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## Association between early lead exposure and externalizing behaviors in adolescence: A developmental cascade

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4 **1 Association between early lead exposure and externalizing behaviors in adolescence:**  
5 **2 a developmental cascade**  
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8 **3**

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39 32 **Keywords:** lead; children and adolescents; externalizing behaviors; binge drinking;  
40 33 **cannabis use.**  
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4 34 **Abstract**

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6 35 **Background:** Lead (Pb) exposure is associated with adverse neurological development.  
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9 36 Most notably, it has been observed through externalizing behavior symptoms, as  
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11 37 observed among Inuit children from northern Québec. Evidence for a persistent  
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14 38 neurological impact of early Pb exposure later in life is however scarce. Pb exposure may  
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16 39 initiate a developmental cascade that increases the risk of long-term behavior problems.  
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19 40 **Objectives:** Testing for direct associations between childhood Pb concentrations and  
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22 41 adolescent externalizing symptoms and substance use, as well as indirect associations  
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24 42 through childhood behavior assessments.  
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27 43 **Methods:** The study sample is a longitudinal cohort of Inuit children (n=212) followed  
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30 44 since birth. Blood Pb concentrations were measured during childhood (median age = 11.4  
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32 45 years) and adolescence (median age=18.5 years). Externalizing/inattentive behavior were  
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35 46 teacher-assessed through the Teacher Report Form and the Disruptive Behavior Disorders  
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37 47 Rating Scale for children. At the adolescence follow-up, behavior problems were self-  
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40 48 reported by filling Achenbach's Youth Self-Report, the Barkley Adult ADHD-IV Rating  
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42 49 Scale, and the Diagnostics Interview Schedule for Children. Adolescent substance use  
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44 50 was also self-assessed through the DEP-ADO. Direct and indirect associations of child  
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47 51 Pb concentrations with adolescent outcomes were tested through mediation models.  
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50 52 **Results:** Child blood Pb concentrations were not directly associated with any adolescent  
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52 53 outcomes. On the contrary, childhood Pb exposure was indirectly associated, through  
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54 54 childhood externalizing behavior assessments, with adolescent externalizing behaviors,  
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57 55 binge drinking, and cannabis use. These indirect associations held after controlling for  
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60 56 adolescents' concurrent Pb blood concentrations.  
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57 **Discussion:** Our results highlight the indirect but lasting effects of child Pb exposure on  
58 adolescent behavior problems, and the importance of childhood externalizing behavior in  
59 this relationship. Adverse early-life environment put children on a riskier developmental  
60 trajectory, increasing their likelihood of lifelong psychological, social and health  
61 problems.

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4 **63 Introduction**

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6 64 Lead (Pb) exposure in children has been associated with negative neurological outcomes  
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8 65 for more than a century (Turner, 1897). In Western countries, policies implemented since  
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10 66 the 1970s were largely successful in reducing Pb exposure. However, certain groups and  
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12 67 subpopulations remain highly exposed to Pb through diverse human-linked sources such  
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14 68 as aged water pipes, dust and paint chips in older neighborhoods, or Pb-based  
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16 69 ammunitions.

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18 70 Pb exposure in children is of particular concern considering its known influence  
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20 71 on developing neurological structures, which may lead to long-lasting cognitive and  
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22 72 behavioral impairments (Télliez-Rojo et al., 2006). Several studies conducted in a variety  
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24 73 of populations, such as major inner cities citizen (Chiodo et al., 2007, 2004; Needleman  
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26 74 et al., 2002) and representative samples in the US (Braun et al., 2006; Froehlich et al.,  
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28 75 2009), South Africa (Naicker et al., 2012), and Inuit children from northern Quebec  
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30 76 (Boucher et al., 2012c), have reported cross-sectional associations between Pb exposure  
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32 77 and numerous externalizing behavior or Attention Deficit Hyperactivity Disorder  
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34 78 (ADHD) symptoms and diagnoses in childhood and adolescence. However, only a  
35  
36 79 handful of longitudinal studies have documented these associations later in adolescence  
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38 80 or early adulthood (Beckley et al., 2018; Burns et al., 1999; Dietrich et al., 2001; Winter  
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40 81 and Sampson, 2017; Wright et al., 2008). Consequences of early Pb exposure throughout  
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42 82 the lifespan still remain largely unknown, in part because of complex interactions with  
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44 83 other determinants of neurodevelopment.

45  
46 84 The long-term effects of early Pb exposure could be explained as a perturbation of  
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48 85 early neurodevelopment that changes the context of later development (Bellinger et al.,  
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50 86 2016). Pb exposure during childhood may not directly cause later behavioral and  
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52 87 cognitive problems; it could instead contribute to putting exposed children on an adverse  
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54 88 developmental path. For this reason, Bellinger et al. (2016) predict that although Pb  
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56 89 exposure is directly associated with childhood behavioral and cognitive outcomes, its  
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58 90 association with adulthood outcomes could be indirect. Thus, instead of a direct  
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60 91 association between Pb exposure during childhood and later problem behaviors, we could  
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62 92 expect a process mediated by the continuation of behavior problems during childhood  
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93 into adolescence, corresponding to the concept of developmental cascade. In this  
94 framework, early Pb exposure would play a role in fostering and maintaining behavior  
95 problems from childhood to early adulthood, highlighting the importance of early-life  
96 environment.

97 In order to incorporate a developmental perspective into the study of effects of  
98 early neurotoxicant exposure, one should take into account the evolution of  
99 manifestations of neurodevelopmental perturbations throughout development. In  
100 adolescence and adulthood, externalizing behaviors manifest themselves as a spectrum of  
101 mental disorders and behaviors, such as substance use and abuse (Krueger et al., 2005),  
102 that children with behavior problems are more likely to develop later in life. A meta-  
103 analysis of longitudinal studies reported that adolescents and young adults who were  
104 diagnosed with ADHD as children were at an increased risk for alcohol use disorder and  
105 cannabis use (Lee et al., 2011). Childhood oppositional defiant/conduct disorder has also  
106 been prospectively associated with later substance use (Groenman et al., 2017). The only  
107 exploratory study, with a limited sample size, investigating the association between  
108 substance use and long-term Pb exposure did not find any significant association  
109 (Fishbein et al., 2008). The mechanisms linking childhood externalizing behaviors with  
110 adolescent or early adulthood substance use remain unclear. One potential mechanism  
111 explaining the increased risk of later substance use may be a vulnerability to disinhibitory  
112 behavior and impulse control (McGue et al., 2001). Accordingly, in this same cohort, our  
113 team has previously published significant results showing an association between child  
114 blood Pb concentrations and impairments in the child's ability to correctly inhibit a  
115 response, resulting in increased impulsivity (Boucher et al., 2012a).

116 In a previous study by our group (Boucher et al., 2012b), we reported a cross-  
117 sectional association between Pb exposure and externalizing symptoms in a sample of  
118 Inuit children with a median age of 11.4 years. The goal of the present study is to expand  
119 these results, which includes a follow-up of the same participants into adolescence. The  
120 Inuit communities in northern Québec practice traditional activities central to their health  
121 and well-being, but some of the practices expose them to multiple environmental  
122 contaminants. The ingestion of Pb ammunition fragments in game meat is their primary

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123 source of Pb exposure (Lévesque et al., 2003). Alongside symptoms of externalizing and  
124 attention problems in adolescence, this study's outcomes include substance use, a  
125 manifestation of externalizing problems in adolescence and adulthood that represent  
126 major public health concern in many indigenous communities across Canada (Firestone  
127 et al., 2015). Therefore, this paper will investigate two processes potentially leading to  
128 the association between child Pb exposure and adolescent externalizing  
129 behaviors/substance use: 1) direct association between child Pb concentrations and  
130 adolescent outcomes and 2) indirect association in which childhood behavior problems  
131 mediate the link between child Pb concentrations and adolescent outcomes, as expected  
132 in a developmental cascade framework.

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5 133 **Methods**

6 134 ***Participants***

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8 135 The participants were Inuit children from the 14 coastal villages of Nunavik, in northern  
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10 136 Québec. Between November 1993 and December 1996, 491 mothers were recruited as  
11  
12 137 part of the Cord Blood Monitoring Program designed to document prenatal exposure to  
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14 138 environmental contaminants and a range of nutrients in Arctic Québec (Dewailly et al.,  
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16 139 1993). An additional 221 mothers were recruited between November 1995 and March  
17  
18 140 2002 as part of the National Institutes of Health (NIH) prospective infancy study  
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20 141 (Jacobson et al., 2008; Muckle et al., 2001). At school age, a subsample of these children  
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22 142 and their primary caregiver ( $n=294$ : 247 from the Cord Blood Monitoring Program and  
23  
24 143 47 from the NIH-infancy study) participated in the Nunavik Child Development Study  
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26 144 (NCDS-childhood), a follow-up designed to examine effects of pre- and postnatal  
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28 145 exposure to environmental contaminants on child behavior and cognitive abilities, which  
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30 146 took place between September 2005 and February 2010. Recruitment methodologies for  
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32 147 both the Cord Blood Monitoring Program and NCDS-childhood samples were reported in  
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34 148 previous studies based on this cohort (Dallaire et al. 2014; Dewailly et al. 1993; Jacobson  
35  
36 149 et al. 2008). The participants were met again during adolescence (NCDS-adolescence)  
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38 150 between January 2013 and February 2016. Inclusion criteria for the NCDS-adolescence  
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40 151 follow-up were participation in the previous two follow-ups, living in Nunavik, and  
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42 152 ability to meet with the research team in one of Nunavik's three main villages. Those  
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44 153 who were identified as suffering from severe health or neurological problems unrelated to  
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46 154 exposure at the NCDS-childhood interview (epilepsy  $n=2$ ; head trauma  $n=1$ ; meningitis  
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48 155  $n=1$ ; multiple sclerosis  $n=1$ ) were excluded from the NCDS-adolescence follow-up. An  
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50 156 additional 49 children of the NCDS-childhood study were not eligible for the follow-up  
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52 157 because they were either deceased, incarcerated, had moved away or were unreachable.  
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54 158 An additional 28 adolescents declined to participate in the follow-up. Thus, a remaining  
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56 159 212 adolescents participated in the NCDS-adolescence study (Fig. 1). As compensation,  
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58 160 the adolescent participants received an electronic device worth \$50 USD.

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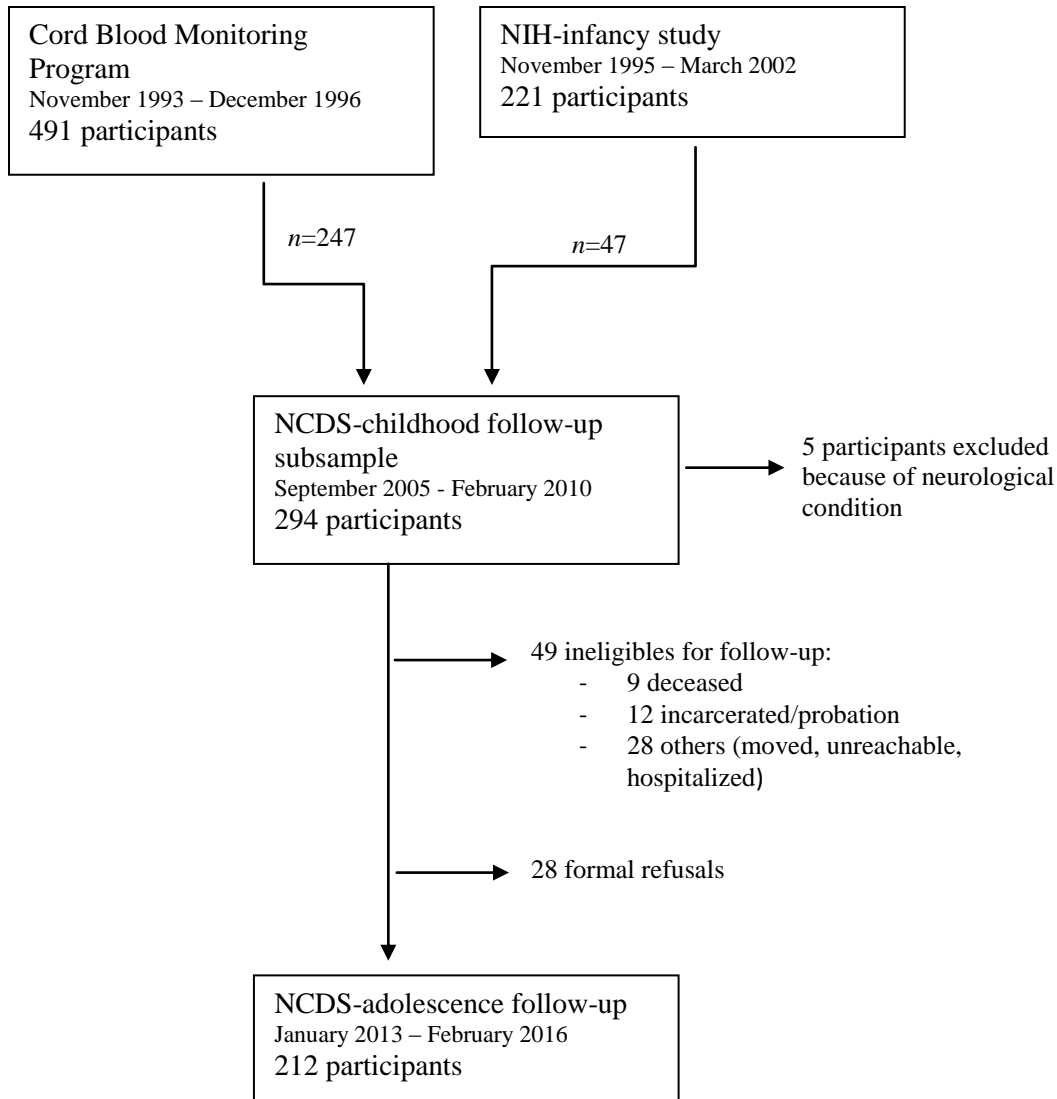


Figure 1. Flow chart for recruitment and follow-up of study participants from November 1993 to February 2016 including reasons and number of excluded participants through follow-ups. Note: NIH, National Institutes of Health; NCDS, Nunavik Child Development Study.

164 The interviews and cognitive/behavioral assessments for the child and adolescent  
 165 follow-ups were conducted in the three largest villages of the region. Participants from  
 166 smaller communities were transported by plane to meet with the research team. Written  
 167 informed consent was provided by the biological mother at recruitment, the primary  
 168 caregiver at the child follow-up, and the participants themselves at the adolescent follow-  
 169 up. The children also gave verbal consent at the childhood follow-up. The Université

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4 170 Laval and Wayne State University ethics committees approved the Infancy and NCDS-  
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6 171 childhood follow-ups, and the ethics committee of the Centre de recherche du CHU de  
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8 172 Québec-Université Laval approved the consent and study procedures at the adolescence.  
9

10 173 ***Biological samples***

11 174 Contaminants and nutrients, including mercury (Hg), Pb and, docosahexaenoic acid  
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13 175 (DHA, an omega-3 fatty acid) were measured in umbilical cord blood samples at birth  
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15 176 (30 mL) and in venous blood samples of children (20 mL) and adolescents (30 mL).  
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17 177 Analyses were performed at the Centre de Toxicologie, Institut National de Santé  
18  
19 178 Publique du Québec (Québec, Canada) for all cord, child, and adolescent contaminant  
20  
21 179 concentrations. Cord and child omega-3 fatty acid composition of plasma phospholipids  
22  
23 180 were analyzed at the University of Guelph Lipid Analytical Laboratory (Guelph, Canada)  
24  
25 181 and at the CHU de Québec for adolescent blood (see Supplemental Material for details of  
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27 182 blood samples analytical procedures).  
28

29 183 ***Child behavior assessment***

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31 184 ***Child externalizing.*** The Child Behavior Checklist (CBCL) from the Achenbach  
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33 185 System of Empirically Based Assessments was used to evaluate externalizing behavior  
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35 186 during childhood (Achenbach and Rescorla, 2001). Each participant's classroom teacher  
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37 187 assessed symptoms through the Teacher Report Form obtained from the research team  
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39 188 via the school principal. The Teacher Report Form includes 112 items rated from 0 to 2  
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41 189 (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). It allows for  
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43 190 computing various syndrome scores by summing the scores of specific items. The  
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45 191 externalizing problems score was obtained by combining both the aggressive behavior  
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47 192 and the rule-breaking behavior scores (sum of 32 of the 112 items). The Teacher Report  
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49 193 Form had never been used with the Inuit population before the NCDS-childhood study  
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51 194 (Boucher et al. 2012), but internal consistency of the externalizing subscale was high  
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53 195 ( $\alpha_{\text{ordinal}} = 0.97$ ). No normative data was available for Inuit children, thus raw scores were  
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55 196 used in all statistical analyses as in the childhood study.

56 197 ***Child hyperactivity-impulsivity.*** The Disruptive Behavior Disorders Rating Scale  
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58 198 (DBD), designed to be completed by parents and teachers, provides the information  
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60 199 necessary for clinical diagnoses of disruptive behaviors in children (Pelham et al., 1992).  
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4 200 The questionnaire is composed of 45 behavioral descriptors rated on a four-point  
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6 201 frequency scale ('never', 'sometimes', 'often', 'very often') based on the *Diagnostic and*  
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8 202 *Statistical Manual of Mental Disorders, 4<sup>th</sup> edition* (DSM-IV). A symptom was  
9  
10 203 considered present if reported as 'often' or 'very often' by the participant's classroom  
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12 204 teacher, and the symptom score (continuous) was computed as the count of hyperactivity-  
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14 205 impulsivity symptoms. This assessment tool has never been validated in the Inuit  
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16 206 population; however, internal consistency was high ( $\alpha_{\text{ordinal}} = 0.92$ ). Even though Boucher  
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18 207 et al. (2012) used the diagnostic/dichotomous scores, we used the continuous scores to  
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20 208 maximize statistical power in the context of a mediation model.

21  
22 209 ***Child oppositional defiant and conduct disorder (OD/CD).*** The DBD was also  
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24 210 used to evaluate symptoms of oppositional defiant disorder and conduct disorder in  
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26 211 children. The DBD has two separate scales for oppositional defiant disorder (8 items) and  
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28 212 conduct disorder (15 items; Pelham et al. 1992). A symptom was considered present if  
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30 213 reported as 'often' or 'very often' by the participant's classroom teacher. Because most  
31  
32 214 (88%) children identified as CD were also identified as OD, children meeting criteria for  
33  
34 215 either of these diagnoses were grouped together in the statistical analyse (Boucher et al.,  
35  
36 216 2012c). Internal consistency was high ( $\alpha_{\text{ordinal}} = 0.95$ ) and the continuous score was  
37  
38 217 retained in analyses.

### 38 218 ***Adolescent behavior assessment***

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40 219 ***Adolescent externalizing.*** The Youth Self-Report 2001-revision (YSR) from the  
41  
42 220 Achenbach System of Empirically Based Assessments was used to evaluate externalizing  
43  
44 221 behavior during adolescence (Achenbach and Rescorla, 2001). This screening tool is  
45  
46 222 intended for use with youths up to 18 years of age. The interviewer asked the participant  
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48 223 to rate the frequency of their symptoms from 0 to 2 (0 = not true, 1 = somewhat or  
49  
50 224 sometimes true, 2 = very true or often true) for each of the 112 items included in the self-  
51  
52 225 report form. The externalizing problems score was obtained by combining the aggressive  
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54 226 behavior and the rule-breaking behavior scores (sum of 32 of the 112 items).The YSR  
55  
56 227 has never been used in the Inuit population before, but internal consistency of the  
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58 228 externalizing subscale was high ( $\alpha_{\text{ordinal}} = 0.88$ ). No normative data was available for Inuit  
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60 229 adolescents, thus raw score were used in all statistical analyses.

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230           **Adolescent hyperactivity-impulsivity.** The Barkley Adult ADHD-IV Rating Scale  
231 (BAARS) is a questionnaire based on the DSM-IV-TR diagnostic criterion for ADHD,  
232 which also assesses ADHD symptoms and subtypes (inattention, hyperactivity-  
233 impulsivity) and total ADHD in American adults aged 18 to 81 years of age (Barkley,  
234 2011). The subtype hyperactivity-impulsivity was used for its similarity with the  
235 childhood measure of hyperactivity-impulsivity. The interviewer asked participants to  
236 rate how often they exhibited each symptom ('never', 'sometimes', 'often', 'very often').  
237 A symptom was considered present if reported as present 'often' or 'very often', and a  
238 symptom score was computed as the count of symptoms present for hyperactivity-  
239 impulsivity items (5 and 4 items, respectively). The BAARS has never been validated in  
240 the Inuit population, but the internal consistency of the selected subscale was acceptable  
241 ( $\alpha_{\text{ordinal}} = 0.76$ ).

242           **Adolescent conduct disorder.** The Diagnostic Interview Schedule for Children  
243 (DISC-IV) is a structured diagnostic instrument originally developed to assess 34  
244 psychiatric disorders in epidemiological studies on children and adolescents. Designed to  
245 collect information corresponding to the DSM-IV diagnostic criterion, it has since been  
246 used in clinical studies and service settings (Shaffer et al., 2000). The eight-item  
247 subsection of the DISC-IV on conduct disorder was included in the adolescent follow-up.  
248 We included it in our analyses for its similarity with the childhood measure of OD/CD.  
249 The participants were asked if the behavior described in each item applied to them  
250 (yes/no). The count of items present was used as an adolescent conduct disorder score.  
251 Neither the DISC-IV nor any subsection were validated in the Inuit population, but  
252 internal consistency in our sample was moderate ( $\alpha_{\text{ordinal}} = 0.77$ ).

253           **Adolescent substance use.** The DEP-ADO 3.2 is a substance use evaluation grid  
254 originally developed and tested for use among Quebec's French-speaking adolescents (12  
255 to 18 years old; Landry et al. 2004). The seven-question grid evaluates frequency,  
256 intensity and age of initiation of alcohol and drug use. Additional items were added to our  
257 questionnaire to describe the drinking environment (during a meal, at a party, etc.) and  
258 motives. Questions about age of substance use initiation were added at the third of four  
259 data collection trips, therefore age at first use data was available only for half of the

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4 260 participants. The binge drinking score (continuous) was defined as the number of days, in  
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6 261 the last year, where more than five/eight alcohol beverages were consumed in one  
7  
8 262 occasion (for women/men). The cannabis use frequency was modeled at four levels:  
9  
10 263 never,  $\leq$ once a month, 1-6 times per week and daily.

#### 11 264 *Covariates*

12  
13  
14 265 Paths in the mediation analysis (exposure to mediator, mediator to outcome, direct and  
15  
16 266 indirect effect) are modeled by two regression analyses. Therefore, for each regression  
17  
18 267 model, a different set of confounding variables was investigated. An *a priori* list of  
19  
20 268 candidate variables was built for each relation based on previous knowledge and the Inuit  
21  
22 269 population's specificities, including child age and sex (Claycomb et al., 2004),  
23  
24 270 socioeconomic status (SES) (Froehlich et al., 2007), age of biological mother at delivery  
25  
26 271 (Claycomb et al., 2004), maternal tobacco use during pregnancy (Huang et al., 2018),  
27  
28 272 birth weight (Lim et al., 2018), gestational age (Bhutta et al., 2002), adoption status  
29  
30 273 (Decaluwe et al., 2015), and house crowding (Solarig and Mare, 2012).

31 274 *Confounders in the prediction of the child behavior scores.* The same  
32  
33 275 confounding variables as those selected in Boucher et al. (2012) were included in the  
34  
35 276 prediction of childhood behaviors (mediators) from childhood Pb exposure: child age,  
36  
37 277 sex, and birth weight, and childhood socioeconomic status, age of biological mother at  
38  
39 278 delivery, maternal tobacco use during pregnancy, and cord blood Hg

40  
41 279 *Confounders in the prediction of adolescent outcomes.* Age at adolescent testing,  
42  
43 280 sex, and SES of principal care provider at the adolescence follow-up were treated as  
44  
45 281 obligatory covariates. Adolescent schooling level was not considered because of its  
46  
47 282 presence in the hypothetical causal pathway.

48  
49 283 The potential covariates considered for the association between child blood Pb  
50  
51 284 concentrations and adolescent outcomes, as well as for the association between child  
52  
53 285 behavior (mediators) and adolescent outcomes were the same. They included a)  
54  
55 286 participant characteristics: birth weight, adoption status (yes/no), and suicidal thoughts in  
56  
57 287 adolescence (yes/no); b) maternal and family characteristics: gestational age, breast  
58  
59 288 feeding duration, primary caregiver education level, age and parity of biological mother  
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61 289 at delivery, marital status (single or not),maternal non verbal reasoning ability at child

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4 290 follow-up (Raven et al., 1992), and childhood and adolescent domestic crowding (> 1  
5  
6 291 person per room; yes/no); c) contaminants and nutrients: cord, child and adolescent blood  
7  
8 292 Hg concentrations, and DHA expressed in percentage by weight of total fatty acids in  
9  
10 293 plasma phospholipids. Blood lead concentrations measured in cord blood and at  
11  
12 294 adolescent follow-up were also considered.

### 13 14 295 *Statistical analyses*

15  
16 296 Descriptive statistics, t-test, Wilcoxon tests and Pearson's Chi-squared tests were  
17  
18 297 computed with the R 3.5.0 software (R Core Team, 2018). The *psych* and *GPArotation*  
19  
20 298 packages were used to obtain ordinal alphas, Pearson correlations and confidence  
21  
22 299 intervals (Bernaards and Jennrich, 2005; Revelle, 2018). The *RVAideMemoire* package  
23  
24 300 was used to compute Spearman correlations and confidence intervals (Hervé, 2018). The  
25  
26 301 *BaylorEdPsych* package was used to perform missing data pattern analysis and test the  
27  
28 302 missing completely at random (MCAR) assumption (Beaujean, 2012).

29  
30 303 *Assumptions.* Continuous variables' distributions were visually checked for  
31  
32 304 normality and the following variables were log<sub>2</sub>-transformed: contaminant variables,  
33  
34 305 mother's age at delivery, child externalizing problems scores and number of binge  
35  
36 306 drinking days in the last year. We analysed the missing value patterns to assess potential  
37  
38 307 bias. The most common missing data were adolescent domestic crowding (5.2%, *n*=11),  
39  
40 308 binge drinking (4.7%, *n*=10), cannabis use (4.2%, *n*=9) and pregnancy tobacco use  
41  
42 309 (2.8%, *n*=6). Little's MCAR test indicated no systematic bias arising from missingness  
43  
44 310 ( $\chi^2 = 308.81$ , *df* = 324, *p* = 0.72; Little 1988).

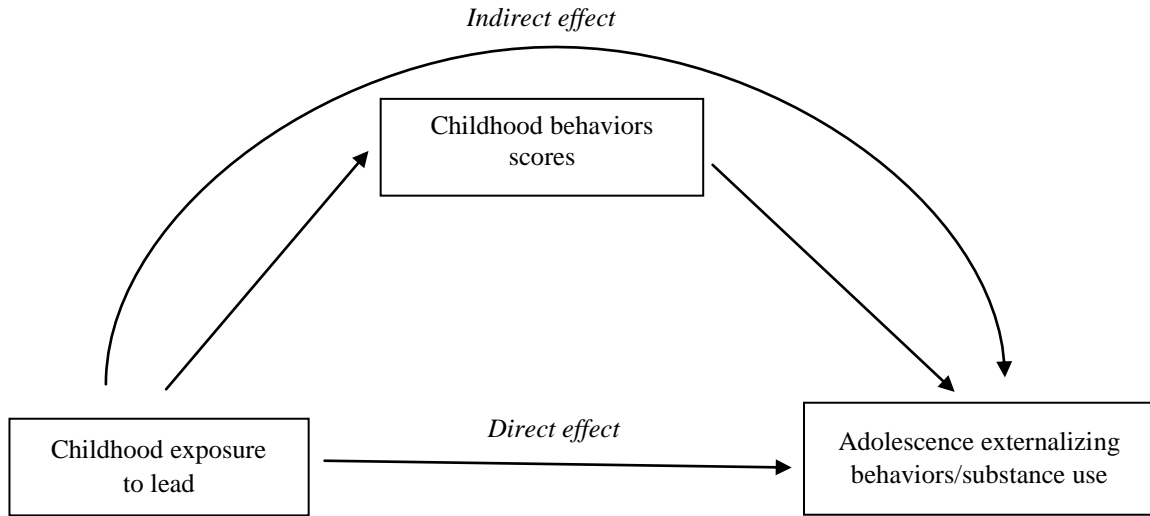
45  
46 311 *Bivariate associations.* We computed either Pearson or Spearman correlations  
47  
48 312 depending on the distribution of the variables to document associations between  
49  
50 313 mediators and outcomes (Table 2). Correlations were also performed to document  
51  
52 314 associations between adolescent blood Pb concentrations and adolescent outcomes.

53  
54 315 *Confounders selection.* Linear and ordinal regressions were performed prior to  
55  
56 316 mediation analysis to evaluate the final inclusion of confounding variables in models.  
57  
58 317 Covariates were included in a forward selection process: variables associated (*p* < 0.20)  
59  
60 318 with both the mediator and the outcome were entered in decreasing order of association  
61  
62 319 with the outcome and were retained if they altered the association by  $\pm 10\%$  (Rothman et

1  
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4 320 al., 2008). When the correlation between two *a priori* potential confounders was greater  
5  
6 321 than  $\rho=0.4$  we only retained the one with the strongest association with the outcome. This  
7  
8 322 selection process of confounding variables followed the same principles and criteria  
9  
10 323 previously used by Boucher et al. (2012).

11  
12 324 **Mediation analyses.** Mediation analyses were conducted to examine the direct  
13  
14 325 and indirect association between child Pb exposure and adolescent externalizing  
15  
16 326 behaviors/substance use by testing three different childhood behaviors scores as  
17  
18 327 mediators based on the results of Boucher et al. (2012; Figure 2). Six mediation analyses  
19  
20 328 were conducted with the three childhood behavior scores as mediators (externalizing,  
21  
22 329 hyperactive-impulsive and OD/CD) to predict their corresponding adolescent behavioral  
23  
24 330 outcomes. Three more were conducted to predict adolescent substance use outcomes  
25  
26 331 (binge drinking and cannabis use) through the same mediators (Figure 2). The parameters  
27  
28 332 were estimated using structural equation modeling in Mplus 8.1 (Muthén and Muthén,  
29  
30 333 2017).

31  
32 334 Within the mediation models, linear regressions were used to model continuous  
33  
34 335 outcomes, whereas probit regression was used for the ordinal outcome (cannabis use).  
35  
36 336 The product of coefficients method was used to estimate the indirect effect in all models  
37  
38 337 (MacKinnon et al., 2007). Full information maximum likelihood (FIML) or weighted  
39  
40 338 least squares means variance adjusted (WLSMV, for the ordinal outcome) estimators  
41  
42 339 were used to minimise the exclusion of participants because of missing values (Enders  
43  
44 340 and Bandalos, 2001). The assumption of missing at random (for FIML) and missing at  
45  
46 341 random with respect to independent variables (for WLSMV) were both met since our  
47  
48 342 data were considered missing completely at random based on Little's MCAR test  
49  
50 343 (Asparouhov and Muthén, 2010). The bias-corrected and accelerated 95% confidence  
51  
52 344 intervals (95% CI) were estimated by bootstrap (10 000 resamples; Hayes & Scharkow,  
53  
54 345 2013). Non-parametric bootstrap methods were preferred to protect against the effects of  
55  
56 346 departure from the normality assumption underlying parametric confidence intervals  
57  
58 347 (Carpenter and Bithell, 2000). Model fit was assessed via three fit statistics: the model  
59  
60 348 chi-square ( $\chi^2$ ), the comparative fit index (CFI) and the root mean square error of  
61  
62 349 approximation (RMSEA; Hooper, Coughlan, & Mullen, 2008).



**Figure 2.** Path diagram showing the associations tested in mediation analyses. Direct effect refer to the association from child blood lead concentrations and externalizing behavior/substance use in the adolescence follow-up. Indirect effect refer to the association of child blood lead concentrations on adolescent's externalizing behaviors/substance use outcomes through childhood behaviors scores.



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351 **Results**

352 *Descriptive analyses*

353 *Sample characteristics.* Participants ranged in age from 9-14 years (median 11.37  
354 years) at the childhood follow-up visit and between 16-22 years at the adolescent follow-  
355 up (median 18.48 years; see Table 1). A third of the participants were still in school at the  
356 adolescent follow-up, whereas more than 35% were fully employed. The median blood  
357 Pb concentrations were higher during childhood (2.07 µg/dL) than at the adolescence  
358 (1.52 µg/dL). The majority of participants showed few symptoms of externalizing  
359 behaviors at both the childhood and adolescent follow-ups. Substance use was very  
360 common among adolescents, with over 40% of participants drinking alcohol at least  
361 weekly and more than half using cannabis at least weekly. Tobacco was the most  
362 widespread substance used, with nearly 8 of 10 participants (79.50%) smoking daily.

363 Of the 294 participants at the childhood follow-up, 212 participated in the  
364 adolescent follow-up (72%). Men were more likely to be lost at follow-up (64.6% vs.  
365 44.3%, p=0.003). Participants with higher scores on the OD/CD scale were more likely to  
366 be lost at follow-up (mean of 2.33 for participants at the adolescent follow-up and of 3.73  
367 for those lost).

Variables	<i>N</i>	Mean ± SD or <i>n</i> (%)	Median	Range
<b>Family/birth characteristics</b>				
Marital status (% married or living with someone)	211	156 (73.90)		
Parity before child birth	212	1.97 ± 1.79	2.00	0.00 – 8.00
Maternal tobacco smoking pregnancy (% yes)	206	177 (85.92)		
Maternal age at delivery (years)	212	23.69 ± 5.67	22.25	15.00 – 42.00
Gestational age (weeks)	212	39.20 ± 1.44	39.00	36.00 – 44.00
Birth weight (kg)	212	3.48 ± 0.46	3.50	2.44 – 4.74
Child sex (% girls)	212	118 (55.66)		
Breast-feeding status (% yes)	207			
None		52 (25.62)		
0 < 3 months		36 (17.73)		
3 < 6 months		24 (11.82)		
≥ 6 months		91 (44.83)		
Cord blood Pb, geomean ± GSD (µg/dL)	204	3.80 ± 1.84	3.73	0.83 – 17.80
Cord blood Hg, geomean ± GSD (µg/dL)	204	1.52 ± 2.15	1.53	0.18 – 9.93
Cord blood DHA (% total fatty acids)	203	1.60 ± 1.29	3.44	1.12 – 7.73
<b>Childhood characteristics</b>				
Age (years)	212	11.34 ± 0.71	11.37	9.32 – 13.97
Adoption status (% adopted)	212	33 (15.57)		
Primary caregiver education (years completed)	211	8.45 ± 2.61	9.00	0.00 – 16.00
SES score <sup>a</sup>	212	28.59 ± 11.38	28.25	8.00 – 66.00
Behaviors (teachers assessment)				
Externalizing - CBCL	205	14.23 ± 12.78	11.00	0.00 – 53.00
Hyperactivity-impulsivity - DBD	207	1.72 ± 2.51	0.00	0.00 – 9.00
Oppositional defiant/conduct disorder - DBD	207	2.33 ± 3.37	1.00	0.00 – 16.00
Blood Pb, geomean ± GSD (µg/dL)	210	2.34 ± 1.86	2.07	0.54 – 12.83
Blood Hg, geomean ± GSD (µg/dL)	210	3.36 ± 2.56	3.41	0.05 – 28.02
Blood DHA (% total fatty acids)	209	2.40 ± 0.97	2.21	0.60 – 4.96
<b>Adolescent characteristics</b>				
Age (years)	212	18.47 ± 1.11	18.48	16.01 – 21.88
Main language at home (% mainly Inuktitut)	210	200 (95.24)		
SES principal provider	207	28.59 ± 13.01	28.00	8.00 – 61.00
In a relationship (% yes)	209	95 (45.45)		
Education	210		3.00	0.00 – 5.00
Secondary 1 or less		46 (21.9)		
Secondary 2 or 3		105 (50.0)		
Secondary 4 or higher		59 (28.1)		
Occupational status (% yes)	210			
Working		75 (35.71)		
School		34 (16.19)		
Both		37 (17.62)		
None		64 (30.48)		
Behaviors (self-reported)				
Externalizing - CBCL	210	15.80 ± 7.46	15.00	0.00 – 40.00
Hyperactivity-impulsivity - BAARS	203	1.59 ± 1.52	1.00	0.00 – 6.00
Conduct disorder - DISC	212	0.94 ± 1.21	1.00	0.00 – 5.00
<b>Substance use</b>				
Age started drugs regular basis (years)	127	14.72 ± 1.93	15.00	7.00 – 19.00
Age started alcohol regular basis (years)	106	15.76 ± 1.63	16.00	10.00 – 19.00
Cannabis use (% , last 12 months)	203			
Never		63 (31.03)		
≤ 1 / month		34 (16.75)		
1-6 times / week		42 (20.69)		
Everyday		64 (31.53)		
Tobacco smoking (% , last 12 months)	200			
None		24 (12.00)		
Occasional		17 (8.50)		
Daily		159 (79.50)		
Alcohol use (% last 12 months)	203	177 (87.19)		
Binge drinking days (number in last year) <sup>b</sup>	176	36.40 ± 47.16	12.00	0.00 – 250.00
Blood Pb, geomean ± GSD (µg/dL)	212	1.63 ± 2.00	1.52	0.35 – 18.13
Blood Hg, geomean ± GSD (µg/dL)	212	3.82 ± 2.76	4.21	0.14 – 36.11
Blood DHA (% total fatty acids)	212	3.35 ± 1.21	3.32	0.60 – 7.12

Note: Pb, lead; Hg, mercury; DHA, docosahexaenoic acid; GSD, geomean standard deviation; CBCL, Child Behavior Checklist; DBD, Disruptive Behavior Disorders Rating Scale; BAARS, Barkley Adult ADHD-IV Rating Scale; DISC, Diagnostic Interview Schedule for Children.

<sup>a</sup>Assessed on the Hollingshead Index, which represents a weighted score of parental occupation (type of work) and education level (Hollingshead, 1975).

<sup>b</sup>Binge drinking, among drinkers, corresponds to consumption of ≥ 5 standard drinks per occasion for women and 8 for men; 1 standard drink ~ 0.5 oz absolute alcohol (~ 350 mL of beer (12 oz), 175 mL of wine (6 oz), or 44 mL of liquor (1.5 oz)).



392 Table 2 – Pearson and Spearman correlation coefficients (95% Confidence Intervals) between mediators and outcomes

	Childhood			Adolescence					
	Externalizing <sup>a</sup>	Hyperactivity-impulsivity <sup>a</sup>	OD/CD <sup>a</sup>	Blood Pb	Externalizing <sup>b</sup>	Hyperactivity-impulsivity <sup>b</sup>	Conduct disorder <sup>b</sup>	Binge drinking <sup>b</sup>	Cannabis use <sup>b</sup>
<b>Childhood</b>									
Blood Pb	<b>0.26</b> (0.12, 0.39)	<b>0.21<sup>SP</sup></b> (0.07, 0.35)	<b>0.20<sup>SP</sup></b> (0.06, 0.32)	<b>0.40 (0.28, 0.51)</b>	0.08 (-0.04, 0.22)	0.10 (-0.04, 0.23)	0.08 <sup>SP</sup> (-0.06, 0.21)	-0.03 (-0.17, 0.08)	0.12 <sup>SP</sup> (-0.02, 0.25)
Externalizing <sup>a</sup>	1	<b>0.73<sup>SP</sup></b> (0.66, 0.79)	<b>0.82<sup>SP</sup></b> (0.77, 0.87)	<b>0.25</b> (0.13, 0.36)	<b>0.20</b> (0.009, 0.32)	-0.003 (-0.13, 0.14)	0.09 <sup>SP</sup> (-0.05, 0.22)	0.14 (-0.02, 0.28)	<b>0.20<sup>SP</sup></b> (0.06, 0.33)
Hyperactivity-impulsivity <sup>a</sup>	-	1	<b>0.65<sup>SP</sup></b> (0.56, 0.72)	<b>0.18<sup>SP</sup></b> (0.04, 0.30)	0.11 <sup>SP</sup> (-0.02, 0.25)	-0.01 <sup>SP</sup> (-0.16, 0.14)	0.07 <sup>SP</sup> (-0.07, 0.21)	0.05 <sup>SP</sup> (-0.09, 0.19)	0.10 <sup>SP</sup> (-0.04, 0.23)
OD/CD <sup>a</sup>	-	-	1	<b>0.21<sup>SP</sup></b> (0.08, 0.33)	<b>0.19<sup>SP</sup></b> (0.05, 0.32)	-0.04 <sup>SP</sup> (-0.17, 0.10)	0.08 <sup>SP</sup> (-0.05, 0.22)	0.10 <sup>SP</sup> (-0.04, 0.24)	<b>0.23<sup>SP</sup></b> (0.08, 0.36)
<b>Adolescence</b>									
Blood Pb	-	-	-	1	0.01 (-0.12, 0.15)	-0.04 (-0.17, 0.09)	0.05 <sup>SP</sup> (-0.08, 0.19)	<b>0.16</b> (0.03, 0.30)	0.13 <sup>SP</sup> (-0.02, 0.27)
Externalizing <sup>b</sup>	-	-	-	-	1	<b>0.44</b> (0.32, 0.57)	<b>0.34<sup>SP</sup></b> (0.21, 0.45)	<b>0.22</b> (0.10, 0.34)	<b>0.32<sup>SP</sup></b> (0.19, 0.43)
Hyperactivity-impulsivity <sup>b</sup>	-	-	-	-	-	1	<b>0.16<sup>SP</sup></b> (0.03, 0.29)	0.10 (-0.04, 0.24)	-0.02 <sup>SP</sup> (-0.15, 0.12)
Conduct disorder <sup>b</sup>	-	-	-	-	-	-	1	0.09 <sup>SP</sup> (-0.05, 0.23)	<b>0.18<sup>SP</sup></b> (0.05, 0.31)
Binge drinking <sup>b</sup>	-	-	-	-	-	-	-	1	<b>0.17<sup>SP</sup></b> (0.03, 0.30)

393 Sample size for individual comparisons varies between 195 and 212 due to missing values.

394 Note: OD/CD, Oppositional defiant/conduct disorder;<sup>a</sup> teachers assessment, <sup>b</sup> self-reported with assistance of interviewer, <sup>SP</sup>, Spearman coefficient.

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4 395 ***Mediation analyses***

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6 396 ***Associations between child Pb and adolescent behavior scores.*** We investigated  
7  
8 397 the effect of child blood Pb concentrations on adolescent behavior scores, directly and  
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10 398 indirectly through their corresponding child behavior scores (Table 3). No direct  
11  
12 399 association was observed between child Pb concentrations and any of the adolescent  
13  
14 400 behavior scores. However, a significant indirect association was observed between child  
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16 401 blood Pb concentrations and adolescent externalizing problem through child externalizing  
17  
18 402 problem scores [0.32 (95% CI: 0.08, 0.72)]. Thus, a 2-fold increase in blood Pb  
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20 403 concentrations units explained on average an increase of 0.25 symptoms on the  
21  
22 404 adolescent externalizing problem score. No indirect association was observed with the  
23  
24 405 adolescent hyperactivity-impulsivity or with adolescent conduct disorder scores. Fit  
25  
26 406 statistics were good for the adolescent externalizing problem and hyperactivity-  
27  
28 407 impulsivity models and acceptable for the adolescent conduct disorder model.

29  
30 408 ***Association between child Pb and adolescent substance use.*** We examined the  
31  
32 409 effect of child blood Pb concentrations on adolescent substance use, directly and  
33  
34 410 indirectly through child behavior scores (Table 4). No direct association was observed  
35  
36 411 between child Pb exposure and any of the adolescent substance use. Significant indirect  
37  
38 412 associations were observed between child blood Pb concentrations and both binge  
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40 413 drinking and cannabis use through child externalizing problem scores [0.09 (95% CI:  
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42 414 0.02, 0.23)] and [0.05 (95% CI: 0.002, 0.14)], respectively. A 2-fold increase in blood Pb  
43  
44 415 concentrations explains on average an increase of 0.06 binge drinking episode per year.  
45  
46 416 There is no straight-forward way to assess the effect size of an ordinal regression  
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48 417 included in a mediation model. The 0.04 indirect association estimate in the cannabis use  
49  
50 418 model can be interpreted as the probability to move from an inferior category of cannabis  
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52 419 use frequency to a superior one for each 2-fold increase in blood Pb concentrations units.  
53  
54 420 Fit statistics were acceptable for binge drinking models and good for cannabis use  
55  
56 421 models.

422 1 Table 3 - Mediation analysis of childhood Pb exposure on adolescent externalizing behaviors, using childhood behavior scores as mediator. Regression coefficients (95% CI) and fit indices ( $n=212$ ).

		Adolescent		
Mediator		Externalizing Estimate (95% CI)	Hyperactivity-impulsivity Estimate (95% CI)	Conduct disorder Estimate (95% CI)
Child externalizing ( $\log_2$ -transformed)				
Child Pb $\rightarrow$ Child externalizing <sup>a</sup>		<b>0.42 (0.15, 0.69)</b>		
Child externalizing $\rightarrow$ Adolescent externalizing <sup>b</sup>		<b>0.77 (0.15, 1.36)</b>		
Direct effect		0.61 (-0.63, 1.96)		
Indirect effect		<b>0.32 (0.08, 0.72)</b>		
$\chi^2$ (df), $p$ -value		10.24(8), 0.25		
CFI		0.92		
RMSEA (90% CI)		0.04 (0.00, 0.09)		
Child hyperactivity-impulsivity				
Child Pb $\rightarrow$ Child hyperactivity-impulsivity <sup>a</sup>			<b>0.58 (0.17, 0.99)</b>	
Child hyperactivity-impulsivity $\rightarrow$ Adolescent hyperactivity-impulsivity <sup>c</sup>			-0.03 (-0.12, 0.06)	
Direct effect			0.11 (-0.14, 0.37)	
Indirect effect			-0.02 (-0.09, 0.03)	
$\chi^2$ (df), $p$ -value			5.01(8), 0.75	
CFI			1.00	
RMSEA (90% CI)			<0.01 (0.00, 0.06)	
Child oppositional defiant/conduct disorder				
Child Pb $\rightarrow$ Child OD/CD <sup>a</sup>				<b>0.67 (0.11, 1.25)</b>
Child OD/CD $\rightarrow$ Adolescent conduct disorder <sup>d</sup>				0.02 (-0.03, 0.08)
Direct effect				0.02 (-0.20, 0.21)
Indirect effect				0.02 (-0.01, 0.07)
$\chi^2$ (df), $p$ -value				7.29(7), 0.40
CFI				0.98
RMSEA (90% CI)				0.01 (0.002, 0.09)

423 37 Note : CI, Confidence interval;  $\chi^2$ (df), chi square (degrees of freedom); CFI, comparative fit index; RMSEA, root mean square error of approximation; OD/CD, Oppositional defiant/conduct disorder.

424 38 <sup>a</sup>Adjusted for child age and sex, SES, age of the biological mother at delivery, maternal tobacco smoking during pregnancy, and birth weight. Models with child hyperactivity-impulsivity and child OD/CD as mediator were also  
 425 39 adjusted for cord Hg ( $\log_2$ -transformed).

426 40 <sup>b</sup>Adjusted for adolescent age and sex, provider SES, and child blood Hg ( $\log_2$ -transformed).

427 41 <sup>c</sup>Adjusted for adolescent age and sex, provider SES, age of the biological mother at delivery and education level of the primary caregiver at child follow-up .

428 42 <sup>d</sup>Adjusted for adolescent age and sex, provider SES, age of the biological mother at delivery, maternal tobacco use during pregnancy, and house crowding at adolescence follow-up.

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430 1 Table 4 - Mediation analysis of childhood Pb exposure on adolescent substance use, using childhood behavior scores as mediator. Regression coefficients (95% CI) and fit indices (n=212).

		Adolescent	
Mediator		Binge drinking (log <sub>2</sub> -transformed) Estimate (95% CI)	Cannabis use Estimate (95% CI)
Child externalizing (log <sub>2</sub> -transformed)			
Child Pb → Child externalizing <sup>a</sup>		<b>0.41 (0.14, 0.69)</b>	0.45 (0.01, 0.85)
Child externalizing → Adolescent substance use <sup>b</sup>		<b>0.22 (0.02, 0.43)</b>	<b>0.11 (0.01, 0.20)</b>
Direct effect		-0.23 (-0.65, 0.21)	0.04 (-0.24, 0.31)
Indirect effect		<b>0.09 (0.02, 0.23)</b>	<b>0.05 (0.002, 0.14)</b>
χ <sup>2</sup> (df), p-value		12.39(9), 0.19	16.69(11), 0.12
CFI		0.92	0.98
RMSEA (90% CI)		0.04 (0.00, 0.09)	0.05 (0.00, 0.10)
Child hyperactivity-impulsivity			
Child Pb → Child hyperactivity-impulsivity <sup>a</sup>		<b>0.57 (0.16, 0.99)</b>	<b>0.59 (0.09, 1.06)</b>
Child hyperactivity-impulsivity → Adolescent substance use <sup>c</sup>		-0.001 (-0.14, 0.14)	0.03 (-0.04, 0.09)
Direct effect		-0.15 (-0.58, 0.31)	0.10 (-0.15, 0.40)
Indirect effect		0.001 (-0.09, 0.09)	0.02 (-0.02, 0.08)
χ <sup>2</sup> (df), p-value		13.06(10), 0.22	9.73(11), 0.56
CFI		0.90	1.00
RMSEA (90% CI)		0.04 (0.00, 0.09)	0.00 (0.00, 0.07)
Child oppositional defiant/conduct disorder			
Child Pb → Child OD/CD <sup>a</sup>		<b>0.66 (0.11, 1.25)</b>	0.68 (-0.02, 1.33)
Child OD/CD → Adolescent substance use <sup>d</sup>		0.04 (-0.07, 0.15)	0.04 (-0.01, 0.08)
Direct effect		-0.17 (-0.59, 0.28)	0.09 (-0.18, 0.38)
Indirect effect		0.02 (-0.04, 0.15)	0.02 (-0.002, 0.08)
χ <sup>2</sup> (df), p-value		20.05(12), 0.07	11.09(10), 0.35
CFI		0.74	0.99
RMSEA(90% CI)		0.06 (0.00, 0.10)	0.02 (0.00, 0.08)

43135 Note : CI, Confidence interval; χ<sup>2</sup>(df), chi square (degrees of freedom); CFI, comparative fit index; RMSEA, root mean square error of approximation; OD/CD, Oppositional defiant/conduct disorder.

43236 <sup>a</sup>Adjusted for child age and sex, SES, age of the biological mother at delivery, maternal tobacco use during pregnancy, and birth weight. Models with child hyperactivity-impulsivity and child OD/CD as mediator were also adjusted  
43337 for cord Hg (log<sub>2</sub>-transformed).

43438 <sup>b</sup>Both models adjusted for adolescent age and sex, provider SES, and adolescent blood Pb (log<sub>2</sub>-transformed). Model with binge drinking as outcome was also adjusted for birth weight, adoption status, and house crowding at  
43539 adolescence follow-up. Model with cannabis use as outcome was also adjusted for breast feeding duration.

43640 <sup>c</sup>Both models adjusted for adolescent age and sex, provider SES, and adolescent blood Pb(log<sub>2</sub>-transformed). Model with binge drinking as outcome was also adjusted for birth weight, adoption status and house crowding at  
43741 adolescence follow-up. Model with cannabis use as outcome was also adjusted for educational level of the primary caregiver at child follow-up and child blood Hg.

43842 <sup>d</sup>Both models adjusted for adolescent age and sex, provider SES, and adolescent blood Pb (log<sub>2</sub>-transformed). Model with binge drinking as outcome was adjusted for adoption status and house crowding at adolescence follow-up.  
43943 Model with cannabis use as outcome was also adjusted for educational level of the primary caregiver at child follow-up

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5 440 **Discussion**  
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8 441 The main objective of this study was to test the developmental cascade linking child  
9 442 blood Pb concentrations with adolescent behavior problems/substance use through  
10 443 behavior problems assessed in childhood. Child blood Pb concentrations were associated  
11 444 with behavioral challenges at the same age as previously reported by Boucher et al.  
12 445 (2012), and these problems, in turn, predicted externalizing behaviors and substance use  
13 446 in adolescence. Direct associations between child blood Pb concentrations and any of the  
14 447 adolescent behavior assessments or with substance use were not significant. Thus, child  
15 448 Pb concentrations were associated with some problem outcomes in adolescence but only  
16 449 indirectly through child externalizing problem score. No indirect associations linked  
17 450 childhood Pb concentrations with adolescent outcomes through child hyperactivity-  
18 451 impulsivity or conduct disorder scores. While the presence of a direct effect was  
19 452 previously considered as the first step in a mediation analysis, it is now recognized that  
20 453 some relationships may be only indirect through a mediator. This is particularly relevant  
21 454 in the longitudinal investigation of externalizing behavior given the persistence from  
22 455 childhood to adolescence/adulthood of behaviors reported in other cohorts (Reef et al.,  
23 456 2011).

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38 457 The indirect associations observed in our study between child Pb concentrations  
39 458 and adolescent outcomes are consistent with the developmental cascades hypothesized by  
40 459 Bellinger et al. (2016). In a developmental framework, such a cascade would start with an  
41 460 early-life neurotoxic exposure affecting some child characteristics, which in turn  
42 461 modifies the neurocognitive development, and consequently cause lifelong impairments.  
43 462 In this context, an intermediary endpoint is considered as a mediating factor between the  
44 463 child's prior exposure and later end-points (Bellinger et al., 2016). The developmental  
45 464 cascades framework predicts direct paths between early exposure and childhood  
46 465 outcomes and indirect paths between the exposure and later impairments, as observed in  
47 466 the present study with externalizing problem score, binge drinking and cannabis use. The  
48 467 underlying mechanisms explaining the persistence of externalizing behaviors (and  
49 468 manifestation of substance use) in adolescence remain unclear. In a previous study, our  
50 469 team reported a significant association between child Pb exposure and increased  
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470 impulsivity showed by impairments in child’s ability to correctly inhibit a response  
471 (Boucher et al. 2012b). These results were consistent with the proposition McGue and  
472 colleagues (2001) that a vulnerability to disinhibitory behavior and impulse control might  
473 explain those associations.

474           The few studies that investigated the effect of child blood Pb concentrations on  
475 adolescent behavior problems only reported total effects without decomposing them in  
476 direct and indirect paths. One such study reported that an increase of 1 µg/dL of the  
477 average child blood Pb concentrations was associated with an increase of 0.06 standard  
478 deviation on the adolescent impulsivity symptoms score (Winter and Sampson, 2017). In  
479 our study, no significant direct or indirect association was observed between child blood  
480 Pb on the adolescent hyperactivity-impulsivity scale. The inclusion of adolescent blood  
481 Pb concentrations did not modify the relationship between child Pb concentrations and  
482 adolescent outcomes even if it was associated with substance use outcomes. However, we  
483 observed indirect associations – through child externalizing behaviors – showing that a 2-  
484 fold increase in blood Pb concentrations can explain 0.25 symptoms on the adolescent  
485 externalizing score and an increase of 0.06 binge drinking episode. As pointed out by  
486 Bellinger et al. (2016), longitudinal studies are able to provide a more complete picture of  
487 the burden of child Pb exposure on later impairments if direct/indirect effects are  
488 considered instead of the traditional approach of only considering the total effect. The  
489 small magnitude of the associations we reported was expected given that adolescent  
490 behavior problems are complex outcomes with multiple predictors; we would not expect  
491 a single contaminant exposure to explain a large proportion of these behaviors,  
492 particularly in Inuit communities where historical and social determinants, coupled with  
493 limited educational and social services, may play a predominant role.

494 ***Strengths***

495           The major strength of this paper is its longitudinal design, which documented  
496 exposure and behavior beyond the critical child developmental period and allowed the  
497 use of mediation analyses as a novel analytic approach in the investigation of Pb  
498 exposure on future impairments, yet well-grounded in Bellinger et al.’s (2016)  
499 developmental cascade framework. Second, externalizing behaviors at the childhood and

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4 500 adolescent follow-up were assessed by different raters, namely the school teachers and  
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6 501 the participants themselves, ensuring independence of behavioral measures. Additionally,  
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8 502 a longitudinal design reduces the potential reverse causation between externalizing  
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10 503 behaviors and substance use; the overwhelming majority of our participants started to  
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12 504 consume alcohol or drugs regularly after the childhood assessment of externalizing  
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14 505 behaviors.

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16 506 *Limitations*

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18 507 One of the key limitations of our study is its relatively small sample size. The  
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20 508 social precariousness in Inuit communities may explain why many participants were not  
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22 509 eligible for the adolescence follow-up. We had a retention rate of 72% between the child  
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24 510 and adolescent follow-up. Most participants ineligible to participate to the adolescent  
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26 511 follow-up were unreachable because of incarceration, hospitalization or death. All of  
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28 512 these are known to be related to gender and oppositional defiant/conduct disorder, which  
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30 513 may explain differences in the adolescent follow-up sample (Begg et al., 1999; Malakieh,  
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32 514 2018; Mordre et al., 2011; Sorenson, 2011). Furthermore, because of limited statistical  
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34 515 power, we were not able to conduct sex effect modification analyses even though  
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36 516 externalizing behaviors and substance use manifestations are likely to differ between  
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38 517 boys and girls (Hammerslag and Gulley, 2016). Additionally, nine mediation models  
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40 518 were tested, which raises the risk of type I error. However, it is important to note that  
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42 519 significant results were not randomly distributed: the indirect associations were  
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44 520 consistently present in models mediated by externalizing behaviors. Next, our sample  
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46 521 was comprised of Inuit children from northern Québec, who are more exposed to Pb than  
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48 522 children from the general Canadian population (2.34 µg/dL compared to 0.8-0.9 µg/dL,  
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50 523 respectively; Health Canada 2010). This and the major historical, cultural and societal  
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52 524 differences of Inuit population with the southern Canadian population, mean that the  
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54 525 generalization of our results is not straightforward. We have consider many potential  
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56 526 covariates measured at different follow-ups, but it is always possible that some were  
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58 527 omitted. Also, lead exposure is usually highest around age 1 to 3, while our measure of  
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60 528 Pb concentration was taken a later age. Using early-life Pb exposure might have shown  
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62 529 stronger associations. Still we were able to observed significant association between later  
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64 530 childhood exposure and behavioral outcomes. Further cohort studies on neurobehavioral  
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531 outcomes should measure blood Pb concentrations at an earlier age, during the peak of  
532 exposition. Finally, the behavior measurement tools used in this study were all developed  
533 for, validated in non-indigenous populations, and administered by non-Inuit interviewers.  
534 Therefore, they may not fully capture behaviors that are considered as problematic by the  
535 Inuit themselves. However, internal consistencies were adequate in our sample (ordinal  
536 alphas higher than 0.76).

537 ***Conclusion***

538 Children exposed to Pb have a higher rate of developmental problems, but uncertainties  
539 remain about what role Pb exposure might play in the relation between childhood  
540 developmental problems and persisting impairments. Our study highlights the indirect but  
541 persistent effects of child Pb exposure on adolescent behavior problems and the  
542 importance of childhood externalizing behavior in this relationship; these early-life  
543 impairments may put children on a impeded developmental trajectory, increasing their  
544 likelihood of lifelong psychological, social and health problems.. Despite the small  
545 contribution of Pb exposure in the prediction of adolescent behavior problems, our results  
546 offer a new perspective in the investigation of the Pb burden on human capital. Further  
547 studies should document the long-term effect of Pb exposure and other neurotoxicants  
548 during adolescence or early adulthood by modelling developmental processes reflecting  
549 the risk of developmental cascades instead of documenting mere associations.

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5 **Supplemental Material - Analytical procedures for contaminant and nutrient**  
6 **analyses**  
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10 Total mercury (Hg) concentrations in umbilical cord blood samples were  
11 determined using cold vapour atomic absorption spectrometry (Pharmacia Model 120;  
12 Pharmacia, Piscataway, NJ, USA). Cord blood lead (Pb) levels were determined by  
13 graphite furnace atomic absorption with Zeeman background correction (Perkin Elmer  
14 model ZL 4100; Perkin Elmer, Norwalk, CT, USA). Concentrations of docosahexaenoic  
15 acid (DHA) in cord blood were expressed as percentages of the total area of all fatty acid  
16 peaks from C14:0 to C24:1 (percent weight). All sample were above the limit of  
17 detection for Hg, Pb and DHA.  
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25 Total Pb and Hg concentrations in child blood samples were determined by ICP-  
26 MS (Perkin Elmer Sciex Elan 6000 ICP-MS instrument for Pb; PE DRC II instrument for  
27 Hg). Concentrations of DHA were expressed as percentages of the total area of all fatty  
28 acid peaks from C14:0 to C24:1 (percent weight). Limits of detection for child blood  
29 sample analyses were 0.1 µg/L for Hg, 0.002 µg/dL for Pb and 0.09 µmol/L for DHA. A  
30 value equal to half the limit of detection of the analytical method was entered in the  
31 database whenever a substance was not detected (child Hg: n = 1; other substances were  
32 detected in all samples).  
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40 All blood samples from the adolescent follow-up were analyzed using inductively  
41 coupled plasma mass spectrometry (PerkinElmer ELAN ICP-MS DRC II) at the Centre  
42 de Toxicologie, Institut National de Santé Publique du Québec (Quebec City, QC,  
43 Canada) for contaminants and at the CHU de Québec (Québec City, QC, Canada) for  
44 DHA. All samples were above the limits of detection for Pb, Hg and DHA.  
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