

Supplementary Online Content

Modesto T, Tiemeier H, Peeters RP, et al. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. *JAMA Pediatr*. Published online July 6, 2015. doi:10.1001/jamapediatrics.2015.0498.

eTable 1. Cognitive and Behavioral Measures in the Generation R Study

eTable 2. Complete Case Analysis

eTable 3. Alternative Cutoff for Thyrotropin Levels (0.03-4.04 mIU/L)

eTable 4. Maternal Thyroid Function in Early Pregnancy and Children's ADHDi Scores at 8 Years of Age

eTable 5. Subanalysis in Pregnant Women Negative for Thyroid Peroxidase Antibodies

eTable 6. Subanalysis Among Pregnant Women With Gestational Age at the Time of Sampling <13 Weeks

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Cognitive and behavioral measures in the Generation R Study

Instrument	Average age of Children	Type of Assessment
Child Behavior Checklist for Toddlers (CBCL/1 ^{1/2} -5)	6 years	Parental report
Social Responsiveness Scale (SRS)	6 years	Parental report
Snijders-Oomen Niet-verbale intelligentie Test – Nonverbal intelligence test	6 years	Observation
Berkley Puppet Interview (BPI)	6 years	Self-report
Teacher Report Form 6-18 (TRF)	6.7 years	Teacher report
Diagnostic Interview Schedule for Children-Young Child version (DISC-YC)	6.7 years	Structured interview with parent
Conners' Parent Rating Scales Revised Short Form (CPRS:R-S)	8.1 years	Parental report

*Children aged 6 to 8 years.

eTable 2. Complete case analysis.

	Parent reported ADHDi scores at age 8 years			
	B	95% CI	P value	Percentage change in scores (95%CI)
Maternal Hypothyroxinemia				
Unadjusted (n=2491)	0.09	0.01, 0.20	0.03	9% (1%, 22%)
Adjusted for age and sex (n=2491)	0.09	0.01, 0.20	0.03	9% (1%, 22%)
Fully adjusted model (n=1967)	0.08	0.01, 0.19	0.04	8% (1%, 21%)
Free T4 per SD				
Unadjusted (n=2528)	-0.01	-0.02, 0.01	0.50	-1% (-2%, 1%)
Adjusted for age and sex (n=2528)	-0.004	-0.02, 0.01	0.84	-0.4% (-2%, 1%)
Fully adjusted model (n=1996)	-0.001	-0.02, 0.02	0.88	-0.1% (-2%, 2%)
Thyrotropin per SD				
Unadjusted (n=2491)	-0.004	-0.02, 0.01	0.60	-0.4% (-2%, 1%)
Adjusted for age and sex (n=2491)	-0.01	-0.02, 0.01	0.41	-1% (-2%, 1%)
Fully adjusted model (n=1967)	-0.01	-0.02, 0.01	0.38	-1% (-2%, 1%)

Maternal thyroid function in early pregnancy and children's Attention-Deficit/Hyperactivity Disorder index (ADHDi) score at age eight years in the Generation R Study.

Abbreviations: ADHDi, Attention-Deficit/Hyperactivity Disorder index; T₄, thyroxine

SD for free T₄: 3.75 pmol/L; SD for thyrotropin: 1.3 mIU/L.

Full models were adjusted for child age, sex, and ethnic background, and maternal educational level, maternal age, maternal history of smoking, maternal psychopathology during pregnancy, parity, marital status, household income, maternal body mass index, and time of blood sampling in pregnancy.

The B's are not easily interpretable since the mathematically transformed scores were used in the analyses. Therefore, coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

Maternal hypothyroxinemia was defined as normal thyrotropin levels and free T₄ concentrations below the 5th percentile (n=127).

ADHDi scores were derived from the Conners' Parent Rating Scales Revised Short Form. Possible ranges for ADHDi score are between 0-16. Higher scores indicate more problems.

eTable 3. Alternative cutoff for thyrotropin levels (0.03-4.04 mIU/L).

	Parent reported ADHDi scores at age 8 years			
	B	95% CI	P value	Percentage change in scores (95%CI)
Maternal Hypothyroxinemia				
Unadjusted	0.05	-0.01, 0.11	0.09	5% (-1%, 12%)
Adjusted for age and sex	0.05	-0.01, 0.11	0.09	5% (-1%, 12%)
Fully adjusted model	0.05	-0.01, 0.11	0.10	5% (-1%, 12%)

Maternal thyroid function in early pregnancy and children's Attention-Deficit/Hyperactivity Disorder index (ADHDi) score at age eight years. The Generation R Study (n = 3873).

Abbreviations: ADHDi, Attention-Deficit/Hyperactivity Disorder index; T₄, thyroxine

Full models were adjusted for child age, sex, and ethnic background, and maternal educational level, maternal age, maternal history of smoking, maternal psychopathology during pregnancy, parity, marital status, household income, maternal body mass index, and time of blood sampling in pregnancy.

The B's are not easily interpretable since the mathematically transformed scores were used in the analyses. Therefore, coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

Maternal hypothyroxinemia was defined as normal as normal thyrotropin levels and free thyroxine concentrations below the 5th percentile (n=161).

ADHDi scores were derived from the Conners' Parent Rating Scales Revised Short Form. Possible ranges for ADHDi score are between 0-16. Higher scores indicate more problems.

eTable 4. Maternal thyroid function in early pregnancy and children’s ADHDi scores at 8 years of age

	Parent reported ADHDi scores at age 8 years			
	B	95% CI	P value	Percentage change in scores (95%CI)
Subclinical Hypothyroidism				
Unadjusted	-0.04	-0.09, 0.04	0.43	-4% (-9%, 4%)
Adjusted for age and sex	-0.03	-0.10, 0.03	0.36	-3% (-10%, 3%)
Fully adjusted model	-0.01	-0.07, 0.05	0.80	-1% (-7%, 5%)

The Generation R Study (n = 3873).

Abbreviation: ADHDi, Attention-Deficit/Hyperactivity Disorder index

Full models were adjusted for child age, sex, and ethnic background, and maternal educational level, maternal age, maternal history of smoking, maternal psychopathology during pregnancy, parity, marital status, household income, maternal body mass index, and time of blood sampling in pregnancy.

The B’s are not easily interpretable since the mathematically transformed scores were used in the analyses. Therefore, coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

We defined maternal subclinical hypothyroidism as free thyroxine within the normal range and high thyrotropin (>2.5 mIU/L).

Attention Deficit/Hyperactivity Disorder index scores were derived from the Conners’ Parent Rating Scales Revised Short Form. Possible ranges for ADHDi score are between 0-16. Higher scores indicate more problems.

eTable 5. Subanalysis in pregnant women negative for thyroid peroxidase antibodies

	Parent reported ADHDi scores at age 8 years			
	B	95% CI	P value	Percentage change in scores (95%CI)
Maternal Hypothyroxinemia				
Unadjusted	0.09	0.01, 0.16	0.02	9% (1%, 17%)
Adjusted for age and sex	0.09	0.01, 0.16	0.02	9% (1%, 17%)
Fully adjusted model	0.08	0.01, 0.16	0.03	8% (1%, 17%)

Maternal hypothyroxinaemia in early pregnancy and children's Attention-Deficit/Hyperactivity Disorder index (ADHDi) score at age eight years, The Generation R Study (n = 3,585).

Full models were adjusted for child age, sex, and ethnic background, and maternal educational level, maternal age, maternal history of smoking, maternal psychopathology during pregnancy, parity, marital status, household income, maternal body mass index, and time of blood sampling in pregnancy.

The B's are not easily interpretable since the mathematically transformed scores were used in the analyses. Therefore, coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

Maternal hypothyroxinemia was defined as normal thyrotropin levels and free thyroxine concentrations below the 5th percentile (n=118).

ADHDi scores were derived from the Conners' Parent Rating Scales Revised Short Form. Possible ranges for ADHDi score are between 0-16. Higher scores indicate more problems.

eTable 6. Subanalysis among pregnant women with gestational age at the time of sampling <13 weeks

	Parent reported ADHDi scores at age 8 years			
	B	95% CI	P value	Percentage change in scores (95%CI)
Maternal hypothyroxinemia				
Unadjusted	0.17	0.03, 0.31	0.01	18% (3%, 36%)
Adjusted for age and sex	0.15	0.01, 0.28	0.04	16%(1%, 32%)
Fully adjusted model	0.13	-0.01, 0.26	0.06	14% (-1%, 29%)
Free T ₄ per SD				
Unadjusted	-0.02	-0.04, -0.004	0.02	-2% (-4%, -0.4%)
Adjusted for age and sex	-0.02	-0.04, -0.001	0.04	-2% (-4%, -0.1%)
Fully adjusted model	-0.02	-0.03, 0.003	0.10	-2% (-3%, 0.3%)
Thyrotropin per SD				
Unadjusted	-0.004	-0.02, 0.01	0.58	-0.4% (-2%, 1%)
Adjusted for age and sex	-0.01	-0.02, 0.01	0.52	-1% (-2%, 1%)
Fully adjusted model	-0.004	-0.02, 0.01	0.59	-0.4% (-2%, 1%)

Maternal thyroid function in early pregnancy and children's Attention-Deficit/Hyperactivity Disorder index (ADHDi) score at age eight years. The Generation R Study (n = 1733).

Abbreviation: T₄, thyroxine

The SD for free T₄: is 0.29 ng/dL. 3.75 pmol/L.

The SD for thyrotropin is 1.3 mIU/L.

Full models were adjusted for child age, sex, and ethnic background, and maternal educational level, maternal age, maternal history of smoking, maternal psychopathology during pregnancy, parity, marital status, household income, maternal body mass index, and time of blood sampling in pregnancy.

The B's are not easily interpretable since the mathematically transformed scores were used in the analyses. Therefore, coefficients were exponentiated and converted to percentage differences. Negative values indicate a decrease in scores.

Maternal hypothyroxinemia was defined as normal thyrotropin levels and free T₄ concentrations below the 5th percentile (N=33).

Attention Deficit/Hyperactivity Disorder index scores were derived from the Conners' Parent Rating Scales Revised Short Form. Possible ranges for ADHDi score are between 0-16. Higher scores indicate more problems.