

1 **Clinical management of nausea and vomiting in**  
2 **pregnancy and hyperemesis gravidarum across primary**  
3 **and secondary care: a population based study**  
4

5 **Running title:** Severe nausea and vomiting in pregnancy management

6 L. Fiaschi\*<sup>1</sup>, C. Nelson-Piercy<sup>2</sup>, S. Deb<sup>3</sup>, R. King<sup>4</sup>, L. J. Tata<sup>1</sup>

7 <sup>1</sup>Division of Epidemiology & Public Health, University of Nottingham, Clinical Sciences Building,  
8 City Hospital, NG5 1PB Nottingham, UK

9 <sup>2</sup> Women's Health Academic Centre, Guy's & St Thomas' Foundation Trust, St Thomas' Hospital,  
10 SE1 7EH London, UK

11 <sup>3</sup> Nottingham University Hospital Department of Obstetrics and Gynaecology Queen's Medical  
12 Centre Derby Road, NG7 2UH Nottingham, UK

13 <sup>4</sup> Sherwood Health Centre, Elmswood Gardens, NG5 4AD Nottingham, UK.

14 \*Corresponding author: Linda Fiaschi (linda.fiaschi@nottingham.ac.uk), Division of  
15 Epidemiology & Public Health, University of Nottingham, Clinical Sciences Building Phase 2, City  
16 Hospital, NG5 1PB Nottingham, UK, Tel. 0044-1158231250. ORCID ID: 0000-0002-3780-5895

17

18

19

20

21

22 **Abstract**

23 **Objectives:** To assess how nausea and vomiting in pregnancy (NVP) and hyperemesis gravidarum  
24 (HG) are managed and treated across primary and secondary care.

25 **Design:** Population-based pregnancy cohort

26 **Setting:** Medical records (CPRD-GOLD) from England

27 **Population:** 417,028 pregnancies, during 1998-2014

28 **Methods:** Proportions of pregnancies with recorded NVP/HG diagnoses, primary care treatment and  
29 hospital admissions were calculated. Multinomial logistic regression was employed to estimate  
30 adjusted relative risk ratios (aRRRs) with 99% confidence intervals (CIs) for the association between  
31 NVP/HG management paths and maternal characteristics.

32 **Main Outcome Measures:** NVP/HG diagnoses, treatments and hospital admissions.

33 **Results:** Overall prevalence of clinically recorded NVP/HG was 9.1%: 2.1% had hospital  
34 admissions, 3.4% were treated with antiemetics in primary care only, and 3.6% had only recorded  
35 diagnoses. Hospital admissions and antiemetic prescribing increased continuously during 1998-2013  
36 (trend  $p < 0.001$ ). Younger age, deprivation, Black/Asian/Mixed ethnicity, multiple-pregnancy were  
37 associated with NVP/HG generally across all levels, but associations were strongest for hospital  
38 admissions. Most comorbidities had patterns of association with NVP/HG levels. Among women with  
39 NVP/HG who had no hospital admissions, 49% were prescribed antiemetics, mainly from first line  
40 treatment (21% prochlorperazine, 15% promethazine, 13% cyclizine) and metoclopramide (10%). Of  
41 those admitted, 38% had prior antiemetic prescriptions (34% first-line, 9% second-line, 1% third-line  
42 treatment).

43 **Conclusion:** Previous focus on hospital admissions has greatly underestimated the NVP/HG burden.  
44 Although primary care prescribing has increased, most women admitted to hospital have no  
45 antiemetics prescribed before this. An urgent call is made to assess whether admissions could be  
46 prevented with better primary care recognition and timely treatment.

47 **Funding**

48 The work was funded by The Rosetrees Trust and the Stoneygate Trust through external peer review  
49 for scientific quality. The funders had no role in study design, data collection, analysis, interpretation  
50 of the results and decision to publish, or preparation of the manuscript. All the authors are  
51 independent from the funders. Grant number RB48AG.

52

53 **Keywords**

54 Nausea and vomiting in pregnancy, Hyperemesis Gravidarum, antiemetics, primary care, secondary  
55 care

56 **Tweetable abstract:**

57 The NVP/HG burden is increasing over time and management optimization should be high priority to  
58 help reduce hospital admissions

59 **Words count:** 3,483

60

61

62

63

64

65

66

67

68

69

## 70 **Introduction**

71 Although nausea and vomiting is a very common symptom in pregnancy (NVP), affecting up to 70%  
72 of women <sup>1</sup> who often do not require treatment, in some cases severity can reach critical levels  
73 requiring hospital admission and need for continuous monitoring <sup>2</sup>. This severe condition, referred to  
74 as hyperemesis gravidarum (HG), has a reported prevalence of around 1.1% worldwide <sup>1</sup> and is  
75 responsible for a range of complications due to malnutrition, dehydration and excessive weight loss.  
76 Maternal and child health are affected by possible adverse effects of HG <sup>3-5</sup> and pregnancy  
77 complications are more likely <sup>6</sup>. These sequelae have substantial financial impact on the health  
78 services and significant burden on professional health care provision <sup>7-9</sup>.

79 In June 2016, the Royal College of Obstetricians and Gynaecologists (RCOG) published the first  
80 national guidelines on the clinical management of NVP and HG for the United Kingdom (UK) <sup>10</sup>  
81 providing an accurate handbook for controversial decision making processes in the management of  
82 this condition with prescribed medications. Although this is supported by international reviews of HG  
83 <sup>11-13</sup>, there is no published evidence of how this condition is actually managed by health professionals  
84 and what common clinical pathways are followed by affected women. In the UK, research based on  
85 surveys <sup>14,15</sup> have shown general dissatisfaction with current clinical care from women experiencing  
86 HG, with a claim that many hospital admissions could have been avoided had they received timely  
87 antiemetic prescribing to curtail worsening severity. It is unknown whether under-prescribing or late  
88 recognition of NVP and HG is widespread as there are no population-based studies showing how this  
89 condition is managed between primary and secondary care.

90 Using the Clinical Practice Research Datalink database (CPRD-HES), we have assessed the spectrum  
91 of NVP and HG across primary and secondary care and described how severity and pathways of  
92 management vary by maternal and pregnancy characteristics and comorbidities. We assessed the  
93 extent to which women are prescribed antiemetics in primary care and how this relates to hospital  
94 admissions.

## 95 **Materials and Methods**

### 96 **Data source**

97 We used primary and secondary care health records linked at individual patient level from the Clinical  
98 Practice Research Datalink (CPRD GOLD),<sup>16</sup> which includes over 15 million patients from 684  
99 general practices (GP) across the UK <sup>17</sup>. Recorded information consists of demographics, symptoms  
100 and diagnoses coded using the Read coding system <sup>18</sup>, clinical tests and drug prescriptions. Over half  
101 of CPRD GOLD patients are linked with the Hospital Episodes Statistics (HES) database <sup>19</sup> which  
102 consists of all admissions to English hospitals. Information within HES includes diagnoses coded  
103 using the International Classification of Diseases system (ICD-10)<sup>21</sup> and hospital procedures coded  
104 using the Office of Population Censuses and Surveys Classification of Interventions and Procedures  
105 (OPCS-4)<sup>22</sup>. Maternity data contained in HES includes extensive information on pregnancy, labour  
106 and delivery; it is the main datasource for monitoring maternity statistics in England<sup>23</sup> and is used to  
107 for perinatal epidemiology research <sup>23,24</sup>. Our previous studies using the CPRD-HES linked population  
108 show maternities are representative of those across the English population<sup>25,26</sup>. Patients were not  
109 involved in the development of the research.

### 110 **Study population**

111 Women with pregnancies ending in live birth or stillbirth between October 1998 and April 2014 who  
112 had active primary care registration were selected by extracting information from GP and HES  
113 records (operational codes of delivery) to obtain the most complete and precise information on each  
114 pregnancy. For live births, a probabilistic matching algorithm was employed to link each mother's  
115 pregnancy records to the corresponding children by matching each delivery date to a child's estimated  
116 birth date or HES birth admission and ensuring they had matching a household code, a unique  
117 identifier indicating which individuals in each practice live together. Gestation and pregnancy details  
118 were extracted from HES maternity data and, when missing, from the child's HES birth record, the  
119 mother's or child's GP records in this order of priority.

## 120 **Diagnoses and hospital admissions for NVP and HG**

121 To capture the full spectrum of severity, as defined in the national guidelines<sup>10</sup>, we identified all  
122 primary care diagnoses and hospital admissions for NVP/HG during pregnancy, using specific Read  
123 codes for primary care (Table S1) and ICD-10 codes for secondary care (Table S2) that were  
124 approved by co-author CNP who is a consultant in obstetric medicine. Due to controversy over a true  
125 distinction between NVP and HG and the lack of a standard approach for the diagnosis and clinical  
126 management of these conditions<sup>4</sup>, the risk that these diagnoses could have been used interchangeably  
127 by health professionals to refer to the same condition was taken in to consideration by carrying out a  
128 comprehensive analysis considering both diagnoses.

129 To exclude presentations of nausea and vomiting for specific reasons, a restrictive criterion was  
130 applied excluding any NVP diagnoses with evidence of differential diagnoses (Table S3 and S4)  
131 recorded in GP data from one week before up to one week after the NVP diagnosis date or in HES  
132 data as a secondary reason of admission. This resulted in 1.9% of GP consultations and 17.6% of  
133 hospital admissions for NVP being excluded.

## 134 **Drug treatment for NVP and HG**

135 Antiemetic prescriptions were extracted from primary care records using selected drugs codes (Table  
136 S5) according to national recommendations from the RCOG,<sup>10</sup> and grouped in the following drug  
137 classes: antihistamines, phenothiazine dopamine antagonists, serotonin antagonists and steroids. As  
138 some drugs have multiple indications, differential diagnostic indications were explored to ensure the  
139 drugs under analysis were prescribed for the purpose of treating NVP/HG, according to the British  
140 National Formulary (BNF)<sup>27</sup>.

## 141 **Grouping women with NVP/HG by their clinical management pathway**

142 We categorised women into 4 mutually exclusive groups (Figure 1), broadly representing their level  
143 of NVP/HG burden, according to their presentation and treatment in primary care or occurrence of  
144 hospital admissions as follows: a primary care diagnosis only, treatment in primary care, early  
145 hospital admissions ( $\geq 20$  weeks gestation), late hospital admissions. We compared these four groups

146 to a control group of all remaining women, i.e. those with no evidence of NVP/HG diagnosis nor  
147 treatment.

### 148 **Maternal characteristics**

149 We assessed maternal characteristics and comorbidities based on their previous evidence as risk  
150 factors for NVP/HG <sup>28,29</sup> and information currently available in the CPRD-HES source dataset. These  
151 were: maternal age at delivery, socioeconomic deprivation as measured by the Index of Multiple  
152 Deprivation (IMD 2010) in quintiles <sup>30</sup>, ethnicity, smoking status during pregnancy, parity, birth  
153 plurality, diabetes, hypertension, pre-eclampsia, parathyroid dysfunction, coronary heart diseases,  
154 anaemia, thyroid dysfunction, hypercholesterolemia and asthma.

### 155 **Statistical analysis**

156 Numbers and proportions of pregnancies for each NVP/HG group (i.e. diagnosis only, antiemetic  
157 treatment, early hospital admission and late hospital admission) were presented overall and the change  
158 in prevalence of each group was shown over time. To assess whether maternal characteristics differed  
159 by NVP/HG group, we used multinomial logistic regression (mlogit<sup>31</sup> with rrr option) to estimate  
160 relative risk ratios (RRR) with 99% confidence intervals (CI) for the association of each level of  
161 NVP/HG burden with maternal characteristics/comorbidities, compared to the control group. RRRs  
162 were adjusted for all the maternal characteristics and pre-existing comorbidities available in the data  
163 except for the risk factor of interest (Table 1). In order to account for potential clustering effects from  
164 including mothers with more than one pregnancy, a cluster option was set in the analysis. Missing  
165 values, present only for three maternal characteristics, namely ethnicity (12.4% missing), smoking  
166 (27.8%) and deprivation status (0.2%), were imputed using the multinomial logistic regression  
167 imputation method available in Stata MPv15 (Stata Corp, College Station, TX) statistical package <sup>32</sup>,  
168 applying the `mi imp mlogit` function<sup>31</sup>, setting 10 imputed datasets and using all maternal  
169 characteristics available as predictor variables. As a sensitivity analysis to assess whether clear clinical  
170 distinctions were actually being made between NVP and HG diagnoses, we conducted stratified  
171 analyses by 1) dividing the primary care diagnosis only group into a) those with HG diagnoses and b)  
172 those with only NVP diagnoses, and 2) dividing the primary care treatment group into those with a)

173 antiemetics prescribed for an HG indication and b) antiemetics prescribed for an NVP indication only.  
174 We assessed the prevalence of these four groups over time and whether they varied by maternal  
175 characteristics.

## 176 **Results**

177 Within the study period there were 417,028 deliveries ending in live births or stillbirths in 300,858  
178 women. The prevalence of NVP/HG overall was 9.1% (37,856): 3.6% (14,815) pregnancies with  
179 primary care diagnoses that did not obtain treatment, 3.4% (14,226) with primary care diagnoses that  
180 were administered antiemetic drug treatment, 1.5% (6,390) with first hospital admission before 20  
181 weeks and 0.6% (2,425) with late hospital admissions from 20 weeks onwards. Between 1999 and  
182 2013 (Figure 2) there were statistically significant increases in early hospital admissions and  
183 antiemetic prescribing such that by 2013, early admissions occurred in 2.1% of pregnancies and  
184 antiemetics were prescribed in primary care in 5.2% of pregnancies compared with 2.5% of  
185 pregnancies with recognised NVP/HG that were left untreated ( $p < 0.001$  for both).

## 186 **Management variation by maternal characteristics**

187 Maternal characteristics varied across the groups (Table 1). In general, compared with control  
188 pregnancies, those among women with NVP/HG had higher proportions of younger women, with  
189 higher socioeconomic deprivation, or with Asian or Black ethnicity, and these proportions increased  
190 with level of NVP/HG burden with the highest among women with hospital admissions. The  
191 prevalence of comorbidities was generally higher in the affected groups compared with control  
192 pregnancies, particularly for pre-existing diabetes, gestational hypertension, pre-eclampsia,  
193 gestational anaemia and thyroid dysfunctions, asthma, and hypercholesterolemia.

194 In the adjusted analysis (Table 1), results showed a clear increased risk of NVP/HG with younger  
195 maternal age across all levels of burden with the magnitude of risk highest for hospital admissions;  
196 whilst women under 25 years were 1.5 times as likely to be treated in primary care compared with  
197 women age 30-34 years, they were over twice as likely to be admitted to hospital. Women from more  
198 deprived socio-economic groups had a comparable prevalence of NVP/HG diagnoses, however they



199 were more likely to be treated with antiemetics in primary care, and to have early hospital admission  
200 compared with women from the least deprived group (test for trend  $p < 0.001$  for all groups other than  
201 diagnosis only). Asian and Black women had considerable increased risks across all levels of  
202 NVP/HG burden, although there was no association between ethnicity and late hospital admission.  
203 Current smoking was associated with a decreased risk of NVP/HG across all levels other than late  
204 hospital admissions. There was no association with multiparity other than a decreased risk in primary  
205 care diagnosis of NVP/HG only. Multiple birth was associated with NVP/HG diagnosed and treated in  
206 primary care but the risk was highest in those with early hospital admissions.

207 Diabetes and hypertension were not associated with NVP/HG diagnosed or treated in primary care,  
208 although they were associated with some increase in late NVP/HG hospital admissions and pre-  
209 existing diabetes increased the risk of early hospital admissions. Pre-eclampsia was associated with  
210 women treated for NVP/HG in primary care, while eclampsia was associated with NVP/HG diagnoses  
211 and late hospital admissions. Asthma and anaemia increased the risk of all levels of NVP/HG. There  
212 was an increased risk of primary care treatment and hospital admissions in women with thyroid  
213 dysfunction or hypercholesterolemia.

#### 214 **Antiemetic prescribing distribution**

215 Distributions of primary care antiemetic prescribing for women with NVP/HG who were and were not  
216 admitted to hospital are shown in Table 2. Of those never admitted to hospital (29,041), antiemetics  
217 were prescribed in 49% of pregnancies; first, second and third-line treatment was prescribed for 42%,  
218 11%, and 1% of pregnancies respectively. The most commonly prescribed antiemetic was  
219 prochlorperazine (21.1%), followed by the other first line drugs promethazine (15.4%) and cyclizine  
220 (13%). While ondansetron and steroids were very rarely prescribed to these women, metoclopramide  
221 was the most commonly prescribed second line treatment (10%) followed by domperidone (1.5%).

222 Of the 6,390 pregnancies with early NVP/HG hospital admission (1.5% overall), only 38% had  
223 evidence of a primary care prescription of antiemetics before the admission and 50% had antiemetics  
224 prescribed following the admission. Overall, 34% received first-line treatment before admission, 9%  
225 second-line and 1% third-line treatment. Individual drugs prescribed were similar to those for

226 unadmitted women, with prochlorperazine being the most common first-line and metoclopramide the  
227 most common second-line treatment. Following admissions, cyclizine, metoclopramide and  
228 prednisolone prescription rates doubled compared to pre-admission rates and ondansetron increased  
229 from 0.4% pre-admission to 4.6% post-admission, reflecting the follow on from the higher level of  
230 treatment lines prescribed in secondary care.

231 Women with late admissions from 20 weeks gestation onwards had even lower prescribing of  
232 antiemetics before their first admission (23% of pregnancies treated pre-admission) and only 8% had  
233 antiemetics prescribed post-admission. First-line treatment was prescribed in 18% of pregnancies pre-  
234 admission, with second and third-line treatment prescribed in 6% and 2% respectively.  
235 Prochlorperazine was still the most common drug prescribed pre-admission, followed by cyclizine,  
236 metoclopramide and promethazine.

### 237 **Sensitivity analysis distinguishing NVP from HG diagnoses made in primary care**

238 Among women with recognised NVP/HG who were never admitted to hospital, the proportions of  
239 pregnancies receiving an HG diagnosis (rather than an NVP diagnosis) were 21% of those without  
240 drug treatment and 41% of those with drug treatment. These proportions remained constant over time  
241 (Figure S1) indicating that NVP and HG diagnoses may have been used interchangeably in the  
242 medical records. Furthermore, the distribution of key maternal characteristics and comorbidities were  
243 very similar between those with HG diagnosed and those with only NVP diagnosed (Figure S2 and  
244 Table S6) again providing the rationale for NVP/HG being considered as the same clinical group.

245

## 246 **Discussion**

### 247 **Main findings**

248 We found that 9.1% of pregnancies had NVP/HG that was clinically recognised in primary or  
249 secondary care; 7% did not result in hospital admission but was treated by GPs with antiemetics half  
250 of the time, and 2.1% resulting in hospital admissions. 38% of women admitted to hospital had  
251 received previous antiemetics in primary care. The prevalence of affected women prescribed

252 antiemetics in primary care has increased over time with a turning point at 2008 after which affected  
253 women were more likely to be treated than not. Hospital admissions, however, also increased over  
254 time, showing an overall increase in the recognised clinical burden of NVP/HG. Moreover, NVP and  
255 HG diagnoses were used in a similar way both for antiemetic prescribing and hospital admissions,  
256 likely reflecting health professionals considering them on a spectrum of illness, despite distinguishing  
257 clinical criteria for hyperemesis gravidarum diagnosis.

### 258 **Strengths and limitations**

259 The CPRD-HES is a well validated data source<sup>33</sup> widely used for epidemiological research<sup>34</sup>, broadly  
260 nationally representative<sup>17,35</sup> and internationally recognised as an extremely meaningful source of  
261 clinical information for studying pregnancy complications and prescribed treatments in England.

262 To our knowledge, this is the first large epidemiological study evaluating the prevalence of clinically  
263 recognised and managed NVP/HG within primary and secondary care.

264 One of the major strengths of this study was the possibility to assess the antiemetic treatments offered  
265 to women with NVP/HG in primary care. However, secondary care prescribing was not available and  
266 although discharge prescriptions are usually short supply, results on prescribing after admission need  
267 to be interpreted cautiously. Whilst it is possible that we overestimated treatments used for NVP/HG,  
268 considering antiemetics have multiple indications, we think this is unlikely as we assessed differential  
269 diagnoses for each consultation where antiemetics were prescribed and carefully excluded  
270 prescriptions referred for treating other conditions including corticosteroids used for asthma, Crohn's  
271 disease and other auto-immune conditions. Some antihistamines are available without prescription,  
272 however, we do not think this underestimated prescriptions as no antiemetics were licensed for use  
273 in pregnancy in England during the study period and pregnant women receive free prescriptions from  
274 the GP. We also applied rigorous exclusion criteria for NVP diagnoses that had differential diagnoses  
275 for these symptoms, such as gastrointestinal, metabolic or genitourinary conditions, as indicated in  
276 RCOG national guidelines for NVP/HG( RCOG, 2016). We acknowledge that NVP is a common  
277 symptom in many diseases and potentially also attributable to other conditions such as diabetes or pre-

278 eclampsia, however, as these are not differential diagnoses, it is also possible that there is co-existence  
279 of NVP/HG with other comorbidities.

280 We have included an extensive analysis of risk factors, however, results could have been affected by  
281 residual confounding as we did not include certain factors such as BMI or family support which were  
282 not comprehensively recorded in the data and there was sub-optimal recording of certain  
283 demographics or life style factors such as ethnicity or smoking status. However quality of data has  
284 improved over time <sup>35</sup> and robust information on pre-existing comorbidities and pregnancy  
285 complications was available <sup>33</sup>. Moreover imputation of missing values for the affected variables was  
286 used to minimise this limitation.

287 We have included women firstly admitted for NVP/HG after 20 weeks of gestation and although the  
288 classic presentation of HG is a hospital admission prior to 20 weeks <sup>36</sup>, some women remain  
289 symptomatic throughout pregnancy <sup>37</sup> so it was important to capture this group, who may represent a  
290 severe and sustained burden of HG. However we acknowledge that those women could have been  
291 admitted for excessive NVP due to other underlying conditions such as diabetes, gestational  
292 hypertension, eclampsia or hypercholesterolemia, revealed to be strong risk factors of late admissions.

293 It is important to acknowledge that our findings represent the clinical prevalence of NVP/HG in  
294 pregnancies ending in live and stillbirths only, as we did not include pregnancies ending in  
295 spontaneous or non-spontaneous abortion. Although some studies have indicated that HG can lead to  
296 pregnancy terminations<sup>38</sup>, more research is needed to assess how severe NVP and HG may relate to  
297 both early or late pregnancy losses.

## 298 **Interpretation**

299 We have shown that the actual prevalence of clinically recognized NVP/HG is higher than previously  
300 reported in agreement with a recently published study based on eight English primary care settings. <sup>39</sup>  
301 Using the linked CPRD-HES data source we have been able to provide this important missing  
302 information to complete the picture of NVP and HG management. Most of the current literature that  
303 describes the prevalence of HG or NVP is either based on medical records of hospital admissions <sup>28,40-</sup>

304 <sup>42</sup> or questionnaires filled in by the affected women to assess the severity of symptoms in an attempt to  
305 detect the actual occurrence of HG or NVP, for which women may not always consult a healthcare  
306 professional <sup>9,43-45</sup>. We found that overall, HG was diagnosed and managed in primary care alone in  
307 2.5% of pregnancies, of which 75% were treated with antiemetics, showing an higher HG burden  
308 than previously reported figures.

309 In our study the level of NVP/HG burden varied by maternal characteristics and comorbidities  
310 consolidating the current knowledge <sup>29</sup> that young mothers, women of Black and Asian ethnic origin,  
311 those from more deprived socioeconomic groups, and with multiple pregnancies are generally more  
312 likely to be affected across the whole severity spectrum. In particular, women from more deprived  
313 backgrounds were much more likely to be admitted to hospital, slightly more likely to be treated with  
314 antiemetics, but had similar risk of diagnosis-only to women from less deprived backgrounds,  
315 indicating that earlier treatment may prevent later hospital admissions.

316 An Australian review <sup>46</sup> revealed the suboptimal management offered to women affected by NVP was  
317 due to the lack of national standard guidelines, concerns about drug teratogenicity and  
318 underestimation of the impact of NVP on women's lives. A pregnancy Sickness Support survey  
319 recently published in the UK also reported significant problems accessing treatment and high levels of  
320 dissatisfaction with care. <sup>14</sup> General failure of an appropriate HG treatment provision was reported  
321 nationally <sup>15,47,48</sup> and internationally <sup>49</sup> with a consequent feeling of isolation and dissatisfaction among  
322 the affected women, exacerbated by further evidence of lack of high-quality studies to support any  
323 particular intervention. <sup>50</sup> Despite a general consensus that some women are denied access to  
324 antiemetics that could help relieve the severe symptoms of these conditions <sup>47</sup>, we found that use of  
325 antiemetics in pregnancy has increased over time. This could be a sign of rising awareness of the  
326 impact of these conditions on the quality of life together with a growing confidence in GPs'  
327 prescribing, supported by growing evidence for the safety of antiemetics in pregnancy <sup>10</sup>. However,  
328 we also found that women with early hospital admissions were much less likely to be treated in  
329 primary care before their admission compared with women who never experienced hospital

330 admissions (38% versus 49%), potentially supporting the hypothesis that some hospital admissions  
331 may be preventable with timely treatment.

### 332 **Conclusions**

333 The actual burden of clinically recognised NVP/HG is larger than reported figures, currently affecting  
334 almost 10% of pregnancies due to a proportion of women reporting clinically relevant symptoms that  
335 are managed at primary care level, half of which are treated with antiemetics. Higher NVP/HG  
336 severity levels generally confirm the consolidated knowledge of which women are more at risk of  
337 developing this condition, with no relevant differences between NVP and HG diagnosis. Doctors'  
338 confidence in prescribing antiemetic drugs to pregnant women is increasing, although 62% of women  
339 with hospital admissions were not prescribed an antiemetic, raising urgent calls to clarify whether  
340 optimal and timely treatments could help prevent hospital admissions.

### 341 **Acknowledgements**

342 None.

### 343 **Disclosure of interests**

344 All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)  
345 (available on request from the corresponding author) and declare: CNP reports personal fees from  
346 Alliance Pharma, during the conduct of the study; personal fees from Sanofi aventis, grants from Leo  
347 Pharma, personal fees from warner chilcott, personal fees from UCB, outside the submitted work; she  
348 is also one of the co-developers of the RCOG Green Top Guideline on HG.; all other authors did not  
349 report any potential conflicts of interest.

### 350 **Contribution to Authorship**

351 LF conducted data management and the analysis. CNP, SD, RK and LJT contributed to the design and  
352 analysis and interpretation of the data; and preparation, critical review, and approval of the  
353 manuscript. The corresponding author attests that LF, CNP, SD, RK and LJT meet authorship criteria  
354 and that no others meeting the criteria have been omitted.

### 355 **Details of Ethics Approval**

356 The study was approved by ISAC (Independent Scientific Advisory Committee) for MHRA Database  
357 Research (protocol number 14\_165R) on the 23<sup>rd</sup> of September 2014.

358 **Funding**

359 The work was funded by The Rosetrees Trust and the Stoneygate Trust through external peer review  
360 for scientific quality. The funders had no role in study design, data collection, analysis, interpretation  
361 of the results and decision to publish, or preparation of the manuscript. All the authors are  
362 independent from the funders. Grant number RB48AG.

363

364

365

366 **References**

- 367 1. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of  
368 pregnancy: a meta analysis. *J Popul Ther Clin Pharmacol*. 2013;20(2):e171-183.
- 369 2. Jarvis S, Nelson-Piercy C. Management of nausea and vomiting in pregnancy. *BMJ*. 2011 Jun  
370 17;342(1):d3606–d3606.
- 371 3. Heitmann K, Nordeng H, Havnen GC, Solheimsnes A, Holst L. The burden of nausea and  
372 vomiting during pregnancy: severe impacts on quality of life, daily life functioning and  
373 willingness to become pregnant again - results from a cross-sectional study. *BMC Pregnancy  
374 Childbirth*. 2017 Feb 28;17(1):75.
- 375 4. London V, Grube S, Sherer DM, Abulafia O. Hyperemesis Gravidarum: A Review of Recent  
376 Literature. *Pharmacology*. 2017;100(3–4):161–71.
- 377 5. Mitchell-Jones N, Gallos I, Farren J, Tobias A, Bottomley C, Bourne T. Psychological  
378 morbidity associated with hyperemesis gravidarum: a systematic review and meta-analysis.  
379 *BJOG*. 2017 Jan;124(1):20–30.
- 380 6. Fiaschi L, Nelson-Piercy C, Gibson J, Szatkowski L, Tata LJ. Adverse Maternal and Birth  
381 Outcomes in Women Admitted to Hospital for Hyperemesis Gravidarum: a Population-Based  
382 Cohort Study. *Paediatr Perinat Epidemiol*. 2017 Oct 6;(32):40–51.
- 383 7. Trovik J, Vikanes Å. Hyperemesis Gravidarum is associated with substantial economic burden  
384 in addition to severe physical and psychological suffering. *Isr J Health Policy Res*. 2016;5:43.
- 385 8. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, et al.  
386 Hospitalizations During Pregnancy Among Managed Care Enrollees. *Obstetrics & Gynecology*.  
387 2002 Jul;100(1):94–100.
- 388 9. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of  
389 illness of severe nausea and vomiting of pregnancy in the United States. *American Journal of  
390 Obstetrics and Gynecology*. 2002 May 1;186(5, Supplement 2):S220–7.
- 391 10. RCOG. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum  
392 (Green-top Guideline No. 69) [Internet]. Royal College of Obstetricians & Gynaecologists. 2016  
393 [cited 2017 May 17]. Available from: [https://www.rcog.org.uk/en/guidelines-research-  
394 services/guidelines/gtg69/](https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/)
- 395 11. Jueckstock JK, Kaestner R, Mylonas I. Managing hyperemesis gravidarum: a multimodal  
396 challenge. *BMC Medicine*. 2010 Jul 15;8(1):46.
- 397 12. Sheehan P. Hyperemesis gravidarum--assessment and management. *Aust Fam Physician*. 2007  
398 Sep;36(9):698–701.
- 399 13. Practice Bulletin Summary No. 153: Nausea and Vomiting of Pregnancy. *Obstet Gynecol*. 2015  
400 Sep;126(3):687–8.
- 401 14. Dean C, Marsden J. Satisfaction for treatment of hyperemesis gravidarum [Internet]. MIDIRS.  
402 2017 [cited 2017 Sep 27]. Available from: [https://www.midirs.org/satisfaction-treatment-  
403 hyperemesis-gravidarum-day-settings-hospital/](https://www.midirs.org/satisfaction-treatment-hyperemesis-gravidarum-day-settings-hospital/)
- 404 15. Power Z, Thomson AM, Waterman H. Understanding the stigma of hyperemesis gravidarum:  
405 qualitative findings from an action research study. *Birth*. 2010 Sep;37(3):237–44.



- 406 16. NIHR, MHRA. Clinical Practice Research Datalink - CPRD; [Internet]. 2017 [cited 2017 Sep  
407 27]. Available from: <https://www.cprd.com/intro.asp>
- 408 17. Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution  
409 of clinical computer systems in primary care in England in 2016 and implications for primary  
410 care electronic medical record databases: a cross-sectional population study. *BMJ Open*. 2018  
411 Feb 1;8(2):e020738.
- 412 18. Benson T. The history of the Read Codes: the inaugural James Read Memorial Lecture 2011.  
413 *Inform Prim Care*. 2011;19(3):173–82.
- 414 19. NHS Digital 1 Trevelyan Square. Hospital Episode Statistics [Internet]. 2012 [cited 2017 Sep  
415 27]. Available from: <http://content.digital.nhs.uk/hes>
- 416 20. N. H. S. NHS Choices - Your health, your choices [Internet]. 2015 [cited 2015 May 28].  
417 Available from: <http://www.nhs.uk/pages/home.aspx>
- 418 21. World Health Organization. International Classification of Diseases, Version 10 [Internet].  
419 2010. Available from: <http://apps.who.int/classifications/icd10/browse/2010/en>
- 420 22. NHS Connecting for Health. Office of Population, Censuses and Surveys Classification 4.4.  
421 [Internet]. 2012. Available from:  
422 [http://webarchive.nationalarchives.gov.uk/20130502102046/http://connectingforhealth.nhs.uk/s](http://webarchive.nationalarchives.gov.uk/20130502102046/http://connectingforhealth.nhs.uk/systemsandservices/data/clinicalcoding/codingstandards/opcs4/index_html)  
423 [ystemsandservices/data/clinicalcoding/codingstandards/opcs4/index\\_html](http://webarchive.nationalarchives.gov.uk/20130502102046/http://connectingforhealth.nhs.uk/systemsandservices/data/clinicalcoding/codingstandards/opcs4/index_html)
- 424 23. Dattani N, Datta-Nemdharry P, Macfarlane A. Linking maternity data for England 2007:  
425 methods and data quality. *Health Stat Q*. 2012;(53):4–21.
- 426 24. Bragg F, Cromwell DA, Edozien LC, Gurol-Urganci I, Mahmood TA, Templeton A, et al.  
427 Variation in rates of caesarean section among English NHS trusts after accounting for maternal  
428 and clinical risk: cross sectional study. *BMJ*. 2010 Oct 6;341:c5065–c5065.
- 429 25. Ban L, Sprigg N, Abdul Sultan A, Nelson-Piercy C, Bath PM, Ludvigsson JF, et al. Incidence of  
430 First Stroke in Pregnant and Nonpregnant Women of Childbearing Age: A Population-Based  
431 Cohort Study From England. *J Am Heart Assoc*. 2017 Apr 21;6(4).
- 432 26. Sultan AA, Tata LJ, Grainge MJ, West J. The Incidence of First Venous Thromboembolism in  
433 and around Pregnancy Using Linked Primary and Secondary Care Data: A Population Based  
434 Cohort Study from England and Comparative Meta-Analysis. *PLoS ONE*. 2013 Jul  
435 29;8(7):e70310.
- 436 27. NICE. BNF: British National Formulary - NICE; [Internet]. 2018 [cited 2018 Feb 20]. Available  
437 from: <https://bnf.nice.org.uk/drug/>
- 438 28. Fiaschi L, Nelson-Piercy C, Tata LJ. Hospital admission for hyperemesis gravidarum: a  
439 nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies.  
440 *Hum Reprod*. 2016 May 31;31(8):1675–84.
- 441 29. Louik C, Hernandez-Diaz S, Werler MM, Mitchell AA. Nausea and vomiting in pregnancy:  
442 maternal characteristics and risk factors. *Paediatr Perinat Epidemiol*. 2006 Jul;20(4):270–8.
- 443 30. Department for Communities and Local Government and The Rt Hon Eric Pickles. English  
444 indices of deprivation - Publications [Internet]. 2010 [cited 2015 May 28]. Available from:  
445 <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010>

- 446 31. Stata Bookstore | Base Reference Manual, Release 15 [Internet]. [cited 2019 Jan 3]. Available  
447 from: <https://www.stata.com/bookstore/base-reference-manual/>
- 448 32. STATA. Data Analysis and Statistical Software; [Internet]. 2018 [cited 2018 Jun 18]. Available  
449 from: <https://www.stata.com/>
- 450 33. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses  
451 in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010  
452 Jan;69(1):4–14.
- 453 34. Abdul Sultan A, Tata LJ, Fleming KM, Crooks CJ, Ludvigsson JF, Dhalwani NN, et al.  
454 Pregnancy complications and adverse birth outcomes among women with celiac disease: a  
455 population-based study from England. *Am J Gastroenterol*. 2014 Oct;109(10):1653–61.
- 456 35. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource  
457 Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015 Jun;44(3):827–36.
- 458 36. McParlin C, O'Donnell A, Robson SC, Beyer F, Moloney E, Bryant A, et al. Treatments for  
459 Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy: A Systematic Review.  
460 *JAMA*. 2016 Oct 4;316(13):1392.
- 461 37. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of  
462 its frequency, intensity, and patterns of change. *Am J Obstet Gynecol*. 2000 Apr;182(4):931–7.
- 463 38. Poursharif B, Korst LM, Macgibbon KW, Fejzo MS, Romero R, Goodwin TM. Elective  
464 pregnancy termination in a large cohort of women with hyperemesis gravidarum. *Contraception*.  
465 2007 Dec;76(6):451–5.
- 466 39. Gadsby R, Rawson V, Dziadulewicz E, Rousseau B, Collings H. Nausea and vomiting of  
467 pregnancy and resource implications: the NVP Impact Study. *Br J Gen Pract*. 2018 Dec  
468 18;bjgp18X700745.
- 469 40. Bolin M, Åkerud H, Cnattingius S, Stephansson O, Wikström A. Hyperemesis gravidarum and  
470 risks of placental dysfunction disorders: a population-based cohort study. *BJOG: An  
471 International Journal of Obstetrics & Gynaecology*. 2013 Apr;120(5):541–7.
- 472 41. Bailit JL. Hyperemesis gravidarum: Epidemiologic findings from a large cohort. *Am J Obstet  
473 Gynecol*. 2005 Sep;193(3 Pt 1):811–4.
- 474 42. Vikanes ÅV, Støer NC, Magnus P, Grjibovski AM. Hyperemesis gravidarum and pregnancy  
475 outcomes in the Norwegian mother and child cohort – a cohort study. *BMC Pregnancy and  
476 Childbirth*. 2013 Sep 3;13(1):169.
- 477 43. Emelianova S, Mazzotta P, Einarson A, Koren G. Prevalence and severity of nausea and  
478 vomiting of pregnancy and effect of vitamin supplementation. *Clin Invest Med*. 1999  
479 Jun;22(3):106–10.
- 480 44. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Epidemiology of nausea and vomiting of  
481 pregnancy: prevalence, severity, determinants, and the importance of race/ethnicity. *BMC  
482 Pregnancy Childbirth*. 2009 Jul 2;9:26.
- 483 45. Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of  
484 pregnancy among Canadian and American women with nausea and vomiting of pregnancy. *J  
485 Psychosom Obstet Gynaecol*. 2001 Mar;22(1):7–12.

- 486 46. Tan A, Foran T, Henry A. Managing nausea and vomiting in pregnancy in a primary care  
487 setting. *Australian Family Physician*. 2016 Aug;45(8):564.
- 488 47. Gadsby R. General practitioners are wary of treating sickness in pregnancy. *BMJ*. 2004 Feb  
489 28;328(7438):505–6.
- 490 48. Gadsby R. Pregnancy nausea and vomiting--the role of the midwife. *Pract Midwife*. 2012  
491 Oct;15(9):17–9.
- 492 49. Heitmann K, Solheimsnes A, Havnen GC, Nordeng H, Holst L. Treatment of nausea and  
493 vomiting during pregnancy -a cross-sectional study among 712 Norwegian women. *Eur J Clin  
494 Pharmacol*. 2016 May;72(5):593–604.
- 495 50. Matthews A, Haas DM, O’Mathúna DPO, Dowswell T, Doyle M. Interventions for nausea and  
496 vomiting in early pregnancy. *Cochrane Database Syst Rev*. 2014 Mar 21;(3):CD007575.

#### 497 **List of Figures:**

498 **Figure. 1** [Categorisations of NVP/HG clinical management within he study population](#)

499 **Figure. 2** [Change in proportion of pregnancies with clinically recognised NVP/HG by level of burden](#)

#### 500 **List of Tables:**

501 **1** [Relative risk ratios of NVP/HG level of burden according to maternal characteristics in 417,028 pregnancies](#)

502 **Table 2** [Distribution of different antiemetics prescribed in pregnancy for women with NVP/HG](#)

#### 503 **Supplemental Material:**

504 **Table S1** [Read codes for NVP and HG diagnoses](#)

505 **Table S2** [ICD10 codes for NVP and HG diagnoses](#)

506 **Table S3** [Read codes for NVP differential diagnoses](#)

507 **Table S4** [ICD10 codes for NVP differential diagnoses](#)

508 **Table S5** [Antiemetics codes used for extracting antiemetic prescriptions](#)

509 **Figure S1** [Change in proportion of pregnancies with clinically recognised NVP/HG by level of burden, distinguishing  
510 NVP diagnosis from HG diagnosis](#)

511 **Figure S2** [Distribution of Maternal characteristics across different HG and NVP level of burden groups](#)

512 **Table S6** [Distribution of hyperemesis gravidarum level of burden according to maternal comorbidities for women  
513 with NVP diagnosis \(with or without treatment\) and HG diagnosis \(with and without treatment\)](#)

