Supplemental material

Association of maternal iodine status with child IQ: a meta-analysis of individual-participant data

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Methods of urinary iodine measurements

In Generation R, urinary iodine was measured by the Sandell-Kolthoff method. Iodine calibration was performed using certified reference materials (CRM) Seronorm urine Levels one and two (Nycomed, Norway), and four EQUIP samples certified for urinary iodine concentration (Centers for Disease Control and Prevention, USA). At a level of 1.7 µmol/l iodine the within-assay CV was 5.1% and the between-assay CV was 14.3% (n= 30). In INMA, urinary iodine was measured using paired-ion reversed-phase, high-performance liquid chromatography (HPLC) with electrochemical detection at a silver working electrode (Waters Chromatography, Milford, MA). The accuracy of the results was verified using the CRM Seronorm urine Levels one and two (Nycomed, Norway), and internal quality control samples. Within run precision was 4.5% relative standard deviation (RSD) at 50 µg/L, 3.2% at 100 µg/L and 2.0% at 300 µg/L. Between run precision was 7.9% RSD at 50 µg/L, 3.5% at 100 µg/L and 2.5 % at 300 µg/L. In ALSPAC, iodine (^{127}I) was measured on a dynamic reaction cell inductively-coupled plasma (ICP) mass spectrometer. The accuracy of the results was verified using the CRM Seronorm urine Levels one and two (Nycomed, Norway), and accuracy was also monitored by measurement of EQUIP samples at regular intervals throughout the analysis. Within run precision was 0.83% RSD at 42 µg/L, 2.47% at 84 µg/L, 0.56% at 149 µg/L and 2.01% at 297 µg/L. Between run precision was 8.69% RSD at 42 µg/L, 6.54% at 84 µg/L, 7.2% at 149 µg/L and 6.8% at 297 µg/L.

eTable 1 Distribution and comparison of maternal and child characteristics in the included and excluded population

	Generation R			INMA			ALSPAC		
	included (n=1931)	**not included (n=7818)**	***P*-value**	**Included (n=1269)**	**not included (n=881)**	***P*-value**	**Included (n=2980)**	**not included (n=11752)**	***P*-value**
Female sex, n(%)	963 (49.9)	3846 (49.2)	0.605	632 (49.8)	348 (46.5)	0.150	1514 (50.8)	5312 (47.6)	0.002
Educational level, n(%)									
Low	154 (8.4)	791 (12.0)	<0.001	270 (21.3)	293 (34.4)	<0.001	573 (19.8)	3183 (33.1)	<0.001
Middle	760 (41.4)	3117 (47.2)		525 (41.5)	337 (39.6)		1810 (62.7)	5318 (55.4)	
High	921 (50.2)	2692 (40.8)		470 (37.2)	221 (26.0)		505 (17.5)	1104 (11.5)	
Maternal ethnicity/country of birth, n(%)									
Spanish	NA	NA	0.001	1184 (93.5)	731 (85.8)	<0.001	NA	NA	<0.001
Latin-american	NA	NA		56 (4.4)	80 (9.4)		NA	NA	
European/other	NA	NA		26 (2.1)	41 (4.8)		NA	NA	
Dutch	1012 (53.2)	3490 (49.5)		NA	NA		NA	NA	
Indonesian	69 (3.6)	198 (2.8)		NA	NA		NA	NA	
Cape verdian	58 (3.1)	314 (4.5)		NA	NA		NA	NA	
Moroccan	115 (6.0)	487 (6.9)		NA	NA		NA	NA	
Surinamese	154 (8.1)	636 (9.0)		NA	NA		NA	NA	
Turkish	170 (9.0)	617 (8.7)		NA	NA		NA	NA	
Other, non-western	150 (7.9)	724 (10.3)		NA	NA		NA	NA	
Other, western	174 (9.1)	589 (8.3)		NA	NA		NA	NA	
White	NA	NA		NA	NA		2841 (98.7)	9234 (97.0)	
Non-white	NA	NA		NA	NA		36 (1.3)	290 (3.0)	
Maternal age, years, mean (SD)	30.5 (4.8)	29.8 (5.5)	<0.001	31.6 (3.9)	30.7 (4.8)	<0.001	28.6 (4.5)	26.9 (5.1)	<0.001
Parity, n(%)									
0	1121 (58.1)	3986 (51.8)	<0.001	727 (57.4)	441 (51.8)	0.018	1346 (46.8)	4527 (44.2)	0.018
1	564 (29.2)	2231 (29.0)		458 (36.1)	335 (39.4)		992 (34.5)	3596 (35.1)	
≥2	246 (12.7)	1480 (19.2)		82 (6.5)	75 (8.8)		539 (18.7)	2124 (20.7)	

eTable 1 Distribution and comparison of maternal and child characteristics in the included and excluded population (continued)

	Generation R			INMA			ALSPAC		
	included (n=1931)	**not included (n=7818)**	***P*-value**	**Included (n=1269)**	**not included (n=881)**	***P*-value**	**Included (n=2980)**	**not included (n=11752)**	**P-value**
Smoking during pregnancy , n(%)									
Never	1319 (75.6)	4648 (72.9)	<0.001	870 (69.4)	478 (64.2)	0.055	2434 (83.2)	7446 (71.4)	<0.001
In the beginning of pregnancy	168 (9.6)	523 (8.2)		168 (13.4)	116 (15.6)		125 (4.3)	682 (6.5)	
Continued	257 (14.7)	1208 (18.9)		216 (17.2)	151 (20.3)		367 (12.5)	2305 (22.1)	
Pre-pregnancy BMI, kg/m^2, median (IQR)	22.6 (20.8-25.2)	22.6 (20.7-25.5)	0.926	22.5 (20.8-25.0)	22.6 (20.7-25.3)	0.670	22.2 (20.5-24.4)	22.1 (20.4-24.4)	0.077

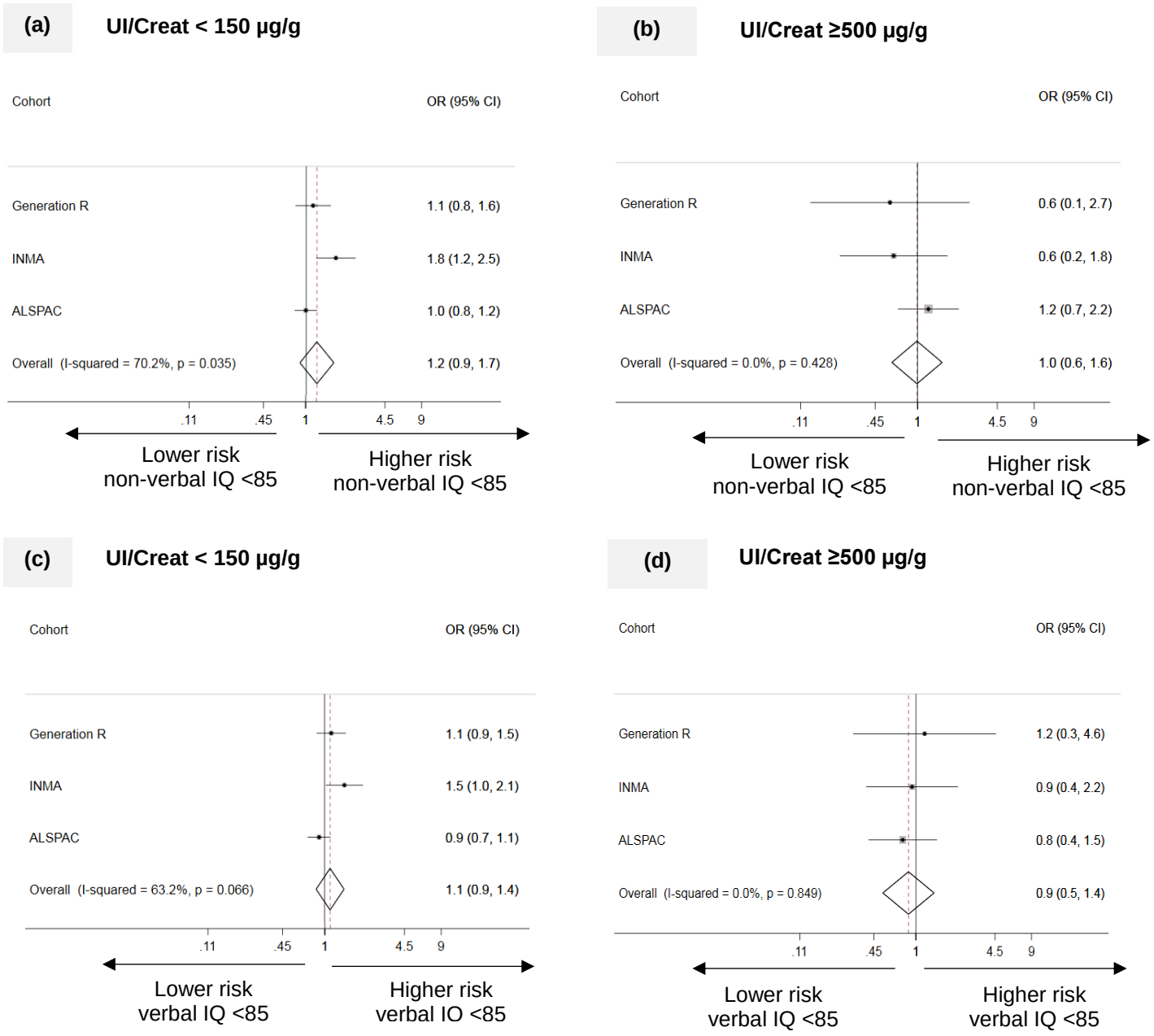
P-value for differences calculated using Chi-square test for categorical variables, Student´s t-test for continuous normal-distributed variables, and Kruskal-Wallis test for continuous non-normal distributed variables. NA: not applicable. Numbers are based on unimputed data; percentages add up to 100% without taking into account missing values.

eTable 2 Continuous analysis of the association of maternal iodine status during pregnancy with child non-verbal and verbal IQ using standard linear regression models.

		Non-verbal IQ		verbal IQ	
Type of model	**Variables in the model**	Beta (95%CI)	*P*-value	Beta (95%CI)	*P*-value
linear model	UI/Creat	0.602 (-0.007 to 1.210)	0.053	1.061 (0.450 to 1.672)	0.001
non-linear model	UI/Creat	0.632 (-5.848 to 7.113)	0.848	10.011 (3.499 to 16.523)	0.003
	UI/Creat^2	-0.003 (-0.651 to 0.644)	0.993	-0.898 (-1.549 to -0.247)	0.007

Reported beta and 95%CI are increase in mean child IQ per natural log increase in UI/Creat. UI/Creat^2 refers to the addition of a squared logtransformed UI/Creat variable in the model. Analyses were performed using linear regression models. Analyses were adjusted for gestational age at urine sampling, child sex, maternal ethnicity/country of birth, maternal education, parity, maternal age, pre-pregnancy BMI, and smoking during pregnancy.

eFigure 1 Association of UI/Creat < 150 µg/g and UI/Creat ≥ 500 µg/g during pregnancy with child suboptimal non-verbal and verbal IQ.



eFigure 1 Association of UI/Creat < 150 µg/g and UI/Creat ≥ 500 µg/g during pregnancy with child suboptimal non-verbal and verbal IQ.

Figure shows the association of UI/Creat <150 µg/g ("deficiency") with a) non-verbal IQ score <85 and c) verbal IQ score <85, and UI/Creat >=500 µg/g ("excess") with b) non-verbal IQ score <85 and d) verbal IQ score <85 as compared to the reference group (UI/Creat ≥150 to <500 µg/g). Associations are depicted as effect estimate (dot) with 95%CI per cohort and overall as estimated by random-effects meta-analysis (diamond). Models are adjusted for gestational age, child sex, maternal ethnicity/country of birth, maternal education, parity, maternal age, pre-pregnancy BMI, smoking during pregnancy, child age and region in INMA.

eTable 3 Continuous analysis of the association of maternal iodine status during pregnancy with child verbal IQ stratified by tertile of gestational age using standard linear regression models.

Type of model	Variables in the model	Gestational age (weeks)	Beta (95%CI)	*P*-value
non-linear model	UI/Creat	≤12	18.276 (6.923 to 29.628)	0.002
	UI/Creat^2		-1.786 (-2.953 to -0.620)	0.003
Linear model	UI/Creat	>12 and ≤14	1.333 (0.230 to 2.436)	0.018
Linear model	UI/Creat	>14	0.444 (-0.601 to 1.489)	0.405

Reported beta and 95%CI are increase in mean child verbal IQ per log increase in UI/Creat. UI/Creat^2 refers to the addition of a squared UI/Creat variable in the model. Analyses were performed using linear regression models. UI/Creat was transformed by the natural logarithm. Analyses were adjusted for gestational age at urine sampling, child sex, maternal ethnicity/country of birth, maternal education, parity, maternal age, pre-pregnancy BMI, and smoking during pregnancy.

eTable 4 Comparison of the ALSPAC study population included in the current study and in the previous publication of Bath et al. 2013

	this study cohort	this study cohort restricted to ≤13 weeks gestation	Bath et al. 2013
No.	2980	1845	958
gestational age, median (IQR)	12 (8-16)	9 (7-11)	10 (9-12)
UI/Creat, µg/g, median (IQR)	124 (82-199)	108 (75-161)	110 (74-170)
UI/Creat < 150 µg/g , %	61.4	70.1	67.4
UIC, µg/L, median (IQR)	96 (57-153)	96.8 (60-149)	91.1 (53.8-143)

eTable 5 Association of maternal iodine status with a child verbal IQ score in the lowest quartile as studied in the current ALSPAC study population and as in the previous publication of Bath et al. 2013

this study cohort [OR (95%CI), *P*-value]	this study cohort restricted to ≤13 weeks gestation [OR (95%CI), *P*-value]	Bath et al. 2013 [OR (95%CI), *P*-value]
1.13 (0.92 to 1.39), 0.259	1.42 (1.06 to 1.91), 0.019	1.58 (1.09 to 2.30), 0.02

Reported OR and 95%CI for a verbal IQ score in the bottom quartile when exposed to a maternal UI/Creat < 150 µg/g vs ≥ 150 µg/g (reference group) during pregnancy. Analyses with un-imputed data were performed using logistic regression models and were adjusted as similarly as possible as compared to the fully adjusted model (model 3) as reported in the publication of Bath et al. Analyses were adjusted for preterm birth, birthweight, child sex, maternal education, paternal education, maternal ethnicity (instead of child ethnicity), parity, age at delivery, smoking, maternal alcohol intake, breastfeeding, iron intake, and omega-3 fatty acid intake estimated from the Food Frequency Questionnaire completed at 32 weeks' of gestation. Missing information that was corrected for in model 3 of Bath et al but lacking in the analysis of this study cohort, were: mothers parenting score (seven-factor measure of cognitive stimulation at 6 months of age), home observation for measurement of environment (HOME) score (six-factor measure of the emotional and cognitive environment at 6 months of age), the family adversity index (18-factor measure of hardship during pregnancy), life-event score (exposure to 41 stressful events during pregnancy), maternal depression since birth, fish-oil supplements during pregnancy, housing status, and crowding.