

Iodine supplementation improves cognition in mildly iodine-deficient children¹⁻³

Rosie C Gordon, Meredith C Rose, Sheila A Skeaff, Andrew R Gray, Kirstie MD Morgan, and Ted Ruffman

ABSTRACT

Background: The effects of severe iodine deficiency during critical periods of brain development are well documented. There is little known about the consequences of milder forms of iodine deficiency on neurodevelopment.

Objective: The objective was to determine whether supplementing mildly iodine-deficient children with iodine improves cognition.

Design: A randomized, placebo-controlled, double-blind trial was conducted in 184 children aged 10–13 y in Dunedin, New Zealand. Children were randomly assigned to receive a daily tablet containing either 150 μg I or placebo for 28 wk. Biochemical, anthropometric, and dietary data were collected from each child at baseline and after 28 wk. Cognitive performance was assessed through 4 subtests from the Wechsler Intelligence Scale for Children.

Results: At baseline, children were mildly iodine deficient [median urinary iodine concentration (UIC): 63 $\mu\text{g}/\text{L}$; thyroglobulin concentration: 16.4 $\mu\text{g}/\text{L}$]. After 28 wk, iodine status improved in the supplemented group (UIC: 145 $\mu\text{g}/\text{L}$; thyroglobulin: 8.5 $\mu\text{g}/\text{L}$), whereas the placebo group remained iodine deficient (UIC: 81 $\mu\text{g}/\text{L}$; thyroglobulin: 11.6 $\mu\text{g}/\text{L}$). Iodine supplementation significantly improved scores for 2 of the 4 cognitive subtests [picture concepts ($P = 0.023$) and matrix reasoning ($P = 0.040$)] but not for letter-number sequencing ($P = 0.480$) or symbol search ($P = 0.608$). The overall cognitive score of the iodine-supplemented group was 0.19 SDs higher than that of the placebo group ($P = 0.011$).

Conclusions: Iodine supplementation improved perceptual reasoning in mildly iodine-deficient children and suggests that mild iodine deficiency could prevent children from attaining their full intellectual potential. The trial was registered with the Australia New Zealand Clinical Trials Register as ACTRN12608000222347. *Am J Clin Nutr* 2009;90:1264–71.

INTRODUCTION

The most serious iodine-deficiency disorder is cretinism, characterized by physical abnormalities and profound mental impairment. Such consequences of severe iodine deficiency during critical periods of brain development are well-known (1,2), but less is understood about the effects of milder forms of iodine deficiency. A meta-analysis by Bleichrodt and Born (3) using studies of children living in moderately and severely iodine-deficient areas estimated that iodine deficiency results in an average 13.5-point reduction in the intelligence quotient (IQ). Another meta-analysis of Chinese studies by Qian et al (4) reported an approximate difference of 10 IQ points between moderate to severely iodine-deficient and iodine-sufficient or

iodine-supplemented populations. A cross-sectional study of mildly iodine-deficient Spanish schoolchildren observed an increased likelihood of children with a lower IQ with poorer iodine status (5). A limitation of such studies is that they were observational, and differences in factors that may affect cognitive ability other than the severity of iodine deficiency, such as socioeconomic status, cannot be eliminated.

Until 2006, the results of randomized trials, in which iodine was given as a single bolus dose in the form of iodized oil, were equivocal. Four of these studies were conducted in children from severely iodine-deficient populations (6–9) and one study in moderately iodine deficient children (10). In 3 of these studies, there was a significant increase in iodine supply in the control groups as well as in the iodine groups, potentially masking the effect of iodine supplementation (6, 8, 9). This led to changes in the planned analyses, with Bautista et al (6) reporting increasing IQ with decreasing goiter size, and van den Briel et al (9) reporting improved cognition with improved iodine status. In the 2 remaining studies, iodine contamination was not an issue; however, the treatment groups remained iodine deficient at the end of the interventions (7, 10). The most convincing evidence comes from a randomized controlled trial conducted by Zimmermann et al (11) in moderately iodine-deficient Albanian children, which found that children in the iodine group performed significantly better on tests of cognitive function than did children in the placebo group. To date, there has not been a similar study in a mildly iodine-deficient population.

The reemergence of iodine deficiency in New Zealand is believed to be a consequence of: lower concentrations of iodine in milk because of the discontinuation of iodine-containing sanitizers in the dairy industry, declining use of iodized salt, and an increased consumption of processed foods not made with iodized salt. A study by Skeaff et al (12) of 300 New Zealand schoolchildren aged 8–10 y reported a median urinary iodine con-

¹ From the Departments of Human Nutrition (RCG, MCR, and SAS), Preventive and Social Medicine (ARG), and Psychology (KMDM and TR), University of Otago, Dunedin, New Zealand.

² Supported by the Maurice and Phyllis Paykel Trust and the University of Otago. The iodine and placebo supplements were provided by Blackmores Australia.

³ Address correspondence to SA Skeaff, Department of Human Nutrition, University of Otago, Dunedin, New Zealand. E-mail: sheila.skeaff@otago.ac.nz.

Received May 29, 2009. Accepted for publication August 5, 2009.

First published online September 2, 2009; doi: 10.3945/ajcn.2009.28145.

centration (UIC) of 66 $\mu\text{g/L}$ and goiter prevalence of 11%; a median UIC between 50 and 99 $\mu\text{g/L}$ and a goiter rate of 5–19.9% is indicative of mild iodine deficiency (13). This was confirmed in a larger ($n = 1700$) more nationally representative sample of schoolchildren in the 2002 National Children's Nutrition Survey (14), which observed the same median UIC of 66 $\mu\text{g/L}$. The functional consequences of mild iodine deficiency during childhood are unknown, and research in this age group is needed. The aim of this study was to investigate the effect of iodine supplementation on cognition in mildly iodine-deficient children.

SUBJECTS AND METHODS

Subjects and study design

This study was a randomized, placebo-controlled, double-blind intervention trial undertaken in schoolchildren living in Dunedin, New Zealand, between August 2007 and October 2008. All schools in Dunedin with ≥ 2 classes of intermediate-aged (ie, middle school) children were approached to take part in the study; 2 schools agreed to participate. Year 7 (ie, grade 7) children were recruited from schools through presentations in their classrooms. One school had 5 grade 7 classes and the other school had 7 grade 7 classes; children were not streamed by ability. To provide an opportunity for children from non-participating schools to take part, advertisements for intermediate-aged children were also placed in local newspapers. Recruitment occurred at 2 time points; from August to October in 2007 (cohort 1) and from February to March in 2008 (cohort 2). Eligibility criteria were as follows: children aged 10–13 y with no known history of thyroid conditions and not taking an iodine-containing dietary supplement. Interested children and their parents provided a postal address and were sent an information sheet, brochure, and consent form in the mail. Children were block-randomized (block size = 20) according to sex and method of recruitment (ie, school or advertisement) to receive a daily supplement containing either 150 μg I or an identical placebo. All participants and their parents or guardians provided informed written consent, and ethical approval for this study was obtained from the University of Otago Human Ethics committee.

Data collection

Testing sessions were carried out at the 2 schools, and, for those children recruited by advertisement, at a clinic at the University of Otago. Dietary, anthropometric, biochemical and cognitive data were collected for each participant at baseline and at 28 wk. Before the baseline testing session, the primary caregiver of each child completed a questionnaire that asked about the child's age and ethnicity (New Zealand European or other ethnicities; Maori or Pacific Island descent), household income (<\$30,000, \$30,000–\$50,000, or >\$50,000), child's supplement use, child's medical conditions, child's medication use, and perceived health status of the child. The questionnaire also included an iodine-specific food-frequency questionnaire (FFQ), which asked caregivers to describe the frequency of consumption by the child of foods that we considered the main source of iodine for New Zealand children (ie, dairy products, milk, red meat, poultry, fish, shellfish, pulses and legumes, fruit,

eggs, and iodized salt). The frequency categories were as follows: "never," "less than once a week," "1–3 times per month," "once a week," "2–4 times a week," "5–6 times per week," "once per day," or "2 or more times a day." At 28 wk, caregivers again completed the FFQ and were also asked to indicate whether they knew their child's supplement allocation (ie, iodine or placebo). Dietary iodine intake was calculated by using data obtained from the New Zealand Food Composition Database for each food group (15).

Anthropometric measurements were obtained according to standardized techniques (16) by using calibrated equipment while the children were wearing light indoor clothing and no shoes. Height was measured to the nearest 0.1 cm with a portable stadiometer designed and built by the University of Otago. Weight was measured to the nearest 100 g with Seca digital platform scales (model 770; Alpha, CMS Weighing Equipment Ltd, London, United Kingdom). A nonfasting 1-mL finger-prick blood sample was collected from each child for the measurement of serum thyroglobulin and total thyroxine (TT_4) concentrations. To facilitate blood flow, a wheat bag was heated in a microwave and wrapped around the child's hand for 2 min before blood was collected into a 1.5-mL Eppendorf tube with a disposable lancet (Tenderlett; International Technidyne Corporation, Edison, NJ). Whole blood was left to clot at room temperature for 60 min and centrifuged in a microcentrifuge at $4000 \times g/\text{min}$ for 10 min, and the serum was isolated and frozen at -20°C . Children were asked to void urine into a clean plastic bowl that was fitted into the toilet bowl. Urine was then transferred to a 5-mL plastic test tube and frozen at -20°C . Thyroid volume was not assessed.

Cognitive testing

Four subtests from the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV), Australian standardized edition (Harcourt Assessment, Marrickville, Australia), were used to assess cognition in the children. Each test was chosen on the basis of 3 criteria: 1) the likelihood of the test to respond to iodine supplementation in mildly iodine-deficient children based on previous research (11), 2) the aspect of cognition assessed by the test, and 3) the relative ease of administration of the test. Two researchers (RCG and MCR) were trained in the administration of the tests by psychologists with a background in developmental (KMDM and TR) and clinical (TR) psychology and carried out all of the cognitive assessments. Testing was conducted in a quiet room free of distractions and took ≈ 30 min to complete. Raw scores obtained from tests were subsequently scaled for age according to the WISC-IV Manual (17). The 4 cognitive tests chosen were picture concepts, letter-number sequencing, matrix reasoning, and symbol search, which have a test-retest reliability of 0.74, 0.59, 0.73, and 0.55, respectively (17). All of the subtests except for symbol search are new to WISC-IV and are described briefly below.

Picture concepts

This test assesses perceptual reasoning. The objective of the test is to select one picture from each of 2 or 3 rows of 3 to 4 pictures that are linked through a common characteristic. As the test progresses, the concepts linking the pictures become more



abstract, and the number of pictures in each row and the number of rows increases.

Letter-number sequencing

This test assesses working memory. The researcher reads the child a jumbled list of letters and numbers at the rate of one letter or number per second. The child is asked to recall the sequence, saying the numbers first in ascending order and then the letters in alphabetical order. As the test progresses, the difficulty increases as the sequences increase in length.

Matrix reasoning

This test is based on Raven's Colored Progressive Matrices and assesses perceptual reasoning. The objective of the test is to select the missing section from an incomplete matrix from 5 possible options, which become progressively more difficult as the test proceeds.

Symbol search

This test assesses processing speed. The child scans 2 symbols and is asked to identify whether either of those 2 symbols is present in a target group of symbols. The child completes as many items as possible in 120 s.

Supplements

Supplements were provided by Blackmores (Warriewood, Australia). The tablets had a digestion time of 8 min and were composed of plant cellulose, and the active tablets contained 150 μg I as potassium iodate. Quality assurance for Blackmores was undertaken by LIPA Pharmaceuticals Ltd (Minto, Australia), who reported a mean iodine content of 156 μg (range: 139–161 μg) for active tablets ($n = 20$). The iodine content of both iodine ($n = 10$) and placebo ($n = 10$) supplements was independently analyzed in New Zealand by Hill Laboratories (Hamilton, New Zealand) using microdigestion with tetramethylammonium hydroxide and inductively coupled plasma mass spectrometry (18). The placebo tablets contained <0.1 μg I per tablet, and the iodine tablets contained a mean (\pm SD) iodine content of 136.0 ± 7.7 μg I per tablet. At the end of the baseline testing session, children were provided with 4 wk worth of supplements in 28-d compliance packaging blister packs (Medico Pak; Douglas Pharmaceuticals, Auckland, New Zealand), and an information sheet on how to take their supplements. Every 4 wk a new blister pack of supplements was posted to each child, and a return envelope was provided so that the previous month's supplements could be collected and counted to assess compliance. If a pack of supplements was not returned, the compliance was assumed to be zero for that month. Movie vouchers, small stationary items, or shopping vouchers were sent out with supplements during the study to aid with compliance.

Biochemical analysis

Analysis of UIC was carried out using Method A, as recommended by the World Health Organization (WHO)/United Nations Children's Fund (UNICEF)/International Council for Control of Iodine Deficiency Disorders (ICCIDD) (13). Internal and external standards were run with each batch of samples. The

internal standard used was a pooled urine sample (72.9 ± 3 $\mu\text{g/L}$), which had a CV of 4.2% ($n = 88$). Seronorm (Sero As, Asker, Norway) was used as an external standard, which had a mean iodine concentration of 137 ± 8 $\mu\text{g/L}$ (expected range: 131–150 $\mu\text{g/L}$) and a CV of 5.5% ($n = 176$).

Serum thyroglobulin and TT_4 concentrations were measured with a radioimmunoassay by EndoLab, Christchurch Hospital, Christchurch. Samples were screened for the amount of serum antibodies to thyroglobulin, because these antibodies can interfere with serum thyroglobulin measurement. Both immunoassays were run with an internal and external reference standard. The thyroglobulin assay had an analytic detection limit of 0.1 $\mu\text{g/L}$ and accuracy checked by using CRM 457 (Institute for Reference Materials and Measurement, Geel, Belgium). The interassay CV was 25% at 0.2 μg thyroglobulin/L, 8% at 40.4 μg thyroglobulin/L, and 5% at 333 μg thyroglobulin/L. Intraassay CVs were 5% at 0.2 μg thyroglobulin/L, 2% at 40.4 μg thyroglobulin/L, and 2% at 333 μg thyroglobulin/L. The TT_4 assay was run with a standard reference material that was produced in-house by the Nuclear Medicine Laboratory (EndoLab). The interassay CV was 4.5%. The intraassay CVs were 7.1% at 41 nmol TT_4/L , 4.4% at 70 nmol TT_4/L , 4.3% at 115 nmol TT_4/L , and 4.2% at 168 nmol TT_4/L .

Statistical analysis

The primary outcome for this study was a difference in cognitive test scores between the iodine and placebo groups. Because the WISC-IV has not been previously used to assess cognition in iodine supplementation studies in children, sample size was determined conservatively by assuming a 0.3-SD difference in mean cognitive test scores ($\alpha = 0.05$ and $\beta = 0.20$). After accounting for 15% attrition, 155 children were needed in each group, giving a total sample size of 310.

Data were analyzed by using STATA software (version 9.0 for Mac; StataCorp, College Station, TX). Log transformations were used on data (UIC, serum thyroglobulin, and dietary iodine) when the residuals from models exhibited positive skew and/or heteroscedasticity. Unpaired t tests were used to test for group differences at each time point, and paired t tests were used to assess differences between baseline and 28 wk for the iodine and placebo groups. The effect of supplementation was evaluated by using multiple linear regression for each of the 4 cognitive tests and biochemical indexes, with control for baseline score, sex, age (for biochemical indexes only), method of recruitment, cohort, household income, and ethnicity; P values were not adjusted for multiple comparisons. Mixed model regression was performed on the cognitive test scores to obtain an estimate of the overall effect of iodine supplementation on cognition, with control for baseline scores (standardized by using baseline SD), sex, method of recruitment, cohort, household income, and ethnicity and by using a random-subjects effect to control for pairs of cognitive scores (ie, at baseline and 28 wk) from each participant. Tester effects (ie, researchers who administered cognitive tests; either RCG or MCR) were examined in all models, but were not significant for both overall cognitive score (baseline: $P = 0.347$; 28 wk: $P = 0.611$) and any of the individual test scores (all $P \geq 0.112$) and were not included as a covariate in the final models. Statistical significance was set at $P < 0.05$.



RESULTS

A total of 184 children ($n = 93$ in cohort 1 and $n = 91$ in cohort 2) participated in the study; 88% ($n = 162$) were recruited from the 2 intermediate schools, with the remaining children ($n = 22$) recruited by advertisement. It was not possible to recruit additional cohorts of children because of the introduction of mandatory iodine fortification of bread in 2009. The average (range) age of the sample was 11.2 (10–13.3) y, and 55% of the children were boys. A household income greater than NZ\$50,000 was reported by 47% of the sample; 22% did not disclose their household income. Approximately 58% of households in New Zealand report an income of >NZ\$50,000 (19). Sixteen percent of children were of Maori or Pacific descent, with the other 84% of the sample comprising New Zealand European and other ethnicities. Approximately 9% of the population in Dunedin is of Maori or Pacific descent (19). The mean (\pm SD) height-for-age z score at baseline was 0.31 ± 1.07 , and the mean (\pm SD) weight-for-age z score at baseline was 0.62 ± 1.14 (20).

There were 18 children who withdrew from the study and did not attend the second testing session, 11 in the iodine group and 7 in the placebo group, which left 166 children who completed the study. Reasons given for withdrawal were as follows: moved away ($n = 4$), no longer wanting to take tablets ($n = 10$), not wanting to give another urine or blood sample ($n = 2$), parent withdrawing consent ($n = 1$), and away from school at 28 wk ($n = 1$). At baseline, 96% of participants provided a urine sample, and 97% provided a finger-prick blood sample. After 28 wk, 96% of participants provided a urine sample, and 99% provided a blood sample. At baseline, 14 of the blood samples collected yielded insufficient serum for analysis; however, at the second testing session, only 2 samples provided insufficient serum. Median compliance for those who remained in the study over the 28 wk was 76% in the iodine group and 77% in the placebo group. At the end of the intervention, 5% of the children correctly identified the supplement group they were in, 86%

specified that they did not know, and 9% incorrectly identified which supplement group they were in.

UIC, serum thyroglobulin, and TT_4 at baseline and 28 wk for the iodine and placebo groups are presented in **Table 1**. At baseline, the median UIC of the children was 63 $\mu\text{g/L}$, which indicated mild iodine deficiency according to the criteria recommended by WHO/UNICEF/ICCIDD (13) (median UIC: 50–99 $\mu\text{g/L}$). Additionally, 87% of the children in this study had a UIC <100 $\mu\text{g/L}$, and 32% had a UIC <50 $\mu\text{g/L}$, greater than the recommendation that no more than 20% of the populations have a UIC below this cutoff (13). After 28 wk, the median UIC in both the placebo and iodine groups had increased significantly ($P < 0.001$); however, the median UIC of 81 $\mu\text{g/L}$ in the placebo group still categorized these children with mild iodine deficiency, whereas the UIC of 145 $\mu\text{g/L}$ in the iodine group was indicative of adequate iodine status. Using linear regression, iodine supplementation was significantly associated with final UIC after the baseline concentration, age, sex, method of recruitment, cohort, ethnicity, and household income were controlled for ($P < 0.001$).

At baseline, the median serum thyroglobulin concentration of the children was 16.4 $\mu\text{g/L}$, greater than the 10.0- $\mu\text{g/L}$ WHO/UNICEF/ICCIDD cutoff (21) for mild iodine deficiency. After 28 wk, the serum thyroglobulin concentration of both groups had significantly decreased ($P < 0.001$); however, the thyroglobulin concentration of 11.6 $\mu\text{g/L}$ in the placebo group was still >10.0 $\mu\text{g/L}$, whereas the concentration of 8.5 $\mu\text{g/L}$ in the iodine group was below this cutoff, which indicated adequate iodine status. There was a significant difference in the final serum thyroglobulin concentration between the groups after the baseline concentration, age, sex, method of recruitment, cohort, ethnicity, and household income were controlled for ($P < 0.001$). The mean (\pm SD) serum TT_4 concentration at baseline was 104 ± 28.1 nmol/L. After 28 wk, there was no significant change in TT_4 in either the iodine or placebo groups, nor was the

TABLE 1

Concentrations of urinary iodine, serum thyroglobulin, and serum total thyroxine (TT_4) at baseline and at 28 wk in children aged 10–13 y from Dunedin, New Zealand

Variable and assessment time	Iodine			Placebo			<i>P</i> for group difference ²
	<i>n</i>	Value	<i>P</i> ¹	<i>n</i>	Value	<i>P</i> ¹	
Urinary iodine concentration ($\mu\text{g/L}$) ³							
Baseline	89	66 (45, 88) ⁴	<0.001	87	62 (47, 78)	<0.001	<0.001
28 wk	77	145 (93, 298)		82	81 (60, 102)		
Thyroglobulin concentration ($\mu\text{g/L}$) ⁵							
Baseline	75	16.5 (9.9, 28.1)	<0.001	71	15.2 (10.7, 24.0)	<0.001	<0.001
28 wk	71	8.5 (5.5, 14.4)		73	11.6 (8.4, 17.6)		
TT_4 concentration (nmol/L) ⁶							
Baseline	75	103 ± 18 ⁷	0.803	73	106 ± 36	0.320	0.728
28 wk	71	101 ± 18		74	101 ± 14		

¹ Within-group differences between baseline and 28 wk by paired *t* test.

² Between-group differences at 28 wk by multiple linear regression after adjustment for baseline values, age, method of recruitment, cohort, ethnicity, household income, and sex.

³ A median urinary iodine concentration of 50–99 $\mu\text{g/L}$ indicates mild iodine deficiency, and >100 $\mu\text{g/L}$ indicates adequate iodine status (13).

⁴ Median; interquartile range (25th–75th percentile) in parentheses (all such values).

⁵ A mean thyroglobulin concentration of 10–19.9 $\mu\text{g/L}$ indicates mild iodine deficiency, and <10 $\mu\text{g/L}$ indicates adequate iodine status (21).

⁶ The normal reference range for 11–15-y-old females is 69–149 nmol/L and for males is 63–147 nmol/L (22).

⁷ Mean \pm SD (all such values).

final serum TT_4 concentration associated with iodine supplementation in the regression analysis ($P = 0.904$).

The median dietary iodine intake for the children at baseline was 54 (interquartile range: 42–65) $\mu\text{g}/\text{d}$, and there was no significant difference between the 2 supplement groups ($P = 0.902$). After 28 wk, the median dietary iodine intake for the children was 54 (interquartile range: 38–65) $\mu\text{g}/\text{d}$, which was not different from baseline ($P = 0.621$), nor was there a difference between the iodine and placebo group ($P = 0.179$). Regular use of iodized salt at the table was reported by 36% and 34% of the iodine and placebo groups at baseline, respectively. After 28 wk, there was no significant change in the proportion of either group using iodized salt at the table (31% and 38% for the iodine and placebo group, respectively). Use of iodized salt in cooking was reported by 65% of the iodine and 59% of the placebo group at baseline; after 28 wk, there was no significant change in the percentage of children in the iodine group (64%) who reported using iodized salt during cooking; however, a significantly higher proportion of the placebo group (68%) reported using iodized salt in cooking ($P = 0.032$).

For each of the cognitive tests, age-standardized cognitive test scores are presented at baseline and 28 wk for the iodine and placebo groups in **Table 2**; the treatment effect (ie, comparison of the difference between the final score and the baseline score) is also reported. There were no significant differences between test scores of the iodine and placebo groups for any of the subtests at baseline. Iodine supplementation resulted in significantly improved performance in the iodine group relative to the placebo group on 2 of the 4 subtests after sex, method of recruitment, cohort, ethnicity, and household income were controlled for: the picture concepts test was associated with a 0.81 age-standardized point improvement in iodine relative to placebo ($P = 0.023$) and matrix reasoning with an improvement of 0.63 age-standardized points ($P = 0.040$). There was no association between supplementation and test scores on the letter-number sequencing ($P = 0.480$) or symbol search ($P = 0.608$)

subtests. Both the iodine and placebo groups significantly improved their baseline scores at 28 wk for symbol search, with an increase in the mean age-standardized score of 1.1 points in both groups ($P < 0.001$). After baseline scores, sex, method of recruitment, cohort, ethnicity, and household income were controlled for, the overall cognitive score was 0.19 (95% CI: 0.04, 0.34) SD higher in iodine-supplemented children than in children who received the placebo at 28 wk ($P = 0.011$). The change in cognitive scores as a result of iodine supplementation presented as effect sizes (ie, SD) of both individual subtests and overall cognitive score is shown in **Figure 1**.

DISCUSSION

Consistent with reports that iodine deficiency is widespread in New Zealand (12, 14), children enrolled in this study were mildly iodine deficient (median UIC: 63 $\mu\text{g}/\text{L}$; serum thyroglobulin: of 16.4 $\mu\text{g}/\text{L}$). Supplementation with 150 μg I/d for 28 wk corrected iodine deficiency, increasing the median UIC (145 $\mu\text{g}/\text{L}$) and decreasing serum thyroglobulin (8.5 $\mu\text{g}/\text{L}$). There was a small improvement in the iodine status of the placebo group, but these children were still categorized as mildly iodine deficient at the end of the study. The iodine content of the diet, as estimated by the FFQ, did not differ between the 2 groups nor did the use of iodized salt at the table; however, a higher proportion of children in the placebo group than in the supplemented group reported using iodized salt in cooking (68% compared with 59%). At baseline, the TT_4 concentration was 104 nmol/L, which was within the normal reference range (22), and there was no change in either group after 28 wk. A limitation of many previous trials was the concurrent improvement in iodine status in the control group that necessitated a post hoc change in data analysis; this was not required in our study because a clear distinction in iodine status between the supplemented and control groups was maintained after 28 wk.

TABLE 2
Age-standardized cognitive test scores at baseline and at 28 wk in children aged 10–13 y from Dunedin, New Zealand

Test and assessment time	Iodine group (n = 84)		Placebo group (n = 82)		Treatment effect ³	P ⁴
	Score ¹	P ²	Score ¹	P ²		
Picture concepts						
Baseline ⁵	9.4 ± 2.4	0.020	9.5 ± 2.7	0.880	0.81 (0.1, 1.5)	0.023
28 wk	10.2 ± 3.0		9.6 ± 2.4			
Matrix reasoning						
Baseline ⁵	9.7 ± 2.4	0.064	9.7 ± 2.5	0.447	0.63 (0.02, 1.2)	0.040
28 wk	10.2 ± 2.4		9.6 ± 2.5			
Symbol search						
Baseline ⁵	9.7 ± 2.5	<0.001	9.3 ± 2.3	<0.001	0.16 (−0.5, 0.8)	0.608
28 wk	10.8 ± 3.1		10.4 ± 2.7			
Letter-number sequencing						
Baseline ⁵	9.5 ± 1.8	0.113	9.6 ± 1.8	0.513	0.18 (−0.3, 0.7)	0.480
28 wk	9.9 ± 1.9		9.7 ± 2.0			

¹ Values are means ± SDs.

² Within-group differences between baseline and 28 wk by paired *t* test.

³ Values are β coefficients (95% CIs) from linear regression analysis and indicate the difference (ie, final – baseline) in age-standardized test scores between the groups as a result of supplementation.

⁴ Between-group differences by multiple linear regression after adjustment for baseline scores, method of recruitment, cohort, ethnicity, household income, and sex.

⁵ No significant difference in baseline scores between the iodine and placebo groups.

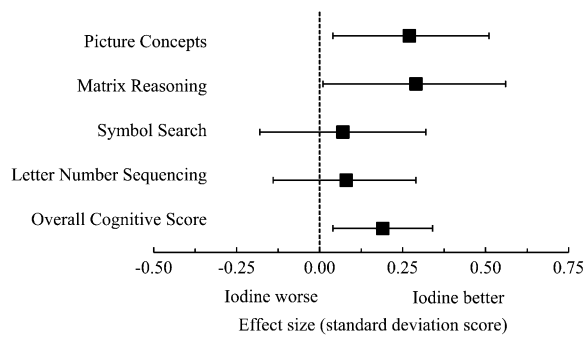


FIGURE 1. Mean (95% CI) effect of iodine supplementation on final scores for each individual Wechsler Intelligence Scale for Children (fourth edition) cognitive subtest and overall cognitive score ($n = 166$). For individual subtests, between-group differences were determined by multiple linear regression after adjustment for baseline scores, sex, method of recruitment, cohort, ethnicity, and household income. For overall cognitive score, a mixed model regression was performed to obtain an estimate of the overall effect of iodine supplementation on cognition, with control for baseline scores, sex, method of recruitment, cohort, ethnicity, and household income and with the use of a random subject effect to control for pairs of cognitive scores (ie, baseline and 28 wk) for each participant. Children who were supplemented with iodine had better scores for picture concepts ($P = 0.023$), matrix reasoning ($P = 0.040$), and overall cognitive score ($P = 0.011$) than did children who received the placebo.

Iodine supplementation was associated with significant improvements in performance on 2 of the 4 cognitive tests relative to the placebo. Iodine supplementation increased the age-standardized score obtained in picture concepts by 0.81 points (ie, 8.6%) and the score in matrix reasoning by 0.63 points (ie, 6.5%). Both the picture concepts and matrix reasoning tests assess perceptual reasoning, which has been previously shown to improve with iodine supplementation in Albanian children assessed with Raven's Colored Progressive Matrices test (11). Perceptual reasoning is a higher-order cognitive ability that relies on development in the frontal lobes of the brain (23). Thyroid hormones are involved in myelination of the central nervous system (24), which begins at ≈ 16 wk of gestation and continues throughout childhood, adolescence, and adulthood (25). The frontal cortex is the area of the brain slowest to fully myelinate and is responsible for higher-order cognitive activities such as problem-solving, planning, reasoning, and focusing attention—processes that comprise fluid intelligence (23). If the beneficial effect of iodine supplementation seen in this study is a result of increased myelination, then such changes in neural architecture are likely to be long term (26). Although thyroid hormones can play a role in brain development, they may also affect brain function via neurotransmitters and aspects of metabolism such as glucose production, which would have short-term effects on cognition (26).

Performance on the letter-number sequencing test and the symbol search test was not affected by iodine supplementation. The letter-number sequencing test is a test of working memory and attention (27). Zimmermann et al (11) used a digit span test of short-term memory and found no improvement in scores as a result of iodine supplementation. Together, these studies suggest that iodine supplementation of mild to moderately iodine-deficient children has little effect on memory. The symbol search test measures processing speed and was the only test in which both the iodine and placebo groups improved on their baseline scores, exhibiting a learning effect. Such learning or practice

effects are not uncommon with cognitive tests, particularly when they are reassessed within a relatively short period of time (ie, < 1 y) (28). The symbol search test is self-administered; it consists of 4 printed pages and has a definite end (ie, 120 items)—a testing format more familiar to these children than the other subtests. Noncognitive factors such as mood, effort, and motivation can also affect performance on cognitive tests (26); at the second testing session we observed that many children were motivated to complete more items in the symbol search test, expressing a desire to improve on their previous performance by finishing the third page and moving onto the fourth and last page. A more likely explanation, however, was an age-related improvement in processing speed (29). In contrast with the findings in our study, moderately iodine-deficient Albanian children supplemented with iodine showed a significant improvement in scores for the symbol search test compared with the children in the placebo group (11). The lower unadjusted mean test scores, even after iodine supplementation of Albanian children, and their poorer baseline iodine status may mean that they had a greater capacity to improve on their symbol search scores than did the New Zealand children.

At 28 wk, children who received the iodine supplement had a small but significant improvement in the overall cognitive score of 0.19 SD compared with children who received the placebo. Zimmermann et al (11) proposed that improvements in cognition in late childhood after iodine supplementation are mediated through higher TT_4 concentrations, which increase intracerebral triiodothyronine (T_3), and suggested that circulating T_4 might be a good indicator of cerebral T_3 status. Contrary to this view, we did not detect a change in TT_4 , indicating that changes in T_3 in the brain may not always be mirrored by the TT_4 concentration. This is not surprising when one considers that T_3 activity in the brain is a result of a complex interplay of factors, including total and free T_4 and T_3 concentrations, thyroid hormone transport, cerebral blood flow, thyroid hormone nuclear receptors, and the activity of the iodothyronine deiodinase enzymes (30–32). Furthermore, studies in animal models and human fetal brain tissue have shown that thyroid hormone metabolism varies in different regions of the brain (31, 33). Much of the research on the effects of iodine deficiency and brain development has focused on pregnancy and infancy, but more studies are needed to determine how the amelioration of mild iodine deficiency improves cognition in late childhood and whether improvements are permanent or reversible. Such research would help address the widely held view that there are no functional consequences of mild iodine deficiency because thyrotropin, TT_4 , and total T_3 concentrations fall within the normal reference range—a school of thought challenged by our findings.

This study had many strengths: its randomized, placebo-controlled, double-blind design; its use of a daily supplement mimicking the effect of iodine fortification; good compliance over the study period; a dietary measure of iodine intake; and the inclusion of new cognitive subtests designed to reflect current clinical knowledge and practice (34). A limitation of the study was its relatively short duration of 28 wk. However, the main limitation was that the original sample size was not achieved because of difficulties recruiting participants and time constraints because of the imminent introduction of mandatory iodine fortification of bread in New Zealand in 2009. As a consequence, the study may have been underpowered to detect a difference

between the iodine and placebo groups on the letter-number sequencing and symbol search subtests. Despite the smaller sample size, we were able to find a small but significant improvement in scores for the other 2 cognitive tests and overall cognitive score. It would be useful to conduct a larger study in another setting to confirm these findings. If feasible, a follow-up study of children to assess cognition after the cessation of supplementation would be of interest to ascertain whether the changes seen are reversible or permanent.

The elimination of iodine deficiency by the year 2005 was a World Fit for Children target (35), yet a large proportion of children worldwide still have inadequate iodine intakes. Although the percentage of households consuming adequately iodized salt has increased in the past 2 decades, particularly in developing countries where moderate to severe iodine deficiency is prevalent, countries such as the United States (36), Australia (37), and New Zealand (14) have reported declining iodine intakes over this same period. The lack of data on the adverse effects of mild iodine deficiency might explain why some governments have been slow to implement strategies to improve iodine intakes in these countries. To our knowledge, this is the first randomized controlled trial to show that iodine supplementation of mildly iodine deficient children improves cognition and suggests that mild iodine deficiency could prevent children from attaining their full intellectual potential.

We thank the principals and teachers of both intermediate schools and the children and their parents who participated in this study.

The authors' responsibilities were as follows—RCG: participated in the collection, analyses, and interpretation of the data with the assistance of MCR; ARG: provided expertise on statistical analysis and interpretation; SAS: designed, supervised, and secured funding for the study and assisted in the interpretation of the data; KMDM and TR: provided expertise on cognitive assessment and trained RCG and MCR in cognitive testing; TR: provided expertise on interpretation of cognitive data; RCG: wrote the first draft of the manuscript; and SAS: edited the manuscript. All authors provided input on versions of the manuscript. None of the authors had any conflicts of interest.

REFERENCES

- Hetzel BS, Dunn JT. The iodine deficiency disorders: their nature and prevention. *Annu Rev Nutr* 1989;9:21–38.
- Boyages SC. Clinical review 49: iodine deficiency disorders. *J Clin Endocrinol Metab* 1993;77:587–91.
- Bleichrodt N, Born MP. A meta-analysis of research on iodine and its relationship to cognitive development. In: Stanbury JB, ed. *The damaged brain of iodine deficiency*. New York, NY: Cognizant Communication, 1994:195–200.
- Qian M, Wang D, Watkins WE, et al. The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. *Asia Pac J Clin Nutr* 2005;14:32–42.
- Santiago-Fernandez P, Torres-Barahona R, Muela-Martinez JA, et al. Intelligence quotient and iodine intake: a cross-sectional study in children. *J Clin Endocrinol Metab* 2004;89:3851–7.
- Bautista A, Barker PA, Dunn JT, Sanchez M, Kaiser DL. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *Am J Clin Nutr* 1982;35:127–34.
- Shrestha R. Effect of iron and iodine supplementation on physical, psychomotor and mental development in primary school children in Malawi. PhD thesis. Wageningen Agricultural University, Wageningen, Netherlands, 1994.
- Isa ZMD, Alias IZ, Kadir KA, Ali O. Effect of iodized oil supplementation on thyroid hormone levels and mental performance among *Orang Asli* schoolchildren and pregnant mothers in an endemic goitre area in Peninsular Malaysia. *Asia Pac J Clin Nutr* 2001;9:274–81.
- van den Briel T, West CE, Bleichrodt N, van de Vijver FJ, Ategbro EA, Hautvast JG. Improved iodine status is associated with improved mental performance of schoolchildren in Benin. *Am J Clin Nutr* 2000;72:1179–85.
- Huda SN, Grantham-McGregor SM, Tomkins A. Cognitive and motor functions of iodine deficient but euthyroid children in Bangladesh do not benefit from iodized poppy seed oil (Lipioidol). *J Nutr* 2001;131:72–7.
- Zimmermann MB, Connolly KJ, Bozo M, Bridson J, Rohner F, Grimci L. Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. *Am J Clin Nutr* 2006;83:108–14.
- Skeaff SA, Thomson CD, Gibson RS. Mild iodine deficiency in a sample of New Zealand schoolchildren. *Eur J Clin Nutr* 2002;56:1169–75.
- World Health Organization/United Nations Children's Fund/International Council for the Control of Iodine Deficiency Disorders. *Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers*. Geneva, Switzerland: World Health Organization, 2001. (WHO/NHD/01.1.)
- Parnell W, Scragg R, Wilson N, Schaff D, Fitzgerald ENZ. *Food NZ children: key results of the 2002 National Children's Nutrition Survey*. Wellington, New Zealand: Ministry of Health, 2003.
- FOODfiles. Datafiles of the New Zealand Food Composition Database. Palmerston North, New Zealand: New Zealand Institute for Crop and Food Research Limited, 2006.
- Lohman TG, Roche AF, Martorell R. *Anthropometric standardisation reference manual*. Champaign, IL: Human Kinetics Books, 1988.
- Wechsler D. *Wechsler Intelligence Scale for Children—fourth edition Australian*. In: Hannan T, ed. *Australian administration and scoring manual*. Marrickville, Australia: Harcourt Assessment, 2005.
- Fecher PA, Goldmann I, Nagengast A. Determination of iodine in food samples by inductively coupled plasma mass spectrophotometry and alkaline extraction. *J Anal Atom Spectrom* 1998;977–82.
- Statistics New Zealand. 2006 Census data. Version current 12 May 2009. Available from: <http://www.stats.govt.nz/census/census-outputs/default.htm> (cited 15 May 2009).
- US Department of Health and Human Services, CDC, National Center for Health Statistics. *CDC growth charts: United States*. Version current 4 June 2009. Available from: <http://www.cdc.gov/GrowthCharts> (cited 11 July 2009).
- World Health Organization/United Nations Children's Fund/International Council for the Control of Iodine Deficiency Disorders. *Indicators for assessing iodine deficiency disorders and their control through salt iodization*. Geneva, Switzerland: World Health Organization, 1994. (WHO/NUT/94.6.)
- Zurakowski D, Di Canzio J, Majzoub JA. Pediatric reference intervals for serum thyroxine, triiodothyronine, thyrotropin, and free thyroxine. *Clin Chem* 1999;45:1087–91.
- Hughes D, Bryan J. The assessment of cognitive performance in children: considerations for detecting nutritional influences. *Nutr Rev* 2003; 61:413–22.
- Dussault JH, Ruel J. Thyroid hormones and brain development. *Annu Rev Physiol* 1987;49:321–34.
- Bryan J, Osendarp S, Hughes D, Calvaresi E, Baghurst K, van Klinken J. Nutrients for cognitive development in school-aged children. *Nutr Rev* 2004;62:295–306.
- Isaacs E, Oates J. Nutrition and cognition: assessing cognitive abilities in children and young people. *Eur J Clin Nutr* 2008;47:4–24.
- Crowe SF. Does the letter number sequencing task measure anything more than digit span. *Assessment* 2000;7:113–7.
- Schmitt JAJ, Benton D, Kallus KW. General methodological considerations for the assessment of nutritional influences on human cognitive functions. *Eur J Nutr* 2005;44:459–64.
- Kail R. Developmental change in speed of processing during childhood and adolescence. *Psychol Bull* 1991;109:490–501.
- Bianco AC, Kim BW. Deiodinases: implications of the local control of thyroid hormone action. *J Clin Invest* 2006;116:2571–9.
- Obregon M-J, Escobar del Rey F, Morreale de Escobar G. The effects of iodine deficiency on thyroid hormone deiodination. *Thyroid* 2005;15: 917–29.
- Kohrle J. Thyroid hormone metabolism and action in the brain and pituitary. *Acta Med Austriaca* 2000;27:1–7.
- Kester MH, Martinez de Mena R, Jesus Obregon M, et al. Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. *J Clin Endocrinol Metab* 2004; 89:3117–28.

34. Williams PE, Weiss LG, Rolfhus E. Theoretical model and test blueprint. WISC-IV Technical Report #1. The Psychological Corporation, Harcourt Assessment Company, 2003.
35. United Nations Children's Fund. A World Fit for Children, 2002. New York, NY. Version current 14 May 2009. Available from: http://www.unicef.org/specialsession/docs_new/documents/wffc-en.pdf (cited 14 May 2009).
36. Hollowell JG, Staehling NW, Hannon WH, et al. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III. *J Clin Endocrinol Metab* 1998;83:3401-8.
37. Li M, Eastman CJ, Waite KV, et al. Are Australian children iodine deficient? Results of the Australian National Iodine Nutrition Study. *Med J Aust* 2006;184:165-9.

