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## Prenatal and Neonatal Thyroid Stimulating Hormone Levels and Autism Spectrum Disorders

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### Abstract

Thyroid hormones are critical for normal brain development. This study examined autism spectrum disorders (ASD) and thyroid stimulating hormone (TSH) levels measured in mid-pregnancy maternal serum and infant blood after birth. Three groups of children born in Orange County, CA in 2000–2001 were identified: ASD (n = 78), developmental delay (n = 45), and general population controls (GP) (n = 149). Samples were retrieved from prenatal and newborn screening specimen archives. Adjusted logistic regression models showed inverse associations between ASD and log transformed TSH levels in maternal serum samples (ASD vs. GP: OR [95 %

CI] 0.33 [0.12–0.91], Early Onset ASD vs. GP: 0.31 [0.10–0.98]). Results for thyroid levels in newborn blood samples were similar though not significant (ASD vs. GP:0.61 [0.18–2.04]).

## Keywords

Thyroid; Thyroid stimulating hormone; Autism; Pregnancy; Developmental delay

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## Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders that include autism, Asperger syndrome, and pervasive developmental disorder, not otherwise specified (PDD-NOS). Individuals with ASD may demonstrate impairments in social interaction and communication, and restricted, stereotyped interests and behaviors (American Psychiatric Association 2000; Lord et al. 2000). The currently estimated prevalence of ASD in the United States is 1 in 68 (CDC 2014). The etiology of ASD is not well understood, but based on family and twin studies, there is a clear genetic contribution (Szatmari et al. 1998; Nordenbæk et al. 2013; Posthuma and Polderman 2013). However, several other studies have strongly suggested that environmental factors are also likely involved in ASD etiology (Lawler et al. 2004). In a twin study conducted by Hallmayer et al. 2011, lack of complete ASD concordance among monozygotic twins and higher than expected ASD concordance among dizygotic twins indicated a significant contribution from a shared environment to ASD etiology. Additionally, a growing body of evidence linking ASD and non-genetic factors such as prenatal maternal antidepressant use (Croen et al. 2011), infections (Atladóttir et al. 2010; Zerbo et al. 2013), proximity to air pollution (Volk et al. 2013) and low periconceptional folic acid intake (Surén et al. 2013) has emerged as well. Research has shown that prenatal and early-life are the critical windows of vulnerability to neurodevelopmental disruption (Beverdors et al. 2005; Rodier 2004).

Thyroid hormones are critical for normal human brain development (Morreale de Escobar et al. 2004). During the prenatal period, the fetus is solely dependent on maternal thyroid hormones until gestational week 12–14, and then partially dependent until birth. Animal studies have shown that thyroid hormones are involved in the formation of the hippocampus, and cytoarchitecture of the somatosensory cortex (Lavado-Autric et al. 2003), and that deficiency of thyroid hormone during certain periods of brain development can lead to brain defects (Bernal et al. 2003). The mechanism by which thyroid hormones may influence brain development is thought to be by influencing cell migration, cortical layer development, and cell differentiation. Differentiation of oligodendrocytes, astrocytes, and microglia have all been linked to thyroid hormone levels, and indirectly, thyroid hormones influence myelination and gene expression (Bernal et al. 2003). Maternal thyroid dysfunction in pregnant women has been linked to neurological deficits in offspring (Williams 2008; Morreale de Escobar et al. 2004; Haddow et al. 1999).

The importance of thyroid hormones for normal brain development has resulted in almost universal newborn screening for hypothyroidism. Thyroid stimulating hormone (TSH) is one measure used as an indicator of thyroid function. TSH and thyroid hormone levels (T3,

known as triiodothyronine, and T4, known as thyroxine) are linked via a negative regulatory feedback loop. Increased production of TSH is often triggered by low thyroid hormone levels. According to the National Academy of Clinical Biochemistry (NACB), TSH levels steadily decrease from infancy to adulthood, with a normal range at birth between 1.3 and 19 IU/mL and at adulthood between 0.4 and 2.5 IU/mL (Baloch et al. 2003; Baskin et al. 2002).

A limited number of studies have examined the potential association between thyroid function and ASD. One study found that family history of autoimmune thyroid disease was associated with ASD with developmental regression (Molloy et al. 2006) while another study showed no differences between thyroid hormone levels measured in children already diagnosed with autism compared with typically developing controls (Cohen et al. 1980). In an animal model of neonatal hypothyroidism, changes in brain were suggestive of the neuropathology seen in individuals with autism (Sadamatsu et al. 2006). Only two studies have examined thyroid concentrations at birth in relation to ASD status; one found that very low T4 levels (3rd percentile) in children was associated with higher ASD risk (Hoshiko et al. 2011), while the other found no association between neonatal T4 levels and ASD or any other neurological condition (Soldin et al. 2003). In the Generation R study of pregnancy, severe early gestation maternal hypothyroxinemia was associated with autistic symptoms at age 6 (Román et al. 2013).

To take advantage of an existing newborn screening database and prenatal screening specimen archive, we conducted a case–control study to investigate the potential association between the risk of autism spectrum disorders and TSH levels measured in maternal serum from mid- pregnancy and in newborn blood spots. We hypothesized that high TSH levels would be associated with increased risk of ASD.

## Methods

### Subjects

Study participants were from the Early Markers for Autism (EMA) study, a population-based, nested case–control study described in detail elsewhere (Croen et al. 2008a, b). EMA utilizes archived maternal mid-pregnancy and neonatal blood specimens from the same mother-baby pairs to examine early biomarkers and their relationship with autism spectrum disorders. Women were eligible for EMA if they participated in the prenatal expanded alpha-fetoprotein screening program (XAFP) in Orange County, California, and delivered a live born infant from July 2000 to September 2001. Three groups of children born to women in the cohort were identified: children with ASD, children with developmental delay or intellectual disability (DD), and general population controls (GP). Children with ASD or DD were recruited from one of the 21 Regional Centers (RC) contracted by the California Department of Developmental Services (DDS), a statewide service delivery system that coordinates the diagnosis and provision of services for individuals with developmental disabilities. Eligibility is determined on the basis of diagnostic parameters without financial or citizenship stipulations. GP controls were randomly sampled from the birth certificate files at a 2:1 ratio after excluding all past or current DDS/RC clients. Controls were frequency matched to ASD cases by gender, birth month, and birth year. At the time of case

and control selection, children were between 3 and 4 years old. The institutional review boards of the California Department of Public Health and Kaiser Permanente Northern California approved the study protocol and methods.

### Diagnostic Verification

Following a protocol developed by the Metropolitan Atlanta Developmental Disabilities Surveillance Program (Yeargin-Allsopp et al. 2003), expert medical record abstractors reviewed and collected detailed diagnostic and clinical data from RC records for all children receiving services for ASD or DD. Following expert clinical review of abstracted data, children with ASD were categorized based on disease onset type and cognitive status using DSM-IV criteria. Early Onset ASD, ASD with regression, or unknown onset type was determined using information from parental report or clinical observations recorded in the RC medical record. “Early onset ASD” was defined by no statement of loss of social and/or language skills, or early and sustained delays or plateauing of skills without actual loss. “ASD with Regression” was defined as clear loss of previously acquired language and/or social skills. Determination of cognitive status was based on composite scores from standardized cognitive and functional tests (DD defined as Mullen Scales of Early Learning and Vineland Adaptive Behavior Scales composite score  $\leq 70$ ; no DD defined as all scores  $\geq 70$  or some scores  $\leq 70$  and others  $\geq 70$ ; unknown: no standardized scores in chart). The final analytic sample consisted of 78 children with ASD, 45 children with DD, and 149 GP controls (Table 1).

### Specimen Collection

Maternal mid-pregnancy and neonatal blood specimens were retrieved from the California Department of Public Health’s prenatal and newborn screening specimen archives. The neonatal specimen archive contains dried bloodspots on nearly every infant, approximately 500,000 per year, born in California since 1980. All newborn blood specimens taken from children were obtained by the heel-stick method usually within 24–48 h of birth. The blood specimens were collected on special S&S filter paper and allowed to dry at room temperature prior to transport to the regional laboratory for routine screening. Blood spots remaining after routine testing were catalogued and stored at  $-20^{\circ}\text{C}$ .

Also included in the archive are approximately 200,000 maternal serum and blood cell pellet specimens collected for routine prenatal Expanded Alpha-fetoprotein (XAFP) screening at 15–19 weeks gestation. The samples were collected from pregnant women living in three Southern California counties in 2000–2001. Specimens were stored by obstetrical care service providers in serum separator tubes which underwent XAFP testing within 7 days of collection at a central laboratory (median time = 3 days). Leftover specimens were stored at  $-20^{\circ}\text{C}$  after 1–2 days under refrigeration. Consent forms for the XAFP Screening program were distributed at the time of the blood collection which stipulated that specimens and results from prenatal testing could be used for legitimate research purposes given appropriate IRB approval.

## Measuring TSH

As part of the state's Neonatal Screening Program, California Department of Health Services Genetic Diseases Branch routinely tests newborn blood for TSH levels. Blood spots are analyzed with a solid-phase, time-resolved sandwich fluoroimmunoassay dissociation enhanced lanthanide fluoroimmunoassay (DELFLIA) (AutoDELFLIA; PerkinElmer, Wellesley, MA) using a lanthanide metal europium (Eu) label. Maternal serum samples from this study were measured using an I-labeled immunoradio-metric assay (IRMA).

## Statistical Methods

Demographic differences between the ASD, DD, and GP groups were tabulated and t tests (for means) as well as Chi squared tests (for frequencies) were calculated. Correlation of TSH levels in maternal and newborn blood was tested using Pearson correlation coefficients. The distributions of TSH levels in maternal mid-pregnancy serum and newborn blood spots in the ASD group were compared to the distributions in the GP and DD groups using two-sample t-tests and  $\log_{10}$ -transformed TSH concentrations. Additional comparisons were made for the DD versus the GP group. No samples in this study were below the limit of detection, so no imputations methods were necessary.

To examine the association of TSH levels in maternal mid-pregnancy and newborn blood with child outcome after adjustment for possible confounders, we fit separate conditional and unconditional logistic regression models. Conditional logistic regression models were used to analyze matched data (matched on child sex, birth month, and birth year) for ASD versus GP analyses. Unconditional logistic regression models were used to compare ASD to DD populations as well as DD to GP populations. TSH levels were  $\log_{10}$  transformed in order to normalize the skewed values, and case versus control status was regressed on transformed TSH levels with adjustment for several factors either associated with autism in previous epidemiologic studies or related to the maternal and neonatal blood draw. Maternal and neonatal models were fit adjusting for mother's age, mother's race (white, Asian, other), Hispanic (yes/no), mother's place of birth (US, Mexico, Other), and mother's weight at blood draw. Maternal models were additionally adjusted for gestational age at maternal blood draw, while neonatal models were adjusted for gestational age at birth and baby's age at blood draw. Maternal weight and gestational age at time of mid-pregnancy blood draw were used because they were related to the maternal blood draw, while maternal age, race/ethnicity, and country of origin have been associated with autism in previous epidemiologic studies (Croen et al. 2002; Magnusson et al. 2012).

An additional set of adjusted logistic regression models were fit comparing the log odds of ASD for individuals with TSH levels in various quartiles. First, quartile cutoff points were based on the distribution of TSH in the control population. These cutoff points were then used to categorize individuals in the ASD group into various quartiles. Logistic regression analyses were then run comparing odds of ASD for individuals with TSH levels in the second, third, or fourth quartile compared to the first quartile representing the lowest levels.

Complete ascertainment of thyroid levels in neonatal blood samples was achieved, while 12.3 % of maternal samples (24 GP mothers, 6 ASD mothers) were missing thyroid values.

## Results

The characteristics of the study population are shown in Table 1. Mothers of children with ASD were less likely to be Hispanic or to be born in Mexico compared to GP or DD mothers. Mothers of children with ASD were older than GP and DD mothers (Table 1). The distribution of maternal race was similar across the three groups.

Arithmetic mean concentrations and 95 % confidence intervals for TSH in maternal and neonatal samples are presented in Table 2. The majority of mothers had second trimester TSH levels within the normal range of 0.4 and 2.5 International Micro Units per Milliliter (IU/mL) (Baloch et al. 2003). As expected, neonatal TSH concentrations were much higher than concentrations in maternal serum samples, and the majority fell within the normal range of 1.3 and 19 IU/mL (Baskin et al. 2002).

In both maternal and neonatal specimens, TSH levels were lower in the ASD group compared to GP controls, though differences were not significant (Maternal ASD vs. GP means: 1.69 vs. 1.99, *p* value 0.18, Neonatal ASD vs. GP means: 6.44 vs. 6.71, *p* value 0.65) (Table 2; Fig. 1). Neonatal TSH concentrations were significantly lower in the DD group compared to the ASD and GP groups.

The correlation of TSH levels between maternal prenatal and newborn specimens was significant, though weak, in the GP population (correlation coefficient 0.21, *p* value = 0.02), and were non-significant in the ASD and DD populations (Table 3).

After adjustment for covariates, maternal mid-pregnancy TSH levels were inversely associated with ASD risk in the child (ASD vs. GP: AOR = 0.33 [0.12–0.91]), and for Early Onset ASD (Early Onset ASD vs. GP: AOR = 0.31 [0.10–0.98], Table 4). Comparing the DD to the GP population, mothers of children with DD had significantly lower TSH during pregnancy (DD vs. GP: AOR = 0.09 [0.02–0.42]). A similar pattern was seen for neonatal TSH levels, although associations were not statistically significant (Table 4). As a sensitivity analysis, neonatal regression models were run excluding gestational age at birth, and resulting AOR's were all similar in direction and magnitude (data not shown). Another sensitivity analysis excluding individuals in small strata (other race/ethnicity, Mexico/Other maternal country of birth) yielded similar results (Appendix Table 7). Additional analyses were conducted for quartiles of TSH levels (Table 5). In maternal samples, TSH levels in the second, third, and fourth quartiles were associated with reduced risk for both ASD and Early Onset ASD in children, though only the third quartile demonstrated statistical significance. TSH levels in the fourth quartile were associated with a significantly reduced risk for DD compared to GP. In neonatal samples, no significant associations were seen for quartiles of TSH comparing ASD children to GP children. While neonatal TSH levels in the second, third, and fourth quartiles were associated with AOR's below 1.0 for DD versus GP, confidence intervals were wide and the reduced risk of DD achieved borderline significance only among children with exposure levels in the third quartile (Table 5). One final analysis fitting an interaction term between gestational age at blood draw and maternal TSH models yielded no significant results (*p* value for ASD vs. GP model = 0.95), and similar results

were seen for the interaction term between gestational age at birth and neonatal TSH models (p value for ASD vs. GP model = 0.68).

## Discussion

In this population-based, nested case-control study with banked biospecimens from the mother during pregnancy and the child shortly after birth, higher TSH levels in mid-pregnancy maternal serum were associated with decreased odds of a child being diagnosed with an ASD. This association was statistically significant for the overall ASD population, the subpopulation of children diagnosed with Early Onset ASD, and the children diagnosed with DD, after adjustment for confounders. Additionally, odds of a child having DD were significantly decreased when maternal TSH levels were elevated compared to control children. While unadjusted results were not statistically significant, they were similar in magnitude to the adjusted results. While quartile analyses did not yield any significant results, the odds ratios comparing second, third, and fourth quartiles of maternal TSH concentrations to the lowest quartile in ASD versus GP populations were all below the null hypothesis of OR = 1, and thus suggest that particularly low maternal TSH levels during pregnancy may be associated with future diagnosis of ASD in the child. In our population, 4.8 % of mothers and 5.5 % of children were below the recommended normal TSH range (Baloch et al. 2003; Baskin et al. 2002).

A limited number of studies have examined thyroid hormone levels in relation to ASD or DD, but to our knowledge, this is the first study to examine TSH levels during pregnancy and the newborn period. One recent study found a strong relationship between maternal hypothyroxinemia with normal TSH levels during gestational weeks 6–18 and having a child with probable autistic symptoms 6 years later (as defined by the Pervasive Developmental Problems subscale of the Child Behavior Checklist and/or the Social Responsiveness Scale) (OR 3.89, 95 % CI [1.83–8.20]) (Román et al. 2013). Another study found that infants with very low thyroxine (T4) (<3rd percentile) at birth had higher risk of being diagnosed with ASD, although findings were not statistically significant for the entire study population (Hoshiko et al. 2011). One animal study found that some of the developmental delays associated with prenatal alcohol exposure were prevented with thyroid hormone replacement therapy, suggesting that perinatal hypothyroidism could contribute to developmental delays (Gottesfeld and Silverman 1990). This is consistent with human studies which found that women who had hypothyroxinemia during pregnancy had children with delayed mental and motor function when compared to controls (Pop et al. 2003), while another study found that maternal hypothyroxinemia during pregnancy led to higher risk of expressive language delay and non-verbal cognitive delay in the child (Henrichs et al. 2010). A large Danish cohort study reported a significant association between maternal hypothyroidism diagnosed after the birth of the child and increased risk of ASD (Andersen et al. 2014). Combined, these results suggest that low thyroid hormone levels in the perinatal period and/or dysfunctional thyroid hormone regulation could be associated with increased risk of ASD and DD. Because TSH and T3/T4 are linked in a negative feedback loop, thyroid function in a normal individual would typically trigger increased TSH when thyroid hormone levels were low, and vice versa. However, the findings from this study indicate that lower maternal TSH levels are associated with increased risk of ASD in the child. We could not determine if the

lower TSH levels were a response to high T3/T4 levels or if TSH levels were chronically low due to a dysfunctional feedback loop.

Results from several studies seem to support dysfunctional thyroid hormone regulation as a risk factor associated with ASD in the child. Familial history of autoimmune thyroid disease has been associated with pervasive developmental disorders including ASD (Sweeten et al. 2003) as well as ASD with regression (Molloy et al. 2006). In our study, TSH levels were not associated with regressive ASD, although the sample size for regressive ASD was very small and effect estimates were imprecise. Two other studies examined TSH levels in children already diagnosed with ASD and found either no difference between children with ASD and controls (Cohen et al. 1980) or that children with ASD have lower levels of TSH (Hashimoto et al. 1991).

The findings of low mid-pregnancy maternal TSH as well as a pattern of lower neonatal TSH being associated with increased risk for ASDs and DD's in the child is plausible given that thyroid hormones are essential for normal fetal brain development. The fetus is completely dependent on maternal thyroid hormone in early- and midgestation (De Escobar et al. 2004), and late fetal brain development requires normal fetal thyroid production.

Another potential mechanism linking risk of ASD and DD to perinatal TSH levels is through placental abnormalities. Placental abnormalities have been associated with neurological diseases (Scher 2001), including ASDs (Walker et al. 2013). Additionally, placental abnormalities directly influence levels of placental chorionic gonadotropin (Cole 2009; Pillitteri and Pillitteri 2010) which have the capacity to modulate maternal TSH levels (Hershman 2008). Placental chorionic gonadotropin also plays a pivotal role in supporting the fetal adrenal zone (Serón-Ferré et al. 1978) which may play a key role in the normal maturation and development of the fetus (Ishimoto and Jaffe 2011).

Our study has several unique strengths. First, TSH concentrations were assessed during mid-pregnancy in the mother and at birth in the child, two biologically relevant time periods during which neurodevelopment occurs. Second, TSH levels were obtained for mother-child pairs, allowing an examination of maternal versus child effects of TSH levels on ASD and DD risk. Third, analyses were adjusted for a broad set of covariates, thus reducing the likelihood of biased risk estimates due to confounding.

However, several study limitations are worthy of mention. First, we did not directly measure free T4 or T3 thyroid hormone levels, and were thus unable to determine if reduced TSH was a consequence of elevated T4/T3 or related to a dysfunctional TSH-thyroid hormone negative feedback loop. Second, we did not have information on the presence of thyroid conditions during pregnancy, nor on treatment for those conditions. Third, TSH in the mother was measured at only one time point during pregnancy. If the critical effects of TSH on child development occur before or after the second trimester measurement, then a mid-pregnancy measurement may not completely capture the relationship between TSH and ASDs. Fourth, ASD, DD, and control designations were not based on a standardized clinical assessment, but relied on information recorded in service agency records. The use of a standard protocol for expert review of RC records likely minimized misclassification of final



ASD and DD status. Some children selected as controls at 3–4 years of age may have been diagnosed at a later age with ASD. This potential misclassification of control status could affect 1–2 children at most, assuming a background ASD prevalence of \*1 %.

Any such misclassification of case or control status should be non-differential with respect to TSH levels, and therefore potentially bias our risk estimates toward the null value. Finally, the limited sample size resulted in imprecise estimates of risk for ASD and its subtypes in relation to TSH levels in the mother and the child.

In conclusion, risk of ASD and DD were associated with reduced levels of maternal TSH measured during mid-pregnancy. Given that some causes of thyroid dys-function such as thyroid autoimmunity and thyroid tumors can be regulated during pregnancy, these findings provide additional motivation to treat thyroid disorders (Groot et al. 2012). Future studies including larger sample sizes, direct measurement of TSH and other thyroid hormone levels throughout pregnancy, analysis of ASD phenotypic subgroups, and information on maternal thyroid clinical conditions during pregnancy and their treatment are warranted.

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## Appendix

See Tables 6 and 7.

Table 6

Arithmetic mean TSH concentrations (ng/mL) by Demographic and Diagnostic Group

	ASD				DD				GP			
	N	Untransformed 5-95 % interval	Arithmetic mean	95 % CI	N	Untransformed 5-95 % interval	Arithmetic mean	95 % CI	N	Untransformed 5-95 % interval	Arithmetic mean	95 % CI
<i>Maternal serum</i>												
Total	72	(0.32-3.91)	1.69	(1.37-2)	38	(0.07-2.97)	1.44	(1.2-1.68)	127	(0.42-3.69)	1.99	(1.46-2.52)
Country of origin												
US	40	(0.35-3.79)	1.62	(1.2-2.04)	10	(0.04-2.97)	1.68	(1.04-2.31)	53	(0.42-3.73)	1.72	(1.47-1.96)
Mexico	6	(0.32-3.91)	1.97	(0.42-3.51)	17	(0.07-3.2)	1.51	(1.12-1.89)	50	(0.42-3.22)	1.67	(1.39-1.96)
Other	26	(0.37-5.63)	1.73	(1.18-2.28)	11	(0.72-2.09)	1.12	(0.83-1.42)	24	(0.56-10.14)	3.26	(0.47-6.05)
Sex of child												
Male	62	(0.37-3.8)	1.72	(1.42-2.03)	22	(0.07-2.97)	1.40	(1.04-1.77)	113	(0.42-3.73)	2.03	(1.43-2.62)
Female	10	(0.32-7.21)	1.48	(0-2.95)	16	(0.72-2.8)	1.49	(1.17-1.81)	14	(0.86-3.01)	1.72	(1.29-2.14)
Race												
White	47	(0.32-3.8)	1.70	(1.3-2.09)	27	(0.07-2.97)	1.54	(1.22-1.86)	102	(0.47-3.47)	1.81	(1.57-2.06)
Asian	17	(0.31-2.66)	1.44	(1.11-1.76)	9	(0.72-2.09)	1.18	(0.83-1.54)	22	(0.31-3.39)	2.82	(-0.18 to 5.82)
Other	6	(0.4-5.73)	2.55	(-0.02-5.11)	2	(1-1.5)	1.25	(-1.93 to 4.43)	3	(0.88-3.69)	2.04	(-1.61 to 5.69)
Ethnicity												
Hispanic	16	(0.32-3.91)	1.62	(1.04-2.2)	21	(0.07-2.8)	1.46	(1.09-1.83)	60	(0.39-3.21)	1.59	(1.34-1.84)
Non-Hispanic	56	(0.32-5.63)	1.71	(1.33-2.08)	17	(0.72-2.97)	1.41	(1.09-1.73)	67	(0.56-3.81)	2.36	(1.37-3.34)
Maternal age												
<20	2	(0.96-2.7)	1.83	(-9.22-12.88)	2	(1.63-1.97)	1.80	(-0.36 to 3.96)	7	(0.29-3.2)	1.67	(0.62-2.72)
20-24	5	(0.83-2.72)	1.49	(0.58-2.39)	5	(0.71-2.16)	1.63	(0.9-2.36)	27	(0.35-3.69)	1.80	(1.36-2.24)
25-29	16	(0.04-5.73)	1.81	(0.87-2.75)	15	(0.07-2.8)	1.34	(0.97-1.71)	38	(0.42-3.12)	1.37	(1.12-1.62)
30-34	33	(0.32-3.91)	1.66	(1.18-2.14)	12	(0.04-3.2)	1.30	(0.76-1.84)	41	(0.76-3.81)	2.69	(1.13-4.24)
35+	16	(0.32-3.8)	1.66	(1.11-2.22)	4	(0.72-2.97)	1.81	(0.32-3.3)	14	(0.42-10.14)	2.19	(0.8-3.57)
<i>Newborn blood spots</i>												
Total	78	(1.27-13.62)	6.435897	(5.49-7.38)	45	(0.55-11.11)	4.862	(3.79-5.93)	149	(2.02-14.25)	6.709195	(5.87-7.55)
Country of origin												
US	41	(1.27-12.99)	5.894634	(4.76-7.02)	12	(0.27-17)	6.480833	(3.75-9.21)	63	(2.52-12.63)	6.303016	(5.48-7.12)

	ASD				DD				GP			
	N	Untransformed 5-95 % interval	Arithmetic mean	95 % CI	N	Untransformed 5-95 % interval	Arithmetic mean	95 % CI	N	Untransformed 5-95 % interval	Arithmetic mean	95 % CI
Mexico	8	(1.55-10.57)	6.55875	(4.08-9.04)	22	(0.71-11.11)	4.347273	(2.8-5.9)	57	(1.25-15.75)	7.177368	(5.27-9.09)
Other	29	(2.17-16.83)	7.167241	(5.21-9.13)	11	(0.55-7.81)	4.125454	(2.58-5.67)	29	(1.29-15.63)	6.671379	(5.24-8.11)
Sex of child												
Male	68	(1.44-12.99)	6.369706	(5.37-7.37)	27	(0.27-9.26)	4.21963	(3.05-5.39)	133	(1.96-14.32)	6.860451	(5.94-7.78)
Female	10	(1.27-18.42)	6.886	(3.42-10.35)	18	(0.55-17)	5.825556	(3.73-7.92)	16	(2.05-14.25)	5.451875	(3.93-6.98)
Race												
White	51	(1.44-12.99)	6.063922	(5.12-7.01)	33	(0.71-12.56)	5.15	(3.78-6.52)	118	(1.96-14.32)	6.919576	(5.9-7.94)
Asian	19	(0.42-16.83)	6.635263	(4.78-8.49)	9	(0.55-7.81)	4.128889	(2.31-5.95)	27	(2.35-10.17)	6.072222	(4.84-7.3)
Other	6	(2.41-27.06)	9.551667	(-0.11-19.22)	3	(0.27-6.13)	3.893333	(-3.97-11.76)	4	(3.3-6.32)	4.8025	(2.67-6.94)
Ethnicity												
Hispanic	18	(1.04-10.57)	6.105556	(4.7-7.51)	26	(0.71-12.56)	4.904231	(3.22-6.58)	69	(1.96-14.32)	7.221449	(5.61-8.83)
Non-Hispanic	60	(1.36-15.23)	6.535	(5.37-7.7)	19	(0.27-11.11)	4.804211	(3.54-6.06)	80	(2.36-12.73)	6.267375	(5.52-7.02)
Maternal age												
<20	2	(6.01-6.19)	6.1	(4.96-7.24)	3	(4.9-11.11)	9.04	(0.13-17.95)	8	(0.72-16.18)	8.31875	(3.51-13.13)
20-24	7	(5.24-9.37)	6.857143	(5.49-8.22)	6	(0.1-8.19)	3.698333	(0.59-6.8)	31	(2.77-13.53)	7.336774	(4.07-10.61)
25-29	18	(1.67-27.06)	7.213333	(4.37-10.06)	17	(0.27-17)	4.921176	(2.88-6.96)	44	(2.02-12.63)	6.524318	(5.43-7.62)
30-34	34	(0.96-16.83)	6.586176	(5.09-8.08)	14	(0.71-12.56)	4.116429	(2.42-5.82)	48	(2.77-14.32)	6.578333	(5.53-7.63)
35+	17	(1.04-10.33)	5.178235	(3.7-6.66)	5	(1.88-9.26)	5.638	(1.27-10.01)	18	(0.09-11.98)	5.713889	(4.3-7.13)

Odds ratios and 95 % confidence intervals for ASD associated with log10-transformed maternal and newborn TSH concentrations, the EMA study

**Table 7**

	N	ASD versus GP <sup>d</sup>	N	ASD w/regression versus GP <sup>d</sup>	N	Early Onset ASD versus GP <sup>d</sup>	N	ASD versus DD <sup>b</sup>	N	DD versus GP <sup>b</sup>
<i>Maternal serum TSH</i>										
Unadjusted	130	0.41 [0.14–1.21]	50	0.41 [0.04–4.23]	114	0.47 [0.15–1.42]	79	1.35 [0.34–5.46]	93	0.30 [0.07–1.38]
Adjusted	126	0.25 [0.07–0.84]	50	0.64 [0.07–6.11]	110	0.27 [0.07–1.01]	75	2.18 [0.39–12.39]	92	0.07 [0.01–0.69]
<i>Neonatal bloodspot TSH</i>										
Unadjusted	149	0.61 [0.18–2.10]	61	0.88 [0.09–8.68]	129	0.53 [0.13–2.06]	84	1.69 [0.34–8.43]	108	0.26 [0.04–1.58]
Adjusted <sup>3</sup>	143	0.42 [0.10–1.80]	60	1.62 [0.03–85.82]	127	0.35 [0.07–1.74]	82	0.83 [0.07–9.13]	106	0.77 [0.05–13.13]

Populations excluded from regressions: Mexico/Other as birth country, “Other” race/ethnicity status

<sup>a</sup>Conditional logistic regression: adjusted model uses mother’s age, mother’s race (white, Asian) Hispanic (yes/no), and mother’s weight at blood draw. Maternal models also adjust for gestational age at maternal blood draw, while Neonatal models adjust for gestational age at birth and baby’s age at blood draw. Unadjusted models also use conditional logistic regression, accounting for matching by sex, birth month, and birth year

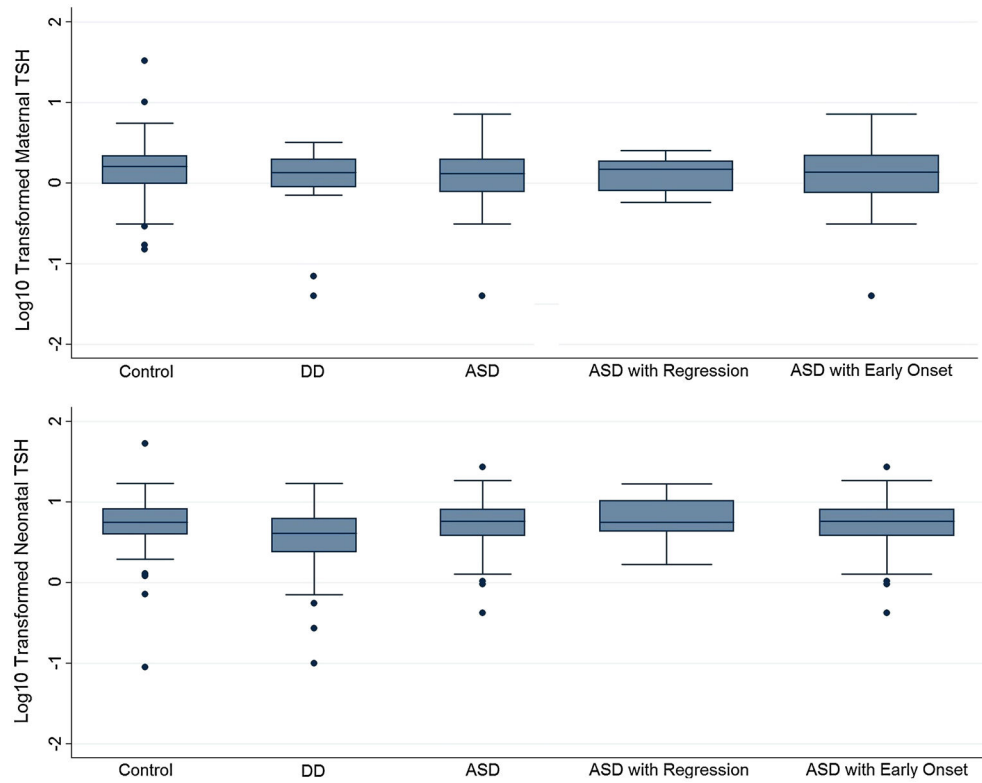
<sup>b</sup>Unconditional logistic regression: adjusted for birth month, birth year, and sex as well as above confounders

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**Fig. 1.** Log10 transformed boxplots of maternal and neonatal TSH levels, by diagnosis category. The median is represented by the center line within each box. The upper and lower boundaries of the solid box are the upper and lower interquartile range. The upper whisker represents the most extreme value within  $Q3 + 1.5*(Q3 - Q1)$  and the lower whisker represents the most extreme value within  $Q1 - 1.5*(Q3 - Q1)$



**Table 1**

EMA demographic characteristics

	ASD (N = 78)		DD (N = 45)		GP (N = 149)		Autism versus GP <i>p</i> value <sup>a</sup>	Autism versus DD <i>p</i> value <sup>a</sup>
	n	%	n	%	n	%		
Child's sex								
Male	68	87.18	27	60	133	89.26	0.664 <sup>b</sup>	0.001 <sup>b</sup>
Female	10	12.82	18	40	16	10.74		
Birth year								
2000	22	28.21	23	51.11	31	20.81	0.248 <sup>b</sup>	0.019 <sup>b</sup>
2001	56	71.79	22	48.89	118	79.19		
Plurality								
Singleton	75	96.15	43	95.56	146	97.99	0.416 <sup>b</sup>	1 <sup>b</sup>
Multiple	3	3.85	2	4.44	3	2.01		
Mother's race								
White	51	67.11	33	73.33	118	79.19	0.074	0.771
Asian	19	25	9	20	27	18.12		
Other	6	7.89	3	6.67	4	2.68		
Mother's ethnicity								
Non-Hispanic	60	76.92	19	42.22	80	53.69	0.001	<0.001
Hispanic	18	23.08	26	57.78	69	46.31		
Maternal birth Country								
US	41	52.56	12	26.67	63	42.28	<0.001	<0.001
Mexico	8	10.26	22	48.89	57	38.26		
Other	29	37.18	11	24.44	29	19.46		
Maternal age (years) mean (SD)	30.7 (5.3)		28.5 (5.1)		28.3 (5.6)		0.0016	0.0285
Maternal age (years)							0.027	0.146
<20	2	2.56	3	6.67	8	5.37		
20-24	7	8.97	6	13.33	31	20.81		
25-29	18	23.08	17	37.78	44	29.53		
30-34	34	43.59	14	31.11	48	32.21		
35+	17	21.79	5	11.11	18	12.08		

	ASD (N = 78)		DD (N = 45)		GP (N = 149)		Autism versus GP <i>p</i> value <sup>a</sup>	Autism versus DD <i>p</i> value <sup>a</sup>
	n	%	n	%	n	%		
Maternal weight prior to XAFP blood draw (lbs) mean (SD)	143.6 (26.4)		147.3 (35.3)		144.6 (27.2)		0.7997	0.5186
Gestational age at XAFP blood draw (days) mean (SD)	119.9 (8.2)		118.8 (8.7)		118.8 (7.4)		0.3057	0.4962
Gestational age at birth (days) mean (SD)	271.0 (14.5)		265.2 (29.0)		271.7 (19.0)		0.753	0.1385
Gestational age at birth (weeks)							0.849	0.239
<33	2	2.56	4	9.09	4	2.68		
33 to <37	7	8.97	5	11.36	17	11.41		
37	69	88.46	35	79.55	128	85.91		

<sup>a</sup> t test for means, Chi squared for frequencies (of non-missing/unknown categories), excluding missing data

<sup>b</sup> Fisher's exact test, excluding missing data

**Table 2**

Arithmetic mean TSH concentrations (ng/mL) by diagnostic group

Maternal serum		N	Untransformed 5–95 % range	Arithmetic mean	95 % Confidence interval	p value for <i>t</i> test, versus GP <sup>a</sup>	p value for <i>t</i> test versus DD
GP		127	(0.42–3.69)	1.99	(1.46–2.52)	-	-
DD		38	(0.07–2.97)	1.44	(1.2–1.68)	0.09	-
ASD		72	(0.32–3.91)	1.69	(1.37–2.0)	0.18	0.62
ASD w/regression		10	(0.58–2.54)	1.41	(0.92–1.90)	0.48	0.81
ASD w/Early Onset		59	(0.32–5.63)	1.76	(1.39–2.14)	0.25	0.61
Newborn blood spots		N	Untransformed 5–95 % range	Arithmetic mean	95 % Confidence interval	<i>t</i> test versus GP	<i>t</i> test versus DD
GP		149	(2.02–14.25)	6.71	(5.87–7.55)	-	-
DD		45	(0.55–11.11)	4.86	(3.79–5.93)	0.00	-
ASD		78	(1.27–13.62)	6.44	(5.49–7.38)	0.65	0.01
ASD w/regression		14	(1.67–16.83)	6.86	(4.49–9.22)	0.76	0.07
ASD w/Early Onset		61	(1.27–12.99)	6.40	(5.30–7.51)	0.56	0.02

<sup>a</sup> *t* tests were done comparing using log<sub>10</sub>-transformed TSH concentrations to achieve normality

**Table 3**

Correlation of maternal and neonatal TSH levels

	<b>ASD</b>	<b>DD</b>	<b>GP</b>	<b>Total population</b>
Correlation <sup>a</sup>	0.08	0.08	0.21	0.15
<i>p</i> value	0.50	0.61	0.02	0.02
n	72	38	127	237

<sup>a</sup>Pearson correlation coefficients

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Odds ratios and 95 % confidence intervals for ASD associated with log10-transformed maternal and newborn TSH concentrations, the EMA study

**Table 4**

	N	ASD versus GP <sup>a</sup>	N	ASD w/regression versus GP <sup>a</sup>	N	Early Onset ASD versus GP <sup>a</sup>	N	ASD versus DD <sup>b</sup>	N	DD versus GP <sup>b</sup>
<i>Maternal serum TSH</i>										
Unadjusted	198	0.53 [0.22–1.29]	86	0.58 [0.07–4.85]	182	0.58 [0.23–1.45]	110	1.31 [0.45–3.86]	165	0.40 [0.13–1.19]
Adjusted	192	0.33 [0.12–0.91]	86	0.81 [0.09–6.99]	176	0.31 [0.10–0.98]	108	1.73 [0.43–7.08]	162	0.09 [0.02–0.42]
<i>Neonatal bloodspot TSH</i>										
Unadjusted	226	0.72 [0.29–1.80]	111	1.19 [0.18–7.75]	205	0.67 [0.25–1.82]	123	4.06 [1.33–12.35]	194	0.21 [0.07–0.57]
Adjusted <sup>a</sup>	216	0.61 [0.18–2.14]	109	1.25 [0.07–21.22]	200	0.56 [0.15–2.16]	120	2.00 [0.34–11.66]	189	0.36 [0.08–1.61]

<sup>a</sup>Conditional logistic regression: adjusted model uses mother’s age, mother’s race (white, Asian, other), Hispanic (yes/no), mother’s place of birth (US, Mexico, Other), and mother’s weight at blood draw. Maternal models also adjust for gestational age at maternal blood draw, while Neonatal models adjust for gestational age at birth and baby’s age at blood draw. Unadjusted models also use conditional logistic regression, accounting for matching by sex, birth month, and birth year

<sup>b</sup>Unconditional logistic regression: adjusted for birth month, birth year, and sex as well as above confounders

Odds ratios and 95 % confidence intervals associated with quartiles of maternal and newborn TSH concentrations, the EMA study

**Table 5**

	ASD versus GP <sup>a</sup>	ASD w/regression versus GP <sup>a</sup>	Early Onset ASD versus GP <sup>a</sup>	ASD versus DD <sup>b</sup>	DD versus GP <sup>b</sup>
<i>Maternal serum TSH</i>					
Second quartile	0.41 [0.15–1.12]	0.29 [0.02–3.73]	0.53 [0.18–1.54]	0.78 [0.19–3.27]	0.57 [0.15–2.08]
Third quartile	0.38 [0.15–0.98]	1.32 [0.15–11.8]	0.35 [0.13–0.98]	0.60 [0.13–2.71]	0.49 [0.13–1.83]
Upper quartile	0.4 [0.16–1.02]	0.6 [0.05–6.97]	0.41 [0.15–1.13]	1.34 [0.25–7.30]	0.22 [0.05–0.94]
<i>Neonatal bloodspot TSH</i>					
Second quartile	0.83 [0.31–2.19]	0.57 [0.05–5.96]	0.88 [0.31–2.49]	1.48 [0.31–7.20]	0.35 [0.11–1.18]
Third quartile	1.1 [0.43–2.8]	1.19 [0.18–7.83]	0.96 [0.33–2.74]	2.25 [0.42–12.07]	0.26 [0.07–0.98]
Upper quartile	0.88 [0.33–2.34]	0.91 [0.12–6.96]	0.92 [0.32–2.66]	2.18 [0.47–10.20]	0.55 [0.16–1.89]

<sup>a</sup>Conditional logistic regression (maternal models): adjusted model uses mother’s age, mother’s race (white, Asian, other), Hispanic (yes/no), mother’s place of birth (US, Mexico, Other), and mother’s weight at blood draw. Maternal models also adjust for gestational age at maternal blood draw, while Neonatal models adjust for gestational age at birth and baby’s age at blood draw. Unadjusted models also use conditional logistic regression, accounting for matching by sex, birth month, and birth year

<sup>b</sup>Unconditional logistic regression: adjusted for birth month, birth year, and sex as well as above confounders