

## Mild Iodine Deficiency During Pregnancy Is Associated With Reduced Educational Outcomes in the Offspring: 9-Year Follow-up of the Gestational Iodine Cohort

Kristen L. Hynes, Petr Otahal, Ian Hay, and John R. Burgess

Menzies Research Institute Tasmania (K.L.H., P.O.), Faculty of Education (I.H.), and School of Medicine (J.R.B.), University of Tasmania, Sandy Bay, Tasmania 7005, Australia; and Department of Endocrinology (J.R.B.), Royal Hobart Hospital, Hobart, Tasmania 7000, Australia

**Context:** Severe iodine deficiency (ID) during gestation is associated with neurocognitive sequelae. The long-term impact of mild ID, however, has not been well characterized.

**Objective:** The purpose of this study was to determine whether children born to mothers with urinary iodine concentrations (UICs)  $<150 \mu\text{g/L}$  during pregnancy have poorer educational outcomes in primary school than peers whose mothers did not have gestational ID (UIC  $\geq 150 \mu\text{g/L}$ ).

**Design:** This was a longitudinal follow-up (at 9 years old) of the Gestational Iodine Cohort. Pregnancy occurred during a period of mild ID in the population, with the children subsequently growing up in an iodine-replete environment.

**Setting and Participants:** Participants were children whose mothers attended The Royal Hobart Hospital (Tasmania) antenatal clinics between 1999 and 2001.

**Main Outcome Measures:** Australian national curriculum and Tasmanian state curriculum educational assessment data for children in year 3 were analyzed.

**Results:** Children whose mothers had UIC  $<150 \mu\text{g/L}$  had reductions of 10.0% in spelling ( $-41.1$  points, 95% confidence interval [CI],  $-68.0$  to  $-14.3$ ,  $P = .003$ ), 7.6% in grammar ( $-30.9$  points, 95% CI,  $-60.2$  to  $-1.7$ ,  $P = .038$ ), and 5.7% in English-literacy ( $-0.33$  points, 95% CI,  $-0.63$  to  $-0.03$ ,  $P = .034$ ) performance compared with children whose mothers' UICs were  $\geq 150 \mu\text{g/L}$ . These associations remained significant after adjustment for a range of biological factors (maternal age at birth of child, gestational length at time of birth, gestational age at time of urinary iodine collection, birth weight, and sex). Differences in spelling remained significant after further adjustment for socioeconomic factors (maternal occupation and education).

**Conclusions:** This study provides preliminary evidence that even mild iodine deficiency during pregnancy can have long-term adverse impacts on fetal neurocognition that are not ameliorated by iodine sufficiency during childhood. (*J Clin Endocrinol Metab* 98: 1954–1962, 2013)

Iodine is essential for neurodevelopment in utero and in childhood, with deficiency being a major cause of preventable intellectual impairment (1). The serious neurodevelopmental consequences of severe iodine deficiency (ID) on the fetus are well documented and include cretin-

ism, which manifests as motor, cognitive, and auditory defects (2). ID, however, results in a spectrum of disorders with many speculating that even mild maternal ID has subtle impacts on fetal development. Recent reviews are not conclusive as to whether low maternal dietary iodine

intake in areas of mild deficiency leads to measurable effects on cognition and neurodevelopment of the offspring (3, 4).

Clinical trials of iodine supplementation in pregnancy in regions of mild ID have typically focused on positive changes in maternal and fetal thyroid function and volumes but have not examined long-term developmental consequences in the offspring. To our knowledge, there are only three studies reporting neurodevelopmental outcomes in offspring after supplementation of mothers with mild ID. Berbel et al (5) reported significantly delayed neurobehavioral performance in children (aged 18 months) if their mothers did not receive iodine supplementation by 4 to 6 weeks of gestation. Similarly, Velasco et al (6) found that children (aged 3–18 months) had higher psychomotor development scores if their mothers were given supplements from the first trimester. Both interventions provide preliminary evidence that even mild gestational ID may have an adverse impact on fetal neurodevelopment and subsequent infant functioning. In contrast, Murcia et al (7) reported that higher maternal intake of iodine-containing supplements was associated with lower scores on the Psychomotor Development Index of the Bayley Scales of Infant Development in their children (aged 1 year).

In addition to gestational studies, there is increasing evidence from observational population studies that less severe cognitive and motor impairment occurs in apparently normal individuals from areas of ID (8). Children without cretinism from iodine-deficient regions of Iran were found to have growth retardation and neurological, auditory, and psychomotor impairments (9). Boyages et al (10) reported impaired intellectual and neuromotor development in apparently normal Chinese children, with a shift in the distribution of cognitive skills to a lower level. Furthermore, randomized controlled trial data show that postgestational supplementation can lead to significantly improved mental performance of children from areas of mild (11), moderate (12), and severe ID (13).

We compared educational outcomes of children (aged 9 years) born to women assessed as being iodine deficient (urinary iodine concentration [UIC]  $<150 \mu\text{g/L}$ ) or sufficient (UIC  $\geq 150 \mu\text{g/L}$ ) during pregnancy. Gestation occurred during 1999–2001, a documented period of mild ID (median UIC,  $77.5 \mu\text{g/L}$ ) in the Tasmanian population (14), with the children subsequently growing up in an environment considered to be replete (14, 15) (median UIC,  $108.0 \mu\text{g/L}$ ) after introduction of voluntary iodine fortification (16). We investigate whether mild gestational ID has long-term effects on educational outcomes.

## Materials and Methods

Urinary iodine (UI) samples were collected from volunteers in a study documenting the impact of advancing gestation on UIC. The methods have been published previously (17). In brief, women attending antenatal clinics at the Royal Hobart Hospital (Tasmania, Australia) consented to give between 1 and 3 random urine samples. Samples were analyzed by the Institute of Clinical Pathology and Medical Research at Westmead Hospital (Sydney, Australia), which complies with International Organization for Standardization/International Electrotechnical Commission standard 17025. UIC was determined using the modified Sandell-Kolthoff reaction (18) and is reported as micrograms of iodine per liter of urine. Gestational age at UI collection was recorded and retrospectively confirmed postdelivery. For mothers providing more than 1 sample, mean UIC and gestation age were calculated. World Health Organization (WHO) indicators of iodine nutrition during pregnancy were used to classify the women as having adequate ( $\geq 150 \mu\text{g/L}$ ) or insufficient iodine ( $<150 \mu\text{g/L}$ ) (19). Birth weight and maternal date of birth were obtained from medical records. No information regarding use of iodine supplements or exposure to iodine-based antiseptics during delivery was consistently available. Offspring from singleton pregnancies are reported.

Longitudinal follow-up of 2 sources of education assessment (provided by the Tasmanian Government Department of Education) was conducted when the offspring were in Grade 3 (in 2009 and 2010) at aged 9 years. Ethics approval to link individual education data with the Gestational Iodine Cohort data was granted by the Tasmanian Health and Medical Human Research Ethics Committee (Ref. No. H11592).

### National Assessment Program—Literacy and Numeracy (NAPLAN)

NAPLAN tests are standardized criteria-referenced measures of individual student's performance in literacy (reading, writing, and language conventions [spelling, grammar, and punctuation]) and numeracy. Testing is conducted annually by the Australian Federal Government in all schools for Grades 3, 5, 7, and 9.

### Student Assessment and Reporting Information System (SARIS)

SARIS is used by Tasmanian State Government schools to record individual student's academic achievement in assessments in English-literacy and Mathematics-numeracy. The system records students' progress in speaking and listening, reading and viewing, and writing and the capacity to work mathematically, understanding numbers, algebra, function and pattern, space and measurement, and chance and data.

In contrast to the Wechsler Intelligence Scale for Children (WISC), which is a measure of students' cognitive ability and intellectual capabilities and designed to provide an individual's intelligence quotient score; the NAPLAN and SARIS are group-measures of students' school-based performance with reference to the Australian and Tasmanian literacy and numeracy curriculum.

Stata/IC12.1 was used for statistical analysis. Means (SD) are presented for continuous measures and percentages for categorical measures. UIC was skewed; thus, median and interquartile range are presented. The Pearson correlation was used to show

associations (the Spearman correlation was used if data were skewed).  $\chi^2$  tests were used to show group differences for categorical data and *t* tests were used for continuous data. Univariable regression models between educational outcome measures at follow-up and continuous gestational UICs were examined initially. Model building of educational outcomes with categorical gestational UIC ( $\geq 150$ / $<150$   $\mu\text{g/L}$ ) followed, initially unadjusted and then with adjustment for biological covariates (gestational age at UI collection, maternal age, gestational length, birth weight, and sex) and with further adjustment for socioeconomic status (SES) covariates (maternal education and maternal occupation). Model covariates were only included in models for reasons of clinical importance or a demonstrated confounding effect (assessed by a 10% change in gestational UIC coefficient and association with outcome and gestational UIC).

## Results

From the original cohort ( $n = 433$ ), 228 offspring were traced and linked to educational data. Examination of gestational measures revealed no statistical differences between those followed-up at 9 years and those lost to follow-up.

During gestation, 367 urine samples (collected between October 1999 and November 2001) were provided (123 women provided 1 sample, 71 provided 2 samples, and 34 provided 3 samples). The overall median UIC, using the mean UI value for each pregnancy ( $n = 228$ ), was 81  $\mu\text{g/L}$  (interquartile range, 46.5–166  $\mu\text{g/L}$ ), indicating mild ID. Mean gestational age at UI collection was 24.6 (SD 9.8) weeks (range, 8–41 weeks).

Using the WHO (19) cut point for adequate iodine nutrition during pregnancy, 71.1% (162 of 228) of women had UICs  $<150$   $\mu\text{g/L}$ . Table 1 details characteristics of children whose mothers had adequate UIC ( $\geq 150$   $\mu\text{g/L}$ ) and insufficient UIC ( $<150$   $\mu\text{g/L}$ ). There were no statistically significant differences ( $P < .05$ ) between the 2 groups in any characteristics measured during gestation and birth or for the SES measures recorded when the children were at school. Statistically significant differences were found in NAPLAN spelling and grammar scores and in SARIS English-literacy scores; children born to mothers with insufficient iodine nutrition had poorer outcomes. The results for NAPLAN reading approached signifi-

**Table 1.** Characteristics of Children by Maternal UIC During Pregnancy: Data for the Cohort of Children (Aged 9 Years) Followed-Up in 2009–2010 in Year 3 ( $n = 228$ )

	UIC $\geq 150$ $\mu\text{g/L}$	n	UIC $<150$ $\mu\text{g/L}$	n	P Value <sup>a</sup>
Gestational measures					
Maternal age at birth of child, y	28.2 (5.8)	66	28.2 (6.1)	162	.957
Gestational length, wk <sup>b</sup>	38.9 (2.2)	65	39.1 (1.8)	161	.543
Preterm birth ( $<37$ wk), %	12.3	8/65	7.5	12/161	.245
Birth weight, g <sup>c</sup>	3405 (501)	66	3408 (602)	159	.971
Low birth weight ( $\leq 2500$ g), %	6.1	4/66	7.6	12/159	.693
Male sex, %	40.9	27/66	49.4	80/162	.245
Gestational age at time of UI collection, wk	24.2 (9.6)	66	24.7 (9.9)	162	.718
School age measures					
Maternal education ( $>$ year 10), %	65.6	42/64	68.8	108/157	.648
Maternal occupation, % <sup>d</sup>	20.3	12/59	22.1	33/149	.775
Paternal education ( $>$ year 10), %	73.2	41/56	68.2	92/135	.488
Paternal occupation, % <sup>d</sup>	37.3	19/51	26.6	33/124	.162
Indigenous status <sup>e</sup>	11.1	7/63	13.8	22/159	.587
2009/2010 Grade 3 education measures					
NAPLAN					
Spelling score	412.0 (104.9)	62	370.9 (84.5)	155	.003
Grammar score	408.1 (103.0)	62	377.2 (97.0)	155	.038
Reading score	413.0 (97.7)	62	387.2 (87.2)	155	.058
Writing score	409.8 (73.0)	62	395.9 (70.6)	155	.197
Numeracy score	385.8 (86.1)	59	378.5 (80.6)	152	.564
SARIS					
English-literacy score	5.78 (1.12)	66	5.45 (1.03)	162	.034
Mathematics-numeracy score	5.67 (1.07)	66	5.45 (1.09)	162	.158

Data are means (SD) for continuous variables and percentages for categorical variables.

<sup>a</sup> P values were calculated using *t* tests for continuous variables and  $\chi^2$  tests for categorical variables.

<sup>b</sup> Length of gestation was unknown for 2 children.

<sup>c</sup> Birth weight was unknown for 3 children.

<sup>d</sup> Occupation was divided into 2 categories: unemployed/manual vs professional/paraprofessional/managers. The percentage in the latter group is given.

<sup>e</sup> Indigenous status: percentage shown is for those indicating Aboriginal, Torres Strait Islander, or both Aboriginal and Torres Strait Islander status.

**Table 2.** Relationship Between Education Outcomes and Possible Confounders

	NAPLAN			SARIS: English-Literacy	n <sup>a</sup>
	Spelling	Grammar	Reading		
Gestational measures					
Maternal age at birth of child, y	0.0816	0.1023	0.1565 <sup>b</sup>	0.1190	217, 228
Gestation					
Gestational age at time of UI collection, wk	-0.0022	-0.0624	-0.0075	-0.0023	217, 228
Gestational length, wk	0.0522	0.0533	0.1033	0.0111	216, 226
Birth weight, g	0.1970 <sup>c</sup>	0.1696 <sup>b</sup>	0.1529 <sup>b</sup>	0.1426 <sup>b</sup>	214, 225
Sex					
Male	367.2 (89.9) <sup>b</sup>	376.0 (95.8)	378.9 (97.7) <sup>b</sup>	5.31 (1.02) <sup>c</sup>	103, 107
Female	396.6 (92.9)	395.0 (102.3)	408.7 (82.1)	5.75 (1.07)	114, 121
School age measures					
Maternal education					
≤Grade 10	369.1 (88.3)	376.7 (91.6)	379.5 (75.9)	5.32 (0.92) <sup>b</sup>	66, 71
>Grade 10	390.1 (92.2)	391.7 (103.2)	403.3 (95.8)	5.68 (1.11)	144, 150
Maternal occupation <sup>d</sup>					
1	381.4 (90.5)	384.0 (96.8)	388.4 (83.7) <sup>c</sup>	5.49 (0.99) <sup>c</sup>	154, 163
2	407.3 (90.3)	414.0 (101.8)	431.5 (98.4)	6.00 (1.20)	44, 45
Paternal education					
≤Grade 10	376.0 (90.0)	364.7 (104.0) <sup>b</sup>	374.6 (81.7) <sup>b</sup>	5.30 (1.04) <sup>b</sup>	46, 58
>Grade 10	393.4 (93.2)	399.9 (98.9)	410.5 (90.6)	5.71 (1.05)	127, 133
Paternal occupation <sup>d</sup>					
1	386.2 (93.9)	379.5 (96.2) <sup>c</sup>	389.8 (80.3) <sup>b</sup>	5.47 (1.05) <sup>c</sup>	116, 123
2	404.8 (86.2)	423.1 (107.0)	425.5 (96.1)	5.99 (1.04)	52, 52
Indigenous					
Yes	352.1 (81.5)	353.5 (109.6)	367.8 (80.7)	5.05 (1.01) <sup>c</sup>	27, 29
No	387.3 (94.0)	390.4 (98.4)	399.4 (92.7)	5.62 (1.07)	185, 193

For continuous variables (ie, maternal age, gestational age at the time of UI collection, gestational length, and birth weight), correlation coefficients are shown. The Spearman rank correlation was used if variables were skewed. For categorical variables (ie, sex, parental education and occupation, and indigenous status), mean values (SD) are shown. *t* tests were used to calculate the *P* value.

<sup>a</sup> The number of children with each education outcome varied. The first *n* is for NAPLAN outcomes, and the second is for SARIS outcomes.

<sup>b</sup> *P* < .05.

<sup>c</sup> *P* < .01.

<sup>d</sup> Occupation was divided into 2 categories: 1, unemployed/manual; 2, professional/paraprofessional/managers.

cance, but NAPLAN writing and both numeracy measures were not significantly different.

Table 2 shows the relationship between each education outcome (which showed an association with UIC in Table 1) and the biological and SES characteristics. Characteristics that were significant (*P* = .05 or *P* = .01) may indicate possible confounding of the association between educational outcomes and UIC. All four education measures (NAPLAN spelling, grammar, and reading and SARIS English-literacy) had small, but significant, positive correlations with birth weight; low-birth-weight children (data not shown) had significantly reduced scores in all outcomes. Sex was observed to be significantly related to spelling, reading, and English-literacy, with boys scoring lower than girls. Significant associations between reading and English-literacy were seen with respect to maternal occupation, but only with English-literacy for maternal education. Paternal occupation and education were significantly associated with grammar, reading, and English-literacy.

Univariable examination of UIC as a continuous variable showed a significant positive association with spelling ( $\beta = 0.049$ , *P* = .033). No associations were found with grammar ( $\beta = 0.026$ , *P* = .295), reading ( $\beta = 0.040$ , *P* = .080), numeracy ( $\beta = 0.044$ , *P* = .100), English-literacy ( $\beta = 0.0003$ , *P* = .198), or Mathematics-numeracy ( $\beta = 0.0002$ , *P* = .321), although writing approached significance ( $\beta = 0.034$ , *P* = .056).

Table 3 shows the associations between UIC and education outcomes using the UIC 150  $\mu\text{g/L}$  cut point. In unadjusted models, spelling, grammar, and English-literacy showed significant associations with UIC and approached significance for reading. No significant associations were found for writing, numeracy, or Mathematics-numeracy. When the associations were significant, the children whose mothers had insufficient UIC had lower education outcome scores. These represent a 10.0%, a 7.6%, and a 5.7% reduction in spelling, grammar, and English-literacy scores, respectively, for the insufficient group.

**Table 3.** Differences in Educational Outcome Scores for Children of Mothers With Inadequate UIC (<150  $\mu\text{g/L}$ ) During Pregnancy Compared With Mothers With Adequate UIC ( $\geq 150 \mu\text{g/L}$ )

Educational Outcome	Unadjusted			Adjusted for Biological Factors <sup>a</sup>			Adjusted for Biological and Socioeconomic Factors <sup>b</sup>		
	$\beta$ (95% CI)	P	n	$\beta$ (95% CI)	P	n	$\beta$ (95% CI)	P	n
NAPLAN									
Spelling	-41.1 (-68.0 to -14.3)	.003	217	-42.2 (-68.4 to -15.9)	.002	214	-38.6 (-65.5 to -11.6)	.005	193
Grammar	-30.9 (-60.2 to -1.7)	.038	217	-30.3 (-59.5 to -1.2)	.042	214	-29.1 (-59.9 to 1.8)	.065	193
Reading	-25.8 (-52.6 to 0.9)	.058	217	-27.7 (-54.0 to -1.4)	.039	214	-18.5 (-45.7 to 8.6)	.179	193
Writing	-13.9 (-35.0 to 7.2)	.197	217	-11.9 (-32.8 to 9.1)	.267	214	-7.9 (-30.2 to 14.2)	.487	193
Numeracy	-7.3 (-32.1 to 17.6)	.564	211	-5.0 (-29.9 to 20.0)	.697	208	+1.4 (-24.2 to 26.9)	.915	188
SARIS									
English-literacy	-0.33 (-0.63 to -0.03)	.034	228	-0.31 (-0.61 to -0.008)	.045	224	-0.30 (-0.62 to 0.01)	.059	202
Mathematics-numeracy	-0.22 (-0.54 to 0.09)	.158	228	-0.23 (-0.54 to 0.09)	.155	224	-0.25 (-0.58 to 0.08)	.140	202

<sup>a</sup> Adjusted for gestational age at the time of UI collection, maternal age at birth of child, gestational length at time of birth, birth weight, and sex.

<sup>b</sup> Adjusted for all the above and for maternal education and occupation.

Associations with spelling, grammar, and English-literacy remained significant and reading became significant after adjustment for gestational and birth factors. In the models adjusted for these biological factors, for both spelling and English-literacy, birth weight and sex were significant factors, with higher-birth-weight children and girls having better education outcomes. For grammar, none of the adjustment factors were significant; for reading, older mother, higher birth weight, and female sex had significant positive associations.

After further adjustment for possible confounding by maternal education and occupation, the association between insufficient UIC and poorer spelling remained significant. Grammar and English-literacy were borderline significant and showed little change in the coefficients. Reading was no longer significant. Further adjustment for paternal education and occupation and for indigenous status (data not shown) did not materially change the coefficients.

## Discussion

This study demonstrates a reduction in spelling, grammar, and general English-literacy performance in children of mothers with a gestational UIC below the current established cut point for sufficiency (150  $\mu\text{g/L}$ ) (19) in comparison with performance of the offspring of mothers with adequate levels. It is well established in areas of severe ID that insufficient maternal iodine during gestation can result in severe and irreversible impairment of fetal neurocognitive development (20). Our findings add support to previous studies reporting that maternal ID in areas of mild-to-moderate deficiency can result in less severe, but measurable, long-lasting impacts (21).

Determining the severity of gestational ID is problematic. Thyroid volume measurement does not indicate recent intake; and thyroid hormone measurements are insensitive. To examine impacts on the fetus, a measure of recent maternal iodine levels is needed. UIC from a spot urine sample reflects intake of ingested iodine for the past 24 hours, although variation due to circadian rhythm influence and postmeal UIC peaks does occur (22). Whereas median UIC from spot samples is the recommended method for determining population iodine status, the large variability in iodine concentration makes it a less than ideal tool for determining individual status. König et al (23) have suggested that to be used as an individual measure, a minimum of 10 spot samples are required. Although not ideal, our study uses UIC to classify pregnant women as being sufficient ( $\geq 150 \mu\text{g/L}$ ) or deficient (<150  $\mu\text{g/L}$ ) in iodine. For approximately half (46%) of the women, status was based on the mean of 2 or 3 samples. The effect of combining multiple UICs was to increase the overall median value of the cohort. This regression to the mean results in any misclassification of iodine status toward a higher, rather than a lower, level.

Our finding of a difference in educational outcomes using UIC  $\geq 150 \mu\text{g/L}$  as the cut point for sufficiency lends support for this current WHO recommendation (19) for pregnant women, which is higher than the general population cut point of UIC  $\geq 100 \mu\text{g/L}$ . Iodine utilization increases by up to 50% during pregnancy, with a concomitant increase in renal iodine clearance. Consequently, women from communities with apparently normal iodine nutrition are at risk of inadequate iodine nutrition during pregnancy (24, 25). This fact has led to recommendations for routine supplementation of pregnant women in North America and Australia with estimated adequate require-

ments of 160  $\mu\text{g}$  of iodine/day and a Recommended Dietary Allowance of 220  $\mu\text{g}/\text{day}$  (26–28).

Restoration of normal fetomaternal iodine nutrition as early as possible in gestation appears to be associated with the greatest benefits for long-term neurodevelopmental outcomes in areas of severe (3) and mild to moderate ID (5, 6). Studies have shown improvements in neurocognitive and psychomotor indices for children of mildly iodine-deficient women who receive supplementation. Previous findings from the Gestational Iodine Cohort provided evidence that supplementation throughout pregnancy is necessary because of the influence of gestational stage on UI excretion. Stilwell et al (17) reported that a range of factors resulted in decreasing iodine excretion with advancing gestation. Whereas median UICs early in pregnancy were higher than the population median, levels fell below the population level by week 16. Similar decreases in UIC from the first to the third trimester have been described by Smyth et al (29) and Brander et al (30), with both also finding that first trimester UICs were significantly higher than the UICs from mildly deficient population controls. This elevation in UIC in early pregnancy to levels of apparent sufficiency, in women from areas of mild ID, is due partly to increases in renal iodine excretion and may give a false indication of iodine adequacy for the developing fetus. Caution is therefore needed when associations between UIC and later neurodevelopmental outcomes are examined; adjustment for gestational stage at time of UI collection (as applied to Table 3 adjusted models) is required to account for UI variation. These studies provide support for current Australian and North American supplementation recommendations and suggest that maintenance of continuous adequate iodine nutrition during pregnancy is required to ensure that preventable adverse consequences do not occur.

Our study focuses on the impacts of mild deficiency during pregnancy but not during childhood. Children were born between March 2000 and December 2001, with the majority of pregnancies occurring during a time of documented mild ID in Tasmania (14, 31). In October 2001, a voluntary iodine fortification program was implemented whereby bread manufacturers substituted regular salt with iodized salt (16). Most children (82.9%) were born before October 2001, with the remaining 39 (17.1%) arriving within 6 weeks of the fortification program being implemented, having had the greater part of their gestation occur in a deficient environment. After fortification, surveys indicated that general population iodine levels had increased to be within the optimal range (median UIC, 108.0  $\mu\text{g}/\text{L}$ ) (14, 15). The timing of the change from population ID to sufficiency assists us in separating the impacts of mild ID on neurodevelopment dur-

ing gestation from those that might occur during childhood. Unfortunately, we are unable to examine the important role of breastfeeding on early development, because data were not available. Mammary tissue is known to concentrate iodine (32) for the purpose of supplying the offspring, which necessitates an increase in maternal dietary intake for sufficiency to be assured. A review of iodine nutrition and breastfeeding (33) highlights the importance of adequate maternal iodine nutrition to ensure that breastfed neonates are not at risk of impaired neurological development. It is likely, both before and after bread fortification, that some exclusively breastfed children whose mother's diets were low in iodine may have continued developing in a suboptimal iodine environment.

Persistence, in our cohort, of reduced outcomes in areas of literacy (particularly spelling), but not reading or numeracy, suggests some gestational neurocognitive processes specific to spelling are affected and may be difficult to remediate via adequate iodine nutrition during childhood. The association with spelling, but not other outcomes, suggests there is not a general cognitive delay or confounding by SES factors. Indeed, our modeling proposes that parental education and occupation have no material impact on spelling outcomes. This finding is supported by the results of a spelling intervention of 8-year-old Australian children in which phonological awareness and oral language interventions were more important than parental education levels and family literacy practices in predicting measures of spelling (34).

The NAPLAN spelling instrument in this study required Grade 3 students to read a sentence and identify and correct errors in frequently used one-syllable words and some frequently used two-syllable words with double letters. This regimen tests both phonological (auditory pathways) and orthographical (visual pathways) capacity and involves elements of working memory and processing speed. To successfully complete the tasks, children must hold multiple ideas in their heads (ie, knowledge of sentence meaning and knowledge of the incorrect and correct words), while working quickly to complete the tasks; this necessitates high-level working memory and fast processing speed, respectively. Ormrod and Cochran (35) reported that although measures of reading and verbal ability accounted for a large proportion of the variability in spelling ability, working memory capacity was a significant predictor for learning to spell and spelling ability. Learning to spell has a large phonological component involving auditory blending of sounds (36), as well as cognitive processing and memory recall abilities to understand and recognize differences between 2 phonetically similar words (37). These results are consistent with the

idea that specific spelling disability is a residual problem for individuals who have slow verbal and auditory processing speed and auditory short-term memory difficulties (38). Severe ID is known to result in deaf-mutism and mild ID in reductions in hearing thresholds (39, 40) that can be improved by supplementation (41, 42). Given that spelling was remediated by exposure to an iodine-fortified environment in our cohort, we propose that a central auditory processing disorder influencing working memory, rather than a hearing threshold deficit, may be at work.

Support for this theory can be found in the NAPLAN numeracy testing at Grade 3. Children use one-to-one correspondence techniques requiring use of visual processing skills to identify patterns. Use of visual processing skills for numeracy tasks and combined use of visual (orthographical) and auditory (phonological) processing skills for spelling tasks provide possible evidence that visual pathways are either not affected by ID during gestation or that any impact may be improved by childhood supplementation, whereas auditory pathways affected during gestation do not recover with subsequent supplementation.

Further support for a hypothesis involving deficits in processing and working memory can be found in populations with mild ID, in whom childhood supplementation has resulted in improvements in some, but not all, areas of cognition and motor performance. Gordon et al (11) reported that supplementation of mildly deficient New Zealand 10- to 13-year-olds resulted in improvements in 2 cognitive subtests (picture concepts and matrix reasoning) from the WISC, but no improvements in subtests for letter-number sequencing or symbol search. The picture concepts and matrix reasoning tests assess perceptual reasoning, whereas the letter-number sequencing and the symbol search tests assess working memory and processing speed. The WISC picture concepts and matrix reasoning tests require visual processing skills similar to those tested in the NAPLAN numeracy test. Improvements in perceptual reasoning but not in working memory have similarly been shown after supplementation of moderate to severely iodine-deficient 10- to 12-year-old Albanian children (12) using the Raven's Colored Progressive Matrices test and WISC Digit Span (Forwards and Backwards) test, respectively. Results for processing speed, however, varied with no associations found using the WISC Coding test, but improvement in the supplemented group using the WISC Symbol Search, the Rapid Object Naming, and Rapid Target Marking tests.

The Generation R Study from The Netherlands, which examined executive functioning in children (aged 4 years) using the Behavior Rating Inventory of Executive Function provides further evidence that working memory is affected by mild gestational ID (43). Children whose

mothers were in the lowest decile of UIC during pregnancy had higher problems scores on 2 of the 5 scales (inhibition and working memory) compared with those of children of mothers in the highest decile; no significant differences were reported for other 3 scales.

Although the evidence is not conclusive, it suggests that working memory and processing speed are affected by ID during gestation and are resistant to supplementation during childhood. It is not possible from the data available to determine definitively whether a central auditory processing disorder, as opposed to a more pervasive neurodevelopmental defect, is responsible for the observed association. Although our study is not a random sample, it does suggest that despite restitution of adequate iodine nutrition in early childhood, ID during embryonic and fetal development has a demonstrable long-term impact on educational performance. Findings from this study and others provide support for the theory that even mild ID at critical periods of fetal development can lead to deficits that are extremely resistant to restoration by later iodine sufficiency or even irreversible.

Further research on the long-term impacts of mild ID during pregnancy on offspring and studies to determine the prevalence of iodine supplementation during pregnancy and lactation appear warranted. Despite introduction of mandatory iodine fortification in Australia in 2009, awareness among women of the role of iodine nutrition is low (44), and the impact of a recent recommendation from the Australian National Health and Medical Research Council that pregnant and breastfeeding women take a daily iodine supplement (45) is unknown. Whereas our study was able to demonstrate that the 150  $\mu\text{g/L}$  cut point enables us to distinguish between sufficiency and deficiency with respect to educational outcomes, it also adds weight to the call for reexamination of current recommendations to ensure that it is truly sufficient for avoiding fetal brain damage in regions of mild ID. As highlighted by the review of Zimmermann and Andersson (46), use of the median UIC of school-aged children cannot be considered a good proxy for the general population and is inappropriate for pregnant and lactating women. Their suggestion that UIC be extrapolated using iodine intake and then interpreted using the estimated adequate requirements cut point method would provide for more robust estimations of population sufficiency. It seems vital that a prospective iodine supplementation intervention of pregnant and breastfeeding women at risk of mild ID, with longitudinal follow-up of their offspring, be conducted to determine appropriate recommendations for supplementation. Although mandatory fortification in Australia may have led to sufficiency in the general population (based on UIC surveys of children), pregnant women are still at risk

of deficiency, which may result in long-term irreversible, but preventable, consequences for their offspring.

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Address all correspondence and requests for reprints to: Dr Kristen Hynes, Menzies Research Institute Tasmania, Medical Science 1 Building, Private Bag 23, Hobart, Tasmania 7000, Australia. E-mail: k.l.hynes@utas.edu.au.

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