Thyroid Function in Monozygotic Twins with Intra-twin Birth Weight Differences: A Prospective Longitudinal Cohort Study

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Objective To analyze the long-term impact of birth weight (BW) on thyroid function in genetically identical twins with intra-twin BW differences from birth to adolescence.

Study design In total, 52 monozygotic twin pairs underwent at least one analysis of thyroid function at mean ages of 10.1 years (27 pairs), 15.1 years (35 pairs), and 17.4 years (36 pairs); 18 pairs donated blood at all time points. BW difference of <1 SDS was defined as concordant, BW difference ≥1 SDS as discordant.

Results In concordant twins, no significant differences were observed. In the discordant group, smaller twins had higher mean thyroid-stimulating hormone (TSH) than their larger co-twins at 10.1 years (3.6 vs 2.5 μU/mL; P = .04) and 15.1 years (2.6 vs 2.2 μU/mL; P = .08). Smaller twins showed lower mean thyroxine than larger co-twins at 10.1 years (7.8 vs 8.2 μg/dL P = .05) and 17.4 years (7.7 vs 8.4 μg/dL; P = .03), and a tendency at 15.1 years (6.9 vs 7.4 μg/dL; P = .09). Calculation of TSH-thyroxine ratio revealed significant differences in the discordant group, with greater ratios in the smaller twin at 10.1 years (0.5 vs 0.3; P = .006) and 15.1 years (0.4 vs 0.3; P = .04).

Conclusions In this group of monozygotic twins with intra-twin BW differences, BW seemed to exert a long-lasting impact on thyroid function. This may be due to a delay in hypothalamic–pituitary–thyroid axis maturation, with TSH resistance during childhood and early adolescence in children with low BW. *(J Pediatr 2019;211:164-71)*.

Low birth weight (BW), unfavorable intrauterine conditions, and rapid postnatal catch-up growth have been associated with a subsequent impairment of growth, acceleration of pubertal maturation, and metabolic disturbances later in life.[1-3] Very little is known about the impact of the perinatal environment on thyroid function. Studies performed in fetuses with intrauterine growth restriction or born small for gestational age (SGA) indicated differences in prenatal thyroid metabolism, with elevated concentrations of thyroid-stimulating hormone (TSH) and lower concentrations of thyroxine (T4),[4] or lower concentrations of free triiodothyronine, and free thyroxine (fT4) without elevated TSH.[5] These changes were interpreted as a sign of adaptive intrauterine thyroid function with the aim of decreasing both metabolic rate and oxygen consumption.[6] The few studies carried out to investigate whether these changes persist up to birth and during the first few months of life showed conflicting results.[7-12] Very few studies have investigated the long-term effects up to childhood, but again with variable results.[13-17] There are even fewer studies on thyroid function in children with former low BW at adulthood, but also with opposing findings.[18,19]

To prevent genetic heterogeneity from exerting a potentially confounding effect of an adverse environment on subsequent thyroid function, we recruited a study cohort solely composed of monozygotic twins who suffered from twin-to-twin transfusion syndrome during pregnancy. Twin-to-twin transfusion syndrome is characterized by the development of unbalanced, chronic blood transfer through placental anastomoses; the recipient twin is adequately nourished, but the donor suffers from growth restriction due to impaired blood flow and nutrient exposure.[20,21] Thus, our cohort has an identical genetic background and the same maternal environment, but differs regarding prenatal nutrient exposure, which led to a significant intra-twin BW difference. Therefore, these monozygotic twin pairs provide an excellent model for examining the impact of genes and environment,[22-24] here the impact of lower BW and prenatal growth restriction on thyroid function in later life.

AIC	Akaike information criterion	T3	Triiodothyronine
AMR	Analytical measurement range	T4	Thyroxine
BMI	Body mass index	TBG	Thyroxine-binding globulin
BW	Birth weight	TgAb	Thyroglobulin antibodies
Δ	Delta value	TPOAb	Thyroid peroxidase antibodies
fT4	Free thyroxine	TSH	Thyroid-stimulating hormone
SGA	Small for gestational age		

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Methods

This study is part of a longitudinal study of twins who suffered from twin-to-twin transfusion syndrome during pregnancy and therefore were treated with intrauterine selective fetoscopic laser coagulation. Initially, all 254 infants (n = 104 females) surviving of 200 consecutive twin pregnancies were enrolled in the Twin-to-Twin Transfusion Syndrome study between 1995 and 1999 and were invited to take part in this long-term follow-up, with annual follow-up examinations until the age of 4 years, then at 10 years of age, during puberty, and post-pubertally. The exact details of this study are described in a previous paper dealing with a special subgroup of 30 pairs with longitudinal clinical follow-up to evaluate growth and pubertal development.[25]

For this study, 52 twin pairs were recruited for extended endocrine and metabolic long-term follow-up if they had at least one test of thyroid function during the last follow-up. All twin pairs were seen in Bonn at the endocrine clinic or visited by the same members of our staff all over Germany at birth, at a mean age of 10.1 years (n = 27 pairs; 15 discordant), 15.1 years (n = 35 pairs, 16 discordant), and 17.4 years (n = 36 pairs; 15 discordant). Eighteen pairs donated blood at all 3 of the aforementioned time points. A BW difference of <1 SDS was defined as concordant, a BW difference of ≥1 SDS was defined as discordant.[23,25] Mean gestational age at birth in the concordant group was 33.82 weeks (range, 27.71-38.0), in the discordant group 33.88 weeks (26.86-37.43). All twin pairs grew up in the same family environment.

The Institutional Ethics Committee of the University Hospital in Bonn approved the study. Informed consent was obtained from all parents and participants. Physical examinations were performed and data concerning general health were collected. All participants were measured with the same standardized stadiometer and automatic weighing machine. To determine whether catch-up growth occurred, data from the German preventive check-up examination (so-called U-exam) at 2 years of age were obtained from all twin pairs.

Collection of Samples

Fasting blood sampling was performed between 8 and 10 a.m. At 10.1 years, the blood sample volume obtained from one concordant twin allowed only analysis of TSH concentration but not other thyroid functions. At the age of 15.1 and 17.4 years, we excluded 2 discordant female twin pairs from the laboratory analysis of thyroid functions for manifest thyroid pathology and levothyroxine treatment in both twins but still included them for analysis of thyroid antibody concentrations (15.1 years, n = 37 pairs, 18 discordant and 17.4 years, n = 38 pairs, 17 discordant). In total, 21 twin pairs donated blood once, 13 donated blood twice, and 18 twin pairs participated in blood sampling at all 3 follow-ups (8 discordant pairs). The samples were centrifuged and stored at −20°C for further study.

Immunoassays

All hormone concentrations and thyroxine-binding globulin (TBG) were measured by chemiluminescent immunoassays using commercially available kits from Siemens Healthcare Diagnostics (Erlangen, Germany): Dimension Vista System Flex reagent cartridge TSH (analytical measurement range [AMR]: 0.005-100mIU/L); Dimension Vista System Flex reagent cartridge FT3 (AMR: 0.50-30.00 pg/mL [0.77-46.1 pmol/L]); Dimension Vista System Flex reagent cartridge fT4 (AMR: 0.1-8.0 ng/dL [1.3-103 pmol/L]); IMMULITE 2000 total triiodothyronine (T3; calibration range: 40-600 ng/dL [0.61-9.2 nmol/L]; IMMULITE 2000 Total T4 (calibration range: 1.0-24 μg/dL [13-309 nmol/L]); and IMMULITE 2000 TBG (reportable range: 3.5-80 μg/mL [65-1480 nmol/L]).

Thyroid antibodies were measured by chemiluminescent immunoassays using commercially available kits from Abbott (Chicago, Illinois): Abbott ARCHITECT Anti-TPO (calibration range: 0.16-1000 IU/mL, positive: >5.61 IU/mL) and B·R·A·H·M·S Thermo SCIENTIFIC: B·R·A·H·M·S anti-Tgn KRYPTOR (AMR: 10-850 U/mL, positive: >33 U/mL).

Statistical Analyses

Statistical analysis was performed by SPSS Statistics (version 24 and 25; IBM Corp, Armonk, New York) and SAS 9.4 (SAS Institute, Cary, North Carolina). SDS were calculated for height, weight, and body mass index (BMI), based on German reference values. Clinical data and hormone concentrations are reported as means and SD and medians and IQR. Delta values (Δs) indicate differences between the co-twins. To calculate Δ, eg, for BW difference, the data of the initially larger twin were always subtracted from the data of the initially smaller co-twin (Δ intra-twin). Before testing, each set of measurements was evaluated for normal distribution. If the assumption of normality did not hold, nonparametric testing was performed. For measurements on ratio scales (auxological data and hormone concentrations), a paired *t* test or the Wilcoxon signed-rank test was used to compare values within twin pairs. Spearman rho tests were carried out to calculate intra-twin correlations.

To further analyze determinants of difference in thyroid function, we performed mixed linear model analyses in all twin pairs using SAS. The concentrations of the smaller twins were analyzed and the concentrations of the larger twins and time were included as fixed factors for each analysis. We analyzed several other potentially contributing factors to the model: BMI-SDS of the smaller twin, sex, if the twin belonged to the concordant or discordant group, BW-SDS of the smaller twin, intra-twin BW-SDS difference, weeks of gestation at delivery, and appropriate catch-up growth of one SDS to his or her co-twin. Akaike information criterion (AIC) was used to measure model quality. A lower AIC signifies an improvement of model quality. All models were checked for potential relevance of second- and third-order interactions. When serum concentrations were below the

reportable range of the respective assay (thyroid antibodies), the lowest reportable value divided by 2 was used for statistical analysis.

Results

Height

At 2 years of age, 52% (13/25) of the former smaller twin had caught up less than 1 SDS in the discordant pairs. The former smaller twin in these discordant pairs remained smaller at all 3 examination times (10.1 years: −0.09 vs 0.39 SDS, $P = .001$; 15.1 years: 0.1 vs 0.61 SDS, $P = .001$; 17.4 years: −0.02 vs 0.45 SDS, $P < .001$).

BMI

In all twin pairs and at all time points, the smaller twins had a significantly lower BMI-SDS than their larger co-twins (10.1 years: −0.70 vs −0.17 SDS, $P = .002$; 15.1 years: −0.55 vs −0.15 SDS, $P < .001$; 17.4 years: −0.26 vs 0.14 SDS, $P < .001$). We observed the same results when analyzing the discordant pairs (10.1 years: −0.71 vs 0.04 SDS, $P = .001$; 15.1 years: −0.46 vs −0.16 SDS, $P = .048$; 17.4 years: −0.36 vs 0.08 SDS, $P = .003$).

Thyroid Function

Table I illustrates thyroid function in our cohort. We found no differences in thyroid function studies in concordant twin pairs at any time point but detected significant differences in discordant pairs at several time points (Table I). Whereas initially smaller twins exhibited greater mean TSH concentrations than their larger co-twins, at 17.4 years no significant TSH differences were found between the twins (Figure 1 and Figure 2; Figure 2 available at www.jpeds.com). In addition, significant differences in T4 concentrations were observed in the discordant twin pairs at 10.1 years and 17.4 years, and a tendency to differ significantly was found at 15.1 years, with the smaller twins exhibiting lower T4 mean concentrations than their larger co-twins at all time points (Figure 3 and Figure 4; Figure 4 available at www.jpeds.com). Calculation of the TSH-T4 ratio revealed significant differences, with a greater ratio in the smaller twins at 10.1 years and at 15.1 years. (Figure 5 and Figure 6; available at www.jpeds.com). Mean trends remained identical regarding discordant pairs who donated blood at all 3 points of examination (n = 8 twin pairs, Figures 7-9; available at www.jpeds.com).

TBG was measured at 10.1 and 15.1 years, and no significant differences were found in any twin pairs. Some twins showed isolated hyperthyrotropinemia, with TSH elevations >4 μU/mL but normal T4 levels. Eight subjects (1 twin pair and 1 former smaller twin from the concordant group, 2 twin pairs, and 1 former smaller twin form the discordant group) had an elevated TSH >4 μU/mL concentration at 10.1 years. At 15.1 years, yet another concordant twin pair and the aforementioned 2 female discordant twin pairs (n = 6) had TSH concentrations >4 μU/mL. At 17.4 years, no twin showed a TSH concentration >4 μU/mL.

Thyroid Autoantibodies

At 17.4 years, we measured thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) in all available blood samples. We found no significant intra-twin differences regarding thyroid autoantibodies in any of the twin pairs, whether concordant or discordant. Instead, in all twins, a highly significant intra-twin correlation was found for TPOAb (rho = 0.609, $P < .001$) and TgAb (rho = 0.735, $P < .001$). Two twin pairs (one from each group) were positive for TPOAb and concordant for thyroid antibody presence. Eight pairs—5 concordant, 3 discordant—were positive for TgAb. The 3 discordant pairs included one of the aforementioned female pairs with Hashimoto thyroiditis and levothyroxine treatment. All twins were always concordant for thyroid antibody presence.

Mixed Linear Model Analyses

To further analyze determinants of difference in thyroid function in our twin pairs, we performed mixed linear model analyses in all twin pairs (Table II). TSH, T4, and TSH-T4 ratio of the smaller twins were analyzed. The concentrations of the larger twins and time were included as fixed factors for each analysis. We analyzed several other potentially contributing factors to the model: BMI-SDS of the smaller twin, sex, if the twin belonged to the concordant or discordant group, BW-SDS of the smaller twin, intra-twin BW-SDS difference, weeks of gestation at delivery, and appropriate catch-up growth of one SDS to his or her co-twin. AIC was used to measure model quality. A lower AIC signifies an improvement of model-quality. All models were checked for potential relevance of second- and third-order interactions.

For all thyroid functions analyzed, neither BMI-SDS, BW-SDS of the smaller twin, nor gestational age at delivery improved the model. Regarding the sex of the twins, we cannot rule out minor influences on TSH and T4 concentrations, but the AIC decreased only minimally (Table II). For TSH concentrations, belonging to the concordant or discordant group and the intra-twin BW-SDS difference were the only other factors further improving the model apart from the TSH concentrations of the larger co-twins and time (Table II). Regarding T4 concentrations of the smaller twins, again, belonging to the concordant or discordant group and the intra-twin BW-SDS difference showed an improvement of the model, and catch-up growth as well (Table II). Regarding TSH-T4 ratios of the smaller twins, belonging to the concordant or discordant group and the intra-twin BW-SDS difference as well showed an improvement of the model, but only if interaction with the time factor was included (Table II).

Discussion

In this longitudinal study of genetically identical monozygotic twins, we found long-lasting differences in thyroid function between twins in association with differences in

Table I. Thyroid measures for all twin pairs

Thyroid measures		10.1 y, n = 27				15.1 y, n = 35				17.4 y, n = 36			
		Concordant n = 12	*P*	Discordant n = 15	*P*, Δ, (ΔSD)/ <ΔIQR>	Concordant n = 19	*P*	Discordant n = 16	*P*, Δ, (ΔSD)/ <ΔIQR>	Concordant n = 21	*P*, Δ, (ΔSD)/ <ΔIQR>	Discordant n = 15	*P*, Δ, (ΔSD)/ <ΔIQR>
TSH, μU/mL	ST	2.85 [0.86]	ns	3.62 [3.77]	**.041, Δ = 1.1 (3),**	2.22 [1.24]	ns	2.60 <1.92>	.083, Δ = 0.36 (1.1),	1.88 [0.80]	ns	1.96 [1.02]	ns
		2.68 <1.2>		2.51 <1.40>	**Δ = 0.17**	2.02 <1.58>		2.06 <1.39>	Δ = 0.33 <0.86>	1.72 <1.21>		1.71 <1.60>	
	LT	2.85 [1.02]		2.52 [1.07]	**<1.08>**	2.21 [1.09]		2.25 [1.33]		2.0 [0.70]		1.98 [0.85]	
		2.63 <1.18>		2.22 <1.49>		2.04 <1.52>		1.82 <1.71>		1.99 <0.99>		1.85 <1.39>	
fT3, pg/mL	ST									3.3 [0.45]	ns	3.38 [0.41]	ns
										3.34 <0.47>		3.33 <0.52>	
	LT									3.39 [0.29]		3.38 [0.53]	
										3.39 <0.24>		3.26 <0.5>	
fT4, ng/dL	ST					1.07 [0.16]	ns	1.05 [0.13]	ns	13.39 .17 [0.16]	ns	1.18 [0.09]	ns
						1.06 <0.24>		1.06 <0.26>		1.14 <0.27>		1.19 <0.14>	
	LT					1.06 [0.12]		1.08 [0.14]		1.18 [0.14]		1.20 [0.13]	
						1.04 <0.13>		1.08 <0.26>		1.18 <0.2>		1.21 <0.21>	
T3, ng/dL	ST	136.5 [18.22]	ns	148.47 [22.47]	ns	133.63 [24.62]	ns	136.69 [22.29]	ns	127.73 [27.49]	.092, Δ =	124.38 [33.2]	ns
		131.5 <28.25>		156 <32>		125 <25>		137 <29>		125 <38>	−6.22 (16.11),	116 <28.1>	
	LT	138.3 [16.12]		153.33 [21.82]		134.64 [21.82]		141.46 [25.99]		133.96 [28.85]	Δ = −1 <19>	127.39 [30.43]	
		143.5 <22.0>		154 <33>		129 <30>		138.5 <40.25>		129 <54>		115 <45>	
T4, μg/dL	ST	7.52 [1.14]	ns	7.77 [1.29]	**.050, Δ =**	7.44 [2.13]	ns	6.95 [1.40]	.085, Δ =	8.3 [1.79]	ns	7.71 [1.51]	**.028, Δ =**
		6.88 <1.97>		7.73 <2.11>	**−0.4 (0.73),**	7.18 <2.53>		6.88 <2.58>	−0.47 (1.03),	8.44 <2.98>		7.35 <1.67>	**−0.70 (1.15),**
	LT	7.81 [1.22]		8.17 [0.89]	**Δ = −0.38**	7.37 [1.66]		7.43 [1.59]	Δ = −0.47	8.39 [2.11]		8.43 [1.36]	**Δ = −0.9,**
		7.71 <1.34>		8.38 <1.42>	**<1.47>**	7.35 <1.53>		7.46 <1.81>	<1.25>	8.82 <3.1>		8.64 <1.74>	**<1.65>**
TSH/T4 ratio	ST	0.37 [0.12]	ns	0.5 [0.58]	**.006, Δ =**	0.33 [0.22]	ns	0.37 [0.23]	**.039, Δ =**	0.25 [0.14]	ns	0.26 [0.13]	ns
		0.37 <0.16>		0.37 <0.16>	**0.19 (0.47),**	0.26 <0.22>		0.31 <0.19>	**0.06 (0.13),**	0.22 <0.16>		0.23 <0.2>	
	LT	0.38 [0.16]		0.31 [0.14]	**Δ = 0.04**	0.33 [0.21]		0.31 [0.18]	**Δ = 0.08**	0.26 [0.13]		0.24 [0.11]	
		0.31 <0.19>		0.28 <0.19>	**<0.1>**	0.3 <0.23>		0.26 <0.28>	**<0.15>**	0.22 <0.17>		0.26 <0.15>	
TBG, μg/mL	ST	22.04 [3.78]	ns	20.88 [3.26]	ns	20.99 [7.17]	ns	19.39 [3.16]	ns				
		21.1 <4.9>		19.6 <3.5>		20.1 <6.05>		19.95 <4.75>					
	LT	21.45 [5.08]		21.45 [2.83]		21.65 [7.67]		20.66 [4.58]					
		20.4 <4.4>		21.4 <4>		19 <13.1>		19.85 <6.85>					
TPOAb, U/mL	ST									5.33 [23.18]	ns	13.28 [53.25]	ns
										0.25 <0.26>		0.34 <0.43>	
	LT									4.15 [17.93]		8.06 [30.54]	
										0.23 <0.20>		0.41 <0.48>	
TgAb, U/mL	ST									20.67 [19.09]	ns	39.94 [48.21]	ns
										16.54 <25.56>		15.24 <52.33>	
	LT									27.33 [36.31]		40.38 [53.68]	
										18.96 <30.91>		25.32 <38.23>	

fT3, free triiodothyronine; *ns*, not significant.

Data expressed as mean [SD], median <IQR>, *P*, Δ = difference ST − LT, (ΔSD = SD of difference ST–LT), Δ = median difference ST–LT, ΔIQR = IQR of difference ST–LT.

Values in bold represent statistically significant results.

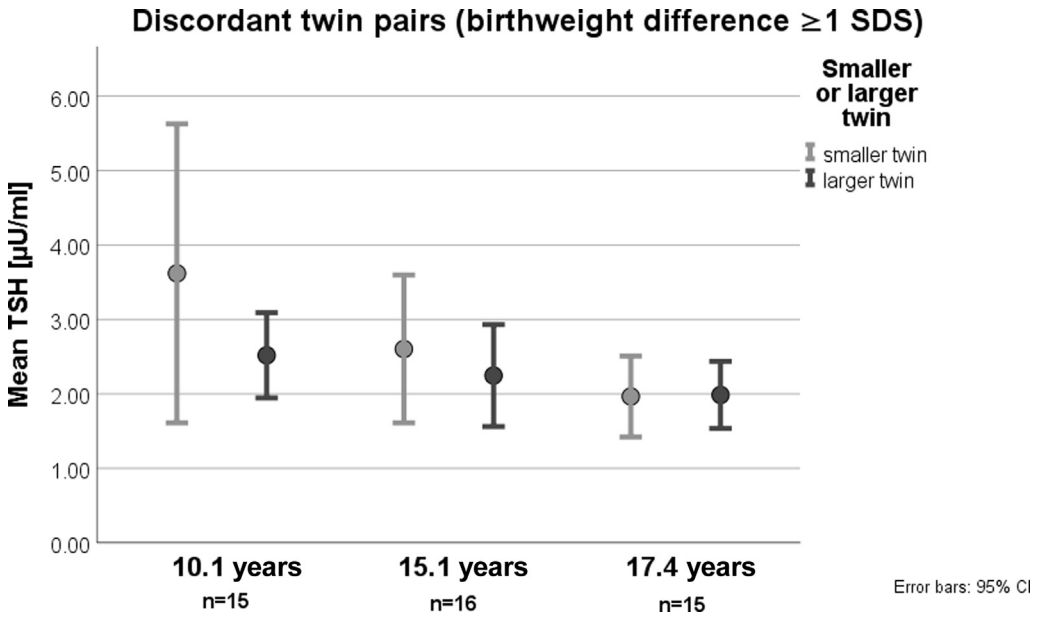

Figure 1. Mean TSH concentrations at 10.1, 15.1, and 17.4 years in discordant twin pairs. *Light gray lines and dots* represent the concentrations in the smaller twins, and *dark gray lines and dots* represent the larger twins. Error bars: 95% CI.

BW, permitting the conclusion that low BW may have a long-term impact on thyroid function in later life.

In the smaller twins of discordant monozygotic twins born with larger BW differences, we found significantly greater TSH levels than those of the larger co-twins during childhood and young adolescence. This accords with the findings of other authors.[13,14,16,17] In contrast, although we found no differences in free T3 or T3 concentrations in these smaller twins, they invariably exhibited lower T4 concentration and lack of TBG differences between twins, which persisted into late adolescence. These results match those of some other studies[11,12] reporting the same constellation of elevated TSH and low T4 concentrations in SGA newborns during the neonatal period.

Radetti et al reported a persisting low fT4 concentration in these smaller twins during childhood (7.9 ± 2.4 years).[15] We

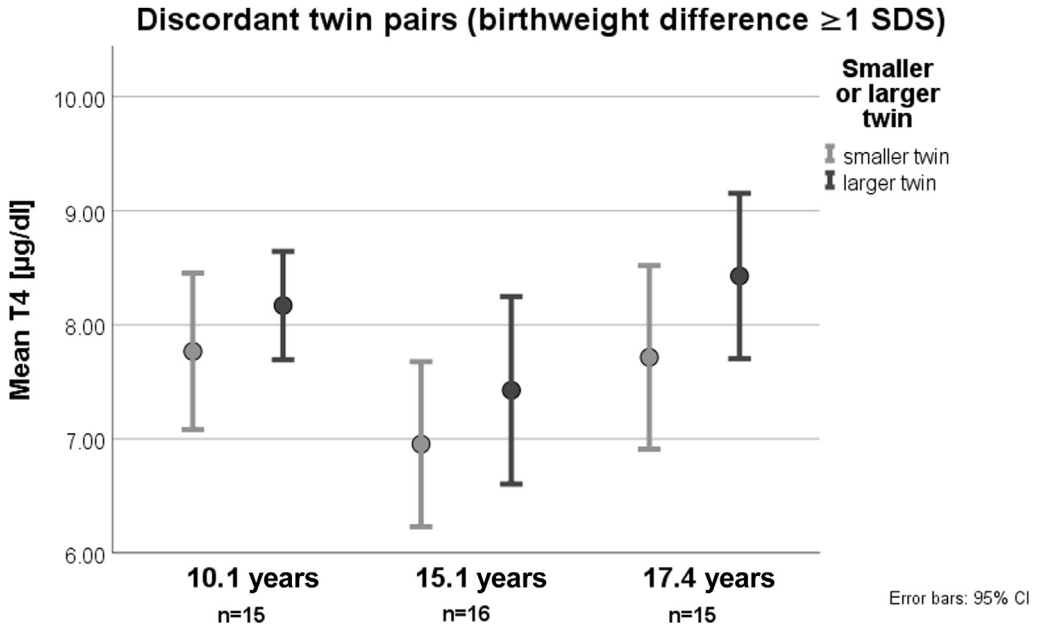

Figure 3. Mean T4 concentrations at 10.1, 15.1, and 17.4 years in discordant twin pairs. *Light gray lines and dots* represent the concentrations in the smaller twins, and *dark gray lines and dots* represent the larger twins. Error bars: 95% CI.

Table II. Mixed linear model for thyroid measures

Mixed linear model - AIC	TSH ST	T4 ST	TSH-T4 ratio ST
Concordant larger co-twin | time	**330.8**	**286.9**	**−26.0**
+ BMI SDS ST	332.9	289.6	−20.0
+ BMI SDS ST | conc. LT + BMI SDS ST | time	338.8	295.1	−10.4
Concordant LT | time | BMI SDS ST (full model)	342.5	299.2	−7.3
+ sex	**330.1**	**286.8**	−22.5
+ sex | conc. LT + sex | time	**329.1**	290.7	−20.3
Concordant LT | time | sex	**328.8**	293.4	−22.9
+ conc./discordant	**329.5**	**283.3**	−25.5
+ conc./discordant | conc. LT + conc./discordant | time	**324.9**	**286.7**	**−30.4**
Concordant LT | conc./discordant | time	**310.8**	289.5	**−56.5**
+ BW-SDS ST	332.3	289.0	−20.3
+ BW-SDS ST | conc. LT + BW SDS ST | time	337.6	295.5	−11.5
Concordant LT | BW-SDS ST | time	340.7	299.5	−8.7
+ ΔBW-SDS	331.5	**282.9**	−22.3
+ ΔBW-SDS | conc. LT + ΔBW SDS | time	**327.1**	287.2	−26.0
conc. LT | ΔBW-SDS | time	**308.2**	290.7	**−56.3**
+ gestational age	333.9	291.4	−18.5
+ gestational age | conc. LT + gestational age | time	338.6	302.4	−6.9
Conc. LT | gestational age | conc. LT | time	340.0	309.1	−4.2
+ catch-up	331.6	**275.8**	−23.5
+ catch-up | conc. LT, catch-up | time	334.5	**282.0**	−19.6
conc. LT | catch-up | time	331.2	**285.8**	**−28.6**

Conc., concordant.
Smaller AIC indicates an improvement of the model by adding another variable. Every new variable was analyzed for the additional co-factor, and possible interactions up to Three-way interaction. A |B stands for A, B, and the interaction between A and B. A |B |C includes all 2-way and the 3-way interaction.

were unable to confirm this, which might have been due to the older age of our study population. It is possible that cold storage affects measured serum concentrations of free thyroid hormones, possibly due to a deterioration in the stability of binding proteins[26] that may be reflected in our results for fT4.

Our calculation of the TSH-T4 ratio as a measure of TSH resistance showed significantly greater ratios in the discordant former smaller twins at 10.1 and 15.1 years, indicating the presence of mild TSH resistance at least into early adolescence. Fisher et al examined thyroid functions from 22 weeks of gestation to adulthood to further evaluate maturation of the hypothalamic−pituitary−thyroid axis. They speculated that maturation was manifested as a progressive decrease in the TSH-fT4 ratio with age, ie, with decreasing TSH and constant fT4 levels.[27] Similarly, our results suggest a delayed maturation of the hypothalamic−pituitary−thyroid axis in infants with former low BW resulting in greater TSH-resistance than that of their co-twins. In contrast, the slightly increased TSH also might be the expression of a reduced biological activity of TSH secondary to the intrauterine environment, which as well may improve over the time.

Regardless of mechanism, these differences seem to become smaller with age; we showed an assimilation over time. In mixed linear model analysis, for the TSH-T4 ratio of the smaller twins, we found that concordance and discordance or the intra-twin difference in BW-SDS showed an improvement of the model only when interaction with time was included. At all time points, however, the corresponding serum concentration of the co-twin was the main determinant in each model of mixed linear model analysis for TSH, T4, and the TSH-T4 ratio. This is in accordance with the results of other twin studies and underlines the importance of the individual genetic background for thyroid function.[28,29]

TSH serum concentrations might also be influenced by environmental conditions. However, all twin pairs lived in the in the same household with similar environmental conditions and nutritional customs. Other studies have described an association between greater BMI and greater TSH[30] or greater TSH and lower fT4 concentrations.[31] In our study, conversely, the former smaller twins always presented with a significantly lower BMI-SDS at all examination times, and the BMI-SDS showed no influence in any model of mixed linear model analysis.

Some authors have reported an influence of gestational age on TSH concentrations in former SGA children[15] or have found differences in thyroid function only in former SGA children born preterm.[16] Because our twins have the same intra-twin gestational age, this cannot explain intra-twin differences in thyroid function. Furthermore, gestational age showed no influence on the smaller twins' thyroid functions in mixed linear model analysis—a result also reported by other authors.[14]

A greater presence of thyroid antibodies in children with former low BW has been frequently reported as an explanation for differences in thyroid function.[32-34] However, we found no significant differences for any of the thyroid antibodies. In contrast, we found a highly significant intra-twin correlation, underlining again a major role of the genetic background, which is in agreement with the results of Brix et al.[35,36]

The only remaining difference between our twins was the pronounced BW difference in the discordant group. Being concordant or discordant and the intra-twin BW difference were the only factors improving the model quality of all thyroid functions analyzed in mixed linear model analysis. Over and above this, our mixed linear model analysis of T4 appeared to indicate that early catch-up growth also has an association with thyroid function. These results are consistent with those of Cianfarani et al, who reported greater TSH concentrations only in children formerly SGA who did not experience catch-up growth, suggesting that thyroid function may affect postnatal growth.[17]

The role of low normal thyroid function is still under discussion, with conflicting results. Considering the fact that fetal programming, besides maximizing the chance of in utero survival,[1] has been interpreted as a useful tool for preparing the fetus for postnatal life,[2] it would be reasonable to have a lower metabolic rate and less energy consumption later in life, if a limited supply of nutrition is expected.

One limitation of our study is its relatively small sample size, as not all 52 twin pairs participated in all 3 follow-ups. However, longitudinal data that were obtained in the subgroup that participated at all 3 time points were congruent with the mean trend of all twins and mixed linear model analyses are relatively resistant when dealing with missing values.

Another possible limitation of this study is that we carried out biochemical analyses with frozen serum samples after they had been stored at −20° C for several years, thus raising the possibility of degradation of some proteins or affectation of measured biological agents.

A major strength of this study, in contrast, is that it was carried out with monozygotic twins who shared identical genetic backgrounds and were raised in the same family environment. The only individual difference regarding these pairs was their fetal environment, with a discordant nutrient exposure, which led to significant intra-twin BW differences that were more pronounced in the discordant group. These monozygotic twin pairs thus provided an excellent model for examining the impact of genes and environment[22-24] without the confounding variables which most singleton studies—even with matched controls—cannot rule out.

In this special group of monozygotic twins, our study showed that BW differences were associated with twin-co-twin differences in thyroid function until adolescence. The fact that TSH concentrations were significantly greater, T4 concentrations lower, and TSH-T4 ratios were greater in the smaller twins of pairs with a greater BW difference indicates the possibility of a delayed maturation of the hypothalamic−pituitary axis and TSH resistance during childhood and early adolescence in former low-BW children and a persisting low T4 in later life. ■

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50 Years Ago in *The Journal of Pediatrics*

Sonar as a Method for Studying Prenatal Development

Donald I. J Pediatr 1969;75:326-33.

Ten years after presenting pulsed sonar technology as a means to evaluate abdominal masses,[1] Ian Donald, a Scottish obstetrician, described the use of ultrasound in monitoring pregnancy progression and fetal growth. Starting with a characteristic ring in early pregnancy and noting the reliable and reproducible measures of biparietal diameter in the second half of pregnancy, Donald's 1969 report was an indicator of the growth potential of ultrasound technology in fetal medicine and a major advance in obstetric history.

Now, fetal ultrasound is part of routine prenatal care and has become robust enough in imaging resolution that standard ultrasound captures, at minimum, multiple measures of fetal growth, evaluation of fetal position, movement, respiration, heart rate, assessment of amniotic fluid volume, placental positioning, and assessment of more than 20 fetal anatomic structures.[2] Further uses, such as Doppler technology, fetal echocardiogram, and 3-dimensional ultrasonography support diagnosis and evaluation of further care management needs.[3]

With advancement of medical technology, ultrasound also serves as a screening tool for additional methods of assessment. Recent studies suggest that evaluation of suspected fetal intracranial anomalies with in-utero magnetic resonance imaging, for example, can facilitate better prognostication and alter management decisions.[4] And although fetal echocardiogram has improved the prenatal diagnosis of congenital cardiac defects, fetal magnetic resonance imaging is being discussed as an adjunctive imaging modality to offer management guidance.[5]

Despite technological evolution, 50 years later, ultrasound technology remains an important mainstay in the evaluation of maternal and fetal health and has even made its way into popular culture as the well-known printed black and white fetal images that parents take home. These advances in imaging are built upon Dr Donald's early work measuring fetal growth.

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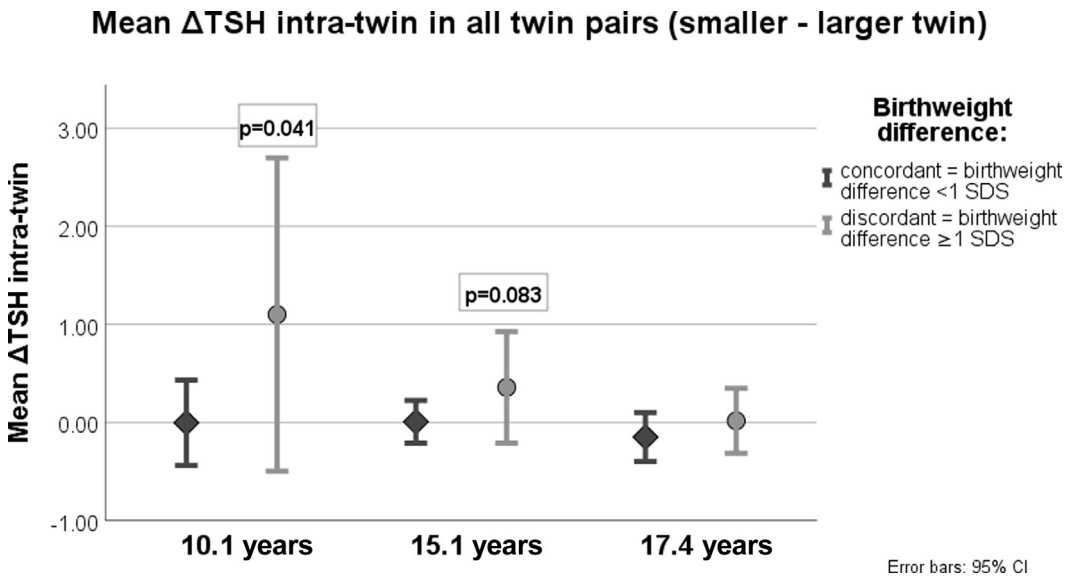

Figure 2. Mean TSH differences between the co-twins in the concordant and discordant group at 10.1, 15.1, and 17.4 years (smaller twin–larger twin = Δ intra-twin). *Light gray lines and dots* represent the mean intra-twin difference in the discordant group, and *dark gray lines and rhombus* represent the mean intra-twin difference in the concordant group. Error bars: 95% CI.

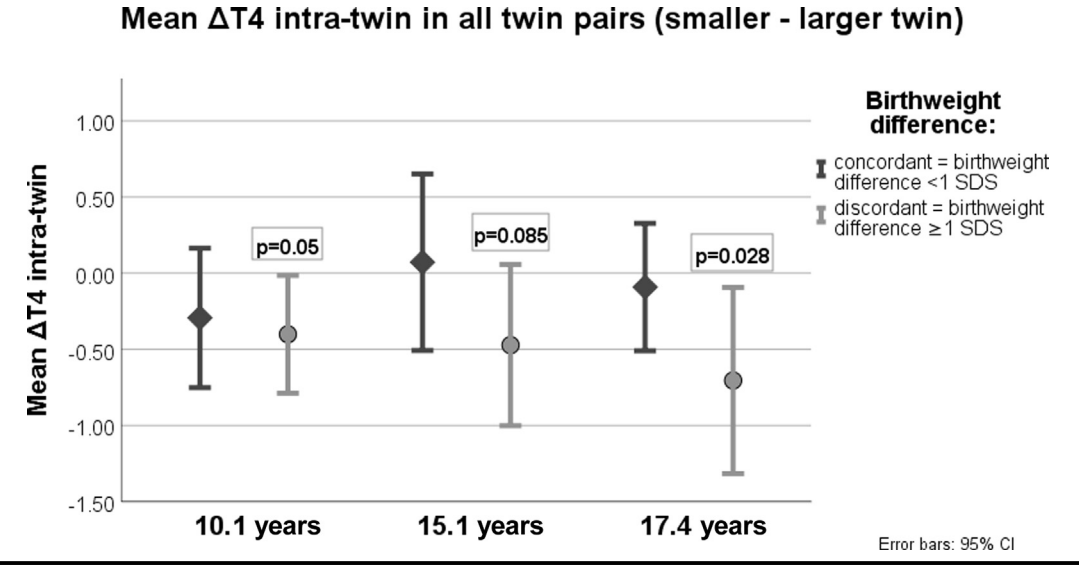

Figure 4. Mean T4 differences between the co-twins in the concordant and discordant group at 10.1, 15.1, and 17.4 years (smaller twin–larger twin = Δ intra-twin). *Light gray lines and dots* represent the mean intra-twin difference in the discordant group, and *dark gray lines and rhombus* represent the mean intra-twin difference in the concordant group. Error bars: 95% CI.

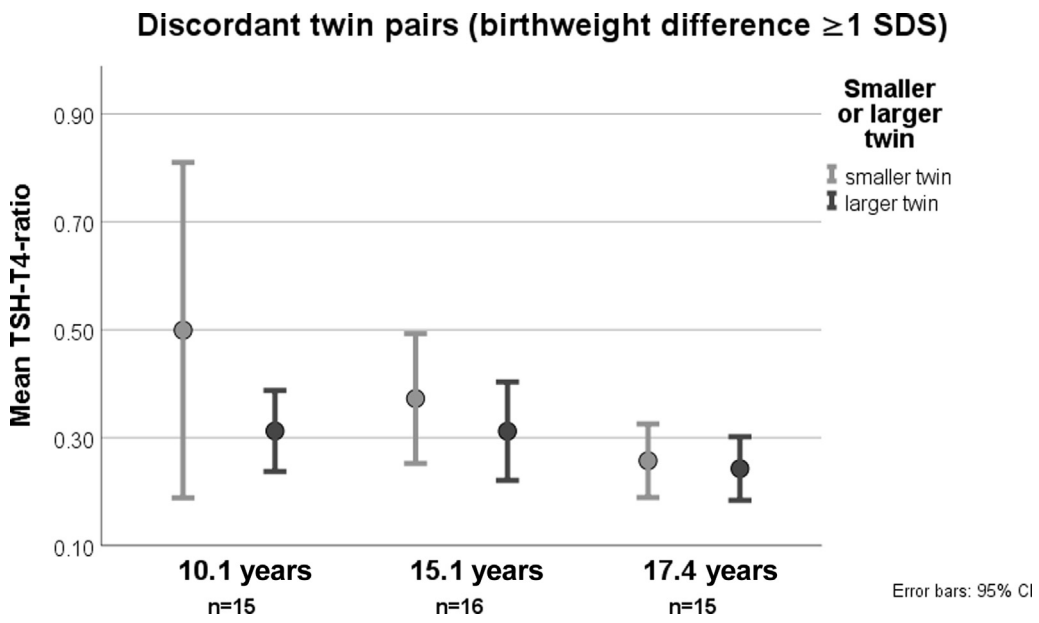

Figure 5. Mean TSH-T4 ratio at 10.1, 15.1, and 17.4 years in discordant twin pairs. *Light gray lines and dots* represent the concentrations in the smaller twins, and *dark gray lines and dots* represent the larger twins. Error bars: 95% CI.

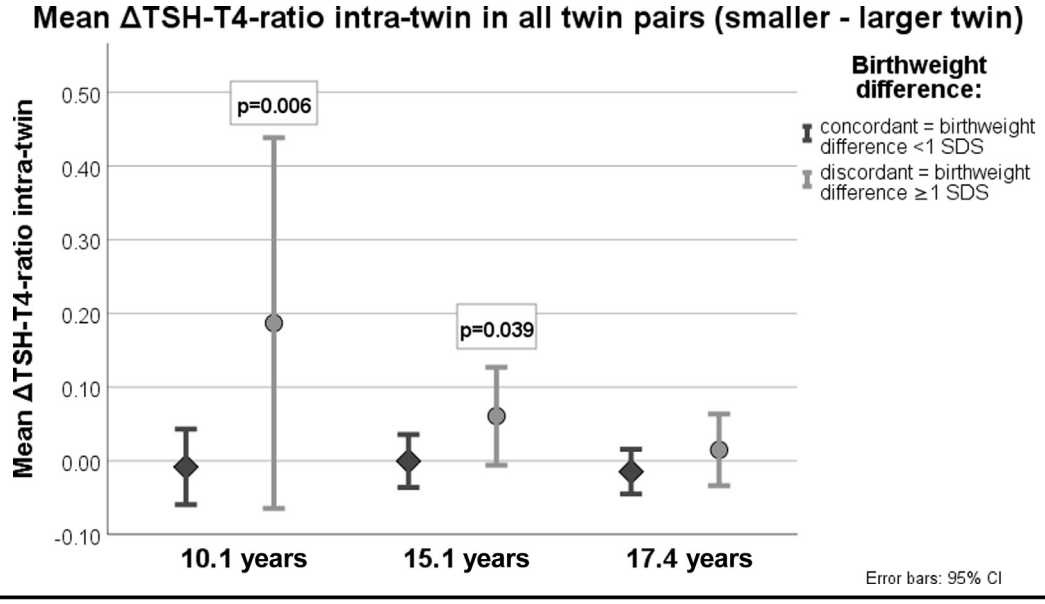

Figure 6. Mean differences in TSH-T4 ratios between the co-twins in the concordant and discordant group at 10.1, 15.1, and 17.4 years (smaller twin–larger twin = Δ intra-twin). *Light gray lines and dots* represent the mean intra-twin difference in the discordant group, and *dark gray lines and rhombus* represent the mean intra-twin difference in the concordant group. Error bars: 95% CI.

Figure 7. Mean TSH concentrations at 10.1, 15.1, and 17.4 years in longitudinal discordant twin pairs who donated blood at all time points. *Light gray lines and dots* represent the concentrations in the smaller twins, and *dark gray lines and dots* represent the larger twins. Error bars: 95% CI.

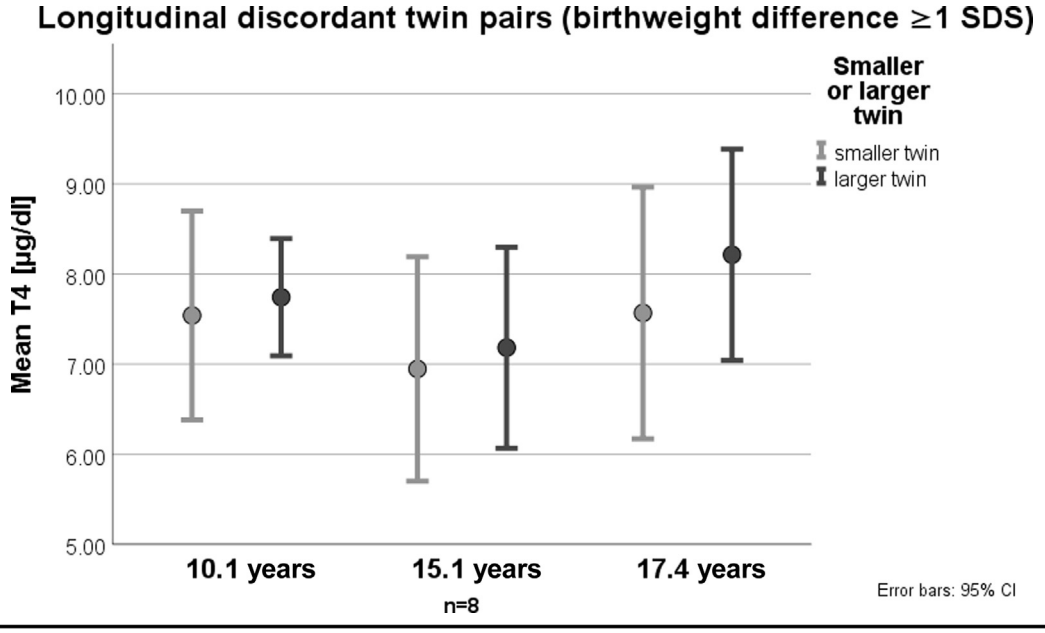

Figure 8. Mean T4 concentrations at 10.1, 15.1, and 17.4 years in longitudinal discordant twin pairs who donated blood at all time points. *Light gray lines and dots* represent the concentrations in the smaller twins, and *dark gray lines and dots* represent the larger twins. Error bars: 95% CI.

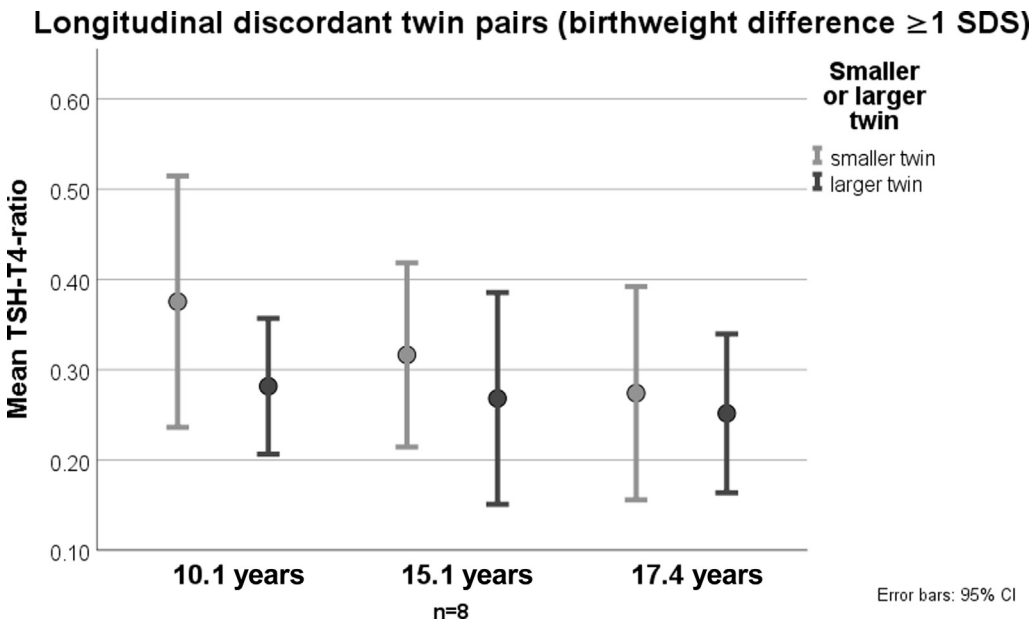

Figure 9. Mean TSH-T4 ratio at 10.1, 15.1, and 17.4 years in longitudinal discordant twin pairs who donated blood at all time points. *Light gray lines and dots* represent the concentrations in the smaller twins, and *dark gray lines and dots* represent the larger twins. Error bars: 95% CI.