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# An adaptive significance of morning sickness? Trivers–Willard and *Hyperemesis Gravidarum*

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## ABSTRACT

Nausea during pregnancy, with or without vomiting, is a common early indication of pregnancy in humans. The severe form, *Hyperemesis Gravidarum* (HG), can be fatal. The aetiology of HG is unknown. We propose that HG may be a proximate mechanism for the Trivers–Willard (T-W) evolutionary hypothesis that mothers in poor condition should favor daughters. Using Swedish linked registry data, 1987–2005, we analyze all pregnancies that resulted in an HG admission and/or a live birth, 1.65 million pregnancies in all. Consistent with the T-W hypothesis, we find that: (i) HG is associated with poor maternal condition as proxied by low education; (ii) HG in the first two months of pregnancy is associated with a 7% point increase in live girl births; and (iii) HG affected pregnancies have a 34-percent average rate of inferred pregnancy loss, higher among less educated women.

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## 1. Introduction

Nausea of pregnancy affects some two thirds of human pregnancies, with typical onset in the first trimester (Louik et al., 2006). In about 1% of pregnancies, the nausea and vomiting in pregnancy (NVP) results in hospitalization and the diagnosis *Hyperemesis Gravidarum* (HG).

Despite its ubiquity, the function of NVP remains poorly understood (Pirisi, 2001). Mild manifestations of NVP have been associated with positive pregnancy outcomes (Weigel and Weigel, 1989). For instance, NVP may steer the pregnant woman away from potentially harmful foods and substances (Flaxman and Sherman, 2000). (For smoking, see Hook (1974); alcohol and tobacco, see Little (1980); and teratogens, see Profet (1988).) However, food aversions or

cravings, also known to occur during pregnancy, guide food choice without impairing functionality or wasting food. Another possibility is that NVP serves no particular purpose (Vikanes et al., 2008).

Curiously, HG has been associated with girl births (Askling et al., 1999; Melero-Montes and Jick, 2001). Trivers and Willard (1973) (T-W) proposed that natural selection would favor mothers' ability to adjust the sex ratio at birth according to condition: mothers in poor condition would produce more daughters, and mothers in good condition more sons. The proposed reason was that (i) lower male (than female) parental investment makes male reproductive success more variable than female such and as a result males in poor condition would not be able to mate; and (ii) that maternal condition is predictive of adult offspring condition. T-W further proposed that the sex regulating mechanism would be sex-differential mortality and pointed out that generally it would be advantageous for such mortality to occur as early as possible.

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Thus, if HG afflicts mothers of low socio-economic status disproportionately, then HG may be a proximate mechanism for the T-W hypothesis. In this paper we bring a large data set to bear on the question. Using Swedish linked registry data we analyze all pregnancies in the period 1987–2005 that resulted in an HG admission and/or a live birth, 1.65 million pregnancies in all.

Consistent with HG being a proximate mechanism for the T-W hypothesis, we find that: (i) HG is associated with poor maternal condition as proxied by low education; (ii) HG in the first two months of pregnancy is associated with a 7% point increase in live girl births; and (iii) HG affected pregnancies have an 34-percent average rate of inferred pregnancy loss, higher among less educated women.

Our findings are consistent with a growing body of evidence that women in poor condition give birth to more daughters (Almond and Edlund, 2007); the nutritional status around conception and early pregnancy possibly being a key mechanism (Cameron, 2004; Mathews et al., 2008; Almond and Mazumder, 2011). To the best of our knowledge, ours is the first study to document in a large sample a significant effect on the sex ratio at birth from a maternal medical condition that varies systematically with social status.

## 2. Methods

We analyzed data from three Swedish registers: the Natality Register, the LISA data set (*Longitudinell Integrationsdatabas för Sjukförsäkrings och Arbetsmarknadsstudier*), and the Inpatient Register (1987–2005). LISA is a large data set containing register data and basic demographic information such as sex and date of birth (month) as well as a unique personal identifier which allows the linking of mothers to live births.

Our primary population consists of 2,531,239 women born in Sweden between 1940 and 1985 and observed in the 1986 population census. We matched these women to all hospitalization and birth records occurring between 1987 and 2005.

We have 1,646,571 singleton live births to 922,073 women (see Table 1). Among the 1,646,571 live births, 8322 women experienced HG in at least one pregnancy, and 11,712 (0.7%) live births were affected by HG.

The inpatient register shows that 15,421 women developed HG during at least one of their pregnancies, a total of 17,840 HG-affected pregnancies, leaving 6128 (17,840–11,712) pregnancies with HG but no live birth.

We capture 83% (1,646,571/1,977,084) of the total live births in Sweden over the 1987–2005 period (as reported by Statistics Sweden). The 17% loss occurs for four reasons.

First, the Swedish Medical Birth Register omits about 1.4% of births “when documents relating to delivery are not sent by the delivery hospital to the register.”<sup>1</sup> Second, we exclude multiple births. Third, we require mothers to be born 1940–85 in Sweden, which excludes the foreign born, as well as young mothers in the later years (e.g., a mother born in 1986 and herself giving birth in 2005 is excluded). Fourth, the 1986 Census is used as a sampling frame and we therefore lose women not enumerated in that Census.

Information on the age and educational attainment (as of 2003) was obtained from the LISA dataset. Advanced maternal age has been found to affect the sex ratio at birth and therefore we include an indicator variable that takes on the value 1 if the mother was older than 35 at the time of giving birth and 0 otherwise. LISA also provides information on maternal education in five educational categories ranging from “compulsory or less” to “Masters or PhD.”

From the Inpatient Register, we identified all hospital admissions for HG (diagnosis code 643 in the International Classification of Diseases, revision 9 (ICD-9), and code O21 in revision 10 (ICD-10)), as well as date (day) of admission. The Natality Register contains information for all pregnancies that resulted in a birth (live or still). From this register we obtain information about date of giving birth (month) and birth outcomes (gestation length, birth weight, Apgar score). For HG for pregnancies that ended with a live birth we can thus calculate gestation length at first admission. Further, we can infer the rate of pregnancy loss among pregnancies with HG. In the case of repeat admissions, the date of the first admission per pregnancy was used.

Three statistical analyses were carried out.

1. The proportion of pregnancies affected by HG was calculated in each of the five categories of completed education. We do not condition on a live birth since pregnancy loss is one consequence of HG and thus conditioning would disproportionately exclude the most severely affected women.
2. To investigate the relationship between HG and a live girl birth we regress the latter on the former employing a linear probability model. A sensitivity analysis was also carried out using a logit model. The analysis was done in two separate comparisons: (i) a conventional between-subject design; and (ii) a within-subject design (Ludwig and Currie, 2010).

The within-subject (or mother fixed effects) design compares outcomes to the same woman. That is, for the same woman, we compare the outcomes (boy or girl) in pregnancies with and without HG. This design thus removes the effect of differences across women, whether observed (e.g., educational attainment), or unobserved (e.g., “concern for her children”), as well as any time-invariant characteristic of the woman (e.g., cohort), thereby further reducing the possibility of

**Table 1**  
Sample description.

Universe	Unit of analysis	HG cases	Denominator
Pregnancies	Pregnancy	17,840	1,652,699
	Woman	15,421	929,172
Live births	Pregnancy	11,712	1,646,571
	Woman	8322	922,073

<sup>1</sup> The Swedish Medical Birth Register – A Summary of Content and Quality. Centre for Epidemiology, National Board of Health and Welfare, 2003.

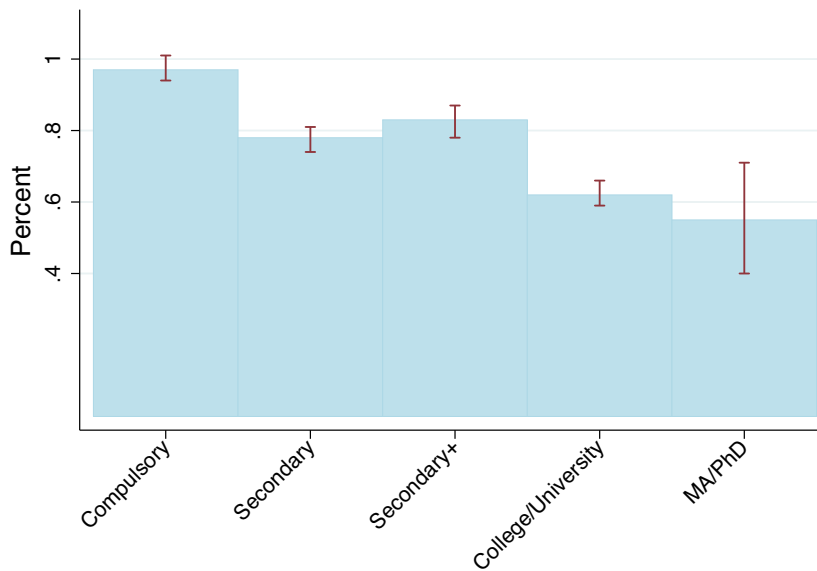


Fig. 1. Probability of *Hyperemesis Gravidarum* by maternal education. The education categories, in ascending order are: *Folkskola/Grundskola*; *Yrskesskola/Gymnasium*; *Gymnasium* plus one or two additional years of education; and *Högskoleexamen*; *Doktors- eller Licentiatexamen*.

confounding. The within-subject design requires variation at the subject level. Therefore, for this analysis, our sample is restricted to women who have had more than one pregnancy with a live birth and had experienced HG in at least one, but not all, of them.

Both of these analyses were carried out unadjusted, or adjusted for advanced maternal age and educational attainment.

- We inferred the proportion of HG pregnancies ending in a miscarriage or stillbirth from pregnancies that resulted in hospital admission for HG but not in a subsequently observed live birth. We also considered whether miscarriage/stillbirth following HG varied with educational attainment.

### 3. Results

#### 3.1. Educational attainment and HG

The relationship between educational attainment and admission for HG is shown in Fig. 1, which reports coefficients and confidence intervals from regressing HG on educational attainment categories and year-of-birth dummy variables (1940–1985).<sup>2</sup>

There is a clear educational gradient. Women with more schooling are less likely to manifest HG. The 95% confidence intervals are narrow courtesy of the large number of observations and we can confidently reject equality of HG rates across education levels.

Women with the lowest schooling level were 76% (0.97/0.55–1) more likely to manifest HG than those with the

highest schooling levels. Women with vocational schooling were 24, 16, and 56% more likely to have had HG than those with secondary, secondary plus, and college/university education, respectively.

#### 3.2. Secondary sex ratio

The relationship between HG by gestation age at first admission and the probability of a girl birth is shown in Fig. 2. There is a marked increase in the probability of observing a girl at (live) birth among those admitted for HG in the first trimester. The coefficient estimates indicate that HG in the first two months of pregnancy raises the proportion of girls at birth by 7% points, from 48.7% to approximately 56% (upper left panel). These results are essentially unchanged with adjustment for advanced maternal age and education (upper right panel). There was no association between girl birth and maternal education (results available on request). In the within-subject analysis, the findings were qualitatively similar (lower panels). The sensitivity analysis using a logit instead of a linear probability model gave very similar results (available on request), unsurprising given that the mean of the dependent variable, girl birth, is close to 0.5.

#### 3.3. Pregnancy loss

Among the 17,840 HG cases, we observed a subsequent live birth for 11,712 cases, implying a 34.3% mortality rate. We have also considered the possibility of an education gradient to the (the inferred) pregnancy loss. While the estimates are less precise due to smaller sample sizes, there is a consistent pattern that maternal schooling increases the likelihood that an HG pregnancy will result in a live birth. A joint *F*-test that the education coefficients are all equal is rejected.

<sup>2</sup> The HG rates by education shown in Fig. 1 are normalized to women born in the 1978 birth cohort, which had HG rates typical of the 1950–1985 cohorts.

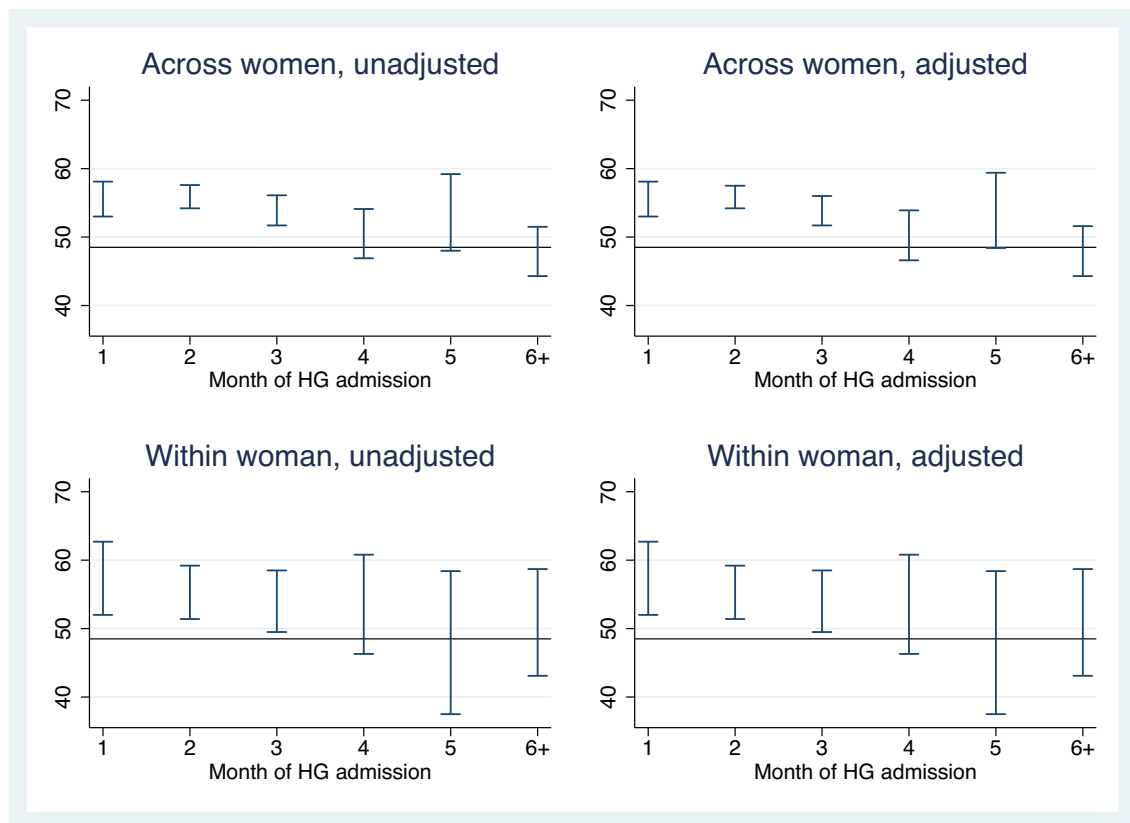


Fig. 2. The percent girl births among live births by gestation month of 1st hospital admission for *Hyperemesis Gravidarum*. The figure graphs 95% c.i. for coefficient estimates from regressing the dummy variable “girl” on HG occurrence in specified month. Top panels are based on the entire sample (1.6 million pregnancies). The bottom panels are based on the sibling subsample (375 thousand pregnancies). Adjusted regressions include controls for advanced maternal age ( $\geq 35$  years) and educational attainment (five categories).

#### 4. Discussion

We have shown that women with low educational attainment are more likely to be admitted to hospital for HG in the first trimester than other pregnant women. Further, we have confirmed previous findings (Askling et al., 1999; Melero-Montes and Jick, 2001) of a pronounced tendency of HG pregnancy to result in live girl births. Combined, these two observations suggest that morning sickness may be a proximate mechanism for the T-W hypothesis that mothers in poor condition would favor daughters.

Our results on maternal condition are broadly consistent with recent findings by Roseboom et al. (2011); although NVP outside the first trimester (less common) has been more strongly associated with low maternal socio-economic status than NVP in the first trimester (Louik et al., 2006).

Our finding that HG is associated with a 34% pregnancy loss suggests that sex-differential mortality may be an important mechanism through which HG lowers the fraction of boys observed at birth. We also find that HG pregnancies are more likely to yield a live birth if the woman is better educated.

While it is theoretically possible that socio-economic status is a factor in hospital admission for HG, we find it reasonable to assume the admission threshold to be similar

across educational levels, considering that in Sweden, all health care is free of charge and access is universal.

To complete the picture, it would be necessary to explain how poor maternal condition leads to this endocrine change, which is likely to involve the hypothalamo-pituitary axis, possibly through the stress pathway. This is plausible in the light of findings from the social determinants of health literature (Marmot, 2004).

The finding that women admitted for HG are more likely to give birth to girls holds up when comparing pregnancies for the same woman, further suggestive of a role of HG in sex-differential prenatal mortality, because time-invariant background characteristics of the woman cannot account for the relationship between HG and the secondary sex ratio of offspring. The consistency of our estimates across multiple sets of control variables suggests that the effect of HG on offspring sex is unlikely to be confounded.

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