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Rates of nausea and vomiting in pregnancy and dietary characteristics across populations

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Nausea and vomiting in pregnancy (NVP) is a pervasive and debilitating phenomenon in humans. Several adaptive explanations for NVP occurrence have been recently proposed, the two most prominent of which predict associations with nutritional intake or specific dietary components. Here we extend previous cross-cultural analyses by analysing associations between NVP prevalence in 56 studies (21 countries) and quantitative estimates of *per capita* intake across major dietary categories, measured for the year of study by the Food and Agriculture Organisation (FAO). Rates of nausea and vomiting in pregnancy were correlated with high intake of macronutrients (kilocalories, protein, fat, carbohydrate), as well as sugars, stimulants, meat, milk and eggs, and with low intake of cereals and pulses. Restricting analyses to studies from North America and Europe caused relationships between macronutrient intake and NVP to disappear, suggesting that they might be influenced by non-dietary confounds associated with geographical region of study. However, factor analysis of dietary components revealed one factor significantly associated with NVP rate, which was characterized by low cereal consumption and high intake of sugars, oilcrops, alcohol and meat. The results provide further evidence for an association between diet and NVP prevalence across populations, and support for the idea that NVP serves an adaptive prophylactic function against potentially harmful foodstuffs.

Keywords: pregnancy sickness; evolutionary medicine; aversion; teratogen; embryo protection

1. INTRODUCTION

Nausea and vomiting in pregnancy (NVP), often termed pregnancy sickness, occurs in the first trimester in up to 80% of pregnancies (Flaxman & Sherman 2000). Symptoms range from mild nausea (often accompanied by aversions to certain foods) to frequent vomiting and hyperemesis (Furneaux *et al.* 2001). Until recently, NVP was thought to be simply an unfortunate by-product of dramatic hormonal changes during early pregnancy (Masson *et al.* 1985; Lagiou *et al.* 2003), with potentially negative consequences on offspring intrauterine growth and health in later life through resulting undernutrition (e.g. Godfrey *et al.* 1996; Fall *et al.* 2003). However, recent reviews have proposed adaptive explanations for the phenomenon (Hook 1976; Profet 1992; Huxley 2000; Flaxman & Sherman 2000; Fessler 2002; Sherman & Flaxman 2002) in light of studies demonstrating favourable prognostic associations, such as reduced risk of spontaneous abortion (Brandes 1967; Pettiti 1986; Weigel & Weigel 1989*b*; Chatenoud *et al.* 1998).

One of the adaptive explanations for an association between NVP and positive pregnancy outcomes is that NVP may indirectly induce higher levels of placental growth (Huxley 2000) by lowering maternal energy intake and levels of insulin and insulin growth factor IGF-1, effectively channelling nutrients away from maternal tissue synthesis and towards the developing placenta. In support of this, reduced maternal energy intake in pregnancy correlates with increased placental weight (Schuster *et al.* 1985; Godfrey *et al.* 1996; Lumey 1998), at least for mild levels of dietary limitation (Barker *et al.* 1993). According to this hypothesis, NVP is more likely to occur in individuals with high preconceptional body-mass index (BMI; Huxley 2000). However, evidence for this is mixed: one study reports more frequent vomiting in heavier than lighter women (Klebanoff *et al.* 1985), another fails to find this relationship (Lagiou *et al.* 2003), while another finds the opposite (Ben-Aroya *et al.* 2005).

A second prominent adaptive explanation for NVP is that it may serve a prophylactic function against ingestion of potentially harmful foodstuffs (Hook 1976; Profet 1992; Flaxman & Sherman 2000; Fessler 2002; Sherman & Flaxman 2002). Among other evidence, this idea is consistent with the timing of peak NVP symptoms during embryonic organogenesis and with commonly observed aversions to certain foods (MacIntyre 1983; Rodin & Radke-Sharpe 1991). In the initial formulation of this idea, NVP was thought to protect the embryo principally against toxins such as those present in caffeinated beverages (Hook 1976; see also Lawson *et al.* 2004). However, its scope was subsequently widened to include pathogens and teratogens (Weigel & Weigel 1989*a*), in particular the defensive secondary compounds produced by plants and found in strong-tasting vegetables, caffeinated drinks, tobacco and alcohol (Little & Hook 1979; Profet 1992).

More recently, Flaxman & Sherman (2000) reformulated this idea as the 'maternal and embryo protection hypothesis' (see also Sherman & Flaxman 2002), extending the benefits of NVP to include the mother, in view of maternal immunosuppression during pregnancy.

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They suggest that NVP triggers aversions to any food likely to contain teratogens and pathogens, especially those that could compromise pregnancy before plants were bred to be 'bland' (lower levels of phytotoxins) and before electric refrigeration became widespread. In their cross-cultural analysis of 27 traditional societies, those in which NVP occurs at low frequencies typically consume less meat than those with higher rates (Flaxman & Sherman 2000). These societies typically have corn as a staple, possibly conferring additional benefits in reducing iron bioavailability to iron-limited pathogens through binding by phytic acid (Fessler 2002). The particular danger of meat-borne pathogens in NVP has also been emphasized by Fessler (2002), who notes that meat is singularly subject to dietary taboos in many human societies (Fessler & Navarrete 2003).

Here we investigate further the link between NVP and diet by comparing rates of NVP prevalence across 56 studies in 21 countries with mean consumption of macronutrients and specific foodstuffs in each country. Our analysis is complementary to and extends the approach of Flaxman & Sherman (2000) in comparing NVP prevalence across different populations, but also offers an opportunity to test predictions generated by different adaptive explanations. We first compare estimates of macronutrient intake (gross calorie, protein, fat, carbohydrate intake), as this is pertinent to the compensatory placental growth hypothesis (Huxley 2000). Relationships noted above between pre-conceptional BMI and NVP symptoms imply that relatively high levels of gross nutrient intake might indirectly predict incidence of NVP. We then proceed to examine broad-level dietary categories to contrast the phytotoxin avoidance hypothesis (Hook 1976; Profet 1992) with the food-borne pathogen avoidance ideas of Flaxman & Sherman (2000) and Fessler (2002). Correlations between NVP incidence and consumption of stimulants (including caffeinated drinks), vegetables and alcohol are predicted by the former, while the latter would predict associations with low intake of cereals and high consumption of meat.

2. MATERIAL AND METHODS

(a) *Nausea and vomiting in pregnancy prevalence*

Data on NVP prevalence across countries were collated using studies cited in prominent reviews (Weigel & Weigel 1989*a*; Profet 1992; Flaxman & Sherman 2000) and by extensive literature search. Studies were included if they provided frequencies of NVP for a specific country. We noted NVP rates, study location and year(s) of data collection. Of the studies found, 17 were conducted in the USA, 13 in the UK and 27 in another 19 countries: Australia (3), Canada (2), Ecuador (1), Greece (1), Hungary (1), India (1), Israel (2), Italy (1), Japan (1), Kenya (1), Korea (1), Netherlands (1), Nepal (1), Norway (1), Saudi Arabia (1), South Africa (1), Sri Lanka (1), Sweden (5) and Tanzania (1; for the full list of studies and NVP rates, see the electronic supplementary material). Two papers (Klebanoff *et al.* 1985, 1999) used data from the Collaborative Perinatal Project during the same time period. To avoid pseudo-replication, we used the former since it included a larger sample size, giving a total sample of 56 studies. In studies where the years of data collection were not stated, we used the year of submission to the publishing journal.

(b) *Dietary characteristics*

Dietary data were obtained from the FAO's (FAOSTAT) Food Balance Sheets (http://faostat.fao.org), which list mean daily *per capita* intake of calories (kcal), protein and fat (g) in each country, allowing comparison with contemporary NVP rates. FAOSTAT does not provide data for carbohydrates, but an estimate of daily intake (g) can be obtained by subtraction from calorie intake using the Atwater general factor system (protein, 4 kcal g^{-1}; fat, 9 kcal g^{-1}; carbohydrate 4 kcal g^{-1}). In addition, we extracted data on 16 major food categories (kilogram *per capita per annum*): cereals, starchy roots, sugars/sweeteners, pulses, oilcrops, vegetable oils, vegetables, fruits, stimulants, spices, alcohol, meats, animal fats, milk, eggs and fish/seafood.

FAOSTAT data are available for each calendar year since 1961. For studies where NVP data were collected over several years, mean values for relevant years were calculated. Where NVP data were collected before 1961, FAOSTAT data for 1961 was used as a best estimate. To confirm this did not influence results, we also carried out analyses excluding the seven studies completed before 1961.

This cross-study approach assumes that national level dietary characteristics reflect the individual diets of women in the relevant studies. While individual diets will naturally vary widely from national averages, they should correlate with national figures, especially in larger studies. While our correlational approach can therefore only indicate trends between diet and NVP and should be treated with appropriate caution, it gains statistical power from the large number of studies involved and any resulting trends are likely to be conservative.

(c) *Analyses*

Data were log-transformed before analysis (we added a constant of 0.01 to allow transformation of zeros). To explore bivariate correlations between NVP prevalence and macronutrients we used least-squares regressions, weighted for sample size. Sample sizes in the original studies varied widely, between 20 and 38 151, so we divided the studies into quartiles (the first quartile weighted by a factor of 1 and the fourth by 4; qualitatively similar results are obtained using unweighted analyses).

For analyses of the 16 major foodstuffs, we first carried out a factor analysis on these data with varimax extraction and rotation (Field 2000), retaining factors with eigen values ≥ 1. We then entered these factors as orthogonal variables into backward stepwise linear regressions, again weighted by sample size, with NVP rate as the response variable. All analyses were done in SPSS v. 12, and all tests were non-directional.

3. RESULTS

(a) *Macronutrients*

Regressions between NVP rates and vegetal intake were not significant for any macronutrient except fat, which was positively associated with NVP rates. In contrast, quantities of macronutrients obtained from animal produce were all positively associated with NVP rates. More variance in NVP for each regression was explained when analysis was restricted to studies for which concurrent dietary data were available (table 1), so all further analyses used the refined dataset of 49 studies.

Table 1. Weighted least-squares bivariate regressions between NVP and measures of daily macronutrient intake

macronutrient	r^2	β	t	p
calories (total)	0.348	0.590	5.01	<0.001
calories (vegetal produce)	0.014	0.117	0.81	0.422
calories (animal produce)	0.400	0.632	5.59	<0.001
protein (total)	0.332	0.577	4.84	<0.001
protein (vegetal produce)	0.071	−0.267	−1.90	0.063
protein (animal produce)	0.351	0.592	5.04	<0.001
fat (total)	0.428	0.654	5.93	<0.001
fat (vegetal produce)	0.179	0.423	3.20	0.002
fat (animal produce)	0.401	0.633	5.61	<0.001
carbohydrate (total)	0.002	−0.202	−0.308	0.759
carbohydrate (vegetal produce)	0.023	−0.151	−1.048	0.300
carbohydrate (animal produce)	0.307	0.554	4.562	<0.001

(b) *Food categories*

Correlations were also found between NVP rates across studies and a number of major dietary components (table 2). Nausea and vomiting in pregnancy was unrelated to intake of starchy roots or oilcrops. Intake of cereals and pulses were negatively related to NVP prevalence. Particularly strong positive correlations (Pearson $r>0.5$) were obtained for sugars and sweeteners, stimulants, meat, milk and eggs.

As dietary categories may be inter-correlated, we carried out a factor analysis to identify a set of orthogonal variables to correlate against NVP rates. This analysis revealed four principal factors with eigen values ≥ 1, together explaining 74.9% of the variance in dietary difference across studies. Backward stepwise regressions revealed significant positive relationships between each of the first two factors and NVP, with the final model accounting for 31.6% of the variance in NVP rate ($F_{2,46}=10.64$ and $p<0.001$). Factor 1 ($t=3.76$ and $p<0.001$) was associated with low intake of pulses (−0.782) and cereals (−0.659) and with high intake of stimulants (0.930), sugars and sweeteners (0.852), milk (0.883), eggs (0.644), meat (0.634), vegetable oils (0.547), fish/seafood (0.546), fruits (0.473) and alcohol (0.447). Factor 2 ($t=2.26$ and $p=0.029$) was associated with high intake of vegetables (0.855) and vegetable oils (0.677). The other two factors, which were not related with NVP, were associated with high intake of starchy roots (0.785) and low spice intake (−0.523; Factor 3) and with high intake of oilcrops (0.876; Factor 4).

Table 2. Weighted least-squares bivariate regressions between NVP and major dietary categories

food category	r^2	β	t	p
cereals	0.129	−0.360	−2.64	0.011
starchy roots	0.007	−0.086	−0.59	0.557
sugars and sweeteners	0.369	0.608	5.25	<0.001
pulses	0.160	−0.399	−2.99	0.004
oilcrops	0.000	0.019	0.127	0.899
vegetable oils	0.235	0.485	3.80	<0.001
vegetables	0.100	0.317	2.29	0.027
fruits	0.133	0.365	2.68	0.010
stimulants	0.366	0.605	5.21	<0.001
spices	0.110	−0.332	−2.41	0.020
alcohol	0.189	0.435	3.31	0.002
meat	0.315	0.561	4.65	<0.001
animal fat	0.076	0.275	1.96	0.056
milk	0.257	0.507	4.03	<0.001
eggs	0.489	0.700	6.71	<0.001
fish/seafood	0.160	0.399	2.99	0.004

(c) *Regional effects*

Although some of these results support previously published findings, correlations could be confounded by an unknown third factor; for example, by non-dietary lifestyle characteristics which also correlate with certain dietary patterns. We therefore carried out further analyses controlling for the geographical region of study. In view of the predominance of North American and European studies in the dataset, we repeated analyses for these two regions (i.e. omitting the others).

In contrast to the global results (table 1), we found no significant relationships between NVP prevalence and macronutrient intake (either total, or from animal and vegetal sources; $p>0.1$ in all cases). However, this was not the case for particular dietary categories. Factor analysis revealed four principal factors, explaining 80.9% of the variance in dietary differences. We again regressed each of these factors on NVP rate, revealing a significant positive relationship between NVP and one factor (Factor 4, $F_{1,33}=5.07$ and $p=0.031$; $r^2=0.133$), which was associated with low cereal consumption (−0.644) and high intake of sugars/sweeteners (0.577), oilcrops (0.511), alcohol (0.380) and meat (0.355).

4. DISCUSSION

Our results provide further evidence for links between diet and NVP. In the initial global analysis, positive correlations were found between NVP rates and intake of all macronutrients. Derivation from animal rather than vegetal produce seems to be important in predicting NVP rate. With respect to major dietary components, NVP was positively correlated with mean intake of sugars/sweeteners, stimulants, vegetables, meats, milk and eggs, and negatively related to cereals and pulses. These patterns are broadly consistent with results of gestational food aversion studies (MacIntyre 1983; Rodin & Radke-Sharpe 1991; Crystal *et al.* 1999) and NVP rates across traditional societies (Flaxman & Sherman 2000; Sherman & Flaxman 2002).

Despite this consistency with previous research, it remains possible that correlations between dietary characteristics and NVP prevalence are confounded by an unknown third variable: a non-dietary effect which correlates with both dietary patterns and NVP. This may be particularly true since the original studies are drawn from across a range of geographical regions which vary markedly in stage of development, and hence economic and medical infrastructure (in contrast to the relatively uniform nature of the traditional societies studied by Flaxman & Sherman (2000)). We could not rule out this possibility, but our regional analyses considering only North American and European studies go some way toward controlling for this potential problem. In these more controlled analyses, NVP rates were related negatively to cereal consumption and positively to intake of sugars/sweeteners, oilcrops (used in frying food), alcohol and meat. These results complement the broader analysis and are again consistent with previous research (Rodin & Radke-Sharpe 1991; Flaxman & Sherman 2000; Lawson *et al.* 2004), suggesting that these particular dietary characteristics are relatively robustly correlated with NVP prevalence. In contrast, the analysis of macronutrient intake and corresponding NVP rate revealed no significant relationships. This suggests that, unlike specific dietary categories discussed above, correlations between NVP rate and gross calorie, protein and fat intake in the initial analyses may likely be explained by a third factor.

Do our results contribute to ongoing debate concerning possible adaptive explanations for NVP? Both hypotheses concerning compensatory placental growth (Huxley 2000) or maternal/embryo protection (Hook 1976; Profet 1992; Flaxman & Sherman 2000; Fessler 2002) draw links to diet, though the latter is more directly linked to diet and makes predictions regarding specific dietary components. Although we found correlations between NVP and macronutrient intake in the global analysis, these correlations disappeared in the regional analysis. There is thus only limited support from our dataset for Huxley's idea, or for a simple relationship between general nutritional status and NVP independent of any adaptive function.

In contrast to macronutrients, significant effects of specific foodstuffs previously implicated in NVP occurrence persisted in the restricted geographical sample. Our results thus appear more consistent with a prophylactic function for NVP. The exact nature of the associations also allows us to further dissect the leading ideas. Although there is some support from the global analysis for the phytotoxin avoidance hypothesis (Hook 1976; Profet 1992) through associations with stimulants (which includes caffeinated drinks), vegetables and alcohol, only the latter remains a predictor in the regional analysis. Alcoholic beverages are thought to have been fermented since the Neolithic (Patrick 1952), giving sufficient time for adaptive responses to develop, and aversions to alcohol are reported by approximately half of women in their first trimester (Lawson *et al.* 2004). Recent evidence suggests population variation in expression of genes coding for alcohol dehydrogenase and aldehyde dehydrogenase, enzymes involved in alcohol metabolism. Unique alleles and haplotypes occur in East Asians, which, after alcohol consumption, lead to characteristically high levels of toxic acetaldehyde and facial flushing (Oota *et al.* 2004). It might therefore be expected that the power of alcohol to evoke NVP is particularly marked in East Asian populations. While a robust test of this prediction awaits more data, we note that the East Asian populations in our dataset have very high NVP prevalence (90 and 84% for Korea and Japan, respectively) compared to other Asian populations (35, 37 and 38% for India, Sri Lanka and Nepal), and that there is a strong positive correlation between alcohol intake and NVP across Asian countries ($r=0.916$, $n=5$ and $p=0.029$), but not in North America or Europe (both $p>0.28$).

Lack of a strong association between NVP and intake of vegetables in the regional analysis is consistent with a previous study (Brown *et al.* 1997). In addition to these results, the significant effects of high meat intake in both the global and regional analyses are predicted by proponents of the food-borne pathogen avoidance idea (Flaxman & Sherman 2000; Fessler 2002), as is that of low cereal consumption if it helps regulate iron levels in blood (Fessler 2002). The specific significance of sugars/sweeteners and oilcrops are perhaps less easy to explain and suggest avenues for further research. It remains possible that either could be selected in the factor analysis as a result of correlations with causal variables, perhaps particularly so for oilcrops, intake of which did not predict NVP prevalence in the wider sample.

Taken together, our results add to a growing body of evidence suggesting links between NVP and diet. Although our results are based on population-level average intakes rather than individual diets, this approach enables standard comparison across a large number of NVP studies for which dietary data were not reported. Furthermore, this approach should be conservative with respect to individual variation and thus provides a reasonable basis for investigating correlations between NVP and diet. However, our results require confirmation from a greater number of more detailed studies in which such dietary information is recorded from individual women, and suggest the need for more research into this important and intriguing area.

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