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UNIVERSITY OF TURKU

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Studies with Pregnancy-Unique Quantification of Emesis Questionnaire

Linda Laitinen

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To my family

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ABSTRACT

Majority of women experience at least some degree of nausea and vomiting of pregnancy (NVP). The severity of the condition ranges from mild symptoms to intractable nausea and vomiting, hyperemesis gravidarum (HG). An internationally widely used questionnaire, the Pregnancy-Unique Quantification of emesis (PUQE), has been developed to categorise the severity of NVP. The present study aimed to assess the usability of the PUQE both in inpatient and outpatient settings for the first time in Finland. Moreover, associations between NVP and maternal factors, physical quality of life (QoL), mental QoL and sleep quality were assessed.

The PUQE was applied in two cohorts of pregnant women: 106 hospitalised women with HG and 2411 women recruited from maternal health care clinics (MHCC). At the hospital, among women with HG, the PUQE scores decreased from admission to discharge, reflecting the alleviation of HG. The change in PUQE scores was associated with improved physical QoL and in repeated admissions also with improved mental QoL.

The women recruited from MHCCs recalled the worst NVP in their current pregnancy and replied to the PUQE accordingly. In general, NVP was frequent and most often rated as moderate. The severity of NVP was mainly associated with higher gravidity and previous nausea related to motion sickness, migraine, and other kind of headache. In addition, family history of NVP was associated with more severe NVP. Further, women with more severe NVP had worse physical QoL, worse mental QoL and worse sleep quality. Moreover, the women replied the PUQE at different gestational weeks, but the PUQE total scores were comparable whether the scores were given in early or in late pregnancy.

The findings of the present study support clinical use of the PUQE also in Finland. The PUQE scores were usable at hospital in HG treatment follow-up. In outpatient care the PUQE could be used as a screening tool to assess the severity of NVP. Using the PUQE for the severity assessment of NVP, the present study found various associative factors for NVP. Notably, along increasing severity of NVP the present study highlighted the deterioration of QoL and sleep quality. These results are important in antenatal counselling.

KEYWORDS: pregnancy, nausea, vomiting, hyperemesis gravidarum, PUQE, quality of life, sleep

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TIIVISTELMÄ

Suurin osa odottajista kokee jonkinasteista raskauspahoinvointia, jonka vaikeusaste vaihtelee lievästä aina hallitsemattomaan pahoinvointiin ja oksenteluun nimeltään hyperemesis gravidarum (HG). Raskauspahoinvoinnin vaikeusasteen luokitteluun on kehitetty kansainvälisesti laajasti käytetty kyselykaavake Pregnancy-Unique Quantification of Emesis (PUQE). Tässä väitöstutkimuksessa selvitettiin PUQEn käytettävyyttä sekä sairaalassa että avoterveydenhuollossa ensimmäistä kertaa Suomessa. Lisäksi tutkittiin äidin ominaisuuksien, fyysisen ja psyykkisen elämänlaadun sekä unen laadun yhteyttä raskauspahoinvointiin.

PUQEa käytettiin kahdessa eri raskaana olevien aineistossa: 106 naisella, jotka olivat HG:n vuoksi sairaalahoidossa ja 2411 neuvoloista rekrytoiduilla odottajilla. Sairaalassa PUQE-pisteet laskivat tulopäivästä lähtöpäivään kuvastaen HG:n lieventymistä. Tämä muutos oli yhteydessä kohentuneeseen fyysiseen elämänlaatuun ja toistuvissa hoitojaksoissa myös kohentuneeseen psyykkiseen elämänlaatuun.

Neuvoloista rekrytoidut odottajat vastasivat PUQEn raskauden pahimman pahoinvointijakson mukaisesti. Raskauspahoinvointi oli yleistä ja PUQEn mukaan yleisimmin keskivaikeaa. Aiemmat raskaudet, matkapahoinvointitausta ja taipumus pahoinvointiin migreenin tai muun päänsäryn yhteydessä sekä sukulaisilla esiintynyt raskauspahoinvointi olivat yhteydessä voimakkaampaan raskauspahoinvointiin. Niillä naisilla, joilla raskauspahoinvointi oli voimakkaampaa, oli myös sekä huonompi fyysinen ja psyykkinen elämänlaatu että huonompi unen laatu. Odottajat vastasivat PUQEn eri raskausviikoilla, mutta PUQE-pisteet olivat vertailukelpoisia alkuraskauden ja loppuraskauden vastausten välillä.

Väitöstutkimuksen mukaan PUQE sopii hyvin kliiniseen käyttöön myös Suomessa. PUQE soveltuu sairaalahoidossa HG potilaiden hoitovasteen seurantaan. Avoterveydenhuollossa PUQE soveltuu raskauspahoinvoinnin voimakkuuden seulontaan. Väitöstutkimus toi esiin useita raskauspahoinvoinnin taustatekijöitä sekä sen elämänlaatua ja unen laatua heikentävän vaikutuksen. Tuloksia voidaan hyödyntää odottajien neuvonnassa.

AVAINSANAT: raskaus, pahoinvointi, oksentelu, hyperemesis gravidarum, PUQE, elämänlaatu, uni

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Abbreviations

AOR	adjusted odds ratio
BMI	body mass index
BNSQ	basic Nordic sleep questionnaire
CI	confidence interval
GDF15	growth and differentiation factor 15
GWK	gestational week
hCG	human chorionic gonadotropin
HG	hyperemesis gravidarum
HELP	hyperemesis level prediction score
HIS	hyperemesis impact of symptoms questionnaire
IQR	interquartile range
INVR	index of nausea, vomiting and retching
MHCC	maternal health care clinic
NVP	nausea and vomiting of pregnancy
NVP-QOL	health-related quality of life for nausea and vomiting of pregnancy
NVPI	nausea and vomiting in pregnancy instrument
OR	odds ratio
PUQE	pregnancy-unique quantification of emesis questionnaire
QoL	quality of life
PSQI	Pittsburgh sleep quality index
RCT	randomised controlled trial
SF-12	12-item short form health survey
SF-36	36-item short form health survey
SGA	small for gestational age
VAS	visual analogue scale

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Laitinen L, Nurmi M, Kulovuori N, Koivisto M, Ojala E, Rautava P, Polo-Kantola P. Usability of pregnancy-unique quantification of emesis questionnaire in women hospitalised for hyperemesis gravidarum: a prospective cohort study. *BMJ Open*, 2022; 12: e058364.

II Laitinen L, Nurmi M, Rautava P, Koivisto M, Polo-Kantola P. Recalling the severity of nausea and vomiting of pregnancy: a study using pregnancy-unique quantification of emesis questionnaire. *Journal of Obstetrics and Gynaecology*, 2023;43:1

III Ellilä P*, Laitinen L*, Nurmi M, Rautava P, Koivisto M, Polo-Kantola P. Nausea and vomiting of pregnancy: A study with pregnancy-unique quantification of emesis questionnaire. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2018; 230: 60–67.

IV Laitinen L, Nurmi M, Ellilä P, Rautava P, Koivisto M, Polo-Kantola P. Nausea and vomiting of pregnancy: associations with personal history of nausea and affected relatives. *Archives of Gynecology and Obstetrics*, 2020; 302: 947–955.

V Laitinen L, Nurmi M, Rautava P, Koivisto M, Polo-Kantola P. Sleep quality in women with nausea and vomiting of pregnancy: a cross-sectional study. *BMC Pregnancy and Childbirth*, 2021; 21: 152.

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1 Introduction

Women face many uncomfortable symptoms that are considered 'just part of a normal pregnancy' (Nazik & Eryilmaz, 2014). Most women experience at least some degree of nausea, vomiting, or both during pregnancy (Gadsby et al., 1993). Indeed, nausea and vomiting of pregnancy (NVP) can even be an anticipated, reassuring sign of pregnancy. Historically, vomiting has been described as a sign of pregnancy already in an Egyptian papyrus dated around 2000 B.C. (Fairweather, 1968). However, NVP may proceed to extremely severe nausea and continuous vomiting. This rare condition is called hyperemesis gravidarum (HG) (Fejzo et al., 2019; Källén, 1987). In the medical literature database of the United States National Library of Medicine, HG was mentioned at the first time in a journal article in 1898 (Das, 1898).

Even nowadays, the exact pathogenesis of NVP is not completely resolved. The historical hypothesis emphasised strong mental component in the etiology of NVP (Fairweather, 1968). However, currently NVP and HG are considered multifactorial, since several genetic, environmental, pregnancy-related, hormonal, gastrointestinal and psychological factors have been shown to be associated with NVP, contributing to individual woman's susceptibility to NVP (Fejzo et al., 2019; Goodwin, 2002; C. Liu et al., 2022). Recently, modern molecular biology methods have revealed new insights especially regarding genetics (Fejzo et al., 2018).

NVP and HG are clinical diagnoses based on excluding other causes that might cause similar symptoms (American College of Obstetricians and Gynecologists, 2018; The Royal College of Obstetricians and Gynaecologist, 2016). In general, NVP symptoms start and peak in the first trimester and mostly resolve around mid-pregnancy (Lacroix et al., 2000). However, it is possible that NVP continues throughout pregnancy (Lindseth & Vari, 2005; Mullin et al., 2012). Contrary to more ordinary NVP, intractable vomiting in HG may lead to dehydration, electrolyte imbalances and substantial weight loss, leading to hospitalization (Bailit, 2005; Fejzo et al., 2019). So far, no curative treatment is available. Therefore, treatment is targeted to alleviate NVP symptoms, at first with dietary and lifestyle modifications and, if needed, with antiemetic medications (Ebrahimi, 2010; Matthews et al., 2015).

Further, dehydration and nutritional deficiencies in HG often require intravenous hydration and even parenteral nutrition (Maslin & Dean, 2022).

NVP, in all severity levels, has been shown to decrease the quality of life (QoL) in pregnant women (Heitmann et al., 2017; Mazzotta et al., 2000). The consequences are evident in daily functioning at home, at work and in social activities (O'Brien & Naber, 1992; Wood et al., 2013). Both physical and mental wellbeing can be compromised (Attard et al., 2002; Mitchell-Jones et al., 2017). In general, NVP is associated with a positive obstetric outcome (Koren et al., 2014). However, in addition to severely decreased quality of life, HG may lead to serious maternal and fetal complications during pregnancy (Fiaschi et al., 2018). Rarely, HG may be a manifestation of abnormal pregnancy, for instance in case of hydatidiform mole (Soto-Wright et al., 1995). Notably, after HG, maternal mental consequences may continue postpartum (Nijsten et al., 2022). Accordingly, psychosocial support is an essential part of management to help women to cope with NVP and HG (Dean et al., 2018).

Thus, NVP and HG share overlapping symptoms, but HG often warrants more intensive treatment and evaluation of possible pregnancy complications. Therefore, it is essential that health care professionals assess the severity of NVP symptoms to be able to optimally manage these conditions. The pregnancy-unique quantification of emesis questionnaire (PUQE) is a simple and practical tool to assess the severity of NVP (Koren et al., 2002). Internationally, the PUQE has been widely used and the usage is recommended in many clinical management guidelines (American College of Obstetricians and Gynecologists, 2018; Lowe et al., 2019; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014). However, in Finland, any structured tool for assessing the severity of NVP have not yet been used routinely. Therefore, the present study applied the PUQE for the first time in Finland.

2 Review of the Literature

2.1 Nausea and vomiting of pregnancy

2.1.1 Overview of nausea and vomiting

Nausea is described as a feeling of discomfort mostly in the abdominal area. Associated symptoms may include fatigue and excessive salivation, and the need to lie down and rest. Notably, nausea is a subjective experience and thus, several definitions exist. Feeling of nausea stems from the brain. A specific site called 'the vomiting centre', area postrema, is located in the brainstem. (Ganong, 2003; Koch & Hasler, 2017)

Various pathways can evoke nausea, for instance gastro-intestinal disorders, specific visual, olfactory and taste stimuli, movement or an illusion of movement, emotions, and toxins. Nauseating stimuli are mediated to the brainstem via sympathetic nerves and by several receptors. In addition, vagal nerve contributes by mediating stimuli from the gastrointestinal tract. (Balaban & Yates, 2017; Ganong, 2003; Koch & Hasler, 2017)

Nausea often precedes vomiting. Vomiting, however, is a reflex. Vomiting cascade, which leads to expelling of gastric contents, is launched in the brain if emetic stimuli increase enough. (Fejzo et al., 2019; Ganong, 2003; Koch & Hasler, 2017)

2.1.2 Definitions of nausea and vomiting of pregnancy and hyperemesis gravidarum

NVP and HG are clinically defined in the absence of other factors that could explain the symptoms (American College of Obstetricians and Gynecologists, 2018; The Royal College of Obstetricians and Gynaecologist, 2016). In general, NVP is defined according to typical symptoms (nausea and/or vomiting in a pregnant woman) and typical occurrence of the symptoms in early pregnancy (**Table 1**). Mostly, NVP symptoms present as mild or moderate. (Aitokallio-Tallberg & Pakarinen, 2005; American College of Obstetricians and Gynecologists, 2018; Fejzo et al., 2019;

Gadsby et al., 1993; The Royal College of Obstetricians and Gynaecologist, 2016; Whitehead et al., 1992)

HG, on the contrary, is rare and is considered to represent the most severe end in the spectrum of NVP symptoms (Fejzo et al., 2019). Clinically, HG is defined in most studies as intractable NVP with dehydration, electrolyte imbalances and starvation leading to weight loss of more than 5% of pre-pregnancy weight. Some women may have ketonuria. (Fejzo et al., 2019; Källén, 1987; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014) Compared to more ordinary NVP, HG symptoms may arise in earlier gestational weeks (gwk) and last throughout pregnancy (Mullin et al., 2012). High proportion of women suffering from HG need hospital admissions, often repeatedly (Fiaschi et al., 2016; Gazmararian et al., 2002; Nurmi et al., 2022).

As the symptoms of NVP and HG are overlapping and definitions are clinical, no single international definition has existed in scientific literature. Thus, some studies combine both NVP and HG, whereas others have tried to strictly focus on women with only NVP or only HG leading to mixed definitions. Therefore, the lack of universal definitions has hampered the comparison of the results in meta-analyses (Grooten et al., 2015; Koot et al., 2018).

However, during recent years, considerable efforts have been made to reach a consensus definition of HG to unify reporting in clinical studies. As a result, in 2021, Jansen et al.(Jansen et al., 2021) published a consensus definition of HG called the Windsor definition **(Table 1**), which was made in cooperation by researchers, clinicians and patient representatives. The Windsor definition of HG emphasises the clinical severity of symptoms and their effect on managing daily routines, but excludes any strict limit of weight loss and the presence of urine ketones (Jansen et al., 2021). Similar patient–clinician cooperation has generated a list of research priorities and core outcome set in HG (Dean et al., 2021; Jansen et al., 2020).

Table 1. Clinical definitions of nausea and vomiting of pregnancy and hyperemesis gravidarum.

Clinical definition of NVP	Clinical definition of HG	The Windsor definition of HG
Pregnant woman with • Nausea and/or vomiting • Symptoms have started in the first trimester • Other possible causative factors can sufficiently be ruled out	Pregnant woman with • Severe nausea and vomiting • Symptoms have started in the first trimester • Other possible causative factors can sufficiently be ruled out • Dehydration • Electrolyte imbalances • Weight loss > 5% (from pre-pregnancy weight) • Ketonuria	Each of the following criteria required: • Severe nausea and/or vomiting • Symptom start in early pregnancy ≤ 16 gwk • Inability to eat and/or drink normally • Strongly limits daily living activities Contributory but not mandatory: signs of dehydration

gwk gestational week; HG hyperemesis gravidarum; NVP nausea and vomiting of pregnancy

2.1.3 Aspects of nausea and vomiting of pregnancy

The clinical presentation of NVP varies. Women may experience only nausea, nausea accompanied with vomiting or only vomiting. Nausea seems to be more common compared to vomiting but most women with NVP suffer from both (Chan et al., 2011; Choi et al., 2018; Gadsby et al., 1993; Källén et al., 2003; Kramer et al., 2013; Whitehead et al., 1992). A smaller proportion of women present only nausea (Chortatos et al., 2013; Gadsby et al., 1993) or only vomiting (Emelianova et al., 1999; Gadsby et al., 2020). In addition, dry retching occurs (Fejzo et al., 2008; Smith et al., 2000; Thaxter Nesbeth et al., 2016; Wong et al., 2022). Further, women report hypersalivation, sensitivity to odours, gastrointestinal reflux, headache and fatigue as accompanying symptoms (Bai et al., 2016; Fejzo et al., 2008; Gill et al., 2009a; Lacasse et al., 2009b; Swallow et al., 2005).

Contrary to a general phrase of ‘morning sickness’, most women experience NVP variedly during the day and also night time, although vomiting may occur more frequently in the morning (Gadsby et al., 1993, 2020; Lacroix et al., 2000; Whitehead et al., 1992). Daily symptom diaries have revealed nausea lasting predominantly all day (Gadsby et al., 1993, 2020; Lacroix et al., 2000).

2.1.3.1 Onset and duration of symptoms

When assessed with daily symptoms diaries, the onset of NVP may be as early as 11 to 20 days after ovulation (Gadsby et al., 2021). When the last menstrual period was used as a reference, the mean onset of NVP was reported to be after 39 days (Gadsby et al., 1993). Assessed with gwk, typical onset of NVP has been reported to occur between gwk 5 to 7, with the symptoms peak around gwk 9–13 (Chan et al., 2011; Lacroix et al., 2000).

Typical duration of NVP has been reported to be 8–9 weeks (Chan et al., 2011; Källén et al., 2003). Women with only nausea had shorter duration of symptoms compared to women with both nausea and vomiting (Chortatos et al., 2013). Cessation of symptoms may be sudden (Gadsby et al., 1993) or NVP may resolve after intermittent symptoms (Lacroix et al., 2000). More than 90% women reported NVP symptoms cessation after 112 days from the last menstrual period (Gadsby et al., 1993) or near gwk 20 (Choi et al., 2018; Whitehead et al., 1992) or after gwk 22 (Lacroix et al., 2000).

Thereby, the course of NVP is mostly limited to the first or early second trimester. However, estimations of the frequency of prolonged, beyond mid-pregnancy lasting NVP vary from 1.1% (Chan et al., 2011) to nearly 10% (Whitehead et al., 1992) or even up to 20–32% (Lindseth & Vari, 2005; Louik et al., 2006; Parker et al., 2014). Moreover, the symptoms may last considerably longer, even until delivery (Kramer et al., 2013; Mullin et al., 2012).

2.1.4 Epidemiology

The reported occurrence of NVP has varied from 33% to over 90% of pregnant women depending on different study designs, study populations and methods of estimating NVP (**Table 2**). In their meta-analysis, Einarson et al. (Einarson et al., 2013) have counted a median global NVP rate of 69%. When assessing nausea and vomiting separately, Petry et al. (Petry et al., 2018) reported the percentages of 38.3% and 38.2%, respectively (total n=1218). Furthermore, Klebanoff et al. (Klebanoff et al., 1985) investigated only the occurrence of vomiting in the absence of hyperemesis (56%, total n=9098) in early pregnancy. Moreover, in a study of Gadsby et al., 256 women kept record of their NVP symptoms with daily diaries in early pregnancy (Gadsby et al., 2020). In their study, the reported percentage for both nausea and vomiting was 58.6%, for nausea only 34.8% and for vomiting only 0.8% (Gadsby et al., 2020). By adding up the numbers, the overall symptom prevalence was calculated to be as high as 94.2%.

Instead, a considerable lower occurrence of NVP (6.4%) was reported by Temming et al. (Temming et al., 2014) in a large sample of women (n=81 486) in their first singleton pregnancy from the USA, derived from a voluntary pregnancy

risk screening and education programme established by the employer or insurance plan. In their study, only the existence of NVP affecting quality of life (QoL) was inquired which possibly led to underestimation of the overall NVP and overlapping with HG.

Similarly, studies regarding the incidence of HG have yielded variable results. Overall, the estimations of the incidence of HG have been reported between 0.3–3.6% (Bailit, 2005; Fiaschi et al., 2016; Källén, 1987; Matsuo et al., 2007; Vikanes et al., 2008) but up to 10.8% was reported in one Chinese study (Zhang & Cai, 1991). In the Finnish population, the incidence of HG was 1.3% in a nation-wide register-based study (Nurmi et al., 2020).

Table 2. Occurrence of nausea and vomiting of pregnancy in previous studies.

Author	Year	Country	Total n	NVP rate	Study design	Method of assessing NVP
Weigel et al.	1988	USA	825	71%	Retrospective cohort	Nausea and/or vomiting (yes/no)
Whitehead et al.	1992	UK	1000	85%	Retrospective cohort	Nausea and/or vomiting (yes/no)
Gadsby et al.	1993	UK	363	80%	Prospective cohort	Daily diaries
Emelianova et al.	1999	Canada	193	67%	Prospective cohort	Nausea or vomiting (yes/no)
Lacroix et al.	2000	Canada	160	74%	Prospective cohort	Daily diaries and McGill Nausea Questionnaire
Lindseth et al.	2005	USA	116	70% 32% late pregnancy	Prospective cohort	NVPI
Louik et al.	2006	USA	22 487	67%	Retrospective cohort	Nausea and vomiting (yes/no)
Chou et al.	2008	Taiwan	243	77%	Cross-sectional cohort	INVR
Lacasse et al.	2009	France	367	79%	Prospective cohort	Modified-PUQE
Chan et al.	2011	USA	2407	89%	Prospective cohort	Nausea and/or vomiting (yes/no)
Chortatos et al.	2013	Norway	51 675	33% 39% only nausea	Population-based cohort	Nausea or vomiting (yes/no)
Kramer et al.	2013	Canada	648	63% early pregnancy 45% late pregnancy	Prospective cohort	NVPI
Parker et al.	2014	USA	560	63%	Retrospective cohort	Nausea and/or vomiting (yes/no)
Nazik et al.	2014	Turkey	909	88%	Retrospective cohort	Nausea and/or vomiting (yes/no)
Temming et al.	2014	USA	81 486	6%	Retrospective cohort	NVP that affected QoL (yes/no)
Dochez et al.	2016	France	399	60%	Retrospective cohort	Modified-PUQE
Yilmaz et al.	2016	Turkey	200	74%	Cross-sectional cohort	Rhodes score
Tan et al.	2017	Australia	116	72%	Prospective cohort	PUQE
Choi et al.	2018	Korea	527	81%	Retrospective cohort	PUQE
Petry et al.	2018	USA	1218	38% nausea	Prospective cohort	Nausea or vomiting (yes/no)

Author	Year	Country	Total n	NVP rate	Study design	Method of assessing NVP
				38% vomiting		
Muchanga et al.	2020	Japan	11 028	85%	Retrospective cohort	Nausea and/or vomiting (yes/no)
Gadsby et al.	2020	UK	256	59% 35% only nausea	Prospective cohort	Daily diaries

INVR index of nausea, vomiting and retching; NVP nausea and vomiting of pregnancy; NVPI nausea and vomiting in pregnancy instrument; PUQE pregnancy unique quantification of emesis; QoL quality of life; UK United Kingdom; USA United States of America

2.2 Evaluation of symptoms

NVP is one discussion topic during routine visits in maternity health care clinics (MHCC). Yet, the estimation of the severity of symptoms, treatment monitoring and follow-up may be challenging without a structured instrument. Evaluation of symptoms by interviewing the patient face to face or by telephone is the traditional method for clinicians but with emerging telemedicine, also mobile apps are being tested (Ngo et al., 2022).

Several questionnaires to assess the severity and aspects of NVP, and the impact of NVP on QoL have been developed for research purposes and for clinicians (**Table 3**). Initially, NVP symptoms have been evaluated with questionnaires originally developed for estimating chemotherapy-induced nausea in cancer patients, for instance with the Rhodes Index of Nausea, Vomiting and Retching (INVR, the Rhodes score) (Rhodes et al., 1984; Rhodes & McDaniel, 1999) and McGill Nausea Questionnaire (Melzack et al., 1985). The Rhodes score includes eight questions concerning duration, frequency, and distress of the symptoms of nausea, vomiting and retching, as well as the amount of vomits (Rhodes et al., 1984; Rhodes & McDaniel, 1999). McGill Nausea Questionnaire consists of three parts: a nausea rating index, where different words describing nausea are selected and ranked by numbers, a numerical overall nausea intensity estimation and a visual analogue scale (VAS) rating of the intensity of nausea (Melzack et al., 1985).

Table 3. Different questionnaires used for assessing nausea and vomiting of pregnancy and hyperemesis gravidarum.

Questionnaire	Abbreviation	Author	Year	Country	Symptom domains	Number of questions / items	Description / Comment
(Rhodes) Index of Nausea and Vomiting	INV / INV-2 / Rhodes score	Rhodes et al.	1984	USA	Duration, frequency, and distress from nausea, vomiting and retching and the amount of vomiting	8	Developed originally to assess nausea, vomiting and retching in cancer patients receiving chemotherapy
McGill Nausea Questionnaire	-	Melzack et al.	1985	Canada	Nausea rating index, overall nausea by VAS	11	Developed originally to assess nausea in cancer patients receiving chemotherapy
(Rhodes) Index of Nausea, Vomiting and retching	INVR / Rhodes score	Rhodes et al.	1999	USA	Duration, frequency, and distress from nausea, vomiting and retching and the amount of vomiting	8	Developed originally to assess nausea, vomiting, and retching in cancer patients receiving chemotherapy
Nausea and Vomiting in Pregnancy Instrument	NVPI	Swallow et al.	2002	USA	Frequency of nausea, vomiting and retching	3	To assess NVP symptoms from the past week
Motherisk[1] Pregnancy-Unique Quantification of Emesis	PUQE	Koren et al.	2002	Canada	Duration of nausea, frequency of vomiting and retching; general wellbeing by VAS	3	The 'original' PUQE to assess NVP symptoms and general wellbeing from previous 12 hours
Health-Related Quality of Life for Nausea and Vomiting of Pregnancy	NVP-QOL	Magee et al.	2002	Canada	Physical symptoms / aggravating factors, fatigue, emotions, limitations	30	To assess QoL in NVP

Questionnaire	Abbreviation	Author	Year	Country	Symptom domains	Number of questions / items	Description / Comment
24-hour Pregnancy-Unique Quantification of Emesis	PUQE-24	Ebrahimi et al.	2009	Canada	Nausea, vomiting, retching	3	To assess NVP symptoms from previous 24 hours
Modified Pregnancy-Unique Quantification of Emesis	Modified-PUQE	Lacasse et al.	2009	Canada	Nausea, vomiting, retching	3	To assess NVP symptoms over the whole first trimester
Hyperemesis Impact of Symptoms	HIS Score	Power et al.	2010	UK	Ability to tolerate food and fluids, fatigue, emotional state, social dysfunction, psychosocial distress	10	To holistically assess the impact of physical and psychosocial symptoms of HG
HyperEmesis Level Prediction Score	HELP Score	MacGibbon et al.	2021	USA	Nausea, vomiting, retching, urinary output, medication, general coping and social dysfunction, weight loss, course of symptoms	12	To assess HG symptoms in more detail. Mobile app piloted.

[1]Motherisk: a former clinical and research program in the Hospital of Sick Children in Toronto, Canada

HG hyperemesis gravidarum; HIS hyperemesis impact of symptoms; HELP hyperemesis level prediction; INV index of nausea and vomiting; INVR index of nausea, vomiting and retching; NVP nausea and vomiting of pregnancy; PUQE pregnancy-unique quantification of emesis; QoL quality of life; UK United Kingdom; USA United States of America; VAS visual analogue scale

2.2.1 Pregnancy-Unique Quantification of Emesis Questionnaire

Pregnancy-Unique Quantification of Emesis questionnaire (PUQE) (**Table 4**) was originally developed around two decades ago by Canadian researchers from a NVP Healthline in need for a simpler tool than the Rhodes score to assess the severity of NVP. The researchers belonged to the former Motherisk program, a research and counselling service of potentially harmful substances during pregnancy at The Hospital of Sick Children in Toronto. After prospectively collecting Rhodes scores from 283 women, the researchers explored the correlations of the answers to each question to the total score and compared the distribution of the severity of different combinations of questions to the total score. Finally, three questions concerning the duration of nausea in hours and the frequency of both vomiting and retching episodes were selected to form a new NVP scoring system named the PUQE. (Koren et al., 2001, 2002; Koren & Cohen, 2021; Rhodes et al., 1984; Rhodes & McDaniel, 1999)

Table 4. The Motherisk PUQE scoring system. Reprinted from Koren et al. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. Am J Obstet Gynecol 2002;186(5):S228–S231, with permission from Elsevier.

Pregnancy-Unique Quantification of Emesis (PUQE)				
1. In the last 12 hours, for how long have you felt nauseated or sick to your stomach				
Not at all	1 hour or less	2 to 3 hours	4 to 6 hours	More than 6 hours
(n=1)	(n=2)	(n=3)	(n=4)	(n=5)
2. In the last 12 hours, have you vomited or thrown up				
7 or more times	5 to 6	3 to 4	1 to 2	1 did not throw up
(n=5)	(n=4)	(n=3)	(n=2)	(n=1)
3. In the last 12 hours, how many times have you had retching or dry heaves without bringing anything up				
No time	1 to 2	3 to 4	5 to 6	7 or more
(n=1)	(n=2)	(n=3)	(n=4)	(n=5)
Total score (summary of n): no symptoms 3; mild 4–6; moderate 7–12; severe ≥13.				

The three PUQE questions are all rated separately in a scale of 1 to 5, where higher number indicates longer duration and more frequent symptoms. In the second PUQE question the item is phrased in descending order. The PUQE score is the sum of the points of the three questions. Total of 3 points equal no NVP, 4–6 points mild

NVP, 7–12 points moderate NVP and ≥ 13 points indicate severe NVP. (Koren et al., 2002)

In the original version of the PUQE, the symptoms were inquired from the past 12 hours, similarly as in the Rhodes score (Koren et al., 2002). Two extensions of the PUQE have been generated. Firstly, to better encompass symptoms from the entire previous day, a 24-hour PUQE (PUQE-24) was developed by the Motherisk research team (Ebrahimi et al., 2009). Secondly, the researchers developed the Modified-PUQE encompassing symptoms from the entire first trimester of pregnancy (Lacasse et al., 2008b).

In addition to the evaluation of physical symptoms, a single 10 centimetre VAS scale for rating overall wellbeing from 'worst possible' to 'best possible', was added to the original PUQE (Koren et al., 2002). Still, a tool to assess QoL impairment especially in women with NVP was needed, leading to the development of the Health-Related Quality of Life for Nausea and Vomiting of Pregnancy (NVP-QOL) also by the researchers of the Motherisk program (Magee et al., 2002). NVP-QOL has been mainly targeted for research purposes as it is more extensive compared to the PUQE. NVP-QOL includes altogether 30 questions from four different domains: physical symptoms and aggravating factors, fatigue, emotions, and limitations (Magee et al., 2002). NVP-QOL was validated a few years after the first introduction in a prospective cohort study of 367 women for internal consistency and against 12-item Short-Form Health Survey (SF-12) (Lacasse & Bérard, 2008).

2.2.1.1 Clinical and research applications

The original PUQE has been validated in prospective cohorts of pregnant women for each studied endpoint. The women were recruited from callers to NVP Healthline, and medical details were collected by interview. The PUQE scores and women's (n=223) intake of multivitamin tablets, number of emergency room visits and rates of hospitalization in different PUQE categories (n=200), and general wellbeing estimations by VAS were compared showing that more severe NVP was associated with discontinuation of vitamins, more frequent hospitalizations and lower general wellbeing estimations (Koren et al., 2005). From 200 women studied, 21 women had HG and they were all hospitalised. Further, 2.5%–6% of women who rated mild to moderate NVP (n=2/16 and n=11, respectively) were hospitalised compared to 33% of women rating severe NVP (n=8/24). In addition, the estimated weekly direct health care costs of NVP management were shown to be associated with the severity of NVP. (Koren et al., 2005).

Similarly, in a prospective cohort of 315 women, more severe PUQE-24 scores were associated with women's inability to continue taking vitamins, more frequent hospitalizations and lower QoL estimations (Ebrahimi et al., 2009). However, no

association was found between NVP and liquid intake (Ebrahimi et al., 2009). Moreover, to validate the Modified-PUQE, comparisons of simultaneously filled scores of the original PUQE and Modified-PUQE by 287 pregnant women showed substantial concordance (Lacasse et al., 2008b).

Several studies have applied the PUQE for assessing the severity and determinants of NVP **(Figure 1**) (Choi et al., 2018; Dochez et al., 2016; Heitmann et al., 2017; Lacasse et al., 2009b; Tan et al., 2018), the impact of NVP on QoL (Clark et al., 2013; Heitmann et al., 2017; Lacasse et al., 2008a; Munch et al., 2011) and the medication used for NVP (Heitmann et al., 2016; Lacasse et al., 2009a). Instead of categorising the severity of NVP, some NVP studies have used only continuous PUQE scores (Gill et al., 2009a; Jafari-Dehkordi et al., 2017; Lehmann et al., 2013; Metz et al., 2022; Zhang et al., 2021). Moreover, in the study of Gadsby et al. where the women filled in daily diaries of NVP symptoms, the PUQE was mentioned as a model for their study questionnaire (Gadsby et al., 2021). Furthermore, the PUQE has been used in randomised controlled trials (RCT) investigating management of NVP. One RCT evaluated the effect of compression stockings for relieving NVP (Mendoza & Amsler, 2017), one study tested acupressure as adjacent therapy in NVP (Adlan et al., 2017), another study compared inpatient and outpatient care in severe NVP/HG (Mitchell-Jones et al., 2017), and one study evaluated the impact of mobile app for tracking NVP symptoms (Ngo et al., 2022). Moreover, the PUQE has been used for comparing NVP symptoms in pregnancies conceived from different assisted reproduction techniques (Wong et al., 2022).

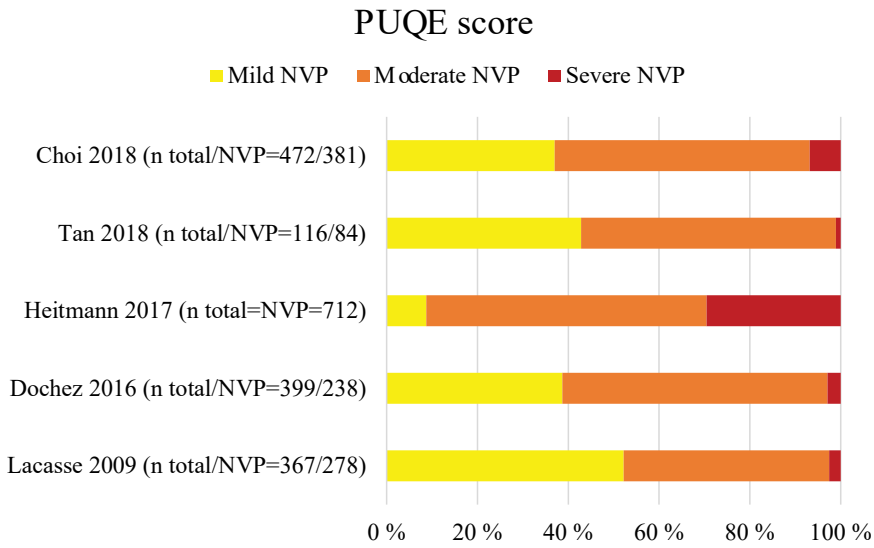

Figure 1. The severity of NVP according to PUQE in previous cohort studies. NVP nausea and vomiting of pregnancy; PUQE pregnancy-unique quantification of emesis questionnaire

The PUQE has also been used in cohort studies of HG (Koot et al., 2020; Koot, Grooten, et al., 2020; Nijsten et al., 2022). The Norwegian PUQE has been validated as a robust indicator for poor nutritional intake in women with HG (n=38), showing also a decrease in PUQE scores along inpatient treatment (Birkeland et al., 2015), similarly as a study of women hospitalised due to HG (n=81) in Nepal (Chhetry et al., 2016). Further, Munch et al. have compared the QoL of women with NVP and HG (Munch et al., 2011). Furthermore, several RCTs investigating HG medication and treatment arrangements have based their comparisons on PUQE scores (Fletcher et al., 2015; Grooten et al., 2017; Guttuso et al., 2020; Maina et al., 2014; Maltepe & Koren, 2013; McParlin, Carrick-Sen, et al., 2016; Mohd Nafiah et al., 2022; Ostenfeld et al., 2020).

Internationally, the PUQE has been implemented in many NVP management guidelines and clinical recommendations (American College of Obstetricians and Gynecologists, 2018; Laitinen & Polo, 2019; Lowe et al., 2019; The Royal College of Obstetricians and Gynaecologist, 2016; Å. Vikanes et al., 2014). Accordingly, the PUQE has been translated into several languages, for instance into Dutch, Finnish, French, Japanese, Norwegian, Korean, Spanish and Turkish (Birkeland et al., 2015; Choi et al., 2018; Dochez et al., 2016; Ebrahimi et al., 2009; Grooten et al., 2017; Hada et al., 2021; Lacasse et al., 2008b; Yilmaz et al., 2022).

2.2.2 Other questionnaires

Although the PUQE is widely used by researchers and clinicians, other questionnaires have been developed, as well. The Nausea and Vomiting in Pregnancy Instrument (NVPI) was introduced around the same time as the PUQE with similar intention to develop a concise tool specifically for NVP, mainly for research purposes (Swallow et al., 2002). The NVPI consists of three questions concerning the frequency of nausea, vomiting, and retching during the past week in a six-point scale corresponding 'not at all', 'occasionally, '3–6 days during the week', 'daily', 'more than once a day' and 'all the time', with total NVPI sum score ranging 0–15 points (Swallow et al., 2002). In addition to other studies of the severity of NVP and associative factors by the original developer (Swallow et al., 2004, 2005), also Kramer et al. (Kramer et al., 2013) used the tool in their prospective cohort study of the severity and determinants of NVP in 648 women filling the NVPI repeatedly in two time points during pregnancy. In their study (Kramer et al., 2013), the NVPI scores were lower in late pregnancy compared to early pregnancy and a considerably high proportion of women (45%) experienced NVP also in late pregnancy (mean gwk 31).

Two questionnaires are developed particularly for HG. The first one, the Hyperemesis Impact of Symptoms questionnaire (HIS score) (Power et al., 2010), has been targeted to nurses and midwifes. HIS score aims to gain a more holistic approach to HG leading to individualised care. The HIS score consists of 10 questions scored from 0 to 3 concerning inability to keep down food and liquids, social dysfunction and psychosocial distress from the past 24 hours. In the validation study, HIS scores have been compared to PUQE scores and two other tools, the Hospital Anxiety and Depression score and SF-12, showing strong correlations (Power, Campbell, et al., 2010). HIS score has been used in one RCT of 273 hospitalised HG women comparing the usual care to individualised midwifery support tailored by HIS score (Fletcher et al., 2015). However, after two weeks follow-up, no significant differences were found between groups in HIS scores, and neither in the PUQE scores or QoL scores of the women (Fletcher et al., 2015).

The second one, HyperEmesis Level Prediction score (HELP score) (Macgibbon et al., 2021) has recently been developed to gain more thorough evaluation of symptoms and disease course especially of severe NVP and HG. It consists of 12 questions of domains considered as indicators of severe disease: the frequency of vomiting and retching episodes, the amount of urine output, the severity of nausea or vomiting 1 hour after medication or after eating or drinking, ability to work, coping with symptoms, estimation of intake, tolerance and number of prescribed medications, weight loss and the course of symptoms. The total HELP score has a wide range from mild (≤ 19 points), moderate (20–32 points), to severe (33–60 points). In the validation study, HELP scores of 445 women with HG were compared

to the PUQE scores, showing HELP scores of women with severe symptoms being more often in the severe category compared to PUQE score categories (Macgibbon et al., 2021).

2.3 Etiology and pathogenesis

Along with many other complex medical entities affecting only females, historically NVP was considered of psychologic origin. From the late 19th century, the predominant theories of the etiology of NVP have evolved from 'hysteria and toxins', psychological theories and hormonal explanations to genetics (Fejzo et al., 2019; Munch, 2002; O'brien & Newton, 1991) (**Figure 2**). From an evolutionary point of view, it has been suggested that NVP has protected the fetus from exposure of potentially harmful substances, for instance via spoiled food (Sherman & Flaxman, 2002).

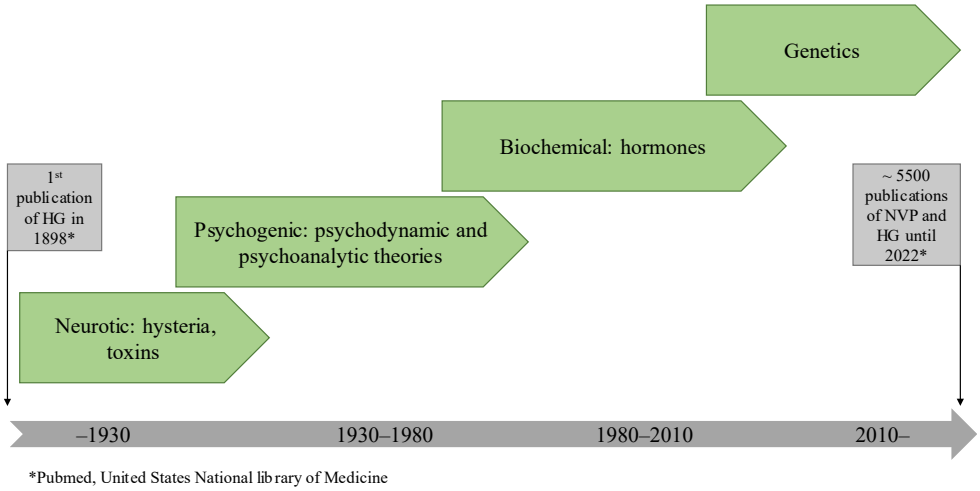

Figure 2. Predominant theories of the etiology of nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG).

Despite decades of research, the exact comprehensive explanation of the etiology and pathogenesis of NVP remains unknown. While several pathways induce nausea in general, also multiple pathways may lead to NVP. Thus, the condition is considered multifactorial as several maternal, genetic, hormonal, gastrointestinal and psychological factors play a role. Emerging progress has been seen especially in genetic studies in recent years. All in all, NVP is nowadays considered to be based on biological origins. (Fejzo et al., 2019; Goodwin, 2002; Liu et al., 2022)

2.4 Associative factors

Several factors have been shown to be associated with occurrence, severity and recurrence of NVP and HG (**Figure 3**). However, conflicting results concerning some of these factors have been reported. Variation can be explained with different NVP definitions, study designs and populations, but it may also reflect the multifactorial origin of NVP. In view of the pathophysiology of general nausea, many factors may share common mechanisms and pathways. On the other hand, each woman may have unique sensitivity to NVP based on several mechanisms and pathways, and each pregnancy of these women may be different in terms of the existence and severity of NVP.

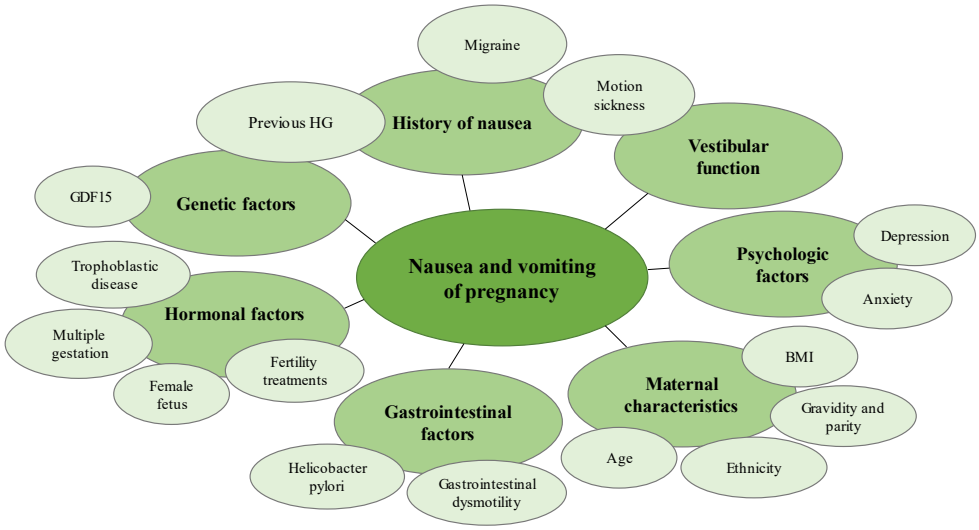

Figure 3. Factors associated with nausea and vomiting of pregnancy. BMI body mass index; GDF15 growth and differentiation factor 15; HG hyperemesis gravidarum

2.4.1 Maternal characteristics

Maternal young age has been associated with increased risk of NVP (Bailit, 2005; Klebanoff et al., 1985; Mullin et al., 2012; Roseboom et al., 2011). Higher gravidity (Louik et al., 2006; Nurmi et al., 2020; Vilming & Nesheim, 2000) has been associated with NVP. Primiparity (Bashiri et al., 1995; Roseboom et al., 2011) but also on the other hand multiparity (Järnfelt-Samsioe et al., 1985) have been associated with NVP. Underweight women with body mass index (BMI) less than 18.5 kilograms (kg)/square meters (m^2) (Nurmi et al., 2020) or BMI less than 20 kg/m^2 (Cedergren et al., 2008), women with lower pre-pregnancy weight (under 50.5 kg or under BMI 20.2 kg/m^2) (Matsuo et al., 2007) and on the other hand overweight

women with BMI ≥ 25 kg/m^2 have been identified having increased risk of NVP and HG (Chortatos et al., 2013; Nurmi et al., 2020; Vikanes et al., 2010). Weight over 150 pounds (68 kg) was associated with prolonged HG, compared to non-HG controls with mean weight of 138 pounds (63 kg) (Mullin et al., 2012). Hence, normal body weight may be considered as protective. Maternal allergies, asthma and immune disorders, as well as hyperthyroidism and pre-existing diabetes have been associated with HG (Ashebir et al., 2022; Fell et al., 2006; Tian et al., 2017). Maternal allergies prior to pregnancy have been associated with prolonged HG (Mullin et al., 2012).

Several studies report partly conflicting associations concerning ethnicity. Non-western (Roseboom et al., 2011), black and Asian women have been less likely to have NVP (Lacasse et al., 2009b), whereas Eastern Asian women (Matsuo et al., 2007), black women (Chan et al., 2011; Louik et al., 2006), non-white women (Bailit, 2005) and Hispanic women have been reported susceptible to NVP (Weigel & Weigel, 1988). Further, immigrants have been identified as a risk group (Lacasse et al., 2009b; Vikanes et al., 2008; Vilming & Nesheim, 2000).

Regarding socioeconomic factors, low socioeconomic status including low household income (Lacasse et al., 2009b; Lacroix et al., 2000; Louik et al., 2006; Roseboom et al., 2011) has been associated with NVP. Further, less-educated women (Lacroix et al., 2000; Louik et al., 2006), women working part-time (Lacroix et al., 2000), unemployed women (Kramer et al., 2013), housewives (Weigel & Weigel, 1988), and single women (Bailit, 2005) have been reported having increased likelihood of NVP.

Besides during pregnancy, nausea and vomiting can be experienced in several other circumstances. Thus, previous history of nausea in another context may predispose to NVP. Women having experienced nausea as a side effect of oral contraceptives and migraineurs have been reported to be more likely to vomit in pregnancy (Tian et al., 2017; Whitehead et al., 1992). Similarly, women suffering from motion sickness have been identified as a risk group (Gadsby et al., 1997; Järnfelt-Samsioe et al., 1985; Tian et al., 2017; Whitehead et al., 1992). As the vestibular system is known to affect nausea in general, it has been suggested to be involved also in NVP (Black, 2002). In women with HG some vestibular abnormalities, like differences in vestibulo-ocular reflex assessed by vestibular autorotation test and video head impulse test, have been found compared to women without HG (Goodwin et al., 2008; Tulmaç et al., 2021).

In addition, women's own history of NVP or HG in previous pregnancies have been reported as risk factors (Gadsby et al., 1997; Nurmi et al., 2018). Estimations of the recurrence of HG have varied considerably, from 15% up to 89% depending on study designs and populations (Fejzo et al., 2011; Nijsten et al., 2021; Nurmi et al., 2018; Trogstad et al., 2005), highlighting the differences between the same

woman's subsequent pregnancies, and thus reflecting the multifactorial origin of NVP. In a Finnish register-based study, the recurrence rate of HG was 24% (Nurmi et al., 2018). In addition, change of partner has not been found to have an significant effect on recurrence (Einarson et al., 2007; Fejzo et al., 2012).

Lifestyle factors may exacerbate or decrease the risk of NVP. Nutritional habits may contribute as high intake of carbohydrates and fibre has been associated with NVP (Chortatos et al., 2013; Latva-Pukkila et al., 2010; Reijonen et al., 2022). In addition, higher intake of fat has been reported in women with NVP compared to symptom-free women (Chortatos et al., 2013) and women with NVP have been shown to eat less protein than women without NVP (Latva-Pukkila et al., 2010). Restrictive diet (lactose-free, vegan, kosher) has been associated with prolonged HG (Mullin et al., 2012). Substance abuse prior to pregnancy has been associated with NVP (Roseboom et al., 2011). However, also lower risk of NVP with pre-pregnancy alcohol consumption (> 5 drinks/week in the six months prior conception) have been reported (Weigel & Weigel, 1988). Decreased risk of NVP in smokers versus non-smoking women has been noted in several studies (Källén et al., 2003; Nurmi et al., 2020; Vikanes et al., 2010).

2.4.2 Genetics

Genetic predisposition of NVP and HG have been suspected since several studies have shown familiar accumulation. Increased risk of NVP and HG have been reported in women whose mothers had been suffering from severe NVP (Fejzo et al., 2008; Gadsby et al., 1997; Vikanes et al., 2010; Whitehead et al., 1992; Zhang et al., 2011). Also, increased risk with affected sisters have been found (Fejzo et al., 2008; Zhang et al., 2011). An international twin study by Colodro-Conde et al. (Colodro-Conde et al., 2016) have reported high hereditary estimates.

Whole genome sequencing techniques have further revealed certain genes to be more frequently expressed in women with HG (Fejzo et al., 2017, 2018, 2022). Especially, association with an appetite-mediating, cachexia-related hormone of placental origin, called the growth and differentiation factor 15 (GDF15), has been discovered (Fejzo et al., 2019; Fejzo et al., 2018; Walker & Thompson, 2018). High levels of serum GDF15 have been measured in women reporting NVP lasting up to second trimester and in women using antiemetics during pregnancy (Petry et al., 2018).

2.4.3 Hormones

Significant hormonal changes occur already in early pregnancy compared to non-pregnant state. Human chorionic gonadotropin (hCG) is a hormone secreted by

placental cells with increasing concentrations from early pregnancy, almost simultaneously with the rise of NVP symptoms. This finding has led to studies of the associations between hCG and NVP and brought up speculations of the role of hCG in the pathophysiology of NVP (Furneaux et al., 2001). Higher concentrations of hCG have been measured in women with HG compared to healthy pregnant controls (Goodwin et al., 1992; Kauppila et al., 1979; Korevaar et al., 2015). In addition, conditions associated with high hCG levels such as multiple pregnancy and molar pregnancy (hydatidiform mole, a trophoblastic disease with exceptionally high concentrations of hCG (Soto-Wright et al., 1995)), have been associated with HG (Bailit, 2005; Fell et al., 2006; Fiaschi et al., 2016; Källén, 1987).

On the contrary, other studies have not found an association between elevated hCG levels and HG (Dypvik et al., 2018; Niemeijer et al., 2014; Verberg et al., 2005). Maternal and fetal determinants affect total hCG concentrations which have been shown to vary substantially in different gwks (Korevaar et al., 2015). Further, genetic studies referred above have not reported associations between hCG genes and HG (Fejzo et al., 2018).

During pregnancy, a marked increase can be seen in levels of serum estradiol and progesterone, as well. Their concentrations, however, rise towards the end of pregnancy, contrary to the typical timing of NVP. Nevertheless, the associations of these hormones and NVP have been investigated showing differences in women with NVP (Järnfelt-Samsioe et al., 1986; Walsh et al., 1996).

Carrying a female fetus have been reported to be associated with an increased risk of NVP and HG (Fell et al., 2006; Fiaschi et al., 2016; Nurmi et al., 2020; Schiff et al., 2004; Vilming & Nesheim, 2000; Young et al., 2021). However, opposite findings concerning fetal gender has also been reported (Chan et al., 2011). In addition, assisted reproduction techniques may contribute to the risk of NVP and HG (Bazargani et al., 2021; Nurmi et al., 2020; Roseboom et al., 2011; Wong et al., 2022).

The thyroid gland is stimulated by hCG in early pregnancy, in some women leading to transient biochemical hyperthyroidism, which may co-occur with HG (Goodwin et al., 1992; Guo et al., 2022; Nijsten et al., 2021). Despite this, changes in thyroid hormones are generally not considered to be associated with the severity of NVP or HG (Niemeijer et al., 2014; Nijsten et al., 2021). In general, nausea is not a typical symptom of hyperthyroidism (De Leo et al., 2016).

2.4.4 Gastrointestinal factors

Changes in gastric motility have effects on the feeling of nausea in general, thereby, gastric dysrhythmias have been studied in NVP (Koch, 2002; Walsh et al., 1996). Regarding gastrointestinal symptoms, heartburn, acid reflux, chronic constipation

and diarrhea, and irritable bowel have been associated with more severe NVP and HG (Fell et al., 2006; Gill et al., 2009a; Tian et al., 2017).

Helicobacter pylori, a gram-negative bacterium adapted to survive in the acidic environment of gastric mucosa, has been recognised as a risk factor for vomiting in pregnancy and HG (Golberg et al., 2007; Grooten et al., 2017; Mansour & Nashaat, 2009; Ng et al., 2018). However, the clinical significance of helicobacter pylori might be negligible in Western countries due to its declining overall prevalence compared to developing countries (Hooi et al., 2017). Interestingly, in women with HG, also changes in the gut microbiota based on faecal samples have been observed (Jin et al., 2020; Nilsen et al., 2020).

2.4.5 Psychological factors

Prior depression, as well as depressive and anxiety symptoms during pregnancy have been associated with NVP and HG in several studies (Balik et al., 2015; Chou et al., 2003; Kjeldgaard et al., 2017; Köken et al., 2008; Kramer et al., 2013; Mitchell-Jones et al., 2017; Mitchell-Jones et al., 2020; Poursharif et al., 2008; Swallow et al., 2004; Tan et al., 2010; Yildirim & Demir, 2019; Yilmaz et al., 2016). These associations certainly point to a psychologic dimension in NVP. Notably, depression and anxiety have been shown to diminish along the treatment of HG (Tan et al., 2014). Given that depression is such a prevalent condition in pregnant women (Woody et al., 2017), the incidence of HG in depressed women has been estimated to be low (Fejzo, 2017; Kjeldgaard et al., 2017).

As mentioned above, historically psychological factors were regarded as major determinants of NVP (Fairweather, 1968). This has cast a long shadow over the topic, as affected women still have reported feeling stigmatised, leading to a call for a more comprehensive, holistic approach (Dean, 2016; Dean et al., 2018; Power et al., 2010). Current consensus regards psychological symptoms more as secondary manifestations caused by NVP and HG, not vice versa (Buckwalter & Simpson, 2002; Fejzo et al., 2019; Kjeldgaard et al., 2017; Mitchell-Jones et al., 2017; Mitchell-Jones et al., 2020).

Summary of associative factors for NVP in previous cohort studies using the PUQE is presented in **Table 5**.

Table 5. Associations of selected variables and NVP in previous studies using the PUQE.

Author, year, country	n total / n NVP	Age	Gravidity	Parity	BMI	Smoking	Marital status	Employment
Lacasse et al., 2009, Canada	367 / 288	Mean age 32±5 years. Age was not associated with NVP.	Primigravida women had less severe NVP OR 0.39 95% CI 0.20–0.78.	Parity of ≥ 2 was associated with more severe NVP OR 6.92 95% CI 2.47–19.36.	Pre-pregnancy BMI <25 n=193 (69%), ≤25<30 n=65 (23%), ≥35 n=23 (8%). BMI was not associated with NVP.	Pre-pregnancy smokers n=37 (13%) and n=9 (3%) during 1st trimester. Smoking was not associated with NVP.	Cohabiting n=281 (98%), single n=6 (2%). Living arrangement was not associated with NVP.	Working n=215 (75%), student or not working n=72 (25%). Employment was not associated with NVP.
Dochez et al., 2016, France	399 / 238	Mean age 31±4 years. Age was not associated with NVP.	-	Nulliparous n=83 (35%). Parity was not associated with NVP.	Mean pre-pregnancy BMI 24±6. Women with more severe NVP had higher BMI (p=0.008).	Smoking during 1st trimester n=45 (19%). Smokers had less NVP OR 0.68 95% CI 0.47–0.97, p=0.04.	Cohabiting n=233 (98%), single n=5 (2%). Living arrangement was not associated with NVP.	Working n=214 (90%), student / not working n=24 (10%). Employment was not associated with NVP.
Heitmann et al., 2017, Norway	712	Age ranged from under 25 (20%) to over 40 years (2%). Mean age not reported. Age was not associated with NVP.	-	Nulliparous n=382 (54%). Parity was not associated with NVP.	Pre-pregnancy BMI <18.5 n=33 (4%), >18.5≤24.9 n=421 (59%), <25≤29.9 n=139 (20%), ≥30 n=118 (17%). BMI was not associated with NVP.	Smokers n=27 (4%). Smoking was not associated with NVP.	Married / cohabiting n=661 (93%), not married / cohabiting n=51 (7%). Marital status was not associated with NVP.	Working n=570 (80%), unemployed / student / other n=142 (20%). Employment was not associated with NVP.

Author, year, country	n total / n NVP	Age	Gravidity	Parity	BMI	Smoking	Marital status	Employment
Tan et al., 2018, Australia	116 / 84	Mean age 32±4 years. Age was not associated with NVP.	Primigravida n=31 (37%). Gravidity was not associated with NVP.	Nulliparous n=51 (61%) and multiparous n=29 (35%). Parity was not associated with NVP.	Mean BMI 23±4. BMI was not associated with NVP.	Smokers n=3 (4%). Smoking was not associated with NVP.	-	Employed n=57 (68%), unemployed / student / other n=18 (22%). Employment was not associated with NVP.
Choi et al., 2018, Korea	472 / 381	<35 years n=225 (59%) and ≥ 35 years n=156 (41%). Age was not associated with NVP.	Gravidity 1 n=170 (45%), 2 n= 167 (44%), ≥ 3 n=44 (11%). Higher gravidity was associated with NVP in univariate analysis (p<0.001) but not in adjusted analysis.	-	-	Smokers n=11 (3%) vs n=8 (9%) in women with no NVP. Smoking was associated with no NVP in univariate analysis (p=0.010) but not in adjusted analysis.	Married n=377 (99%), unmarried n=4 (1%). Marital status was not associated with NVP.	Employed n=225 (53%), unemployed n=156 (41%). Employment was not associated with NVP.

BMI body mass index; NVP nausea and vomiting of pregnancy; OR odds ratio; PUQE pregnancy-unique quantification of emesis questionnaire
Variables shown in this table are selected to match with the variables assessed in the present study.

2.5 Diagnosis

Generally, NVP can be diagnosed if a pregnant woman suffers from nausea and/or vomiting in early pregnancy and other causative factors can be sufficiently ruled out. Predominantly, the diagnosis can be made mainly by interviewing. Clinical examination should focus on evaluation of signs of dehydration and starvation and simultaneously excluding differential diagnoses. The severity of NVP should be evaluated, for instance using a structured questionnaire. The PUQE is recommended in many international management guidelines. In addition, current medication, and history of other medical conditions, particularly conditions requiring absolute continuation of essential medications, should be recorded. (American College of Obstetricians and Gynecologists, 2018; Lowe et al., 2019; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014)

In the initial estimation, only few diagnostic tests, including clinical abdominal examination, laboratory tests (complete blood count, serum electrolytes and urine sample to detect ketonuria and infections) and obstetric ultrasonographic scan, are usually adequate (**Table 6**). Additional diagnostic tests, including further laboratory tests and radiological imaging may be required in women with atypical signs or symptoms, for instance fever, intensive headache or abdominal pain. Any findings pointing out to differential diagnoses should be recognised. (**Table 7**). Weight loss should be regularly monitored in prolonged NVP and with severe symptoms suggesting HG. At least in severe NVP/HG, additional laboratory tests are needed (**Table 7**). (American College of Obstetricians and Gynecologists, 2018; Lowe et al., 2019; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014)

Table 6. Basic diagnostic evaluation in nausea and vomiting of pregnancy.

Method	Purpose
Estimation of symptoms	To assess the severity of NVP. To exclude other causes of nausea and vomiting.
Interview, questionnaires	
Clinical examination	To assess general state and signs of dehydration. Compare current weight to pre-pregnancy weight. Additional examinations if any atypical findings (specified in Table 7).
Abdominal examination (inspection, auscultation, percussion, palpation)	
Blood pressure, pulse, temperature	
Weight	
Laboratory tests	To assess signs of dehydration and exclude other causes of nausea and vomiting. Additional laboratory tests should be considered if indicated by interview/clinical examination (specified in Table 7) or in case of prolonged symptoms.
Complete blood count	
Electrolytes	
Urine sample	
Ultrasonographic scan	To confirm: • intrauterine pregnancy, fetal viability and gwk • number of fetuses To exclude trophoblastic disease. May be scheduled for suitable time.

gwk gestational week; NVP nausea and vomiting of pregnancy

Table 7. Differential diagnoses in nausea and vomiting of pregnancy.

Differential diagnosis	Other symptoms	Additional clinical tests / radiology	Laboratory tests
Infections			
Gastroenteritis	Fever, abdominal pain, diarrhoea	-	CBC, CRP, fecal or blood culture for listeriosis
Hepatitis	Fever, jaundice, upper abdominal pain	Upper abdominal US	CBC, CRP, liver enzymes, serological tests
Appendicitis	Fever, lower abdominal pain	Abdominal US	CBC, CRP
Urinary tract infections	Fever, pain while urinating, back pain	In pyelonephritis urinary tract US	CBC, CRP, urinalysis
Gastrointestinal diseases[1]			
Gastric ulcer	Upper abdominal pain, hematemesis, melena	Gastroscopy	Helicobacter pylori testing
Cholecystolithiasis	Upper abdominal pain	Upper abdominal US	CBC, CRP, liver enzymes
Endocrine diseases			
Hyperthyroidism[2]	Goitre, palpitations, nervousness, sweating	Palpation of thyroid gland, US if needed	Thyroid function tests
Hyperparathyroidism	Constipation, tiredness, muscle weakness	-	Levels of calcium and parathyroid hormone
Diabetic ketoacidosis	Tiredness, headache	-	Blood glucose
Other			
Vestibular diseases, tumours (brain, gastrointestinal), intoxication, medication side effects, eating disorders, Addison's disease, porphyria			

This table summarises only the basic examinations during pregnancy and detailed recommendations can be found in clinical guidelines of each diagnosis.
CBC complete blood count including red and white blood cells and platelets; CRP C-reactive protein; NVP nausea and vomiting of pregnancy; US ultrasonographic scan
[1]Elevated liver enzymes may be present in NVP
[2]Transient biochemical hyperthyroidism may be present in NVP

2.6 Treatment

Treatment options of NVP depend on the severity of symptoms. In the assessment of the severity of NVP, woman's own subjective perception of her disease may differ from the objective evaluation by health care professionals (Chandra et al., 2002). So far, no curative option is available, and the treatment is focused on relieving the symptoms and improving hydration and nutritional status.

Usually, in mild cases, women can cope with dietary and lifestyle modifications. More intensive treatment includes antiemetic medications. Further, intravenous hydration or even nutritional therapy may be needed in severe NVP and HG. (American College of Obstetricians and Gynecologists, 2018; Campbell et al., 2016; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014) Importantly, psychosocial support and empathetic attitude of the healthcare professionals are warranted (Dean et al 2018; Power et al., 2010). In case of previous HG, pre-pregnancy planning of care and active pharmacological management in the following pregnancy is essential (Campbell et al., 2016; Dean et al., 2018; Lacasse et al., 2009a; Maltepe & Koren, 2013).

NVP management is mostly organised at primary health care level and carried out in outpatient care (Clark et al., 2014). However, local arrangements and health care organizations differ globally. HG is the most common reason for hospitalization in early pregnancy and repeated admissions may be needed (Fiaschi et al., 2016; Gazmararian et al., 2002). Consequently, HG causes substantial burden to the health care system, leading to high estimated costs (Konikoff et al., 2016; Nurmi et al., 2022; Trovik & Vikanes, 2016). Optimal arrangements with respect to cost-effectiveness and patient preference have been studied (Fiaschi et al., 2019; McParlin et al., 2016; Murphy et al., 2016; Ucyigit, 2020).

2.6.1 Non-pharmacological treatment

Various dietary interventions and lifestyle modifications are recommended for women with NVP (Ebrahimi, 2010). These instructions include, for instance, eating small frequent meals high in protein and avoiding fatty or spicy foods. Also, good air condition at home to avoid unpleasant odours or a change of scenery, and resting are recommended (Ebrahimi, 2010). For many women, these interventions are helpful (Lacroix et al., 2000; O'Brien & Naber, 1992). However, no RCT of dietary or lifestyle modifications in HG exists (Boelig et al., 2018). Therefore, these instructions are regarded suitable mainly for mild or moderate NVP.

Use of prenatal vitamins has been associated with decreased existence of vomiting (Emelianova et al., 1999). However, on the contrary, discontinuation of iron-containing pregnancy multivitamins has been associated with improved NVP symptoms (Gill et al., 2009b). Pyridoxin, vitamin B6, is recommended as first-line

treatment for NVP in the USA and Canadian clinical guidelines (American College of Obstetricians and Gynecologists, 2018; Campbell et al., 2016). Parenteral supplementation of water soluble B1 vitamin thiamine is important in prolonged NVP before administration of dextrose solutions to avoid Wernicke's encephalopathy, a serious neuropsychiatric syndrome (Oudman et al., 2019).

Traditionally, ginger has been found to alleviate NVP (Ebrahimi, 2010). However, in Finland, ginger supplements are considered unsafe during pregnancy because available preparations also contain other herbal agents with unknown effects (Malm, 2018). Furthermore, the application of acupuncture or acupressure using wristbands at the Nei Guan point P6 on the palmar surface of wrist has been found to be effective (Sridharan & Sivaramakrishnan, 2020), however, also RCTs with opposite findings have been published (Knight et al., 2001; Mohd Nafiah et al., 2022). In addition, two RCTs investigating the effect of aromatherapy (lemon and mint oil) included in systematic Cochrane review have found no significant effect (Matthews et al., 2015). Moreover, based on a review of six studies, hypnosis cannot be recommended as an effective therapy in NVP (McCormack, 2010). Use of compression stockings alleviated the symptoms of NVP in one study (Mendoza & Amsler, 2017).

Although not officially recommended, a minority of women have used cannabis sativa (marijuana) during pregnancy to relieve NVP (American College of Obstetricians and Gynecologists, 2017; Badowski & Smith, 2020). In a study by Metz et al., 5.8% of 9250 women were urine tested positive for cannabis exposure, with higher levels associated with more severe NVP, possibly reflecting intentions to self-medicate (Metz et al., 2022). Besides being an illegal drug in most countries, marijuana is also related to adverse pregnancy and foetal outcomes (American College of Obstetricians and Gynecologists, 2017; Badowski & Smith, 2020).

Psychosocial support should be offered in the management of NVP and HG (Balik et al., 2015; Dean et al., 2018). In lack of sufficient treatment and psychosocial support, even suicidal ideation has been reported and women have ended up terminating otherwise wanted pregnancies (Dean et al., 2018; Nana et al., 2022). The effect of NVP on mental QoL is discussed in more detail in Chapter 2.7.1.2. Sensitive approach is needed when recommending psychological interventions as some women may find those offensive considering the historical beliefs of the origin of NVP (Dean et al., 2018; Power et al., 2010). However, besides affirming the biological basis of NVP, also the apparent mental burden of the condition must be taken into account (Mitchell-Jones et al., 2017). An RCT of 86 women by Faramarzi et al. showed improvement in NVP measured by INVR scores when three weeks of mindfulness-based cognitive psychotherapy was added to treatment, compared to conventional treatment with only pyridoxin (Faramarzi et al., 2015). The differences were also evident after one month follow-up. Besides interventions given by mental

health professionals (psychologists, psychiatric nurses, psychiatrics), peer support may enhance coping. Active patient associations act in several countries and online (Dean et al., 2018). Further, in Finland, a NVP/HG webpage has been founded and is updated by a HG researcher (Nurmi, 2011).

There is a need for more research concerning nutritional status of women with HG and nutritional interventions of HG, a gap in knowledge which has been highlighted in HG research priorities (Dean et al., 2021; Elkins et al., 2022; Maslin & Dean, 2022). Limited data suggests that women with severe NVP and HG are at risk for malnutrition (Maslin et al., 2021). Generally, women with NVP and HG should be encouraged to eat and drink what they can, and intravenous hydration with electrolyte and thiamine replacements, if needed, should be used in dehydrated women (Lowe et al., 2019; Vikanes et al., 2014). Initial 12-hour fasting during inpatient treatment of HG have not shown to be useful compared to expedite oral feeding (Tan et al., 2020). Comparisons were made concerning patient satisfaction and nausea scores and the frequency of vomiting episodes (Tan et al., 2020). Enteral nutrition may be needed if weight loss in NVP and HG continues despite of relevant treatment with intravenous hydration and antiemetics. The recommended first line choice would be nasogastric or nasojejunal tube feeding (American College of Obstetricians and Gynecologists, 2018; Elkins et al., 2022; Stokke et al., 2015). One challenge in this otherwise safe treatment option may be patients' acceptance (Grooten et al., 2017). On the contrary, intravenous total parenteral nutrition is associated with pregnancy risks and should only be considered as a last reserve (Elkins et al., 2022).

2.6.2 Medication

Safe medication to relieve the symptoms of NVP and HG can be offered. However, the thalidomide tragedy in the 1950–60s, when this former NVP medicine with previously unknown teratologic potential led to thousands of malformed infants, had far-reaching effects (Vargesson, 2015). Obviously, the attitudes of women and professionals towards medication in pregnancy have changed to even overcautious. Hence, suspicion of potential risks may overcome the need of remedy for NVP (Baggley et al., 2004; Heitmann et al., 2016). Safety data of several antiemetic medicines used during pregnancy has been building up over years or decades of reported use (Austin et al., 2019). In fact, this reflects that fewer new ones have been introduced. In the future, genetic studies in HG might offer new promising therapeutic agents, potentially targeting GDF15 (Fejzo et al., 2022).

Previous Cochrane systematic reviews addressing the treatment of NVP and HG (Boelig et al., 2018; Matthews et al., 2015) have concluded that the main challenge is the lack of high-quality evidence to perform reliable meta-analyses and thus to

recommend any antiemetic treatment over another. This limitation should be noticed when making clinical management decisions. Finding effective or even curative treatment for HG have been ranked top priorities in future HG research (Dean et al., 2021).

Recommendations of which medicine is the first line choice vary in the international management guidelines (Wong et al., 2022). Importantly, treatment response should be evaluated. Most clinical guidelines include stepwise instructions or algorithms of medication according to the severity (assessed with the PUQE) and persistence of symptoms. Medicines with different pharmacological actions can be combined. Oral administration route is favoured in mild to moderate NVP leaving parenteral treatment for more severe cases. (Campbell et al., 2016; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014)

Treatment usually consists of antiemetics, generally metoclopramide, ondansetron, or antihistamines with antiemetic function, for instance cyclizine, doxylamine, meclizine or promethazine. Combination of doxylamine and pyridoxin is widespread. Corticosteroids are recommended as a third line option or for refractory cases. (American College of Obstetricians and Gynecologists, 2018; Boelig et al., 2018; Matthews et al., 2015; McParlin et al., 2016; The Royal College of Obstetricians and Gynaecologist, 2016) In addition, small RCTs have been conducted investigating the use of transdermal clonidine (Maina et al., 2014) and gabapentin (Guttuso et al., 2020). Another RCT concerning the use of mirtazapine and ondansetron in HG is ongoing (Ostenfeld et al., 2020). Thromboprophylaxis with low molecular weight heparin is recommended during hospitalization for HG (Fiaschi et al., 2018; The Royal College of Obstetricians and Gynaecologist, 2016; Vikanes et al., 2014).

Prochlorperazine and chlorpromazine are traditional psychiatric medicines which in addition to their antiemetic function also relieve anxiety. Further, diazepam has been used in women suffering from NVP or HG (Lowe et al., 2019). However, diazepam, or benzodiazepines overall, are not generally recommended during pregnancy because of reported perinatal adverse outcomes (Grigoriadis et al., 2020; The Royal College of Obstetricians and Gynaecologist, 2016). Clinical depression warrants adequate treatment with counselling and sometimes antidepressants. Selective serotonin reuptake inhibitors can be used as well as mirtazapine (Campbell et al., 2016).

Another common accompanying symptom in NVP is heartburn. Antacids and histamine H2 receptor blockers, ranitidine, and famotidine are regarded safe during pregnancy. In case when more effective anti-reflux medication is needed, proton pump inhibitors can be used, primarily omeprazole. Constipation is a frequent discomfort during pregnancy, and it may accompany NVP and HG with poor intake. Non-absorbent stool softeners, laxatives and fibre-containing bulking agents can be

used. Further, Helicobacter pylori eradication is possible also during pregnancy. (Lowe et al., 2019; The Royal College of Obstetricians and Gynaecologist, 2016)

Receiving adequate medication is another concern. According to a large population-based cohort study from the UK accounting 417 028 pregnancies from years 1998–2013, only 34% to 63% women had been prescribed antiemetic medication prior to hospitalization for HG in 1999–2013 (Fiaschi et al., 2019). Further, in another cohort of 33 439 women from the UK, only half (51%) of them had received a prescription after being discharged from the hospital (Fiaschi et al., 2018). A Norwegian study retrospectively reviewed all HG patients' (n=1064) medical files from one large university hospital, the Haukeland University Hospital in Bergen, revealing a steady yearly increase (1.5% to 2.6%) in prescribed antiemetic medication from 2002 to 2019 (Erdal et al., 2022). A recent study in which 786 women with previous HG were recruited online evaluated the women's experiences of the treatment of HG (Mares et al., 2022). The majority (68%) of women had found HG medication ineffective despite active treatment efforts with combinations of several medicines (57% ≥ three preparations) which were, in turn, related to intolerable side effects (Mares et al., 2022).

Medications have some side effects, but benefits should outweigh harms. The risk of teratogenicity must be carefully considered when using medication during the first trimester, simultaneously with fetal organogenesis. The European Medical Agency has launched a warning in 2019 concerning ondansetron and potentially a 1.2 to 1.4 fold risk of cardiac anomalies and cleft palate, leading to prohibition of the use of ondansetron during the first trimester (European Medical Agency, 2019). However, these associations have been considered controversial due to conflicting results and thus, the warning has been disputed (Damkier et al., 2021; Huybrechts et al., 2019; Kaplan et al., 2019). The potential risks related to medicines should also be balanced against the outcome of worsened NVP or HG if not properly treated (Trovik & Vikanes, 2019).

The medications available and used for NVP in Finland are presented in **Table 8**. Notably, only the combination of pyridoxin and doxylamine is specifically licenced for use in NVP. Overview of NVP treatment is presented in **Figure 4.**

Table 8. Treatments for nausea and vomiting of pregnancy available in Finland.

Preparation	Dosage	Gravbase category*
Antiemetic medications		
Combination (antihistamine + vitamin B_6)		
Doxylamine + Pyridoxin[1]	2 x 1–2 po	C1
Antihistamines		
Meclizine	25 mg x 1–2 po	A
Cyclizine	50 mg x 1–3 po	A
Dopamine D_2-receptor antagonist		
Metoclopramide	10 mg x 1–3 po / iv	C2
Serotonin 5-HT_3-receptor antagonist		
Ondansetron[2]	4 mg x 1–3 po / iv	C1
Anti-anxiety / antiemetic medication		
Prochlorperazine	5–10 mg x 1–3 po	C2
Corticosteroids[3]		
Methylprednisolone, Hydrocortisone, Prednisone, Prednisolone	Methylprednisolone 16 mg x 3 / 40 mg x 1 iv or hydrocortisone 100 mg x 2 iv 1-3 days, followed by tapered regimen of prednisone or prednisolone from 40 mg x 1 po for 1-2 weeks	C1
Anti-reflux medications		
Antacids		
Salts of calcium, sodium, and magnesium	1–2, several doses a day	A
Sucralfate	1 x 3–4 5 ml x 3–4	B
H_2-receptor blockers		
Ranitidine	150 mg x 2 po 50 mg x 1–2 iv	A
Famotidine	10–40 mg x 1 po	A
Proton pump inhibitors		
Omeprazole	20–40 mg x 1–2 po / iv	A
Esomeprazole	20–40 mg x 1–2 po / iv	B
Lansoprazole	15–30 mg x 1 po	B

Preparation	Dosage	Gravbase category*
Pantoprazole	20–40 mg x 1–2 po	B
Vitamins		
Thiamine[4](B_1)	100 mg x 1, 3 days iv	A
Pyridoxin[5] (B_6)	10– 25 mg x 3 po (available only in combination with doxylamine)	A
Prenatal multivitamins	1 x day	-
Intravenous hydration		
Crystalloids[4]	Individual dose. Basic requirements: Water 30–35 ml/kg Glucose 1.5 g/kg Sodium 1.5 mmol/kg Potassium 1 mmol/kg	-
Enteral / parenteral nutrition		
Products providing liquid nutrients. Vitamins and trace elements need to be added.	Individual dose. Energy requirement ~25–35 kcal/kg/day	-

Gravbase Finnish decision support database for health care professionals of the safety of drug treatment during pregnancy; iv intravenous; kcal kilocalories; kg kilogram; mg milligram; ml millilitre; mmol millimole; NVP nausea and vomiting of pregnancy; po per oral; pr per rectum

*Gravbase categories refer to the safety of medications during pregnancy indicated by coloured letters:

A = Considered safe during pregnancy.

B = Limited data, no signs of teratology or adverse effects.

C1 = Limited or conflicting data, teratogenic or adverse effects found in animal testing, or no animal testing conducted.

C2 = No signs of teratology but use in (late) pregnancy may lead to neonatal or infant adverse effects.

D = Generally contraindicated during pregnancy for suspected or known teratogenic effects.

[1]The only medicine specifically licenced for NVP available in Finland.

[2]Use prohibited during the first trimester by European Medical Agency due to suspected risk of cardiac malformations and cleft palate.

[3]May be considered for refractory cases.

[4]Recommended to give thiamine before dextrose solutions to avoid Wernicke's encephalopathy.

[5]No supplements containing only pyridoxin available in Finland with similar low dosage as recommended in international NVP guidelines.

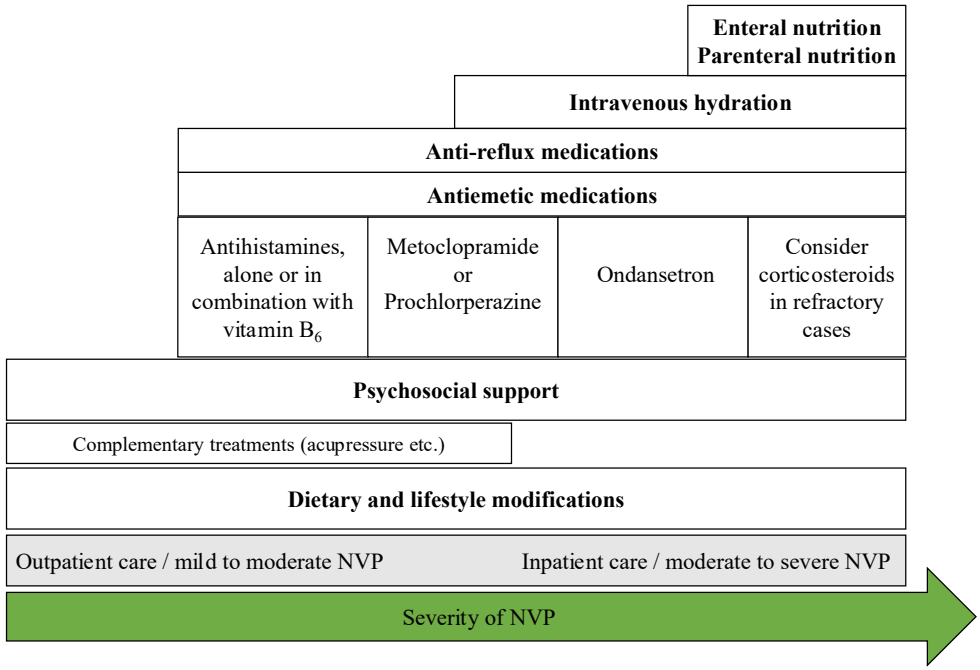

Figure 4. Overview of treatment of nausea and vomiting of pregnancy (NVP). Summary of the medications and dosages are presented in **Table 8**.

2.7 Impact on the mother and the fetus

2.7.1 Maternal quality of life

QoL is a broad concept of perceived adequate physical, mental, and social functioning. Further, health related QoL can be described as QoL related to specific illness and it can also be assessed concerning pregnancy. (Lagadec et al., 2018) Several factors have been identified to be associated with QoL in women with NVP in studies using structured QoL questionnaires as well as qualitative methods (Wood et al., 2013). Besides obvious physical impairment, also mental, social, and domestic aspects of QoL have been shown to be affected (**Figure 5**). Considering the mostly self-limiting course of NVP, it has been shown to cause a substantial impact on QoL, since not only severe NVP but also mild and moderate NVP are associated with lower QoL (Attard et al., 2002; Heitmann et al., 2017; Mazzotta et al., 2000).

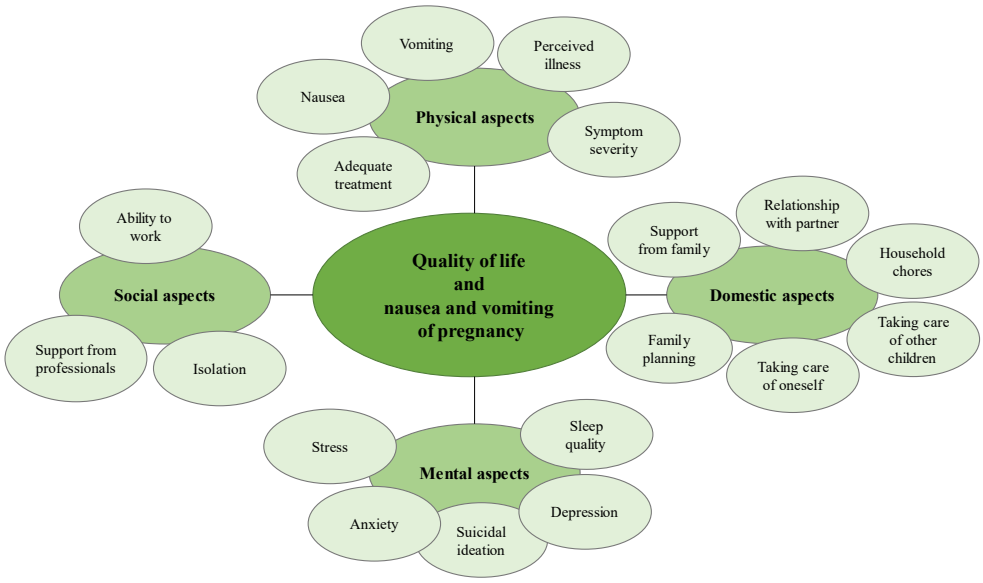

Figure 5. Factors associated with quality of life in nausea and vomiting of pregnancy.

2.7.1.1 Physical aspects and daily functioning

Nausea has been reported as the most bothersome physical symptom of NVP (Clark et al., 2013; Magee et al., 2002; Smith et al., 2000). Several studies which have applied generic QoL questionnaires, the SF-36 or the SF-12, have found especially lower physical component scores in women with NVP and HG (Attard et al., 2002; Bai et al., 2016; Lacasse et al., 2008a; Munch et al., 2011; Smith et al., 2000; Tan et al., 2018). In more disease-specific estimations, higher scores in the NVP-QOL questionnaire corresponding poorer QoL, have also been associated with more severe NVP (Dochez et al., 2016; Lacasse et al., 2008a).

Similar findings have been reported in longitudinal studies. Hirose et al. estimated the QoL of 153 NVP women with SF-12 between gwk 5–20 (Hirose et al., 2020). During the follow-up period, lower physical component score of SF-12 was associated with more severe NVP at three time points (gwk 5–8, gwk 9–12 and gwk 13–20, respectively) (Hirose et al., 2020). Further, Liu et al. (Liu et al., 2019) evaluated the QoL of 101 pregnant women with the NVP-QOL in each trimester. In their study, higher NVP-QOL scores were associated with more severe NVP, and furthermore, the QoL scores were the highest at the first trimester, reflecting the peak occurrence and symptom course of NVP (Liu et al., 2019). In addition, Munch et al. (Munch et al., 2011) compared the SF-36 scores of 48 women with NVP (recruited from outpatient clinics) and 29 women with HG (recruited when hospitalised for HG but evaluated later after discharge) in the first trimester in their cross-sectional study.

Interestingly, the physical component QoL scores were similarly low in both groups (NVP vs HG), highlighting that not only HG but also NVP affects QoL (Munch et al., 2011).

NVP has been shown to have varying effects to daily functioning. More severe NVP has shown to correlate with lower social functioning scores measured with general health questionnaire (Swallow et al., 2004). Lower social functioning scores in women with NVP have also been measured with SF-36 (Attard et al., 2002; Smith et al., 2000). In qualitative studies, the women have reported isolation from their previous social life (O'Brien & Naber, 1992) and lack of support (Chou et al., 2003). As for occupational functioning, NVP leads to sick leave and altered work schedules, both causing increased time lost from work (Attard et al., 2002; Heitmann et al., 2017; O'Brien & Naber, 1992; Smith et al., 2000; Tan et al., 2018). Additionally, NVP has many effects on family life. The women have described inability to perform household scores, for instance cooking, and difficulties in taking care of other children (O'Brien & Naber, 1992; Smith et al., 2000). Further, negative impact to the relationship with partner (Mazzotta et al., 2000; Poursharif et al., 2008) as well as being disbelieved of the severity of their illness by partner or other family members (O'Brien & Naber, 1992) have been reported.

2.7.1.2 Mental aspects

Similarly to physical component scores, also decreased mental component scores of QoL assessed with SF-36 or SF-12 questionnaires have been reported in several studies (Attard et al., 2002; Bai et al., 2016; Lacasse et al., 2008a; Munch et al., 2011). Of mental symptoms, increased stress (Chou et al., 2008; Liu et al., 2019; Tan et al., 2014; Yildirim & Demir, 2019), depressive symptoms (Chou et al., 2008; Swallow et al., 2004; Tan et al., 2014) and anxiety (Tan et al., 2014; Yildirim & Demir, 2019) have been associated with NVP and HG (McCarthy et al., 2011). A systematic review with meta-analysis of 12 studies concerning the psychological morbidity in HG pointed out significantly higher depression and anxiety scores in women with HG compared to non-HG controls (Mitchell-Jones et al., 2017). However, these associations have been criticised for overlapping of the symptoms included in specific questionnaires, for instance tiredness, hopelessness and isolation, with symptoms that are part of HG and caused by the disease, not depression or anxiety despite high scores in specific questionnaires (Fejzo, 2017).

One cohort study comparing the QoL of 84 women with NVP and 32 women without NVP at gwk 9–16 did not find differences in the mental component scores of SF-12 between the groups (Tan et al., 2018). On the contrary, Tan et al. (Tan et al., 2014) conducted a study of 121 women hospitalised for HG for the first time and 120 non-HG controls with matching gwks and assessed their psychological distress

at two time points, during hospitalization and in the third trimester by using the 21-item Depression, Anxiety and Stress Scale. Their study revealed a decline in all perceived symptoms (depression, anxiety and stress) in HG women in the scores at third trimester (≥ gwk 28) compared to their scores in the first trimester during hospitalization (Tan et al., 2014). Actually, the depression, anxiety and stress scores in HG women were lower at third trimester than the same scores of the control women. Thus, it revealed reassuring improvement in psychological distress along treatment and, simultaneously, reflected the natural course of the decline of HG symptoms with increasing gwks (Tan et al., 2014). Also in a prospective cohort study of 164 women with HG examined at gwk 15 and gwk 20 (McCarthy et al., 2011), the depression and stress scores decreased but anxiety scores remained high during follow-up, for weeks after vomiting had stopped.

As mentioned earlier in this literature review in chapter 2.2.1., also the PUQE has been complemented with a well-being score with a single VAS rating of feeling 'worst possible' to 'best possible' (Koren et al., 2002). It was designed to give an estimate of women's emotional and physical health, with intention to reflect the overall distress of NVP to QoL. In the validation studies of the PUQE (Koren et al., 2005) and the PUQE-24 (Ebrahimi et al., 2009) decreased well-being by VAS was associated with more severe NVP.

In qualitative studies, women with HG have described feeling isolated with even suicidal ideation, and left unsupported and uncared by healthcare professionals (Dean et al., 2018; Poursharif et al., 2008; Power et al., 2010). Further, reports on effects to future family planning have been striking including fear of future pregnancies and even terminations of wanted pregnancies due to HG, mediated by experience of inadequate support, compassion and treatment by healthcare professionals (Nana et al., 2021, 2022; Poursharif et al., 2007, 2008). Immigrant women have been recognised as a special risk group of receiving less support from family members and health care professionals (Groleau et al., 2019). While adapting to a new culture, these women may have struggled with isolation and stress already before pregnancy. Hence, facing a rare condition such as HG may be an overwhelming experience which, in turn, poses a challenge for far away relatives to understand. During treatment, both the women and health care professionals may encounter misunderstandings in communication due to language problems, but professionals should focus on carefully explaining HG to the women and also to family members (Groleau et al., 2019).

2.7.1.3 Sleep quality

Sleep quality is one important aspect of QoL. Pregnancy changes sleep already from the first trimester because of hormonal changes and physical pregnancy-related

symptoms disturbing sleep (Hedman et al., 2002; Sedov et al., 2018). All kind of insomnia symptoms, difficulties falling asleep, nocturnal awakenings and too early morning awakenings increase (Aukia et al., 2020). Also nocturnal breathing disturbances, especially snoring, increase (Bourjeily et al., 2011). All these symptoms have been shown to be associated to pregnancy complications (Lu et al., 2021). In addition, depressive and anxiety symptoms have been associated with sleep disturbances during pregnancy (Aukia et al., 2020; Polo-Kantola et al., 2017). Furthermore, fatigue is another common complaint in early pregnancy (Nazik & Eryilmaz, 2014).

Several studies have addressed sleep quality on NVP or HG with various methods and findings (**Table 9**). The main aim in some studies have been to assess sleep quality specifically in women with NVP or HG (Pengsheng & Haiyan, 2021; Yildirim & Demir, 2019; Zhang et al., 2021), whereas in others to assess the determinants of sleep problems in pregnancy in general (Ertmann et al., 2020; Kadloğlu et al., 2022; Mindell et al., 2015) or contributing factors to women's QoL (Clark et al., 2013; Heitmann et al., 2017; Swallow et al., 2004).

In the validation studies of PUQE-24, reported 'poor or broken sleep' (defined as anything other than undisturbed continuous sleep) was not associated with PUQE score (Ebrahimi et al., 2009). Further, Heitmann et al. evaluated self-reported sleep problems and NVP with PUQE with no associations. However, in a cohort study of 621 women by Clark et al. (Clark et al., 2013), more severe NVP assessed by PUQE was associated with worse sleep quality.

On the contrary, Yildirim et al. (Yildirim & Demir, 2019) studied sleep disorders in 46 women with HG compared to 52 non-HG controls and found higher Pittsburgh Sleep Quality Index (PSQI) scores indicating worse sleep quality in women with HG. In addition, in a Chinese cross-sectional study with 2494 women whose NVP was categorised with the Modified-PUQE, women with moderate and severe NVP reported poor sleep quality assessed with the PSQI (Pengsheng & Haiyan, 2021). And, in another Chinese cross-sectional study with the PUQE-24 and the PSQI of 2281 women in different pregnancy trimesters, women with high PUQE score also had high scores in PSQI and overall higher prevalence of poor sleep across pregnancy (Zhang et al., 2021).

Table 9. Previous studies assessing nausea and vomiting of pregnancy and sleep quality.

Author	Year	Country	Study design	N	Study aim	NVP scale	Sleep scale	Results
Swallow et al.	2004	UK	Cohort study	273	To assess psychological health and NVP in early pregnancy.	NVPI	General Health Questionnaire; insomnia/anxiety symptoms	Nausea/vomiting severity correlated with insomnia/anxiety ($r=0.16$, $p<0.01$).
Lindseth et al.	2005	USA	Cohort study	116	To assess NVP in late pregnancy (> gwk 20).	NVPI	Reported total hours of sleep	NVP women slept less hours per night (mean NVP 5.3 vs no NVP 7.2, $p=0.03$).
Ebrahimi et al.	2009	Canada	Cohort study	311	To validate PUQE-24.	PUQE-24	Reported total hours of sleep; continuous or broken/poor sleep	Broken/poor sleep (44–52%) was not associated with PUQE score.
Clark et al.	2013	USA	Cohort study	621	To assess symptoms related to NVP and to quantify its impact on QoL.	PUQE	Difficulty of getting a good night's sleep (yes/no)	More severe NVP was associated with difficulty getting a good night's sleep ($p<0.05$).
Mindell et al.	2015	USA	Prospective cohort study	2427	To assess sleep quality across pregnancy.	Existence of nausea (yes/no)	PSQI	Nausea disturbed sleep (sometimes/often) during pregnancy ($p<0.001$).
Heitmann et al.	2017	Norway	Cohort study	712	To assess the burden of NVP to QoL.	PUQE-24	Self-estimation of sleep problems (yes/no)	Sleep problems occurred 53–64% with all severity of NVP ($p=0.24$).

Author	Year	Country	Study design	N	Study aim	NVP scale	Sleep scale	Results
Yildirim et al.	2019	Turkey	Case-control study	98 (46 HG, 52 controls)	To assess sleep disorders, anxiety, and depression in women with HG.	HG: vomiting >3 times a day, poor oral intake, weight loss >5% since inclusion, ketonuria >1+	PSQI	PSQI sores were higher in women with HG (p<0.001).
Ertmann et al.	2020	Denmark	Cross-sectional study	1338	To assess sleep quality in early pregnancy (< gwk 16).	Existence of nausea and/or vomiting (yes/no)	Selected questions from Nottingham Health Profile	Nausea or vomiting were not associated with sleep complaints in the multivariable analysis including physical and mental health status.
Pengchen et al.	2021	China	Cross-sectional study	2494	To examine the association between NVP and poor sleep quality.	Modified-PUQE	PSQI	Women with moderate and severe NVP reported poor sleep quality (p<0.0001).
Zhang et al.	2021	China	Cross-sectional study	2281	To investigate the prevalence and risk factors of poor sleep quality.	PUQE	PSQI	Women with PUQE score >11 had high PSQI mean scores and prevalence of poor sleep (p<0.001).
Kadloglu et al.	2022	Turkey	Prospective cohort study	189	To determine the frequency of sleep problems and underlying factors.	Existence of HG (yes/no)	PSQI	Sleep disorders were found more often in women with HG than in women without HG (p=0.032).

gwk gestational week; NVPI Nausea and vomiting in pregnancy instrument; NVP nausea and vomiting of pregnancy; PUQE Pregnancy-unique quantification of emesis; PSQI Pittsburgh sleep quality index; QoL quality of life; UK United Kingdom; USA United States of America

2.7.2 Maternal complications

Severe NVP and HG can lead to maternal complications during pregnancy, including dehydration, electrolyte imbalances, malnutrition and weight loss (Fejzo et al., 2019). Prolonged inadequate nutrition and persistent vomiting increase the risk of vitamin depletions, most importantly concerning thiamine, a water soluble B1 vitamin which is essential in carbohydrate metabolism in the brain. Malnutrition increases the risk of thiamine deficiency which, if untreated, may lead to acute neuropsychiatric syndrome called Wernicke's encephalopathy (Oudman et al., 2019). Wernicke's encephalopathy is a triad of ocular symptoms, ataxia, and altered mental status (Oudman et al., 2019). Prevention of this possibly permanent brain damage is warranted, therefore, administration of thiamine before infusion of dextrose solutions is recommended in the international management guidelines (American College of Obstetricians and Gynecologists, 2018; Lowe et al., 2019; The Royal College of Obstetricians and Gynaecologist, 2016). In addition, vitamin K deficiency is rare but may also occur in HG leading to severe coagulopathies (Nijsten et al., 2022). Further, other severe maternal complications related to HG include oesophageal rupture, splenic avulsion, pneumothorax, acute tubular necrosis and refeeding syndrome as a complication of too rapid feeding after starvation (American College of Obstetricians and Gynecologists, 2018; Elkins et al., 2022; Popa et al., 2021).

The associations between NVP, HG and mental symptoms during pregnancy have been discussed in previous chapters of this literature review. However, the mental health consequences may continue postpartum. More severe NVP assessed with PUQE has been associated with postpartum depression (Muchanga et al., 2022). In a prospective cohort study assessing psychological morbidity of women with HG pre- and postnatally (n=85/56), postpartum depressive symptoms were common (29% vs 7%) compared to non-HG controls (Mitchell-Jones et al., 2020). Other studies have also found symptoms of depression, anxiety and posttraumatic stress disorder after HG pregnancies (Nijsten et al., 2022; Poursharif et al., 2008). Concerning even more long term maternal consequences, Fossum et al. (Fossum et al., 2017) have studied maternal mortality in their population based cohort study from Norway with data from the Medical Birth Registry of Norway linked with the Cause of Death Registry (n=13 397 women with HG, median follow-up 26 years). In their study, previous HG was associated with reduced risk of death from cancer. Although with no association, mortality from cardiovascular disease was also evaluated since HG has been associated with high blood pressure and pre-eclampsia during pregnancy which, in turn, are linked with increased risk of later cardiovascular diseases (Fossum et al., 2017).

2.7.3 Obstetric outcome

Generally, NVP can be considered as a positive sign since NVP has been associated with lower incidence of miscarriages in cohort studies (Bashiri et al., 1995; Chan et al., 2010; Hinkle et al., 2016) and in a systematic review of 10 studies evaluating fetal outcomes (Koren et al., 2014). Further, based on the same systematic review, NVP has been associated with generally favourable pregnancy outcomes concerning the rates of malformations, fetal growth restriction and preterm birth (Koren et al., 2014). However, Chortatos et al. (Chortatos et al., 2015) reported in the large Norwegian Mother and Child Cohort (total n=51 675) higher odds for pre-eclampsia, proteinuria and high blood pressure, as well as for pelvic girdle pain in women with NVP (n=17 070) and women with only nausea (n=20 371). Their data were linked with the Medical Birth Register of Norway. In their study, and similarly as mentioned earlier, reduced odds for prematurity and small for gestational age (SGA) babies were found.

However, opposite to NVP, HG has been connected to adverse obstetric outcomes, but studies have reported contradictory findings. Several small cohort studies have found no differences in obstetric outcomes of women with HG compared to non-HG controls (Agmon et al., 2019; Bashiri et al., 1995; Kuru et al., 2012; Tan et al., 2007; Tsang et al., 1996). On the other hand, associations with severe vomiting, HG and pre-eclampsia (J. Zhang & Cai, 1991), low birthweight (Koudijs et al., 2016; Petry et al., 2018) and preterm birth (McCarthy et al., 2011) have been reported. Insufficient total maternal weight gain during pregnancy, especially not regaining pre-pregnancy weight before mid-pregnancy, has been associated with adverse outcomes, particularly SGA (Meinich & Trovik, 2020; Temming et al., 2014).

Consistently, in larger cohort studies and register-based studies, HG has been associated with pregnancy complications and poor obstetric outcomes. In a population-based cohort study reporting pregnancy complications related to HG in the UK (data from total n=83 679 HG admissions), women with HG had increased odds for anaemia, pre-eclampsia and eclampsia, venous thromboembolism, induction of labour, preterm delivery, caesarean section, low birth weight and SGA. However, decreased odds for stillbirth and post term delivery were found (Fiaschi et al., 2018). Further, Bolin et al. (Bolin et al., 2013) reported findings based on the Swedish Medical Birth Register in women hospitalised for HG (n=10 186). HG was associated with increased odds for pre-eclampsia and, in women hospitalised for HG for the first time in the second trimester (n=2084), with increased odds of placental abruption, preterm birth (< gwk 37) and SGA. Moreover, a study based on the Netherlands Perinatal Registry reported that women with HG had more often also diabetes and hypertension during their pregnancies (Roseboom et al., 2011). In addition, associations with prematurity and low birth weight (<10th percentile) were

found. Similar findings of HG and higher incidence of low birthweight (<2500 grams), SGA, prematurity and higher female/male offspring ratio were concluded in a systematic review and meta-analysis of 24 studies (Veenendaal et al., 2011).

Thus, a recent review concluded that it is still uncertain if HG is associated with adverse fetal outcomes (Varela & Deltsidou, 2021). Overall, the clinical meaningfulness of the statistically significant findings may be limited, as pointed out in the results by Vandraas et al. (Vandraas et al., 2013). Indeed, in their large register-based study of altogether 2.2 million pregnancies, women with HG had lower infant birthweight and deliveries at earlier gwk, but the actual calculated differences were 21 to 34 grams and less than one day, respectively. However, if HG persist to the late second trimester or continues throughout pregnancy, ultrasound scans for fetal growth are recommended (The Royal College of Obstetricians and Gynaecologist, 2016).

2.7.4 Offspring future health

Intrauterine conditions do matter in later life (Ismail-beigi et al., 2006). As discussed in the previous chapter, fetal outcome is considered generally favourable despite of mother's NVP (Ayyavoo et al., 2014; Koren et al., 2014; Nulman et al., 2009). Contradictory results regarding early childhood sex-dependant growth of children after mother's NVP have been published (Gu et al., 2021; Ong et al., 2021). In one study, boys of mothers with NVP were taller and heavier than girls at infancy and in early childhood (Ong et al., 2021), whereas in another study, girls of mothers with NVP were taller and heavier than boys at the age of one to two years (Gu et al., 2021).

Limited data are available concerning children's long term outcomes after HG (Veenendaal et al., 2011). Metabolomic programming towards cardiovascular diseases in adulthood after in utero exposure to maternal starvation due to severe HG has been considered parallel to the outcomes of children born after famine (Ismail-beigi et al., 2006). However, a prospective follow-up study of the Northern-Finland Birth Cohort found no signs of negative cardiovascular health (based on physical examination, anthropometric measurements, blood pressure and laboratory tests) in adolescents aged 16 born from HG pregnancies (n=42) compared to controls (n=6420) (Koot et al., 2017). Further, some studies have raised concerns of children's abnormal neurodevelopment after prolonged NVP and HG but more evidence is needed (Fejzo et al., 2019; Parker et al., 2014).

3 Aims

The present study was conducted to assess the clinical usability of the PUQE and to evaluate the severity of NVP assessed with the PUQE in Finnish women. More specifically, the PUQE was applied both in inpatient and in outpatient settings. Further, the PUQE was used to study the associations between several maternal factors and the severity of NVP, as well as various aspects of NVP.

The specific aims were as follows:

1. To assess the usability of PUQE in hospital setting. (**Study I**)
2. To assess the usability of PUQE across pregnancy in outpatient setting. (**Study II**)
3. To evaluate the associations between the severity of NVP assessed with the PUQE and maternal basic characteristics. In addition, to estimate various aspects of NVP. (**Study III**)
4. To evaluate the associations between the severity of NVP assessed with the PUQE and maternal previous susceptibility to nausea and NVP in relatives. In addition, to estimate various aspects of NVP. (**Study IV**)
5. To evaluate the associations between the severity of NVP assessed with the PUQE and physical QoL, mental QoL and sleep quality. (**Study V**)

4 Materials and Methods

4.1 Participants, data collection and study designs

This thesis includes five publications (**Studies I–V**) based on two cohorts of pregnant women; one cohort of women hospitalised for HG and the other cohort of women recruited from MHCCs. The participants, the study designs, and the main aims of **Studies I–V** are summarised in **Figure 6**.

4.1.1 Study I

Study I was a prospective cohort study. The women were recruited between January 2011 and March 2019 from the antenatal ward of Turku University Hospital, Turku, Finland. The nurses in the ward were instructed by the researchers to recruit women hospitalised for HG. Finnish language skills were required since the study questionnaire was available only in Finnish. Other inclusion criteria were singleton pregnancy and hospital admission lasting at least overnight. Altogether 106 women participated of whom 95 were included in the final study cohort after excluding multiple pregnancies and admissions lasting less than overnight.

In **Study I**, during the years of recruitment, there were annually 32 to 68 admission periods for HG (including readmission periods of the same woman), resulting in 433 admission periods, which gives an estimated participation rate of 37% (162 periods/433 periods). Further, the number of deliveries in Turku University Hospital varied annually from 3708 to 4214, which gives an estimated admission rate due to HG of 0.8%–1.7%.

The diagnosis of HG was set according to the International Statistical Classification of Diseases and Related Health problems 10th Revision (World Health Organisation, 2016). Admittance criteria were based on clinician's assessment of the general sickness of the women, clinical signs or laboratory findings of dehydration or presence of urine ketones. At discharge, the overall alleviation of HG symptoms were evaluated as well as women's self-judgement of the improvement of their condition. All women were treated with intravenous hydration and the majority of women also received antiemetic medication.

Demographic data of the women were collected from the hospital medical records, including gwk at admission, parity (nulliparous/multiparous), body mass index (BMI, kg/m^2, calculated by pre-pregnancy weight and height), smoking (no/yes), marital status (cohabited/single), the total length of all admissions (days), the number of readmissions and urine ketone results as well as details of treatment. Age (years) was calculated by comparing the date of birth and the answering date.

Basic characteristics of the women in **Studies I**, **III–V** are described in **Table 10.** Details of admission periods and treatment in **Study I** are described in **Table 11**.

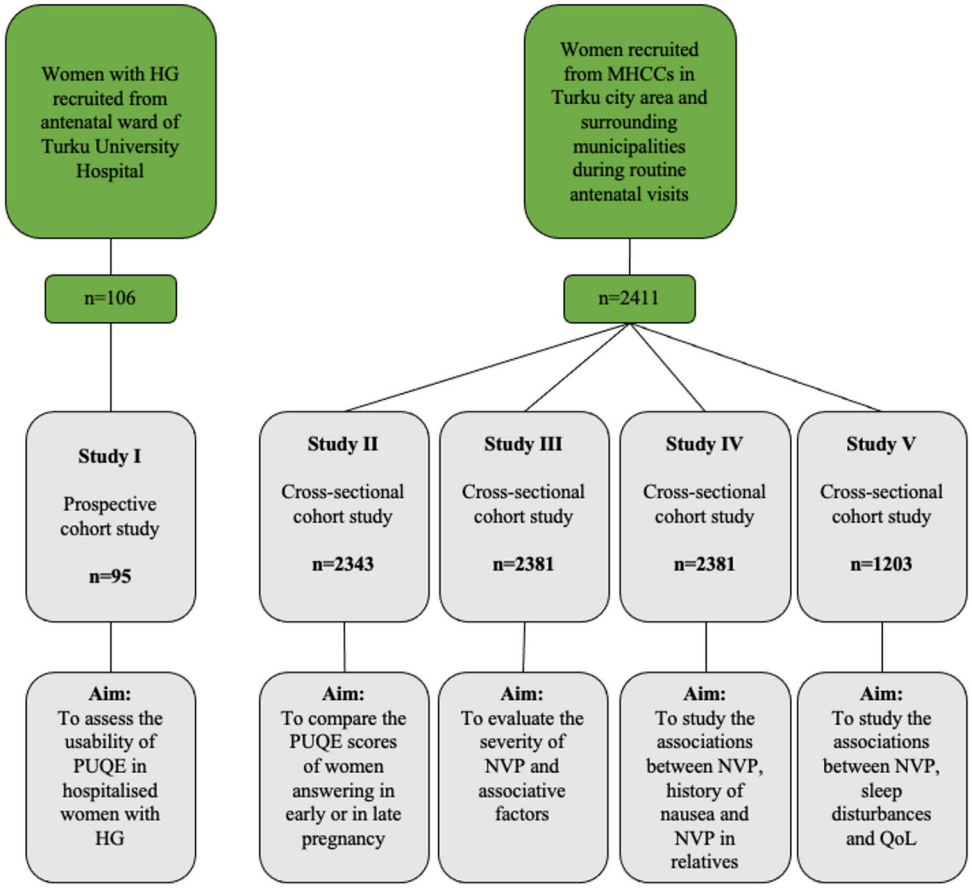

Figure 6. Flowchart of Studies I–V. HG hyperemesis gravidarum; MHCC maternal health care clinic; NVP nausea and vomiting of pregnancy; PUQE pregnancy-unique quantification of emesis; QoL quality of life

Table 10. Basic characteristics of women in Studies I, III–V.

	Women hospitalised for HG n=106	Women recruited from MHCCs n=2411		
	Study I	**Studies III–IV**		**Study V**
		All women	Subanalysis of women ≤ 20 gwk	Women ≤ 20 gwk
n	95	2381	1247	1203
	Mean (SD, range) or n (%)	**Mean (SD, range) or n (%)**	**Mean (SD, range) or n (%)**	**Mean (SD, range) or n (%)**
Gwk	9.8 (2.5, 6–20)	20.2 (4.5, 7–40)	16.6 (2.0, 7–20)	16.6 (2.0, 7–20)
Age (years)	29.5 (5.0, 19–43)	30.3 (4.7, 15–46)	30.0 (4.8, 18–44)	30.0 (5.0, 18–44)
BMI (kg/m^2)	25.2 (5.4, 18–41)	24.6 (4.8, 15–58)	24.4 (4.8, 17–58)	24.4 (4.8, 17–58)
Previous pregnancies		1.3 (1.4, 0–15)	1.3 (1.4, 0–15)	
0	35 (37.6)	802 (34.5)	416 (34.3)	400 (34.2)
1	38 (40.9)	776 (33.4)	408 (33.7)	396 (33.9)
≥ 2	20 (21.5)	747 (32.1)	388 (32)	373 (31.9)
Previous miscarriages[1]	0.3 (0.7, 0–3)	0.3 (0.7, 0–5)	0.3 (0.7, 0–5)	0.3 (0.6, 0–5)
0	71 (78.0)	1778 (76.5)	910 (75.1)	876 (74.9)
≥ 1	20 (22.0)	547 (23.5)	302 (24.9)	293 (25.1)
Previous abortions		0.1 (0.4, 0–4)	0.1 (0.4, 0–3)	
0		2048 (88.1)	1062 (87.6)	1025 (87.7)
≥ 1		277 (11.9)	150 (12.4)	144 (12.3)
Previous deliveries		0.8 (1.0, 0–12)	0.8 (1.0, 0–12)	
Parity				
Nulliparous	35 (37.6)	1069 (46.0)	556 (45.9)	536 (45.9)
Multiparous	58 (62.4)	1256 (54.0)	656 (54.1)	633 (54.2)
Nationality				
Finnish		2326 (98.8)	1214 (98.7)	1174 (98.7)
Other		29 (1.2)	16 (1.3)	16 (1.3)
Smoking				
No	87 (96.7)	2018 (87.0)	1049 (86.8)	1014 (87.0)
Yes	3 (3.3)	301 (13.0)	159 (13.2)	152 (13.0)
Marital status				
Cohabited	85 (92.4)	2218 (96.2)	1156 (96.3)	1115 (96.4)
Single	7 (7.6)	88 (3.8)	44 (3.7)	42 (3.6)
Employment				
Working		1697 (83.1)	875 (82.1)	847 (82.3)
Not working		346 (16.9)	191 (17.9)	182 (17.7)

[1]including ectopic pregnancies

BMI body mass index; gwk gestational week; MHCC maternal health care clinic; n number; SD standard deviation

Table 11. Details of admission periods and treatment in Study I. Total n=95.

	n	Mean±SD or n (%)	Range
Number of admissions:	95		
1		60 (63.2)	
≥ 2		35 (36.8)	2–14
Length of admissions (days)	160*	3.1±2.2	1–12
HG treatment:	93		
Intravenous fluids		93 (100)	
Antiemetic medication		75 (80.6)	
Metoclopramide		32 (42.7)	
Ondansetron		12 (16.0)	
Both		31 (41.3)	
Parenteral nutrition		5 (5.4)	

*Total number of all admission periods with available data. HG hyperemesis gravidarum; n number; SD standard deviation

4.1.2 Studies II-V

Studies II–V were cross-sectional retrospective cohort studies. The women were enrolled between October 2011 and November 2014 in Turku city area and surrounding municipalities in Finland, from total of 33 MHCCs in Turku, Kaarina, Lieto, Masku, Mynämäki, Naantali, Nousiainen, Paimio, Rusko and Sauvo. All MHCCs in Turku city area and surrounding municipalities were included. First, the MHCC nurses were instructed by the researchers about the study. Accordingly, the nurses recruited the women. All women attending to routine MHCC visits in mid-pregnancy were eligible to participate in the study. However, capability to understand Finnish language was required since the study questionnaire was available only in Finnish but there were no further specific inclusion or exclusion criteria. Thus, the purpose was to collect a large sample of women with wide range of severity of NVP. Altogether 2411 women with gwk 7–40 were recruited. The women filled in the PUQE once according to the worst 12-hour period of their NVP.

During the recruitment period of **Studies II–V** in 2011–2014, there were annually around 1800 children born in Turku and 1200 children born in surrounding municipalities, which gives a rough estimation of 26% participation rate.

In **Study II**, the PUQE scores of 2343 women answering in different gwks were compared. Four groups of women were formed according to the gwk at reply: ≤ 16 gwk (n=554), ≤ 20 gwk (n=1209), > 20 gwk (n=1134) and ≥ 24 gwk (n=495). In this grouping method, one woman could belong to several groups.

In **Studies III–IV**, 2381 women with complete PUQE scores were included in analyses. In addition, a sub-analysis of only women answering ≤ 20 gwk (n = 1247) were performed in **Studies III–IV**, to further assess the results in women who presumably had shorter time from the worst NVP.

In **Study V**, women > 20 gwk and incomplete questionnaires were excluded to target the study population below mid-pregnancy which was compatible with the time frame given in the sleep questionnaire (chapter 4.2.1.3). Thereafter, a total of 1203 women answering ≤ 20 gwk were included in analysis.

Demographic data of the women in **Studies II–V** were collected from the Medical Birth Register of Finnish Institute for Health and Welfare, including previous pregnancies (number), previous deliveries (number), previous miscarriages including ectopic pregnancies (number), previous pregnancy terminations (number), pre-pregnancy body mass index (BMI, kg/m^2, calculated by pre-pregnancy weight and height), smoking (no/yes), marital status (cohabited/single) and employment (working/not working). Age (years) was calculated by comparing the date of birth and the answering date. Gwk and nationality were enquired in the study questionnaire.

Basic characteristics of the women in subgoups of **Study II** are described in **Table 12**.

Table 12. Basic characteristics of women in Study II.

	Women recruited from MHCCs n=2411			
	Study II (n=2343)			
Subgroup	≤ 16 gwk	≤ 20 gwk	> 20 gwk	≥ 24 gwk
n	554	1209	1134	495
	Mean (SD, range) / Median [IQR]	**Mean (SD, range) / Median [IQR]**	**Mean (SD, range) / Median [IQR]**	**Mean (SD, range) / Median [IQR]**
Gwk	15 [14, 16]	17 [15, 18]	23 [22, 25]	26 [25, 28]
Age (years)	29.5 (4.7, 18–44)	30.0 (4.7, 18–44)	30.6 (4.7, 15–46)	30.8 (4.7, 15–44)
BMI (kg/m^2)	23.2 [20.9, 26.4]	23.3 [21.2, 26.4]	23.7 [21.5, 26.5]	23.7 [21.7, 26.4]
Previous pregnancies	1 [0, 2]	1 [0, 2]	1 [0, 2]	1 [0, 2]
Previous deliveries	0 [0, 1]	1 [0, 1]	1 [0, 1]	1 [0, 1]
	n (%)	**n (%)**	**n (%)**	**n (%)**
Smoking				
No	457 (93.8)	1019 (94.4)	972 (94.3)	432 (96.4)
Yes	30 (6.2)	60 (5.6)	59 (5.7)	16 (3.6)
Marital status				
Cohabited	514 (96.6)	1121 (96.4)	1062 (96.0)	464 (96.1)
Single	18 (3.4)	42 (3.6)	44 (4.0)	19 (3.9)
Employment				
Working	371 (79.8)	852 (82.4)	822 (84.1)	358 (83.5)
Not working	94 (20.2)	182 (17.6)	155 (15.9)	71 (16.5)

BMI body mass index; gwk gestational week; IQR interquartile range; n number; SD standard deviation

4.2 Methods

4.2.1 Study questionnaires

The basic structure of the study questionnaire was similar in the hospital and in the MHCCs. The study questionnaire consisted of the PUQE, three VAS scales to estimate separately physical QoL, mental QoL and general sleep quality, four selected questions from the Basic Nordic Sleep Questionnaire (BNSQ) concerning distinct sleep disturbances, and questions of personal history of nausea and history of NVP in relatives (Appendices). In addition, the women hospitalised for HG (**Study I**) filled in daily the PUQE and physical QoL and mental QoL VAS scales, of which the replies of the admission and discharge days were included into the analyses.

The variables assessed in Studies **I–V** are illustrated in **Figure 7**.

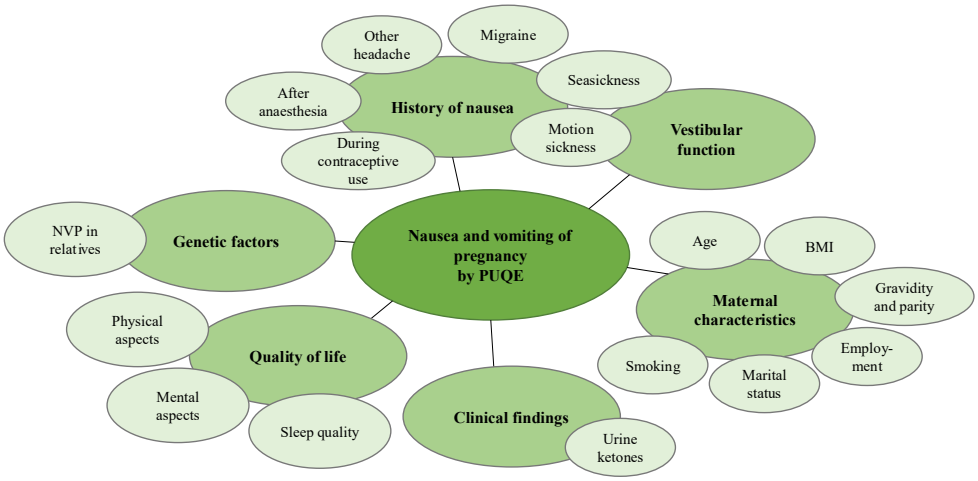

Figure 7. Variables assessed in Studies I–V. BMI body mass index; NVP nausea and vomiting of pregnancy; PUQE pregnancy-unique quantification of emesis questionnaire

4.2.1.1 Pregnancy-Unique Quantification of Emesis Questionnaire

The severity of NVP was assessed by the PUQE (Koren et al., 2002)**Table 4**. In **Study I**, the daily severity of NVP was estimated with the PUQE and the replies of the admission and discharge days were included into the analyses. In **Studies II–V**, the women replied the PUQE encompassing the worst 12-hours of NVP in their current pregnancy.

The PUQE consists of three questions rating the symptoms of NVP: duration of nausea in hours and the quantity of both vomiting and retching episodes. In each

question the points range from 1–5. Thus, the PUQE total score ranges between 3 and 15. According to the PUQE, the severity of NVP is categorised into four categories: no NVP (3 points), mild NVP (4–6 points), moderate NVP (7–12 points) and severe NVP (13–15 points).

For the present study, the PUQE was translated into Finnish by professional translator (M.N.) with permission from the original PUQE developer (Gideon Koren) and the Finnish version was back translated by another professional translator (E.O.).

4.2.1.2 Quality of life and general sleep quality

Physical QoL and mental QoL were assessed in **Study I**, whereas physical QoL, mental QoL and also general sleep quality were all included in **Study V**. The estimations were reported by VAS from 0–10, where higher number in scales indicated better QoL and better general sleep quality in the study questionnaire. In **Study I** the QoL VAS were daily estimations of which only replies of the admission day and the discharge day were used in analyses, whereas the women in **Study V** were instructed to give VAS ratings according to their QoL/general sleep quality during the worst 12-hours of NVP of the current pregnancy.

All VAS items were later reversed in the statistical analyses to better correlate with other context in clinical medicine where VAS lines are used (Jensen et al., 1986) and thus, higher number in VAS scales indicated worse QoL and worse general sleep quality in **Studies I and V**. In addition, in statistical analyses, the VAS scales were rescaled from 0–10 to 0–100.

4.2.1.3 Basic Nordic Sleep Questionnaire

The BNSQ is a Scandinavian questionnaire to evaluate the prevalence and the severity of sleep disorders from the past three months (Partinen & Gislason, 1995). The original version encompasses 21 questions. Answers to each question are rated in a five-point scale: ‘never or less than once per month’ (1 point), ‘less than once per week’ (2 points), ‘on 1–2 nights per week’ (3 points), ‘on 3–5 nights per week’ (4 points) and ‘every night or almost every night’ (5 points).

In **Study V**, distinct sleep disturbances during the past three months were enquired with four selected questions from the BNSQ, including questions of ‘difficulties falling asleep’, ‘night awakenings’, ‘too early morning awakenings’ and ‘sleepiness during the day’. The answers were dichotomised to represent clinically relevant sleep disturbances (yes: ≥ 3 times a week vs no: ≤ 1–2 times a week), similarly as in previous studies using the questionnaire in pregnant women (Aukia et al., 2020; Polo-Kantola et al., 2017).

4.2.1.4 Personal history of nausea

In **Study IV**, personal history of nausea in various situations was inquired with 'yes'/'no' answer options. In the study questionnaire, the situations with previous concomitant nausea were 'motion sickness', 'seasickness', 'migraine' 'other kind of headache', 'after anaesthesia', 'during contraceptive use' and 'other kind of nausea'. The context of other kind of nausea could be specified with an open answer, as well as the method of contraception which had caused nausea.

4.2.1.5 Nausea and vomiting of pregnancy in relatives

In **Study IV**, history of NVP in relatives was asked with 'yes' / 'no' / 'not known' answer options and with an open question to specify who that relative was. In the analyses, the relatives were grouped into 'first-degree relatives' (mother, sister) and into 'second-degree relatives' (grandmother, aunt, or more distant relatives).

4.2.1.6 The Medical Birth Register

Basic demographic data of the women in **Studies II–V** were obtained from the Medical Birth Register which is maintained by the Finnish Institute for Health and Welfare. This national register is for statistical and research use and contains data of the new-borns and their mothers. The variables obtained included number of previous pregnancies, previous deliveries, previous miscarriages and ectopic pregnancies, previous pregnancy terminations, pre-pregnancy body mass index (BMI, kg / m^2, calculated using pre-pregnancy weight and height), smoking, marital status, and employment status.

4.2.2 Laboratory measurements

In **Study I**, urine ketones were measured at admission and subsequently daily during the admission period using urinalysis reagent strips (Mission®, Acon Laboratories, Inc, San Diego, USA). The urine ketones categories were – (no detectable ketones), + (15 mg/dL=1.5 mmol/L), ++ (40 mg/dL=4.0 mmol/L) and +++ (80 mg/dL=8.0 mmol/L). In the present study, only the results of the admission and discharge days were analysed.

4.3 Statistical analyses

Summary of the statistical methods in Studies **I–V** is presented in **Table 13**. Power calculations aiming for power of 80% and alpha 5% were performed when planning the optimal sizes of the study cohorts. In the hospital data, the difference of three

PUQE points between admission and discharge was considered clinically relevant. The change of three points (from 12 to 9) was used with standard deviation (SD) of 8 which resulted 58 women (nQuery Advisor 4.0: paired t-test). In the MHCC data, power calculation was based on the following variables: NVP no/yes (PUQE points 0–3 = no NVP / ≥ 4 = having NVP) and parity (the probability of NVP for primiparas 75% and multiparas 80% (Louik et al., 2006)) which resulted 1094 women per group and altogether 2192 women (nQuery Advisor 4.0: $\chi 2$ test (equal n's).

First, descriptive analysis of the data was performed. Continuous variables were characterised using means, SD, and ranges of values or with medians and interquartile ranges (IQR). Categorical variables were characterised using frequencies and percent. In all studies, the severity of NVP was categorised according to the PUQE score. Four PUQE categories were formed: 'no NVP', 'mild NVP', 'moderate NVP' and 'severe NVP'. The distributions of each variable and the assumptions of each statistical model were ensured before applying. The results were presented as p values and odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$. All analyses were calculated with 9.4 version of SAS for Windows (SAS Institute Inc. Cary, NC, USA).

In all analyses of **Study I**, the results from the admission day were compared to the results of the discharge day. In addition to PUQE score categories, PUQE total points (continuous PUQE scores) were used as a continuous variable. Physical and mental QoL and urine ketones categories on admission and discharge days were compared to PUQE score categories and to PUQE total points. The analyses were performed separately for women having only the first admission period and thereafter including women having readmissions, to roughly reflect milder HG (the first admission) and prolonged HG (repeated admissions). In addition, all admissions were analysed together in the present study. The number of values in urine ketones categories when readmissions were included were too low for calculations, and thus, only the first admission and all admissions were eligible for comparisons of urine ketones.

In **Study II**, the continuous and categorised PUQE scores, as well as basic characteristics of the women, were compared in early and in late pregnancy. The comparisons were performed between subgroups formed according to the gwk of answering the PUQE: ≤ 20 gwk vs > 20 gwk, ≤ 20 gwk vs ≥ 24 gwk and ≤ 16 gwk vs ≥ 24 gwk.

In **Study III**, the basic characteristics were at first compared in univariate analysis with the PUQE score and with the PUQE questions. Thereafter, the variables with $p < 0.1$ in univariate analysis with the PUQE score (previous pregnancies, previous deliveries, previous miscarriages, and marital status) were entered into multivariate analysis. Because of intercorrelations, previous pregnancies were considered both as a continuous variable and a categorised variable (0, 1, ≥ 2

previous pregnancies). The same analyses were performed in the subgroup of women answering ≤ 20 gwk.

In **Study IV**, the personal history of nausea variables and family history of NVP (first-degree relatives and second-degree relatives) were at first compared in univariate analysis with the PUQE score and the PUQE questions. Secondly, the results were adjusted for age, parity, BMI, smoking and employment because these variables have been associated with NVP in previous studies. Third, multivariate analysis was performed including all personal history of nausea variables and the PUQE score. The same analyses were performed in the subgroup of women answering ≤ 20 gwk.

In **Study V**, the associations between the physical and mental QoL, general sleep quality and sleep disturbances and the PUQE score were analysed. The results were adjusted for basic characteristics (age, parity, BMI, smoking and employment) because these variables have been associated with both NVP and sleep quality in previous studies. Thereafter, three different multivariable analyses (Models 1–3) were performed. Model 1 encompassed the PUQE score, basic characteristics, sleep disturbances and physical QoL. Model 2 included the PUQE score, basic characteristics, sleep disturbances and mental QoL. Model 3 included the PUQE score, basic characteristics, sleep disturbances and both physical and mental QoL. General sleep quality was not included in the Models because of apparent interaction with sleep disturbances.

Table 13. Summary of the statistical analyses in Studies I–V.

Study I	
Dependent variables	PUQE categories, PUQE total points and the change (delta, Δ) of PUQE categories between admission and discharge days.
Independent variables	Physical QoL, mental QoL, urine ketones categories.
Adjusted for	Age, BMI, and parity.
Statistical methods	**ANOVA** **Multinomial logistic regression analysis** **Linear mixed model** 1) Analyses including only the first admission period 2) Analyses including readmission periods 3) Analyses including all admissions **GEE estimation** was used in comparisons with PUQE categories when including readmissions and all admissions. **Linear mixed model with random intercept for patient** was used in comparisons with PUQE total points when including readmissions and all admissions. **Tukey-Kramer method** was used when adjusting *p*-values in comparisons of the urine ketones categories.
Study II	
Main variables	PUQE categories, PUQE questions and PUQE total points in subgroups according to gwk when answering the PUQE: • ≤ gwk 16 • ≤ gwk 20 • > gwk 20 • ≥ gwk 24
Other variables	Basic characteristics (age, BMI, previous pregnancies, previous deliveries, smoking, marital status, employment).
Statistical methods	**Two sample t-test, Mann-Whitney *U* test or Chi-Square test** Comparisons of the variables in groups: • ≤ 20 gwk vs > 20 gwk • ≤ 20 gwk vs ≥ 24 gwk • ≤ 16 gwk vs ≥ 24 gwk
Study III	
Dependent variables	PUQE categories and PUQE questions.
Independent variables	Basic characteristics (age, previous pregnancies, previous deliveries, previous miscarriages, previous pregnancy terminations, nationality, BMI, smoking, marital status, employment).
Subgroup	Subgroup analyses of women ≤ 20 gwk.

Statistical methods	**Multinomial logistic regression analysis**: 1) Univariate analyses PUQE categories and basic characteristics PUQE questions and basic characteristics 2) Multivariate analysis PUQE categories and basic characteristics with $p < 0.1$ in univariate analysis (previous pregnancies, previous, deliveries, previous miscarriages, marital status)
Study IV	
Dependent variables	PUQE categories and PUQE questions
Independent variables	Personal history of nausea, NVP in first-degree and second-degree relatives.
Subgroup	Subgroup analyses of women ≤ 20 gwk.
Adjusted for	Age, BMI, employment, parity, smoking.
Statistical methods	**Multinomial logistic regression analysis**: 1) Univariate analyses PUQE categories and personal history of nausea PUQE questions and personal history of nausea PUQE categories and family history of NVP PUQE questions and family history of NVP 2) Multivariate analyses PUQE categories and personal history of nausea PUQE questions and personal history of nausea PUQE categories and family history of NVP PUQE questions and family history of NVP
Study V	
Dependent variables	PUQE categories
Independent variables	General sleep quality, sleep disturbances, physical QoL, mental QoL.
Adjusted for	Basic characteristics (age, BMI, parity, smoking, employment).
Statistical methods	**Multinomial logistic regression analysis:** 1) Univariate analyses PUQE categories and general sleep quality by VAS PUQE categories and sleep disturbances PUQE categories and physical QoL by VAS PUQE categories and mental QoL by VAS 2) Multivariate analyses Model 1: PUQE categories, basic characteristics, sleep disturbances, physical QoL Model 2: PUQE categories, basic characteristics, sleep disturbances, mental QoL Model 3: PUQE categories, basic characteristics, sleep disturbances, physical QoL and mental QoL
All analyses were performed using 9.4 version of SAS Institute Inc. (Cary, NC, USA) for Windows.	

ANOVA analysis of variance; BMI body mass index; gwk gestational week; GEE generalised estimating equation; PUQE pregnancy-unique quantification of emesis questionnaire; QoL quality of life; VAS visual analogue scale

4.4 Ethics

In **Study I**, all women gave written informed consent after receiving oral and written information about the study. The Joint Ethics Committees of University of Turku and Turku University Hospital gave ethical approval (60/180/2011).

All women in **Studies II–V** received oral and written information about the study before enrolment and returning the study questionnaire implied informed consent. The Joint Ethics Committees of University of Turku and Turku University Hospital gave ethical approval (58/180/2011). The permission to use the Medical Birth Register was admitted by the Finnish Institute for Health and Welfare (THL/658/5.05.00/2012).

All studies were performed in concordance with the declaration of Helsinki from 1964 and its later amendments.

5 Results

5.1 The usability of Pregnancy-Unique Quantification of Emesis Questionnaire

5.1.1 Pregnancy-Unique quantification of Emesis Questionnaire in hospital setting (Study I)

The PUQE scores were higher on admission day and lower on discharge day (p<0.0001 for the first admission, readmissions, and all admissions) (**Table 14**).

To further estimate the usability of PUQE in hospitalised women with HG, the physical QoL and mental QoL ratings by VAS scores, as well as urine ketones categories were compared with the PUQE score categories and continuous PUQE scores on admission day and on discharge day. Only the first admission, readmissions and all admissions were all analysed separately.

Accordingly, physical QoL VAS and mental QoL VAS were higher at admission and lower at discharge (p<0.0001 for first admission, readmissions, and all admissions).

Table 14. Continuous PUQE scores in Study I.

	HG women (n=106)					
	Study I (n=95)					
	Admission day			Discharge day		
	First admission	Readmissions	All admissions	First admission	Readmissions	All admissions
n[1]	68	54	122	65	57	122
	Mean (SD, range)					
PUQE score	11.6 (2.3, 5–15	12.3 (2.7, 4–15)	11.9 (2.5, 4–15)	6.5 (2.4, 3-12)	6.1 (2.8, 3–13)	6.3 (2.6, 3–13)

[1]number of available data.

HG hyperemesis gravidarum; n number; PUQE pregnancy-unique quantification of emesis questionnaire

5.1.1.1 Quality of life and Pregnancy-Unique Quantification of Emesis Questionnaire

When analysing only the first admission period, on admission day according to VAS estimations worse physical QoL was associated with higher PUQE score category. Coherently, on discharge day of the first admission period, better physical QoL was associated with lower PUQE score category. However, no association with mental QoL and PUQE emerged.

When analysing only readmissions, the associations between physical QoL and NVP were similar as during the first admission: the associations were shown both on admission day and discharge day. On the contrary, worse mental QoL was not associated with higher PUQE score category on admission day but on the discharge day, better mental QoL was associated with lower PUQE score category.

When all admissions were included, worse physical QoL was associated with higher PUQE score category on admissions day and better physical QoL with lower PUQE score category on discharge day. As for mental QoL, on admission day of all admission periods, women with worse mental QoL fell into higher PUQE score category in unadjusted analysis but in adjusted analysis the results showed only a tendency. On discharge day of all admissions, women with better mental QoL fell into lower PUQE score category in adjusted analysis.

During the first admission, readmissions and all admissions, the decrease (indicating better QoL as higher scores in VAS scales indicated worse QoL in analyses) in both physical QoL and mental QoL VAS was associated with decrease in the PUQE score category.

The associations between physical QoL, mental QoL and PUQE score categories on admission and discharge days are presented in **Table 15**.

Table 15. Physical and mental QoL on admission and discharge days and the probability to fall into higher or lower PUQE score category[1].

	PUQE admission day			PUQE discharge day			Δ		
	AOR	**95% CI**	***p***	**AOR**	**95% CI**	***p***	**AOR**	**95% CI**	***p***
First admission									
Physical QoL VAS	1.09	1.03–1.16	0.003	0.94	0.91–0.98	0.003	0.93	0.90–0.97	<0.001
Mental QoL VAS	1.01	0.97–1.04	0.765	0.97	0.94–1.00	0.062	0.97	0.94–0.99	0.011
Readmissions									
Physical QoL VAS	1.13	1.02–1.25	0.016	0.93	0.90–0.97	<0.001	0.96	0.93–0.99	0.013
Mental QoL VAS	1.04	0.99–1.09	0.166	0.93	0.89–0.97	0.002	0.95	0.92–0.98	0.001
All admissions									
Physical QoL VAS	1.10	1.05–1.15	<0.0001	0.94	0.92–0.97	<0.0001	0.95	0.93–0.98	<0.001
Mental QoL VAS	1.03	1.00–1.06	0.063	0.96	0.93–0.98	<0.001	0.96	0.94–0.98	<0.0001

AOR Adjusted odds ratio: adjusted for age, body mass index and parity; PUQE Pregnancy Unique Quantification of Emesis Questionnaire; QoL Quality of life; VAS Visual analogue scale; Δ, delta, indicates the change in PUQE score categories

[1]Higher PUQE score category on admission day and lower PUQE score category on discharge day

When PUQE scores were considered as continuous scores, the results concerning physical QoL were similar during the first admission, readmissions, and all admissions: worse physical QoL according to VAS was associated with higher continuous PUQE scores. Instead, mental QoL was associated with continuous PUQE scores only on readmissions and when all admissions were included: worse mental QoL was associated with higher continuous PUQE scores at admission and better mental QoL was associated with lower continuous PUQE scores at discharge. The improvement in both physical QoL and mental QoL (the mean difference in VAS values between admission and discharge days) was associated with the change in continuous PUQE score during the first admission, readmissions, and all admissions. (**Figure 8**, **Figure 9**, **Figure 10**)

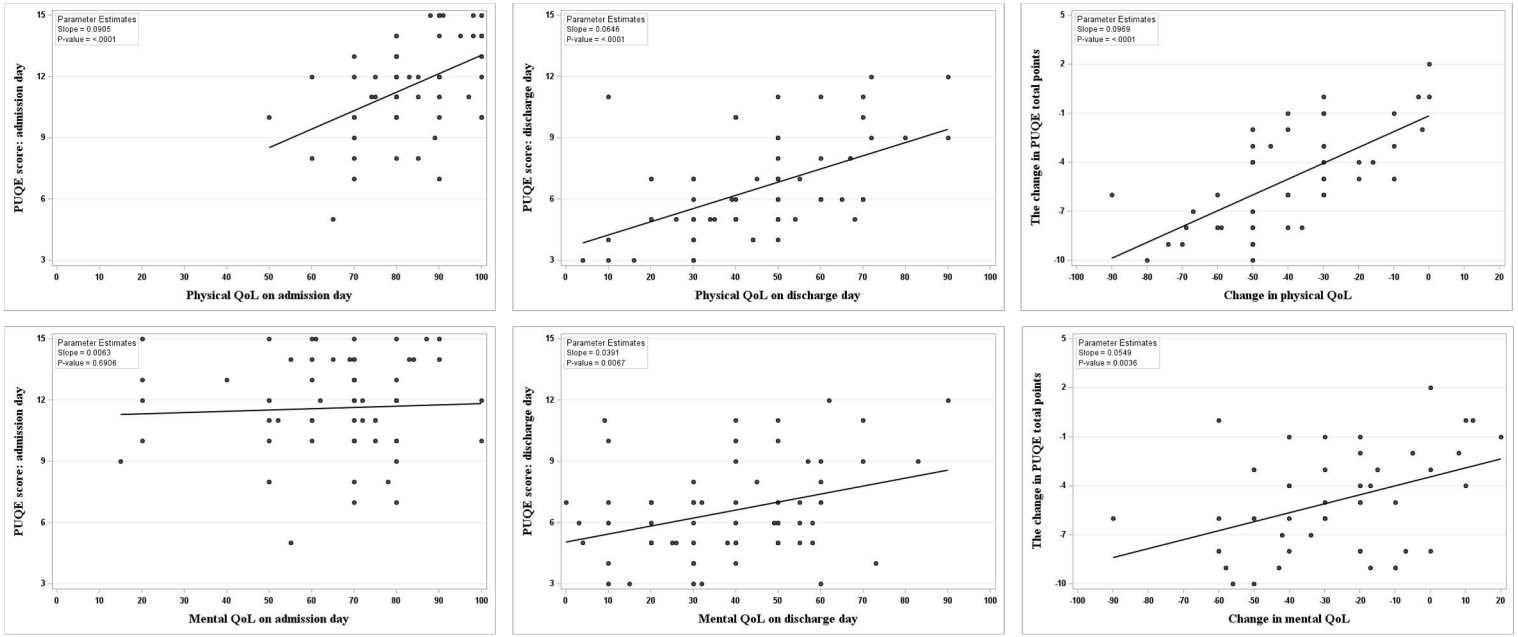

Figure 8. Associations between continuous PUQE scores, physical QoL and mental QoL including only the first admission. Higher number in QoL scales indicate worse QoL and higher PUQE score indicate worse NVP. NVP nausea and vomiting of pregnancy; PUQE Pregnancy-unique quantification of emesis questionnaire; QoL quality of life.

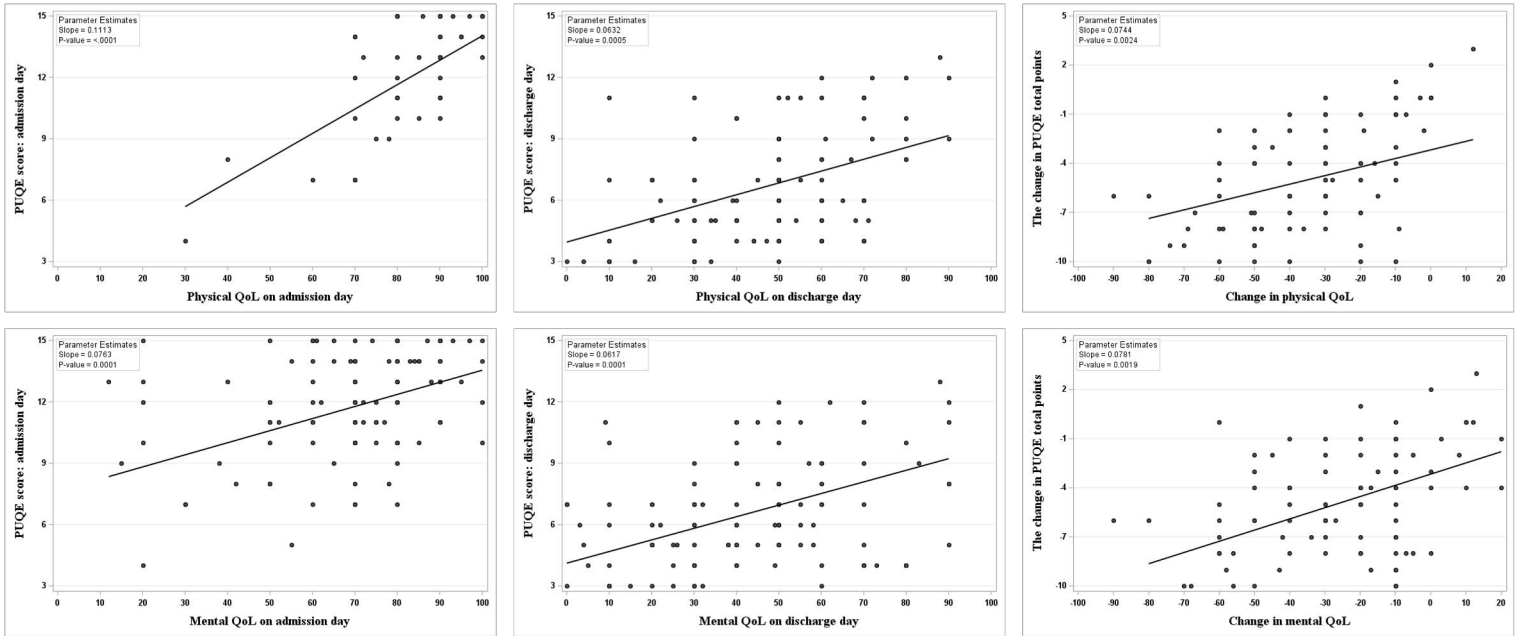

Figure 9. Associations between continuous PUQE scores, physical QoL and mental QoL including only readmissions. Higher number in QoL scales indicate worse QoL and higher PUQE score indicate worse NVP. NVP nausea and vomiting of pregnancy; PUQE Pregnancy-unique quantification of emesis questionnaire; QoL quality of life.

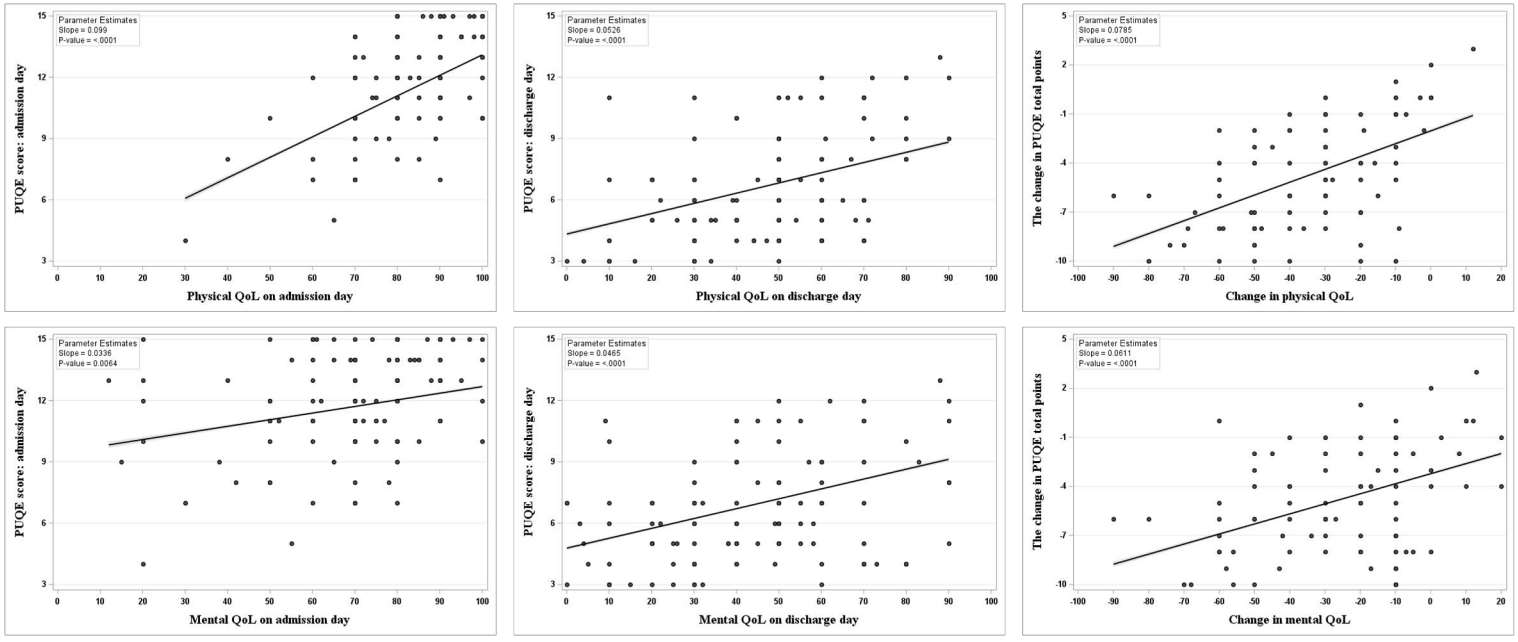

Figure 10. Associations between continuous PUQE scores, physical QoL and mental QoL including all admissions. Higher number in QoL scales indicate worse QoL and higher PUQE score indicate worse NVP. NVP nausea and vomiting of pregnancy; PUQE Pregnancy-unique quantification of emesis questionnaire; QoL quality of life.

5.1.1.2 Urine ketones and Pregnancy-Unique Quantification of Emesis Questionnaire

Ketonuria was frequent as the women had various urine ketones categories on admission and discharge days. Almost three quarters of women had some urine ketones (+/++/+++) on admission day and practically the same proportion of women had negative urine ketones on discharge day. Notably, none of the women had severe urine ketones (+++) on discharge day. (**Figure 11**)

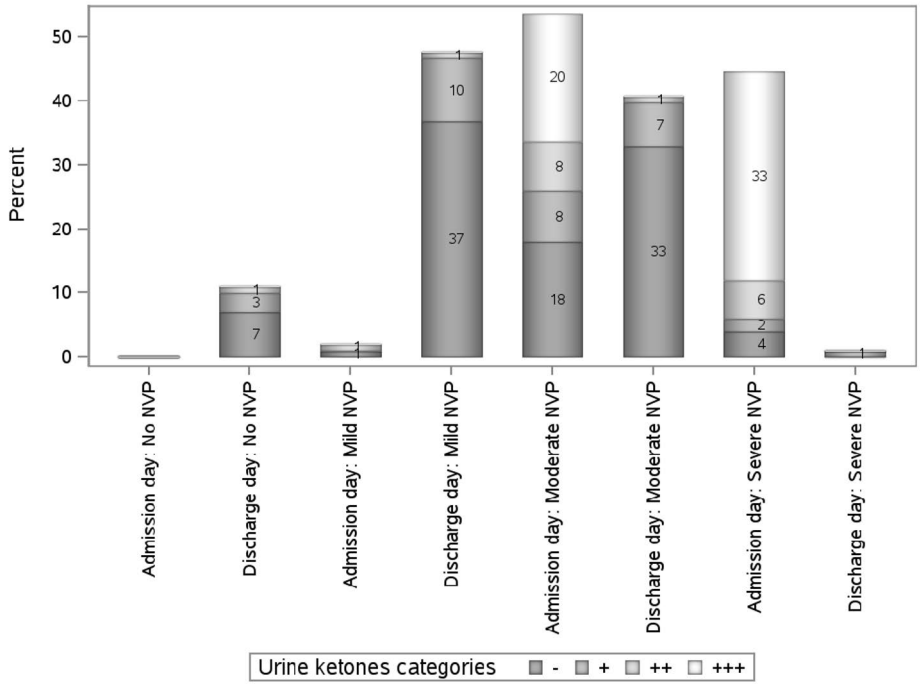

Figure 11. Urine ketones according to PUQE categories on admission and discharge days. PUQE Pregnancy-unique quantification of emesis questionnaire.

On admission day of the first admission period, presence of severe ketonuria (+++) was associated with higher PUQE score. Otherwise, urine ketones were not associated with the severity of NVP. (**Table 16**). The results were similar when PUQE scores were considered both as categorised and continuous scores, and also when only readmissions were included in the analyses with continuous PUQE scores. Instead, urine ketones were not associated with continuous PUQE scores on admission day when all admissions were analysed.

Table 16. Urine ketones categories on admission and discharge days and the probability to fall into higher or lower PUQE score category[1].

Urine ketones	PUQE admission day			PUQE discharge day				Δ		
	AOR	**95% CI**	***p***	**AOR**	**95% CI**	***p***	**Change in urine ketones category[1]**	**AOR**	**95% CI**	***p***
First admission										
+ vs -	5.11	0.22–118.15	0.542	2.07	0.24–17.80	0.709	-3 vs -2	1.44	0.12–17.75	0.982
++ vs -	1.69	0.10–29.43	0.965	NA			-3 vs -1	12.07	0.69–210.64	0.113
+++ vs -	16.00	1.44–177.82	0.016	NA			-3 vs 0	2.55	0.26–25.58	0.722
							-2 vs -1	8.38	0.38–184.74	0.290
							-2 vs 0	1.77	0.15–20.78	0.933
							-1 vs 0	0.21	0.01–3.71	0.504
All admissions										
+ vs -	2.65	0.16–44.99	0.814	0.75	0.20–2.87	0.874	-3 vs -2	2.69	0.44–16.38	0.496
++ vs -	3.26	0.32–32.97	0.556	5.85	0.11–316.49	0.553	-3 vs -1	14.88	1.38–160.59	0.019
+++ vs -	14.97	1.67–134.00	0.008				-3 vs 0	4.25	0.48–37.79	0.323
							-2 vs -1	5.54	0.51–60.60	0.256
							-2 vs 0	1.58	0.19–12.99	0.944
							-1 vs 0	0.29	0.02–3.66	0.587

Urine ketones categories: -/+/++/+++. [1]Presented as the number and the direction of changed categories between admission and discharge days. Only the first admission and all admissions were analysed. Δ, delta, indicates the change in PUQE score categories.
AOR adjusted odds ratio: adjusted for age, body mass index and parity; PUQE Pregnancy-Unique Quantification of Emesis Questionnaire; QoL quality of life; VAS visual analogue scale; NA not applicable.
[1]Higher PUQE category on admission day and lower PUQE category on discharge day

5.1.2 Pregnancy-Unique Quantification of Emesis Questionnaire in outpatient setting (Study II)

In comparisons of the PUQE scores in the four groups, ≤ 16 gwk vs ≥ 24 gwk, ≤ 20 gwk vs > 20 gwk and ≤ 20 gwk vs ≥ 24 gwk, there were no differences in the PUQE scores, neither when the PUQE scores were analysed as categorised PUQE scores nor as continuous PUQE scores. (**Figure 12**, **Table 17**)

However, concerning the various aspects of NVP enquired in different PUQE questions, the women answering in early pregnancy rated longer duration of nausea compared to women answering in late pregnancy. Otherwise, no differences emerged in the answers to the PUQE questions. (**Table 17**)

Table 17. Comparisons of PUQE scores and points of PUQE questions according to different gestational weeks. Total n=2343.

	≤ 20 gwk (n=1209)	> 20 gwk (n=1134)		≤ 20 gwk (n=1209)	≥ 24 gwk (n=495)		≤ 16 gwk (n=554)	≥ 24 gwk (n=495)	
	Mean (SD) Median [IQR]	**Mean (SD) Median [IQR]**	***p***	**Mean (SD) Median [IQR]**	**Mean (SD) Median [IQR]**	***p***	**Mean (SD) Median [IQR]**	**Mean (SD) Median [IQR]**	***p***
PUQE score	7.4 (3.1) 7 [5, 10]	7.4 (3.1) 7 [5, 10]	*0.683*	7.4 (3.1) 7 [5, 10]	7.3 (3.1) 7 [5, 10]	*0.386*	7.6 (3.0) 7 [5, 10]	7.3 (3.1) 7 [5, 10]	*0.109*
PUQE Question 1	3.3 (1.4) 3 [2, 5]	3.2 (1.4) 3 [2, 5]	*0.081*	3.3 (1.4) 3 [2, 5]	3.1 (1.4) 3 [2, 5]	*0.014*	3.4 (1.4) 3 [2, 5]	3.1 (1.4) 3 [2, 5]	*0.005*
PUQE Question 2	1.7 (1.1) 1 [1, 2]	1.8 (1.1) 1 [1, 2]	*0.084*	1.7 (1.1) 1 [1, 2]	1.8 (1.1) 1 [1, 2]	*0.138*	1.8 (1.0) 1 [1, 2]	1.8 (1.1) 1 [1, 2]	*0.484*
PUQE Question 3	2.4 (1.4) 2 [1, 3]	2.4 (1.4) 2 [1, 3]	*0.682*	2.4 (1.4) 2 [1, 3]	2.3 (1.4) 2 [1, 3]	*0.576*	2.4 (1.4) 2 [1, 3]	2.3 (1.4) 2 [1, 3]	*0.253*

Mann-Whitney *U* test. PUQE total score (range 3–15) is the sum of the points of the three PUQE questions (range 1–5 points per question).
gwk gestational week; IQR interquartile range; PUQE Pregnancy-Unique Quantification of Emesis Questionnaire

5.2 The severity of nausea and vomiting of pregnancy

The PUQE categories in **Studies II–V** are presented in **Figure 12**. The mean PUQE scores in **Studies II–V** are presented in **Table 18**.

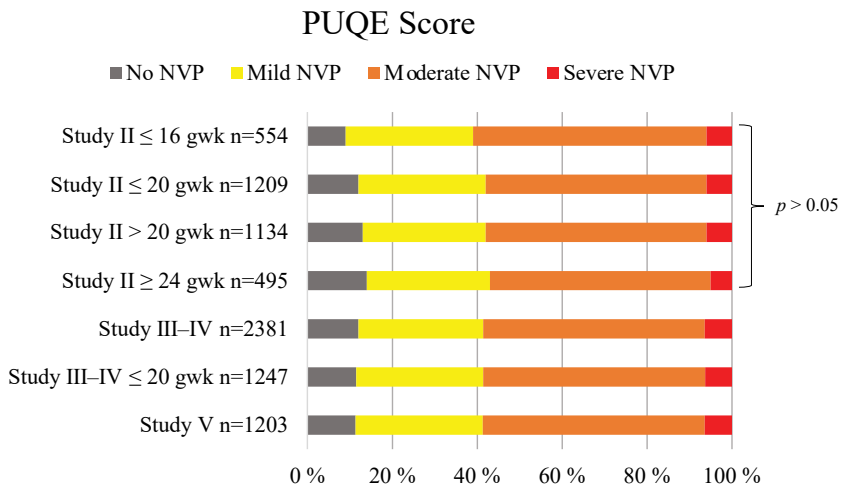

Figure 12. PUQE categories in Studies II–V. Chi-Square test for comparisons of PUQE categories between groups ≤ 20 gwk vs > 20 gwk, ≤ 20 gwk vs ≥ 24 gwk and ≤ 16 gwk vs ≥ 24 gwk. Gwk gestational week; n number; PUQE pregnancy-unique quantification of emesis questionnaire.

Table 18. Continuous PUQE scores and points of PUQE questions in Studies II–V.

	MHCC women n=2411						
	Study II				**Studies III-IV**		**Study V**
	≤ 16 gwk	≤ 20 gwk	> 20 gwk	≥ 24 gwk	All women	Subanalysis ≤ 20 gwk	**Women ≤ 20 gwk**
n	554	1209	1134	495	2381	1247	1203
Mean (SD, range)							
PUQE score	7.6 (3.0, 3–15)	7.4 (3.1, 3–15)	7.4 (3.1, 3–15)	7.3 (3.1, 3–15)	7.4 (3.1, 3–15)	7.4 (3.1, 3–15)	7.4 (3.1, 3–15)
PUQE Question 1	3.4 (1.4, 1–5)	3.3 (1.4, 1–5)	3.2 (1.4, 1–5)	3.1 (1.4, 1–5)	3.3 (1.4, 1–5)	3.3 (1.4, 1–5)	
PUQE Question 2	1.8 (1.0, 1–5)	1.7 (1.0, 1–5)	1.8 (1.1, 1–5)	1.8 (1.1, 1–5)	1.8 (1.1, 1–5)	1.7 (1.1, 1–5)	
PUQE Question 3	2.4 (1.4, 1–5)	2.4 (1.4, 1–5)	2.4 (1.4, 1–5)	2.3 (1.4, 1–5)	2.4 (1.4, 1–5)	2.4 (1.4, 1–5)	

PUQE score (range 3–15) is the sum of the points of the three PUQE questions (range 1–5 points per question). Gwk gestational week; MHCC maternal health care clinic; n number; PUQE pregnancy-unique quantification of emesis questionnaire; SD standard deviation

5.2.1 The severity of nausea and vomiting of pregnancy in women with hyperemesis gravidarum (Study I)

On admission day, NVP was the most often moderate or severe according to PUQE. On admission day of the first admission period, most women rated their NVP moderate according to PUQE. The same held true during all admissions. Instead, concerning readmissions, on admission day severe NVP was the most prevalent PUQE score category. However, on discharge day, most of the women had mild NVP both in the first admission, in readmissions and in all admissions. (**Figure 13**)

5.2.2 The severity of nausea and vomiting of pregnancy in outpatient women (Studies II–IV)

According to PUQE, NVP was most often categorised as moderate or mild in the women recruited from the MHCCs. The proportions of women with no NVP were the same in all women and in the subgroup analysis of women answering ≤ 20 gwk. Likewise, the proportions of women reporting severe NVP were similar in all women and in the subgroup analysis of women ≤ 20 gwk. Accordingly, the percentages of the PUQE categories were similar in the subgroups of **Study II.** (**Figure 12**)

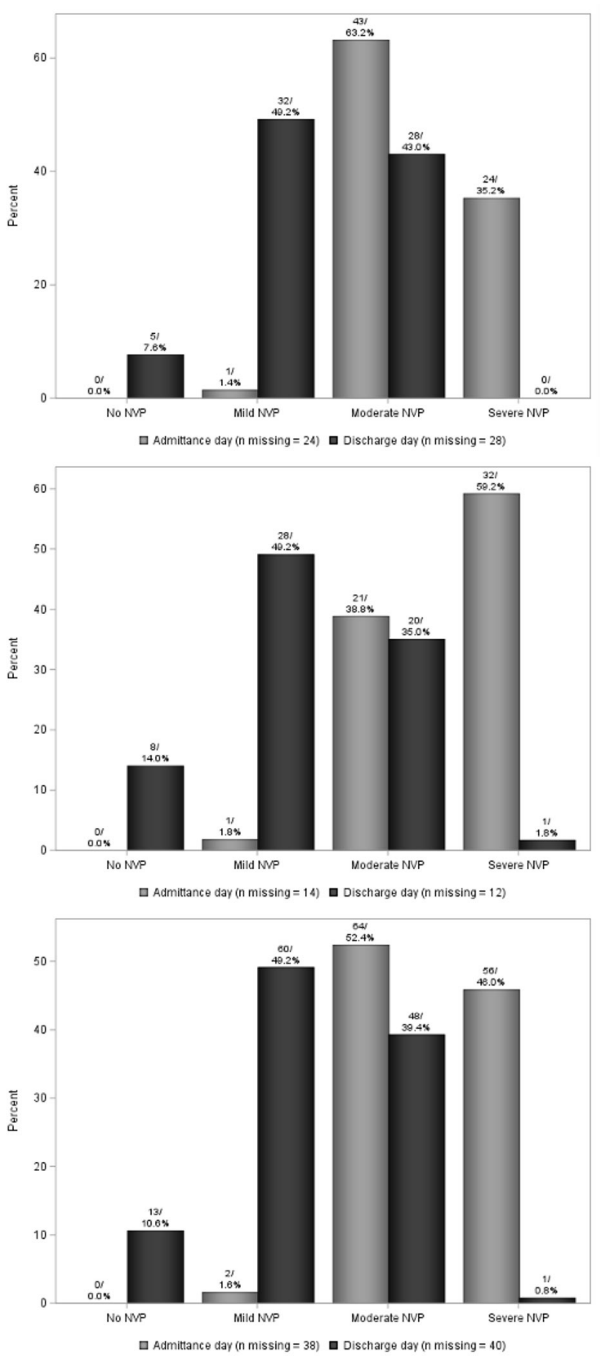

Figure 13. PUQE categories on admission and discharge days in Study I including only the first admission (upper), readmissions (middle), and all admissions (bottom). NVP nausea and vomiting of pregnancy; PUQE pregnancy-unique quantification of emesis questionnaire

5.3 Associative factors for the severity of nausea and vomiting of pregnancy (Studies III–V)

Summary of the factors associated with the severity of NVP in Studies **I–V** is presented in **Figure 14**.

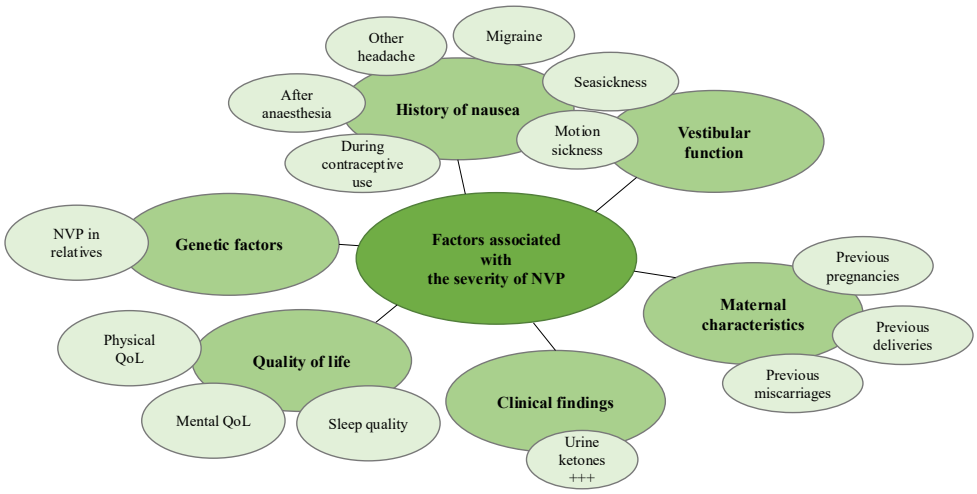

Figure 14. Factors associated with the severity of nausea and vomiting of pregnancy (univariate analysis). NVP nausea and vomiting of pregnancy; QoL quality of life

5.3.1 Maternal characteristics

Concerning the basic characteristics of all women, only previous pregnancies were associated with all PUQE categories: women with higher gravidity were more likely to have more severe NVP. In addition, having previous deliveries were associated with mild and moderate NVP and having previous miscarriages with moderate and severe NVP. Age, BMI, previous pregnancy terminations, smoking, marital status, employment, and nationality were not associated with the severity of NVP.

To further explore the effect of previous pregnancies, it was categorised demonstrating that women with higher gravidity (≥ 2 previous pregnancies) had more severe NVP than nulliparous women. However, no associations were found in multivariate analysis between previous pregnancies, previous deliveries, previous miscarriages, marital status, and the severity of NVP. (**Table 19**)

In the subgroup analysis of women ≤ 20 gwk, having previous pregnancies was associated with more severe NVP. Similarly, in analysis with categorised previous pregnancies, women with one or more previous pregnancies had more severe NVP compared to nulliparous women. Further, having previous deliveries was associated

with moderate NVP. The other maternal characteristics studied were not associated with NVP. (**Table 20**)

5.3.2 Personal history of nausea

When associations between personal history of nausea in various situations and the severity of NVP were studied, history of nausea in context of motion sickness, seasickness and other kind of headache were associated with more severe NVP in univariate analysis. In addition, history of nausea in migraine, nausea after anaesthesia, nausea related to the use of contraception and other kind of nausea were associated with moderate and severe NVP. These results remained the same in adjusted analysis. (**Table 19**)

To consider the interrelations, multivariate analysis including all personal history of nausea variables was conducted. In multivariate analysis, history of motion sickness was associated with more severe NVP (mild NVP OR 1.59, 95% CI 1.06–2.40; moderate NVP OR 2.19, 95% CI 1.49–3.23; severe NVP 3.17, 95% CI 1.81–5.56, $p<0.0001$). In addition, history of nausea in migraine was associated with severe NVP (OR 3.18, 95% CI 1.86–5.45, $p<0.0001$)) and history of nausea with other type of headache with moderate NVP (OR 1.80, 95% CI 1.34–2.72, $p=0.001$).

In the subgroup analysis of women ≤ 20 gwk, in univariate analysis, history of nausea in context of motion sickness, seasickness and other type of headache were associated with more severe NVP. Further, history of nausea in migraine was associated with moderate and severe NVP. In adjusted analysis, the results remained the same. (**Table 20**)

In multivariate analysis of all personal history of nausea variables in the subgroup of women ≤ 20 gwk, history of motion sickness was associated with more severe NVP (mild NVP OR 1.97, 95% CI 1.09–3.55; moderate NVP OR 2.45, 95% CI 1.39–4.30; severe NVP OR 2.93, 95% CI 1.26–6.79, $p=0.013$). Further, history of nausea in migraine with moderate NVP (OR 1.84 95% CI 1.02–3.32, $p=0.002$) and severe NVP (OR 3.37, 95% CI 1.49–7.60, $p=0.002$) and history of nausea with other headache with moderate NVP (OR 2.01, 95% CI 1.22–3.30, $p=0.033$).

5.3.3 Nausea and vomiting of pregnancy in relatives

Women who reported NVP in first-degree relatives suffered from more severe NVP compared to women with no NVP. Further, the women with affected second-degree relatives were more likely to suffer from moderate NVP or severe NVP compared to women with no NVP. These results were the same in adjusted analysis. (**Table 19**)

In subgroup analysis of women ≤ 20 gwk, history of NVP in first-degree relatives was associated with more severe NVP. Further, women with affected second-degree

relatives were more likely to suffer from moderate or severe NVP compared to women with no NVP. In the adjusted analysis, the results concerning associations between first-degree relatives and NVP were the same. However, NVP in second-degree relatives was associated with only severe NVP in adjusted analysis. (**Table 20**)

Table 19. Statistically significant associations with the severity of nausea and vomiting of pregnancy in Studies III–IV. Total n=2381.

				No	Mild NVP		Moderate NVP		Severe NVP	
	n	***p*[1]**	***p*[2]**	**OR**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**
Basic characteristics										
Previous pregnancies	2325	<0.001		1	1.15 (1.02–1.30)		1.24 (1.11–1.39)		1.26 (1.08–1.46)	
1 vs 0	776	<0.001		1	1.67 (1.20–2.33)		1.78 (1.30–2.43)		1.63 (1.00–2.67)	
≥ 2 vs 0	747	<0.001		1	1.57 (1.11–2.22)		2.02 (1.47–2.79)		2.17 (1.34–3.51)	
Previous deliveries	2325	0.005		1	1.19 (1.01–1.41)		1.31 (1.12–1.53)		1.21 (0.97–1.51)	
Previous miscarriages[3]	2325	0.020		1	1.25 (0.97–1.60)		1.34 (1.06–1.70)		1.58 (1.17–2.14)	
Personal history of nausea										
Motion sickness	1091	<0.001	<0.001	1	1.82 (1.35–2.46)	1.67 (1.21–2.31)	2.65 (2.00–3.52)	2.54 (1.87–3.45)	3.81 (2.50–5.81)	3.93 (2.48–6.23)
Seasickness	731	<0.001	<0.001	1	1.81 (1.29–2.52)	1.72 (1.20–2.47)	1.96 (1.43–2.69)	1.94 (1.37–2.74)	2.29 (1.47–3.57)	2.65 (1.63–4.31)
Migraine	687	<0.001	<0.001	1	1.19 (0.85–1.66)	1.28 (0.89–1.84)	1.76 (1.29–2.41)	1.79 (1.27–2.51)	3.39 (2.19–5.24)	4.23 (2.62–6.84)
Other headache	904	<0.001	<0.001	1	1.70 (1.24–2.34)	1.66 (1.17–2.35)	2.46 (1.83–3.32)	2.50 (1.80–3.47)	2.30 (1.50–3.54)	2.32 (1.44–3.73)
Other nausea[4]	271	0.033	0.007	1	1.47 (0.89–2.43)	1.33 (0.77–2.28)	1.83 (1.14–2.94)	1.73 (1.01–2.97)	2.23 (1.17–4.23)	2.30 (1.15–4.58)

After anaesthesia	262	0.014	0.044	1	1.27 (0.77–2.10)	1.19 (0.70–2.04)	1.79 (1.12–2.86)	1.64 (1.00–2.71)	2.10 (1.11–3.99)	2.09 (1.05–4.17)
Use of contraception	95	0.003	0.007	1	2.80 (0.83–9.45)	2.22 (0.64–7.65)	4.83 (1.50–15.52)	3.72 (1.14–12.10)	7.57 (2.07–27.62)	6.87 (1.84–25.59)
NVP in relatives[5]										
First-degree	874	<0.001	<0.001	1	2.06 (1.43–2.97)	2.04 (1.37–3.03)	3.84 (2.72–5.40)	4.23 (2.91–6.15)	3.19 (1.92–5.28)	3.56 (2.05–6.20)
Second–degree	60	<0.001	<0.001	1	1.54 (0.52–4.55)	1.37 (0.45–4.16)	3.97 (1.51–10.40)	3.16 (1.17–8.53)	4.28 (1.28–14.38)	3.84 (1.08–13.62)

AOR adjusted odds ratio; BMI body mass index; CI confidence interval; n number; NVP nausea and vomiting of pregnancy; OR odds ratio; vs versus

[1] univariate analysis

[2] adjusted analysis: adjusted for age, parity, BMI, smoking and employment

[3]including both spontaneous abortions and ectopic pregnancies

[4]Other context of nausea: in rotating motion n=27, during gastroenteritis or other illness n=26, hunger n=24, pain n=20, with repulsive odours n=18.

[5]First-degree relatives: mother or sister, second-degree relatives: more distant relatives (aunt, cousin, grandparents).

Table 20. Statistically significant associations with the severity of nausea and vomiting of pregnancy in subgroup ≤ 20 gwk of Studies III–IV. Total n=1247.

				No	Mild NVP		Moderate NVP		Severe NVP	
	n	***p*[1]**	***p*[2]**	**OR**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**
Basic characteristics										
Previous pregnancies	1212	0.005		1	1.22 (1.03–1.45)		1.33 (1.13–1.56)		1.26 (1.01–1.57)	
1 vs 0	408	0.004		1	1.62 (1.02–2.57)		1.88 (1.22–2.90)		1.40 (0.71–2.79)	
≥ 2 vs 0	388	0.004		1	1.98 (1.20–3.26)		2.53 (1.58–4.06)		2.53 (1.28–5.00)	
Previous deliveries	1212	0.011		1	1.25 (0.98–1.60)		1.43 (1.13–1.81)		1.28 (0.93–1.76)	
Personal history of nausea										
Motion sickness	573	<0.0001	<0.0001	1	2.51 (1.62–3.90)	2.60 (1.63–4.15)	3.14 (2.07–4.76)	3.31 (2.12–5.16)	5.50 (2.99–10.1)	6.34 (3.22–12.5)
Seasickness	385	<0.0001	<0.0001	1	2.96 (1.76–4.99)	3.10 (1.78–5.40)	2.90 (1.76–4.80)	3.08 (1.80–5.25)	4.91 (2.55–9.45)	6.80 (3.29–14.1)
Migraine	364	<0.0001	<0.0001	1	1.38 (0.85–2.24)	1.33 (0.79–2.22)	2.16 (1.37–3.39)	1.96 (1.21–3.17)	4.15 (2.21–7.78)	4.56 (2.28–9.11)
Other headache	489	0.0001	0.001	1	1.94 (1.24–3.01)	1.72 (1.07–2.76)	2.51 (1.53–5.16)	2.38 (1.51–3.72)	2.81 (1.53–5.16)	2.33 (1.18–4.60)

NVP in relatives										
First-degree	482	<0.0001	<0.0001	1	2.17 (1.31–3.59)	2.15 (1.26–3.69)	3.83 (2.38–6.17)	4.20 (2.52–7.00)	2.81 (1.41–5.60)	3.10 (1.46–6.60)
Second-degree	30	<0.0001	<0.0001	1	3.94 (0.46–33.64)	3.15 (0.36–28.10)	9.86 (1.29–75.60)	7.36 (0.93–58.30)	10.93 (1.15–103.87)	10.83 (1.11–105.46)

AOR adjusted odds ratio; BMI body mass index; CI confidence interval; n number; NVP nausea and vomiting of pregnancy; OR odds ratio; vs versus

[1] univariate analysis

[2] adjusted analysis: adjusted for age, parity, BMI, smoking and employment

First-degree relatives: mother or sister, second-degree relatives: more distant relatives (aunt, cousin, grandparents).

5.3.4 Sleep quality

Women rating worse general sleep quality by VAS suffered from more severe NVP compared to women with no NVP (**Figure 18**).

Sleepiness during the day was associated with more severe NVP. Further, women with moderate NVP and severe NVP had more night awakenings and too early morning awakenings. Furthermore, difficulty falling asleep was associated with moderate NVP. In adjusted analysis, the results remained the same except the association between difficulty falling asleep and moderate NVP and the association between too early morning awakenings and severe NVP which lost their significance. (**Table 21**)

Table 21. Associations between distinct sleep disturbances and nausea and vomiting of pregnancy. Total n=1203.

				No	Mild NVP		Moderate NVP		Severe NVP	
	n	***p*[1]**	***p*[2]**	**OR**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**	**OR (95% CI)**	**AOR (95% CI)**
Sleep disturbances according to BNSQ										
Difficulty falling asleep	85	0.005	0.026	1	1.05 (0.37–2.98)	1.00 (0.30–3.18)	2.66 (1.04–6.75)	2.46 (0.86–7.07)	3.01 (0.95–9.57)	3.00 (0.80–11.29)
Night awakenings	837	<0.0001	<0.0001	1	1.34 (0.90–2.01)	1.33 (0.86–2.05)	2.39 (1.62–3.52)	2.08 (1.38–3.15)	3.87 (1.95–7.70)	3.90 (1.79–8.47)
Too early morning awakenings	143	<0.001	0.013	1	2.02 (0.82–4.95)	1.81 (0.72–4.53)	3.82 (1.64–8.91)	3.16 (1.33–7.49)	3.97 (1.42–11.04)	3.05 (0.99–9.37)
Sleepiness during the day	427	<0.0001	<0.0001	1	2.87 (1.67–4.95)	2.90 (1.60–5.28)	4.93 (2.93–8.29)	5.07 (2.86–8.97)	4.15 (2.11–8.15)	4.67 (2.20–9.94)

AOR = adjusted odds ratio; BNSQ basic Nordic sleep questionnaire; BMI body mass index; CI confidence interval; n number; NVP nausea and vomiting of pregnancy; OR odds ratio

[1]univariate analysis

[2]adjusted analysis: adjusted for age, parity, BMI, smoking, employment

5.4 Aspects of nausea and vomiting of pregnancy (Studies III–IV)

The mean points of each PUQE questions in **Studies II–IV** are presented in **Table 18**.

In **Studies III–IV**, in the first PUQE question evaluating the duration of nausea, the answers of all women accumulated to the severe end of the answer options. Thus, over third of all women had nausea over six hours during the worst 12 hours of NVP. However, in the second PUQE question evaluating the number of vomiting episodes during the worst 12 hours of NVP, over half of all women had only one to two vomiting episodes. Instead, as seen in PUQE question 3, retching was more frequent than vomiting. Over third of all women had retching episodes more than three times during the worst 12 hours of NVP. (**Figure 15**)

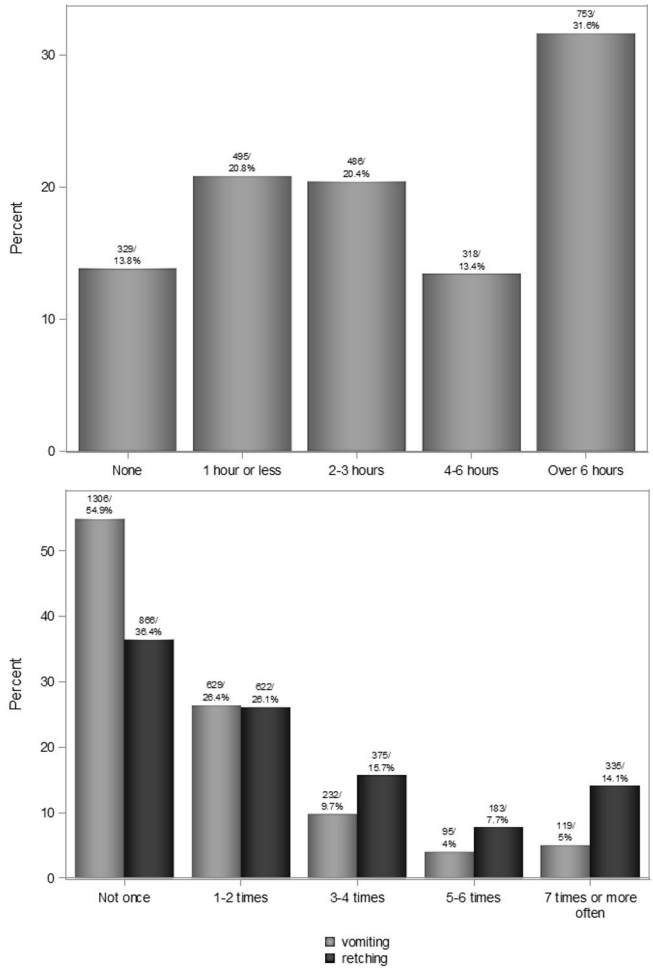

Figure 15. Duration of nausea in hours and frequencies of vomiting and retching episodes in Studies III–IV. Reprinted from Study III with the permission from Elsevier.

In the subgroup analysis of women ≤ 20 gwk, the proportions were essentially the same. (**Figure 16**)

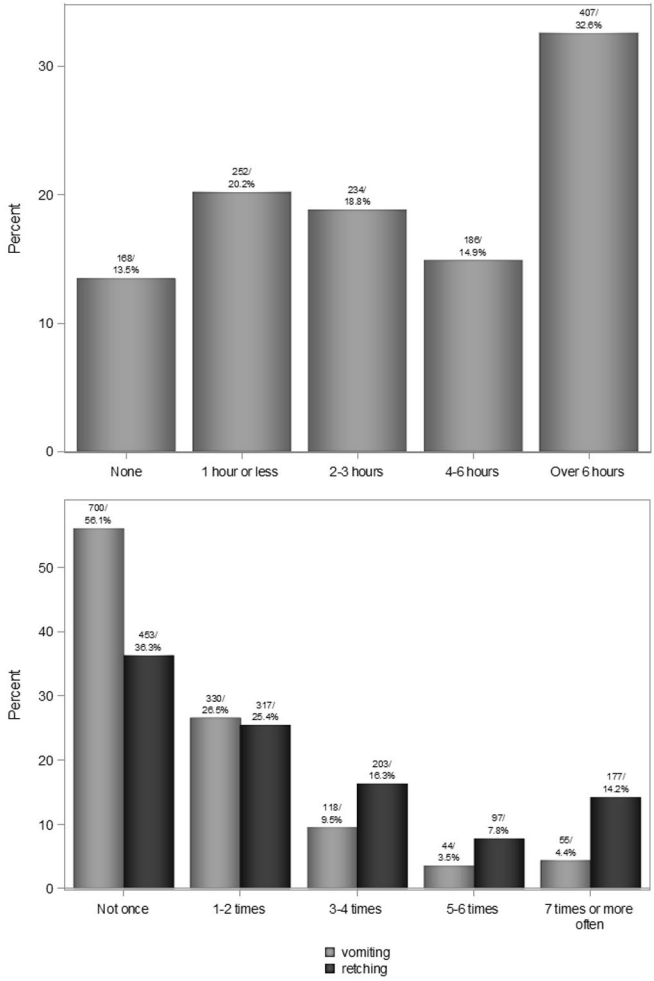

Figure 16. Duration of nausea and frequencies of vomiting and retching episodes in the subgroup of ≤ 20 gwk in Studies III–IV. gwk gestational week.

5.5 Associative factors for various aspects of nausea and vomiting of pregnancy (Studies III–IV)

Summary of factors associated with various aspects of NVP is presented in **Figure 17**.

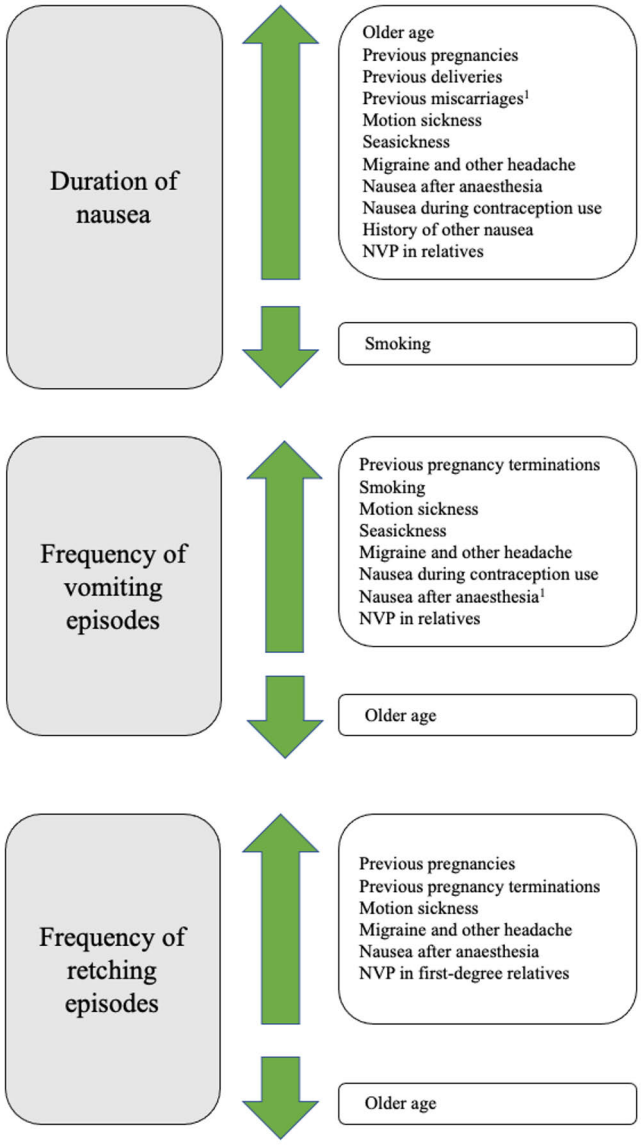

Figure 17. Factors associated with aspects of nausea and vomiting of pregnancy (univariate analysis). [1]only in subgroup ≤ 20 gwk. gwk gestational week; NVP nausea and vomiting of pregnancy.

5.5.1 Maternal characteristics

Age was associated with daily nausea over six hours. However, older women had less vomiting and retching. Having previous pregnancies and previous deliveries were associated with longer duration of nausea. In addition, women with previous pregnancies had retching episodes over three times during the worst 12 hours of NVP. Further, having previous pregnancy terminations were associated with vomiting episodes three to four times and with retching episodes three to six times during the worst 12 hours of NVP. On the other hand, smokers had overall shorter duration of nausea, but smoking was associated with vomiting three to four times during the worst 12 hours of NVP. Instead, BMI and marital status were not associated with aspects of NVP. (**Table 22**)

Table 22. Statistically significant associations between basic characteristics and various aspects of NVP in Study III.

	All women (n=2381)				
	Age	Previous pregnancies	Previous deliveries	Previous pregnancy terminations	Smoking
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
PUQE Question 1: Duration of nausea					
p	*0.004*	*<0.001*	*<0.001*	*0.674*	*<0.0001*
None	1	1	1	1	1
≤ 1h	0.99 (0.96–1.02)	1.14 (1.01–1.28)	1.13 (0.95–1.34)	1.21 (0.86–1.69)	1.12 (0.77–1.62)
2–3 h	1.00 (0.97–1.03)	1.21 (1.07–1.36)	1.29 (1.10–1.52)	1.00 (0.70–1.43)	0.65 (0.43–0.98)
4–6 h	0.99 (0.95–1.02)	1.23 (1.09–1.40)	1.28 (1.07–1.53)	1.14 (0.78–1.66)	0.72 (0.46–1.12)
> 6 h	1.03 (1.00–1.06)	1.29 (1.16–1.44)	1.38 (1.19–1.62)	1.16 (0.85–1.60)	0.49 (0.33–0.73)
PUQE Question 2: Frequency of vomiting					
p	*<0.0001*	*0.471*	*0.473*	*0.007*	*0.021*
No	1	1	1	1	1
1–2 times	0.96 (0.94–0.98)	1.01 (0.94–1.09)	1.02 (0.92–1.12)	1.07 (0.85–1.35)	1.35 (1.02–1.80)
3–4 times	0.93 (0.90–0.96	1.09 (0.99–1.19)	1.05 (0.92–1.20)	1.62 (1.25–2.12)	1.83 (1.26–2.66)
5–6 times	0.93 (0.89–0.97)	0.98 (0.84–1.15)	0.89 (0.70–1.12)	1.15 (0.71–1.87)	1.17 (0.63–2.21)
≥ 7 times	0.93 (0.89–0.97)	1.05 (0.93–1.20)	0.87 (0.70–1.08)	1.35 (0.91–1.98)	1.14 (0.65–2.02)
PUQE Question 3: Frequency of retching					
p	*<0.0001*	*0.012*	*0.317*	*0.023*	*0.209*
No	1	1	1	1	1
1–2 times	0.97 (0.95–0.99)	1.06 (0.98–1.15)	1.08 (0.97–1.21)	1.16 (0.89–1.51)	1.05 (0.76–1.46)
3–4 times	0.96 (0.93–0.98)	1.11 (1.02–1.22)	1.09 (0.96–1.23)	1.51 (1.15–1.98)	1.36 (0.95–1.94)
5–6 times	0.93 (0.90–0.96)	1.19 (1.07–1.32)	1.16 (1.00–1.35)	1.51 (1.08–2.11)	1.55 (0.99–2.41)
≥ 7 times	0.96 (0.94–0.99)	1.10 (1.00–1.20)	1.07 (0.94–1.22)	1.19 (0.87–1.62)	1.25 (0.86–1.82)

CI confidence interval; n number; OR odds ratio; PUQE pregnancy-unique quantification of emesis questionnaire.

In subgroup analysis of women ≤ 20 gwk, the results were similar concerning age, previous pregnancies, previous deliveries, and previous pregnancy terminations. Instead, having previous miscarriages was associated with nausea over four hours during the worst 12 hours of NVP. Smoking, however, was associated with shorter duration of nausea but with one or two vomiting episodes during the worst 12 hours of NVP. (**Table 23**)

Table 23. Statistically significant associations between basic characteristics and various aspects of NVP in subgroup analysis of Study III.

	Subanalysis of ≤ 20 gwk (n=1247)					
	Age	Previous pregnancies	Previous deliveries	Previous miscarriages[1]	Previous pregnancy terminations	Smoking
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
PUQE Question 1: Duration of nausea						
p	*0.006*	*0.005*	*0.006*	*0.017*	*0.881*	*0.025*
None	1	1	1	1	1	1
≤ 1 h	0.99 (0.95–1.04)	1.21 (1.02–1.43)	1.23 (0.96–1.57)	1.58 (1.08–2.31)	0.95 (0.59–1.53)	1.13 (0.66–1.94)
2–3 h	0.99 (0.94–1.03)	1.25 (1.05–1.48)	1.35 (1.06–1.71)	1.42 (0.96–2.09)	1.05 (0.66–1.68)	0.81 (0.46–1.45)
4–6 h	0.98 (0.93–1.02)	1.29 (1.08–1.53)	1.26 (0.98–1.63)	1.84 (1.26–2.70)	1.10 (0.67–1.80)	0.95 (0.53–1.72)
> 6 h	1.04 (1.00–1.08)	1.35 (1.15–1.58)	1.48 (1.18–1.85)	1.72 (1.21–2.46)	0.90 (0.58–1.40)	0.52 (0.30–0.91)
PUQE Question 2: Frequency of vomiting						
p	*<0.0001*	*0.920*	*0.867*	*0.187*	*0.034*	*0.039*
No	1	1	1	1	1	1
1–2 times	0.95 (0.93–0.98)	1.02 (0.93–1.12)	1.05 (0.93–1.19)	1.01 (0.82–1.24)	0.86 (0.61–1.23)	1.78 (1.21–2.58)
3-4 times	0.93 (0.89–0.97)	1.02 (0.89–1.17)	0.97 (0.79–1.19)	0.88 (0.63–1.23)	1.64 (1.12–2.40)	1.67 (0.96–2.89)
5–6 times	0.92 (0.86–0.98)	1.08 (0.90–1.31)	0.98 (0.71–1 35)	1.47 (1.02–2.11)	0.89 (0.38–2.05)	1.15 (0.44–3.02)
≥ 7 times	0.90 (0.85–0.96)	1.05 (0.88–1.26)	0.93 (0.69–1.25)	1.21 (0.84–1.76)	1.47 (0.86–2.53)	1.66 (0.78–3.54)
PUQE Question 3: Frequency of retching						
p	*<0.0001*	*0.012*	*0.317*	*0.089*	*0.023*	*0.174*
No	1	1	1	1	1	1
1–2 times	0.97 (0.95–0.99)	1.06 (0.98–1.15)	1.08 (0.97–1.21)	1.02 (0.86–1.20)	1.16 (0.89–1.51)	1.08 (0.68–1.70)
3–4 times	0.96 (0.93–0.98)	1.11 (1.02–1.22)	1.08 (0.96–1.23)	1.12 (0.93–1.35)	1.51 (1.15–2.00)	1.69 (1.05–2.72)
5–6 times	0.93 (0.90–0.96)	1.19 (1.07–1.32)	1.16 (1.00–1.35)	1.29 (1.04–1.62)	1.51 (1.08–2.11)	1.40 (0.74–2.66)
≥ 7 times	0.96 (0.94–0.99)	1.10 (1.00–1.20)	1.07 (0.94–1.22)	1.20 (1.00–1.45)	1.19 (0.87–1.62)	1.51 (0.91–2.51)

CI confidence interval; gwk gestational week; n number; OR odds ratio; PUQE pregnancy-unique quantification of emesis questionnaire

[1]including ectopic pregnancies

5.5.2 Personal history of nausea

In adjusted analysis, history of motion sickness was associated with all aspects of NVP. Likewise, women with seasickness had longer duration of nausea, vomiting episodes over five times and retching episodes over three times during the worst 12 hours of NVP. In addition, women with history of nausea in migraine or other kind of headache had longer duration of nausea. Further, women with migraine had vomiting over three times and retching over five times during the worst 12 hours of NVP. Nausea in other headache was associated with more frequent retching episodes. Furthermore, nausea after anaesthesia was associated with duration of nausea over six hours and nausea related to the use of contraception was associated with duration of nausea for over four hours and over seven vomiting episodes during the worst 12 hours of NVP. Also having history of other kind of nausea was associated with duration of nausea over four hours during the worst 12 hours of NVP. (**Table 24**)

In adjusted analysis of the subgroup of women answering ≤ 20 gwk, history of motion sickness was associated with all aspects of NVP: the women had longer duration of nausea, over seven vomiting episodes and over three retching episodes during the worst 12 hours of NVP. Further, women with seasickness had longer duration of nausea and over four vomiting episodes during the worst 12 hours of NVP. Likewise, having migraine was associated with all aspects of NVP: nausea over two hours, and over seven times of vomiting and retching episodes during the worst 12 hours of NVP. Furthermore, history of other kind of headache was associated with over four hours of nausea in 12 hours, and more frequent retching episodes in 12 hours. In addition, history of nausea after anaesthesia was associated with over seven vomiting episodes during the worst 12 hours of NVP. (**Table 25**)

Table 24. Statistically significant associations between personal history of nausea, NVP in relatives and aspects of NVP in Study IV.

	All women (n=2381)								
	Personal history of nausea							NVP in relatives	
	Motion sickness	Seasickness	Migraine	Other headache	After anaesthesia	During contraception use	Other nausea	First-degree relatives	Second-degree relatives
	AOR (95% CI)	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**
PUQE Question 1: Duration of nausea									
p	*<0.0001**	*<0.001**	*<0.0001**	*<0.0001**	*0.005**	*0.029**	*0.017**	*<0.0001**	*<0.0001**
None	1	1	1	1	1	1	1	1	1
≤ 1 h	1.41 (1.02–1.96)	1.52 (1.06–2.20)	1.56 (1.08–2.27)	1.59 (1.13–2.24)	1.20 (0.69–2.09)	2.79 (0.79–9.92)	1.31 (0.76–2.26)	1.72 (1.15–2.56)	1.17 (0.35–3.97)
2–3 h	1.98 (1.43–2.73)	1.73 (1.20–2.49)	1.61 (1.11–2.33)	1.71 (1.21–2.42)	1.26 (0.73–2.19)	3.06 (0.87–10.81)	1.23 (0.71–2.12)	2.21 (1.47–3.32)	1.83 (0.57–5.83)
4–6 h	2.98 (2.08–4.26)	2.01 (1.35–2.98)	1.62 (1.08–2.43)	2.59 (1.79–3.77)	1.45 (0.80–2.61)	4.61 (1.29–16.46)	1.90 (1.07–3.39)	5.97 (3.56–10.01)	5.78 (1.74–19.19)
> 6 h	2.65 (1.95–3.60)	2.09 (1.49–2.93)	2.39 (1.70–3.38)	2.38 (1.72–3.28)	2.11 (1.29–3.46)	5.26 (1.59–17.38)	1.97 (1.20–3.24)	3.68 (2.51–5.37)	4.19 (1.51–11.58)
PUQE Question 2: Frequency of vomiting									
p	*<0.0001**	*0.008**	*<0.0001**	*0.077**	*0.057*	*0.039**	*0.549*	*<0.0001**	*<0.0001**
No	1	1	1	1	1	1	1	1	1
1–2 times	1.47 (1.19–1.82)	1.17 (0.93–1.47)	1.12 (0.88–1.41)	0.93 (0.74–1.16)	0.91 (0.64–1.30)	1.37 (0.79–2.37)	1.14 (0.82–1.59)	2.06 (1.52–2.78)	1.68 (0.80–3.52)
3-4 times	1.36 (1.00–1.85)	1.07 (0.76–1.52)	1.59 (1.15–2.21)	1.48 (1.08–2.03)	1.41 (0.89–2.25)	1.49 (0.69–3.19)	1.18 (0.72–1.95)	1.62 (1.07–2.46)	1.71 (0.65–4.49)
5–6 times	1.70 (1.07–2.70)	2.02 (1.26–3.23)	1.85 (1.16–2.96)	0.99 (0.61–1.58)	1.15 (0.55–2.38)	1.70 (0.58–4.95)	1.22 (0.60–2.47)	1.90 (1.02–3.53)	2.19 (0.59–8.17)
≥ 7 times	2.02 (1.32–3.12)	1.74 (1.12–2.71)	3.40 (2.20–5.28)	1.27 (0.82–1.95)	2.09 (1.18–3.72)	3.45 (1.58–7.51)	1.68 (0.90–3.14)	1.48 (0.88–2.49)	2.24 (0.78–6.46)

PUQE Question 3: Frequency of retching									
p	*<0.0001**	*0.024*	*<0.0001**	*<0.0001**	*0.099**	*0.213*	*0.111*	*<0.0001**	*<0.0001**
No	1	1	1	1	1	1	1	1	1
1–2 times	1.31 (1.04–1.65)	1.11 (0.86–1.42)	1.19 (0.92–1.53)	1.51 (1.19–1.92)	1.30 (0.90–1.88)	1.48 (0.80–2.76)	1.13 (0.78–1.64)	2.04 (1.48–2.81)	2.45 (1.13–5.32)
3–4 times	1.58 (1.21–2.07)	1.39 (1.04–1.86)	1.28 (0.95–1.72)	1.61 (1.22–2.13)	1.31 (0.85–2.02)	1.34 (0.65–2.78)	1.43 (0.94–2.19)	2.36 (1.62–3.43)	2.75 (1.15–6.58)
5–6 times	1.96 (1.36–2.82)	1.63 (1.10–2.42)	1.56 (1.06–2.30)	1.74 (1.19–2.54)	1.85 (1.07–3.19)	2.21 (0.98–5.01)	1.89 (1.11–3.20)	2.44 (1.46–4.06)	2.35 (0.71–7.76)
≥ 7 times	1.95 (1.47–2.59)	1.42 (1.05–1.91)	2.48 (1.85–3.33)	1.85 (1.39–2.47)	1.63 (1.06–2.51)	2.03 (1.02–4.02)	1.41 (0.90–2.19)	1.98 (1.37–2.86)	1.49 (0.55–4.06)

AOR adjusted odds ratio (adjusted for age, parity, BMI, smoking and employment); BMI body mass index; CI confidence interval; n number; PUQE pregnancy-unique quantification of emesis questionnaire

*signicant in univariate analysis

5.5.3 Nausea and vomiting of pregnancy in relatives

In adjusted analysis, history of NVP in first-degree relatives was associated with longer duration of nausea, vomiting episodes up to six times and more frequent retching episodes during the worst 12 hours of NVP compared to women with no NVP. Further, history of NVP in second-degree relatives was associated with duration of nausea over four hours and up to four retching episodes during the worst 12 hours of NVP. (**Table 24**)

In adjusted subgroup analysis of women ≤ 20 gwk, history of NVP in first-degree relatives was associated with nausea over two hours, one or two vomiting episodes and more frequent retching during the worst 12 hours of NVP. Further, history of NVP in second-degree relatives was associated with four to six hours of nausea and three to four retching episodes in 12 hours. (**Table 25**)

Table 25. Statistically significant associations between personal history of nausea, NVP in relatives and aspects of NVP in subanalysis of Study IV.

	Subgroup ≤ 20 gwk (n=1247)						
	Personal history of nausea				NVP in relatives		
	Motion sickness	Seasickness	Migraine	Other headache	After anaesthesia	First-degree relatives	Second-degree relatives
	AOR (95% CI)	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**	**AOR (95% CI)**
PUQE Question 1: Duration of nausea							
p	*<0.0001**	*<0.0001**	*<0.001**	*0.003**	*0.078**	*<0.0001**	*<0.0001**
None	1	1	1	1	1	1	1
≤ 1 h	1.83 (1.15–2.91)	2.62 (1.50–4.57)	1.41 (0.83–2.39)	1.58 (0.99–2.54)	1.30 (0.59–2.85)	1.67 (0.97–2.87)	1.75 (0.15–19.97)
2–3 h	2.53 (1.59–4.04)	2.78 (1.59–4.86)	1.83 (1.08–3.08)	1.57 (0.97–2.53)	1.61 (0.75–3.48)	2.59 (1.45–4.63)	3.89 (0.39–39.32)
4–6 h	3.72 (2.26–6.12)	3.24 (1.81–5.82)	1.98 (1.14–3.43)	1.97 (1.20–3.24)	1.91 (0.87–4.22)	6.53 (3.16–13.48)	18.87 (2.01–177.1)
> 6 h	3.34 (2.17–5.15)	3.69 (2.20–6.20)	2.62 (1.62–4.24)	2.31 (1.49–3.58)	2.36 (1.18–4.72)	2.73 (1.64–4.54)	9.18 (1.14–73.30)
PUQE Question 2: Frequency of vomiting							
p	*0.001**	*0.001**	*<0.001**	*0.881*	*0.041*	*0.009**	*0.009**
No	1	1	1	1	1	1	1
1–2 times	1.48 (1.10–1.99)	1.34 (0.97–1.85)	1.31 (0.95–1.81)	0.97 (0.71–1.32)	1.29 (0.82–2.04)	1.89 (1.25–2.85)	1.61 (0.56–4.63)
3-4 times	1.10 (0.70–1.70)	0.88 (0.53–1.46)	1.35 (0.84–2.16)	0.92 (0.58–1.46)	1.42 (0.74–2.74)	1.55 (0.88–2.73)	1.77 (0.45–6.96)
5–6 times	1.49 (0.74–2.97)	2.24 (1.11–4.52)	1.44 (0.70–2.98)	0.82 (0.39–1.69)	1.24 (0.42–3.68)	1.48 (0.62–3.55)	1.43 (0.16–12.64)
≥ 7 times	2.51 (1.32–4.75)	3.06 (1.60–5.85)	4.12 (2.17–7.80)	1.29 (0.69–2.41)	3.50 (1.58–7.77)	1.04 (0.51–2.11)	2.37 (0.58–9.66)
PUQE Question 3: Frequency of retching							
p	*0.002**	*0.062*	*0.007**	*0.008**	*0.286*	*0.004**	*0.004**
No	1	1	1	1	1	1	1
1–2 times	1.36 (0.98–1.87)	1.24 (0.87–1.77)	1.23 (0.86–1.77)	1.55 (1.11–2.18	1.44 (0.87–2.40)	1.89 (1.23–2.91)	2.08 (0.64–6.82)
3–4 times	1.79 (1.23–2.59)	1.64 (1.10–2.44)	1.41 (0.95–2.11)	1.81 (1.24–2.64)	1.61 (0.92–2.84)	2.81 (1.68–4.69)	4.07 (1.21–13.72)
5–6 times	1.75 (1.06–2.89)	1.76 (1.01–3.05)	1.35 (0.78–2.34)	1.19 (0.69–2.06)	1.59 (0.71–3.52)	2.89 (1.42–5.87)	1.52 (0.17–13.84)
≥ 7 times	1.98 (1.34–2.93)	1.51 (0.99–2.30)	2.19 (1.45–3.31)	1.68 (1.12–2.53)	1.76 (0.98–3.19)	2.26 (1.33–3.85)	3.36 (0.94–11.96)

AOR adjusted odds ratio (adjusted for age, parity, BMI, smoking and employment); BMI body mass index; CI confidence interval; n number; PUQE pregnancy-unique quantification of emesis questionnaire

*signicant in univariate analysis

5.6 Quality of life, sleep quality and nausea and vomiting of pregnancy (Study V)

5.6.1 Quality of life and nausea and vomiting of pregnancy in outpatient women

Women estimating worse physical QoL, and worse mental QoL by VAS suffered from more severe NVP compared to women with no NVP (**Figure 18**).

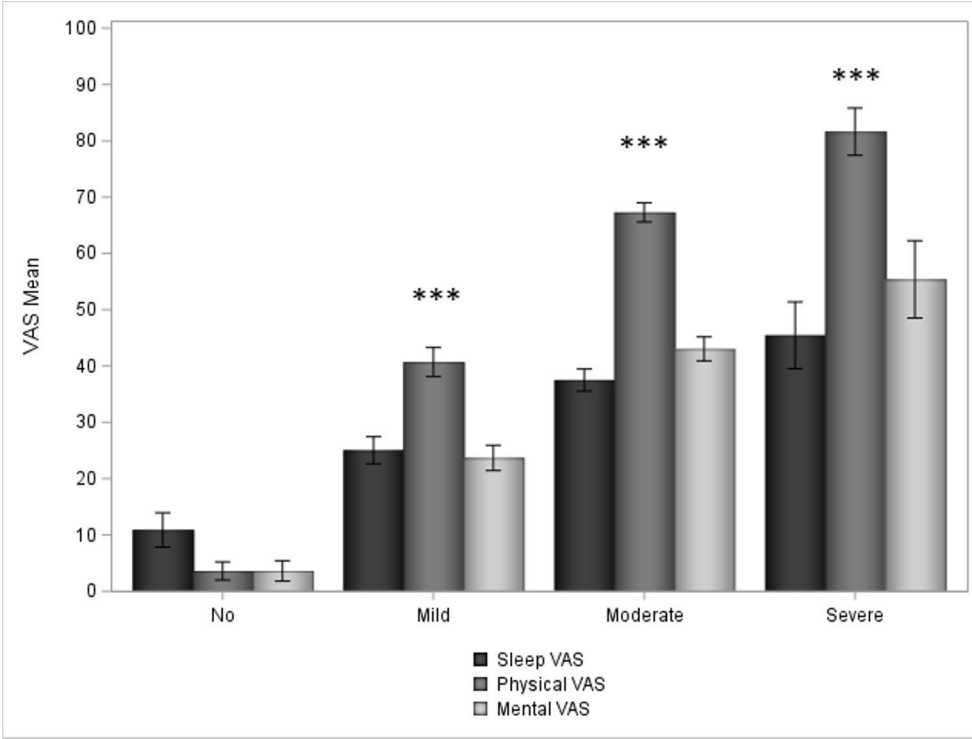

Figure 18. General sleep quality, physical QoL and mental QoL by VAS in NVP categories. Presented as means and confidence intervals. Higher scores in scales indicates worse quality. *** p<0.001 for all comparisons with no NVP. QoL quality of life; NVP nausea and vomiting of pregnancy; VAS visual analogue scale.

5.6.1.1 Quality of life, sleep quality and nausea and vomiting of pregnancy

To further evaluate the connections between sleep disturbances, QoL and the severity of NVP, multivariate models were conducted. The association between worse physical QoL exceeded that of sleep disorders to the severity of NVP. In addition, when only mental QoL, sleep disorders and the severity of NVP were

included, worse mental QoL was associated with more severe NVP, night awakenings were associated with moderate NVP and severe NVP and sleepiness during the day with mild NVP and moderate NVP. However, when physical QoL and mental QoL were both included in the multivariate model, their effect to the severity of NVP exceeded that of sleep disorders. (**Table 26**)

Table 26. Multivariate associations between sleep disturbances, physical QoL, mental QoL and the severity of NVP in Study V. Total n=1203.

	Model 1	Model 2	Model 3	No	Mild NVP			Moderate NVP			Severe NVP		
	p[1]	**p[2]**	**p[3]**	**AOR**	**AOR[1] (95%CI)**	**AOR[2] (95%CI)**	**AOR[3] (95%CI)**	**AOR[1] (95%CI)**	**AOR[2] (95%CI)**	**AOR[3] (95%CI)**	**AOR[1] (95%CI)**	**AOR[2] (95%CI)**	**AOR[3] (95%CI)**
Difficulty falling asleep	0.367	0.466	0.339	1	0.26 (0.03–1.92)	0.33 (0.08–1.39)	0.20 (0.03–1.56)	0.46 (0.06–3.54)	0.49 (0.12–2.00)	0.34 (0.04–2.69)	0.43 (0.04–4.21)	0.48 (0.09–2.59	0.29 (0.03–2.92)
Night awakenings	0.421	0.011	0.396	1	0.77 (0.39–1.52)	1.30 (0.79–2.14)	0.81 (0.40–1.62)	0.88 (0.42–1.84)	1.84 (1.10–3.09)	0.94 (0.44–1.99)	1.42 (0.51–3.96)	3.52 (1.49–8.35)	1.57 (0.56–4.44)
Too early morning awakenings	0.730	0.842	0.582	1	0.50 (0.10–2.51)	0.62 (0.21–1.89)	0.34 (0.06–1.92)	0.50 (0.10–2.64)	0.63 (0.21–1.92)	0.32 (0.05–1.88)	0.36 (0.06–2.29)	0.55 (0.14–2.17)	0.25 (0.04–1.76)
Sleepiness during the day	0.321	0.024	0.290	1	1.67 (0.60–4.63)	2.37 (1.16–4.83)	1.67 (0.58–4.77)	1.72 (0.60–4.95)	2.88 (1.41–5.90)	1.65 (0.56–4.89)	1.06 (0.32–3.52)	2.04 (0.82–5.10)	0.98 (0.29–3.36)
Physical QoL	<0.0001	NA	<0.0001	1	1.21 (1.16–1.26)	NA	1.19 (1.14–1.25)	1.26 (1.20–1.31)	NA	1.23 (1.18–1.29)	1.33 (1.27–1.40)	NA	1.30 (1.24–1.37)
Mental QoL	NA	<0.0001	0.007	1	NA	1.13 (1.10–1.17)	1.03 (0.99–1.07)	NA	1.16 (1.12–1.20)	1.04(1.00–1.08)	NA	1.19 (1.15–1.23)	1.05 (1.01–1.09)

AOR adjusted odds ratio; BMI body mass index; NA not applicable; NVP nausea and vomiting of pregnancy; PUQE Pregnancy Unique Quantification of Emesis questionnaire; QoL = quality of life; Sleep disturbances were assessed with Basic Nordic Sleep Questionnaire. [1]Model 1: PUQE score, sleep disturbances, physical QoL, basic characteristics (age, parity, BMI, smoking, employment); [2]Model 2: PUQE score, sleep disturbances, mental QoL, basic characteristics; [3]Model 3: PUQE score, sleep disturbances, physical QoL, mental QoL, basic characteristics

6 Discussion

6.1 The usability of Pregnancy-Unique Quantification of Emesis Questionnaire

The present study applied the PUQE in two different settings: prospectively with hospitalised women with HG and in retrospective assessment of the worst NVP in the current pregnancy of women attending to routine MHCC visits.

Originally, the PUQE has been validated in a prospective cohort study of 200 women with NVP, of whom 21 women had HG (Koren et al., 2005), as referred in chapter 2.2.1.1. Additionally, previous studies have applied the PUQE and its extensions (PUQE-24 and the Modified-PUQE) also in women with HG (Birkeland et al., 2015; Chhetry et al., 2016) and in prospective (Lacasse et al., 2009b; Tan et al., 2018) and retrospective (Choi et al., 2018; Dochez et al., 2016; Heitmann et al., 2017) assessment of NVP. Indeed, as severe NVP and HG are overlapping, and HG is considered to represent the far end in the severity spectrum of NVP (Fejzo et al., 2019), it seems reasonable that the PUQE can be applied for both NVP and HG.

However, specific questionnaires to assess particularly HG and to consider wider spectrum of symptoms than the PUQE may certainly be needed. The PUQE has been criticised for having a too narrow rating scale for the most severe symptoms, thus neglecting some important features of HG, like inadequate intake of food or liquids (Macgibbon et al., 2021). Indeed, detailed questionnaires provide more information, invaluable for scientific purposes and suitable for patient self-monitoring, but lengthy questionnaires are more time-consuming and thus less practical for clinicians. Dealing with this limitation, it all comes back to the original idea of the PUQE as a simple, short questionnaire. Therefore, balancing in clinical practice remains a challenge.

6.1.1 Pregnancy-Unique Quantification of Emesis Questionnaire in women with hyperemesis gravidarum (Study I)

The PUQE categorises the severity of NVP and women rating the most severe PUQE score certainly need thorough medical evaluation as they potentially have HG.

However, as in the present study, not all women hospitalised for HG rate severe NVP category by PUQE at admittance. The rate of hospitalisation in different PUQE categories was evaluated in the validation studies of the original PUQE which showed that third of the women who were admitted had severe NVP and only few women rated mild or moderate NVP (Koren et al., 2005). Furthermore, in their study, women with HG had a mean PUQE score of 11 which equals moderate NVP. Instead, in a Norwegian study of hospitalised women with HG, the most prevalent PUQE category at admission was severe NVP (58%) (Birkeland et al., 2015). In the present study, moderate NVP was the most prevalent PUQE category at first admission, but when only readmissions were considered, the most prevalent PUQE category was severe NVP. Notably, thus far, the present study was the first study to assess the first admission and readmissions separately revealing higher PUQE scores at admission in readmissions which roughly reflected prolonged, more severe HG.

Similarly, as in the present study, the PUQE scores have been shown to decrease along HG treatment in other studies. In a study of hospitalized women with HG from Nepal, mean continuous PUQE score at admission was 12.3 and after three days the mean score was 5.4 (mean length of hospitalisation was three days) (Chhetry et al., 2016). In the above-mentioned Norwegian study of hospitalised women with HG, the median continuous PUQE score at admission was 13 and at discharge 6, and the median length of hospitalisation was two days (Birkeland et al., 2015). Further, an RCT from the UK compared treatment of HG with intravenous hydration and antiemetics in inpatient (n=76) and outpatient (n=74) settings and used the PUQE scores for comparisons (Mitchell-Jones et al., 2017). In both groups, the mean reduction in PUQE scores after 24 hours were 4.7 and 4.6 points from moderate (mean 12.9) and severe (mean 13.7) PUQE scores, showing a similar decrease in PUQE scores along treatment (Mitchell-Jones et al., 2017). In the present study, as well as in previous studies, the continuous PUQE scores in HG reflected the overall improvement of the condition, suggesting that the PUQE score could serve as a valuable instrument for individual recovery assessment in the hospital setting.

6.1.1.1 Pregnancy-Unique Quantification of Emesis Questionnaire in hospital setting

The present study evaluated the usability of PUQE in hospital setting and compared the PUQE scores to clinically meaningful measurements: estimations of physical QoL and mental QoL assessed by VAS scores and to urine ketones, which were routinely measured in clinical care.

The original PUQE included a single VAS score for the estimation of general wellbeing (Koren et al., 2002). In the validation studies, this wellbeing score has been shown to correlate with more severe NVP (Ebrahimi et al., 2009; Koren et al.,

2005). By using two separate scores, physical QoL VAS and mental QOL VAS, the QoL could be estimated more comprehensively, yet in an easy way to fill in. Many general QoL questionnaires, like SF-12 or SF-36, as well as the NVP-specific NVP-QOL, are considerably longer and more time-consuming, and therefore less practical in daily recordings at the hospital. A Norwegian study of hospitalised women with HG (Birkeland et al., 2015) applied a single wellbeing VAS score similar to one in the original PUQE studies, showing lower wellbeing scores associated with higher PUQE scores but improved wellbeing scores along treatment. Similarly, the UK study comparing inpatient and outpatient treatment of severe NVP/HG applied a single wellbeing rating by VAS which improved along treatment, although the VAS scores were compared only between the groups and not with PUQE scores (Mitchell-Jones et al., 2017).

As far as we know, no other study except the present study have applied two separate VAS scores, one for physical QoL and one for mental QoL in hospitalised women with HG and compared the ratings to the PUQE scores. In a previous study using SF-36 in women with HG (n=29), HG was shown to relate to both lower physical and mental QoL but the estimations were given only after discharge (Munch et al., 2011). The present study found that lower physical QoL was associated with higher PUQE scores in women admitted for HG which is intuitive as the PUQE score questions are concentrated on physical symptoms. This is also comparable to a previous Norwegian study which applied a single wellbeing rating (Birkeland et al., 2015).

However, a novel finding was that also mental QoL was associated with PUQE scores in women with HG, although only in readmissions, and not during the first admission. The determinants of lower mental QoL may be complex and higher PUQE score seems not that straightforwardly reflective for lower mental QoL unless a woman is repeatedly hospitalised. The findings concerning mental QoL in the present study indicate the distress in women with HG who suffer from more prolonged HG as they are repeatedly hospitalised, which evidently also warrants psychological support. In context of previous reports of mental consequences of HG, feelings of depression, anxiety, isolation and even suicidal ideation have been related to insufficient care and support from health care professionals (C. Dean, Bannigan, et al., 2018; Poursharif et al., 2008). However, in the present study, mental QoL scores decreased indicating improved QoL during treatment which, along with decreased PUQE scores, can be interpreted as a reassuring finding concerning improvement in overall wellbeing of the women.

Urine ketones are often related to HG since ketones can be detected in urine in starvation when the body metabolises fatty acids from adipose tissue due to lack of carbohydrates in nutrition (Mitchell et al., 1995). Therefore, ketonuria is mentioned in clinical guidelines as a sign of HG (American College of Obstetricians and

Gynecologists, 2018; The Royal College of Obstetricians and Gynaecologist, 2016). However, controversial evidence exists regarding the clinical value of urine ketones in HG since not all women with HG present ketonuria and ketonuria has not been associated with the severity of HG (Koot et al., 2020; Niemeijer et al., 2014; Tayfur et al., 2017). A Dutch study with 215 women with HG of which 181 gave urine samples for the detection of ketones at admission found that most women (90%) had some degree of ketonuria, but it was not associated with the severity of NVP measured by PUQE (Koot et al., 2020). In their study, the urine ketones were only measured once at admission. In a retrospective cohort study of 433 women with HG, severe ketonuria (+++) at admission was associated with moderate and severe PUQE scores (Tayfur et al., 2017). Similarly, in the present study, only severe ketonuria (+++) was associated with higher PUQE score at admission. However, no urine ketones categories were associated with PUQE at discharge. The women presented different urine ketones categories but in none of the women urine ketones increased in categories along treatment. In addition, negative urine ketones were not demanded for discharge but in clinical practice, the decrease in ketones is often noted which may have influenced the treatment of the women in the present study and thereby the results.

6.1.2 Pregnancy-Unique Quantification of Emesis Questionnaire in outpatient setting (Study II)

The validation studies of the original PUQE have been conducted in a prospective setting by analysing the PUQE scores of women who called the Motherisk NVP Healthline when they were seeking advice for NVP (Koren et al., 2005). Thereby, those women had coexisting NVP when they answered the PUQE.

Since the initial introduction of the PUQE, it has been also used in retrospective assessment of NVP during pregnancy or soon after delivery (Choi et al., 2018; Heitmann et al., 2017). For comparison, the existence, duration and severity of NVP has been enquired even years or decades after the particular pregnancy (Colodro-Conde et al., 2016). Still, based on a study by Koren et al. (Koren et al., 2004), there has been suspicion of recall bias in retrospective assessment of NVP, even though the estimations were given while pregnant. In their study, the same women who had initially called NVP Healthline and rated their NVP by PUQE were contacted again a few weeks later (mean three weeks). At that later time point, the women recalled longer duration of nausea and more frequent vomiting episodes than they had estimated initially (Koren et al., 2004).

In the present study, the individual women answered the PUQE in different gwks but all recalled the worst 12-hour episode of NVP. Accordingly, the PUQE scores were compared in early and in late pregnancy to evaluate estimations given with

shorter and longer time interval from the worst NVP. There were no differences between the PUQE total scores, although the scores at different gwks were not the scores of the same women.

However, in the present study, there was a difference in one aspect of NVP: the women who recalled the worst NVP in early pregnancy rated longer duration of nausea compared to women recalling the worst NVP in late pregnancy. Interestingly, even though the study designs were not totally comparable, this was an opposite finding to the study by Koren et al. (Koren et al., 2004), where the women recalled the duration of nausea longer after more time had elapsed since their initial estimation.

6.2 The severity and aspects of nausea and vomiting of pregnancy (Studies III–IV)

6.2.1 The occurrence of nausea and vomiting of pregnancy

The overall occurrence of NVP assessed by PUQE in the present study was 88% which is slightly higher than the reported occurrences in previous cohort studies with the PUQE (60–81%) (Choi et al., 2018; Dochez et al., 2016; Lacasse et al., 2009b; Tan et al., 2018). The variation may be explained by differences in the study designs. Although all the beforementioned studies used the PUQE, Dochez et al. (Dochez et al., 2016), Lacasse et al. (Lacasse et al., 2009b) and Tan et al. (Tan et al., 2018) applied the Modified-PUQE which encompasses NVP from the whole first trimester whereas Choi et al. (Choi et al., 2018) enquired NVP from the worst day of the current pregnancy. Notably, the recalled period of NVP in the study of Choi et al. (Choi et al., 2018) resembled the present study for the most and also their NVP occurrence (81%) was most similar. On the contrary, the lowest NVP occurrence (60%) by the Modified-PUQE was reported by Dochez et al. (Dochez et al., 2016). The women in their study were recruited at the hospital after delivery, and who therefore presumably had the longest time interval to recall their NVP from the first trimester compared to the other cohorts which were recruited during pregnancy (Choi et al., 2018; Dochez et al., 2016; Lacasse et al., 2009b; Tan et al., 2018).

Further, the occurrence of NVP in the present study was higher compared to median global occurrence of NVP (69%) calculated in a previous meta-analysis (Einarson et al., 2013). In general, previous prospective cohort studies have partly reported higher NVP occurrence compared to retrospective studies, probably because of more accurate reporting compared to possibly inaccurate recall of especially mild symptoms in some retrospective studies. In addition, in previous studies, the existence of NVP has been enquired using varied methods, and not

always by a validated questionnaire such as the PUQE. Moreover, ethnic variation may, in part, explain the global variation.

6.2.2 The severity of nausea and vomiting of pregnancy

The most prevalent PUQE category in outpatient setting in the present study was moderate NVP, followed by mild NVP, similarly as in previous cohort studies with PUQE (**Figure 1**) (Choi et al., 2018; Dochez et al., 2016; Heitmann et al., 2017; Lacasse et al., 2009b; Tan et al., 2018). On the contrary, the highest rate of severe NVP by PUQE (29%) was presented in a study of Heitmann et al (Heitmann et al., 2017). However, they recruited only women who had suffered from NVP in the current pregnancy or their prior pregnancy (which had occurred less than a year ago) through an anonymous online survey. Thus, their study could be prone to selection of more severely affected women.

6.2.3 The aspects of nausea and vomiting of pregnancy

In the present study, the percentages of various aspects of NVP (nausea, vomiting and retching) were similar as reported by Choi et al. (Choi et al., 2018). Duration of nausea was long, in third of all women over six hours. Interestingly, retching was more frequent than vomiting but the frequencies of both vomiting and retching were lower compared the duration of nausea which lasted for most of the day. Certainly, our findings support previous reports that NVP is more than 'morning' sickness (Gadsby et al., 1993, 2020; Lacroix et al., 2000). In addition, as nausea lasts for hours and vomiting may actually relieve nausea for a moment, not surprisingly nausea has been reported as the most disturbing symptom in NVP (Clark et al., 2013).

6.3 Associative factors for the severity and various aspects of nausea and vomiting of pregnancy (Studies III–IV)

In the present study, some maternal factors were associated with more severe NVP, corresponding association with all PUQE categories whereas other factors were only associated with a single PUQE category. Similarly, some maternal factors were associated with all aspects of NVP (nausea, vomiting and retching) by PUQE and others only with a single aspect. However, the comparisons to aspects of NVP by PUQE in the present study were unique since no other study has performed similar evaluations with different PUQE questions. From clinical perspective, presumably the factors associated with more severe NVP and with several aspects of NVP are the most relevant.

6.3.1 Associations between basic characteristics and nausea and vomiting of pregnancy

Of the basic characteristics, only higher gravidity was associated with more severe NVP. Similarly in two other cohort studies with PUQE, higher number of previous pregnancies and previous deliveries were associated with NVP (Choi et al., 2018; Lacasse et al., 2009b). This finding is also comparable to other studies of NVP (Järnfelt-Samsioe et al., 1985; Louik et al., 2006). In the present study, higher gravidity and multiparity were also associated with various aspects of NVP. On the contrary, in some previous studies particularly primiparous women have been affected (Bashiri et al., 1995; Roseboom et al., 2011), but these studies have been mainly focused on HG. The exact reason behind our finding remains to be determined, but multiparous women encounter more daily family responsibilities, which diminishes the possibility for resting and, in turn, may exacerbate NVP.

In the present study, some associations emerged regarding various aspects of NVP, but otherwise basic characteristics of the women were not associated with the severity NVP. The same held true in most of the previous cohort studies with the PUQE (**Table 5**). Previously, in one study with the PUQE, higher BMI was shown to be associated with more severe NVP (Dochez et al., 2016). This finding, however, emerged only when moderate NVP and severe NVP were compared to mild NVP, not to women with no NVP like in the present study. BMI was not associated with NVP in the present study. Further, in Dochez et al. study (Dochez et al., 2016), smoking in the first trimester was associated with less NVP compared to women with no NVP. Similar finding of smoking but only in univariate analysis was reported by another cohort study with PUQE (Choi et al., 2018). In the present study, association with smoking emerged only in comparisons of the various aspects of NVP: smokers had both less nausea and less vomiting.

6.3.2 Associations between history of nausea and nausea and vomiting of pregnancy

Regarding personal history of nausea and the severity of NVP, associations with motion sickness, nausea in migraine and in other kind of headache emerged. These factors were associated also with various aspects of NVP. The associations between personal history of nausea and NVP have not been previously studied similarly as in the present study using the PUQE.

Susceptibility to NVP may be linked with previous susceptibility to nausea since multiple pathways lead to nausea in general, and thus, the factors may share common pathways in NVP. The present study confirmed the findings of earlier cohort studies of the association between history of motion sickness and NVP (Gadsby et al., 1997; Järnfelt-Samsioe et al., 1985; Whitehead et al., 1992). These studies were also based

on survey data. As the vestibular system is involved in motion sickness, it may also play a role in susceptibility to NVP (Black, 2002). Further, a linkage between HG and motion sickness is supported by abnormalities, although preliminary, in the vestibulo-ocular reflex of HG women (Goodwin et al., 2008; Tulmaç et al., 2021), but more research is needed in women with different severity of NVP. Motion sickness and seasickness are closely related and probably share similar underlying mechanisms, explaining why in the present study the association with seasickness was lost in multivariate analyses with all history of nausea variables.

As for previous vulnerability to headache, some women who reported nausea related to other headache may have suffered from undiagnosed migraine. The present study confirmed findings from a previous cohort study concerning history of migraine and NVP (Whitehead et al., 1992). Further, in one previous cohort study with the PUQE, headache during pregnancy was associated with more severe NVP, and previous migraine was recorded, but all chronic illnesses were grouped together in analyses (Heitmann et al., 2017). Generally, migraine is more prevalent in females which may, in part, be related to hormonal factors which certainly change during pregnancy, but also to genetic and psychosocial factors (Buse et al., 2013).

6.3.3 Associations between affected relatives and nausea and vomiting of pregnancy

Evidence of inherited susceptibility to NVP has been found in previous genetic (Fejzo et al., 2018) and twin studies (Colodro-Conde et al., 2016). Similarly, increased likelihood of NVP if particularly mother or sister had been affected have been reported in earlier cohort studies (Gadsby et al., 1997; Whitehead et al., 1992). Especially, the likelihood of HG has been reported to be substantially increased if also mother or sister had HG, compared to the otherwise low incidence of HG in general population (Fejzo et al., 2008; Zhang et al., 2011). The findings of the present study were thus in line with previous studies, confirming increased odds for NVP if family members, mother or sister, but also, if even more distant relatives, had been affected. This held also true when the various aspects of NVP were assessed. However, the low number in more distant relatives limit more detailed interpretations, for instance comparisons between maternal and paternal lines.

6.4 Quality of life, sleep quality and nausea and vomiting of pregnancy (Study V)

The present study confirmed that not only HG but NVP at all severity levels was associated with decreased QoL, confirming previous findings (Heitmann et al., 2017; Lacasse et al., 2008a; Munch et al., 2011). Both physical QoL and mental QoL

decreased along increasing severity of NVP: the women with severe NVP reported the worst physical QoL as well as the worst mental QoL. Even though the present study used simple VAS ratings, the results were similar to studies using lengthier general QoL questionnaires or the NVP-QOL (Dochez et al., 2016; Lacasse et al., 2008a; Lacasse & Bérard, 2008; Liu et al., 2019).

In the present study also worse general sleep quality, assessed by one VAS question, was associated with more severe NVP. This finding emphasises the importance of sleep quality as part of QoL. In previous studies, general sleep quality has been estimated with various methods, for instance with reported total hours of sleep (Lindseth & Vari, 2005) or by asking difficulty of getting a good night's sleep (Clark et al., 2013). Nevertheless, worse sleep quality has been associated with NVP in previous studies (Clark et al., 2013; Lindseth & Vari, 2005; Mindell et al., 2015; Swallow et al., 2004). Only one study in which sleep quality was estimated as good or poor/broken sleep based on the number of hours of continuous sleep found no association between sleep quality and the severity of NVP (Ebrahimi et al., 2009). Additionally, self-estimation of existence of sleep problems was not associated with the severity of NVP in another study but the estimations were partly given after delivery which may have influenced the accuracy of recall (Heitmann et al., 2017). However, in both of these studies, the percentages of women with poor sleep were quite high, more than half of all women, which further highlights the overall high prevalence of sleep problems during pregnancy (Aukia et al., 2020; Ebrahimi et al., 2009; Hedman et al., 2002; Heitmann et al., 2017).

So far, the present study is the only one using the PUQE and the BNSQ to estimate sleep disturbances in more detail in women with NVP. Additionally, the present study revealed novel association of sleep maintenance disturbances and more severe NVP. With another specific sleep questionnaire, the PSQI to evaluate sleep quality and PUQE for NVP, two recent large studies have found that women with more severe NVP had worse sleep quality (Pengsheng & Haiyan, 2021; Zhang et al., 2021). Another study with PSQI also found worse sleep quality in women with HG (Yildirim & Demir, 2019).

Although the present study revealed detailed associations of sleep disturbances and NVP, sleep quality is interdependent with both physical QoL and mental QoL. Physical discomforts during pregnancy may exacerbate sleep disturbances but also sleep disturbances may induce physical symptoms (Roth, 2007). And further, mental symptoms, like anxiety and depressive symptoms, have been shown to decrease sleep quality during pregnancy, but also sleep disturbances may induce mental symptoms (Pietikäinen et al., 2019; Polo-Kantola et al., 2017). Hence, in the present study, the effect of physical QoL and mental QoL to NVP exceeded the effect of sleep in the multivariate analysis.

6.5 Methodological considerations

The strengths and limitations of the present study are discussed in the following chapters.

6.5.1 Data management and participation

The present study was conducted following good scientific practice according to the declaration of Helsinki. Required permissions were obtained from the Ethical Committee and for the use of register data from the Finnish Institute for Health and Welfare. All women were given oral and written information about the study before participating. Written informed consent was obtained from all women in **Study I**. In **Studies II–V**, a separate written informed consent form was obtained, though not used in all MHCCs, and therefore returning the questionnaire was considered as informed consent. All data were securely stored, including the original study questionnaires and the data keyed to excel format. Only research group members had access to the original questionnaires and all electrical data were handled as anonymous identification numbers.

Participation was voluntary and interested women who were offered participation took part. In addition, participation was made as easy as possible for the women. In **Study I**, women admitted for HG were invited and in **Studies II–V**, all women attending to routine MHCC visits were eligible. In **Study I**, the women filled in study questionnaires daily in the hospital. In addition, they gave daily urine samples for urine ketones detection, which was included as normal routines for all HG patients. Part of the women were repeatedly hospitalised which on one hand added up the number of filled questionnaires. On the other hand, however, filling the questionnaire several times could have been prone to learning effect. On the contrary, in **Studies II–V**, the study questionnaire was filled only once.

The information of the number of women who refused to participate and the reasons for declining were, however, not systematically collected in **Studies I–V** and therefore, calculation of the exact participation rate or drop-out analyses were not possible to perform.

6.5.2 Recruitment

The recruitment was performed by nurses who were carefully instructed by the researchers. Originally, the recruitment in the MHCCs was planned to target to mid-pregnancy. Eventually, the gwk of the women in **Studies II–V** ranged from 7 to 40, meaning that the nurses recruited the women in visits at different gwk or that some women accepted to participate but returned the questionnaire later than originally intended. However, the wide range of gwk enabled the comparisons made in **Study**

II. In addition, the purpose was to collect a large sample of women, but in the **Studies III–V**, additional subgroup analyses ≤ 20 gwk were performed to limit possible recall bias.

The recruitment by the nurses had advantages. In **Study I**, the women were admitted to the hospital in different times of the day, many of them in the evening. Therefore, it was not possible for the researchers to be present at the ward all day, but the nurses working in different shifts were available. However, the recruitment was dependent on the activity of the nurses, although the researchers reminded of the study regularly. The nurses recruited the women on top of their other duties without any extra compensation. This was reflected as long recruitment period, for several years. Despite the delay, the recruitment was continued until the number estimated in power calculations was achieved.

In **Studies II–V**, the estimated sample size was quite large and therefore, the recruitment was conducted in several MHCCs. However, the activity of the nurses varied in different MHCCs and some MHCC nurses recruited more women than the others. On the other hand, the activity of the women to participate may have varied in different MHCC areas. These challenges were partly expected, and by including several MHCCs, the number of women estimated by power calculation was achieved. Again, this would not have been possible if the recruitment would have been carried out only by the researchers themselves. Practically all women in Finland attend to MHCCs for free of cost routine pregnancy follow-up (Finnish Institute for Health and Wellfare, 2015), and therefore, the only possibility to recruit a large sample of women with different severity of NVP, including women with no NVP, was the recruitment from MHCCs.

6.5.3 Participants

In the present study most of the participants were Finnish women. Overall, the percentage of foreigners in Finland was low during the recruitment years (around 4% (Official Statistics of Finland, 2021)), and hence, the MHCC cohort could be considered representative for average Finnish pregnant women. However, considering the evidence of ethnic variation associated with NVP and HG, as Finnish language skills were required in taking part to the present study, NVP and HG in other ethnicities could not reliably be assessed.

In **Study I**, the possibility that only the women with milder symptoms participated and those with more severe symptoms did not, or vice versa, could not be ruled out. Similar risk of selection bias applied to **Studies II–V**. However, in **Study I**, the severity of NVP by PUQE was comparable to previous studies, and the PUQE scores decreased similarly during admissions. In **Studies II–V**, the severity of NVP by PUQE ranged from mild NVP to severe NVP, but also women with no

NVP were recruited. Importantly, the number of women in **Studies II–V** was high compared to previous cohort studies with the PUQE (**Figure 1**)(Choi et al., 2018; Dochez et al., 2016; Heitmann et al., 2017; Lacasse et al., 2009b; Tan et al., 2018).

Further, the women in **Study I** were recruited from a single centre. However, Turku University Hospital is a large tertiary hospital with the highest number of patients compared to other regional hospitals in Western-Finland. Furthermore, the treatment protocol in HG in **Study I** was not standardised, but current treatment practice was followed, and the women received approximately similar treatment. In addition, the diagnosis of HG was established by physicians, either by specialists in obstetrics and gynaecology or by residents working under supervision of specialists. Therefore, contrary to the assessment of the severity of NVP by PUQE, the existence of HG in **Study I** was not self-reported. Moreover, the PUQE scores and VAS estimations in **Study I** were recorded only for the researchers and the scores were not used to guide treatment or the decision of admittance and discharge.

6.5.4 Study design

The prospective study design in **Study I** enabled to compare the PUQE scores at admission and at discharge, and to include the answers of the same women also from readmissions. The cross-sectional study design in **Studies II–V** enabled to recruit a large cohort with all severity of NVP. The evaluation of NVP was retrospective, as the recruitment was targeted to mid-pregnancy, where the occurrence of the worst NVP symptoms is supposed to be over in most women. However, the exact gwk of the worst 12-hour period of NVP recalled in the study questionnaire were not recorded. Accordingly, the recall bias could not be estimated exactly. Therefore, the results of **Study II** cannot be straightforwardly compared to longitudinal studies, but our results should be confirmed in a setting with the same women recalling the worst NVP in early and in late pregnancy.

6.5.5 Questionnaires

The main merit of the present study was the use of validated questionnaires. The present study applied the PUQE for the first time in Finnish pregnant women and in women with HG. The original PUQE which enquires NVP symptoms in a 12-hour time frame was selected because it was developed specifically for NVP and used widely. However, PUQE-24 would have better covered the whole day.

In addition, the present study gathered new insights of sleep quality in women with NVP by using the BNSQ. However, the time frame for the sleep disorders could have been narrowed to match even better with the duration of NVP. The original

version of the BNSQ enquires sleep quality from the past three months, and therefore it was chosen also in the present study.

Survey data is always self-reported and therefore prone to reporting bias. However, the severity of NVP could not have been gathered from medical files and self-reported data was the only option for this kind of study. Notably, the basic characteristics of the women were obtained from the Finnish Medical Birth Register. The Finnish register data is considered highly accurate (Sund, 2012). As mentioned before, HG was diagnosed by health care professionals, according to the 10th version of the international classification of diseases (World Health Organisation, 2016). Further, QoL and general sleep quality were rated by VAS which is generally applied in medicine (Jensen et al., 1986).

In the study questionnaire, also the personal history of nausea and NVP in relatives were self-reported. However, information of many of these conditions and concomitant nausea would have been impossible to gather from medical files or registers. Undoubtedly, the NVP in relatives could be prone to bias, since women with more severe NVP might be more likely to discuss the topic with relatives compared to women with milder NVP. However, the women could also tick an option of not knowing whether their relatives had NVP. Furthermore, the information of chronic somatic and mental illnesses, and medications of the women were lacking. Another missing yet important history variable was previous HG. However, around third of the women in **Study I** and almost half of the women in **Studies II–V** did not have previous pregnancies.

6.5.6 Statistical considerations

In the present study, the statistical methods were chosen in cooperation with professional biostatistician who performed the analyses accordingly. Basic characteristics, which in previous studies have been associated with NVP, were used as adjusting factors. In addition, different multivariate analyses were conducted to assess the connections between variables. Also, data obtained from the same woman in readmittances were considered when applying suitable statistical methods. Naturally, some missing data existed, but, in all studies, complete PUQE score was required in the analyses. In all **Studies I–V**, questionnaires with missing data of the dependent variables were excluded in each study.

6.6 Clinical implications

The PUQE was used in Finland for the first time in the present study. For the women, it is quick and easy to fill in. For the healthcare professionals, it is practical, as its

interpretation is straightforward. Therefore, the PUQE can be recommended for both inpatient and outpatient settings.

In the hospital, PUQE scores of women with HG decreased during treatment, and thus the PUQE scores could be used as one indicator of recovery. As the PUQE is short and simple, it can be used even daily. In outpatient care, the PUQE could serve as a screening tool for NVP and help to identify women with the most severe symptoms, as severe NVP was shown to be associated with higher burden of illness both physically and mentally. In addition, many international clinical treatment guidelines have already implemented the PUQE for guiding the selection of suitable treatment based on symptom severity. Although treatment options are limited, women with severe NVP certainly would benefit from prompt symptom assessment to get timely medical treatment.

The present study applied the PUQE during pregnancy mostly retrospectively when the worst symptoms had relieved in most of the women, with no significant differences in the PUQE scores between early and late pregnancy. Hence, the PUQE can be considered suitable for use during pregnancy also after the peak of the most severe symptoms.

In the present cohort of Finnish pregnant women, the occurrence of NVP was high and the symptoms, especially nausea, lasted for hours when the women estimated the worst 12-hour period of their NVP. A significant decrease in physical QoL, mental QoL and sleep quality was also observed. This means a substantial effect on everyday lives of the majority of pregnant women, also affecting their families and occupational responsibilities.

Several maternal factors were associated with the severity and various aspects of NVP. These findings may be used in prenatal care when counselling women regarding their individual potential risk for NVP or excluding it. In addition, the present study hopefully raises general awareness of NVP among women and healthcare professionals, thus contributing to mitigating any underestimation of the illness.

6.7 Future aspects

Recently, considerable efforts have been made to recognise top priorities in HG research and to elucidate any knowledge gaps (Dean et al., 2022; Dean et al., 2021). One topic, listed as number nine in top ten of the research priorities is '*What clinical measurements and markers are most useful in assessing, diagnosing, managing and monitoring HG?*' (Dean et al., 2021). In the present study, the PUQE reflected alleviation of HG during treatment but whether the PUQE scores, alone or combined with other measurements, could predict, or guide the optimal length of

hospitalisation or the probability for readmission remains to be investigated in future studies.

In future NVP research, use of a validated questionnaire such as the PUQE would help compare results between studies and enable reliable meta-analyses. Further, special attention should be given to selecting a suitable time frame of the PUQE as there are three extension options: the 'original' PUQE (Koren et al., 2002), PUQE-24 (Ebrahimi et al., 2009) and the Modified-PUQE (Lacasse et al., 2008b). In addition, reliability of the recall of NVP should be further assessed with the same women answering the PUQE repeatedly during pregnancy.

In Finland, practically all women attend MHCCs during pregnancy. Routine visits already consist of filling in several forms and questionnaires. In the future, the PUQE could be included, since NVP, especially in the severe form, may inflict the entire pregnancy (Kramer et al., 2013; Mullin et al., 2012), postpartum period (Mitchell-Jones et al., 2020) and even the future family planning of the woman (Nijsten et al., 2021; Poursharif et al., 2008).

7 Conclusions

The main conclusions of the present study were as follows:

1. The PUQE was shown to be a clinically usable tool in inpatient setting: in hospitalised women with HG, the PUQE scores improved from admission to discharge. The improvement of the PUQE scores was associated with improved physical QoL. Further, similar association with improved mental QoL was found, but only when readmissions were considered.
2. The PUQE total scores were similar in women who recalled their NVP during the worst 12 hours of current pregnancy whether the scores were given in earlier gwk or in later gwk. Only detailed differences emerged in the recalled daily duration of nausea, but otherwise the PUQE questions were rated similarly. Hence, the consistency of the PUQE scores across pregnancy support the usability of the PUQE for retrospective assessment of NVP in outpatient setting.
3. Overall, NVP was frequent, and the severity of NVP was most often rated as moderate according to the PUQE. Further, daily duration of nausea was long, whereas only few times of vomiting and retching were reported. However, retching was experienced more frequently than vomiting. Of the maternal basic characteristics, higher gravidity was associated with more severe NVP and with several aspects of NVP.
4. Maternal previous susceptibility to nausea, especially related to motion sickness, migraine and other kind of headache was associated with more severe NVP as well as with various aspects of NVP. Further, having affected relatives increased the likelihood to suffer from more severe NVP.
5. The women with more severe NVP also demonstrated worse physical QoL, worse mental QoL and worse general sleep quality. Further, distinct sleep disturbances were associated with the severity of NVP; however, the associations between QoL and NVP were more dominant.

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Appendices

Appendix 1. Study questionnaire.
Name: _____ Personal identification number: _____
Nationality: _____
Date of filling: _____ Gestational week: _____
Place of filling: _____
Study code (researcher fills) _____

Answer to all questions on this page according to the worst 12 hours of the worst nausea. Consider nausea during whole pregnancy even if your nausea has already been relieved.

1. For how long have you felt nauseated or sick to your stomach?

Not at all	□
1 hour or less	□
2–3 hours	□
4–6 hours	□
More than 6 hours	□

2. Have you vomited or thrown up?

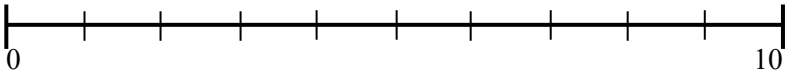
7 or more times	□
5–6 times	□
3–4 times	□
1–2 times	□
I did not throw up	□

3. How many times have you had retching or dry heaves without bringing anything up?

None	□
1–2 times	□
3–4 times	□
5–6 times	□
7 or more times	□

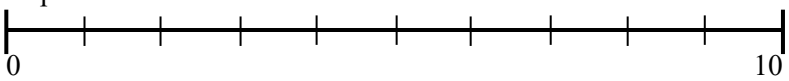
4. During the worst 12 hours of nausea, how would you have rated your physical well-being? Please mark to suitable point on the scale.

I felt sick. I felt healthy.

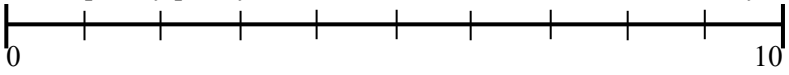


5. During the worst 12 hours of nausea, how would you have rated your mental well-being? Please mark to suitable point on the scale.

Depressed. Normal / satisfied.



6. I slept very poorly. Very well.



7. Have you had difficulties to fall asleep during the past three months?

1. Never or less than once per month. □
2. Less than once per week. □
3. On 1–2 days per week. □
4. On 3–5 days per week. □
5. Daily or almost daily. □

8. How often have you awakened at night during the past three months?

1. Never or less than once per month. □
2. Less than once per week. □
3. On 1–2 days per week. □
4. On 3–5 days per week. □
5. Daily or almost daily. □

9. How often have you awakened too early in the morning without being able to fall asleep again during the past three months?

1. Never or less than once per month. □
2. Less than once per week. □
3. On 1–2 days per week. □
4. On 3–5 days per week. □
5. Daily or almost daily. □

10. Do you feel excessively sleepy during daytime?

1. Never or less than once per month.	□
2. Less than once per week.	□
3. On 1–2 days per week.	□
4. On 3–5 days per week.	□
5. Daily or almost daily.	□

11. Have you had nausea in the following context?

		No	Yes
Motion sickness		□	□
Seasickness		□	□
Migraine		□	□
Other headache		□	□
After anaesthesia		□	□
Use of contraception		□	□,
	method: _____		
Other		□	□,
	when? _____		

12. Have any of your relatives (mother, grandmother, aunt, sister etc.) suffered from nausea in pregnancy?

No	□
Yes	□,
	who? _____
I don´t know	□

Appendix 2. Kyselykaavake.

Nimi: _____ Henkilötunnus: _____
Kansalaisuus: _____
Lomakkeen täyttöpäivämäärä: _____ Raskausviikko: _____
Lomakkeen täyttöpaikka: _____
Tutkimuskoodi (tutkija täyttää) _____

Vastaa kaikkiin tämän sivun kysymyksiin niiden 12 tunnin ajalta, jolloin pahoinvointi oli pahimmillaan. Vastatessasi ota huomioon koko raskauden aikainen pahoinvointi, vaikka pahoinvointi olisi jo ohi.

1. Kuinka monta tuntia pahoinvointi kesti?

Ei yhtään	□
Tunnin tai alle tunnin	□
2–3 tuntia	□
4–6 tuntia	□
Yli kuusi tuntia	□

2. Kuinka monta kertaa oksensit?

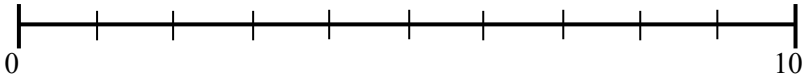
7 kertaa tai useammin	□
5–6 kertaa	□
3–4 kertaa	□
1–2 kertaa	□
En kertaakaan	□

3. Kuinka monta kertaa yökkäilit ilman, että oksensit?

En kertaakaan	□
1–2 kertaa	□
3–4 kertaa	□
5–6 kertaa	□
7 kertaa tai useammin	□

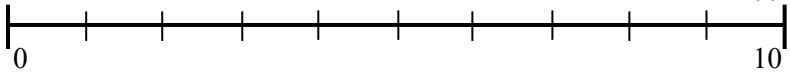
4. Millaiseksi arvioisit fyysisen vointisi niiden 12 tunnin aikana, jolloin pahoinvointi oli pahimmillaan? Merkitse arviosi sopivaan kohtaan janalle.

Tunsin olevani sairas. Tunsin olevani terve.

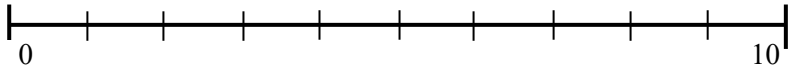


5. Millaiseksi arvioisit henkisen vointisi niiden 12 tunnin aikana, jolloin pahoinvointi oli pahimmillaan? Merkitse arviosi sopivaan kohtaan janalle.

Masentunut Normaali/tyytyväinen.



6. Nukuin
erittäin huonosti. erittäin hyvin.



7. Onko sinulla ollut vaikeuksia nukahtaa viimeksi kuluneen kolmen kuukauden aikana?

1. Ei koskaan tai harvemmin kuin kerran kuussa. □
2. Harvemmin kuin kerran viikossa. □
3. 1–2 päivänä viikossa □
4. 3–5 päivänä viikossa □
5. Päivittäin tai lähes päivittäin □

8. Kuinka usein olet herännyt yöllä viimeisten kolmen kuukauden kuluessa?

1. En koskaan tai harvemmin kuin kerran kuussa. □
2. Harvemmin kuin kerran viikossa. □
3. 1–2 päivänä viikossa. □
4. 3–5 päivänä viikossa. □
5. Päivittäin tai lähes päivittäin. □

9. Kuinka usein olet herännyt liian aikaisin aamulla pystymättä enää nukahtamaan uudelleen kuluneen kolmen kuukauden aikana?

1. En kertaakaan tai harvemmin kuin kerran kuussa. □
2. Harvemmin kuin kerran viikossa. □
3. 1–2 päivänä viikossa. □
4. 3–5 päivänä viikossa. □
5. Päivittäin tai lähes päivittäin. □

10. Tunnetko itsesi liian uneliaaksi päivällä?

1. En koskaan tai harvemmin kuin kerran kuussa. □
2. Harvemmin kuin kerran viikossa. □
3. 1–2 päivänä viikossa. □
4. 3–5 päivänä viikossa. □
5. Päivittäin tai lähes päivittäin. □

11. Oletko kärsinyt pahoinvoinnista seuraavissa tilanteissa?

	En	Kyllä
Matkapahoinvointi	□	□
Merisairaus	□	□
Migreeni	□	□
Muu päänsärky	□	□
Anestesian jälkeen	□	□
Ehkäisyn yhteydessä	□	□,
ehkäisymenetelmä: _____		
Muussa tilanteessa	□	□,
missä? _____		

12. Onko joku sukulaisistasi (esim. äiti, isoäiti, täti, sisar) kärsinyt raskauspahoinvoinnista?

Ei	□
Kyllä	□,
	kuka? _____
En tiedä	□

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