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Maternal Thyroid Function and Autoimmunity and Risk of Problem Behavior: The Generation R Study

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Disclosure

Nothing to disclose

At the conclusion of this presentation, the participant should be able to:

- 1. Name one consequence of thyroid autoimmunity during pregnancy on maternal health**
- 2. Name two pregnancy complications related to thyroid autoimmunity in pregnancy**
- 3. Name two adverse effects of maternal thyroid autoimmunity on children's mental health**
- 4. Answer whether euthyroid women with Thyroid Peroxidase Antibodies need any intervention during pregnancy?**
- 5. Answer whether the children who are born to euthyroid mothers with Thyroid Peroxidase Antibodies need early monitoring for Attention Deficit/Hyperactivity Disorders**



Background

**Maternal hypothyroidism
in pregnancy**



Child's cognitive deficits

**Hypothyroxinemia in first
trimester of pregnancy**



**(low-for-gestational age free T4 with
normal TSH)**

**•Animals: Alterations of brain
cortical cytoarchitecture**

•Humans: Cognitive deficits

**Elevated TPO-Abs
in mothers**



•Miscarriage/preterm delivery

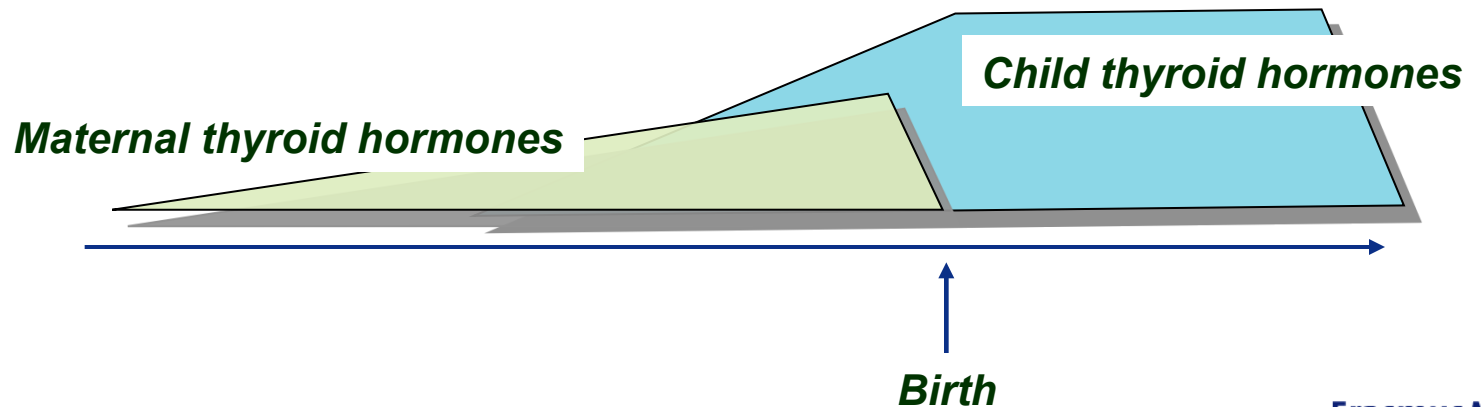
•Pre and postnatal depression

**•Deficits in child's cognitive
function and motor
development**

Thyroid Hormones and Brain

Neurogenesis
Neural migration

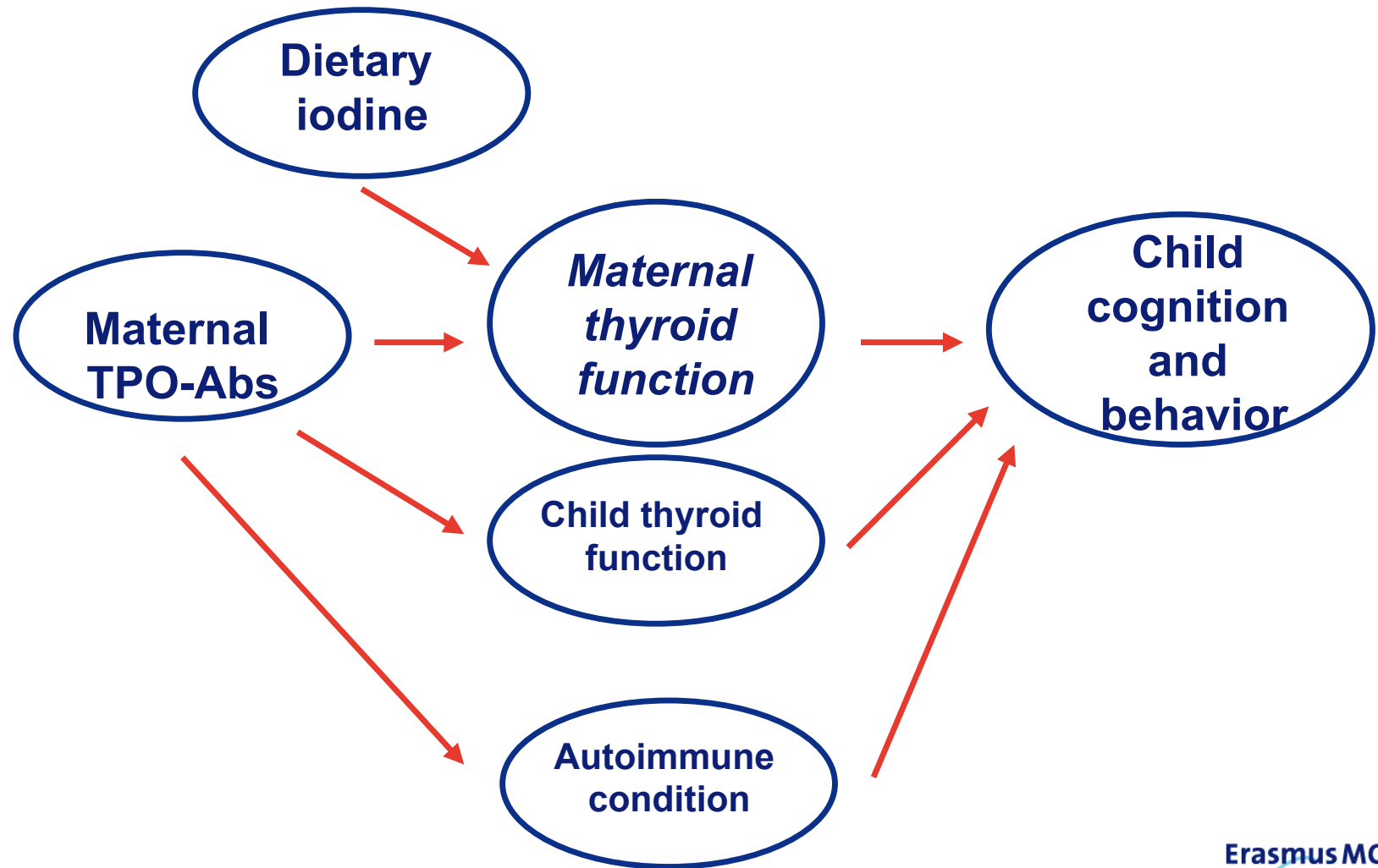
Synapse formation
Myelination



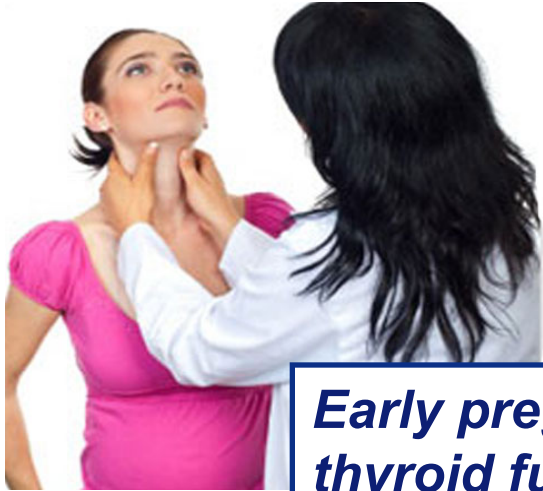
Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum

- Overt hypothyroidism should be treated in pregnancy.
- TPOAb⁺ Women and subclinical hypothyroidism should be treated.
- There is insufficient evidence to recommend for or against universal treatment of TAb⁻ pregnant women with subclinical hypothyroidism.
- Isolated hypothyroxinemia should not be treated in pregnancy.

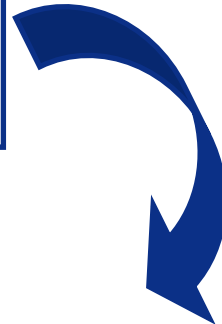
Background



Aim



***Early pregnancy
thyroid function
and autoimmunity***



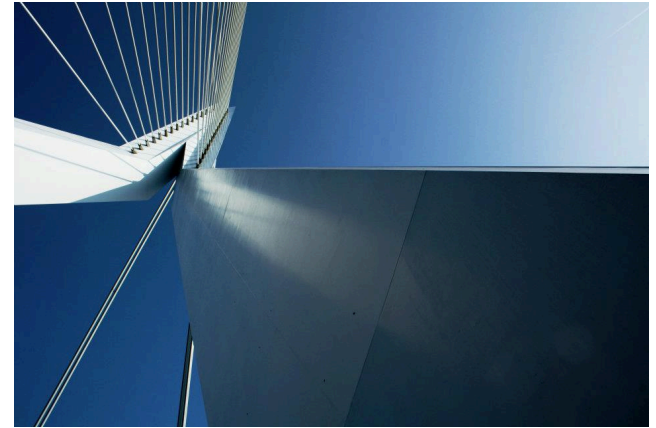
***Attention deficit/
hyperactivity problems
Language delay
Autistic symptoms***

The Generation R Study

- Prospective cohort study
- From fetal life onwards
- 9,778 mothers and their children
- Urban, multi-ethnic population in Rotterdam



The Generation R Study



< 18 wks

Birth

• **TSH**

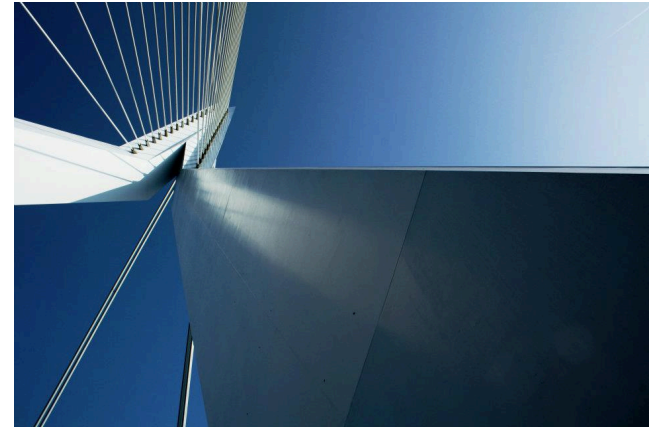
• **Free T4**

• **Thyroid Peroxidase
Antibodies**

N~5200



The Generation R Study



N~1000

• *Iodine and creatinine in urine samples*

< 18 wks

Birth

• *TSH*

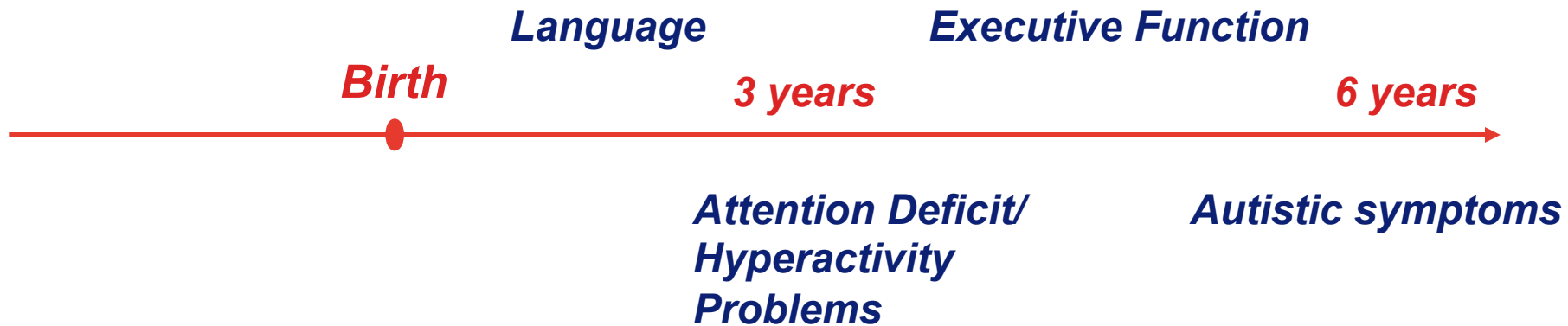
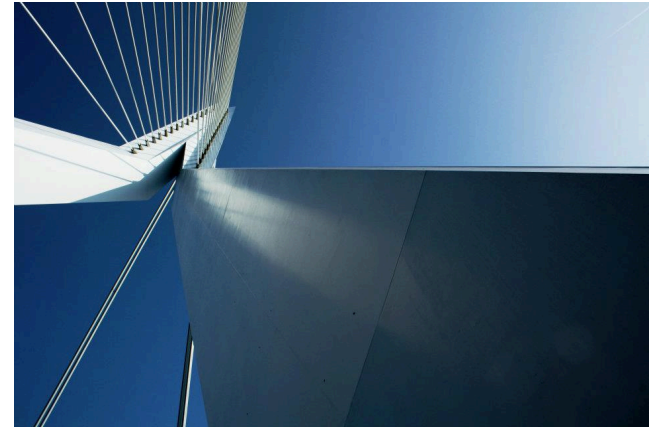
• *Free T4*

• *Thyroid Peroxidase Antibodies*

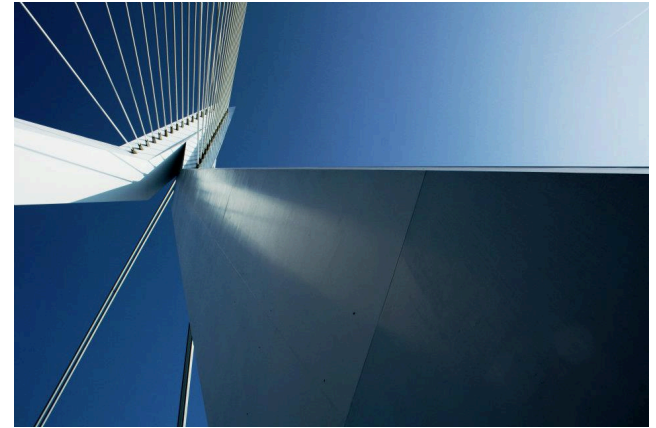
N~5200



The Generation R Study



The Generation R Study



*Parental
Psychopathology*

Apgar score

Household income

Sex *Birth* *Mode of Delivery*



Birth weight

Parental education

*Maternal
smoking*

Ethnic background



Externalizing problems & Attention Deficit Hyperactivity Problems

- *Cannot concentrate, cannot pay attention for long*
- *Cannot sit still, restless, or hyperactive*
- *Destroys property belonging to others*

Executive Function

- *Inhibition: to stop his/her own behavior*
- *Working memory: to hold information in mind to complete a task*

Autistic symptoms

- *Avoids eye contact, or has unusual eye contact*
- *Has repetitive, odd behaviors such as hand flapping or rocking*



Maternal hypothyroxinemia and language development in children up to age 2.5 years

Maternal thyroid function in early pregnancy and expressive language delay at 18 and 30 months

Maternal thyroid function measure	One time point				Across ages	
	Expressive language delay at age 18 months ^a		Expressive language delay at age 30 months ^b		Expressive language delay at 18 and 30 months	
	n	OR (95% CI), P	n	OR (95% CI), P	n	OR (95% CI), P
TSH, per SD	3384	0.91 (0.81–1.03), 0.136	2757	0.92 (0.81–1.06), 0.249	3614	0.92 (0.84–1.02), 0.100
FT ₄ , per SD	3409	0.95 (0.83–1.09), 0.430	2779	0.84 (0.71–0.99), 0.039	3643	0.90 (0.80–1.01), 0.069
Mild hypothyroxinemia ^c	2736 ^e	1.33 (0.91–1.94), 0.143	2225 ^e	1.47 (1.00–2.17), 0.051	2926 ^e	1.44 (1.09–1.91), 0.010
Severe hypothyroxinemia ^d	2736 ^e	1.77 (1.10–2.84), 0.018	2225 ^e	1.78 (1.07–2.94), 0.024	2926 ^e	1.80 (1.24–2.61), 0.002

Adjusted for maternal and child factors

Henrichs et al. JCEM 2010, 95 (9), 4227-4234

Maternal hypothyroxinemia and language development in children up to age 2.5 years

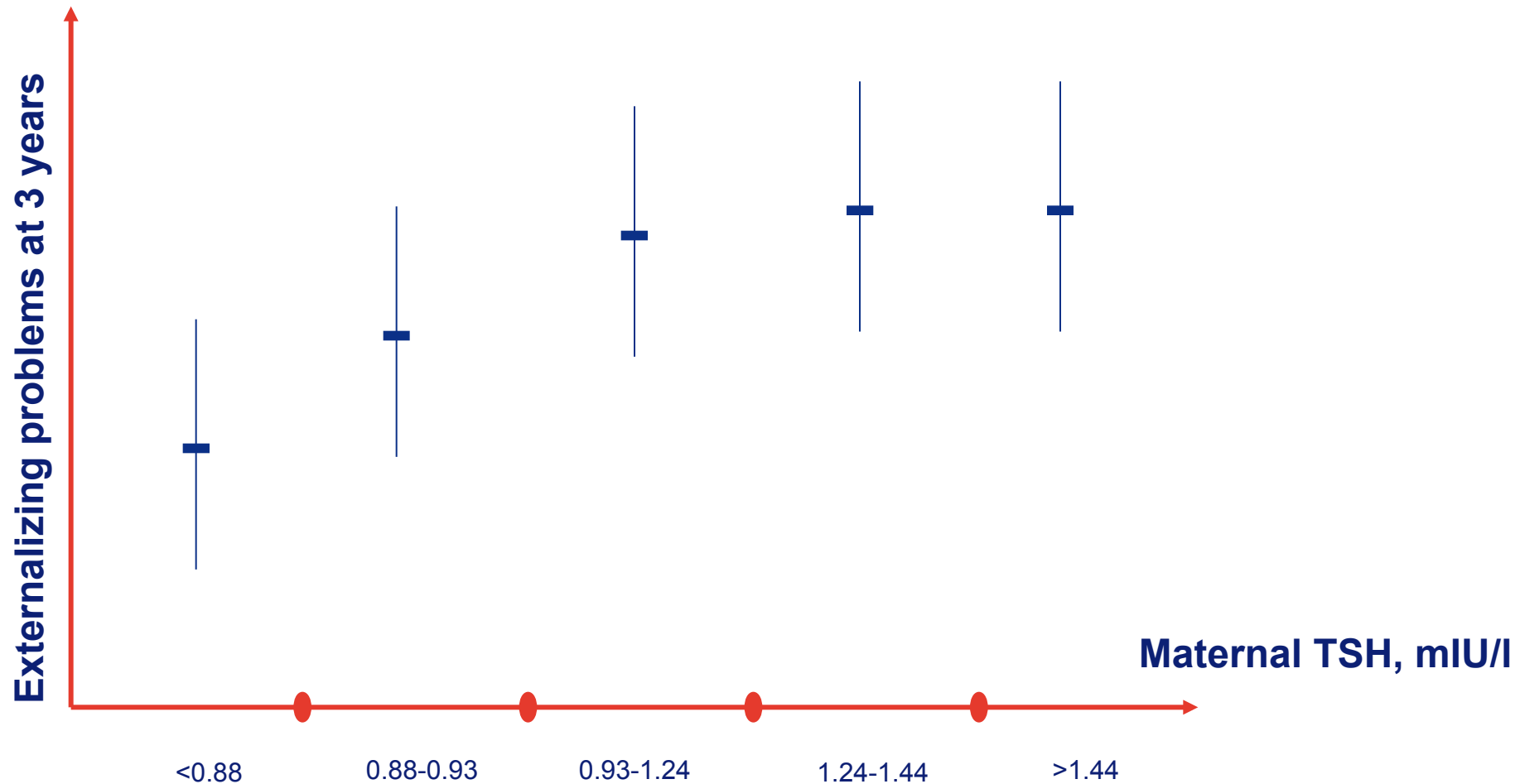
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Maternal TSH levels and externalizing problems in children at age 3 years



Maternal Thyroid Peroxidase Antibodies in early pregnancy and problem behavior in the children at age 3 years

	Problem Behavior at the age of 3 years		
Maternal Thyroid Parameters	Maternal Rating	Paternal Rating	<i>Maternal and Paternal Rating</i>
Outcomes	<i>OR (95%CI)</i>	<i>OR (95%CI)</i>	<i>OR (95%CI)</i>
Attention Deficit/Hyperactivity Problems	1.60 (0.90-2.87)	1.89* (1.16-3.07)	1.77* (1.15-2.72)
Oppositional Deviant Problems	1.46 (0.91-2.34)	1.36 (0.73-2.52)	1.39 (0.95-2.03)

Adjusted for maternal and child factors

Ghassabian et al. Thyroid 2012, 22 (2), 178-186

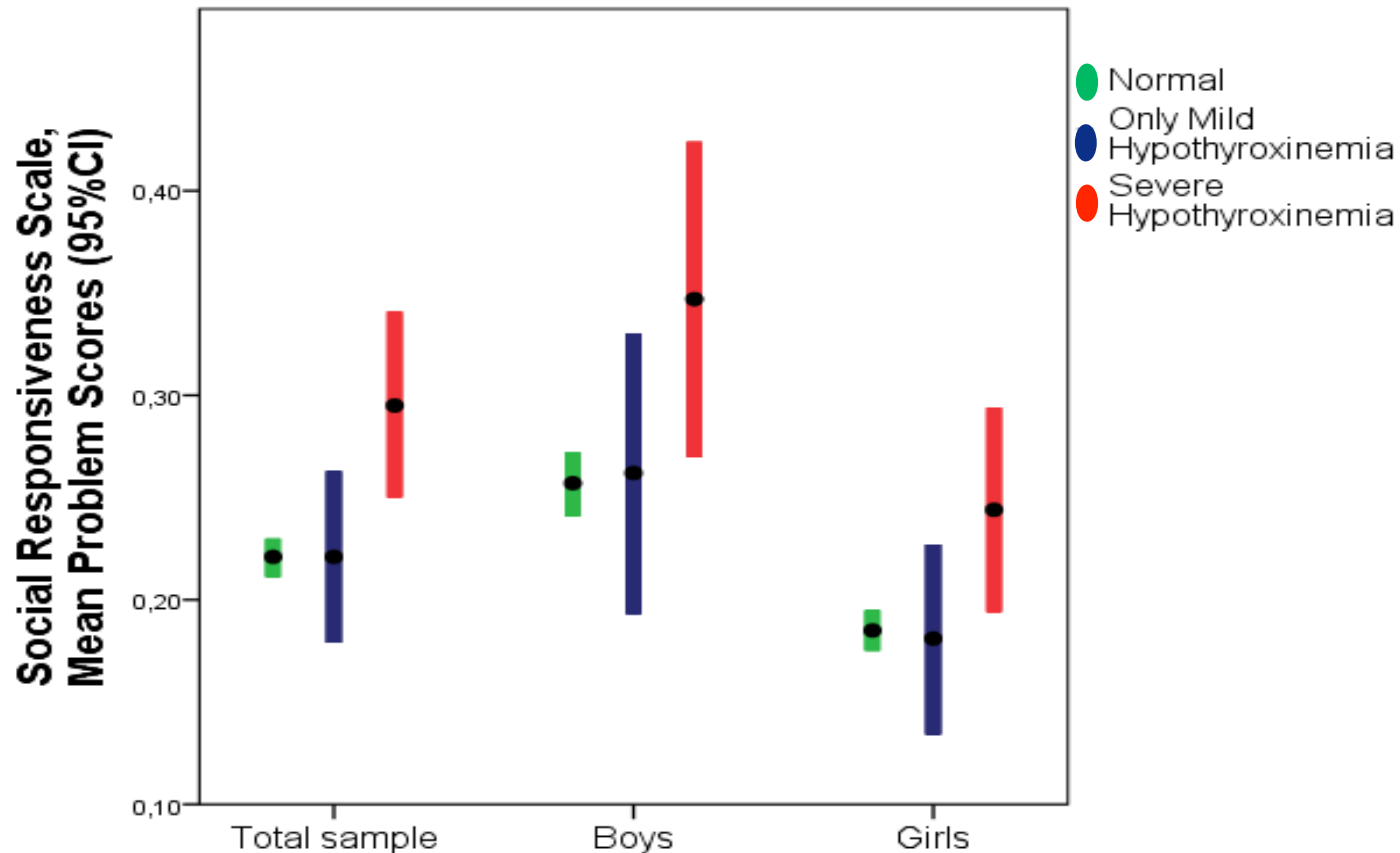
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Adjusted for maternal and child factors

Ghassabian et al. *Thyroid* 2012, 22 (2), 178-186

Maternal hypothyroxinemia in early pregnancy and autistic symptoms in the children at age 6 years



Low maternal urinary iodine and children's scores on executive function at 4 years

	All women (<i>n</i> = 692)			
	Adjusted ^{2,4}		Additionally adjusted ²⁻⁴	
	β (95% CI)	<i>P</i> value	β (95% CI)	<i>P</i> value
Inhibition	0.05 (0.01, 0.10)	0.03	0.04 (−0.00, 0.09)	0.07
Shifting	−0.01 (−0.05, 0.03)	0.64	−0.02 (−0.06, 0.02)	0.41
Emotional control	0.01 (−0.04, 0.06)	0.63	0.00 (−0.05, 0.05)	0.94
Working memory	0.07 (0.03, 0.12)	0.003	0.06 (0.01, 0.10)	0.01
Planning/ organization	0.03 (−0.02, 0.08)	0.19	0.02 (−0.03, 0.07)	0.43
Global executive composite	0.05 (0.00, 0.10)	0.05	0.03 (−0.01, 0.08)	0.16

Adjusted for maternal and child factors

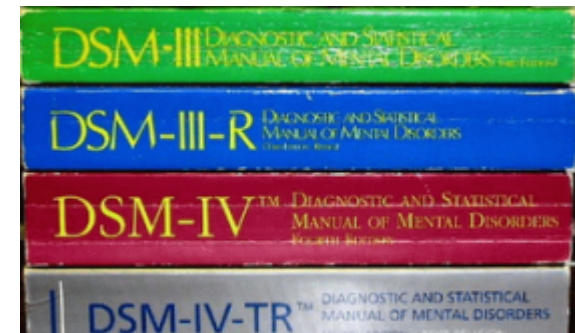
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Limitations

- Maternal thyroid parameters, but not child thyroid function
- Parental rating of behavior and cognition but not clinical diagnosis



Conclusion

Observational studies suggest the effect of maternal low thyroid function (within the normal range) and thyroid autoimmune disease on child outcomes.

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Observational studies suggest the effect of maternal low thyroid function (within the normal range) and thyroid autoimmune disease on child outcomes.

So far Randomized Trials failed to show the effectiveness of thyroid screening and treatment at population level.

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Antenatal Thyroid Screening and Childhood Cognitive Function

John H. Lazarus, M.D., Jonathan P. Bestwick, M.Sc., Sue Channon, D.Clin.Psych., Ruth Paradise, Ph.D.,
Aldo Maina, M.D., Rhian Rees, M.Sc., Elisabetta Chiusano, M.Psy., Rhys John, Ph.D.,
Varvara Guaraldo, M.S.Chem., Lynne M. George, H.N.C., Marco Perona, M.S.Chem., Daniela Dall'Amico, M.D.,
Arthur B. Parkes, Ph.D., Mohammed Joomun, M.Sc., and Nicholas J. Wald, F.R.S.

Future investigations...



- Brain imaging

Structural and functional abnormalities (e.g. hippocampus and cerebellum) in humans

- Genetics (Mendelian randomization)

Acknowledgment

All the participating children and their parents

Department of Child and Adolescent Psychiatry

Department of Internal Medicine

Department of Immunology

Department of Obstetrics and Gynecology

Department of Epidemiology

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