Nausea and vomiting in pregnancy and the impact upon dietary intakes and birth outcomes – a study performed in the Norwegian Mother and Child Cohort Study

Master Thesis

of

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Yahweh, Yahweh,
always pain before the child is born
Yahweh, tell me now
Why the dark before the dawn?
U2

Arthur Chortatos, 2011

Executive Summary

Background: Nausea and vomiting during pregnancy (NVP) is often experienced by women during gestation. Most studies report up to 80% of women experience one or both of these phenomena, and symptoms of NVP have been recorded from 2000 B.C. to the present time. Favorable birth outcomes are often reported for pregnancies experiencing NVP whilst simultaneously having negative effects upon quality of life of the expectant mother during pregnancy.

At the present time the etiology of NVP is unknown, yet there are many hypotheses from different fields of science and with various explanations addressing why NVP occurs, and how it may be triggered in the body.

It is also common during periods of NVP for women to alter their diet, whether it is owing to a pregnancy-related craving or aversion to certain foods or by the inability to eat as desired owing to the associated symptoms.

The aim of this study was to explore the occurrence of nausea alone or NVP in the Norwegian population, and to explore the dietary changes that may occur to pregnant women experiencing these symptoms. Furthermore, the reported favorable birth outcomes associated with NVP were to be assessed.

Subjects and Methods: Using data collected in the Norwegian Mother and Child Cohort study (MoBa), maternal demographic data and dietary intakes were cross-referenced with those reporting nausea alone and NVP. The MoBa cohort contains many variables related to mother and child, and these provided data regarding the pattern of nausea and NVP, as well as birth outcomes. Statistical methods were used to test for associations between the variables.

Results: In total, 62 416 women were included in the study sample. Of these, 17 185 women (27.5%) experienced no symptoms, 27 642 women (44.3%) experienced nausea only, and 17 589 women (28.2%) experienced NVP. The NVP women experienced the least gestational weight gain, whilst simultaneously having the largest dietary intake of all macronutrients. A larger proportion of the no symptom group started to eat probiotic foods and chocolate during pregnancy. The NVP group represented the largest proportion of those beginning to eat foods rich in sugar, foods rich in sour/salt taste, milk, fruit, vegetables, and sugared soft drinks.

The nausea and NVP group had more babies born large for gestational age (LGA), and the no nausea group had more small for gestational age (SGA) babies. The no nausea group gave birth to a higher number of male babies, as well as babies with the lightest mean birth weight. Babies born to the nausea group of women were the heaviest of all three groups.

Conclusion: The results from the study show that women experiencing nausea or NVP have a significantly different dietary profile compared to those women without symptoms. Additionally, the nausea and NVP women had a higher proportion of birth outcomes such as birth weight and length of gestation that were within normal parameters, supporting studies reporting nausea and NVP to be associated with favorable birth outcomes. Questions regarding the different dietary habits of the three groups, especially in association with probiotic foods, water, salty foods and chocolate intakes, should be addressed in future studies.

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Figures and tables

Clarification of terms/Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AgRP	Agouti-related peptide; a brain neuropeptide with orexigenic properties
B.C.	Before Christ; an epoch used in dating years in antiquity
BMI	Body Mass Index; the body weight divided by the square of height, universally used in nutrition to produce a unit of measure (kg/m^2)
BPH	By-Product Hypothesis; a hypothesis of eating-related embryo protection
E%	Energy percent; the proportion of the total energy intake from different macronutrients
n/N	Number of people used in data; used in the table presentations
EPH	Embryo Protection Hypothesis; a hypothesis of eating-related embryo protection
FFQ	Food Frequency Questionnaire; a tool for assessing amount of food and energy eaten by an individual
g	Grams, unit of weight
hCG	Human chorionic gonadotrophin; a hormone produced during pregnancy
HG	Hyperemesis Gravidarum; an extreme form of NVP
IGF	Insulin-like growth factor; proteins similar to insulin the body uses for a variety of internal signaling
kJ	Kilojoule; international unit for energy intake
LBW	Low Birth Weight; birth weight less than 2 500 grams
LGA	Large for Gestational Age; weight of baby above the 90th percentile for the gestational age
MBRN	Medical Birth Registry of Norway; a compulsory national health registry recording data of all live births and stillbirths in Norway since 1967

MJ	Megajoule; international unit for energy intake
MoBa	The Norwegian Mother and Child Cohort Study; one of the largest ongoing pregnancy cohort studies in the world to date.
mRNA	Messenger ribonucleic acid; carries genetic information for coding information to the sites of protein synthesis
N	Nausea alone; state experienced by some women in this study
NK	Natural Killer Cells; cytotoxic lymphocytes that are a major component of the innate immune system
NKB	Neurokinin B; a hormone produced during pregnancy
NN	No Nausea; state experienced by some women in this study
NPY	Neuropeptide Y; a brain neuropeptide with orexigenic properties
NVP	Nausea and Vomiting during Pregnancy; state experienced by some women in this study. A condition pregnant women experience during pregnancy characterized by periods of both nausea and vomiting
Q1-4	Questionnaires used in MoBa; numbered 1 to 4
Q31	Question 31; contained in questionnaire 2 of MoBa, provided data regarding the way diet had changed for pregnant women in this study
Q38	Question 38; contained in questionnaire 2 of MoBa, provided data regarding the intake of foods begun to be eaten by pregnant women in this study
QOL	Quality of Life, health tool used to evaluate the general well-being of individuals
SGA	Small for Gestational Age; weight of baby below the 10th percentile for the gestational age
Th1/Th2	T helper cells 1 and 2; a sub group of lymphocytes involved in activating and directing other immune cells
U.S.	United States of America
vs.	versus; used for comparison

1 Introduction

1.1 The master thesis as a part of The Norwegian Mother and Child Cohort Study

The master thesis is based upon data from The Norwegian Mother and Child Cohort Study (MoBa). MoBa was planned in the 1990s partly by researchers at the Medical Birth Registry of Norway (MBRN), and partly by researchers at the National Institute of Public Health (1). The main aim of MoBa is to achieve better health for mothers and children in the future by focusing primarily upon adverse pregnancy outcomes, as well as diseases affecting mother, father, or child, with an aim of future prevention. Possible causal factors are explored from data obtained via questionnaires, blood samples from mother, father, and child, and medical registries. Norway has approximately 4.8 million inhabitants, and over 60 000 births a year (2). The target population of the study has been all women who gave birth in Norway; from mid-year 1999 to the end of 2008, with over 100 000 women included (3).

1.2 Background

The human race has endured for many millennia thanks to the successful ability the species has for reproduction. It is therefore of vital importance that the processes of conception, gestation, and healthy infant delivery are continuously investigated and thoroughly understood. A woman during pregnancy has many challenges to overcome, yet one of the prime necessities is that of obtaining adequate nutrition to satisfy her needs and the needs of the developing fetus (> 8 weeks from fertilization). During the first trimester of pregnancy (from conception to approximately week 13), up to 90% of women will experience symptoms of nausea alone or nausea and vomiting (4). The usual range of symptoms span from mild nausea (with mild aversions to particular foods accompanying), to frequent episodes of vomiting, with extreme cases developing into hyperemesis gravidarum (HG), which can lead to hospitalization and even death in some cases (4;5). There is a current level of agreement among researchers and midwives suggesting that nausea and vomiting in pregnancy (NVP) is the norm rather than the exception during early pregnancy (6). Although studies have shown that many risk factors are associated with NVP, the fact that up to 90% of pregnant women

experience symptoms of NVP to some extent suggest that the main risk for NVP is pregnancy itself (7).

1.2.1 History

That the phenomena of nausea and NVP have plagued the gestating woman since the beginning of written record-keeping should come as no surprise. Evidence from ancient papyrus scrolls written in approximately 2000 B.C. details an episode of NVP (8-10). One famous victim of NVP is the 19th century English author Charlotte Brontë, who died from starvation and dehydration after suffering very severe NVP four months into her first pregnancy (11). In the 21st Century, nausea and NVP seldom progresses to a condition that is life-threatening, however, it potentially presents a challenge to nutrient intake in the most vulnerable period of gestational development (12). Furthermore, it appears that nausea and NVP are uniquely related to the pregnant state of human beings. After constant interrogation of animal investigators in the U.S. regarding primate pregnancy and NVP- like symptoms, Hook (13) pointed out that the phenomena of a gestating female having symptoms of nausea or NVP is exclusive only to human beings. Sherman & Flaxman (14) went deeper into this phenomena by consulting veterinary textbooks, zoo yearbooks, actual veterinarians and animal researchers in fields regarding appetites of primates, swine, sheep, cats, dogs, rats, rabbits, horses and goats during pregnancy. They found only references to a sharp drop in food consumption during weeks 3 to 5 for domestic dogs (Canis familiaris) and captive rhesus macaques (Macaca mulatta).

1.3 Profile on NVP

Literature on this topic in past decades has straddled between old and new terminologies and subsequently caused the definition of NVP to become non-precise. In order to avoid any ambiguity on the subject, a brief examination of the definition is necessary. Järnfelt-Samsioe (15) has used the term Emesis Gravidarum or Emetic Pregnancy (16) to define either nausea alone, or the combination of both nausea with retching and occasional vomiting during early pregnancy. Although some sources define ‘morning sickness’ as nausea occurring in the early part of the day during the first months of pregnancy (17), others define it as nausea and vomiting during pregnancy (14). The fact that classic morning sickness (using whichever definition) does not necessarily occur exclusively in the morning hours (18-20) further

necessitates a better name for this malady. The term ‘pregnancy sickness’ was used by Profet in the early 1990’s as a collective term describing food aversions, nausea, vomiting, ‘one or all of which occur in the first months of pregnancy’ (21); this provides a useful yet generous definition embracing a little too much. Nausea and Vomiting in Pregnancy (NVP), was used by Fairweather in 1968 (8) to describe ‘nausea or vomiting that is commonly observed during the first 14 or 16 weeks of pregnancy’. However, Niebyl (22) recently used the term NVP to differentiate ‘nausea and vomiting in early pregnancy’ from ‘nausea alone’. With such a variety of names describing such an array of symptoms (sometimes exclusive or inclusive of each other), it is perhaps necessary to clearly state that for the purposes of the master thesis, the NVP condition shall refer to pregnant women experiencing both nausea and vomiting (either simultaneously or at differing moments during pregnancy), and shall furthermore delineate from those pregnant women experiencing nausea alone, or symptom free. How episodes of nausea with gagging, dry retching (dry heaving) and/or resistance to the vomiting reflex were translated by the women when filling out the questionnaire, is impossible to assess.

1.3.1 Confirming diagnosis

The diagnosis of NVP is clinical in nature, and although other causes of persistent nausea, retching and/or vomiting are rarely encountered, a failure to distinguish them from NVP can easily occur, resulting in misclassification at best, and serious complications at worst (4). Gastrointestinal disorders have been shown to cause nausea and vomiting, whether it be via an inflammatory process (such as appendicitis, cholecystitis or pancreatitis), obstructions, motility disorders or peptic ulcers (7). The incidence of gastro-esophageal reflux disease in pregnancy is estimated to be between 40% and 85% (23). It is also possible nausea and vomiting could stem from neurological conditions, motion sickness, extreme migraines, depression, anxiety, or metabolic conditions such as acidosis, hyperthyroidism, parathyroid or adrenal disorders. NVP is diagnosed with typical symptomatic characteristics in the absence of abdominal pain, change in bowel habits, bilious emesis or other symptoms (24). Other causes of pregnancy related nausea can include preeclampsia, HELLP syndrome (Hemolytic anemia, Elevated Liver enzymes and Low Platelet count), and acute fatty liver of pregnancy (AFLP). While causes of nausea and vomiting unrelated to pregnancy can occur at any time, preeclampsia, HELLP syndrome and AFLP typically occur in the third trimester (25). In practice, NVP is usually diagnosed in one of three classes: mild (nausea only), moderate

(nausea and vomiting) or severe (where the extent of vomiting is so severe and prolonged that it can induce maternal weight loss, electrolyte imbalance and dehydration) (12). Symptoms of NVP include nausea, gagging, retching, and vomiting, although women suffering from NVP may not experience all of these symptoms (26). Several factors can worsen NVP, such as poor sleep, Helicobacter pylori infection, or the presence of peptic or duodenal ulcers (27). Approximately 0.5% to 3% of pregnant women develop HG (28;29).

1.3.2 Hyperemesis Gravidarum (HG)

HG is a severe form of NVP usually requiring hospitalization to reverse dehydration, electrolyte imbalances, and nutritional deficiencies. It is a condition that is similar yet much more severe than NVP. HG is defined as intractable vomiting associated with weight loss of more than 5% of pre-pregnancy weight, dehydration, ketonuria, and hypokalemia (28;30). NVP on the other hand, is not usually associated with a significant weight loss or a significant change in nutritional status. Additionally, HG may persist throughout the entire gestation period, as opposed to NVP, which usually decreases in the second trimester (31). HG was found to be the most common reason for hospitalization during the first trimester of pregnancy (32), and can lead to complications such as neurologic disturbance, retinal hemorrhage, and liver and renal damage if left untreated (33). Women experiencing HG suffer an inability to eat or retain food, which results in a significant change in nutritional status and a dramatic weight loss (8). More than 50 000 pregnant women are hospitalized each year in the United States alone due to HG (33). The reported incidence varies because of different diagnostic criteria and ethnic variations in study populations (34).

1.3.3 Timing

In most cases, the onset of pregnant related nausea occurs within 5 weeks of conceiving following the last menstrual period (35). In one prospective study following 363 women, NVP peaked at approximately 9 weeks of gestation. Of these, 60% of cases resolved by the end of the first trimester, and 91% resolved by week 16 of gestation (19). Cessation of symptoms occurred at approximately the same time for all the women in this study, regardless of whether symptoms had begun early or late in the first trimester or whether early symptoms were severe or mild. This caused the researchers to suggest that one agent might be involved in the etiology of the condition and a different agent responsible for its cessation (19). Another study reported 80% of their sample either experiencing symptoms continuously or

episodically throughout the day (12;36). Although NVP is usually experienced as a complication of the first trimester of pregnancy, a small proportion of women experience symptoms throughout the entire pregnancy (7). When relating the timing of NVP onset with embryogenesis and the phases of fetal development, remarkable parallels are seen. Vulnerability for various organ systems of the developing embryo (≤ 8 weeks post fertilization) begins at about week five, when the developing central nervous system and heart become critically sensitive. The peak of organogenesis and embryonic susceptibility to teratogens occurs during weeks 6 to 12, with the embryo's central nervous system continuing to be sensitive through to week 18 (14).

1.3.4 Ethnographic profile

Although Semmens (37) indicates NVP to be more common in Westernized countries, predominantly in urban populations compared with rural populations, and rare in African, Native American, Eskimo, and some Asian populations except for the industrialized Japanese, contraindications are abundant. Reports exist of NVP occurring in populations from such diverse locations as Ghana (38), China (39;40), Tonga (41), with Indigenous North Americans, Pacific islanders, Iranians, and Mexicans also noted as having experienced symptoms (42). This anomaly in results is most likely caused by both the age of Semmen's paper (1971), as well as the limited availability and access to clinical documents from non-westernized cultures. A more recent investigation addressing ethnicity and NVP found that Black and Asian women were less likely to have 1st trimester NVP when compared with Caucasian women in the same phase of gestation (43). The authors were, however, aware that their findings confirmed previous studies yet contraindicated other studies, only to finally conclude that different study populations, study designs, evaluations of NVP symptoms, and confounders considered could partly explain the disparity between the different studies (43). In Scandinavia, although current epidemiological figures are scarce, one Swedish study found 70% of their sample to have experienced symptoms of nausea during their pregnancy (44), whilst another Swedish study reported 79% of their sample to have experienced NVP (45).

1.3.5 Affected maternal quality of life (QOL) and other costs of NVP

It has been demonstrated that the impact of NVP on health-related QOL in pregnant women is an issue that tends to be minimized (27;46). Research has shown that NVP has a significant impact on family life and employment, as well as social life, stress levels, the intent to have

other children, and economic burdens, particularly with regard to productivity losses (24;46-48). NVP can even lead in some cases to depressive feelings and elective termination of pregnancy (48-50). As one review written by a registered nurse stated:

"…qualitative descriptions of the experience of nausea and vomiting of pregnancy….are difficult to summarize….any provider who cares for pregnant women is strongly urged to read their stories…these stories describe the world of severe nausea and vomiting of pregnancy as one of isolation, loneliness, guilt, thoughts of pregnancy termination, frustration at being unable to complete activities of daily living and role function, delay in maternal role attainment, concern for the effects on the unborn child, lowered self-efficacy, and alternations in relationships with family, partners, and friends." (51)

A 2002 study calculated a hypothetical economic cost of $US 2 947 per woman with moderate to severe NVP, and $US 17 000 per woman experiencing severe NVP in the United States (this figure includes reduced productivity, visits to health care professionals, and the cost of medications and other remedies). This figure is relatively high, especially when compared to $US 8 095, the estimated cost of a case of influenza in patients who were hospitalized but did not die (27). The duration of symptoms would naturally affect these estimates. Another estimate of the cost severe nausea and vomiting places on the U.S. health system is approximately $US 130 million (28), based on costs associated with an estimated annual average of 39 000 hospital admissions. Unlike the previous estimate, this estimate did not include physician fees or the loss of productivity at home or employment, nor the cost of other patient treatment, making it a much higher estimate.

1.4 The placenta

The placenta is an organ that connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply. The functional unit of the placenta is the chorionic villus, which creates a tremendous absorptive surface to facilitate transport. The word placenta comes from the Greek language, meaning 'flat, slab-like' in reference to its round, flat appearance in humans (52). The remarkable endocrine alterations that are characteristic of human pregnancy are attributable either directly or indirectly to the placenta, which produces steroid and peptide hormones in amounts that are unparalleled in the placentas of other mammals (53).

During pregnancy, the placenta synthesizes and secretes massive amounts of estrogens and progesterone into the circulation of the gestating mother, together with peptide hormones such as human placental lactogen (hPL) and human chorionic gonadotrophin (hCG). It has also been observed that the placenta synthesizes hormones normally of hypothalamic and pituitary origin; these include adrenocorticotrophin, thyrotrophin-releasing hormone, luteinizing hormone-releasing hormone, corticotrophin releasing hormone and somatostatin. Inhibin, growth factors, cytokines, and leptin, the latter being involved in the regulation of metabolic efficiency, energy expenditure and food intake, are also released from the placenta (53). The specific roles of all of these factors in the mother and fetus remain uncertain, although the role of some factors is discussed in section 1.5.2. The placenta grows throughout pregnancy, and development of the maternal blood supply to the placenta is suggested to be complete by the end of the first trimester of pregnancy (54).

The complex invasive processes accompanying implantation of the embryo to the uterine wall are controlled at the embryo–maternal interface by factors from both the endometrium and the embryonic trophoblast itself (the trophoblast later combines with the endometrium to form the placenta) (55). The maternal immune response to embryo implantation is discussed further in section 1.5.2. The immunologic changes occurring in pregnancy alters the susceptibility to and severity of infectious diseases for the gestating mother; for example, pregnancy may increase susceptibility to toxoplasmosis and listeriosis (56).

It is well recognized that it is mainly the placenta and not the fetus or mother that orchestrates the progress of a pregnancy, as is seen when a viable fetus is not present, and a hydatidiform mole forms instead, the placenta will continue to term, and in some cases cause pathologies such as preeclampsia (57). Pregnancies with a complete hydatidiform mole have also been associated with clinically significant nausea and vomiting, again indicating that the stimulus is produced by the placenta, not the fetus (22;24;58). Further evidence of involvement of the placenta in NVP comes from observations that women suffering NVP until term report immediate relief of symptoms once the placenta has been delivered (59). In some studies, the mean weight of placenta of women experiencing NVP was heavier than those not experiencing this condition (6;60), although this has been contested by others (16;61).

Animal models have shown that different maternal nutrient levels cause varying sizes of placental mass (62-65). It seems the placenta may undergo an adaptive compensatory

response to mild maternal undernutrition, causing a larger mass that optimizes placental exchange efficiency (12). This is discussed in more detail in section 1.5.1.

1.5 Etiology

Although the phenomenon of NVP has affected women for nearly 4000 years, there still remains no clear understanding of the etiology nor underlying mechanism of the condition (9;10;66). During the decades it has been under investigation, it has metamorphosized through a number of epochs. Here the thread of analysis shall be briefly outlined from antiquity to the modern day.

In their 1991 paper, O'Brien and Newton outlined what they considered to have been the three central phases of theory development relating to NVP (66). From antiquity until circa 1929 was what they call 'The early Somatic era'. The early Somatic era proposed sometime in the late 1600's that NVP was either due to some neurological reflex between the abdominal region of the woman and her uterus, or else caused by some unknown toxin involved in gestation. From the 1930's until the 1980's the somatic theories were disregarded, and 'The Intrapsychic era' came into fruition. These theories moved away from the abdomen toward the mind, accusing the psyche and mental state of the pregnant woman for her malady (employing terms such as 'neurotic' and 'hysterical'). The 'hysteria' causing NVP was suggested to be a manifestation of unconscious loathing the woman had for her husband, child, or both. In the early 1980's a resurgence of interest in NVP emerged, giving us the present era, 'The Metabolic and Social Stress era'. This era supports an endocrine etiology of the malady, although a refinement and selective conglomeration of the previous eras seems closer to the truth (67). It is in this era that we find hypotheses focusing upon hormonal and gastro-electric etiologies (68). Hypotheses and ideas concerning NVP are not simply investigating underlying mechanisms of causality (the 'how'), but also questions regarding the adaptive or functional role (if any) of such a malady (the 'why'). Borrowing terminology used in other papers, there are many 'levels of analysis' (69) used when investigating NVP. Hypotheses addressing, the functional/adaptive role are termed 'functional mechanism' hypotheses, whilst questions addressing the causative mechanisms are termed 'proximate mechanism' hypotheses.

1.5.1 Functional mechanism hypotheses

The Embryo Protection Hypothesis (EPH)

This hypothesis (sometimes called the Prophylaxis Hypothesis) (70), originating in the 1970's (71), is based upon the following logic: Plants contain a variety of chemicals and other enzymes, providing flavors, aromas and other qualities, many of which have evolved to assist the plant when faced with parasitic or herbivorous enemies (72). These phytochemicals are usually ingested by humans as a daily part of vegetable, herbal or spice consumption. Spices in particular are known to contain a variety of powerful antimicrobial properties (73). Large quantities of these phytochemicals can begin to act in teratogenic ways, and it is in order to shield the developing fetus from such embryotoxic substances that the EPH points to NVP's functional mechanism.

The EPH was later broadened to include other foods such as caffeinated drinks, tobacco and alcohol (74). Caffeine has been associated with spontaneous abortions (75), and supporters of the EPH regularly point to caffeine as one of the most prominent food aversions during early pregnancy (21). Furthermore, it is suggested that the expression of NVP is an adaptation that was favored by natural selection, as NVP causes pregnant women to expel and subsequently learn to avoid potentially harmful foods likely to contain parasites, pathogens, and plant toxins (70).

Fessler (76) recently advanced the hypothesis further, implying that it is not so much plant-based toxins that pose a threat to the fetus, rather, it is the pathogen content specifically found in meat which poses a threat (76). Critics of the hypothesis refer to studies that have found no relationship between NVP and the ingestion of certain foods that the EPH considers toxic for the embryo (77). Although the EPH initially focused on the health of the embryo, it was later reformulated into the 'maternal and embryo protection hypothesis' (35), extending the benefits of NVP to include the mother also, especially in view of maternal immunosuppression during pregnancy.

The By-Product Hypothesis (BPH)

This hypothesis, sometimes known as the 'parent-offspring conflict' (78) has origins in the beginning of the 21st century with behavioral ecologist Scott Forbes (79), and follows the logic that conflicts of interest over the division of resources between the mother and the

embryo she is carrying exist. This conflict of interest would manifest in a physiological tug-of-war (80) within the pregnant woman's body, potentially producing visible side effects. Thus, NVP symptoms might be an inevitable consequence of a mother-offspring physiological conflict (79). The conflict is said to begin in the moments following conception as the embryo struggles to wrest control of pregnancy from the mother and obtain more nourishment from her than she can spare, triggering morning sickness, diabetes, and high blood pressure. Mothers, in return, may often spontaneously abort embryos with severe genetic defects, allowing for a hypothesized prenatal quality control of offspring (81).

A spin-off to the BPH is the Honesty-signal hypothesis (79). The hypothesis posits that hormonal signals such as hCG have developed over evolutionary time, and are used in some way to communicate with the mother the viability and/or quality of the embryo. Evolution has necessitated these signals as an assurance that the pregnancy is a good investment (in terms of fitness) (70). The BPH as well as the honesty-signal hypothesis continue to attract much criticism (82), particularly since NVP seems to be neither necessary nor sufficient for a viable pregnancy (35). Forbes' pointing to potential hormonal mechanisms (e.g., the possibility that the conflict is mediated by hCG) in BPH provides a convenient link between Functional Mechanism and Proximate Mechanism hypotheses.

Alternative Hypotheses

1) Studies have shown that early food restriction and under-nutrition during pregnancy stimulates placental growth – especially when these restrictions have been during the first trimester of pregnancy (51;65), which is thought to be responsible for a variety of favorable pregnancy outcomes (44;83). The resultant endocrine response to restricted dietary intake in animal studies has shown that the reduced nutrient intake lowers maternal levels of the anabolic hormones insulin and Insulin-like growth Factor 1 (IGF-1) (84). These results have also been seen in observational studies on humans (65). NVP in humans may be the means by which a reduction in maternal energy intake is achieved.

   The usual timing of NVP correlates with rapid placental growth and the production of hCG; hCG has been shown to stimulate the release of thyroxine, which also contributes to stimulating placental growth (85). Insulin has been reported to inhibit hCG production in first-trimester placenta in vitro (86), which adds further support to the hypothesis that maintaining low levels of insulin in the first trimester of pregnancy may be vital to early

placental development. Critics of this hypothesis are quick to point out that pregnant women crave energy-rich foods and find energy-poor foods aversive (35). A prospective study found that women who had high carbohydrate intakes in early pregnancy gave birth to infants with lower birth and placental weights, concluding that a high carbohydrate intake in early pregnancy suppresses placental growth (64).

The potential effect of the differing levels of maternal nutrition at different stages of pregnancy, and the subsequent influence on the growth of the fetus is a complex subject, as outlined by various related studies (87-90), and is worthy of a study in itself.

2) It may be that NVP acts as a signal, either to a woman's family that she will soon need additional food and protection, or to her mate of the desirability of reducing sexual intercourse (91). This communication hypothesis has also received criticism, least of all owing to the fact NVP usually peaks 6 to 10 weeks after conception, which follows other, equally unambiguous indications of pregnancy such as cessation of menstruation (usually occurring 4 to 8 weeks earlier) (35).

1.5.2 Proximate mechanism hypotheses

The array of causative mechanisms for NVP tends to focus mainly on the role of circulating hormones in the gestating woman. The mechanism of hormones in the etiology of NVP remains mostly speculative and unknown; timing is an important factor in supporting these theories as the onset and peak of symptoms seem to mirror closely the changes in the levels of these hormones (92). It is important when examining these various etiologies proposed that most researchers consider the etiology of NVP for any individual to be multifactorial, comprising of several independent variables that will be unique for each pregnancy. This is also applicable to the same individual during subsequent pregnancies (26).

Sex hormones - Progesterone and Estrogen

Estradiol (the predominant estrogen in humans) increases early in pregnancy and slowly rises throughout the remainder of pregnancy (93). Progesterone also increases early in the first trimester and remains elevated until delivery (94;95). When these hormones were artificially introduced to healthy non-pregnant women, both agents – especially progesterone, caused nausea to occur in some women (96). Artificial exposure to these hormones usually occurs

when using oral contraceptives, and many women report nausea in the first few months of use. Other studies report first trimester levels higher than those resulting from oral contraceptive use, although the steroid load on the liver might be of the same magnitude (15;97). Since the steroid load on the liver during early pregnancy and when using oral contraceptives is postulated as being similar, the common denominator between NVP and oral contraceptive nausea is assumed to be these steroid effects upon liver function (15).

Progesterone and estrogen have also been shown to inhibit the activity of smooth muscles (97-99). Smooth muscle interactions with progesterone and estrogen have been shown to delay gastric emptying and reduce the patency of the lower esophageal sphincter, thereby increasing gastric reflux and emptying of the stomach (12;97). Other studies have found no evidence that progesterone or estrogen play a major role in the occurrence of nausea with or without vomiting in early pregnancy (100;101).

Human chorionic gonadotrophin (hCG)

hCG is a hormone released by placental trophoblasts very early in pregnancy and has attracted attention as a possible cause of NVP, owing primarily to the near-identical timing of hCG release and the onset of NVP (5). Since the 1930's it was believed that the sole function of hCG during pregnancy was as a replacement for pituitary luteinizing hormone in controlling progesterone production at the initiation of pregnancy (102). In the past decade it has since been shown to be involved in maintaining maternal blood supply and nutritional support to the developing fetus (102), and to activate the thyroid, stimulating the production and release of thyroxine (85) a potent stimulator of placental growth (84;103). The thyroid activation is believed to occur because hCG, sharing some structural similarities with thyroid-stimulating hormone, acts as a thyroid-stimulating factor (85). Although secretion of hCG by the placental trophoblasts has been proposed as the most likely endocrine contributor to NVP, data to support this are far from conclusive (8;93;102).

A review by Goodwin (100) looking at hCG and NVP revealed a relationship in 13 of 17 studies, prompting speculation that the failure of some studies to show a relationship may be due to varying biologic activity of different forms of hCG. Women with twins or hydatidiform moles have higher circulating hCG levels than other pregnant women, and are therefore at a higher risk for NVP-like symptoms (22). It has also been observed that higher hCG levels were reported in women who were pregnant with female fetuses, and higher

amniotic fluid hCG concentrations were also reported during early pregnancy in women bearing female fetuses (104).

Although hCG is today's likely endocrine culprit for NVP, researchers cannot even say with any certainty what receptor it binds, thus more findings are certain to surface in the near future (102).

Hyponatremia

During the first trimester of pregnancy, there are a number of changes in the body's biochemical environment taking place, such as plasma volume expanding and total body water increasing, creating lower sodium concentrations and a reduced plasma osmolality; since it takes several weeks for the body's osmoreceptors to reset to the lower values, researchers have suggested that these changes may cause symptoms of hyponatremia to develop (105). A decrease in plasma osmolality, stimulation of thirst, and persistent anti diuretic hormone (ADH) release are features of normal pregnancy, as is renal sodium and water retention (106). Chapman et al. (107) found serum sodium and serum osmolality levels decreased significantly by the 6th week of gestation, a time which generally coincides with NVP onset. Furthermore, they found that complete placentation is not necessary for these initial hemodynamic changes to occur in normal human pregnancy, indicating that maternal factors possibly related to changes in ovarian function may be responsible (107). Since mild hyponatremia symptoms include lethargy, headache, nausea and vomiting, muscle cramps, and depressed neural reflexes (108), all of which are a part of most pregnancies, this hypothesis is not without merit.

Gastric dysrhythmias

As mentioned earlier in this section, progesterone and estrogen during pregnancy impair the esophageal, gastric, and small bowel motility, through smooth muscle relaxation catalyzed by the increased levels of these hormones. It is thought that this motility disturbance (collectively known as dysmotility or dysrhythmia in various literature) may contribute to NVP. Some of the key areas of disturbances are as follows:

Lower Esophageal Sphincter (LES): it is postulated that the hormone's effect upon the LES contributes to heartburn and NVP. One study found that progesterone alone or in conjunction

with estrogen may cause LES relaxation, causing an increased incidence of symptomatic heartburn, and possibly NVP (109).

Stomach: Delays in gastric emptying during pregnancy may be associated with NVP. In the early stages of pregnancy progesterone inhibits gastric emptying, when levels of this hormone are highly elevated. In normal conditions, the stomach has a rhythmical electrical depolarization mechanism at work known as a Slow Wave (110). The Slow Wave propagates at 3 cycles per minute, and variations from this frequency are called gastric dysrhythmias (7). One study used healthy non-pregnant women with a history of nausea during a previous pregnancy and administered estradiol and progesterone (alone and in combination) to test whether NVP may be mediated by elevated levels of these hormones (110). Their results showed progesterone to cause slow wave dysrhythmic effects that mimic the abnormalities observed in early pregnancy. By itself, estradiol had no effect on slow wave rhythmicity, however, the co-administration of estradiol with progesterone significantly potentiates the dysrhythmic effects of progesterone alone (110), demonstrating that although progesterone clearly produces disruptions, no single mediator may be responsible. As many of the hormonal studies performed upon NVP have indicated, a complex interaction of elevated circulating hormones may underlie the development of NVP during the first trimester.

Helicobacter Pylori

Common symptoms of Helicobacter pylori infection include nausea, vomiting, and heartburn, however, these symptoms also occur in 50 to 90% of pregnancies (111). In many studies, Helicobacter pylori infection has been significantly associated with HG, similarly in various degrees of significant nausea and vomiting, although other studies have found no specific correlation between infection with Helicobacter pylori and gastrointestinal symptoms during pregnancy (34;112). Contraindications from studies may result from different testing procedures used to determine the presence of Helicobacter pylori, or from lack of controlling for possible confounding factors that may influence the prevalence of Helicobacter pylori (34). A systematic review addressing HG and Helicobacter pylori infection performed in 2007 suggested an association between the two, yet also highlighted study limitations as causative of the differing results (31).

Leptin

Leptin, a hormone predominantly secreted by white adipose tissue, is also secreted by the human placenta during pregnancy (113). Leptin is proposed to act on the hypothalamus in order to regulate food intake and the signals that produce the feeling of satiety (113). It has been shown that messenger RNA (mRNA) for leptin appears on the human placenta, with maximum numbers peaking at 8 weeks gestation (114), causing researchers to postulate that in early pregnancy placental leptin production may act to suppress appetite and reduce maternal energy intake (84;115;116). While some researchers have found there is no relationship between leptin and NVP symptoms (117;118), others have found a significantly higher level in women with HG (119), and one study showed leptin to have a more important role for NVP severity than hCG (120).

Corpus luteum position

Ultrasound assessments performed on women seeking a legal abortion revealed that nausea and vomiting was associated with the corpus luteum situated on the right ovary rather than on the left, a finding possibly due to differences in venous drainage on the left and the right and vein caliber differences (121).

Mother's immune system

There has been some speculation that nausea and vomiting of pregnancy might be the result of an immunologic response, but there have been limited investigations or direct support for this idea. The human immune system has the function of eliminating infections that penetrate the body's outer defenses. Environmental insults engage inflammatory processes that activate the innate and adaptive arms of the immune system through complex and highly localized molecular and cellular interactions (122). It is of interest to keep in mind that during pregnancy, the placenta is, in effect, an allograft; in normal pregnancy it only shares half the genes of the mother, and in the case of a surrogacy it is a xenograft sharing none of its genes with the mother (57). For this reason, the placenta should elicit an immune response causing it to be rejected, and yet in most cases normal pregnancy develops unhindered. This, coupled to the fact that the health of the mother can be compromised for the benefit of the feto-placental unit, means that for all intents and purposes it is behaving as a parasite (57). Research has continued over the past 50 years to understand by what means the fetus avoids attack and

rejection by their mother's immune system (122). Although the effects of some infectious agents during pregnancy are well known, knowledge about many others is limited (56).

The full spectrum of altered immune response during pregnancy basically involves changes in T lymphocyte subpopulations, immunosuppressive serum factors, circulating immune complexes, and maternal immunologic recognition mechanisms (123). Briefly, lymphocytes of the immune system are components which compose specific and non-specific defenses. Lymphocytes produce two general, opposing, types of cytokines; Th1 and Th2, the former a cell mediated pro-inflammatory response, the latter a humoral/antibody mediated anti-inflammatory response (124). After conception occurs, high progesterone levels are indirectly responsible for stimulating Th2 cytokines. The imbalance favoring Th2 cytokines creates a profound decrease in non-specific cytokines, especially natural killer (NK) cells, and in doing so alleviates major threats to the developing organism (125).

Support for this idea comes from studies showing altered Th1 and Th2 immune responses as etiological factors in recurrent miscarriage, with recurrent miscarriages showing a predominant cell-mediated/Th-1 immune response (124). The rising progesterone levels, now being produced by the developing placenta in addition, continues throughout pregnancy, restraining lymphocyte activity and allowing development of the feto-placental unit (125;126). The suppressed immune-reactivity of NK cells throughout the body is the cost of this adaptive immunosuppression, increasing the woman's susceptibility to infectious diseases (123;126). According to Sherman & Flaxman (35), temporary immunosuppression is essential for a successful pregnancy, for if the mother's immune system functioned normally, she might reject her own offspring (127).

The changes to the mother's immune response are known to occur locally at the maternal-fetal interface but may also affect systemic immune responses to infection. It has also been observed that the neuropeptide Neurokinin B (NKB) is released by the placenta during pregnancy, and that this neuropeptide has a post-translational modification causing the placenta to be phosphocholinated (57). Phosphocholination is used by nematodes to avoid immune surveillance from the invaded host, leading to the situation found in many 'infections' where the invader hijacks one of the host's systems for the benefit of its own survival (57). Researchers have speculated this NKB phosphocholination is also used by the placenta to avoid triggering a maternal immune response during pregnancy (57). The attraction to the idea that the immune system somehow triggers NVP seems to stem from the

general idea that 2 persons temporarily occupying the same body will have some struggles (51).

Psychological

Little evidence exists that NVP represents a psychiatric or psychosomatic disorder; in the 1970's one study found that 50% of obstetricians believed that NVP was a psychologically based malady (37). Two main hypotheses at that time regarding the psychological element in NVP were quite contrasting. One hypothesis (128) claimed vomiting represented an unconscious attempt to reject the developing child. The idea followed that as awareness of the reality of the situation became apparent, and the fetus and its independent existence were accepted by the mother, the symptoms ceased. Evidence to support this theory was lacking. The other hypothesis focused not upon the women experiencing NVP, but on those without symptoms of NVP, speculating the symptom free group represented a demonstration that the reality of the pregnancy was being denied (128).

Support for this hypothesis was provided by a Swedish epidemiological study that found non-NVP women to be less likely than NVP women to see themselves as similar to their mother, to have more difficulties during pregnancy, and to have more adjustment problems after the birth (129). They concluded that a total absence of pregnancy nausea may indicate psychological conflicts in the woman.

The role of the expectant mother's own mother is deeply rooted in psychoanalytic theory (130). Psychoanalysis provides possibly the most pervasive theory for the etiology of NVP, describing NVP as a conversion or somatization disorder (8;131-133). Conversion disorders can be broadly defined as transformation of purely psychic trauma into physical symptoms. The individual attempts to control an overwhelming psychic disturbance by converting it to physical symptomatology (130). It has also been proposed that NVP is a symptom of the pregnant woman's dissatisfaction with her relationship to her husband (134). This attitude was central to the psychoanalysis written about Charlotte Brontë, where it was stated that Brontë was 'fearful, conflicted, and reluctant to accept her future marriage and childbearing' and that 'pernicious vomiting . . . always has psychogenic features' (135). The stress associated with marital relationships has been previously shown to be associated with nausea in pregnancy (18;60).

There is support for psychological etiologies to NVP from evidence that psychological treatments (e.g. hypnosis) have been shown to help some individuals (130;136;137). Apfel et al. also found that women with NVP were more hypnotizable than women in a control group, implying that they are more suggestible (138). Buckwalter & Simpson pointed out that the apparent success of hypnosis and other psychotherapeutic approaches in treating NVP suggested an intricate relationship between biological, psychological, and sociocultural factors, claiming (in 2002) it 'premature to conclude that there are no psychological aspects of NVP' (130). Yet in 2004, the American College of Obstetricians and Gynecologists (ACOG) stated that 'it is likely that the concept that nausea and vomiting of pregnancy reflect a psychologic disorder has impeded progress toward a greater understanding of the true etiology of the condition' (139).

Genetic

Genetic causes have been suggested owing to observations that NVP is more frequent in monozygotic twins; is more common in women whose siblings and mothers are affected by NVP; shows ethnic variation; and is correlated with other genetically determined conditions, such as taste sensation, anosmia (loss of smell), and glycoprotein receptor defects (19;100;140-142), although differences in race/ethnicity have been suggested to be accounted for by socioeconomic variables instead (143). One study noted that the East Asian populations in their data (such as Japan and Korea) had a very high NVP prevalence when compared to other Asian populations (such as India, Sri Lanka and Nepal), and showed a strong positive correlation between alcohol intake and NVP across Asian countries, but not in North America or Europe (144). Although the suggestion supposes the results are most likely owing to population variation in the expression of genes coding for alcohol dehydrogenase and aldehyde dehydrogenase, unique haplotypes in Eastern Asians characteristically leading to toxic reactions after alcohol ingestion (145), it is indicative of the genetic variation possibly underlying the etiology of NVP. Other examples suggesting genetic etiologies are studies showing significantly lower incidences of NVP in samples of U.S. Southern black teenagers when compared with Southern white teenagers (67), and the incidence of NVP to be slightly lower in samples of South African blacks as compared to South African whites (146).

One study used a large prospective cohort to test whether different male partners would affect the severity of NVP experienced by the same woman in different pregnancies (59). They concluded that changes in partners did not affect the severity of NVP, that the NVP severity

experienced by women generally remained stable from one pregnancy to the next. This suggests that factor(s) responsible for NVP, if genetic, are controlled for by the maternal genome (i.e. a maternal X chromosome, or by other chromosome(s) originating in the mother).

1.6 Maternal variables and pregnancy outcomes

One of the great paradoxes concerning NVP are the findings that show a positive outcome of pregnancy when NVP was experienced in the first trimester (12). For example, the risk of a miscarriage occurring is reduced when NVP is present (61), as are risks such as perinatal death and premature delivery (12). Likewise, studies of various strengths and designs have shown factors such as maternal age, socio-economic status, smoking status, parity and infant gender to affect maternal NVP (45;51;147), whilst other studies were unable to show these as having any influence upon maternal NVP (26;148). For every study showing an outcome connected to NVP, there are invariably studies finding the opposite or no effect.

What follows is a brief delineation of variables associated with differing outcomes in pregnancy for NVP:

Maternal BMI and gestational weight gain

Studies have shown underweight women will experience less severe symptoms of NVP compared to women of normal pre-conception weight (84;143;149), whereas the opposite was shown by another study (150). Other studies have claimed obesity to be related with NVP (26), while others have found no association (101). Some studies report associations between NVP and a smaller weight gain in pregnancy (43;51;151). Researchers have found that women who experienced no symptoms tended to have a lower pre-pregnancy weight, and the pattern of maternal weight gain during the course of pregnancy was almost identical for women who experienced no symptoms and women who experienced only nausea (83;149). One study report has shown more frequent vomiting in heavier than lighter women (143), whilst another fails to find this relationship (101), and yet another finds the opposite (150). Vellacott, Cook & James (18) and Gadsby, Barnie-Adshead & Jagger (60) found maternal weight to have no statistical significance for NVP symptoms.

Maternal demographics and histories

Various studies have found the presence of NVP associated with a young maternal age (22;26;45;143;148;152;153), although many other studies have found no such association (18;40;60;154;155). NVP has also been associated with maternal employment as manual or service workers (45;156), lower education (143), and maternal cigarette smoking (26;143;152). Lower education's association with NVP has been contested by another study group (153), as has the mother's employment status (155). Findings that smoking is associated with NVP has been frequently contested (20;22;45;60;148), with some of these groups suggesting maternal smoking as having a protective mechanism effect against NVP.

An increased risk for NVP has also been reported for those with a reproductive history such as women with multiparity (16;43;59;148;153), plurality (> 1 infant birth per pregnancy) (157-159), whilst others have found NVP risks are higher in primiparous women (22;26;143;157). Other studies (40;60) found no difference between parity and NVP symptoms. An increased risk of NVP was also shown to be associated with a previous intolerance to estrogen-containing oral contraceptives (26;44;45;60;160), with NVP experienced in previous pregnancies (59;60;161;162), having a mother who had also experienced NVP (60), and having multiple prior miscarriages (148). One study has reported that women were prone to develop NVP if the interval between pregnancies were short (16).

Miscarriage

Several studies have shown that women with NVP have a lower risk of miscarriage than women who did not experience NVP (61;153;163;164). A meta-analysis of 11 studies found that a highly significant association exists between NVP and a decreased risk of miscarriage (165). A later prospective cohort study also observed that women experiencing nausea alone or NVP had a significantly decreased miscarriage risk (6).

Infant's birth

It has been observed that women with NVP were likely to have a slightly longer gestation and less likely to have preterm births (< week 37) than women who do not experience NVP (143;159;165;166). Gadsby, Barnie-Adshead & Jagger (60) have also shown a heavier placenta to be associated with NVP. The association between preterm births and NVP has not been observed by other studies (16;40;44;61;143).

Women with no symptoms of NVP delivered a higher proportion of low birth weight (LBW) infants (< 2500 g) (83;159;167;168). However, others have shown no significance between NVP and LBW (16;61;101;143;166). In addition, following a review of 7 studies performed by the ACOG (139), no increase in incidence of low birth weight among those with nausea and vomiting was found, and 3 studies actually found a decreased incidence of low birth weight. The presence of NVP has also been correlated with infant gender (43;51;168-171), whereby females seem to be born to those women experiencing symptoms. The ratio varies slightly in the different studies, but the findings consistently show a higher ratio of female fetus and NVP, with only one study showing a higher ratio of males born for women suffering NVP (184). However, there are a number of other studies that have found no association between NVP and gender (148;153;155;172).

1.6.1 Suggested treatments for NVP

The management of NVP, depending upon the severity of symptoms, ranges from conservative dietary modifications in the mildly symptomatic woman, to pharmacologic drug therapy and total parenteral nutrition for those with severe intractable symptoms (7). According to the ACOG, it is important to intervene early when symptoms present themselves, as 'failure to treat early manifestations of nausea and vomiting of pregnancy increases the likelihood of hospital admissions' (139). Treatment generally begins with non-pharmacologic interventions; if symptoms do not improve, drug therapy is added.

Non pharmacological interventions

Common lifestyle changes recommended comprise of resting or napping more frequently during the day, and avoiding sensory stimuli that may provoke NVP symptoms. Sleep requirements increase during pregnancy, therefore rest is usually encouraged as fatigue may exacerbate NVP (92). Protein-containing snacks at night and crackers at the bedside also have been suggested. In NVP, nausea has been shown to decrease significantly, and gastric dysrhythmias significantly reduced following ingestion of a high-protein meal compared with a high-fat or high-carbohydrate meal (24). While there has been no evidence-based research on the effectiveness of these approaches, their safety has never been in question (173).

Alternative treatments for NVP have included natural ingredients such as the powdered root of ginger (Zingiber officinale) (7), used for centuries in eastern cultures for NVP symptom

relief (174). Various studies have shown B6 administration sometimes alleviate symptoms of NVP (148;175). A Cochrane review looking at treatments for NVP found that pyridoxine caused the fewest side effects of those drugs found to be of benefit.

As clinical evidence regarding NVP is limited, as well as the moral and ethical issues surrounding any testing of substances upon pregnant women, it seems appropriate to investigate what those practitioners observing and dealing with pregnant women recommend. In a recent study investigating the types of advice and support that midwives give to women regarding NVP, almost all the midwives who were questioned recommended ginger for NVP, followed by vitamin B6 and peppermint. Less commonly prescribed was chamomile, also recommended for its calming/relaxing effects (176).

Pharmacological interventions

Several different categories of pharmaceuticals either singly or in combination are used to treat NVP. The drug categories, based upon their different mechanisms of action include antiemetics, antinauseants, antihistamines (H1 blockers), anticholinergics, promility agents (such as dopamine antagonists), serotonin antagonists, and corticosteroids (173).

1.7 Dietary impact of NVP

A pregnant women's diet may be modified either by unintentional elimination or unintentional introduction of foods, or else an intentional selection or rejection of foods in an attempt to improve their well-being (177). The consequences of these modifications and restrictions of food and nutrient intakes in pregnant women during the course of the pregnancy, are unknown (177). Adding further impact upon the dietary changes of pregnant women are the observations that pregnancy in general, and especially where symptoms of NVP are present, is usually strongly associated with food cravings and aversions (178).

1.7.1 Cravings and aversions

That pregnancy has long been associated with food cravings can be found in medical literature as early as 1893, where it was observed that about one-third of pregnant women surveyed in one study reported 'longings' for specific foods (179), whereas the first detailed list of aversions during pregnancy stems back to 1725 (180). The desire for craved foods by

pregnant women can be quite intense; one study analyzing letters sent in response to a radio show found that some women expressed a willingness to steal the food items they craved in order to obtain them, in addition to the sensation that most women mentioned a sense of secrecy and shame surrounding the phenomenon (181).

Women have previously reported cravings for foods which include sweets (especially chocolate), fruits and fruit juices, ice cream, milk and other dairy products (182;183), whereas the most commonly reported aversions were for drinks containing caffeine, strong tasting and smelling foods, and fatty or greasy foods (178). Food cravings are reported to be especially prominent during the first and third trimesters of pregnancy (183;184), although Tierson, Olsen & Hook reported the most significant changes in diet occurred specifically in the first trimester (83). Food cravings and aversions have already been discussed as part of the EPH, which predicted aversions to strong-tasting vegetables, beverages containing alcohol and caffeine, as well as meat, fish, poultry and eggs. The latter foods, in accordance with the EPH, are more likely to be contaminated with parasites and pathogens at a time when pregnancy causes immunosuppression, leaving women more vulnerable to infection (12). This has been supported in numerous studies on diet and NVP showing a general trend toward craving fruit and fruit juices, and sweet foods (sweets, chocolate, biscuits), with the most common aversions towards tea and coffee, spicy/high flavored foods and meat/high protein foods (185).

Sherman & Flaxman's (14) examination of the EPH in depth confirmed pregnant women most often reported aversions to 'meat, fish, poultry, and eggs', with aversions to these animal products nearly double those of the second most aversive food category 'non-alcoholic beverages'. In regard to food cravings, they found pregnant women most often reported cravings for 'fruit and fruit juice' and 'sweets, desserts, and chocolate'. They also noted the non-alcoholic (caffeinated) beverage aversion was significantly higher in the first trimester of pregnancy than in the second or third trimesters, again emphasizing the timing for embryo organogenesis as the cause of rejection (14).

Since it seems that meats are more dangerous than vegetables (due to meat spoiling faster as animal immune systems cease to function at death), meats are more often associated with foodborne illnesses (186-188). As shown previously, the immune response of gestating women becomes depressed during pregnancy, and the susceptibility to embryo damage in the first trimester is postulated as the cause for meat-fish-egg aversions, manifesting as NVP.

1.7.2 Macronutrient overview

Fat

In a study conducted upon women who had experienced HG or very severe NVP, Signorello et al. (33) found that of all of the studied nutrients, only pre-pregnancy intake of dietary fat seemed to influence the risk of HG. In particular it was the levels of saturated fat which were suggestive as a risk, which, when combined with previous findings reporting that saturated fat creates an increase in the circulating levels of estrogen (189;190), may suggest a link between symptoms and saturated fat intake.

Protein

Voda & Randell (191) have suggested that high protein meals and snacks might be more effective than high carbohydrate meals in controlling NVP. When studying gastric dysrhythmias and nausea, Jednak et al. (192) found that nausea and gastric dysrhythmias were significantly reduced by feeding patients high-protein meals, but not by feeding them high-fat or high-carbohydrate meals. Women experiencing NVP reported in another study that high protein food such as dairy products, tuna, and roast beef were items most helpful in relieving nausea and vomiting (46). Another recent study reported that women who have higher protein portions in their diet experience less severe NVP symptoms (177). It has been reported many times in research that total protein in plasma is reduced during pregnancy (193-195). This effect seems mainly due to a serum albumin decline, yet the biological effects of this reduced osmolarity have proven difficult to understand (16), although it may be reasonable to suppose that the abnormally high hormone surges associated with pregnancy tax the body for serum proteins. Further support for protein comes from a study showing that an increased protein intake negatively correlated with number of days of nausea experienced (149).

There is a large body of growing evidence exploring the mechanism of protein intake as protective for nausea in general and NVP in particular. Levine et al. (196) suggests that by reducing gastric dysrhythmia, the feelings of nausea would minimize or disappear completely. They reported protein-rich meals especially those in liquid form), were most suppressive of gastric dysrhythmia and subsequent nausea and other motion sickness symptoms. This is supported by Jednak et al.'s studies with protein and the effect on nausea in first trimester pregnant women (192). Rieber et al. (197) recently exposed female subjects to experimental

nausea conditions (using a rotation device) after ingesting a protein drink either with or without the amino acid tryptophan. They found that with the tryptophan depleted subjects, increased symptoms of nausea were recorded, as well as an increase in hunger reported throughout the nausea, indicating an orexigenic effect of the tryptophan depletion. This latter finding had not been demonstrated previously in any studies. What associations, if any, these results have to food cravings or aversions during pregnancy, has yet to be explored.

Carbohydrate

Since carbohydrate intake has previously been suggested to relieve feelings of depression, it has been proposed that individuals suffering discomfort (such as NVP) 'self-medicate' their depression with carbohydrates (182). The biochemical mechanism behind carbohydrate craving is speculated to result from the dysphoria resulting from low serotonin levels (182). Carbohydrate-rich foods are thought to elevate production and release of brain serotonin which, in turn, elevates mood (198;199). This hypothesis is supported by demonstrations that carbohydrate cravings are reduced by drugs which enhance serotonin release or synthesis (200). In addition, some have linked carbohydrate craving to neuropeptide Y (NPY), since this orexigenic agent was shown to produce an increase in the intake of carbohydrate-containing foods (201). Studies that support the link between cravings and mood have suggested that mood changes may be components of the mechanisms that shape ingestive behavior during pregnancy (76). Tepper & Crystal-Mansour, commenting upon Fessler's paper (76) suggest that 'mood changes during pregnancy may be more predictive of food cravings and aversions than pregnancy sickness.' A high carbohydrate diet was shown to be very effective in completely eliminating or reducing the symptoms of NVP in one study (58). When Pepper & Roberts (144) investigated the link between NVP and diet by comparing rates of NVP prevalence across 56 studies in 21 countries against mean consumption of macronutrients and specific foodstuffs in each country, they found NVP was negatively related to the consumption of cereals and pulses, although their results are based on population-level average intakes rather than individual diets and should be interpreted appropriately. Godfrey et al. (64) found that women who had a high intake of carbohydrate during early pregnancy, as well as a low intake of dairy protein in late pregnancy, tended to have infants that were thin at birth. Thinness at birth is reported to be associated with insulin resistance and with the development of non-insulin dependent diabetes and coronary heart disease in adult life (202). In addition, women consuming high carbohydrate intakes in early

pregnancy have been shown to give birth to infants with low birth and placental weights, this being independent of the mother's height and BMI (64).

1.7.3 Mother-Fetus dietary bond

Adequate nutrition during pregnancy is important to enable the fetus to grow and develop physically and mentally to full potential (202;203). It is widely believed that fetal nutrition plays a key role in the well-being of the newborn infant, and further impacts on health during childhood and adulthood, with possible effects into the next generation (204-206). Recent evidence suggests the influence of early nutrition programming on a child's long-term health (207-209). It has been proposed that a limited or unbalanced supply of nutrients in pregnancy may permanently change the physiology and metabolism of the fetus, increasing the risk of chronic diseases such as coronary heart disease and diabetes later in life (87). One study looking at maternal diet and glucose insulin metabolism in the offspring concluded that high intakes of protein and fat during pregnancy may impair development of the fetal pancreatic beta cells, and thereafter lead to insulin deficiency in the offspring. The authors are clear to stress that these findings are not the basis for recommending alterations to current dietary advice (210).

Another research group (149) looked at how infant birth weight varied with women experiencing NVP. Those women with no NVP had a larger proportion of infants born with low birth weight, which they attributed to a shortened gestation time. By translating niacin intake levels as protein intake, they noticed a negative correlation between intake of protein during week 12 and the total days of nausea. They also reported an increased intake of protein was associated with a decreased infant birth weight, which they postulated as being mostly accounted for by shortened gestation length. In other words, the increased protein intake caused a faster maturation of the fetus resulting in earlier delivery (149).

Studies investigating the association of NVP with physical and psychosocial disorders later in childhood (211) hypothesized dietary protein level reductions for weeks during gestation could lead to subtle neurobehavioral defects apparent later in life. They reported that children of mothers with NVP during gestation had lower sensory thresholds, higher levels of activity and emotional intensity, lower scores in task persistence at age 5, and were viewed as more careless in their schoolwork at 12 years of age. Prolonged nausea and vomiting was hypothesized as an interference with proper fluid intake and nutrition, leading to various

blood chemistry abnormalities, such as increased blood urea nitrogen and ketones (211). It has been demonstrated in animal studies that a high salt intake by gestating mammals is linked to a high offspring salt intake, programming for future hypertension and other related chronic disease (212).

1.8 Aims and research questions

Using the data in MoBa, it is the aim of this master thesis to explore the dietary characteristics of pregnant women experiencing nausea and NVP. In particular, the study aims to detect increases or decreases in macronutrient intake during the course of the first trimester, and to detect patterns of increase or decrease in intake for selected food groups and items. The three main categories of pregnant women to be researched here shall be those with no symptoms of either nausea or NVP (NN), those women experiencing nausea alone (N), and those women reporting both nausea and vomiting (NVP)

The study aims:

- to detect modifications in macronutrient intake during the course of the first trimester
- to detect patterns of increase or decrease in intake for selected food groups and items
- to detect if pregnancy outcomes such as infant birth weight and gestational weight gain are affected by nausea and/or NVP.

The motivation for doing such research is the current absence of a clear understanding to the phenomenon surrounding nausea and vomiting during pregnancy. Although this research may not concern itself directly with the etiology of NVP, results obtained may reinforce and support the validity of some hypotheses over others.

2 Subjects and methods

2.1 Subjects

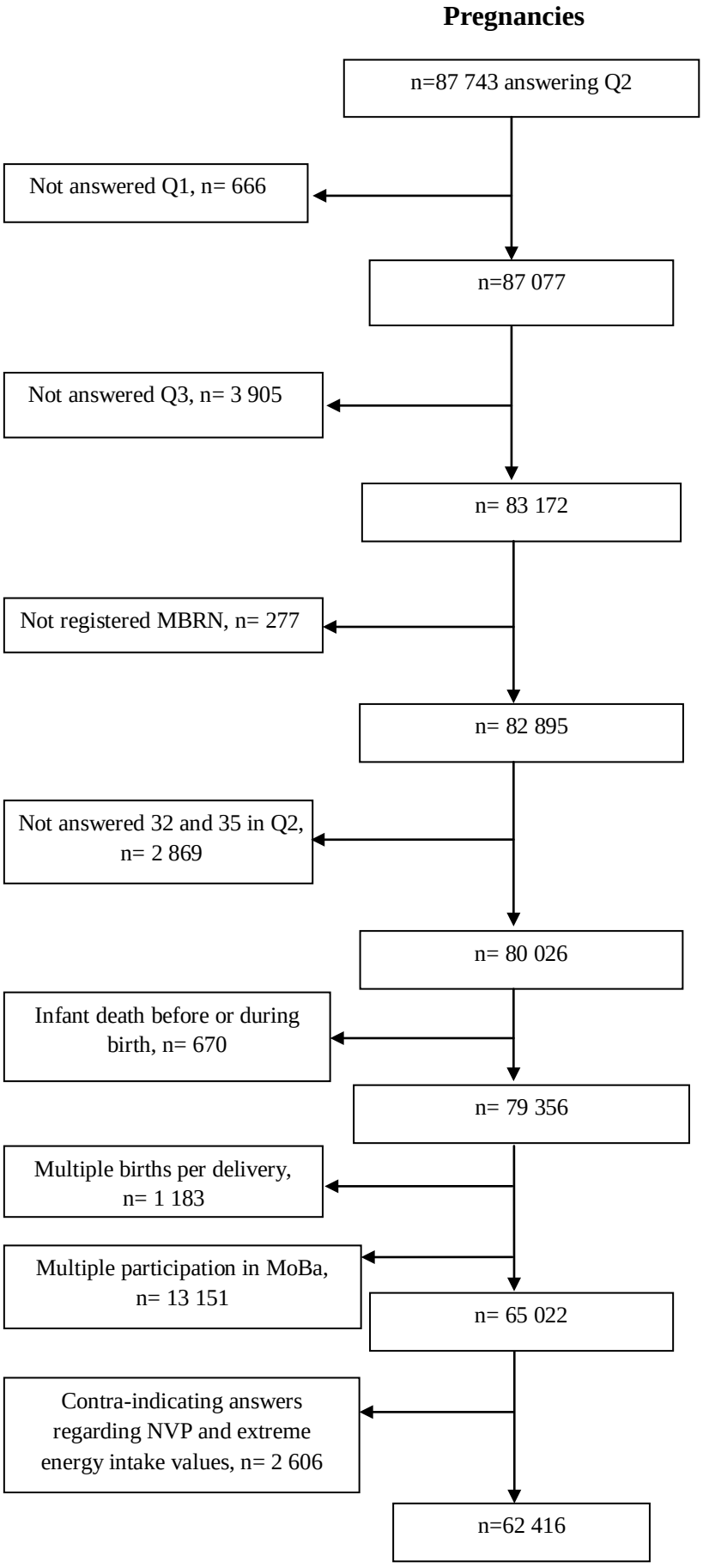
The Mother and Child Cohort study (MoBa) had a target population comprising of all women who gave birth in Norway, without exclusion criteria other than the ability to comprehend the Norwegian language, and were recruited between 1999 and 2008 (3). Data needed for the master thesis was found in questionnaire 2 (Q2), answered by 87 743 participants (figure 1, page 29). In addition to Q2, data from questionnaire 1 (Q1) and questionnaire 3 (Q3) were included. Thus women who had failed to answer those two booklets were excluded, leaving 83 172 women.

The Medical Birth Registry of Norway (MBRN) is a national health registry in which registration of all live births and stillbirths in Norway has been compulsory since 1967. Data from MBRN has been linked to the data of MoBa participants using the national identification number of the participants (1). There were instances where data was found to be missing for some women, and it thus became necessary to exclude these from the study sample, leaving 82 895 women.

Although only women who had answered Q2 were included, some had failed to answer questions 32 and 35 within Q2, questions which specifically related to nausea and vomiting. Those women not answering questions 32 and 35 were therefore also excluded. Women who had not given birth to living infants were excluded, as were those women who had not had singleton births (i.e. twins, triplets). Women who had participated with several pregnancies during the cohort study were included, being represented only by their first participating birth. Women who had a reported daily energy intake of < 4.5 and > 20 MJ per day were excluded from the sample (213), as were women who had answered questions with obvious inconsistencies and errors (for example negative body weight values, and issues concerning the presence of nausea and vomiting). The final sample studied for the master thesis included 62 416 women.

A detailed description of the MoBa study and the various questionnaires used is available in literature (1), or else by visiting the project's web site (www.fhi.no).

Figure 1. Flow diagram for inclusion of participants for the study from the Norwegian Mother and Child Cohort



2.2 MoBa questionnaires

A series of questionnaires were used to obtain information from women participating in the MoBa cohort. Questionnaire 1 (Q1) was completed by mothers between weeks 13 – 17 of pregnancy, questionnaire 2 (Q2) in week 22 of pregnancy, questionnaire 3 (Q3) in week 30 of pregnancy, and questionnaire 4 (Q4) when the child was at age 6 months. In total, there are currently six questionnaires in the MoBa cohort. The content of Q1 to Q4 dealt with themes such as previous pregnancies, medical histories of the women, a food frequency questionnaire (FFQ) and dietary habits, the women's health status during pregnancy, exposures in the home and work environment, and maternal disorders, amongst many other themes. The bulk of data investigated in the master thesis came from Q2, in particular the FFQ, and the reported dietary changes due to the pregnancy. Page 13 of Q2 dealt specifically with the latter theme, and can be inspected in appendix 2.

2.3 Questions central to this study

Of all the questions in the MoBa study, those which appeared on page 13 in Q2 (questions 31 to 38) were the ones most probing into dietary change, nausea and vomiting. Question 31 presented 17 food and drink items, and the women were asked to indicate via a series of tick boxes as to whether they had begun to eat more, or the same amount, or less, of these items compared with their diet before becoming pregnant. They also had the chance to indicate if they never ate/drank the item before pregnancy, or if they had stopped consuming this item completely since pregnancy. Question 32 asked whether the women had experienced nausea during the pregnancy. Question 33 as a follow-up to question 32, asked 'if yes (to experiencing nausea), have you eaten more or less than before?'. Still following on with the nausea theme, question 34 asked from which pregnancy week nausea had begun, and which pregnancy week nausea had ended; there was also a tick box available for the women to indicate if nausea was still being experienced. Question 35 asked if the women had experienced vomiting in this pregnancy, and question 36 asked from which pregnancy week vomiting had begun, and which pregnancy week vomiting had ended; there was also a tick box available for the women to indicate if vomiting was still being experienced. Question 37, using a yes/no tick box, asked whether the women had begun to eat or drink certain food items during the pregnancy. Question 38, as a follow-up to question 37, asked 'if yes (to eating certain foods), write the name of the food item(s)'.

2.4 Formatting of Q2, Question 38

As shown on page 13 of Q2, question 38 was a follow-up to question 37, asking 'Have you started to eat or drink certain food items during this pregnancy? Yes /No'. Question 38 asked 'If yes, name the two most important food items you have started to eat/drink', followed by two empty spaces where the women were expected to write the food/drink items. These open answers were not available from the MoBa database, thus were coded and entered by the master student. In the process of categorizing these open answers, it became necessary to classify foods for further analysis. Foods were listed into these main categories: Milk and milk products; Breads and cereals; Biscuits, Buns and cakes; Fat; Meats; Fish; Egg; Vegetables; Fruit; Chocolate; Sweets (non-chocolate); Coffee; Teas; Juice; Carbonated drinks; Water; Alcohol; Spreads; Unspecified; Pica; General food types. The categories and complete list of foods used can be seen in table 1, appendix 2.

From the complete list, there are some items requiring further explanation:

Salt/salty foods: some food items were described by the women more for their effect on the palate rather than just a food item, e.g. salty pickles. These foods were classified under this section rather than 'unspecified/other vegetable', as the saltiness of the food seemed more essential to the consumer than the food item itself.

Sour foods-unspecified/other: as with salty foods, these foods were chosen seemingly for their overall sourness rather than for the actual food.

Words/products unrecognizable: occasionally a food reported was unknown or the word recorded read as gibberish, and were therefore ignored.

Water with ice – as opposed to simply water alone, water with ice required a category of its own as it seemed extremely popular amongst pregnant women.

Pica – the consumption of non-food items or peculiar methods of eating are well known for pregnant women (76;180). All such cases were categorized here.

In addition to the exhaustive categorization of the foods reported in question 38, some reported foods were also tagged into broader categories relating to pregnant women and their food choices in an effort to detect various trends in consumption. These broader categories are as follows: Foods that help reduce nausea; Foods helping digestion (dried fruits etc.); Foods

containing probiotics; Foods rich in proteins; Foods rich in fat; Foods rich in sugar; Foods using artificial sweeteners; and Foods rich in sour/salt taste. The individual food items used to create the broader categories can be found at the end of table 1, appendix 2.

2.5 The Food Frequency Questionnaire (FFQ)

The FFQ used in Q2 (week 22) asked questions about the intake of over 200 food items and was designed to illustrate dietary habits and intake levels of foods and dietary supplements since the woman had become pregnant. This FFQ was designed for use in MoBa, and was subsequently validated (214). The validation study found that the MoBa FFQ produced a realistic and relatively precise estimate of the habitual intake of energy, nutrients and food groups among the pregnant Norwegian women featured in the MoBa cohort. Further information regarding the FFQ and validation details can be read elsewhere (214).

2.6 Study sample selections for certain variables

The following variables contained data with unrealistic or extreme values, and were treated in the following ways: The analysis of the variable 'length of gestation' included only those women reporting a length ≥ 28 and ≤ 42 weeks; The analysis of the variable 'gestational weight gain' included only those women reporting a loss of weight ≤ 30 kg, or a gain of weight ≤ 50 kg; The variable 'Height' had values of zero marked as 'system missing'; The analysis of the variable 'Weight of placenta' included only values ≥ 200 grams and ≤ 1000 grams; The analysis of the variables 'number of weeks of nausea experienced' and 'number of weeks of vomiting experienced' included only women reporting a value between 0 and 26 weeks; Where women had indicated 'still nauseous' or 'still vomiting' (question 34 and question 36 in Q2, respectively) yet had no value present for 'number of weeks of nausea' or 'number of weeks of vomiting', a value of 22 weeks was inserted; The analysis of the variable 'Weight of baby' included only values higher than 1 gram.

2.7 Statistical analysis

In the preliminary phase, analyses were run to check for missing values and the normality of the continuous data. The variables 'Large for gestational age' (LGA) and 'Small for gestational age' (SGA) were created by calculating the 10th percentile and 90th percentile of

each gestational week, as well as for different parities (primiparous vs. multiparous) for each gestational week between weeks 34 to 42 taken from the MoBa data. Data for weeks 28 to 34 used the 10th and 90th percentiles with data collected from the MBRN (215). Data were transferred to OpenOffice Spreadsheet software (v.3.2.1, Oracle Corp., Redwood, CA) for graph construction, which involved continuous values converted to percentage of group values. Nominal data were analyzed by the chi-squared (χ^2) test. Continuous data that were assumed normally distributed were analyzed by one-way analysis of variance (ANOVA). If the comparison of the three groups was significant, pair wise comparisons between groups (post hoc tests) were performed for maternal demographics, macronutrient intakes, and birth related variables, using the Bonferroni correction. If the three pairwise comparisons were not significant, this is included as a footnote in the table. Where only two groups were compared, an independent sample t-test was performed. When continuous data were not normally distributed, a Kruskal–Wallis test was used. The significance level was set at 5%, and all analyses were performed using PASW version 18.0 (SPSS, Inc., Chicago, IL).

3 Results

In total, 62 416 women were included in the study sample. The women were distributed as follows: No Nausea (NN) 17 185 women (27.5%), Nausea (N) 27 642 women (44.3%), and Nausea and Vomiting during Pregnancy (NVP) 17 589 women (28.2%), which included 687 women whose condition developed into hyperemesis gravidarum (HG).

3.1 Maternal demographics

Table 1 in appendix 1 shows selected maternal demographics.

The mean age of the women with NVP was younger compared to the other groups (29.1 years vs. 30.6 years N and 30.1 years NN, table 1 in appendix 1).

The median pre pregnancy weight of women with NVP was higher when compared with the other groups (66.0 kg vs. 65.0 kg N and 65.0 kg NN), as was the BMI. The women with NVP were shorter than the other groups (167.8 cm vs. 168.3 cm N and 168.2 cm NN). Gestational weight gain was lowest for the NVP group (14.3 kg vs. 15.1 kg N and 15.2 kg NN).

Maternal age at delivery was lowest amongst the NVP group, both for the under 25 year old category (16.6% vs. 10.4% NN and 8.8% N), and the 25-29 year old category (36.7% vs. 35.7% NN and 32.0% N). Conversely, the N and NN groups represented the highest proportion of over 30 year old women.

Women from the NVP group represented a higher proportion of those with a BMI < 18.5 kg/m² (3.2% vs. 2.9% NN and 2.7% N), as well as the category 24.9-29.9 kg/m² (22.3% vs. 20.8% N and 20.4% NN), and the category 30kg/m² and over (11.0% vs. 8.7% N and 8.3% NN). The 18.5-24.9 kg/m² category had the highest proportion of the NN group (66.3% vs. 65.3% N and 60.9% NVP).

Women with NVP represented a higher proportion of those with less than 12 years education (35.9% vs. 29.5% for both N and NN groups). Married women represent the highest proportion of the N group (47.7% vs. 45.4% NVP and 41.1% NN), while women with NVP represented the highest proportion of single/widowed women (2.7% vs. 2.4% NN and 1.9% N). Women who were co-habiting had the highest proportion in the NN group (54.9% vs. 50.2 % NVP and 49.0% N).

The NVP and N group represented the highest proportion of non-smokers amongst the category of those smoking 3 months prior to pregnancy (72.4% and 71.7%, respectively, vs. 67.5% NN). This pattern continued for women who smoked during pregnancy, where the N and NVP groups dominated the non-smokers (92.6% N and 92.0% NVP vs. 89.7% NN).

Women from the NN group represented the highest proportion that were pregnant for the first time (primiparous) (67.7% vs. 56.4% NVP and 50.0% N). When reporting on previous births, the N group had the highest proportion (32.2% vs. 29.3% NVP and 21.1% NN), a pattern that continues with 2 or more previous children born (17.9% N vs. 14.2% NVP and 11.2% NN).

3.2 Nausea and vomiting related characteristics

When exploring the mean number of weeks of nausea experienced by the groups, those women with NVP experienced significantly more weeks when compared with the N group (10.5 weeks vs. 7.8 weeks N, table 2 in appendix 1). The mean number of weeks of vomiting for the NVP group was 6.4 weeks.

Women from the N group represent the highest proportion of women with nausea during weeks 1-4 (18.9% vs. 8.8% NVP), as well as in weeks 5-10 (63.7% vs. 52.2% NVP), however, in all categories from week 11 through to week 26, it is the NVP group with the highest proportion of women with nausea (weeks 11-16 23.0% vs. 12.6% N). NVP represents the only group with weeks of vomiting reported, showing the highest proportion of women in weeks 5-10 (50.9%), and the lowest prevalence in the latter weeks (17-21 weeks 1.3%, 22-26 weeks 0.1%, figures 5 and 6 in appendix 1).

Of those women who had answered yes to experiencing nausea, the highest proportion who reported eating less as a result of the nausea was the NVP group (68.2% vs. 51.6% N and 3.0% NN), whereas the highest proportion who reported eating more was the Nausea group (48.1% vs. 31.4% NVP and 4.8% NN).

When asked in question 37 if the women had begun to eat any certain foods during the pregnancy, the NVP group had the highest proportion responding ‘yes’ (29.3% vs. 26.0% N and 22.9% NN).

3.3 Daily intakes of macronutrients for women based on FFQ

The NVP group had the highest mean energy intake (9 862.5 kJ vs. 9 710.2 kJ N and 9 535.5 kJ NN, table 3 in appendix 1). This same pattern was found for carbohydrate (316.5 g vs. 308.6 g N and 301.8 g NN), added sugar (65.8 g vs. 61.3 g N and 59.6 g NN), protein (87.5 g vs. 87.2 g N and 86.3 g NN), and fat (80.4 g vs. 80.1 g N and 78.9 g NN).

The NVP group had the highest proportion of saturated fat (31.0 g vs. 30.8 g N and 30.5 g NN), as well as trans-fat (2.4 g vs. 2.3 g NN and N), and poly-unsaturated fat (15.2 g vs. 15.1 g N and 14.8 g NN). Mono-unsaturated fat had the highest proportion with the N group (25.8 g vs. 25.6 g NVP and 25.4 g NN).

3.4 Daily intakes of macronutrients as energy percent for women based on FFQ

When overall energy percent values for macronutrients are compared, carbohydrate's energy percent is highest for the NVP group (53.7% vs. 53.2% N and 53.0% NN, table 4 in appendix 1), as well as added sugars (10.9% vs. 10.3% N and 10.2% NN). Although the carbohydrate energy percent is significantly different for all three groups, added sugar is statistically different between the NVP group and the other two groups only.

The NN group represents the highest energy percent values for protein (15.4% vs. 15.3% N and 15.2% NVP), and for fat (31.4% vs. 31.3% N and 30.9% NVP). The protein distribution is statistically different for all groups, however fat is only statistically different between the NVP group and the other two groups.

Of the fat components, only saturated fat was statistically different between all groups, with trans-fat and mono-unsaturated fat statistically different between the NVP group and the other two groups. There was no significant difference in poly-unsaturated fats.

3.5 Daily intakes of selected foods for women based on FFQ

The mean milk intake was highest in the NVP group (350.0 g vs. 337.0 g N and 334.7 g NN, table 5 in appendix 1), and a similar distribution was also apparent with vegetable intake (48.9 g vs. 47.2 g N and 45.6 g NN), and fruit (295.1 vs. 280.4 N and 272.0 NN).

The NN group had the highest levels, and NVP the lowest levels, for the intake of Biola/Cultura (34.1 g vs. 28.2), juice (1.5 g vs. 0.9 g), chocolate (19.4 g vs. 17.8 g), and drinking water (1,221.0 g vs. 1,182.8 g).

Fish intake was highest amongst the N group (45.1 g vs. 44.2 g NVP and 43.7 NN), whilst meat intake was highest amongst the NN group (77.3 g vs. 77.2 NVP and 76.7 g N), although this was not statistically significant. Sugared soft drink intake was highest in the NVP group (104.9 g vs. 77.8 g NN and 76.6 g N).

3.6 Dietary trends of those starting to eat general food types during pregnancy (Q38)

Of those women answering ‘yes’ to starting to eat certain food types during pregnancy, the NVP group had the highest proportion eating ‘foods that help reduce nausea’ (5.4% vs. 4.1% N and 2.1% NN, table 6 in appendix 1).

The N group had the highest proportion of women eating ‘food helping digestion’ (4.9% vs. 4.6% NN and 4.4% NVP), though this was not statistically significant. Of the ‘foods containing probiotics’, the NN group had the highest proportion (14.8% vs. 11.2% N and 7.0% NVP).

Of the ‘foods rich in proteins’, the NVP group had the highest proportion (6.8% vs. 6.4% NN and 6.1% N), though this was not statistically significant. With the categories ‘foods rich in fat’, ‘foods rich in sugar’, ‘foods using artificial sweeteners’ and ‘foods rich in sour/salt taste’, the NVP group consistently had the highest proportion of the group distribution, and the NN group had the smallest proportion.

3.7 Dietary trends of those starting to eat certain foods for women based on Q38 responses

Of those women answering ‘yes’ to starting to eat certain foods during pregnancy, the NVP group had the highest proportion consuming milk during the pregnancy (14.6% vs. 13.5% NN and 13.2% N, table 7 in appendix 1).This group also had the highest proportion for water intake (7.8% vs. 6.7% N and 4.7% NN), vegetable intake (10.9% vs. 9.5% N and 8.6% NN), fruit (31.8% vs. 29.9% N and 29.1% NN), fish (6.2% vs. 6.2% NN and 5.9% N), and sugared soft drinks (4.5% vs. 2.8 % N and 2.5% NN).

The NN group had the highest proportion of consumption of Biola/Cultura (14.8% vs. 11.2% N and 7.0% NVP). This trend continued for juice (8.2% vs. 8.1% N and 7.6% NVP), chocolate (2.5% vs. 1.8% N and 1.3% NVP).

The N group represented the higher proportion of meat intake (6.2% vs. 5.9% NVP and 5.0% NN), although this was not found to be statistically significant.

3.8 Birth-related variables

The majority of women gave birth after a ‘normal’ gestation (37-42 weeks, table 8 in appendix 1), with the N and NVP groups representing the highest proportions (95.7% and 95.4% respectively vs. 94.9% NN). ‘Early births’ (35-36 weeks) were highest amongst NN groups (3.3% vs. 3.0% NVP and 2.8% N), as were ‘very early births’ (28-34 weeks) (1.8% vs. 1.6% NVP and 1.5% N).

Of the babies born ‘large for gestational age (LGA)’ (birth weight above the 90th percentile between 28-42 weeks gestation), the highest proportion was amongst the N group (10.1% vs. 9.8% NVP and 9.0% NN). Conversely, babies born ‘small for gestational age (SGA)’ (birth weight below the 10th percentile between 28-42 weeks gestation), had the NN group representing the highest proportion (11.6% vs. 10.5% NVP and 9.8% N).

There were a high proportion of males born in the NN group (54.3% vs. 51.0 N and 48.3% NVP). The mean weight of the placenta was lowest amongst the NN group (654.7 g vs. 670.4 g N and 668.4 g NVP). This pattern is reflected in the weight of baby at birth, where the NN babies were born lightest (3 540.5 g), and the N babies born heaviest (3 619.1 g).

3.9 Question 31

Question 31 (Q31) asked women about 17 different food groups and their relationship (in week 22) to those food groups. Of the 17 food groups explored in Q31, all were grouped into a panel according to a prevailing food type, except alcohol, which was omitted as this had an almost uniform abstinence from the sample population.

Figures 1 to 4 in appendix 1 show the results of Q31. Of the 16 food groups the women responded to, there was on average 99% response. Food groupings from question 31 were further grouped into one of four panels representing protein-rich foods (figure 1), carbohydrate-rich foods (figure 2), fat-rich foods (figure 3), and beverages (figure 4).

In response to food groups which subjects had 'Stopped eating completely', the majority of women in all 3 condition groups reported 0%. Exceptions include eggs, fish and fat, where NVP reported a higher proportion compared to N and NN (1% vs. 0%). With biscuits, chocolate and other sweets, similar patterns prevailed (3% vs. 1%). This pattern continued for juice (2% vs. 1% N and 0% NN), sugared drinks (6% vs. 5% N and 4% NN), artificially sweetened drinks (10% vs. 8% N and 6% NN), and tea (4% vs. 3% N and 2% NN). The largest results for 'Stopped eating completely' came for coffee, again with NVP reporting the highest proportion of all 3 condition groups (17% vs. 13% N and 9% NN).

In response to food groups which the subjects reported 'Ate less', the general trend showed the NVP condition consistently having a greater proportion when compared to the other 2 women's conditions. Smaller proportions prevailed for groups such as milk, cheeses (9% vs. 4% N and 2% NN), bread (6% vs. 3% N and 1% NN), fruit (3% vs. 1% N and NN), vegetables (5% vs. 2% N and 1% NN). Higher proportions for 'Ate less' occurred for meat (15% vs. 8% N and 5% NN), fish (10% vs. 6% N and 3% NN), eggs (14% vs. 9% N and 6% NN), biscuits (19% vs. 16% N and 14% NN), fat (25% vs. 17% N and 15% NN), chocolate (39% vs. 31% N and 26% NN), other sweets (37% vs. 30% N and 26% NN). This pattern continued with all beverages, except coffee, which had the NN condition prevailing (47% vs. 46% N and 38% NVP).

In response to food groups which the subjects reported 'Ate more', there appeared no general pattern between the 3 women's conditions, in most cases proportions were very similar, or else NVP had a higher proportion. The most pronounced differences with NVP having the greater proportion appeared for milk, cheese (42% vs. 41% N and 39% NN), eggs (12% vs.

10% N and 8% NN), biscuits (15% vs. 10% N and 7% NN), and sugared drinks (9% vs. 7% N and 5% NN).

In response to food groups which the subjects reported ‘Ate as before’, the general pattern showed women with NN having consistently higher proportional values when compared to the other 2 women’s conditions. The most pronounced differences show NN having the greater proportion for meat (90% vs. 85% N and 78% NVP), eggs (84% vs. 79% N and 71% NVP), biscuits (66% vs. 62% N and 53% NVP), fat (76% vs. 73% N and 64% NVP), chocolate (54% vs. 47% N and 41% NVP), other sweets (57% vs., 51% N and 44% NVP), and juice (60% vs. 56% N and 49% NVP).

In response to food groups where the women reported ‘Never ate before’, the majority of women in all 3 condition groups reported very low or similar values (under 5%). Exceptions include biscuits where women with NN had a greater proportion (12% VS. 11% N and 10% NVP), and sugared drinks (19% vs. 19% N and 14% NVP). Coffee was the only example where NVP had a clearly higher proportion (38% vs. 28% N and 27% NN).

4 Discussion

4.1 Summary of results

The results from the study show that women with nausea and vomiting (NVP) experience the least gestational weight gain, whilst simultaneously having the largest dietary intake of all macronutrients, except mono-unsaturated fat. Of the foods the women began to eat during gestation, a larger proportion of the no nausea (NN) group started to eat probiotic foods and chocolate. The NVP group started to eat foods rich in sugar, foods rich in sour/salt taste, milk, fruit, vegetables, and sugared soft drinks. The nausea (N) group closely resembled eating patterns of the NVP group.

The N and NVP group had more babies born large for gestational age (LGA), and the NN group had more small for gestational age (SGA) babies. The NN group gave birth to a higher number of male babies, as well as babies with the lightest mean birth weight. Babies born to the N group were the heaviest of all three groups. The majority of comparisons were significant in this large cohort study.

4.2 Study sample and methods

4.2.1 Strengths

Strengths of the study include the prospective design and large population based cohort which has women from nearly every county in Norway represented.

The data from the Norwegian Mother and Child Cohort study (MoBa) has been linked to the Medical Birth Registry of Norway (MBRN), that provides information on all births in Norway (with a gestational age of 16 weeks) since 1967, including data on birth weight, birth length, gestational age, parity, parental age and complications. These data are of high quality since virtually all data are collected by health personnel, removing the possibility of errors or bias through self-reporting.

A validated food frequency questionnaire (FFQ) was used (214), and FFQ's have been proven as an effective tool in nutrition studies to assess and approximate the diet of people over a lengthy duration of time (216;217).

4.2.2 Weaknesses

Although the FFQ was validated, the accuracy of the food intake data is always suspect of misreporting. Misreporting (both under and over reporting) of energy intake values has been previously described in many population groups including pregnant women (218;219). This is in accordance with a recent Swedish study that concluded that it is common for pregnant women to under-report their energy intake (218). However, there are no reasons to believe that diet was reported differently for women experiencing no symptoms, nausea, or nausea and vomiting. Since questions from the FFQ and question 38 (Q38) were both contained in the same questionnaire, it is difficult to determine how much (if any) reporting overlap has occurred between regular intakes of foods and foods women have started to eat.

Selection biases are distortions that result from procedures used to select subjects and from factors that influence study participation (220). The decision to use Norwegian as the only language of the study effectively means that the chances of enrolling the many non-ethnic Norwegians residing in Norway as participants would be limited. Other examples of potential selection bias are the decision to exclude women who chose to terminate pregnancy or who had experienced a spontaneous abortion or prenatal death. These women may have been subject to previous or current nausea and vomiting related effects and their exclusion may have affected results. This sample only included women with single gestation, and trends more indicative of NVP characteristics may have been more apparent if the variables for women with multiple gestations had been included. Loss to follow-up bias is unlikely in this study. Only 4.5% of those answering Q1 and Q2 did not answer Q3. Moreover, birth outcome data came from the MBRN. Nilsen et al. suggests that prevalence estimates of exposures and outcomes may be biased in MoBa due to selection bias (221). They found a 43.5% response rate from women invited to participate in MoBa, furthermore, determined that MoBa had a strong underrepresentation of the youngest women (< 25 years), those living alone, mothers with more than two previous births, and those with previous stillbirths (221).

Timing of the answers provided for the questionnaires may vary due to the responsibility of completion and delivery being with the participant. This affects Q2 in particular, since it is accepted as a representation of dietary profile at week 22 of gestation.
One limitation of this study is the possibility of reverse causality. It is difficult to assess with certainty if the dietary habits of women experiencing nausea and NVP were owing to the lifestyle of that person, or to the effects of the malady. The questions seeking information

about nausea and vomiting were contained in the same booklet as the dietary questions (Q2), therefore placing both in the same time frame.

Relying on self-assessment and recall, and the unreliability of memory remains the central inherent problem. The inconsistencies and errors encountered as answers to some of the questions analyzed in the MoBa data may have been a manifestation of disturbed cognitive mechanisms or simple recording errors often reported in association with the pregnant state of mind (222-224). There were instances of women who were excluded for reporting either no nauseous symptoms, only to later state a number of weeks of nausea experienced, and vice versa (for example, table 2 in appendix 1 has 1 056 NN women answering a question aimed at those who reported nausea). These and other errors were only detected due to their extreme nature (such as birth weight of 1g), yet the occurrence of errors with plausible data may have gone undetected and may affect the quality of the results.

Another weakness of this study is the self-reporting of nausea and vomiting. Without a validated test to quantify the presence and severity of nausea, it remains a subjective report. Likewise for vomiting; how episodes of nausea with gagging, dry retching (dry heaving) and/or resistance to the vomiting reflex were translated by the women when filling out the questionnaire is impossible to assess. The lack of a clinical diagnosis also raises the question of whether the vomiting and/or nausea were due to normal 'morning sickness' and not owing to some other ailment, such as food poisoning or one of the many other non-pregnancy related causes.

Since the issue of frequency or severity of vomiting have not been addressed in the MoBa questionnaires, it is impossible to estimate how much of the ingested nutrition consumed by the NVP group has been retained. This data gap has the potential to bring into question all associations related to the dietary intake of the NVP group and the subsequent changes to their gestational weight and birth outcomes. Since a precise estimation of their intake is impossible from the data supplied, the information obtained from the N group of women is of invaluable use here. Although the symptoms of nausea and NVP are not exactly the same, the intakes and appetite changes of the N group can still be used as a guideline to highlight differences between the N and NVP group, and the NN group.

Statistically, there were many analyses and tests performed. The concern with multiple comparisons must be kept in mind when drawing conclusions. Significance may be owing to

chance. Thus, any associations must be evaluated on their own merits, and must be discussed with the respect to results from prior studies. Moreover, the study sample is large, providing high statistical power to detect small differences between the three groups. Findings in the study, though of statistical relevance, may not necessarily represent any clinical relevance.

4.3 Maternal demographics

4.3.1 Age

The results show that it was the women who were younger that were most likely to experience NVP. In the category '< 25 years', the NVP group had a higher proportion, while higher proportions were observed above 30 years in the N group. Although this supports the numerous studies naming younger women as being most likely to experience NVP, an effective discussion of age comparisons is difficult when the mean difference between the three groups spans 1.5 years.

4.3.2 Weight and BMI

The weight and BMI of the women showed that it was the heavier women who were prone to experience NVP symptoms. Though the median difference between the groups was only 1 kg, the categories for 25-29.9 kg/m^2 (overweight) and $\geq$ 30 kg/m^2 (obese) both feature the NVP group as a majority, supporting O'Brien & Zhou's claim that NVP symptoms are related to obesity (26).

4.3.3 Height

Height values suggest that the shorter women are statistically more likely to experience NVP. Though the difference is small, this is a finding that, to our knowledge, has never been reported before. When conducting a socio-demographic study for hyperemesis gravidarum (HG) on pregnant women in Oslo, Vilming & Nesheim (225) found that the HG women had a mean height 4 cm shorter than the non-HG women, although no significance was reported.

4.3.4 Gestational weight gain

Gestational weight gain was significantly lowest amongst the NVP group. The fact that vomiting with nausea caused the lowest weight gain in this sample is perhaps not surprising since the women who reported NVP also had the highest proportion reported as eating less in answer to question 33. Studies have shown that vomiting will reduce appetite in pregnant women (226), and reduced weight gain for women suffering NVP was also reported by other studies (149). Latva-Pukkila et al. (177) found in pregnant women with and without NVP no significant differences in gestational weight gain for the groups. Weigel & Weigel found women with only vomiting gained less weight during the first 20 weeks when compared to those experiencing nausea alone or no symptoms, however there were no significant differences in weight gain at the time of delivery (165). A discussion of gestational weight gain's role with infant birth weight follows in section 4.6 below.

4.3.5 Maternal education

We found a significant difference in education between the three groups: women experiencing NVP had a lower education. This confirms the findings of Klebanhoff et al. (143) who found a statistically higher number of women experiencing vomiting during pregnancy that had an education less than 12 years in a sample representing mixed socio-economic and race variables in the U.S. These results contradict the findings of Petitti (153) who also had a sample from the U.S., and found no statistical difference for education between women who experienced nausea in pregnancy and those who did not, although women with nausea and vomiting were not included in either study.

4.3.6 Marital status

The majority of the women in the sample were married or co-habitants, and the marital status was significantly different between the three groups. The N group had the highest proportion married, whilst the NN group had the highest proportion co-habitating. Why marriage should seem to trigger nausea and NVP more than co-habitation is difficult to speculate. Iatrakis et al. (134) found that stress related to poor communication with the women's husbands influenced the severity of nausea and vomiting. Although Iatrakis et al.'s study supports these findings, it is important to take note of the different attitudes to marriage vs. co-habitation amongst different populations. Co-habitation and marriage are both common in Norway, and

it has been reported that co-habitation has become an institutionalized alternative to a formal marriage in Norway (227). Whether the level of communication in co-habitant relationships is of a different quality, or somehow less stressful for a pregnant woman in Norway, is both difficult to ascertain and outside the scope of this study.

4.3.7 Smoking

The N and NVP groups had the highest proportion of non-smokers three months before pregnancy, and during pregnancy. These numbers contradict Goecke et al. (152), and support the many studies which suggest smoking to have a protective mechanism against nausea and NVP (20;22;45;60;148). The suggested protective mechanism seems to be connected to the hormones hCG and estradiol (the predominant estrogen in humans). As discussed in the introduction, these two hormones are amongst the most suspected in causing symptoms of nausea and NVP in women. One study has shown that smoking while pregnant significantly decreases the levels of these hormones, as well as finding there to be a steady decline with increasing cigarette consumption (228). Another study explains the reduced nausea and NVP for smoking mothers is possibly due to cigarettes damaging placental cells thought to be responsible for triggering NVP (229). Leptin is another hormone also suspected of being involved with NVP (120), and research has shown that cigarette smoke reduces the circulating levels of leptin, causing a stronger interest in this hormone's role in pregnancy since the functional reason for raised leptin is not yet fully understood (230;231).

4.3.8 Parity

Literature regarding nausea during pregnancy and NVP has been divided over the subject of parity. The results from this study suggest the women who were pregnant for the first time were more likely to avoid symptoms of nausea or NVP. Multiparous women had a higher risk of experiencing nausea. These findings support Pettiti (153) who found multiparous women to be statistically more likely to experience nausea than primiparous women. These findings contradict those claiming NVP severity increases as parity increases (59), and those claiming to have found no significant relationship between nausea and parity (60). These diverse results may be likely due to the sample size differences between these studies, the latter having only 363 women enrolled in the study compared to the 62 416 in this study.

4.3.9 Weeks of nausea and vomiting

The average length of nausea in our sample was 7.8 weeks in the N group and 10.5 weeks in the NVP groups (figures 5 and 6, appendix 1). These figures are similar to that reported by Gadsby et al.(19), where 9 weeks was reported as the peak for women experiencing nausea. However, other studies have reported longer durations, for example Zhou et al. (155) report their sample to have had a mean nausea length (with or without vomiting) of 3.8 months (approximately 15 weeks). This may reflect the difficulty in recording symptoms such as nausea, as well as in developing a classification tool for interpreting the length and severity of nausea. Zhou stated that classifying women as 'nauseous', regardless of whether they'd experienced 10 minutes or 10 hours per day, as an example of this difficulty (155). The discrepancy in the various research findings may be accounted for by the increasing sophistication in methods for measuring the variables. It may also be explained by differing methods used to investigate nausea and vomiting in pregnancy (26).

The mean length of vomiting for the NVP group is 10.5 weeks, a figure which supports previous literature, such as Vellacott et al. (18) who found a peak incidence of NVP occurring between week 8 and 12 of their sample. When observing the intensity of nausea and vomiting for the NVP group, our study found more women reporting vomiting than nausea up to week 10, yet from week 10 onwards there was a greater proportion of the NVP group experiencing nausea than vomiting. This is clearly illustrated in figure 6, appendix 1.

4.3.10 Nausea's effect on eating

Of the women who reported nausea, there was a near-equal division as to whether they began to eat more or less food as a result of that condition (48.1% More vs. 51.6% Less, table 2, appendix 1). The group that experienced NVP on the other hand had a higher proportion answering 'less' (68.2%). That vomiting and nausea should affect the appetite of women and cause them to eat less should perhaps come as no surprise.

Cancer patients experiencing nausea and vomiting from chemotherapy have reported a loss of appetite as a common side effect (232). A poor appetite and reduced food intake for women with nausea and/or NVP was also reported by Taggart (226) and others (233). Focus group studies on NVP are often full of expressions of distaste for food from the suffering women: *"…if I even think of food it makes me gag. That's when I vomit..."* (191). Yet the physiological contradictions which the NVP women seem to undergo are clearly expressed by

the same woman further in the interview where she states *"...the nausea seems to get worse if I don't eat.....I have pains in my stomach like I'm hungry, but the thought of food doesn't appeal to me..."* (191). This may explain why the NVP group, when asked if they'd begun to eat certain foods during the pregnancy, represented the highest proportion of those answering 'yes'. It has been reported in previous papers that during pregnancy there is an increased expression of the orexigenic peptide NPY and agouti-related peptide (AgRP) mRNA (234). It is thought that these changes result in an increase in food intake, despite the increased leptin levels produced by the placenta (leptin being an appetite suppressor). Contrary to expectation, pregnancy-induced leptin levels are not associated with a decrease of food intake in the gestating woman, instead, a pregnancy related leptin resistant state occurs (230;234). Whitehead et al. (36) reports that the development of dietary cravings was significantly associated with pregnant women experiencing nausea, although a loss of appetite has been shown to be just as likely. Evolutionary biologists such as Margie Profet, expounding the hypothesized prophylactic qualities NVP has in protecting the developing embryo from toxins contained in foods, suggests the decreased food intake is the body's way to protect the embryo and should therefore be adhered to *"…pregnancy sickness is supposed to alter a woman's diet radically…"* (21).

4.4 Dietary impact

4.4.1 Macronutrients

In the present study, there was a significant difference in energy intake between the three groups. The NN group ingested the lowest mean amount of kilojoules of the three (9 536 kJ), with the N group having a higher mean intake (9 710 kJ) and the NVP group having the highest mean intake (9 863 kJ, table 3). Of the few studies which exist in literature to examine dietary intake of nauseous and NVP women, this result corresponds with the findings of Pepper & Roberts (144). After obtaining dietary data from the United Nations Food and Agriculture Organization's food balance sheets for 21 countries and correlated that data with 56 NVP studies, they found a positive correlation between NVP rates and intakes of all macronutrients. Coad et al. (12) postulated that women suffering NVP may be increasing their nutrient intake to alleviate symptoms, which would also correspond to the intake distribution between groups such as those found here. Their research found that just over 30% of women reported their symptoms were alleviated by continually snacking, usually on carbohydrate-

rich foods (12). Most of the popular information sources aimed at women experiencing NVP, as well as most midwives' advice, usually recommend many frequent small snacks to help alleviate symptoms of nausea and/or NVP (24;176). On a study investigating pregnancy and eating behavior, Clark & Ogden (235) found pregnant women reported an improved body satisfaction, lowered attempts to control their food intake and eating more. In addition, they mentioned overeating as a method to relieve nausea. Furthermore, the reason a women in pregnancy modifies her diet may stem from different reasons. Schwab & Axelson (262) report women sometimes modify their diet due to concern for personal health, indigestion, or appetite changes related to aversions and cravings. Of interest are the studies which have found contradicting results. Latva-Pukkila et al. (177) compared diets of women with and without NVP (n=187). They found women with NVP to be consuming less energy overall, although this was not statistically significant.

When studying the dietary intake of pregnant women in North America, Picone et al. (236) concluded that low weight gain in pregnancy is associated with a lower food intake by the gestating woman. Yet the NVP group in our study had the lowest gestational weight gain, and the highest caloric intake. The differing results with Picone et al. (236) may be owing to the NVP condition, as their study made no mention of nausea or NVP, but on smoking and stress during pregnancy. Of particular note is their finding that stress negatively correlated with weight gain, but not with calorie intake. As many women who have experienced NVP testify, NVP is found to be a stressful episode by the gestating woman (24;134). Thought of in this way, these reported results present a profile of NVP much more in accordance with findings from this study, that is, a woman with high stress levels, eating more, yet gaining less weight than women with an uncomplicated pregnancy. Picone et al. (236) suggests it is due to stress causing an increased secretion of corticoids, catecholamines, growth hormones and prolactins, hormones known to impair insulin release and cause an increase in metabolic rate. If this metabolic scenario is combined with episodes of vomiting and food aversions, a low gestational weight gain amongst the NVP group seems easier to accept.

To illustrate the complexity of this issue, when observing the dietary intake of women during the course of their pregnancy, Beal (237) reported that nausea and NVP created an effect upon the caloric dietary intake that was not consistent in pattern or trend. Beal reports that of those women with minimal or moderate nausea, half the group ate more frequently while the other half reacted with less appetite and more aversions to food. Progressing into the third month

however, the majority had increased their intake. This exposes the importance of timing in the present study, as discussed earlier. Are the women in the master study sample answering questions in Beal's early 'half-half' phase, or have they shifted to the 'majority consuming more' phase? Whitehead et al. (36) reports that of 1000 women surveyed, over half of those who were nauseated reported that eating improved the symptom while only a third of the women who vomited said that eating improved their symptom. A similar complexity was noted by Taggart (226) who showed NVP-affected women sometimes had a poor appetite, although it being usual for their appetite to remain normal or even increased in spite of nausea and vomiting, concluding finally that the 'range of individual variation was wide'.

4.4.2 Carbohydrates

The women in the NVP group had the highest mean consumption of carbohydrates in actual weight (316.5 g), as well as energy percent (53.7%), differences that were statistically significant, as were the differences for added sugars (tables 3 and 4). That the NVP group consumes highest amounts of carbohydrate is supported by a number of papers and for differing reasons.

Jednak et al. (192) reported high carbohydrate meals exasperating gastric dysrhythmias, which can lead to nauseous effects. They found nausea was significantly reduced when subjects were fed high protein meals instead. The findings of this study suggest support for the results of the master study.

Carbohydrate-rich foods have previously been shown to elevate the production and release of brain serotonin which, in turn, elevates mood (198;199). It has also been discussed (see section 1.7.2) that people under periods of depression or distress tend to 'self-medicate' their depression with carbohydrate-rich foods (182). This strengthens the findings of the highest carbohydrate intakes being with the NVP group. Duncan & Harding (58) also reported carbohydrate to be effective in controlling or reducing the symptoms of NVP. As opposed to overall energy intake findings, Latva-Pukkila et al. (177) found that the women with NVP also consumed a higher amount of carbohydrates, although this was not statistically significant.

Of the food items explored from the FFQ (table 5), and Q38 (table 7), sugared soft drinks, foods rich in sugar, juices, vegetables and fruits are the highest carbohydrate containing items

(chocolate varies in sugar content and is considered a fat-containing food in this study). The NVP group had significantly higher intake of all these items from the FFQ analysis, except for juice. Likewise, the NVP group had significantly higher intakes of all these items based on the Q38 analysis, except for juice. These food items correspond with previous studies exploring foods which alleviate symptoms of NVP (58;185). When looking at the results of question 31 (Q31) concerning intake of carbohydrate rich foods (figure 2), the NVP group are observed as having the highest proportion 'eating more' of all the carbohydrate-rich foods, supporting the results of the FFQ and Q38.

4.4.3 Protein

The women from the NN group had a significantly higher intake of protein as energy percent (15.4%) whilst the NVP group had the lowest (15.2%, table 4). Even though the differences are small, this finding supports the literature showing that a high protein intake tended to reduce nausea and vomiting symptoms (24;191;192;196;197). It also supports the embryonic hypotheses theories, claiming NVP women tend to have aversions to protein meals (fish and meat in particular) (14;185).

Of the food items explored from the FFQ (table 5) and Q38 (table 7), milk, fish, meat, and the general food type 'foods rich in protein' (table 6) are the highest protein-containing food items in this study. In the FFQ, the NN group the highest intake of meat, the N group had the highest intakes of fish, and the NVP group the highest intake of milk. The Q38 food items showed the N group having the highest number choosing meat, and the NVP group having the highest number choosing milk and equal highest number (with NN group) choosing fish. Unlike previous studies showing lower intakes of meat and fish for NVP women (177), this present study shows no clear trend in food item consumption. Milk has often been cited as a food item craved during pregnancy, regardless of NVP condition (182;183;191), so the results concerning milk may possibly be disguising any trend. These results lend no support to the claims that nausea and vomiting in pregnancy act in a prophylactic capacity in order for the woman to avoid foods potentially high in toxins, such as meat and fish (14;21;76;185).

When looking at the results of Q31 concerning intake of protein-rich foods (figure 1), the NVP group represents the highest proportion as 'eating more' as well as 'eating less' of these food items. Perhaps the clearest indicator of an absence of a trend regarding protein-rich food items is the result from Q38 for 'foods rich in proteins'. Here it was observed that NVP had

the highest proportion of women choosing these foods, with the next highest being NN women, with the N group having the lowest proportion, although these differences were not statistically significant. Once again the results may be affected by the dietary intake patterns from the NVP group, described by Beal as being one 'that was not consistent in pattern or trend' (237).

4.4.4 Fat

Energy percent derived from fat was significantly highest in the NN group (31.4%), and lowest in the NVP group (30.9%). These findings are supported by reports that fatty foods are often avoided by women with nausea and NVP (185). This pattern is perhaps easier to see in Q31 results for fat-rich foods (figure 3), where the highest response to 'eating less' and 'stopped eating completely' concerning fat comes from the NVP group (25% and 1% respectively), as well as the smallest proportion 'eating as before' (64%). These findings also support research showing that nausea is related to delayed gastric emptying thought to be induced by the fat content of meals (192), although some papers relate fat directly to nausea, independent of gastric emptying rates (238).

When observing the results for fat constituents, saturated fat is perhaps the most interesting, since previous research has shown that the risk for HG increases considerably with higher saturated fat intake pre-pregnancy (33). Although the results from the FFQ are indicative of the dietary habits in week 22, it is tempting to believe the diet in week 22 is a loose reflection of the pre-pregnancy diet; this then lends some support to the relationship between saturated fat and NVP. Further support for this relationship comes from the studies showing saturated fat creating an increase in the circulating levels of estrogen (189;190). Estrogens are thought not only to cause nausea in vomiting directly (96), but also shown to delay gastric emptying and cause nausea and vomiting by inducing gastric reflux (12;97). Latva-Pukkila et al. (177) also found their NVP group to have less overall energy percent from fat when compared to those without symptoms, as well as lower energy percent from fat constituents.

4.5 Particular foods

4.5.1 Probiotics

It is of interest to note in the FFQ results (table 5) and in the Q38 results (tables 6 and 7), that the NN group consistently expressed significantly highest intakes of probiotic foods, mainly in the form of Biola and Cultura products. Research is presently ongoing regarding the benefits of probiotic consumption for humans, although few seem to focus upon the pregnant state. Of those relating to pregnancy, studies are focused upon the effect on spontaneous preterm delivery, necrotizing enterocolitis, and bacterial vaginosis (239-241). Unrelated to pregnancy, research suggests that probiotics may have a place as treatment in Helicobacter pylori infections and possibly as a prophylaxis against infection (242;243). It is tempting to speculate that the high intakes of probiotics by the NN group has a relevant connection to Helicobacter pylori protection, given that Helicobacter pylori has been suggested to be causative in symptoms of morning sickness (112), as well as HG (34). Additionally, research by Rautava et al. (244) into the probiotic effects upon anti- and pro- inflammatory cytokines, and the capacity probiotics have to modulate skewness in the Th1 and Th2 balance, provides a tangible basis to suggest probiotics may be causing a reduction in the symptoms of nausea or NVP suggested to be triggered by the immunological changes post conception.

4.5.2 Chocolate

Another food item of interest is chocolate (here chocolate refers to all confectionary, milk and dark chocolates consumed). The FFQ results (table 5) and the Q38 results (table 7), showed significantly higher intakes of chocolate and significantly highest proportion of women beginning to eat chocolate in the NN group. This finding is somewhat surprising, as the notion of pregnant women in distress ‘self-medicating’ themselves with carbohydrates and sweets (as discussed with carbohydrates) is a profile better suited to the N and NVP sufferers. Indeed, those groups have the highest intakes of sugared soft drinks (tables 5 and 7), and the highest proportion consuming ‘foods rich in sugar’ (table 6). Why is chocolate not included in this pattern? The results of Q31 regarding chocolate consumption (figure 3) show the NN group as the highest proportion ‘eating as before’ and lowest proportion ‘eating less’. This suggests that it may not be due to the NN women eating more chocolate, rather, the women in the N and NVP groups reducing their intake of chocolate. This idea is further supported by

the NVP group reporting the highest percent answering ‘stopped eating completely’ (3%), as well as in the ‘eating less’ category (39%). The aversion to chocolate as a mechanism of feto-protection was actually suggested by Profet (21), although the idea that chocolate contains toxins is only implied and not shown in studies, referring to the bitterness of unsweetened chocolate as ‘nature’s warning’ (21). This finding does, however, contradict the numerous mentions of chocolate as a food item craved by pregnant women (14;182;183;233), as well as a Finnish study that showed chocolate consumption during pregnancy was higher among those who felt themselves most stressed (245). More research may be needed to examine whether the ingestion of chocolate actually offers any protection from nausea and NVP. That chocolate has protective benefits for other pregnancy related maladies (hypertension and preeclampsia for instance) has been discussed in previous research (245;246).

4.5.3 Water and salty food

It has been suggested that pregnant women should consume 8-12 cups of fluids a day for adequate hydration (this amount includes fluids such as milk and juice, fluids in fruit and vegetables) (207). In this study, water refers to all water taken exclusively, regardless of whether it was tap, bottled, carbonated or otherwise. The results from the FFQ (table 5) showed the NN group consumes the highest amount of water, however, the results from Q38 (table 7) showed the NVP group as the highest proportion choosing to increase their intake of water. If the diet in week 22 is accepted as a loose reflection of the pre-pregnancy diet, these results represent a profile suggesting a relative lower intake of water pre-conception, with a large increase post-conception for NVP and N groups. That women in early pregnancy crave water has been shown in numerous studies (226;247), and it is mainly believed to be owing to the osmotic changes in early gestation and the consequent resetting of osmotic receptors and thirst thresholds, as well as the actions of the placental hormone relaxin (105;226;248-251). Additionally, conditions such as nausea and vomiting have also been shown to release hormones that act as a stimulus for drinking water, independent of the osmotic changes occurring during pregnancy (252;253). A related reflex to these osmotic changes in the gestating woman is the inducement of salt appetite (254-258) and increases in salty food intake (equated as a decreased salt sensitivity) have previously been reported (259-262). Salt appetite has also been shown to increase with increasing levels of estradiol and progesterone (263), both circulating in high levels in pregnant women, and in pregnant women experiencing vomiting (212). Table 6 showed the NVP group to have the highest increase in

foods rich in sour/salt taste, while the NN group had the least increase. The significance of the water and salt intake for the N and NVP group shall be discussed in section 4.7.2.

4.6 Birth outcomes

The main birth outcomes studied were length of gestation and size for gestational age, as well as sex of child, placenta weight and birth weight.

4.6.1 Length of gestation

The majority of all three groups of women delivered their child in the normal range of gestation (37-42 weeks), although there were significant differences. The NN group had the largest proportion of preterm births (early: 35-36 weeks, and very early births: 28-34 weeks). NVP has previously had conflicting reports in regards to gestation length. Latva-Pukkila et al. (177) reported that their NVP group had a shorter length of gestation compared to those without symptoms. Other studies found no association whatsoever (40;61), yet others have shown an association with a slightly longer duration of gestation (143;159;166;169). The present finding supports these latter studies. Tierson (149) maintained that a higher protein energy intake would result in a faster maturation of the infant, resulting in shorter gestation and a lighter birth weight. Energy from protein intake was significantly higher in the NN group, and these women did have the highest group proportion of the early and very early births, as well as the lightest babies. These results therefore add support to that theory, whilst simultaneously highlighting the importance of the mother-fetus dietary bond.

4.6.2 Size for gestational age

The NN group had the smallest proportion of large for gestational age (LGA) births, and the highest proportion of small for gestational age (SGA) births. These findings contradict most of the findings in related research to date. Bailit (264) found that the infants born to women suffering HG were more likely to be significantly small for gestational age, while Zhang & Cai (265) found that severe vomiting during pregnancy was modestly associated with infants who were small for gestational age.

Of related interest is a study by Ricci et al. (266), whose group recently investigated prenatal diet and size for gestational age. They found that women eating more fish and less meat are

associated with a lower risk of delivering an SGA baby. The results from the FFQ (table 5) and Q38 (table 7) show that the NN women had the highest intake of meat (in FFQ) and the lowest intake of fish (in FFQ), although significance was only found for fish. It should be noted that there are conflicting results regarding maternal diet and size for gestational age, usually due to issues such as confounders, pollutants contained in fish and geographic diversity (267-269).

4.6.3 Sex of child

There was a significantly higher birth of males amongst the NN group, a finding which corresponds with the previous studies observing gender and the incidence of nausea/NVP (43;51;168-171). The global long standing male-female birth ratio has been approximately 52% male: 48% female (270;271), although this study found a 48% male: 52% female ratio for the NVP group. Bremme et al. (104) has observed higher levels in both plasma and amniotic fluid of human chorionic gonadotrophin (hCG) to have been related to female gender during pregnancy. This finding together with the numerous findings linking elevated hCG with nausea and NVP strengthens the etiological suspicion of hCG's role in nausea and NVP. Schiff (271) suggested it may be elevated levels of serum estradiol, believed to be implicated with HG, which may also be connected to the altered sex ratio.

Rosenfeld & Roberts (272), performed experiments with mice, and found that a diet high in saturated fats but low in carbohydrate lead to the birth of significantly more male than female offspring. According to the FFQ results (table 4), the NN group consumed the least energy percent from carbohydrates and the highest energy percent from saturated fat compared to the other groups, as well as giving birth to a larger distribution of males, lending support to those laboratory findings.

4.6.4 Placental weight

In the present study the NN group had significantly lower mean placenta weight at the time of delivery than the N and NVP groups. Although this corresponds with theories claiming that NVP will cause a large placenta, the reasoning is based on NVP experiencing food restrictions (51;65). Unlike most other studies, this study found that the NVP group actually had the highest caloric intake, which ultimately contradicts that theory. Regardless of the functional process responsible for the correlation, a significantly heavier placental weight for

NVP women was previously found in another study (6). Other research reported that women consuming high intakes of carbohydrates, especially in the first trimester, produced small placentas at birth (64), a finding which this study does not support.

4.6.5 Birth weight

The mean birth weight was highest in the N group of women (3 619.1 g), and lowest in the NN group (3 540.5 g). This result tends to confirm the previous observations that nausea and NVP are associated with higher birth weights (16;61;83;159;167). These findings again support Tierson's (149) hypothesis of a high maternal protein intake resulting in faster maturation of the infant, shorter gestation and a lighter birth weight. Energy intake from protein was significantly higher in the NN group, who also had the highest group representation in preterm births, however another study focusing on maternal diet during gestation found no association regarding protein and birth weight (273). That the N group gave birth to the heaviest babies, and yet had the second highest mean energy intake (with NVP the highest), may be indicative of the level of nutrient loss the NVP group experienced through vomiting. As discussed in 4.2.2, the data gap between mean intake amounts reported by the NVP group and actual digested amounts may differ. Since nausea and nausea and vomiting are similar maladies (yet not exactly the same), it is expected the N and NVP groups will display similar intake values. If, in fact, the N group had the mean highest energy intake, having babies with the heaviest birth weight would be in accord with other studies (159;274;275).

Of interest are the many studies investigating maternal weight gain and infant birth weight. The epidemiologic evidence has clearly demonstrated a linear association between maternal weight gain and infant birth weight (276-278), although our results show the women with the highest gestational weight gain delivered infants with the lowest birth weight. There is a conspicuous absence of questions and research regarding the influence of nausea and NVP upon gestational weight gain and infant birth weight. Brawarsky et al. (276) investigated risk factors for excessive or inadequate gestational weight gain but failed to fully assess the role of nausea and or vomiting, stating only that 'nausea during the first trimester was common and not associated with weight gain'. Wells et al. (279) mentioned nausea as a risk factor for inadequate weight gain in pregnancy, although they make no mention of vomiting, or whether vomiting is implied in their definition of nausea. Latva-Pukkila et al. (177) found the women

with NVP in their study to have least gestational weight gain and the lightest infant birth weight when compared to women without NVP, however, neither outcome was statistically significant. The stress experienced by women with gestational nausea and NVP may explain the lower weight gain found in this study. Chomitz et al. (277) have illustrated that anxiety may increase metabolic expenditure or cause a mediated change in catecholamine or hormonal balances and may result in a lower gestational weight gain during pregnancy.

4.7 Etiological questions

Of the many etiological mechanisms hypothesized to be somehow associated with nausea and NVP, there are some that the present results are able to make comment upon.

4.7.1 Functional mechanism hypotheses

Embryo protection hypothesis

The embryo protection hypothesis (EPH) stated that the high toxins found in certain foods would cause more nausea/NVP symptoms in order to protect the embryo and mother from embryotoxic substances, thereby assigning better birth outcomes to women with NVP. Although the list of foods accused of containing potential embryotoxins is vast (14), most were classified as vegetables or meats (the latter in particular). The N and NVP groups consumed the highest amounts of vegetables and meat (although the NN group also had a high meat intake according to the FFQ), and had the heaviest and largest for gestational age babies, as well as the most births with a normal gestational age. If we accept that the N and NVP groups experienced aversions due to the toxins in their diet, then the results of this study would suggest some support for this hypothesis.

One alternative hypothesis claims food restrictions due to NVP, and the resultant lower insulin levels accompanying this situation, would equate to a larger placental growth (in compensation), as well as a larger birth weight. The N and NVP groups had the largest placentas and largest birth weights, but no food restrictions reported (in fact, they displayed the highest energy intake, although how much was actually digested, in particular regarding the NVP group, is difficult to assess). Little in this study supports this hypothesis.

4.7.2 Proximate mechanism hypotheses

Hyponatremia

As detailed in section 1.5.2, during the onset of pregnancy a number of changes in the body's biochemical environment take place resulting in a resetting of the body's homeostatic osmoreceptors. Homeostasis is mainly achieved via the hormones ADH and aldosterone (280). ADH release retains water in dehydration states, and aldosterone increases the reabsorption of sodium ions and water. As healthy women increase plasma volume during pregnancy, the increased plasma volume - which is also proportional to the size of the fetus - creates a hemodilution and subsequent state of hyponatremia, as the increased plasma volume creates an environment of decreased plasma osmolality (191). In the pregnant woman this decrease in plasma osmolality begins early in pregnancy, and is at its lowest by week 10, remarkably coinciding with the pattern of nausea and vomiting onset (248). Relaxin is a hormone also implicated in hyponatremia during pregnancy. Relaxin is secreted from the corpus luteum of the ovary and the placenta during pregnancy, with plasma levels elevated throughout pregnancy and dropping sharply at birth. Relaxin has been implicated in the resetting of osmoreceptors and the release of ADH (248). Circulating relaxin has also been shown to stimulate thirst, even in a hyponatremic state (249). A combination of hyponatremia and excessive thirst is prolonged by progesterone acting as a competitive binder to aldosterone receptors (281), a competition hypothesized to continue until aldosterone levels overcome the progesterone levels (184). The high aldosterone concentration further induce salt appetite in adults, and experiments using estradiol and progesterone report these hormones alone are adequate to produce an increase in salt appetite (263;282). Estradiol and progesterone have both been shown to be high in the first trimester of pregnancy (section 1.5.2). This evidence lends support to the salt and water intake modifications seen in the N and NVP group's diet.

Many studies have shown nausea and vomiting in non-pregnant people to be symptoms of mild to severe hyponatremia (108;253;283), and nausea itself has been shown to further stimulate the release of ADH, exasperating the hyponatremic state further (250;253).

Haugen et al. (284) recently found a protective effect against the risk of HG from the intake of water of approximately 200-450 g per day more than those women developing HG pre-conception. The results of our study indicate the NVP and N group may have consumed

relatively less amounts of water pre-conception than the NN group. Since the delay in resetting osmoreceptors is suggested as being the cause for extended hyponatremia in the pregnant state with nausea and/or vomiting resulting, it seems likely that an increased water intake pre-conception may prime the osmoreceptors for the changes forthcoming with pregnancy. Previous research has found an increased water intake to cause reductions in plasma osmolality and create a mild hyponatremia (285;286), which may be inducing the osmoreceptors to reset to a lower plasma osmolality, a model which would hypothetically prepare the body for the larger homeostatic changes to come with pregnancy and possibly avoid the nausea and NVP symptoms. The salt and water modifications of the N and NVP group's diet suggest the symptoms of some imbalance, most likely in connection with electrolyte homeostatic adjustment.

Gastric dysrhythmias

Gastric dysrhythmias are supposedly caused by the estrogen and progesterone hormones. This study unfortunately had no access to blood tests of the sample. However, a high dietary protein intake was believed to alleviate the dysrhythmia mechanism and cause reduced nausea and NVP symptoms. The NN group had significantly higher amounts of protein energy intake. There seems to be some support for this hypothesis in the study results.

Helicobacter Pylori

Helicobacter Pylori is suspected of being associated with nausea, NVP and HG. The NN group had significantly higher intakes of probiotic foods, shown to be effective against the helicobacter pylori bacteria strain. If Helicobacter pylori is implicated in nausea, NVP and HG, then there seems to be some support for this in the study results.

Mother's immune system

The maternal immune system has been claimed to have a role in NVP. Probiotics have been shown to modulate the Th1/Th2 cytokine balance, theoretically easing the immunologic response from the mother, thereby reducing NVP symptoms. Considering that the NN women had the highest intakes of probiotics, there seems to be some support for this hypothesis in the study results.

Psychological etiology

Psychological elements such as stress have been implicated in the etiology of nausea and NVP. The stress associated with marriage, if different to that in a co-habitant relationship, may account for why more married women are with nausea and NVP in this study compared to the other groups. Further support for stress related hormone surges have been their connection with lower gestational weight gain, and higher overall energy and carbohydrate intakes, both of which are applicable to the NVP group in this study.

4.8 Conclusion and future directions for research

The results of this study show there are statistical differences between the three groups of women profiled, concerning maternal demographics, dietary intakes and birth outcomes. What follows is a brief profile of each group:

Women with no symptoms: tended to be lighter in weight pre-pregnancy, and taller than the NVP group. They had the largest gestational weight gain, were higher educated and tended to be in a co-habitant relationship. They represented the highest proportion of smokers, both before and during pregnancy, and the highest proportion giving birth for the first time. Concerning diet, they had the least energy intake, yet their diet consisted of the highest protein and fat percent energy intake by comparison to the other groups. According to the FFQ they consumed the most probiotics, water, juice and chocolate; according to Q38 they again chose the highest probiotics, juice and chocolate, as well as equal highest amount of fish and least amount of meat. They were more likely to have a preterm birth, a child small for gestational age, a male child with the lightest placenta and lightest birth weight.

Women with nausea: tended to be the oldest and tallest women, with a gestational weight gain comparable to the NN group. They tended to be educated over 13 years and married, representing the highest proportion of non-smokers during pregnancy. They were the highest proportion having given birth previously. The majority experienced 5-10 weeks of nausea, and had the highest proportion eating more due to nausea. Concerning diet, they had an energy intake between NN and NVP, as with the energy percent intake of macronutrients. According to the FFQ they consumed the most fish and the least meat and sugared soft drinks; according to Q38 they chose the most foods helping with digestion, the least fish and the most meat. They had the highest proportion of deliveries in the 37-42 week range, the highest large

for gestational age births, an even sex ratio leaning towards males (51%), with the heaviest placenta and birth weight.

Women with nausea and vomiting: tended to be the youngest, with the highest proportion under 30 years old. They also tended to be the heaviest and shortest, and educated the least amount of years. They had the highest proportion of non-smokers three months prior to pregnancy and amongst the highest proportion non-smoking during pregnancy. The majority experienced most nausea in weeks 5-10, also vomiting the most in weeks 5-10. They had the highest proportion eating less due to nausea, yet had the highest proportion beginning to eat certain foods in the pregnancy (Q38). Concerning diet, they had the highest energy intake values of the three groups, with highest macronutrient intakes, except for mono-unsaturated fat. According to the FFQ they consumed the most milk, vegetables, fruit and sugared soft drinks; according to Q38 they chose the most foods reducing nausea, foods rich in proteins, foods rich in fat, foods rich in sugar, foods rich in artificial sweeteners, and foods rich in sour/salt taste. They consumed the most milk, water, vegetables, fruit, sugared soft drinks, and equal highest fish (shared with NN group). They tended to give birth to a female (51.7%), with a placenta weight and birth weight relatively high by comparison to the other groups.

Although this study has uncovered a great number of statistically significant findings in the course of analyses, the issue of clinical relevance has to be addressed in future studies. There are three areas which seem of clinical relevance:

1) Firstly, the field investigating probiotics and their exposure to women during gestation is still developing, and it is of interest to see whether the results here could be developed further. What effect does a high probiotic intake have on pregnant women? By what mechanisms could probiotics be protecting women from the symptoms of nausea and NVP?

2) Secondly, studies focusing upon the pre-adjustment of a woman's osmoreceptors prior to conceiving by virtue of water intake may provide beneficial assistance to women prone to nausea or NVP.

3) Third, if the effects of nausea and NVP are causing a higher birth weight and more incidences of babies being delivered large for gestational age, what effects in regards to

fetal programming (if any) does the nausea and NVP have upon the development or protection of chronic adult disease?

Conceiving and carrying a growing child inside is said to be one of the most exciting events in a woman's life. It also happens to be a period when her body is undergoing an enormous number of hormonal and physiological changes. What can be clearly seen in the results of this study is that the onset of symptoms for nausea and NVP has roots in many of these underlying changes taking place during gestation. It is as though the symptoms seen are an iceberg, indicative of some events larger and of greater importance that lurk beneath the surface. The notion that nausea and NVP can cause such distress for the mother to be, and yet – as can be seen here – bring forth positive birth outcomes, remains one of the most mystifying puzzles in obstetrics. Owing to the elusive nature of the proposed etiological mechanisms behind nausea and NVP, the suspicion that there are more than one trigger to this malady, and perhaps another agent responsible for its cessation, seems plausible.

The study has aimed to explore the relationship between nausea, with and without vomiting, in the pregnant state, and the resultant changes in the maternal diet. In addition, these changes have been related to resultant birth outcomes evidenced. The interactions between all three of these variables have proven to be entwined in such a way, that the continuity between cause and effect of NVP require further questioning. Future research on the interactions of these variables needs to address the problem in its entirety, and not just in the sum of its parts.

Reference List

1. Magnus P, Irgens LM, Haug K, Nystad W, Skjærven R, Stoltenberg C. Cohort profile: the Norwegian mother and child cohort study (MoBa). Int J Epidemiol 2006;35:1146.

2. Statistics Norway2010, *Statistical yearbook of Norway 2010*, [Online], Available: http://www.ssb.no/english/yearbook/yearbook_2010.pdf

3. Norwegian Institute of Public Health 2010, *Norwegian Mother and Child Cohort Study: revised protocol, end of enrolment - protocol II*, [Online], Available:http://www.fhi.no/dokumenter/be3db266ca.pdf

4. Ebrahimi N, Maltepe C, Einarson A. Optimal management of nausea and vomiting of pregnancy. International Journal of Women's Health 2010;2:241.

5. Furneaux EC, Langley-Evans AJ, Langley-Evans SC. Nausea and vomiting of pregnancy: endocrine basis and contribution to pregnancy outcome. Obstetrical & gynecological survey 2001;56:775.

6. Margaret Weigel M, Reyes M, Caiza ME, Tello N, Castro NP, Cespedes S, Duchicela S, Betancourt M. Is the nausea and vomiting of early pregnancy really feto-protective? J Perinat Med 2006;34:115-22.

7. Broussard CN, Richter JE. Nausea and vomiting of pregnancy. Gastroenterol Clin North Am 1998;27:123-51.

8. Fairweather DV. Nausea and vomiting in pregnancy. Am J Obstet Gynecol 1968;102:135.

9. *Kahun medical papyrus: manuscript for the health of mother and child*, [Online], 2010, Available: http://www.digitalegypt.ucl.ac.uk/med/birthpapyrus.html [accessed 17 January 2011]

10. Bayon HP. Ancient Pregnancy Tests in the Light of Contemporary Knowledge:(Section of History of Medicine). Proc R Soc Med 1939;32:1527.

11. Rhodes P. A medical appraisal of the Brontes. Bronte Soc Trans 1972;16:101-9.

12. Coad J, Al-Rasasi B, Morgan J. Nutrient insult in early pregnancy. Proc Nutr Soc 2002;61:51-9.

13. Hook EB. Influence of pregnancy on dietary selection. Int J Obes 1980;4:338.

14. Flaxman SM, Sherman PW. Morning sickness: A mechanism for protecting mother and embryo. The Quarterly Review of Biology 2000;75:113-48.

15. Järnfelt-Samsioe A. Nausea and vomiting in pregnancy: a review. Obstetrical & gynecological survey 1987;42:422.

16. Järnfelt-Samsioe A, Eriksson B, Waldenstrøm J, Samsioe G. Some new aspects on emesis gravidarum. Gynecol Obstet Invest 1985;19:174-86.

17. Merriam-Webster's Medical Dictionary. Merriam-Webster, Inc., *"morning sickness"*, [Online], 2010, Available: http://dictionary.reference.com/browse/morning sickness [accessed 9 January 2011]

18. Vellacott ID, Cooke EJA, James CE. Nausea and vomiting in early pregnancy. International Journal of Gynecology & Obstetrics 1988;27:57-62.

19. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. The British Journal of General Practice 1993;43:245.

20. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol 2000;182:931-7.

21. Profet M. Protecting your baby-to-be: preventing birth defects in the first trimester. Addison-Wesley, 1995.

22. Niebyl JR. Nausea and Vomiting in Pregnancy. N Engl J Med 2010;363:1544-50.

23. Gill SK, Maltepe C, Koren G. The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy. Can J Gastroenterol 2009;23:270.

24. Koch KL, Frissora CL. Nausea and vomiting during pregnancy. Gastroenterol Clin North Am 2003;32:201.

25. Scorza K, Williams A, Phillips JD, SHAW J. Evaluation of nausea and vomiting. Am Fam Physician 2007;76:76-84.

26. O'Brien B, Zhou Q. Variables related to nausea and vomiting during pregnancy. Birth 1995;22:93-100.

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

28. Miller F. Nausea and vomiting in pregnancy: the problem of perception--is it really a disease? Am J Obstet Gynecol 2002;186:S182.

29. Bashiri A, Neumann L, Maymon E, Katz M. Hyperemesis gravidarum: epidemiologic features, complications and outcome. European Journal of Obstetrics & Gynecology and Reproductive Biology 1995;63:135-8.

30. Arsenault MY, Lane CA, MacKinnon CJ, Bartellas E, Cargill YM, Klein MC, Martel MJ, Sprague AE, Wilson AK, The management of nausea and vomiting of pregnancy. Journal of obstetrics and gynaecology Canada: JOGC 2002;24:817.

31. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstetrics & Gynecology 2007;110:695.

32. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL. Hospitalizations during pregnancy among managed care enrollees. Obstetrics & Gynecology 2002;100:94.

33. Signorello LB, Harlow BL, Wang S, Erick MA. Saturated fat intake and the risk of severe hyperemesis gravidarum. Epidemiology 1998;9:636.

34. Penney DS. Helicobacter pylori and severe nausea and vomiting during pregnancy. The Journal of Midwifery & WomenÆs Health 2005;50:418-22.

35. Sherman PW, Flaxman SM. Nausea and vomiting of pregnancy in an evolutionary perspective. Am J Obstet Gynecol 2002;186:S190-S197.

36. Whitehead SA, Andrews PLR, Chamberlain GVP. Characterisation of nausea and vomiting in early pregnancy: a survey of 1000 women. Journal of Obstetrics & Gynecology 1992;12:364-9.

37. Semmens JP. Female sexuality and life situations: an etiologic psycho-socio-sexual profile of weight gain and nausea and vomiting in pregnancy. Obstetrics & Gynecology 1971;38:555-63.

38. Tayie FAK, Lartey A, Asibey-Berko E. Effects of pregnancy sickness on infant birth-weight and maternal weight-gain among Ghanaian women. Ecology of Food and Nutrition 2001;40:143-57.

39. Dundee JW, Chestnutt WN, Ghaly RG, Lynas AG. Traditional Chinese acupuncture: a potentially useful antiemetic? Br Med J (Clin Res Ed) 1986;293:583.

40. Chin RKH. Antenatal complications and perinatal outcome in patients with nausea and vomiting-complicated pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 1989;33:215-9.

41. Ostraff M, Anitoni K, Nicholson A, Booth GM. Traditional Tongan cures for morning sickness and their mutagenic/toxicological evaluations. J Ethnopharmacol 2000;71:201-9.

42. O'Brien B. Use of indigenous explanations and remedies to further understand nausea and vomiting during pregnancy. Health Care Women Int 1999;20:49-61.

43. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Epidemiology of nausea and vomiting of pregnancy: prevalence, severity, determinants, and the importance of race/ethnicity. BMC pregnancy and childbirth 2009;9:26.

44. Järnfelt-Samsioe A, Samsioe G, Velinder GM. Nausea and vomiting in pregnancy: a contribution to its epidemiology. Gynecol Obstet Invest 1983;16:221-9.

45. Källén B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. Acta Obstet Gynecol Scand 2003;82:916-20.

46. O'Brien B, Naber S. Nausea and vomiting during pregnancy: effects on the quality of women's lives. Birth 1992;19:138-43.

47. Kuo SH, Wang RH, Tseng HC, Jian SY, Chou FH. A comparison of different severities of nausea and vomiting during pregnancy relative to stress, social support, and maternal adaptation. The Journal of Midwifery & Women's Health 2007;52:e1-e7.

48. Mazzotta P, Maltepe C, Navioz Y, Magee LA, Koren G. Attitudes, management and consequences of nausea and vomiting of pregnancy in the United States and Canada. International Journal of Gynecology & Obstetrics 2000;70:359-65.

49. Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. Journal of Psychosomatic Obstetrics & Gynecology 2001;22:7-12.

50. Mazzotta P, Magee L, Koren G. The association between abortion and nausea and vomiting of pregnancy. Nausea and Vomiting of Pregnancy: State of the Art 2000;1:149-56.

51. Davis M. Nausea and vomiting of pregnancy: an evidence-based review. The Journal of Perinatal & Neonatal Nursing 2004;18:312.

52. Dictionary.com Unabridged. Random House, Inc., *"placenta"*, [Online], 2010, Available: http://dictionary.reference.com/browse/placenta [Accessed 18 January 2011]

53. Evain Brion D. Maternal endocrine adaptations to placental hormones in houmans. Acta Paediatr 1999;88:12-6.

54. Demir R, Kaufmann P, Castellucci M, Erbengi T, Kotowski A. Fetal vasculogenesis and angiogenesis in human placental villi. Cells Tissues Organs 1989;136:190-203.

55. Duc-Goiran P, Mignot TM, Bourgeois C, Ferre F. Embryo-maternal interactions at the implantation site: a delicate equilibrium. European Journal of Obstetrics & Gynecology and Reproductive Biology 1999;83:85-100.

56. Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. Emerg Infect Dis 2006;12:1638-43.

57. Lowry PJ. The placenta is simply a neuroendocrine parasite. J Neuroendocrinol 2008;20:700-4.

58. Duncan JW, Harding VJ. A report on the effect of high carbohydrate feeding on the nausea and vomiting of pregnancy. Can Med Assoc J 1918;8:1057.

59. Einarson TR, Navioz Y, Maltepe C, Einarson A, Koren G. Existence and severity of nausea and vomiting in pregnancy (NVP) with different partners. Journal of Obstetrics & Gynecology 2007;27:360-2.

60. Gadsby R, Barnie-Adshead AM, Jagger C. Pregnancy nausea related to women's obstetric and personal histories. Gynecol Obstet Invest 1997;43:108-11.

61. Weigel M, Weigel RM. Nausea and vomiting of early pregnancy and pregnancy outcome. An epidemiological study. BJOG: An International Journal of Obstetrics & Gynaecology 1989;96:1304-11.

62. Robinson J, Chidzanja S, Kind K, Lok F, Owens P, Owens J. Placental control of fetal growth. Reproduction, Fertility and Development 1995;7:333-44.

63. Gadd TS, Aitken RP, Wallace JM, Wathes DC. Effect of a high maternal dietary intake during mid-gestation on components of the utero-placental insulin-like growth factor (IGF) system in adolescent sheep with retarded placental development. Reproduction 2000;118:407.

64. Godfrey K, Robinson S, Barker DJP, Osmond C, Cox V. Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. BMJ 1996;312:410.

65. Lumey LH. Compensatory placental growth after restricted maternal nutrition in early pregnancy. Placenta 1998;19:105-11.

66. O'Brien B, Newton N. Psyche versus soma: Historical evolution of beliefs about nausea and vomiting during pregnancy. Journal of Psychosomatic Obstetrics & Gynecology 1991;12:91-120.

67. Dilorio C. First trimester nausea in pregnant teenagers: Incidence, characteristics, intervention. Nurs Res 1985;34:372.

68. O'Brien B, Relyea MJ, Taerum T. Efficacy of P6 acupressure in the treatment of nausea and vomiting during pregnancy. Am J Obstet Gynecol 1996;174:708-15.

69. Sherman PW. The levels of analysis. Anim Behav 1988.

70. Flaxman SM, Sherman PW. Morning sickness: adaptive cause or nonadaptive consequence of embryo viability? The American Naturalist 2008;172:54-62.

71. Hook EB. Nausea and Vomiting of Pregnancy-A Feto-Protective Mechanism Against Embryotoxins? Pediatr Res 1974;8:344.

72. Koul O. Plant allelochemicals and insect control: an antifeedant approach. Chemical Ecology of Phytophagous Insects Oxford and IBH, New Delhi 1993;51-80.

73. Walker JRL. Antimicrobial compounds in food plants. Natural Antimicrobial Systems and Food Preservation Wallingford (UK): CAB International 1994;181-204.

74. Profet M. Pregnancy sickness as adaptation: A deterrent to maternal ingestion of teratogens. The adapted mind: Evolutionary psychology and the generation of culture 1992;327.

75. Hook EB. Changes in tobacco smoking and ingestion of alcohol and caffeinated beverages during early pregnancy: Are these consequences, in part, of feto-protective mechanisms diminishing maternal exposure to embryotoxins. Birth defects: Risks and consequences 1976;173.

76. Fessler DMT, Reproductive immunosuppression and diet. An evolutionary perspective on pregnancy sickness and meat consumption. Current anthropology 2002;43:19-61.

77. Brown JE, Kahn ES, Hartman TJ. Profet, profits, and proof: Do nausea and vomiting of early pregnancy protect women from. Am J Obstet Gynecol 1997;176:179-81.

78. Sherman P, Flaxman S. Protecting Ourselves from Food Spices and morning sickness may shield us from toxins and microorganisms in the diet. American Sci 2001;89:142-51.

79. Forbes S. Pregnancy sickness and embryo quality. Trends in Ecology & Evolution 2002;17:115-20.

80. Moore T, Haig D. Genomic imprinting in mammalian development: a parental tug-of-war. Trends Genet 1991;7:45-9.

81. Forbes S. A natural history of families. Princeton Univ Pr, 2005.

82. Flaxman SM, Sherman PW. Is morning sickness maladaptive? Trends in ecology and evolution 2002;17:359-0.

83. Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with pregnancy outcome. Am J Obstet Gynecol 1986;155:1017.

84. Huxley RR. Nausea and vomiting in early pregnancy: its role in placental development. Obstetrics & Gynecology 2000;95:779.

85. Mori M, Amino N, Tamaki H, Miyai K, Tanizawa O. Morning sickness and thyroid function in normal pregnancy. Obstetrics & Gynecology 1988;72:355.

86. Barnea ER, Neubrun D, Shurtz-Swirski R. Effect of insulin on human chorionic gonadotrophin secretion by placental explants. Hum Reprod 1993;8:858.

87. Barker DJP. Fetal origins of coronary heart disease. BMJ 1995;311:171.

88. Godfrey KM. The Role of the Placenta in Fetal Programming--A Review. Placenta 2002;23:S20-S27.

89. Bauer MK, Harding JE, Bassett NS, Breier BH, Oliver MH, Gallaher BH, Evans PC, Woodall SM, Gluckman PD,Fetal growth and placental function. Mol Cell Endocrinol 1998;140:115-20.

90. Kind KL, Moore VM, Davies MJ. Diet around conception and during pregnancy-effects on fetal and neonatal outcomes. Reproductive biomedicine online 2006;12:532-41.

91. Deutsch JA. Pregnancy sickness as an adaptation to concealed ovulation. Riv Biol 1994;87:277.

92. Badell ML, Ramin SM, Smith JA. Treatment options for nausea and vomiting during pregnancy. Pharmacotherapy 2006;26:1273-87.

93. Soules MR, Hughes Jr CL, Garcia JA, Livengood CH, Prystowsky MR, Alexander III E. Nausea and vomiting of pregnancy: role of human chorionic gonadotropin and 17-hydroxyprogesterone. Obstetrics & Gynecology 1980;55:696.

94. Johansson EDB. Progesterone levels in peripheral plasma during the luteal phase of the normal human menstrual cycle measured by a rapid competitive protein binding technique. Acta Endocrinol (Copenh) 1969;61:592.

95. Soldin OP, Guo T, Weiderpass E, Tractenberg RE, Hilakivi-Clarke L, Soldin SJ. Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. Fertil Steril 2005;84:701-10.

96. Ingemanson CA, Jägerhorn M, Zizala J, Nilsson B, Zador G. Preliminary Results from a Swedish Multicenter Trial of a New Low Dose Combined Oral Contraceptive. Acta Obstet Gynecol Scand 1976;55:71-5.

97. Fisher RS, Roberts GS, Grabowski CJ, Cohen S. Altered lower esophageal sphincter function during early pregnancy. Gastroenterology 1978;74:1233.

98. Ylöstalo P, Kirkinen P, Heikkinen J, Mäentausta O, Järvinen PA. Gall bladder volume and serum bile acids in cholestasis of pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology 1982;89:59-61.

99. Johnson P, Samsioe G, Gustafson A. Studies in Cholestasis of Pregnancy. Acta Obstet Gynecol Scand 1975;54:77-84.

100. Goodwin M. Nausea and vomiting of pregnancy: an obstetric syndrome. Am J Obstet Gynecol 2002;186:S184-S189.

101. Lagiou P, Tamimi R, Mucci LA, Trichopoulos D, Adami HO, Hsieh CC. Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone: a prospective study. Obstetrics & Gynecology 2003;101:639.

102. Cole LA. New discoveries on the biology and detection of human chorionic gonadotropin. Reprod Biol Endocrinol 2009;7.

103. Spencer GSG, Robinson GM. Stimulation of placental, fetal and neonatal growth by thyroxine administration to pregnant rats. J Endocrinol 1993;139:275.

104. Bremme K, Eneroth P, Nilsson B. Hormone levels in amniotic fluid and fetal sex. Gynecol Obstet Invest 1982;14:245-62.

105. Dilorio C. The management of nausea and vomiting in pregnancy. The Nurse Practitioner 1988;13:23.

106. Schrier RW. Decreased effective blood volume in edematous disorders: What does this mean? J Am Soc Nephrol 2007;18:2028.

107. Chapman AB, Abraham WT, Zamudio S, Coffin C, Merouani A, Young D, Johnson A, Osorio F, Goldberg C, Moore LG, Dahms T, Schrier RW. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. Kidney Int 1998;54:2056-63.

108. Schrier RW. Does' asymptomatic hyponatremia'exist? Nature Reviews Nephrology 2010;6:185.

109. Van Thiel DH, Gavaler JS, Stremple J. Lower esophageal sphincter pressure in women using sequential oral contraceptives. Gastroenterology 1976;71:232.

110. Walsh JW, Hasler WL, Nugent CE, Owyang C. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. American Journal of Physiology-Gastrointestinal and Liver Physiology 1996;270:G506.

111. Jacoby EB, Porter KB. Helicobacter pylori infection and persistent hyperemesis gravidarum. Am J Perinatol 1999;16:85-8.

112. Reymunde A, Santiago N, Perez L. Helicobacter pylori and severe morning sickness. The American Journal of Gastroenterology 2001;96:2279-80.

113. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes 2002;26:1407-33.

114. Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T, Nakao K, Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nat Med 1997;3:1029-33.

115. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM, Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543.

116. Considine RV, Caro JF. Leptin: genes, concepts and clinical perspective. Hormone Research in Paediatrics 1996;46:249-56.

117. Unsel N, Benian A, Erel T. Leptin levels in women with hyperemesis gravidarum. International Journal of Gynecology & Obstetrics 2004;84:162-3.

118. Arslan EO, Cengiz L, Arslan M. Thyroid function in hyperemesis gravidarum and correlation with serum leptin levels. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2003;83:187.

119. Aka N, Atalay S, Sayharman S, Kiliç D, Köse G, Küçüközkan T. Leptin and leptin receptor levels in pregnant women with hyperemesis gravidarum. Aust N Z J Obstet Gynaecol 2006;46:274-7.

120. Chou FH, Chan TF, Chin CC, Chen YL, Shen CJ, Kuo SH. Biomarkers and Perceived Emotional Stress in Early-Stage Pregnant Taiwanese Women With Nausea and Vomiting. Biological Research For Nursing 2010.

121. Samsioe G, Crona N, Enk L, Järnfelt-Samsioe A. Does position and size of corpus luteum have any effect on nausea of pregnancy? Acta Obstet Gynecol Scand 1986;65:427-9.

122. Mellor, A. L. and Munn, D. H. Extinguishing maternal immune responses during pregnancy: implications for immunosuppression. Seminars in Immunology 13(4), 213-218. 2001.

123. Brabin BJ. Epidemiology of infection in pregnancy. Review of Infectious Diseases 1985;7:579.

124. Lim KJH, Odukoya OA, Li TC, Cooke ID. Cytokines and immuno-endocrine factors in recurrent miscarriage. Hum Reprod Update 1996;2:469.

125. Szekeres-Bartho J, Halasz M, Palkovics T. Progesterone in pregnancy; receptor-ligand interaction and signaling pathways. J Reprod Immunol 2009;83:60-4.

126. Szekeres-Bartho J. Endocrine regulation of the immune system during pregnancy. Immunology of Pregnancy 1992;151.

127. Haig D. Altercation of generations: genetic conflicts of pregnancy. American journal of reproductive immunology (New York, NY: 1989) 1996;35:226.

128. Wolkind S, Zajicek E. Psycho-social correlates of nausea and vomiting in pregnancy. J Psychosom Res 1978;22:1-5.

129. Uddenberg N, Nilsson A, Almbren PE. Nausea in pregnancy: psychologic and psychosomatic aspects. J Psychosom Res 1971;15:269.

130. Buckwalter JG, Simpson SW. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. Am J Obstet Gynecol 2002;186:S210-S214.

131. Deuchar N. Nausea and vomiting in pregnancy: a review of the problem with particular regard to psychological and social aspects. BJOG: An International Journal of Obstetrics & Gynaecology 1995;102:6-8.

132. El-Mallakh RS, Liebowitz NR, Hale MS. Hyperemesis gravidarum as conversion disorder. The Journal of nervous and mental disease 1990;178:655.

133. Iancu J, Kotler M, Spivak B, Radwan M, Weizman A. Psychiatric aspects of hyperemesis gravidarum. Psychother Psychosom 1994;61:143-9.

134. Iatrakis GM, Sakellaropoulos GG, Kourkoubas AH, Kabounia SE. Vomiting and nausea in the first 12 weeks of pregnancy. Psychother Psychosom 1988;49:22-4.

135. Dooley L. Psychoanalysis of Charlotte Bronte, as a Type of the Woman of Genius. The American Journal of Psychology 1920;31:221-72.

136. Seng JS, Schrot JA, van De Ven C, Liberzon I. Service use data analysis of pre-pregnancy psychiatric and somatic diagnoses in women with hyperemesis gravidarum. Journal of Psychosomatic Obstetrics & Gynecology 2007;28:209-17.

137. Simpson SW, Goodwin TM, Robins SB, Rizzo AA, Howes RA, Buckwalter DK, Buckwalter JG. Psychological factors and hyperemesis gravidarum. Journal of Women's Health & Gender-Based Medicine 2001;10:471-7.

138. Apfel RJ, Kelley SF, Frankel FH. The role of hypnotizability in the pathogenesis and treatment of nausea and vomiting of pregnancy. Journal of Psychosomatic Obstetrics & Gynecology 1986;5:179-86.

139. Goodwin TM. Nausea and vomiting of pregnancy. ACOG Practice Bulletin 52. American College of Obstetricians and Gynecologists. Obstet Gynecol 2004;103:803-15.

140. Verberg MFG, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update 2005;11:527.

141. Minturn L, Weiher AW. The influence of diet on morning sickness: a cross-cultural study. Med Anthropol 1984;8:71.

142. Corey LA, Berg K, Solaas MH, Nance WE. The epidemiology of pregnancy complications and outcome in a Norwegian twin population. Obstetrics & Gynecology 1992;80:989.

143. Klebanhoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstetrics & Gynecology 1985;66:612.

144. Pepper GV, Craig Roberts S. Rates of nausea and vomiting in pregnancy and dietary characteristics across populations. Proceedings of the Royal Society B: Biological Sciences 2006;273:2675.

145. Oota H, Pakstis AJ, Bonne-Tamir B, Goldman T, Grigorenko E, Kajuna SL, Karoma NJ, Kungulilo S, Lu RB, Odunsi K, Okonufua F, Zhukova OV, Kidd JR, Kidd KK.The evolution and population genetics of the ALDH2 locus: random genetic drift, selection, and low levels of recombination. Ann Hum Genet 2004;68:93-109.

146. Walker ARP, Walker BF, Jones J, Verardi M, Walker C. Nausea and vomiting and dietary cravings and aversions during pregnancy in South African women. BJOG: An International Journal of Obstetrics & Gynaecology 1985;92:484-9.

147. Zhang J, Cai W. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. Epidemiology 1991;2:454.

148. Louik C, Hernandez Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy: maternal characteristics and risk factors. Paediatr Perinat Epidemiol 2006;20:270-8.

149. Tierson FD. Nausea and Vomiting of Pregnancy and its Association with Pregnancy Outcome. Nausea and Vomiting of Pregnancy, State of the Art 2000.

150. Ben-Aroya Z, Lurie S, Segal D, Hallak M, Glezerman M. Association of nausea and vomiting in pregnancy with lower body mass index. European Journal of Obstetrics & Gynecology and Reproductive Biology 2005;118:196-8.

151. Linseth G, Vari P. Nausea and vomiting in late pregnancy. Health Care Women Int 2005;26:372-86.

152. 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.Two naturally occurring variants of the serotonin receptor gene HTR3C are associated with nausea in pregnancy. Acta Obstet Gynecol Scand 2010;89:7-14.

153. Petitti DB. Nausea and pregnancy outcome. Birth 1986;13:223-6.

154. Paarlberg KM, Vingerhoets A, Passchier J, Heinen A, Dekker GA, Van Geijn HP. Psychosocial factors as predictors of maternal well-being and pregnancy-related complaints. Journal of Psychosomatic Obstetrics & Gynecology 1996;17:93-102.

155. Zhou Q, O'Brien B, Relyea J. Severity of Nausea and Vomiting During Pregnancy: What Does It Predict? Birth 1999;26:108-14.

156. Weigel M, Weigel RM. The association of reproductive history, demographic factors, and alcohol and tobacco consumption with the risk of developing nausea and vomiting in early pregnancy. Am J Epidemiol 1988;127:562.

157. Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. Am J Perinatol 2000;17:207-18.

158. Basso O, Olsen J. Sex ratio and twinning in women with hyperemesis or pre-eclampsia. Epidemiology 2001;12:747-9.

159. Brandnes JM. First-trimester nausea and vomiting as related to outcome of pregnancy. Obstetrics & Gynecology 1967;30:427.

160. Järnfelt-Samsioe A, Eriksson B, Leissner KH, Samsioe G. Gallbladder disease related to use of oral contraceptives and nausea in pregnancy. South Med J 1985;78:1040.

161. Trogstad LIS, Stoltenberg C, Magnus P, Skjærven R, Irgens LM. Recurrence risk in hyperemesis gravidarum. BJOG: An International Journal of Obstetrics & Gynaecology 2005;112:1641-5.

162. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. Obstetrics & Gynecology 2006;107:285.

163. Medalie JH. Relationship between nausea and/or vomiting in early pregnancy and abortion. Lancet 1957;273:117.

164. Fenster L, Eskenazi B, Windham GC, Swan SH. Caffeine consumption during pregnancy and fetal growth. Am J Public Health 1991;81:458.

165. Weigel RM, Weigel M. Nausea and vomiting of early pregnancy and pregnancy outcome. A meta analytical review. BJOG: An International Journal of Obstetrics & Gynaecology 1989;96:1312-8.

166. Ananth CV, Rao PS. Epidemiology of nausea and vomiting of pregnancy and its relation to fetal outcome in a rural area. J Trop Pediatr 1993;39:313.

167. Little RE, Hook EB. Maternal alcohol and tobacco consumption and their association with nausea and vomiting during pregnancy. Acta Obstet Gynecol Scand 1979;58:15-7.

168. Källén B. Hyperemesis during pregnancy and delivery outcome: a registry study. European Journal of Obstetrics & Gynecology and Reproductive Biology 1987;26:291-302.

169. Czeizel AE, Puho E. Association between severe nausea and vomiting in pregnancy and lower rate of preterm births. Paediatr Perinat Epidemiol 2004;18:253-9.

170. Hsu CD, Witter FR. Fetal sex and severe hyperemesis gravidarum. Int J Gynaecol Obstet 1993;40:63-4.

171. Askling J, Erlandsson G, Kaijser M, Akre O, Ekbom A. Sickness in pregnancy and sex of child. The Lancet 1999;354:2053.

172. Chan RL, Olshan AF, Savitz DA, Herring AH, Daniels JL, Peterson HB, Martin SL. Maternal influences on nausea and vomiting in early pregnancy. Maternal and child health journal 2009;1-6.

173. King TL, Murphy PA. Evidence-based approaches to managing nausea and vomiting in early pregnancy. Journal of midwifery & women's health 2009;54:430-44.

174. Ulbricht CE, Basch EM, Standard N. Natural Standard herb & supplement reference: evidence-based clinical reviews. Mosby, 2005.

175. Vutyavanich T, Wongtrangan S, Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: A randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol 1995;173:881-4.

176. Wills G, Forster D. Nausea and vomiting in pregnancy: what advice do midwives give? Midwifery 2008;24:390-8.

177. Latva-Pukkila U, Isolauri E, Laitinen K. Dietary and clinical impacts of nausea and vomiting during pregnancy. Journal of Human Nutrition and Dietetics 2010;23:69-77.

178. Al-Rasasi, B., Siegler, R., Nichols, J., Coad, J., and Morgan, J. Dietary cravings and aversions in pregnancy. Proceedings-Nutrition Society of London 60, 136.

179. Giles A. The longings of pregnant women. Obstetrical Society of London Transactions 1893;35:242-9.

180. Dickens G, Trethowan WH. Cravings and aversions during pregnancy. J Psychosom Res 1971;15:259-68.

181. Harries JM, Hughes TF. Enumeration of the "cravings" of some pregnant women. Br Med J 1958;2:39.

182. Weingarten HP, Elston D. The phenomenology of food cravings. Appetite 1990;15:231-46.

183. Fairburn CG, Stein A, Jones R. Eating habits and eating disorders during pregnancy. Psychosom Med 1992;54:665.

184. Worthington-Roberts B, Little RE, Lambert MD, Wu R. Dietary cravings and aversions in the postpartum period. J Am Diet Assoc 1989;89:647.

185. Bayley TM, Dye L, Jones S, DeBono M, Hill AJ. Food cravings and aversions during pregnancy: relationships with nausea and vomiting. Appetite 2002;38:45-51.

186. Bryan FL. Risks of practices, procedures and processes that lead to outbreaks of foodborne diseases. Journal of food protection (USA) 1988.

187. Roberts D. Trends in food poisoning. Food Science and Technology Today 1990;2:28-34.

188. Sockett PN. The epidemiology and costs of diseases of public health significance, in relation to meat and meat products. Journal of food safety 1995;15:91-112.

189. Goldin BR, Adlercreutz H, Gorbach SL, Woods MN, Dwyer JT, Conlon T, Bohn E, Gershoff SN. The relationship between estrogen levels and diets of Caucasian American and Oriental immigrant women. The American journal of clinical nutrition 1986;44:945.

190. Rose DP, Boyar AP, Cohen C, Strong LE. Effect of a low-fat diet on hormone levels in women with cystic breast disease. I. Serum steroids and gonadotropins. J Natl Cancer Inst 1987;78:623.

191. Voda AM, Randall MP. Nausea and vomiting of pregnancy:" Morning sickness.". Concept clarification in nursing 1982;133-66.

192. Jednak MA, Shadigian EM, Kim MS, Woods ML, Hooper FG, Owyang C, Hasler WL. Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. American Journal of Physiology-Gastrointestinal and Liver Physiology 1999;277:G855.

193. Collins PA. Serum constituents in pregnancy including 4 cases with elevated alkaline phosphatase levels. Clin Biochem 1981;14:98.

194. Newman RL. Serum electrolytes in pregnancy, parturition, and puerperium. Obstetrics & Gynecology 1957;10:51.

195. Robertson EG, Cheyne GA. Plasma biochemistry in relation to oedema of pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology 1972;79:769-76.

196. Levine ME, Muth ER, Williamson MJ, Stern RM. Protein predominant meals inhibit the development of gastric tachyarrhythmia, nausea and the symptoms of motion sickness. Alimentary pharmacology & therapeutics 2004;19:583-90.

197. Rieber N, Mischler D, Schumacher V, Muth E, Bischoff S, Klosterhalfen S, Zipfel S, Enck P. Acute tryptophan depletion increases experimental nausea but also induces hunger in healthy female subjects. Neurogastroenterology & Motility 2010;22:752-e220.

198. Pelchat ML. Of human bondage: Food craving, obsession, compulsion, and addiction. Physiology & Behavior 2002;76:347-52.

199. Wurtman RJ, Wurtman JJ. Carbohydrate craving, obesity and brain serotonin. Appetite 1986.

200. Wurtman JJ. Neurotransmitter control of carbohydrate consumption. Ann N Y Acad Sci 1985;443:145-51.

201. Morley JE, Blundell JE. The neurobiological basis of eating disorders: some formulations. Biol Psychiatry 1988;23:53-78.

202. Godfrey KM, Barker DJP, Robinson S, Osmond C. Maternal birthweight and diet in pregnancy in relation to the infant's thinness at birth. BJOG: An International Journal of Obstetrics & Gynaecology 1997;104:663-7.

203. Anderson AS. Pregnancy as a time for dietary change? Proc Nutr Soc 2001;60:497-504.

204. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. Br Med J 1991;303:1019.

205. Barker DJ. The fetal and infant origins of adult disease. Br Med J 1990;301:1111.

206. Law CM, Gordon GS, Shiell AW, Barker DJP, Hales CN. Thinness at birth and glucose tolerance in seven year old children. Diabet Med 1995;12:24-9.

207. Shapira N. Prenatal nutrition: a critical window of opportunity for mother and child. 2008.

208. Kunz, L. H. and King, J. C. Impact of maternal nutrition and metabolism on health of the offspring. Seminars in Fetal and Neonatal Medicine 2007; 12(1):71-77.

209. Nijland MJ, Ford SP, Nathanielsz PW. Prenatal origins of adult disease. Curr Opin Obstet Gynecol 2008;20:132.

210. Campbell DM, Hall MH, Barker DJP, Cross J, Shiell AW, Godfrey KM. Diet in pregnancy and the offspring's blood pressure 40 years later. BJOG: An International Journal of Obstetrics & Gynaecology 1996;103:273-80.

211. Martin RP, Noyes J, Wisenbaker J, Huttunen MO. Prediction of early childhood negative emotionality and inhibition from maternal distress during pregnancy. Merrill-Palmer Quarterly 1999;45.

212. Nicolaidis S, Galaverna O, Metzler CH. Extracellular dehydration during pregnancy increases salt appetite of offspring. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 1990;258:R281.

213. Meltzer HM, Brantsæter AL, Ydersbond TA, Alexander J, Haugen M. Methodological challenges when monitoring the diet of pregnant women in a large study: experiences from the Norwegian Mother and Child Cohort Study (MoBa). Maternal & Child Nutrition 2008;4:14-27.

214. Brantsæter AL, Haugen M, Alexander J, Meltzer HM. Validity of a new food frequency questionnaire for pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). Maternal & Child Nutrition 2008;4:28-43.

215. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand 2000;79:440-9.

216. Chen Y, Ahsan H, Parvez F, Howe GR. Validity of a food-frequency questionnaire for a large prospective cohort study in Bangladesh. Br J Nutr 2004;92:851-9.

217. Heath ALM, Skeaff CM, Gibson RS. The relative validity of a computerized food frequency questionnaire for estimating intake of dietary iron and its absorption modifiers. Eur J Clin Nutr 2000;54:592-9.

218. Forsum E, Kabir N, Sadurskis A, Westerterp K. Total energy expenditure of healthy Swedish women during pregnancy and lactation. The American journal of clinical nutrition 1992;56:334.

219. De Vries JH, Zock PL, Mensink RP, Katan MB. Underestimation of energy intake by 3-d records compared with energy intake to maintain body weight in 269 nonobese adults. The American journal of clinical nutrition 1994;60:855.

220. Rothman KJ, Greenland S. Validity and generalizability in epidemiologic studies. 1988.

221. Nilsen RM, Vollset SE, Gjessing HK, Skjærven R, Melve KK, Schreuder P, Alsaker ER, Haug K, Daltveit AK, Magnus P.Self selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol 2009;23:597-608.

222. Wilson DL, Barnes M, Ellett L, Permezel M, Jackson M, Crowe SF. Compromised verbal episodic memory with intact visual and procedural memory during pregnancy. J Clin Exp Neuropsychol 2011:1-12.

223. Janes C, Casey P, Huntsdale C, Angus G. Memory in pregnancy. I: Subjective experiences and objective assessment of implicit, explicit and working memory in primigravid and primiparous women. Journal of Psychosomatic Obstetrics & Gynecology 1999;20:80-7.

224. Keenan PA, Yaldoo DT, Stress ME, Fuerst DR, Ginsburg KA. Explicit memory in pregnant women. Am J Obstet Gynecol 1998;179:731-7.

225. Vilming B, Nesheim BI. Hyperemesis gravidarum in a contemporary population in Oslo. Acta Obstet Gynecol Scand 2000;79:640-3.

226. Taggart N. Food habits in pregnancy. Proc Nutr Soc 1961;20:35-40.

227. Mastekaasa A. Is marriage/cohabitation beneficial for young people? Some evidence on psychological distress among Norwegian college students. Journal of community & applied social psychology 2006;16:149-65.

228. Bernstein L, Pike MC, Lobo RA, Depue RH, Ross RK, Henderson BE. Cigarette smoking in pregnancy results in marked decrease in maternal hCG and oestradiol levels. BJOG: An International Journal of Obstetrics & Gynaecology 1989;96:92-6.

229. Arnholdt H, Meisel F, Fandrey K, Löhrs U. Proliferation of villous trophoblast of the human placenta in normal and abnormal pregnancies. Virchows Archiv B Cell Pathology Zell-pathologie 1991;60:365-72.

230. Caprio M, Fabbrini E, Isidori AM, Aversa A, Fabbri A. Leptin in reproduction. Trends in Endocrinology and Metabolism 2001;12:65-72.

231. Reseland JE, Mundal HH, Hollung K, Haugen F, Zahid N, Anderssen SA, Drevon CA. Cigarette smoking may reduce plasma leptin concentration via catecholamines. Prostaglandins, leukotrienes and essential fatty acids 2005;73:43-9.

232. Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM, Tattersall MH. On the receiving end--patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol 1983;19:203-8.

233. Pope JF, Skinner JD, Carruth BR. Adolescents' self-reported motivations for dietary changes during pregnancy. Journal of Nutrition Education 1997;29:137-44.

234. Grattan DR, Ladyman SR, Augustine RA. Hormonal induction of leptin resistance during pregnancy. Physiology & Behavior 2007;91:366-74.

235. Clark M, Ogden J. The impact of pregnancy on eating behaviour and aspects of weight concern. Int J Obes 1999;23:18-24.

236. Picone TA, Allen LH, Schramm MM, Olsen PN. Pregnancy outcome in North American women. I. Effects of diet, cigarette smoking, and psychological stress on maternal weight gain. The American journal of clinical nutrition 1982;36:1205.

237. Beal VA. Nutritional studies during pregnancy. I. Changes in intakes of calories, carbohydrates, fat, protein, and calcium. J Am Diet Assoc 1971;58:312.

238. Feinle C, Grundy D, Read NW. Fat increases vection-induced nausea independent of changes in gastric emptying. Physiology & Behavior 1995;58:1159-65.

239. Myhre R, Brantsæter AL, Myking S, Gjessing HK, Sengpiel V, Meltzer HM, Haugen M, Jacobsson B. Intake of probiotic food and risk of spontaneous preterm delivery. The American journal of clinical nutrition 2011;93:151.

240. Braga TD, da Silva GAP, de Lira PIC, de Carvalho Lima M. Efficacy of Bifidobacterium breve and Lactobacillus casei oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. The American journal of clinical nutrition 2011;93:81.

241. Shalev E. Ingestion of probiotics: Optional treatment of bacterial vaginosis in pregnancy. IMAJ-RAMAT GAN- 2002;4:357-60.

242. Yasar B, Abut E, Kayadibi H, Toros B, Sezikli M, Akkan Z, Keskin O, Ovunc-Kurdas O. Efficacy of probiotics in Helicobacter pylori eradication therapy. Turkish Journal of Gastroenterology 2010;21:212-7.

243. Hamilton-Miller JMT. The role of probiotics in the treatment and prevention of Helicobacter pylori infection. Int J Antimicrob Agents 2003;22:360-6.

244. Rautava S, Kalliomäki M, Isolauri E. New therapeutic strategy for combating the increasing burden of allergic disease: Probiotics--A Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota (NAMI) Research Group report. J Allergy Clin Immunol 2005;116:31-7.

245. Strandberg T, Järvenpä AL, Vanhanen H, McKeigue PM. Does chocolate relieve Christmas season stress? Duodecim; lääketieteellinen aikakauskirja 1999;115:2653.

246. Triche EW, Grosso LM, Belanger K, Darefsky AS, Benowitz NL, Bracken MB. Chocolate consumption in pregnancy and reduced likelihood of preeclampsia. Epidemiology (Cambridge, Mass) 2008;19:459.

247. Ershow AG, Brown LM, Cantor KP. Intake of tapwater and total water by pregnant and lactating women. Am J Public Health 1991;81:328.

248. Weisinger RS, Burns P, Eddie LW, Wintour EM. Relaxin alters the plasma osmolality-arginine vasopressin relationship in the rat. J Endocrinol 1993;137:505.

249. McKinley MJ, Cairns MJ, Denton DA, Egan G, Mathai ML, Uschakov A, Wade JD, Weisinger RS, Oldfield BJ. Physiological and pathophysiological influences on thirst. Physiology & Behavior 2004;81:795-803.

250. Lindheimer MD, Barron WM, Davison JM. Osmoregulation of thirst and vasopressin release in pregnancy. American Journal of Physiology-Renal Physiology 1989;257:F159.

251. Davison JM, Gilmore EA, Durr J, Robertson GL, Lindheimer MD. Altered osmotic thresholds for vasopressin secretion and thirst in human pregnancy. American Journal of Physiology-Renal Physiology 1984;246:F105.

252. Fried LF, Palevsky PM. Hyponatremia and Hypernatremia. Med Clin North Am 1997;81:585-609.

253. Kawai N, Baba A, Suzuki T, Shiraishi H. Roles of arginine vasopressin and atrial natriuretic peptide in polydipsia-hyponatremia of schizophrenic patients. Psychiatry Res 2001;101:39-45.

254. Barelare B, Richter CP. Increased sodium chloride appetite in pregnant rats. American Journal of Physiology--Legacy Content 1937;121:185.

255. Pike RL, Yao C. Increased sodium chloride appetite during pregnancy in the rat. The Journal of nutrition 1971;101:169.

256. Crystal SR, Bernstein IL. Infant salt preference and mother's morning sickness. Appetite 1998;30:297.

257. Gardenswartz MH, Berl T, National Kidney Foundation. Drug induced changes in water excretion. National Kidney Foundation, 1981.

258. Robertson GL. Thirst and vasopressin function in normal and disordered states of water balance. The Journal of laboratory and clinical medicine 1983;101:351.

259. Skinner JD, Pope JF, Carruth BR. Alterations in adolescents' sensory taste preferences during and after pregnancy. J Adolesc Health 1998;22:43-9.

260. Brown JE, Toma RB. Taste changes during pregnancy. The American journal of clinical nutrition 1986;43:414.

261. Kolble N, Hummel T, von Mering R, Huch A, Huch R. Gustatory and olfactory function in the first trimester of pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 2001;99:179-83.

262. Schwab EB, Axelson ML. Dietary changes of pregnant women: compulsions and modifications. Ecology of Food and Nutrition 1984;14:143-53.

263. Kensicki E, Dunphy G, Ely D. Estradiol increases salt intake in female normotensive and hypertensive rats. J Appl Physiol 2002;93:479.

264. Bailit JL. Hyperemesis gravidarium: Epidemiologic findings from a large cohort. Am J Obstet Gynecol 2005;193:811-4.

265. Zhang J, Cai W. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. Epidemiology 1991;454-7.

266. Ricci E, Chiaffarino F, Cipriani S, Malvezzi M, Parazzini F. Diet in pregnancy and risk of small for gestational age birth: results from a retrospective case control study in Italy. Maternal & Child Nutrition.

267. Mitchell E, Robinson E, Clark PM, Becroft DM, Glavish N, Pattison NS, Pryor JE, Thompson JM, Wild CJ. Maternal nutritional risk factors for small for gestational age babies in a developed country: a case-control study. Archives of Disease in Childhood Fetal and Neonatal Edition 2004;89:F431.

268. Olsen SF, Secher NJ. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. BMJ 2002;324:447.

269. Halldorsson TI, Meltzer HM, Thorsdottir I, Knudsen V, Olsen SF. Is high consumption of fatty fish during pregnancy a risk factor for fetal growth retardation? A study of 44,824 Danish pregnant women. Am J Epidemiol 2007;166:687.

270. Davis DL, Gottlieb MB, Stampnitzky JR. Reduced ratio of male to female births in several industrial countries. JAMA: The Journal of the American Medical Association 1998;279:1018.

271. Schiff MA, Reed SD, Daling JR. The sex ratio of pregnancies complicated by hospitalisation for hyperemesis gravidarum. BJOG: An International Journal of Obstetrics & Gynaecology 2004;111:27-30.

272. Rosenfeld CS, Roberts RM. Maternal diet and other factors affecting offspring sex ratio: a review. Biol Reprod 2004;71:1063.

273. Mathews F, Yudkin P, Neil A. Influence of maternal nutrition on outcome of pregnancy: prospective cohort study. BMJ 1999;319:339.

274. Doyle W, Crawford MA, Wynn AHA, Wynn SW. Maternal nutrient intake and birth weight. Journal of Human Nutrition and Dietetics 1989;2:415-22.

275. Clausson B, Granath F, Ekbom A, Lundgren S, Nordmark A, Signorello LB, Cnattingius S. Effect of caffeine exposure during pregnancy on birth weight and gestational age. Am J Epidemiol 2002;155:429.

276. Brawarsky P, Stotland NE, Jackson RA, Fuentes-Afflick E, Escobar GJ, Rubashkin N, Haas JS. Pre-pregnancy and pregnancy-related factors and the risk of excessive or inadequate gestational weight gain. International Journal of Gynecology & Obstetrics 2005;91:125-31.

277. Chomitz VR, Cheung LWY, Lieberman E. The role of lifestyle in preventing low birth weight. The Future of Children 1995;121-38.

278. Abrams B, Selvin S. Maternal weight gain pattern and birth weight. Obstetrics & Gynecology 1995;86:163.

279. Wells CS, Schwalberg R, Noonan G, Gabor V. Factors influencing inadequate and excessive weight gain in pregnancy: Colorado, 2000–2002. Maternal and child health journal 2006;10:55-62.

280. Gauer OH, Henry JP, Behn C. The regulation of extracellular fluid volume. Annu Rev Physiol 1970;32:547-95.

281. Quinkler M, Meyer B, Bumke-Vogt C, Grossmann C, Gruber U, Oelkers W, Diederich S, Bahr V. Agonistic and antagonistic properties of progesterone metabolites at the human mineralocorticoid receptor. European journal of endocrinology 2002;146:789.

282. Epstein AN, Sakai RR. Angiotensin-aldosterone synergy and salt intake. Brain peptides and catecholamines in cardiovascular regulation in normal and disease states JP Buckley &C M Ferrarlo eds New York: Raven Press 1986.

283. Agrawal V, Agarwal M, Joshi SR, Ghosh AK. Hyponatremia and hypernatremia: Disorders of water balance. JAPI 2008;56.

284. Haugen M, Vikanes Å, Brantsæter AL, Meltzer HM, Grjibovski AM, Magnus P. Diet before pregnancy and the risk of hyperemesis gravidarum. Br J Nutr 2011;*FirstView Article*X:1-7.doi: 10.1017/S0007114511000675, Available on CJO 2011.

285. Armstrong LE, Maresh CM, Gabaree CV, Hoffman JR, Kavouras SA, Kenefick RW, Castellani JW, Ahlquist LE. Thermal and circulatory responses during exercise: effects of hypohydration, dehydration, and water intake. J Appl Physiol 1997;82:2028.

286. Adrogué HJ, Madias NE. Hyponatremia. The New England journal of medicine 2000;342:1581.

Appendix 1

Table 1. Maternal demographics, mean (SD)[a], number (%)

	Total	No nausea	Nausea	NVP	
	62 416	n=17 185	n=27 642	n=17 589	*p*-value[b]
		Mean (SD)	Mean (SD)	Mean (SD)	
Maternal age at delivery (y)	62 416	30.1 (4.5)	30.6 (4.5)	29.1 (4.7)	<0.001
Pre pregnancy maternal weight (kg)	61 127	65.0[c]	65.0[c]	66.0[c]	<0.001[d]
Pre pregnancy BMI (kg/m²)	60 877	23.0[c]	23.1[c]	23.4[c]	<0.001[d]
Height of mother (cm)	61760	168.2 (5.9)	168.3 (5.8)	167.8 (6.1)	<0.001[e]
Gestational weight gain (kg)	47 153	15.2 (5.7)	15.1 (5.8)	14.3 (6.5)	<0.001[e]
Missing	15 263	4224	6 591	4 448	
		n (%)	n (%)	n (%)	
Maternal age at delivery (y)					
< 25	7 137	1 785 (10.4)	2 436 (8.8)	2 916 (16.6)	
25-29	21 453	6 141 (35.7)	8 854 (32.0)	6 458 (36.7)	<0.001[f]
30-34	26 317	7 204 (41.9)	12 472 (45.1)	6 641 (37.8)	
≥ 35	7 509	2 055 (12.0)	3 880 (14.0)	1 574 (8.9)	
Pre pregnancy BMI category (kg/m²):					
18.5-24.9	40 142	11 389 (66.3)	18 039 (65.3)	10 714 (60.9)	
< 18.5	1 798	497 (2.9)	743 (2.7)	558 (3.2)	<0.001[f]
25-29.9	13 171	3 498 (20.4)	5 747 (20.8)	3 926 (22.3)	
≥ 30	5 766	1 418 (8.3)	2 418 (8.7)	1 930 (11.0)	
Missing[g]	1 539				
Maternal education years:					
≤ 12 y	19 140	4 956 (29.5)	8 007 (29.5)	6 177 (35.9)	
13 - 16 y	26 125	7 204 (42.9)	11 808 (43.6)	7 113 (41.3)	<0.001[f]
≥ 17 y	15 861	4 647 (27.6)	7 299 (26.9)	3 915 (22.8)	
Other/missing[g]	1 290				
Marital status:					
Married	28 233	7 057 (41.1)	13185 (47.7)	7 991 (45.4)	
Single/widow	1 389	399 (2.4)	520 (1.9)	470 (2.7)	<0.001[f]
Co-habitants	31 815	9 441 (54.9)	13 553 (49.0)	8 821 (50.2)	
Other or not known[g]	979				
Smoking 3 months prior to pregnancy:					
No	44 140	11 595 (67.5)	19 815 (71.7)	12 730 (72.4)	
Occasionally	6 412	1 886 (11.0)	2 861 (10.4)	1 665 (9.5)	<0.001[f]
Daily	11 331	3 560 (20.7)	4 751 (17.2)	3 020 (17.2)	
Missing[g]	533				

Table 1 continues overleaf

Table 1. (cont.)

	Total	No nausea	Nausea	NVP	
	62 416	17 185	27 642	17 589	*p*-value[b]
		n (%)	n (%)	n (%)	
Smoking during pregnancy (Week 22):					
No	57 207	15 414 (89.7)	25 607 (92.6)	16 186 (92.0)	
Occasionally	1 627	568 (3.3)	646 (2.3)	413 (2.3)	<0.001[f]
Daily	3 154	1 089 (6.3)	1 211 (4.4)	854 (4.9)	
Missing[g]	428				
Parity:					
First pregnancy	35 356	11 629 (67.7)	13 809 (50.0)	9 918 (56.4)	
1	17 685	3 628 (21.1)	8 895 (32.2)	5 162 (29.3)	<0.001[f]
2 or more	9 375	1 928 (11.2)	4 938 (17.9)	2 509 (14.2)	

[a]SD, standard deviation

[b]One-way ANOVA with post hoc tests

[c]Median value

[d]Kruskal–Wallis test

[e]Significance between NVP and No Nausea/Nausea only

[f]χ^2-test

[g]Not included in percent distribution

Table 2. Nausea and vomiting related characteristics, mean (SD)[a], number (%)

	Total 62 416	No nausea 17 185	Nausea 27 642	NVP 17 589	*p*-value[b]
		Mean (SD)	Mean (SD)	Mean (SD)	
Number of weeks of nausea	62 416	0	7.8 (4.2)	10.5 (5.5)	<0.001
Number of weeks of vomiting	62 416	0	0	6.4 (4.2)	
		n (%)	n (%)	n (%)	
Number of weeks of nausea:					
None	17 185	17 185 (100.0)	0	0	
1-4 weeks	6 679	0	5 147 (18.9)	1 532 (8.8)	
5-10 weeks	26 451	0	17 363 (63.7)	9 088 (52.2)	
11-16 weeks	7 441	0	3 433 (12.6)	4 008 (23.0)	<0.001[c]
17-21 weeks	1 662	0	458 (1.7)	1 204 (6.9)	
22-26 weeks	2 430	0	863 (3.2)	1 567 (9.0)	
Missing[d]	568				
Number of weeks of vomiting:					
None	44 827	17 185 (100.0)	27 642 (100.0)	0	
1-4 weeks	4 951	0	0	4 951 (30.8)	
5-10 weeks	8 182	0	0	8 182 (50.9)	
11-16 weeks	2 727	0	0	2 727 (17.0)	
17-21 weeks	208	0	0	208 (1.3)	
22-26 weeks	18	0	0	18 (0.1)	
Missing [d]	1 503				
If yes to nausea, have you begun to eat:					
More	17 811	51 (4.8)	12 441 (48.1)	5 319 (31.4)	
Less	24 949	31 (3.0)	13 346 (51.6)	11 572 (68.2)	<0.001[c]
More/Less	1 131	974 (92.2)	85 (0.3)	72 (0.4)	
Missing [d]	18 525				
Q37'Have you begun to eat certain foods during this pregnancy?'					
Yes	15 819	3 720 (22.9)	7 006 (26.0)	5 093 (29.3)	
No	44 793	12 547 (77.1)	19 973 (74.0)	12 273 (70.6)	<0.001[c]
Yes/No	33	6 (0.0)	16 (0.0)	11 (0.1)	
Missing [d]	1 771				

[a]SD, standard deviation

[b]Independent sample t-test

[c]χ^2-test

[d]Not included in percent distribution

Table 3. Daily intakes of macronutrients calculated from the FFQ for 62 416 women, mean (SD)[a]

	No nausea		Nausea		NVP		
	Mean (SD)	Median (Q1, Q3)[b]	Mean (SD)	Median (Q1, Q3)[b]	Mean (SD)	Median (Q1, Q3)[b]	*p*-value[c]
Energy intake (kJ)	9 535.5 (2 510.5)	9 193 (7 767, 10 912)	9 710.2 (2 522.1)	9 390 (7 952, 11 145)	9 862.5 (2 747.5)	9 486 (7 913, 11 387)	<0.001
Carbohydrate intake (g)	301.8 (89.9)	289 (201, 350)	308.6 (89.9)	297 (204, 358)	316.5 (98.6)	302 (203, 372)	<0.001
Added sugar (g)	59.6 (36.8)	51 (36, 73)	61.3 (37.0)	53 (37, 76)	65.8 (42.9)	56 (37,82)	<0.001
Protein intake (g)	86.3 (20.8)	84 (72, 98)	87.2 (20.9)	85 (73, 99)	87.5 (22.7)	85 (72, 100)	<0.001[d]
Fat intake (g)	78.9 (23.6)	75 (62, 92)	80.1 (23.9)	77 (63, 93)	80.4 (25.6)	76 (62, 94)	<0.001[d]
Saturated fat (g)	30.5 (9.7)	29 (24. 36)	30.8 (9.8)	29 (24. 36)	31.0 (10.6)	29 (24. 37)	<0.001[d]
Trans fat (g)	2.3 (1.1)	2 (2,3)	2.3 (1.1)	2 (2,3)	2.4 (1.2)	2 (2,3)	<0.001[e]
Mono-unsaturated fat (g)	25.4 (7.9)	24 (20, 30)	25.8 (8.1)	25 (20, 30)	25.6 (8.6)	24 (20, 30)	<0.001[d]
Poly-unsaturated fat (g)	14.8 (5.7)	14 (11, 17)	15.1 (5.8)	14 (11, 18)	15.2 (6.1)	14 (11, 18)	<0.001[d]

[a]SD, standard deviation

[b]Q1 25thpercentile; Q3 75th percentile

[c]One-way ANOVA with post hoc tests

[d]Significance between No Nausea and Nausea/NVP only

[e]Significance between NVP and No Nausea/Nausea only

Table 4. Daily intakes of macronutrients as energy percent (E%) calculated from the FFQ for 62 416 women; (SD)[a]

	No nausea	Nausea	NVP	*p*-value[b]
Carbohydrate intake (E%)	53.0 (4.7)	53.2 (4.7)	53.7 (5.0)	<0.001
Added sugar (E%)	10.2 (4.7)	10.3 (4.7)	10.9 (5.4)	<0.001[c]
Protein intake (E%)	15.4 (2.1)	15.3 (2.0)	15.2 (2.2)	<0.001
Fat intake (E%)	31.4 (4.5)	31.3 (4.5)	30.9 (4.7)	<0.001[c]
Saturated fat (E%)	12.2 (2.1)	12.1 (2.1)	11.9 (2.2)	<0.001
Trans fat (E%)	0.9 (0.3)	0.9 (0.3)	0.9 (0.4)	<0.001[c]
Mono-unsaturated fat (E%)	10.2 (1.9)	10.1 (1.9)	9.9 (1.9)	<0.001[c]
Poly-unsaturated fat (E%)	5.9 (1.6)	5.9 (1.6)	5.9 (1.6)	0.006[d]

[a]SD, standard deviation

[b]One-way ANOVA with post hoc tests

[c]Significance between NVP and No Nausea/Nausea only

[d]Significance between Nausea and No Nausea/NVP only

Table 5. Daily intakes of selected foods calculated from the FFQ for 62 416 women, (SD)[a]

	No nausea 17 185		Nausea 27 642		NVP 17 589		
	Mean(SD)	Median (Q1, Q3)[b]	Mean(SD)	Median (Q1, Q3)[b]	Mean(SD)	Median (Q1, Q3)[b]	*p*-value[c]
Milk (g)	334.7 (324.3)	242 (86, 431)	337.0 (327.0)	242 (82, 436)	350.0 (354.3)	249 (74, 442)	0.332
Biola/Cultura (g)	34.1 (89.7)	0 (0, 20)	33.3 (89.2)	0 (0, 20)	28.2 (84.2)	0 (0, 13)	<0.001
Juice (orange, apple) (g)	1.5 (9.0)	0 (0, 0)	1.3 (9.2)	0 (0, 0)	0.9 (8.5)	0 (0, 0)	<0.001
Chocolate (g)	19.4 (18.1)	15 (8, 25)	19.0 (18.4)	12 (8, 25)	17.8 (18.7)	12 (6, 25)	<0.001
Water(all types) (g)	1 221.0 (713.4)	1 071 (552, 1 714)	1 219.0 (709.6)	1 071 (552, 1 695)	1 182.8 (740.2)	1 036 (535, 1 643)	<0.001
Vegetables (g)	45.6 (36.0)	36 (23, 58)	47.2 (36.6)	38 (24, 60)	48.9 (40.3)	38 (23, 63)	<0.001
Fruit (g)	272.0 (192.1)	230 (137, 357)	280.4 (193.3)	240 (144, 369)	295.1 (223.5)	242 (141, 390)	<0.001
Fish (g)	43.7 (25.3)	41 (26, 57)	45.1 (25.9)	42 (27, 59)	44.2 (27.6)	41 (25, 78)	<0.001
Meat (g)	77.3 (26.5)	75 (60, 92)	76.7 (26.8)	75 (60, 92)	77.2 (29.2)	75 (59, 93)	0.073
Sugared soft drinks (g)	77.8 (186.0)	25 (8, 71)	76.6 (179.2)	25 (8, 71)	104.9 (229.6)	33 (8, 107)	<0.001

[a]SD, standard deviation

[b]Q1 25thpercentile; Q3 75th percentile

[c]Kruskal–Wallis test

Table 6. Women who chose to start eating general food types during pregnancy based on Q38 responses, number (%)

	No nausea 17 185	Nausea 27 642	NVP 17 589	Total 62 416	*p*-value[a]
Total number of the sample answering 'yes' to eating more (Q37)	3 720 (21.7)[b]	7 006 (25.4)[b]	5 093 (29.0)[b]	15 819 (25.3)[b]	
Foods that help reduce nausea	77 (2.1)	287 (4.1)	276 (5.4)	640 (4.1)	<0.001
Foods helping digestion (dried fruits etc.)	172 (4.6)	342 (4.9)	226 (4.4)	740 (4.7)	0.60
Foods containing probiotics	551 (14.8)	785 (11.2)	357 (7.0)	1 693 (10.7)	<0.001
Foods rich in proteins	238 (6.4)	429 (6.1)	344 (6.8)	1 011 (6.4)	0.42
Foods rich in fat	335 (9.0)	664 (9.5)	488 (9.6)	1 487 (9.4)	0.38
Foods rich in sugar	410 (11.0)	833 (11.9)	766 (15.0)	2 009 (12.7)	<0.001
Foods using artificial sweeteners	26 (0.7)	69 (1.0)	65 (1.3)	160 (1.0)	0.007
Foods rich in sour/salt taste	184 (5.0)	434 (6.2)	343 (6.7)	961 (6.1)	0.001

[a]χ^2-test

[b]Percent of group total

Table 7. Women who chose to start eating certain foods during pregnancy based on Q38 responses, number (%)

	No nausea	Nausea	NVP	Total	
Women answering 'yes' to eating more (Q37)	3 720 (23.5)	7 006 (44.3)	5 093 (32.2)	15 819 (100)	*p*-value[a]
Milk	502 (13.5)	923 (13.2)	743 (14.6)	2 168	0.01
Biola/Cultura	551 (14.8)	785 (11.2)	357 (7.0)	1 693	<0.001
Juice (orange, apple)	301 (8.2)	569 (8.1)	387 (7.6)	1 257	0.40
Chocolate	92 (2.5)	129 (1.8)	67 (1.3)	288	<0.001
Water (all types)	176 (4.7)	472 (6.7)	396 (7.8)	1 044	<0.001
Vegetables	321 (8.6)	665 (9.5)	557 (10.9)	1 543	<0.001
Fruit	1 084 (29.1)	2 094 (29.9)	1 618 (31.8)	4 796	0.006
Fish	231 (6.2)	410 (5.9)	317 (6.2)	958	0.90
Meat	184 (5.0)	434 (6.2)	299 (5.9)	917	0.10
Sugared soft drinks	91 (2.5)	197 (2.8)	227 (4.5)	515	<0.001

[a]χ^2-test.

Table 8. Birth-related variables, mean (SD)[a], number(%)

	Total 62 416	No nausea 17 185	Nausea 27 642	NVP 17 589	*p*-value[b]
		n (%)	n (%)	n (%)	
Length of gestation:					
Normal range 37-42 weeks	59 127	16 180 (94.9)	26 276 (95.7)	16 671 (95.4)	
Early birth 35-36 weeks	1 851	567 (3.3)	764 (2.8)	520 (3.0)	0.018
Very early birth 28-34 weeks	1 006	306 (1.8)	424 (1.5)	276 (1.6)	
Missing[c]	432				
Large for gestational age (LGA)	6 035	1 543 (9.0)	2 781 (10.1)	1 711 (9.8)	0.02
Others[c]	56 088				
Missing[c]	293				
Small for gestational age (SGA)	6 520	1 988 (11.6)	2 702 (9.8)	1 830 (10.5)	<0.001
Others[c]	55 603				
Missing[c]	293				
Sex of child:					
Male	31 916	9 334 (54.3)	14 086 (51.0)	8 496 (48.3)	<0.001
Female	30 500	7 851 (45.7)	13 556 (49.0)	9 093 (51.7)	
		Mean (SD)	Mean (SD)	Mean (SD)	
Weight of placenta at birth (g)[b]	59 837	654.7 (134.2)	670.4 (134.3)	668.4 (133.1)	<0.001[e]
Missing[c]	2 579				
Weight of baby at birth (g)[b]	62 382	3 540.5 (550.9)	3 619.1 (539.7)	3 585.9 (548.1)	<0.001
Missing[c]	34				

[a]SD standard deviation

[b]One-way ANOVA with post hoc tests or χ^2-test

[c]Not included in percent distribution

[d]Not adjusted for length of gestation

[e]Significance between No Nausea and Nausea/NVP only

Figure 1. Q31 Protein-rich foods.

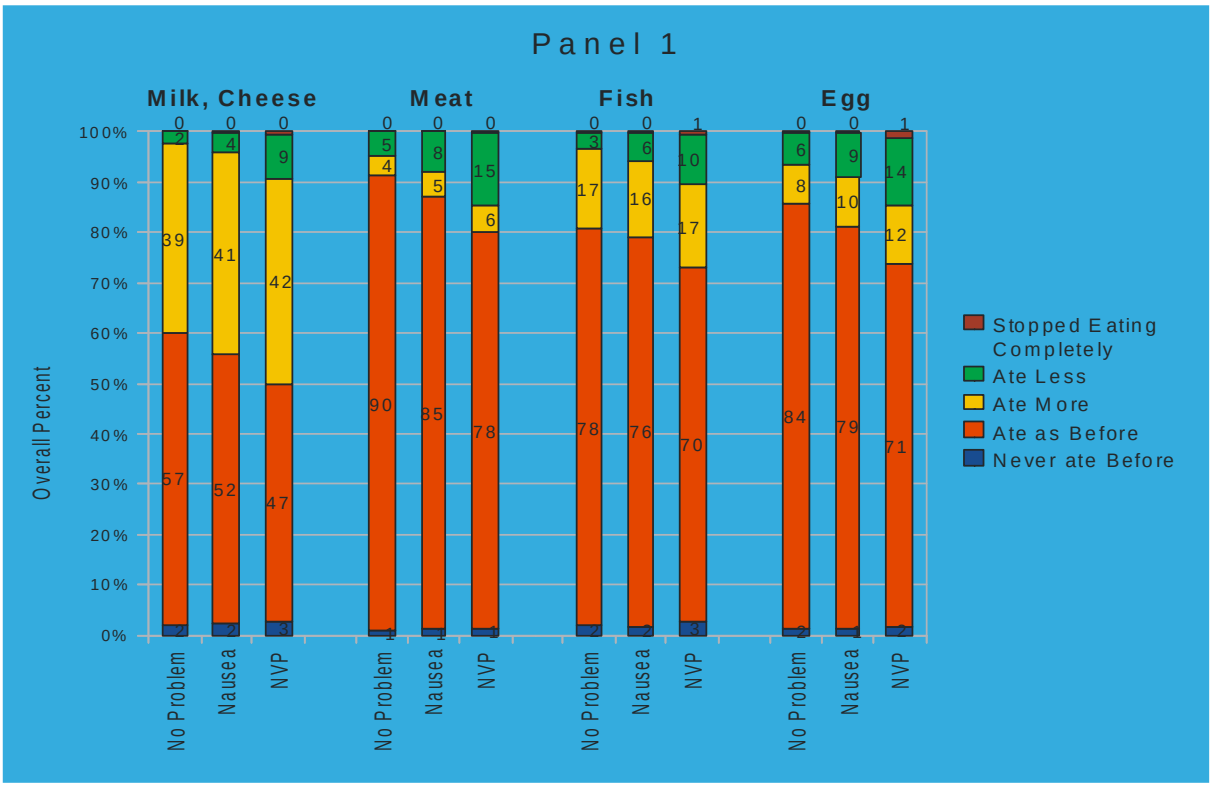


Figure 2. Q31 Carbohydrate-rich foods.

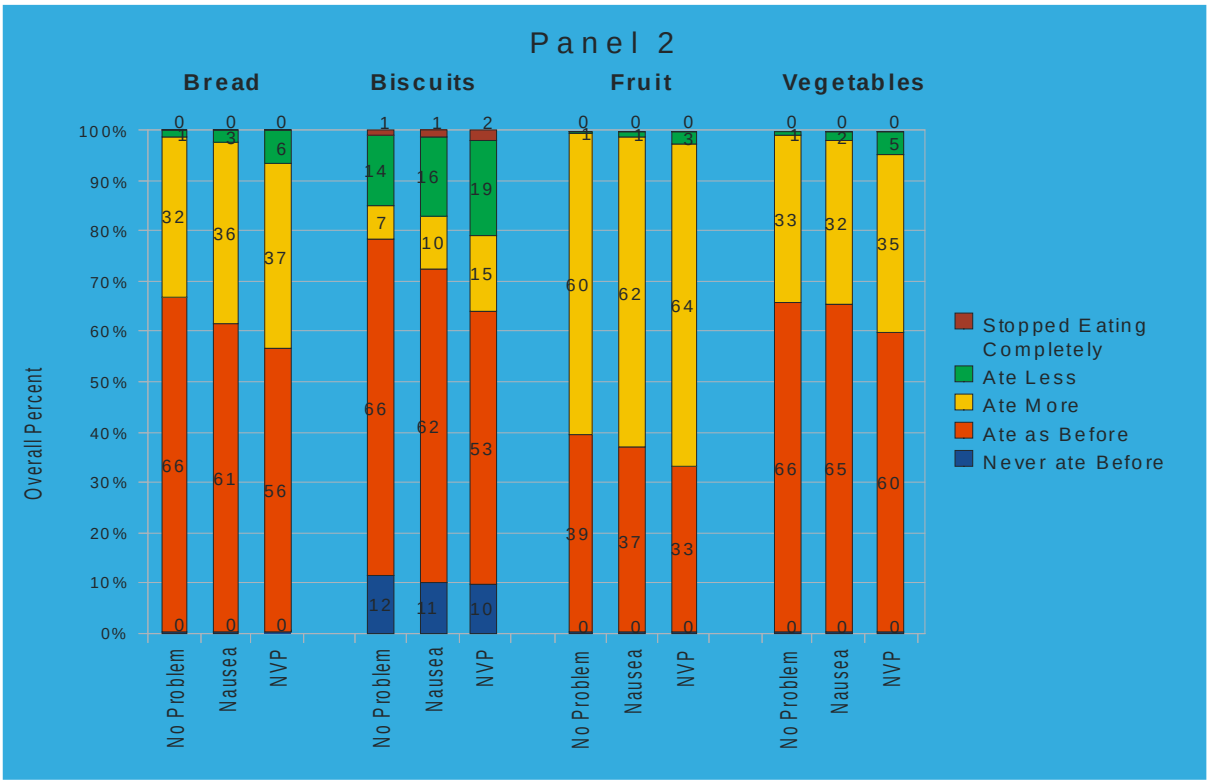


Figure 3. Q31 Fat-rich foods.

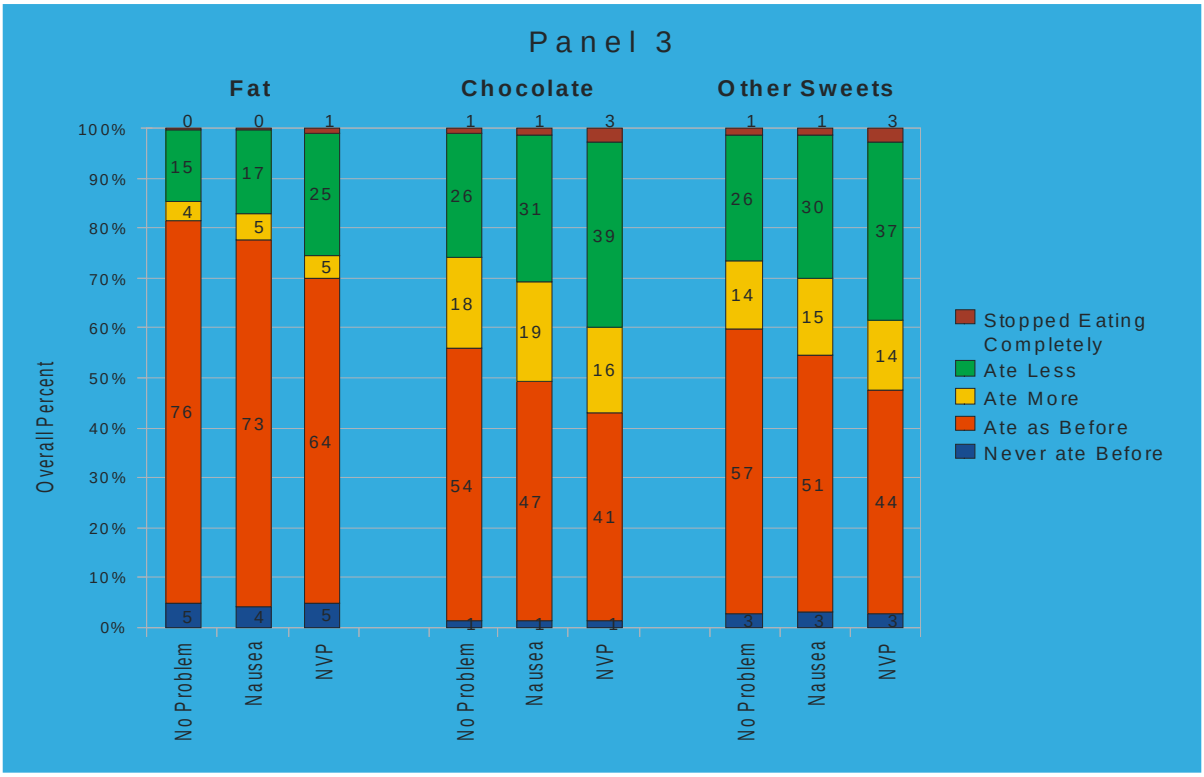
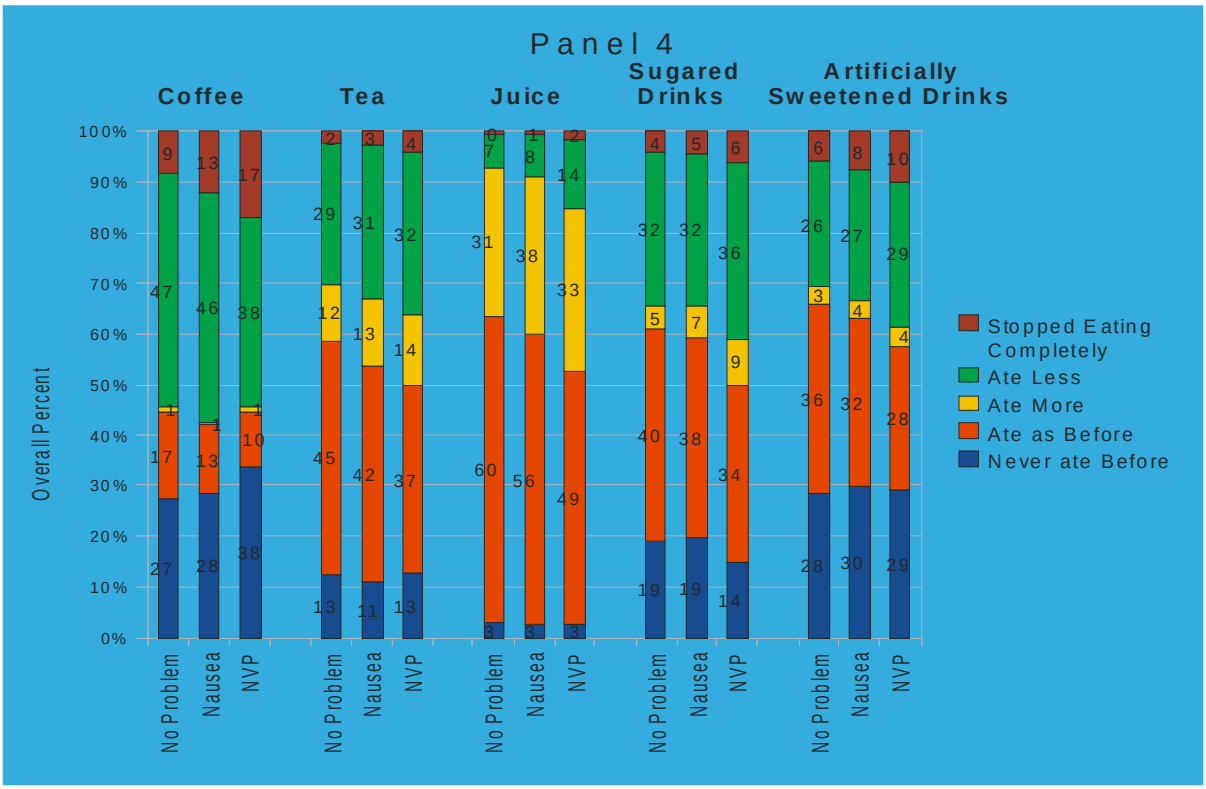


Figure 4. Q31 Beverages.



All categories had an average 99% participation from the 62416 women; those answering more than one category (on average 0.1% of sample) were omitted.

Figure 5. Nausea group's pattern of nausea week 0-26

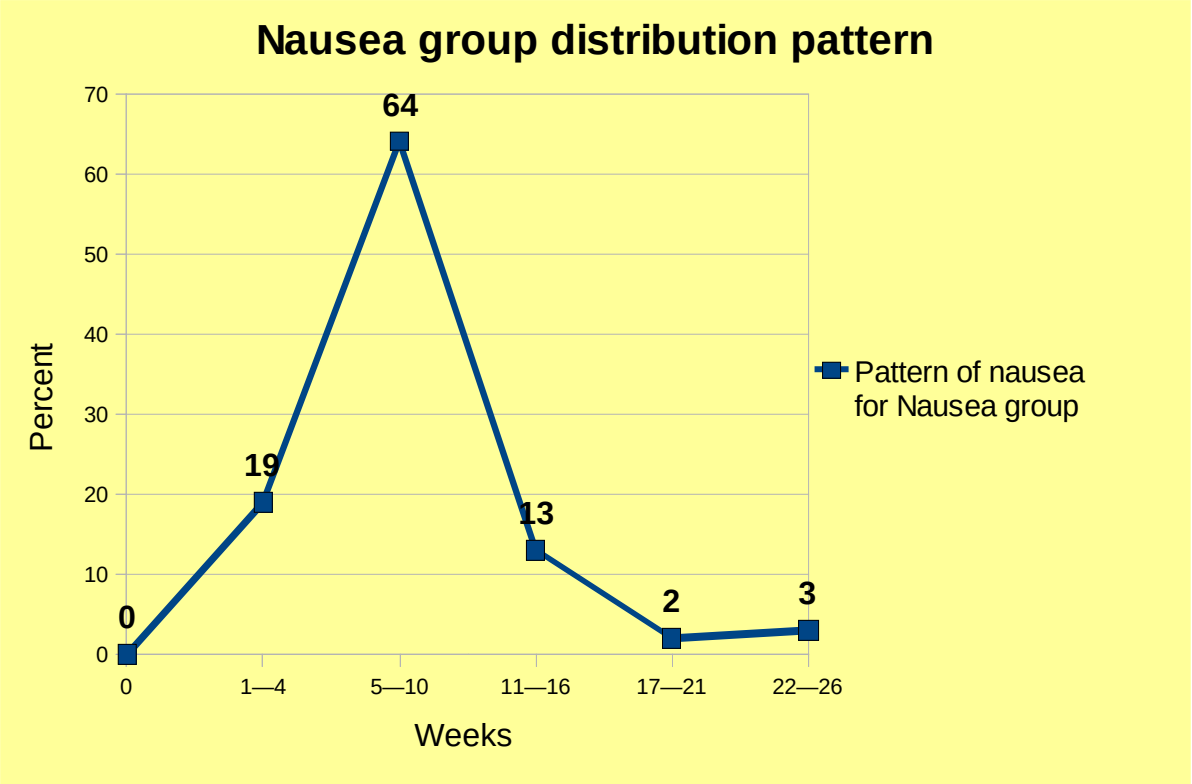
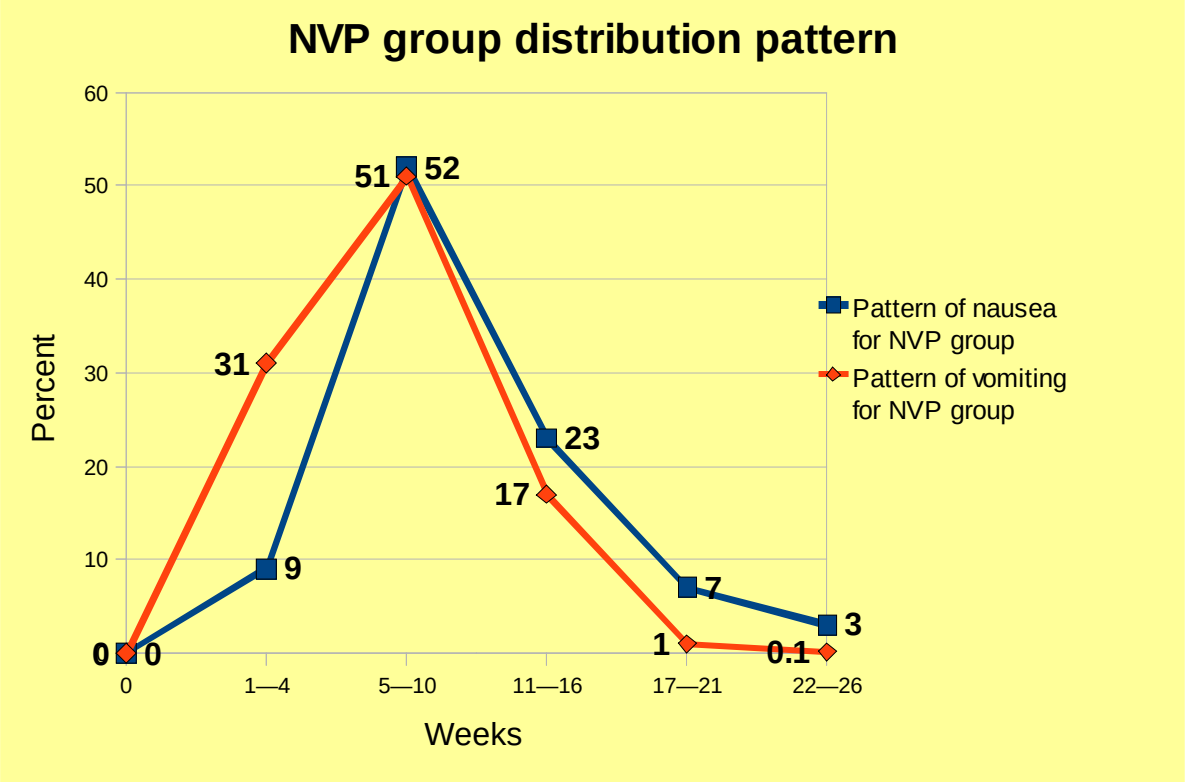


Figure 6. NVP group's pattern of nausea and vomiting week 0-26



Appendix 2

Item 1. Page 13 from Q2

Dietary changes due to this pregnancy

31. Please mark if you have eaten more, less or the same amount of the following food items compared to before you became pregnant

Food item	Did not eat or drink this before pregnancy	As before	More	Less	Stopped completely
1. Milk, dairy products	☐	☐	☐	☐	☐
2. Bread and cereals	☐	☐	☐	☐	☐
3. Biscuits	☐	☐	☐	☐	☐
4. Fat	☐	☐	☐	☐	☐
5. Meat	☐	☐	☐	☐	☐
6. Fish	☐	☐	☐	☐	☐
7. Eggs	☐	☐	☐	☐	☐
8. Vegetables	☐	☐	☐	☐	☐
9. Fruit	☐	☐	☐	☐	☐
10. Chocolate	☐	☐	☐	☐	☐
11. Other sweets	☐	☐	☐	☐	☐
12. Coffee	☐	☐	☐	☐	☐
13. Tea	☐	☐	☐	☐	☐
14. Juice	☐	☐	☐	☐	☐
15. Soft drinks with sugar	☐	☐	☐	☐	☐
16. Soft drinks sugar free	☐	☐	☐	☐	☐
17. Alcohol	☐	☐	☐	☐	☐

32. Have you experienced nausea during this pregnancy? ☐ Yes ☐ No

33. If yes; have eaten more or less than before? ☐ More ☐ Less

34. In which week(s) have you been most bothered with nausea?

From pregnancy week	To pregnancy week	Still nauseated
		☐

35. Have you been throwing up (vomiting) during this pregnancy? ☐ Yes ☐ No

36. In which week(s) have you been throwing up (vomiting)?

From pregnancy week	To pregnancy week	Still throwing up
		☐

37. Have you started to eat or drink certain food items during this pregnancy? ☐ Yes ☐ No

38. If yes, name the two most important food items you have started to eat/drink.

Write the name of the food item

13

Table 1. Categorized food groups used to format Question 38. All asterisks explained at end of table.

Food Groups	**Codes**
Milk and Milk products	**1000**
Full fat (3.9)	1001
Low fat (1.5)	1002
Extra low fat (0.7)	1003
Skimmed (0.1)	1004
Unspecified milk type	1005
Biola natural /Activia	1006**
Biola – fruit variety	1007**
Cultura natural	1008**
Cultura – fruit variety	1009**
Kefir	1010
Other fermented drinks/unspecified	1011*******
Yoghurt plain/unspecified	1012
Yoghurt – fruit variety	1013
Yoghurt – low fat	1014
Yoghurt – drinking variety	1015
Other milk based drink/food	1016
Ice cream	1017****
Cheese yellow/white	1018
Cheese yellow/white – low fat	1019
Cheese brown/prim spread	1020
Creamed cheese varieties	1021****
Cheese – unspecified/other	1022
Milk – non dairy	1023
Milkshake – non chocolate	1024*****
Cream	1025****
Smoothies with fruit/berries	1026
Smoothies unspecified	1027
Breads and Cereals	**2000**
Bread – whole grain	2001
Bread – white	2002
Bread – unspecified/other	2003
Crisp bread	2004*
Rice crisp bread	2005
Oatmeal/Oat soup	2006
Semolina/wheatmeal/Maizenameal	2007
Grain products	2008
Cereal blend (4 corn) - sweetened	2009

Cereal blend (4 corn) - unsweetened	2010
Breakfast cereal – unspecified/other	2011
Rice	2012
Pasta	2013
Seeds	2014*
Crusts, dry bread, toast, bran	2015#
Noodles	2016
Biscuits, Buns and Cakes	**3000**
Sweet Biscuits	3001*****
Sweet biscuits – with filling	3002*****
Sweet biscuits – with chocolate	3003*****
Biscuits – salt type	3004#
Biscuits – unspecified/other	3005*****
Pepper cake biscuits	3006*****
Buns – plain	3007
Buns – with raisins/chocolate	3008
Sponge Cake – Plain	3009*****
Sponge Cake – with chocolate	3010*****
Cream Cake	3011*****
Cake – unspecified/other	3012*****
Muffins	3013*****
Waffles	3014
Jelly	3015*****
Hi sugar/Sweet foods – other/unspecified	3016*****
Fat	**4000**
Butter	4001****
Margarine	4002****
Food Oils	4003****
Cod liver oil (liquid and capsules)	4004
Mayonnaise and mayo based foods	4005****
Mayonnaise – light	4006
Unspecified/other fats	4007****
Mayonnaise based foods/salads	4008****
Meats	**5000**
Chicken	5001***
Turkey	5002***
Other fowl	5003***
Lamb	5004***
Beef	5005***

Pig	5006***
Game (moose, reindeer)	5007***
Organs/blood	5008***
Meat cakes/hamburger	5009****
Processed meat slices incl. Salami etc.	5010****
Smoked meats	5011
Sausages/wieners	5012****
Processed Liver	5013****
Processed Liver – low fat	5014
Unspecified/other meats	5015****
Fish	**6000**
Salmon	6001***
Tuna	6002***
Mackerel	6003***
Cod	6004***
Unspecified/other fresh fish	6005***
Mussels	6006***
Lobster	6007***
Crab	6008***
Prawns/shrimps	6009***
Shellfish unspecified/other	6010***
Fish Cakes/puddings	6011
Processed fish (incl. Spreads)	6012***
Caviar	6013*******
Egg	**7000**
Eggs (boiled, fried, omelette)	7001***
Egg (yellow)	7002***
Egg (white)	7003***
Vegetables	**8000**
Carrots / turnips / swede	8001
Cauliflower	8002
Broccoli	8003
Salads	8004
Tomatoes	8005
Mushrooms	8006
Corn	8007
Unspecified/other fresh vegetables	8008
Canned beans/lentils	8009
Canned peas	8010

Olives	8011
Tomato sauce/ ketchup/soup	8012
Unspecified/other processed vegetables	8013
Potatoes - cooked	8014
Potatoes – processed	8015
Cabbages	8016
Corn based products (corn chips, popcorn)	8017*******
Fruit	**9000**
Oranges	9001
Grapefruits	9003
Other citrus fruits	9004
Banana	9005
Grapes	9006
Kiwi	9007
Melon – all types	9008
Avocado	9009
Apples	9011
Unspecified/other fruits	9012
Berries – all types	9013
Raisins	9014*
Prunes	9015*
Dried fruits - other	9016*
Canned fruits	9017
Jams/marmalades	9018
Nuts	9019
Chocolate	**10000**
Dark Chocolate	10001****
Milk Chocolate	10002****
Confectionary/choc bars	10004*****
Hot Cocoa / Chocolate milk/milkshakes	10005
Chocolate – unspecified/other	10006*****
Sweets (non-chocolate)	**11000**
Caramels	11001*****
Sweet lollies	11002*****
Salt/sour lollies	11003*******
Licorice – sweet	11004*****
Licorice – salt	11005*******
Chewing Gum	11006
Honey	11007

Unspecified/other sweets	11008*****
Licorice - unspecified	11009*****
Coffee	**12000**
Milk-based coffee	12002
Coffee – black/unspecified/other	12003
Coffee – caffeine free	12004
Teas	**13000**
Black tea	13001
Green tea	13002
Herbal and Fruit teas	13004
Ice Tea	13005*****
Tea – unspecified/other	13006
Juice	**14000**
Orange juice	14001
Apple juice	14002
Unspecified/other fruit juices	14003
Concentrated nectar (saft)	14004*****
Concentrated nectar (saft) – light	14005******
Carbonated Drinks	**15000**
Carbonated sugared drinks	15001*****
Carbonated sweetner drinks	15002******
Water	**16000**
Water – carbonated	16001#
Water – still	16002
Water – unspecified	16003
Alcohol	**17000**
Beer	17001
Beer – low alcohol	17002
Beer – zero alcohol	17003
Wine – alcohol free	17004
Wine – red	17005
Wine – white	17006
Wine – unspecified	17007
Spirits	17008
Vorterol	17009*****
Spreads	**18000**

Peanut Butter	18001****
Spreads - other	18002****
Chocolate based spreads	18003****
Unspecified	**19000**
Salt / salty foods	19001*******
Sour foods – unspecified/other	19002*******
Strong/Hot Spices - foods	19003*******
Pizza/ calzone	19004
Ginger and ginger products (not drinks)	19005#
Malt Extract	19006
Eddik/Vinegar	19008*******
Soups various	19010
Soya Products (non-liquid)/Tofu	19011
Ginger based soft drinks	19012#
Fast Foods (Burgers, kebabs)	19013****
Words/products uncategorizable (Feil)	19014
Water with ice	19015
Pica	**20000**
Pica (non-foods, ice, unusual eating habits)	20001
General Food types	**21000**
High Fat foods – unspecified/increased intake	21001****
High Carbohydrate foods – unspecified/increased intake	21002#
High Protein foods – unspecified/increased intake	21003***
Artificially sweetened foods – unspecified/increased intake	21005******
High Fiber foods – unspecified/increased intake	21006*

Guide to the broader Categorizations

Foods that help reduce nausea (20) = #
Foods helping digestion (dried fruits etc.) (30) = *
Foods containing probiotics (40) = **
Foods rich in Proteins (50) = ***
Foods rich in Fat (60) = ****
Foods rich in Sugar (70) = *****
Foods using artificial Sweeteners (80) = ******
Foods rich in Sour/salt taste (90) = *******