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Nausea and Vomiting during Pregnancy and Neurodevelopmental Outcomes in Offspring

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Abstract

Background—Nausea and vomiting of pregnancy (NVP) is the most common complication of pregnancy. NVP has been associated with improved fetal outcomes, but its association with childhood neurodevelopmental outcomes has rarely been studied.

Methods—Subjects were children aged 5–12 years (n=560) who were controls in a previously conducted case-control study of prenatal risk factors for craniofacial malformations. Information on NVP, including trimester, duration, and treatment, was collected through a maternal interview conducted within three years of delivery. Neurocognition was assessed using the Peabody Picture Vocabulary Test (PPVT-III) and the Beery-Buktenica Test of Visual Motor Integration (VMI-5). Psychosocial outcomes, including internalizing and externalizing behavior problems, were measured by maternal-report using the Child Behavior Checklist (CBCL) and teacher-report, using the Teacher Report Form (TRF). Linear regression models were used to calculate adjusted mean differences (adjMD) and 95% confidence intervals (CI) on test scores for children exposed and unexposed to NVP in-utero. Differences based on trimester, duration, and treatment were assessed.

Results—NVP was reported among 63% of women and was most common in early pregnancy. Children exposed to NVP performed worse on the VMI-5 (adjMD:−3.04; CI: −5.02, −1.06), but exhibited few other differences from unexposed children. Durations of NVP ≥ 4 months were associated with poorer scores on PPVT-III (adjMD: −2.52), VMI-5 (adjMD: −5.41), and CBCL (adjMD:3.38(Internalizing) and adjMD:4.19(Externalizing)).

Conclusions—Overall there were few differences between children exposed and unexposed to NVP. NVP was associated with slightly worse visual-motor performance, and prolonged NVP and NVP extending late into pregnancy were associated with poorer scores on several neurodevelopmental measures.

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Keywords

nausea and vomiting; pregnancy; neurocognitive; psychosocial; childhood

Nausea and vomiting during pregnancy (NVP) is the most common pregnancy complication, affecting an estimated 50% to 80% of all pregnancies.^{1–3} NVP peaks between 8 and 12 weeks of gestation and usually subsides by the beginning of the second trimester. Approximately 90% of women with NVP report no further symptoms after 20 weeks of gestation.⁴ NVP is viewed as a marker of a healthy pregnancy and has been linked to improved fetal outcomes, including reduced risks of spontaneous abortion,^{5, 6} preterm birth⁷ and birth defects.⁸ Suggested explanations for this fetoprotective effect of NVP include stimulation of placental growth through reduced energy intake and nutrient partitioning due to changes in hormone secretion⁹ and reduced exposure to teratogens.¹⁰

NVP is thought to be the consequence of hormonal changes as a result of pregnancy, specifically increased levels of human chorionic gonadotrophin (hCG) and free thyroxine (FT4), and decreased levels of thyroid-stimulating hormone (TSH).¹¹ FT4, a thyroid hormone, is essential in fetal brain development, with reports of delayed mental and motor function in children of women with hypothyroxinaemia.^{12–14} It follows that children of women who experienced NVP may have improved neurocognitive outcomes if their levels of FT4 are increased. In a recent study, children of women who experienced NVP had higher scores on several measures of intelligence compared with children of women that did not experience NVP.¹⁵ On the other hand, the most severe form of NVP, hyperemesis gravidarum (HG), has been associated with psychological disorders in offspring.¹⁶ Although associations between NVP and improved fetal outcomes have been demonstrated, little is known about its association with subsequent childhood neurocognitive and psychosocial outcomes.

The objective of this study was to examine the association between maternal NVP and measures of childhood neurocognitive and psychosocial outcomes using a contemporary cohort of children in the United States.

Methods

Eligible participants were children aged 5 to 12 whose mothers previously participated in a case-control study of risk factors for hemifacial microsomia (HFM), a type of structural birth defect. The case-control study included children born in 1996 through 2002, and details of that study are described elsewhere.¹⁷ Mothers of the children that participated in the case-control study were contacted by phone and invited to participate in a follow-up study when their child reached an age of 5 to 6 years old. Of the 1106 subjects eligible for follow-up, 704 (64%) participated in the follow-up study. The present analysis is restricted to singleton control children (n=560). To isolate the effects of NVP on neurodevelopment, we excluded children with HFM, who have elevated risks for prenatal abnormalities¹⁸ and developmental delays in childhood.¹⁹ This study was approved by the Institutional Review Board at Boston University and was completed in compliance with HIPAA standards.

Outcome Measures

Neurocognitive—Verbal and nonverbal functions were assessed using the Peabody Picture Vocabulary Test – Third Edition (PPVT-III) and the Beery-Buktenica Developmental Test of Visual Motor Integration- Fifth Edition (VMI-5), respectively. These tests were administered by classroom teachers and have been demonstrated to be both reliable and accurate.^{20,21} Details regarding the testing procedures are described elsewhere.¹⁹ Standardized scores with a normative mean of 100 and a standard deviation of 15 were calculated for each test.

Psychosocial

The Child Behavior Checklist (CBCL) and the Teacher Report Form (TRF) were used to provide measures of psychosocial outcomes from parent-report and teacher-report, respectively. Item content is similar and both tests provide measures of internalizing behavior problems (e.g. shy, withdrawn) and externalizing behavior problems (e.g. hyperactive, disruptive). T-scores are calculated for Internalizing and Externalizing composite scores (mean=50, SD=10). Information regarding the administration and internal consistency of these tests has been detailed elsewhere.²²

Nausea and Vomiting

Data on NVP was collected as part of the case-control study through a structured maternal interview conducted within three years of delivery, with an average time to interview of one year after delivery. Mothers were asked if they had nausea with or without vomiting at any point from the month prior to their last menstrual period (LMP) through five months after the LMP. Since nausea and vomiting occurs most frequently in the earliest weeks of pregnancy, this assessment is expected to capture the most relevant time period with respect to onset of NVP. Children were classified as exposed to NVP if their mother reported experiencing an onset of NVP prior to 20 weeks of gestation, otherwise they were considered unexposed. Information on duration of NVP and treatment, including medication type and start and stop dates of medication usage, was also obtained. Duration of NVP was categorized as either long or short. Long durations were defined as those lasting ≥ 4 lunar months independent of timing of onset.³ Mothers that reported treating their NVP were classified into the treated NVP group, while those with NVP and no treatment were in the untreated NVP group. Data on hyperemesis gravidarum was not specifically asked, but mothers reporting NVP requiring treatment with intravenous fluids were excluded (n=1).

Statistical Analysis

Demographic and reproductive characteristics were summarized for mother-child pairs with and without any reported NVP during pregnancy. Average mean scores on the neurocognitive tests, PPVT-III and VMI-5, and psychosocial tests, CBCL and TRF, were calculated for children exposed to NVP and those unexposed to NVP. Multivariable linear regression models adjusted for child's sex, maternal age (< 25, 26–34, ≥ 35), maternal race/ethnicity (white, black, Hispanic, other), maternal education (<12, 12, 13–15, ≥ 16 years) and household income (<25,000, 25–34,999, 35–64,999, ≥ 65,000), were used to calculate the mean difference (adjMD) between the two groups on neurocognitive and psychosocial

outcome measures. Covariates were identified a priori based on known associations with both NVP and neurodevelopment and were included in all regression models.

In secondary analyses planned a priori, adjusted linear regression models were also used to assess how associations of NVP with neurodevelopmental outcomes varied with trimester of NVP, categorized into 5 groups: (1) 1st trimester only; (2) 1st and 2nd trimester; (3) 1st, 2nd, and 3rd trimester; (4) 2nd trimester only; (5) 2nd and 3rd trimester. Due to small numbers of women in groups (4) and (5), these were combined creating a category of women with NVP onset in the 2nd trimester. NVP onset beyond the 2nd trimester, which is expected to be a very rare event, was not captured due to the structure of the interview. AdjMDs between test scores based on duration of NVP, regardless of timing, were also calculated for children exposed to (1) long durations of NVP (≥ 4 months) and (2) short durations (<4 months) of NVP. We also assessed whether outcome measures differed for offspring whose mothers were (1) treated for NVP and (2) untreated for NVP. Children of women with no NVP were used as the reference group for all analyses.

Models were weighted using the inverse probability of participation to assess the potential impact of participation bias due to measured covariates. Inverse probability weights (IPW) were determined from fitting a logistic regression model in which participation was predicted by: maternal age, race, education, marital status, household income, and child sex. We also performed a sensitivity analysis removing children of mothers with hypothyroidism due to the association between hypothyroidism with both NVP and neurodevelopment. All analyses were performed using SAS Software Version 9.3.

Results

Among the 560 singleton children included in this study, 63% of their mothers reported NVP. Women with NVP were more often white non-Hispanic (76.8% versus 73.4%) and were more highly educated than women without NVP. NVP occurred less frequently in older mothers and mothers with a previous miscarriage. Pre-pregnancy BMI, multivitamin use, and infant sex were similar between the two groups (Table 1).

Among mothers with NVP, nearly 96% experienced NVP in their 1st trimester (Table 2). Less than 20% of women had NVP extending into the 3rd trimester. The majority of NVP lasted less than 4 months. Mothers with short durations of NVP tended to be white, non-Hispanic, older, and more educated, and they less frequently reported cigarette smoking during the pregnancy, among other differences (Supplemental Table 1). Among the 21% of mothers that treated their NVP, antihistamine-antiemetics were used most frequently. There were few differences in covariate distributions for mothers who treated their NVP compared to those who did not (Supplemental Table 2).

Neurocognitive Outcomes

Adjusted mean PPVT-III scores were similar among children exposed to NVP and children unexposed to NVP with an adjMD of −0.58 (95% CI: −3.10, 1.94), while VMI-5 scores were lower (i.e., worse) among children with NVP (adjMD: −3.04; 95% CI: −5.02, −1.06). Compared with children unexposed to NVP, children exposed to NVP in all trimesters of

pregnancy had poorer outcomes on both neurocognitive measures, but differences were most notable for the VMI-5 test (adjMD: -5.78). NVP in the 1st trimester only was associated with slightly improved PPVT-III scores and worse VMI-5 scores. Long durations of NVP were associated with poorer outcomes with adjMDs of -2.52 (95% CI: $-6.59, 1.54$) and -5.41 (95% CI: $-8.62, -2.20$) for PPVT-III and VMI-5 scores, respectively, while smaller differences of -0.22 ($-2.86, 2.43$) for the PPVT-III test and -2.57 ($-4.66, -0.48$) for the VMI-5 test were observed for short durations of NVP. Treatment differences were associated with lower scores for children with mothers who did not treat NVP than those with mothers who used any treatment when both were compared to those without any NVP (Table 3).

Psychosocial Outcomes

Adjusted mean scores for mother-reported internalizing and externalizing behavior problems were slightly higher, i.e. there were greater behavior problems, for children exposed to NVP compared with children unexposed to NVP, while there was less difference in behavior problems according to teacher-report. Compared with children unexposed to NVP, children exposed to NVP in all trimesters of pregnancy had poorer outcomes on most psychosocial measures. Differences were most notable for the CBCL scales (adjMDs: 3.23 ; 95% CI: $0.54, 5.92$ for internal and 3.67 ; 95% CI: $0.94, 6.41$ for external). TRF scores were poorer in the group of children exposed to NVP onset in the 2nd trimester, but this assessment was based on only 12 children (Table 4).

Long durations of NVP were more strongly associated with mother-reported behavior problems than were short durations of NVP, with adjMDs of 3.38 (95% CI: $0.82, 5.94$) and 0.38 (95% CI: $-1.37, 2.12$) for internalizing behavior problems and 4.19 (95% CI: $1.58, 6.79$) and 0.55 ($-1.22, 2.32$) for externalizing behavior problems. Results for duration of maternal NVP and TRF scores were less pronounced and, in the case of internalizing behavior problems, the mean difference was largest for the short duration group.

Using children unexposed to NVP as the referent group, there was little difference between psychosocial outcomes for either treated or untreated NVP. Treatment of NVP with antihistamine-antiemetics, specifically, was associated with slightly poorer scores on all tests than the overall treated group, when both were compared to children unexposed to NVP. However, the null value was within the 95% confidence limits for all these associations (Table 4).

Sensitivity Analyses

Weighting linear regression models by the inverse probability of participation did not greatly alter findings of associations between any NVP and neurodevelopmental outcomes, although there was some attenuation in mean differences for TRF tests. Approximately 2% of mothers with NVP and 3% of mothers without NVP reported taking medication for hypothyroidism during their pregnancy. Removing children of mothers with a reported thyroid condition ($n=14$), did not meaningfully change overall results (data not shown).

Comments

Children exposed to NVP did not differ from children unexposed to NVP with respect to the majority of neurocognitive and psychosocial outcomes evaluated. However, those exposed to NVP scored lower than unexposed children on the VMI-5, a measure of visual-motor performance. These associations were relatively small in magnitude ($\sim .2$ to $.4$ standard deviations), and average scores for children in both groups were within the normative range. Nonetheless, a shift of this magnitude for an entire population would likely have clinically meaningful effects, particularly in relation to a risk factor as common as NVP. Poorer outcomes on most measures were observed for long durations and late timing of NVP, although these observations were based on small numbers. Children exposed to longer durations of NVP had lower adjusted mean scores on both neurocognitive tests and had more behavior problems, with the exception of teacher-reported internalizing behavior, than those unexposed to NVP. NVP later in gestation was associated with poorer scores on most measures of neurocognition and psychosocial behavior.

Shorter durations of NVP and NVP limited to the 1st or 1st and 2nd trimesters were associated only with poorer outcomes on the VMI-5, a measure of visual-motor integration. Mechanisms that might account for an NVP association restricted to visual-motor skills, but not receptive language, are unclear. Neurocognitive functions might be differentially affected depending on the type and timing of nutritional deficiencies and similar insults during pregnancy.²³ NVP might represent such an insult, though plasticity in fetal/infant brain development and environmental influence may offset the effects of such insults by ages 5–12 years. To our knowledge, there are no studies that have investigated timing and duration of NVP in relation to cognitive performance. Our findings regarding 2nd and 3rd trimester exposure to NVP are consistent with another study in which NVP late in pregnancy was associated with teacher-reported behavior problems.²⁴ NVP later in pregnancy may have a different underlying etiology, with greater consequences for fetal development. Alternatively, regardless of the biological underpinnings, the fetus may be more susceptible at this time due to the brain growth and formation that takes place toward the end of pregnancy.²⁵

In this study, children whose mothers received treatment for NVP had slightly better visual-motor scores than those whose mothers did not treat their NVP, although both groups still had poorer scores than children of women with no NVP. This finding stands in contrast to that of a Canadian study, in which children of women with untreated NVP had the highest scores on tests of visual-motor integration.¹⁵ In the present study, approximately 23% of mothers reported treatment of NVP, which is similar to that reported in two prior studies (15% and 20%).^{2, 26} The higher rate of 49% in the Canadian study is likely due to the study sample, which contained women who were ascertained through a pregnancy information service. One possible reason why associations with neurodevelopment could differ for treated versus untreated NVP is that treatment may be a marker of greater severity or longer duration of NVP, either of which may magnify the strength of association with development. Although we do not have information on severity, treatment of NVP was more common among women with a long duration of NVP, 31.1%, compared to 18.0% of those with short durations of NVP. If the sample of women in the Canadian study had more severe NVP on

average, it may explain the discrepant findings. It is also possible that the treatment itself has an effect on fetal brain development, but the mechanism by which this might occur is unknown.

Because we did not measure severity of NVP, the exposure definition was broad and captured illness ranging from minor nausea alone to severe nausea with vomiting. As a result, we were unable to assess the association between severity of NVP and outcome measures. Additionally, because we asked about NVP onset in the first half of pregnancy we could not investigate associations with late onset NVP. In the present study information on NVP onset was only asked with regard to the first five months of pregnancy, but late onset NVP would affect < 5% of pregnancies.³ We collected information on treatment of NVP, though the number of women using medications other than antihistamine-antiemetics was small, limiting our ability to evaluate treatment of NVP with other medications. Data on NVP were self-reported by the mother up to 3 years after delivery, which may be subject to bias or poor recall. However, the prevalence of 61% in our study is very comparable to a recent meta-analysis reporting a prevalence of 69% in the United States.²⁷

A strength of our study was the use of a well-developed structured interview that collected detailed information on NVP and confounders prior to childhood neurodevelopmental testing. Any misclassification of NVP is expected to be non-differential with respect to the outcome, since this information was collected prior to outcome measurement. If anything, such misclassification could have attenuated findings. PPVT-III, VMI-5, and TRF tests are all standardized measures, administered by classroom teachers under uniform guidelines, with excellent reliability and validity. We assessed potential participation bias by applying inverse probability weights, with minimal change in results. Lastly, the evaluation of several outcomes and multiple different classifications of exposures raises the possibility of chance findings in sub-groups analyzed.

These findings did not support the hypothesis that in-utero exposure to NVP is associated with improved neurocognitive and psychosocial outcomes in childhood. NVP was associated with worse visual-motor skills, but only minimally associated with other neurocognitive and psychosocial measures. Longer durations of NVP and NVP late in pregnancy were associated with worse performance on several outcome measures. Future research should focus on the complex combination of onset, duration, treatment and severity of NVP and address the potential mechanisms by which NVP affects neurocognitive and psychosocial outcomes in offspring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and Reproductive Characteristics of Women with and without Nausea and Vomiting during Pregnancy

	NVP (n=353)		No NVP (n=207)	
	n	%	n	%
Maternal Race/Ethnicity				
White, non-Hispanic	271	76.8	152	73.4
Hispanic	42	11.9	25	12.1
Black, non-Hispanic	27	7.6	21	10.1
Other	13	3.7	9	4.3
Maternal Age at Conception				
25	89	25.2	51	24.6
26–34	210	59.5	116	56.0
35	54	15.3	40	19.3
Maternal Education (years)				
<12	31	8.8	25	12.1
12	70	19.8	44	21.3
13–15	84	23.8	49	23.7
16	167	47.3	89	43.0
Missing	1	0.3	0	0.0
Marital Status				
Married/Cohabiting	315	89.2	183	88.4
Single/Divorced/Separated	38	10.8	24	11.6
Family Income (USD)				
<25,000	52	14.7	40	19.3
25–34,999	43	12.2	25	12.1
35–64,999	116	32.9	60	29.0
65,000	124	35.1	70	33.8
Missing	17	4.8	12	5.8
Pre-pregnancy BMI (kg/m²)				
<18.5	11	3.1	8	3.9
18.5–24.9	222	62.9	128	61.8
25–29.9	74	21.0	41	19.8
30	42	11.9	26	12.6
Missing	4	1.1	4	1.9
Gravidity				
0	119	33.7	70	33.8
1	117	33.1	63	30.4
2	117	33.1	74	35.7
Previous Miscarriage				

	NVP (n=353)		No NVP (n=207)	
	n	%	n	%
No	298	84.4	165	79.7
Yes	55	15.6	42	20.3
Cigarette Use at Conception				
None/Unknown	299	84.7	172	83.1
10/day	28	7.9	17	8.2
>10 /day	26	7.4	18	8.7
Multivitamin Use				
Yes	116	32.9	68	32.9
No	237	67.1	139	67.1
Infant Sex				
Male	175	49.6	104	50.2
Female	178	50.4	103	49.8
Hypothyroidism				
Yes	8	2.3	6	2.9
No	345	97.7	201	97.1

Table 2
Characteristics of Nausea and Vomiting of Pregnancy by Trimester, Duration, and Treatment

Any NVP (n=353)	Total n (%)	Duration		Treatment	
		4 months n (%)	<4 months n (%)	Yes n (%)	No n (%)
Trimester					
1st only	90 (25.5)	0 (0.0)	90 (100.0)	12 (13.3)	78 (86.7)
1st, 2nd	183 (51.8)	7 (3.8)	176 (96.2)	38 (20.8)	145 (79.2)
1st, 2nd, 3rd	65 (18.4)	64 (98.5)	1 (1.5)	21 (32.3)	44 (67.7)
2nd only	8 (2.3)	0 (0.0)	8 (100.0)	1 (12.5)	7 (87.5)
2nd, 3rd	4 (1.1)	2 (50.0)	2 (50.0)	1 (25.0)	3 (75.0)
Duration					
4 months	73 (20.7)	---	---	23 (31.5)	50 (68.5)
<4 months	277 (78.5)	---	---	50 (18.1)	227 (81.9)
Treatment					
Yes	73 (20.7)	23 (31.5)	50 (68.5)	---	---
No	280 (79.3)	50 (17.9)	227 (81.1)	---	---

3 women missing information on duration

Table 3

Adjusted Mean Differences for Neurocognitive Outcomes by Trimester, Duration, and Treatment of Nausea and Vomiting of Pregnancy

		PPVT-III		VMI-5	
		Mean (SE) ^a	Difference ^a (95%CI)	Mean (SE) ^a	Difference ^a (95%CI)
NVP					
No (n=207)		102.4 (1.4)	0.0 (Reference)	97.7 (1.1)	0.0 (Reference)
Yes (n=353)		101.9 (1.3)	-0.58 (-3.10, 1.94)	94.6 (1.0)	-3.04 (-5.02, -1.06) ^c
Trimester of NVP					
1st Only (n=90)		103.6 (1.9)	1.20 (-2.44, 4.85)	94.1 (1.5)	-3.64 (-6.52, -0.75) ^c
1st and 2 nd (n=183)		101.0 (1.5)	-1.35 (-4.29, 1.59)	95.4 (1.2)	-2.29 (-4.60, 0.03)
1st, 2nd, and 3 rd (n=65)		100.0 (2.1)	-2.34 (-6.61, 1.93)	91.9 (1.7)	-5.78 (-9.14, -2.41) ^c
2nd Only, 2nd and 3 rd (n=12)		105.0 (4.2)	2.62 (-5.69, 10.93)	97.8 (3.3)	0.10 (-6.47, 6.66)
Duration					
Long (4 months) (n=73)		99.9 (2.0)	-2.52 (-6.59, 1.54)	92.4 (1.6)	-5.41 (-8.62, -2.20) ^c
Short (<4 months) (n=277)		102.3 (1.4)	-0.22 (-2.86, 2.43)	95.2 (1.1)	-2.57 (-4.66, -0.48) ^c
Treatment					
Treated NVP (n=73)		101.7 (2.3)	0.36 (-3.46, 4.18)	96.1 (1.6)	-1.58 (-4.62, 1.46)
Antihistamine-antiemetics ^b (n=32)		103.2 (2.8)	0.50 (-4.91, 5.91)	94.2 (2.1)	-3.40 (-7.55, 0.76)
Untreated NVP (n=280)		100.1 (1.9)	-1.31 (-3.93, 1.32)	94.2 (1.1)	-3.46 (-5.55, -1.37) ^c

^a Adjusted for child's sex, maternal age, maternal race, maternal education, and household income

^b Antihistamine-antiemetic group is a subgroup of subjects in the any treatment group

^c p-value < 0.05

Table 4

Adjusted Mean Differences for Psychosocial Outcomes by Trimester, Duration, and Treatment of Nausea and Vomiting of Pregnancy

	CBCL: Internal			CBCL: External			TRF: Internal			TRF: External		
	Mean ^d (SE)	Difference ^d (95%CI)	Mean ^d (SE)	Difference ^d (95%CI)	Mean ^d (SE)	Difference ^d (95%CI)	Mean ^d (SE)	Difference ^d (95%CI)	Mean ^d (SE)	Difference ^d (95%CI)	Mean ^d (SE)	Difference ^d (95%CI)
NVP												
No (n=207)	47.4 (0.9)	0.0 (Reference)	47.3 (0.9)	0.0 (Reference)	47.3 (0.9)	0.0 (Reference)	48.9 (0.8)	0.0 (Reference)	48.9 (0.8)	0.0 (Reference)	48.9 (0.8)	0.0 (Reference)
Yes (n=353)	48.5 (0.9)	1.13 (-0.53, 2.79)	48.7 (0.9)	1.46 (-0.23, 3.15)	48.1 (0.8)	0.81 (-0.81, 2.43)	49.6 (0.8)	0.70 (-0.83, 2.23)	49.6 (0.8)	0.70 (-0.83, 2.23)	49.6 (0.8)	0.70 (-0.83, 2.23)
Trimester of NVP												
1st Only (n=90)	47.7 (1.3)	0.37 (-2.04, 2.78)	47.7 (1.3)	0.60 (-1.86, 3.04)	49.7 (1.2)	2.31 (-0.03, 4.64)	49.8 (1.2)	1.08 (-1.13, 3.29)	49.8 (1.2)	1.08 (-1.13, 3.29)	49.8 (1.2)	1.08 (-1.13, 3.29)
1st and 2nd (n=183)	48.2 (1.0)	0.80 (-1.14, 2.73)	47.9 (1.0)	0.80 (-1.17, 2.77)	47.8 (1.0)	0.43 (-1.48, 2.33)	48.7 (1.0)	-0.05 (-1.85, 1.75)	48.7 (1.0)	-0.05 (-1.85, 1.75)	48.7 (1.0)	-0.05 (-1.85, 1.75)
1st, 2nd, and 3rd (n=65)	50.6 (1.3)	3.23 (0.54, 5.92) ^c	50.8 (1.4)	3.67 (0.94, 6.41) ^c	46.8 (1.3)	-0.54 (-3.22, 2.14)	50.3 (1.3)	1.51 (-1.02, 4.04)	50.3 (1.3)	1.51 (-1.02, 4.04)	50.3 (1.3)	1.51 (-1.02, 4.04)
2nd Only, 2nd and 3rd (n=12)	44.9 (2.8)	-2.44 (-8.15, 3.27)	49.2 (2.9)	2.04 (-3.78, 7.85)	50.1 (2.9)	2.75 (-3.04, 8.54)	52.8 (2.7)	4.08 (-1.39, 9.56)	52.8 (2.7)	4.08 (-1.39, 9.56)	52.8 (2.7)	4.08 (-1.39, 9.56)
Duration												
Long (4months) (n=73)	50.6 (1.3)	3.38 (0.82, 5.94) ^c	51.3 (1.3)	4.19 (1.58, 6.79) ^c	47.0 (1.2)	-0.40 (-2.94, 2.14)	50.4 (1.2)	1.53 (-0.87, 3.93)	50.4 (1.2)	1.53 (-0.87, 3.93)	50.4 (1.2)	1.53 (-0.87, 3.93)
Short (<4months) (n=277)	47.6 (0.9)	0.38 (-1.37, 2.12)	47.7 (0.9)	0.55 (-1.22, 2.32)	48.6 (0.9)	1.17 (-0.54, 2.88)	49.3 (0.9)	0.45 (-1.17, 2.07)	49.3 (0.9)	0.45 (-1.17, 2.07)	49.3 (0.9)	0.45 (-1.17, 2.07)
Treatment												
Treated NVP (n=73)	49.2 (1.3)	1.81 (-0.80, 4.42)	48.3 (1.4)	1.02 (-1.64, 3.69)	47.9 (1.3)	0.54 (-2.02, 3.09)	50.1 (1.2)	1.19 (-1.21, 3.60)	50.1 (1.2)	1.19 (-1.21, 3.60)	50.1 (1.2)	1.19 (-1.21, 3.60)
Antihistamine-antiemetics ^b (n=32)	50.1 (1.9)	2.82 (-0.85, 6.50)	48.7 (1.9)	1.51 (-2.30, 5.33)	49.4 (1.8)	1.88 (-1.67, 5.43)	57.3 (1.7)	3.28 (-0.10, 6.66)	57.3 (1.7)	3.28 (-0.10, 6.66)	57.3 (1.7)	3.28 (-0.10, 6.66)
Untreated NVP (n=280)	48.4 (0.9)	0.96 (-0.77, 2.69)	48.8 (0.9)	1.57 (-0.20, 3.34)	48.2 (0.9)	0.88 (-0.82, 2.58)	49.5 (0.8)	0.57 (-1.03, 2.17)	49.5 (0.8)	0.57 (-1.03, 2.17)	49.5 (0.8)	0.57 (-1.03, 2.17)

^a Adjusted for child's sex, maternal age, maternal race, maternal education, and household income

^b Antihistamine-antiemetic group is a subgroup of subjects in the any treatment group

^c p-value < 0.05