Behav Genet
DOI 10.1007/s10519-016-9781-7

ORIGINAL RESEARCH

# Nausea and Vomiting During Pregnancy is Highly Heritable

**Lucía Colodro-Conde[1,2] · Patrick Jern[3,4] · Ada Johansson[1,3,4] · Juan F. Sánchez-Romera[5] · Penelope A. Lind[1] · Jodie N. Painter[1] · Juan R. Ordoñana[2] · Sarah E. Medland[1]**

Received: 29 September 2015 / Accepted: 5 January 2016


**Abstract** Nausea and vomiting during pregnancy (NVP) affects about 70 % of all expectant mothers and commonly impacts their physical health and psychosocial functioning. The aim of this study was to estimate the heritability of the presence, duration and severity of NVP. The sample consisted of 1723 women ($M_{age} = 41.78$, $SD = 11.67$) including twins in both complete and incomplete pairs and their sisters from two cohorts participating in the NVP Genetics Consortium. The sample comprised 159 monozygotic and 140 dizygotic complete twin pairs, and 69 twin-sister pairs. We applied an extended twin design using OpenMx and Mx for secondary analysis. Individual differences in NVP were best explained by additive genetic and unique environmental effects. Heritability estimates were 73 % (95 % CIs = 57–84 %) for presence, 51 % (95 % CIs = 36–63 %) for duration and 53 % (95 % CIs = 38–65 %) for severity of NVP. The genetic correlation between duration and severity was almost perfect. Our results show that genes play an important role in different aspects of NVP and justify the importance of searching for genetic variants.

**Keywords** Nausea and vomiting during pregnancy · Morning sickness · Twin study · Heritability · Women's health · NVP Genetics Consortium

## Introduction

Nausea and vomiting during pregnancy (NVP) is a common condition that affects about 70 % of all expectant mothers (Einarson et al. 2013). Although NVP typically occurs in the first trimester, around 23.5 % of women have NVP continuing into the third trimester. There is also high variability in the severity with which NVP symptoms are presented. The severity of NVP can be conceptualized as a continuum (Munch et al. 2011), being classified as mild in 40 %, moderate in 46 % and severe in 14 % of cases (Einarson et al. 2013). Relatively rarely (in 1.1 % of pregnant women), NVP can progress to hyperemesis gravidarum (HG) (Einarson et al. 2013). HG is defined as persistent and excessive vomiting starting before the end of the 22nd week of gestation, characterized by prolonged and severe nausea and vomiting, dehydration, ketonuria and >5 % bodyweight loss (World Health Organization 2010). If untreated, or if treatment is unsuccessful, HG can lead to irreversible maternal renal, neurologic, and hepatic damage, in addition to negative effects on the fetus, such as low birth weight, lower size for gestation age and prematurity in the child (Fejzo et al. 2009; Matsuo et al. 2007; Veenendaal et al. 2011). The condition is also costly, with economic costs of NVP and HG were estimated at almost 1.8 billion USD in the USA in 2012 (Piwko et al. 2013).

Edited by Yoon-Mi Hur

✉ Lucía Colodro-Conde
lucia.colodroconde@qimrberghofer.edu.au; lucia.c.c@um.es

[1] Quantitative Genetics Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Australia

[2] Department of Human Anatomy and Psychobiology, University of Murcia and IMIB Arrixaca, Murcia, Spain

[3] Department of Psychology, Åbo Akademi University, Turku, Finland

[4] Department of Psychology and Speech-Language Pathology, University of Turku, Turku, Finland

[5] Department of Developmental and Educational Psychology, University of Murcia and IMIB Arrixaca, Murcia, Spain

Published online: 22 January 2016

However, a recent systematic review highlights that NVP is associated with favorable fetal outcomes in terms of decreased risk of miscarriages, congenital malformations and prematurity (Koren et al. 2014). The latest data from the Norwegian Mother and Child Cohort Study ($N = 51{,}675$) corroborated this, showing that NVP was associated with favorable delivery and birth outcomes, such as birth weight and gestational age (Chortatos et al. 2015). NVP has been hypothesized to be an evolved mechanism for protecting the mother and her embryo, having an adaptive and prophylactic function (Flaxman and Sherman 2000). NVP may have evolved, along with food aversions, to motivate women to avoid exposure to diseases and other toxins when they are immunosuppressed and when the fetus is at a critical stage of development (McKerracher et al. 2015). Symptoms of NVP peak when embryonic organogenesis is most susceptible to chemical disruption (i.e., weeks 6–18), lending support to the adaptive hypothesis. On the other hand, women with NVP are more likely to develop pregnancy complications, including pelvic girdle pain, proteinuria, high blood pressure and preeclampsia (Chortatos et al. 2015). NVP not only affects the physical health of pregnant women but can also affect their psychosocial functioning, resulting in a lower health-related quality of life (Munch et al. 2011) that can be compared to that of individuals with chronic illnesses (Smith et al. 2000). In an Australian study of 593 women with NVP (Smith et al. 2000), 70 % reported that the condition decreased their ability to parent their other children effectively. Of those in employment, 65 % reported being less attentive to their work, with 28 % changing their schedule and 4 % resigning. Mazzotta et al. (2001) reported that 3.3 % of women with NVP had terminated a pregnancy and 12.9 % had considered termination due to severe NVP. Women are significantly more likely to terminate pregnancy if NVP progresses to HG: Poursharif et al. (2008) reported that 15.2 % of women suffering HG had terminated a pregnancy due to the symptoms. As might be expected, the unremitting nausea and vomiting experienced by women with severe NVP and HG is associated with exhaustion, anxiety and depression (Attard et al. 2002; Koren et al. 2005; Hizli et al. 2012), which are known risk factors for postnatal depression (Hizli et al. 2012; Uguz et al. 2012). Most women first try dietary and other lifestyle modifications to control their NVP symptoms (Clark et al. 2013), but up to 10 % will require pharmacotherapy (Niebyl 2010). However, since the pathogenesis of NVP is not well understood, treatments have a limited success (Poursharif et al. 2008).

There are individual differences in the likelihood of presenting with NVP, how long NVP symptoms occur during pregnancy, and the severity of the associated impairment. Levels of human chorionic gonadotrophin (hCG) reach their peak when the incidence of NVP is most elevated, and hCG concentrations are higher in multiple and molar pregnancies or when the fetus is female, all conditions in which NVP is more common (Veenendaal et al. 2011; Basso and Olsen 2001; Danzer et al. 1980). Younger age of the mother has been found to increase NVP risk, as does a higher number of previous pregnancies (Louik et al. 2006), high body mass index (Cedergren et al. 2008), not smoking (Louik et al. 2006; Jueckstock et al. 2010) and having nutrient deficiencies, alterations in lipid levels, or *Helicobacter pylori* infections (Jueckstock et al. 2010). NVP is a condition linked to the mother, and is not affected by a change of partner (Einarson et al. 2007).

There is currently only one twin study on NVP, conducted in the population-based Norwegian Twin Panel by Corey et al. (1992). With a sample of 830 monozygotic (MZ) twins and 902 dizygotic (DZ) twins, they showed a higher concordance of the presence of NVP in MZ than in dizygotic DZ twins, with tetrachoric correlations being about twice as high in identical twins compared to fraternal twins ($r_{MZ} = .54$ and $r_{DZ} = .24$; $p < .05$ in both cases). For having used medication to treat NVP, the tetrachoric correlations were $r_{MZ} = .63$ and $r_{DZ} = .26$ ($p < .05$ in both cases). Although heritability was not reported in their paper, using the tetrachoric correlations and sample sizes, we used the Mx program (Neale et al. 2006) to estimate heritabilities for NVP (53 %) and for taking nausea medication (73 %). Another study by Fejzo et al. (2008) reported a high prevalence of severe NVP and HG among relatives of a sample of self selected women affected by HG: approximately 28 % reported their mother had severe NVP or HG when expecting them, and 19 % of their sisters with a pregnancy history had HG. A significant increase in nausea in early pregnancy was also found by Gadsby et al. (1997) in women whose mothers experienced nausea in their pregnancies.

Despite the high frequency of NVP and the clinical, economical and psychosocial consequences of NVP, its causes remain unknown. The NVP Genetics Consortium (Colodro Conde et al. in press), a collaborative project created in 2013, aims to identify risk factors for NVP, with a special focus on the genetic risk factors. In the present study, we applied an extended twin design to two twin cohorts, from two different countries, currently participating in the Consortium. The aim was to shed light on the etiology of NVP by (i) estimating the relative magnitude of the environmental and genetic sources of variance in the presence, duration and severity of NVP and (ii) analyzing the sources of variance shared by the duration and severity of NVP.

## Methods

### Participants

The original study sample consisted of 1725 women from 1331 families from the Genetics of Sexuality and Aggression (GSA) and the Murcia Twin Registry (MTR) cohorts which participate in the NVP Genetics Consortium (Colodro Conde et al. in press). The GSA cohort provided data from female twins in same sex and opposite sex pairs and their sisters (non-twin female siblings of twins), while the MTR cohort had collected data from same sex female twins. Samples were unselected and both sample cohorts are population-based. The original data collections have been described elsewhere-see Johansson et al. (2013) and Zietsch et al. (2015) for the GSA cohort and Ordoñana et al. (2006, 2013) for the MTR cohort.

The participants in this study were women who had at least one full-term pregnancy and had reported data on their experience with NVP. Zygosity was determined either by genotyping or questionnaire. Zygosity was unknown for 23 pairs from the GSA study; in these pairs we used data from the first born twin. Only data of the oldest non-twin sibling in each family was considered for the analyses. The sample consisted of 540 women from MZ twin pairs, 769 from DZ twin pairs (534 from same sex twin pairs) and 390 sisters of twins, resulting in 159 MZ and 140 DZ complete pairs and 69 twin-sister pairs. Age at survey time ranged from 25 to 73 years ($M_{age} = 41.8$, $SD = 11.7$).

### Procedure, variables and instruments

Data were collected in September-December of 2013 by a secure, online questionnaire in the case of the GSA sample and by telephone interview for the MTR sample. The questionnaires were back translated from English into Finnish or Spanish and were equivalent between cohorts.

Women were asked whether they had suffered from nausea and vomiting during any of their pregnancies (see Appendix). For those women endorsing this item, further information was collected with reference to the most affected pregnancy, including the trimester(s) in which the symptoms took place as well as the level of associated impairment. The variables analyzed in this study were: (1) presence of NVP in any pregnancy, (2) duration of NVP in the most affected pregnancy and (3) severity of NVP in the most affected pregnancy. Presence of NVP was a dichotomous question, defined as the absence of NVP or NVP for <7 days versus NVP for 7 or more days. Duration was calculated summing the number of trimesters in which NVP was reported and thus had four categories (from those who did not have NVP or did for less than 7 days to three trimesters with symptoms). Finally, the data on severity was collected following the method described by Zhang et al. (2011). Participants were asked to rate their degree of NVP using qualifiers including the number of days with NVP during the pregnancy, impact on normal daily routine, consultation with medical professionals, prescription of medication, use of nutritional support (IV or nasogastric tube) and weight loss. This variable was categorised on four levels of severity: (1) no NVP or NVP for <7 days and minor impairment; (2) NVP for more than 7 days, no medical consultation and minimal impact; (3) NVP for more than 7 days, no use of medication and minor role impairment; and (4) NVP for more than 7 days, use of mediation, loss of weight, and major disruption of the daily routine. The three variables were treated as categorical.

### Data analyses

Descriptive statistics were obtained using SPSS v.22 (IBM Corp. 2013). All subsequent analyses were employed using the statistical package OpenMx (Boker et al. 2011) in R Studio Version 0.98.507 or the Mx software package (Neale et al. 2006). Thresholds, twin–twin and twin-sister correlations, and genetic and environmental variances were estimated using a liability-threshold model, which allows calculations with both complete and incomplete pairs of twins and siblings. Analyses were performed on raw binary and ordinal data, where it is assumed that thresholds delimiting the ordered categories (i.e. no NVP or NVP for <7 days versus NVP 7 days or more) overlay a normally distributed continuum of liability (i.e. likelihood of experiencing NVP).

Assumptions of the twin design (see Neale and Cardon 1992) were checked, including the homogeneity of the thresholds of first- and second-born twins, across zygosity groups and across twins and sisters. For presence of NVP, thresholds could be equated between twins of the same pair, across zygosity (including opposite sex twins) and across twin and siblings. This was also the case for duration and severity of NVP, but only when the data was separated by cohort. Age at survey time was modeled in all analyses as a covariate, effectively partialling out age from the twins and sisters. Thresholds and age effects were equated between cohorts in the analyses conducted with the presence of NVP. However, the direction of the age effects was positive for the GSA cohort and negative for the MTR cohort for both duration and severity of NVP. Thus, for the analyses performed with these variables, thresholds and

age effects were allowed to vary between cohorts, but were the same across zygosity within cohort.

Twin and twin-sister tetrachoric (for the dichotomous trait presence of NVP) and polychoric correlations (NVP duration and symptom severity) and their 95 % confidence intervals (CIs) were estimated (for more information about twin modeling with categorical data, see Rijsdijk and Sham (2002)). Phenotypic correlations generally reflect a combination of additive genetic (*A*), dominant genetic (*D*), shared environmental (*C*), and residual (*E*) variation. In addition to increasing the statistical power, the inclusion of data from sisters allows testing for twin-specific environmental influences (*S*) (Verweij et al. 2012). Additive genetic variation results from the sum of allelic effects. Non-additive genetic variation includes that due to dominance and epistasis. Shared environmental variance results from environmental influences shared by family members. Residual variation includes measurement error and environmental influences that are not shared between twin pairs, such as idiosyncratic experiences (Verweij et al. 2012). We tested whether MZ correlations were higher than those of DZ twin pairs, which would suggest a genetic influence on individual differences in this trait. We also tested if the twin-sister correlations were lower than the DZ twin correlations, which would point to the influence of twin-specific environmental factors (Neale and Maes 2004). It is not possible to estimate *C* and *D* simultaneously with twin and sibling data only, because *C* and *D* are negatively confounded. The choice of modeling *C* or *D* depends on the pattern of MZ and DZ correlations; *C* is estimated if the DZ twin correlation is more than half the MZ twin correlation, and *D* is estimated if the DZ twin correlation is less than half the MZ correlation (Neale et al. 2006).

Structural equation modeling was used to determine the sources of variation that best matched the observed data (Posthuma et al. 2003). Variance component model-fitting was conducted to partition the variation in NVP into genetic and environmental sources by means of three univariate analyses, one for each dependent variable. Since the goodness-of-fit of a model to the observed data is distributed as Chi square ($\chi^2$), by testing the change in Chi square ($\Delta\chi^2$) against the change in degrees of freedom ($\Delta$df) we can test whether dropping or equating specific model parameters significantly worsens the model fit. The best-fitting model was chosen in each case by deducting the residual deviance of the compared models and by comparing Akaike's information criterion (AIC). Twin correlations and variance component estimates could be equated between cohorts without a significant loss of fit established at $p < .05$.

We also conducted a bivariate analysis to examine the phenotypic variation and the sources of covariance between duration of the symptoms present during the pregnancy and the level of impairment associated with them. That is, we estimated the extent to which the observed correlations between these two variables were due to overlap in genetic influences (genetic correlation, $r_g$) or residual factors (residual correlation, $r_e$), since *A* and *E* were the factors that better explained the variance in duration and severity. The A and E matrices were specified in a Cholesky decomposition.

Additionally, we modeled the tetrachoric correlations and the sample size reported in the Norwegian study (Corey et al. 1992) in conjunction with those obtained in the present study to check if the heritability estimates of the presence of NVP, that is, the magnitude of genetic effects, could be equated between the different cohorts.

## Results

Basic demographic information and data on NVP are shown in Table 1. Women in our sample had 2.2 children on average and around 60 % women suffered from NVP in at least one of their pregnancies. In the most affected pregnancy of those women reporting NVP, the symptoms were present only in the first trimester for 54.7 % while 14.5 % had symptoms persisting until the end of the pregnancy. NVP resulted in minor role impairment in 33.3 % and major impact in 16.5 % of women presenting NVP.

Table 2 presents the intra-pair correlations for presence, duration and severity of NVP. The MZ correlations were consistently at least twice as high as the DZ correlations for the three NVP phenotypes ($r_{MZ} = .75$ vs. $r_{DZ} = .29$ for presence, $r_{MZ} = .52$ vs. $r_{DZ} = .20$ for duration and $r_{MZ} = .55$ vs. $r_{DZ} = .13$ for severity of NVP). Twin-sister correlations ($r_{TS} = .43$ for presence, $r_{TS} = .31$ for duration and $r_{TS} = .33$ for severity of NVP) were not significantly different from the DZ correlations. This pattern of correlations suggested the presence of genetic effects in all studied aspects of NVP. Additionally, no evidence of a twin-specific shared environment was found.

We fit univariate models to disentangle the sources of variance of the three phenotypes. In Table 3 we show the model fitting results and the proportions of variance explained by the full ACE and ADE models. Since the twin correlations were suggestive of a dominant genetic effect, the nested submodels, where some of the parameters were dropped, were tested against the ADE model. For the three variables, the best fitting models revealed a similar structure of the underlying variance, including additive genetic and residual non-shared environmental sources of variation. Additive genetic factors accounted for 73 % (95 % CIs = 57–84 %) of the variance of the presence of NVP,

**Table 1** Descriptive statistics of the participants of the Finnish (GSA) and Spanish (MTR) NVP cohorts and the total sample [valid %, (frequency), unless otherwise stated]

| | GSA (n = 1154) | MTR (n = 545) | Total (N = 1699) |
|---|---|---|---|
| Year of birth (range) | 1957–1988 | 1940–1966 | 1940–1988 |
| Age (*M*, *SD*, range) | 34.8 (4.9, 25–56) | 56.6 (7.4, 47–73) | 41.8 (11.7, 25–73) |
| Number of children (*M*, *SD*, range) | 2 (1, 1–9) | 2.5 (1.1, 1–8) | 2.2 (1.1) |
| Zygosity | | | |
| MZ twin pairs | 21.7 (251) | 53 (289) | 31.8 (540) |
| DZ (same sex) twin pairs | 24.1 (278) | 47 (256) | 31.4 (534) |
| DZ (opposite sex) twin pairs | 20.4 (235) | 0 | 13.8 (235) |
| Non twins (sisters) | 33.8 (390) | 0 | 23 (390) |
| NVP for 7 or more days | 59.9 (691) | 55.2 (301) | 58.4 (992) |
| Duration | | | |
| No NVP/NVP < 7 days | 40.1 (463) | 44.9 (244) | 41.7 (707) |
| 1 trimester | 32.1 (370) | 31.7 (172) | 31.9 (542) |
| 2 trimesters | 22.4 (258) | 8.5 (46) | 17.9 (304) |
| 3 trimesters | 5.5 (63) | 14.9 (81) | 8.5 (144) |
| Severity | | | |
| No NVP/NVP < 7 days, minor impact | 40.1 (463) | 45.5 (244) | 41.8 (707) |
| NVP ≥ 7 days, no medical consultation, minimal impact | 30.7 (354) | 26.1 (140) | 29.3 (494) |
| NVP ≥ 7 days, no medication, minor role impairment | 25 (289) | 7.1 (38) | 19.3 (327) |
| NVP ≥ 7 days, medication/IV/feeding tube, weight loss, moderate/major role impairment | 4.2 (48) | 21.3 (114) | 9.6 (162) |

Tests for differences between cohorts for presence, duration and severity of NVP, accounting for relatedness, are presented in the main text

*NVP* nausea and vomiting during pregnancy, *MZ* monozygotic, *DZ* dizygotic

**Table 2** Monozygotic (MZ), dizygotic (DZ) twin and twin–sister (TS) thetracoric and polychoric correlations with 95 % confidence intervals (CI) for three NVP phentoypes

| | $r_{MZ}$ (95 % CIs) | $r_{DZ}$ (95 % CIs) | $r_{TS}$ (95 % CIs) |
|---|---|---|---|
| Presence | 0.75 (0.58, 0.86) | 0.29 (0.03, 0.52) | 0.43 (0.06, 0.70) |
| Duration | 0.52 (0.37, 0.64) | 0.20 (0.01, 0.37) | 0.31(−0.04, 0.57) |
| Severity | 0.55 (0.40, 0.67) | 0.13 (−0.07, 0.31) | 0.33 (−0.01, 0.57) |

*NVP* nausea and vomiting during pregnancy. $r_{DZ}$ and $r_{TS}$ could be equated, yielding in estimates of 0.34 (95 % CI: 0.13, 0.52) for presence, 0.22 (95 % CI: 0.06, 0.37) for duration and 0.17 (95 % CI: 0.02, 0.32) for severity

51 % (95 % CIs = 36–63 %) of its duration and 53 % (95 % CIs = 38–65 %) of the severity of NVP.

Bivariate analysis was performed using Cholesky decomposition of duration and severity of NVP. The phenotypic correlation between traits was $r_{ph} = .92$ (95 % CIs = .91–.93). Due to the results of the univariate analyses, we present the results of the bivariate analysis with only two sources of variance, A and E. Figure 1 shows the first genetic factor ($A_1$) loaded on duration and severity, accounting for 51 % (95 % CIs = 37–64 %) and 53 % (95 % CIs = 40–66 %) of their variation, respectively. The specific genetic contribution to severity of the second genetic factor ($A_2$) accounted for 1 % (95 % CIs = 0–7 %) of its variance and could be dropped from the model without worsening fit ($\Delta\chi^2_1 = 0.275$, $p = .6$). Decomposition of the residual non-shared environmental variation showed that the first factor ($E_1$) accounted for 49 % (95 % CIs = 37–63 %) of the variance for duration and also accounted for 32 % (95 % CIs = 22–46 %) of the variance in severity. The specific residual contribution to severity ($E_2$) accounted for 13 % (95 % CIs = 8–16 %) of the variance of severity. The genetic correlation was $r_g = .99$ (95 % CIs = .93–1) and the residual non-shared environmental correlation was $r_e = .85$ (95 % CIs = .78–.88).

**Table 3** Model-fitting results for univariate models for NVP phenotypes and proportions of variance explained by additive genetic (A), common environment (C) or dominant genetic effects (D) and residual variation (E) with 95 % confidence intervals (CI)

| Parameter estimates (CIs = 95 %) | | | | Goodness-of-fit index | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Model | A | C/D | E | *−2LL* | *df* | *AIC* | $\Delta X^2$ | $\Delta df$ | *p* |
| Presence | | | | | | | | | |
| ACE | 0.73 (0.30, 0.84) | 0 (0, 0.35) | 0.27 (0.16, 0.44) | 2249.337 | 1694 | −1138.663 | | | |
| ADE | 0.73 (0.38, 0.84) | 0 (0, 0.34) | 0.27 (0.16, 0.43) | 2249.337 | 1694 | −1138.663 | – | – | – |
| **AE** | **0.73 (0.57, 0.84)** | **–** | **0.27 (0.16, 0.43)** | **2249.337** | **1695** | **−1140.663** | **0.00** | **1** | **1** |
| E | – | – | 1 (1,1) | 2303.371 | 1696 | −1088.629 | 54.03 | 2 | <0.001 |
| Duration | | | | | | | | | |
| ACE | 0.51 (0.11, 0.63) | 0 (0, 0.31) | 0.49 (0.37, 0.65) | 4094.47 | 1688 | 718.47 | | | |
| ADE | 0.51 (0, 0.63) | 0 (0, 0.62) | 0.49 (0.36, 0.64) | 4094.47 | 1688 | 718.47 | | | |
| **AE** | **0.51 (0.36, 0.63)** | **–** | **0.49 (0.37, 0.64)** | **4094.47** | **1689** | **716.47** | **0** | **1** | **1** |
| E | – | – | 1 (1,1) | 4131.77 | 1690 | 751.77 | 37.30 | 2 | <0.001 |
| Severity | | | | | | | | | |
| ACE | 0.53 (0.23, 0.65) | 0 (0, 0.21) | 0.47 (0.35, 0.62) | 4049.210 | 1681 | 687.21 | | | |
| ADE | 0.23 (0, 0.64) | 0.32 (0, 0.67) | 0.45 (0.33, 0.60) | 4048.39 | 1681 | 686.39 | 4 | | |
| **AE** | **0.53 (0.38, 0.65)** | **–** | **0.47 (0.35, 0.62)** | **4049.21** | **1682** | **686.21** | **0.82** | **1** | **0.37** |
| E | | | 1 (1,1) | 4088.03 | 1683 | 722.03 | 39.64 | 2 | <0.001 |

*df* degrees of freedom, *−2LL* twice negative log-likelihood, ΔX2 difference in X2 as compared to ADE model, Δdf difference in degrees of freedom as compared to ADE model. Bold values indicates best fitting model

## Discussion

The present study aimed to examine the sources of variance underlying NVP, the most common condition in pregnancy. We analyzed data from 159 MZ and 140 DZ complete twin pairs, 69 twin-sister pairs, 573 incomplete twin pairs and 414 sisters on the presence of NVP and its duration and severity in the most affected pregnancy and showed that genetic factors play an important role in NVP.

The prevalences of the three phenotypes studied here are commensurate with those reported in Einarson et al. (2013) meta-analysis. The prevalence of NVP lasting for at least 7 days was 58.4 % in the present study. Einarson et al. reported 70 %, although this figure corresponds to symptoms of NVP of any duration. In our study, 14.5 % of women reported experiencing NVP over three trimesters, which is lower than the 23.5 % figure reported by Einarson et al. (2013), but this prevalence fall within the 95 % confidence interval (12.8–34.2 %). Lastly, 16.5 % of women reported the NVP in their most affected pregnancy implied a major impairment, which is very similar to the corresponding figure in the meta-analysis, 14.4 %.

While the prevalence of NVP was similar between cohorts, the distribution of the duration of the symptoms and their severity among the affected women was statistically different when comparing data from the two cohorts. Women from the Spanish MTR cohort reported more severe symptoms and a longer duration of NVP than did women from the Finnish GSA cohort. Moreover, an older age at survey time was associated with an increase in the duration and severity of NVP symptoms for women in the GSA cohort and a decrease for women from the MTR cohort. Phenotypic differences could be due to differences between the countries in terms of diet, socio-economic status, health systems, socio-cultural environment and/or clinical management that can affect the experience of NVP. In particular, medication prescription by medical personnel appears to be far more common in Spain, which would be expected given a higher number of participants in the extreme category of severity. The use of prescription drugs could also facilitate a perception of persistence in time if women continued taking medication in order to prevent new episodes of NVP. We also cannot rule out a recall bias for women, especially from the MTR cohort, reporting data about experiences that could have happened years ago. However, the twin correlations and sources of variance were equivalent between cohorts.

Our results indicate that experiencing NVP is highly heritable, since genetic effects accounted for 73 % of the variance. Additionally, we tested if the magnitude of the heritability estimates from the Spanish, Finnish and Norwegian cohorts were equivalent across cohorts. We used raw data for the Spanish and Finnish cohorts and the sample size and twin correlations reported in the paper by Corey et al. (1992) for the Norwegian data. The heritability estimates could be equated without loss of model fit ($-2LL = 0.41$, $df = 2$, $p = .81$) as calculated in Mx, showing that the estimates were equivalent across cohorts.

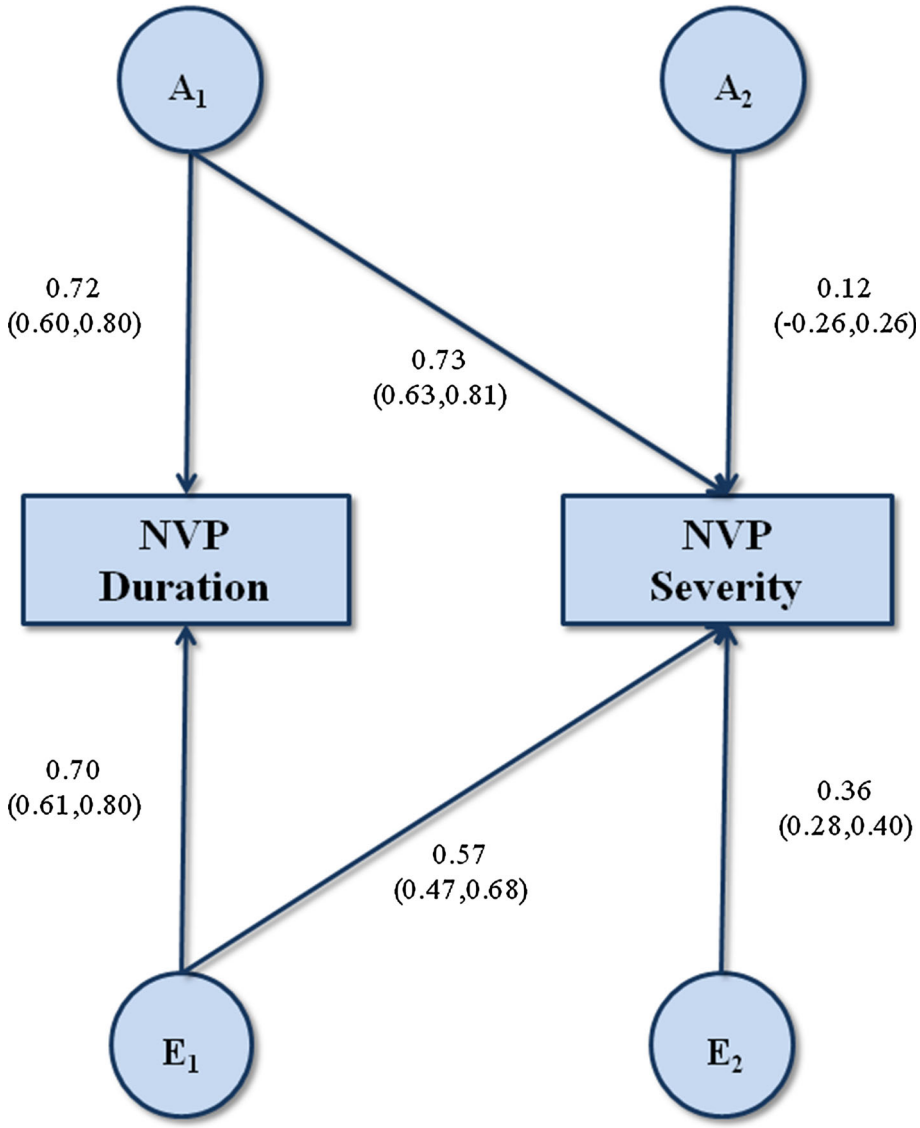


**Fig. 1** Cholesky decomposition for latent variables, showing the standardised path coefficients. They need to be squared to compute the variance components. *A1* and *A2*: Additive genetic factors, *E1* and *E2*: residual factors

These data collected from women born between 1915 and 1988 in three different countries provide consistent evidence that supports the existence of a genetic effect on the presence of NVP. This is also consistent with the familial aggregation reported for NVP in other studies (Fejzo et al. 2008; Gadsby et al. 1997). These findings motivate international efforts to analyze genetic data on NVP, such as the established Consortium.

We also analyzed the sources of variation of the duration and the severity of NVP. In both variables, the heritability estimates were moderate (51 and 53 % for duration and severity, respectively). That is, the degree to which symptoms of NVP occur is also heritable. The phenotypic, genetic and environmental correlations of both phenotypes were extremely high. However, the correlations were mainly driven by the women who did not have NVP symptoms or had them for less than 7 days, with a minor impact (n = 716). That is, if this first category was omitted from the analyses, the phenotypic correlation was reduced to .54 (95 % CIs = .47–.60). Thus, the duration and the severity of NVP are similar in nature and the same genetic and environmental risk factors likely contribute to both phenotypes. It is possible there is a recall bias so those who had severe NVP tend to report longer durations and those who had a mild one tend to report shorter duration of the symptoms. If so, it is likely that this pattern is a reflection of the course of NVP over pregnancy in the absence of efficient treatments for those with more severe symptoms. This finding offers clues for the design of future projects, so for example it may be possible to jointly study both traits in a genome wide association study, that is, to combine in GWAS meta-analysis data from different cohorts

that have collected information on either severity or duration of NVP or to use data from one of the phenotypes as a replication for the findings of the other.

Our findings justify the importance of searching for genetic variants influencing NVP. Genetic variants influencing the serotonin neurotransmitter (Goecke et al. 2010) and hCG have been proposed as candidates for the development of NVP. There is also a higher frequency of severe NVP in patients with certain genetically-determined conditions such as disorders in taste sensation, in the glycoprotein hormone receptor or in fatty acid transport (Outlaw and Ibdah 2005; Rodien et al. 1998, 2004; Bartoshuk et al. 1996; Sipiora et al. 2000). However, the genetic pathways that influence NVP have not yet been elucidated.

NVP is a universal condition in pregnancies. There is documentation of vomiting in pregnancy dating back to ancient Egypt (2000 BC) and works by Hippocrates dated around 300 BC (O'Brien and Newton 1991) and NVP is common in both industrialized and non- industrialized societies. Additionally, food rejection at the beginning of pregnancy has been reported in rhesus monkeys (Czaja 1975). It is hyphotesised the influence of genes on NVP may have evolved to ensure pregnancies with better general outcomes. While NVP can limit maternal and fetal access to energy and nutrients, it is associated with reduced risk of spontaneous abortion and other complications (Koren et al. 2014; Chortatos et al. 2015).

There are a number of limitations that should be considered. Firstly, there may be recall bias in those women reporting data about NVP from pregnancies that took place some years ago. However, pregnancy-related events are less susceptible to recall bias than other kind of events (Attard et al. 2002). Secondly, as many of the participants were still within child bearing age, it is possible that we may be underestimating prevalence and severity as there is the potential for additional more affected pregnancies. Lastly, we were unable to control for some potential variables that are relevant in the experience of NVP, such as the fact of having a multiple pregnancy or the age at the most affected pregnancy.

In summary, NVP and HG are important health outcomes in terms of their high frequency, clinical and psychosocial consequences for women, adverse pregnancy outcomes and financial burden. Our results indicate that a significant part of the individual differences in NVP are due to genetic variation. Future work should identify specific factors to understand the causes of NVP, which may help with the development of more effective treatments acting in new biological targets and preventing the progression from mild to severe NVP or HG. A better prediction of which women will be at risk for NVP and HG, would allow for informing women about their personal risk levels so they can make better decisions about when and how to seek treatment, with the aim of increasing the number of women who receive medical assistance prior to progression to severe NVP thereby reducing the prevalence of HG.

**Acknowledgments** The GSA group is grateful to the twins and siblings of twins for their participation. We are indebted all GSA staff, past and present. MTR is grateful to the twins for their participation in the Murcia Twin Registry. We are grateful to Nicholas G. Martin for his comments on previous versions of this work and to Baptiste Couvy-Duchesne for his support in the data analyses.

**Compliance with ethical standards**

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** Informed consent was obtained from all individual participants included in the study. Data collections were approved by the relevant Ethics Committees in each of the participant institutions (Ethics Committee of the Åbo Akademi University and Committee of Research Ethics of the University of Murcia) and follow the relevant national regulations regarding data protection. The Helsinki Declaration, as well as applicable institutional and governmental regulations concerning the ethical use of human volunteers, were followed during all the phases of this research.

**Funding** The GSA data collection was funded by The Academy of Finland [Grant Number 138291]. The MTR is funded by Fundación Séneca - Agencia de Ciencia y Tecnología de la Región de Murcia, Murcia, Spain [08633/PHCS/08, 15302/PHCS/10] and the Spanish Ministry of Science and Innovation [Grant Numbers PSI2009–11560]. The NVP Genetics Consortium is supported by the Australian National Health and Medical Research Council [Grant Number APP1084325]. This work was also supported by Fundación Séneca - Agencia de Ciencia y Tecnología de la Región de Murcia, Murcia, Spain [19151/PD/13 to L.C.C.] and by The Academy of Finland [284385, 274521 to P.J.].

## Appendix: Questionnaire

Have you ever experienced any nausea or vomiting or morning sickness while pregnant?

- ❍ No, I've never experienced any nausea or vomiting or morning sickness while pregnant, or I did for less than 7 days.
- ❍ Yes, I have experienced some nausea or vomiting or morning sickness while pregnant for 7 or more days.

Thinking of your most affected pregnancy, did you have any morning sickness during your

- ❍ 1st trimester
- ❍ 2nd trimester
- ❍ 3rd trimester

Using the following scale which of the following best describes your experiences during your most affected pregnancy?

- ❍ I had some nausea and/or vomiting for more than 7 days, but I didn't see a doctor about this. It didn't disrupt my daily routine.
- ❍ It disrupted my daily routine but it didn't affect my weight and I didn't need medication to manage it.
- ❍ It really disrupted my daily routine and I was prescribed medication (or was put on a drip) but it didn't lead to weight loss.
- ❍ It really disrupted my daily routine. I lost weight. I was prescribed medication or was put on a drip or feeding tube.
- ❍ I don't remember or am unsure.

## References


Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, Torrance GW (2002) The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol 186(5 Suppl Understanding):S220–S227

Bartoshuk LM, Duffy VB, Reed D, Williams A (1996) Supertasting, earaches and head injury: genetics and pathology alter our taste worlds. Neurosci Biobehav Rev 20(1):79–87

Basso O, Olsen J (2001) Sex ratio and twinning in women with hyperemesis or pre-eclampsia. Epidemiology 12(6):747–749

Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, Spies J, Estabrook R, Kenny S, Bates T, Mehta P, Fox J (2011) OpenMx: an open source extended structural equation modeling framework. Psychometrika 76(2):306–317

Cedergren M, Brynhildsen J, Josefsson A, Sydsjö A, Sydsjö G (2008) Hyperemesis gravidarum that requires hospitalization and the use of antiemetic drugs in relation to maternal body composition. Am J Obstet Gynecol 198412(e411-412):e415

Chortatos A, Haugen M, Iversen PO, Vikanes A, Eberhard-Gran M, Bjelland EK, Magnus P, Veierod MB (2015) Pregnancy complications and birth outcomes among women experiencing

nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study. BMC Pregnancy Childbirth 15:138

Clark S, Hughes B, McDonald SS (2013) The impact of nausea and vomiting of pregnancy on quality of life: report of a national consumer survey and recommendations for improving care. Obstet Gynecol Surv 68(9):S1–S10

Colodro-Conde L, Cross SM, Lind PA, Painter JN, Gunst A, Jern P, Johansson A, Maegbaek ML, Munk-Olsen T, Nyholt DR, Ordoñana JR, Paternoster L, Sánchez-Romera JF, Wright MJ, Medland SE (in press) Cohort profile: nausea and vomiting during pregnancy genetics consortium (NVP genetics consortium). Int J Epidemiol. doi:10.1093/ije/dyv360

Corey LA, Berg K, Solaas MH, Nance WE (1992) The epidemiology of pregnancy complications and outcome in a Norwegian twin population. Obstet Gynecol 80(6):989–994

Corp. I (Released 2013.) IBM SPSS Statistics for Windows, Version 22.0.. In. IBM Corp., Armonk, NY

Czaja JA (1975) Food rejection by female rhesus monkeys during the menstrual cycle and early pregnancy. Physiol Behav 14(5):579–587

Danzer H, Braustein GD, Rasor J, Forsythe A, Wade ME (1980) Maternal serum human chorionic gonadotropin concentrations and fetal sex prediction. Fertil Steril 34(4):336–340

Einarson TR, Navioz Y, Maltepe C, Einarson A, Koren G (2007) Existence and severity of nausea and vomiting in pregnancy (NVP) with different partners. J Obstet Gynaecol 27(4):360–362

Einarson TR, Piwko C, Koren G (2013) Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol 20(2):e171–e183

Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, Goodwin TM (2008) High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod Biol 141(1):13–17

Fejzo MS, Poursharif B, Korst LM, Munch S, MacGibbon KW, Romero R, Goodwin TM (2009) Symptoms and pregnancy outcomes associated with extreme weight loss among women with hyperemesis gravidarum. J Womens Health (Larchmt) 18(12):1981–1987

Flaxman SM, Sherman PW (2000) Morning sickness: a mechanism for protecting mother and embryo. Q Rev Biol 75(2):113–148

Gadsby R, Barnie-Adshead AM, Jagger C (1997) Pregnancy nausea related to women's obstetric and personal histories. Gynecol Obstet Invest 43(2):108–111

Goecke TW, Ekici AB, Niesler B, Loehberg CR, Hammer C, Rappold G, Schanze D, Straub V, Altmann HH, Strissel P, Strick R, Beckmann MW, Fasching PA (2010) Two naturally occurring variants of the serotonin receptor gene HTR3C are associated with nausea in pregnancy. Acta Obstet Gynecol Scand 89(1):7–14

Hizli D, Kamalak Z, Kosus A, Kosus N, Akkurt G (2012) Hyperemesis gravidarum and depression in pregnancy: is there an association? J Psychosom Obstet Gynaecol 33(4):171–175

Johansson A, Jern P, Santtila P, von der Pahlen B, Eriksson E, Westberg L, Nyman H, Pensar J, Corander J, Sandnabba NK (2013) The genetics of sexuality and aggression (GSA) twin samples in Finland. Twin Res Hum Genet 16(1):150–156

Jueckstock JK, Kaestner R, Mylonas I (2010) Managing hyperemesis gravidarum: a multimodal challenge. BMC Med 8:46

Koren G, Piwko C, Ahn E, Boskovic R, Maltepe C, Einarson A, Navioz Y, Ungar WJ (2005) Validation studies of the pregnancy unique-quantification of emesis (PUQE) scores. J Obstet Gynaecol 25(3):241–244

Koren G, Madjunkova S, Maltepe C (2014) The protective effects of nausea and vomiting of pregnancy against adverse fetal outcome–a systematic review. Reprod Toxicol 47:77–80

Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA (2006) Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr Perinat Epidemiol 20(4):270–278

Matsuo K, Ushioda N, Nagamatsu M, Kimura T (2007) Hyperemesis gravidarum in Eastern Asian population. Gynecol Obstet Invest 64(4):213–216

Mazzotta P, Stewart DE, Koren G, Magee LA (2001) Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynaecol 22(1):7–12

McKerracher L, Collard M, Henrich J (2015) The expression and adaptive significance of pregnancy-related nausea, vomiting, and aversions on Yasawa Island, Fiji. Evol Hum Behav 36(2):95–102

Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM (2011) Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. J Perinatol 31(1):10–20

Neale MC, Cardon LR (1992) Methodology for genetic studies of twins and families. Kluwer Academic Publishers, Dordrecht, The Netherlands.

Neale MC, Maes HH (2004) Methodology for genetic studies of twins and families. Kluwer Academic Publishers, The Netherlands

Neale MC, Boker SM, Xie G, Maes HH (2006) Mx: statistical modeling. Department of Psychiatry, VCU Box 900126, Richmond, VA 23298 http://www.vcu.edu/mx/

Niebyl JR (2010) Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med 363(16):1544–1550

O'Brien B, Newton N (1991) Psyche versus soma: historical evolution of beliefs about nausea and vomiting during pregnancy. J Psychosom Obstet Gynaecol 12(2):91–120

Ordoñana JR, Perez-Riquelme F, Gonzalez-Javier F, Carrillo E, Gomez-Amor J, Martinez-Selva JM (2006) An initiative in Spain for the study of women's health: the Murcia Twin Registry. Twin Res Hum Genet 9(6):865–867

Ordoñana JR, Rebollo-Mesa I, Carrillo E, Colodro-Conde L, Garcia-Palomo FJ, Gonzalez-Javier F, Sanchez-Romera JF, Aznar Oviedo JM, de Pancorbo MM, Perez-Riquelme F (2013) The Murcia Twin Registry: a population-based registry of adult multiples in Spain. Twin Res Hum Genet 16(1):302–306

Outlaw WM, Ibdah JA (2005) Impaired fatty acid oxidation as a cause of liver disease associated with hyperemesis gravidarum. Med Hypotheses 65(6):1150–1153

Piwko C, Koren G, Babashov V, Vicente C, Einarson TR (2013) Economic burden of nausea and vomiting of pregnancy in the USA. J Popul Ther Clin Pharmacol 20(2):e149–e160

Posthuma D, Beem AL, de Geus EJ, van Baal GC, von Hjelmborg JB, Iachine I, Boomsma DI (2003) Theory and practice in quantitative genetics. Twin Res 6(5):361–376

Poursharif B, Korst LM, Fejzo MS, MacGibbon KW, Romero R, Goodwin TM (2008) The psychosocial burden of hyperemesis gravidarum. J Perinatol 28(3):176–181

Rijsdijk FV, Sham PC (2002) Analytic approaches to twin data using structural equation models. Brief Bioinform 3(2):119–133

Rodien P, Bremont C, Sanson ML, Parma J, Van Sande J, Costagliola S, Luton JP, Vassart G, Duprez L (1998) Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. N Engl J Med 339(25):1823–1826

Rodien P, Jordan N, Lefevre A, Royer J, Vasseur C, Savagner F, Bourdelot A, Rohmer V (2004) Abnormal stimulation of the thyrotrophin receptor during gestation. Hum Reprod Update 10(2):95–105

Sipiora ML, Murtaugh MA, Gregoire MB, Duffy VB (2000) Bitter taste perception and severe vomiting in pregnancy. Physiol Behav 69(3):259–267

Smith C, Crowther C, Beilby J, Dandeaux J (2000) The impact of nausea and vomiting on women: a burden of early pregnancy. Aust N Z J Obstet Gynaecol 40(4):397–401

Uguz F, Gezginc K, Kayhan F, Cicek E, Kantarci AH (2012) Is hyperemesis gravidarum associated with mood, anxiety and personality disorders: a case-control study. Gen Hosp Psychiatry 34(4):398–402

Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ (2011) Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG 118(11):1302–1313

Verweij KJ, Mosing MA, Zietsch BP, Medland SE (2012) Estimating heritability from twin studies. Methods Mol Biol 850:151–170

World Health Organization (2010) International statistical classification of diseases and related health problems, 10th revision. World Health Organization, Geneva

Zhang Y, Cantor RM, Macgibbon K, Romero R, Goodwin TM, Mullin PM, Fejzo MS (2011) Familial aggregation of hyperemesis gravidarum. Am J Obstet Gynecol 204(3):230 e231–230 e237

Zietsch BP, Lee AJ, Sherlock JM, Jern P (2015) Variation in women's preferences regarding male facial masculinity is better explained by genetic differences than by previously identified context-dependent effects. Psychol Sci 26(9):1440–1448. doi:10.1177/0956797615591770