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Letters to the Editor

Lack of a Relation Between Human Neonatal Thyroxine and Pediatric Neurobehavioral Disorders: Neonatal Total Thyroxine Is Not a Good Proxy Measure of Maternal Thyroid Hormone Insufficiency

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Dear Editor:

We were struck by the title of the paper recently published by Soldin et al. in the February issue of *Thyroid* ("*Lack of a relation between human neonatal thyroxine and pediatric neurobehavioral disorders*" (1) for its provocative, if unintended, implication that neonatal thyroxine (T_4) is not associated with specific neurobehavioral deficits. Clearly, neonatal thyroxine may be associated with a variety of neurobehavioral deficits (2–5), and new research is revealing associations between neuropsychological outcome and subtle maternal thyroid hormone insufficiency (6–9).

In contrast to the implication of the title, the hypothesis under investigation was that "intrauterine thyroid dysfunction is an early factor in the development of neurobehavioral disorders" in humans. Clearly, this hypothesis has important implications for human health. To test this hypothesis, Soldin et al. (1) utilized a case-control study design in which the hypothesized causal pathway of interest (insufficient levels of free T_4 during fetal brain development leading to deficiencies in central nervous system [CNS] development) was presumed to be represented adequately by relationships between neonatal levels of T_4 and a hospital clinic diagnosis of any of the following: attention-deficit hyperactivity disorders (ADHD), autism spectrum disorder, behavioral disorder, cognitive disorder, developmental delay, emotional disorder, learning disability, or speech/language disorder. However, we contend that the choices of neonatal T_4 as a proxy measure of intrauterine thyroid status, and the use of hospital diagnoses of broad and heterogeneous neurobehavioral disorders limits the ability to adequately test this hypothesized causal pathway of interest. In the first case, the choice of neonatal T_4 as a proxy measure of intrauterine thyroid status is not appropriate for reason of (at least) the findings of Haddow et al. (8), who observed that neonatal T_4 is not reflective of maternal thyroid status, and that of Calvo et al. (10) who observed that the fetus is exposed to biologically relevant levels of free T_4 that are likely to be affected by subtle changes (e.g., hypothyroxinemia) in maternal free T_4 rather than in neonatal T_4 (11).

The issues germane to the use of hospital diagnoses are more complex. Soldin et al. (1) identified cases based on the sole criterion of a hospital clinic diagnosis—rendering the cases a disproportionate representation of higher severity disease; this has implications for the generalizability of study findings. Although the controls were intended to be identified as children without a hospital clinic diagnosis of a neurobehavioral disorder and with neonatal T_4 determinations made at the same time as those of the cases, there was no assessment of the "controls" to verify his or her control status as having no diagnosis of disease made elsewhere (e.g., pediatric practices) in any year up to the time when the matched case was diagnosed. Moreover, no information was collected on potential confounders and modifiers of the relationships between neonatal T_4 and neurobehavioral disorder. Therefore, the data collected were biased toward the null in that, among the cases, some normal levels of neonatal T_4 are likely "misrepresentations" of potentially low, or infrequently high, levels of free T_4 *in utero*, rendering cases spuriously similar to controls; and the controls likely include some children with a neurobehavioral disorder, the diagnosis being made in a nonhospital setting, rendering the controls spuriously similar to the cases.

Finally, the available data include no low levels of T_4. This precludes the discovery of any of the relationships of interest and the reported odds ratios are estimates of relationships that are not of interest; namely those between disease and variations in normal levels of T_4 on the second day after birth. Further confusing the interpretation of the reported odds ratios is that it is not known what they are actually

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measuring; the "referent" and "comparison" exposure histories that are being compared in these calculations are not defined. The small counts of cases for each of the diseases indicated in Table 1 reveals that the study was not adequately powered for the estimation of any of the relationships of interest. Thus the null findings in Table 2 are as expected and the missing confidence intervals are undoubtedly too wide to permit meaningful interpretation.

We are reminded that the issues that were the intended focus of this report are timely and important. The study by Haddow et al. (8) showing that maternal hypothyroidism, as well as hypothyroxinemia, are associated with specific neuropsychological deficits in the offspring that may represent a turning point in our thinking about this issue, which began several decades ago with the systematic studies of Man et al. (12–14). This body of literature indicates clearly that thyroid hormone of maternal origin affects fetal brain development, as is also indicated by the work of Cao et al. (15,16) who demonstrated that the clinical syndrome of neurologic cretinism is caused by thyroid hormone insufficiency during the first trimester of pregnancy. Fewer experimental studies have focused on the relationship between maternal thyroid status and fetal brain development. Dowling et al. (17–19) found that thyroid hormone of maternal origin can regulate the expression of specific genes expressed in the fetal brain and that may affect specific developmental processes occurring prior to the onset of fetal thyroid function. Perhaps more compelling, however, is the work of Lavado-Autric et al. (20) that shows that maternal hypothyroxinemia can result in migration defects of cortical neurons, resulting in the presence of many ectopic neurons as well as disarray of cortical lamina. This topic has been reviewed extensively by Chan and Rovet (21).

Likewise, we know more about the vulnerability of the neonate to thyroid hormone insufficiency than we do about the fetus. For example, congenital hypothyroidism (CH), which is a relatively prevalent disorder of newborns, was a leading cause of mental retardation but because of newborn screening and early treatment, outcome is significantly improved (2,22). However, affected children still exhibit subtle selective persisting impairments (23–26) and may have mild behavioral problems (27). Their IQ levels on average are about 6 points below expectation (28) and they show mild selective deficits on tests of visuospatial, motor, language, memory, and attention abilities (26,29–34) as well as some underachievement at school and increased risk of math disabilities (27,35–40). A recent study reported these effects persisted into adulthood (41). Thus, thyroid hormone is clearly essential for normal brain development over a broad developmental period, and identifying the proxy measures that reveal associations between thyroid status of the mother, fetus, or neonate and neurobehavioral disorders will lead to a better understanding of treatment options.

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Authors' Response

We appreciate the opportunity to respond to the letter to the opinions expressed by Zoeller, Bigelow, and Rovet. We were surprised by the authors' suggestion that in our paper we somehow implied neonatal thyroxine (T_4) screening was unnecessary. Clearly, these authors misunderstood our paper (1). We believe neonatal screening is important for early diagnosis of congenital hypothyroidism, inborn errors of metabolism, and other disorders. Neonatal screening is fortunately an accepted part of routine neonatal health care in almost all countries with well-developed medical services and has undoubtedly proven beneficial to the health of the newborn. Furthermore, we advocate and have promoted early maternal thyroid insufficiency screening for pregnant mothers as early as the first trimester of pregnancy, and have presented this position at several scientific conferences (2–4).

We do concur with Zoeller et al. on the importance of T_4 to fetal neurodevelopment and the importance of this supply from the maternal thyroid. In our paper, we pointed out a number of circumstances in which insufficient fetal supplies of free T_4 can cause neurocognitive disorders, including untreated hypothyroidism in pregnant women, moderate iodine deficiency, women with low free T_4 (hypothyroxinemia) in the first trimester of pregnancy, and women with antithyroid peroxidase antibodies. If anything, our statement that: "Any combination of these factors, which alone may not be detectable, may lead to a synergistic effect that may result in a disruption leading to neurobehavioral

disorders" (p. 196) implies that screening programs should be expanded to include maternal thyroid status, rather than discontinued.

Adequate functioning of both the maternal and fetal thyroid gland is critical to ensure adequate fetal neurologic and neuro-psycho-intellectual development. Clinical studies of endemic cretinism in iodine-deficient regions and of children with sporadic congenital hypothyroidism have demonstrated that thyroid hormone is essential for normal brain development. Further studies have illustrated that there is a fine interplay dependent on precise timing and concentrations of thyroid hormone in the developing brain and the relative sensitivity of the fetal brain cells to maternal thyroid hormone insufficiency (5–8). Haddow et al. (9) and Pop et al. (10) have highlighted the complex relationship between maternal thyroid dysfunction during pregnancy and its possible consequences for the neuro-psycho-intellectual development of the fetus and child. However, the women in the study by Haddow were hypothyroid defined by thyrotropin (TSH), not T_4, or had mild hypothyroidism not hypothyroxinemia. The transfer of thyroid hormones from the mother to the fetus plays an important role both before and after the onset of fetal thyroid function at midgestation. It is presently considered that 30% of serum T_4 levels measured at birth in cord blood are still of maternal origin (11). Maternal thyroid hormones cross the placenta and can be found in low but detectable levels in the fetus at 4–6 weeks' gestation (12,13).

Thyroid hormone supply to the growing fetus is almost exclusively of maternal origin at least until midgestation. At this stage brain development is a complex process involving neuronal multiplication, migration, and architectural organization. As a result, severe maternal hypothyroidism during the second trimester will result in irreversible neurologic deficits. Thyroid insufficiency in the pregnant rat disrupts the migration of neurons in the fetal cortex and hippocampus, leading to the presence of neurons in aberrant locations of the adult offspring's brain (14). From the third trimester, the supply of thyroid hormones to the fetus is essentially of fetal origin, and fetal brain development involves glial cell multiplication, migration, and myelinization. Material hypothyroxinemia occurring at these later stages will therefore result in less severe, and partially reversible, fetal brain damage than what is expected with earlier maternal thyroid deficiencies.

We speculate that the authors' misunderstanding of our work could be the result of confusion over the hypothesis we were investigating, specifically the relationship between T_4 concentrations measured by the Neonatal Screening Program during the first few days of life and various neurobehavioral deficits later on in childhood. The purpose of our paper was not to challenge the relevance of fetal thyroid hormone levels to neurodevelopment, but to assess whether the data from the neonatal screening programs could be used to predict who are the children who would subsequently develop one of the major neurobehavioral conditions of childhood. Low neonatal T_4 would reflect newborn thyroidal insufficiency, which may or may not have been compensated by adequate maternal supply of T_4 to the fetus *in utero*, whereas low maternal thyroid hormone supply to the fetus prior to fetal thyroid hormone synthesis may not be detected by newborn T_4 concentrations.

The authors are correct to point out that the cases in this case control study were identified on the basis of outpatient clinic diagnoses and that the controls were selected despite the absence of diagnoses, and we agree that the potential bias introduced by these criteria are legitimate issues for further study. However, we do not believe the mere possibility of such a bias in assessing disorders of the sort we considered sufficient to undermine our results. While this may be a limitation of the study, it is a common limitation in case/control epidemiologic studies rather than a fatal flow.

We have pointed out that the strength of the evidence for a lack of association between specific neurobehavioral disorders and neonatal T_4 concentrations varies by disorder and for some of the disorders is only suggestive. We invite those with larger numbers of patients with specific outcomes to replicate our study and to determine whether they find an association where we did not.

Zoeller et al. would have preferred that the neonatal T_4 distributions included subjects with low levels of T_4. We can only comment that these are the data. Nonetheless, it is a reasonably important observation that none of the 227 cases of pediatric neurobehavioral disorders had an abnormally low neonatal T_4 level. This observation alone suggests that low neonatal T_4 is not a major factor for subsequent pediatric neurobehavioral disorders.

As explained in the statistical analysis section, T_4 was treated as both a categorical and as a continuous variable in the conditional logistic regression analysis. When the logistic regression analysis was performed, T_4 was treated as a categorical variable and the lower levels of T_4 were the reference group. Thus, this group would not appear in any of the tables. When T_4 was treated as a continuous variable, "low levels of T_4" would not appear in the regression model either. Odds ratios were used as an expression of the strength of any association. Although confidence intervals are useful, *p* values also provide important information as to whether an association could be explained by chance alone.

Finally, it seems that the authors did not understand the function of the conditional logistic regression model. Although some of the numbers of cases were not large, the sample sizes were the sum of the number of cases plus the number of controls, which was not small. More importantly, for all disorders, including some with large numbers of cases (such as ADHD, behavioral disorder, and learning disorder), the conditional logistic regression analyses revealed the same results: lack of association between the disorders and T_4.

We again stress our finding that the occurrence of the conditions in the study population did not correlate with neonatal T_4 concentrations, is in no way to dismiss the role of earlier (*in utero*) T_4 supplies and neurologic and behavioral outcomes. Here, too, we concur completely with Zoeller et al., and acknowledged as much when we said that even early treatment of congenital hypothyroidism can have "subtle yet measurable neurocognitive and psychomotor deficits" (p. 196). Ours is a more modest point, and should not be confused with the genuinely radical position that Zoeller et al. represent us as defending.

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Dissertation Experiences

Dear Editor:

I am writing to tell you how much I enjoyed reading the dissertation abstracts in your September issue. I very much hope you will keep this feature. Indeed, I share many of your experiences voiced in your editorial except I was doing this in labor, after delivery, and between feeds! But I too had to do two drafts. I have only two copies, one that is yellow—like parchment— and the other is the same except that half was eaten by a very smart dog.

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Lack of a Relation Between Human Neonatal Thyroxine and Pediatric Neurobehavioral Disorders

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The growth and differentiation of the central nervous system are closely related to the presence of iodine and thyroid hormones. It has been hypothesized that neurobehavioral disabilities of childhood, such as attention deficit hyperactivity disorder (ADHD), learning disorders, and autism can be attributed to fetal thyroidal endocrine disruption *in utero.* To determine whether there is an association between neonatal thyroid status and a subsequent diagnosis of a neurobehavioral disability, neonatal thyroxine (T_4) levels have been used as the indicator of the presence of intrauterine thyroidal dysfunction. Neonatal T_4 levels were obtained from the neonatal hypothyroidism screening program. All cases were diagnosed at medical school diagnostic clinics, the diagnostic categories being ADHD, autism spectrum disorder, behavioral disorder, cognitive disorder, developmental delay, emotional disorder, learning disability, and speech/language disorder. Conditional logistic regression analysis was performed for each clinical condition. Odds ratios for the conditions ranged from 0.92 to 1.13 with p values ranging between 0.19 and 0.84. No significant differences were detected between neonatal T_4 values of the cases and the controls for any of the neurobehavioral conditions. All neonatal T_4 values were within normal ranges. The data provide no evidence to suggest that intrauterine thyroid status as reflected by the neonatal T_4 values had an impact on the neurologic disorders diagnosed in childhood.

Introduction

Insufficient levels of thyroid hormones, mainly free thyroxine (FT_4), during fetal brain development lead to deficiencies in differentiation and maturation of the central nervous system, later resulting in poor motor skills and deficient intellectual and behavioral development (1). The human fetal thyroid begins to produce thyroid hormones by approximately week 10 of gestation. The fetus is dependent on maternal thyroid hormones during those first weeks of gestation and at least the first part of the second trimester of pregnancy (2,3). During the later gestational period the fetal thyroid has the capacity to make sufficient thyroxine (T_4) on its own (1). It has been suggested that fetal neurologic damage is inversely related to maternal serum T_4 levels in the first and second trimesters. Triiodothyronine (T_3) is the main form of thyroid hormone that regulates fetal brain development by its binding to brain nuclear receptors. Maternal T_4 and T_3 that cross the placenta are converted to T_3 at the fetal brain tissue level (4).

Iodine plays a central role in thyroid physiology, being both a major constituent of thyroid hormones and a regulator of thyroid gland function. Iodine deficiency has been shown to result in decreased serum T_4 levels and in increased thyroid stimulating hormone (thyrotropin [TSH]) levels (5). In mildly iodine-deficient areas (median urinary iodine [UI], 50–99 μg/L) and in iodine-sufficient areas where maternal T_4 concentrations are in the low-normal range, mild and subclinical neuropsychomotor deficits have been observed in neonates (6). Congenital hypothyroidism can cause motor and cognitive development abnormality in children (7), such motor and cognitive development abnormalities have occurred when blood T_4 levels failed to reach a threshold level of 43 nmol/L at the neonatal screening after birth (8,9). It is assumed that when T_4 levels fall below such a threshold at a critical time of development and for an extended length of time there will be a neurobehavioral effect.

Newborns with congenital hypothyroidism who are identified by screening programs and treated promptly by T_4 supplementation usually have IQs in the normal range at 5 to 7 years of age, as well as normal growth and development (1). Even children born without a thyroid have normal intellect if the absence is detected early enough after birth and thyroid hormone replacement is initiated early. Autism may

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also be a disease of early fetal brain development (approximately day 20–24 of gestation) (10). We examined the hypothesis that intrauterine thyroid dysfunction may be an early factor in the development of neurobehavioral disorders by testing whether T_4 levels of newborns who were subsequently diagnosed with neurobehavioral disorders differed from T_4 levels of the general community of newborns.

Methods

Study design

This matched case-control study was designed to determine whether children who were subsequently diagnosed with specific neurobehavioral disorders had abnormal T_4 levels as newborns. The methodology has previously been described (11). Cases diagnosed at the pediatric neurodevelopmental diagnostic clinics of the three medical schools in Washington, D.C., served as potential cases. The data from the Washington, D.C. neonatal screening program were reviewed to identify the records of cases that had been born in Washington, D.C., and to record their neonatal T_4 values. The controls were those newborns born and screened on the same day as the case and at the same hospital. The neonatal T_4 values of the controls were identified and compared to those of the cases.

The pediatric neurodevelopmental diagnostic clinics of the three medical schools in Washington, D.C., were recruited for participation in this study. The institutional review board of each medical school approved the protocol, as did the director of the D.C. Department of Health. Each clinic prepared a list of children diagnosed there as having a neurobehavioral disorder along with their date of birth. These lists were submitted to the Neonatal Screening Laboratory at Howard University Hospital that had conducted the screening for the Division of Maternal Child Health, D.C. Department of Health, Washington, D.C. Laboratory records were searched to identify the screening results for each case. Neonatal T_4 level measurements were retained in this laboratory as numeric date with actual values, in contrast to laboratories elsewhere that retained only the categorical information of normal or abnormal.

Matched controls for each case were all children who were born in the same Washington, D.C., hospital as the case and had their neonatal screening blood sample taken on the same day as the case. Neonatal T_4 level as well as the date of sampling, date of birth, race, and gender of each case and all of its controls were recorded as a set with study numbers replacing personal identifiers. Cases or controls who were born prematurely were noted and excluded from the analysis. Because all the children who met the matching criteria were retained as controls, the number of matched controls per case varied. The data from the three centers were pooled for analysis.

Subject recruitment, screening, and diagnosis

Diagnostic clinics of the three medical schools in Washington, D.C. (Howard University, George Washington University Childrens' National Medical Center, and Georgetown University) diagnosed the cases independent of this analysis. Assessments involved a full psychiatric interview with each child and each parent, and supplementary parental, teacher, and child interview materials and questionnaires. The children included in this study were diagnosed by an interdisciplinary team. Diagnostic teams consisted, at a minimum, of a psychologist and a developmental pediatrician, with additional team members, such as a physical therapist, occupational therapist, special educator, and speech and language specialist, added based on the specific needs of each individual child. All children received a neuropsychologic assessment designed to be age appropriate and to address the presenting symptoms of the child. This study was designed to maintain confidentiality with the specific diagnoses of individual cases maintained by the child's clinic. Informed consents were not required as this study was limited to the analysis of currently existing datasets and did not involve patient contact or follow-up.

Diagnosis of cases was performed according to usual clinical standards. All case children met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders IV* (*DSM-IV*). While the test procedures varied among institutions, the domains measured included abstract and concept formation, complex problem solving, cognitive speed, verbal learning, long- and short-term memory, attention and alertness, visuospatial relationships, sensory function, and motor function. Age and presenting questions influenced the choice of evaluation tools in most instances.

Laboratory methods

Newborn thyroxine laboratory measurements

Collection of samples. All newborn blood specimens were obtained by the heel-stick method, within 48–72 hours of birth. The blood specimens were collected at the nursery on a special S & S #903 filter paper. The specimens were allowed to dry at room temperature prior to transport of the dry blood specimen (DBS) to the laboratory.

T_4. Newborn T_4 was measured using an immunoassay for T_4 ICN neonatal (^{125}I) T_4 solid phase radioimmunoassay system (ICN Biomedicals, Irvine, CA) (12) which had a reference (normal) range of 7 μg/dL to 25 μg/dL. Values lower than 7 μg/dL were considered abnormal. The abnormal specimens were then assayed for TSH.

TSH. TSH was measured with ICN ImmunoChem™ Neonatal hTSH IRMA kit (ICN Biomedicals) (13). The same procedure and equipment were used to measure the samples of all of the cases and all of the controls. The TSH assays were performed on a one-quarter inch disc of the DBS using ICN ImmunoChem Neonatal hTSH IRMA kit (13).

Reference ranges

The reference ranges for T_4 were: 7–25 μg/dL (90–276 nmol/L), and values lower than 7 μg/dL (90 nmol/L) were considered abnormal. The reference ranges quoted were supplied by the kit manufacturers and were used throughout the study. The abnormal specimens are then assayed for TSH. The reference ranges for TSH 0–30 μIU/mL are the normal limits, and TSH values above 40 μIU/mL are suggestive of hypothyroidism. The reference values for T_4 and TSH were derived from six controls: three controls from the specific manufacturer of these kits and three controls from the Center for Disease Control (CDC). Additionally, five controls from the CDC were assayed quarterly for the proficiency testing. All the participating laboratories performing the

neonatal newborn screening internationally and in the United States assay these CDC proficiency-testing samples.

The reference values for T_4 and TSH were derived from six standards: three standards from the specific manufacturer of the kits and three standards from the CDC. Additionally, five standards from CDC were assayed quarterly for the proficiency testing.

Statistical analysis

To explore the relation between neonatal blood thyroid hormone levels (T_4) and subsequent diagnosis of each of the neurobehavioral disorders, a matched case-control design was used. In order to improve generalizability, multiple sets of matched controls were defined to compare with cases in terms of neonatal blood thyroid hormone levels. Matched controls were created as follows: (1) controls matched for age, gender, and race; (2) controls matched for age and gender; (3) controls matched for age and race; and (4) controls matched for gender and race. Distribution of cases and controls can be found in Table 1.

Conditional logistic regression analysis with unequal numbers of controls was performed because this is a matched case-control study with unequal numbers of controls (14). Controls/case ratio average was 4.2, the maximum, 9. Conditional logistic regression analyses were performed separately for different sets of controls.

To examine the relation between T_4 and disease status, T_4 was treated both as a categorical and as a continuous variable in the logistic regression analysis. Using T_4 as a categorical variable, quantiles were calculated (the first, 25th percentile; the second, 50th percentile or median; and the third, 75th percentile) of T_4. The values of T_4 above the third quantile were used as a reference group. Thus, three dummy variables were then created and were put into the logistic regression analysis. Statistical tests were considered to be significant at an α level of 0.05 on a two-tailed test.

Results

The children included in this study were $5^1/_2$ to 12 years of age at the time of diagnosis and had been diagnosed with neurobehavioral disorders at three independent medical school diagnostic clinics in Washington, D.C. (Table 1). The disorders included in this study include (1) ADHD, (2) autism spectrum disorder, (3) behavioral disorder, (4) cognitive disorder, (5) developmental delay, (6) emotional disorder, (7) learning disability, and (8) speech/language disorder.

Table 1. Distribution of Cases and Controls by Diagnosis

Disorder	*No. cases*	*No. controls*
Attention deficit (ADHD)	53	231
Autism (ASD)	6	23
Behavioral disorder	37	154
Cognitive disorder	22	95
Developmental disorder	9	36
Emotional disorder	7	27
Learning disorder	67	286
Speech/language disorder	26	96
Total (1175)	227	948

Table 2. Odds Ratios and p Values by Diagnosis

Disorder/disability	*Odds ratio*	p *value*
Attention deficit (ADHD)	0.99	0.81
Autism (ASD)	1.08	0.73
Behavioral disorder	1.01	0.84
Cognitive disorder	0.95	0.47
Developmental delay	0.92	0.42
Emotional disorder	1.13	0.58
Learning disorder	0.95	0.19
Speech/language disability	0.93	0.25
Total (n = 1175)		

Matched controls were those newborns whose neonatal screening occurred on the same day and in the same hospital as the case, with one to five matched controls per case. Information on cases and controls included age at time of T_4 sampling, race, and gender. Analysis took these variables into consideration. The odds ratios and p values by diagnosis are charted in Table 2, and more specifically, including matching by varying sets of demographic variables in Figure 1. All cases of neurobehavioral disorders seen here were found to have neonatal T_4 levels within the normal range for newborns, as did the controls.

The actual T_4 values for the cases were (Table 3): mean T_4 was 13.95 μg/dL and standard deviation (SD) (3.94 μg/dL). The T_4 concentration range was 2.6–25.3 μg/dL; the quantiles: 11.2, 14.0, 16.5. For the controls, the mean T_4 (SD) was 14.47 μg/dL (3.38 μg/dL), and the T_4 concentration range, 2.4–25.1 μg/dL; the quantiles: 12.3, 14.5, 16.7.

As illustrated in Figure 1, no differences were found between the odds ratio of the different neurobehavioral dysfunctions and none were found to have any statistical significance.

Table 2 lists the different disorders, their odds ratio, and p values. The odds ratios range from 0.92 to 1.13. As noted in Table 2, the odds ratio and p values by diagnosis show no significant differences for any of the disorders or disabilities.

These results illustrate that although the children who served as cases in our study had neurobehavioral disorders that manifested during childhood, their levels of T_4 as neonates (as measured by the neonatal screening program) were within the normal pediatric T_4 reference range (11). There is no evidence to suggest that neonatal T_4 level had a prominent impact and was the cause of later manifestation of neurobehavioral disorders of interest in this study. All analytic sets found no difference in the neonatal T_4 levels for all the neurobehavioral disorders for the cases as well as for their controls, whether T_4 was analyzed as a categorical or continuous variable.

Discussion

It is well established that thyroid hormones play a critical role in brain development (15–18). Both maternal and neonatal thyroid glands play an important role in normal neuropsychointellectual development. Lesser degrees of thyroid dysfunction do not cause frank mental retardation, but can

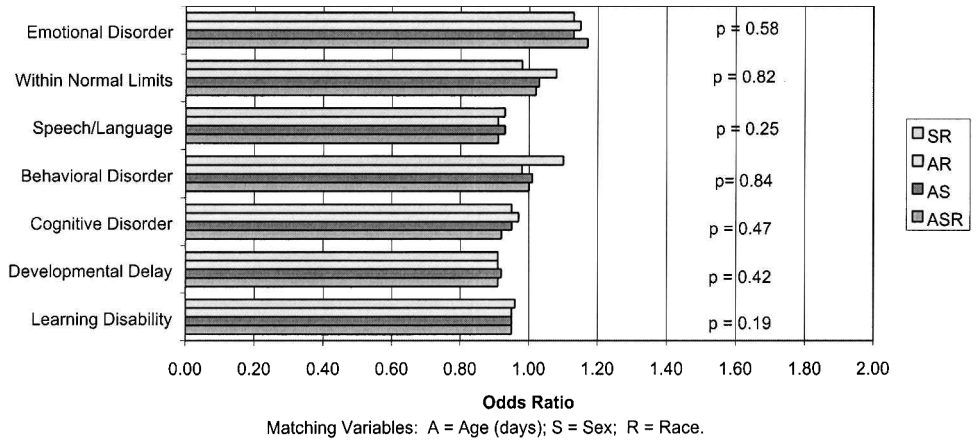

FIG. 1. Odds ratio for neurobehavioral disorders of children by neonatal thyroxine (T_4) as a continuous variable and matched on varying set of demographic variables.

result in more subtle yet measurable neurocognitive and psychomotor deficits, as observed in some children with early-treated congenital hypothyroidism (7,19–23). There will only be an adverse effect if these factors cause FT_4 insufficiency (hypothyroxinemia) during development fetus. Consistent with these observations, pregnant women with untreated hypothyroidism (24,25), women in geographical areas of moderate iodine deficiency (26), women with first trimester but low FT_4 (27), and women with antithyroid peroxidase antibodies (28) may give birth to children who subsequently demonstrate mild but measurable neurocognitive and psychomotor deficits in early childhood. Any combination of these factors, which alone may not be detectable, may lead to a synergistic effect that may result in a disruption leading to neurobehavioral disorders.

The fundamental causes of many of the neurobehavioral disorders are not known; however, many researchers agree that these may be a manifestation of brain disorders with a biologic basis (29,30). Genetic and environmental elements are believed to be important contributors to the etiology of some neurobehavioral disorders (31,32). In light of observations that intrauterine thyroid dysfunction can lead to neurobehavioral disturbances (33–37), the fact that premature birth accompanied by transient hypothyroidism increases the risk of neurologic development ADHD (38), and the comorbidity of ADHD with learning disabilities (30) we studied the relation between newborn T_4 levels and neurobehavioral disorders. Although free triiodothyronine (FT_3) is the physiologically active hormone that binds to the nuclear receptors (and is estimated as 0.2%–0.4% of the total T_3) in this study T_4 served as a surrogate for the active form of the hormone. It has been found that motor and cognitive impairment was correlated with the degree of maternal hypothyroxinemia, and not with circulating T_3 or TSH levels. The concentrations of all T_4 and T_3 hormones tend to change together, although the ultimate regulation of thyroid hormone metabolic activity is derived by the relative rates of formation of T_3 and reverse triiodothyrone (rT_3) from T_4.

Fetal total T_4 and FT_4 production do not clearly increase until week 20–24, and fetal serum FT_3 is undetectable until gestational week 32 (1). Although the fetal thyroid can synthesize its own T_4, maternal T_4 may still contribute significantly to fetal needs, at levels 20%–50% of normal values until term (39). We did not assess maternal thyroid function during pregnancy although the study's underlying hypothesis was that intrauterine thyroid dysfunction would be a contributing factor for subsequent neuropsychiatric disorders. Because neonatal T_4 levels reflect primarily T_4 levels produced by the neonate's thyroid gland on the second or third day of life, differences in T_4 levels between cases and controls would have suggested a pattern continuous with that of fetal T_4 levels during gestation. However, all analytic sets found no difference in the neonatal T_4 concentrations for all the neurobehavioral disorders for the cases as well as for their controls, whether T_4 was analyzed as a categorical or as a continuous variable. It is likely that neurobehavioral deficits result from complex processes and result from exposure to multiple factors in the internal and external environment. Because T_4 concentrations of the cases and of the controls in our study were all within normal range (Table 3), although we have no record of the maternal T_4 concentrations at weeks 0–12 of gestation, it is highly unlikely that it is the intrauterine T_4 concentrations of the mothers that are responsible for the resulting neurobehavioral disorders in their offspring.

The number of cases of autism in this study (6 cases, 11 controls) is only sufficient to yield an indication rather than a strong finding that neonatal T_4 concentrations cannot predict autism. Similarly, in the other groups, the numbers are only suggestive of no relation between the disorder and newborn T_4 concentrations. Each of the cases in this study had

TABLE 3. T_4 CONCENTRATIONS, MEANS, RANGES, AND QUANTILES FOR CASES AND CONTROLS

T_4 concentrations ($\mu g/dL$)	*Cases (SD) ($\mu g/dL$)*	*Controls (SD) ($\mu g/dL$)*
Mean	13.95 (3.94)	14.47 (3.38)
Range	2.6–25.3	2.4–25.1
Quantiles	11.2, 14.0, 16.5	12.3, 14.5, 16.7

T_4, thyroxine; SD, standard deviation.

normal neonatal T_4 concentrations that did not differ from the neonatal T_4 levels of their matched controls, demonstrating no relation between neonatal T_4 levels at birth and the development of neurobehavioral disorders later on in childhood. Studies similar in methodology to this study might be more conclusive.

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