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Cognitive deficits at age 22 years associated with prenatal exposure to methylmercury

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Abstract

Prenatal exposure to mercury has been associated with adverse effects on child neurodevelopment. The present study aims to determine the extent to which methylmercury-associated cognitive deficits persist into adult age. In a Faroese birth cohort originally formed in 1986–1987 (N=1,022), prenatal methylmercury exposure was assessed in terms of the mercury concentration in cord blood and maternal hair. Clinical examinations of 847 cohort members at age 22 years were carried out in 2008–2009 using a panel of neuropsychological tests that reflected major functional domains. Subjects with neurological and psychiatric diagnoses were excluded from the data analysis, thus leaving 814 subjects. Multiple regression analysis included covariates previously identified for adjustment. Deficits in Boston Naming Test and other tests of verbal performance were significantly associated with the cord-blood mercury concentration. Deficits were also present in all other tests applied, although most were not statistically significant. Structural equation models were developed to ascertain the possible differences in vulnerability of specific functional domains and the overall association with general intelligence. In models for individual domains, all of them showed negative associations, with crystallized intelligence being highly significant. A hierarchical model for general intelligence based on all domains again showed a highly significant negative association with the exposure, with an approximate deficit that corresponds to about 2.2 IQ points at a 10-fold increased prenatal methylmercury exposure. Thus, although the cognitive deficits observed were smaller than at examinations at younger ages, maternal seafood diets were associated with adverse effects in this birth cohort at age 22 years. The deficits affected major domains of brain functions as well as general intelligence. Thus, prenatal exposure to this marine contaminant appears to cause permanent adverse effects on cognition.

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Conflict of interest statement

Otherwise the authors have no competing interests to declare.

Supplementary data

Supplementary data related to this article are attached.

Keywords

Environmental exposure; Methylmercury compounds; Neuropsychological measures; Prenatal exposure delayed effects; Structural equation modeling

1. Introduction

Methylmercury contamination of seafood occurs world-wide (United Nations Environmental Programme (UNEP), 2002), and its neurotoxic effects during human brain development have been well documented (Karagas et al., 2012). Neurodevelopmental consequences are likely to be permanent (Grandjean & Landrigan, 2006), as illustrated, e.g., cognitive deficits in adults with elevated childhood exposure to lead (Mazumdar et al., 2011). While congenital methylmercury poisoning is known to cause irreversible effects to the brain (Harada, 1995), little information is available on the long-term repercussions on cognitive development associated with elevated maternal methylmercury exposure from seafood intake during pregnancy.

We established a birth cohort in the Faroe Islands in 1986–1987, where dietary methylmercury exposure mainly originates from traditional consumption of meat from the pilot whale; the child's prenatal exposure was assessed from the mercury concentration in cord blood, and maternal hair-mercury concentrations were also determined (Grandjean et al., 1992). Cognitive effects were first studied at age 7 (Grandjean et al., 1997) and then again at age 14 years (Debes, Budtz-Jørgensen, Weihe, White, & Grandjean, 2006). These studies suggested that the cognitive effects first determined at age 7 persisted through to age 14. We now examine whether negative associations are still detectable eight years later, at age 22. We chose to focus on major functional domains and a hierarchical model that allowed assessment of general intelligence.

2. Materials and methods

2.1. Study population and exposure assessment

A birth cohort of 1,022 subjects was generated from singleton deliveries in 1986–1987 at the three hospitals in the Faroe Islands. Cord blood and maternal hair (length, 6–9 cm) were collected for mercury analysis (Grandjean et al., 1992). Follow-up has now been extended to age 22 years, where 847 cohort members (83%) participated in the clinical examinations. All cohort members underwent physical examination and completed a questionnaire on past medical history and current health status to determine any diagnoses that might affect the subject's psychological performance. Of the cohort members examined, 31 were excluded from the analyses due to neurological diagnoses and two due to psychiatric diagnoses, thus rendering a total of 814 study subjects for analysis.

Concomitant methylmercury exposure was determined from mercury analysis of the subject's whole blood and hair. Mercury in whole blood was analyzed on a Direct Mercury Analyzer (DMA-80, Milestone Inc, Sorrisole, Italy), while hair was analyzed on a Flow Induction Mercury System (FIMS-400, Perkin-Elmer, Waltham, MA). Both analyses have an imprecision better than 4%, and the quality is secured by inclusion of quality controls and

standard reference material samples in each analytical series, as well as participation successfully in external quality assessment schemes. The very small laboratory variance has no impact on the overall imprecision of the exposure assessments (Budtz-Jørgensen, Grandjean, & Weihe, 2007). Additional exposure information available included the concentration of polychlorinated biphenyls (PCBs) in cord blood (Grandjean et al., 2012) and lead in cord blood (Yorifuji, Debes, Weihe, & Grandjean, 2011).

2.2. Neuropsychological tests

For the purpose of this study, we aimed at a nomothetic approach as used in the psychometric modeling of interindividual differences, while emphasizing tests of fundamental cognitive processes relevant to cognitive and neuropsychological models of the processing architecture of the mind (Deary, 2005). The test selection was guided by an overall objective to sample broadly from the universe of human mental abilities by specific tests with good psychometric properties in order to represent a number of broad ability domains, which could be organized into a hierarchical model of abilities as described by modern psychometric theorists (Carroll, 1993; Floyd, Shands, Rafael, Bergeron, & McGrew, 2009; Gustafsson, 1984; Jensen, 1994, 1998; McGrew, 2009; Undheim, 1987), thereby obtaining theoretical (Borsboom, 2005, 2006) and practical (Gignac, 2014; Gignac & Watkins, 2013) benefits in regard to validity and reliability of latent variable theory, confirmatory factor analytic methods, and structural equation modeling. Although this approach deviates from our previous means of designing a test battery, several tests had already been administered in the two previous examinations of the cohort. Several tests were taken from well reputed test scales, i.e. WISC-R (Wechsler, 1974), WAIS-R (Wechsler, 1981), WMS-III (Wechsler, 1997), WJ III (Woodcock, McGrew, & Mather, 2001) and the computer facilitated test system NES2 (Letz & Baker, 1988).

Within the time limits of the clinical examinations, our test battery was classified and categorized by the taxonomy used in the Cattell-Horn-Carroll Three Stratum Theory (CHC-theory) of intelligence (Floyd et al., 2009; McGrew, 2009; Schneider & McGrew, 2012) under eight broad ability domains. The latent first-order factors reflecting these domains were Gf (Fluid Reasoning, often referred to as fluid intelligence), Gc (Comprehension-knowledge, often referred to as crystallized intelligence), Gv (Visual processing), Gsm (Short-term memory), Glr (Long-term storage and retrieval), Gs (Cognitive processing speed), Gt (Decision and reaction speed), Gps (Psychomotor speed). All selected tests were feasible for application in both Faroese and Danish languages, and instructions and test materials were translated by FD. The tests were administered in uniform sequence by two psychologists (FD and Arne Ludvig) at two stations.

2.2.1. WJ III Concept Formation—The test measures Fluid Reasoning (Gf) by the cognitive process of Induction (Schrank, McGrew, & Woodcock (2001). The stimulus material is visual (drawings), and the task is identifying, categorizing and determining rules. The problem solving requires rule-based categorization; rule switching and induction/inference. The response is oral (words).

2.2.2. Raven Standard Progressive Matrices Plus—The test is a parallel form of the Raven Standard Progressive Matrices (Raven, 1958) with some more difficult items to secure better discrimination at the high end. The subject is asked to identify the missing item that completes a pattern by indicating it in a multiple choice format. After an initial individual instruction, the test was self-administered with no time limit while alone in a room. The test is thought to measure g, and in factor analytical models, this test reflects Gf and Gv.

2.2.3. Boston Naming Test—The 60-item Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983) is a visual confrontation naming test which measures the word retrieval or word finding performance of a subject. Stimuli are line drawings of a wide category of objects of increasing difficulty. Scores are obtained for number of correct items without cueing, and correct number of items after stimulus and phonemic cueing by the examiner.

2.2.4. WJ III, Picture Vocabulary (suppl.), Synonyms, Antonyms, Verbal Analogies—Together these tests comprise Verbal Comprehension in WJ III and contribute to the CHC-factor Comprehension-Knowledge (Gc) by measuring the narrow abilities of Lexical Knowledge and Language Development (Schrack, 2001). Responses are oral (words). Nine items at adult level of difficulty from Picture Vocabulary, not overlapping with the Boston Naming Test, were also administered, but only included in scores of the Incidental Memory condition of the BNT.

2.2.5. WISC-R, Block Design (+ 3 last items from WAIS-R)—To be consistent with the administration at age 14 years, where the three most difficult items from the adult version (WAIS-R) (Wechsler, 1981) were added to the children's version (WISC-R) (Wechsler, 1974), the same combination of items was used at age 22 years. By an unfortunate error of administration, the three items from WAIS-R were not administered in the first part of the study, so that number of scores obtained for these items was reduced. The test measures Visual-Spatial Thinking (Gv) by narrow abilities for visuospatial perception, analysis, abstraction, synthesis and construction.

2.2.6. WJ III, Spatial Relations—The test measures Visual-Spatial Thinking (Gv) by the narrow abilities of Visualization and Spatial relations (Schrack, 2001). The stimuli are visual (drawings). The tests requires visual feature detection, manipulation of visual images in space and matching. Responses are oral (letters) or motoric (pointing).

2.2.7. WJ III, Numbers Reversed—The test measures Short-Term Memory (Gsm) and Working memory (Schrack, 2001). The stimuli are Auditory (numbers) and require holding a span of numbers in immediate awareness while reversing the sequence by the cognitive processes of span of apprehension and recoding in working memory. Responses are Oral (numbers).

2.2.8. WJ III, Memory for words—The test measures Short-Term Memory (Gsm) by the narrow ability of auditory memory span (Schrack, 2001). Stimuli are auditory (words). The

test requires repeating a list of unrelated words in a correct sequence by the formation of echoic memories and by the verbalizable span of echoic store. Responses are oral (words).

2.2.9. WMS III, Spatial Span—The tests measures Short-Term Memory (Gsm) by the narrow ability of visual spatial span in a forward and in a backward condition (Schrunk, 2001). The test is intended as a visual analogue to the Digit Span Test in the Wechsler scales. Stimuli are ten blue blocks randomly placed on a white form board. The examiner points out sequences of increasing length by touching a number blocks at a pace of one block per second. The subject has to reproduce a demonstrated sequence in the same order in the first condition, and in reverse order the second condition.

2.2.10. California Verbal Learning Test (CVLT)—The test measures learning, short-term and long-term retrieval as well as recognition (Glr) of a shopping list of sixteen items by cognitive component processes of maintaining information in immediate memory, learning by coding into long-term memory, recall by retrieval from long-term memory, semantic categorization, and matching of stimuli with newly stored content in long-term memory (Delis, Kramer, Kaplan, & Ober, 1994).

2.2.11. Incidental Memory—This added test condition measures long term memory and retrieval (Glr). After about 45 minutes the subjects were asked what pictures they incidentally could remember from the Boston Naming Test and the Picture Vocabulary previously presented to the subject as described above.

2.2.12. WJ III, Visual matching—The test measures Processing Speed (Gs) by the narrow ability of Perceptual speed. Stimuli are visual (numbers) (Schrunk, 2001). The task requires rapidly locating and circling identical numbers from a defined set of numbers by the process of speeded visual perception and Matching. The response is motoric (circling).

2.2.13. WJ III, Decision Speed—The test measures Processing Speed (Gs) by the narrow ability of Semantic processing speed (Schrunk, 2001). Stimuli are visual (pictures). The test requires Locating and circling two pictures most similar conceptually in a row by processes of object recognition and speeded symbolic/semantic comparisons. The response is Motoric (circling).

2.2.14. NES2, Continuous Performance Test (CPT)—The test is a choice reaction time test measuring decision and reaction speed (Gt) requiring vigilance and sustained attention over a time span of 10 minutes (Letz & Baker, 1988). The subjects were presented with black and white silhouettes of animals appearing briefly on the computer screen (Dahl et al., 1996). The subject was required to press a button on a response box as fast as possible every time a cat appeared on the screen. The first 12 of 60 target responses were considered practice trials and the following 48 responses were considered test trials. Speed and stability of the responses were measured by the mean and the standard deviation of the reaction times. The number of false positive and false negative responses was also obtained.

2.2.15. NES2, Finger Tapping Test—The task measures elementary manual motor speed without any ongoing mental problem solving (Letz & Baker, 1988). The subjects were

given practice trials. The subjects then performed two rounds of finger tapping in the sequence of dominant, non-dominant and alternating hands for 15 seconds. The greatest result in each condition was taken as the final score.

2.2.16. CPT-90—The test is supposed to measure attentional control, switching and inhibition (Debes, 2008). Although likely reflecting Gt, the exact placement of this test in the CHC-taxonomy is yet unclear, and the results were therefore not entered into factor analytical measurement models. The test was developed in the freeware program DMDX (Forster, 2002) by the examiner (FD) and was adjusted and calibrated for use at the age of the present cohort members. Six hundred stimuli in the form of one-digit numbers were presented on a computer screen with an inter-stimulus interval of 708 msec. Ninety percent of the stimuli were the target stimulus (one-digit number 9), and 10 % were non-target stimuli (numbers from 0 to 8) that the subjects were not required to respond to. In order to reduce the usual trade-off between speed and accuracy, rhythmical responding was required to an audible beep between the stimuli. The proportion of successful reaction-inhibitions to non-target stimuli was corrected for the tendency not to react on target stimuli, since this tendency might falsely inflate the success-rate of response-inhibition for non-target stimuli. The first 20 non-target stimuli were considered practice trials, and the remaining 40 non-target trials were taken as test-items.

2.3. Covariates and statistical analysis

The methylmercury concentrations were converted to a logarithmic scale to obtain reasonable approximation to normally distributed residuals. Covariates were chosen, as based on previous examinations at ages 7 and 14 years (Budtz-Jørgensen et al., 2007; Debes et al., 2006; Grandjean et al., 2012; Grandjean et al., 1997; Yorifuji et al., 2011): age, sex, maternal fish intake during pregnancy (number of fish dinners per week), maternal Raven score, employment of mother and father at age 14, school grade at age 14, tested in Faroese (or Danish), examination am or pm, PCB exposure [$\log(\text{PCB concentration in cord blood})$] and lead exposure [$\log(\text{lead in cord blood})$]. As prenatal methylmercury exposures were much higher than postnatal levels, and because indicators of postnatal methylmercury exposure appear to contribute only little to exposure-associated deficits (Grandjean, Weihe, Debes, Choi, & Budtz-Jørgensen, 2014), we included exposure data at age 22 years only in sensitivity analyses. As potential confounders previously considered, we also considered maternal smoking and mother's and father's education in additional analyses.

As a first approach, multiple regression analyses were performed using each of the neuropsychological test variables as outcomes. These analyses were conducted for complete cases only and therefore depended on the availability of covariate data. As several related outcome variables were available, structural equation models were developed to extract information on the overall association of prenatal methylmercury exposure with domain-related performance. Structural equation models were defined, and an initial, brief model relied on selected tests considered to be the best indicators of general mental ability to ascertain the impact on g (Fig. 1). An extended model included all tests separated according to functional domain to examine the full breadth of the impact of methylmercury on the universe of mental abilities, including the g as defined by all of the domains included (Fig

2). The psychometric measurement models were defined in accordance with substantive theory in the field (McGrew, 2009). No data driven techniques were used. In addition, a first-order model examined the association with the first order orthogonal factors, without a general ability factor. As before, the prenatal methylmercury exposure was modeled from the mercury concentrations in cord blood and hair and the number of whale meat dinners consumed by the mother per month during pregnancy (all values were logarithmically transformed) (Debes, 2008). Covariate adjustment of the outcomes was included, and covariate adjustment also of the latent exposure was included in sensitivity analyses. The estimation method was Full Information Maximum Likelihood, using the observed information matrix with missing data, which utilizes all information in the dataset and avoids list-wise deletion due to missing information.

IBM SPSS Statistical 20.0 (SPSS 20.0) was the program used for descriptive and multiple regression analyses. Mplus 7.3 was used for confirmatory factor analyses and structural equation modeling.

3. Results

Descriptive data for the subjects examined at age 22 years about their mercury exposure at delivery and at 22 years are presented in Table 1. Geometric mean levels for blood-mercury at ages 7 and 14 were 8.67 µg Hg/L and 4.22 µg Hg/L, respectively. Thus, exposures decreased with age and current exposure levels were almost an order of magnitude lower than prenatal exposures. Concomitant exposures showed only weak, though positive associations with prenatal levels (Pearson's $r = 0.17$ for blood and $r = 0.15$ for hair, after log transformation). When postnatal exposures are low, their possible impact on neurodevelopment is dubious and difficult to determine (Grandjean et al., 2014), and the cord-blood mercury concentration as the most appropriate reflection of prenatal exposure (Grandjean & Budtz-Jørgensen, 2010) is therefore considered as the main predictor of neurotoxic risk.

Descriptive data for the important covariates are presented in Table 2. The results are similar to those reported for cohort subjects who participated in previous examinations (Debes, 2008; Grandjean et al., 1997). Of main interest in regard to confounding is the maternal Raven score, which was considered a mandatory covariate for adjustment. In regard to other neurotoxicant exposures, lead correlated weakly with mercury ($p = 0.07$), while PCB showed a significant association ($p > 0.001$).

Descriptive data for the neuropsychological outcome variables are presented in Table 3. The results are similar to expectations, and all tests showed wide ranges of performance, thus rendering the tests selected appropriate for the purposes of this study.

3.1 Multiple regression analyses

The multiple regression results confirmed the associations with cord blood mercury for tests of verbal comprehension, Boston Naming Test, Synonyms and Antonyms (Table 4). Further, a significant negative association was found for cord blood mercury and supraspan reproduction in the first trial of CVLT. Moreover all coefficients were in the direction of

poorer performance, except for Spatial Span, which showed a slightly positive value in the forward and backward condition for mercury in cord blood. Parallel calculations for maternal hair-mercury showed similar patterns, although with higher p values (Appendix Table 1). A significant negative association was seen for Synonyms and, at a weaker level of statistical significance, Antonyms, Spatial Span forward condition, as well as the first trial of CVLT and the Long Delay Recognition. However, maternal hair was positively associated with Block Design, Face Recognition Delayed, and Decision Speed. Because the positive associations are weak and non-significant, the true direction of these associations is uncertain. When comparing to regressions without covariate adjustments, the full model generally resulted in smaller estimated mercury effects.

3.2 A higher-order brief structural model

A brief higher-order measurement model was defined comprising a general intellectual factor, g , reflecting in two broad first-order factors G_f (fluid intelligence, standardized coefficient 0.804) and G_c (crystallized intelligence, standardized coefficient 0.897). G_f was reflected in Raven's Standard Progressive Matrices and in Concept Formation (with standardized coefficients of 0.774 and 0.618, respectively), and G_c was reflected in Verbal Analogies, Boston Naming Test (where the residuals of the two conditions, without and with cueing, were allowed to co-vary), Synonyms, and Antonyms (with standardized coefficients of 0.632, 0.753, 0.751, 0.818, and 0.734, respectively, and a correlation between the residuals of the two conditions of the Boston Naming Test of 0.860). For reasons of identification, latent variables with just two indicators (g and G_f) had both unstandardized indicator paths fixed to 1.00. All factor loadings were statistically significant, and all variables were considered good indicators of their respective constructs. The fit of the model was acceptable with regard to Chi Square = 72.614, $df = 13$, $p = 0.000$ and RMSEA = 0.075. Other indices showed excellent fit with CFI = 0.983 and SRMR = 0.040.

A structural equation model was then defined, where the g -factor was affected by a latent variable for the prenatal exposure to methylmercury (Hg^*). This variable had cord blood mercury and mercury in maternal hair at delivery as indicators, and was formed by maternal whale meat dinners consumed per month during pregnancy. The model fit was good. The standardized effect of the latent mercury variable on the g factor was -0.140 and was highly significant ($p = 0.001$). The a priori selected set of covariates was then entered into the model, each covariate correcting every manifest psychometric test variables (Figure 1). The cognitive measurement model was thus based on the residualized manifest variables. The fit of this model was from acceptable to good (Chi Square = 258.987; $df = 66$; $p = 0.000$; RMSEA = 0.060; CFI = 0.958; SRMR = 0.047). The standardized effect of the latent mercury variable on the g factor was -0.145 and was highly significant ($p = 0.002$). At 10-fold higher methylmercury exposure the performance was therefore 14.5% lower, thus indicating a strong negative association between prenatal exposure to methylmercury and the general intellectual ability at age 22 years. Inclusion of covariates only slightly modified the size of the regression coefficient, strengthening it from -0.14 to -0.15 .

3.3 A higher-order broad structural model

An extended higher-order measurement model with a broader nomothetic span was defined, comprising a general second-order factor, g , affecting eight first-order factors: G_f , G_c , G_v , G_{sm} , G_{lr} , G_{lr} , G_t , G_p . Eight correlations between residuals of manifest indicators (outcome variables) were allowed in order to correct for local dependence of highly similar tests (Table 5). This model produced a so called Heywood case with a small negative standardized residual (-0.047) for G_f , and a standardized coefficient slightly above one (1.023) for the path from g to G_f . The standard errors could not be computed, and no estimates were yielded. After fixing the negative residual to zero, the coefficient from g to G_f then necessarily became 1.000 , meaning that there was identity between g and G_f , thereby rendering either of the two redundant. Also, this attempt rendered the computation of standard errors impossible, and no estimates were produced. This particular phenomenon of identity occurring between g and G_f is well-known in the literature, and has been dealt with in different ways. Wendy Johnson and colleagues (Johnson & Bouchard, 2005a, 2005b; Major, Johnson, & Deary, 2012) have classified tests solely by their content, and thereby all tests with visual stimulus material were considered visuospatial in the taxonomy of her VPR-model. Also in the most recent version of the Wechsler Adult Intelligence Scale, the Perceptual Reasoning Index is a mixture of visuospatial and fluid reasoning tests.

The present measurement model was then redefined, and the indicators for G_f were taken as indicators for G_v instead. This yielded an error free model with $N = 814$ and a good overall fit, Chi-Square = 827.509, $df = 337$, $p = 0.000$; RMSEA = 0.042; CFI = 0.952; SRMR = 0.059. The loadings on g range from 0.278 and 0.302 for G_t and G_p in a lower category and from 0.753 to 0.865 at the higher end. The loadings of the manifest tests on their respective broad ability factors range from 0.220 to 0.915. All coefficients of the measurement model were statistically significant.

A more advanced structural equation model was then defined, where the g -factor was again affected by the latent variable for the prenatal exposure to methylmercury (Hg^*) described earlier. The coefficient for this path was -0.106 , $p = 0.011$. The overall model fit was good with Chi-Square 922.255, $df = 420$, $p = 0.000$; RMSEA = 0.038; CFI = 0.955; SRMR = 0.055. The covariates were then entered into the model, correcting the manifest variables, as described earlier (Figure 2). The unstandardized estimate for this the path from mercury to g was -0.226 ($p = 0.045$), thus meaning that a 10-fold increase in the latent variable for mercury reduced g by 0.2 on the scale of the Analogies subtest from WJ III. The standardized coefficient for Hg^* on g was -0.093 , $p = 0.041$. The overall model fit was good also with Chi-Square = 1001.346, $df = 453$, $p = 0.000$; RMSEA = 0.039; CFI = 0.953; SRMR = 0.042. A statistically significant negative association was found between prenatal methylmercury exposure and general intellectual ability. Again, the covariates only slightly modified the size of the regression coefficient, weakening it from -0.11 to -0.09 .

3.4 A first-order broad structural model

A modification of the model in Figure 2 made with no g -factor and with the latent mercury variable affecting every orthogonal first-order factor. The model fit was good $N = 814$, Chi-Square = 1851.969, $df = 429$, $p = 0.000$, RMSEA = 0.064, CFI = 0.875, SRMR = 0.098. The

latent variable for prenatal exposure to methylmercury has a negative effect on all seven ability domains (Table 6), manifesting significantly in Gc, near significantly in Gv and Glr but only weakly and non-significantly in the other four ability domains.

3.5 Domain specific associations

The pattern of results in the models above indicates a negative effect from methylmercury specifically on Gc beyond the effect on g. There was not enough power in the data to test for the effect of mercury on g and on the residuals of all the first-order factors simultaneously in one structural equation model, since such a model did not converge. In a simpler model the latent variable of prenatal exposure to methylmercury was specified to simultaneously affect the g-factor and the Gc-factor of the broad measurement model. For simplicity the model was run without covariates. The model fit was good and the paths from Hg* to g and from Hg* to Gc had standardized coefficients of -0.086 and -0.084 with p values 0.042 and 0.015 respectively. Tested in the same way, the associations with mercury for each of the other first-order factors did not reach statistical significance, while the negative association with the g factor remained significant.

Extended analyses that included the current methylmercury exposure showed results for prenatal exposure that did not materially differ from the results presented above. The same was the case in additional sensitivity analyses where maternal smoking during pregnancy and maternal and paternal education were added as covariates.

4. Discussion

The present study extends our follow-up of Faroese birth cohort members up to age 22 years. The prenatal exposure was characterized by means of the cord-blood mercury concentration, which is more precise than the concentration in maternal hair collected at parturition (Grandjean & Budtz-Jørgensen, 2010). The follow-up examination at age 7 years of this cohort (Grandjean et al., 1997) provided data on developmental neurotoxicity that were used to calculate a safe exposure limit for methylmercury (National Research Council, 2000). With participation rates of 83%–90% on the three follow-up examinations, the validity of the results are only minimally affected by attrition. In addition, postnatal exposures were much lower than prenatal exposures and therefore did not affect the neurodevelopmental outcomes (Grandjean et al., 2014). Concomitant exposures to PCBs (Grandjean et al., 2012) and lead (Yorifuji et al., 2011) also affected these effect variables only to a minimal extent.

The results from age 22 suggest that cognitive deficits associated with prenatal methylmercury exposure remain through young adult age, with effect sizes somewhat lower than those observed at ages 7 and 14 years. Again, the Boston Naming Test appeared to be the outcome that was most sensitive to the neurotoxicant exposure, as was previously seen at ages 7 and 14 years (Debes et al., 2006; Grandjean et al., 1997). This finding, along with the similar associations with related WC III outcomes, suggests that Gc may be particularly vulnerable to developmental methylmercury toxicity. Perhaps development of Gc function allows discrete impairments in ability to leave a more discernible trace in the performance of

exposed subjects. This domain may also be less sensitive to situational noise, and tests, such as the BNT, may have a high sensitivity due to the large number of items.

While continued brain development, stimulation, education, head trauma, alcohol usage, depression, and many other factors have likely influenced cohort members' brain functions, and while potential compensation mechanisms that may have limited the impact of developmental neurotoxicity, the deficits seem to remain and extend into young adulthood. This notion is in accordance with current knowledge on the permanent nature of neurotoxic damage during early development (Grandjean, 2013; Grandjean & Landrigan, 2006), and it is in accordance with findings on other neurotoxicants, such as lead (Mazumdar et al., 2011), arsenic (Dakeishi, Murata, & Grandjean, 2006), and alcohol (Streissguth et al., 2004). One other cohort, recruited in the Seychelles, has aimed at assessing long-term implications of developmental neurotoxicity, now up to age 19 years (van Wijngaarden et al., 2013). However, in addition to slight differences in the outcome measures, prenatal methylmercury exposure was determined only in maternal hair collected up to 6 months after parturition, and information on maternal fish intake and pesticide exposure was unavailable. Although the Seychelles study has sometimes been highlighted as evidence that methylmercury from marine food is not associated with neurodevelopmental toxicity (Myers et al., 2003), other prospective studies with better exposure assessment (Freire et al., 2010; Lederman et al., 2008; Oken et al., 2008) support the results from the Faroes. In addition, the neuropsychological test findings are supported by neurophysiological results (Murata, Weihe, Budtz-Jørgensen, Jørgensen, & Grandjean, 2004; White et al., 2011).

The test battery was designed to allow assessment of mercury associations with deficits in a wide range of abilities, while structural equation modeling techniques allowed estimation of associations with first-order factors for broad ability domains and the second-order general mental ability *g* in hierarchical models. Multiple regression analyses showed significant negative effects of methylmercury on tests in the domain of verbal comprehension (*Gc*), and partly in memory for verbal material (*Glr*). Analyses with structural equations models confirmed the pattern from the regression analyses with a significant effect on *Gc* in a model with seven first-order factors. Structural equation models with a general ability factor also showed a significant negative effect on *g*. As the mercury concentration in the full-length hair sample may better reflect the average exposure during the whole gestational period (Grandjean, Jørgensen, & Weihe, 2002), the negative association between hair-mercury and memory scores (*Glr*) may indicate that these functions are vulnerable also prior to the third trimester represented by the cord blood concentration.

The domain-based approach to neuropsychological testing and the analysis using structural equations is in accordance with modern classification of tests and advanced modeling of intelligence in population studies (McGrew, 2009). However, most epidemiological studies of neurotoxicity have focused on brief omnibus tests or limited test batteries based on feasibility and prior knowledge on sensitivity to neurotoxicant effects (Grandjean, 2013). Thus, although conclusions from such studies may be drawn in regard to effects on IQ, they do not provide information on the domains contributing to such effects. Still, the functional classification of tests often presents a challenge, as more than one domain may be involved in the test performance. In addition, the structural equation analysis requires that a latent

factor can be generated based on a factor analysis of the results from tests thought to represent the domain. With only two or three tests for each domain, the evidence may be insufficient to appropriately represent the particular function intended. In the present study, the weak association of prenatal methylmercury exposure with several outcomes may reflect this concern, given that the tests were not selected with the main purpose of identifying functions that were suspected of being vulnerable to this neurotoxicant. However, some of the tests were already administered in previous studies of the cohort (Debes, 2008; Grandjean et al., 1997) and were suspected of being sensitive to methylmercury-mediated neurotoxicity. It is noteworthy that the Boston Naming Test, which was the outcome most clearly affected at ages 7 and 14 years (Debes et al., 2006; Grandjean et al., 1997) was also the test that showed the strongest associations at age 22. This result appears not to be specifically related to this particular test, as similar associations with mercury exposure were obtained for the WJIII Synonyms and Antonyms tests that relates to the same functional domain.

Still, the changes associated with a 10-fold increase in prenatal methylmercury exposure appear fairly low in comparison with the results from previous examinations (Debes et al., 2006; Grandjean et al., 1997). Thus, even at age 14 years, a doubled exposure was associated with a decrease in BNT scores of several points. In contrast, at age 22, a ten-fold increased exposure results in a loss of less than 2 points. In terms of g , if expressed in IQ points, the Beta of -0.145 for the brief SEM corresponds to 2.2 IQ points, again for a 10-fold increased exposure. A difference of this magnitude may easily be missed in epidemiological studies, but the low p values must be ascribed to the thorough neuropsychological testing and the approach to the statistical analysis.

The pattern of results observed also supports the conclusion that the negative associations likely reflect true adverse effects on the general factor and thereby on the general partition of the variance in the underlying first-order factors. In addition, a clear negative mercury association was apparent with the domain-specific variance in G_c beyond the g variance partition, as supported by the structural equation model showing significant negative effects on both g and G_c . The latter, along with G_f , is often considered the most important broad ability domain, and both are included in tests commonly used in clinical practice for estimation of the general intellectual ability of a subject (e.g., Raven's matrices, Mill-Hill Vocabulary Scale and Reynolds Intellectual Assessment Scales). Similarly, broader Intelligence test batteries like WAIS-IV and WJ III also include subtests or brief versions that reflect G_f and G_c .

The finding of a significant negative associations with general mental ability in different estimation models adds to the public health concern about methylmercury as an environmental neurotoxicant, as the g variance is thought to contribute to every more specific, particular or narrow ability. The associations appeared relatively robust with regard to covariates, which do not seem to moderate the effect to any substantial degree. Inclusion of neither prenatal PCB nor lead exposure cause any attenuation of the calculated mercury associations with the outcomes, thus confirming previous findings that these pollutants do not cause any important confounding (Grandjean et al., 2012; Yorifuji et al., 2011).

5. Conclusions

Cognitive deficits associated with prenatal methylmercury exposure from maternal seafood diets remained detectable in a Faroese birth cohort re-examined at age 22 years. The deficits appeared to be less serious than at previous examinations at ages 7 and 14 years, although they affected major domains of brain functions as well as general intelligence. As has been seen with other neurodevelopmental toxicants, such as lead and alcohol, prenatal exposure to methylmercury appears to cause permanent adverse effects on cognition.

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Abbreviations

CPT	Continuous Performance Test
CVLT	California Verbal Learning Test
Gf	Fluid Intelligence/Reasoning
Gc	Crystallized Intelligence / Verbal comprehension – knowledge
Gv	Visual-Spatial Processing
Gsm	Short-Term Memory
GlR	Long-Term Storage and Retrieval
Gs	Cognitive Processing Speed
Gt	Timed Reaction and Decision Speed
Gps	Psychomotor Speed and Dexterity
Hg	mercury
Hg*	latent mercury exposure
NES2	Neuropsychological Examination System 2
WAIS-R	Wechsler Adult Intelligence Scale, Revised
WISC-R	Wechsler Intelligence Scale for Children, Revised
WJ III	Woodcock-Johnson III Tests of Cognitive Abilities

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Appendix

Table 1

Test score change associated with mercury in mother's hair (logarithmically transformed), as indicated by multiple regression analysis with adjustment for covariates.

Cognitive domain	Test variable	N	Change	Standardized	p
Gf	WJ III Concept Formation	830	-.694	-.041	.303
	Raven Standard Progressive Matrices Plus	828	-.434	-.016	.677
Gc	Boston Naming Test , without cues	830	-.417	-.020	.615
	Boston Naming Test, w. stim. and phon. cues	830	-.495	-.027	.493
	Synonyms, WJ III	830	-.775	-.087	.028
	Antonyms, WJ III	830	-.504	-.071	.078
	Verbal Analogies, WJ III	830	-.069	-.010	.813
Gv	Block Design WISC-R	826	.603	.021	.598
	Block Design WISC-R + 3 WAIS-R	426	.588	.018	.726
	Spatial Relations, WJ III	824	-.031	-.002	.964
Gsm	Numbers Reversed, WJ III	826	-.456	-.035	.395
	Memory for words, , WJ III	826	-.401	-.053	.192
	Spatial Span Forward, WMS-III	826	.327	.051	.206
	Spatial Span Backwards, WMS-III	826	-.097	-.017	.680
Glr	CVLT, Trial 1, Correct	830	-.423	-.066	.099
	CVLT, Learning trials 1–5	830	-1.350	-.039	.310
	CVLT, List B, Correct	830	-.183	-.027	.499
	CVLT, Short Delay, Free Recall	830	-.301	-.031	.435
	CVLT, Long Delay, Free Recall	830	-.105	-.011	.786
	CVLT, Long Delay, Recognition	827	-.349	-.074	.070

Cognitive domain	Test variable	N	Change	Standardized	p
	Incidental Memory for Boston Naming and Picture Vocabulary, WJ-III	830	-.757	-.053	.186
	Warrington's Face Recognition Test, Set2, Immediate Recall	822	-.099	-.006	.872
	Warrington's Face Recognition Test, Set 2, Delayed Recall	822	.074	.004	.915
Gs	Visual Matching, WJ III *)	826	-.191	-.009	.831
	Decision Speed, WJ III*)	826	1.304	.054	.177
Gt	CPT, NES2, Mean RT of 4 last Blocks	823	9.074	.057	.164
	CPT, NES2, SD of 4 last Blocks	823	.584	.009	.826
	CPT, NES2, false negative errors last 4 blocks	823	.150	.043	.288
	CPT, NES2, false positive errors last 4 blocks	823	.037	.008	.842
	CPT-90, Proportion correct non-target (minus first 20 stimuli)	803	-.026	-.030	.460
	CPT-90, Noise corrected proportion correct non-target (minus first 20 stimuli)	803	-.027	-.031	.442
Gps	Finger Tapping, NES2, preferred hand	823	-2.337	-.061	.102
	Finger Tapping, NES2, non-preferred hand	823	-1.480	-.030	.411
	Finger Tapping, NES2, alternate hands	823	-2.585	-.038	.324

Fig. 1.

A structural equation model showing the standardized negative effect of a latent variable for prenatal exposure to methylmercury on a second-order latent variable for general mental ability in a measurement model with two first-order factors, and with the manifest test variables corrected for a set of covariates. $LogWhale = \text{Log}_{10}(\text{Maternal Whale Dinners} + 1)$; $LogHgB = \text{Log}_{10}(\text{Hg in Cord Blood} + 1)$; $LogHgH = \text{Log}_{10}(\text{Hg in Mother Hair} + 1)$; Hg^* = Latent Hg-variable; g = Latent variable for general mental ability; Gf = Latent variable for fluid reasoning; Gc = Latent variable for verbal comprehension. Coefficients are standardized values. Double headed arrow indicates correlation of residuals. Numbers at arrows are residual variances. For simplicity, covariates are only shown schematically with no values or intercorrelations. Covariates are: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead exposure, and PCB exposure.

Fig. 2.

A Structural Equation Model (SEM) showing the standardized negative effect of a latent variable for prenatal exposure to methylmercury on a second-order latent variable for general mental ability in a measurement model with seven first-order factors, and with the manifest test variables corrected for a set of covariates. Parameter names are as in Fig. 1. For Gsm , Glr , Gs , Gt , and Gps , see Table 3 footnote. Coefficients are standardized values. Double headed arrows indicate correlation of residuals. Numbers at arrows are residual variances. As in Figure 1, residual variances for manifest variables, and covariates, are not shown. Covariates are: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead exposure, and PCB exposure.

Table 1

Methylmercury exposure biomarker results for 831 members of a Faroese birth cohort examined at age 22 years.

Prenatal	N	Geometric Mean	Interquartile Range	Total Range
Cord Blood (µg Hg/L)	793	22.91	13.45 – 40.95	1.00 – 350.50
Maternal Hair (µg Hg/g)	812	4.24	2.61 – 7.70	2.00 – 39.10
Age 22 years				
Blood (µg Hg/L)	803	2.53	1.39 – 4.55	0.14 – 46.33
Hair (µg Hg/g)	750	0.68	0.35 – 1.36	0.00 – 9.02

Geometric mean and interquartile range for cord blood mercury concentrations ($\mu\text{g/L}$) in relation to predictors of neurobehavioral performance with p for association with the cord-blood mercury concentration.

Table 2

Predictor	Categories	N	Geometric Mean	Interquartile range	p^*
Sex	Female	404	21.60	12.83 – 39.78	0.040
	Male	389	24.36	14.50 – 42.38	
Number of maternal fish dinners during pregnancy	0 – 2	400	20.69	12.90 – 37.50	0.001
	> 2	393	25.42		
Maternal Raven	< 44	235	26.15	14.70 – 45.60	0.002
	44 – 49	255	22.75	13.65 – 38.45	
	> 49	244	19.90	10.93 – 38.25	
Mother employed (age 14)	No	137	23.59	13.80 – 38.80	0.655
	Yes	590	22.64	13.35 – 41.85	
Father employed (age 14)	No	45	28.75	14.60 – 57.05	0.054
	Yes	674	22.61	13.40 – 41.00	
Age at examination (years)	20.95 – 21.80	263	23.30	15.10 – 40.10	0.841
	21.81 – 22.34	264	22.28	13.10 – 43.73	
	22.34 – 23.74	266	23.17	13.00 – 39.40	
Tested in language	Faroese	748	23.51	14.00 – 41.08	0.001
	Danish	45	14.91	7.35 – 37.40	
School Grade (age 14)	6	52	21	1.16 – 1.54	0.482
	7	636	23	1.16 – 1.63	
	8	44	21	1.16 – 1.54	

^{*)} P-value is for the association with the logarithmic transformation of cord blood mercury ($\text{Log}_{10}(\text{Hg}+1)$)

Table 3

Raw scores for neurobehavioral function tests administered at age 22 years.

Cognitive domain	Test variable	N	Mean	Standard deviation	Interquartile range	Total range
Gf ^{a)}	WJ III ^{b)} Concept Formation	813	33.78	4.38	31 – 37	7 – 40
	Raven Standard Progressive Matrices Plus	811	37.32	6.83	33 – 42	14 – 56
Gc ^{a)}	Boston Naming Test without cues	813	47.27	5.46	44 – 51	18 – 58
	Boston Naming Test with cues	813	50.50	4.72	48 – 54	21 – 59
	Synonyms, WJ III	813	7.98	2.30	6 – 9	1 – 15
	Antonyms, WJ III	813	12.67	1.84	11 – 14	5 – 18
	Verbal Analogies, WJ III	813	8.70	1.89	8 – 10	3 – 15
Gv ^{a)}	Block Design WISC-R ^{c)}	809	55.38	7.45	53 – 61	6 – 62
	Block Design WISC-R + 3 WAIS-R ^{d)}	417	73.00	8.17	69 – 79	39 – 83
	Spatial Relations, WJ III	807	73.47	4.35	71 – 77	49 – 81
Gsm ^{a)}	Numbers Reversed, WJ III	809	15.53	3.43	13 – 17	8 – 28
	Memory for words, WJ III	809	19.02	1.98	18 – 20	9 – 24
	Spatial Span Forward, WMS-III	809	9.09	1.66	8 – 10	5 – 14
	Spatial Span Backwards, WMS-III	809	8.83	1.50	8 – 10	3 – 14
	CVLT ^{e)} Trial 1, Correct	813	5.71	1.68	5 – 7	0 – 13
Glr ^{a)}	CVLT, Learning trials 1–5	813	49.37	8.87	43 – 56	24 – 77
	CVLT, List B, Correct	813	5.66	1.74	4 – 7	0 – 12
	CVLT, Short Delay, Free Recall	813	10.92	2.51	9 – 13	1 – 16
	CVLT, Long Delay, Free Recall	813	11.19	2.49	10 – 13	3 – 16
	CVLT, Long Delay, Recognition	810	14.88	1.22	14 – 16	9 – 16
	Incidental Memory for Boston Naming and Picture Vocabulary, WJ-III	813	9.45	3.69	7 – 12	1 – 24
	Warrington's Face Recognition Test, Immediate Recall	805	44.01	3.94	42 – 47	25 – 50
	Warrington's Face Recognition Test, Delayed Recall	805	41.91	4.43	39 – 45	13 – 50

Cognitive domain	Test variable	N	Mean	Standard deviation	Interquartile range	Total range
Gs ^{a)}	Visual Matching, WJ III ^{f)}	809	49.17	5.75	45 – 53	33.00 – 67.50
	Decision Speed, WJ III ^{f)}	809	38.06	6.22	34.00 – 41.62	19.00 – 64.29
Gt ^{a)}	CPT ^{g)} , NES II ^{h)} , Mean RT of 4 last Blocks	806	381.66	40.88	352.98 – 404.83	291.33 – 540.94
	CPT, NES II, SD of 4 last Blocks	806	54.98	16.91	42.95 – 63.52	22.90 – 142.67
	CPT, NES II, false negative errors last 4 blocks	806	0.29	0.92	0 – 0	0 – 11
	CPT, NES II, false positive errors last 4 blocks	806	0.73	1.18	0 – 1	0 – 10
	CPT-90 ⁱ⁾ , Proportion correct non-target (minus first 20 stimuli)	787	0.59	0.23	0.43 – 0.78	.02 – 1.00
	CPT-90, Noise corrected proportion correct non-target (minus first 20 stimuli)	787	0.53	0.22	0.37 – 0.71	.03 – 1.00
Gps ^{a)}	Finger Tapping, NES II, preferred hand	806	85.66	9.91	79 – 91	61 – 132
	Finger Tapping, NES II, non-preferred hand	806	80.44	12.78	72 – 86	54 – 158
	Finger Tapping, NES II, alternate hands	806	121.00	17.71	109 – 134	69 – 203

^{a)} Gf = Fluid Intelligence/Reasoning; Gc = Crystallized Intelligence / Verbal comprehension – knowledge; Gv = Visual-Spatial Processing; Gsm = Short-Term Memory; Glr = Long-Term Storage and Retrieval; Gs = Cognitive Processing Speed; Gt = Timed Reaction and Decision Speed; Gps = Psychomotor Speed and Dexterity

^{b)} WJ III = Woodcock-Johnson III Tests of Cognitive Abilities

^{c)} WISC-R = Wechsler Intelligence Scale for Children, Revised

^{d)} WAIS-R = Wechsler Adult Intelligence Scale, Revised

^{e)} CVLT = California Verbal Learning Test

^{f)} Subjects, who finished all items before the time limit of 3 minutes; had their score adjusted by adding the number of items they would have achieved in the time remaining, based on their performed items per second [Adjusted Score = Score + Score/sec. x No. secs. remaining]

^{g)} CPT = Continuous Performance Test

^{h)} NES2 = Neuropsychological Examination System 2

ⁱ⁾ CPT-90 = Continuous Performance Test w. 90 % target stimuli and 10 % non-target stimuli.

Test score change associated with mercury in cord blood (logarithmically transformed), as indicated by multiple regression analysis with adjustment for covariates.

Table 4

Cognitive domain	Test variable	N	Change associated with 10-fold increase	Standardized coefficient (Beta)	p
Gf	WJ III Concept Formation	662	-.284	-.022	.585
	Raven Standard Progressive Matrices Plus	662	-1.295	-.079	.046
Gc	Boston Naming Test, without cues	662	-1.295	-.079	.046
	Boston Naming Test, with cues	662	-1.382	-.097	.014
	Synonyms, WJ III	662	-.769	-.112	.005
	Antonyms, WJ III	662	-.453	-.080	.046
	Verbal Analogies, WJ III	662	-.137	-.024	.547
Gv	Block Design WISC-R	659	.015	.001	.986
	Block Design WISC-R + 3 WAIS-R	333	-1.579	-.065	.247
	Spatial Relations, WJ III	657	-.551	-.043	.290
Gsm	Numbers Reversed, WJ III	659	-.289	-.028	.491
	Memory for words, , WJ III	659	-.196	-.034	.403
	Spatial Span Forward, WMS-III	659	.266	.052	.197
	Spatial Span Backwards, WMS-III	659	.073	.016	.696
	CVLT, Trial 1, Correct	662	-.489	-.097	.015
Glr	CVLT, Learning trials 1-5	662	-.170	-.006	.869
	CVLT, List B, Correct	662	-.081	-.015	.706
	CVLT, Short Delay, Free Recall	662	-.135	-.018	.657
	CVLT, Long Delay, Free Recall	662	-.093	-.013	.751
	CVLT, Long Delay, Recognition	659	-.157	-.043	.293
	Incidental Memory for Boston Naming and Picture Vocabulary, WJ-III	662	-.517	-.047	.248
	Warrington's Face Recognition Test, Set2, Immediate Recall	656	-.476	-.041	.319
	Warrington's Face Recognition Test, Set 2, Delayed Recall	656	-.056	-.004	.918

Cognitive domain	Test variable	N	Change associated with 10-fold increase	Standardized coefficient (Beta)	p
Gs	Visual Matching, WJ III	659	-.748	-.043	.285
	Decision Speed, WJ III	659	.926	.049	.225
Gt	CPT, NES II, Mean RT of 4 last Blocks	656	4.082	.033	.432
	CPT, NES II, SD of 4 last Blocks	656	.861	.017	.685
	CPT, NES II, false negative errors last 4 blocks	656	.047	.016	.693
	CPT, NES II, false positive errors last 4 blocks	656	-.066	-.019	.645
	CPT-90, Proportion correct non-target (minus first 20 stimuli)	641	-.022	-.033	.419
Gps	CPT-90, Noise corrected proportion correct non-target (minus first 20 stimuli)	641	-.019	-.028	.491
	Finger Tapping, NES2, preferred hand	656	-1.218	-.041	.275
	Finger Tapping, NES2, non-preferred hand	656	-1.381	-.035	.338
	Finger Tapping, NES2, alternate hands	656	-1.199	-.023	.551

For explanation of acronyms, see Table 3.

Covariates: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead logarithmic, PCB's logarithmic

Table 5

Change associated with a 10-fold increase in prenatal methylmercury exposure in regard to seven latent variables, each reflecting a cognitive domain, in a structural equation model with an orthogonal first-order factor measurement model after adjustment for covariates.

Cognitive domain	Measurement scale	Change associated with 10-fold increase in exposure	Standardized coefficient (Beta)	<i>P</i>
Gc	Verbal Analogies, WJ-III	−0.555	−0.164	0.000
Gv	Raven Plus	−1.364	−0.093	0.057
Gsm	Numbers Reversed, WJ III	−0.560	−0.062	0.198
Glr	CVLT, Trials 1 –5	−1.628	−0.075	0.079
Gs	Visual Matching, WJ III	−0.498	−0.037	0.457
Gt	CPT, Reaction Time, NES2	−1.815	−0.025	0.582
Gps	Finger Tapping, pref. hand, NES2	−1.280	−0.052	0.260

For explanation of acronyms, see Table 3.

Covariates: Sex, Maternal fish dinners during pregnancy, Maternal Raven, Mother employed (age 14), Father employed (age 14), Age at examination, Tested in language, School grade (age 14), Lead logarithmic, PCB's logarithmic