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Increased nuchal translucency thickness and risk of neurodevelopmental disorders

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KEYWORDS: increased nuchal translucency; neurodevelopmental disorders; normal karyotype; prenatal screening

ABSTRACT

Objective *To investigate the association between fetal nuchal translucency (NT) thickness and neurodevelopmental disorders in euploid children.*

Methods *This study included 222 505 euploid children who had undergone routine first-trimester screening during fetal life. Children were divided according to prenatal NT into three groups: NT < 95th percentile (*n = *217 103 (97.6%)); NT 95th–99th percentile (*n = *4760 (2.1%)); and NT > 99th percentile (*n = *642 (0.3%)). All children were followed-up to a mean age of 4.4 years. Information on diagnoses of intellectual disability, autism spectrum disorders (ASD), cerebral palsy, epilepsy and febrile seizures was obtained from national patient registries.*

Results *There was no excess risk of neurodevelopmental disorders among euploid children with first-trimester NT 95th–99th percentile. For children with NT > 99th percentile, there were increased risks of intellectual disability (odds ratio (OR), 6.16 (95% CI, 1.51–25.0), 0.31%) and ASD (OR, 2.48 (95% CI, 1.02–5.99), 0.78%) compared with children with NT < 95th percentile (incidence of 0.05% for intellectual disability and 0.32% for ASD), however, there was no detected increase in the risk of cerebral palsy (OR, 1.91 (95% CI, 0.61–5.95), 0.47%), epilepsy (OR, 1.51 (95% CI, 0.63–3.66), 0.78%) or febrile seizures (OR, 0.72 (95% CI, 0.44–1.16), 2.65%).*

Conclusions *In a large unselected cohort of euploid children, there was no increased risk of neurodevelopmental disorders among those with a first-trimester NT 95th–99th percentile. Among euploid children with first-trimester NT > 99th percentile, there were increased risks of intellectual disability and ASD, but the absolute risk was reassuringly low (< 1%).*

INTRODUCTION

Associations between increased nuchal translucency (NT) and congenital malformations, chromosomal abnormalities, genetic syndromes and adverse pregnancy outcome have been demonstrated in numerous studies[1–5]. The long-term outcome in euploid children with increased prenatal NT is, however, still undetermined. Some previous studies have shown an association between increased NT and neurodevelopmental delay in up to 7.4% of euploid children[6–8], while others found no difference in development when compared with children with prenatal NT < 95th and < 99th percentiles[9,10]. These studies were based on clinical examination, parental questionnaire or a combination of both[6,9,11,12]. However, different cut-offs for increased NT were used and the length of follow-up varied greatly (8–120 months).

Overall, studies on this matter are scarce and heterogeneous and have been performed mainly on small cohorts. Therefore, the information provided to pregnant women and their partners in the case of a fetus with increased NT and normal karyotype is limited.

In 2004, a national screening program was introduced in Denmark, offering to all pregnant women a first-trimester risk assessment for the most common chromosomal abnormalities, free of charge. Screening consists of a NT scan and measurement of pregnancy-associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotropin (β-hCG). The program has a

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participation rate greater than 90%[13]. Since 2008, all data from the screening program have been collected in the Danish Fetal Medicine Database. Furthermore, all inpatient and outpatient visits within the Danish healthcare system are recorded in the National Patient Register (NPR). In combination, these two databases provide a unique opportunity to perform a large-scale follow-up study of children who had a NT measurement in fetal life, and the information derived may improve the counseling of parents in the case of a fetus with increased NT and a normal karyotype.

The aim of this study was to investigate in euploid children the association between increased prenatal NT and neurodevelopmental disorders, defined as intellectual disability, autism spectrum disorders (ASD), cerebral palsy, epilepsy or febrile seizures.

METHODS

This was a nationwide, register-based study and was approved by the Danish Data Protection Agency (RH-2015-111). At birth, all children are assigned a unique personal registration number, which is used for identification in the Danish social and healthcare system[14]. This centralized registration system enables follow-up of individuals through public registries.

Study cohort

All liveborn singleton infants in Denmark who had a NT measurement when fetal crown–rump length (CRL) was 45–84 mm, between 1 January 2008 and 31 March 2012, were included. NT measurement is part of the first-trimester risk assessment and was performed by sonographers or specialists in fetal medicine, certified by, and in accordance with, the guidelines of The Fetal Medicine Foundation. All 17 national departments of obstetrics and gynecology use the same software (Astraia, Munich, Germany) and report to the Danish Fetal Medicine Database, from which data were retrieved.

Data were obtained on maternal characteristics (maternal age at NT scan, ethnicity, prepregnancy body mass index, smoking status, method of conception), first-trimester risk assessment (NT thickness, levels of PAPP-A and β-hCG, risk assessment for trisomies 21, 18 and 13) and neonatal outcome (gestational age at delivery, birth weight, gender, results of any pre- or postnatal chromosomal analysis and any structural abnormalities detected on first- or second-trimester ultrasound scan). Gestational age was based on CRL at the 11–14-week scan[15].

Children were divided by prenatal NT thickness into three groups: NT < 95th percentile (Group 1), NT 95th–99th percentile (Group 2) and NT > 99th percentile (Group 3). The 99th percentile was defined as NT ≥ 3.5 mm for all gestational ages, while the 95th percentile was adjusted for gestational age[16]. A second-trimester anomaly scan was offered to all pregnant women at 18–20 weeks' gestation. The presence of a structural malformation was not an exclusion criterion.

Chorionic villus sampling or amniocentesis was offered to women with a first-trimester risk of trisomy 21 of > 1:300 or of trisomies 18 or 13 of > 1:150. Invasive testing was also performed if a fetal malformation was detected. Standard prenatal testing included molecular rapid aneuploidy detection of chromosomes 13, 18, 21, X and Y (by quantitative fluorescent polymerase chain reaction or multiplex ligation-dependent probe amplification (MLPA)) and G-banded karyotyping. In the case of a fetal malformation with a suspected genetic disorder, standard prenatal testing was supplemented with MLPA for microdeletions (P064), subtelomere MLPA (P036 + P069) or array comparative genomic hybridization (CGH).

Postnatal chromosome analysis included G-banded karyotyping, MLPA for microdeletions, subtelomere MLPA or array CGH. Array CGH was performed primarily in cases with delayed development and in some cases with malformations or dysmorphic features. MLPA was performed when there was suspicion of a specific syndrome.

Information about chromosomal abnormalities was retrieved from the Danish Central Cytogenetic Register (DCCR). In Denmark, all prenatal and postnatal chromosome analysis is undertaken at five departments of clinical genetics, and the results are submitted to the DCCR. Specialists in clinical genetics from the five departments reviewed the results of their analyses and classified chromosomal abnormalities as pathogenic or not. We excluded all children with mosaicism or chromosomal abnormalities with evidence of pathogenicity, including those associated with genetic syndromes. Liveborn children with no prenatal or postnatal genetic analyses were considered not to have manifestations leading to genetic analysis during the period of observation, and are referred to as euploid in this study. Thus, the cohort consisted of children for whom no pathology was expected.

Follow-up

All children in the cohort were followed prospectively from birth until 31 December 2014, providing a follow-up of 2–6 years. In Denmark, children are enrolled automatically at birth as patients of the maternal family doctor. Within the first 5 years of age, all children are offered seven health assessments by the doctor, free of charge. This program follows a standardized protocol by The National Board of Health and includes an assessment of developmental stages.

Data were retrieved from the NPR and the Danish Psychiatric Central Register (DPCR), both nationwide registries of all inpatient and outpatient visits to the healthcare system, including all diagnoses and dates of admission within the follow-up period. Diagnoses were categorized using the International Classification of Diseases, tenth revision (ICD-10). We investigated

diagnoses of intellectual disability, cerebral palsy, epilepsy and febrile seizures (ICD-10: F70–79, G80–83, G40 and R560, respectively) from the NPR and diagnoses of ASD (ICD-10: F84.0, F84.1, F84.5, F84.8 and F84.9) from the DPCR. Diagnoses of childhood autism (ICD-10: F84.0) were analyzed separately. Childhood autism differs from the other diagnoses as it has a specific criterion of manifestation before 3 years of age, and thus most children in the cohort were the required age for a diagnosis.

We did not investigate genetic syndromes owing to the varying degrees of neurological impairment among affected individuals[17,18]. Furthermore, the exclusion of children with pathogenic chromosomal abnormalities eliminated most of these cases from our cohort.

Statistical analysis

Means and SD were calculated for continuous and normally distributed data, and differences between means were tested by Student's *t*-test. Data were expressed as median (interquartile range) when non-normally distributed, and compared by Wilcoxon's signed-rank test. The chi-square test was used for intergroup comparison of categorical data. Logistic regression was used to estimate the odds ratios (ORs) of diagnoses of intellectual disability, ASD, cerebral palsy, epilepsy and febrile seizures in children in Groups 2 and 3 compared with children in Group 1; $P < 0.05$ was considered statistically significant. All statistical analysis was performed using STATA 13.1 (Statistic Data Analysis, STATA Corp., College Station, TX, USA).

RESULTS

Between 1 January 2008 and 31 March 2012, a total of 230 230 first-trimester NT scans were performed in singleton pregnancies in Denmark, and 229 688 met the inclusion criterion of fetal CRL of 45–84 mm. Of these, 222 964 (97.1%) resulted in a live birth and 3718 (1.6%) resulted in miscarriage, termination of pregnancy or stillbirth. The outcome of pregnancy was unknown for 3006 (1.3%) pregnancies that were lost to follow-up. Prenatal or postnatal chromosome analysis was performed in 10 719 (4.8%) of the 222 964 liveborn children, of whom 459 (4.3%) had an abnormal karyotype, resulting in a cohort of 222 505 children that were assumed to be chromosomally normal (Figure 1).

The distribution of prenatal NT thickness among liveborn euploid children was as follows: 217 103 (97.6%) with NT < 95th percentile (Group 1), 4760 (2.1%) with NT 95th–99th percentile (Group 2) and 642 (0.3%) with NT > 99th percentile (Group 3). Table 1 shows the characteristics of the mothers and infants in the three groups. There were no differences in maternal characteristics between Groups 1 and 3, except for a smaller proportion of ovulation-induced conceptions in Group 3. Maternal age, body mass index and proportion of smokers were significantly higher in Group 2 than in Group 1. Median NT measurement was 1.6 (range, 0.1–2.7) mm, 2.8 (range, 2.2–3.5) mm and 4.0 (range, 3.6–9.4) mm in Groups 1, 2 and 3, respectively. The prevalence of male infants, chromosomal analyses and structural abnormalities at the 20-week scan were significantly higher in Groups 2 and 3 than in Group 1. Mean age at follow-up was 4.2–4.4 years among the three groups, and was significantly lower in Group 2 than in Group 1.

A total of 10 424 children had a diagnosis of intellectual disability, ASD, cerebral palsy, epilepsy or febrile seizures (Table 2). The prevalence of children with one or more diagnoses was similar in all groups, with 4.7% in Groups 1 and 2 and 4.8% in Group 3.

Fetal NT > 99th percentile was associated with intellectual disability, with an OR of 6.16 (95% CI, 1.51–25.0). Two (0.31%) out of 642 infants with NT > 3.5 mm (Group 3) were diagnosed with intellectual disability compared with 110/217 103 (0.05%) infants with NT < 95th percentile (Group 1). The NT in these two cases was 3.9 mm and 7.3 mm, and both had normal standard prenatal chromosome analysis (46,XY). Standard prenatal analyses were performed in 13/110 and 2/4 cases of intellectual disability in Groups 1 and 2, respectively. Postnatal array CGH was performed in five cases of intellectual disability in Group 1.

The prevalence of ASD was 0.32% ($n = 686$), 0.32% ($n = 15$) and 0.78% ($n = 5$) in Groups 1, 2 and 3, respectively (Table 2). There was an association between NT > 99th percentile and ASD (OR, 2.48 (95% CI, 1.02–5.99)). The OR of childhood autism in infants with NT > 99th percentile (Group 3) was based on only two cases (OR, 1.82 (95% CI, 0.45–7.32); NT, 3.7 mm and 4.0 mm). The frequency of standard prenatal chromosomal analyses among children with ASD was 28/686, 7/15 and 5/5 in Groups 1, 2 and 3, respectively. Twelve children in Group 1 had postnatal array CGH.

The overall prevalence of diagnoses belonging to the ICD-10 G-group (diseases of the neurological system) was higher in Group 3 at 3.3% (21/642; OR, 2.0 (95% CI, 1.30–3.11)) than in Groups 1 (1.7% (3591/217 103)) and 2 (1.9% (89/4760)). A summary of the ICD-10 G-group diseases diagnosed in Group 3 is given in Table S1.

Cerebral palsy, epilepsy and febrile seizures showed no association with NT > 99th percentile (Table 2), and we found no association between NT 95th–99th percentile and any of the investigated neurological or psychiatric diagnoses.

DISCUSSION

In euploid children, NT > 99th percentile at first-trimester screening was associated with an increased risk of intellectual disability and ASD. There was no association between NT > 99th percentile and cerebral palsy, epilepsy or febrile seizures. We found no correlation between fetal NT 95th–99th percentile and neurodevelopmental disorders. Thus, based on this very large unselected cohort, we can reassure parents of an expected normal outcome for euploid fetuses with NT 95th–99th percentile. Based on our findings, parents should be informed that

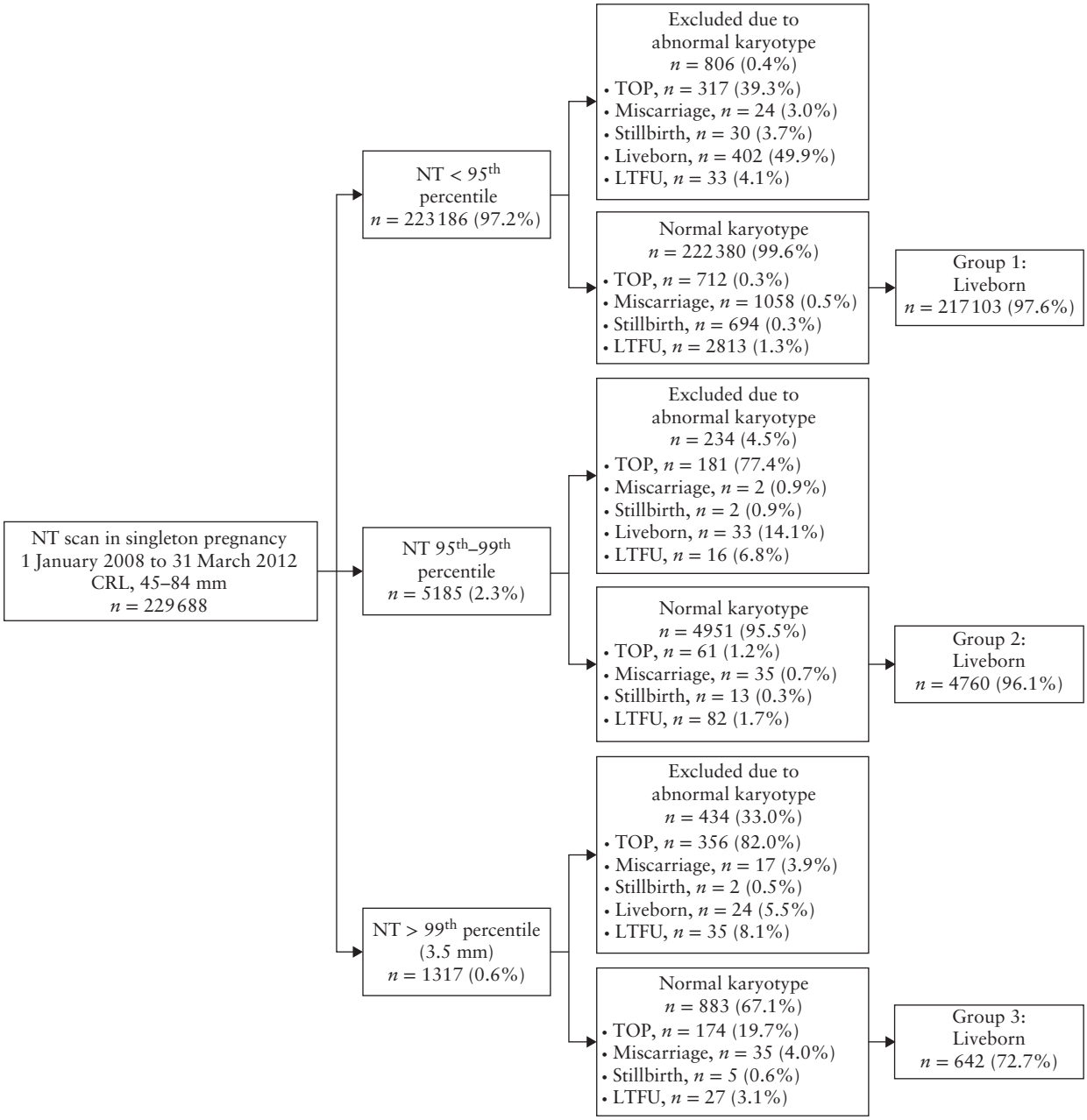

Figure 1 Flowchart of study inclusion of children with first-trimester nuchal translucency (NT) assessment. CRL, crown–rump length; LTFU, lost to follow-up; TOP, termination of pregnancy.

the risk of intellectual disability and ASD is increased in euploid fetuses with NT > 99th percentile, but the absolute risk is reassuringly low (< 1%).

In a review in 2010, Bilardo *et al.*[11] addressed the difficulties in parental counseling when increased NT is detected in euploid children. They emphasized the need for large-scale studies with long-term follow-up of infants to provide reliable data and prevent underestimation of neurodevelopmental disorders. Our study provides complementary information to prior research on neurodevelopment in euploid children through longer follow-up and investigation of specific neurological diagnoses.

In a long-term follow-up study, Äyräs *et al.*[8] investigated 691 children with NT > 95th percentile at a mean age of 6.5 years, identified through national Finnish databases. Based on ICD-10 codes, neurodevelopmental disorders were found in 4.2% of children, which is comparable with our estimate of 4.7% (253/5402) of children with NT > 95th percentile. The Finnish study, however, did not include a control group. We found that as many as 4.7% (10 171/217 103) of controls had an ICD-10 code suggesting a neurodevelopmental disorder.

Senat *et al.*[12] assessed the development of 160 euploid children with fetal NT > 99th percentile by clinical examination and questionnaire at 2 years of age. Developmental delay was detected in 1.2% of cases, as well as in controls. Miltoft *et al.*[9] found a similar prevalence in a questionnaire-based study of 80 children

Table 1 Characteristics of study groups of euploid children according to prenatal nuchal translucency (NT) thickness

Characteristic	*Group 1: NT < 95th percentile (n = 217 103)*	*Group 2: NT 95th–99th percentile (n = 4760)*	P*	*Group 3: NT > 99th percentile (n = 642)*	P†
Maternal age (years)	29.9 ± 4.9	30.1 ± 4.9	0.001	30.0 ± 5.1	0.348
Maternal BMI (kg/m^2)‡	23 (21–26)	23 (21–26)	0.001	23 (20–27)	0.967
Smoker§	22 757 (10.5)	598 (12.6)	< 0.001	81 (12.6)	0.070
Mode of conception¶					
Spontaneous	197 350 (90.9)	4310 (90.5)	0.249	590 (91.9)	0.441
Intrauterine insemination	3101 (1.4)	76 (1.6)	0.336	10 (1.6)	0.790
Ovulation induction	1977 (0.9)	38 (0.8)	0.417	1 (0.2)	0.044
IVF	8309 (3.8)	199 (4.2)	0.212	24 (3.7)	0.895
NT thickness (mm)	1.6 (1.4–1.9)	2.8 (2.6–3.0)		4.0 (3.7–4.5)	
Risk for trisomy 21 (1 in *n*)**	8806 (3637–15 002)	538 (190–1204)		46 (14–111)	
Fetal malformation on 20-week scan	1200 (0.6)	58 (1.2)	< 0.001	10 (1.6)	0.001
GA at delivery (days)	281 (273–287)	281 (273–287)	0.780	280 (272–288)	0.704
Birth weight (g)††	3508.7 ± 562.6	3584.2 ± 568.9	< 0.001	3551.9 ± 626.7	0.053
Male neonate	110 753 (51.0)	2985 (62.7)	< 0.001	397 (61.8)	< 0.001
Chromosomal analysis	8021 (3.7)	1648 (34.6)	< 0.001	591 (92.1)	< 0.001
Age at follow-up (years)	4.4 ± 1.2	4.2 ± 1.2	< 0.001	4.3 ± 1.2	0.072

Data are given as mean ± SD, median (interquartile range) or *n* (%). *Group 2 *vs* Group 1. †Group 3 *vs* Group 1. Data missing for: ‡5733 (Group 1), 138 (Group 2), 23 (Group 3) cases; §1213 (Group 1), 35 (Group 2), 7 (Group 3) cases; ¶6366 (Group 1), 137 (Group 2), 17 (Group 3) cases; **1104 (Group 1), 26 (Group 2), 5 (Group 3) cases; ††1617 (Group 1), 33 (Group 2), 7 (Group 3) cases. BMI, body mass index; GA, gestational age; IVF, *in-vitro* fertilization.

Table 2 Neurodevelopmental outcome in study groups of euploid children according to prenatal nuchal translucency (NT) thickness

Outcome	*All (n = 222 505)* (n)	*Reference Group 1: NT < 95th percentile (n = 217 103)* (n (%))	*Group 2: NT 95th–99th percentile* (n = 4760)		*Group 3: NT > 99th percentile* (n = 642)	
			n (%)	OR (95% CI)	n (%)	OR (95% CI)
No impairment	212 081	206 932 (95.32)	4538 (95.34)		611 (95.17)	
Any impairment	10 424	10 171 (4.68)	222 (4.66)	1.00 (0.87–1.14)	31 (4.83)	1.03 (0.72–1.48)
Intellectual disability	116	110 (0.05)	4 (0.08)	1.72 (0.63–4.67)	2 (0.31)	6.16 (1.51–25.0)
ASD	706	686 (0.32)	15 (0.32)	1.00 (0.60–1.66)	5 (0.78)	2.48 (1.02–5.99)
Childhood autism	338	327 (0.15)	9 (0.19)	1.10 (0.57–2.14)	2 (0.31)	1.82 (0.45–7.32)
Cerebral palsy	547	533 (0.25)	11 (0.23)	0.94 (0.52–1.71)	3 (0.47)	1.91 (0.61–5.95)
Epilepsy	1148	1120 (0.52)	23 (0.48)	0.94 (0.62–1.42)	5 (0.78)	1.51 (0.63–3.66)
Febrile seizures	8141	7950 (3.66)	174 (3.66)	1.00 (0.86–1.16)	17 (2.65)	0.72 (0.44–1.16)
ICD-10 G-group diagnosis	3701	3591 (1.65)	89 (1.87)	1.13 (0.92–1.40)	21 (3.27)	2.01 (1.30–3.11)

ASD, autism spectrum disorder; ICD-10, International Classification of Diseases, tenth revision; OR, odds ratio.

with fetal NT > 99th percentile. At 2 years of age, 1.3% of children presented developmental delay, the same prevalence as in the control group with fetal NT < 95th percentile. The finding of uniform rates of overall neurodevelopmental impairment in children with NT > 99th percentile and in the control group is similar to our findings. The discordant incidence of developmental delay between the former two studies and ours is probably due to differences in outcome assessment and follow-up time; in our study, only 2.1% (15/706) of ASD cases were diagnosed at 2 years of age.

In accordance with previous studies, we found a larger proportion of male fetuses among children with increased NT[19,20], as well as a larger proportion of fetal malformations[3,5]. No children with NT > 99th percentile and a diagnosis of intellectual disability or ASD had a prenatally detected malformation.

If children with structural malformations ($n = 2483$) had been excluded, our results would have remained the same, though the association between NT > 99th percentile and intellectual disability and ASD would have been statistically stronger (OR, 7.2 (95% CI, 1.77–29.18) and OR, 2.6 (95% CI, 1.09–6.37), respectively).

In our population, only 2.8% of fetuses had a NT > 95th percentile, and 0.6% had a NT > 99th percentile, which is lower than expected but similar to the findings of Miltoft *et al.*[9].

We found a lower prevalence of intellectual disability in our cohort (0.05%, 116/222 505) compared with the 0.3–1.4% prevalence reported in previous studies[21–24]. However, these studies investigated

unselected populations, which is the probable cause of the discordance. It is noteworthy that the lowest previously reported prevalences of intellectual disability (0.3%) are from two Scandinavian studies on unselected children, indicating a lower prevalence in this region than in other parts of the world[22,23].

Strengths and limitations of the study

Our study investigated the general population and includes the largest such sample to date, followed-up to a mean of 4.4 years. The size of the sample enabled us to examine separately the impact of NT > 99th percentile and NT 95th–99th percentile. We compared all results with our control group of children with normal prenatal NT, which further strengthens the study. The results are based on diagnoses made by physicians and are thus less prone to bias than are studies based on parental evaluation. This register-based study has the advantage of a low rate of missing data compared with studies assessing long-term outcome by questionnaire or clinical examination. The 1.3% of pregnancies that were lost to follow-up can, for the most part, be attributed to migration and Danish citizens who lived and gave birth in Sweden after having first-trimester risk assessment in Denmark.

Outcome assessment was based exclusively on ICD-10 codes from the NPR and DPCR and was not verified by other independent sources. However, validation studies of these registries have shown high positive predictive value for the diagnoses of interest[25–27]. Our risk assessment included only diagnoses with certain neurological impairment and thus did not include the risk of genetic syndromes that may affect neurodevelopment. However, exclusion of children with chromosomal abnormalities resulted in the inclusion of very few children with genetic syndromes in the cohort.

We defined children as euploid if they had no pathogenic chromosomal analysis reported in the DCCR. The inclusion of children with undiagnosed chromosomal abnormalities might bias the estimates. However, because of the size of the control group and the expected few cases, this bias is expected to be small owing to dilution. Prenatal array CGH is now offered to cases with NT > 99th percentile, but this was not the case during our study period.

Bias may result if the NT estimate was associated with a propensity to discovering neurodevelopmental disorders, e.g. if parents with a fetus with NT > 99th percentile had a higher propensity for seeking medical care for their child. However, in a system with universal, free healthcare, this scenario is unlikely for severe neurodevelopmental disorders.

Importantly, even in a study with more than 220 000 pregnancies, few were diagnosed with intellectual disability among those with NT > 99th percentile, and the statistical power is consequently limited for some of the key outcomes. On the other hand, the low occurrence and low absolute risk of neurodevelopmental disorders are reassuring from a parental perspective. Neurodevelopmental disorders are diagnosed rarely in early childhood, thus the relatively short follow-up will result in unidentified cases within our study cohort. Future follow-up of our cohort would validate our findings and contribute valuable information.

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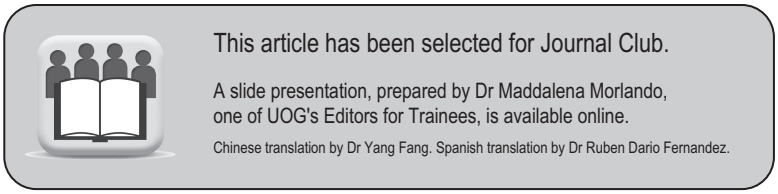
SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Diagnoses belonging to the ICD-10 G-group (diseases of the neurological system) among children with nuchal translucency thickness > 99th percentile



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El aumento del grosor de la traslucencianucal y el riesgo de trastornos del desarrollo neurológico

RESUMEN

Objetivo Investigar la asociación entre el grosor de la traslucencia nucal (TN) fetal y los trastornos del desarrollo neurológico en niños/as euploides.

Métodos Este estudio incluyó a 222 505 niños/as euploides que habían sido objeto de un cribado rutinario fetal durante el primer trimestre. Los niños/as se separaron en tres grupos, de acuerdo con la TN prenatal: TN < percentil (p) 95° (n = 217 103 (97,6%)); percentil 95°-99° (n = 4760 (2,1%)) para la TN; y TN > percentil 99° (n = 642 (0,3%)). Se dio seguimiento a todos los niños/as hasta una edad promedio de 4,4 años. La información sobre el diagnóstico de discapacidad intelectual, trastornos del espectro autista (TEA), parálisis cerebral, epilepsia y convulsiones febriles se obtuvo de registros nacionales de pacientes.

Resultados No se encontró un exceso de riesgo de trastornos del desarrollo neurológico en niños/as euploides con TN en percentil 95°-99° en el primer trimestre. Para los niños/as con TN > percentil 99° se encontró un mayor riesgo de discapacidad intelectual (razón de momios (RM) 6,16 (IC 95%, 1,51–25,0), 0,31%) y de TEA (RM 2,48 (IC 95%, 1,02–5,99), 0,78%) en comparación con niños/as con TN < p 95° (incidencia del 0,05% para la discapacidad intelectual y del 0,32% para los TEA); sin embargo, no se detectó un incremento del riesgo de parálisis cerebral (RM 1,91 (IC 95%, 0,61–5,95), 0,47%), epilepsia (RM 1,51 (IC 95%, 0,63–3,66), 0,78%) o convulsiones febriles (RM 0,72 (IC 95%, 0,44–1,16), 2,65%).

Conclusiones En una cohorte no seleccionada de gran tamaño de niños/as euploides no se encontró un riesgo mayor de trastornos del desarrollo neurológico entre aquellos con un percentil 95°-99° de la TN en el primer trimestre. Entre los niños/as euploides con TN > percentil 99° en el primer trimestre se encontraron mayores riesgos de discapacidad intelectual y TEA, pero el riesgo absoluto fue tranquilizadoramente bajo (<1%).

颈项透明层增厚和神经发育障碍的风险

目的：研究整倍体儿童中胎儿颈项透明层（nuchal translucency，NT）厚度和神经发育障碍间的关系。

方法：研究纳入在胎儿期进行常规孕早期筛查的 222 505 例整倍体儿童。根据产前 NT，将儿童分为 3 组：NT<第 95 百分位数（*n*=217 103，97.6%），NT 为第 95 百分位数~第 99 百分位数（*n*=4760，2.1%），NT>第 99 百分位数（*n*=642，0.3%）。对所有儿童进行随访，至平均年龄 4.4 岁。从国家患者登记处获得智障、自闭症谱系障碍（autism spectrum disorders，ASD）、脑性瘫痪、癫痫及热性惊厥的诊断信息。

结果：孕早期 NT 为第 95 百分位数~第 99 百分位数的整倍体儿童中，未见神经发育障碍风险过高。NT>第 99 百分位数的儿童与 NT<第 95 百分位数的儿童相比，发生智障[比值比（odds ratio，OR），6.16（95% CI，1.51~25.0），0.31%]和 ASD[OR，2.48（95% CI，1.02~5.99），0.78%]的风险增加（智障的发生率为 0.05%，ASD 为 0.32%），然而未见脑性瘫痪[OR，1.91（95% CI，0.61~5.95），0.47%]、癫痫[OR，1.51（95% CI，0.63~3.66），0.78%]及热性惊厥[OR，0.72（95% CI，0.44~1.16），2.65%]的风险增加。

结论：在大型未经选择的整倍体儿童队列中，孕早期 NT 为第 95 百分位数~第 99 百分位数的儿童中神经发育障碍风险未见增加。孕早期 NT>第 99 百分位数的整倍体儿童中，智障和 ASD 风险增加，所幸的是绝对风险较低（<1%）。