# **Preconception maternal iodine status is associated with IQ but not with measures of executive function in childhood**

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**Supplemental Tables 1–4 and Figures 1-2** are available from the Online Supporting Material

**Short running head**: Maternal iodine status and cognitive function

**Abbreviations**: CANTAB: Cambridge Neuropsychological Test Automated Battery; DMS:Delayed Matching to Sample; I/Cr:iodine: creatinine ratio; IED:Intra-Extra Dimensional Set Shift; IQR:interquartile range; SSP:Spatial Span; SWS:Southampton Women’s Survey; UIC:urinary iodine concentration; WASI:Wechsler Abbreviated Scale of Intelligence.

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**ABSTRACT**

**Background:** Adverse effects of severe maternal iodine deficiency in pregnancy on fetal brain development are well-established, but the effects of milder deficiency are uncertain. Most studies examine iodine status in pregnancy; less is known about iodine nutrition before conception.

**Objective:** We examined relationships between maternal preconception iodine status with offspring cognitive function, within a prospective mother-offspring cohort.

**Design:** Maternal iodine status was assessed using the ratio of iodine:creatinine concentrations (I/Cr) in spot urine samples (median period before conception 3.3 (interquartile range 2.2,4.7) years). Childhood cognitive function was assessed at age 6-7 years. Full scale IQ was assessed using the Wechsler Abbreviated Scale of Intelligence, and executive function using tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Analyses (n=654 mother-child dyads) were adjusted for potential confounders including maternal intelligence, education and breastfeeding duration.

**Results:** Median (interquartile range) urinary iodine concentration was108.4 µg/L (62.2-167.8) and I/Cr ratio 114 µg/g (76-164). Preconception I/Cr ratio was positively associated with child IQ, before and after (β=0.13 (95%CI 0.04, 0.21) /SD, *P*=0.003) adjustment for potential confounding influences. 8.9% of women had a preconception urinary I/Cr ratio <50 µg/g; compared to those with an I/Cr ratio ≥150 µg/g, their offspring IQ was 0.49 (95% CI 0.79, 0.18) SD lower. There were no associations with the executive function outcomes assessed using CANTAB, before or after adjustment for confounders.

**Conclusions**: The association between iodine status before conception and child IQ provides some support for demonstrated links between low maternal iodine status in pregnancy and poorer cognitive function reported in other studies. However, given the negative effects on school performance previously observed in children born to iodine-deficient mothers, the lack of associations with measures of executive function in the present study was unexpected. Further data are needed to establish the public health importance of low preconception iodine status.

**Keywords:** iodine, development, cognition

**INTRODUCTION**

Iodine is an essential nutrient, required for the synthesis of thyroid hormones, known to be critical for cellular metabolism, growth, psychomotor and physical development, and function at all stages of life [1]. In pregnancy, the increased synthesis of thyroid hormones, essential for optimal fetal neurodevelopment, increases iodine requirements [2]. The fetus is known to be very vulnerable to the effects of iodine deficiency; the effects of severe deficiency on fetal brain development and the risk of cretinism in childhood are well-established [2,3]. However, there is a growing body of evidence that links milder forms of thyroid dysfunction to adverse pregnancy outcomes [4], suggesting that there may be important effects of mild or moderate maternal iodine deficiency on fetal development. At present, there is a lack of good evidence, and any effects on cognitive function of children born to mildly deficient women are not well understood [2].

In recent years, the UK has been categorised as mildly iodine deficient [5], although, based on new data from the UK National Diet and Nutrition Survey (NDNS), status is now considered to be adequate, as all groups studied in the NDNS met the WHO criteria for adequate iodine intake (median urinary iodine concentration within the range 100-299μg/L and fewer than 20% of samples below 50μg/L [6]), including women of childbearing age [7]. But it is a concern that high rates of mild to moderate iodine deficiency have been reported in other contemporary UK studies (ranging between 51% in young girls [8], and 40% [9] to 53% [10] among pregnant women), suggesting that deficiency may still be a problem in some sub-groups [5]. There is no UK recommendation to increase iodine intake in pregnancy, set on the premise that most women have an adequate status that will enable them to meet the additional iodine demands of pregnancy without supplementation [11]. However, the marked increase in maternal production of thyroxine in early gestation, at a time when the fetus is wholly dependent on maternal supply to support normal brain development [12,13], means that maternal iodine status needs to be sufficient before conception to support this increase. And it is a therefore a concern that low iodine status may be common in women of childbearing age.

These concerns have been heightened by findings of recent studies from developed populations, including the UK; low maternal iodine status in pregnancy has been linked to poorer cognitive function [14] and poorer school performance in children [15], and associations shown between low maternal iodine intakes in pregnancy and language delay and behaviour problems in the offspring [16]. However, to our knowledge, the role of preconception iodine status as an influence on fetal brain development has not been evaluated. Using preconception data from a general population sample of women, we describe maternal preconception iodine status, and examine how it relates to measured cognitive function of their children when aged 6-7 years.

**SUBJECTS AND METHODS**

*Southampton Women’s Survey (SWS)*

The SWS is a prospective study of mothers and children [17]. 12,583 non-pregnant women, aged 20-34 years, were interviewed at home when diet and lifestyle were assessed. 3158 became pregnant within the period of the study and had a live singleton infant. These women were followed up in pregnancy; their children have been assessed in ongoing follow-up studies [17]. The SWS was approved by the Southampton and South West Hampshire Local Research Ethics Committee (307/97, 153/99w, 005/03/t, 06/Q1702/104 and 10/H0504/30); written informed consent was obtained from all participants. Details of maternal educational attainment (defined in 6 groups according to highest academic qualification) were obtained at the preconception interview. Height and weight were measured, and used to calculate BMI (kg/m2). Maternal smoking status was recorded before conception and in pregnancy. Maternal diet was assessed using an administered food frequency questionnaire, before conception and in early and late pregnancy [18,19] to record average consumption of 100 foods over the preceding three months. Food iodine intake was estimated using national food composition data [18,20]. Detailed information on supplement use was collected; supplementary iodine intakes were calculated using manufacturers’ composition data, together with participants’ reported supplement frequency, dose and duration of use. At birth, the baby was weighed; gestational age was determined using a computerized algorithm based on menstrual data or using ultrasound assessment of fetal anthropometry in early pregnancy. The infants were visited at the ages of 6, 12 and 24 months; duration of breastfeeding was defined according to the date of the last feed reported at these visits [21].

*Assessment of iodine status*

A single spot urine sample was provided by each SWS woman at clinic visits, following their initial interviews, in the period before conception. The samples were collected at a median of 3.3 (IQR 2.2, 4.7) years before conception. The time of day was recorded. Urine samples were frozen and stored at -80oC from the date of collection until being thawed and assayed for iodine and creatinine contents in 2016 by the Trace Element Unit, Southampton General Hospital, Southampton, UK. Urinary iodine and creatinine concentrations are stable during prolonged frozen storage [14]. Urinary iodine concentration was assessed using inductively coupled plasma mass spectrometry (NexION 300D, PerkinElmer); creatinine concentrations were determined by a Beckman Coulter AU5800 using the Jaffe reaction. Urinary iodine concentration was measured in duplicate using rhodium as an internal standard (VWR International). Samples were analyzed against a urine calibration curve with the addition of 0, 1, 2, 5 and 10 µmol/l iodine (potassium iodide, Fisher Chemicals). Samples for calibration, test and quality control were diluted 1:15 with diluent containing 0.3% ammonia, 0.4 g/l ethylenediaminetetraacetic acid disodium salt dehydrate and 1.2 g/l ammonium dihydrogen orthophosphate (Fisher Chemicals). Results were verified by measurement of certified reference material, Seronorm Trace Elements Urine Levels 1 and 2 (Sero, Norway). Within-run precision was 2.17% (coefficient of variation) at 0.66 µmol/l for Seronorm Urine Level 1 and 1.21% at 2.30 µmol/l for Seronorm Urine Level 2. Between-run precision was 7.05% (coefficient of variation) at 0.66 µmol/l for Seronorm Urine Level 1 and 2.20% at 2.30 µmol/l for Seronorm Urine Level 2. To correct measures of iodine concentration for differences in urine volume, an iodine: creatinine ratio (I/Cr) was calculated for each participant; this measure of iodine status was used in all statistical analyses. However, in order to compare our study with new iodine status data available for a national sample of women of childbearing age [7], we also present descriptive data on urinary iodine concentration (UIC).

*Assessment of cognitive function at 6-7 years of age*

From August 2010, trained research nurses administered a variety of tests of cognitive function at the 6-7 year home visit, supervised by an educational psychologist; there were 942 children in this sub-group (**Figure 1**) Full scale IQ - an estimate of general cognitive ability - was assessed using the 2-subtest form of the Wechsler Abbreviated Scale of Intelligence [22]. This scale has been shown to have excellent reliability, with an average reliability coefficient (internal consistency) for full scale IQ of 0.93 and average inter-rater agreement >0.90 for verbal and non-verbal subtests. In the present study, inter-rater reliability statistics, determined from comparison of nurse-assessed video interviews were very similar (>0.9). Specific components of executive function were assessed using tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, UK) [23]. Delayed Matching to Subject (DMS) and Spatial Span (SSP) are both tests of memory. DMS assesses forced choice recognition memory for novel non-verbalisable patterns, and tests both simultaneous and short term visual memory. SSP assesses working memory capacity. Intra-Extra Dimensional Set Shift (IED) is a test of rule acquisition and reversal that assesses the ability to engage in deliberate, goal-directed action. Several outcome measures are available for each CANTAB test. In the current analysis, to reduce the likelihood of chance findings, and consistent with earlier analyses [23], we used the following outcomes: DMS, total correct (12 second delay); IED, total errors (adjusted for each stage not attempted due to failure); SSP, span length (longest sequence successfully recalled). Maternal intelligence (full scale IQ) was also assessed, using the Wechsler Abbreviated Scale of Intelligence [22].

*Statistical analysis*

Of the children who had an assessment of cognitive function when they were aged 6-7 years, 58 were excluded as they were born preterm (<37 weeks’ gestation). Of the remaining 884 children, 654 (74%) were born to mothers who had provided preconception urine samples (Figure 1.). Iodine status (I/Cr), was used as a continuous variable throughout the analyses, but categorised for presentation. I/Cr values and CANTAB IED total errors (adjusted) values were positively skewed and therefore transformed using Fisher-Yates normal scores [24]. Full scale IQ (WASI), CANTAB DMS total correct (12 second delay) and CANTAB SSP span length were standardised for analyses so the results could be interpreted in terms of standard deviation changes; Pearson correlations were used to compare these measures. Linear regression models were used to assess the association between I/Cr and cognitive function as measured by full scale IQ (WASI) and executive function (CANTAB); the analyses are presented unadjusted and adjusted for confounders. The choice of confounders was informed by a Directed Acyclic Graph (**Supplemental Figure 1**); this suggested adjusting for maternal IQ, maternal education and maternal pre-pregnancy BMI. In addition, breastfeeding duration, smoking in pregnancy (yes/no), sex, age and maternal iodine intakes in pregnancy were included to improve the accuracy of the model. Only the CANTAB outcomes were adjusted for age in the analysis, as the derivation of full scale IQ includes adjustment for age. A sample size of 422 participants (the smallest number included in the fully adjusted models) would have 80% power to detect a regression coefficient of 0.135 in measured cognitive outcome for a 1SD increase in iodine:creatinine ratio, at a 5% significance level. The data were analysed using Stata version 14.1 (StataCorp LP).

**RESULTS**

*Participant characteristics*

The characteristics of 654 mothers and children in the sub-sample of SWS for whom preconception maternal iodine status and cognitive function data were available are shown in **Table 1**, together with data for the remaining SWS mothers and children (born at term) who were not included in the analyses. In comparison with the rest of the cohort, the mothers in the sub-sample were of similar age and BMI. The majority of women in both groups did not take iodine-containing supplements in the preconception period. However, there were some differences when women in the sub-sample were compared with the rest of the cohort: they had slightly lower iodine intakes, were less likely to smoke in pregnancy and more likely to have breastfed for longer (all *P*<0.05). There was also a difference in average maternal IQ between the two groups; in the sub-sample, maternal IQ was higher and a greater proportion of mothers had educational qualifications at least to 18 years (both *P*<0.05). Children in the sub-sample did not differ in weight at birth or duration of gestation when compared with the rest of the SWS children and the proportion of boys was similar.

*Maternal iodine status*

**Figure 2** shows the distributions of maternal urinary iodine concentration and the I/Cr ratio. Median I/Cr ratio was 114 µg/g (IQR) 76-164); median urinary iodine concentration was108.4 µg/L (IQR, 62.2-167.8). 17.8% of women had a preconception urinary iodine concentration below 50 µg/L. The timing of urine collections ranged between 9.00am and 8.00pm, although the majority (85%) of samples were collected after 12.00pm. Urinary iodine concentration was inversely related to time of sample collection (*P=*0.018), but there was no association between time of sample collection and I/Cr ratio (*P=*0.87). We therefore did not consider time of collection of sample further in the analyses of I/Cr ratio data.

The characteristics of mothers and children studied are shown in **Supplemental Table 1,** according to maternal preconception iodine status (I/Cr ratio). Maternal iodine status was positively related to age and inversely related to preconception BMI, although the differences were small. As expected, iodine status was positively related to iodine intake and to use of iodine-containing supplements; almost a fifth of women who had an I/Cr ratio ≥150 µg/g were taking iodine-containing supplements. There were no differences in maternal educational attainment or IQ in relation to iodine status in the preconception period. No differences were found in the weight of the baby or gestational age at birth in relation to maternal iodine status; higher iodine status tended to be associated with longer duration of breastfeeding but this did not achieve statistical significance.

*Preconception iodine status and cognitive function in childhood*

**Table 2**. shows the associations between maternal preconception iodine status (I/Cr ratio) and children’s cognitive function outcomes at the age of 6-7 years, before and after adjustment for potential confounders. Preconception iodine status was positively associated with child’s full scale IQ; this association was robust to adjustment for the potential confounding influences including adjustment for the effects of maternal IQ. When we included quadratic terms to the adjusted model, we found no evidence of non-linearity in this association (data not shown). Full scale IQ was not strongly correlated with DMS, total correct (12 second delay) (r = 0.10, *P* = 0.03), IED, total errors (adjusted) (r = -0.16, *P* < 0.001) or SSP, span length (r = 0.27, *P* < 0.001). In contrast to the association seen with full scale IQ, maternal iodine status was not related to any of the executive function outcomes assessed using CANTAB – either before or after adjustment for confounders. The contrasting associations between maternal preconception iodine status and child IQ and assessed executive function are illustrated in **Figure 3**;the non-standardised IQ data are shown in **Supplemental Figure 2.** 8.9% of women had a preconception urinary I/Cr ratio <50 µg/g; compared to those with an I/Cr ratio ≥150 µg/g, their offspring IQ was 0.49 (95% CI 0.79, 0.18) SD lower, equivalent to a difference of 7.5 points (Supplemental Figure 2).

Because iodine status was assessed before conception, we also considered changes in iodine intakes in pregnancy from the preconception period (**Supplemental Table 2**). There was a small increase in the use of iodine-containing supplements in early pregnancy. However, the more notable change was an overall increase in dietary iodine intake in early pregnancy (*P<*0.001) followed by a further increase in late pregnancy (*P<*0.001). These changes were partly explained by an increase in milk intake in pregnancy, as we have previously reported [19]. The proportion of women who had iodine intakes below the UK reference nutrient intake (140 µg/day) fell from almost half the group before conception to less than a third by late pregnancy. In the next analyses we therefore further adjusted the models for differences in maternal iodine intake in pregnancy. The findings were largely unchanged: maternal preconception iodine status was still positively associated with child IQ, but was not related to any of the executive function outcomes examined (**Supplemental Table 3**).

Our final analyses considered the timing of assessment of preconception iodine status. As it is possible that more distant assessments may be a weaker marker of iodine status at conception, we tested for interactions between preconception iodine status and time to conception; we found no evidence of differential effects (**Supplemental Table 4**).

**DISCUSSION**

In a general population sample of UK women, lower iodine status before conception was related to lower IQ in their child at the age of 6-7 years. The association provides some support for links between maternal iodine status in pregnancy and child IQ that have been previously reported [14], and importantly, we found the association to be robust to adjustment for a range of potential confounding factors, including maternal IQ. To our knowledge, associations between iodine status in the preconception period and children’s cognitive function have not been reported before. However, in light of the reported links between maternal iodine insufficiency in pregnancy and children’s school performance [14,15] an unexpected finding of our study was that there were no associations between maternal iodine status in the preconception period and measures of executive function.

Although mild to moderate iodine deficiency is common in many parts of the world, clear evidence of effects of maternal insufficiency on child neurodevelopment is lacking [25]. Recent observational studies have started to address this gap in knowledge. They show deficits in child IQ and school performance [14,15] in relation to lower maternal iodine status in pregnancy, and most recently, child language delay and behaviour problems at the age of 3 years among children born to women who had low iodine intakes in pregnancy [16]. Whilst we cannot compare our preconception data directly with the findings from studies of pregnant women, the variations in iodine status we describe across our study population are very comparable to other UK studies. For example, median UIC in our study was 108 µg/L, which compares with values of 91 µg/L in ALSPAC cohort in pregnancy [14] and 117 µg/L among a national sample of non-pregnant women of childbearing age in the recent data collection in the NDNS [7]. A median UIC value >100 µg/L in our study, together with the findings that 18% of SWS women had UIC values below 50 µg/L would categorise this group as having adequate iodine intake, using WHO criteria [6]. Consistent with these indications of iodine sufficiency, median iodine intakes were close to the RNI in the preconception period. Furthermore, intakes increased, in line with greater milk consumption in pregnancy (Supplemental Table 2), such that less than a third of women had intakes below the RNI by late pregnancy. However, despite these positive indications of iodine sufficiency, some of the women studied had low iodine status, and lower status was related to sizeable deficits in child IQ when assessed at 6-7 years. In terms of effect size, the differences in child IQ (Supplemental Figure 2) appear greater than the differences observed in the ALSPAC cohort, which did not take account of differences in maternal IQ [14]. But it is important to note that the group of SWS women who had I/Cr below 50 µg/g was relatively small in our study, and the confidence intervals were wide.

One interpretation of our findings is that maternal iodine status was insufficient to support optimal fetal neurodevelopment for some women in the study population. Iodine is required for the synthesis of thyroid hormones and adverse effects of maternal hypothryoxinemia on fetal brain development are known [13], although this relationship may be complex as both low and high maternal free thyroxine concentrations have been linked to deficits in child IQ [26]. However, it is also important to highlight the negative findings from our study; contrary to expectation, we found no differences in other measures of cognitive ability, namely scores on three tests of executive function. Executive function describes various cognitive processes that coordinate, monitor and maintain other more basic cognitive processes involved in learning, reasoning and goal-directed behaviour. Measured executive function has been shown to be associated with better performance in tests of reading and maths in childhood [27]. There is evidence that measured executive function is associated with intelligence although, as in the present study, correlations between scores are modest [28]. Given the demonstrated links between low maternal iodine status and poorer school performance in other studies that point to negative effects on working memory capacity and visual processing skills [15,29], we would have expected to see comparable patterns of associations as we observed for child IQ. It is not clear why the associations with different measures of cognitive function were not consistent, and further data are needed. One possibility is that the variability in the CANTAB measures selected for analysis was modest. While we had an *a priori* analysis plan, that included a specified set of outcomes, and we used a directed acyclic graph approach to identify confounding factors to consider, these are observational data and we cannot exclude the possibility of residual confounding, or that the single association we found between iodine status and child IQ was a chance finding. However, our data add to earlier evidence [14] that also showed links between lower maternal iodine status and lower offspring IQ; the consistency of findings raises concerns.

A strength of this study is that we studied a large general population sample of women and children; the women had been characterised in detail in the period before conception, and we collected data on a range of measures of their child’s cognitive function at age 6-7 years. But the study also has some limitations. Firstly, we defined iodine status using single spot urine samples. While spot samples are commonly used to describe iodine status in population studies, and are considered to provide a good index of iodine intake over the past day, 24-hour samples and/or repeat spot samples are recommended for individual studies to take account of variations in iodine excretion [30,31]. Our analyses therefore used the iodine:creatinine ratio in order to correct for differences in urine volume; I/Cr has been demonstrated to have better agreement with 24-hour iodine excretion than UIC [32,33]. A second limitation is that for some women in the group, significant time had elapsed between the date of the urine sample and the date of conception. We have previously described stability in dietary habits in the preconception period in this population, such that the women’s dietary patterns when re-assessed after 2 years were very similar (correlation between dietary pattern (‘prudent’) scores=0.81; average change in score =0.13SD) [34]. As these data suggest that iodine status would not have changed markedly by the time women conceived, the analysed samples should provide reasonable indication of iodine status at conception. However, although we found no evidence of differential effects, according to length of time between assessment of iodine status and conception, it is possible that changes had occurred. A third limitation is that we studied a sub-group of women who were taking part in the SWS, and some characteristics, such as maternal IQ and educational attainment, differed from the women who were not included in the analyses. This could affect the generalisability of our findings, although the variations in iodine status of the SWS women that we describe are comparable to recent status data from a nationally-representative sample of women of child-bearing age [7]. A final limitation is that we did not collect urine samples from the children. As we are unable to take account of differences in iodine status in childhood, we cannot exclude the possibility of postnatal effects of differences in status on cognitive function.

The benefits of iodine supplementation for mildly deficient women are uncertain [2], and further data are needed [25,35]. The high rates of unplanned pregnancy in the UK [36], together with the known vulnerability of the fetus to the effects of iodine deficiency in early gestation, may limit the effectiveness of iodine supplementation starting in pregnancy, suggesting that the time to optimise iodine status is before conception. Additionally, a recent analysis from the Norwegian Mother and Child Cohort Study [16] showed no protective effects of iodine supplementation during pregnancy on offspring neurodevelopment; there was also some suggestion of harmful effects of supplementation among women who had low dietary iodine intakes [16]. While ongoing research will be key to defining the prevalence and public health importance of low iodine status, our study adds further data to a body of evidence that focuses attention on the importance of nutrition in the preconception period.

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**Table 1. Characteristics of 654 mother-child pairs studied and the rest of the SWS cohort**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Analysis sample**  **(*n = 654*)1** |  | **Rest of SWS cohort**  **(*n = 2297*)** | ***P*-value for difference** |
| **Maternal characteristics** |  |  |  |  |
|  |  |  |  |  |
| Age at preconception assessment (years)2 | 27.5 ± 3.8 |  | 27.8 ± 3.9 | 0.11 |
|  |  |  |  |  |
| Preconception BMI (kg/m2)3 | 24.3 (21.9, 26.9) |  | 24.1 (21.9, 27.5) | 0.82 |
|  |  |  |  |  |
| Total iodine intake (µg/day)3 | 147 (116, 193) |  | 155 (116, 210) | 0.01 |
|  |  |  |  |  |
| - % women taking iodine supplements in preconception period (%) | 12 |  | 10 | 0.12 |
|  |  |  |  |  |
| % women who smoked: |  |  |  |  |
| - in preconception period (%) | 24 |  | 29 | 0.007 |
| - in pregnancy (%) | 10 |  | 18 | < 0.001 |
|  |  |  |  |  |
| % women with qualifications to at least A-level (%)4 | 66 |  | 57 | < 0.001 |
|  |  |  |  |  |
| Maternal IQ2,5,6 | 108.4 ± 12.6 |  | 105.0 ± 13.3 | 0.02 |
|  |  |  |  |  |
| **Child characteristics** |  |  |  |  |
|  |  |  |  |  |
| Boys (%) | 51 |  | 52 | 0.85 |
|  |  |  |  |  |
| Gestational age at birth (weeks)2 | 40.2 ± 1.2 |  | 40.1 ± 1.2 | 0.05 |
|  |  |  |  |  |
| Birthweight (kg)2 | 3.5 ± 0.5 |  | 3.5 ± 0.5 | 0.84 |
|  |  |  |  |  |
| Duration of breastfeeding (weeks)3 | 13.0 (2.0, 30.4) |  | 8.7 (0.4, 26.1) | < 0.001 |
|  |  |  |  |  |
| Age at assessment of cognitive function (years)2 | 6.9 ± 0.2 |  |  |  |
| Full scale IQ2 | 103.7 ± 15.3 |  | - |  |
|  |  |  |  |  |
| DMS, total correct (12 second delay)2 | 2.6 ± 1.2 |  | - |  |
|  |  |  |  |  |
| IED, total errors (adjusted)2 | 58 (37, 63) |  | - |  |
|  |  |  |  |  |
| SSP, span length2 | 3.9 ± 0.9 |  | - |  |

1children who had measured cognitive function at 6-7 years and whose mother’s iodine status was assessed; 2mean ± SD and all such values; 3median (interquartile range) and all such values; 4school examinations taken at age 18 years; 5maternal intelligence assessed when children were aged 6-7 years using the Wechsler Abbreviated Scale of Intelligence [22]; 6data available for 243 women in the ‘rest of SWS cohort’ group. CANTAB outcomes (CANTAB®, Cambridge Cognition, Cambridge, UK) DMS: Delayed Matching to Sample, IED: CANTAB Intra-Extra Dimensional Set Shift, SSP: CANTAB Spatial Span

**Table 2. Maternal preconception iodine status (iodine:creatinine ratio) as a predictor of cognitive function at age 6-7 years1,2 in 654 mother-child pairs studied**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Unadjusted** | | |  | **Adjusted3** | | |
|  | **Beta (95% CI)** | ***P-*value** | ***n*** |  | **Beta (95% CI)** | ***P-*value** | ***n*** |
|  |  |  |  |  |  |  |  |
| Full scale IQ (z-score) | 0.09 (0.02, 0.17) | 0.02 | *647* |  | 0.13 (0.04, 0.21) | 0.003 | *507* |
| *Executive function* |  |  |  |  |  |  |  |
| CANTAB DMS total correct (12 sec delay) (z-score) | 0.03 (-0.06, 0.11) | 0.52 | *540* |  | 0.01 (-0.09, 0.10) | 0.90 | *453* |
|  |  |  |  |  |  |  |  |
| CANTAB IED total errors (adjusted4)  (z-score) | -0.07 (-0.15, 0.02) | 0.12 | *538* |  | -0.04 (-0.14, 0.05) | 0.36 | *451* |
|  |  |  |  |  |  |  |  |
| CANTAB SSP span length (z-score) | 0.00 (-0.08, 0.09) | 0.95 | *505* |  | 0.00 (-0.10, 0.09) | 0.93 | *422* |

1Cognitive function assessed using the Wechsler Abbreviated Scale of Intelligence (full-scale IQ) [22] and Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, UK) [23]; 2Iodine:creatinine ratio (z-score); 3adjusted for maternal IQ, maternal education, pre-pregnancy BMI, duration of breastfeeding, smoking in pregnancy, sex and age (for CANTAB outcomes); 4adjusted by adding 25 for each stage not attempted due to failure. CANTAB DMS: Delayed Matching to Sample, CANTAB IED: Intra-Extra Dimensional Set Shift, CANTAB SSP: Spatial Span. Beta values represent the slope of association between maternal iodine status and children’s cognitive outcomes.

**Figure 1. Flow chart showing the 654 children assessed at 6-7 years in the Southampton Women’s Survey**

**Figure 2. Frequency distributions of preconception urinary iodine concentration and iodine:creatinine ratio, determined in spot samples from 654 women in the Southampton Women’s Survey**

**Figure 3. Adjusted differences in cognitive function at 6-7 years in 654 chidren in the Southampton Women’s Survey, according to maternal preconception iodine status (iodine:creatinine ratio).** Numbers of mother-child pairs: I/Cr <50, n=58; ≥ 50 to < 100, n=222; ≥ 100 to < 150, n=188; ≥ 150, n=186.Cognitive function assessed using the Wechsler Abbreviated Scale of Intelligence [22] (A) and Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, UK) [23] (B,C,D); data adjusted for maternal IQ, maternal education, pre-pregnancy BMI, duration of breastfeeding, smoking in pregnancy, sex and age (for CANTAB outcomes); reference group I/Cr ≥150µg/g; Values are means and 95% confidence intervals. IEDadjusted by adding 25 for each stage not attempted due to failure. CANTAB DMS: Delayed Matching to Sample, CANTAB IED: Intra-Extra Dimensional Set Shift, CANTAB SSP: Spatial Span.