Severity of nausea and vomiting in pregnancy and early childhood neurobehavioral outcomes: the Growing Up in Singapore Towards Healthy Outcomes study

Running Title: Vomiting in pregnancy and child behaviors

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Synopsis

Study question

What is the relationship of nausea and vomiting in pregnancy (NVP) with the social-emotional, behavioural, and cognitive development of the offspring?

What's already known

The existing literature demonstrates the psychosocial burden of NVP on pregnant mothers. A few studies have shown the contribution of NVP to emotional behavioral difficulties in school-age and adult offspring. Neurobehavioral outcomes in early childhood have not been thoroughly explored.

What this study adds

Severe NVP in this multi-ethnic Asian cohort correlates with a variety of neurobehavioral impairments in the offspring. The behavioral phenotype shifts from predominantly externalizing symptoms in the first 2 years to internalizing symptoms after 2 years of life. No associations are found between NVP and cognitive intelligence at 4.5 years.

ABSTRACT

Background: Nausea and vomiting of pregnancy (NVP) affects 50 to 80 percent of women. The existing literature has examined NVP from the perspective of the mother, and relatively less is known about offspring outcomes.

Objectives: To study the relationships of NVP with social-emotional, behavioral, and cognitive outcomes of the offspring in a multi-ethnic Asian cohort.

Methods: In the Growing Up in Singapore Towards Healthy Outcomes prospective mother-offspring cohort study, mothers responded to a structured NVP questionnaire at 26-28 weeks' gestation (n=1172) and participants with severe NVP were confirmed using medical records. Children underwent multiple neurodevelopmental assessments throughout childhood. We conducted multivariable regressions with post-estimation predictive margins to understand the associations of NVP with offspring neurobehavioral outcomes, which included 1-year Infant-Toddler Social and Emotional Assessment, 1.5-year Quantitative Checklist for Autism in Toddlers, 2-year Bayley Scales of Infant and Toddler Development, 2- and 4-year Child Behavior Checklist, and 4.5-year Kaufman Brief Intelligence Test. Analyses were adjusted for household income, birth variables, maternal mental health, and other relevant medical variables. Cohen's *d* effect sizes were calculated using standardized mean differences (μ_d).

Results: Mothers were categorized into no (n=296, 25.3%), mild-moderate (n=686, 58.5%), and severe NVP (n=190, 16.2%), of whom 67 (5.7%) required admission. Compared to children of mothers who had no or mild-moderate NVP, children with exposure to severe NVP exhibited more externalizing behaviors (μ_d 2.0, 95% CI 0.3, 3.6; Cohen's *d*=0.33) and social communication difficulties before 2 years (μ_d 4.1, 95% Cl 0.1, 8.0; *d*=0.38), both externalizing (μ_d 1.5, 95% CI 0.4, 2.6; *d*=0.43) and internalizing behaviors at 2 years (μ_d 1.2,

95% CI 0.1, 2.2; *d*=0.35), and only internalizing behaviors after 2 years (μ_d 1.1, 95% CI 0.4, 2.0; *d*=0.37).

Conclusions: Severe NVP is highly prevalent in this Asian cohort and may be adversely associated with multiple offspring neurobehavioral outcomes.

Keywords: Nausea in pregnancy; vomiting in pregnancy; behaviours; child development; hyperemesis gravidarum

Word count: 3219

BACKGROUND

Nausea and vomiting of pregnancy (NVP) is characterized by a spectrum of severity and affects 50 to 80 percent of women during pregnancy.[1-3] Symptoms typically peak during the first trimester and remit by the 20th week of gestation.[4-6] The pathophysiology of NVP remains incompletely understood but is likely multifactorial with hormonal, environmental, psychological, evolutionary and genetic etiologies.[4-6] Hyperemesis gravidarum represents the most morbid clinical presentation across the spectrum of NVP and has been variably defined as persistent nausea and vomiting leading to weight loss in excess of 5% of pre-pregnancy weight[2,7] and/or warranting hospital admission based on the Fairweather criteria. The Fairweather criteria defines hyperemesis gravidarum as "vomiting occurring in pregnancy before the 20th week of gestation, not associated with coincidental conditions as appendicitis, pyelitis, etc., and of such severity as to require the patient's admission to hospital".[8] The reported incidence of hyperemesis gravidarum is 0.3 to 1.0 percent in Caucasian populations[9, 10] and up to 3.0 to 10.8 percent in Asian populations,[4, 6] hinting at potentially distinct biological mechanisms governing NVP in different races, ethnic aggregation, or genetic susceptibility.[11]

Hyperemesis gravidarum and its impact on maternal physical and mental well-being have been extensively studied. Hitherto, much of the existing literature on the psychosocial burden of NVP has been examined from the perspective of the mother,[12-16] and relatively less is known of pregnancy and offspring outcomes. Whereas milder symptoms have been considered inconsequential or even protective of adverse outcomes such as miscarriage,[17-20] accumulating evidence has suggested a link between hyperemesis gravidarum and placental dysfunction disorders, including preeclampsia, abruption, stillbirth, small for gestational

age, and preterm birth.[13, 21] Considering that weight loss, poor diet quality, nutritional deficiencies, and ketonuria are complications after protracted vomiting, hyperemesis gravidarum imposes physiological and metabolic stresses which recapitulate a state of starvation or malnutrition *in utero*, which in turn has been postulated to account for the developmental origins of many adult diseases.[22]

Prenatal exposure to hyperemesis gravidarum has been reportedly associated with mental health disorders in adult offspring, as well as a variety of attention, learning, and language problems in children.[1, 20, 23-27] Two studies have reported differences in developmental outcomes only for protracted NVP that continued into the mid-late second trimester.[1, 24] Other studies have also emerged recently that described the relationship between NVP and autism spectrum disorders.[28-31] Accordingly, this study was conducted in a prospective mother-offspring cohort to examine a wider range of early childhood outcomes, consisting of social-emotional, behavioural and cognitive outcomes, after exposure to different severity of NVP *in utero.*

METHODS

Study population

The Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort is a population-based, prospective longitudinal study of pregnancies and children with the aim of studying how antenatal and early childhood conditions influence the long-term health of women and children. Briefly, women aged 18 years or older across all socioeconomic backgrounds were recruited from KK Women's and Children's Hospital (KKH) and National University Hospital (NUH) in Singapore between 2009 and 2010 during their first trimester of pregnancy, as

described previously.[32] GUSTO inclusion criteria required both biological parents to be one of the three major ethnicities in Singapore (i.e. Chinese, Malay or Indian) and are Singaporeans (i.e. not recent immigrants). Participants were followed up through and beyond delivery, and their children tested regularly over childhood.

Exposures

Severity of vomiting in the first and second trimester was recorded in a structured interview-administered questionnaire at 26-28 weeks' gestation. Electronic medical records maintained by the hospitals were utilized to confirm the severity of vomiting, including prescription of anti-emetic medications and hospital admissions. Seventy-four women were admitted due to non-infectious nausea and vomiting and all of them had "hyperemesis gravidarum" as the discharge diagnosis. Congruence between mothers' reports and medical records for severe NVP was 90.5%. Sixty seven participants with congruent records were included. As weight loss was not systematically obtained, we did not categorize pregnant mothers into hyperemesis gravidarum. Instead, the severity of nausea and vomiting was classified into none, mild-moderate (defined as nausea and/or vomiting occasionally), and severe (defined as regular vomiting with inability to retain meals).

Outcomes

The outcomes analysed in this study were scores from the 1-year Infant-Toddler Social and Emotional Assessment (ITSEA; n=542);[33] 1.5-year Quantitative Checklist for Autism in Toddler (Q-CHAT; n=208),[34, 35] 2-year Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; n=397);[36] 2- and 4-year Child Behavior Checklist (CBCL; 2-year n=506, 4-year mother n=666, 4-year father n=586)[37] and the Kaufman Brief Intelligence

Test, Second Edition (KBIT-2) at 4.5 years (n=476).[38] The cognitive assessments were completed by blinded research staff and the questionnaires were completed by mothers, except for the 4-year CBCL, which were completed by both mothers and fathers individually. The inclusion of father-reported CBCL was to reduce any reporter bias that might arise when mothers report both the exposure and the outcome. To avoid dependency and intra-subject correlation in the neurobehavioral outcomes of multiple-birth siblings and repeated measurement of maternal variables, we only included mothers with singleton pregnancies.

Statistical analyses

Multivariable linear regression models were used to delineate the relationships between NVP and child outcomes, and analyses were adjusted for the following covariates: gestational age, birthweight (World Health Organization (WHO) gestational age and sex-specific Z-scores), maternal age at delivery, monthly household income, gestational diabetes (defined by WHO 1999 criteria), hypertensive disorders of pregnancy (i.e. preeclampsia, eclampsia, or pregnancy-induced hypertension), positive smoking or tobacco smoke exposure (self-reported or plasma cotinine blood test >0.17 ng/mL), sex of baby, and the changes in maternal general mood from pregnancy to 3-months postpartum. The maternal general mood variable was taken from an exploratory bifactor analysis (EFA) combining items from the State-Trait Anxiety Inventory (STAI),[39, 40] Beck Depression Inventory (BDI-II),[41, 42] and Edinburgh Postnatal Depression Scale (EPDS)[43, 44], as reported previously.[45] Briefly, this EFA was fitted with the individual items of the mental health scales as manifest variables, and factors were retained if the eigenvalue from observed data was larger than eigenvalues from parallel analysis (1000 randomly-generated correlation matrices).[45] An

oblique rotation (bi-geomin) was used to permit correlation between subfactors, and estimates were obtained under maximum likelihood with robust standard errors.[45]

Unadjusted mean scores and their 95% confidence intervals for the three categories of NVP were obtained using the post-estimation predictive margins command immediately after fitting regression models. To further facilitate interpretation regarding the clinical significance, we reported Cohen's *d* for effect sizes. Statistical analyses were completed in Stata version 16.0 (StataCorp, College Station, TX).[46]

Sensitivity analyses

Since women with severe NVP were grouped together in the multivariable regression regardless of admission into the hospital, we conducted sensitivity analyses to test the uncertainty around whether there were differences in child outcomes between mothers with severe NVP who sought care in the hospital versus those who did not. We found that the 123 mothers with severe NVP who were not hospitalized accounted for our results in Tables 2 and 3, and not the 67 women with severe NVP who were hospitalized (**eTable 1**).

Missing data

Our missing data tabulation showed that 37% of children born to mothers with NVP data did not have data related to neurodevelopment, while only 15% had dropped out entirely from the GUSTO cohort at 4.5 years. This was because approximately 22% of the children in the cohort were not asked to attend the neurodevelopment visits, as a way to reduce time burden on the families. Those who attended the neurodevelopmental visits were randomly selected from the 1172 mothers, except for the 4-year visit, when children with more

consistent attendance in prior visits were prioritized to ensure a higher sample of complete data. To assess for potential bias due to missing data, we compared the demographic characteristics and the NVP distribution of mothers whose children had missing or non-missing outcomes. We did not find any differences between the two groups, except for a small difference in ethnicity at the 1-year follow up visit (**eTable 2**).

Missing data were handled by multiple imputations (*m* = 50) on the independent and dependent variables using chained equations. Before re-calculating the multivariable regression estimates from the imputed data, we deleted imputed data of the dependent variables and left only the observed data to minimize bias introduced by a misspecified imputation model for the outcomes.[47]

Ethics approval

The study protocol was approved by the SingHealth Centralized Institutional Review Board and National Healthcare Group Domain Specific Review Board, and all participants gave written informed consent prior to study enrolment.

RESULTS

Description of cohort

Of 1247 mother-child dyads in the GUSTO study, 1172 mothers completed a structured interview-administered questionnaire at 26-28 weeks' gestation with information about first and second trimester nausea and vomiting (**Figure 1**). Altogether 296 (25.3%) women reported no vomiting, 686 (58.5%) had mild or moderate vomiting, and 190 (16.2%) reported severe vomiting. Of the 74 women classified as severe vomiting and required

rehydration in the hospital for pregnancy-related vomiting, 67 (90.5%) of them reported congruent degree of NVP as the hospital records. Baseline maternal demographics, adverse intra-uterine exposures (including smoking exposure, hypertensive disorders of pregnancy, and gestational diabetes mellitus), pre- and postnatal mood scores of mothers, and birthweight were comparable across women with varying degrees of NVP (**Table 1**). However, there were differences in child's sex, ethnicity, gestational age and breast feeding across the three categories of vomiting severity (**Table 1**). Mothers who conceived sons were, as a group, less likely to report severe NVP than mothers who conceived daughters. In our multi-ethnic cohort, Indian mothers were more likely to report severe vomiting as compared with Chinese mothers, while Malay ethnicity did not appear to be associated with severity of vomiting. No inter-group differences were found in maternal mood from antenatal to postnatal period based on ethnicity of the women. Finally, mothers with severe NVP were less likely to report breast feeding for at least 3 months as compared with mothers with no, mild, and moderate NVP, which was likely related to unmeasured confounders.

Child outcomes after exposure to nausea and vomiting in pregnancy

In our multivariable regression models, we observed more pronounced externalizing behaviours at 1 year and more social communication difficulties at 1.5-year in children born to mothers who reported severe vomiting as compared to those who reported no or milder NVP (**Table 2**). Dysregulated behaviours were also elevated at 1-year, along with negative emotionality (i.e. tendency to react to stressful situations with unpleasant emotions) and sleep disturbances in infants born to mothers with severe NVP (**Table 2**). The models for data deleted listwise and for imputed data produced the same results.

It is important to note that regression models were consecutively run for all domains and subscales (over 30 in total) in the ITSEA and CBCL without selective searching for notable associations. We elected to display only domains with meaningful effect sizes based on inspection of 95% confidence intervals. The reader may therefore interpret all ITSEA and CBCL outcomes not shown in the tables as having 95% confidence intervals that crossed zero.

To afford a more comprehensive and longitudinal assessment, we used the Childhood Behavior Checklist (CBCL) at 2- and 4-year time points (**Table 3**). At age 2, we found more externalizing and internalizing problems in children with exposure to severe NVP as compared to those whose mothers reported no or mild-moderate NVP during pregnancy. The most prominent areas of difficulty were related to regulation of emotions and attention, e.g., emotional reactivity and attention problems. In addition, consistent with age 1, higher scores in sleep problems were reported. In the DSM-oriented scales, children exposed to severe NVP had higher symptoms of attention-deficit hyperactivity disorder and affective disorder.

At 4 years, children exposed to severe NVP exhibited mainly internalizing behaviours such as anxiety and depressive symptoms. It is notable that both mother and father corroborated this finding in separate reports. In addition, when compared to children born to mothers without or with milder NVP, those born to mothers who experienced severe vomiting during their pregnancy had more impairments based on several DSM-oriented scales, including in

affective and anxiety conditions (**Table 3**). We compared the models obtained from our imputed data with the observed data and found minimal changes in the estimates.

Severe vomiting was not associated with language and motor scores in 2-year-old children based on the Bayley-III scale (**Table 4**). However, reductions of 5.4- and 5.1-ponts in the non-missing and imputed Bayley cognitive scores, respectively, were found, which corresponded to 1/3 of a standard deviation in this instrument. By 4.5 years of age, there were no differences in verbal, nonverbal, and composite IQ scores based on the KBIT-2 between the 3 groups of children. It is important to note that KBIT-2 was conducted in English in this cohort. Since only 36.9% of Singaporean children speak English as their first language, the verbal IQ score (Mean 86.2, SD 16.1) was therefore much lower than nonverbal IQ score (100.0, SD 14.7) at age 4.5.[48]

COMMENT

Principal findings

In this large Asian prospective mother-offspring cohort, children born to mothers with severe NVP during pregnancy showed worse emotional and behavioural functioning, as compared to children without exposure to NVP.

Strengths of the study

To date, there has been no other study using a non-clinical cohort with such a wide range of outcomes in early childhood and in an Asian population, which is important considering potential biological and etiological differences between women from different ethnic backgrounds. Our present study has important policy, clinical, and research implications, as

our findings suggest that the *in utero* environment of fetuses exposed to severe NVP may set a trajectory of increased risk for poorer developmental outcomes. Other strengths include the prospective longitudinal study design, rigorous phenotyping of mother-child dyads, adjustments for multiple covariates, and the use of validated tests for assessing early childhood neurocognitive and behavioural profiles.

Limitations of the data

Limitations of the study include self-reporting of vomiting severity, which is subjective and may be associated with recall bias. However, medical record details have been used to ensure accuracy of the women's self-report with a congruence of 90.5% in this study. Inherent in cohorts, there are up to 50 percent of missing neurodevelopment data in the later years, which may bias our findings based on participants who are left in the cohort. Hence, we have employed multiple imputations and conducted sensitivity analyses. We did not find differences between our sample and the overall GUSTO cohort in terms of NVP categories of mothers, medical conditions during pregnancy, and child variables including gestational age and birthweight, except for a larger percentage of Singaporean Chinese families attending the 1-year infant visit.

Interpretation

A novel finding from this study is that children born to mothers with severe NVP initially demonstrate mainly externalizing symptoms in infancy and toddlerhood, while children present with more internalizing symptoms by preschool age. Although the association between NVP and internalizing symptoms in adult offspring has been consistently reported,[2, 9, 25] little is known about internalizing symptom profile from 1 to 4 years of age.

In this study, the association of NVP and internalizing symptoms can be observed as early as 2 to 4 years of age. Consistent with recent studies linking NVP and autism spectrum disorder, we have replicated similar results at 1.5-years. Instead of using an ASD diagnosis as the outcome, this study uses social communication skills from the Q-CHAT, which allows for a more granular understanding of the relationship between NVP and social communication as a continuum.

Severe NVP is highly prevalent in our cohort (16.2%), which has been suggested to be epidemiologically associated with Asian ethnicity.[4,6] Nevertheless, it is notable that rates have varied widely across studies. Possible explanations for between-study heterogeneity in prevalence estimates include differences in the criteria used to define hyperemesis gravidarum, insufficient sample sizes, self-reporting and recall bias, differences in the specific ethnic composition, and country-specific sociocultural attitudes, guidelines and accessibility to healthcare institutions. It is intriguing to note that in our sensitivity analyses (**eTable 1**), mothers with NVP admitted into the hospital and received treatment have children with similar outcomes as those born to mothers with no, mild, or moderate NVP. Consistent with two prior studies, poorer outcomes are identified in children whose mothers have not sought aggressive treatment for NVP.[26, 27] As further described below, lack of treatment for NVP likely entrenches the condition of persistent ketouria and starvation during pregnancy, while early rehydration or use of antiemetics may help to restore a normal *in utero* environment.

In this study, mothers with severe NVP also have infants born at earlier gestational age. This corroborates previously established risk factors and reinforces the need for awareness

regarding the psychosocial burden of NVP.[10, 12-16, 49] The exact mechanisms which drive NVP remain an area of investigation. Emerging evidence suggests a multifactorial pathogenesis involving an interaction between genetic, hormonal and gastrointestinal factors.[50] Previously, NVP was attributed to hCG production; however, a review of 31 papers showed conflicting evidence.[51] There has been more support for the role of genetic factors in the pathogenesis of NVP. A genome-wide association study (GWAS) of European mothers identifies GDF15 (encoding growth/differentiation factor 15), which delays gastric emptying and contributes to nausea, as a risk factor. GFRAL, the receptor of GDF15, in the vomiting center of the brainstem (i.e. postrema), which signals loss of appetite and taste aversion, is another risk factor.[52] The GWAS also implicates IGFBP7 (encoding insulin-like growth factor-binding protein 7), a placental protein and biomarker of cachexia, and PGR, a hormone receptor involved in reducing gastrointestinal motility during pregnancy, in the etiology of NVP. Interestingly, all three identified risk genes (GDF15, IGFBP7 and PGR) are expressed in the placenta, which points to the importance of a placental component of NVP. Additionally, a familial aggregation study has found that NVP risk is increased in women with affected mothers or sisters, again strongly suggesting a genetic association in NVP.[11] A GWAS study related to this topic in Asia may prove valuable for elucidating the genetic bases of these interethnic differences and may open new opportunities for modulation of NVP.

A possible explanation for the associations between NVP and neurobehavioral outcomes of children relates to the “fetal programming hypothesis”,[22] which posits that negative stimuli to the fetus during a critical window of development can program long-term health. Indeed, severe vomiting in pregnancy is often associated with rapid weight loss, malnutrition, poor diet quality,[22] restricted eating patterns and ketonuria (which is a marker of acute

starvation), potentially mimicking a state of famine. Studies have suggested that such phenotypic pliability may be enacted through epigenetic modifications e.g., DNA methylation *in utero.*[53] To paint a more conclusive picture regarding the epigenetic alterations induced by NVP in the offspring, epigenome-wide association studies should be undertaken to identify differences in genome methylation between children with or without exposure to NVP.

In contrast to the observation that hyperemesis gravidarum is associated with worse placental dysfunction[13, 21] and negatively influences offspring development,[20, 23-25] there is growing acceptance of the idea that milder symptoms may be protective of pregnancy outcomes such as miscarriage and congenital malformation.[17, 19, 54] These ostensibly opposing effects on perinatal outcomes allude to the complex biology of NVP. Further studies are warranted to understand the possibility of NVP providing feto-protection while *in utero* and simultaneously setting an unfavourable development trajectory in the offspring after birth.

Conclusions

Severe NVP is highly prevalent in this Asian cohort and is associated with a multitude of unfavourable neurobehavioral outcomes in the offspring.

ACKNOWLEDGEMENTS

We would like to thank Dimple Rajgor for helping with formatting and submission of this manuscript. We also acknowledge the GUSTO study group, which includes Allan Sheppard, Amutha Chinnadurai, Anne Eng Neo Goh, Anne Rifkin-Graboi, Anqi Qiu, Arijit Biswas, Bee Wah Lee, Birit F.P. Broekman, Boon Long Quah, Borys Shuter, Chai Kiat Chng, Cheryl Ngo, Choon Looi Bong, Christiani Jeyakumar Henry, Claudia Chi, Cornelia Yin Ing Chee, Yam Thiam Daniel Goh, Doris Fok, E Shyong Tai, Elaine Tham, Elaine Quah Phaik Ling, Evelyn Chung Ning Law, Evelyn Xiu Ling Loo, Fabian Yap, Falk Mueller-Riemenschneider, George Seow Heong Yeo, Helen Chen, Heng Hao Tan, Hugo P S van Bever, Iliana Magiati, Inez Bik Yun Wong, Ivy Yee-Man Lau, Izzuddin Bin Mohd Aris, Jeevesh Kapur, Jenny L. Richmond, Jerry Kok Yen Chan, Joanna D. Holbrook, Joanne Yoong, Joao N. Ferreira., Jonathan Tze Liang Choo, Jonathan Y. Bernard, Joshua J. Gooley, Keith M. Godfrey, Kenneth Kwek, Kok Hian Tan, Krishnamoorthy Niduvaje, Kuan Jin Lee, Leher Singh, Lieng Hsi Ling, Lin Lin Su, Ling-Wei Chen, Lourdes Mary Daniel, Lynette P Shek, Marielle V. Fortier, Mark Hanson, Mary Foong-Fong Chong, Mary Rauff, Mei Chien Chua, Melvin Khee-Shing Leow, Michael Meaney, Mya Thway Tint, Neerja Karnani, Ngee Lek, Oon Hoe Teoh, P. C. Wong, Paulin Tay Straughan, Peter D. Gluckman, Pratibha Agarwal, Queenie Ling Jun Li, Rob M. van Dam, Salome A. Rebello, Seang-Mei Saw, See Ling Loy, S. Sendhil Velan, Seng Bin Ang, Shang Chee Chong, Sharon Ng, Shiao-Yng Chan, Shirong Cai, Shu-E Soh, Sok Bee Lim, Stella Tsotsi, Chin-Ying Stephen Hsu, Sue Anne Toh, Swee Chye Quek, Victor Samuel Rajadurai, Walter Stunkel, Wayne Cutfield, Wee Meng Han, Wei Wei Pang, Yap-Seng Chong, Yin Bun Cheung, Yiong Huak Chan and Yung Seng Lee.

Financial Support

This research is funded by the Singapore Ministry of Health's National Medical Research Council and Singapore National Research Foundation (NMRC/TCR/004-NUS/2008; NMRC/TCR/ 012-NUHS/2014), UK Medical Research Council (MC_UU_12011/4), the Department of Health, National Institute for Health Research (NF-SI-0515-10042), and the European Union's Erasmus+ Programme Early Nutrition eAcademy Southeast Asia (ENeASEA-573651-EPP-1-2016-1-DE-EPPKA2-CBHE-JP). Additional funding was provided by the Singapore Institute for Clinical Sciences and the NIHR Southampton Biomedical Research Centre.

Conflict of Interest

S-Y Chan, KM Godfrey and Y-S Chong are part of the Epigen Academic Consortium that has received funding for research studies outside of this submitted work. All other authors declare no conflicts of interest.

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Figure legends

Figure 1: Study flow diagram of the population-based cohort

Table 1. Characteristics of participants in the Growing Up Towards Healthy Outcomes (GUSTO) study and relative risks between mothers with severe vomiting and no vomiting

Characteristic	Severity of vomiting			Relative risk (95% confidence interval)
	None (n=296)	Mild-Moderate (n=686)	Severe (n=190)	
Maternal age, median (IQR), years	31.3 (27.9-35.3)	31.2 (27.6-34.9)	31.3 (27.2-34.6)	--
Gestational age, median (IQR), week	39.0 (38.1-39.7)	38.9 (38.0-39.7)	38.7 (37.6-39.6)	--
Pregnancy Edinburgh post-natal depression scale (EPDS) score, mean (SD)	6.93 (4.54)	7.55 (4.30)	7.86 (4.91)	--
Pregnancy state-trait anxiety inventory (STAI) score, mean (SD)	70.04 (18.29)	71.42 (17.65)	72.54 (18.04)	--
3-month postnatal EPDS score, mean (SD)	5.86 (4.43)	6.54 (4.69)	7.13 (5.23)	--
3-month postnatal STAI score, mean (SD)	69.0 (18.4)	70.8 (19.4)	71.5 (20.4)	--
Birthweight in kilograms, mean (SD)	3.08 (0.43)	3.11 (0.56)	3.03 (0.46)	--
Birthweight z-score, mean (SD)[a]	0.06 (1.17)	0.179 (1.25)	0.155 (1.21)	--
Maternal race, %				
Chinese	58.5	58.2	47.3	Reference
Malay	22.3	26.5	26.1	1.44 (0.92, 2.26)
Indian	19.3	15.3	26.6	1.71 (1.08, 2.70)
Smoke exposure in pregnancy, %	14.2	16.0	14.7	0.95 (0.66, 1.38)
Breastfeeding for ≥ 3 months, %	57.6	57.7	43.5	0.62 (0.47, 0.82)
Gestational diabetes mellitus, %	17.0	19.0	19.0	1.03 (0.73, 1.45)
Hypertensive disorders of pregnancy, %	7.8	5.4	6.3	1.03 (0.60, 1.76)
Household income per month (SGD $), %				
0-1999	14.0	15.3	16.2	Reference
2000-3999	30.9	28.5	38.0	1.06 (0.60, 1.89)
4000-5999	25.9	25.3	22.4	0.75 (0.40, 1.38)
>6000	29.1	31.0	23.5	0.70 (0.38, 1.28)
Male child, %	54.0	55.2	41.9	0.65 (0.50, 0.84)

[a]Standardized for gestational age and sex
Abbreviations: SGD$, Singapore Dollars

Table 2. Severe NVP and its relationships with 1-year ITSEA subscales and 1.5-year QCHAT total score

Outcome[a]	Severity of vomiting	Unadjusted means (95% CI)	Adjusted difference in means (95% CI)[b]	Cohen's d
Activity and impulsivity	None (n=132)	5.2 (4.7, 5.7)	0.0 (Reference)	
	Mild-moderate (n=312)	5.2 (4.9, 5.5)	0.0 (-0.6, 0.6)	
	Severe (n=81)	6.0 (5.4, 6.7)	0.9 (0.1, 1.7)	0.38
Externalizing Behaviours	None (n=126)	11.1 (9.8, 12.3)	0.0 (Reference)	
	Mild-moderate (n=307)	10.6 (9.8, 11.3)	-0.5 (-2.0, 1.0)	
	Severe (n=81)	12.6 (11.1, 14.0)	2.0 (0.3, 3.6)	0.33
Negative emotionality	None (n=131)	6.7 (5.7, 7.7)	0.0 (Reference)	
	Mild-moderate (n=317)	7.1 (6.5, 7.7)	0.4 (-0.8, 1.5)	
	Severe (n=85)	8.9 (7.3, 9.6)	1.8 (0.2, 3.3)	0.37
Sleep problems	None (n=130)	2.4 (1.9, 2.8)	0.0 (Reference)	
	Mild-moderate (n=315)	2.8 (2.6, 3.1)	0.5 (-0.1, 1.0)	
	Severe (n=85)	3.3 (2.7, 3.8)	0.9 (0.2, 1.6)	0.47
Dysregulation domain	None (n=131)	17.0 (15.1, 18.8)	0.0 (Reference)	
	Mild-moderate (n=316)	17.3 (16.2, 18.4)	0.3 (-1.9, 2.5)	
	Severe (n=85)	20.0 (17.8, 22.3)	3.1 (0.1, 6.0)	0.41
Q-CHAT total score	None (n=54)	34.7 (32.4, 37.0)	0.0 (Reference)	
	Mild-moderate (n=150)	33.5 (32.2, 37.9)	-1.2 (-3.9, 1.5)	
	Severe (n=24)	38.8 (35.5, 42.0)	4.1 (0.1, 8.0)	0.38

[a]The ITSEA questionnaire comprises numerous subscales; only domains with meaningful effect sizes based on inspection of 95% confidence intervals are displayed in this table.
[b]Covariates included gestational age, birthweight Z-scores, maternal age, household monthly income, gestational diabetes, hypertensive disorders of pregnancy, history of smoking exposure and/or positive plasma cotinine, sex of child, maternal general mood factor from pregnancy to 3-month post-partum, and parity.

Table 3. Severe NVP and its relationship with 2-year mother-rated behaviors, 4-year father-reported behaviors, and 4-year mother-reported behaviors from CBCL

Outcome[a]	Severity of vomiting	Unadjusted means (95% CI)	Adjusted difference in means (95% CI)[b]		Cohen's d
			Observed	Imputed	
2-year Emotionally reactive	None (n=93)	1.6 (1.0, 2.1)	0.0 (Reference)		
	Mild-moderate (n=245)	2.1 (1.8, 2.4)	0.5 (-0.1, 1.2)	0.5 (-0.1, 1.2)	
	Severe (n=55)	2.7 (2.0, 3.4)	1.1 (0.3, 2.0)	1.1 (0.2, 2.0)	0.43
2-year Attention problems	None (n=93)	2.5 (2.0, 3.0)	0.0 (Reference)		
	Mild-moderate (n=245)	2.9 (2.7, 3.2)	0.4 (-0.1, 1.0)	0.4 (-0.1, 1.0)	
	Severe (n=55)	3.7 (3.1, 4.3)	1.2 (0.4, 2.0)	1.2 (0.4, 2.0)	0.49
2-year Sleep problems	None (n=93)	2.6 (2.0, 3.3)	0.0 (Reference)		
	Mild-moderate (n=245)	2.9 (2.6, 3.3)	0.3 (-0.4, 1.0)	0.3 (-0.4, 1.0)	
	Severe (n=55)	3.7 (2.9, 4.5)	1.1 (0.1, 2.1)	1.1 (0.1, 2.1)	0.35
2-year DSM Attention-deficit	None (n=93)	4.3 (3.6, 5.0)	0.0 (Reference)		
	Mild-moderate (n=245)	4.9 (4.5, 5.3)	0.6 (-0.2, 1.4)	0.6 (-0.2, 1.4)	
	Severe (n=55)	5.8 (4.9, 6.7)	1.5 (0.4, 2.6)	1.5 (0.4, 2.6)	0.43
2-year DSM Affective	None (n=93)	2.1 (1.4, 2.7)	0.0 (Reference)		
	Mild-moderate (n=245)	2.4 (2.0, 2.8)	0.3 (-0.4, 1.1)	0.3 (-0.4, 1.1)	
	Severe (n=55)	3.2 (2.4, 4.1)	1.2 (0.1, 2.2)	1.2 (0.1, 2.2)	0.35
4-year Anxious-depressive symptoms (paternal report)	None (n=136)	2.7 (2.2, 3.2)	0.0 (Reference)		
	Mild-moderate (n=354)	3.0 (2.6, 3.3)	0.2 (-0.4, 0.8)	0.2 (-0.4, 0.8)	
	Severe (n=91)	3.8 (3.2, 4.5)	1.1 (0.3, 1.9)	(0.3, 1.9)	0.37

4-year Anxious-depressive symptoms (maternal report)	None (n=152)	2.9 (2.4, 3.3)	0.0 (Reference)		
	Mild-moderate (n=394)	2.8 (2.5, 3.1)	-0.1 (-0.6, 0.5)	-0.1 (-0.6, 0.5)	
	Severe (n=111)	3.7 (3.1, 4.3)	0.6 (0.0, 1.2)	0.6 (0.0, 1.2)	0.28
4-year DSM Affective (maternal report)	None (n=152)	2.1 (1.6, 2.6)	0.0 (Reference)		
	Mild-moderate (n=394)	2.4 (2.1, 2.7)	0.3 (-0.3, 0.9)	0.3 (-0.2, 0.9)	
	Severe (n=111)	2.8 (2.3, 3.4)	0.8 (0.0, 1.5)	0.8 (0.0, 1.5)	0.22
4-year DSM Anxiety (maternal report)	None (n=152)	3.5 (3.0, 4.0)	0.0 (Reference)		
	Mild-moderate (n=394)	3.7 (3.4, 4.0)	0.3 (-0.3, 0.9)	0.3 (-0.3, 0.9)	
	Severe (n=111)	4.6 (4.0, 5.2)	1.1 (0.4, 2.0)	1.1 (0.3, 1.9)	0.37

[a]The CBCL questionnaire comprises numerous subscales; only domains with meaningful effect sizes based on inspection of 95% confidence intervals are displayed in this table.
[b]Covariates included gestational age, birthweight Z-scores, maternal age, household monthly income, gestational diabetes, hypertensive disorders of pregnancy, history of smoking exposure and/or positive plasma cotinine, sex of child, maternal general mood factor from pregnancy to 3-month post-partum, and parity.
Abbreviations: DSM, Diagnostic and Statistical Manual for Mental Disorders

Table 4. A reduction in the Bayley cognitive score was found at 2 years in children with exposure to severe NVP. The cognitive scores in the KBIT-2 at 4.5 years were not different based on severity of NVP.

Outcome	Severity of vomiting	Unadjusted means (95% CI)	Adjusted difference in means (95% CI)[a]	
			Observed	Imputed
Bayley Composite cognitive (2 year)	None (n=117)	105.6 (102.6, 108.5)	0.0 (Reference)	
	Mild-moderate (n=296)	103.0 (101.2, 104.7)	-2.6 (-6.0, 0.9)	-2.4 (-5.9, 1.2)
	Severe (n=69)	100.2 (96.5, 103.9)	-5.4 (-10.1, -0.6)	-5.1 (-9.9, -0.3)
Bayley Composite language (2 year)	None (n=117)	97.2 (93.8, 100.5)	0.0 (Reference)	
	Mild-moderate (n=296)	96.4 (94.5, 98.4)	-0.7 (-4.6, 3.2)	-0.7 (-4.6, 3.3)
	Severe (n=69)	95.7 (91.6, 99.9)	-1.4 (-6.7, 3.9)	-1.4 (-6.7, 4.0)
Bayley Composite motor (2 year)	None (n=115)	108.0 (104.8, 111.2)	0.0 (Reference)	
	Mild-moderate (n=291)	107.8 (106.0, 109.7)	-0.1 (-3.9, 3.6)	0.0 (-3.7, 3.8)
	Severe (n=69)	103.2 (99.3, 107.1)	-4.8 (-9.8, 0.3)	-4.6 (-9.7, 0.4)
KBIT verbal (4.5 year)	None (n=114)	87.0 (83.5, 90.6)	0.0 (Reference)	
	Mild-moderate (n=290)	86.0 (83.8, 88.1)	-1.1 (-5.2, 3.1)	-1.1 (-5.3, 3.1)
	Severe (n=65)	86.2 (81.6, 90.8)	-0.9 (-6.6, 4.9)	-0.8 (-6.6, 5.0)
KBIT non-verbal (4.5 year)	None (n=114)	101.3 (98.0, 104.6)	0.0 (Reference)	
	Mild-moderate (n=293)	100.9 (98.9, 102.9)	0.3 (-4.2, 3.6)	0.2 (-3.7, 4.2)
	Severe (n=65)	100.4 (96.1, 104.8)	-0.8 (-6.3, 4.6)	-0.3 (-5.8, 5.1)
KBIT IQ composite (4.5 year)	None (n=114)	93.5 (90.3, 96.8)	0.0 (Reference)	
	Mild-moderate (n=290)	92.7 (90.7, 94.7)	-0.8 (-4.6, 3.1)	-0.4 (-4.3, 3.5)
	Severe (n=65)	92.5 (88.2, 96.7)	-1.0 (-6.4, 4.4)	-0.7 (-6.1, 4.7)

[a]Covariates included gestational age, birthweight Z-scores, maternal age, household monthly income, gestational diabetes, hypertensive disorders of pregnancy, history of smoking exposure and/or positive plasma cotinine, sex of child, maternal general mood factor from pregnancy to 3-month post-partum, and parity.

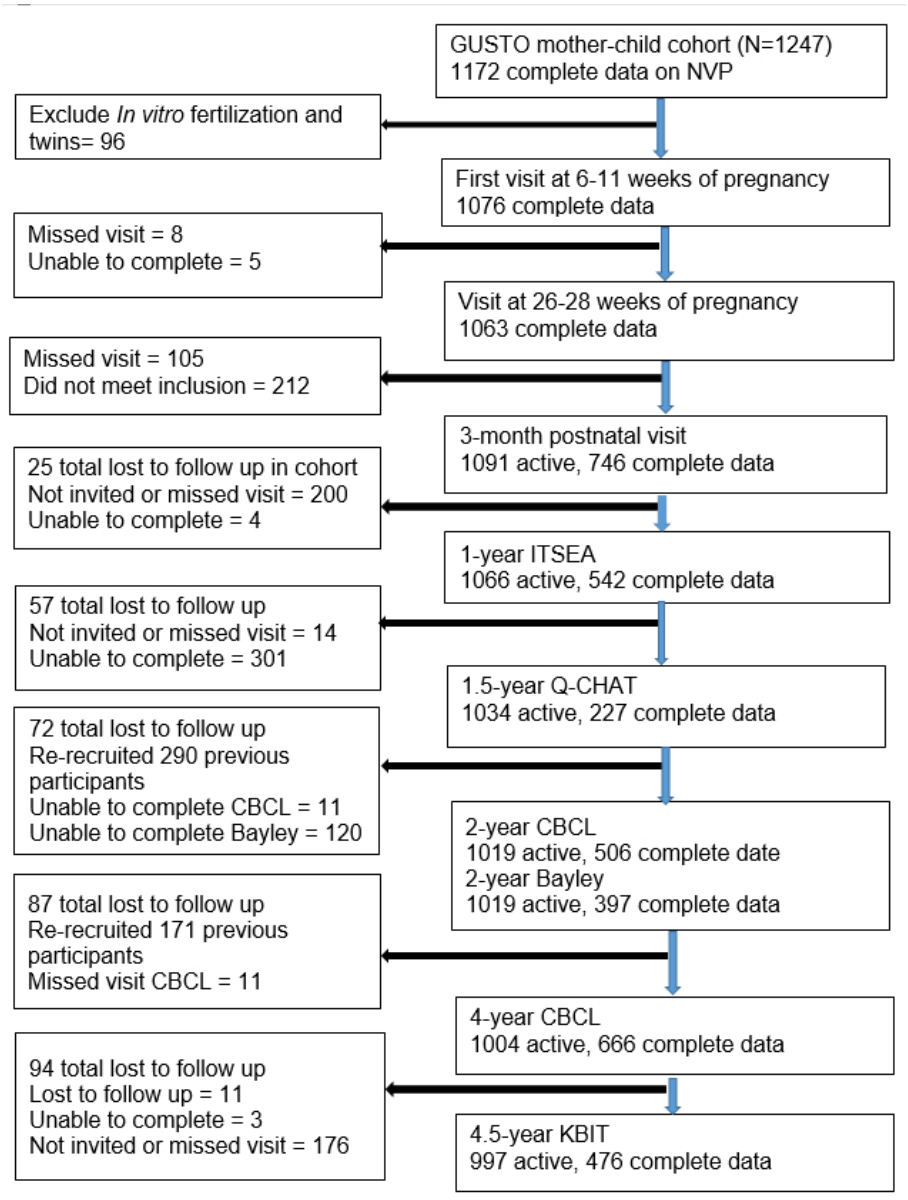

Figure 1: Study flow diagram of the population-based cohort

167x222mm (96 x 96 DPI)

eTable 1: In the sensitivity analyses, severe NVP without hospital admission is associated with a wider range of child outcomes than severe NVP with hospital admission

Outcome	Severity of vomiting	Model-adjusted means (95%CI)	Adjusted difference in means (95% CI)[a]
1-year ITSEA Activity & impulsivity	None	5.08 (4.85, 5.30)	0.0 (Reference)
	Severe: with admission	6.00 (5.31, 6.69)	0.9 (-0.2, 1.7)
	Severe: no admission	6.28 (5.24, 7.32)	1.2. (0.1, 2.3)
1-year ITSEA Externalizing Behaviours	None	10.05 (9.48, 10.61)	0.0 (Reference)
	Severe: with admission	11.48 (8.85, 14.11)	1.5 (-1.3, 4.3)
	Severe: no admission	12.77 (11.05, 14.49)	2.7 (0.9, 4.5)
1-year ITSEA Negative emotionality	None	7.16 (6.83, 7.49)	0.0 (Reference)
	Severe: with admission	8.95 (7.70, 10.20)	1.8 (0.5, 3.1)
	Severe: no admission	9.67 (7.85, 11.48)	2.0 (0.1, 4.0)
1-year ITSEA Sleep problems	None	2.44 (2.26, 2.61)	0.0 (Reference)
	Severe: with admission	2.96 (2.10, 3.82)	0.5 (-0.5, 1.4)
	Severe: no admission	3.18 (2.59, 3.77)	0.7 (0.1, 1.4)
1-year ITSEA Dysregulation	None	16.57 (15.88, 17.26)	0.0 (Reference)
	Severe: with admission	21.38 (17.72, 25.04)	4.2 (0.3, 8.2)
	Severe: no admission	20.40 (17.92, 22.88)	3.8 (1.2, 6.4)
1.5-year QCHAT total	None	36.09 (35.89, 36.29)	0.0 (Reference)
	Severe: with admission	38.28 (37.03, 39.49)	2.2 (1.2, 3.3)
	Severe: no admission	39.57 (38.30, 40.84)	3.5 (2.2, 4.8)
2-year CBCL Emotional reactivity	None	2.30 (2.22, 2.38)	0.0 (Reference)

	Severe: with admission	3.30 (3.07, 3.53)	1.1 (0.8, 1.4)
	Severe: no admission	4.10 (3.79, 4.42)	1.6 (1.2, 2.0)
2-year CBCL Attention problems	None	2.98 (2.92, 3.04)	0.0 (Reference)
	Severe: with admission	3.06 (2.88, 3.24)	0.3 (-0.1, 0.6)
	Severe: no admission	3.76 (3.48, 4.04)	0.8 (0.5, 1.1)
2-year CBCL Sleep problems	None	3.08 (2.30, 3.16)	0.0 (Reference)
	Severe: with admission	3.00 (2.75, 3.24)	0.3 (-0.1, 0.6)
	Severe: no admission	4.63 (4.25, 5.01)	1.6 (1.2, 1.9)
2-year CBCL DSM ADHD	None	4.91(4.83 ,4.99)	0.0 (Reference)
	Severe: with admission	5.50 (5.27, 5.73)	1.2 (-0.2, 2.0)
	Severe: no admission	7.01 (6.65, 7.37)	2.1 (1.7, 2.5)
2-year CBCL DSM affective	None	2.56 (2.47, 2.65)	0.0 (Reference)
	Severe: with admission	2.07(1.82, 2.33)	-0.3 (-0.6, 0.1)
	Severe: no admission	5.25 (4.85, 5.64)	2.7 (2.3, 3.1)
4-year CBCL anxious-depressive (paternal report)	None	2.90 (2.83, 2.96)	0.0 (Reference)
	Severe: with admission	2.96 (2.75, 3.17)	-0.2 (-0.4, 0.1)
	Severe: no admission	3.75 (3.53, 3.96)	0.9 (0.6, 1.1)
4-year CBCL anxious-depressive (maternal report)	None	3.07 (3.01, 3.12)	0.0 (Reference)
	Severe: with admission	2.85 (2.66, 3.03)	-0.4 (-0.7, 0.2)
	Severe: no admission	4.15 (3.96, 4.33)	1.1 (0.9, 1.3)
4-year CBCL DSM Affective (maternal report)	None	2.53 (2.47, 2.59)	0.0 (Reference)
	Severe: with admission	2.82 (2.62, 3.01)	0.1 (-0.1, 0.3)
	Severe: no admission	3.26 (3.07, 3.46)	0.7 (0.5, 0.9)

4-year CBCL DSM Anxiety (maternal report)	None	3.82 (3.76 ,3.88)	0.0 (Reference)
	Severe: with admission	3.59 (3.39, 3.78)	-0.5 (-0.8, 0.2)
	Severe: no admission	5.22 (5.03, 5.41)	1.4 (1.2, 1.6)

[a] Covariates included gestational age, birthweight Z-scores, maternal age, household monthly income, gestational diabetes, hypertensive disorders of pregnancy, history of smoking exposure and/or positive plasma cotinine, sex of child, maternal general mood factor from pregnancy to 3-month post-partum, and parity.

Abbreviations: ITSEA, Infant Toddler Social and Emotional Assessment; Q-CHAT, Quantitative Checklist for Autism in Toddlers; CBCL, Child Behavior Checklist; DSM, Diagnostic and Statistical Manual of Mental Disorders

eTable 2: Comparison between participants with complete data and missing data based on demographic data and early medical variables

Characteristic		1-year complete (N=542)	1-year missing (N=630)	2-year complete (N=397)	2-year missing (N=775)	4.5-year complete (N=476)	4.5-year missing (N=696)
Severity of nausea and vomiting (NVP)	No	25.2	25.3	23.7	26.1	24.2	26.0
	Mild-moderate	59.4	57.8	62.3	56.6	62.0	56.1
	Severe	15.4	16.9	14.0	17.3	13.8	17.9
Ethnicity	Chinese	64.4	51.7	56.8	56.2	56.0	56.5
	Malay	21.7	27.3	27.5	24.4	27.9	24.0
	Indian	13.9	21.0	15.7	19.4	16.1	19.5
Male sex		50.9	54.1	51.6	53.2	52.3	52.9
Gestational diabetes during pregnancy		18.1	20.1	19.5	19.1	18.1	19.9
Pregnancy-induced hypertension		5.3	6.5	4.8	6.4	5.7	6.0
Smoke exposure (self-report and/or positive plasma cotinine level)		14.9	14.6	17.2	13.6	18.5	12.4
Number of siblings	0	45.5	45.2	45.3	45.3	46.4	44.6
	1	33.7	35.3	30.5	36.6	29.0	38.2
	2 or more	21.8	19.5	24.2	18.1	24.6	17.2
Gestational age in weeks, mean (SD)		38.83 (1.45)	38.41 (2.07)	38.86 (1.29)	38.46 (2.03)	38.83 (1.33)	38.44 (2.08)
Birthweight Z-score, mean (SD)		0.16 (1.20)	0.10 (1.26)	0.12 (1.20)	0.13 (1.24)	0.16 (1.21)	0.10 (1.24)