


# BMJ Open Systematic evidence map of evidence addressing the top 10 priority research questions for hyperemesis gravidarum

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## ABSTRACT

**Objective** Knowledge gaps regarding hyperemesis gravidarum (HG) are substantial. We aimed to systematically identify and map recent evidence addressing the top 10 priority questions for HG, as published in 2021 in a James Lind Alliance Priority Setting Partnership.

**Design** Systematic evidence map.

**Methods** We searched MEDLINE and EMBASE on 12 January 2021 and CINAHL on 22 February 2021 with search terms hyperemesis gravidarum, pernicious vomiting in pregnancy and their synonyms. Results were limited to 2009 onwards. Two reviewers independently screened titles and abstracts to assess whether the studies addressed a top 10 priority questions for HG. Differences were discussed until consensus was reached. Publications were allocated to one or more top 10 research questions. Study design was noted, as was patient or public involvement. Two reviewers extracted data synchronously and both cross-checked 10%. Extracted data were imported into EPPI-Reviewer software to create an evidence map.

**Outcome measures** The number and design of studies in the search yield, displayed per the published 10 priority questions.

**Results** Searches returned 4338 results for screening; 406 publications were included in the evidence map. 136 publications addressed multiple questions. Numerous studies address the immediate and long-term outcomes or possible markers for HG (question 8 and 9, respectively 164 and 82 studies). Very few studies seek a possible cure for HG (question 1, 8 studies), preventative treatment (question 4, 2 studies) or how to achieve nutritional requirements of pregnancy (question 10, 17 studies). Case reports/series were most numerous with 125 (30.7%) included. Few qualitative studies (9, 2.2%) were identified. 25 (6.1%) systematic reviews addressed eight questions, or aspects of them. 31 (7.6%) studies included patient involvement.

**Conclusions** There are significant gaps and overlap in the current HG literature addressing priority questions. Researchers and funders should direct their efforts at addressing the gaps in the top 10 questions.

## BACKGROUND

Hyperemesis gravidarum (HG) affects approximately 1.1% of pregnant women

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The 10 questions mapped were identified and prioritised by patients and clinicians using the James Lind Alliance method, thereby ensuring their relevance and importance.
- ⇒ A broad overview of the research landscape of the top 10 priority questions for hyperemesis gravidarum is provided, and gaps can be easily identified in this visual presentation.
- ⇒ We translated 21 articles but were unable to translate 18 foreign language studies, particularly those in Arabic and Iranian, which may be seen as a limitation.
- ⇒ Many of the excluded studies were abstracts which had not been published as an article, highlighting the need for researchers to ensure their research is published.
- ⇒ Search results were limited to 2009 onwards. Older literature may be informative but was not in the scope of this review.

globally.<sup>1</sup> The condition is characterised by extreme levels of nausea and vomiting leading to complications such as dehydration and malnutrition.<sup>2</sup> HG accounts for severe physical and psychological morbidity for women affected,<sup>3–5</sup> and where symptoms lead to malnutrition in the mother, there may be lifelong consequences for the exposed offspring.<sup>6,7</sup>

Prior to the rapid advance of intravenous therapies in the early 1960s, HG was well documented and researched as it was a common cause of death in early pregnancy.<sup>8,9</sup> However, with the dawn of the psychosomatic era and with the invention of intravenous therapy, interest in the condition declined and HG patients were commonly mislabelled as psychiatric; an attitude which has persisted into the current century.<sup>10</sup> The incorrect psychiatric labelling of HG can lead to further stigmatisation and consequently a lack of interest in HG research.<sup>11</sup> Additionally, the little research that has been done

into HG has been hampered by factors such as a lack of definition and standard outcomes rendering research too heterogeneous and unfit for meta-analysis.<sup>12</sup> Two recent systematic reviews of treatments for nausea and vomiting in pregnancy (NVP) and HG were unable to draw conclusions due to the heterogeneity of the studies included.<sup>13,14</sup> However, researchers are now seeking to lay solid foundations for future research such as with an internationally agreed definition and by mandating a set of core study outcomes required for publication, which could each contribute to limit heterogeneity of individual studies.<sup>15</sup>

The chasm between the questions patients and clinicians want answers to and the questions research has been seeking to answer, is an important underlying factor for research waste.<sup>16</sup> The recent introduction of patient and public involvement (PPI) in the research process from question development to outcome dissemination is aimed at closing this chasm.<sup>17</sup> Ensuring that research funding is directed to the most important and useful projects can significantly reduce research waste.<sup>18</sup> A recent James Lind Alliance (JLA) Priority Setting Partnership (PSP) for HG, which benefited from thorough PPI throughout, identified the top 10 priority questions for researchers to address over the coming years.<sup>19</sup>

The aim of the present evidence mapping project was to systematically identify the number and design of published literature addressing the top 10 priority questions for HG. The systematic evidence map (SEM) we aimed to produce should help researchers and funders identify the areas of greatest need and potential benefit thereby reducing research waste and maximising value. We additionally aimed to map PPI in HG research.

## METHODS AND ANALYSIS

### Study design

SEM methodology is a systematic approach to identifying gaps in knowledge and future research needs of a particular topic using transparent and robust methods.<sup>20,21</sup> It aims to create a visual matrix of current evidence without further appraisal of the quality of the evidence.<sup>22</sup>

A preliminary search of PROSPERO and key databases for published studies and protocols was conducted to rule out other SEM projects or similar scoping review for HG; no such studies or protocols were identified.

A methodological framework combining the Arksey and O'Malley<sup>23</sup> scoping studies approach and the Campbell Collaboration<sup>24</sup> protocol template for evidence maps was adopted, which at the time of development was a pragmatic approach to use the most established methods to date for SEMs. The Campbell Collaboration is an organisation promoting the use of systematic evidence synthesis for positive social and economic policy and practice change.<sup>25</sup> It has produced standards for SEMs which we have incorporated into this project such as defining the search strategy, objectives, inclusion criteria, eligibility criteria, categories, restrictions and so on, in advance in order to expand the below stages.<sup>24</sup>

The Arksey and O'Malley steps which were incorporated in our approach are as follows<sup>23</sup>:

Stage 1: identifying the research question(s).

Stage 2: identifying relevant studies, that is, conducting the searches.

Stage 3: study selection, that is, screening and selecting those fitting the eligibility criteria.

Stage 4: charting the data.

Stage 5: collating, summarising and reporting the results.

### Patient public involvement

The authors of this SEM are fully committed to patient involvement in HG research which adds significant relevance to research findings.<sup>26</sup> The lead author (CRD) and MO are both HG patients themselves and are experienced advocates of patients with HG. Patients have cocreated this work with clinicians and academics; an HG patient and advocate, created the concept, conducted the research and wrote the manuscript, while experienced academics and clinicians acted as supervisors and collaborators. Additional patients and clinicians were consulted throughout the process (see the acknowledgements section): researchers and clinicians opinions were sought during online meetings and phone calls and patients from England were shown early versions of the SEM during informal volunteer online meet-ups on the usefulness of the map and the categories for them. Trustees of the charities Pregnancy Sickness Support (UK) and Hyperemesis Ireland, whose boards consist of patient representatives, clinicians and/or researchers, provided feedback after the final SEM was presented during an online meeting.

### Stage 1: identifying the research questions

A JLA PSP for HG was conducted between 2017 and 2019, which brought together patients, their caregivers and offspring and healthcare professionals involved in HG care, to identify the top 10 most pressing, unanswered research questions.<sup>19</sup> Table 1 provides the resulting top 10 questions which form the basis for this project. For full details of the JLA project, including methods, data collection, participant recruitment, countries represented, the prioritisation process and how the questions were developed, refer to the published research available online (doi: 10.1136/bmjopen-2020-041254).

### Stage 2: identifying relevant studies

#### Search strategy

The original search strategy was devised and conducted electronically by a Medical Information Specialist (author RS) in 2019 as part of the JLA PSP evidence check process. This search sought to identify if any questions could be considered answered with enough evidence of sufficient quality. This has been described in detail previously and includes the protocol.<sup>19</sup> For this SEM, the searches were repeated. MEDLINE and EMBASE were searched from inception to 12 January 2021 by RS using the following broad terms: hyperemesis gravidarum/ or (“excessive

**Table 1** Top 10 unanswered research priority questions\* for hyperemesis gravidarum, in ranked order of importance from one as the most important<sup>19</sup>

Ranking	Question*
1	Can we find a cure? What novel or new treatments are being developed/tested/used elsewhere which could have a curative effect and to address all the symptoms of HG rather than just the vomiting?
2	How can we most effectively manage HG? What clinical support measure is most important to people who have had hyperemesis and what did they find most beneficial? For example, medical management, pharmaceutical review, nutrition support, rehydration, psychological support
3	What causes HG?
4	Is HG preventable? What is the effect of preventative treatment or early intervention on the severity and duration of HG in a subsequent pregnancy?
5	What are the immediate† and long-term effects‡ of HG (including malnutrition§ and dehydration¶, stress**) on the developing fetus (offspring)?
6	What are the immediate† and long-term effects‡ of the various medications/treatments on the developing fetus (offspring) throughout the various stages of pregnancy and in varying doses or combinations of treatments?
7	What are relative†† efficacies of the current medications and treatment options available? What is the optimal dose, route, timing and combination of the medications and what are the related side effects?
8	What are the immediate† and long term‡, physical, mental and social consequences and complications of HG (including malnutrition and dehydration) on the pregnant person's body? (ie, metabolic impact, DVT, depression, effects of dehydration)
9	What clinical measurements and markers are most useful in assessing, diagnosing, managing and monitoring HG?
10	What are the nutritional requirements of the 1st, 2nd and 3rd trimesters and how can people with HG achieve these goals? That is, oral supplements, fortifying food, dietary measures

\*The phrasing of the questions was established using the James Lind Alliance consensus method therefore we were not able to alter the phrasing in the writing of this manuscript.  
 †Immediate effects relates to those during the perinatal period.  
 ‡Long-term effects relates to any time after the perinatal period.  
 §Example indicators of malnutrition include weight loss or nutritional intake.  
 ¶Example indicators of dehydration include need for intravenous rehydration or urine output.  
 \*\*Stress could be measured with questionnaires.  
 ††Relative to each other.  
 ‡‡  
 DVT, Deep Vein Thrombosis; HG, hyperemesis gravidarum.

vomiting” or (pernicious adj3 vomiting) or hyperemesis) and (gravid\* or pregn\* or gestation or antenatal)).mp.

Additionally, the Cochrane Library was searched electronically by CRD in collaboration with RS, using the term “hyperemesis gravidarum”. A further CINAHL search was conducted with the same strategy by RS on 22 February 2021, as a deviation from the protocol, because the reviewers noticed that certain papers from nursing and midwifery journals had not been returned in the original searches.

The searches are detailed in online supplemental file 2.

### Eligibility criteria

#### Inclusion and exclusion criteria

To be eligible, publications had to study women with HG, or their offspring, and address any aspect of any of the top 10 questions. All study designs and languages were eligible. We did not apply a minimum study size for eligibility. The steering group for the PSP agreed that due to the paucity of HG research and changing attitudes to HG treatment in the last decade, a 10-year limit was most appropriate.<sup>19</sup> Since the first search was performed in 2019, we excluded articles published prior to 2009.

Abstracts (from conference oral presentations or posters) were excluded if full texts for the same study were not found. Review articles in which search methods were not described were excluded as narrative reviews. Reviews which describe their study as a systematic review were included as such. Reviews which described their methods including databases and search terms used, but did not fit generally accepted criteria for a systematic review such as following a protocol, screening and data extracting in duplicate or assessing risk of bias,<sup>27</sup> were labelled as literature reviews. Protocols for systematic reviews, randomised controlled trials, cohort or case–controlled studies and qualitative studies, which were published in peer-review journals and did not yet have a corresponding publication of results, were included. The addition of protocols was aimed at offering researchers information about research currently underway in order to reduce research waste and potentially aid collaboration.

#### Defining HG

Other systematic review protocols have highlighted the challenge of defining the condition of HG itself.<sup>28</sup> A historic lack of clinical definition has hampered HG research efforts globally and made meta-analysis difficult due to heterogeneity within the studies.<sup>12 29</sup> This review took the same approach as other systematic reviews which have included articles that describe HG, regardless of how that is defined. We excluded studies which only included mild to moderate NVP, but included studies where severe NVP was explicitly described.

#### Stage 3: study selection

Two reviewers (CRD and KN) independently screened titles and abstracts to establish if they may be eligible for inclusion according to the criteria above, using Rayyan



software,<sup>30</sup> and met to discuss differences, such as whether the study relates to a top 10 question or not. In case of disagreement, a third reviewer was consulted (RCP). The reviewers labelled relevant references with the top 10 priority question they related to. Full texts were retrieved for full screening. Foreign language papers were translated using Google Translate online where possible and authors were contacted where full texts were unfindable via online library sources. Full text eligibility screening was conducted independently by the two reviewers for 50% of the texts each, followed by checking 10% of each others. Discrepancies were discussed until consensus was reached. Publications meeting the inclusion criteria detailed above were included.

#### Stage 4: charting the data

The two reviewers independently extracted data from the full texts, completing 50% each, again checking 10% of each others. An Excel data charting form was used to extract key information which included:

- ▶ The top 10 question it addressed.
- ▶ Author(s), full reference, year of publication.
- ▶ Country.
- ▶ Abstract
- ▶ Aims of the study
- ▶ Study design
- ▶ Reporting of PPI
- ▶ Outcome measures
- ▶ Results

#### Defining PPI and patient authorship

INVOLVE is a UK government funded programme established to support active PPI in medical, health service and social care research; it defines PPI in research as ‘research being carried out ‘with’ or ‘by’ members of the public rather than ‘to’, ‘about’ or ‘for’ them’<sup>31</sup> They further define the term ‘public’ as patients, potential patients, carers and people who use health and social care services as well as people from organisations that represent people who use services.<sup>31</sup>

PPI was considered to be included if a manuscript explicitly describes how it was included, if one of the author’s affiliation was a patient organisation for HG, or if an author specified that they experienced HG within the manuscript.<sup>32</sup>

#### Stage 5: collating, summarising and reporting the results

Research was categorised according to the top 10 priority questions and some questions were further labelled with subcategories which were identified and constructed from the studies during the data extraction process (see table 2). These categories were discussed with clinical research colleagues to ensure they were relevant and reflective of the research. Studies with ambiguity around its categorisation were also discussed with clinical research colleagues and a patient representative. Research was next categorised according to study designs: Reviews, randomised control trials (RCTs), cohort studies,

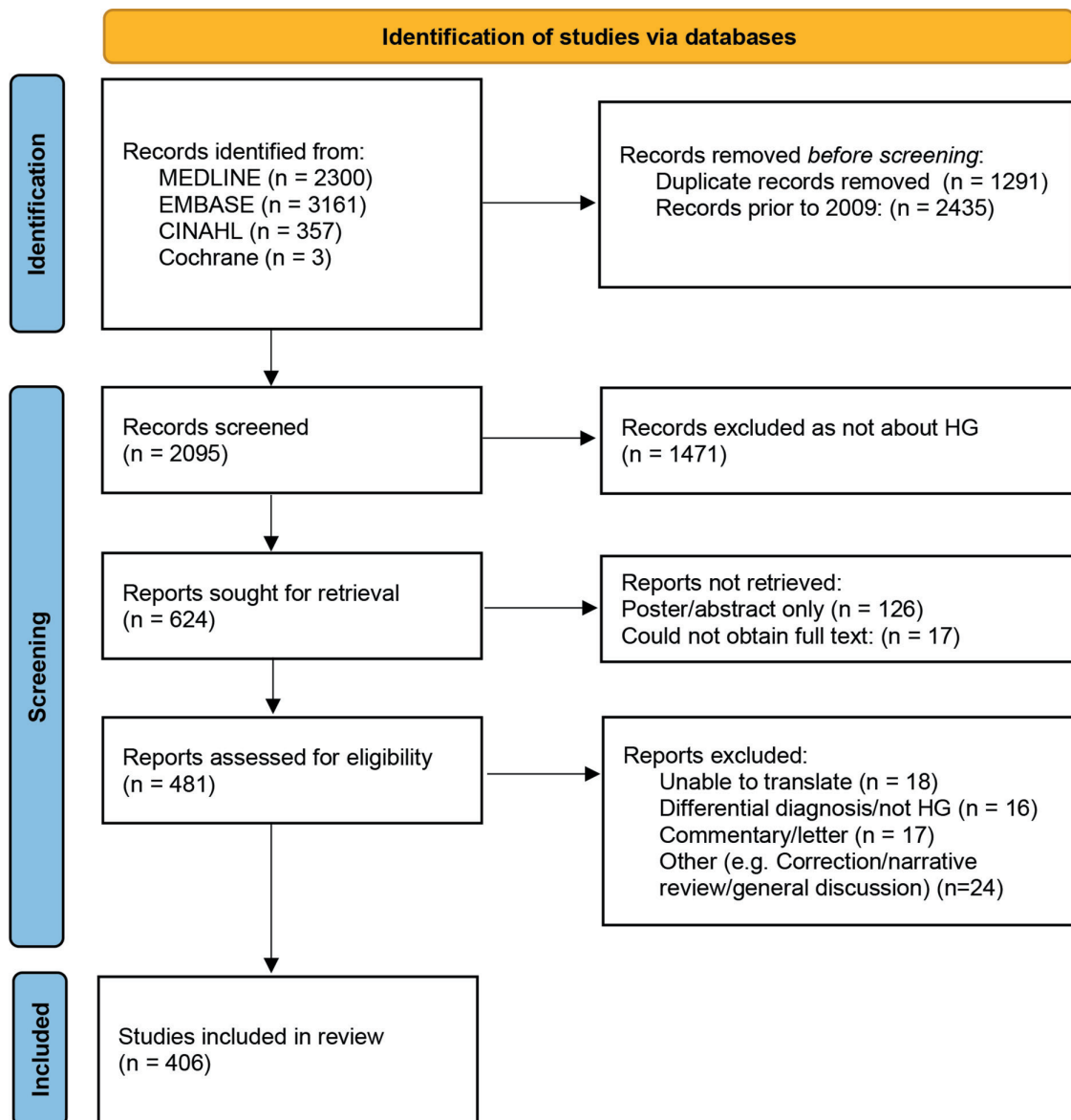
**Table 2** Question subcategories which emerged during data extraction

Question*	Subcategories
Q2: How can we most effectively manage HG?	<ol style="list-style-type: none"> <li>1. Outpatient treatment</li> <li>2. Intravenous treatment</li> <li>3. Tube feeding</li> <li>4. Other treatments</li> </ol>
Q3: What causes HG?	<ol style="list-style-type: none"> <li>1. Genetic studies</li> <li>2. <i>Helicobacter pylori</i></li> <li>3. Laboratory studies of other factors, for example, hCG</li> <li>4. Psychosocial factors</li> <li>5. Other causes</li> </ol>
Q5: What are the immediate and long-term effects of HG on the fetus?	<ol style="list-style-type: none"> <li>1. Perinatal outcomes</li> <li>2. Long-term outcomes</li> </ol>
Q7: What are the relative efficacies of current treatments?	<ol style="list-style-type: none"> <li>1. Anti-emetics</li> <li>2. Steroids</li> <li>3. Other treatments</li> </ol>
Q8: What are the immediate and long-term effects of HG on pregnant people?	<ol style="list-style-type: none"> <li>1. Psychosocial effects</li> <li>2. Wernicke’s encephalopathy</li> <li>3. Other maternal complications due to HG</li> <li>4. Long-term maternal health</li> <li>5. Metabolic impact (laboratory results)</li> <li>6. Other outcomes</li> </ol>
Q9: What clinical measurements and markers in HG are available and most useful in assessing, diagnosing, managing and monitoring HG?	<ol style="list-style-type: none"> <li>1. Psychosocial measurements</li> <li>2. <i>Helicobacter pylori</i> as marker</li> <li>3. Other laboratory markers</li> <li>4. HG assessment questionnaires</li> <li>5. Other assessments</li> </ol>

\*Questions 1, 6 and 10 did not require subcategories. hCG, human chorionic gonadotrophin; HG, hyperemesis gravidarum.

case–control studies, qualitative studies, surveys and case reports/series. These were further categorised as either systematic or literature reviews, either prospective or retrospective for cohorts and case–control studies, and either case reports or case series. Other designs did not require further subcategories.

Data were then imported into the EPPI-Reviewer software<sup>33</sup> which is an online tool designed to generate a bubble map. Bubble maps present evidence visually with circles whose size represents the number of studies. The top 10 questions and their subcategories are on the x-axis and methodologies used in the studies are on the y-axis. Inclusion of PPI in research categories were assigned colours for a third-dimension representation within the map. Additionally, the country of the studies was labelled for convenient identification of research output by country through the filter function of the software.



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of inclusions and exclusions. HG, hyperemesis gravidarum.

Where there was potential ambiguity over categorisation articles were discussed with a third author (RCP) and external justification for labelling sought, for example, a treatment was considered new or novel if it does not currently appear in national guidelines in the UK, USA or Netherlands (ie, gabapentin, clonidine, cannabis and mirtazapine).

## RESULTS

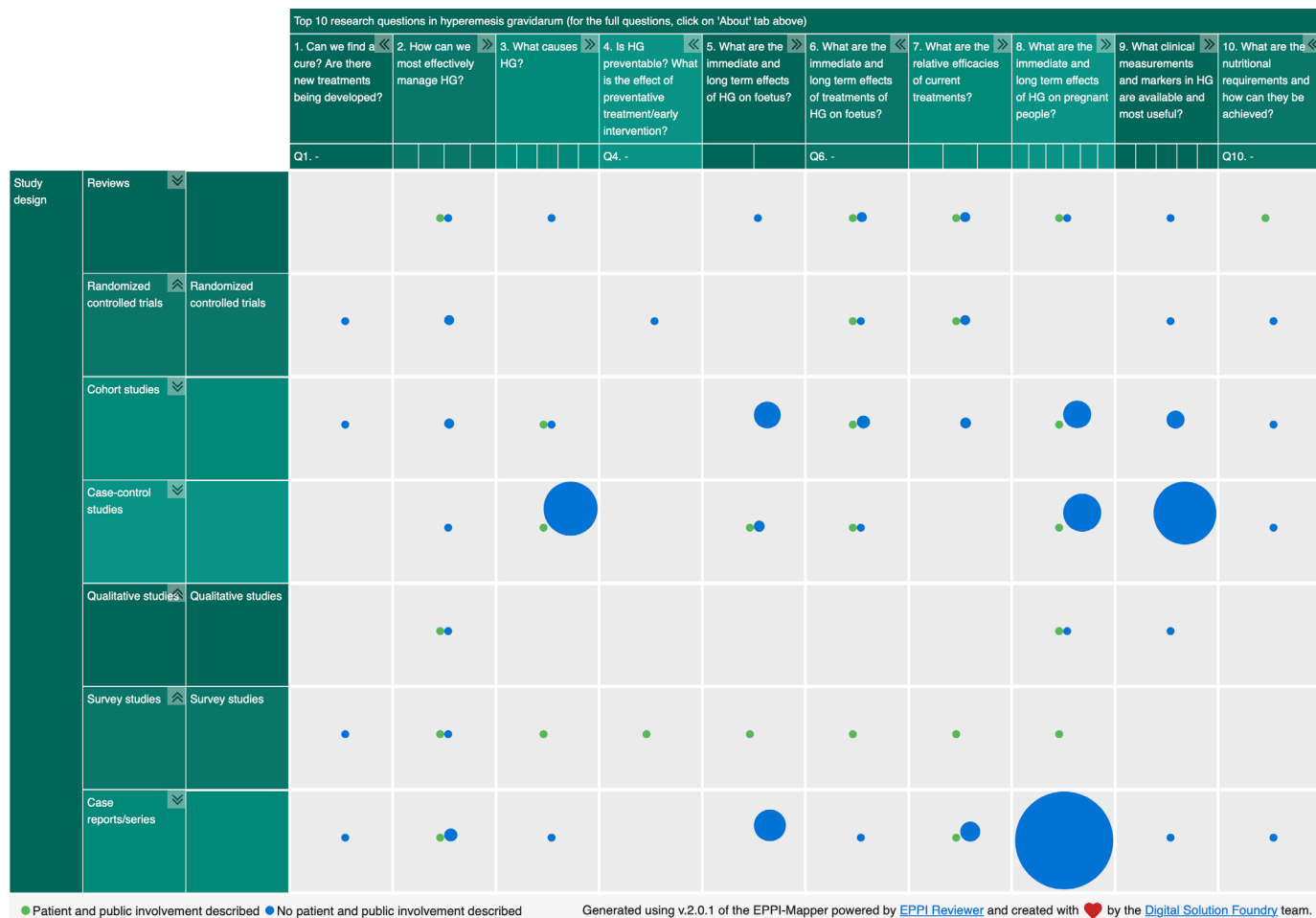
### Identification of studies

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the selection process. The combined searches yielded 5821 eligible citations, of which 2435 were excluded because of being published before 2009. After initial screening of title and abstract, 624 remained for full text assessment.

### Reasons for exclusions

Of the 624 a further 218 studies were excluded (see online supplemental file 3). While 21 included articles were translated, we were unable to translate a further 18 articles which were predominantly written in Persian or Arabic. One hundred and twenty-six studies were presented only as an abstract or poster and were therefore excluded, and we were unable to obtain full texts for a further 17 articles despite requests to the authors. Sixteen of the 624 studies were deemed not to be about HG when the full text was reviewed. A further 17 articles were commentaries or letters referring to other research and 24 were excluded for other reasons such as being a general discussion, background article or narrative review.

A total of 406 studies were included in the final SEM. See online supplemental file 4 for the full list with labels.



**Figure 2** Bubble map charting the available evidence according to the question it relates to, the study design and the involvement of patient and public involvement. HG, hyperemesis gravidarum.

Interactive spreadsheets are available online (<https://www.hgresearch.org/hgmapfiles>).

### BUBBLE MAP

The interactive map is available online at [www.hgresearch.org/hgmapfiles](http://www.hgresearch.org/hgmapfiles), and as [figure 2](#) as a static image without expanding subcategories.

### CHARACTERISTICS OF STUDIES

**Table 3** shows the number of studies according to study design. There was some overlap as five studies incorporated more than one design, for example, a prospective case-control study which also included a qualitative element.<sup>34</sup> Case reports/series and case-control studies were most numerous with 125 and 124 identified respectively. Of the 406 included papers, only 25 were systematic reviews and 21 were RCTs. The majority of the studies included originated from Europe and the USA (66%, 275/406).

### RESULTS PER QUESTION

**Figure 3** shows the number of studies identified per question which ranged from two studies addressing preventing HG (question 4) to 164 studies addressing the effects and complications of HG (question 8). One hundred and thirty-six studies addressed more than one question. Where more than nine references are described refer to online supplemental file 4.

#### Question 1: can we find a cure? What novel or new treatments are being developed/tested/used elsewhere which could have a curative effect and to address all the symptoms of HG rather than just the vomiting?

Eight studies assessed whether four different novel treatments could have a beneficial or curative effect on HG. Of these, two were RCTs (one assessing transdermal clonidine<sup>35</sup> and one assessing gabapentin,<sup>36</sup> two were prospective cohort studies also assessing clonidine<sup>37</sup> and gabapentin,<sup>38</sup> one was a survey study of cannabis use in pregnancy for sickness,<sup>39</sup> and three were case reports (one of cannabis<sup>40</sup> and two of mirtazapine).<sup>41 42</sup> The RCTs and cohort studies also reported fetal outcomes while the other studies did not.

**Table 3** Studies included in systematic evidence map for hyperemesis gravidarum, presented according to their method

Method*	Number of studies	Method subcategory	Number of studies
Reviews	34	Systematic review	25
		Literature review	9
RCT†	21		
Cohort studies	85	Prospective cohort study	41
		Retrospective cohort study	44
Case-control studies	124	Prospective case-control study	109
		Retrospective case-control study	15
Qualitative study†	9		
Surveys†	13		
Case reports/Series	125	Case reports	115
		Case series	10
<b>Total</b>	<b>411</b>		

\*RCT, qualitative studies and surveys did not require subcategories.

†Method categories were not mutually exclusive. RCT, randomised control trial.

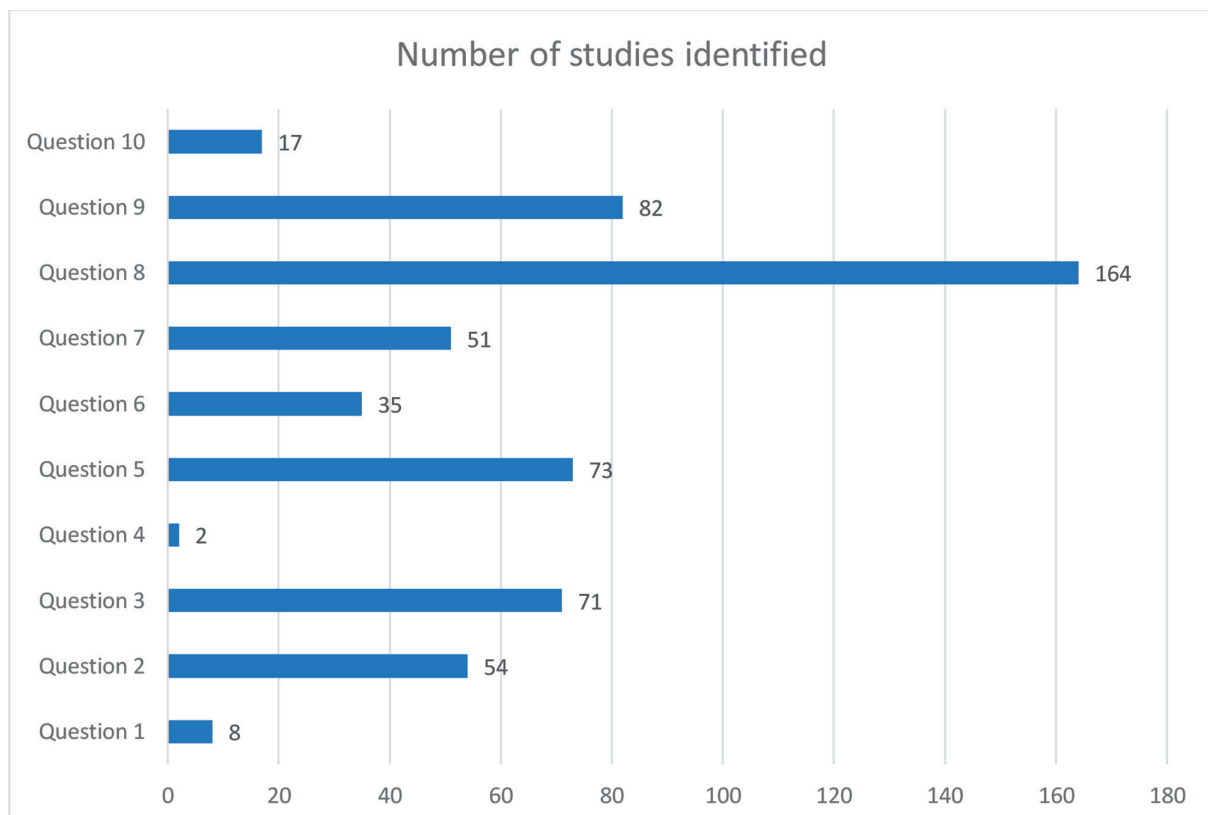
**Question 2: how can we most effectively manage HG? What clinical support measure is most important to people who have had hyperemesis and what did they find most beneficial? For example, medical management, pharmaceutical review, nutrition support, rehydration, psychological support**

A total of 54 studies were identified regarding management of HG. Five systematic reviews were identified, four of which were almost identical assessing interventions for HG.<sup>13 14 43 44</sup> The last was a systematic review of the effect of acustimulation on NVP and HG.<sup>45</sup> Nine RCTs were identified on a variety of topics regarding how best to manage HG, including three studies assessing outpatient care,<sup>46-48</sup> one on tube feeding,<sup>49</sup> two assessed intravenous therapies<sup>50 51</sup> and three studies reported other types of clinical support measures, including a 12-hour fasting approach and relaxation methods.<sup>52-54</sup>

Question two contained the most qualitative studies with six identified describing women's experiences of the condition and its treatments.<sup>55-60</sup>

**Question 3: what causes HG?**

Seventy-one studies have attempted to find a cause for HG. Of these, eight have sought to identify genetic causes,<sup>61-68</sup> 17 researched the role of *Helicobacter pylori* in the aetiology of HG, 23 looked at a variety of laboratory markers, 18 studies assess psychosocial factors as a cause and five studies assessed other possible causes such as nervous system dysfunction, dietary factors and the vestibular system. Laboratory studies were included under



**Figure 3** The number of studies identified per top 10 question included in the evidence map for hyperemesis gravidarum.

question three if the authors of the study stated that they were specifically looking at possible aetiology, rather than for diagnostics, assessment or monitoring purposes.

Of the 17 studies assessing *H. pylori*, three systematic reviews have been published<sup>69–71</sup> and the remaining 14 studies are all prospective case–control studies.

To date, no systematic review has been conducted of the published reports regarding genetic factors, laboratory markers and possible psychosocial causes of HG, although one systematic review assessed polyunsaturated fatty acids in HG.<sup>72</sup>

#### **QUESTION 4: IS HG PREVENTABLE? WHAT IS THE EFFECT OF PREVENTATIVE TREATMENT OR EARLY INTERVENTION ON THE SEVERITY AND DURATION OF HG IN A SUBSEQUENT PREGNANCY?**

Only two studies sought to assess if HG is preventable, either during a pregnancy or prior to a subsequent one. Of these, one was an RCT assessing the effect of pre-emptive medication on the incidence and severity of HG in a subsequent pregnancy.<sup>73</sup> The other was a survey study exploring the experiences of HG in a subsequent pregnancy and how factors such as increased support, or early treatment affected symptoms.<sup>74</sup>

#### **Question 5: what are the immediate and long-term effects of HG (including malnutrition and dehydration, stress) on the developing fetus (offspring)?**

We identified 73 studies assessing perinatal and/or long-term offspring outcomes following HG. Of these, 60 assessed perinatal outcomes and 15 assessed health in later life among offspring; two studies assessed both.<sup>6 75</sup> Three systematic reviews have been conducted which describe perinatal outcomes for the fetus, one of which also reported long-term outcomes.<sup>6 76 77</sup> Among the 60 studies describing perinatal outcomes, 28 were case reports.

#### **Question 6: what are the immediate and long-term effects of the various medications/treatments on the developing fetus (offspring) throughout the various stages of pregnancy and in varying doses or combinations of treatments?**

Thirty-five studies reported fetal outcomes following HG treatment with a range of medications and interventions, of which nine were systematic reviews<sup>13 14 43 78–83</sup> and one was a literature review.<sup>84</sup> Four of these assessed the safety of ondansetron specifically.<sup>78 80 81 84</sup> Six were RCTs,<sup>35 36 46 49 85 86</sup> ten were retrospective cohort studies and two were prospective cohort studies.<sup>37 38</sup> There were also three retrospective case–control studies,<sup>87–89</sup> two surveys<sup>90 91</sup> and two case reports/series.<sup>92 93</sup>

#### **Question 7: what are relative efficacies of the current medications and treatment options available? What is the optimal dose, route, timing and combination of the medications and what are the related side effects?**

Fifty-one studies assessed the efficacy of treatments, of which eight were systematic reviews<sup>13 14 43 44 79 82 83 94</sup> and

ten were RCTs. Of the studies assessing treatments, 30 assessed the efficacy of anti-emetics, 5 assessed corticosteroids specifically<sup>79 95–98</sup> and 20 studied ‘other treatments’. Other treatments included gabapentin, clonidine, cannabis, ginger, antacids, diazepam, mirtazapine, B vitamins, Chinese medicines and Japanese herbal Kampo medicines, as well as routes of administration including peripheral central catheters and transdermal application.

#### **Question 8: what are the immediate and long-term, physical, mental and social consequences and complications of HG (including malnutrition and dehydration) on the pregnant person’s body? (ie, metabolic impact, Deep Vein Thrombosis, depression, effects of dehydration)**

One hundred and sixty-four studies addressed aspects of this question, however, 90 of these are case reports of serious complications such as thyrotoxicosis, refeeding syndrome, cardiac arrest and hepatorenal failure. In total, there were 56 case reports and one systematic review on Wernicke’s encephalopathy.<sup>77</sup> Forty studies assessed the psychosocial effects of HG on women, including two systematic reviews: one of quantitative studies<sup>29</sup> and one of qualitative studies.<sup>3</sup>

#### **Question 9: what clinical measurements and markers are most useful in assessing, diagnosing, managing and monitoring hyperemesis?**

Eighty-two studies sought to assess clinical measurements and markers for HG, of which 59 were searching for altered serum levels of a vast array of markers, predominately with prospective case–control studies (n=42). In addition to laboratory markers, six studies sought to validate assessment questionnaire tools<sup>34 99–103</sup> and six studies looked at the effect that HG had on other assessments conducted during pregnancy, such as screening for gestational diabetes, urinary tract infections and the triple test screen.<sup>104–109</sup> There was one systematic review which summarised diagnostic laboratory markers for HG in general<sup>110</sup> as well as two systematic reviews on *H. pylori* and HG<sup>69 70</sup> and one specifically on nucleic acids in pregnancy complications.<sup>111</sup>

#### **Question 10: what are the nutritional requirements of the first, second and third trimesters and how can people with HG achieve these goals? That is, oral supplements, fortifying food, dietary measures**

The effect of HG on nutritional intake and methods for addressing deficiencies were addressed by 17 studies, including a scoping review on the nutritional intake of women with HG<sup>112</sup> and an RCT to assess the effect of early enteral tube feeding.<sup>49</sup>

#### **PPI and patient authorship**

PPI was included in 31 studies, of which 12 explicitly described how patients were involved in the development of the research and 25 had an author who was also a patient. Of the studies with patient authors, 19 did not describe the scope of the PPI in the development, design or production of the research, beyond listing the



affiliation. The remainder of the included studies did not mention PPI or explicitly stated that it was not included. See online supplemental file 1 for the full reference list for each category.

Of those that included PPI, four were systematic reviews<sup>3 14 94 112</sup> (of which one was a systematic review of qualitative studies), four were survey studies,<sup>55 74 113 114</sup> two were prospective case-control studies,<sup>115 116</sup> one was a protocol for an RCT<sup>86</sup> and one was a qualitative study.<sup>60</sup> Of the remaining 20 studies that included a patient author, but did not report PPI, seven were survey studies,<sup>75 90 91 117–120</sup> four were cohorts,<sup>63 121–123</sup> three were case-control studies,<sup>61 87 124</sup> two were case reports,<sup>125 126</sup> two were qualitative studies<sup>56 58</sup> and one was a literature review.<sup>11</sup>

## DISCUSSION

We systematically searched the literature for studies on HG and identified 406 studies, addressing the top 10 unanswered research priorities for HG and mapped them according to study design and patient involvement. While all the questions have at least two papers addressing them, the JLA PSP found all questions ‘remain unanswered by sufficiently robust and conclusive systematic review’ and were thus included in the prioritisation process.<sup>19</sup> Where many individual (small) reports exist, a systematic review can help provide robust summary answers to questions. Identifying a presence of a wealth of small individual studies, in the absence of a systematic review could trigger future systematic review and meta-analysis development. For many other questions there simply is a dearth of evidence, and primary research is needed. To our knowledge, this is the first time a SEM has followed a JLA PSP and it is the first SEM for HG. SEMs are a relatively new type of evidence synthesis product but are increasingly recognised for their ability to identify gaps in the literature and informing future research efforts, thereby addressing need and reduce research waste.<sup>127 128</sup>

### Gaps in the literature

In this SEM, substantial gaps in the literature were identified as well as duplicate systematic reviews. For example, only two studies were identified for question four, regarding prevention of HG, suggesting a serious need for original research to address the effect of early or preventative treatment. In total, there were only 25 (5.9%) systematic reviews included, of which 13 contained meta-analysis addressing various topics including *H. pylori*, infant outcomes, diagnostic markers, interventions and medications, psychosocial factors and traditional Chinese therapies. By comparison, an evidence map of social, behavioural and community engagement interventions for reproductive, maternal, newborn and child health, conducted by the WHO in 2017<sup>129</sup> found systematic reviews accounted for 23% of their 612 included studies. Our SEM also identified notable overlap on systematic review topics, specifically

for *H. pylori* in association with HG (two of which were less than 3 years apart,<sup>69 70</sup> and on treatments for NVP/HG, including multiple reviews published in the same year or within 1 year of each other.<sup>14 43 44 79 82 94 130</sup> Five separate recent systematic reviews on treatments or interventions for HG assessed the efficacy of medications and all found that trials to date were small and of low quality and high heterogeneity, and all concluded with the need for large, high quality trials with consistent outcome measures.<sup>14 43 44 130 131</sup> This suggests that researchers are not assessing what is already known and where the gaps are before embarking on new systematic reviews or original research which is a necessary step in reducing research waste.<sup>132</sup> Yet since the publication of these systematic reviews, only one large trial of prednisolone versus placebo has been published and one RCT protocol for mirtazapine versus ondansetron and no others are currently registered with clinicaltrials.gov.<sup>86 96</sup>

### Methods underpinning the literature

Some gaps within the bubble map are unlikely to be filled as some methods would not be appropriate to answer the question, such as using qualitative methods to address the aetiology, while other gaps quite clearly need to be filled with future research, such as RCTs for treatment efficacy. There is a demand for large, well designed RCTs rather than yet more systematic reviews of the same heterogeneous, low-quality studies. However, two more systematic reviews are now registered on PROSPERO to assess the effectiveness of acupuncture for HG, despite all five of the recent systematic reviews published including acupuncture as a treatment and finding conflicting results from low quality studies.<sup>133 134</sup> This problem of redundancy of reviews is not limited to HG. A survey of 73 randomly selected meta-analyses from 2010 found that two-thirds (67%) had at least one duplicate meta-analysis published concurrently within 3 years of the original meta-analysis. This survey found that, on four topics, there were more than eight overlapping meta-analyses with the same subject.<sup>135</sup> While some overlap can be justified and, indeed, necessary for updating and independent replication, the degree of overlap we found in the course of this SEM likely reflects substantial wasted efforts and funds.<sup>135</sup> Registering systematic reviews on PROSPERO, which has been established since 2011, may help to reduce unnecessary duplication.<sup>136</sup> However, only two of the five systematic reviews on treatments we identified had been registered on PROSPERO, which hampers authors in their ability to gain timely awareness of concurrent duplicate efforts.<sup>14 44</sup> A survey of authors who published a systematic review and/or meta-analysis between 2010 and 2016 found almost half (44.9%) did not register their protocols, primarily due to a lack of knowledge of the need and importance of protocol registration.<sup>137</sup> Increasingly journals are requiring registration of protocols, which should begin to raise awareness of the importance of this practice.



## PPI tracking

Like ours, some other SEMs have included PPI in their design, methods, conduction and publication.<sup>138 139</sup> However, they did not extract information on whether the studies they mapped had included PPI and to the best of our knowledge, no other evidence map has specifically extracted data on PPI. The body of evidence in support of PPI in research is ever growing and positive impacts have been found throughout the research process.<sup>26 140 141</sup> It is particularly notable for reducing research waste by ensuring that questions are meaningful and methods appropriate to answer them, improving recruitment and aiding dissemination.<sup>18 26</sup> We hope that this will act as a stimulant for future research to include PPI.

## Strengths and limitations

This was the first SEM on HG and it was conducted from a patient-centred perspective with an innovative approach to evidence synthesis combining two established methods. Another strength of our study is the broad terms used to conduct the search in multiple databases, ensuring a wide net for studies to fall into. We were able to translate 22 foreign language articles, however, we were unable to translate a further 18 articles. We also limited our study to 2009 onwards which on the one hand ensures the map is current, but conversely means that some key studies published prior to 2009 were excluded. While we contacted many authors for full texts that were otherwise unavailable, 17 authors did not reply. Furthermore, we did not contact the authors of conference oral/poster abstracts (n=126) to request if full texts had been published due to resource limitations.

Due to the wide variety of study methods included it was not possible to extract data on population sizes in studies. Additionally, other SEMs extracted data on additional features, which we did not, such as 'open access availability' of published studies which could be useful for researchers using the map.

Although we had clearly defined categories and two researchers conducted the labelling and checked each other to reduce bias, there was a degree of subjectivity when labelling many papers which could fit in multiple categories or did not describe methods explicitly enough to know exactly how to categorise it. Additionally, due to the broad nature of the top 10 questions there was substantial overlap and potential for subjectivity.

Individual questions would benefit from wider searching with individually designed strategies and different methodology. For example, research addressing question 10 may exist within the wider field of pregnancy nutrition and epidemiological studies of antiemetics that address question seven may not have shown up in our HG specific search. We took a pragmatic approach to inclusion of research where participants are described as having HG or clearly defined severe NVP. Differences in HG or severe NVP diagnosis leads to heterogeneity in included studies and hampers aggregation of evidence, as previously demonstrated.<sup>142</sup> Hopefully the publication of the internationally agreed

Windsor definition for HG the next decade will enhance research homogeneity and reduce waste.<sup>143</sup>

Many of the individual questions would benefit from having the quality of their available evidence appraised, however, due to the nature of SEMs,<sup>127</sup> we did not attempt to quality assess included studies, which can be seen as a limitation.

## CONCLUSIONS

This SEM provides an overview of the current evidence addressing the top 10 priority questions for HG. While all the questions have at least two papers addressing them, all questions remain unanswered and would benefit from either original research or systematic review. The SEM presents a useful, interactive tool for researchers seeking to address one of these questions and could save valuable finite resources to justify, or rule out, planned studies. The SEM highlights significant gaps in the literature, requiring original research, particularly in the fields of cure and prevention of HG as well how to address the nutritional challenges of HG. We aim for this SEM to be updated annually through the International Collaboration on Hyperemesis Gravidarum.

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