BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

Sick leave and medication use in pregnancy - a European web-based study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014934
Article Type:	Research
Date Submitted by the Author:	28-Oct-2016
Complete List of Authors:	Truong, Bich; University of Oslo, School of Pharmacy, PharmacoEpidemiology and Drug Safety Research Group Lupattelli, Angela; University of Oslo, School of Pharmacy, PharmacoEpidemiology and Drug Safety Research Group Kristensen, Petter; National Institute of Occupational Health; Univeristy of Oslo, Institute of Health and Society Nordeng, Hedvig; University of Oslo, School of Pharmacy, PharmacoEpidemiology and Drug Safety Research Group; Norwegian Institute of Public Health,
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Sick leave, Maternal medicine < OBSTETRICS, PUBLIC HEALTH, Pregnancy

SCHOLARONE™
Manuscripts

For peer review only

Sick leave and medication use in pregnancy - a European web-based study

Bich Thuy Truong,[1] Angela Lupattelli,[1] Petter Kristensen,[2,3] Hedvig Nordeng[1,4]

[1]PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway

[2]National Institute of Occupational Health, Oslo, Norway

[3]Institute of Health and Society, University of Oslo, Oslo, Norway

[4]Norwegian Institute of Public Health, Oslo, Norway

Corresponding author

Bich Thuy Truong, MScPharm

School of Pharmacy, University of Oslo

Sem Sælands vei 3, 0371 Oslo, Norway

E-mail: b.t.h.truong@farmasi.uio.no

Tel.: +47 98 42 68 20

Keywords: Sick leave, maternal medicine, pregnancy, public health

Running title: Sick leave and medication use in pregnancy

Word count (excluding title page, abstract, references, figures and tables): 3983

For peer review only

ABSTRACT

Background and objective: Inter-country comparability of sick leave in pregnancy is difficult since most studies have been conducted on individual country level in Scandinavia. The objective of this study was to explore patterns of and reasons for sick leave during pregnancy on a multinational level, focusing on medication use but also the differences in sick leave schemes.

Design and setting: Cross-sectional, web-based study in 12 European countries within the period of October 2011 to February 2012. Data were collected via an electronic questionnaire.

Participants: Pregnant women and mothers of children under the age of one year.

Primary outcome measure: Sick leave prevalence in pregnancy.

Results: Of 6686 women included, 3385 (50.6%) had been on sick leave during pregnancy. The rates of sick leave varied across countries, ranging from 31.7-34.8% in Sweden and the United Kingdom, to 62.4-71.3% in Norway, Serbia, Croatia and Poland. The most common reasons for being on sick leave were pregnancy complications (26.5%), pain in the neck, back or pelvic girdle (16.2%), and nausea and vomiting (NVP, 16.0%). Women using medications for NVP, pain or sleeping problems were more likely to be on sick leave during pregnancy compared to women not experiencing these conditions (adjusted odds ratio (aOR): 1.59, 95% confidence interval (95% CI): 1.31-1.92, aOR: 1.24, 95% CI: 1.04-1.49 and aOR: 1.82, 95% CI: 1.17-2.82 respectively). Women from countries with "Low" sick leave schemes were less likely to have multiple sick leaves compared to women from countries with "Medium" schemes (aOR: 0.63, 95% CI: 0.49-0.82).

Conclusion: The rates of sick leave in pregnancy vary greatly across European countries. Women using medications for NVP, pain or sleeping problems were more likely to be on sick leave. The differences in sick leave patterns across countries could only to a limited extent reflect the differences in sick leave schemes.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection methodology, allowing inter-country comparison of sick leave in pregnancy.
- Insights into patterns of sick leave in pregnancy for countries outside Scandinavia.
- No detailed information about sick leave, i.e. exact timing, duration and whether it was part-time or full-time.
- A web-based survey as a study method impedes calculation of a conventional response rate and may cause selection bias of the target population.
- Self-report data on dependent and independent variables.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Multiple studies conducted in Scandinavia have identified generally high rates of sick leave among pregnant women (range 48.0-67.7%),[1-5] and pregnancy-related conditions, such as back pain and nausea and vomiting (NVP), were found to be the most common reasons for sick leave.[3, 4, 6, 7] Sick leave in pregnancy may also be required on the basis of risky occupational exposures or work related duties that may negatively impact pregnancy outcomes.[8-11] Interestingly, research on sick leave in pregnancy is almost non-existing for countries outside Scandinavia, which makes inter-country comparison challenging. Taken into consideration the high extent of sick leave seen in the Scandinavian countries, it is crucial to gain knowledge about patterns and factors associated with sick leave during pregnancy in order to initiate preventive measures. Such knowledge would not only be a huge economic interest for the society, but it would also be beneficial for clinicians/physicians who encounter pregnant women in antenatal care. It also calls for attention to elucidate patterns of sick leave among pregnant women in other European countries as such knowledge can contribute to a better understanding of maternal health across countries. National differences in work participation by women of fertile age, as well as thresholds and attitudes towards sick leave may differ across countries despite the presence of the same diseases/conditions among pregnant women.[12, 13]

The concept of paid sick leave is included in most Western countries welfare systems and it is intended to provide employees with financial protection during sickness and disability.[14] However, the qualifications for receiving sick leave benefits vary greatly between countries. The World Health Organization (WHO) has described the concept of paid sick leave from a global perspective, revealing that 145 countries provide paid sick leave and that the wage replacement ranges between lump sums in 14.0% of the countries, to 100% of wages in 21.0% of the countries.[14]

Many medical conditions occur during pregnancy and pregnant women may need medical treatment to ensure maternal-fetal health.[15] However, pregnant women tend to overestimate the teratogenic risk associated with medication treatment,[16] which can result in untreated conditions due to fear of harming the unborn child.[17] As some untreated maternal conditions e.g. diabetes and epilepsy, can pose a risk to the fetus, it is essential that pregnant women are empowered to make safe decision about treatment options in pregnancy.[15] Furthermore, none

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of the previous studies above have distinguished between treated and untreated conditions among pregnant women in relation to sick leave. Sociodemographic and lifestyle factors, such as age, gender and education,[18] self-reported health[19] and work-related conditions[4, 20-22] have been described as potential determinants of sick leave in general, but no previous studies have investigated the extent of sick leave in pregnancy with respect to maternal medication use. The role of medication use in relation to sick leave in pregnancy therefore remains elusive.

The objective of the study was to describe patterns of and reasons for sick leave in pregnancy on a multinational European level, focusing on maternal illnesses and related medication use. In addition, we explored sick leave in relation to the differences in European sick leave schemes.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS

Study design, data collection and study population

This is a sub-study of the "Multinational Medication Use in Pregnancy Study", a cross-sectional, web-based study carried out in Europe, North and South America, and Australia in the period of October 2011 to February 2012, with the purpose to investigate patterns of medication use in pregnancy. The study has been described in detail elsewhere.[23] In brief, member countries of the European Network of Teratology Information Services (ENTIS), Organization of Teratology Information Specialist (OTIS) in North and South America, Mothersafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated. Data was collected via an anonymous, self-administrated, questionnaire (www.questback.com), accessible in each participating country for two months in the period mentioned above. The full questionnaire has previously been published.[23] Invitation to participate in the study (presented as banner/ads) was available on 2-3 national pregnancy-related web pages and/or social networks, selected according to the number of daily users in each participating country. Pregnant women at any gestational age and new mothers of children under the age of one year were eligible for inclusion. The women were instructed to answer the questions related to their current or latest pregnancy. Detailed information regarding recruitment tools utilized and internet penetration rates on individual country level have been described previously.[23]

This sub-study sample was restricted to women with residence in European countries only. Eligible countries were divided into three regions: 1) Western Europe: Austria, France, Italy, Switzerland, the Netherlands and the United Kingdom (UK), 2) Northern Europe: Iceland, Finland, Norway and Sweden and 3) Eastern Europe: Croatia, Poland, Russia, Serbia and Slovenia. Unemployed women, women from European countries with less than 100 participants and women who did not answer the question "Have you been on sick leave during this pregnancy?" were excluded (Supplementary figure 1).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Measures

Sick leave during pregnancy

Our main outcome measure was sick leave during pregnancy. All women were asked to state whether or not they had been on sick leave during pregnancy (yes/no). Women answering "yes" could also report the reason(s) for being on sick leave as free-text entries (Supplementary table 1) and the trimester when the sick leave occurred (weeks 0-12, 13-24 and/or 25 – delivery, which correspond to first, second and third trimester respectively). The rates of overall sick leave consist of women who reported to have been on sick leave in at least one trimester. The extension of sick leave indicates the number of women being on sick leave in more than one trimester.

Illnesses and related medication use

Maternal illnesses and related medication use during pregnancy were the main independent variables in this study. Participants were presented with a list of nine common acute pregnancy-related conditions (i.e. common cold, constipation, heartburn and reflux problems, headache, NVP, other infections, pain in the neck, back or pelvic girdle, sleeping problems and urinary tract infection) and nine chronic conditions (i.e. allergy, anxiety, asthma, depression, diabetes, epilepsy, hypothyroidism, cardiovascular and rheumatic disorders). In addition, the women could report as a free text if she had any other chronic conditions not previously listed. Women confirming to have experienced any condition were asked to report any related medication use as a free-text entry. For the acute pregnancy-related conditions we mainly focused on NVP, pain and sleeping problems. The chronic conditions were categorized as no conditions, somatic conditions only and any mental conditions (anxiety and depression), i.e. women with both somatic and mental conditions were categorized in the mental group.

The questionnaire also included a list of common over-the-counter (OTC) medication groups (i.e. analgesics, nasal spray/drops, antacids, antiemetics and laxatives) and participants could report whether these OTC medications were used. Women reporting any medication use were asked to specify the timing of usage according to pregnancy weeks (weeks 0-12, 13-24 and 25 – delivery). Medication use did not include vitamins, mineral supplements and herbal or supplementary products.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Each country's sick leave scheme categorization was in addition an independent variable of interest. The schemes were categorized into "High", "Medium" or "Low" based on the percentage of wages replacement during sick leave and the number of waiting days prior to wage replacement in each country. Information from "Social Security Programs Throughout the World 2012" was used in the categorization.[24] The categorization criteria were: "High"; Full (100%) wage replacement for everyone and no waiting days, "Medium"; 60-100% wage replacement and no waiting days and "Low"; <100% wage replacement and 1-3 waiting days.

Maternal sociodemographic and lifestyle factors

Several maternal characteristics and health related factors were assessed as potential confounders as they may be risk factors for sick leave in pregnancy and also be associated with medication use in pregnancy and country of residence and hence sick leave scheme. These variables included age, maternal status (pregnant or mother of the time of awnsering the questionnaire), parity, marital status, employment status, highest level of education, folic acid use before and/or during pregnancy, smoking during pregnancy, alcohol consumption after awareness of pregnancy and whether or not the pregnancy was planned or secondarily to infertility treatment. These variables were categorized as presented in Table 1.

Ethics

The study was approved by the South-East Regional Ethics Committee in Norway. Additional ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by the national legislation. Informed consent was considered given when the women answered "Yes" to the question "Are you willing to participate in the study?" before accessing the online questionnaire. All data were handled and stored anonymously.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Statistical analysis

Descriptive analyses on the prevalence of sick leave, by timing in gestation and country of residency, as well as reasons for being on sick leave were performed. The Chi-square and the Fisher's exact test were used to compare women's sociodemographic, lifestyle and pregnancy related factors according to overall prevalence of sick leave and the extension of sick leave during pregnancy. Univariate and multivariate Generalized Estimating Equation (GEE) with logit link function accounting for clustering on country level was used to estimate the association of: 1) Maternal medication use and 2) Sick leave scheme categorization with: a) Overall sick leave during pregnancy (yes/no) and b) Extension of sick leave in pregnancy (in one trimester only/in any two or all three trimesters). The associations were presented as crude (OR) and adjusted odds ratios (aOR) with 95% confidence interval (95% CI). All potential confounders presented in Table 1 were first entered in the multivariate models. Then, the multivariate models were fitted by removing all variables having no role in the model, i.e. variables yielding <10% change of the beta coefficients of the independent variables (i.e., medication use and sick leave scheme categorization). The final multivariate models contained covariates as shown in Table 3. Since only new mothers had full overview of the pregnancy in relation to sick leave in this study, a sensitivity analysis restricted to this group was conducted. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using the Data Analysis and Statistical Software Stata/MP version 14.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

RESULTS

Population characteristics

A total of 9615 women replied to the informed consent question after reading the study description. Of these, 9483 (98.7%) completed the online questionnaire. This sub-sample was restricted to 6686 (69.5%) women from 12 European countries; Croatia, Finland, France, Italy, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland and the UK. Flowchart of women who met the inclusion and exclusion criteria for this final study sample, along with the number of participants from each country is summarized in Supplementary figure 1. Maternal health and lifestyle factors, sick leave scheme categorization for each country and sociodemographic characteristics of the study sample in relation to sick leave are summarized in Table 1.

Fifty-two percent (n=3486) of the included women were pregnant at the time of accessing and answering the questionnaire, while the remaining were new mothers of children under the age of one year (n=3200). Pregnant women were often younger and primiparous compared to new mothers (Supplementary table 2). The average gestation week (GW) among pregnant women were 23 (range 1-42), while almost half (48.5%) of the new mothers had a child over 6 months of age. Detailed information regarding maternal status and GW on individual country level is presented in Supplementary table 3.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1 Maternal health and lifestyle factors, sociodemographic characteristics and sick leave scheme categorization in relation to sick leave in pregnancy.

	Total population n=6686	Sick leave in pregnancy		No sick leave versus sick leave
		No (n=3301)	Yes (n=3385)	
Health and lifestyle factors	n (%)	n (%)	n (%)	P-value
Alcohol in pregnancy*				
Yes	1069 (16.0)	562 (17.0)	507 (15.0)	0.022
No	5562 (83.2)	2707 (82.0)	2854 (84.4)	
Smoking in pregnancy*				
Yes	539 (8.1)	235 (7.1)	304 (9.0)	0.005
No	6133 (91.7)	3061 (92.7)	3072 (91.0)	
Infertility treatment				
Yes	476 (7.1)	181 (5.5)	295 (8.7)	<0.001
No	6210 (92.9)	3120 (94.5)	3090 (91.3)	
Folic acid use*				
Yes	6151 (92.6)	3020 (92.3)	3131 (93.0)	0.300
No	489 (7.4)	252 (7.7)	237 (7.0)	
Medication for chronic indications				
Yes	1371 (20.5)	577 (17.5)	794 (23.5)	<0.001
No	5315 (79.5)	2724 (82.5)	2591 (76.5)	
Medication for acute indications				
Yes	5254 (78.6)	2465 (74.7)	2789 (82.4)	<0.001
No	1432 (21.4)	836 (25.3)	596 (17.6)	
Number of acute conditions				
Mean (SD), range 0-9	4.2 (1.6)	3.9 (1.6)	4.4 (1.5)	<0.001
Chronic conditions				
No chronic conditions	5279 (79.0)	2708 (51.3)	2571 (48.7)	<0.001
Somatic conditions	1167 (17.5)	507 (43.4)	660 (56.6)	
Mental conditions	240 (3.6)	86 (35.8)	154 (64.2)	
Country of residence				
Paid sick leave scheme**				
High	1179 (17.6)	443 (37.6)	736 (62.4)	<0.001
Medium	3128 (46.8)	1494 (47.8)	1634 (52.2)	
Low	2379 (35.6)	1364 (57.3)	1015 (42.7)	
Region of residence				
Western Europe	2379 (35.6)	1364 (41.3)	1015 (30.0)	<0.001
Northern Europe	2351 (35.2)	1133 (34.3)	1218 (36.0)	
Eastern Europe	1956 (29.3)	804 (24.4)	1152 (34.0)	
Sociodemographic and maternal characteristics				
Maternal age (years)				
≤20	168 (2.5)	107 (3.2)	61 (1.8)	0.001
21-30	3704 (55.4)	1792 (54.3)	1912 (56.5)	
31-40	2698 (40.4)	1344 (40.7)	1354 (40.0)	
≥41	116 (1.7)	58 (1.8)	58 (1.7)	
Marital status				
Married/cohabitant	6375 (95.4)	3132 (94.9)	3243 (95.8)	0.073
Single/divorced/other	311 (4.7)	169 (5.1)	142 (4.2)	

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Employment*				
Employed in other sectors	4893 (73.3)	2356 (71.6)	2537 (75.0)	<0.001
Healthcare personnel	1,088 (16.3)	445 (13.5)	643 (19.0)	
Student	695 (10.4)	492 (14.9)	203 (6.0)	
Highest level of education				
Primary school	191 (2.9)	97 (2.9)	94 (2.8)	0.438
High-school	1736 (26.0)	845 (25.6)	891 (26.3)	
University or college	3,985 (59.6)	1994 (60.4)	1991 (58.8)	
Other education	774 (11.6)	365 (11.1)	409 (12.1)	
Maternal status at the time of answering the questionnaire				
New mothers	3200 (47.9)	1432 (44.8)	1768 (55.3)	<0.001
Pregnant in 1st trimester	724 (10.8)	511 (70.6)	213 (29.4)	
Pregnant in 2nd trimester	1177 (17.6)	642 (54.6)	535 (45.5)	
Pregnant in 3rd trimester	1585 (23.7)	716 (45.2)	869 (54.8)	
Primiparious				
Yes	3603 (53.9)	1830 (55.4)	1773 (52.4)	0.012
No	3083 (46.1)	1471 (44.6)	1612 (47.6)	
Pregnancy planned*				
Yes	4657 (69.9)	2229 (67.7)	2428 (72.0)	0.001
No, but expected	1491 (22.4)	788 (23.9)	703 (20.8)	
No	519 (7.8)	277 (8.4)	242 (7.2)	

*Total numbers do not add up due to missing values; folic acid n=46 (0.7%), employment n=10 (0.2%), alcohol in pregnancy n=55 (0.8%), smoking in pregnancy n=14 (0.2%) and pregnancy planned n=19 (0.3%). **__High__; Norway, __Medium__; Croatia, Finland, Poland, Russia, Serbia, Slovenia and Sweden, and __Low__; Italy, France, the United Kingdom and Switzerland.

Sick leave during pregnancy

A total number of 3385 (50.6%) women had been on sick leave at some point in pregnancy, with a higher reported rate among new mothers (55.3%) than in the pregnant women (46.4%). The prevalence of sick leave in each individual country is presented in Figure 1. The proportions of women being on sick leave in first, second and/or third trimester were 38.5%, 48.1% and 52.1% respectively. Most women (64.1%) had been on sick leave in one trimester only (n=2170), whereas 32.3% (n=1095) had been in any two or all three trimesters. Timing of sick leave for the remaining 120 women (0.04%) was unknown.

The rates of overall prevalence and the extension of sick leave in each individual country are presented in Supplementary table 4. The most common reasons for being on sick leave were pregnancy complications (26.0%), pain in the neck, back or pelvic girdle (16.2%) and NVP (16.0%) (Figure 2). Reasons for sick leave were categorized into the 16 most prevalent categories as shown in Supplementary table 1.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Illnesses and related medication use

Women on sick leave had a significantly higher number of reported acute conditions (mean (SD): 4.4 (1.5) vs 3.9 (1.6), p<0.001) and chronic conditions (0.7 (0.6) vs 0.2 (0.5), p<0.001) compared to women not being on sick leave. The same trends were seen among women with multiple sick leaves and medicated women compared to women being on sick leave in one trimester only and non-medicated women respectively (data not shown).

Women medicated for NVP, pain or sleeping problems had significantly higher rates of being on sick leave due to the indication of medication use compared to non-medicated women with the same conditions (Table 2). These women had also higher rates of sick leave due to any reason (data not shown).

Table 2 Proportions of women being on sick leave due to nausea and vomiting (NVP), pain or sleeping problems according to medication use to the mentioned conditions.

Conditions	Total	Sick leave due to the mentioned condition		Yes vs No P-value
		Yes	No	
NVP, n (%)	4841	535 (11.1)	4306 (89.0)	
Medicated, n (%)	781	186 (23.8)	595 (76.2)	<0.001
Non-medicated, n (%)	4060	349 (8.6)	3711 (91.4)	
Pain*	5396	858 (15.9)	4538 (84.1)	
Medicated, n (%)	3320	631 (19.0)	2689 (81.0)	<0.001
Non-medicated, n (%)	2076	227 (10.9)	1849 (89.1)	
Sleeping problems	3748	198 (5.3)	3550 (94.7)	
Medicated, n (%)	105	11 (10.5)	94 (90.0)	0.016
Non-medicated, n (%)	3643	187 (5.1)	3456 (94.9)	

*Reasons for sick leave categorized as pain in the neck, back or pelvic girdle, other pain and headache.

Within the group of women medicated for NVP (n=781), almost half (45.1%) were treated with antihistamines (both first and second generation), while 24.7% were treated with metoclopramide, domperidone or bromopride. The remaining women (30.3%) were treated with other medications. Women using other medications for NVP had a significantly lower rate of being on sick leave due to NVP (14.5%) compared to women using antihistamines (51.1%), or metoclopramide, domperidone or bromide (34.4%, p<0.001). However, there was no significant difference in sick leave due to NVP between women using antihistamines and women using metoclopramide, domperidone or bromide (p=0.130). The same trends were seen among women medicated for any pain (pain in the neck, back or pelvic girdle, headache or other pain, n=3320). Paracetamol (including combinations), non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic (including combinations) were the most

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

used medications for this indication and were used by 2829 (85.6%), 279 (7.4%) and 97 (2.6%) women respectively. Women using other medications than those mentioned for pain had significantly lower rates of sick leave due to pain (4.9%) compared to women using paracetamol (19.3%) or NSAIDs (19.3%, p<0.001).

Sick leave schemes

The categorization of countries according to sick leave schemes was as follows: "High"; Norway (n=1179), "Medium"; Croatia, Finland, Poland, Russia, Serbia, Slovenia and Sweden (n=3128), and "Low"; Italy, France, the UK and Switzerland (n=2379). Women from countries with "High" sick leave schemes had the highest rates of both overall prevalence and extensions of sick leave.

Factors associated with sick leave

Women using medications for NVP, pain or sleeping problems were more likely to be on sick leave during pregnancy compared to women not experiencing the conditions (aOR: 1.59, 95% CI: 1.31-1.92, aOR 1.24, 95% CI: 1.04-1.49 and aOR: 1.82, 95% CI: 1.17-2.82, respectively). Maternal medication use for NVP was in addition significantly associated with sick leave in more than one trimester (aOR: 1.76, 95% CI: 1.36-2.31). Women from countries with "Low" sick leave schemes were less likely to have multiple sick leaves in pregnancy compared to women from countries with "Medium" sick leave schemes (aOR: 0.63, 95% CI: 0.49-0.82). Crude and adjusted ORs for all variables are shown in Table 3.

Sensitivity analysis

In the sensitivity analysis restricted to new mothers the magnitude of the association between medication use for pain (compared to not experiencing pain) and sick leave was 47.3% lower than the one observed in the main analysis and were no longer significant. Medication use for sleeping problems was also no longer significantly associated with sick leave in pregnancy. The remaining factors associated with overall sick leave in pregnancy and the corresponding ORs were mainly the same (±20%) (data not shown).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3 Independent variables and the association with sick leave during pregnancy, presented as crude (OR) and adjusted odds ratios (aOR) with 95% confidence interval (95% CI).

Independent variables	Sick leave during pregnancy			
	Yes vs no		In any two or all three trimesters vs any one trimester only	
Medication use for chronic indications	**OR** (95% CI)	**aOR**[1] (95% CI)	**OR** (95% CI)	**aOR**[2] (95% CI)
Yes	1.47 (1.31-1.66)	1.16 (0.89-1.40)	1.53 (1.29-1.81)	1.00 (0.72-1.39)
No	Reference	Reference	Reference	Reference
Nausea and vomiting (NVP)	**OR** (95% CI)	**aOR**[3] (95% CI)	**OR** (95% CI)	**aOR**[1] (95% CI)
No	Reference	Reference	Reference	Reference
NVP non-medicated	1.27 (1.14-1.42)	0.94 (0.83-1.06)	1.26 (1.05-1.51)	0.96 (0.78-1.18)
NVP medicated	2.29 (1.92-2.72)	1.59 (1.31-1.92)	2.30 (1.81-2.94)	1.76 (1.36-2.31)
Pain	**OR** (95% CI)	**aOR**[3] (95% CI)	**OR** (95% CI)	**aOR**[4] (95% CI)
No	Reference	Reference	Reference	Reference
Pain non-medicated	1.65 (1.36-1.99)	1.19 (0.99-1.42)	1.42 (1.05-1.92)	1.09 (0.79-1.51)
Pain medicated	2.08 (1.78-2.41)	1.24 (1.04-1.49)	1.96 (1.46-2.62)	1.29 (0.92-1.79)
Sleeping problems (SP)	**OR** (95% CI)	**aOR**[3] (95% CI)	**OR** (95% CI)	**aOR**[5] (95% CI)
No	Reference	Reference	Reference	Reference
SP non-medicated	1.48 (1.32-1.66)	1.32 (1.19-1.46)	1.25 (1.07-1.46)	1.12 (0.95-1.32)
SP medicated	2.78 (1.83-4.21)	1.82 (1.17-2.82)	1.91 (1.82-3.08)	1.32 (0.79-2.21)
Sick leave scheme categorization	**OR** (95% CI)	**aOR**[6] (95% CI)	**OR** (95% CI)	**aOR**[7] (95% CI)
High	1.35 (0.56-3.27)	1.12 (0.46-2.74)	1.46 (1.06-2.02)	1.31 (0.95-1.81)
Medium	Reference	Reference	Reference	Reference
Low	0.68 (0.40-1.13)	0.60 (0.35-1.05)	0.64 (0.50-0.83)	0.63 (0.49-0.82)

Missing data <5% as presented in Table 1.
[1]Adjusted for all variables as in 2 with the exceptions of maternal age, folate use and parity.
[2]Adjusted for maternal status, employment, education, smoking in pregnancy, infertility treatment, acute conditions, chronic conditions, planned pregnancy, maternal age, folate use, alcohol in pregnancy, parity and marital status.
[3]Adjusted for all variables as in 2 with the exceptions of maternal age, folate use, alcohol in pregnancy and marital status.
[4]Adjusten for all variables as in 2 with the exceptions of maternal age and marital status.
[5]Adjusted for all variables as in 2 with the exceptions of maternal age, folate use, parity and marital status.
[6]Adjusted for all variables as in 2 with the exceptions of parity.
[7]Adjusted for all variables as in 2 with the exceptions of planned pregnancy, maternal age and folate use.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

To our knowledge, this is the first study investigating patterns of sick leave in pregnancy on a multinational level, focusing on maternal medication use. The results indicate that the rates of sick leave in pregnancy vary greatly within Europe, ranging from 31.7% in Sweden to 71.3% in Poland. The most common reason for sick leave was pregnancy complications, but the most frequent reason did differ according to country and region of residence. Women using medications for NVP, pain or sleeping problems were more likely to be on sick leave during pregnancy compared to women not experiencing the conditions. Residence in countries with "Low" sick leave schemes seems to decrease the likelihood of multiple sick leaves.

Eastern Europe had the highest rates of work-related sick leave, but had on the other hand, lowest rates of sick leave due to pain and NVP (Supplementary table 4). These findings may reflect the differences in women's perception towards own health[19] and the need of sick leave during pregnancy. Women on long-term sick leave seem to have a lower self-rated health, as well as lower quality of life compared to women not on sick leave or on short-term sick leave.[19] Studies have also shown that there is also a great variety in physicians practice in prescribing sick leave,[13] where clinical specialist tend to prescribe shorter sick leave compared to general practitioners and more sick days are often prescribed in smaller municipalities than larger ones.[12] A difference in sick leave prescribing practice between European countries are therefore plausible. We had no information regarding the prescribing physician, the number of sick days prescribed, nor if the women were from a suburban or urban area which may have contributed to the differences in patterns of sick leave seen in this study.

Women medicated for NVP, pain or sleeping problems had an increased likelihood of being on sick leave during pregnancy compared to non-medicated women with the same conditions (Table 2). These conditions are common pregnancy-related conditions and previous studies have shown that they can have a huge impact on pregnant women's daily activities, such as walking, standing or changing position, as well as quality of life.[3, 25, 26] A possible explanation for our findings is that medicated women may have had a more severe condition and hence be more disabled compared to non-medicated women. As such, medication use may be a proxy for the severity of the conditions.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Our results suggest that sick leave schemes may have an impact on both the rates and the extensions of sick leave, especially in countries with limited benefits. A "High" sick leave scheme was not significantly associated with increased rates of sick leave compared to "Medium" sick leave schemes. Interestingly, "Low" sick leave schemes seems to decrease the likelihood of being on multiple sick leaves in pregnancy even after adjusting for maternal characteristics and sociodemographic and lifestyle factors. These findings are consistent with a report from WHO which states that countries with a medium scope of benefits had the highest number of sick leave days in Europe.[14] However, there was no doubt that countries with limited benefits had the lowest rates of sick leave like in our study.

We found that the majority of women on sick leave were so during the last trimester in alignment with a study conducted in Sweden.[2] However, in countries like Russia and the UK maternity leave can be taken in the beginning of the third trimester and during the second trimester, respectively, which may explain the relatively low rates of sick leave seen in these countries compared to other countries in this study. The Swedish study did also report that a large proportion of pregnant women were on maternity leave during the last trimester.[2] An underestimation of sick leave rates in the third trimester in these countries can therefore not be ruled out.

The main strength of this study lies in the large sample size and the uniform data collection methodology utilized across all participating countries, allowing inter-country comparison of sick leave in pregnancy. Our estimates of sick leave could be estimated with a precision whitin ±5.0% in each country with the exception of France, Croatia, Serbia and Slovenia where the precision ranged from ±6-8%. We had detailed information regarding maternal health, including medication use and co-morbidities which could be risk factors for sick leave in pregnancy. In addition, we took into consideration the differences in sick leave schemes across the participating countries using external sources. Our previous study have also shown that the study sample were sufficiently representative of the general birthing population in each individual country with regards to age and smoking habits. However, they had on average a higher level of education and were more likely to be primiparous.[23]

The limitations of this study include the lack of detailed information regarding sick leave in pregnancy, i.e. exact timing, duration and whether if it was part-time or full-time sick leave. Also, we were not able to distinguish between sick leave among women employed in private

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

and public sectors. Considering that differences in benefit scheme in the different sectors could affect sick leave rates, a distinguishing of these sectors could have yielded another sick leave pattern. The categorization of the sick leave schemes was also solely based on the percentage of wage replacement and the number of waiting days prior to wage replacement. It is conceivable that other factors also should have been taken into consideration in such a categorization, e.g. the scope of maternity leave and the number of days prior to due date this leave can be taken. Moreover, data was collected via a questionnaire posted on web-pages and social networks and hence a conventional response rate could not be calculated. However, there are examples of web-based recruitment methods that show reasonable validity in epidemiology studies.[27, 28] Furthermore, the web-recruitment approach could introduce the possibility of selection bias as only women with internet access and women who visited the web-pages where the invitation to participate were posted could participate. However, some studies have showed that a large proportion of pregnant women tend to use the internet, including discussion forums and social networks, when in need of pregnancy information.[29, 30] Also, internet access in households in our European target population were generally high in 2012, ranging from 63.0% in Italy to 93.0% in Norway.[31] Another limitation of our study is that all data were self-reported and therefore depended on the women´s perception and recall rather than validated data. The use of medications and sick leave during pregnancy may have been underestimated due to recall bias, especially among women who were not pregnant at the time of answering the questionnaire. A study showed that retrospectively self-reported sick leave data due to musculoskeletal diseases has been found to be sufficient when compared to registered sick leave.[32] However, other studies have reported discrepancies of sick leave rates in self-reported data when compared to register data, especially for long-term sick leave.[33, 34] The inclusion of pregnant women at any gestation may also have underestimated the rates of sick leave as women in early gestation may have not had the chance to be on sick leave at the time of answering the questionnaire but later on in pregnancy. As shown in the sensitivity analysis, restricted to new mothers only, the association between maternal medication use for pain and sleeping problems were no longer significantly associated with sick leave in pregnancy. Also, the French and the Russian study sample represented a small proportion of the general birthing in France and Russia, respectively and hence the generalizability of our results should be interpreted with caution especially in those countries.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

CONCLUSION

A large proportion of pregnant women were on sick leave during pregnancy, but the rates varied greatly across European countries. Maternal medication use for NVP, pain and sleeping problems were associated with sick leave in pregnancy, most likely because medication use is a proxy for the severity of the conditions. The differences in sick leave patterns across European countries could only to a limited extent reflect the differences in each country's sick leave scheme, which implies that sick leave in pregnancy is also affected by other national differences.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Acknowledgement The authors would like to thank the Organisation of Teratology Information Servises (OTIS), the European Network of Teratology Information Services (ENTIS) Scientific Board and website providers who contributed to the recruitment phase of the main study "Medication Use in Pregnancy: a cross-sectional, multinational web-based study". They would also like to thank all study national coordinators (Twigg MJ, Zagorodnikova K, Mårdby AC, Moretti ME, Drozd M, Panchaud A, Hameen-Anttila K, Rieutord A, Gjergja Juraski R, Odalovic M, Kennedy D, Rudolf G, Juch H, Passier JLM and Björnsdóttir I). They are greatful to all the women who took part of this study.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

A funding statement The main study was supported by the Norwegian Research Council grant number 216771/F11, the Foundation for Promotion of Norwegian Pharmacies and the Norwegian Pharmaceutical Society.

Contributors AL and HN conceived the idea and participated in the design and coordination of the main study. BT performed the initial analysis, with AL contributing substantially to the final analysis for this sub-study. BT drafted the first manuscript. AL, PK and HN contributed to the interpretation of the results and revised the manuscript critically for important intellectual content. All authors have read and approved the final version of the manuscript and are in agreement to be accountable for all aspects of the work.

Data sharing statement No additional data are available. Researchers can apply for data access for sub-projects within the overall aims of the main study "The Multinational Medication Use in Pregnancy Study".

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

REFERENCES

1 Sydsjo A, Sydsjo G, Kjessler B. Sick leave and social benefits during pregnancy-a Swedish-Norwegian comparison. *Acta Obstet Gynecol Scand* 1997;76(8):748-54.

2 Mogren I. Perceived health, sick leave, psychosocial situation, and sexual life in women with low-back pain and pelvic pain during pregnancy. *Acta Obstet Gynecol Scand* 2006;85(6):647-56.

3 Malmqvist S, Kjaermann I, Andersen K, et al. The association between pelvic girdle pain and sick leave during pregnancy; a retrospective study of a Norwegian population. *BMC Pregnancy and Childbirth* 2015;15:237.

4 Dorheim SK, Bjorvatn B, Eberhard-Gran M. Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. *Bjog* 2013;120(5):521-30.

5 Robinson HS, Eskild A, Heiberg E, et al. Pelvic girdle pain in pregnancy: the impact on function. *Acta Obstet Gynecol Scand* 2006;85(2):160-4.

6 Heitmann K, Holst L, Lupattelli A, et al. Treatment of nausea in pregnancy: a cross-sectional multinational web-based study of pregnant women and new mothers. *BMC Pregnancy Childbirth* 2015;15(1):321.

7 Sivertsen B, Hysing M, Dorheim SK, et al. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. *BMC Pregnancy Childbirth* 2015;15:129.

8 Khojasteh F, Arbabisarjou A, Boryri T, et al. The Relationship between Maternal Employment Status and Pregnancy Outcomes. *Glob J Health Sci* 2016;8(9):53533.

9 Xu G, Wu Y, Yang L, et al. Risk factors for early miscarriage among Chinese: a hospital-based case-control study. *Fertility and Sterility* 2014;101(6):1663-70.

10 Axelsson G, Rylander R, Molin I. Outcome of pregnancy in relation to irregular and inconvenient work schedules. *British Journal of Industrial Medicine* 1989;46(6):393-8.

11 Bodin L, Axelsson G, Ahlborg G, Jr. The association of shift work and nitrous oxide exposure in pregnancy with birth weight and gestational age. *Epidemiology* 1999;10(4):429-36.

12 Kankaanpaa AT, Franck JK, Tuominen RJ. Variations in primary care physicians' sick leave prescribing practices. *Eur J Public Health* 2012;22(1):92-6.

13 Rudbeck M. Variation in patients' sick leave between general practitioner practices. *Scand J Public Health* 2014;42(7):621-6.

14 Scheil-Adlung X, Sandner L. The case for paid sick leave - Word Health Report Background Paper No. 9 2010 [Date accessed: October 2016 http://www.who.int/healthsystems/topics/financing/healthreport/SickleaveNo9FINAL.pdf?ua=1].

15 Nordeng H. Drug utilization in pregnant women. In: Elseviers M, Wettermakr B, Almarsdottir A, et al., eds. Drug Utilization Research Methods and Applications. West Sussex, UK: Wiley-Blackwell 2016:240-7.

16 Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2010;66(2):207-14.

17 Petersen I, McCrea RL, Lupattelli A, et al. Women's perception of risks of adverse fetal pregnancy outcomes: a large-scale multinational survey. *BMJ Open* 2015;5(6):e007390.

18 Dekkers-Sanchez PM, Hoving JL, Sluiter JK, et al. Factors associated with long-term sick leave in sick-listed employees: a systematic review. *Occup Environ Med* 2008;65(3):153-7.

19 Eriksson HG, von Celsing AS, Wahlstrom R, et al. Sickness absence and self-reported health a population-based study of 43,600 individuals in central Sweden. *BMC Public Health* 2008;8:426.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

20 Kristensen P, Nordhagen R, Wergeland E, et al. Job adjustment and absence from work in mid-pregnancy in the Norwegian Mother and Child Cohort Study (MoBa). *Occup Environ Med* 2008;65(8):560-6.

21 Strand K, Wergeland E, Bjerkedal T. Work load, job control and risk of leaving work by sickness certification before delivery, Norway 1989. *Scandinavian Journal of Public Health* 1997;25(3):193-201.

22 Werner EL, Cote P. Low back pain and determinants of sickness absence. *Eur J Gen Pract* 2009;15(2):74-9.

23 Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open* 2014;4(2).

24 Social Security Administration and the International Social Security Association. Social Security Programs Throughout the World: Europe 2012 [Date accessed: June 2016 https://www.ssa.gov/policy/docs/progdesc/ssptw/2010-2011/europe/ssptw10europe.pdf].

25 Heitmann K, Svendsen HC, Sporsheim IH, et al. Nausea in pregnancy: attitudes among pregnant women and general practitioners on treatment and pregnancy care. *Scand J Prim Health Care* 2016:1-8.

26 Rezaei E, Moghadam ZB, Saraylu K. Quality of Life in Pregnant Women with Sleep Disorder. *Journal of Family & Reproductive Health* 2013;7(2):87-93.

27 Ekman A, Dickman PW, Klint A, et al. Feasibility of using web-based questionnaires in large population-based epidemiological studies. *Eur J Epidemiol* 2006;21(2):103-11.

28 Huybrechts KF, Mikkelsen EM, Christensen T, et al. A successful implementation of e-epidemiology: the Danish pregnancy planning study 'Snart-Gravid'. *Eur J Epidemiol* 2010;25(5):297-304.

29 O'Higgins A, Murphy OC, Egan A, et al. The use of digital media by women using the maternity services in a developed country. *Ir Med J* 2014;107(10):313-5.

30 Bert F, Gualano MR, Brusaferro S, et al. Pregnancy e-health: a multicenter Italian cross-sectional study on Internet use and decision-making among pregnant women. *J Epidemiol Community Health* 2013;67(12):1013-8.

31 Internet use in households and by individuals in 2012. Eurostat Statistics in focus. 2012 [Date accessed: October 2016 http://ec.europa.eu/eurostat/documents/3433488/5585460/KS-SF-12-050-EN.PDF].

32 Fredriksson K, Toomingas A, Torgen M, et al. Validity and reliability of self-reported retrospectively collected data on sick leave related to musculoskeletal diseases. *Scand J Work Environ Health* 1998;24(5):425-31.

33 Stapelfeldt CM, Jensen C, Andersen NT, et al. Validation of sick leave measures: self-reported sick leave and sickness benefit data from a Danish national register compared to multiple workplace-registered sick leave spells in a Danish municipality. *BMC Public Health* 2012;12:661.

34 Pole JD, Franche RL, Hogg-Johnson S, et al. Duration of work disability: a comparison of self-report and administrative data. *Am J Ind Med* 2006;49(5):394-401.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGENDS

Figure 1 Sick leave rates in each participating country. The numbers of participants in each country were: Poland n=533, Croatia n=237, Serbia n=173, Norway n=1179, Finland n=438, France n=287, Slovenia n=135, Russia n=878, Switzerland n=486, Italy n=720, the United Kingdom n=886 and Sweden n=734.

Figure 2 Reasons for sick leave in pregnancy (n=3385). A woman could report several reasons for being on sick leave. For more categorization details, see Supplementary table 1.

Supplementary figure 1 Flow-chart of women who met the inclusions and exclusions criteria for the final study sample.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

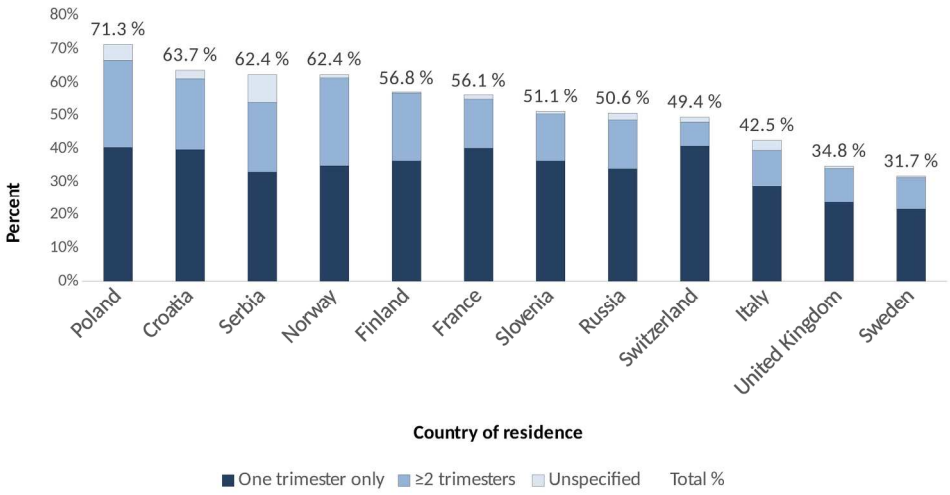


Figure 1: Sick leave rates in each participating country. The numbers of participants in each country were: Poland n=533, Croatia n=237, Serbia n=173, Norway n=1179, Finland n=438, France n=287, Slovenia n=135, Russia n=878, Switzerland n=486, Italy n=720, the United Kingdom n=886, and Sweden n=734.

190x142mm (300 x 300 DPI)

w only

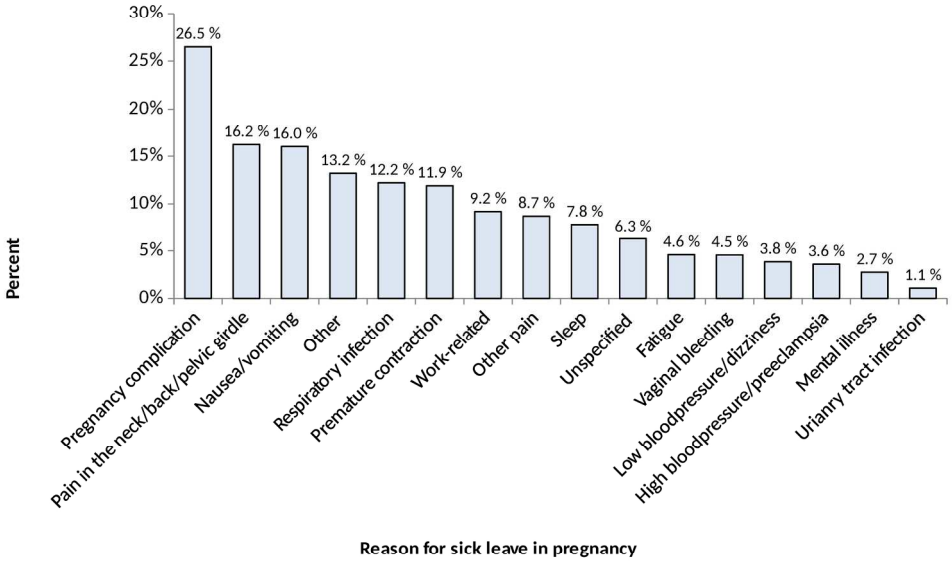
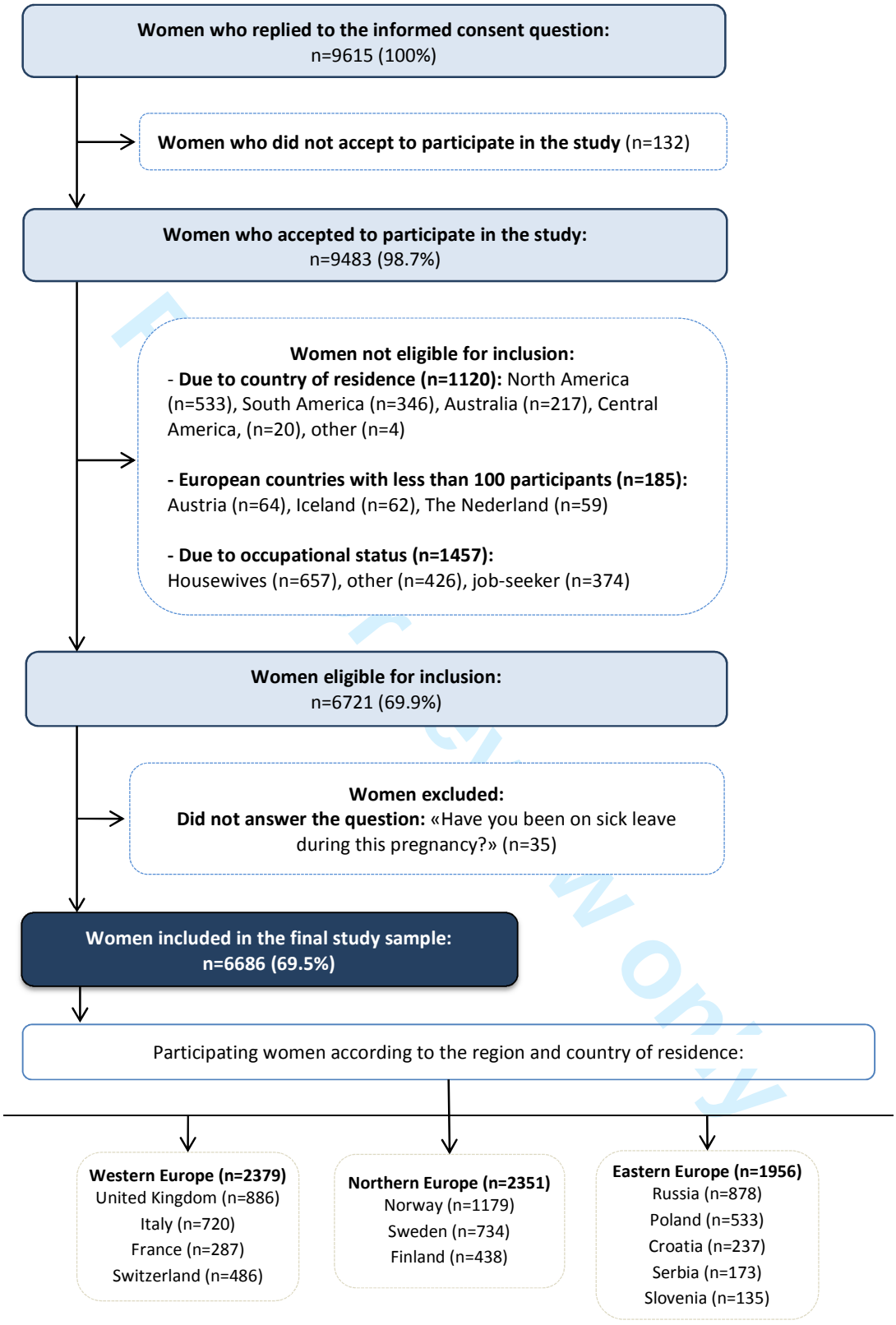


Figure 2 Reasons for sick leave in pregnancy (n=3385). A woman could report several reasons for being on sick leave. For more categorization details, see Supplementary table 1.

190x142mm (300 x 300 DPI)

For peer review only



Supplementary figure 1 Flow-chart of women who met the inclusions and exclusions criteria for the final study sample.

Supplementary table 1 Reasons for sick leave categorization. A woman could report several reasons for being on sick leave during pregnancy. The remaining categories were: pain in the neck, back or pelvic girdle (16.2%), nausea/vomiting (16.0%), sleep (7.8%), fatigue (4.6%), vaginal bleeding (4.5%), low blood pressure/dizziness (3.8%), and high blood pressure/preeclampsia (3.6%).

Category	Free-text entries
Pregnancy complications, n=896 (26.5%)	Epilepsy, carpal tunnel syndrome, cervix insufficiency, complications, gestosis, glucose intolerance, HELLP syndrome, hematoma, in vitro fertilization, high maternal age, leakage of amniotic fluid, low placenta, low position of the baby, malnutrition of the fetus, maternal diabetes, medical procedure, multiple pregnancy, obesity, prenatal, previous abortion, ovarian hyperstimulation, placenta abruption, placenta previa, Rhesus-disease, shortened cervix, swollen legs, threatened miscarriage, thrombophilia, varicose veins, water in the body
Other, n=447 (13.2%)	Allergy, anemia, angina, appendicitis, asthenia, cough, death in the family, difficulties walking, endometriosis, fever, end of pregnancy, gastritis, hernia, hospitalization, hypertonia, inflammation in the legs, kidney stone, mononucleosis, operation, ovarian cysts, poisoning, stomach upset, streptococcus, vaginal inflammation, viral infection, weight loss
Respiratory infections, n=413 (12.2%)	Bacterial infections of the airway, bronchitis, chest infection, cold virus, flu, infection of the lungs, influenza, laryngitis, pneumonia, rhinitis, sinusitis, sinus trouble, throat infection, tonsillitis, upper respiratory infection
Premature contractions, n=343 (11.9%)	Increased uterine tone, preterm labor, suspicion of premature birth
Work-related, n=311 (9.2%)	Accident at work, difficulty in sitting for a long time, harmful working conditions, hard work, heavy lifting, night work, overtime work, too much standing at work, too long commuting to work, stressful job, working in kindergarten
Other pain, n=295 (9%)	Headache, joint pain, Migraine, neuralgia, sciatica
Mental illnesses, n=93 (2.7%)	Anorexia, anxiety, depression, mental stress
Urinary tract infections, n=36 (1.1%)	Includes pyelonephritis and protein in the urine

For peer review only

Supplementary table 2 Maternal health and lifestyle factors, sociodemographic characteristics and sick leave scheme categorization according to country of residence among pregnant women and new mothers.

Independent variables	Total population, n=6686	Pregnant women, n=3486	New mothers, n=3200	Pregnant women vs new mothers
Health and lifestyle factors	n (%)	n (%)	n (%)	p-value
Alcohol in pregnancy*				
Yes	1069 (16.0)	494 (14.2)	575 (18.0)	<0.001
No	5562 (83.2)	2958 (84.9)	2604 (81.4)	
Smoking in pregnancy*				
Yes	539 (8.1)	268 (7.7)	271 (8.5)	0.243
No	6133 (91.7)	3210 (92.1)	2923 (91.3)	
Pregnant after infertility treatment				
Yes	476 (7.1)	269 (7.7)	207 (6.5)	0.047
No	6210 (92.9)	3217 (92.3)	2993 (93.5)	
Folic acid use*				
Yes	6151 (92.6)	3199 (92.4)	2952 (92.9)	0.449
No	489 (7.4)	263 (7.6)	226 (7.1)	
Medication for chronic indications				
Yes	1371 (20.5)	720 (20.7)	651 (20.3)	0.754
No	5315 (79.5)	2766 (79.4)	2549 (79.7)	
Medication for acute indications				<0.001
Yes	5254 (78.6)	2610 (74.9)	2644 (82.6)	
No	1432 (21.4)	876 (25.1)	556 (17.4)	
Number of acute conditions				
Mean (SD), range 0-10	4.2 (1.6)	4.2 (1.6)	4.1 (1.6)	<0.001
Chronic conditions				
No chronic conditions	5279 (79.0)	2762 (79.2)	2517 (78.7)	0.828
Somatic conditions	1167 (17.5)	599 (17.2)	568 (17.8)	
Mental conditions	240 (3.6)	125 (3.6)	115 (3.6)	
Country of residence				
Sick leave scheme				
High	1179 (17.6)	674 (19.3)	505 (15.8)	<0.001
Medium	3128 (46.8)	1536 (44.1)	1592 (49.8)	
Low	2379 (35.6)	1276 (36.6)	1103 (34.5)	
Region				
Northern Europe	2351 (35.2)	1349 (38.7)	1002 (31.3)	<0.001
Eastern Europe	1956 (29.3)	861 (24.7)	1095 (34.2)	
Western Europe	2379 (35.6)	1276 (36.3)	1103 (34.5)	
Sociodemographic and maternal characteristics				
Maternal age (years)				
≤20	168 (2.5)	112 (3.2)	56 (1.8)	<0.001
21-30	3704 (55.4)	1974 (56.6)	1730 (54.1)	
31-40	2698 (40.4)	1351 (38.8)	1347 (42.1)	
≥41	116 (1.7)	49 (1.4)	67 (2.1)	
Marital status				
Married/cohabitant	6375 (95.4)	3333 (95.6)	3042 (95.1)	0.287
Single/divorced/other	311 (4.7)	153 (4.4)	158 (4.9)	

For peer review only

Employment*				
Student	695 (10.4)	342 (9.8)	353 (11.0)	0.014
Healthcare personnel	1088 (16.3)	607 (17.4)	481 (15.0)	
Employed in other sectors	4893 (73.2)	2530 (72.6)	2363 (73.8)	
Highest level of education				
Primary school	191 (2.9)	96 (2.8)	95 (2.9)	0.858
High-school	1736 (26.0)	916 (26.3)	820 (25.6)	
University or collage	3985 (59.6)	2077 (59.6)	1908 (59.6)	
Other education	774 (11.6)	397 (11.4)	377 (11.8)	
Primiparity				
Yes	3603 (53.9)	2085 (59.8)	1518 (47.4)	<0.001
No	3083 (46.1)	1401 (40.2)	1682 (52.6)	
Pregnancy planned*				
Yes	4657 (69.7)	2443 (70.1)	2214 (69.2)	0.076
No, but expected	1491 (22.3)	788 (22.6)	703 (22.0)	
No	519 (7.8)	246 (7.1)	273 (8.5)	

*Total numbers do not add up due to missing values; Folic acid n=46 (0.7%), employment n=10 (0.2%), alcohol in pregnancy n=55 (0.8%), smoking in pregnancy n=14 (0.2%), and pregnancy planned n=19 (0.3%). **__High__; Norway, __Medium__; Croatia, Finland, Poland, Russia, Serbia, Slovenia, and Sweden, and __Low__; Italy, France, the United Kingdom, and Switzerland.

For peer review only

Supplementary table 3 Information regarding maternal status of the women at the time of answering the questionnaire in each participating country.

Country	New mothers (n=3200)	Pregnant women (n=3486)				
	Total	Total	1st trimester	2nd trimester	3rd trimester	Average GW
	n	n	n (%)	n (%)	n (%)	Week (range)
Croatia	144	93	24 (25.8)	30 (32.3)	39 (41.9)	22 (4-40)
Finland	145	293	38 (13.0)	107 (36.5)	148 (50.5)	24 (5-42)
France	94	193	45 (23.2)	64 (33.2)	84 (43.5)	22 (1-40)
Italy	227	493	122 (24.8)	206 (41.8)	165 (33.5)	20 (2-41)
Norway	505	674	188 (27.9)	204 (30.3)	282 (41.8)	21 (1-41)
Poland	248	285	50 (17.5)	105 (36.8)	130 (45.6)	23 (1-41)
Russia	553	325	70 (21.5)	88 (27.1)	167 (51.4)	24 (1-41)
Serbia	108	65	5 (7.7)	25 (38.5)	35 (53.9)	25 (5-39)
Slovenia	42	93	24 (25.8)	32 (34.4)	37 (39.8)	21 (5-41)
Sweden	352	382	90 (23.6)	124 (32.5)	168 (44.0)	22 (4-42)
Switzerland	226	260	52 (20.0)	84 (32.3)	124 (47.7)	23 (4-41)
United Kingdom	556	330	16 (4.9)	108 (32.7)	206 (62.4)	27 (3-41)

GW: Gestational week.

For peer review only

Supplementary table 4 Percentage of overall prevalence and extensions of sick leave in addition to top three reasons for sick leave in each country.

Country of residence	Total sick leave	Sick leave in ≥ 2 trimesters	Most frequent reason for sick leave
	% (n)	% (n)	Reason (%)
Eastern Europe			
Poland	71.3 (355)	39.4 (140)	Pregnancy complications (27.6) Due to work (20.8) Other (13.7)
Croatia	63.7 (145)	35.2 (51)	Pregnancy complications (43.7) NVP (11.3) Vaginal bleeding (10.6)
Serbia	62.4 (93)	38.7 (36)	Pregnancy complications (26.9) Other (19.4) Due to work (15.7)
Slovenia	51.1 (68)	27.9 (19)	Pregnancy complications (33.3) Vaginal bleeding (18.8) Respiratory infections & other (11.6)
Russia	50.6 (128)	30.1 (128)	Pregnancy complications (46.2) Respiratory infections (32.9) Premature contractions (8.1)
Northern Europe			
Norway	62.4 (724)	43.2 (313)	Pain in the neck, back, or pelvic girdle (42.9) NVP (29.5) Sleeping problems (16.4)
Finland	56.8 (248)	35.9 (89)	Respiratory infections (23.3) Premature contractions (22.9) Pain in the neck, back, or pelvic girdle (20.5)
Sweden	31.7 (230)	31.3 (72)	Pregnancy complications (31.3) NVP (22.8) Pain in the neck, back, or pelvic girdle (10.3)
Western Europe			
France	56.1 (157)	26.8 (42)	Premature contractions (22.2) Sleeping problems (19.3) Pain in the neck, back, or pelvic girdle (13.0)
Switzerland	49.4 (233)	15.0 (35)	Premature contractions (23.6) Pregnancy complications (20.0) Other (16.7)
Italy	42.5 (284)	27.1 (77)	Pregnancy complications (34.0) NVP (11.8) Respiratory infection (10.4)
The UK	34.8 (302)	30.8 (93)	NVP (33.8) Respiratory infections (22.1) Other pain (16.9)

The UK=the United Kingdom

For peer review only

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

"Sick leave and medication use in pregnancy - a European web-based study"

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	Supplementary table 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8, 9, Table 1
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not relevant
		(*e*) Describe any sensitivity analyses	9

For Peer Review Only

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary figure 1
		(b) Give reasons for non-participation at each stage	Supplementary figure 1
		(c) Consider use of a flow diagram	Supplementary figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10, Table 1, Supplementary table 2
		(b) Indicate number of participants with missing data for each variable of interest	Page 10, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	12, Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18, 19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

BMJ Open

Sick leave and medication use in pregnancy - a European web-based study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014934.R1
Article Type:	Research
Date Submitted by the Author:	17-May-2017
Complete List of Authors:	Truong, Bich; University of Oslo, School of Pharmacy, PharmacoEpidemiology and Drug Safety Research Group Lupattelli, Angela; University of Oslo, School of Pharmacy, PharmacoEpidemiology and Drug Safety Research Group Kristensen, Petter; National Institute of Occupational Health; Univeristy of Oslo, Institute of Health and Society Nordeng, Hedvig; University of Oslo, School of Pharmacy, PharmacoEpidemiology and Drug Safety Research Group; Norwegian Institute of Public Health,
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	Sick leave, Maternal medicine < OBSTETRICS, PUBLIC HEALTH, Pregnancy

SCHOLARONE™
Manuscripts

For peer review only

Sick leave and medication use in pregnancy - a European web-based study

Bich Thuy Truong,[1] Angela Lupattelli,[1] Petter Kristensen,[2,3] Hedvig Nordeng[1,4]

[1]PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway

[2]National Institute of Occupational Health, Oslo, Norway

[3]Institute of Health and Society, University of Oslo, Oslo, Norway

[4]Norwegian Institute of Public Health, Oslo, Norway

Corresponding author

Bich Thuy Truong, MScPharm

School of Pharmacy, University of Oslo

Sem Sælands vei 3, 0371 Oslo, Norway

E-mail: b.t.h.truong@farmasi.uio.no

Tel.: +47 98 42 68 20

Keywords: Sick leave, maternal medicine, pregnancy, public health

Running title: Sick leave and medication use in pregnancy

Word count (excluding title page, abstract, references, figures, and tables): 3994

For peer review only

ABSTRACT

Background and objective: A comparison of sick leave in pregnancy between countries is difficult since most studies have been conducted in single countries in Scandinavia. The objective of this study was to explore patterns of and reasons for sick leave during pregnancy on a multinational level, focusing on medication use but also differences in sick leave policies.

Design and setting: Cross-sectional, web-based study in 12 European countries from October 2011 to February 2012. Data were collected via an electronic questionnaire.

Participants: Pregnant women and mothers of children under the age of one year.

Primary outcome measure: Sick leave prevalence in pregnancy.

Results: Of 6686 women included, 3385 (50.6%) had been on sick leave during pregnancy. The rates of sick leave varied across countries, ranging from 31.7-34.8% in Sweden and the United Kingdom, to 62.4-71.3% in Norway, Serbia, Croatia, and Poland. The most common reasons for being on sick leave were pregnancy complications (26.5%); pain in the neck, back, or pelvic girdle (16.2%); and nausea and vomiting (NVP, 16.0%). Women using medications for acute illnesses were more likely to be on sick leave than their non-medicated counterparts; while, an opposite trend was observed for women with chronic disorders, where non-medicated women were more likely to be on sick leave. Women from countries with "Low" sick leave policies were less likely to have extensions of sick leaves compared with women from countries with "Medium" schemes (aOR: 0.63, 95% CI: 0.49-0.82).

Conclusion: The rates of sick leave in pregnancy vary greatly across European countries. Women using medications were more likely to be on sick leave, especially for acute illnesses. The differences in sick leave patterns across countries only partially reflected differences in sick leave policies, which implies that sick leave in pregnancy is also affected by other national differences.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

ARTICLE SUMMARY

Strengths and limitations of this study

- Uniform data collection methodology, allowing inter-country comparisons of sick leave in pregnancy.
- New insights into patterns of sick leave in pregnancy for countries outside Scandinavia, as well as into the impact of medication of acute and chronic disorders on sick leave.
- No detailed information about sick leave, i.e. exact timing, duration and whether it was part-time or full-time.
- A web-based survey as a study method impedes the calculation of a conventional response rate and may cause selection bias of the target population.
- Self-reported data used for dependent and independent variables.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

INTRODUCTION

Multiple studies conducted in Scandinavia have identified generally high rates of sick leave among pregnant women (range 48.0-67.7%),[1-5] and pregnancy-related conditions, such as back pain and nausea and vomiting (NVP), were the most common reasons for sick leave.[3, 4, 6, 7] Sick leave in pregnancy may also be required when there are risky occupational exposures or work-related duties that may negatively impact pregnancy outcomes.[8-12] Interestingly, research on sick leave in pregnancy is almost non-existent for countries outside Scandinavia, which makes inter-country comparisons challenging. When considering the high extent of sick leave seen in the Scandinavian countries, it is crucial to gain knowledge about patterns and factors associated with sick leave during pregnancy to initiate preventive measures. Such knowledge would not only be of huge economic interest for society, but it would also be beneficial for clinicians/physicians who encounter pregnant women in antenatal care. Elucidating patterns of sick leave among pregnant women in other European countries can also contribute to a better understanding of maternal health across countries. National differences in work participation by women of fertile age, as well as the thresholds and attitudes towards sick leave, may differ across countries despite the same diseases/conditions affecting pregnant women.[13, 14]

The concept of paid sick leave is included in the welfare systems of most Western countries and it is intended to provide employees with financial protection during sickness and disability.[15] However, the qualifications for receiving sick leave benefits vary greatly between countries. The World Health Organization (WHO) described the concept of paid sick leave from a global perspective, revealing that 145 countries provide paid sick leave and the wage replacement ranges from lump sums, in 14.0% of the countries, to 100% of wages in 21.0% of the countries.[15]

Many medical conditions occur during pregnancy and pregnant women may need medical treatment to ensure maternal-fetal health.[16] However, pregnant women tend to overestimate the teratogenic risk associated with medications,[17] which can result in untreated conditions due to fear of harming the unborn child.[18] As some untreated maternal conditions, e.g. diabetes and epilepsy, can pose a risk to the fetus, it is essential that pregnant women are empowered to make safe decisions about treatment options in pregnancy.[16] Sociodemographic and lifestyle factors, such as age, gender, and education;[19] self-reported

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

health;[20] and work-related conditions[4, 21-23] are potential determinants of sick leave in general, but no previous studies have investigated the extent of sick leave in pregnancy with respect to maternal medication use. Therefore, the role of medication use in sick leave during pregnancy remains elusive.

The objective of this study was to describe patterns of and reasons for sick leave in pregnancy on a multinational European level, focusing on maternal illnesses and related medication use. In addition, we explored sick leave in relation to the differences in European sick leave policies.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

METHODS

Study design, data collection, and study population

This is a sub-study of the "Multinational Medication Use in Pregnancy Study", a cross-sectional, web-based study carried out in Europe, North and South America, and Australia from October 2011 to February 2012, with the purpose to investigate patterns of medication use in pregnancy. The study has been described in detail elsewhere.[24] In brief, member countries of the European Network of Teratology Information Services (ENTIS), Organization of Teratology Information Specialist (OTIS) in North and South America, Mothersafe in Australia and European institutions conducting public health research were invited to take part in the project. Of these, 18 countries participated. Data were collected via an anonymous, self-administrated, questionnaire (www.questback.com), accessible in each participating country for two months in the period mentioned above. The full questionnaire has previously been published.[24] An invitation to participate in the study (presented as banner/ads) was available on two to three national pregnancy-related web pages and/or social networks, selected according to the number of daily users in each participating country. Pregnant women at any gestational age and new mothers of children under the age of one year were eligible for inclusion. The women were instructed to answer the questions related to their current or latest pregnancy. Detailed information regarding the recruitment tools utilized and internet penetration rates for individual countries have been described previously.[24]

This sub-study sample was restricted to women with residence in European countries only. Eligible countries were divided into three regions: 1) Western Europe: Austria, France, Italy, Switzerland, the Netherlands, and the United Kingdom (UK); 2) Northern Europe: Iceland, Finland, Norway, and Sweden; and 3) Eastern Europe: Croatia, Poland, Russia, Serbia, and Slovenia. Unemployed women, women from European countries with less than 100 participants, and women who did not answer the question "Have you been on sick leave during this pregnancy?" were excluded (Supplementary Figure 1).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Measures

Sick leave during pregnancy

Our main outcome measure was sick leave during pregnancy. All women were asked to state whether or not they had been on sick leave during pregnancy (yes/no). Women answering "yes" could also report the reason(s) for being on sick leave as free-text entries (Supplementary Table 1) and the trimester when the sick leave occurred (weeks 0-12, 13-24, and/or 25–delivery, which correspond to the first, second, and third trimester respectively). The rates of overall sick leave consist of women who reported to have been on sick leave in at least one trimester. Extension of sick leave referred to women on sick leave for more than one trimester.

Acute illnesses, chronic disorders, and related medication use

Maternal illnesses and related medication use during pregnancy were the main independent variables in this study. Participants were presented with a list of nine common acute pregnancy-related illnesses (i.e. common cold, constipation, heartburn and reflux problems, headache, NVP, other infections, pain in the neck, back, or pelvic girdle, sleeping problems, and urinary tract infection) and nine chronic disorders (i.e. allergy, anxiety, asthma, depression, diabetes, epilepsy, hypothyroidism, cardiovascular, and rheumatic disorders). In addition, the women could report as free text any other chronic disorders not previously listed. Women who reported they had experienced any illnesses or disorders were asked to report any related medication use as a free-text entry. For the acute pregnancy-related illnesses, we focused on NVP, pain, and sleeping problems because these illnesses were specifically stated as reasons for sick leave in pregnancy (Figure 2). The four most prevalent chronic disorders were also studied, i.e. mood disorders (depression and anxiety), asthma, allergy, and hypothyroidism.

The questionnaire also included a list of common over-the-counter (OTC) medication groups (i.e. analgesics, nasal spray/drops, antacids, antiemetics, and laxatives) and participants could report whether these OTC medications were used. Women reporting any medication use were asked to specify the timing of usage according to pregnancy weeks (weeks 0-12, 13-24, and 25–delivery). Medication use did not include vitamins, mineral supplements, and herbal or supplementary products.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Each country's sick leave policy category was also an independent variable of interest. The policies were categorized into "High", "Medium", or "Low" based on the percentage of wage replacement during sick leave and the number of waiting days prior to wage replacement in each country. Information from "Social Security Programs Throughout the World 2012" was used for the categorization.[25] The criteria were: "High", full (100%) wage replacement for everyone and no waiting days; "Medium", 60-100% wage replacement and no waiting days; and "Low", <100% wage replacement and 1-3 waiting days.

Maternal sociodemographic and lifestyle factors

Several maternal characteristics and health-related factors were assessed as potential confounders as they may be risk factors for sick leave in pregnancy and also be associated with medication use in pregnancy, the country of residence and, hence, the sick leave policy. These variables included age, maternal status (pregnant or mother at the time of answering the questionnaire), parity, marital status, employment status, highest level of education, folic acid use before and/or during pregnancy, smoking during pregnancy, alcohol consumption after awareness of pregnancy, and whether or not the pregnancy was planned or secondary to infertility treatment. These variables were categorized as presented in Table 1.

Ethics

The study was approved by the South-East Regional Ethics Committee in Norway. Additional ethical approval or study notification to the relevant national Ethics Boards was achieved in specific countries as required by the national legislation. Informed consent was considered given when the women answered "Yes" to the question "Are you willing to participate in the study?" before accessing the online questionnaire. All data were handled and stored anonymously.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Statistical analysis

Descriptive analyses on the prevalence of sick leave, by the timing in gestation and country of residency, as well as reasons for being on sick leave were performed. The Chi-square and the Fisher's exact test were used to compare women's sociodemographic, lifestyle, and pregnancy-related factors according to the overall prevalence of sick leave and the extension of sick leave during pregnancy. A univariate and multivariate Generalized Estimating Equation (GEE) with logit link function accounting for clustering on the country level was used to estimate the association of: 1) maternal medication use and 2) categorization of sick leave policies with: a) overall sick leave during pregnancy (yes/no) and b) extension of sick leave in pregnancy (in one trimester only/in any two or all three trimesters). The associations were presented as crude (OR) and adjusted odds ratios (aOR) with the 95% confidence interval (95% CI). Potential confounders were identified according to prior knowledge and current literature, and by using Direct Acyclic Graphs. The same set of confounders (i.e. maternal age, parity, maternal status, marital status, education level, employment, infertility treatment, whether or not the pregnancy was planned, alcohol use in pregnancy, smoking in pregnancy, acute illnesses [other than the one of interest], and chronic disorders [other than the one of interest], was used for all models containing medication use as the independent variable. Potential confounders for the "sick leave policy" model were fitted by removing all variables having no role in the model, i.e. variables yielding <10% change in the beta coefficients of the "sick leave policy" variable. Since only new mothers had full overview of the pregnancy in relation to sick leave, a sensitivity analysis restricted to this group was conducted. Sensitivity analyses were also performed that took into account the differences in maternity leave policies in each country. These analyses were restricted to pregnant women who were not qualified for maternity leave (Supplementary Table 2) according to pregnancy week when the electronic questionnaire was completed. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using the Data Analysis and Statistical Software Stata/MP version 14.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

RESULTS

Population characteristics

A total of 9615 women replied to the informed consent question after reading the study description. Of these, 9483 (98.7%) completed the online questionnaire. This sub-sample was restricted to 6686 (69.5%) women from 12 European countries: Croatia, Finland, France, Italy, Norway, Poland, Russia, Serbia, Slovenia, Sweden, Switzerland, and the UK. A flowchart of women who met the inclusion and exclusion criteria for this final study sample, along with the number of participants from each country is summarized in Supplementary Figure 1. Maternal health and lifestyle factors, sick leave policy categorizations for each country, and sociodemographic characteristics of the study sample in relation to sick leave are summarized in Table 1.

Fifty-two percent (n=3486) of the included women were pregnant at the time of accessing and answering the questionnaire, while the remaining were new mothers of children under the age of one year (n=3200). Pregnant women were often younger and primiparous compared with new mothers (Supplementary Table 3). The average gestation week (GW) among pregnant women was 23 (range 1-42); while, almost half (48.5%) of the new mothers had a child over 6 months of age. Detailed information regarding the maternal status and GW for each individual country is presented in Supplementary Table 4.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 1 Maternal health and lifestyle factors, sociodemographic characteristics, and sick leave categories in relation to sick leave in pregnancy.

	Total population n=6686	Sick leave in pregnancy		No sick leave versus sick leave
		No (n=3301)	Yes (n=3385)	
Health and lifestyle factors	n (%)	n (%)	n (%)	P-value
Alcohol in pregnancy*				
Yes	1069 (16.0)	562 (17.0)	507 (15.0)	0.022
No	5562 (83.2)	2707 (82.0)	2854 (84.4)	
Smoking in pregnancy*				
Yes	539 (8.1)	235 (7.1)	304 (9.0)	0.005
No	6133 (91.7)	3061 (92.7)	3072 (91.0)	
Infertility treatment				
Yes	476 (7.1)	181 (5.5)	295 (8.7)	<0.001
No	6210 (92.9)	3120 (94.5)	3090 (91.3)	
Folic acid use*				
Yes	6151 (92.6)	3020 (92.3)	3131 (93.0)	0.300
No	489 (7.4)	252 (7.7)	237 (7.0)	
Medication for chronic indications				
Yes	1371 (20.5)	577 (17.5)	794 (23.5)	<0.001
No	5315 (79.5)	2724 (82.5)	2591 (76.5)	
Medication for acute indications				
Yes	5254 (78.6)	2465 (74.7)	2789 (82.4)	<0.001
No	1432 (21.4)	836 (25.3)	596 (17.6)	
Number of acute illnesses				
Mean (SD), range 0-9	4.2 (1.6)	3.9 (1.6)	4.4 (1.5)	<0.001
Chronic disorders**				
No chronic disorders	5279 (79.0)	2708 (51.3)	2571 (48.7)	<0.001
Somatic disorders	1322 (19.8)	507 (43.4)	660 (56.6)	
Mood disorders	240 (3.6)	86 (35.8)	154 (64.2)	
Country of residence				
Paid sick leave policy***				
High	1179 (17.6)	443 (37.6)	736 (62.4)	<0.001
Medium	3128 (46.8)	1494 (47.8)	1634 (52.2)	
Low	2379 (35.6)	1364 (57.3)	1015 (42.7)	
Region of residence				
Western Europe	2379 (35.6)	1364 (41.3)	1015 (30.0)	<0.001
Northern Europe	2351 (35.2)	1133 (34.3)	1218 (36.0)	
Eastern Europe	1956 (29.3)	804 (24.4)	1152 (34.0)	
Sociodemographic and maternal characteristics				
Maternal age (years)				
≤20	168 (2.5)	107 (3.2)	61 (1.8)	0.001
21-30	3704 (55.4)	1792 (54.3)	1912 (56.5)	
31-40	2698 (40.4)	1344 (40.7)	1354 (40.0)	
≥41	116 (1.7)	58 (1.8)	58 (1.7)	
Marital status				
Married/cohabitant	6375 (95.4)	3132 (94.9)	3243 (95.8)	0.073
Single/divorced/other	311 (4.7)	169 (5.1)	142 (4.2)	

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Employment*				
Employed in other sectors	4893 (73.3)	2356 (71.6)	2537 (75.0)	<0.001
Healthcare personnel	1,088 (16.3)	445 (13.5)	643 (19.0)	
Student	695 (10.4)	492 (14.9)	203 (6.0)	
Highest level of education				
Primary school	191 (2.9)	97 (2.9)	94 (2.8)	0.438
High-school	1736 (26.0)	845 (25.6)	891 (26.3)	
University or college	3,985 (59.6)	1994 (60.4)	1991 (58.8)	
Other education	774 (11.6)	365 (11.1)	409 (12.1)	
Maternal status at the time of answering the questionnaire				
New mothers	3200 (47.9)	1432 (44.8)	1768 (55.3)	<0.001
Pregnant in 1st trimester	724 (10.8)	511 (70.6)	213 (29.4)	
Pregnant in 2nd trimester	1177 (17.6)	642 (54.6)	535 (45.5)	
Pregnant in 3rd trimester	1585 (23.7)	716 (45.2)	869 (54.8)	
Primiparous				
Yes	3603 (53.9)	1830 (55.4)	1773 (52.4)	0.012
No	3083 (46.1)	1471 (44.6)	1612 (47.6)	
Pregnancy planned*				
Yes	4657 (69.9)	2229 (67.7)	2428 (72.0)	0.001
No, but expected	1491 (22.4)	788 (23.9)	703 (20.8)	
No	519 (7.8)	277 (8.4)	242 (7.2)	

*Total numbers do not add up due to missing values: folic acid n=46 (0.7%), employment n=10 (0.2%), alcohol in pregnancy n=55 (0.8%), smoking in pregnancy n=14 (0.2%), and pregnancy planned n=19 (0.3%).

**Chronic disorders were categorized as no conditions, somatic conditions only (allergy, asthma, diabetes, epilepsy, hypothyroidism, cardiovascular diseases, and rheumatic disorders), and any mood disorders (anxiety and/or depression), i.e. women with both somatic and mood disorders were categorized in the latter group.

***__High:__ Norway, __Medium:__ Croatia, Finland, Poland, Russia, Serbia, Slovenia, and Sweden, and __Low:__ Italy, France, the United Kingdom, and Switzerland.

Sick leave during pregnancy

A total number of 3385 (50.6%) women had been on sick leave at some point in pregnancy, with a higher reported rate among new mothers (55.3%) compared with pregnant women (46.4%). The prevalence of sick leave in each individual country is presented in Figure 1. The proportions of women on sick leave in the first, second, and/or third trimester were 38.5%, 48.1%, and 52.1% respectively. Most women (64.1%) had been on sick leave in one trimester only (n=2170); whereas, 32.3% (n=1095) had been on sick leave in any two or all three trimesters. Timing of sick leave for the remaining 120 women (0.04%) was unknown.

The rates of overall prevalence and the extension of sick leave in each individual country are presented in Supplementary Table 5. The most common reasons for being on sick leave were pregnancy complications (26.0%); pain in the neck, back, or pelvic girdle (16.2%); and NVP

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

(16.0%) (Figure 2). Reasons for sick leave were categorized into the 16 most prevalent categories as shown in Supplementary Table 1.

Acute illnesses, chronic disorders, and related medication use

Women on sick leave had a significantly higher number of reported acute illnesses (mean [SD]: 4.4 [1.5] vs 3.9 [1.6], p<0.001) and chronic disorders (0.7 [0.6] vs 0.2 [0.5], p<0.001) compared with women not on sick leave. The same trends were seen among women with extensions of sick leaves and medicated women compared with women who were sick leave in one trimester only and non-medicated women, respectively (data not shown).

Women medicated for NVP, pain, or sleeping problems had significantly higher rates of sick leave due to the indication for medication use than non-medicated women with the same conditions (Table 2). These women had also higher rates of sick leave due to any reason (data not shown).

Table 2 Proportions of women on sick leave due to nausea and vomiting (NVP), pain, or sleeping problems according to medication use for the reported conditions.

Conditions	Total	Sick leave due to the reported condition		Yes vs No
		Yes	No	P-value
NVP	4841	535 (11.1)	4306 (89.0)	
Medicated, n (%)	781 (16.1)	186 (23.8)	595 (76.2)	<0.001
Non-medicated, n (%)	4060 (84.9)	349 (8.6)	3711 (91.4)	
Pain*	5396	858 (15.9)	4538 (84.1)	
Medicated, n (%)	3320 (62.0)	631 (19.0)	2689 (81.0)	<0.001
Non-medicated, n (%)	2076 (38.0)	227 (10.9)	1849 (89.1)	
Sleeping problems	3748	198 (5.3)	3550 (94.7)	
Medicated, n (%)	105 (2.8)	11 (10.5)	94 (90.0)	0.016
Non-medicated, n (%)	3643 (97.2)	187 (5.1)	3456 (94.9)	

*Reasons for sick leave categorized as pain in the neck, back, or pelvic girdle, other pain, and headache.

Sick leave policies

The categorization of countries according to sick leave policies was as follows: “High” - Norway (n=1179); “Medium” - Croatia, Finland, Poland, Russia, Serbia, Slovenia, and Sweden (n=3128); and “Low” - Italy, France, the UK, and Switzerland (n=2379). Women from Norway with “High” sick leave policies had the highest overall prevalence and extensions of sick leave (data now shown).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Factors associated with sick leave

Having chronic asthma, allergy, hypothyroidism, or mood disorders was positively associated with sick leave in pregnancy regardless of medication use (Table 3). Women who did not report any treatment (non-medicated) for asthma, allergy, or hypothyroidism had a higher likelihood (1.5-2.7-fold) of being on sick leave compared with women without the disorder. These associations were greater than for medicated women (1.3-1.5-fold), whereas, the inverse was observed in relation to mood disorders (non-medicated vs. medicated aOR: 2.1 vs. 3.1). The association between medicated acute illnesses and sick leave was also greater than for non-medicated acute illnesses and sick leave, when compared with no acute illness (Table 3). Women from countries with "Low" sick leave policies were less likely to have extensions of sick leaves in pregnancy compared with women from countries with "Medium" sick leave policies (aOR: 0.63, 95% CI: 0.49-0.82).

Sensitivity analysis

The sensitivity analyses addressing the differences in maternity leave policies in each country showed that the magnitude of the association between having a medicated condition and sick leave did not substantially differ from the main analyses (data not shown).

In the sensitivity analysis restricted to new mothers, the magnitudes of the associations between having a medicated condition and sick leave were generally similar to those of the main analysis (±20% change of the point estimates), with the exception of medicated mood disorders (+57% change) and non-medicated NVP (>35% lower) (data not shown).

These sensitivity analyses could not be done for hypothyroidism and sleeping problems due to small sample sizes.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Table 3 Independent variables and the association with sick leave during pregnancy, presented as crude (OR) and adjusted odds ratios (aOR) with the 95% confidence interval (95% CI).

Independent variables		Sick leave during pregnancy			
		Yes vs. no		In any two or all three trimesters vs any one trimester only	
Chronic disorders	**Total,** n	**OR** (95% CI)	**aOR** (95% CI)	**OR** (95% CI)	**aOR** (95% CI)
Mood disorders*					
No	6.446	Reference	Reference	Reference	Reference
Yes, non-medicated	199	1.82 (1.36-2.43)	2.05 (1.50-2.77)	1.69 (1.17-2.43)	1.77 (1.21-2.58)
Yes, medicated	41	4.11 (1.89-8.90)	3.14 (1.43-6.88)	2.28 (1.12-4.65)	2.27 (1.06-4.85)
Asthma					
No	6.369	Reference	Reference	Reference	Reference
Yes, non-medicated	96	2.33 (1.51-3.60)	2.22 (1.41-3.47)	1.35 (0.82-2.21)	1.74 (1.19-2.55)
Yes, medicated	221	1.40 (1.07-1.82)	1.32 (1.00-1.75)	1.66 (1.14-2.39)	1.33 (0.80-2.23)
Allergy					
No	6.098	Reference	Reference	Reference	Reference
Yes, non-medicated	339	1.55 (1.25-1.93)	1.51 (1.20-1.90)	1.28 (0.95-1.72)	1.38 (1.01-1.88)
Yes, medicated	249	1.62 (1.26-2.10)	1.49 (1.14-1.94)	1.51 (1.09-2.09)	1.50 (1.07-2.10)
Hypothyroidism					
No	6.426	Reference	Reference	Reference	Reference
Yes, non-medicated	17	1.81 (0.63-1.94)	2.68 (0.93-7.73)	0.74 (0.20-2.82)	0.87 (0.22-3.48)
Yes, medicated	243	1.50 (1.16-1.92)	1.41 (1.08-1.84)	1.11 (0.78-1.59)	1.25 (0.86-1.82)
Acute illnesses		**OR** (95% CI)	**aOR** (95% CI)	**OR** (95% CI)	**aOR** (95% CI)
Nausea and vomiting					
No	1.836	Reference	Reference	Reference	Reference
Yes, non-medicated	4.060	1.27 (1.14-1.42)	2.49 (1.58-3.93)	1.26 (1.05-1.51)	1.95 (0.79-4.81)
Yes, medicated	790	2.29 (1.92-2.72)	4.52 (2.01-7.27)	2.30 (1.81-2.94)	3.69 (1.49-9.13)
Pain**					
No	852	Reference	Reference	Reference	Reference
Pain, non-medicated	2.076	1.63 (1.39-1.91)	1.07 (0.85-1.36)	1.42 (1.05-1.92)	1.03 (0.66-1.60)
Pain, medicated	3.758	2.09 (1.80-2.43)	1.38 (1.11-1.71)	1.96 (1.46-2.62)	1.38 (0.91-2.10)
Sleeping problems (SP)					
No	2.938	Reference	Reference	Reference	Reference
SP, non-medicated	3.643	1.51 (1.38-1.67)	3.09 (1.91-5.00)	1.25 (1.07-1.46)	4.07 (1.19-13.92)
SP, medicated	105	2.61 (1.79-3.93)	5.42 (2.88-10.22)	1.91 (1.82-3.08)	5.71 (1.53-21.34)

Missing data <5%, as presented in Table 1. *Depression and/or anxiety. **Pain in the neck, back, or pelvic girdle or headache.

The multivariate models were adjusted for acute illnesses (other than the one of interest), age, alcohol in pregnancy, chronic disorders (other than the one of interest), education, employment, infertility treatment, marital status, maternal status, parity, planned pregnancy, and smoking in pregnancy.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

DISCUSSION

To our knowledge, this is the first study investigating patterns of sick leave in pregnancy on a multinational level, focusing on maternal medication use. The results indicate that the rates of sick leave in pregnancy vary greatly within Europe, ranging from 31.7% in Sweden to 71.3% in Poland. The most common reason for sick leave was pregnancy complications, but this differed according to the country and region of residence. When compared with women without acute illnesses, women using medications for acute illnesses were 1.4-5.4-fold more likely to be on sick leave; while, non-medicated women were 1.1-3.1-fold more likely. The opposite trend was seen for the chronic disorders asthma, allergy, and hypothyroidism. Residence in countries with "Low" sick leave policies seems to decrease the likelihood of extending sick leaves.

Eastern European women had the highest rates of work-related sick leave; on the other hand, they also had the lowest rates of sick leave due to pain and NVP (Supplementary Table 5). These findings may reflect differences in women's perception towards their own health[20] and the need for sick leave during pregnancy. Women on long-term sick leave seem to have a lower self-rated health, and lower quality of life compared with women not on sick leave or on short-term sick leave.[20] Studies have also shown the practice of prescribing sick leave varies greatly.[14] Clinical specialists tend to prescribe shorter sick leaves than practitioners and more sick days are often prescribed in smaller municipalities than larger ones.[13] We had no information regarding the prescribing physician, the number of sick days prescribed, nor if the women were from a suburban or urban area; thus, prescribing practices may have contributed to the different patterns of sick leave seen in this study.

The association between non-medicated chronic disorders (i.e., asthma, allergy, and hypothyroidism) and sick leave was greater than the association for medicated chronic disorders, when both groups were compared with women having no chronic disorder. Yet, the opposite trend was seen for all the acute illnesses investigated as well as for chronic mood disorders. Previous studies have shown that acute pregnancy-related illnesses can have a huge impact on pregnant women's daily activities, such as walking, standing, or changing position, as well as quality of life.[3, 26, 27] On the other hand, perinatal mood disorders can have significant detrimental effects on the mother, child, and whole family.[28] A possible explanation for our findings is that women medicated for acute illnesses or for treatment of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

mood disorders had a more severe condition; hence, they were more disabled than non-medicated women. Indeed, pharmacological treatment with antidepressants in pregnancy is usually reserved for women with a major mood disorder, or as a second line therapy when non-pharmacological therapies have failed.[29] Thus, medication use for acute illnesses as well as for mood disorders may be a proxy for the severity of the conditions. However, studies have shown that common pregnancy-related illnesses, such as NVP, are often mismanaged and neglected by health care personnel.[26] The results of our study may support these findings as the magnitude of the association between non-medicated and medicated acute illnesses, specifically for NVP and sleeping problems, was greater than that for chronic disorders. Reducing sick leave rates among pregnant women is beneficial for public health, and has major economic interest for society. Previous research has mainly focused on preexisting chronic disorders in pregnancy, and these women are generally followed-up adequately. However, our study indicates there is a need to focus on other aspects in pregnancy. Therefore, future research should investigate whether or not sick leave among pregnant women can be prevented by optimizing management of acute pregnancy-related illnesses.

Our results suggest that sick leave policies may have an impact on both the rates and the extensions of sick leave, especially in countries with limited benefits. A “High” sick leave policy was not significantly associated with increased rates of sick leave compared with “Medium” policies. Interestingly, “Low” sick leave policies seem to decrease the likelihood of extending of sick leaves in pregnancy even after adjusting for maternal characteristics and sociodemographic and lifestyle factors. These findings are consistent with a report from WHO, which found countries with a medium scope of benefits had the highest number of sick leave days in Europe.[15] However, there was no doubt that countries with limited benefits had the lowest rates of sick leave, like in our study.

We found the majority of women were on sick leave so during the last trimester, and this is consistent with a study conducted in Sweden.[2] However, in countries like Russia and the UK, maternity leave can be taken in the beginning of the third trimester, which may explain the relatively low rates of sick leave seen in these countries compared with the other countries in this study. However, as shown in the sensitivity analyses restricted to pregnant women who were not qualified to receive maternity leave in each country, the associations between maternal conditions and sick leave did not considerably differ.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

The main strength of this study was the large sample size and the uniform data collection methodology utilized across all participating countries, allowing inter-country comparisons of sick leave in pregnancy. The precision of our estimates of sick leave was within ±5.0% in each country with the exception of France, Croatia, Serbia, and Slovenia where the precision ranged from ±6-8%. We had detailed information regarding maternal health, including medication use and co-morbidities, which could be risk factors for sick leave in pregnancy. In addition, we considered the differences in sick leave policies across the participating countries using external sources. Our previous studies also demonstrated that the study samples were sufficiently representative of the general birthing population in each individual country with regards to age and smoking habits. However, they had on average higher levels of education and were more likely to be primiparous.[24]

The limitations of this study include the lack of detailed information regarding sick leave in pregnancy, i.e. exact timing, duration, and whether if it was part-time or full-time. Also, we were not able to distinguish between sick leave among women employed in private and public sectors, and this could have yielded another sick leave pattern. Moreover, data were collected via a questionnaire posted on web-pages and social networks; hence, a conventional response rate could not be calculated. However, there are examples of web-based recruitment methods that show reasonable validity in epidemiology studies.[30, 31] Furthermore, the web-recruitment approach could introduce the possibility of selection bias as only women with internet access who visited the web-pages where the invitation to participate was posted could participate. However, some studies have shown that a large proportion of pregnant women tend to use the internet, including discussion forums and social networks, when in need of pregnancy information.[32, 33] Also, internet access in households in our European target population were generally high in 2012, ranging from 63.0% in Italy to 93.0% in Norway.[34] Another limitation of our study is that all data were self-reported and therefore depended on the women's perception and recall rather than validated data. The use of medications and sick leave during pregnancy may have been underestimated due to recall bias, especially among women who were not pregnant at the time of answering the questionnaire. A previous study demonstrated that retrospective, self-reported sick leave data due to musculoskeletal diseases were comparable with registered sick leave.[35] However, other studies have reported discrepancies in sick leave rates in self-reported data when compared with register data, especially for long-term sick leave.[36, 37] The inclusion of pregnant women at any gestation may also have underestimated the rates of sick leave, as

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

women in early gestation may not have been on sick leave at the time of answering the questionnaire, but were later on in pregnancy. The sensitivity analyses restricted to new mothers only showed that the magnitude of the association between medication use for NVP and sick leave was reduced and no longer significant. This may be because women reported current illnesses to a larger degree and NVP often occur in the beginning of the pregnancy. Also, the French and the Russian study samples represented a small proportion of the general birthing population in these countries; hence, the generalizability of our results should be interpreted with caution, especially in those countries.

CONCLUSION

A large proportion of women were on sick leave during pregnancy, but the rates varied greatly across European countries. Maternal medication use was associated with sick leave, especially for acute illnesses. The differences in sick leave patterns across European countries only partially reflect the differences in each country's sick leave policy, which implies that sick leave in pregnancy is also affected by other national differences.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Acknowledgement The authors would like to thank the Organisation of Teratology Information Services (OTIS), the European Network of Teratology Information Services (ENTIS) Scientific Board and website providers who contributed to the recruitment phase of the main study "Medication Use in Pregnancy: a cross-sectional, multinational web-based study". They would also like to thank all study national coordinators (Twigg MJ, Zagorodnikova K, Mårdby AC, Moretti ME, Drozd M, Panchaud A, Hameen-Anttila K, Rieutord A, Gjergja Juraski R, Odalovic M, Kennedy D, Rudolf G, Juch H, Passier JLM and Björnsdóttir I). They are grateful to all the women who took part in this study.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

A funding statement The main study was supported by the Norwegian Research Council grant number 216771/F11, the Foundation for Promotion of Norwegian Pharmacies, and the Norwegian Pharmaceutical Society.

Contributors AL and HN conceived the idea and participated in the design and coordination of the main study. BT performed the initial analysis, with AL contributing substantially to the final analysis for this sub-study. BT drafted the first manuscript. AL, PK, and HN contributed to the interpretation of the results and critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript and are in agreement to be accountable for all aspects of the work.

Data sharing statement No additional data are available. Researchers can apply for data access for sub-projects within the overall aims of the main study: "The Multinational Medication Use in Pregnancy Study".

REFERENCES

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 Sydsjo A, Sydsjo G, Kjessler B. Sick leave and social benefits during pregnancy-a Swedish-Norwegian comparison. *Acta Obstet Gynecol Scand* 1997;76:748-54.

2 Mogren I. Perceived health, sick leave, psychosocial situation, and sexual life in women with low-back pain and pelvic pain during pregnancy. *Acta Obstet Gynecol Scand* 2006;85:647-56.

3 Malmqvist S, Kjaermann I, Andersen K, et al. The association between pelvic girdle pain and sick leave during pregnancy; a retrospective study of a Norwegian population. *BMC Pregnancy and Childbirth* 2015;15:237.

4 Dorheim SK, Bjorvatn B, Eberhard-Gran M. Sick leave during pregnancy: a longitudinal study of rates and risk factors in a Norwegian population. *Bjog* 2013;120:521-30.

5 Robinson HS, Eskild A, Heiberg E, et al. Pelvic girdle pain in pregnancy: the impact on function. *Acta Obstet Gynecol Scand* 2006;85:160-4.

6 Heitmann K, Holst L, Lupattelli A, et al. Treatment of nausea in pregnancy: a cross-sectional multinational web-based study of pregnant women and new mothers. *BMC Pregnancy Childbirth* 2015;15:321.

7 Sivertsen B, Hysing M, Dorheim SK, et al. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. *BMC Pregnancy Childbirth* 2015;15:129.

8 Khojasteh F, Arbabisarjou A, Boryri T, et al. The Relationship between Maternal Employment Status and Pregnancy Outcomes. *Glob J Health Sci* 2016;8:53533.

9 Xu G, Wu Y, Yang L, et al. Risk factors for early miscarriage among Chinese: a hospital-based case-control study. *Fertility and Sterility* 2014;101:1663-70.

10 Axelsson G, Rylander R, Molin I. Outcome of pregnancy in relation to irregular and inconvenient work schedules. *British Journal of Industrial Medicine* 1989;46:393-8.

11 Bodin L, Axelsson G, Ahlborg G, Jr. The association of shift work and nitrous oxide exposure in pregnancy with birth weight and gestational age. *Epidemiology* 1999;10:429-36.

12 Hansen ML, Thulstrup AM, Juhl M, et al. Occupational exposures and sick leave during pregnancy: results from a Danish cohort study. *Scand J Work Environ Health* 2015;41:397-406.

13 Kankaanpaa AT, Franck JK, Tuominen RJ. Variations in primary care physicians' sick leave prescribing practices. *Eur J Public Health* 2012;22:92-6.

14 Rudbeck M. Variation in patients' sick leave between general practitioner practices. *Scand J Public Health* 2014;42:621-6.

15 Scheil-Adlung X, Sandner L. The case for paid sick leave - Word Health Report Background Paper No. 9 2010 [Date accessed: October 2016 http://www.who.int/healthsystems/topics/financing/healthreport/SickleaveNo9FINAL.pdf?ua=1].

16 Nordeng H. Drug utilization in pregnant women. In: Elseviers M, Wettermakr B, Almarsdottir A, et al., eds. Drug Utilization Research Methods and Applications. West Sussex, UK: Wiley-Blackwell 2016:240-7.

17 Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2010;66:207-14.

18 Petersen I, McCrea RL, Lupattelli A, et al. Women's perception of risks of adverse fetal pregnancy outcomes: a large-scale multinational survey. *BMJ Open* 2015;5:e007390.

19 Dekkers-Sanchez PM, Hoving JL, Sluiter JK, et al. Factors associated with long-term sick leave in sick-listed employees: a systematic review. *Occup Environ Med* 2008;65:153-7.

20 Eriksson HG, von Celsing AS, Wahlstrom R, et al. Sickness absence and self-reported health a population-based study of 43,600 individuals in central Sweden. *BMC Public Health* 2008;8:426.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

21 Kristensen P, Nordhagen R, Wergeland E, et al. Job adjustment and absence from work in mid-pregnancy in the Norwegian Mother and Child Cohort Study (MoBa). *Occup Environ Med* 2008;65:560-6.

22 Strand K, Wergeland E, Bjerkedal T. Work load, job control and risk of leaving work by sickness certification before delivery, Norway 1989. *Scandinavian Journal of Public Health* 1997;25:193-201.

23 Werner EL, Cote P. Low back pain and determinants of sickness absence. *Eur J Gen Pract* 2009;15:74-9.

24 Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open* 2014;4.

25 Social Security Administration and the International Social Security Association. Social Security Programs Throughout the World: Europe 2012 [Date accessed: June 2016 https://www.ssa.gov/policy/docs/progdesc/ssptw/2010-2011/europe/ssptw10europe.pdf].

26 Heitmann K, Svendsen HC, Sporsheim IH, et al. Nausea in pregnancy: attitudes among pregnant women and general practitioners on treatment and pregnancy care. *Scand J Prim Health Care* 2016:1-8.

27 Rezaei E, Moghadam ZB, Saraylu K. Quality of Life in Pregnant Women with Sleep Disorder. *Journal of Family & Reproductive Health* 2013;7:87-93.

28 Howard LM, Molyneaux E, Dennis CL, et al. Non-psychotic mental disorders in the perinatal period. *Lancet* 2014;384:1775-88.

29 Psychiatric Disorders in Pregnancy and the Postpartum: Principles and Treatment. Hendrick V, editor. Totawa, New Jersey: Humana Press; 2006.

30 Ekman A, Dickman PW, Klint A, et al. Feasibility of using web-based questionnaires in large population-based epidemiological studies. *Eur J Epidemiol* 2006;21:103-11.

31 Huybrechts KF, Mikkelsen EM, Christensen T, et al. A successful implementation of e-epidemiology: the Danish pregnancy planning study 'Snart-Gravid'. *Eur J Epidemiol* 2010;25:297-304.

32 O'Higgins A, Murphy OC, Egan A, et al. The use of digital media by women using the maternity services in a developed country. *Ir Med J* 2014;107:313-5.

33 Bert F, Gualano MR, Brusaferro S, et al. Pregnancy e-health: a multicenter Italian cross-sectional study on Internet use and decision-making among pregnant women. *J Epidemiol Community Health* 2013;67:1013-8.

34 Internet use in households and by individuals in 2012. Eurostat Statistics in focus. 2012 [Date accessed: October 2016 http://ec.europa.eu/eurostat/documents/3433488/5585460/KS-SF-12-050-EN.PDF].

35 Fredriksson K, Toomingas A, Torgen M, et al. Validity and reliability of self-reported retrospectively collected data on sick leave related to musculoskeletal diseases. *Scand J Work Environ Health* 1998;24:425-31.

36 Stapelfeldt CM, Jensen C, Andersen NT, et al. Validation of sick leave measures: self-reported sick leave and sickness benefit data from a Danish national register compared to multiple workplace-registered sick leave spells in a Danish municipality. *BMC Public Health* 2012;12:661.

37 Pole JD, Franche RL, Hogg-Johnson S, et al. Duration of work disability: a comparison of self-report and administrative data. *Am J Ind Med* 2006;49:394-401.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

FIGURE LEGENDS

Figure 1 Sick leave rates in each participating country. The numbers of participants in each country were: Poland n=533, Croatia n=237, Serbia n=173, Norway n=1179, Finland n=438, France n=287, Slovenia n=135, Russia n=878, Switzerland n=486, Italy n=720, the United Kingdom n=886, and Sweden n=734.

Figure 2 Reasons for sick leave in pregnancy (n=3385). A woman could report several reasons for being on sick leave. More details on the sick leave categories are presented in Supplementary Table 1.

Supplementary Figure 1 Flow-chart of women who met the inclusion and exclusion criteria for the final study sample.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

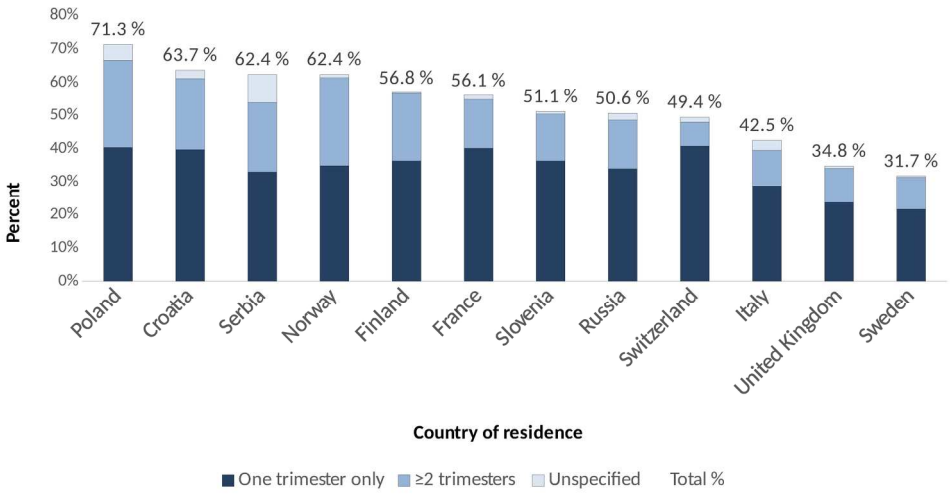


Figure 1: Sick leave rates in each participating country. The numbers of participants in each country were: Poland n=533, Croatia n=237, Serbia n=173, Norway n=1179, Finland n=438, France n=287, Slovenia n=135, Russia n=878, Switzerland n=486, Italy n=720, the United Kingdom n=886, and Sweden n=734.

190x142mm (300 x 300 DPI)

w only

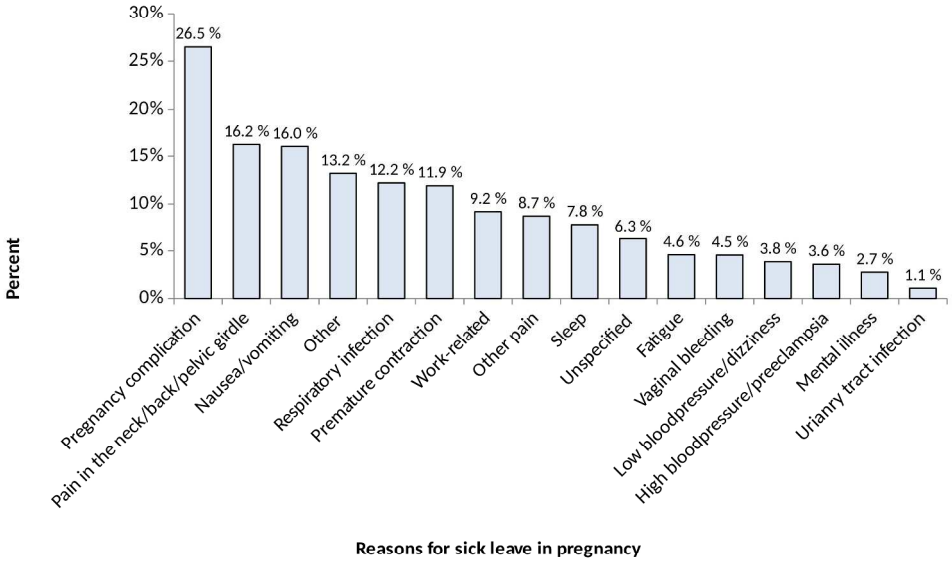
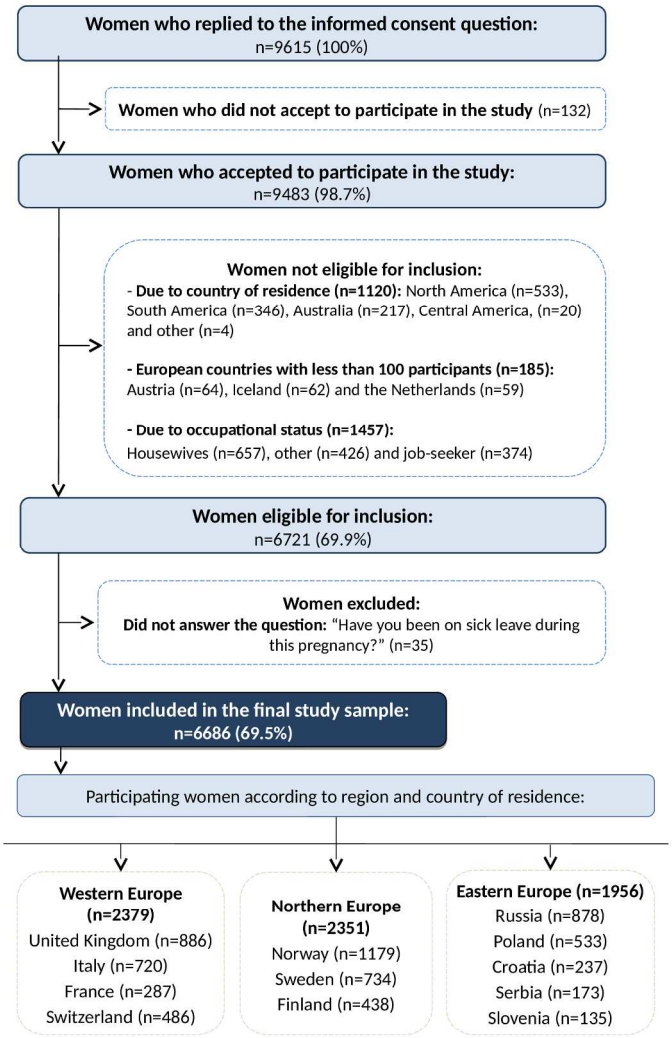


Figure 2: Reasons for sick leave in pregnancy (n=3385). A woman could report several reasons for being on sick leave. More details on the sick leave categories are presented in Supplementary Table 1.

254x190mm (300 x 300 DPI)

For peer review only



Supplementary Figure 1: Flow-chart of women who met the inclusion and exclusion criteria for the final study sample.

190x275mm (300 x 300 DPI)

Supplementary Table 1 Reasons for sick leave.

Category	Free-text entries
Pregnancy complications, n=896 (26.5%)	Epilepsy, carpal tunnel syndrome, cervix insufficiency, complications, gestosis, glucose intolerance, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, hematoma, in vitro fertilization, high maternal age, leakage of amniotic fluid, low placenta, low position of the baby, malnutrition of the fetus, maternal diabetes, medical procedure, multiple pregnancy, obesity, prenatal, previous abortion, ovarian hyperstimulation, placenta abruption, placenta previa, Rhesus-disease, shortened cervix, swollen legs, threatened miscarriage, thrombophilia, varicose veins, water in the body
Other, n=447 (13.2%)	Allergy, anemia, angina, appendicitis, asthenia, cough, death in the family, difficulties walking, endometriosis, fever, end of pregnancy, gastritis, hernia, hospitalization, hypertonia, inflammation in the legs, kidney stone, mononucleosis, operation, ovarian cysts, poisoning, stomach upset, streptococcus, vaginal inflammation, viral infection, weight loss
Respiratory infections, n=413 (12.2%)	Bacterial infections of the airway, bronchitis, chest infection, cold virus, flu, infection of the lungs, influenza, laryngitis, pneumonia, rhinitis, sinusitis, sinus trouble, throat infection, tonsillitis, upper respiratory infection
Premature contractions, n=343 (11.9%)	Increased uterine tone, preterm labor, suspicion of premature birth
Work-related, n=311 (9.2%)	Accident at work, difficulty sitting for a long time, harmful working conditions, hard work, heavy lifting, night work, overtime work, too much standing at work, too long commuting to work, stressful job, working in kindergarten
Other pain, n=295 (9%)	Headache, joint pain, migraine, neuralgia, sciatica
Mental illnesses, n=93 (2.7%)	Anorexia, anxiety, depression, mental stress
Urinary tract infections, n=36 (1.1%)	Includes pyelonephritis and protein in the urine

A woman could report several reasons for being on sick leave during pregnancy. The remaining categories were: pain in the neck, back, or pelvic girdle (16.2%); nausea/vomiting (16.0%); sleep (7.8%); fatigue (4.6%); vaginal bleeding (4.5%); low blood pressure/dizziness (3.8%); and high blood pressure/preeclampsia (3.6%).

For peer review only

Supplementary Table 2 Descriptions of maternity leave in each participating country according to weeks prior to childbirth.

Country	Maternity leave	Weeks before expected date of birth	Trimester
Croatia	28 days before the expected date of birth (45 days if there are complications resulting from the pregnancy)	6.4	3
Finland	50-30 days before the expected date of childbirth	7.1	3
France	Six weeks before	6	3
Italy	Two months before	8	3
Norway	3 weeks before	3	3
Poland	After childbirth	0	-
Russia	70 days before	10	3
Serbia	28 days before (first and second child)	4	3
Slovenia	28 days before	4	3
Sweden	60 days before	8.6	3
Switzerland	up to 196 francs, is paid for up to 98 days (14 weeks) after childbirth	0	-
United Kingdom	Maternity allowance: 15 weeks before Statutory maternity pay after childbirth	15	3

For peer review only

Supplementary Table 3 Maternal health and lifestyle factors, sociodemographic characteristics, and sick leave categorization according to the country of residence among pregnant women and new mothers.

Independent variables	Total population, n=6686	Pregnant women, n=3486	New mothers, n=3200	Pregnant women vs new mothers
Health and lifestyle factors	n (%)	n (%)	n (%)	p-value
Alcohol in pregnancy*				
Yes	1069 (16.0)	494 (14.2)	575 (18.0)	<0.001
No	5562 (83.2)	2958 (84.9)	2604 (81.4)	
Smoking in pregnancy*				
Yes	539 (8.1)	268 (7.7)	271 (8.5)	0.243
No	6133 (91.7)	3210 (92.1)	2923 (91.3)	
Pregnant after infertility treatment				
Yes	476 (7.1)	269 (7.7)	207 (6.5)	0.047
No	6210 (92.9)	3217 (92.3)	2993 (93.5)	
Folic acid use*				
Yes	6151 (92.6)	3199 (92.4)	2952 (92.9)	0.449
No	489 (7.4)	263 (7.6)	226 (7.1)	
Medication for chronic indications				
Yes	1371 (20.5)	720 (20.7)	651 (20.3)	0.754
No	5315 (79.5)	2766 (79.4)	2549 (79.7)	
Medication for acute indications				<0.001
Yes	5254 (78.6)	2610 (74.9)	2644 (82.6)	
No	1432 (21.4)	876 (25.1)	556 (17.4)	
Number of acute conditions				
Mean (SD), range 0-10	4.2 (1.6)	4.2 (1.6)	4.1 (1.6)	<0.001
Chronic conditions**				
No chronic conditions	5279 (79.0)	2762 (79.2)	2517 (78.7)	0.828
Somatic conditions	1167 (17.5)	599 (17.2)	568 (17.8)	
Mental conditions	240 (3.6)	125 (3.6)	115 (3.6)	
Country of residence				
Sick leave policy***				
High	1179 (17.6)	674 (19.3)	505 (15.8)	<0.001
Medium	3128 (46.8)	1536 (44.1)	1592 (49.8)	
Low	2379 (35.6)	1276 (36.6)	1103 (34.5)	
Region				
Northern Europe	2351 (35.2)	1349 (38.7)	1002 (31.3)	<0.001
Eastern Europe	1956 (29.3)	861 (24.7)	1095 (34.2)	
Western Europe	2379 (35.6)	1276 (36.3)	1103 (34.5)	
Sociodemographic and maternal characteristics				
Maternal age (years)				
≤20	168 (2.5)	112 (3.2)	56 (1.8)	<0.001
21-30	3704 (55.4)	1974 (56.6)	1730 (54.1)	
31-40	2698 (40.4)	1351 (38.8)	1347 (42.1)	
≥41	116 (1.7)	49 (1.4)	67 (2.1)	
Marital status				
Married/cohabitant	6375 (95.4)	3333 (95.6)	3042 (95.1)	0.287
Single/divorced/other	311 (4.7)	153 (4.4)	158 (4.9)	

For peer review only

Employment*				
Student	695 (10.4)	342 (9.8)	353 (11.0)	0.014
Healthcare personnel	1088 (16.3)	607 (17.4)	481 (15.0)	
Employed in other sectors	4893 (73.2)	2530 (72.6)	2363 (73.8)	
Highest level of education				
Primary school	191 (2.9)	96 (2.8)	95 (2.9)	0.858
High-school	1736 (26.0)	916 (26.3)	820 (25.6)	
University or collage	3985 (59.6)	2077 (59.6)	1908 (59.6)	
Other education	774 (11.6)	397 (11.4)	377 (11.8)	
Primiparity				
Yes	3603 (53.9)	2085 (59.8)	1518 (47.4)	<0.001
No	3083 (46.1)	1401 (40.2)	1682 (52.6)	
Pregnancy planned*				
Yes	4657 (69.7)	2443 (70.1)	2214 (69.2)	0.076
No, but expected	1491 (22.3)	788 (22.6)	703 (22.0)	
No	519 (7.8)	246 (7.1)	273 (8.5)	

*Total numbers do not add up due to missing values: Folic acid n=46 (0.7%), employment n=10 (0.2%), alcohol in pregnancy n=55 (0.8%), smoking in pregnancy n=14 (0.2%), and pregnancy planned n=19 (0.3%).

**Chronic disorders were categorized as no conditions, somatic conditions only (allergy, asthma, diabetes, hypothyroidism, cardiovascular diseases, and rheumatic disorders), and any mood disorders (anxiety and/or depression), i.e. women with both somatic and mood disorders were categorized in the latter group.

***__High__: Norway, **Medium:** Croatia, Finland, Poland, Russia, Serbia, Slovenia, and Sweden, and **Low:** Italy, France, the United Kingdom, and Switzerland.

For peer review only

Supplementary Table 4 Maternal status of the women at the time of answering the questionnaire in each participating country.

Country	New mothers (n=3200)	Pregnant women (n=3486)				
	Total	Total	1st trimester	2nd trimester	3rd trimester	Average GW
	n	n	n (%)	n (%)	n (%)	Week (range)
Croatia	144	93	24 (25.8)	30 (32.3)	39 (41.9)	22 (4-40)
Finland	145	293	38 (13.0)	107 (36.5)	148 (50.5)	24 (5-42)
France	94	193	45 (23.2)	64 (33.2)	84 (43.5)	22 (1-40)
Italy	227	493	122 (24.8)	206 (41.8)	165 (33.5)	20 (2-41)
Norway	505	674	188 (27.9)	204 (30.3)	282 (41.8)	21 (1-41)
Poland	248	285	50 (17.5)	105 (36.8)	130 (45.6)	23 (1-41)
Russia	553	325	70 (21.5)	88 (27.1)	167 (51.4)	24 (1-41)
Serbia	108	65	5 (7.7)	25 (38.5)	35 (53.9)	25 (5-39)
Slovenia	42	93	24 (25.8)	32 (34.4)	37 (39.8)	21 (5-41)
Sweden	352	382	90 (23.6)	124 (32.5)	168 (44.0)	22 (4-42)
Switzerland	226	260	52 (20.0)	84 (32.3)	124 (47.7)	23 (4-41)
United Kingdom	556	330	16 (4.9)	108 (32.7)	206 (62.4)	27 (3-41)

GW = Gestational week.

For peer review only

Supplementary Table 5 Prevalence overall and of extensions of sick leave and the top three reasons for sick leave in each country.

Country of residence	Total sick leave	Sick leave in ≥ 2 trimesters	Most frequent reason for sick leave
	% (n)	% (n)	Reason (%)
Eastern Europe			
Poland	71.3 (355)	39.4 (140)	Pregnancy complications (27.6) Due to work (20.8) Other (13.7)
Croatia	63.7 (145)	35.2 (51)	Pregnancy complications (43.7) NVP (11.3) Vaginal bleeding (10.6)
Serbia	62.4 (93)	38.7 (36)	Pregnancy complications (26.9) Other (19.4) Due to work (15.7)
Slovenia	51.1 (68)	27.9 (19)	Pregnancy complications (33.3) Vaginal bleeding (18.8) Respiratory infections & other (11.6)
Russia	50.6 (128)	30.1 (128)	Pregnancy complications (46.2) Respiratory infections (32.9) Premature contractions (8.1)
Northern Europe			
Norway	62.4 (724)	43.2 (313)	Pain in the neck, back, or pelvic girdle (42.9) NVP (29.5) Sleeping problems (16.4)
Finland	56.8 (248)	35.9 (89)	Respiratory infections (23.3) Premature contractions (22.9) Pain in the neck, back, or pelvic girdle (20.5)
Sweden	31.7 (230)	31.3 (72)	Pregnancy complications (31.3) NVP (22.8) Pain in the neck, back, or pelvic girdle (10.3)
Western Europe			
France	56.1 (157)	26.8 (42)	Premature contractions (22.2) Sleeping problems (19.3) Pain in the neck, back, or pelvic girdle (13.0)
Switzerland	49.4 (233)	15.0 (35)	Premature contractions (23.6) Pregnancy complications (20.0) Other (16.7)
Italy	42.5 (284)	27.1 (77)	Pregnancy complications (34.0) NVP (11.8) Respiratory infection (10.4)
The UK	34.8 (302)	30.8 (93)	NVP (33.8) Respiratory infections (22.1) Other pain (16.9)

The UK = United Kingdom; **NVP =** nausea and vomiting

For peer review only

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

"Sick leave and medication use in pregnancy - a European web-based study"

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	Supplementary Figrue 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8, 9, Table 1
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Not relevant
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not relevant
		(*e*) Describe any sensitivity analyses	9

For peer review only

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary Figure 1
		(b) Give reasons for non-participation at each stage	Supplementary Figure 1
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10, Table 1, Supplementary Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Page 10, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	Page 12, Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 14, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17, 18, 19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only