PROTECT Pregnancy Study: An Exploratory Study of Self-Reported Medication Use in Pregnant Women

Prepared on behalf of the PROTECT Consortium by

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Abstract

The PROTECT Pregnancy Study was designed to pilot direct-to-patient data collection methods for use in postmarketing surveillance into the foetal effects of maternal medication use in pregnancy. This study which recruited women between October 2012 and January 2014 explored whether women in participating EU countries were willing to provide information via the internet to enable prospective collection of medication exposure data and information about other life style factors during pregnancy. The study's main objective was to assess the extent to which data collected directly from pregnant women via the Internet and an interactive voice response system (IVRS) would provide information on medication use and other potential risk factors throughout pregnancy that is suitable for research purposes.

Pregnant women were recruited for the study using a variety of methods and were asked about use of medications, alcohol and tobacco, recreational drugs, herbals and other factors that could negatively affect birth outcome. The pilot study revealed that women would indeed volunteer to provide information on medication and lifestyle factors during pregnancy, with 2521 women enrolling from four countries over 8-18 months. The four countries include the United Kingdom (UK), The Netherlands (NL), Denmark (DK) and Poland (PL). Of those who enrolled in the PROTECT pregnancy study, only 2066 provided any data, with all but one providing data via internet. Of the 2065 who provided data via the Internet, 23% were recruited during their first trimester of pregnancy, 52% in their second and 25% in their 3rd trimester, showing that it was indeed feasible, though more difficult, to recruit women early in pregnancy.

Eighty-three percent of women used 1 or more medicines (range 0-16) during their pregnancy or in the preceding month, with 19% reporting using 5 or more different medications. Women reported using slightly more medications during the first trimester (36% reported using at least one medication), compared with the second (34%) and third (32%) trimesters. Comparing data reported from the women in PROTECT with their linked data (primarily in the Danish registers) revealed that 83% of self-reported medicines prescribed for chronic conditions that were also recorded in the national prescription medication register. Women also reported taking several drugs which were not in the register during or within the preceding pregnancy. Much of this "non-register" drug use may be explained by non-prescription drug use or use at hospital or medications purchased more than six months prior to pregnancy. Further, 24% of women reported taking non-prescription medications during pregnancy, not counting herbals and dietary supplements; seven percent reported using herbal products during pregnancy. These findings suggest that register or survey data alone will not give a complete and accurate reflection of total drug use during pregnancy since there is both a significant non-prescription medication use and a discrepancy between recorded and reported medicine use. Also, self-reported data contained quite a lot of valuable information on medicines used for short-term conditions and medications used intermittently. Overall about one percent of women reported that they had taken medications that were prescribed for others and given to them, and seven percent reported having decided not to take medications that had been prescribed for them. In addition, seven percent of women reported having received anaesthetics during pregnancy, and five percent reported exposure to x-rays.

Pregnancy outcomes were provided by 464 out of 1555 women whose expected dates of delivery occurred while the study was still actively collecting data. Overall 91% of women who reported a pregnancy outcome had a live birth. Eight of these births were twins which corresponds to population based figures. The frequency of foetal loss before 22 weeks of pregnancy was highest in Denmark 15% compared with 0-8% in the other three countries. Since a

higher percentage of women in Denmark than in other countries were recruited during the first trimester when foetal loss is highest, this result is not surprising. Ten mothers (2.3%) reported that their babies had a birth defect that was "visible" to them at birth. Since the question posed to mothers was about visible defects rather than any defect because we thought that none-visible birth defects might not be immediately detected, it is our interpretation that what we observed is close to the expected range as reported by clinicians.

We also conducted a comparison of self-reported data with data from electronic health records in the UK but were only able to match a small number of records, which precluded much generalization.

This pilot study has provided valuable insights into whether data collected directly from consumers are suitable for research purposes. We found that it was possible to recruit pregnant women without the direct intervention of health care professionals, but that paid advertisements were necessary to recruit a reasonable sample size in a relatively short period of time. We were also able to recruit women earlier in pregnancy than is generally possible using the more traditional methods of data collection. Respondents provided details of prescription medication use. They also reported non-prescription medicine use as well as herbal and homeopathic drug use – all of which have proved difficult to collect by other means. Women were also willing to provide details of life-style choices such as alcohol, smoking and recreational drug use which are frequently not accurate or non-existent in medical records. This means that information on other risk factors and potential confounders can be collected to increase the value of this type of non-interventional research for understanding the teratogenic effects of medications and other exposures during pregnancy.

In summary, direct to consumer studies offer important benefits in obtaining data not found in prescription drug registers and electronic health records, and these type of studies will be most informative when combined with selected data from other sources to validate clinical outcomes of interest, and to corroborate most important exposures.

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1 Introduction

1.1 Introduction to direct pharmacovigilance

The use of therapeutic medication during pregnancy, whilst in many cases essential for the health of the mother, causes concern regarding the potential for deleterious effects on the foetus. Indeed, medicine use in pregnancy can be related to a variety of adverse outcomes, including not only congenital malformations, but also preterm birth, intrauterine growth restriction, spontaneous abortion, late foetal death, neonatal death, or developmental disabilities (behavioural, neurological, motor, intellectual or sensory) that only become apparent in later infancy or childhood.

A priori knowledge of the effects of many medicines taken during pregnancy is often limited. Pregnant women are often excluded or discontinued from pre-marketing clinical trials in humans, so the safety of many drugs in pregnant women has not been established at the time of drug licensing. Unless the medicine is intended to treat pregnancy specific conditions, at the time of licensing information with respect to reproductive toxicity is only available from animal studies. Because of wide variations in species-specific effects, even among mammalian species, such studies in animals do not necessarily predict human teratogenesis.[1] Another complication is that teratogenic effects in humans cannot be fully predicted from the class of a drug or from what is known about its pharmacology and toxicology.[2]

Consequently, many drugs are not recommended for use during pregnancy or have special warnings because their safety during pregnancy has not been studied sufficiently for physicians to be confident that they are safe. While some drugs can be avoided during pregnancy; however, medications for chronic diseases such as diabetes, epilepsy, asthma, and rheumatic diseases may need to be continued because these conditions, left untreated, can be detrimental to both the mother and the foetus.

There is evidence that prescription medication use actually increases during pregnancy, but primarily for the treatment of pregnancy-related symptoms.[3] Estimations of the percentage of women prescribed drugs during pregnancy vary, but several suggest that the frequency may be as high as 84-99%.[3-6] Furthermore, many medications are obtained without prescription and/or may not be perceived as medicines, and therefore are not easily tracked in any standard health record or prescription registry.[7] Women who are concerned about conventional drug use in pregnancy may also turn to alternative therapies, such as homeopathic or herbal medicines. Many of these alternative drugs are less well regulated and information about the potential risks of their use in pregnancy is often lacking even pre-clinical data.

Many pregnancies are unplanned and women initially may not be aware of their pregnancy resulting in inadvertent expose of the foetus to prescribe or over the counter medications. As organogenesis occurs early in pregnancy, detrimental effects on the foetus may have already occurred before pregnancy is suspected or confirmed. Therefore, it is critical to collect information on drug exposure in relation to gestational age to answer questions on whether a medicine may harm the foetus and, if it does, the developmental stage when the foetus is vulnerable to the effects of the drug. There is also increasing awareness that drugs given later on in pregnancy may also have detrimental effects on the foetus.

Given the ethical considerations relating to clinical trials in pregnant women and the difficulties in extrapolating animal reproductive data to humans, information on the safety of medicines during pregnancy can usually only be collected using observational data post authorisation.

For the evaluation of drug safety in pregnancy, different approaches are available. Spontaneous reports can provide a signal of increased risk, cohort studies provide the opportunity of evaluating a range of pregnancy outcomes

associated with exposure, and case-control studies can evaluate an increase in risk of specific birth outcomes. However, all methods are hampered by the fact that for this type of evaluation, drugs cannot be grouped pharmacologically; instead, they need to be evaluated separately; many of the outcomes of interest are rare and similarly cannot be grouped, and as a consequence, the population size needed for any evaluation is substantial.[2]

Acknowledging that no single method of data collection and/or analysis is sufficient to monitor all drug-induced teratogenic effects, various post-marketing surveillance strategies are required to optimise data collection.

For all study designs, collection of accurate information about exposure and outcome is essential. In addition to medication, it is also important to collect data on lifestyle factors including alcohol consumption, smoking and the use of drugs of abuse, all of which have been associated with adverse pregnancy outcomes. Ideally, to avoid bias, complete exposure to medications and risk factor information needs to be collected prospectively at frequent intervals and before the pregnancy outcome is known.[7-10]

The majority of these data sources collect their data on drug exposure during pregnancy either from health care professionals, through direct patient questioning by an interviewer (frequently a midwife) or have utilised prescription or dispensing records. Using researchers to collect information is time consuming and expensive, and can only be performed at relatively infrequent times during the pregnancy, which may lead to lost information.[9] In addition, women may be reluctant to report accurate information about lifestyle behaviours already identified as being potentially harmful to a foetus, or which are in themselves illegal, in a face-to-face interaction.

There is some evidence that using the internet may overcome these issues related to collection of potentially sensitive information. A study on sexually transmitted diseases using an anonymous internet questionnaire successfully collected data on the number of sexual partners and cocaine use.[11]

A Danish study on women trying to conceive collected data on frequency of sexual intercourse, household income, and lifestyle factors, and explored the effect of questionnaire length on willingness to participate and attrition.[12] It found that women were willing to provide the information and that questionnaire length did not influence participation or the amount of missing data.[13] Women were willing to provide identifying information, such as their civil registry number and e-mail address, making it theoretically possible to link them personally to national registries.[12] This indicates that sensitive data can be collected via the internet and can be collected with sufficient identifiers to permit linkage to other sources.

There is evidence that ongoing, prospective collection of drug information in pregnant women linked with congenital malformation registries can be used to evaluate specific drug risks such as has been demonstrated with SSRIs but this used face to face interview with the potential limitations as specified above.[8]

This study will explore and assess whether women in participating EU countries are willing to provide information via the internet to enable prospective collection of medication exposure data and information about other life style factors during pregnancy. It is often assumed that people who are IT-literate and have internet access may not be representative of the general population. This study will also use an alternative method of data capture – an interactive voice response system (IVRS) - to capture data and will compare the demographics and attributes of the two populations. Because of the technical difficulties and differences associated with IVRS, it was not intended that the questionnaires will mirror each other nor that similar numbers using each modality will be recruited but the numbers and information collected will allow comparisons to be made.

1.2 IMI-PROTECT and Work Package 4

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. It does this by facilitating collaboration between the key players involved in healthcare research, including universities, the pharmaceutical and other industries, small and medium-sized enterprises (SMEs), patient organisations, and medicines regulators. IMI is a partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). PROTECT (Pharmacoepidemiological research on outcomes of therapeutics by a European consortium) is one of the programs ongoing at the IMI. The PROTECT project will enhance the monitoring of the safety of medicinal products. It was designed to contribute to better evaluating and communicating their benefit-risk profile throughout their lifecycle. To this end, innovative tools and methodological standards will to be developed. The European Medicines Agency coordinated PROTECT and managed a Consortium of 35 public and private partners and its 7 work packages (WP).

This study report will discuss the objective, methods and results of Work Package 4 (WP-4). The overall objective of WP4 is to explore the feasibility and added value of modern methods for collecting data directly from consumers. Partners involved include; European Medicines Agency (EMA), Lægemiddelstyrelsen (DKMA), GlaxoSmithKline Research and Development LTD (GSK), International Alliance of Patients' Organizations (IAPO), Rijksuniversiteit Groningen (RUG), University of Newcastle upon Tyne (UNEW), Imperial College London (Imperial), Poznan University of Medical Sciences (PUMS), Sanofi-Aventis Research and Development (SARD), Genzyme Europe B.V. (Genzyme), Amgen NV (Amgen), H. Lundbeck A/S (HLU) and Quintiles. Although not formally a partner, significant input was provided by IMS-Cegedim Strategic Data Medical Research.

1.3 PROTECT Pregnancy Study

This study was carried out to test new ways of collecting information on lifestyle factors, health and use of medicines throughout pregnancy in a large number of pregnant women. It was a pilot study to see whether research quality data could be collected directly from pregnant women without the intervention of health care professionals. Among the questions to be answered were:

a) Demographic characteristics and health status of pregnant women at study entry

b) The length of time and consistency with which pregnant women recruited via internet would provide the data requested.

c) Compare the usage, accuracy and completeness of self-reported prescription drug use, self-reported data with data from external sources (pharmacy data bases and electronic health records) in countries where such resources exist, or with national data.

d) The usage of over-the-counter products, as well as homeopathic and herbal medication use in pregnancy.

e) The validity of self-reported pregnancy outcomes, to the extent such data could be verified.

f) The effect, if any, of the frequency of data collection on the completeness and accuracy of reporting

g) The extent to which women would report “sensitive” information about lifestyle and other risk factors for congenital effects

h) The amount of loss to follow up and reasons for discontinuation

Other questions of interest included:

- Can we get data earlier in pregnancy than traditional routes?
- How representative are the women?
- Are there differences between the populations who chose to use IVRS or the internet?
- How important are data *not* captured by EHR or pharmacy databases?
- Is the information collected directly from pregnant women of sufficient quality to be used for pharmacovigilance?

1.4 Methods overview

The study was a non-interventional, prospective study of pregnant women who agreed to provide information about their medication use and certain lifestyle factors on a periodic basis throughout their pregnancy. Volunteers were recruited by measures such as placement of pamphlets in pharmacies and by links from carefully selected websites and social networking sites. In Poland, radio and TV were also used to inform potential participants about the study. Subjects were invited to learn more about the study either through visiting the study web site or phoning a telephone number where a recorded message described the study and invited eligible women to register for participation (see Figure 1-1).

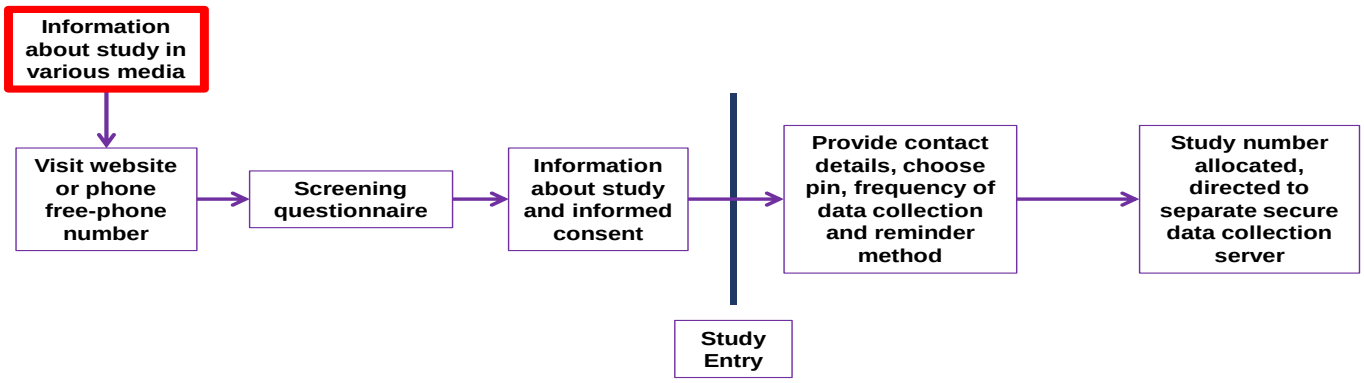


Figure 1-1 Overview of study entry

The screening questionnaire checked that the woman was pregnant, lived in one of the four participating countries and was over the country age of consent. After enrolment, participants were asked whether they prefer to provide data via the internet or by interactive voice response system (IVRS). Participants were also asked to choose between providing data every 2 weeks or every 4 weeks. Women who chose to provide data via the internet were reminded when data collection was due by an e-mail with a secure link. Women using the IVRS system could either phone using a toll free number or the system would phone the number they provided. For logistical reasons, not all phone calls from a mobile could not be made toll free so women were warned about this and the potential loss of included package minutes.

Data were collected in the predominant natural languages of the four study countries: Denmark, the Netherlands, Poland, and the United Kingdom (UK).

Figure 1-2 shows an overview of the study. It was realised that IVRS is not an ideal way to collect data and that collecting data via the internet was much more suitable. One of the main concerns was that, if an IVRS was not used in the future, would we miss a particular segment of the population? Therefore the main question relating to IVRS

was whether the women who chose IVRS as their preferred method of data provision were different from those who chose to use web-based approaches. For this reason, it was decided that women choosing to provide data by IVRS would have a shortened baseline questionnaire and be followed up for pregnancy outcome only. Figure 1-2 shows an overview of the data collection schedule for both systems.

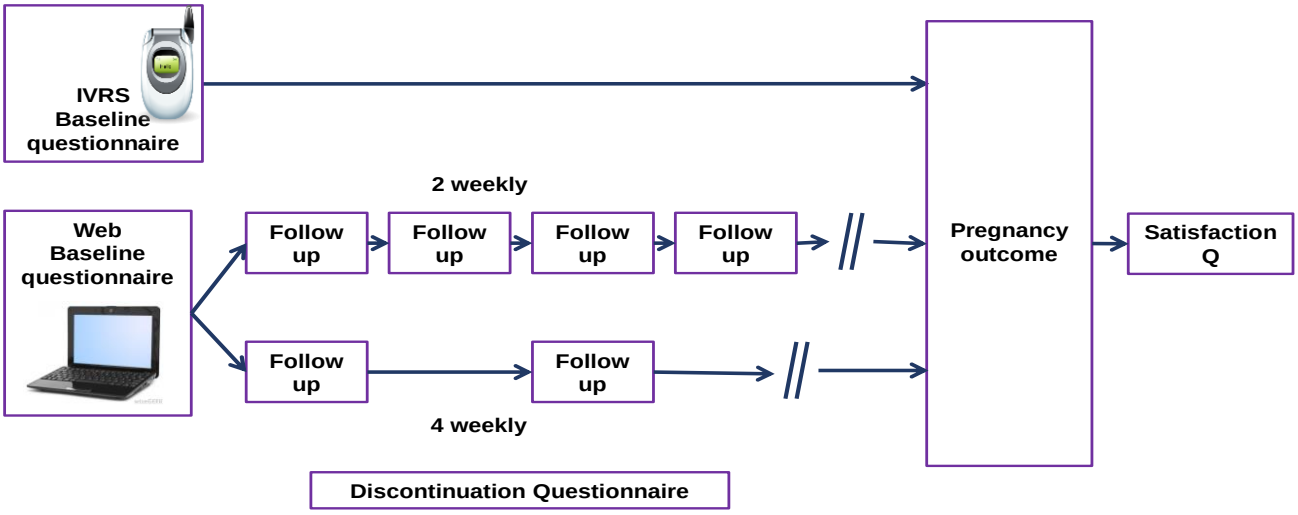


Figure 1-2 Overview of data collection

Data were collected on use of prescription and non-prescription medication, as well as on use of herbals and homeopathic medications and dietary supplements including vitamins, folic acid and iron (see Figure 1-3)

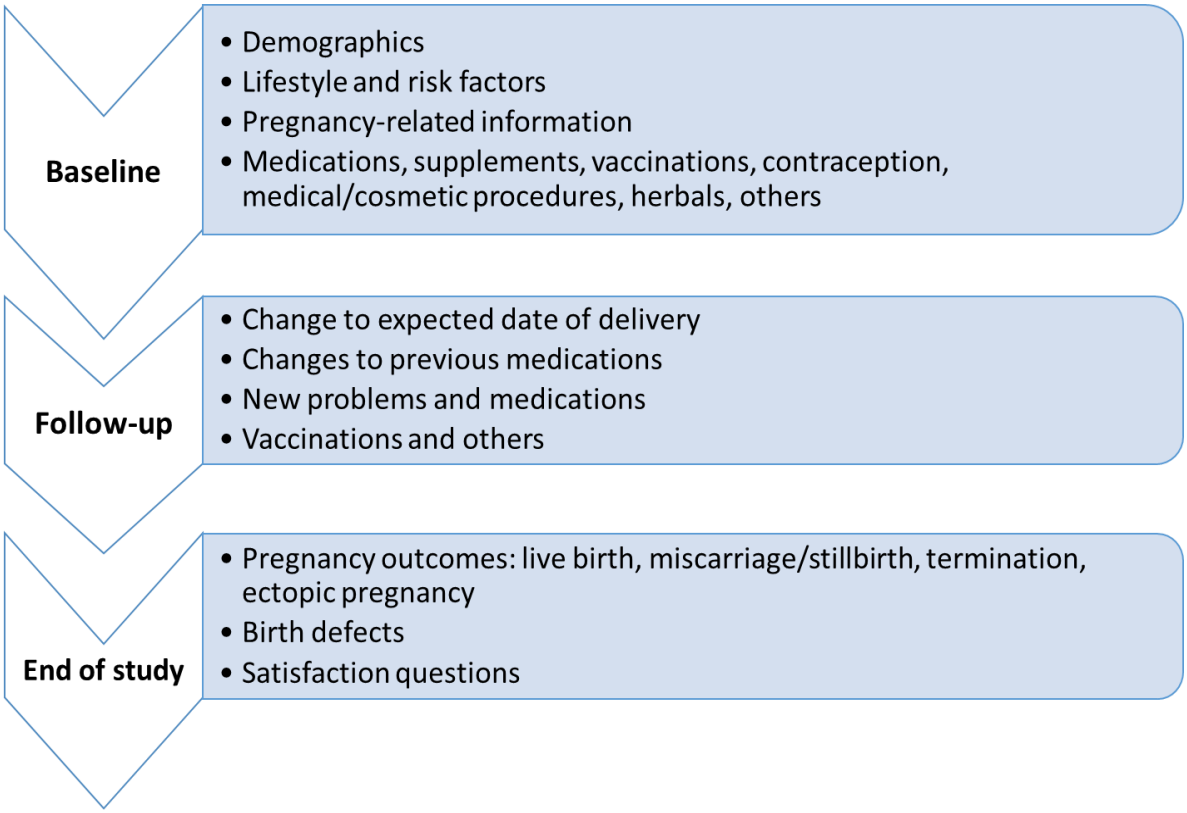


Figure 1-3: Schematic of data collection

More information was collected from women who provided their response over the internet than by phone, in order to best utilise the full capacity of internet- based data collection.

Three of the four countries (Denmark, the Netherlands, the UK) had automated systems of recording prescription data, either on a national (Denmark), regional (the Netherlands) or general practice-specific basis (in the UK, THIN). In the UK and Denmark, where individual matching was possible, analyses was performed to compare self-reported information with that recorded electronically. In The Netherlands, self-reported prescription use was compared with regional data for pregnant women.

2 Recruitment

2.1 Introduction to recruitment

For inclusion in the study participants were required to be currently pregnant, residing in one of the four study countries, have adequate natural language skills for that country, to have internet or phone access and to be of legal age for the provision of their consent to participate (Denmark, Netherlands and Poland – 18 years, UK – 16 years). In Denmark there was an additional requirement for participants to provide their civil registration number. In Denmark, all participants had to provide consent via the secure internet website (SIW) regardless of whether they chose to use the internet or IVRS to provide data. In the Netherlands and the UK, informed consent to participate was provided electronically via the SIW or via the IVRS system. In Poland participants were required to provide hand signed declarations of consent via forms printed from the SIW and mailed to the local study team.

Because this study was a pilot study, the target sample size of 4,800 women (1,200 per study location) was selected based on affordability (data storage and cleaning), with a goal of recruiting participants over a 24 month period. Due to time-delays experienced in gaining data protection approvals, the recruitment period was subsequently reduced to 16 months, with a proportionate (assuming linear recruitment) 33.3% reduction in target sample size (3,200 women – 800 per study location).

Participants were recruited between the 1st October 2012 (recruitment week 1) and 31st January 2014 (recruitment week 70) in Denmark, Netherlands and UK. Due to difficulties in arranging ethical approvals, the start date in Poland was further delayed until 20th May 2013 (recruitment week 34) which proportionately (assuming linear recruitment) decreased the target sample size 47.1% further for this location (423 women). Data were collected from all participants until 28th March 2014. Participants received no incentives for enrolment or providing data. We believe that their main motivation was the altruistic contribution towards improving knowledge surrounding medication use in pregnancy.

2.2 Aims of recruitment

A key recruitment objective was to use direct-to-participant advertisements which did not require healthcare professional interventions/promotion wherever possible to recruit women early in their pregnancy, and at low or no cost.

2.3 Recruitment methods employed

In the first 18 weeks of the recruitment period low/no-cost advertisement methods were used in Denmark, Netherlands and UK. These included posting promotional discussion topics in pregnancy e-forums (UK), placing small hyperlinks on pregnancy related websites (Netherlands), displaying leaflets and posters in community pharmacies and/or obstetric/midwifery units (Netherlands and UK, Poland from week 34), sharing advertisement materials through a social media profile (Facebook - UK), and low-cost banner advertising in pregnancy-specific sections of a popular health and wellbeing website (Denmark). After initial low/no-cost advertising attempts, additional funding was provided for higher cost advertising methods which included large digital banners (Denmark), hyperlinks (Netherlands) and small picture/text graphics (UK) placed on more prominent pregnancy information websites, adverts in emails sent to registered users of widely used pregnancy/health information and parenting websites (all locations), an advert aired on regional/digital-internet television channels (Poland), a full page article in a regional newspaper (Poland) and pregnancy magazine (Poland), and paid advertising on a social media site (Facebook) targeted at women of reproductive age (16-45) with interests related to children, pregnancy and health (UK).

2.4 Enrolment timeline and early study discontinuation

As represented in Figure 2-1 below, a total of 2,521 study participants provided informed consent to participate in the study. Of these only 14 chose to provide data using the IVRS. Because of the small number of women choosing IVRS – of whom only one completed the initial baseline questionnaire figures from now on refer only to the 2507 who chose to provide data using the internet. A significant number of these internet participants also discontinued prior to the completion of the baseline study questionnaire leaving 2065 active study participants.

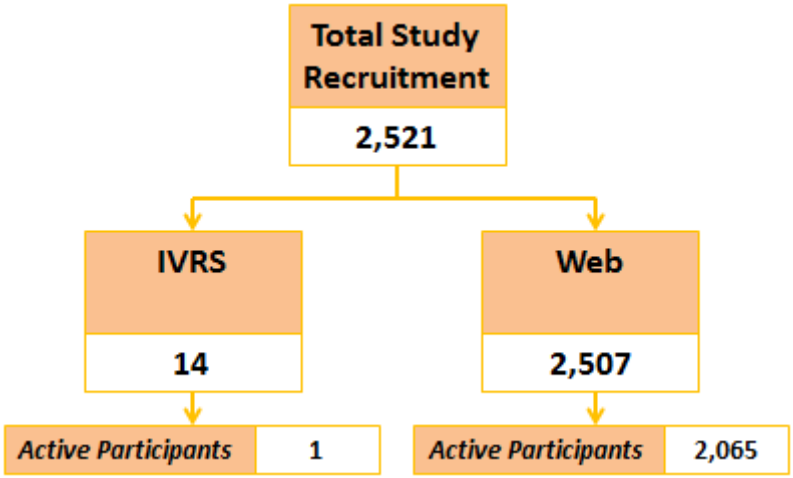


Figure 2-1 Total number of participants recruited to the study and actively participating via the IVRS and website data collection tools

Data for those participating via the website by age and country are provided in Table 2-1 (all women screened) and Table 2-2 (all women who dropped out). The proportion of participants recruited who discontinued participation appeared similar between three of the four study locations (Denmark 17.0%, the Netherlands 16.2% and UK 16.9%). In Poland the rate of study discontinuation was larger (23.7%).

Table 2-1 Total number of women enrolled (screened) by age at screening and country

	Denmark	Netherlands	Poland	United Kingdom	All
All ages (N)	770	568	316	853	2507
<20	0.4% (3)	0.4% (2)	1.9% (6)	1.1% (9)	0.8% (20)
20-24	8.7% (67)	6.7% (38)	15.8% (50)	10.4% (89)	9.7% (244)
25-29	32.7% (252)	35.0% (199)	43.4% (137)	28.0% (239)	33.0% (827)
30-34	36.4% (280)	42.1% (239)	30.7% (97)	36.2% (309)	36.9% (925)
35-39	18.6% (143)	13.6% (77)	7.6% (24)	20.3% (173)	16.6% (417)
40+	3.2% (25)	2.3% (13)	0.6% (2)	4.0% (34)	3.0% (74)
Mean age (SD)	30.7 (4.7)	30.4 (4.3)	28.6 (4.4)	30.8 (5.2)	30.4 (4.8)

Table 2-2 Women enrolled (screened) but dropped out before completing a baseline questionnaire by age at screening

	Denmark*	Netherlands*	Poland*	United Kingdom*	All
All ages (N)	17.0% (131)	16.2% (92)	23.7% (75)	16.9% (144)	17.6% (442)
<20	33.3% (1)	50.0% (1)	66.7% (4)	22.2% (2)	40.0% (8)
20-24	16.4% (11)	15.8% (6)	44.0% (22)	19.1% (17)	23.0% (56)
25-29	13.5% (34)	18.1% (36)	18.3% (25)	18.4% (44)	16.8% (139)
30-34	16.8% (47)	15.5% (37)	21.6% (21)	14.2% (44)	16.1% (149)
35-39	23.1% (33)	11.7% (9)	8.3% (2)	17.3% (30)	17.7% (74)
40+	20.0% (5)	23.1% (3)	50.0% (1)	20.6% (7)	21.6% (16)
Mean age (SD)	31.6 (5.0)	29.8 (4.3)	26.8 (4.6)	30.7 (5.4)	30.1 (5.2)

* Percentage of the total in the age group by country (Table 2-1)

The mean age of participants who discontinued participation before providing study data was lower than that of those who continued to participate in three of the four study locations (the Netherlands 29.8 vs. 30.4, Poland 26.8 vs. 28.6 and UK 30.7 vs. 30.8 years). In Denmark the mean age of study participants who discontinued participation was higher (31.6 vs 30.7).

Following the early discontinuation of the 442 participants, 2065 participants, 82.4% of those enrolled, provided study data (DK=639, NL=476, PL=241, UK=709).

Table 2-3 below provides an age and country adjusted comparison of study discontinuation before providing study data relative to that experienced in the UK. There were no overall age differences between those who discontinued the study early and those who completed at least one questionnaire, but there were age differences within countries. Those who discontinued the study early in Denmark were slightly older, similar in the Netherlands and they were slightly younger in Poland, when compared to the UK.

There were significance differences when comparing the early discontinuation across countries (Table 2-3). Denmark had the lowest incidence rates of early discontinuation, and significantly different from other countries. Poland had the highest incidence rates of early discontinuation. The high rate in Poland may be due to delay with providing printed informed consent and the influx of enrolled participants in the weeks before study closure. However, enrolled participants had at least about 8 weeks between enrolment and study closure on 28th March 2014, when last data were collected.

Table 2-3 Incidence rates ratio of early drop-outs adjusted for age and country

	Number dropped out prior to providing baseline data	Number provided study data	Incidence rates ratio (95% CI)
Denmark	131	639	1.00
Netherlands	92	476	7.36 (1.51 – 35.74)
Poland	75	241	61.90 (10.16 – 377.00)
UK	144	709	3.97 (1.19 – 13.24)
Age, per year	NA	NA	1.04 (1.01 – 1.07)
Interactions with age, UK	NA	NA	1.00
Netherlands	NA	NA	0.94 (0.89 – 0.98)
Poland	NA	NA	0.88 (0.82 – 0.94)
UK	NA	NA	0.96 (0.92 – 0.99)

NA = Not applicable

Figure 2-2 below shows the percentages and number of women, out of those who provided study data, by the frequency they chose to provide follow-up data. Participants in the Netherlands and Poland had greater preferences for less frequent contact with the study, where respectively 70% and 64% chose to provide data every 4 weeks instead of every 2 weeks (NL=30%, PL=36%). About equal proportions of participants in Denmark and the UK chose to provide data every 4 weeks (DK=51%, UK=51%) and every 2 weeks (DK=49%, UK=49%).

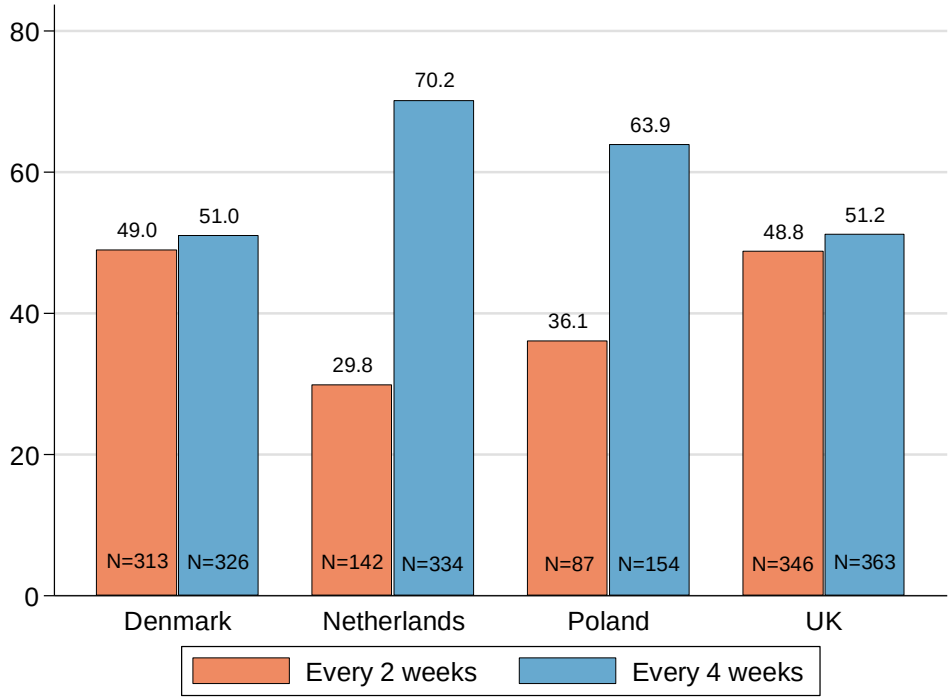


Figure 2-2 Percentages and number (N) of women by country and the chosen frequency to provide follow-up data

Figure 2-3 below describes the cumulative number of study participants recruited over the 70 week recruitment period for each study location. The graphic demonstrates a clear increase in the number of study participants recruited after the implementation of higher cost advertising methods in the UK around February 2013.

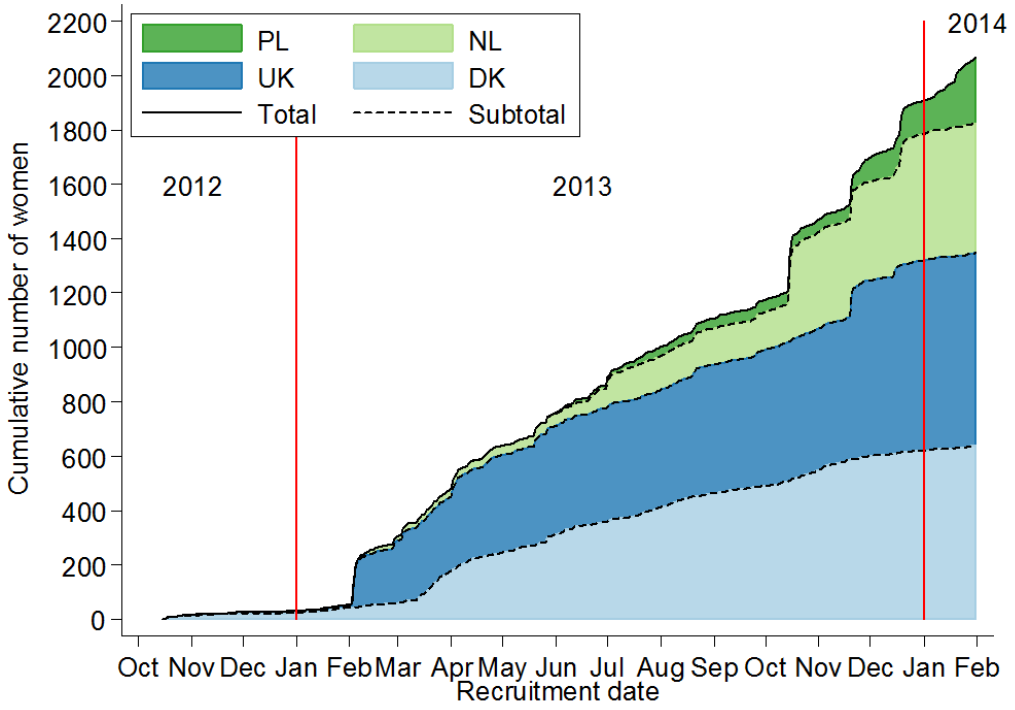


Figure 2-3 Cumulative recruitment by country and month

Although we initially aimed to recruit 1200 women to participate by the website from each country over 24 months, the actual recruitment time was reduced from 24 months to 18 months in 3 countries, and to only 8 months in one country because of unforeseen delays including that caused by data protection issues. Figure 2-4 describes the proportion of the total sample size recruited in each of the four study locations, and the total number of these participants who continued to be active in the study after recruitment.

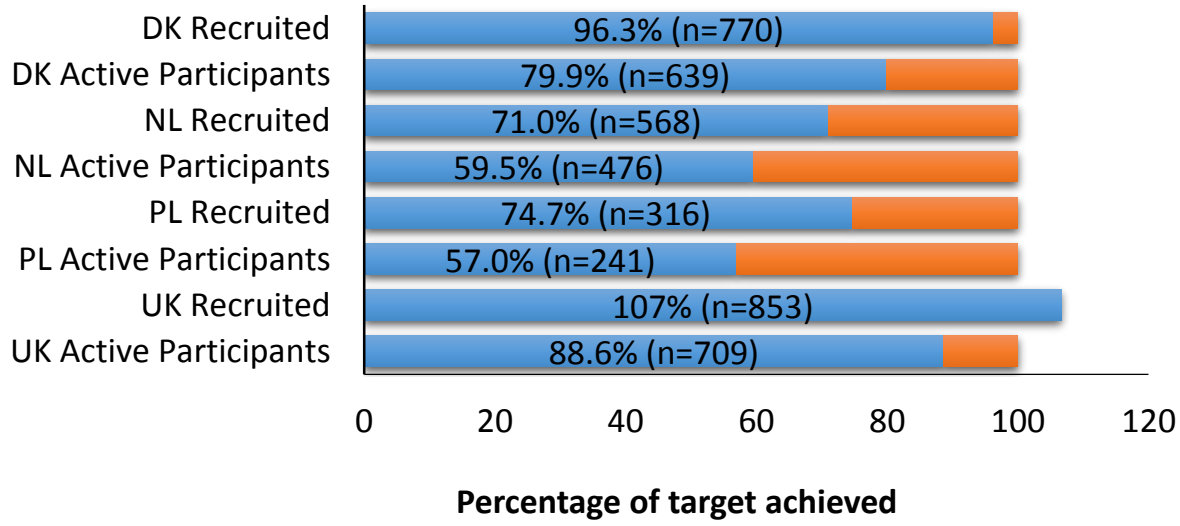


Figure 2-4 Proportion of sample size recruited and actively participating in each study location relative to the target sample size

2.5 Route of recruitment

Study participants were recruited through the various advertisement methods outlined above, and country leads determined which methods should be used based on their local experience with the target population. These individual recruitment methods were crudely grouped into broadly comparable advertisement types. Table 2-4 below provides an overview of the proportion of women recruited by each of these advertisement types and demonstrates the differences between the four study locations which reflect the differences in the way in which country leads predominantly advertised the study. We shaded the predominant recruitment routes in each country in Table 2-4.

Table 2-4: Grouped percentage (frequency) of women recruited by advertising route and country

	Denmark	Netherlands	Poland	United Kingdom
Facebook	0.0% (0)	1.5% (7)	9.1% (22)	1.1% (8)
Leaflet	0.0% (0)	14.3% (68)	19.5% (47)	11.1% (79)
Club e-mail	3.1% (20)	72.7% (346)	19.5% (47)	82.1% (582)
Web advertisement	93.0% (594)	7.4% (35)	9.1% (22)	2.8% (20)
Word of mouth	3.1% (20)	1.1% (5)	9.1% (22)	1.7% (12)
Other	0.8% (5)	3.2% (15)	33.6% (81)	1.1% (8)
Total (N)	**639**	**476**	**241**	**709**

The interactive graph (http://public.tableausoftware.com/views/wp4/Dashboard2?:embed=y&:display_count=no) allows exploration of the cumulative recruitment by country and recruitment strategy. In order to clearly see individual trends, one could select the county of interest, as well as excluded dominant lines.

2.6 Trimester of pregnancy at recruitment

One of the primary aims of the recruitment strategy of this study was to enrol women at an early stage of their pregnancy. During the completion of the baseline questionnaire, all participants were asked to provide their estimated due date (EDD). At each follow up, we asked whether the EDD had changed. We used the last provided EDD to calculate the time of gestation at enrolment in weeks since the first day of their last menstrual period (LMP: EDD-40 weeks) to define gestational trimester at recruitment (first: 1-12 weeks post LMP, second: 13-26 weeks post LMP, third: 27-40 weeks post LMP). Figure 2-5 is a display of the proportion of active study participants recruited in each trimester stratified by study country.

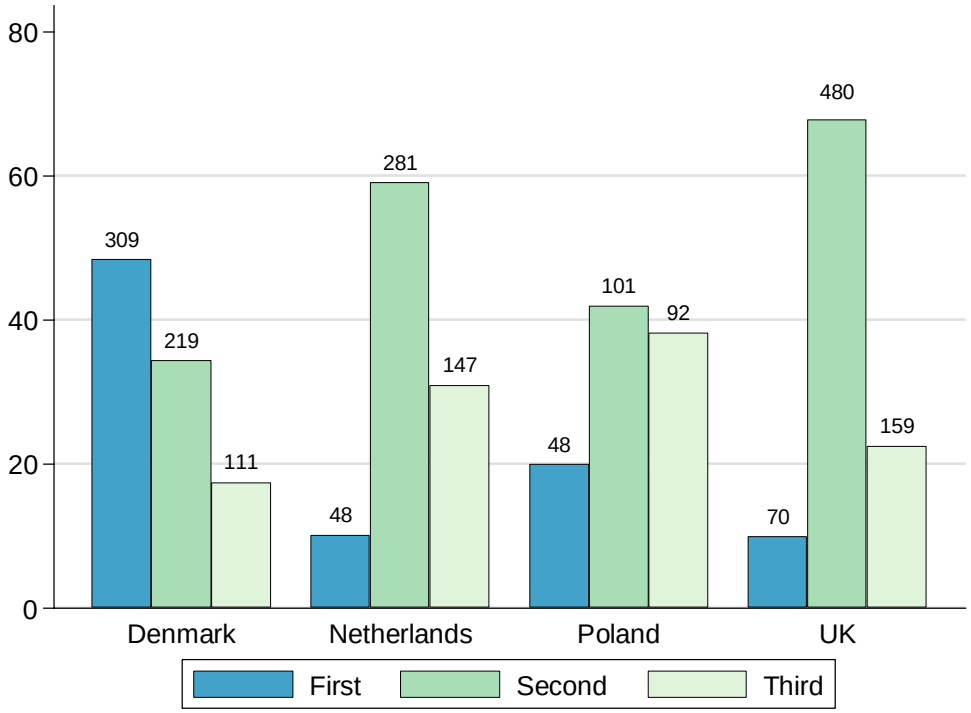


Figure 2-5 Percentage of women recruited by trimester and country

The above graphic clearly indicates that the recruitment strategy employed in Denmark (mainly website banner advertising) recruited a much larger proportion of first trimester study participants than that used in each of the remaining study locations. When the week of pregnancy at enrolment for women recruited in their first trimester was compared between the four study locations (Table 2-5 below), the Danish recruitment strategy recruited the majority of their participants at a much earlier time than what was observed in the other study countries.

Table 2-5: Proportion of active participants recruited at the various stages of pregnancy compared by country

	Denmark		**Netherlands**		**Poland**		**United Kingdom**		**All Locations**	
	% (n)		*% (n)*		*% (n)*		*% (n)*		*% (n)*	
≤4/40	9.08	(58)	0.420	(2)	1.24	(3)	0	(0)	3.05	(63)
5/40	8.29	(53)	0	(0)	1.66	(4)	0.564	(4)	2.95	(61)
6/40	8.29	(53)	0.420	(2)	2.07	(5)	0.564	(4)	3.10	(64)
7/40	5.79	(37)	0.420	(2)	2.07	(5)	0.282	(2)	2.23	(46)
8/40	4.54	(29)	0.840	(4)	3.32	(8)	0.987	(7)	2.32	(48)
9/40	3.60	(23)	3.15	(15)	0.00	(0)	1.97	(14)	2.52	(52)
10/40	3.29	(21)	1.89	(9)	1.66	(4)	1.13	(8)	2.03	(42)
11/40	3.13	(20)	1.26	(6)	3.73	(9)	2.12	(15)	2.42	(50)
12/40	2.35	(15)	1.68	(8)	4.15	(10)	2.26	(16)	2.37	(49)
≥13/40	51.6	(330)	89.9	(428)	80.1	(193)	90.1	(639)	77.0	(1590)
Total	100	(639)	100	(476)	100	(241)	100	(709)	100	(2065)

When the trimester at enrolment for the active study participants recruited was compared between the different grouped advertisement methods and study country (Figure 2-6 below) it became apparent that different advertisement methods in different locations were more suitable at recruiting first trimester participants. In Denmark this was website adverts, in Netherlands leaflet advertising, in Poland both leaflet and social media advertising, and in the UK it was leaflet advertising.

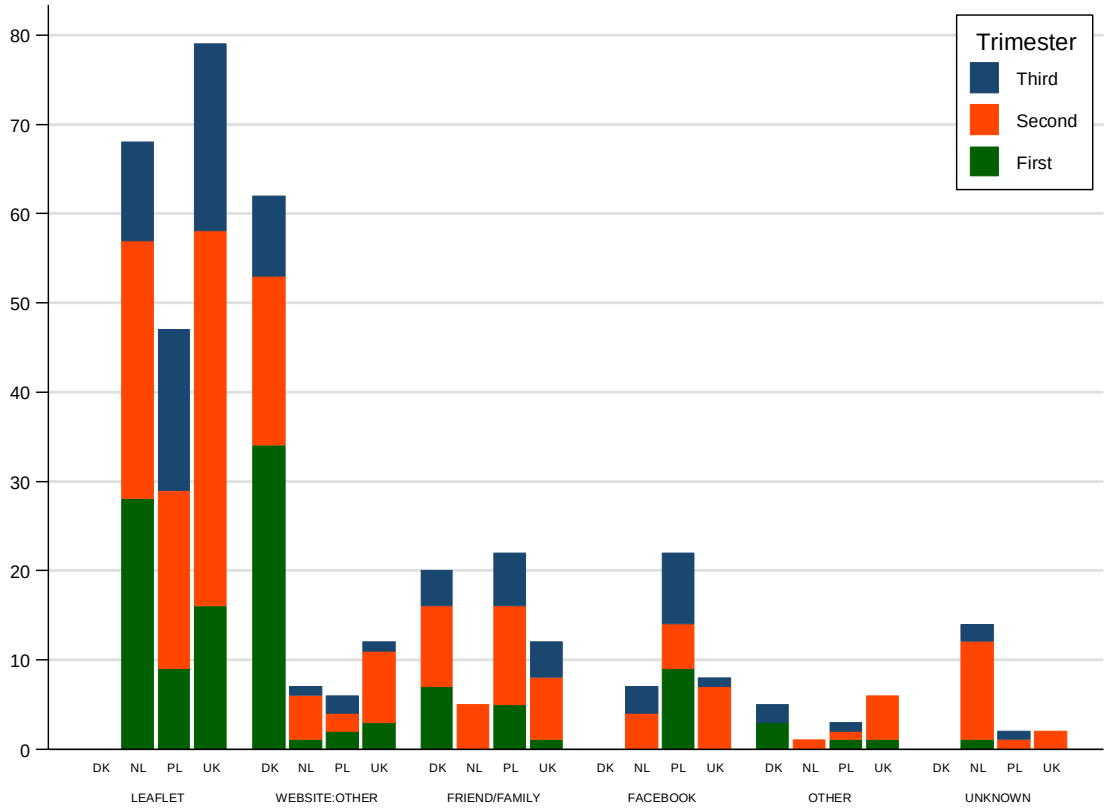


Figure 2-6 Number of women recruited by trimester – breakdown of non-country specific groups

2.7 Recruitment of women expected to deliver during the study period

This study did not screen potential participants to include only those women who were at a stage of pregnancy at recruitment which would allow enough time for the pregnancy to complete prior to the end of the data collection period (31st March 2014). The overall proportion of participants who were recruited in enough time to allow for pregnancy completion was 75.0%. Figure 2-7 provides an overview of the cumulative number of deliveries expected from the recruited study cohort and how the rate of pregnancy completion during the study period differed between the four countries. The highest proportion of non-completed pregnancies was identified in Poland (53.5%) and the lowest in the UK (17.3%). Both the stage of pregnancy at enrolment and the time at which successful advertisement methods were employed will have affected the proportion of the total study cohort which were expected to complete pregnancy during the study period.

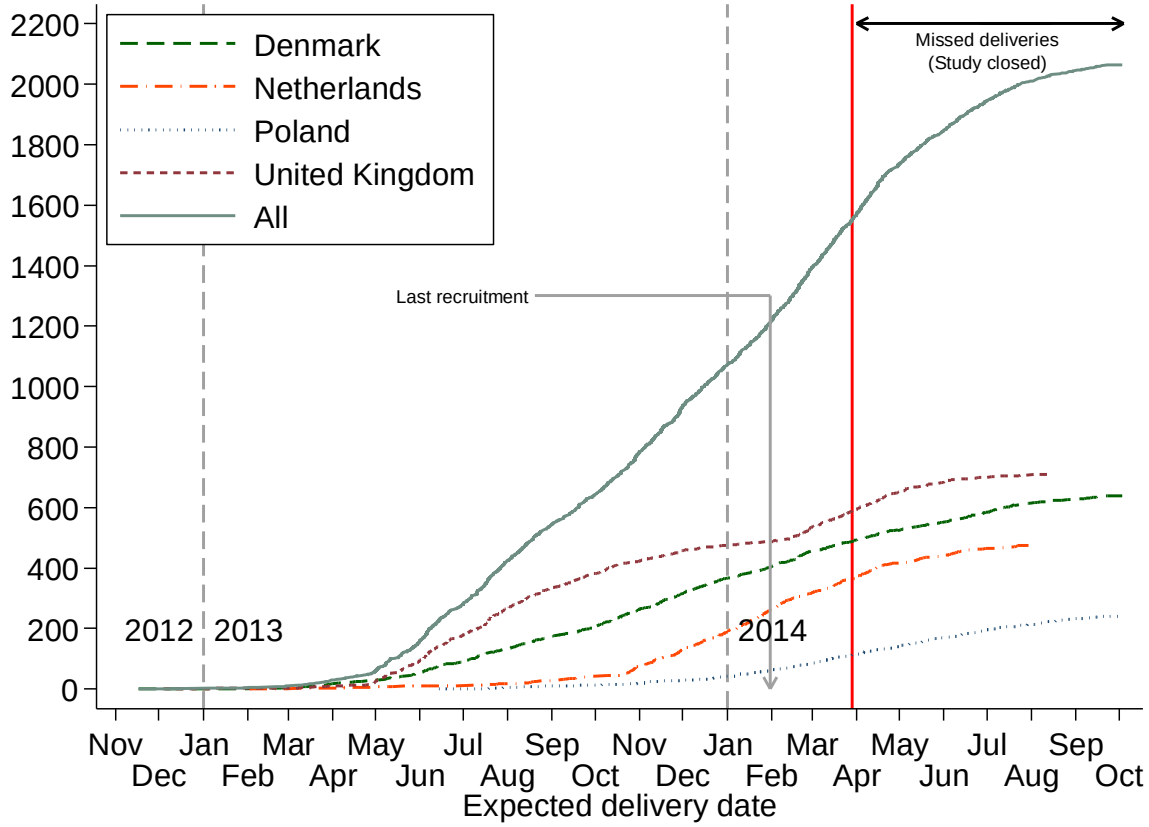


Figure 2-7 Line graph of the expected number of deliveries by country and time (cumulative count)

2.8 Concluding remarks

The main aims of this recruitment strategy were to recruit women in the early stages of pregnancy using low/no-cost, direct-to-participant advertisement methods. Our findings suggest that the recruitment of a suitably large sample of pregnant women to a non-interventional study of self-reported medication use and pregnancy outcomes was not feasible using the low/no-cost advertisement methods which we used.

Higher-cost advertisement methods successfully recruited study participants without the intervention of healthcare professionals. Overall, the total sample size collected represented less than seven in every ten thousand pregnancies estimated to have been recognised by women residing in the four study locations during the recruitment period. For the individual study locations the sample represented 42.6, 10.4, 7.40 and 3.38 of every ten thousand Danish, Dutch, Polish and UK pregnancies respectively.

Our findings suggest that the advertisement methods we used were limited in their ability to enrol women early in their pregnancy with only 23% of the total study cohort being recruited in their first trimester. However, there were considerable international variations with the strategy in Denmark recruiting a higher proportion of first trimester participants (48.4%) than in the other study locations (Netherlands 10.1%, Poland 19.9%, UK 9.87%). We believe that website advertisements have the greatest potential to recruit women early in pregnancy since this was the predominant advertisement method used in Denmark.

Overall our results indicate that recruiting pregnant women to a pharmacovigilance/pharmacoepidemiology pregnancy study via direct-to-participant advertisements is feasible but recruiting women in early pregnancy has additional challenges.

3 Economic analysis of recruitment

3.1 Introduction

A key recruitment objective was to use direct-to-participant advertisements wherever possible to recruit women early in their pregnancy, and at low or no cost.

3.2 No-cost and low-cost strategies

1. The initial strategy for recruitment was low to no cost using leaflets located in pharmacies/midwives (not in Denmark), advertisements on selected healthcare-related internet sites, advertorials in selected magazine or journals and Advertisement bulletins on internet pregnancy forum websites and social network websites

2. In the first 18 weeks of the recruitment period these low/no-cost advertisement methods were used in Denmark, Netherlands and UK. These included posting promotional discussion topics in pregnancy e-forums (UK), placing small hyperlinks on pregnancy related websites (Netherlands), displaying leaflets and posters in community pharmacies and/or obstetric/midwifery units (Netherlands and UK, Poland from week 34), sharing advertisement materials through a social media profile (Facebook - UK), and low-cost banner advertising in pregnancy-specific sections of a popular health and wellbeing website (Denmark).

3.3 Web advertisements

After initial low/no-cost advertising attempts and a somewhat disappointing enrolment rate, additional funding was provided for higher cost advertising methods. These included large digital banners (Denmark), hyperlinks (Netherlands) and small picture/text graphics (UK) placed on more prominent pregnancy information websites and parenting websites (all locations) and paid advertising on a social media site (Facebook) targeted at women of reproductive age (16-45) with interests related to children, pregnancy and health (UK). All online media platforms used to advertise the study are provided in the Table 3-1 below, which also details the estimated number of unique daily visitors to the website and provides the total reach for each of the online advertising methods.

Table 3-1 Online media platforms used to advertise the study with estimated number of unique daily visitors and estimated total advert reach

Website	Study location	Estimated unique visitors/ day*	Total advert reach
www.netdoktor.dk	Denmark	OSU – 9,500	Unavailable
www.min-mave.dk	Denmark	4,600	6,649
www.altomboern.dk	Denmark	6,250	Unavailable
www.gravid.dk	Denmark	1,750	Unavailable
www.voresborn.dk	Denmark	1,800	Unavailable
www.netsundhedsplejersken.dk	Denmark	Unavailable	Unavailable
www.baby.dk	Denmark	2,500	503
www.jongegezinnen.nl	Netherlands	12,500	1,739
www.babyopkomst.nl	Netherlands	5,500	Unavailable
www.mamazone.pl	Poland	OSU – 9,500	183
www.babyboom.pl	Poland	OSU – 10,000	17
www.netmums.com	United Kingdom	310,000	483
www.facebook.com	United Kingdom	-	271

Key: OSU – official statistics unavailable (where details are provided they were estimated from www.trafficestimate.com)

*Information collected from advertising information pages present on the sites at the time of advertisement. Total advert reach describes the number of clicks received on a website/social media advert and the number of adverts distributed in emails adverts

3.4 Direct-to-patient emails

Following the disappointing results of low/no-cost advertising and web advertisement for recruitment it was thought that adverts in emails sent directly to registered users of widely used pregnancy/health information sites could be a viable recruitment option. When pregnant woman register to the following websites they receive periodic emails including pregnancy information, offers, reviews and advertisements. Different arrangements on type of advertisement used, frequency of submission etc. were deployed per website and country (Table 3-2).

Table 3-2 Websites used to advertise the study via email with estimated total advert reach

Website	Study location	Total advert reach
www.min-mave.dk	Denmark	~6,000
www.voresborn.dk	Denmark	~8,000
www.jongegezinnen.nl	Netherlands	80,214
www.mamazone.pl	Poland	40,000
www.fajnamama.pl	Poland	20,000
www.babyonline.pl	Poland	24,000
www.magazynsupermama.pl	Poland	5,000
www.bounty.co.uk	United Kingdom	120,442

3.5 Cost of advertisement methods

Low/no cost advertisement methods were used for the first 18 weeks of the total study recruitment period. Unfortunately these advertisement methods attracted a smaller than expected number of visitors to the study website (n=1,278), of which only 4% (n=52) enrolled and provided study data. As such, advertisement methods with higher costs were subsequently implemented, and as described in Figure 2-3 these improved the recruitment rate of study participants. In total, €56,727 was spent advertising the study which equated to a crude average of €22.63 per participant recruited and €27.47 per active participant enrolled.

Of the total 2,065 active study participants, 1,867 were recruited through paid advertisement methods (website displays, email broadcasts, leaflet printing/delivery, television broadcasts, social media displays). In comparing the overall recruitment strategies undertaken in each of the four different study countries, we observed considerable international differences in the cost per active participant enrolled. The most cost-effective (€ per enrolled active participant) recruitment strategy overall was performed in Denmark (€16.14) and the least in Poland (€86.74).

We also identified international differences in the cost-effectiveness of the grouped advertisement methods which are described graphically in Figure 3-1 below. The cost-per-participant for website advertising in Denmark (€16.03), Poland (€12.54) and UK (€28.80) was low in comparison with the Netherlands (€187.56), whilst email advertising costs in Poland were high (€112.85) in comparison with Denmark (€19.50), the Netherlands (€21.42) and the UK (€17.22). Leaflet advertising costs were similar across the three study locations where the method was used (Netherlands €82.29, Poland €92.66, UK €78.20). Television, print (magazine and newspaper) and paid social media advertising were used in two study locations and did not result in many recruits (television n=9, print n=0, social media n=1).

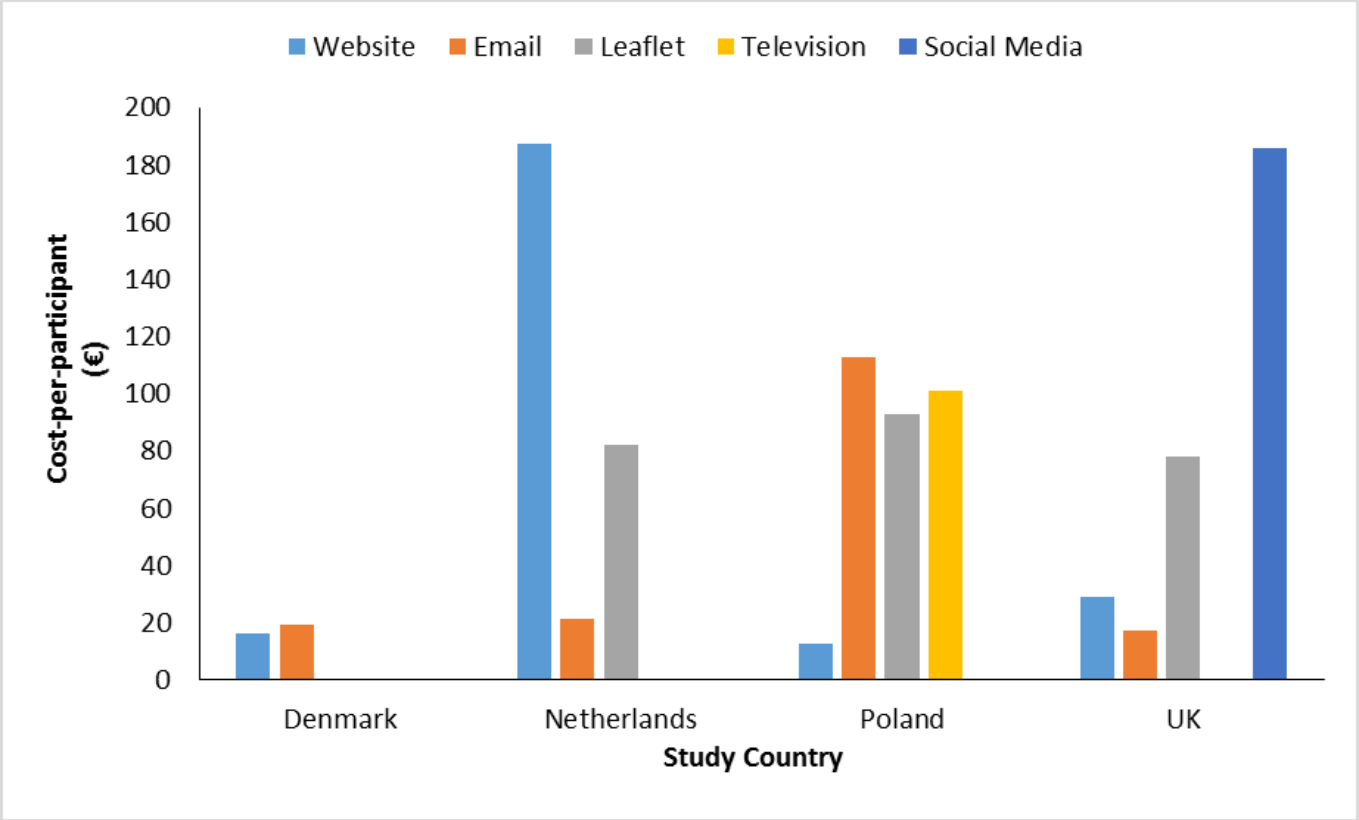


Figure 3-1 Specific cost of recruitment in all countries

3.6 Concluding remarks

The least cost-effective overall recruitment strategy was performed in Poland (€86.74 per participant) which we believe was mainly observed as a result of a large high-cost email campaign (90,000 emails - €4,000) undertaken on the fourth to last week of the recruitment period which only recruited 44 study participants (~€90 per participant). Whilst this low recruitment yield may have been due to the short time which participants had to respond to the advert, because participant enrolment usually happened almost immediately after email broadcast in other study locations it is plausible that this method was simply not cost-effective in Poland. When findings from all study locations were combined, the most cost-effective methods overall were email (except in Poland) and website advertisements. However, international variation in the cost-effectiveness of the individual methods was demonstrated by the high cost of website advertising in the Netherlands (cost-per-participant €171.49), and as previously mentioned, email advertising in Poland (cost-per-participant €112.85).

4 Participants retention in the study

Of the 2521 women who enrolled in the study only 14 (0.5%) chose to answer questions using IVRS. Of these 13 failed to complete the baseline questionnaire compared with 442 (17%) of those who chose the web based system. All subsequent analyses are based on the 2065 women who chose to enter data via the web and completed the baseline questionnaire

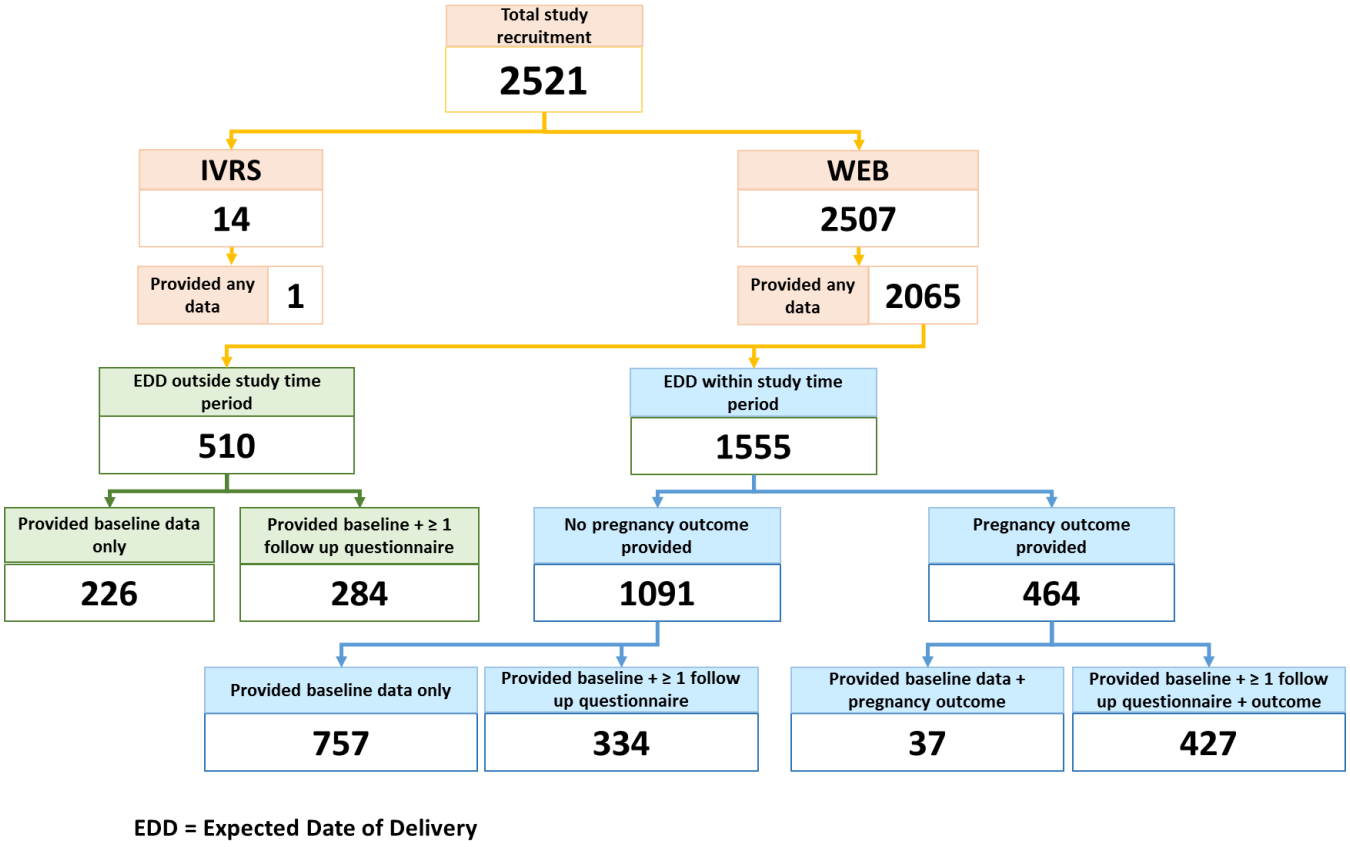


Figure 4-1 Study recruitment and provision of data

4.1 Overview of the retention of participants in the study

Retention of participants was of interest in this pilot study. In this study, participants were given the choice of providing data 2-weekly or 4-weekly, as shown in Table 4-1. For participants who provided follow-up data, the observed frequency of completing subsequent questionnaires was in agreement with the frequency they chose at enrolment. The between-participant variance of the length of time between follow-up questionnaires was 2.05 (95% CI 1.73 – 2.42) weeks, and the within-participant variance was 1.86 (95% CI 1.77 – 1.96) weeks. Therefore, 52% of participants completed the follow-up questionnaires at similar intervals, and about the same percentage (48%), did not.

Table 4-1 Choice of frequency and actual frequency of follow-up questionnaires data provision by country

	Denmark	Netherlands	Poland	United Kingdom	All
Chosen frequency					
Every 2 weeks, % (n)	49.0% (313)	29.8% (142)	36.1% (87)	48.8% (346)	43.0% (888)
Every 4 weeks, % (n)	51.0% (326)	70.2% (334)	63.9% (154)	51.2% (363)	57.0% (1177)
Actual frequency[1]					
2-weekly					
Mean (95% CI), weeks	2.5 (2.3,2.7)	2.3 (2.0,2.7)	2.3 (1.9,2.8)	2.6 (2.4,2.8)	2.5 (2.4,2.6)
Median (IQR), weeks	2.0 (1.9-2.3)	2.0 (1.9-2.3)	2.0 (2.0-2.3)	2.0 (2.0-2.3)	2.0 (2.0-2.3)
4-weekly					
Mean (95% CI), weeks	4.7 (4.5,5.0)	5.1 (4.8,5.4)	4.5 (4.1,4.9)	4.8 (4.6,5.1)	4.8 (4.7,5.0)
Median (IQR), weeks	4.0 (3.9-4.4)	4.0 (4.0-4.5)	4.1 (4.0-4.4)	4.0 (3.9-4.5)	4.0 (3.9-4.5)

[1] Actual frequencies were calculated only for women who provided data to at least one follow-up questionnaire. Means and 95% confidence intervals were estimated using a mixed model with women as random effect. Medians and interquartile ranges (IQR) were estimated as medians of within-woman quantiles.

Figure 4-2 shows the distribution of the time from formal study entry (enrolment and completion of informed consent) to completing the first (baseline) questionnaire by country. The distributions, as expected, are highly skewed with most women completing the baseline questionnaire on the same day they entered the study. About 93% of women from the Netherlands completed the first questionnaire immediately (same day), and the rest completed the questionnaire within the following two weeks. Women in other countries completed the first questionnaire as late as over three weeks.

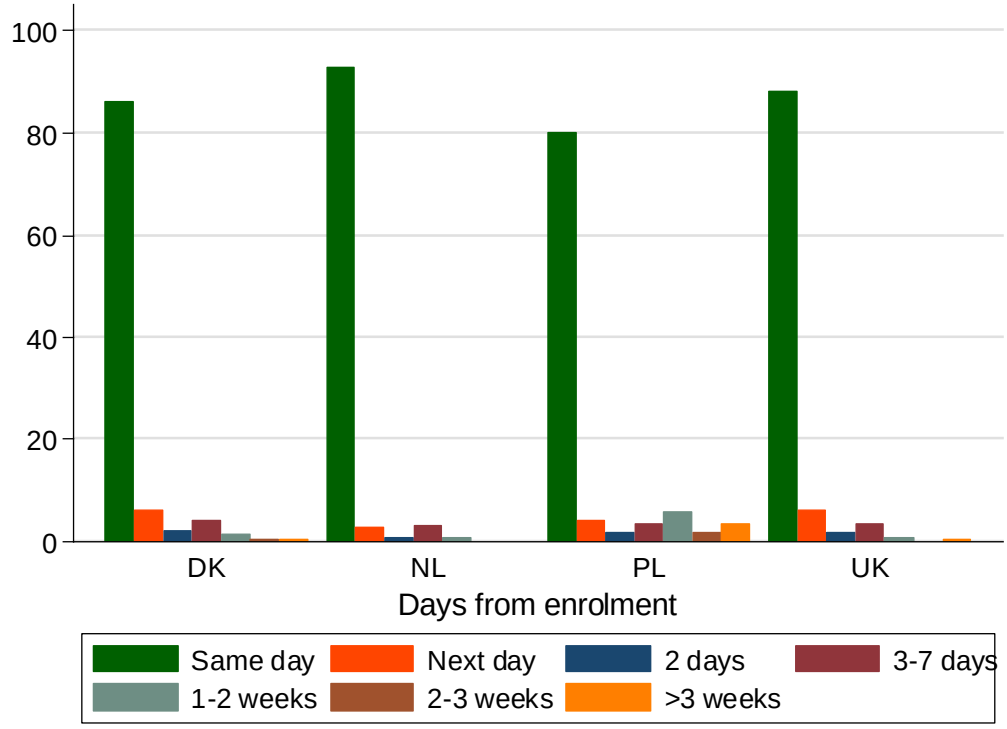


Figure 4-2 Percentage of people by time completion between countries

Most participants (>80%) completed the first questionnaire the same day as enrolment; however, some took longer. Table 4-2 describes the number of days after enrolment to time of submission of completed baseline questionnaire. For those who did not complete the questionnaire on the same day that they enrolled in the study, Polish women took longer to complete the questionnaire, with a median of 10 days from enrolment to submission and the longest time of 12 days. It is possible that participants from Poland completed the first questionnaire slightly later than those in other countries because of the unique legal requirement in Poland that participants mail in a printed consent form.

Table 4-2 Days to complete the first study questionnaire after enrolment

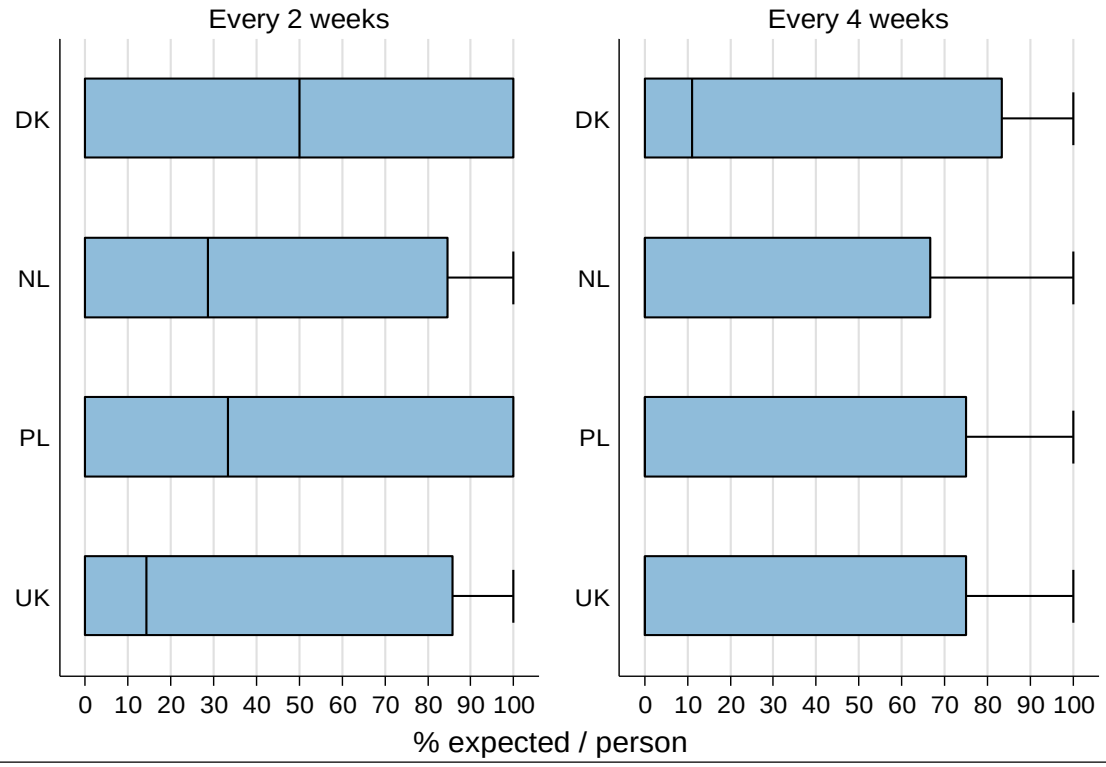
	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
All participants, days					
Mean (SD)	0.6 (3.2)	0.3 (1.3)	2.3 (7.0)	0.3 (1.5)	0.6 (3.2)
Median (IQR)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)
>1 day only, days					44.0
Mean (SD)	4.4 (7.5)	3.8 (3.3)	11.7 (11.6)	2.8 (3.4)	
Median (IQR)	2.0 (1.0 - 4.0)	3.0 (1.0 - 5.0)	9.5 (2.0 - 17.0)	1.0 (1.0 - 3.0)	5.2 (7.7)
Longest	44.0	14.0	43.0	25.0	2.0 (1.0 - 6.0)
Time to complete, by category					
Same day	86.1% (550)	92.9% (442)	80.1% (193)	88.0% (624)	87.6% (1809)
Next day	6.1% (39)	2.7% (13)	4.1% (10)	6.2% (44)	5.1% (106)
2 days	1.9% (12)	0.6% (3)	1.7% (4)	1.6% (11)	1.5% (30)
3-7 days	4.1% (26)	3.2% (15)	3.3% (8)	3.4% (24)	3.5% (73)
1-2 weeks	1.3% (8)	0.6% (3)	5.8% (14)	0.7% (5)	1.5% (30)
2-3 weeks	0.2% (1)	0.0% (0)	1.7% (4)	0.0% (0)	0.2% (5)
Over 3 weeks	0.5% (3)	0.0% (0)	3.3% (8)	0.1% (1)	0.6% (12)

Overall between 45% and 59% of participants completed at least one follow-up questionnaire, including the pregnancy outcome questionnaire (Table 4-3). Women who chose to provide data every 2 weeks were more adherent to completing at least one follow-up, ranging from 58% in the UK to 67% in Denmark. Fewer completed at least one follow-up questionnaire among those who provided data every 4 weeks, ranging from 39% in the Netherlands to 52% in Denmark. The same pattern was also observed in the percentage of completed follow-up questionnaires of the number expected (length of time expected to be in the study at enrolment divided by the chosen frequency). No more than 50% of the expected questionnaires were completed on average in any country. The summary distributions of the completed questionnaires versus expected number of questionnaires by country and follow-up frequency are illustrated in the box plots (box-whiskers diagram) in Figure 4-3. The box plots, limited to those who returned at least one follow-up questionnaire, are provided in Figure 13-9 in Appendix 13.2.

Similarly, more women who chose to provide data every 2 weeks provided data on the outcome of pregnancy compared to those who chose every 4 weeks. More frequent contact with the study may have encouraged women to stay in longer, or women may have more opportunities to report. Danish women also reported most outcomes, and this was mainly driven by miscarriages and that more women in Denmark enrolled in their first trimester.

Table 4-3 Completion of follow-up and end of study questionnaires

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Completed at least one follow-up (all)	59.2% (378)	44.7% (213)	49.8% (120)	52.3% (371)	52.4% (1082)
2-weekly	67.1% (210)	58.5% (83)	63.2% (55)	57.5% (199)	61.6% (547)
4-weekly	51.5% (168)	38.9% (130)	42.2% (65)	47.4% (172)	45.5% (535)
Percentage completed of expected questionnaires					
All, mean (SD)	42.8 (42.9)	32.3 (41.2)	37.1 (42.4)	35.8 (41.3)	37.3 (42.1)
2-weekly	48.6 (42.8)	41.0 (41.7)	45.6 (42.9)	37.0 (41.4)	42.6 (42.3)
4-weekly	37.2 (42.2)	28.6 (40.5)	32.3 (41.5)	34.6 (41.3)	33.3 (41.4)
All, median (IQR)	33.3 (0.0 - 94.1)	0.0 (0.0 - 75.0)	0.0 (0.0 - 85.7)	11.1 (0.0 - 80.0)	14.3 (0.0 - 85.7)
2-weekly	50.0 (0.0 - 100.0)	28.6 (0.0 - 84.6)	33.3 (0.0 - 100.0)	14.3 (0.0 - 85.7)	28.6 (0.0 - 91.7)
4-weekly	11.1 (0.0 - 83.3)	0.0 (0.0 - 66.7)	0.0 (0.0 - 75.0)	0.0 (0.0 - 75.0)	0.0 (0.0 - 75.0)
Reported pregnancy outcome (all)	27.7% (177)	19.3% (92)	15.8% (38)	22.1% (157)	22.5% (464)
2-weekly	32.6% (102)	25.4% (36)	26.4% (23)	23.7% (82)	27.4% (243)
4-weekly	23.0% (75)	16.8% (56)	9.7% (15)	20.7% (75)	18.8% (221)



Note: Vertical lines in the middle of the box indicates the medians (50th percentile). The left end of the box is the 25th percentile and the right end of the box is the 75th percentile. The horizontal line on the right end of each box is the top 25% of participants.

Figure 4-3 Box plot of adherence to frequency for all participants

4.2 Estimates of retention

The length of time in the study was defined as the time of last observed data entry by the participants, and "failure" to complete the study was defined as not providing an end of pregnancy outcome, unless the estimated due date was within one week before the study closure, or after the study closure. The last opportunity to submit data was on the 28th March 2014.

All analyses to estimate the retention rates were adjusted for study design variables: recruitment sites (country), trimester at enrolment, and chosen frequencies. Additionally, we also adjusted the analysis for women who joined the study too late (less than two weeks before the study closure) as they could not be expected to return a follow-up questionnaire. We also explored the effects of interactions between the main effects; these are provided in tables in Appendix 13.2. Retention rates were analysed in terms of the length of time in the study (Section 4.2.1), the number of questionnaires completed (Section 4.2.2), and the adherence to schedule frequency of choice (Section 4.2.3).

4.2.1 Length of time in the study

Table 4-4 shows the results of the survival time women continued to provide data through pregnancy outcome. There were no statistically significant differences between countries in the length of time participants continued to provide data in the study, but those who joined earlier in their pregnancy, not surprisingly, provided more follow-up surveys. The rates of failing to provide pregnancy outcome data were more than doubled in the women who enrolled in the second and third trimesters when compared to those who enrolled in the first trimester. The choice of frequency and joining the study late did not have significant effects on the length of participation.

Table 4-4 Hazard ratio (HR) estimates of not completing the study

	Completed, number (total weeks in study)	Not completed, number (total weeks in study)	Hazard ratio (HR)
Denmark	318 (5438.0)	321 (1449.8)	1.00
Netherlands	203 (2350.9)	273 (734.3)	1.45 (0.70,3.00)
Poland	163 (1024.4)	78 (161.0)	0.26 (0.03,1.97)
United Kingdom	290 (4199.6)	419 (1181.1)	1.63 (0.89,2.98)
Trimesters			
First	313 (4537.8)	162 (1092.1)	1.00
Second	503 (6767.8)	578 (1962.2)	2.04 (1.41,2.94)
Third	158 (1707.2)	351 (471.9)	2.31 (1.48,3.59)
Chosen frequency			
2-weekly	450 (6394.4)	438 (1671.1)	1.00
4-weekly	524 (6618.5)	653 (1855.1)	1.38 (0.95,2.00)
Joined study too close to due date	21 (156.4)	54 (0.2)	1.31 (0.90,1.91)
Those chosen 2-weekly and recruited in the first trimester in Denmark (Constant)	105 (2064.5)	52 (437.0)	0.23 (0.18,0.31)

Note: "completed" is defined as having provided an end of pregnancy outcome data

4.2.2 Number of follow-up questionnaires completed

Table 4-5 shows the incidence rates ratio of the number of follow-up questionnaires completed, estimated from a zero-inflated negative binomial count model. In comparison to the women from Denmark, women from the Netherlands, Poland and the United Kingdom completed 33%, 45% and 59% fewer follow-up questionnaires, respectively. Women enrolled later in their pregnancy, and who chose to provide data every four weeks completed fewer questionnaires, as expected.

Table 4-5 Incidence rate ratio (IRR) estimates of the number of follow-up questionnaires completed by participants

	Mean (SD) of number of questionnaires / person	Median (IQR) of number of questionnaires / person	IRR
Denmark	3.4 (4.5)	2 (0 – 5)	1.00
Netherlands	1.9 (2.9)	0 (0 – 3)	0.67 (0.37,1.21)
Poland	1.6 (2.4)	0 (0 – 2)	0.41 (0.25,0.65)
United Kingdom	2.3 (3.0)	1 (0 – 4)	0.55 (0.37,0.84)
Trimesters			
First	3.8 (4.8)	2 (0 – 6)	1.00
Second	2.5 (3.2)	1 (0 – 4)	0.66 (0.54,0.79)
Third	1.3 (1.8)	0 (0 – 2)	0.31 (0.24,0.40)
Chosen frequency			
2-weekly	3.7 (4.5)	2 (0 – 6)	1.00
4-weekly	1.5 (2.1)	0 (0 – 3)	0.44 (0.37,0.52)
Those chosen 2-weekly and recruited in the first trimester in Denmark (Constant)	6.6 (6.3)	5 (0 – 12)	9.36 (8.37,10.47)

Note: Negative Binomial dispersion, α, is 0.22 (95% CI 0.18 – 0.28). Vuong test against standard negative Binomial model is statistically significant.

We illustrated the number of completed questionnaires by country, choice of frequency and trimester in Figure 4-4. Danish women completed the most number of follow-up questionnaires, and Polish women completed the fewest number of follow-up questionnaires, nor surprising, since data collection is Poland was actively for only 8 months compared with 18 months in other countries. Those who chose to provide data more frequently (2-weekly) and those who enrolled earlier in their pregnancy completed more follow-up questionnaires. A clear difference in the number of follow-up questionnaires completed can be seen between countries among those who enrolled in the first trimester and chose to provide data every 2 weeks. Nonetheless, it is essential to keep in mind that this representation does not account for stage of pregnancy when women joined the study, i.e., a woman who joined at 30 weeks of pregnancy would be eligible to complete fewer follow-up questionnaires that one who joined at 8 weeks of pregnancy.

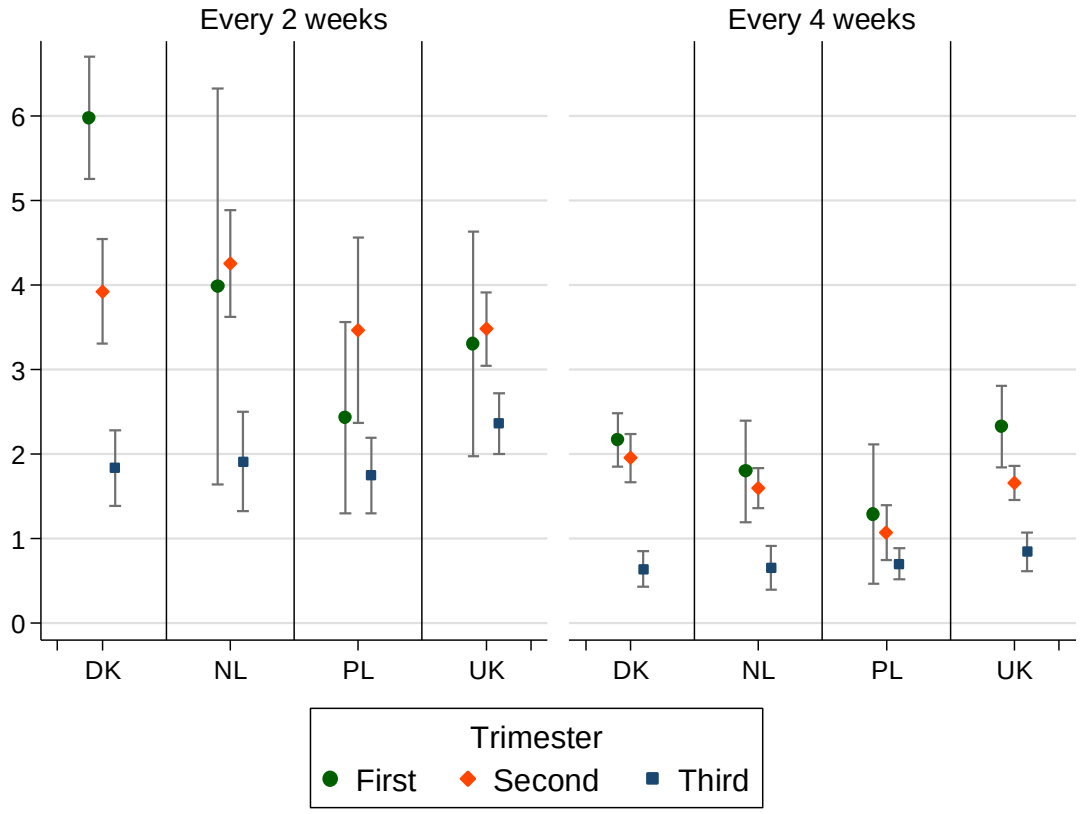


Figure 4-4 Number of follow-up and/or end of pregnancy questionnaires, as predicted by zero-inflated negative binomial model

4.2.3 Adherence to the follow-up frequency schedule

Women may stay longer in the study but they may not provide data as frequent as expected. We conduct a multiple failure survival analysis of not completing a scheduled follow-up questionnaire. Women were regarded as successfully completed a schedule follow-up questionnaire when they completed it before the next expected follow-up date, otherwise they will be regarded as failed at that time point.

Figure 4-5 shows the adjusted survivor curves by country, trimester and chosen frequency. In all countries, the adherence to scheduled questionnaires among those who enrolled in the third trimester is better in the 4-weekly group, which might be because much fewer questionnaires were expected from them.

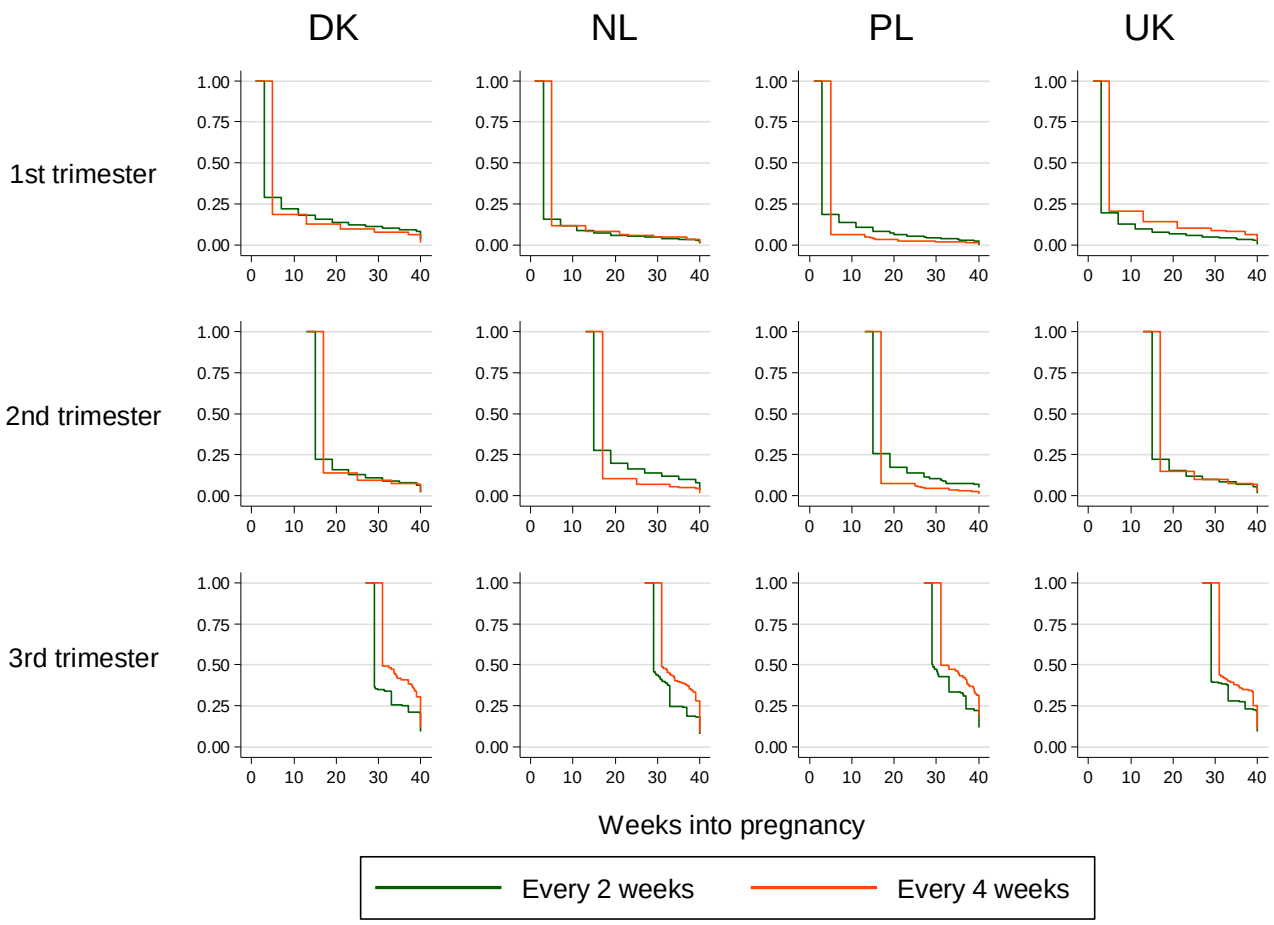


Figure 4-5 Survivor curves adjusted for scheduled response time by country and trimester at recruitment

The hazard ratio estimates are shown in Table 4-6. Overall, women who chose to provide data every 4 weeks failed to complete 42% fewer scheduled follow-up questionnaires compared to those who chose 2-weekly schedule. Danish women were the most adherent to scheduled follow-up questionnaires. By comparison, between 31% and 38% more scheduled follow-up questionnaires were not completed by women in the other countries. Interestingly, women who enrolled earlier in the pregnancy and had more follow-up questionnaires to complete, also had better adherence.

Table 4-6 Hazard ratio (HR) estimates of the adherence to the scheduled follow-up questionnaires

	Adhered to schedule, number (total weeks in study)	Not adhered to schedule, number (total weeks in study)	Hazard Ratio (HR)
Denmark	380 (5313.7)	592 (9472.6)	1.00
Netherlands	219 (2502.4)	445 (5949.1)	1.33 (1.04,1.70)
Poland	122 (1060.7)	216 (1934.7)	1.31 (0.97,1.77)
United Kingdom	376 (4371.6)	665 (9428.6)	1.38 (1.18,1.63)
Trimesters			
First	282 (4181.0)	445 (8060.0)	1.00
Second	582 (7007.0)	1042 (15086.7)	1.12 (0.97,1.30)
Third	233 (2060.4)	431 (3638.3)	0.83 (0.65,1.05)
Chosen frequency			
2-weekly	554 (6247.4)	832 (10538.4)	1.00
4-weekly	543 (7001.0)	1086 (16246.6)	0.58 (0.51,0.65)
Joined study too close to due date	21 (157.3)	54 (287.7)	1.03 (0.83,1.28)
Those chosen 2-weekly and recruited in the first trimester in Denmark (Constant)	111 (1830.6)	149 (2404.9)	0.16 (0.15,0.18)

4.3 Concluding remarks

In evaluating these data, it is essential to keep in mind three key points:

1) Women could enrol in the study at different points during pregnancy and hence, would not be eligible to provide the same amount of follow-up simply by virtue of their stage of pregnancy at enrolment, and

2) This study used very minimal techniques to encourage retention and questionnaire completion. Study participants only received a few email reminders around the time a follow-up questionnaire was due and some also received text messages instead of email.

3) There were no payments or other incentives for completing follow-up data, and a focus group meeting conveyed midcourse during the study revealed that this was the single most potent encouragement that was desired.

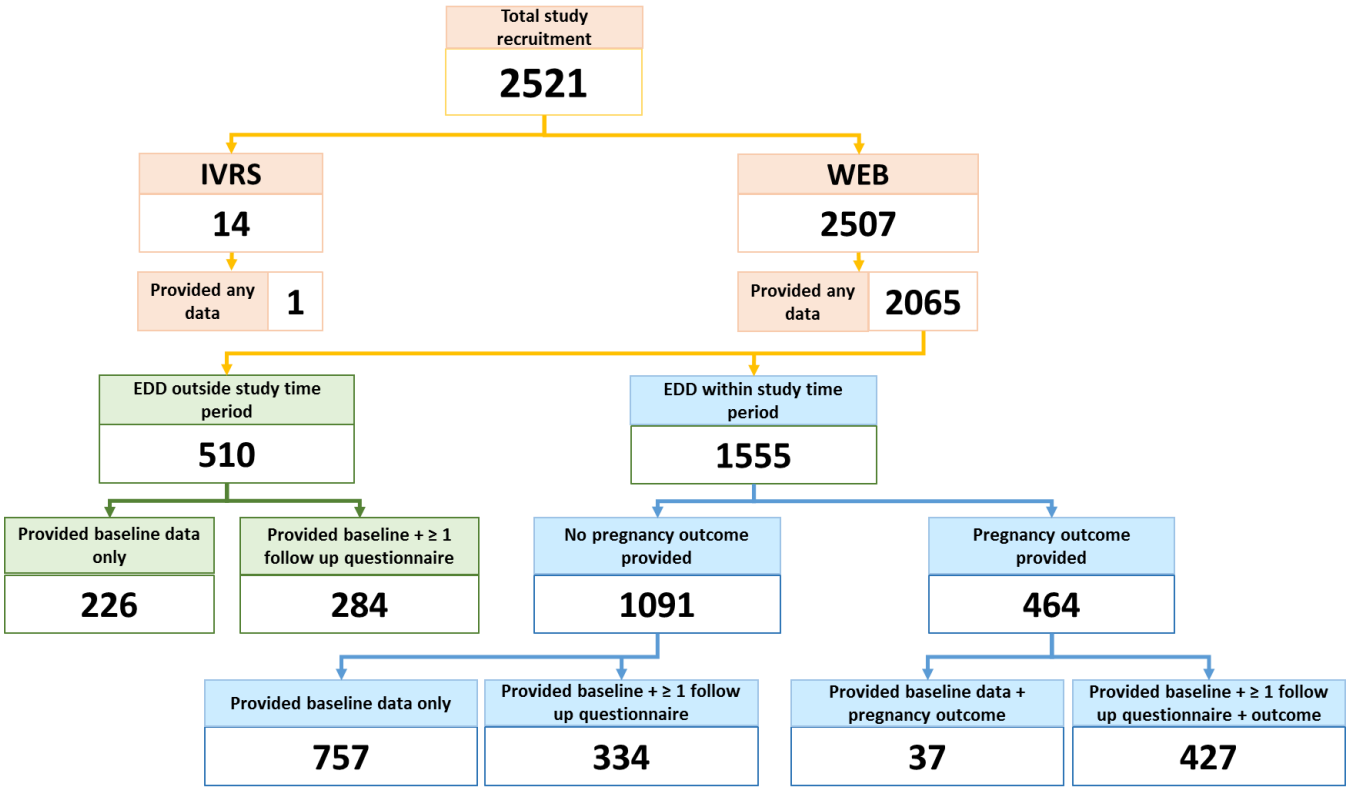
That said, in general, women who enrolled earlier and who chose to provide data more frequently had better study retention. Two-weekly follow-up did not seem to be a burden, and participants were willing to contribute data despite the frequent contact. Danish women complied with the prescribed data collection schedule better than those in other countries. It is also worth noting that the apparent low retention rates in Poland may be explained in large part by the late stage in the study during which they were recruited; those who needed more time to provide data, either baseline or follow-up, may not have had enough time to do so during the period within which the study was open for data collection. Further analyses are needed to investigate the characteristics of women who were retained longer versus who were not and whether data quality varied among those who participated more frequently.

5 Demographics of participants

5.1 Introduction

Ideally a sample should be representative of the target population of interest and differences may not be important provided one is aware of what they are, or the differences relate to a variable of interest which cannot be corrected for during analysis. One of the questions of the IMI-PROTECT pregnancy study was how the demographics of a self-selected cohort of pregnant women, recruited without the direct intervention of health care practitioners would compare with that of the national pregnant population.

Research using internet based methods of data collection permits a greater number of questions to be asked with a greater range of pre-selected answers compared with IVRS. Anyone who has used a telephone call system and been subjected to a series of questions to establish the appropriate person to deal with an enquiry is aware of the limitations and frustrations of these systems. However, there is concern that research that only utilises internet based technology may exclude particular segments of a population e.g. those who are older, lower social class and possibly less literate. Therefore differences in the demographics of women choosing to use IVRS versus the web were of interest as a guide for future research.



EDD = Expected Date of Delivery

5.2 Geographic representation

Figure 5-1 to Figure 5-4 show the numbers of women enrolled from each district in the four countries.

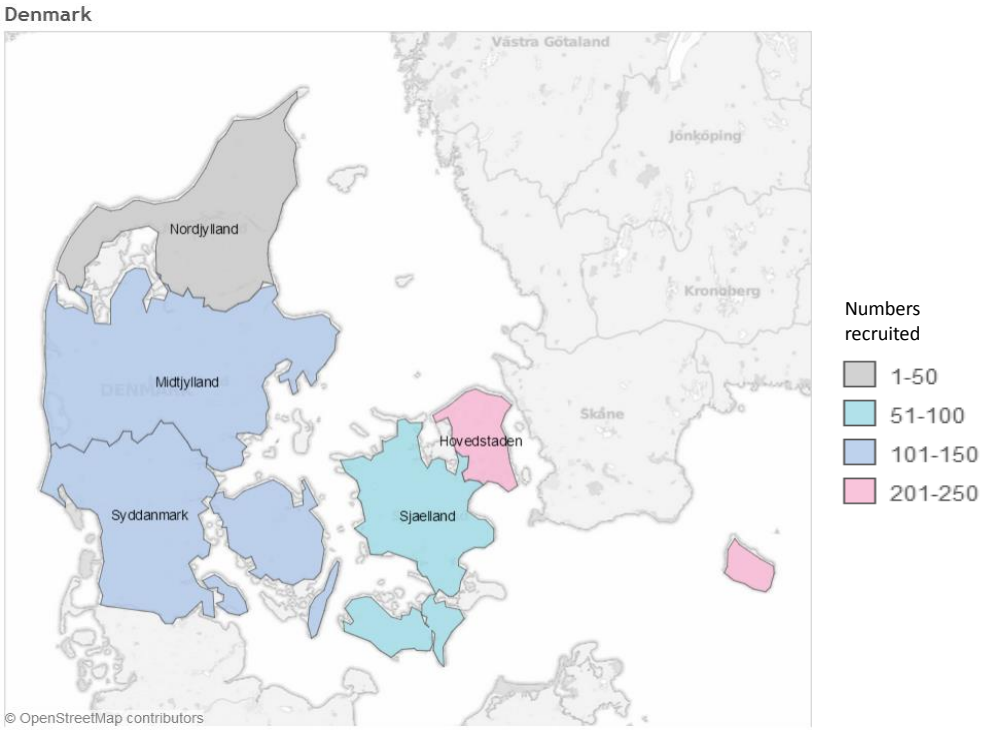


Figure 5-1: Recruitment by regions in Denmark

As can be seen, women were recruited from all over Denmark. The map is also available on http://public.tableausoftware.com/profile/.shmi.#!/vizhome/WP4DK/DKcount.

Figure 5-2: Recruitment by regions in Netherlands

Women were enrolled from across the Netherlands with most women coming from central areas, exploratory map is available on http://public.tableausoftware.com/profile/.shmi.#!/vizhome/WP4NL/NLcount.

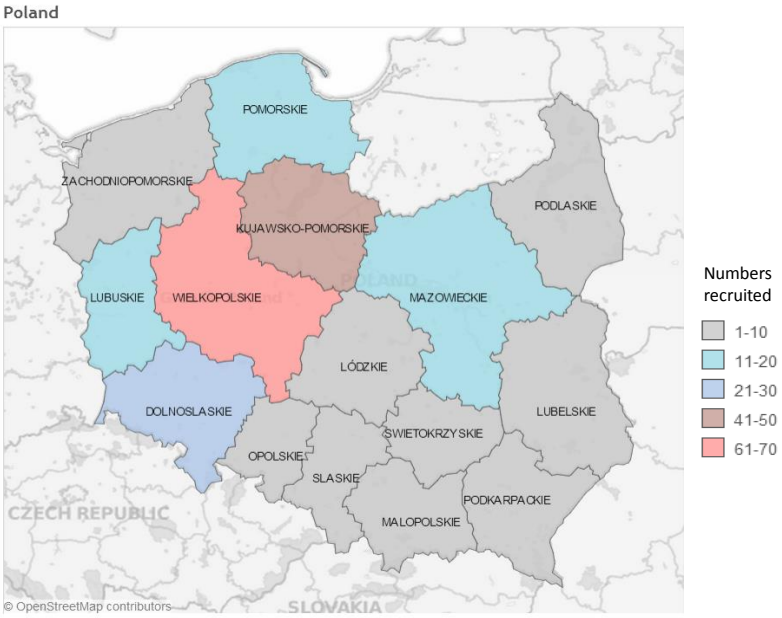


Figure 5-3: Recruitment by regions in Poland

Women were enrolled from across Poland with greater numbers in the East and North; exploratory map is available on http://public.tableausoftware.com/profile/.shmi.#!/vizhome/WP4PL/PLcount.

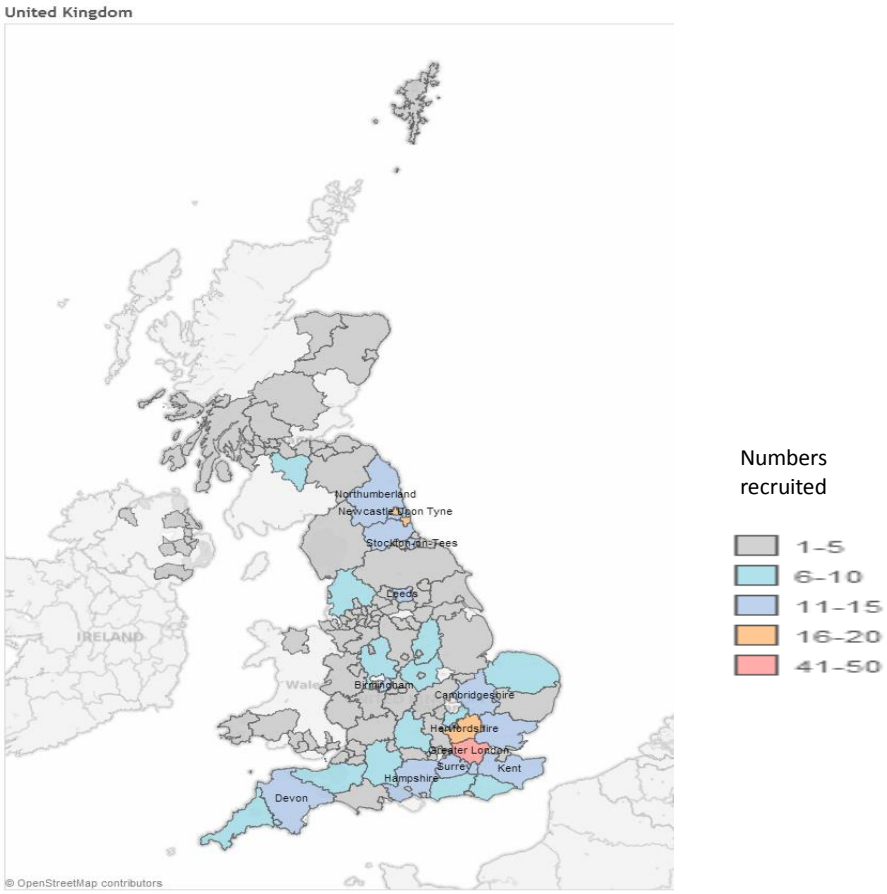


Figure 5-4: Recruitment by regions in the UK

In the UK, leaflets had been targeted at areas where the numbers of GP practices providing data to THIN were greater than average to increase the chances of being able to link the women with data from THIN. However, use of internet recruitment meant that women were recruited from all over the UK. The online version of the map is available on http://public.tableausoftware.com/profile/.shmi.#!/vizhome/WP4UK/UKcount.

5.3 Characteristics of women

Figure 5-5 shows the age distribution of the women at the end of their pregnancy by country. The mode and distribution of age for the four countries was similar except for the UK which was flatter and had was skewed to the left compared with the other countries. Due to legal reasons around the age of informed consent, the lower age limit for inclusion in the study was 16 years for the UK compared with 18 years for the other countries. However, this had no effect on the age range of the UK compared with the other countries.

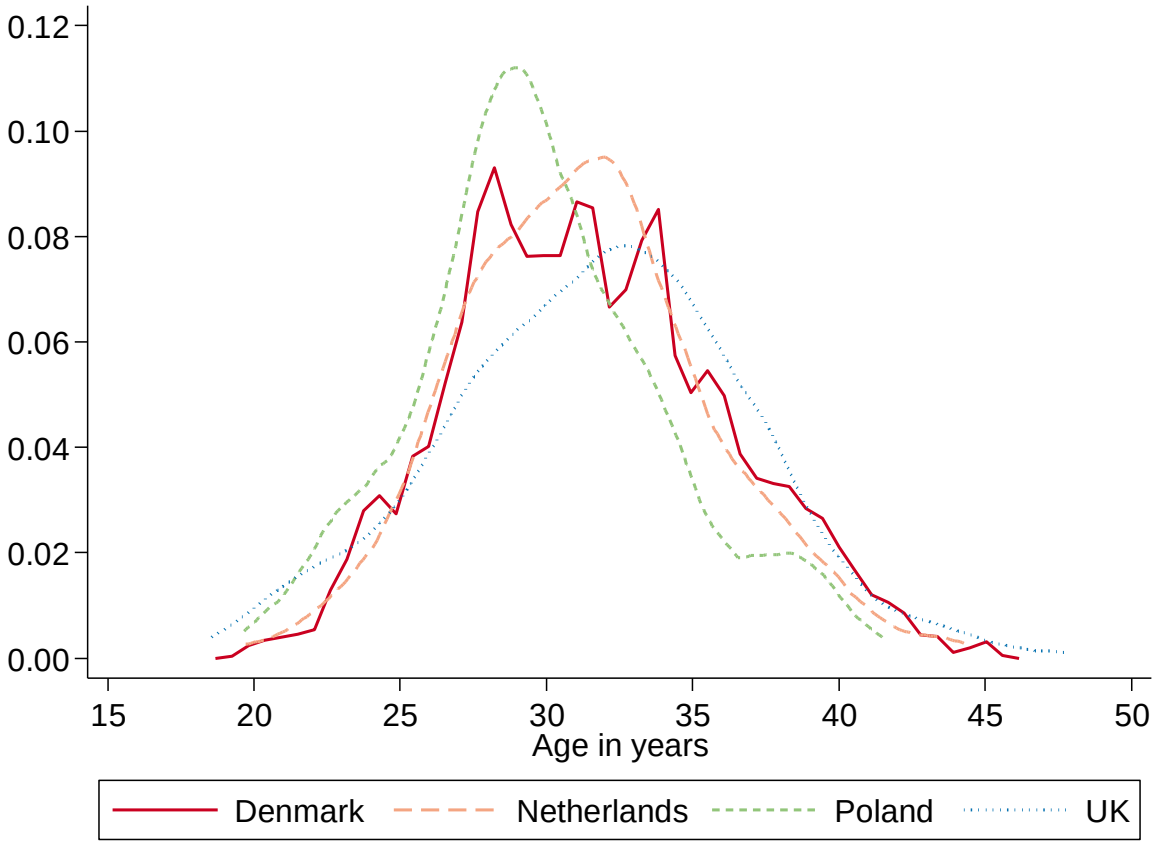


Figure 5-5: Age Distribution at the end of their pregnancy of the PROTECT women

Table 5-1 and Table 5-2 compare the PROTECT population with the national population by age band. The PROTECT population was older in all countries compared with national (England and Wales for the UK) statistics. The age inclusion criteria might have affected the statistics for the under 20 years old age band but the effect is also seen in the 20-25 years old age band where enrolment was lower in all the PROTECT cohorts compared with national statistics.

Table 5-1: Age of PROTECT population compared with national (DK and NL) statistics

Age at end of pregnancy	Denmark				Netherlands			
	PROTECT		National		PROTECT		National 2012	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
	31.5	4.6	30.9	5.1	31.3	4.3	30.9	4.9
	%	No.	%	No.	%	No.	%	No.
<20	0.2	1	1.4	750	0.2	1	1.3	2,257
20-24	6.7	43	11.2	6,192	6.1	29	10.2	17,727
25-29	33.5	214	31.0	17,112	32.1	153	30.7	53,181
30-34	37.1	237	35.0	19,319	43.3	206	37.3	64,498
35-39	18.5	118	17.7	9,769	15.5	74	17.1	29,562
≥40	4.1	26	3.8	2,083	2.7	13	3.4	5,860

Table 5-2: Age of PROTECT population compared with national (PL) and England and Wales (UK) statistics

Age at end of pregnancy	Poland				UK			
	PROTECT		National		PROTECT		England & Wales 2013	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
	29.8	4.2	29.2	NA	31.7	5.1	30.0	NA
	%	No.	%	No.	%	No.	%	No.
<20	0.4	1	3.9	14,552	0.7	5	4.2	29,136
20-24	12.0	29	17.0	63,158	9.4	67	17.1	119,719
25-29	45.2	109	35.4	131,373	25.8	183	28.2	196,693
30-34	32.0	77	29.7	110,192	37.5	266	30.4	212,306
35-39	9.1	22	11.7	43,554	22.4	159	16.0	111,500
≥40	1.2	3	2.2	8,133	4.1	29	4.2	29,158

Table 5-3 shows the height, weight before pregnancy and mean body mass index (BMI) of the PROTECT population. Women from the UK weighed more and were shorter than the women from the other countries which is reflected in the higher mean BMI. This is also reflected in Figure 5-6: Distribution of BMI by country, which shows the BMI distribution by country.

Table 5-3: Height, weight and BMI for the PROTECT population

	DK		NL		PL		UK	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Weight before pregnancy, kg	70.1	14.6	70.7	12.9	62.6	11.7	71.6	17.6
Height, cm	169.3	6.7	170.6	9.2	166.9	6.2	164.8	13.7
BMI	24.4	4.7	24.6	9.1	22.5	3.6	27.4	13.2

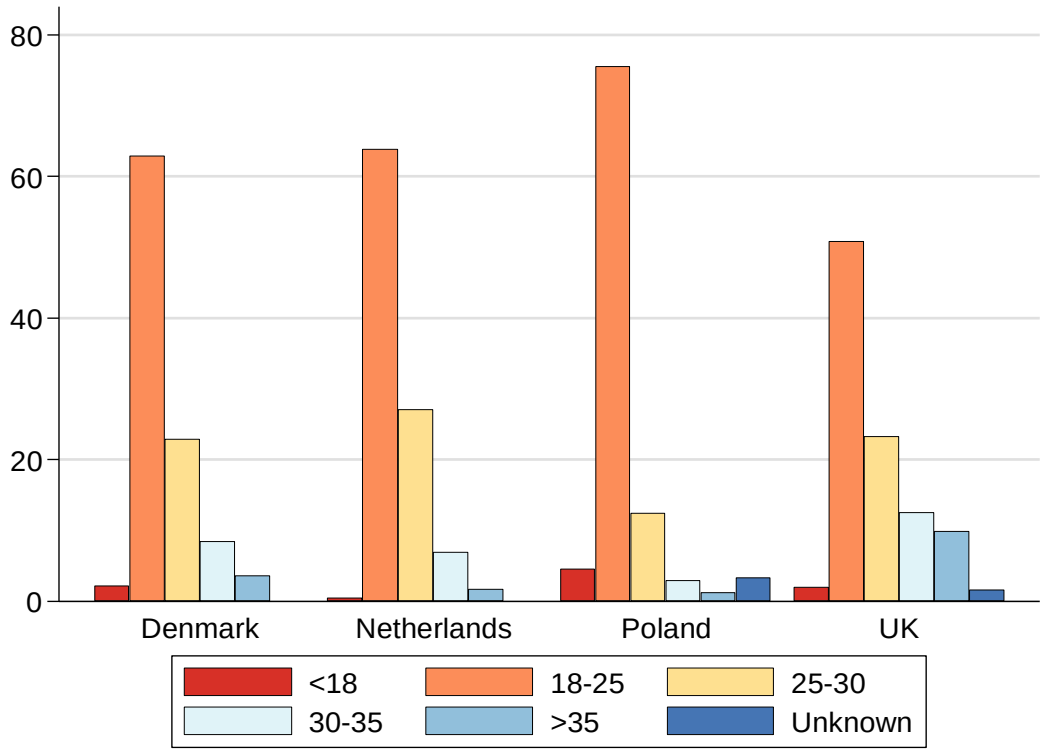


Figure 5-6: Distribution of BMI by country

Table 5-4: Ethnic origin by country

Ethnic group	DK (%)	NL (%)	PL (%)	UK (%)
Asian or Chinese	0.8	1.3	0.0	2.5
Black	0.3	0.0	0.0	0.9
Mixed	1.7	1.7	0.0	1.3
Other ethnic	0.5	0.4	0.0	0.1
White	96.2	95.8	99.6	95.0
Unknown / missing	0.5	0.8	0.4	0.7

Table 5-4 shows the ethnic origin by country. Most women in the PROTECT population were white. In Poland there were no women who declared themselves to be of another ethnic origin whereas in the other countries the population was slightly more mixed.

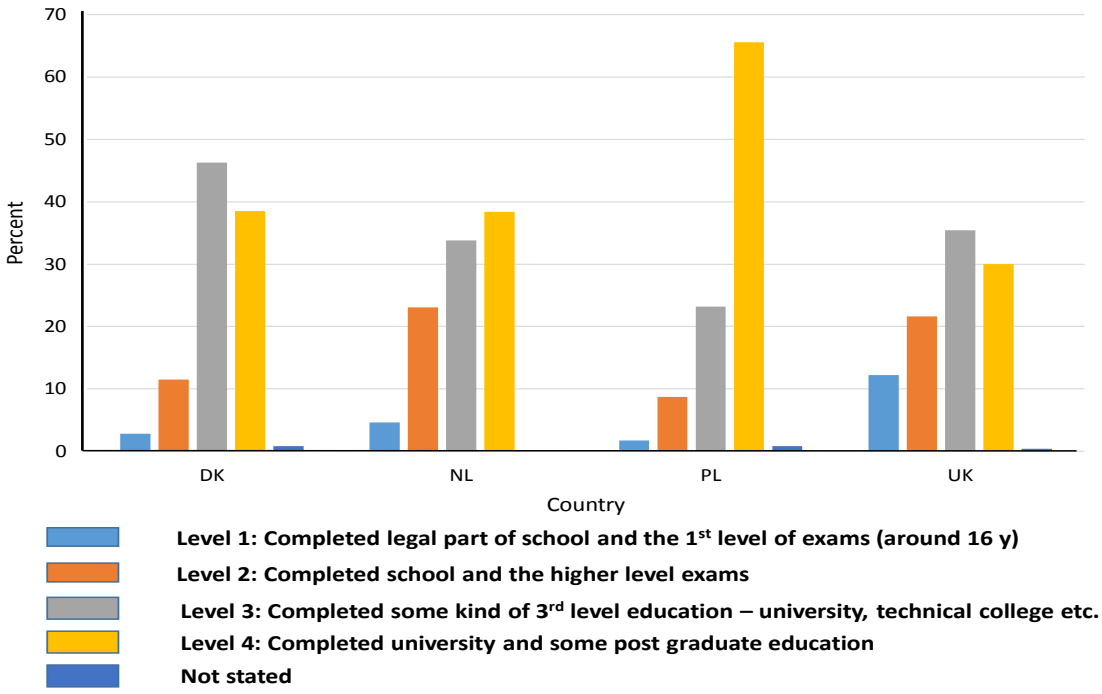


Figure 5-7: Educational status of women in PROTECT by country.

Figure 5-7 and Table 5-5 and Table 5-6 show the educational status of women in PROTECT by country. Poland had a very high proportion of women who had attended university or some other 3rd level education or more compared with the other countries.

Table 5-5: Educational levels of PROTECT women compared with national statistics

Educational level	Denmark[a]			Netherlands[b]		
	PROTECT		National	PROTECT		National
	%	Number	%	%	Number	%
Level 1	2.8	18	15.3	4.6	22	15.3
Level 2	11.7	74	32.8	23.1	110	41.8
Level 3	46.7	296	30.9	33.8	161	25.5
Level 4	38.8	246	14.6	38.4	183	15.3
Not stated	0.8	5	6.3	0.0	0	2.1

[a] Data from Statistics Denmark, Births 2012

[b] Data source: age: Stichting Perinatale Registratie Nederland. Perinatale Zorg in Nederland 2012. Utrecht: Stichting Perinatale Registratie Nederland, 2013; educational level: all women aged 25-45, Statstics Netherlands (cbs.nl)

Table 5-6: Educational levels of PROTECT women compared with national statistics

Educational level	Poland[a]			UK[b]		
	PROTECT		National	PROTECT		National*
	%	Number	%	%	Number	%
Level 1	1.7	4	7.0	12.6	89	44.4
Level 2	8.7	21	55.7	21.6	153	21.8
Level 3	23.2	56	0.6	35.4	251	33.0
Level 4	65.6	158	32.6	30.0	213	
Not stated	0.8	2	4.1	0.4	3	0.8

[a] The national figures for Poland do not correspond completely with the educational levels used in PROTECT since level 4 for the national figures includes licentiate which is included in level 3 for PROTECT. Data source: Central Statistical Office of Poland (http://stat.gov.pl/; http://demografia.stat.gov.pl/bazademografia/Tables.aspx)

[b] The national figures for the UK are for men and women from 2011. UK national figures for post graduate education not available.

The women in PROTECT were better educated than the national averages in all countries. This was particularly noticeable in Poland where almost 89% of women had a university degree. One of the places where leaflets were distributed was in the University medical centre but since the study was advertised by a variety of other means (including radio and TV) in Poland, it is unlikely that this can account for all the difference. Polish national statistics do not use the same cut off points as were used for PROTECT in that "licentiate" is included in level 4 in national statistics but in level 3 for PROTECT but the combined levels 3 and 4 for the Polish PROTECT women was still more than double the combined national levels 3 and 4. The fact that the women in PROTECT were older than the national average may also reflect the fact that they were better educated.

5.4 Pregnancy-related characteristics

Table 5-7 and Table 5-8 describe gravidity and parity for study participants.

Table 5-7: Gravidity

	DK		NL		PL		UK		All	
	%	No	%	No	%	No	%	No	%	No
First pregnancy	38.3	245	47.3	225	50.6	122	41.6	295	43.0	887
Not first pregnancy	61.0	390	51.7	246	46.9	113	58.0	411	56.2	1160
Status unknown	0.6	4	1.1	5	2.5	6	0.4	3	0.9	18

With the exception of Poland, most women had been pregnant before. Table 5-8 shows the number of previous pregnancies and the outcomes.

Table 5-8: Outcomes of previous pregnancies

	DK		NL		PL		UK		All	
Women with number of previous pregnancies - % women, number	100%	390	100%	246	100%	113	100%	411	100%	1160
Total number of previous pregnancies	748		434		165		911		2258	
Median, IQR	1	1-2	1	1-2	1	1-2	2	1-3	1	1-2
Maximum number	12		13		5		12		13	
Live births - % women, number	78.5%	306	75.2%	185	78.8%	89	79.6%	327	78.2%	907
Total number	402		236		107		511		1256	
Median, IQR	1	1-1	1	1-1	1	1-1	1	1-2	1	1-2
Maximum number	5		4		3		9		9	
Miscarriage	35.6%	139	47.6%	117	31.9%	36	39.9%	164	39.3%	456
Total number	219		170		50		289		728	
Median, IQR	1	1-2	1	1-2	1	1-2	1	1-2	1	1-2
Maximum number	10		13		3		11		13	
Elective termination	21.0%	82	6.9%	17	0.9%	1	16.8%	69	14.6%	169
Total number	107		19		1		84		211	
Median, IQR	1	1-1	1	1-1	1	1-1	1	1-1	1	1-1
Maximum number	4		2		1		3		4	
Stillbirths	2.1%	8	2.0%	5	2.7%	3	2.7%	11	2.3%	27
Total number	8		5		3		12		28	
Median, IQR	1	1-1	1	1-1	1	1-1	1	1-1	1	1-1
Maximum number	1		1		1		2		2	
Ectopic	2.8%	11	1.6%	4	3.5%	4	3.6%	15	2.9%	34
Total number	12		41		41		15		351	
Median, IQR	1	1-1	1	1-1	1	1-1	1	1-1	1	1-1
Maximum number	2		1		1		1		2	

Of the women who had been pregnant before, the median number of previous pregnancies was 1 with the exception of the UK where the median was 2. However, the maximum number of previous pregnancies was 12 or 13 in Denmark, the Netherlands and the UK whereas it was lower in Poland at 5. 78.2% of previously pregnant women reported that they had had a live birth. Most women had had only one previous live births. However in the UK the maximum number was 9 whereas in the other countries it ranged between 3 and 5. In the 39.3% of women who had reported miscarriages, the median number was one in all countries but some women had up to 13 miscarriages. The exception again was Poland where the maximum number was lower at 3. There was a marked differences between countries in the number of women who had an elective termination – 21% in Denmark, 16.8% in the UK versus 6.9% in the Netherlands and only 0.9% in Poland. 2.3% of women reported that they had suffered a stillbirth and 2.9% that they had had an ectopic pregnancy.

5.5 Lifestyle behaviour and recreational drug use

In the baseline questionnaire, participating women were asked about their substance use during their pregnancy. Participants were asked whether they were smoking at the moment, and if yes, how many cigarettes they smoked per day. If they stated they were non-smokers, we asked them if they had smoked in the year before their pregnancy. Participating women were also asked how often they drank alcohol during this pregnancy and if they had used recreational drugs up to the time they completed the baseline questionnaire until that moment. If yes to the latter they were asked what drugs they had used. Results are shown in Table 5-9 to Table 5-11.

Table 5-9: Smoking status during and prior to pregnancy

	DK		NL		PL		UK		All	
	%	No	%	No	%	No	%	No	%	No
Current smoker	4.1	26	4.2	20	4.6	11	4.8	34	4.4	91
Smoker before pregnancy	16.6	106	14.3	68	18.7	45	16.1	114	16.1	333
Non smoker before pregnancy	74.2	474	77.3	368	73.9	178	78.7	558	76.4	1578
Unknown	5.2	33	4.2	28	2.9	7	0.4	3	3.1	63

Table 5-10: Alcohol use during pregnancy

	DK		NL		PL		UK		All	
	%	No	%	No	%	No	%	No	%	No
4 or more times per week	0.0	0	0.0	0	0.0	0	0.1	1	0.0	1
2-3 times per week	0.3	2	0.2	1	0.0	0	0.6	4	0.3	7
2-4 times per month	6.1	39	0.6	3	0.0	0	10.7	76	5.7	118
About once per month or less	20.7	132	6.1	29	11.6	28	21.4	152	16.5	341
Never	72..6	464	92.6	441	87.6	211	66.6	472	76.9	1588
Unknown	0.3	2	0.4	2	0.8	2	0.6	4	0.5	10

Table 5-11: Recreational drug use during pregnancy

	DK		NL		PL		UK		All	
	%	No	%	No	%	No	%	No	%	No
Used	0.9	6	0.4	2	0.4	1	1.1	8	0.8	17
Cannabis		4		1		1		5	*(61.1)*	11
Cocaine		0		0		0		2†	*(11.1)*	2†
Heroin		0		0		0		1	*(5.6)*	1
MDMA		1		1		0		1†	*(16.7)*	3†
Unspecified		1		0		0		0	*(5.6)*	1
Did not use	98.3	628	98.9	471	96.3	232	98.2	696	98.2	2027
Preferred not to answer	0.6	4	0.2	1	2.9	7	0.4	3	0.7	15
Unknown	0.2	1	0.4	2	0.4	1	0.3	2	0.3	6

† One woman in the UK reported the use of both MDMA and cocaine during her pregnancy

While the use of alcohol varies a lot between the four participating countries, with alcohol use during pregnancy ranging from 7.0% in the Netherland to 33.0% in the UK, smoking data correspond fairly well, with about 4% of all women confirming they smoke at the time of baseline questionnaire completion. As expected, only a few women (less than 1%) reported recreational drug use during their pregnancy, with cannabis as the drug most commonly used. Another 0.7% indicated that they would rather not answered the question about recreational drug use.

Data about substance use vary a lot in literature. Studies often attract a selected sample of pregnant women and data about a sensitive topic like this, that is obtained by self-reporting to a health care worker or interviewer might be biased because of the propensity to give a social desirable answer. In their 2010 report, EURO-PERISTAT,[14] a European project to monitor and evaluate maternal and child health in the perinatal period, showed data on smoking during pregnancy. Data for the participating countries show percentages of 12.8 for Denmark, 10.5 for the Netherlands, 12.3 for Poland and 12.0 for the UK. Trimester of data collection varied between countries though. Other percentages for the UK found in the literature range from 6.9 in a web-based survey[15] to 20.9 for a cohort where they used pregnancy notes from health care workers.[16] A cohort study in Poland, measuring cotinine in saliva - an indicator for actual smoking - reported 16.1% of participating pregnant women continued to smoke. Data about alcohol use during pregnancy are hard to find, but the data that is published shows even greater variance. For the Netherlands, a cohort study set up in a rural area reported maternal alcohol use during pregnancy reported by the obstetrician or gynaecologist after birth, to be 4.0%,[17] while another cohort study set up in a urban area with self-reported alcohol use during first trimester of pregnancy reported a percentage of 41.8.[18] In Denmark two studies, both using data from the Danish National Birth Cohort, reported 44.6% of pregnant women to have used alcohol during first trimester and 88.7% during the entire pregnancy respectively.[19, 20] The figures of recreational drug use during pregnancy were hard to compare to population data or data about recreational drug use in pregnancy in the literature. For PROTECT, the actual numbers reporting use are low and comparison data were very scarce. One population based cohort study performed in the UK in the early nineties found self-reported cannabis use during pregnancy to be 2.6%.[21] Another study from Denmark tested for cannabis in urine and found a percentage of 0.5%, which was thought to be quite low, because an earlier study based on self-reporting reported cannabis use during pregnancy to be 1.2%.[22] In general, PROTECT data on recreational drug use seem to be quite low.

PROTECT data and data found in the literature show that figures about substance use during pregnancy differ a lot and depend largely on the design of the study performed and the circumstances in which the data were collected. Conclusions about the validity of PROTECT study data and about the validity of comparison data found in literature are very hard to make, due to the differences in study design and absence of population data. Based on the data we have it is likely that data on substance use provided by the participants of the PROTECT pregnancy study is an underestimation of actual substance use of pregnant women in the participating countries, probably due to the self-selection of higher educated, more health-oriented women. Some underreporting may also play a role, despite the anonymity of the web-based approach that encourages people to be honest and not give a social desirable answer.

5.6 Concluding remarks

The women in the PROTECT were, in general, geographically representative of the populations from which they were drawn. However, they were older and better educated than the average woman in each country. This was particularly noticeable in Poland where the figure with a university degree was twice the national average. With the exception of Poland, this was not the first pregnancy for the majority of women. This is possibly to be expected given the older age of the PROTECT women compared with the general population of pregnant women. Whereas most women had only one previous pregnancy, there was a wide range with some women reporting up to 13 previous pregnancies. In Poland the maximum number of previous pregnancies was 5 which was less than half that of the maximum reported in the other 3 countries. This could possibly be explained by the fact that nearly 90% of women from Poland had a university degree which might have delayed starting a family and thus affected the number of previous pregnancies.

Most of the women were white. In Poland, all the women who were prepared to state their ethnic origin were white whereas there was a small percentage of women of other ethnic/racial origins in the other countries.

The women from the UK had a higher mean BMI than the other countries whereas Poland had the lowest mean BMI, which could be associated with the differences in maternal education and maternal age between countries.

For women who had had previous pregnancies there were some notable differences between countries. Perhaps most striking was the percentage of previous elective termination in Denmark and the UK compared with the Netherlands and Poland. The reason for this is unclear but a number of hypotheses could explain it. Firstly there could be fewer unwanted pregnancies in Poland and the Netherlands. Poland had by far the highest level of woman with tertiary education which might explain this. An alternative explanation could be access to contraception but that is widely available in the other three countries so this seems an unlikely explanation. Alternative explanations for the difference in frequency could also be access to elective termination or acceptance by women of it. For example, elective termination in Poland is only possible on three grounds: the pregnancy is dangerous for the life of the mother, the pregnancy is a result of crime (rape and/or incestuous relations with first degree relatives), and the foetus is severely and irreversibly damaged.

Conclusions about the validity of PROTECT data as an example of self-reported data about sensitive topics such as alcohol or recreational drug use during pregnancy, using an anonymous and rather novel collecting method like the internet to avoid bias due to social desirable answering are very hard to make. There is an absence of population data with which to compare the data and comparison data found in the literature vary a lot due to differences in study design and source population. However, our data appear to be in line with what data there are.

6 Medication use in pregnancy

6.1 Background to medications use analysis

"Medications" in this study are defined as any medicinal or healthcare products, which includes prescription only medications, over the counter (OTC) medication, herbal remedies, homeopathic products, fish oil, dietary supplements, multivitamins, iron supplements, and vaccinations.

Women provided information on medications and procedures in two ways: (1) through selection from fixed lists of the most commonly used medications for the medical conditions as pre-specified by the study team, and (2) through open questions. All reported medications were manually coded into ATC codes (level 5, where possible) by the study country leads using WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/).

Throughout, we only report medications and procedures that were used within the month prior to the beginning of pregnancy and during the pregnancy, unless otherwise specified.

Section 6.2 presents an overview of self-reported medication use among pregnant women in the four participating countries as well as overall (4 countries together). The number of different types of medication used varied by woman and country. The prevalence of medication use in the four countries was between 80% and 88% (Section 6.2.1). Women also reported the frequency of medication use and changes to their medications well, but because the study did not collect information on dosage, only simple summaries are provided (Section 6.2.2). Section 6.2.3 summarises the types of medications reported by women at the ATC anatomical group level (level 1) that broadly reflects the indications of the medications. Section 6.2.4 provides an overall (all countries) summary of the types of medications used within trimesters of pregnancy. Prescription-only and over-the-counter medications are reported separately in Sections 6.2.5.

In Section 6.2.6, we present diabetes mellitus status in pregnancy and the medications that women reported to have taken to control the condition in pregnancy.

We present the results on medication use which women self-reported to have been influenced by pregnancy and planning of pregnancy in Section 6.2.7. Although most medications were prescribed or bought for personal use, a small proportion of women also reported using medications prescribed to others. This might include friends or family who experienced similar (or the same) medical symptoms (Section 6.2.8). Section 6.2.9 summarises the percentages of women who decided not to take medications because of being pregnant, either on their own or on their doctor's advice.

We present use of pregnancy-related medicinal products such as folic acid and iron supplements in Section 6.2.10; alternative medications and dietary supplements such as herbal remedies and homeopathy in Section 6.2.11; vaccinations and antimalarial drugs in Section 6.2.12; and contraceptive use prior to pregnancy in Section 6.2.13.

We summarise the reporting of procedures in Section 6.3, both medical (Section 6.3.1) and cosmetic (Section 6.3.2).

The final Section 6.4 discusses the findings of self-reported medications and procedures in general. Appendices 13.5 to 13.16 provide detailed lists of medications reported by levels of ATC codes.

6.2 Self-report medications use

There were a total of 12,915 reports of medication use within PROTECT, including 209 reports of items that the study team considered not to be medications (e.g. plaster, teas, saline spray, or when women did not name the medication), and those that were reported as being used outside the current pregnancy period or within 1 month prior to the start of pregnancy. This section summarises the key findings of self-reported medication use.

6.2.1 Number of medications, excluding vaccines, multivitamins, irons and alternative medications and dietary supplements

Figures about medication use during pregnancy in literature vary a lot, depending on the classes of medication that were included and the study design. A literature review from 2011 included 17 studies (1989 to 2010) investigating drug use during pregnancy in developed countries and reported estimates of overall prescription drug use in pregnancy of 27-93% (excl. vitamins and minerals).[23] The medications reported in this study only covered a shorter period of time depending on when a participant joined and left the study, and therefore may not be directly comparable to those in the literature. Figure 6-1 shows the percentages by country for the number of different medications used (defined by the number of unique ATC codes) within the period of one month prior to and during pregnancy.

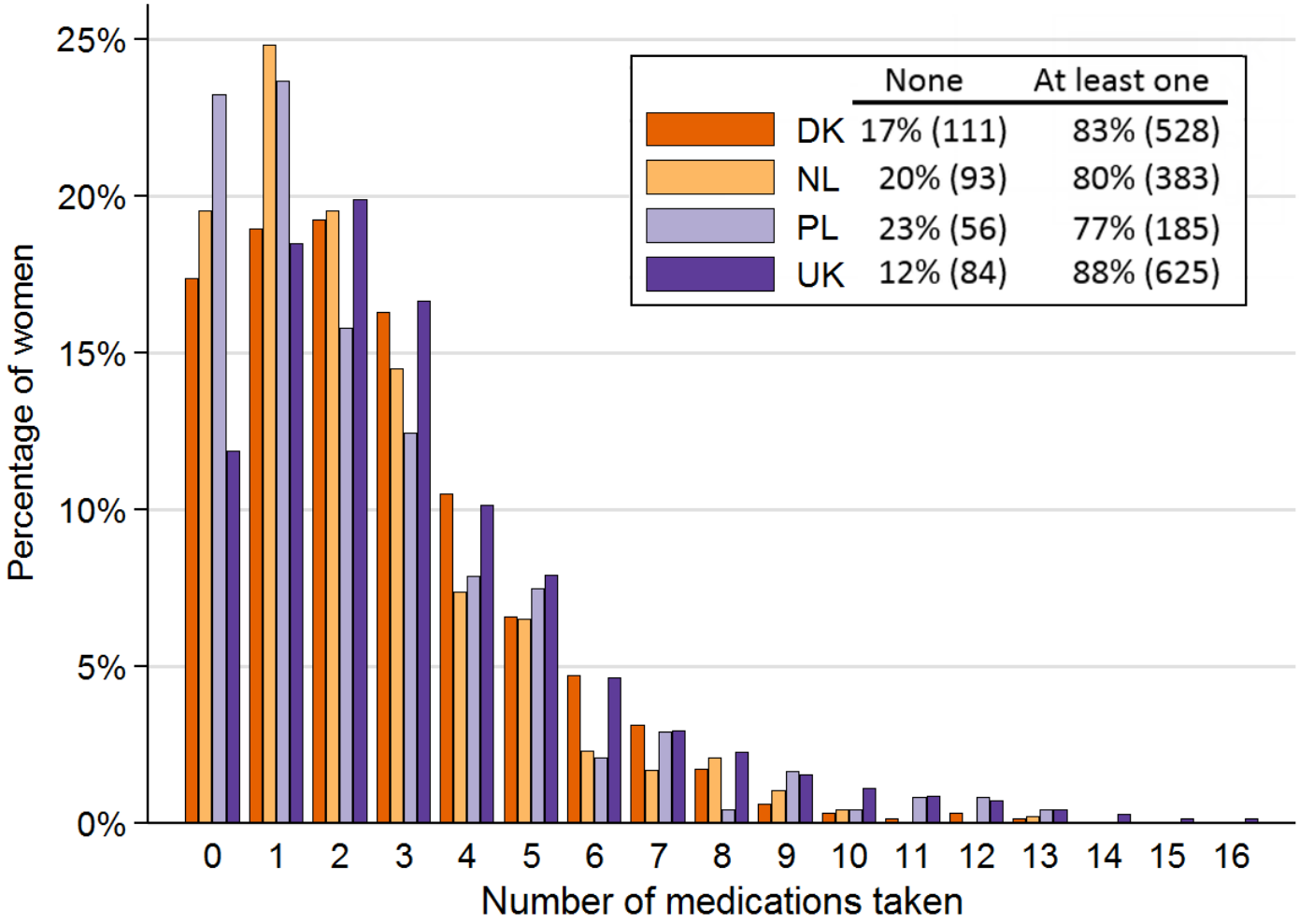


Figure 6-1 Percentages of women by number of different medications used by country

Table 6-1 shows the number of different medications reported by each woman. Women taking 5 or more medications were grouped together since individual numbers for women taking each number of medications above 5 were small. 344 (17%) women did not report any use of medications, and 1721 (83%) reported at least one medication use during and up to one month before pregnancy. Women in Poland and the Netherlands reported use of the fewest different medications and women in the UK reported the most. Overall, the median was 2 and the interquartile range was from 1 to 4.

Table 6-1 Number of different medications (by ATC codes) reported per woman during and up to one month before pregnancy, % (n) of women

Number	DK	NL	PL	UK	All
Total, N	639	476	241	709	2065
None	17% (111)	20% (93)	23% (56)	12% (84)	17% (344)
One	19% (121)	25% (118)	24% (57)	18% (131)	21% (427)
Two	19% (123)	20% (93)	16% (38)	20% (141)	19% (395)
Three	16% (104)	14% (69)	12% (30)	17% (118)	16% (321)
Four	10% (67)	7% (35)	8% (19)	10% (72)	9% (193)
Five and above	18% (113)	14% (68)	17% (41)	23% (163)	19% (385)
Odds ratio[a]	1.00	0.80 (0.65, 0.99)	0.76 (0.58, 0.99)	1.34 (1.11, 1.62)	NA

[a] Ordered logit on number of different medications use by countries (adjusted by choice of the frequency of data provision). An increase from "Four" to "Five and above" is assumed to be a difference of 1 unit. Sensitivity analyses of using the actual number of medications did not alter the results. NA = not applicable.

6.2.2 Reports of frequency of medications use and changes in use

We asked women how frequently they took their medication. Women were given the choices of reporting the frequency as "Less than once a day", "Once a day", "Twice a day", "3 times a day", "4 times a day", or "Only when I need it". A follow up question was asked if the women responded "Only when I need it"; where women could report use of "Several times a day", "Once or twice a day", "Almost daily", "Once or twice a week", or "1-4 times a month".

Table 6-2 Percentage (number) of women who ever reported frequency of medications use or changes in their medications

	DK	NL	PL	UK	All
Total, N	639	476	241	709	2065
Frequencies					
Reported	78% (498)	75% (358)	66% (159)	84% (593)	78% (1608)
Did not report[a]	22% (141)	25% (118)	34% (82)	16% (116)	22% (457)
Changes					
Reported[b]	77% (490)	66% (312)	60% (145)	80% (565)	73% (1512)
Did not report[a]	23% (149)	34% (164)	40% (96)	20% (144)	27% (553)

[a] Include those who did not report any medication use. [b] Include those who reported ongoing use and no changes

In general, when asked about medication frequency, women were willing to report this (Table 6-2). Of the reported frequencies, 42% of the medications were taken as and when needed and 25% were taken once a day. Medications that were taken most frequently (4 times a day) included paracetamol, aciclovir and amoxicillin. Women were also willing to report changes to their previously reported medications (Table 6-2), in terms of whether the amount taken decreased, increased or did not change. Of the 911 instances where details were reported, 40% were reports of no change, 35% of decreased amounts and 25% of increased amounts.

Table 6-3 shows the top 10 medications reported and the amount use changed during pregnancy, across all study countries. However, it is not known what the underlying reasons for these changes were, since we did not specifically ask for the information in the study. It is possible that these were due to a combination of several factors: becoming pregnant, changes in the conditions they were taken for, changes in the benefit-risk perception of the medications, or others.

Table 6-3 Top 10 drugs by amount of changes, % reports by amount of changes (number)

Decreased amount (n=312)	No change (n=367)	Increased amount (n=229)
Ibuprofen: 7.4% (23)	Salbutamol: 9.3% (34)	Levothyroxine sodium: 13.1% (30)
Paracetamol: 7.4% (23)	Budesonide: 4.9% (18)	Salbutamol: 11.8% (27)
Salbutamol: 5.8% (18)	Omeprazole: 4.9% (18)	Alginic acid: 7.4% (17)
Sumatriptan: 5.8% (18)	Sertraline: 4.4% (16)	Paracetamol: 4.8% (11)
Citalopram: 4.5% (14)	Levothyroxine sodium: 4.1% (15)	Insulin aspart: 4.4% (10)
Paracetamol combinations excl psycholeptics: 4.2% (13)	Terbutaline: 4.1% (15)	Acetylsalicylic acid: 3.5% (8)
Fluoxetine: 2.9% (9)	Beclomethasone: 3.3% (12)	Ranitidine: 3.5% (8)
Sertraline: 2.9% (9)	Formoterol and other drugs for obstructive airway diseases: 3.3% (12)	Beclomethasone: 3.1% (7)
Tramadol: 2.9% (9)	Citalopram: 2.7% (10)	Omeprazole: 2.6% (6)
Diclofenac: 2.2% (7)	Paracetamol: 2.5% (9)	Terbutaline: 2.6% (6)
Terbutaline: 2.2% (7)	Venlafaxine: 2.5% (9)	

6.2.3 Types of medications

Overall, 6909 reports of medications (excluding vitamins, fish oils etc) were provided by the study participants as used at any time during pregnancy or in the month prior to becoming pregnant, as shown in Figure 6-2.

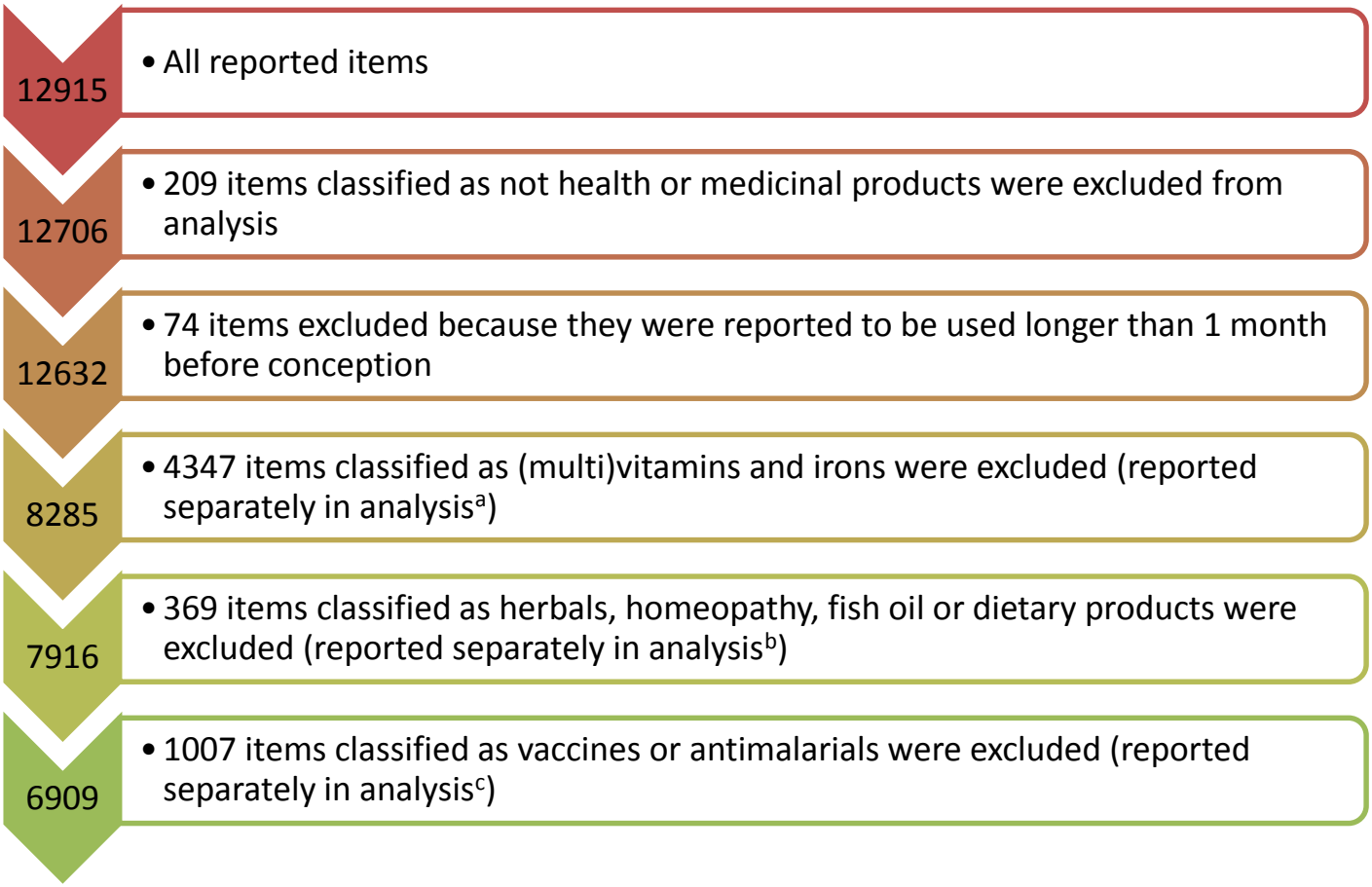


Figure 6-2 Medications included in current analysis

[a] See Section 6.2.10
[b] See Section 6.2.11
[c] See Section 6.2.12

For simplicity, Table 6-4 shows the percentage and number of women who reported any medication within an anatomical group for each country (see Table 13-7 in the Appendix for a detailed list). There were some differences among countries in the pattern of medications use. Women in the UK reported a relatively higher level of medications in category alimentary tract and metabolism, which appear to have been driven by a high rate of use of medications for acid related disorders or constipation. Medications categorised as genito-urinary system and sex hormones were also high, possibly due to reasons such as the high use of hormonal contraceptives in Poland and UK, high rate of unplanned pregnancies in Poland, and a high rate of gonadotrophin use reported in Denmark and the Netherlands. Many obstetricians in Poland would also recommend pregnant women using progesterone to avoid miscarriage due to low hormone levels. The high level of medication use in the nervous system category was mainly attributed to analgesics (ATC code: N02) such as paracetamol.

Table 6-4 Percentage (number) of women who reported medications use during and up to one month before pregnancy, by ATC anatomical group Type

Medications	DK		NL		PL		UK		All	
Number of women	639		476		241		709		2065	
	%	No.	%	No.	%	No.	%	No.	%	No.
A- Alimentary tract and metabolism†	56	357	46	219	52	126	84	594	63	1296
B- Blood and blood forming agents†	3	17	2	11	5	12	6	41	4	81
C- Cardiovascular system†	5	30	4	19	13	31	5	32	5	112
D- Dermatologicals†	14	89	13	64	14	34	9	63	12	250
G- Genito-urinary system and sex hormones†	38	243	32	152	40	97	21	146	31	638
H- Systemic hormonal preparations excluding sex hormones†	4	28	7	33	11	27	4	31	6	119
J- General anti-infectives for systemic use†	23	150	10	49	24	58	39	273	26	530
L- Antineoplastic and immunomodulationg agents†	1	7	3	16	0	1	2	11	2	35
M- Musculoskeletal system	11	72	3	14	7	16	8	54	8	156
N- Nervous system†	69	444	63	298	45	109	89	633	72	1484
P- Anti-parasitic products, insecticides and repellents	0	3	0	1	0	0	1	8	1	12
R- Respiratory system†	33	211	41	197	25	60	45	317	38	785
S- Sensory organs	2	15	3	13	1	3	1	8	2	39
V- Various†	0	3	0	0	3	7	0	0	0	10

† P-value <0.05 for χ^2-test of medication use/no medication use across countries

6.2.4 Types of medications within trimesters of pregnancy

One approach that could address the difference in reporting of medication use between trimesters is to adopt the disproportionality analysis technique used in signal detection, such as the proportional reporting ratios (PRR).[24] PRR may be the simplest disproportionality analysis method but its performance is on par with other more complex methodologies.[25]

To analyse the difference in proportions of medications used over time during pregnancy, we conducted a disproportionality analysis where the proportion of medications used in the first trimester were compared with those used in later trimesters (trimesters 2 and 3 combined). PRR, in this context, denote the ratio of medication use reported in the first trimester in comparison with use reported in the second or third trimester (see Appendix 13.6). A PRR greater than 1 indicates a higher proportion of use, whereas a PRR of less than 1 indicates a lower proportion of use during the first trimester. We adopted the MHRA's criteria for adverse drug reaction signals, and defined an increased or disproportionate use of a medication where PRR ≥ 2, $\chi^2 \geq 4$, and number of cases (use of a particular

medication by a woman in the first trimester) ≥ 3. These criteria restrict the need to evaluate small increases of use due of small numbers and/or higher chance of false signals.

The PRRs listed here refer to "signals" of what may be unusually higher reported use of a particular medication in the first trimester relative to the others in the dataset; and therefore should be interpreted cautiously. These signals of higher usage are not confirmed or validated, but the results do provide us with some clues as to which medications have a higher use in the first trimester and therefore have the potential to do most harm if they were to be subsequently identified as potential teratogens.

The initial disproportionality analysis of reported medication use, (defined by ATC codes regardless of level) within the first trimester compared to later trimesters, identified increased first trimester use of 30 medications (Table 13-8 in Appendix 13.6). We observed, among others, disproportionate use of contraceptive drugs or ovulation-inducing drugs (ATC codes beginning with G03-Sex hormones, H01C-Hypothalamic hormones and L02A-Hormones and related agents) to prevent or stimulate pregnancy). It is expected that higher proportions of these drugs would be used in the first trimester compared to the later trimesters since women who were on these drugs would stop using them when they found out they were pregnant.

In order to avoid masking of signals for increased medications use in the first trimester, we excluded the sex hormones and reran the analysis. After excluding sex hormones, we additionally identified loperamide, bromocriptine (may be used to prevent a prolactinoma preventing pregnancy) and ibuprofen as being used disproportionately during early pregnancy. Table 6-5 shows the list of raised signals for further evaluation (the PRR results are provided in Table 13-9 in Appendix 13.6).

Table 6-5 Raised signals of disproportionate self-reported medications in the first trimester versus the later trimesters

Medications	
A07DA03 – Loperamide	N06AA09 – Amitriptyline
C07AA05 – Propranolol	N06AB03 – Fluoxetine
G02CB01 – Bromocriptine	N06AB04 – Citalopram
M01AB05 – Diclofenac	N06AB06 – Sertraline
M01AE01 – Ibuprofen	N06AX16 – Venlafaxine
M01AE02 – Naproxen	N06BA04 – Methylphenidate
N02CC01 – Sumatriptan	R03DC03 – Montelukast
N02CC04 – Rizatriptan	R06AD03 – Thiethylperazine
N05AH04 – Quetiapine	R06AX18 – Acrivastine
N05CH01 – Melatonin	R06AX27 – Desloratadine

We also explored running the disproportionality analysis with less granularity using only level 3 of ATC codes. The grouping at higher level of ATC codes identified increased use of 13 ATC pharmacological subgroups in the first trimester (Table 13-10 in Appendix 13.6). A detailed list of overall medication use by trimester is also provided in Table 13-11 in Appendix 13.6.

To consider any medications where use only become more pronounced after the first trimester, we reran the analysis with the first trimester as the denominator. The PRRs in this case may indicate reluctance to use the medications during early pregnancy (fears over teratogenicity for example). Using the same criteria to identify signals, we did not observe any disproportionate use of medications reported in the later trimesters.

6.2.5 Prescription-only and over-the-counter medications (OTC)

In order to standardise prescription-only and OTC medications across the four countries, we used the list of OTC medications that are available in Denmark, for all countries. Some medications are available on both prescription and OTC in some countries.

About 83% (1721) of women reported to have used medications during and up to one month before pregnancy (Section 6.2.1). 60% (1235) of all women reported using at least one prescribed medication, and 41% (841) reported using at least one medication that are available over the counter. Figure 6-3 shows the percentage of 2065 women who reported using prescription and OTC medications. Consistently across countries, more women tend to use prescription medications during and up to a month before pregnancy. The actual percentages and numbers are given in the following Table 6-6 and Table 6-7.

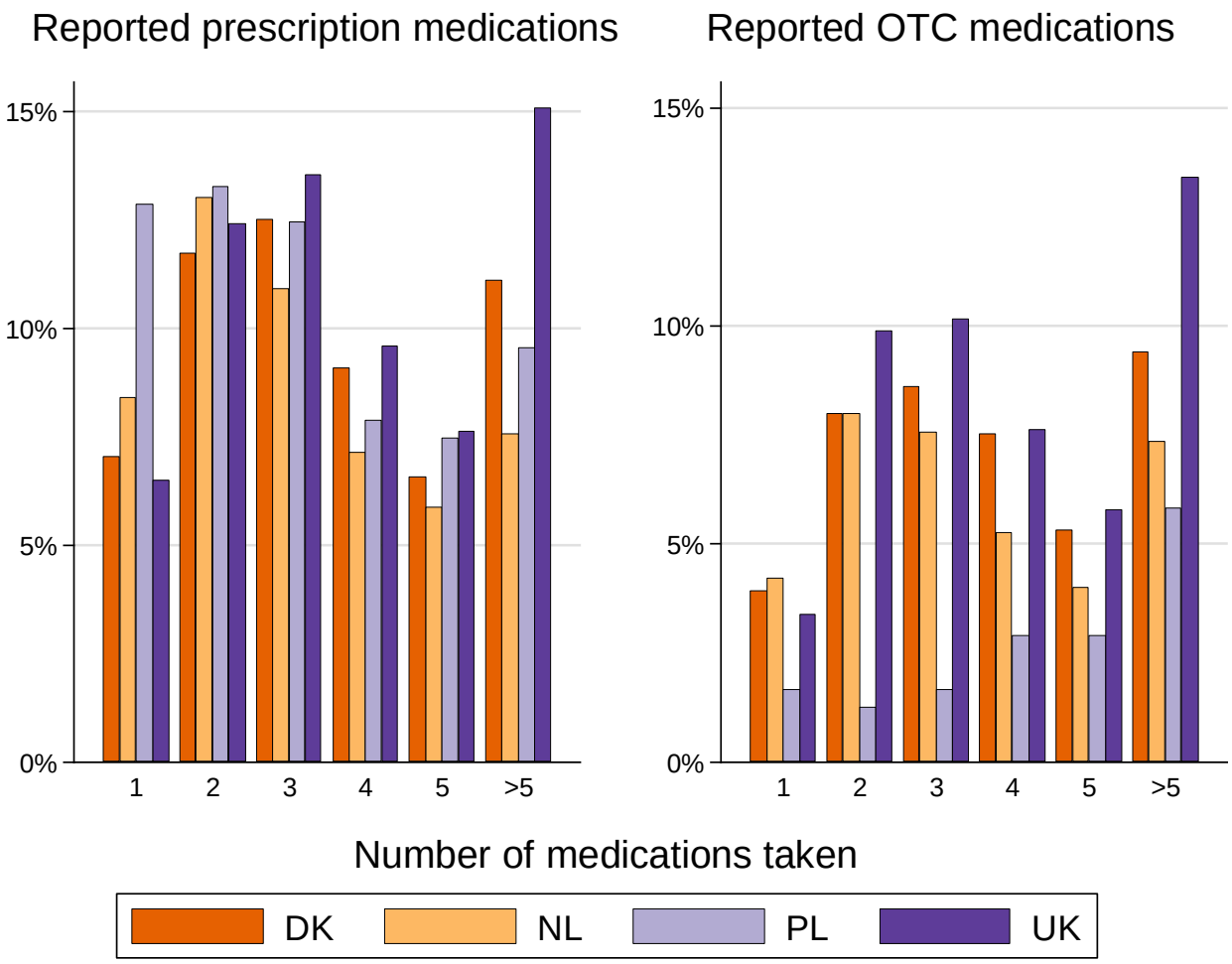


Figure 6-3 Percentage of women by number of medications taken, women who did not report use are not shown

Table 6-6 Number of prescribed medications reported by women

	DK	NL	PL	UK	All
None*	42% (268)	47% (224)	37% (88)	35% (250)	40% (830)
One	7% (45)	8% (40)	13% (31)	6% (46)	8% (162)
Two	12% (75)	13% (62)	13% (32)	12% (88)	12% (257)
Three	13% (80)	11% (52)	12% (30)	14% (96)	12% (258)
Four	9% (58)	7% (34)	8% (19)	10% (68)	9% (179)
Five	7% (42)	6% (28)	7% (18)	8% (54)	7% (142)
Six or more	11% (71)	8% (36)	10% (23)	15% (107)	11% (237)

* Includes women who did not report any medications at all

Table 6-7 Number of over the counter medications reported by women

	DK	NL	PL	UK	All
None*	57% (366)	64% (303)	84% (202)	50% (353)	59% (1224)
One	4% (25)	4% (20)	2% (4)	3% (24)	4% (73)
Two	8% (51)	8% (38)	1% (3)	10% (70)	8% (162)
Three	9% (55)	8% (36)	2% (4)	10% (72)	8% (167)
Four	8% (48)	5% (25)	3% (7)	8% (54)	6% (134)
Five	5% (34)	4% (19)	3% (7)	6% (41)	5% (101)
Six or more	9% (60)	7% (35)	6% (14)	13% (95)	10% (204)

* Includes women who did not report any medications at all

Of particular interest, we show in Table 6-8 below the number of women who reported to have used only medications that are available through prescription, and those reported to have used only medications that are available over the counter. Women in Poland reported only using prescribed medications as much as twice more (29%, 70) than other countries, and also Poland had the fewest number of women (2.5%, 6) who reported only using medications that can be bought over the counter without prescription.

Table 6-8 Reported use of prescription-only medications and over the counter medications (without report of using the other)

	DK	NL	PL	UK	All
Only used prescription medications, without any OTC	13.9% (89)	15.3% (73)	29.0% (70)	10.7% (76)	14.9% (308)
Only used medications available OTC, without any prescribed medications	14.1% (90)	14.7% (70)	2.5% (6)	14.0% (99)	12.8% (265)

Amoxicillin was the most reported prescription-only medication and paracetamol was the most reported OTC medication, with about 8% and 76% of women reporting use of these respectively (Table 6-9). The medians and mean numbers of prescription-only and OTC medications used by each participant are about two per woman, and are shown in Figure 6-4 and a boxplot is shown in Figure 6-5; where "number of medications" is different medications as defined by ATC codes.

Table 6-9 Top 10 medications reported during pregnancy

Prescription-only medications	OTC medications
J01CA04 - Amoxicillin: 8.0% (165)	N02BE01 - Paracetamol: 71.8% (1483)
R03AC02 - Salbutamol: 4.6% (96)	A02BX13 - Alginic acid: 14.1% (291)
H03AA01 - Levothyroxine sodium: 4.0% (83)	A02AD01 - Ordinary salt combinations: 8.4% (173)
G03A - Hormonal contraceptives for systemic use: 3.5% (73)	M01AE01 - Ibuprofen: 7.2% (149)
J01CA08 - Pivmecillinam: 3.2% (67)	G01AF02 - Clotrimazole: 6.5% (135)
J02AC01 - Fluconazole: 3.1% (64)	A06AD11 - Lactulose: 4.9% (101)
G03DA04 - Progesterone: 2.9% (59)	R01AA07 - Xylometazoline: 4.5% (93)
G03GB02 - Clomifene: 2.8% (57)	A06AC01 - Ispaghula (psylla seeds): 4.4% (90)
A10BA02 - Metformin: 2.3% (48)	N02BE51 - Paracetamol, combinations: 3.9% (80)
A03FA01 - Metoclopramide: 2.3% (47)	A02BC01 - Omeprazole: 3.9% (80)

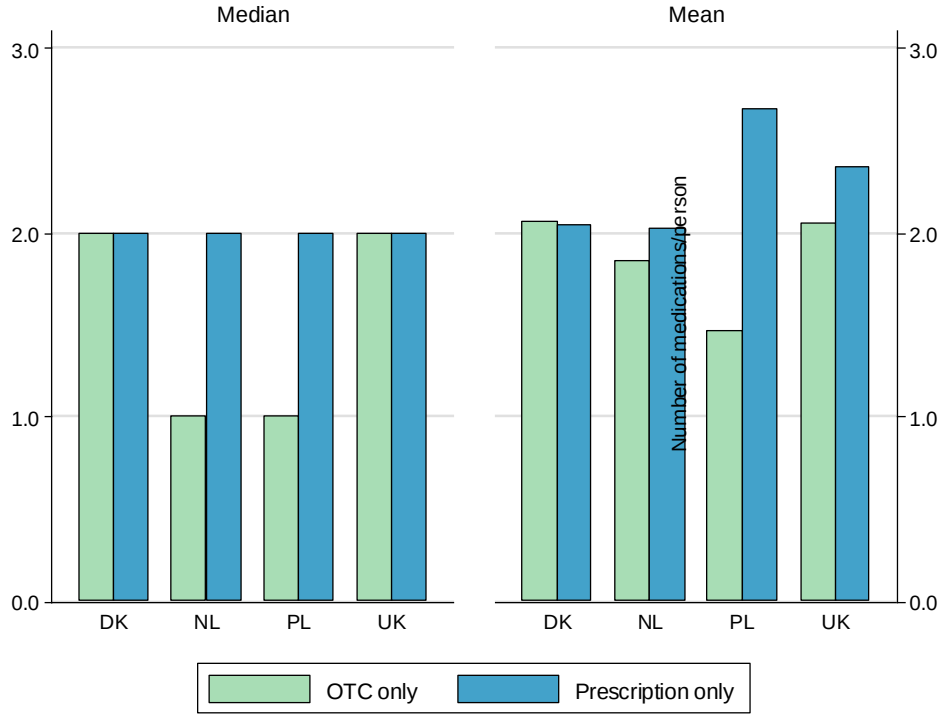


Figure 6-4 Number of medications reported per woman

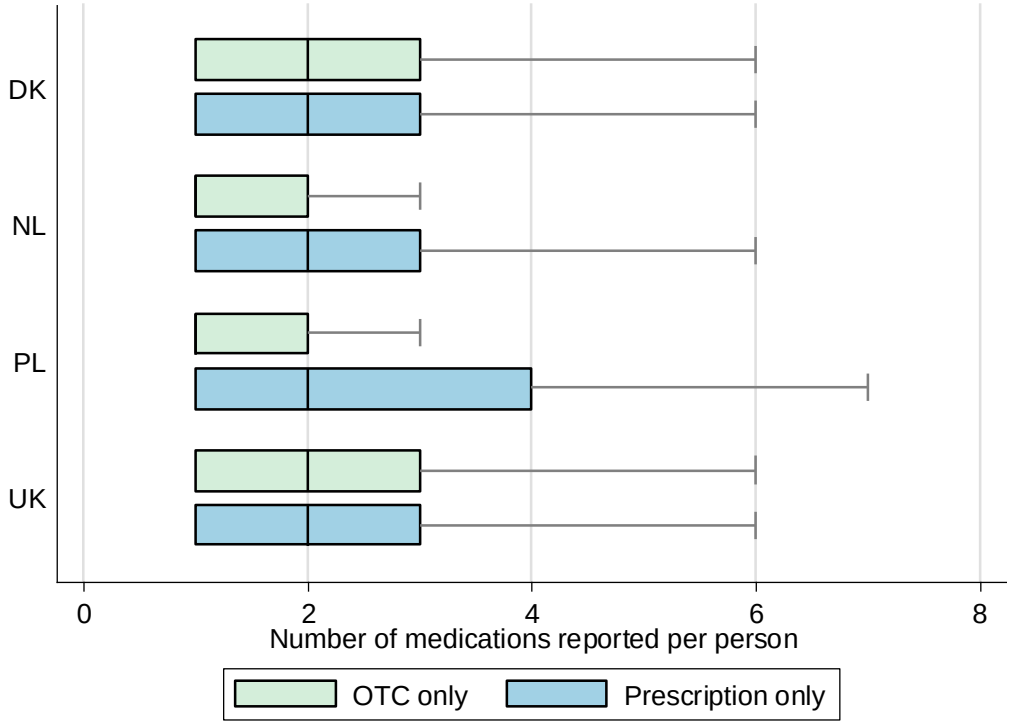


Figure 6-5 Number of medications reported per woman

Overall, there is no difference between the number of OTC medications and prescription-only medications that were reported per woman, with an estimate of 1% (95% CI -8%-12%) more OTC medications (Table 6-10). However, the results in Table 6-10 (last column) show that the number of OTC and prescription-only medications reported per woman significantly differ by country, where Poland had the lowest reported use of OTC medications compared to prescription-only medications.

Table 6-10 Incidence rate ratio (IRR) estimates of medications reported per woman in a random-effect Poisson regression

	IRR (95% CI) main effects	IRR (95% CI) interactions with OTC
Denmark	1.00	1.00
Netherlands	0.99 (0.88, 1.12)	0.90 (0.77, 1.06)
Poland	1.31 (1.16, 1.49)	0.54 (0.44, 0.66)
United Kingdom	1.16 (1.05, 1.27)	0.86 (0.76, 0.98)
Medications availability		
Prescription only	1.00	
OTC[a]	1.01 (0.92, 1.12)	
Prescription-only in Denmark (constant)	*2.00 (1.86, 2.15)*[b]	

[a] Including medications available also through prescription

[b] Rates of prescription-only medications in DK

Table 13-12 and Table 13-13 (available in Appendices 13.7 and 13.8, respectively) show the detailed lists of OTC and prescription-only medications.

The list of chronic medications (medications used long-term) reported are provided in Table 13-14 in Appendix 13.9, and the list of medications for short-term illnesses are provided in Table 13-15 in Appendix 13.10. These lists do not differentiate OTC and prescription-only medications.

6.2.6 Diabetes Mellitus in pregnancy

Diabetes Mellitus (DM) is a serious condition with increasing incidence overall. Concurrently, the incidence of gestational diabetes is increasing as well, resulting in a higher number of pregnancies complicated by diabetes. Diabetes in pregnancy involves several risks for both mother and baby, including miscarriage, stillbirth, pre-eclampsia, pre-term delivery, macrosomia and increased risk of congenital anomalies.[26] Since adequate control of blood-glucose levels substantially decreases these risks of diabetes in pregnancy, adequate perinatal therapy of diabetes is of great importance. In the baseline questionnaire, participating women were asked whether they were using any medication for diabetes. After confirmation, women were asked about the type of diabetes and the medications they used for it. In the follow-up questionnaires women were asked for the development of gestational diabetes since the last questionnaire, whether they used medications for it and about the type of medications. Result are shown in Table 6-11 and Table 6-12.

Table 6-11: Prevalence of Diabetes Mellitus (DM) per country and per type

	Total	DM type 1	%	DM type 2	%	Pre-gestational DM		Gestational DM	%	Unknown	total	%
DK	639	2	0.3	0	0.0	2	0.3	10	1.6	2	14	2.2
NL	476	4	0.8	0	0.0	4	0.8	10	2.1	1	15	3.2
PL	241	2	0.8	0	0.0	2	0.8	8	3.3	1	11	4.6
UK	709	7	1.0	3	0.4	10	1.4	23	3.2	0	33	4.7
All	**2065**	**15**	**0.7**	**3**	**0.1**	**18**	**0.9**	**51**	**2.5**	**4**	**72**	**3.5**

Table 6-12: Medications used for Diabetes in pregnancy

	Total	Insulin (mono-therapy)	%	Metformin (mono-therapy)	%	Insulin + metformin	%	No meds	%	Un-known
Type 1	15	15	100	0	0	0	0	0	0.0	0
Type 2	3	0	0	0	0	3	100	0	0.0	0
Gestational DM	51	12	23.5	7	13.7	4	7.8	27	52.9	1
Unknown	4	2	50	2	50	0	0	0	0.0	0

Medically treated pre-gestational diabetes ranged from 0.3% in Denmark to 1.4% in the UK and all of these women were treated with insulin. Type 2 diabetes was only reported in the UK and was treated with oral antidiabetics together with the insulin therapy. The only oral antidiabetic that was mentioned throughout all types of diabetes was metformin. A recent European study showed a comparable prevalence of insulin-treated pre-gestational Diabetes Mellitus for Denmark of 0.45%, but lower prevalences for the Netherlands and the UK, both being 0.4%.[26] These differences might reflect the higher engagement of pregnant women with a chronic condition or using medications themselves, with a study like the PROTECT pregnancy study, involving health and medication use.

Gestational diabetes was reported by 2.5% of participating women, ranging from 1.6% in Denmark to 3.3% in Poland. These numbers tend to be an underestimation of actual figures, because the risk of gestational diabetes increases with development of pregnancy, and not all participants were followed until the end of their pregnancy. The majority of Gestational diabetes reported was not treated with medication, probably reflecting mild or onset diabetes where dietary adjustments were sufficient to reach an adequate control of blood-glucose levels at time of reporting. During progress of pregnancy gestational diabetes tends to intensify and some of these women might had to change to medication after all. Treatment of gestational diabetes varied between participating countries. In Denmark none of the women reporting gestational diabetes were prescribed any medications. In the Netherlands 2 out of 10 (20%) were on insulin against 3 out of 7 (43%) for Poland and 10 out of 23 (44%) for the UK. Furthermore, in the UK 7 women (30%) reported the use of metformin alone and 4 women used metformin on top of their insulin. The UK was the only country where women reported the use of oral antidiabetics (metformin) for gestational diabetes. These differences might reflect the different stages of pregnancy in which the gestational diabetes was reported as well as national differences in overall treatment of gestational diabetes.

6.2.7 Influence of pregnancy or planning of pregnancy on continuing medications' use

Planning a pregnancy and/or becoming pregnant may also play a role in a mother's decision about using certain medications. The majority of the study participants reported that they planned their pregnancy (76%), with the highest proportion (84%) in the Netherlands, and the lowest (66%) in Poland (Table 6-13). Of the 1576 women who planned their pregnancy, 79% continued medication use and 17% stopped using one or more medications while trying to conceive (Table 6-14).

The lists of medications women decided to stop taking are provided in Appendix 13.11.

Table 6-13 Percentage (frequency) of mothers who planned pregnancy

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Pregnancy planned	75.9% (485)	84.2% (401)	65.6% (158)	75.0% (532)	76.3% (1576)
Pregnancy not planned	20.8% (133)	14.5% (69)	24.1% (58)	24.3% (172)	20.9% (432)
Unknown	3.3% (21)	1.3% (6)	10.4% (25)	0.7% (5)	2.8% (57)

Test of differences χ^2, P < 0.001

Table 6-14 Percentage (frequency) of mothers who stopped using medications while trying to get pregnant, among those who planned pregnancy

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Stopped	16.3% (79)	15.2% (61)	18.4% (29)	17.7% (94)	16.7% (263)
Did not stop	74.6% (362)	82.5% (331)	76.6% (121)	79.5% (423)	78.5% (1237)
Unknown	9.1% (44)	2.2% (9)	5.1% (8)	2.8% (15)	4.8% (76)

Table 6-15 shows the ranks, by country and overall, of the top five medications that the participants chose to stop taking while trying to get pregnant. Citalopram was stopped most frequently – driven by a ranking of 1 and 2 in the UK and Denmark respectively. Women in Poland stopped using drospirenone and ethinylestradiol most frequently while trying to get pregnant (7 women) which is possibly not surprising since it they are used together as an oral contraceptive – likewise levonorgestrel and ethinylestradiol were also stopped by women trying to become pregnant.

Table 6-15 Medications reported to have been stopped while trying to get pregnant and ranks by country among those who planned pregnancy (N=1576)

ATC – Description: % (n)	DK	NL	PL	UK	All
N06AB04 - Citalopram: 1% (17)	2	6	5	1	1
M01AE01 - Ibuprofen: 1% (16)	1	2	4	8	2
N02CC01 - Sumatriptan: 1% (12)	3	2	4	9	3
G03AA07 - Levonorgestrel and ethinylestradiol: 1% (9)	9	5	5	2	4
M01AB05 - Diclofenac: 1% (8)	5	5	5	6	5
N06AB06 - Sertraline: 1% (8)	7	6	5	3	5
R06AE09 - Levocetirizine: 1% (8)	9	1	5	9	5

Table 6-16 Percentage (frequency) of mothers who stopped using medications when the found out they were pregnant

	Denmark	Netherlands	Poland	United Kingdom	All
Total number of women	639	476	241	709	2065
Stopped	14.9% (95)	10.7% (51)	11.2% (27)	17.8% (126)	14.5% (299)
Did not stop	64.9% (415)	75.4% (359)	69.3% (167)	72.8% (516)	70.6% (1457)
Unknown	20.2% (129)	13.9% (66)	19.5% (47)	9.4% (67)	15.0% (309)

Table 6-16 shows whether women reported that they stopped taking medications when they found out they were pregnant; and overall, 71% reported continued medication use, and 15% stopped. The top 5 medications that the pregnant women in the study reported to have stopped using when they found they were pregnant are listed in Table 6-17. Ibuprofen was the top ranked medication that was stopped in all countries except Poland; participants from Poland reported to have stopped using bromocriptine the most often (3 women).

Table 6-17 Medications reported to have been stopped when women found out they were pregnant (ranks by country)

ATC – Description: % (n)	DK	NL	PL	UK	All
M01AE01 - Ibuprofen: 2% (44)	1	1	2	1	1
A10BA02 - Metformin: 1% (11)	3	4	3	6	2
N02AX02 - Tramadol: <0.5% (10)	4	4	4	4	3
N02BE51 - Paracetamol, combinations excl psycholeptics: <0.5% (10)	8	2	4	2	3
N02BE01 - Paracetamol: <0.5% (9)	2	3	4	9	4
N06AB04 - Citalopram: <0.5% (8)	5	3	4	5	5
N06AB03 - Fluoxetine: <0.5% (8)	8	4	4	2	5
M01AE02 - Naproxen: <0.5% (8)	7	4	4	3	5

Table 6-18 shows the top five medications that women stopped on doctor's advice, and whether the women told their doctors when they decided to stop taking the medications. The reasons for stopping medication use would vary but we did not ask the question directly in the study. The reasons may include a combination of no longer needing the medications, changing to a different medication, or for being risk averse (e.g. safety of the foetus, safety of mothers, contra-indications to new medications).

Table 6-18 Ranking of medications that were stopped on doctor's advice, and whether doctors were told or not

ATC – Description	Doctor's advice	Told doctors of stopping	Did not tell doctors of stopping
A10 - Drugs used in diabetes	5		
G03 - Sex hormones and modulators of the genital system		5	
M01 - Antiinflammatory and antirheumatic products	1	2	1
N02 - Analgesics	2	3	2
N06 - Psychoanaleptics	3	1	5
R03 - Drugs for obstructive airway diseases			4
R06 - Antihistamines for systemic use	4	4	3

6.2.8 Medications from other people

A small number of women (~1%) in the study reported using medications prescribed for other people (Table 6-19). The numbers were very small, but 4 women reported sharing analgesics (oxycodone and paracetamol) and 8 reported sharing drugs for acid-related problems. A detailed list of medications obtained from other people are provided in Table 13-18 in Appendix 13.12.

Table 6-19 Use of medications from other people

	Denmark	Netherlands	Poland	United Kingdom	All
Total number of women	639	476	241	709	2065
Used, % (n)	1.7% (11)	0.6% (3)	1.2% (3)	1.4% (10)	1.3% (27)
Did not use, % (n)	97.5% (623)	98.9% (471)	93.8% (226)	98.3% (697)	97.7% (2017)
Unknown	0.8% (5)	0.4% (2)	5.0% (12)	0.3% (2)	1.0% (21)

6.2.9 Decided not to take doctor's prescribed medications

Table 6-20 shows the percentages (and number) of women who decided not to take medications prescribed by their doctor. The overall percentage of those who did not take prescribed medications is 7%, ranging from 6% to 8%. There were no significant differences between countries. The women may have had several reasons for deciding not to take medication, perhaps based on the individual's risk perception or social influence. However, this is only speculation because the study did not ask the reason for their decisions directly.

Table 6-20 Decided not to take doctor's prescribed medications

	Denmark	Netherlands	Poland	United Kingdom	All
Total number of women	639	476	241	709	2065
Did not take, % (n)	7.2% (46)	5.5% (26)	6.2% (15)	8.6% (61)	7.2% (148)
Taken, % (n)	92.8% (593)	94.3% (449)	90.9% (219)	91.3% (647)	92.4% (1908)
Unknown	0.0% (0)	0.2% (1)	2.9% (7)	0.1% (1)	0.4% (9)

The top 10 medications that were reported to have not been taken were ibuprofen, citalopram, sumatriptan, paracetamol, tramadol, diclofenac, fluoxetine, levonorgestrel and ethinylestradiol, metformin and sertraline. A detailed list of the medications women reported to have not been taken is provided in Table 13-19 in Appendix 13.13.

6.2.10 Pregnancy-related medicinal products

Over 90% of women in the study reported the use of at least one pregnancy-related medication, including fertility medications, iron tablets, multivitamins and folic acid. Fewer Polish women reported use of pregnancy-related medications, less than 80%, compared to the other countries (Table 6-21). Iron tablet use in Denmark was considerably more prevalent than in other countries, 63% versus the lowest (Netherlands) of about 9% and a sample average of 30%. Multivitamin use was reported by fewest participants in Poland (about 41%) and by most in Denmark (about 83%).

Just under 75% of women reported use of folic acid tablets; with 400μg tablets being the most popular, reported by almost half of the study participants. In most cases, women reported use of the same folic acid dose throughout the pregnancy. Six women reported use of multiple doses and were double-counted; five reported 400μg and 5mg, and one reported 400μg and 800μg. Another 10 women also reported not knowing the dose or did not report the dose at one occasion, and provided a dose of 400μg (6 women), 800μg (2 women) and 5mg (2 women) at another occasion – these women were not double-counted.

Table 6-21 Percentage (frequency) of mothers who used pregnancy-related medications before and/or during pregnancy

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Use of pregnancy-related medications	91.9% (587)	96.6% (460)	78.8% (190)	95.6% (678)	92.7% (1915)
Fertility medication to get pregnant	8.9% (57)	11.6% (55)	9.1% (22)	6.1% (43)	8.6% (177)
Iron tablets	62.8% (401)	8.8% (42)	22.4% (54)	16.2% (115)	29.6% (612)
Multivitamins	83.1% (531)	70.6% (336)	41.1% (99)	65.0% (461)	69.1% (1427)
Folic acid tablets	65.9% (421)	79.0% (376)	69.3% (167)	78.1% (554)	73.5% (1518)
400 μg	53.7% (343)	39.1% (186)	40.7% (98)	50.1% (355)	47.6% (982)
800 μg	1.4% (9)	3.2% (15)	2.9% (7)	2.0% (14)	2.2% (45)
5000 μg	0.5% (3)	5.0% (24)	2.1% (5)	7.8% (55)	4.2% (87)
Did not know the dose	9.5% (61)	31.1% (148)	23.7% (57)	18.2% (129)	19.1% (395)
Unspecified (missing)	0.8% (5)	0.8% (4)	0.4% (1)	0.7% (5)	0.7% (15)
Did not use any listed	7.8% (50)	3.2% (15)	19.5% (47)	3.8% (27)	6.7% (139)
Unknown	0.3% (2)	0.2% (1)	1.7% (4)	0.6% (4)	0.5% (11)

6.2.11 Alternative medications, fish oil and dietary supplements

Table 6-22 shows the percentage and number of women who reported use of alternative medications (homeopathic and herbal products), fish oil and dietary supplements (not including folate – see Section 6.2.10).

Women in Denmark reported high use of fish oils (11%) compared to other countries; Polish women did not report any fish oil use. The use of homeopathy was similar in all countries at about 1%. Dietary supplement use was highest in Poland at 5%, and lowest in the UK at <1%. Herbal products use was similar across countries with an overall prevalence of 7%. The most reported herbals are raspberry, krauterblut, cranberry, menthol, Curanol, Vivag, Echinacea, aloe vera and zurawit.

Table 6-22 Percentage (number) women who used alternative medications and dietary supplements during pregnancy

Medications	DK	NL	PL	UK	All
Total number of women	639	476	241	709	2065
F - Fish oil	11.0% (70)	3.2% (15)	0.0% (0)	1.4% (10)	4.6% (95)
X - Homeopathic products	1.6% (10)	1.5% (7)	0.4% (1)	0.8% (6)	1.2% (24)
Y - Dietary supplements	2.7% (17)	1.9% (9)	5.0% (12)	0.1% (1)	1.9% (39)
Z - Herbal products	8.1% (52)	7.6% (36)	5.8% (14)	6.2% (44)	7.1% (146)
Neither	76.7% (490)	85.9% (409)	88.8% (214)	91.4% (648)	85.3% (1761)

6.2.12 Vaccinations and antimalarials

Vaccination rates amongst pregnant women were highest in the UK at 62%, double the average; and lowest in Poland at 3% (Table 6-23). The high rate of vaccinations in the UK was mainly driven by flu and pertussis vaccines. Women in the UK also reported significantly more vaccinations for pertussis (33%), tetanus (8%), polio (7%) and diphtheria (7%), compared to <1% women in other countries. Women in Denmark reported significantly more HPV vaccinations (6%) compared to almost none in other countries.

Table 6-23 Percentage (frequency) of mothers who had vaccinations during pregnancy or in the month before becoming pregnant

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Had vaccinations	23.3% (149)	6.1% (29)	2.5% (6)	62.1% (440)	30.2% (624)
Flu	15.5% (99)	4.2% (20)	0.8% (2)	56.1% (398)	25.1% (519)
Seasonal	13.5% (86)	3.6% (17)	0.8% (2)	39.8% (282)	18.7% (387)
Pandemic	0.3% (2)	0.0% (0)	0.0% (0)	1.0% (7)	0.4% (9)
Combined seasonal+pandemic	0.8% (5)	0.0% (0)	0.0% (0)	7.5% (53)	2.8% (58)
Did not know	0.9% (6)	0.2% (1)	0.0% (0)	4.4% (31)	1.8% (38)
HPV – cervix cancer prevention	5.9% (38)	0.0% (0)	0.0% (0)	0.1% (1)	1.9% (39)
Measles	0.0% (0)	0.2% (1)	0.0% (0)	0.6% (4)	0.2% (5)
Mumps	0.0% (0)	0.2% (1)	0.0% (0)	0.6% (4)	0.2% (5)
Rubella	0.0% (0)	0.2% (1)	0.0% (0)	0.6% (4)	0.2% (5)
BCG – tuberculosis prevention	0.0% (0)	0.0% (0)	0.0% (0)	0.3% (2)	0.1% (2)
Pertussis (whooping cough)	0.0% (0)	0.0% (0)	0.0% (0)	32.6% (231)	11.2% (231)
Tetanus	0.8% (5)	0.6% (3)	0.0% (0)	7.6% (54)	3.0% (62)
Polio	0.0% (0)	0.4% (2)	0.0% (0)	6.6% (47)	2.4% (49)
Diphtheria	0.0% (0)	0.4% (2)	0.0% (0)	6.9% (49)	2.5% (51)
Hepatitis A	0.3% (2)	0.4% (2)	0.0% (0)	0.3% (2)	0.3% (6)
Hepatitis B	0.2% (1)	0.2% (1)	0.4% (1)	0.1% (1)	0.2% (4)
Typhoid	0.2% (1)	0.4% (2)	0.0% (0)	0.1% (1)	0.2% (4)
Other	2.7% (17)	0.8% (4)	1.2% (3)	3.0% (21)	2.2% (45)
Did not have vaccination/unsure	76.7% (490)	93.7% (446)	96.3% (232)	37.9% (269)	69.6% (1437)
Unknown	0.0% (0)	0.2% (1)	1.2% (3)	0.0% (0)	0.2% (4)

Table 6-24 shows the reports of antimalarials use. Very few women were able to report the name of malaria medications they took. However, the number of women who reported malaria medications was small. All malaria medications that were taken were for prevention, except for one woman who reported that she did not know whether it was taken for prevention or treatment – which suggests that it was probably taken for prevention.

Table 6-24 Percentage (frequency) of mothers who had malaria medicines

	Denmark	Netherlands	Poland	United Kingdom	All
Had malaria medicines	2.5% (16)	1.1% (5)	0.8% (2)	0.4% (3)	1.3% (26)
Chloroquine	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.1% (1)
Doxycycline	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.1% (1)
Malarone	0.0% (0)	0.2% (1)	0.0% (0)	0.4% (1)	0.3% (2)
Mefloquine	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.1% (1)
Did not have malaria medicines/unsure	97.3% (622)	98.7% (470)	97.5% (235)	98.4% (698)	98.1% (2025)
Unknown	0.2% (1)	0.2% (1)	1.7% (4)	1.1% (8)	0.7% (14)

6.2.13 Birth control (contraceptive) medications

Table 6-25 shows the number of mothers who were (4%) or were not (94%) using contraception when they found out they were pregnant. Oral contraceptives were most used among the women in the study; followed by IUDs, contraceptive rings, contraceptive implants and contraceptive injections. About 1% reported that they did not know if they were using contraceptives when they became pregnant, with a significantly higher proportion in Poland at 7%.

Table 6-25 Percentage (frequency) of mothers who were pregnant while on contraceptive

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Pregnant while using contraceptives	3.3% (21)	3.2% (15)	2.5% (6)	6.1% (43)	4.1% (85)
Oral contraceptive	1.9% (12)	1.9% (9)	2.1% (5)	4.2% (30)	2.7% (56)
Combined (oestrogen/progestogen)	0.8% (5)	0.6% (3)	0.0% (0)	2.1% (15)	1.1% (23)
Progestogen only	0.3% (2)	0.6% (3)	0.4% (1)	1.6% (11)	0.8% (17)
I don't know	0.2% (1)	0.0% (0)	0.8% (2)	0.1% (1)	0.2% (4)
Unspecified	0.6% (4)	0.6% (3)	0.8% (2)	0.4% (3)	0.6% (12)
Vaginal contraceptive ring	0.2% (1)	0.6% (3)	0.0% (0)	0.0% (0)	0.2% (4)
Contraceptive injection	0.0% (0)	0.0% (0)	0.0% (0)	0.1% (1)	0.0% (1)
Contraceptive implant	0.2% (1)	0.0% (0)	0.0% (0)	0.1% (1)	0.1% (2)
IUD	0.5% (3)	0.6% (3)	0.0% (0)	0.3% (2)	0.4% (8)
A copper IUD	0.2% (1)	0.6% (3)	0.0% (0)	0.0% (0)	0.2% (4)
A hormonal IUD	0.2% (1)	0.0% (0)	0.0% (0)	0.3% (2)	0.1% (3)
I can't remember	0.2% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (1)
Other contraceptives	1.1% (7)	0.0% (0)	0.0% (0)	1.3% (9)	0.8% (16)
Did not use contraceptive	94.8% (606)	96.0% (457)	86.7% (209)	92.8% (658)	93.5% (1930)
Did not know if she was using a contraceptive	1.6% (10)	0.6% (3)	6.6% (16)	0.4% (3)	1.5% (32)
Unknown	0.3% (2)	0.2% (1)	4.1% (10)	0.7% (5)	0.9% (18)

Women who used IUD contraception removed it as late in pregnancy as week 9 (Table 6-26). Four women (two in Denmark and two in the UK) did not specify whether the IUD was removed or not. It is possible that they may not have be removed due to the possible risk of mechanical damage and risk of inducing abortion. An estimated 1% of women reported to have taken emergency hormonal contraception to prevent pregnancy but still became pregnant (Table 6-26).

Table 6-26 Other contraceptive information

	Denmark	Netherlands	Poland	United Kingdom	All
IUD users	3	3	0	2	8
Removed IUD when pregnant	2	3	n/a	1	6
Pregnancy week when removed	Week 2 (1)	Week 6 (2) Week 9 (1)	n/a	Unknown	Week 2 – Week 9
Unspecified	2	0	n/a	2	4
Emergency contraception to prevent pregnancy	0.3% (2)	2.1% (10)	0.8% (2)	1.3% (9)	1.1% (23)

6.3 Self-report procedures

Not all medical and cosmetic procedures are captured in electronic healthcare databases. The Pregnancy Study asked women about any procedures that they underwent during pregnancy, either for medical (Section 6.3.1) or cosmetic (Section 6.3.2) purposes.

6.3.1 Medical procedures

Information about medical procedures, such as the use of anaesthetics or X-rays may be of value for safety monitoring. Table 6-27 shows that overall 7% and 5% of women were exposed to anaesthetics and x-rays during pregnancy, respectively. Anaesthetics exposure was significantly different between countries (P=0.003), largely driven by differences in exposure to local anaesthetics.

Table 6-27 Percentage (number) of mothers who had medical procedures during pregnancy

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Anaesthetic use	4.9% (31)	8.8% (42)	11.6% (28)	7.1% (50)	7.3% (151)
General anaesthetics	0.6% (4)	1.1% (5)	0.4% (1)	0.6% (4)	0.7% (14)
Spinal anaesthetic	0.0% (0)	0.0% (0)	0.0% (0)	0.3% (2)	0.1% (2)
Local anaesthetic	4.1% (26)	7.6% (36)	10.0% (24)	5.9% (42)	6.2% (128)
Did not know	0.2% (1)	0.2% (1)	1.2% (3)	0.3% (2)	0.3% (7)
Did not have anaesthetics / procedures	94.8% (606)	90.5% (431)	85.9% (207)	92.1% (653)	91.9% (1897)
Anaesthetics – Unknown	0.3% (2)	0.6% (3)	2.5% (6)	0.8% (6)	0.8% (17)
Had X-rays	6.9% (44)	4.6% (22)	3.7% (9)	4.9% (35)	5.3% (110)
Did not have x-rays	89.8% (574)	93.3% (444)	84.6% (204)	87.4% (620)	89.2% (1842)
X-rays – Unknown	3.3% (21)	2.1% (10)	11.6% (28)	7.6% (54)	5.5% (113)

6.3.2 Cosmetic procedures

Very few women (<1%) reported that they had undergone cosmetic procedures during pregnancy (Table 6-28). There were single reports of each type of cosmetic procedure, except for two women in the UK who had a tattoo during their pregnancy.

However, women also reported anti-D or insulin treatment (1 in DK and 1 in PL), Mantoux tests (1 in NL) and flu vaccinations (1 in UK) as cosmetic procedures, which have been excluded from Table 6-28. This may be that the women only recalled about the interventions when presented with the question on cosmetic procedures, or that because the questionnaire suggested "injections" as a procedure that should be reported here. It is unlikely that women had mistaken these procedures as being non-medical. Other reports of cosmetic procedures appear to be correctly classified.

Table 6-28 Number of mothers who had cosmetic procedures during pregnancy

	Denmark	Netherlands	Poland	United Kingdom	All
Total, N	639	476	241	709	2065
Had cosmetic procedure	0.2% (1)	0.2% (1)	0.4% (1)	0.3% (2)	0.2% (5)
Breast size	1	0	0	0	1
Laser hair removal	0	1	0	0	1
Peeling	0	0	1	0	1
Tattoo	0	0	0	2	2
Did not have cosmetic procedure	99.7% (637)	99.6% (474)	97.5% (235)	99.3% (704)	99.3% (2050)
Unknown	0.2% (1)	0.2% (1)	2.1% (5)	0.4% (3)	0.5% (10)

6.4 Concluding remarks

There are some differences and similarities across countries in the medications and procedures women self-reported in the study. Women in the UK reported more medications use compared to other countries. It is not known with sufficient degree of certainty if the study attracted a less healthy population in the UK than other countries. However, the existing chronic medical conditions women reported (Table 13-6 in Appendix 13.4) do suggest this might be the case.

In general, there are some remarkable differences in the use of some medications between countries that are of interest to the study team. Some highlights are:

- The use of drugs for acid related disorders range from 14% in Poland to 43% in the UK. Women in the UK predominantly reported use of alginic acid for heartburn, whilst in the other countries more antacids were reported.

- The use of insulin for diabetes ranged from 0.6% in the Netherlands to 4% in the UK;[27] and oral anti-diabetics were reported most in the UK (4%) and not at all in the Netherlands. These reports are consistent with the reported chronic medical conditions (Table 13-6 in Appendix 13.4), where there is a higher prevalence of diabetes among UK participants compared to other countries.

- 4% of women in the UK reported metformin use, compared to 2% in Denmark, 1% in Poland and none in the Netherlands. It is possible that higher use of metformin in the UK and Denmark may be due to prescriptions to women with Poly Cystic Ovarian Syndrome (PCOS) to lower the risk of developing diabetes. In DK and the UK the majority of women that use metformin before and during the beginning of their pregnancy indicate they use it for PCO (polycystic ovarian syndrome) instead of for diabetes. While in the Netherlands and Poland it is not reported.

- Antihypertensives had the highest reported use in Poland (4%) and lowest in the UK and Denmark (0.3%). These differences may be due to more Polish (pregnant) women having hypertension. However, the self-reported medical conditions suggested a higher prevalence in the UK. It may be that the treatment policies for hypertension are different between countries.

- Some other differences include thyroid medications use (between 3% in Denmark and 9% in Poland), antibiotics (between 10% in the Netherlands and 29% in the UK), migraine medications (between 0.4% in Poland and 4% in Denmark), asthma medications (between 9% in Poland and 17% in the UK), and antidepressants (between 2% in Poland and 8% in the UK).

- Reports of over-the-counter medications were relatively low in Poland compared to other countries. Historically, the transition to market economy started in 1989 in Poland, before which, only a few OTC medications were available, and women were used to using only prescribed medications. Even though today's OTC market is rich, many young women in Poland are influenced by their mothers, and may still be avoiding unnecessary OTC medications during pregnancy.

- 10% of participants in Poland did not report whether the current pregnancy was planned or unplanned, compared to less than 3% average across all four countries. This lack of reporting may be due to the possibility that the couple did not plan the pregnancy but also did not avoid pregnancy (i.e. not planned but not unplanned). This technical distinctions may prohibit the women in Poland to provide appropriate responses.

- There were also some differences in the self-reported fertility medications use, particularly iron and multivitamins. The reports of folic acid use was lowest in Denmark (66%) and highest in the Netherland (79%), but a higher proportion of women in the Netherlands (31%) reported not knowing the dose of folic acid they were taking, versus 20% overall.

- In the UK, The National Health Service (NHS) advises pregnant women to be vaccinated against flu and pertussis to protect both the mothers and the babies. In Denmark, the Danish Health and Medicines Authority also recommends vaccinations against flu. These recommendations may explain the higher rates of vaccination in Denmark and the UK compared to other countries for these vaccines. See http://www.nhs.uk/conditions/pregnancy-and-baby/pages/whooping-cough-vaccination-pregnant.aspx on pertussis, and http://www.nhs.uk/conditions/pregnancy-and-baby/pages/flu-jab-vaccine-pregnant.aspx on flu in the UK. See https://sundhedsstyrelsen.dk/da/sundhed/vaccination/influenzavaccination/er-du-gravid# on flu vaccinations in Denmark.

There may be several explanations of these observed differences between countries. Differences in the self-reported medications use might occur because of the differences in prevalence of underlying disease, differences in treatment policy, differences in availability of certain medications, or it could be due to the differences in the populations we recruited as well as the variations in the quality of self-reported medications in the different countries.

The benefit-risk balance, or at least the perception of benefit-risk balance, of medications may also play a role in the use and also in the reporting of use. Some medications are not recommended or contra-indicated for use during pregnancy or at different stages of pregnancy. From the analyses on medications use within trimesters (Section 6.2.4), it is possible that the raised signals of medications use in the first trimester were due to necessity because of underlying medical conditions. However, we did not evaluate further these signals to confirm higher rates of use, nor did we investigate whether they were stopped early during the pregnancy.

The medications women reported to have stopped taking either on their own decision or on doctor's advice, and the prescribed medications women decided not take may also reflect the perceived unfavourable benefit-risk balance of these medications. In general, women in the UK reported most stopped and/or not taking prescribed medications; and the least was reported in the Netherlands. Without more examinations of the evidence, these perceived greater risks over benefits of the medication may not reflect the actual benefit risk balance of medication use during pregnancy. This, of course, is not the only possible explanation as women may decide that they no longer need the medications.

In conclusion, our study demonstrated that it is feasible to collect data on medications directly from individuals such as pregnant women. The changing circumstances of the participants, for example decreased quality of life due to pregnancy, and getting busier towards the end of pregnancy may affect the data provision. The quality and willingness to report certain medications may also vary, and we believe further work is required to determine the best way to capture these information better.

7 Outcomes of pregnancy

7.1 Introduction to outcomes of pregnancy

After the due date of their pregnancy had passed, women participating in the PROTECT pregnancy study were asked to fill out a final questionnaire with questions about some aspects of the recent childbirth process and about the health of their baby. Of all women who completed the baseline questionnaire (n=2065), 22.5% (464) completed the outcome questionnaire at the end of pregnancy. The overall proportion of participants who were recruited in enough time to allow for pregnancy completion was 75.0% (n=1555). Across the four different countries, the percentage of outcome questionnaire completion was 19.3% in the Netherlands, 15.8% in Poland, 22.1% for the UK and 27.7% in Denmark (see Table 4-3). These figures are influenced by the differences in the stage of pregnancy at the time of enrolment, by country as well as differences in the average remaining time interval between enrolment and the end of the data collection period. The highest proportion of pregnancies which were ongoing at the end of the study enrolment period was recorded in Poland (53.5%) and the lowest was in the UK (17.3%). Denmark, was among the first countries to start the recruitment but the women were recruited very early in pregnancy compared to the other countries and hence also in Denmark the percentage of ongoing pregnancies at the end of the study is at the higher end of the range.

7.1.1 Outcomes

Outcomes of pregnancy used for this study are: live birth, miscarriage (<22 weeks), stillbirth/late foetal death (>22 weeks), elective termination of pregnancy and ectopic pregnancy.

We will describe the listed variables of these outcomes:

- **Live birth** - number of infants, gestational age (weeks), sex, weight and any visible defects noted at birth.
- **Miscarriage and stillbirth** - number of miscarriages and stillbirths, gestational age at the time of miscarriage or stillbirth and any birth defects.
- **Termination of pregnancy** - number of pregnancies electively terminated, reason for termination (personal, concerns about effects of medications, abnormalities on scan or prenatal screening, etc.), if available and gestational age at the time of termination.
- **Ectopic pregnancy** – number of ectopic pregnancies and the number of weeks pregnant before pregnancy ended.

7.2 Results for study pregnancy outcomes

For all mothers who completed the outcome questionnaire, Table 7-1 shows the number of live births, miscarriages, stillbirths, terminations and ectopic pregnancies per country.

Table 7-1 Percentage (frequency) of mothers with a specified pregnancy outcome

	DK	NL	PL	UK	All
Number of women	177	92	38	157	464
Live birth	83.1% (147)	95.7% (88)	92.1% (35)	96.2% (151)	90.7% (421)
Miscarriage (<22w) [a]	13.0% (23)	0.0% (0)	7.9% (3)	2.5% (4)	6.5% (30)
Late foetal death/stillbirth (≥ 22w)[a]	2.3% (4)	0.0% (0)	0.0% (0)	0.0% (0)	0.9% (4)
Termination of pregnancy	1.1% (2)	2.2% (2)	0.0% (0)	0.0% (0)	0.9% (4)
Ectopic pregnancy	0.6% (1)	0.0% (0)	0.0% (0)	0.0% (0)	0.2% (1)
Unknown	0.0% (0)	2.2% (2)	0.0% (0)	1.3% (2)	0.9% (4)

[a] Unknown date of event: date estimated from the date outcome was reported

There were a higher number of miscarriages in Denmark than the other countries (p<0.001), but in Denmark women were recruited in an earlier phase of their pregnancy (see Section 2.6) with a consequential higher risk of miscarriages during the available reporting period. Population data for miscarriages from the different countries are not available since miscarriages often happen early in pregnancy, before women attend a health care professional for their pregnancy and therefore not all miscarriages are registered. It is estimated though that approximately 10% of all recognised pregnancies end up in a miscarriage, but a lot of women in the PROTECT study were recruited after the 22th week of their pregnancy. Whether the 13% of miscarriage in Denmark is high, can therefore not be concluded.

Denmark was the only country with reported stillbirths. The overall percentage of stillbirths in the participating countries in 2010 was around 0.5%.[14] Numbers in PROTECT are too small to make a valid comparison.

7.2.1 Live births

Most women who completed the outcome questionnaire reported a live birth. Table 7-2 shows the number of infants delivered for women who experienced a live birth.

Table 7-2 Percentage (frequency) of mothers …

	DK	NL	PL	UK	All
Total mothers	147	88	35	151	421
Number of infants, % (n) of total mothers					
One	99.3% (146)	95.5% (84)	97.1% (34)	97.4% (147)	97.6% (411)
Two	0.7% (1)	2.3% (2)	2.9% (1)	2.6% (4)	1.9% (8)
Unknown	0.0% (0)	2.3% (2)	0.0% (0)	0.0% (0)	0.5% (2)
Gestational age, weeks[a] median (95%CI)	40.3 (39.2 - 41.1)	39.4 (37.9 - 40.7)	39.5 (38.5 - 40.0)	39.9 (39.1 - 40.7)	39.9 (38.8 - 40.8)

[a] Missing data for gestational age were imputed using the multiple imputation by chained equation technique

The percentage of multiple births that were registered was higher for the Netherlands, Poland and the UK compared to Denmark but the numbers are very small. Population based percentages of multiple births for 2010 ranged from 1.3 for Poland to 2.1 for Denmark. The overall proportion of women with a multiple birth in the PROTECT pregnancy study of 1.9% appears to correspond fairly well to the population based percentage.[14]

Women participating in the PROTECT pregnancy study were asked to provide information about some characteristics of their child and their baby's health in the days after childbirth. Table 7-3 provides information about gender, birth weight, number of children reported as having a birth defect or as having neonatal complications soon after birth.

Table 7-3 Baby's birth information

	DK	NL	PL	UK	All
Total babies (known)	148	88	36	155	427
Sex, % (n) of total babies					
Female	47.3% (70)	52.3% (46)	44.4% (16)	47.7% (74)	48.2% (206)
Male	50.7% (75)	43.2% (38)	52.8% (19)	51.6% (80)	49.6% (212)
Unknown	2.0% (3)	4.5% (4)	2.8% (1)	0.6% (1)	2.1% (9)
Baby's weight, grams (95%CI)	3447 (3341 - 3554)	3406 (3259 - 3554)	3157 (2891 - 3423)	3423 (3340 - 3507)	3406 (3345 - 3467)
Birth defects					

Reports birth defect	2.0% (3)	0.0% (0)	2.8% (1)	3.9% (6)	2.3% (10)
Reports no defects	94.6% (140)	95.5% (84)	97.2% (35)	94.8% (147)	95.1% (406)
Did not know	2.0% (3)	1.1% (1)	0.0% (0)	0.6% (1)	1.2% (5)
Unspecified	1.4% (2)	3.4% (3)	0.0% (0)	0.6% (1)	1.4% (6)
Complications					
Reports complications when asked	14.2% (21)	21.6% (19)	30.6% (11)	12.9% (20)	16.6% (71)
Reports no complication	84.5% (125)	76.1% (67)	69.4% (25)	86.5% (134)	82.2% (351)
Did not know	1.4% (2)	1.1% (1)	0.0% (0)	0.6% (1)	0.9% (4)
Unspecified	0.0% (0)	1.1% (1)	0.0% (0)	0.0% (0)	0.2% (1)

When women indicated that their child was born with a birth defect, they were asked to describe this. Reported birth defects were coded according to the International Classification of Diseases coding system, 10th revision (ICD-10). Table 7-4 shows the different birth defects that were reported by the women that completed the outcome questionnaire. The total amount of different birth defects exceeds the number of birth defects reported according to Table 7-3 and number of babies with a birth defect showing in Table 7-4, because one child had multiple birth defects and some mothers indicated that their child did not have a birth defect, but then mentioned a birth defect when asked for any other information that they would like to report.

Table 7-4: Details of birth defects reported that could be coded as such according to the ICD-10 coding system (ICD-code Q00-Q99)

	DK	NL	PL	UK	All
Total babies (known)	148	88	36	155	427
Total number of babies with a reported birth defect	**2.7% (4)**	**2.2% (2)**	**2.8% (1)**	**3.9% (6)**	**3.0% (13)**
ankyloglossia	-	1.1% (1)	-	2.6% (4)	1.2% (5)
hypospadia	0.6% (1)	1.1% (1)	-	-	0.5% (2)
heart defect	-	-	-	0.6% (1)	0.2% (1)
absence of hand or finger	-	-	2.8% (1)	-	0.2% (1)
malformation of neck	0.6% (1)	-	-	-	0.2% (1)
deformity of feet	-	-	-	0.6% (1)	0.2% (1)
malformations of tongue, other than ankyloglossia	0.6% (1)	-	-	-	0.2% (1)
malformation of earear	0.6% (1)	-	-	-	0.2% (1)
Down syndrome	-	-	-	0.6% (1)	0.2% (1)

Table 7-5 shows the different neonatal complications that were reported, coded according to the ICD-10 coding system. The total amount of complications exceeds the number of complication reported when asked, according to Table 7-3 because some mothers reported multiple complications and some mothers reported a complication when asked for any other information.

Table 7-5: Details of complication reported that could be coded as conditions originating in the perinatal period according to the ICD-10 coding system (ICD-code P00-P96)

	DK	NL	PL	UK	All
Total babies (known)	148	88	36	155	427
neonatal jaundice	3.9% (6)	3.3% (3)	13.9% (5)	2.6% (4)	4.2% (18)
feeding problems	4.6% (7)	4.3% (4)	-	3.2% (5)	3.7% (16)

disorders related to length of gestation and foetal growth	0.6% (1)	6.5% (6)	2.8% (1)	4.5% (7)	3.5% (15)
transitory endocrine and metabolic disturbance	2.0% (3)	3.3% (3)	-	3.8% (6)	2.8% (12)
respiratory distress	2.0% (3)	1.1% (1)	2.8% (1)	3.2% (5)	2.3% (10)
newborn affected by maternal factors and by complications of pregnancy, labour, and delivery	0.6% (1)	1.1% (1)	-	2.6% (4)	1.4% (6)
infection specific to perinatal period	0.6% (1)	2.2% (2)	2.8% (1)	-	0.9% (4)
meconium aspiration	0.6% (1)	1.1% (1)	-	0.6% (1)	0.7% (3)
disturbance of cerebral status	2.0% (3)	-	-	-	0.7% (3)
intracranial haemorrhage	-	-	-	1.2% (2)	0.5% (2)
other haemorrhagic or haematological disorder	-	1.1% (1)	2.8% (1)	-	0.5% (2)
birth injury to peripheral nervous system	-	-	-	0.6% (1)	0.2% (1)
metabolic academia	0.6% (1)	-	-	-	0.2% (1)
cardiovascular disorder	0.6% (1)	-	-	-	0.2% (1)
digestive system disorder	-	1.1% (1)	-	-	0.2% (1)
disturbance of temperature regulation	-	-	-	0.6% (1)	0.2% (1)

At the end of the outcome questionnaire, women were asked if there was any other information about themselves or the baby that they thought was important to tell us. Birth defects and neonatal complications reported in response to this question were included in Table 7-4 and Table 7-5. Table 7-6 shows details of the information reported that could be coded according to the ICD-10 coding system.

Table 7-6: Other information reported that could be coded as conditions in pregnancy, childbirth and the puerperium according to the ICD-10 coding system (ICD-code O00-O9A)

	DK	NL	PL	UK	All
Total babies (known)	148	88	36	155	427
pre-eclampsia	0.6% (1)	1.1% (1)	-	-	0.5% (2)
umbilical cord complication	1.4% (2)	-	-	-	0.5% (2)
maternal hypertension, unspecified	0.6% (1)	-	-	-	0.2% (1)
obstruction of labour by foetus	0.6% (1)	-	-	-	0.2% (1)
postpartum haemorrhage	-	1.1% (1)	-	-	0.2% (1)

7.2.1.1 Birth defects

In the outcome questionnaire, women were asked to indicate whether their baby had a birth defect, if there were any complications with their baby in the first days after birth and if they had any other information concerning their baby that they would like to share. Overall for 2.3% (n=10) of all offspring, the mother reported that her baby had a birth defect. For two of these children the 'defect' mentioned was not a real birth defect or not confirmed yet. When asked for any other information, a birth defect was reported for another 5 babies (1.2%), giving a total of 3.0% (n=13) of live born children with a reported birth defect. The birth defects that were not mentioned as such were predominantly mild malformations. (3x ankyloglossia, 1x hypospadias, 1 eye malformation).

We compared the prevalence of reported congenital anomalies in this PROTECT cohort with European data on birth defects in EUROCAT (the European surveillance of congenital anomalies). For the years 2008-2012 EUROCAT registered a total prevalence rate of major birth defects of 2.6% for all births (live births, foetal deaths and terminations).[27] Heart defects form the most common group of birth defect with a total prevalence of 0.8%. For our study, numbers were too low for subgroups to be compared with population data. For the PROTECT pregnancy study data, the large numbers of ankyloglossia cases in the UK (2.6%) is noticeable, however EUROCAT does not register ankyloglossia because it is not a major birth defect.

7.2.1.2 Complications

The most common neonatal complications reported in the PROTECT study were jaundice (4.2%), feeding problems (3.7%), problems related to length of gestation and foetal growth (3.5%), mostly preterm birth, endocrine and metabolic problems (2.8%), excessive weight loss, low blood glucose or respiratory distress (2.3%). For some children the mother stated there had not been complications with the baby, but complications were mentioned when other information was asked for.

7.2.2 Miscarriage

Table 7-4 shows the gestational age at the time of miscarriage and stillbirth for women participating in the PROTECT pregnancy study by country. Because of low numbers and differences in distribution of recruitment-time between counties, statistical comparisons are not appropriate.

Table 7-7 Percentage (frequency) of mothers reporting a foetal loss

	DK	NL	PL	UK	All
Total mothers, n	27	0	3	4	34
Gestational age at miscarriage (<22w) [a] , weeks	23	-	3	4	30
Median	10.7	NA	19.3	11.7	11.3
Inter-quartile range	8.1 - 12.7	NA	7.4 - 21.4	11.1 - 14.1	8.6 - 12.9
Minimum - maximum	5.4 - 14.9		7.4 - 21.4	11.1 - 16.0	11.1 - 16.0
Gestational age at foetal death/stillbirth (≥22w)[a]	4	-	-	-	4
Median	35.5	NA	NA	NA	35.5
Inter-quartile range	32.0 - 37.9	NA	NA	NA	32.0 - 37.9
Minimum - maximum	30.7 - 38.0				30.7 - 38.0
Birth defects	None	None	None	None	

[a] Unknown date of events were assumed to be a week before the date outcome was reported up to week 38 of pregnancy
- = Not observed, NA = Not applicable

7.2.3 Termination of pregnancy

For all women that reported pregnancy outcome, only 4 indicated to have had an elective termination, two from Denmark and two for the Netherlands. Two women reported the date of termination (21.9 and 23.6 weeks of pregnancy), for the other the date of termination could be estimated before 14 and 21 weeks of pregnancy. For both countries, one participant indicated that there were abnormalities on a scan or with prenatal screening while the other would not prefer to explain the reason for termination (personal reasons). Because of low numbers and differences in distribution of recruitment-time between counties, statistical comparisons are not appropriate.

Table 7-8 Percentage (frequency) of mothers reporting a termination

	DK	NL	PL	UK	All
Total mothers, n	2	2	0	0	4
Gestational age at event, weeks					
Date reported	21.9w	23.6w	NA	NA	
Date estimated	<21.0w	<14.0w	NA	NA	
Reasons for termination					
There were abnormalities on a scan or prenatal screening	1	1	NA	NA	2
For personal reasons: I would prefer not to explain	1	1	NA	NA	2

7.2.4 Ectopic pregnancy

One participant from Denmark reported an ectopic pregnancy at around nine weeks of pregnancy. The ectopic pregnancy would most likely have happened sooner, but the exact date was not provided. She reported "*kroppen klarede det selv*" when asked about the intervention, which roughly translates to not having any medical intervention (i.e. reabsorption of the foetus).

7.3 Comparison to malformation registries

The Danish Birth Registry (DBR) records data about birth defects for all births registered. We compared the data about birth defects recorded in the DBR for children born to women who participated in PROTECT and completed the outcome questionnaire. We were able to match 120 children based on the civil registration number of the mother and the results are shown in Table 7-9.

Table 7-9 Reporting ratios of reported birth defects in study versus national data for Denmark.

		Number of women
Number of malformation reported in PROTECT pregnancy study :		4
Number of malformations reported in Danish Birth Registry :		8
	malformation:	
Reported in PROTECT as well as in the DBR	hypospadia	1
Malformation in DBR, not in PROTECT (Total=8)*	ankyloglossia	1
	cardiovascular defect(s)	1
	cerebral cysts	1
	hip dislocation	4
	undescended testis	1
Malformation in PROTECT, not in DBR (Total=3)	neck malformation	1
	tongue malformation	1
	ear malformation	1

* For one child 2 different birth defects were registered.

In the PROTECT study, a birth defect was reported for 4 (2.7%) of the Danish children. For the 120 children we were able to trace in the Danish Birth registry, 8 children (6.7%) had a reported birth defect. Comparing the birth defects mentioned in the PROTECT pregnancy study for Denmark with birth defects recorded in the Danish Birth Registry showed little overlap. Only one of these birth defects was recorded in both databases. The malformations registered in the Danish Birth registry might be detected after completion of the outcome questionnaire. Hip dislocation for example is often detected after a few months and heart defects and cerebral cysts might not show at birth as well. Ankyloglossia and undescended testis are not considered as a major birth defect by Eurocat and might not be considered as such by the mother as well.

7.4 Birth Defects in blood Relatives

If a birth defect occurs, it often is the result of a genetic predisposition in combination with environmental exposure. To investigate the possibilities for collecting data about genetic predisposition, we asked the participating women in the baseline questionnaire whether she herself, the father or any other blood relative was born with a birth defect. If the women gave an affirmative answer, we asked them to specify the birth defect and whether this birth defect ran in the family. Reported birth defects were coded according to the ICD-10 coding system. Table 7-10 shows the reported birth defects in blood relatives. The exact kinship of the affected relative was not asked.

Table 7-10: Birth defects in blood relatives

	DK	NL	PL	UK	Total
Total number of women	639	476	241	709	2065
Women indicating birth defects in blood relatives % (n)	5.0% (32)	9.2% (44)	8.3% (20)	7.8% (55)	7.3% (151)
cardiovascular defects	1.3% (8)	2.7% (13)	4.1% (10)	2.8% (20)	2.5% (51)
cleft lip/palate	0.6% (4)	1.9% (9)	0.8% (2)	0.8% (6)	1.0% (21)
deformity of hip	0.3% (2)	1.1% (5)	0	0.6% (4)	0.5% (11)
spina bifida	0	1.3 (6)	0.4% (1)	0.4% (3)	0.5% (10)
malformations of arm/hand	0.6% (4)	0	0.4% (1)	0.4% (3)	0.4% (8)
Down's syndrome	0.2% (1)	0	0	0.6% (4)	0.2% (5)
other musculoskeletal malformations	0.2% (1)	0.2% (1)	0	0.4% (3)	0.3% (5)
malformations of kidney	0.2% (1)	0.4% (2)	0	0.3% (2)	0.3% (5)
other chromosome abnormalities	0.6% (4)	0	0	0	0.2% (4)
male genitourinary malformations	0	0.4% (2)	0	2	0.2% (4)
malformations of feet	0	0.4% (2)	0	0.1% (1)	0.1% (3)
hypertrophic pyloric stenosis	0	0	0	0.4% (3)	0.1% (3)
malformations of intestine	0.2% (1)	0	0	0.1% (1)	0.1% (2)
malformations of the brain	0.3% (2)	0	0	0	0.1% (2)
other birth defects	0.3% (2)	0.2% (1)	0.4% (1)	0.1% (1)	0.2% (5)
Women indicating no birth defects in blood relatives % (n)	92.8% (593)	88.7% (422)	81.3% (196)	90.1% (639)	89.6% (1850)
Do not know %(n)	2.2% (14)	2.1% (10)	9.5% (23)	2.1% (15)	3.0% (62)
Missing (no information) %(n)	0.0% (0)	0.0% (0)	0.8% (2)	0.0% (0)	0.1% (2)

The total number of different birth defects does not add up to the number of women indicating they had a relative with a birth defect. While some women had more than one relative with a birth defect or multiple defects in the same relative, others did not specify what the birth defect was. Besides the birth defects that are shown in table 7-10, some women entered a genetic or acquired disease when asked for birth defects in blood relatives, for example: respiratory distress, different heart diseases, autism, haemophilia, cystic fibrosis and others. Of the women indicating they had a relative with a birth defect, 20% (n=30) confirmed that this birth defect ran in the family, ranging from 9.4% in Denmark to 25% in Poland. The birth defects most mentioned to run in the family were heart defects (n=7), hip deformities (n=5), polydactyly (n=3), kidney malformations (n=2) and cleft lip/palate (n=2).

7.5 Infections that can cause negative birth outcomes

When acquired during pregnancy, certain infectious diseases can be dangerous to the foetus. Viruses that cause typical childhood diseases like chickenpox, measles, mumps and rubella can cause birth defects or miscarriage when caught during the first trimester of pregnancy. In later phases of pregnancy, some of these viruses can cause stillbirth or preterm birth. The listeria bacterium that can be sometimes found in raw milk and its products (mostly cheese) can also cause miscarriage or stillbirth. Toxoplasmosis, a parasite with the cat as primary host can be transmitted by contact with infected faeces or raw meet. When infected during pregnancy, the parasite is known to cause certain birth defects or death of the foetus. In the baseline questionnaire, participating women were asked whether they had encountered any of these diseases during their pregnancy prior to completion of the questionnaire. Table 7-11 shows the number of women per country who reported they had one of these conditions during their pregnancy.

Table 7-11: Infections that can cause negative birth outcomes

Condition:	DK	NL	PL	UK	All
Listeriosis	0	0	0	0	0
Shingles	0.3% (2)	0	0	0.1% (1)	0.1% (3)
Chickenpox	4.2% (27)	0.6% (3)	0	0.8% (6)	1.7% (36)
Measles	1.7% (11)	0.4% (2)	0	0.1% (1)	0.7% (14)
Mumps	0.6% (4)	0.4% (2)	0	0.3% (2)	0.4% (8)
Rubella/German measles	0.8% (5)	0.4% (2)	0	0	0.3% (7)
Toxoplasmosis	0.6% (4)	0.2% (1)	1.2% (3)	0	0.4% (8)
None of the above	85.4% (546)	95.0% (452)	84.6% (204)	94.6% (671)	90.7% (1873)
Missing (no information)	10.0% (64)	4.4% (21)	14.1% (34)	4.4% (31)	7.3% (150)

The number of women reporting one of the infectious diseases during their pregnancy seems to be quite high, especially for Denmark. We suspect that some reporting error may have occurred for the responses. It is possible that some women gave a positive answer to the question when they had only been in contact with someone with for example chickenpox or measles rather than having contracted it themselves. The prevalence data of rubella and measles in Denmark for 2013-2014 shows that no women aged 25-34 were reported as having had rubella, and only five women aged 25-34 were reported to have had measles (http://www.ssi.dk/smitteberedskab/sygdomsovervaagning.aspx). In Denmark, it is mandatory to report these diseases.

7.6 Concluding remarks

- Self-reporting shortly after birth gives a lot of information about events that took place around birth and the health of the child, but result are probably not accurate and complete enough to calculate prevalences of risk factors, complications and birth defects.
- Data on self-reported birth defects are hard to compare to population based prevalences or personalised data from other databases because not all birth defects can be detected soon after birth and distinction between minor and major birth defects is not always clear.
- Asking for birth defects of the baby or birth defects in blood relatives without further specification and without interrogation of the given answers will not give complete and valid information.

8 Record linkage to external electronic healthcare records

8.1 Introduction to record linkage and EHRs

In two countries (Denmark and the United Kingdom), it was possible to compare the information about medications gathered from the questionnaire completed by the women with that obtained from health records or pharmacy dispensing data. The comparison to the registry data at the individual level using outside data sources was conducted as a one-time record linkage at the end of the study period. Because of national differences in availability of data, the comparative studies of prescription drug use and pregnancy outcomes will be unique to each participating country. To our understanding, the information on non-prescription medications is rarely or poorly recorded in EHRs. Therefore, we explored to what extent these types of medicines are recorded in the EHR in UK.

Section 8.2 describes the feasibility of performing data linkage in Denmark and the UK, and the expected number of successful linkage. The conduct and results from the data linkage analyses of self-reported versus EHR/register are presented in Section 8.3 for Denmark, and in Section 8.4 for the UK. We briefly discuss individual results from Denmark and the UK in Section 8.3.3 and Section 8.4.3, respectively. Finally, we make overall concluding remarks on the data linkage analyses in Section 8.5.

8.2 Linkage feasibility

Women contributing data to PROTECT from Denmark were required to consent to the linkage and provide their CPR number. Consequently, all 639 participants in PROTECT were expected to be linked.

In the UK, women were given the option to consent to EHR linkage through The Health Improvement Network (THIN). THIN covered 5.67% of the UK population in 2013, approximately half of which are women (http://www.epic-uk.org/our-data/statistics.shtml). About 30% of THIN population are “active” patients (those who still contribute data, e.g. have not left THIN GP practices). Of the 853 women who enrolled in PROTECT, 674 consented to their data be linked to the EHR. Assuming a slightly higher proportion of active patients among PROTECT participants of about 50%, we estimated about 20 women would be linked in the UK.

The cost for individual record linkage in the UK through a Trusted Third Party is about £10,000 for any number of women. Due to the small number of linkage expected, the cost/person is high. However, as this was one of the deliverable for this work package, we decided that it is in the best interest of the study to conduct the comparative exercise.

8.3 Record linkage in Denmark

Denmark has national registers of prescription medication use as well as a birth register and a hospital register. Linkage between the registers of an individual’s information is possible using the unique 10-digit civil registration number (CPR number) assigned to all citizens.

The Danish Register of Medicinal Product Statistics (http://www.ssi.dk/English, http://medstat.dk/en) contains information on all medicine sales that were prescribed in primary (clinic) and secondary (hospital) care in Denmark. Medications that are purchased on prescription – including those that available over the counter (OTC) – are recorded in the register using the purchasing individual’s encrypted (CPR-number). The information recorded includes, but is not limited to, package ID, the medicinal product’s ATC code, the number of packages sold, the number of tablets within the package, the tablet strength (medicinal dose) and date of purchase is stored alongside. Hereafter the part of the medicine register covering individual medication purchases will be called the prescription register.

The Hospital Register holds information from public and private hospitals on diagnoses (ICD-10), examinations and treatments during a hospital stay and ambulatory care, dates of admissions and discharges, amongst other things.

The birth register collects information from the hospital register and midwives (homebirths) on all births from 22 weeks of pregnancy. The civil registration register is used for establishing the link between the mother and her child. The birth register contains information on both the mother and the child. Among others, details concerning date of birth, the course of pregnancy, the birth, apgar score, umbilical cord pH value, birth weight, treatment in neonatal period and congenital anomalies are included in this register.

All Danish participants in the PROTECT Pregnancy Study gave informed consent to link their PROTECT questionnaire data to the national health registers by using their CPR number. This was mandatory for participation.

Linkage to the prescription register was performed to compare the questionnaire data for medicines bought on prescription with the prescription register data. Linkage to the birth register was performed for comparison of malformations reports (see Section 7.3) between questionnaire data and the birth register.

8.3.1 Methods

This methods section is based on the overall description of the PROTECT pregnancy study as described in this report. The women were enrolled from 19 Oct 2013 to 31 Jan 2014 and data collection ended 28 March 2014. Recruitment was planned to stop by 31 August 2013 to provide time for the women to give birth before study end. The recruitment period was prolonged until end Jan 2014 and consequently not all women gave birth during the study period and therefore could not fill the follow-up questionnaires on medication use and the final outcome questionnaire.

Conception date was calculated as the most recent EDD provided by the mother minus 266 days. Then the CPR number was linked to the prescription register for medication purchases in the period 6 months prior to conception until the date of birth (as recorded in registers) or to date of study end.

In the PROTECT questionnaire data, medication use was reported relative to the medical conditions for which they were taken. For each medical condition the women reported they were treated for with drugs, a top ten list was shown. It was also possible to choose “other medication” and provide details as free text. The top ten lists described both non-proprietary and brand names for medicines available on the market at the time of designing the questionnaire. If the same substance could be used in different administration forms these were also stated. All choices relate to a unique ATC code on level 5 (most specific level e.g. J01AA02 doxycycline for systemic use). This was done in order to enable direct comparison to prescription register data. PROTECT study participants were also asked if any medication were stopped when planning the pregnancy or during pregnancy and if they had any medication prescribed that they chose not to take, if they took any medicine prescribed for another person. These latter options were asked for in free text.

In follow-up questionnaires, medications that were recorded in a previous questionnaire were shown and the woman was asked if she were still taking the medication. Women were also asked for details of any new medications or illnesses and the same “top 10” list of medicines was shown. The number of free text inputs on the PROTECT study questionnaire was considerable, and accounted for almost 25% of all medications recorded in the questionnaire. All free text data was recoded into ATC level 5 using all available information concerning the indication of the medicinal products by investigators who were without knowledge of which medications had been recorded in the Danish prescription register. On several occasions, it was not possible to identify a specific drug (e.g. an answer like antibiotics or antihistamines) and in these cases no comparison were made. For circumstances where the information provided could have related to several ATC level 5 level codes (e.g. if the study participant stated

metronidazole, it could have been for dermatological use; D06BX01, gynecological use; G01AF01 or systemic use; P01AB01), we chose the ATC code which was most commonly recorded in the Danish prescription register in 2013.

The comparisons were performed in two different ways. To test if early recruitment would provide more accurate information than later recruitment, we did the first analysis by the woman dependent on recruitment in first, second or third trimester looking at all medications. Trimesters are expressed as number of weeks of pregnancy counted from last menstrual period. Exposure to medication was calculated for the period from conception date to the date of last follow-up questionnaire. First trimester was defined from week 3-12, second trimester from week 13-26 and third trimester 27+ weeks. An example of how this was done: If the woman stated that, she had taken the drug N03AX01 any time during the first trimester, this was compared to any purchase of the same ATC code at level 5 in the register anytime during first trimester. For the comparison for the complete follow-up period we compared an ATC code at any time during this period. For the second analysis, we likewise compared on drug level- ATC level 5 – though higher levels are shown in the table.

It was only possible to compare the medications registered in the prescription register (so drugs prescribed). In the questionnaires, the women were asked to report on all medications and not divide them between OTC or prescription medications. We decided to include all drugs from the prescription register that were prescription only medications and OTC medication that were available on prescription. We did not include vitamins or minerals even though some of these vitamins were prescription only drugs. Neither did we include contraception and fertility treatments. This was because we expected some confusion from the women's point of view of whether or not to report it as it is obvious that both would be stopped when she realised she was pregnant.

8.3.2 Results

This pilot study intended to recruit 800 women from Denmark. A total of 783 women signed up for the study and 639 women completed the baseline questionnaire. Two women signed up before the conception date of the index pregnancy and were excluded, thereby leaving 637 women for the comparison study. The number of participating women in PROTECT is approximately 1% of all pregnant women in Denmark during the recruitment period of 15 months. One purpose of the study was to recruit women as early as possible; 48% of the participants were recruited in the first trimester (Table 8-1) and of these the most frequent weeks of recruitment were week 5 and week 6 (Table 2-5 in Section 2.6).

Table 8-1 Comparison between register data (R) and PROTECT questionnaire data (Q) per woman. Medication bought on prescription (prescription only and OTC) but not vitamins, minerals, contraception and fertility treatment.

	Women with no medication in R N	Women with at least one medication in R (%)	Women with one medication in R		Women with two medications in R		Women with three or more medications in R		All women with medications
			Complete recall N (% complete)	Non complete recall N	Complete recall N (% complete)	Non complete recall N	Complete recall N (% complete)	Non complete recall N	Complete recall N (% complete)
	Medications taken in total follow-up period (from conception to last follow-up)								
Anytime recruited N = 637	321	316 (50)	111 (66)	56	38(48)	42	11 (16)	58	160 (51)
	Medications taken in first trimester (from conception to conception+76 days)								
Recruited in first trimester N = 307	195	112 (36)	51 (70)	22	11 (46)	13	2 (13)	13	64 (57)
Recruited in second trimester N = 211	139	72 (34)	36 (65)	19	4 (31)	9	0 (0)	4	40 (56)
Recruited in third trimester N = 119	81	38 (32)	15 (75)	5	3 (37)	8	1 (14)	6	19 (50)
Anytime recruited N = 637	415	222 (35)	102 (69)	46	18 (38)	30	3 (12)	23	123 (53)

8.3.2.1 Comparison at the woman level

Information collected from the Danish prescription register was used as the reference point to which we compared the information reported in the PROTECT study questionnaire. We compared all women for the available follow-up period. Some women only reported for a short time period while others gave information for the total pregnancy period. We also compared questionnaire data to the register for drugs used in first trimester for all women together and broken down by trimesters of recruitment to see if first trimester recruited women were better in recalling their medications. This was further divided by one, two or three and more medications taken during first trimester. The women were asked if they bought any prescribed medication that they chose not to take. This question was asked specifically to be sure that any medication not mentioned in the questionnaire was not left out because of non-compliance. Any medication mentioned in questionnaires that was also in the register is considered as remembered in the comparison analyses. E.g. if a woman did not report a drug as taken, but reported the drug as "stopped when recognizing the pregnancy", it was counted as reported/remembered.

Based on register data, the proportion of women using more than one medication does not change by the trimester of recruitment (p-value = 0.2, based of chi-squared test of independence). For women recruited in the first trimester, 36% (CI 95% 31.1%-42.1%) used at least one medication, those recruited in second 34% (CI 95% 27.7%-40.9%), and in, and in the third trimester 32% (CI 95% 23.7%-41.1%). Regardless of how many medications they used, women recruited in first and second trimester had a higher rate of remembering medications compared to women recruited in third trimester (Table 8-1). The percentages are 57%, 56% and 50% for first, second and third trimester respectively (Table 7-1). When these figures are again broken down by number of medications per woman, this pattern disappears. This may be due to the small numbers or it may be that the previous found trend is not "true".

Looking at all women, independent of when recruited and for the total period of observation, we see that the more different drugs the woman took the more difficult to remember all of them. Taking one drug 66% remembered the drug, taking two drugs 48% remembered. For women taking three or more drugs only 16 % remembered to tell about all taken drugs (Table 8-1). Remembered is understood as reported as taken or reported as prescribed but not taken.

8.3.2.2 Comparison on drug level

In the second analysis (Table 8-2), we did a comparison analysis that looked at both how accurately women remembered drugs that had been purchased (drugs in the register) and how much information questionnaires can add to the register data. We did the analysis on drug level for each woman. We included as many drugs as possible in the categories, but some drugs did not fit in. Therefore, Table 8-2 does not show all drugs reported in the questionnaire or the register. Accordingly, Table 8-2 is not a descriptive table of medication use during the participants' pregnancies. In addition many of the women only participated during a part of their pregnancy because they chose to leave the study before the birth, and for other women the study was closed before they reached due date.

Table 8-2 Compatibility and discrepancies between register data (R) and PROTECT questionnaire (Q) data based on whole period of follow-up

Drug group	ATC code	In R	In R and Q (B as % of A)		In Q traced in R up to 6 months prior conception date	In R stated as prescribed but not taken in Q (included in column B)	Not in R stopped because of recognized pregnancy	In Q not in R, unexplained
		A		B	C	D	E	F
Drugs for chronic conditions		**174**	**145**	**(83%)**	**36**	**4**	**43**	**402***
Insulin	A10A	4	4	(100%)	0	0	0	0
Oral diabetes drugs	A10B	5	5	(100%)	2	0	5	1
Cardiovascular drugs	C (ex. C05), B01AC	11	8	(73%)	4	0	2	6
Intestinal anti-inflammatory agents	A07EA, A07EC	8	7	(88%)	0	0	0	0
Thyroid therapy	H03	19	18	(95%)	0	0	0	0
Anti-inflammatory drugs, systemic (glucosamine not included)	M01A	7	4	(57%)	5	1	19	35*
Paracetamol	N02BE01	7	5	(71%)	3	1	0	283*
Opioids	N02A	8	7	(88%)	0	0	0	6
Anti-epileptics	N03A	11	9	(82%)	0	0	0	0
Anti-psychotics	N05A	5	3	(60%)	0	0	0	1
Anti-depressants	N06A	31	29	(94%)	7	2	7	6
ADHD treatment	N06BA	3	2	(67%)	0	0	0	0
Anti-asthmatics	R03	35	29	(83%)	7	0	0	17
Anti-histamines	R06AE07, R06AX	10	9	(90%)	3	0	4	38*
Eye allergy drugs	S01GX	4	1	(25%)	2	0	0	4
Anti-migraine	N02C	6	5	(83%)	3	0	6	5

Drug group	ATC code	In R	In R and Q (B as % of A)		In Q traced in R up to 6 months prior conception date	In R stated as prescribed but not taken in Q (included in column B)	Not in R stopped because of recognized pregnancy	In Q not in R, unexplained
		A	B		C	D	E	F
Drugs for occasional or short term use		**283**	**153**	**(54%)**	**8**	**7**	**3**	**128***
Dermatological preparations (non corticosteroids)	D01 and D06	31	8	(26%)	1	0	1	53*
Corticosteroids (dermatological use)	D07	20	6	(30%)	2	1	0	9*
Acne (dermatological use)	D10A	4	1	(25%)	0	0	0	1*
Malaria	P01B	2	1	(50%)	0	0	0	2*
Antibiotics (systemic)	J01 and P01AB01	174	112	(64%)	1	4	0	8
Anti-fungals (systemic)	J02	13	9	(69%)	1	2	0	2
Anxiolytics, hypnotics and sedatives	N05B and N05C	1	0	(0%)	0	0	1	3
Ear, nose and throat preparations for infections	S01A-S01C, S02, R01, R02A, R05	38	16	(42%)	3	0	2	50*
Pregnancy related medications		**118**	**78**	**(66%)**	**12**	**4**	**0**	**208***
Acid related disorders	A02 (excl. A02AA04)	18	13	(72%)	3	2	1	41*
Anti-emetics	A03FA01, A04A, R06AD	15	10	(67%)	3	2	0	6
Heparin	B01AB	3	3	(100%)	0	0	0	0
Haemorrhoids treatment	C05A	23	11	(48%)	1	0	0	3
Laxatives	A02AA04, A06	2	2	(100%)	1	0	2	93*
Gynaecological anti-infective	G01AF	33	20	(61%)	0	0	0	62*
Progesterone	G03DA04	25	20	(80%)	4	0	0	3

* Some or all of the medications in this group are available as OTC.

Note that this table does not show the total prescription medication use during the participant's pregnancies. The observed period is from conception to last follow-up.

Table 8-2 shows what additional information can be found in the register compared with questionnaire data – the difference between column A and column B. Included in column B are the drugs in column D where the woman told the study that she purchased the drugs (so will be in the register) but did not take them. Columns C, E and F show information not found in the register during the pregnancy period. For example, for anti-migraine drugs, five women out of six that bought the medication during pregnancy reported it in the questionnaire; three women reported taking medication but it was purchased in the 6 months prior to conception so not found in the register during the actual pregnancy duration; six women who didn't buy anti-migraine medication during pregnancy reported that they had stopped taking the drug when they realised they were pregnant, and other five women reported anti-migraine drug use but it was not bought within the six months prior to pregnancy or during pregnancy.

The comparison of questionnaire data with the register (columns A and B) shows that 83% of "Drugs for chronic diseases" in the register were reported in the questionnaire and 54% of "Drugs for occasional or short-term use" were reported. For "Pregnancy related drugs", 66% were reported. Women reported vaccinations but these were not recorded in the prescription register because HPV and flu vaccinations are mainly free, and given at the physician's clinic (data not shown). A linkage to the vaccination register might have revealed register data on these. The women were not asked for hospital medications in a specific question and we consider some of the medication mentioned in column F to be hospital medications. For the drug categories shown, the questionnaire added information to the register data relating to about 15 drugs were recorded in the register but which were actually not taken (Table 8-2, column D). Questionnaire data also added 56 drugs that were only found in the register 6 months prior to the pregnancy but not during pregnancy (Table 8-2, column C).

We specifically asked about use of any prescription drugs that were prescribed for friends or family and not for the woman herself. Three women told the study about these. The drugs are oxycodone and cortisone cream (not shown in the table). Six other drugs were mentioned but none of these were drugs that were only available by prescription.

8.3.3 Discussion

Our results were based on 637 women who provided baseline data, which was around 1% of all pregnant women during the recruitment period in Denmark. Although 637 women is too few for valid comparisons between some of the medication categories and also numbers in Table 8-1 are too small to give any information when women are further categorized by numbers of medications taken, some conclusions can be made. We see a tendency to higher rates of remembering medications if recruited early in pregnancy compared to those recruited later. We also found that the number of medications was very important to the woman's ability to remember all of them and the figures indicate that the number of medications has a greater effect on complete recall than recruitment early or late in pregnancy.

The choice of web advertising for participants was intended to get women into the study as early as possible after recognition of their pregnancy. The results suggest that early recruitment does not have a major impact on recall of medications used in first trimester. However, early Recruitment early in 1st trimester was possible (Figure 2-5, Figure 2-5). Early recruitment enables research in the field of drugs which increase the risk of miscarriage and/or malformations leading to early miscarriages. A study like this does reach women who have early miscarriages who may not have interacted with healthcare professionals regarding their pregnancy and therefore the miscarriage would not have been registered. Such early miscarriages are hardly ever studied and are of great importance.

We showed relatively high rates (83%) of recall for medications usually taken for chronic diseases and only 54% recall for medicines for short-term conditions. Many women were recruited early in pregnancy and the women answered on a 2 or 4 weeks basis which we expected to succeed in high recall. Reason for the women not reporting

all their medications could be how the questionnaire was designed. Although we provided a list of frequently used medications by conditions for which they were used, still one quarter of the medicine information was entered as free text. This will increase the chance of errors. The top 10 lists have been difficult to use, because some medications are very similar in the substance name and if only one of them is on the list it is possible that some women chose from the list instead of using the free text field for writing the correct one. We can see that most of the women only took one or two different prescription medicines, so maybe it was confusing for the women to have to go through all kinds of diseases having perhaps just one new medicine to add – and forgets it. In some instances, we believe that the translation of the diseases was not understandable as everyday language. We realise from feedback that the women were frequent users of tablets and smartphones as a part of modern lifestyle and so use them everywhere, which may not be where they keep their medicine packets. This may cause errors in recall. In addition, if you are not at home, you may be concentrating on other things and you may forget medications. On the other hand, having a tablet or smartphone always with you may enhance the ability to report on a 2 or 4 weeks basis.

The questionnaires added important information on medications purchased up to six months before pregnancy but actually taken during pregnancy. This is very important information as when using only register data it is difficult to know which medication purchased prior to pregnancy is actually taken during pregnancy and which are stopped. Since women did not have total recall when self-reporting medications that we knew about from the register, we suspect that the additional prescription medications they mentioned may therefore not also be 100% of what they actually took. Questionnaire information on medicines taken later in pregnancy was sparse due to many women dropping out of the study before the end of their pregnancy. Unless there are added strategies to enhance retention, this study shows that combining questionnaire data with register data will enhance studies on malformation due to medication use, but may not be helpful with looking at adverse outcomes potentially related to medications taken only later in pregnancy.

Using web-based recruitment seems to be an important, but not the only, possibility for recruiting women into the study. Using online questionnaires where the data goes directly into the database is surely the future as when the questionnaires and the database are established, the main costs would be for recruitment. Moreover, it is possible to imagine the prospect of a survey continuing for years, making it possible to recruit enough women to look at specific drug effects. Questionnaires would need to be updated frequently to account for changes in marketed medicines and most likely it will continue to be necessary to adapt data collection to new modalities and electronic systems as they come into widespread use.

In a country like Denmark, the future for such studies may be the development of a platform for questionnaires running as a parallel system, separate to the electronic registration for all medicines bought on prescription. The electronic system is already available for health personnel and individuals themselves. The electronic system with medicine information is updated daily and an idea could be to use this system to provide data on medicine purchases from pharmacies directly to the research platform and then making the questionnaires interactive. The system could show the women her recent purchase and she is asked to say yes or no as to whether she actually took the medication. In addition, medication that has been prescribed previously but is still active could be shown and asked about. This would remove the problem with recall. However, OTC medications would still have to rely on recall and prescription medicines which were not bought from a pharmacy would not be included.

8.4 Record linkage in the United Kingdom

In the UK there are a number of primary care medical records databases available. The PROTECT Pregnancy Study has access to The Health Improvement Database (THIN), which routinely collects data from primary care through a non-interventional method, using the Vision practice management/records system. The THIN database includes complete data on prescriptions written in primary care. Data on over-the-counter medications are only intermittently recorded and are therefore not suitable for validation studies. However, we include OTC medications in the comparison to demonstrate the added-value of self-report studies, such as ours. We also compared the self-reported lifestyle choices against what are recorded on the women's primary care data.

We obtained ethical approval from the THIN Scientific Research Committee to conduct the analyses (Ref: 14-037R), and a copy of the approval letter is provided in Appendix 13.17.

The methods that we used in the comparative analyses are described in Section 8.4.1, followed by the results (Section 8.4.2), where we report the geographical regions of women in the study that we were able to link to their primary care records in THIN, and a summary of "successful" data linkage. "Successful" data linkage is defined as the number of women whose data are available within the study time period that we could use in subsequent analyses. Section 8.4.2.1 compares the self-reported pregnancy outcomes to the THIN records. We then describe the medications self-reported and prescribed in Section 8.4.2.2 to assess the completeness of direct-to-patient medications report and the amount of information it would add. Section 8.4.2.3 describes the lifestyle choices reported and recorded during pregnancy such as smoking, alcohol consumption and illicit substance use. The results from these analyses are discussed in Section 8.4.3.

8.4.1 Method

Data from THIN practices in England were linked at the person level to the PROTECT Pregnancy Study dataset through one or more available patient identifiers (for example, NHS number, date of birth, and postcode of residence). Patient identifiable information was needed for the linkage procedures, however this information is not collected as part of the THIN research dataset. Linking involves the use of a Trusted Third Party (TTP) that obtains the encrypted and pseudo-anonymised patient identifiable information from the practices directly. The TTP did not have access to any medical data or to unencrypted patient identifiers. Encrypted patient identifiers from the PROTECT study were also sent to the TTP. The linkage was carried out with the TTP attempting to link patients between the two data sources using the encrypted available identifiers. Once the TTP has carried out the linkage procedure and provided the linked IDs, the encrypted and pseudo-anonymised identifiers used for the link were destroyed.

8.4.1.1 Timeframe

In order to capture the medications self-reported by women during pregnancy, we widened the timeframe to include medications prescribed 6 months prior to the start of pregnancy, because women may still consume medications prescribed before pregnancy during pregnancy. This circumstance would not be captured in the THIN database because only the original prescription date (prior to pregnancy) would be captured on THIN, but not the actual consumption date during pregnancy. The pregnancy period was calculated from the latest estimated due date provided by women (it was asked in the first questionnaire and at every follow-up) minus 280, and therefore the study window for THIN medication analyses is at most 460 days (Figure 8-1).

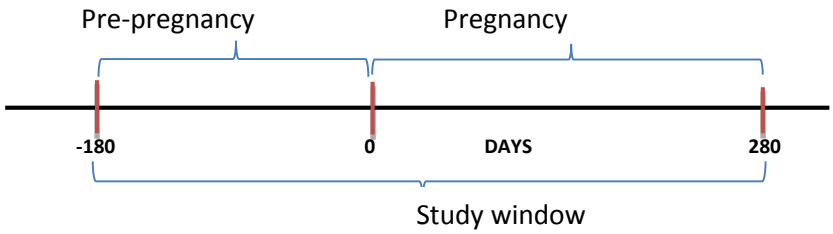


Figure 8-1 Sampling timeframe for data on THIN database

8.4.1.2 Descriptive summary

To compare the pregnancy outcomes and medications, we first located what were self-reported and what were recorded in the two databases. Then we calculated the numbers and percentages of matched and unmatched records.

8.4.1.3 Level of completeness

We measured the level of completeness by benchmarking the number of medications women self-reported to the number of medications in their medical records on THIN. The number of medications recorded on THIN was categorised into one, two and three or more medications. The percentages of self-reported medications versus the recorded were then calculated.

We also selected several types of medication of particular interest that were typically used for chronic medical conditions, short-term medical conditions, and pregnancy-related conditions – the same as those selected for the Denmark analyses. The ATC codes of the medications selected are shown in Table 8-2 above. We calculated the number of women with the medications recorded in the THIN database and who also self-reported the medications. We present the percentage of complete matches by first using the THIN records as denominator, and then by using the PROTECT self-reported data as denominator.

8.4.1.4 Detailed comparison of all medications self-reported and recorded

There is not a gold standard method to measure concordance and discordance between two linked databases that collect data using different methods. Several measures are available but, as always, each comes with strengths and weaknesses as well as adopting different underlying assumptions. We compared the level of concordances and discordances using four indices: Jaccard index, Sorensen's positive and negative agreement indices, and Cohen's Kappa index.

8.4.1.5 Lifestyle choices comparison

We used the Read and medical codes provided by CSD Medical Research UK (now part of IMS Health) on smoking and alcohol use. In order to extract the information on smoking, CSD kindly provided the study team with their in-house algorithm that we adopted in this study. These codes and algorithm were provided in confidence. Following the identification of the required data, we performed descriptive summary on the matched/unmatched data as described in 8.4.1.2 Descriptive summary.

8.4.2 Results

Fifty women in PROTECT were successfully linked to their medical records on THIN database. 38/50 women linked had provided their postcode through the study, and their geographical regions are mapped in Figure 8-2. Among the 50 women linked, three had two THIN unique identifiers assigned from two general practices suggesting that they had moved practice at some point. For these three women, we combined their data from the two practices for analyses. An interactive version of the map with additional features, such as number of women and the regions of those with or without recent THIN data, is available online; to explore the interactive map, readers are encouraged to visit https://public.tableausoftware.com/views/WP4_UKlink/Story1?:embed=y&:display_count=no). The observed higher percentage of matching by region may reflect the number of participants from that region, the size of population in that region, and the concentration of THIN general practices.

About 78% (664/853) of the women enrolled in the UK consented to individual record-linkage and provided accurate information as required (Figure 8-3). Although 50 women were successfully linked, only data from 18 women were usable for comparison because 24 women had left THIN practices before the current pregnancy and therefore there is no data related to current pregnancy on THIN; and eight women did not provide any data to PROTECT (dropped out prior to completing the baseline questionnaire) for comparison (see Figure 8-3).

The analyses in the following sub-sections were based on these 18 women.

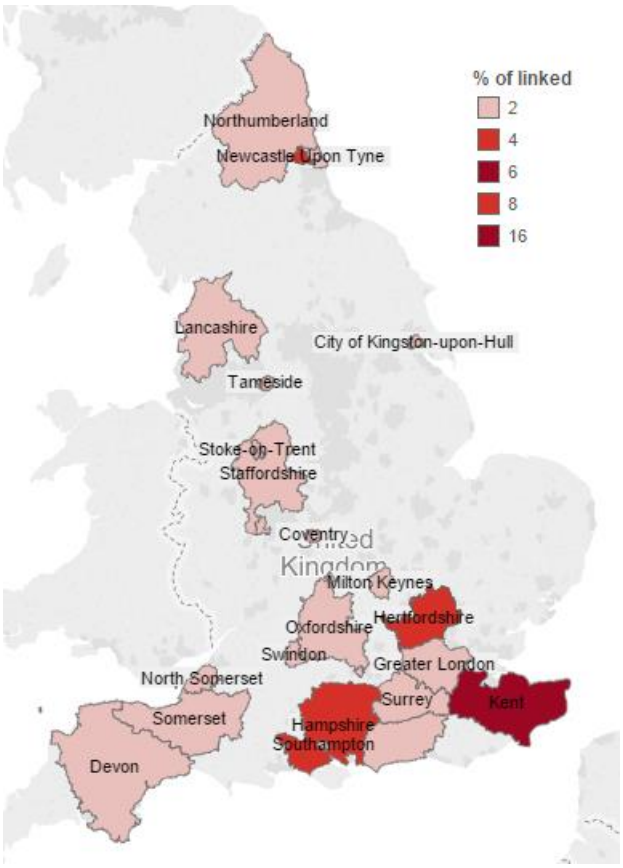


Figure 8-2 Locations of participants with linked data

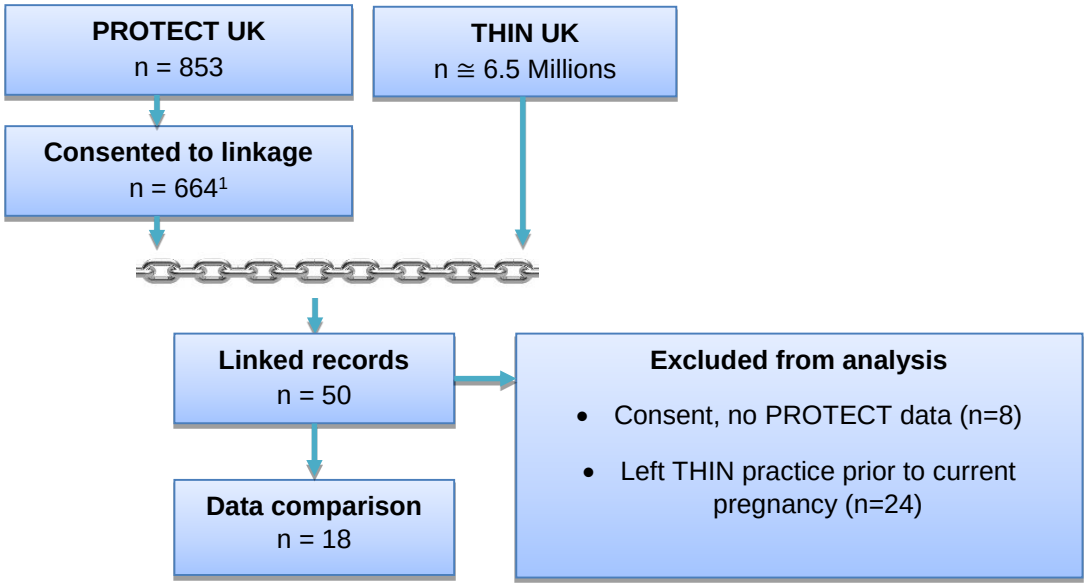
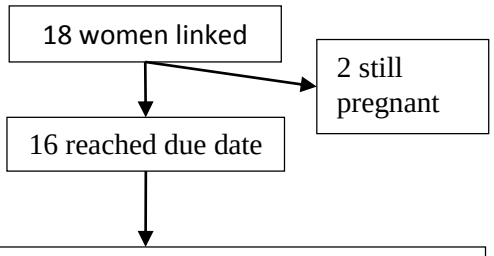


Figure 8-3 Flowchart of women linked to THIN database

[1] Of 674 consented, 664 NHS numbers provided appeared to be accurate; 9 provided NHS numbers "0", and 1 was "not known."

8.4.2.1 Pregnancy outcomes

The pregnancy outcomes in the THIN database are recorded in the Medical and AHD files. We searched through relevant codes for pregnancy outcomes, which were provided by THIN and further validated by the study team, in the two files. Among the 18 women successfully linked, two were still pregnant at the end of the study, and 16 had reached their expected due date. In PROTECT, only 5 reported the pregnancy outcomes (live births), and the remaining 11 discontinued the study before their pregnancy ended (Figure 8-4).



	PROTECT	THIN
No end of pregnancy related information	11 (69%)	6 (38%)[2]
Had end of pregnancy related information	5 (31%)[1]	10 (63%)
Value-added information	3 (19%)	8 (50%)

[1] All live births

[2] Including 2 (13%) who only had pregnancy outcome related information prior to joining the study and therefore irrelevant to this study

Figure 8-4 Flowchart of the availability of the end of pregnancy information

Table 8-3 Self-reported versus recorded information related to pregnancy outcome

		PROTECT		
		Outcome not reported	Outcome Reported	Total
THIN	Outcome not recorded	3 (19%)	3 (19%)	6 (38%)
	Outcome Recorded	8 (50%)	2 (13%)	10 (63%)
	Total	11 (69%)	5 (31%)	16 (100%)

Table 8-3 shows the concordance between the THIN and PROTECT data on an indicator of end of pregnancy among the 16 women who were no longer pregnant at the end of the study. Only two women had agreement in their reporting and medical record. Of these two women, both reported live births and the date of delivery were also in agreement in both databases. We demonstrated that the end of pregnancy information on those who discontinued from the PROTECT study may still be available through THIN linkage; in this case THIN provided additional information on pregnancy outcome for 8 women. Likewise, PROTECT provided additional information on the pregnancy outcome for 3 women.

For the eight women whose outcome data were only available through THIN, six of the eight women had Read codes indicating the actual end of pregnancy, and two only had postnatal examination information (for full list, see Table 13-23 in Appendix 13.18).

8.4.2.2 Compatibility and discrepancies of individual medications

Table 8-4 shows that agreement between data provided by the PROTECT women and that from the THIN record is generally low, with more than half (53%) PROTECT women reporting between 0% and 25% of the medications recorded in THIN. It also appears that women were more likely to report medications when they had more prescriptions. However, the discrepancy between self-reported and GP recorded medications may be due to medications that were prescribed but were not taken, or it may be due to women forgetting to report them to PROTECT.

Table 8-4 Compatibility and discrepancies between THIN data and PROTECT data based on whole period of follow-up for 15/18 women in THIN with at least one medications use

Level of completeness	One medication in THIN	Two medications in THIN	Three or more medications in THIN	Total (At least one medication in THIN)
0 – 25%	0 (0%)	3 (20%)	5 (33%)	8 (53%)
25 – 50%	0 (0%)	0 (0%)	1 (7%)	1 (7%)
50 – 75%	0 (0%)	2 (13%)	2 (13%)	4 (27%)
75 – 100%	1 (7%)	0 (0%)	1 (7%)	2 (13%)

The discrepancies of selected self-reported medications versus THIN records by types of drugs is shown in Table 8-5; (for the ATC related codes, see Table 8-2). In the UK, the number of women linked is much fewer than those in Denmark, and therefore only the higher level categories that appear in bold in Table 8-5 may be informative. The breakdown of the categories are only shown for completeness.

For medications for chronic medical conditions, 50% (3/6) of PROTECT participants reported the medications recorded on their THIN records; but only 38% (3/8) of the participants' THIN records captured what they self-reported in PROTECT.

For medications for occasional or short-term use, only 33% (4/12) PROTECT participants reported the medications recorded on their THIN records; but 67% (4/6) of the participants' THIN records captured what they self-reported in PROTECT.

For pregnancy-related medications, 60% (6/10) PROTECT participants reported the medications recorded on their THIN records; and equal numbers of the participants' THIN records captured what they self-reported in PROTECT.

Although there may be some percentage differences for these selected medications, the absolute numbers of women who self-reported medications recorded THIN are similar (actually, equal).

Table 8-5 Number of women in PROTECT who reported medications recorded in THIN up to six month prior to the start of pregnancy (P=PROTECT, T=THIN)

	N_P/N_T (%)	N_T/N_P (%)
DRUGS FOR CHRONIC CONDITIONS	**3/6 (50)**	**3/8 (38)**
Insulin	-	-
Oral diabetics	-	0/1 (0)
Heart related drugs	1/1 (100)	1/1 (100)
Intestinal anti-inflammatory agents	-	-
Thyroid therapy	2/2 (100)	2/2 (100)
Anti-inflammatory drugs, systemic	-	0/1 (0)
Paracetamol	-	0/4 (0)
Opioids	0/1 (0)	-
Anti-epileptics	0/1 (0)	-
Antipsychotics	-	-
Antidepressants	1/3 (33)	1/1 (100)
ADHD treatments	-	-
Anti-allergies	0/1 (0)	0/1 (0)
Anti-asthmatics	-	0/1 (0)
Antihistamines	-	-
Eye allergy drugs	0/1 (0)	-
Anti-migraines medications	-	-
DRUGS FOR OCCASIONAL OR SHORT-TERM USE	**4/12 (33)**	**4/6 (67)**
Dermatological non-corticosteroids	1/1 (100)	1/2 (50)
Dermatological corticosteroids	0/2 (0)	-
Acne, dermatological treatment	0/1 (0)	-
Malaria drugs	-	-
Antibiotics, systemic	4/9 (44)	4/5 (80)
Antifungals, systemic	-	0/1 (0)

Anxiolytics, hypnotics and sedatives	1/2 (50)	1/1 (100)
Ear, nose and throat preparations for infections	0/4 (0)	0/1 (0)
PREGNANCY-RELATED MEDICATIONS	**6/10 (60)**	**6/10 (60)**
Acid-related disorders	3/6 (50)	3/8 (38)
Anti-emetics	-	-
Antithrombotic agents	1/1 (100)	1/1 (100)
Haemorrhoids	-	-
Laxatives	1/2 (50)	1/1 (100)
Gynaecological anti-infectives	1/2 (50)	1/2 (50)
Progesterone	-	-

Table 8-6 shows the analyses of compatibilities and discrepancies of medications at ATC level 2 where at least one record/report was available in either PROTECT or THIN database. The compatibility between the two databases is generally low, as described by the Jaccard, Sorensen's positive agreement and Cohen's Kappa indices – the lower the index the less compatible the medications recorded/reported in the databases, and vice versa.

Drugs for acid related disorders, and anti-bacterials for systemic use were the only medications that achieved reasonable concordance between self-reporting and GP recording; both drugs with relatively high usage. Higher measures of compatibility for other medications were driven by very few medications recorded/reported. The highest concordance should be expected for medications for chronic diseases. However, of the 18 women matched with THIN data, few had chronic diseases. Interestingly, although no GP prescriptions were recorded for diabetes for these matched women, one self-reported using a medication for diabetes. This suggests that women may not always understand the indication for the medication they are taking. PROTECT performed particularly well in capturing over-the-counter medications such as vitamins, anti-anaemic preparations and analgesics. Very low concordance was expected for over-the-counter medications since they are typically not prescribed in general practices.

Table 8-6 Medications use by ATC therapeutic group

ATC	Both	PROTECT only	THIN only	Not used	J[1]	S_+[2]	κ[3]	S_-[4]
A-Alimentary tract and metabolism								
A02-Drugs for acid related disorders	5	3	1	9	0.56	0.71	0.54	0.82
A06-Drugs for constipation	1	0	1	16	0.50	0.67	0.64	0.97
A10-Drugs used in diabetes	0	1	0	17	0.00	0.00	0.00	0.97
A11-Vitamins	0	12	0	6	0.00	0.00	0.00	0.50
A12-Mineral supplements	0	1	1	16	0.00	0.00	-0.06	0.94
B-Blood and blood forming organs								
B01-Antithrombotic agents	1	0	0	17	1.00	1.00	1.00	1.00
B02-Antihemorrhagics	0	0	1	17	0.00	0.00	0.00	0.97
B03-Antianemic preparations	2	13	1	2	0.13	0.22	-0.08	0.22
C-Cardiovascular system								
C03-Diuretics	1	0	0	17	1.00	1.00	1.00	1.00
C09-Agents acting on the renin-angiotensin system	1	0	0	17	1.00	1.00	1.00	1.00
D-Dermatologicals								
D01-Antifungals for dermatological use	1	1	0	16	0.50	0.67	0.64	0.97
D02-Emollients and protectives	0	0	2	16	0.00	0.00	0.00	0.94
D07-Corticosteroids, dermatological preparations	0	0	2	16	0.00	0.00	0.00	0.94
D10-Anti-acne preparations	0	0	1	17	0.00	0.00	0.00	0.97
D99-Dermatologicals: Sublevel unknown	0	0	1	17	0.00	0.00	0.00	0.97
F-Fish oil								
F99-Fish oil: Sublevel unknown	0	2	0	16	0.00	0.00	0.00	0.94
G-Genito urinary system and sex hormones								
G01-Gynecological antiinfectives and antiseptics	1	1	1	15	0.33	0.50	0.44	0.94
G03-Sex hormones and modulators of the genital system	1	0	3	14	0.25	0.40	0.34	0.90
H-Systemic hormonal prep, excluding sex hormones								
H03-Thyroid therapy	2	0	0	16	1.00	1.00	1.00	1.00
J-General antiinfectives for systemic use								
J01-Antibacterials for systemic use	4	1	5	8	0.40	0.57	0.33	0.73
J02-Antimycotics for systemic use	0	1	0	17	0.00	0.00	0.00	0.97

ATC	Both	PROTECT only	THIN only	Not used	J[1]	S_+[2]	κ[3]	S_-[4]
M-Musculo-skeletal system								
M01-Antiinflammatory and antirheumatic products	0	1	0	17	0.00	0.00	0.00	0.97
M02-Topical products for joint and muscular pain	0	0	1	17	0.00	0.00	0.00	0.97
N-Nervous system								
N02-Analgesics	1	5	2	10	0.13	0.22	0.00	0.74
N03-Antiepileptics	0	0	1	17	0.00	0.00	0.00	0.97
N04-Anti-parkinson drugs	0	0	1	17	0.00	0.00	0.00	0.97
N05-Psycholeptics	1	0	1	16	0.50	0.67	0.64	0.97
N06-Psychoanaleptics	1	0	2	15	0.33	0.50	0.45	0.94
R-Respiratory system								
R01-Nasal preparations	0	1	1	16	0.00	0.00	-0.06	0.94
R03-Drugs for obstructive airway diseases	0	1	0	17	0.00	0.00	0.00	0.97
R05-Cough and cold preparations	0	0	1	17	0.00	0.00	0.00	0.97
R06-Antihistamines for systemic use	2	1	0	15	0.67	0.80	0.77	0.97
S-Sensory organs								
S01-Ophthalmologicals	0	0	2	16	0.00	0.00	0.00	0.94
S02-Otologicals	0	0	2	16	0.00	0.00	0.00	0.94
S03-Ophthalmological and otological preparations	0	0	1	17	0.00	0.00	0.00	0.97
V-Various								
V07-All other non-therapeutic products	0	0	2	16	0.00	0.00	0.00	0.94

[1] Jaccard Index Positive agreement where the medication is found in either or both sources[28]

[2] Positive agreement[29-31]

[3] Cohen's κ (Kappa)[32]

[4] Negative agreement[29-31]

8.4.2.3 Lifestyle choices

8.4.2.3.1 Smoking

The smoking status during pregnancy was recorded and self-reported, as shown in Table 8-7. One woman had a record as a "current smoker" in THIN, but self-reported as an ex-smoker who smoked longer than a year before her current pregnancy. On further examination, the woman's THIN record on smoking was several months earlier than when she reported to PROTECT, which suggests that she may have stopped smoking when she was pregnant and reported accurately. The 33% (6) of women who self-reported to be non-smokers but did not have a smoking status on THIN may also be accurately reported; and the reason it is missing in the THIN database is because smoking status may have been recorded there outside the timeframe of the data we acquired for the study.

Table 8-7 Smoking status reported by women and recorded on THIN

		THIN				
		Current smoker	**Non-smoker**	**Ex-smoker***	**Unknown**	**Total**
PROTECT	**Non-smoker**	0 (0%)	6 (33%)	1 (6%)	6 (33%)	13 (72%)
	Smoker in the year before pregnancy	1 (6%)	0 (0%)	3 (17%)	1 (6%)	5 (28%)

* Ex-smoker in THIN includes women who smoked longer than a year before the current pregnancy

8.4.2.3.2 Alcohol consumption

Of the 18 women linked, given that they had some data during pregnancy and by the time they were able to report to PROTECT (date of the first questionnaire), 18% (3) reported alcohol consumption of "about once a month or less", and likewise of "2-4 times a month". 65% (11) did not consume alcohol during pregnancy, which confirms the accuracy of their records in THIN. One woman's alcohol consumption is unknown.

Only one women from THIN had a code associated with an alcohol consumption, for being an ex-drinker. The same woman reported to PROTECT that she consumed alcohol "about once a month or less" during pregnancy, which was about 20 weeks later than the date recorded on THIN of her having stopped drinking (Table 8-8). It is known that alcohol consumption is not recorded routinely in the general practices.

Table 8-8 Alcohol consumption as reported by women and recorded on THIN

		THIN		
		No alcohol record	**Has alcohol record**	**Total**
PROTECT	**About once a month or less**	2 (12%)	1 (100%)*	3 (17%)
	2-4 times a month	3 (18%)	0 (0%)	3 (17%)
	Never	11 (65%)	0 (0%)	11 (61%)
	No information	1 (6%)	0 (0%)	1 (6%)

* Stopped drinking alcohol about two months post-conception

8.4.2.3.3 Illicit substance use

There was no illicit substance use recorded on THIN among the linked women. All women from PROTECT also reported that they did not use any illicit substance. Therefore, in this case, PROTECT confirms the lack of non-illicit substance user status as there is no mention of any use in the absence of associated records on THIN.

8.4.3 Discussion

The results from data linkage analyses and comparison in the UK demonstrate that no single use of a data source (e.g. THIN only versus PROTECT only) can provide the complete information on the subjects. This includes the information on pregnancy outcomes, medications use and lifestyle behaviour. Several factors may account for these differences seen between the data provided. The questioning method such as active questioning about specific information being sought may result in better data being provided and captured. Set frequency of data collection as in prospective studies may result in more data being collected when compared to opportunistic data collection as in primary care. Prospective studies like ours may be affected by selective recall, perhaps more than the data being recorded in the primary care which. The main potential bias from THIN data in this study is women's behaviour, since data from primary care (and on THIN database) are only recorded at the time of consultation. Therefore the frequency with which a woman visits her general practice would be the major potential bias. It may also be possible that the frequency the more experienced mothers visit their general practices may differ from the less experienced ones; but we have not explored this possibility in our study.

Self-reporting of pregnancy outcomes in PROTECT was quite low in general (22.5% overall; 22.1% in the UK) due to study discontinuation, lost to follow-up and study closure. In theory, all pregnancy outcomes should be recorded on THIN database, but only 63% (10/16 women) of the linked women ever had a record indicating an end of pregnancy in our cut of the data. The pregnancy outcomes may have been recorded retrospectively when the records were updated.

There were some discrepancies between self-reported medications and THIN medical records among the 15 women who had any medications use during pregnancy. Despite rather low medications use, the analyses suggest that women did not report all the medications recorded as completely as they should have when compared to their THIN records. However, these women also reported some medications within the same category that were not recorded on their THIN records. The discrepancies could be for several reasons: women did not report the medications they took, women did not report the decision to not take the medication, and/or women did not report the medications accurately enough to be coded into the correct ATC codes. The latter could happen for some pre-specified medication lists that were not accurate, or more likely if the medication was reported as free text. If the wrong ATC code was chosen (by the study team), it is likely that the medication would not be found in THIN.

Recall bias may also play a role in THIN records, but should not affect data on prescription. Recall bias may affect recorded drugs use history on the occasions when GP asked a patient about drugs they have were taking at the time of the visit. The estimates on rates of prescription may be an over-estimation of the drugs actually taken, and therefore may exaggerate or dilute the effects of drugs.

Another point to take into account is that GPs recorded prescribed medications using the BNF (British National Formulary) coding system into THIN, which were consequently automatically matched to the ATC codes. This indirect coding may also introduce some discrepancies in the data.

The use of different indices to assess compatibility and discrepancies between medications on the two databases did not suggest that any superior index performed better throughout. However, low numbers and high proportions of non-medication users may affect the performance of these indices since none was developed to handle small numbers.

Since pregnancies are managed largely outside GP practices, medications prescribed in hospital may not be captured in THIN data. We also acknowledged that the information on lifestyle factors, cosmetic procedures and alternative treatments may be present in the free text comments on THIN database, and that we did not have access to these comments for confidentiality reasons. Therefore, we expected that PROTECT data would provide more information in our study, but without more thorough examinations of the GP records from THIN, it is difficult to tell to what extent THIN captured these types of information.

The self-reporting of lifestyle factors such as smoking, alcohol use and illicit substance use were generally compatible with the women's most recent THIN records. This might be because being pregnant may have encouraged better lifestyle and more contact with the GPs.

8.5 Concluding remarks

Medications appear to be recorded quite accurately for chronic diseases but less accurately for non-chronic diseases. The comparative analyses conducted in Denmark and the UK show that both direct-to-patient prospective studies and existing electronic healthcare records (e.g. Danish Registry, THIN) have their own strengths and weaknesses. Although the questionnaire data are available throughout the pregnancy, collecting data directly from the women is vulnerable to participants discontinuing the study prior to the end of pregnancy. Neither EHR or register data or self-reported data on medication use are complete by themselves, and these methods can supplement each other. Self-reported data give important information for first trimester exposure that usually cannot be found in a register. Direct-to-participant data collection methods such as used in PROTECT can recruit women at the very early stage in their pregnancy, which can provide information on early miscarriages that ended without the women contacting healthcare professionals. The hospitals and/or general practices are frequently not aware that the woman is pregnant or that she has miscarried, and this information is also usually unknown to researchers. However, self-reporting is less reliable in terms of completeness of reporting and consistency of reporting throughout pregnancy.

The analyses in Denmark show good accuracy in reporting of medications, but there were greater discrepancies in the analyses among UK participants. It may be that Danish women were better self-reporters than the UK women, but it also could be due to the fact that the comparisons were made against dispensed medications in Denmark and prescribed medications in the UK. Additionally, the numbers were far smaller in the UK compared to Denmark; so it is difficult to draw robust conclusions for the reporting of medications in the UK based on this small sample. Because of this reason, it was expected at the start of the study that the medications comparison in Denmark would be more consistent with self-reported medications than other countries.

We believe that direct-to-patient data collection on medications use and electronic healthcare databases can both play a role in pharmacovigilance. But the use of both sources together may contribute to better and richer information by complementing the strengths of each. Direct-to-patient studies with linkage to electronic healthcare records, such as this, could also be used to update the participants' healthcare records provided the participants provided their consent to do so.

9 Assessment of consumer-based tools data collection

9.1 Introduction to consumer-based tools data collection

When data is collected directly from participants, the data entry should be easy to perform as participants will not usually be supported during data entry and there is no possibility then, once data is entered, to post queries to have errors corrected or incomplete data entered. In the absence of training, it is important that the collection tool is user friendly and doesn't require specific training to understand how to complete the questionnaires.

Taking into consideration these requirements, the data collection tools used in this study were developed with these attributes in mind to allow participants to provide data directly register by themselves.

Two data collection systems were developed for this study. The Interactive Voice Response System (IVRS) is a system that allowed the recording of answers provided over the phone by selecting options in the keypad. The electronic Questionnaires were available online via a computer. Participants were given the choice of using either one recording tool or the other. A username and password was created for each participant at enrolment allowing their recognition by the systems and assuring their questionnaires couldn't be completed, or viewed, by anybody else. Both data collection tools were developed by Outcome Sciences Inc. (now Quintiles).

The IVRS option was given to participants to allow participation of women who had no access to computers. Toll free numbers were offered in each country to avoid costs of participating in to participate to the study. There were 2 ways to provide data via the phone: women could call the system directly to access the questionnaire or wait to be called by the system. Women were asked to provide their preferred day and time to be called in the enrolment questionnaire. In Denmark where women had to consent online, participants could then choose their tool while registering. The IVRS option was not proposed for Polish participants as they had to sign the informed consent. For participants in the Netherlands and in the UK, registration was directly accessible via the phone.

The IVRS system has some limitations due to the fact that all questions and options need to be repeated. It can be annoying and the system is thus not adapted to long questionnaire completion. As a consequence, we primarily sought to collect information that would allow us to compare the population using IVRS to those participating online. In the baseline questionnaire, questions on demographics, education level, life style and medication use were asked but with less detail than that for the online questionnaire. No 2 or 4 weekly follow-up questionnaires were sought from the IVRS group. Instead, we only planned for IVRS participants to complete the baseline and the end of pregnancy questionnaires. However, the only respondent who actually completed the baseline questionnaire by IVRS did not complete the pregnancy outcome questionnaire.

The online questionnaires were accessible via a public website where interested women could first receive more information on the study and then, register if they were interested. Once registered, participants could complete the baseline questionnaire directly or log in to the system later on to do so. Reminders were sent to participants via e-mail where participants had to click on a link directly leading them to the login page that would open on the questionnaire they had to complete when the correct identifiers were provided. Participants also had the possibility to receive phone text messages if they provided their phone number while registering.

Questionnaires were developed to help participants to recall the medications they took by proposing common treatment options by medical condition. Free text data entry was restricted as much as possible by proposing medication options per condition but there was the possibility of adding medications or conditions which had not been pre-populated using a free text option. Additionally, information completed in previous questionnaire was carried forward to the following questionnaire to ease data entry.

9.2 Results and Discussion

9.2.1 Comparison between IVRS and web population

From the 2521 patients enrolled, only 14 were IVRS patients (13 in DK and 1 in the Netherlands). Most of those who chose IVRS did not complete the baseline questionnaire. There is therefore insufficient information collected to compare the two populations. The main information is that the use of the phone to complete the questionnaires is of marginal feasibility and that most people do not chose this as their means of providing information. This doesn't mean that IVRS is of no value, but considering the wide usage of the internet, the phone usage may only be of use for specific participant categories, for example elderly persons not used to using the internet, and especially if short questionnaires are administered.

9.2.2 Difference between women choosing a follow-up every 2 or 4 weeks

Women were able to choose the frequency of their follow-up, which was either every two or every four weeks. The influence of frequency on retention and data quality was investigated. It was expected that women answering the questionnaire on a more regular basis would recall better than women that provided information monthly. On the other hand, it was expected that women participating more regularly might have a lower retention rate.

As presented in Section "4. Participants retention in the study", in Table 4-1, women in some countries showed a preference for follow-up every month while in some other countries, follow-up frequency preference was split equally. In term of retention, there was clearly a higher retention rate in the population who chose the follow-up every 2 weeks.

Additionally to the data on the retention rate, women were asked to provide feedback on the questionnaire frequency in the satisfaction survey that was completed at the end of the study. One hundred and thirty six women answered this questionnaire. From this number, 109 were satisfied by the frequency they had chosen and was split equally between the roughly equal numbers of women who responded every two follow-up frequencies – 2 weeks (56) or monthly (53).

Twenty five participants answered that the follow-ups were too frequent (from the 25, 19 had a follow-up every 2 weeks). Conversely, 2 participants answered that the frequency was too low. Surprisingly, those 2 participants provided answers twice a month.

Apparently, most of the participants were satisfied by the frequency they had chosen and only a small percentage would have preferred a lower frequency.

Taking into consideration this feedback, and the retention rate, the best frequency would be every two weeks.

9.2.3 Feedback on questionnaire completion

Participants had several opportunities to provide feedback about the questionnaires. Several criteria were specifically studied. Feedback was collected at different time points.

9.2.3.1 Discontinuation reasons

Participants were allowed to stop participation at any time during the study. They were requested to notify the study that they were discontinuing and if they did they were given a discontinuation questionnaire which asked for the reason they wanted to stop. Apart from the option that they were no longer pregnant, they could chose: no longer interested, questions are too burdensome, questions are too personal and other (with a free text entry).

In total, 85 women completed the discontinuation questionnaire. 16 informed us that they were no longer pregnant. The 69 remaining participants provided the following reasons for discontinuation:

- No longer interested in the study: 37.69% (26)
- The questionnaire was too time consuming: 28.99% (20)
- Questions are too personnel: 4.36% (3)
- Other (with comment): 28.99% (20)

From the 20 answers belonging to the category "Other", 10 explained they had technical issues (4 of which clearly stated the problem was due to loss of information because forms couldn't be saved during completion), a particular problem for the rather lengthy baseline questionnaire; 4 explained that discontinuation was related to their pregnancy status; (3 of which explained that they were close to the end of their pregnancy and that they would have no time to continue participation). Finally, 6 provided other answers that could not be categorized.

9.2.3.2 Results of the Satisfaction Questionnaire.

A satisfaction questionnaire was provided to all women who completed the study (end of pregnancy or discontinuation). Several of the questions asked in the Satisfaction Questionnaire were related to questionnaire completion.

Concerning the Baseline questionnaire, of 132 participants who provided an answer, 52 said that the time to complete the Baseline questionnaire was very little, while 59 answered it was a bit consuming and only 21 answered it was substantial.

Concerning the follow-up questionnaires, from the 133 answers provided, 89 participants said that the time to complete the Follow-up questionnaires was very little, while 35 answered it was a bit consuming and only 9 answered it was substantial.

From the feedback received, it is clear that the time necessary to complete the baseline was considered as being longer than for the follow-ups. Nevertheless, it needs to be kept into mind that answers were only provided by active participants. Participants who considered the duration of the data entry as unacceptable would have stopped earlier. The settings of the system did not allow recording of whether some women who registered, started to complete the baseline questionnaire and discontinued in the middle of completion. This would have been a good indication to know whether length or difficulty of this form would have discouraged some participants.

The difficulty of the questions was also assessed: from the 136 answers received, 3 participants found the questions hard to understand, 1 found that most of the questions were difficult, 38 that some were difficult and 94 had no difficulties at all.

The confidence related to the answers the women provided was evaluated and the following answers were given. From the 139 answers received, 101 participants confirmed they were confident with the information provided.

Twenty three were less confident but considered that they were confident about most of the information provided. Only 3 answered that they were only sometimes confident.

To be taken into account: feedback provided for the satisfaction questionnaire generally concern women who participate until the end and provided information about the pregnancy outcome: 125 from the 139 who completed the satisfaction questionnaire. From those, 111 gave a live birth, 11 had a stillbirth, 1 termination and 1 an ectopic pregnancy and 1 didn't provided any answer on this point.

9.2.3.3 Feedback from registered women not completing the baseline

As a significant number of women were lost between entering the study and completing the baseline questionnaire, web participants in this category were contacted via e-mail to collect their feedback. They were asked to provide the reason why they didn't complete the baseline. Only women who didn't formally discontinue were contacted. The following options were given: Was no longer interested in the study, the questionnaire was too long, the questions were too burdensome, the questions were too personal, I was no longer pregnant, other with free text entry.

In total, 359 women were contacted and 49 women answered (53 options chosen in total). The number of answers received doesn't permit statistical analysis but it provides a good insight and directions for improvement.

The results were as follow:

- Was no longer interested in the study: 3.77% (2)
- The questionnaire was too long: 11.32% (6)
- The commitment required was too burdensome: 9.43% (5)
- The questions were too difficult: 0% (0)
- The questions were too personnel: 0%(0)
- Was no longer pregnant: 15.09% (8)
- Other with comment: 60.38% (32)

From the 53 comments received, 32 were not related to a specific category. The main feedback of this "Other" category concerned technical issues: 62.5% (20) informed they stopped participating for some technical reason. It corresponds to 37.7% of all the answers provided. The most common reason for this was that it was due to the fact that the system couldn't be used on tablets and smart phones (25%-5 participants) while another defined category had issues with the fact that entered data were lost when their computer crashed (20% - 4). The rest of the technical issues (55% - 11) had different causes that were often related to participants inability to log in but were not defined enough to be precisely categorized. From the "Other" category, there were also 4 women who explained their non-participation was related to their pregnancy: tiredness, sickness, etc. Finally, 8 participants, provided other reasons for discontinuation.

9.3 Other parameters to be taken into account:

Women were asked whether the reminders were useful. In the satisfaction questionnaire, 137 participants provided an answer. From this number, 117 found it really useful and 14 sometimes useful. 6 participants were not satisfied for various reasons.

9.4 Feedback from a focus study group

A total of 45 women were interviewed to get feedback on where they looked for information about their pregnancy, the barriers/drivers that would help them to decide whether to participate in the study, their general feedback on the website, etc. The respondents were from the UK (9 participants), Poland 15 participants), Denmark (13 participants) and the Netherlands (8 participants), none of whom participated in the PROTECT Pregnancy Study. A one-to-one guided interview was conducted to collect their feedback by an independent company experienced in conducting consumer surveys. Prior to their interview, women were asked to spend at least 10 minutes on the website.

9.4.1 Information Sources

Women where asked what source of information they consulted to find out more about their pregnancy. In the 4 countries, the use of internet was always close to the top ranging from first place to fourth place in the information sources cited. Women consulted the main local sites speaking about pregnancy or becoming parents.

9.4.2 Barriers and Drivers

Women were asked about what would prevent or instead persuade them to participate in a study.

Concerning the drivers, there were 2 clear patterns. In UK, Denmark and the Netherlands, the “knowledge that your input would help support future practice” was the first choice while “incentives (discount vouchers etc.)” was the last. In Poland, “incentives (discount vouchers etc.)” was the main driver followed by “knowledge that your input would help support future practice”. It is clear that altruism and a positive impact for others is an extremely high driver in all countries. Incentives could also help, depending on the country chosen.

Concerning the barriers, “Amount of time required is too long” was the top reason that would prevent women in the UK and in the Netherlands from participating in a study. In Poland, options related to time involvement was just after the “Inconvenience” option that is related to the extra-step of printing and sending the ICF in this country. In Denmark, the “Worried about security of personal information” came first followed by “Amount of time required is too long”. In this country, participants are obliged to provide their social security number to participate. In UK, this information is also asked but is optional and doesn’t appear as a major barrier.

In all countries, the option “Amount of time required is too long” was in first or second place. Duration of the activities to be performed by women should be below 2 hours per month to be considered as acceptable.

9.4.3 Feedback on the Website

The general feedback received on the website was positive. Most women confirmed that having looked at the websites that they would have participated in the study.

In each country, feedback on areas for improvement was collected.

What was noticed is that the feedback on areas for improvement differed among participants and countries. In the UK, the language was considered as heavy and difficult while in Poland, participants appreciated the way information was provided indicating it was "written in a serious way and inspires trust". In this country, several women considered that the colours chosen for the website were not appropriate as those are "colours associated with physicians". No feedback was received on the colours in other countries. Perception related to the website format or content is driven by local considerations. The content of the website was not developed to take those local considerations into consideration.

The proposals to ameliorate the website that were the most often proposed are:

- Improve the navigation
- Improve the length, difficulty of the text.
- Increase the visual part: more pictures.

9.5 Quality of the data

One of the main criteria to assess the usefulness of a collection tool is the quality of the data collected. It should be confirmed that participants provide data on the long term that are reliable.

For this study, we noticed that the retention rate was low and that participants were lost at each step (see Section 4. Participants retention in the study). Nevertheless, some participants provided information until the end of the study. This level of discontinuation should be taken into account when determining the target of enrolled participants.

In the UK and in Denmark, it was possible to compare the data collected with linked data using either the electronic medical record (UK) or prescription and birth registries (DK). The comparisons cannot exactly match as the national databases only provide information on prescribed drugs (UK) or dispensed drugs (DK) while data collected from the women for the study asked about over the counter medications, medications prescribed but not taken, homeopathic remedies, recreational drugs, etc.

Self-reported data rely on participant's willingness and capability to provide accurate data. It is thus extremely important to develop questionnaires that are clear and easy to answer and enrol a sufficient number of participants to counterbalance the mistakes performed by some of them.

Additionally, the system should be as user friendly as possible and only focus on the main questions to decrease the involvement time of participants.

9.6 Concluding remarks

9.6.1 IVRS versus online data collection

From the two tools used for data collection, it was clear that the online tool was the most used. This might have been influenced by the way the patients were informed about the study, but in Denmark, where all participants had to register online, and could then choose to continue via the phone, only a few participants chose the phone option. Interestingly enough, most of the participants who chose IVRS were from Denmark with only one participant from countries where there was the possibility of entering the study directly using the phone. This suggests that the online data entry is the preferred means for providing information for most pregnant women.

With technological progress, informatics tools are now nearly accessible to everybody. New tools like tablets and smartphones are getting used by people that may not necessarily have a computer at home. One of the feedbacks received regarding limited participation in the study was the incompatibility of the online data collection tool with tablets and smart-phones. For future studies, the online data collection tool should be compatible with the latest informatics tools and programs. This should be considered in the development budget as there will be additional requirements to ensure compatibility and format for these smaller screens.

9.6.2 Parameters related to data entry

Several criteria influenced the willingness to participate and the retention. A special attention should be made to the questionnaires length and complexity.

Frequency of data collection had an impact on data collection as the population who chose to provide data entry every 2 weeks had a better retention rate compared to the population entering data on a monthly basis.

In most cases, reminders were considered as useful. Those should be kept.

9.6.3 Information to patients and website format

The main source of information on the study for women interested in participating is the website. It is therefore important that the website provides the information needed to make a decision and is user friendly enough not to put off potential participants. Feedback advised simplifying the text contained in the website and to have more pictures. An effort should be made to simplify navigation.

From the feedback received from the study group, it appeared that perception was often influenced by culture. It is thus important to take this into account and adapt website content to participating countries. Feedback collected from a larger study group would be useful to customize website to country requirements.

9.6.4 Motivation parameters

Motivation to participate is one of the main parameter influencing participation and retention. The main criteria influencing decision to participate was the desire to influence positively future practice by participating in the study. The goal of data collection should be clearly explained to participants.

Incentives were deliberately not proposed for this study but might be considered for future studies.

Another way to encourage continued participation is to provide information about the study progresses via a newsletter for example.

10 Discussion

10.1 Study results

This study explored whether women in participating EU countries were willing to provide information via the internet to enable prospective collection of medication exposure data and information about other life style factors during pregnancy. Many women volunteered for the study. We learned that women are indeed willing to provide information via the internet, but that most respondents were not willing to provide information using an interactive voice system. Slightly more women (57%) chose to provide responses every four weeks, whereas 43% chose to respond every two weeks. Study retention was slightly better for women who chose to report more frequently. Respondents were well educated and were largely Caucasian, regardless of the underlying distribution of ethnicity in the country where they resided.

It proved challenging to recruit respondents very early in pregnancy, partly due to the relatively slow response to passive-type study recruitment, the compressed time available for recruitment and the very modest budget available for study promotion. Email lists that identified women who had joined pregnancy clubs were used when it appeared that the passive methods of subject recruitment were insufficient, and naturally, these emails targeted women who had already self-identified as pregnant and had joined a club, and thus, were more likely to be in their second trimester of pregnancy or later.

The study results also suggest that data collection was relatively burdensome, particular with regard to the baseline questionnaire since many participants did not contribute any follow-up after completing the baseline questionnaire. Follow-up questionnaires were provided inconsistently, and only a small proportion of those who enrolled actually provided data on birth outcome. We suspect that many of the short-comings of the data collection program related to the complexity of the data being requested, the manner in which the questions were posed, and the lack of functionality of the electronic data capture system on modalities other than personal computers. At the time this electronic data capture system was created, the program was not designed to work on smaller screens like iPhones, i-Pads and other hand-held devices, and use of those hand-held devices proliferated rapidly over the five years during which this study was designed and conducted. Furthermore, this study employed no methods for encouraging patient follow-up other than periodic reminders by email and/or text messaging. Study participation might have been higher with more creative retention efforts and perhaps modest payments for participant reports.

Nonetheless, respondents willingly provided data on medication use, including prescription and non-prescription medications, and herbal products. When compared with prescription register data, we learned that women who took relatively few medications had greater completeness of reporting than those who used many drugs regularly. We also learned that self-reported medication use revealed some deficiencies of exclusive reliance on existing prescription medication data, particularly with regard to medications used intermittently or for short-term conditions. Women also reported using medications that had been prescribed prior to their becoming pregnant, and a very small proportion also reported using medications that had been given to them by others and not prescribed by their own medical care providers. They also were willing to report that in some situations they had received prescriptions but decided not to fill them, so interpretations based solely on prescribing information recorded in electronic health records would not provide a fully accurate picture of medication use. Similarly, women also reported about using alcohol, smoking cigarettes and using illicit drugs like marijuana and cocaine. They also provided data on other exposures that are sometimes difficult to obtain, including vaccinations, surgery and type of anaesthetic administered. However, validity and completeness of this information is not easy to determine due to lack of population data on most exposures.

We also learned that women were willing to provide data on clinical outcomes. Among live births, most reports were healthy babies. Self-reported visible birth defects were less reliable for research and pharmacovigilance purposes because the information was coming from untrained reporters. Information on "visible birth defects" largely lacked the clinical specificity need to draw causal inferences, and based on a small sample of women whose self-reported data were matched with electronic health records, the clinician-reported data was more accurate and specific.

It is also worth noting that a relatively small proportion of participants actually reported the birth outcome among those who were expected to deliver their babies while the study was still active. Different approaches to obtaining birth outcome, including initiating follow-up longer after the expected date of delivery may improve reporting, since having a baby, particularly a first baby, is a major life adjustment and responding to a study questionnaire could be expected to be a lower priority at that point in time.

10.2 Generalisability

10.2.1 Extending to other populations

10.2.1.1 Access to internet

The ability to generalize to other populations for study will depend in part on how much these populations use the internet and how, as well as the cost and ease of internet access for them. For example, the elderly may not use the internet as much or as frequently as those who are younger, and the elderly may need to use software that has large fonts and does not rely on strong familiarity with computers. These are assumptions but were not tested in this study as all participants were of child-bearing age.

This pilot study showed broad geographic response in regions where the study was promoted, and those who responded revealed substantial heterogeneity in terms of the amounts of medications used and in lifestyle factors. These are all positive points suggesting that it is possible to gather a broadly representative study population. The fact that our population was on the whole better educated than the general population may matter for some studies, but this could possibly be overcome by changing advertising methods. Stage of pregnancy at recruitment was influenced by the advertising method or internet site used and this may enable future studies to target women at the early stages of pregnancy.

In summary, it appears that internet data collection is suitable for many applications for many populations who have access to internet, and the mental and physical ability to use those systems – both in terms of finding out about the study and in responding to questionnaires.

10.2.1.2 Generalisability to other geographic zones

The study was performed in four European countries. Performing this kind of study in other regions of the world should be evaluated in relation to internet access and use by the chosen population. While in Europe, the internet is accessible to the majority of the population, there are regions elsewhere in the world where the use of computers or other devices will be restricted to a population with higher economic status. This will bias the selection of the participating population and needs to be evaluated carefully.

10.2.1.3 Restrictions in term of population

As the main criteria to take part to this kind of study is the access to internet, the possibility to be contacted via internet as well as the capability to provide consent to participate, means that the target population remains a population of adults.

Intuitively, this method of study seems ideal for paediatric use given the widespread use of computers in that age group. However, there are particular issues with the paediatric populations which may make participation problematic. For the very youngest ones, they will simply not be actively using the internet and for the population able to use the internet and to be recruited via the internet, there are problems with legal limits on the age for consent. The UK was the only country where it was felt possible to recruit women younger than 18 years of age and then the lower age was restricted to 16. It would be possible to get informed consent from a parent or guardian and then have a child or teenager provide data but that would introduce additional sources of bias. In addition carers might be concerned about the type of questions and/or data being requested and children might be concerned about carers viewing the data provided.

Like with other forms of self-reporting, disabled patients who were unable to give their consent would be excluded as well. Populations not able to manipulate a computer or another device for any reason (handicap, age, etc.) would not be able to participate in a study using the internet to self-report data of interest.

However, internet based research could be used for populations who have difficulty getting to study sites because of illness or work commitments. Internet research, because data can be entered at any time, will permit studies to include people in full-time or shift work who might otherwise be unable to participate. Similarly, those whose mobility is restricted may also be candidates for studies in which it would otherwise be impossible for them to participate.

10.2.2 Data Collected

This study showed that women will provide rich data about medication use and other lifestyle factors that could explain a medication's safety and effectiveness. Systems need to be adapted to use freely entered text since respondents are not always able to recall the indication for which they used the medication, and subjects may not have great patience for drop-down boxes with many drug choices. Also, serious adverse events and clinical outcomes of special interest may need clinician validation since respondents are not medically trained. Moreover, we were informed (Section 9.2.3.3) that several women who were not feeling well or lost their baby after the registration simply stopped their participation in the study. Important information related to safety were thus not recorded in the database as participants emotional and physical status was conflicting with their willingness to participate.

The study set-up is well adapted to collect medication use, lifestyle factors, perform disease registry or burden of care studies provided the questionnaires are simplified to reduce the difficulties related to providing medical data by non- medically trained participants. In its current format this method of data collection is not ideally suited for pharmacovigilance studies due to the low retention rate, potential loss of important information and lack of medical training when detailed medical outcomes are required. However, implementing various modifications to the system and utilising additional data sources would permit this use.

10.3 Recommendations and further work

A lot of information could be collected during the study, showing participants dedication and involvement. Nevertheless, this study also showed several areas where improvement would benefit future studies.

More effort should be made to develop the public website used for participants' registration. The website should be adapted to the participating countries and should be informative and easy to use.

The ability to recruit was also strongly dependent upon advertising. Very low or no-cost methods simply didn't work. The budget available to advertise was very small and future studies need to ensure that this aspect is adequately funded. The country leads chose the methods they thought would work in their particular country. They did not have access to marketing people (or marketing budgets) which might have enabled more strategic placing of adverts. It is possible that the fact that a better educated population responded may reflect the fact that the country leads were scientists (as were most of the work package members) and so used recruitment portals they were either familiar with or had found by internet searches. Use of marketing specialists could be beneficial to future studies.

Questionnaires should focus on the data of interest to reduce time for questionnaires completion and also simplify the way the questions are phrased. It would be desirable to extend this work through development of different approaches to asking about medication use to see if more accurate information could be obtained and if participants would contribute information more consistently. It would be also be helpful to evaluate different methods of obtaining clinically relevant information on adverse outcomes of interest, including seeking clinical confirmation for suspected outcomes of interest or linking to appropriate databases. Once those methods have been refined, it would be desirable to explore other modalities of internet based data collection, e.g. smartphones and tablet based devices, in addition to providing data via a personal computer.

The positive impact of incentives should be tested. It was shown that decision to participate was mainly related to the fact that participants considered they could provide useful information. Nevertheless, some incentive might certainly have a good impact on retention and should be considered. Incentives may not need to be monetary or voucher based but there probably needs to be some "gain" to the data provider. This may be by being part of an on-line community or some form of interactive feedback. This could take several forms. For example regular feedback on the study progress or on their progress within the study would likely be beneficial. Games on smartphones sometimes provide "stars" or awards for completing something on a particular day with additional awards at selected accumulation levels – e.g. 25 stars. Other potential methods to increase retainment of participants throughout the entire pregnancy should be expanded as well.

Many of these things were considered at the study design stage but there were several constraints which prevented implementation. One of the strengths of the PROTECT consortium was that it comprised a mixture of partners: academics, regulators, small and medium sized companies and members of the European Federation of Pharmaceutical Industry Associations (EFPIA). However, the involvement of pharmaceutical companies meant that there were constraints on anything which could possibly be construed as advertising or encouraging medication use. Whilst the involvement of the pharmaceutical industry in the design stage was very important, for practical purposes, it might be better for the study to be actually run by non-pharmaceutical parties which would remove some of these constraints.

There were also practical problems with providing incentives in that anonymity of the study participants was promised and therefore delivery of any baby related, or other gift, might be seen as compromising that. Many of the discussed ideas for retention which avoided gifts at the individual level were simply not feasible because of

budgetary constraints – e.g. online games or interactive pregnancy related information such as pictures of the developing foetus. These are all aspects which need to be considered in future developments.

The timescale for the study was also inadequate given the complexity of the data being collected and the number of regulatory (ethical and data protection) procedures which needed to be completed. No-one anticipated the lengthy start-up time required and this needs to be factored into future studies. Data protection was a major issue and the legal issues relating to this in a multi-partner consortium were considerable and have been published elsewhere.[33] These issues will be multiplied when more countries are included in this type of research. All these issues meant that the time available for recruitment and study participation were curtailed. Future studies would benefit from a much longer time-scale. Once the system is set up and in place, the main costs relate to continued advertising so a longer scale study would actually be relatively more cost efficient.

Another area of further research can be the assessment of possibilities to link the self-reported data on exposures and other possible risk factors before and during pregnancy with other databases, like medical records to acquire additional information. This information can be used to complete the data acquired and create a risk-profile that is as complete as possible that can be used for the assessment of negative or preventive effects of several exposures. Finally this might lead to future prevention of certain birth defects and other negative birth outcomes.

11 Conclusions

The study was really successful in showing that it was possible to collect medical information directly from a specific population without the involvement of physicians or other healthcare professionals. Recruitment through the internet was working well and was cost effective compared to a standard study that would have involved doctors or nurses remunerated for their time at each visit.

This pilot study confirms that a broad variety of respondents can be attracted for internet-based research on medication safety and outcomes, and that the information appears to be reliable, particularly in terms of demographics, lifestyle factors and medications used for to treat chronic diseases, with the limitation that reporting appear to be less complete for those taking a large number of medications for chronic conditions. It is worth cautioning that consumers should not be expected to report medical conditions and other clinical outcomes using the same terminology as clinicians would, suggesting that clinical validation of important outcomes may be needed.

Research into the safety of medication use during pregnancy is an important topic for public health. At the moment, there is a lack of information on both which drugs cause harm but also on which drugs are safe to use. The methods used in this study could provide the basis for a Europe-wide system for collecting data. Use of newer data input modalities such as smartphones and tablets is essential as is the ability to update platforms and software as new technologies emerge and new drugs become licensed. In addition, both the funding and the timescale for the study need to be considerably increased. For this reason, funding via IMI, whilst fine for a pilot study into feasibility, may not be the most appropriate way forward unless both these issues can be addressed.

12 References

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13 Appendix

13.1 Recruitment graphs by country

13.1.1 Recruitment in Denmark

Figure 13-1 Number recruited in Denmark by route of recruitment

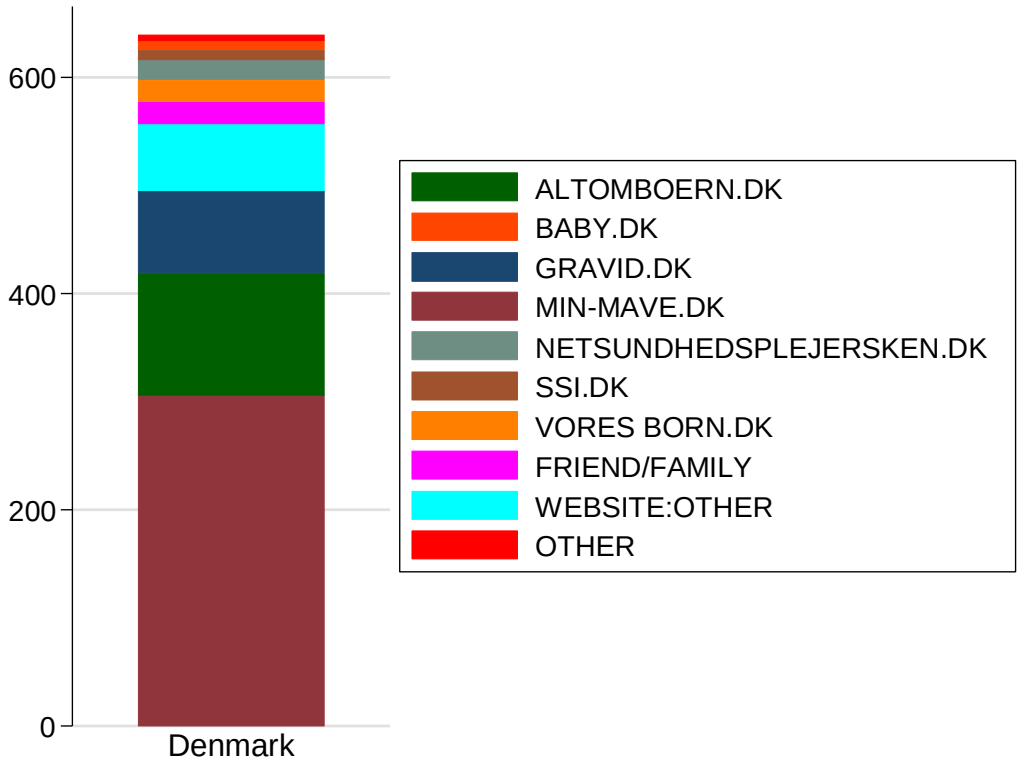
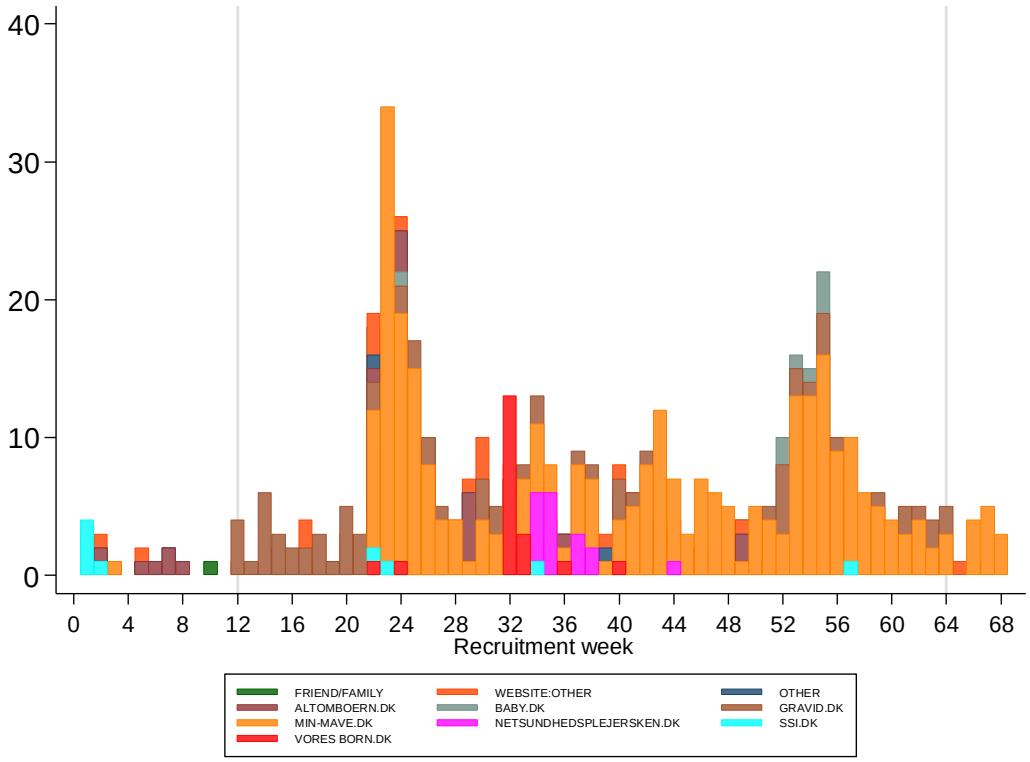


Figure 13-2 Known recruitment routes in Denmark by week



13.1.2 Recruitment in the Netherlands

Figure 13-3 Stacked bar graph of total number recruited in the Netherlands

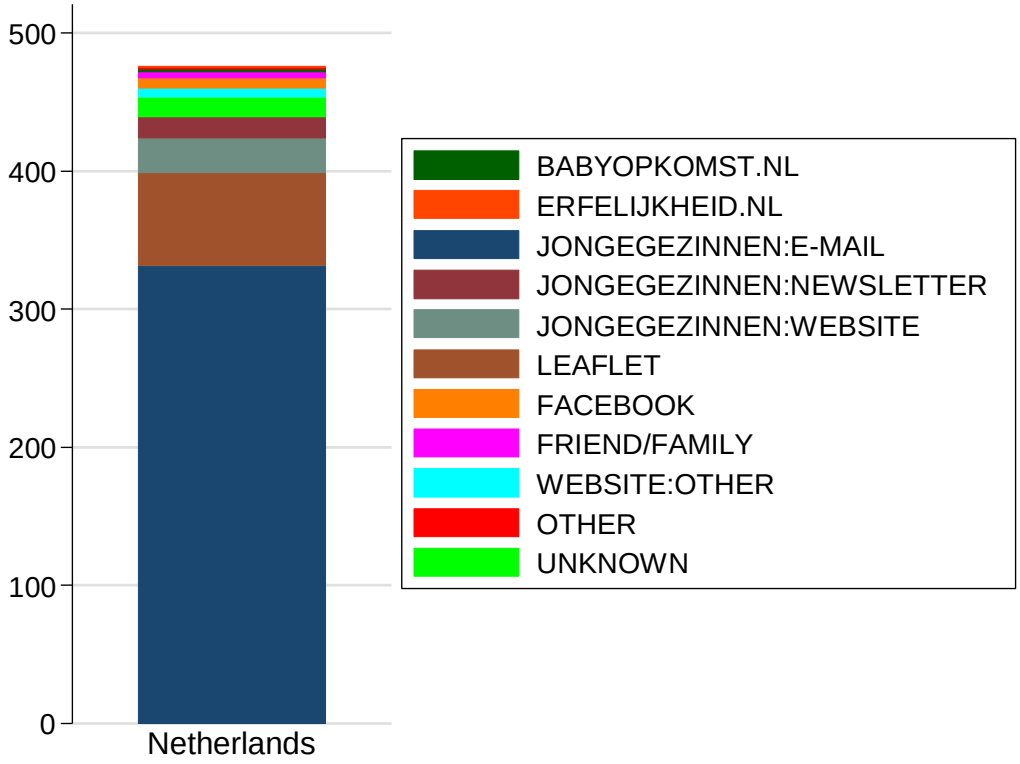
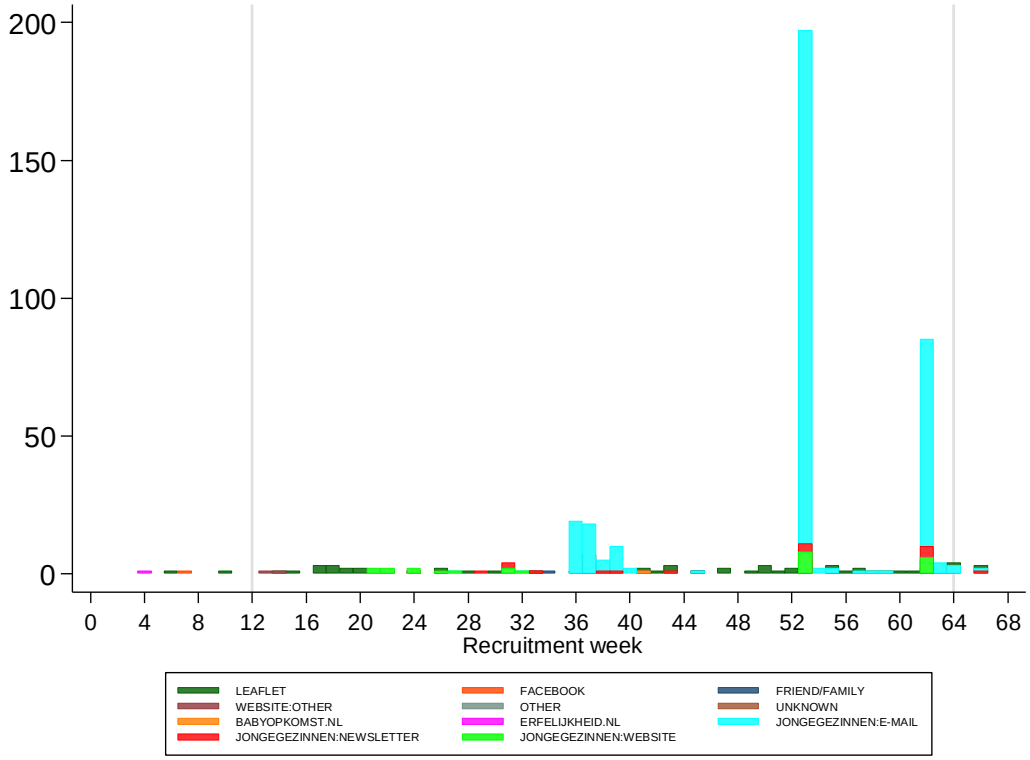


Figure 13-4 Known recruitment routes in the Netherlands by week



13.1.3 Recruitment in Poland

Figure 13-5 Stacked bar graph of total number recruited in the Poland

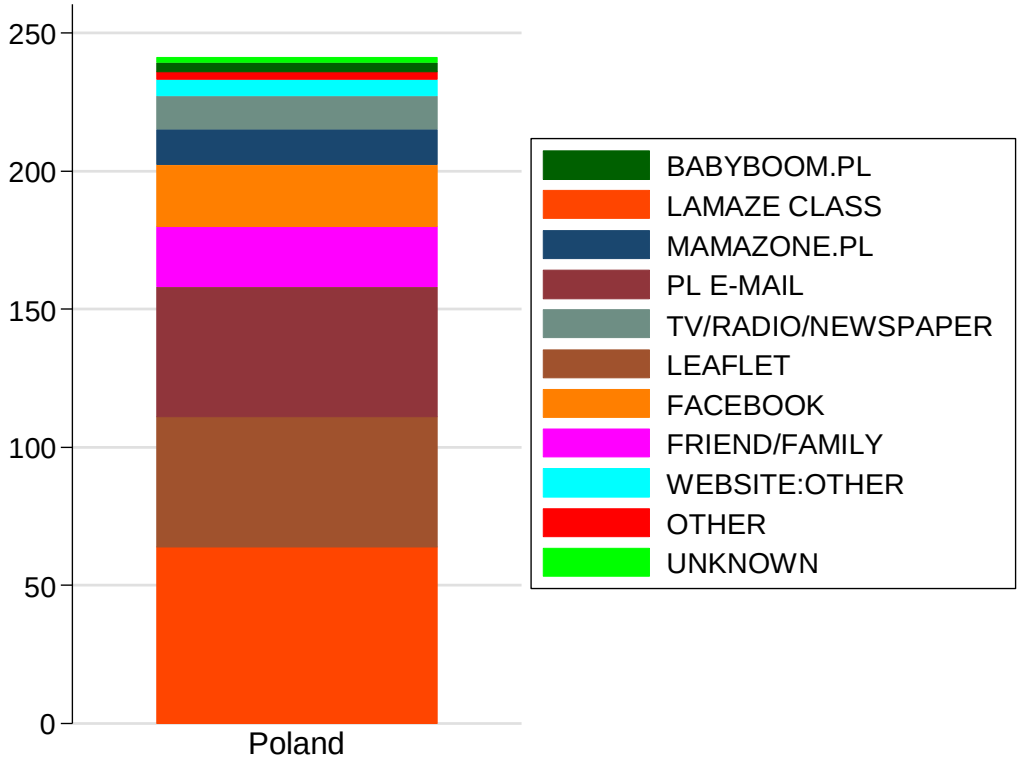
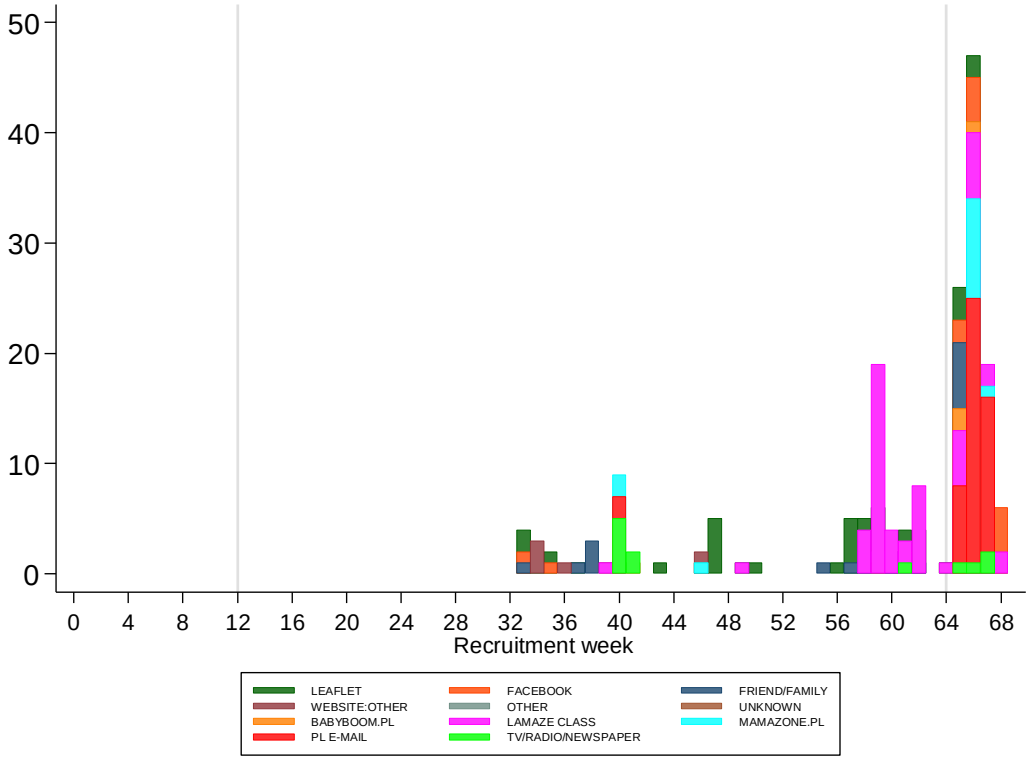


Figure 13-6 Known recruitment routes in the Poland by week



13.1.4 Recruitment in the United Kingdom

Figure 13-7 Stacked bar graph of total number recruited in the United Kingdom

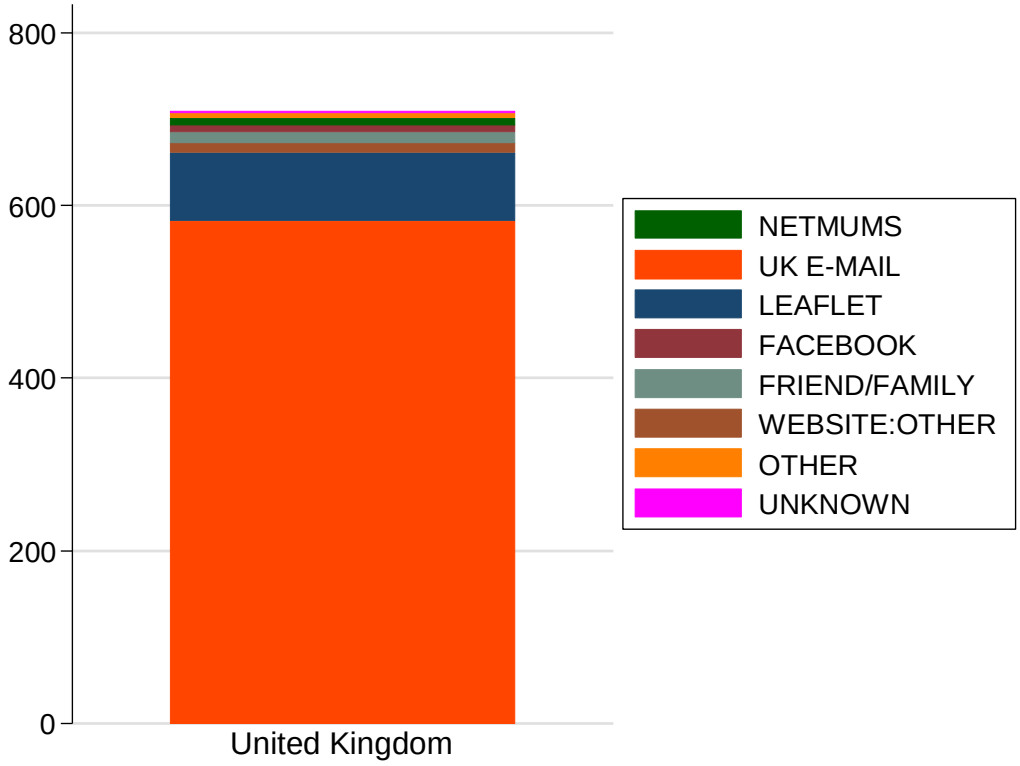
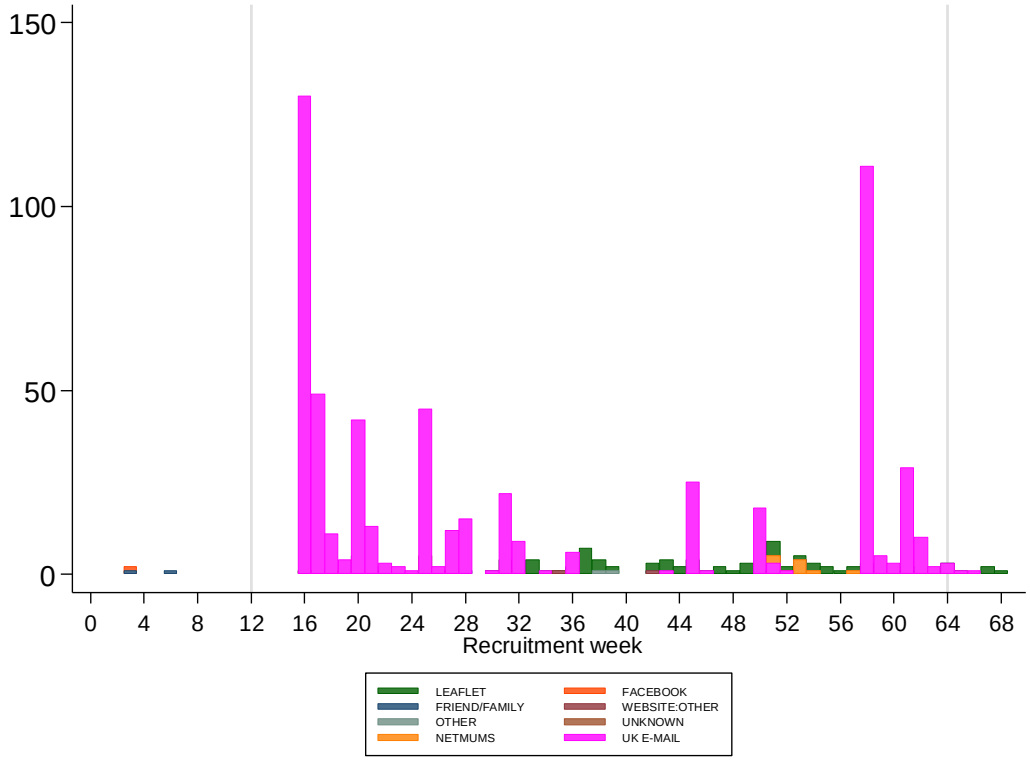
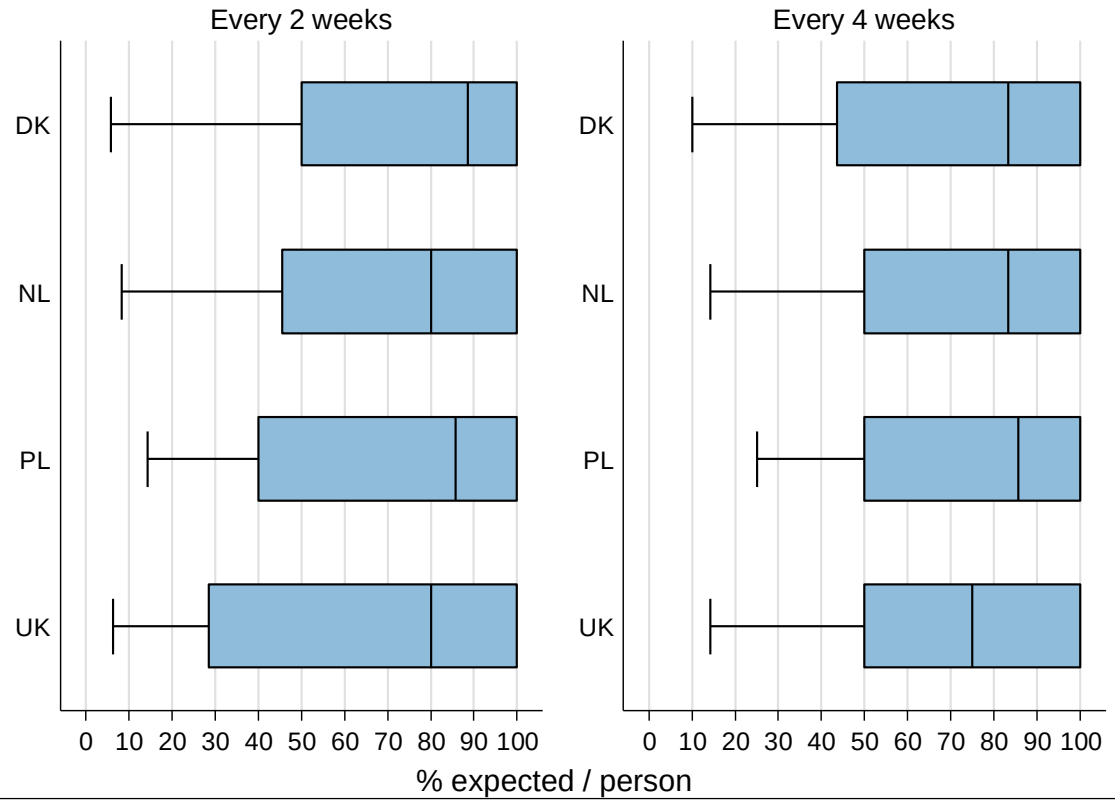


Figure 13-8 Known recruitment routes in the United Kingdom by week



13.2 Retention and adherence



Note: Vertical lines in the middle of the box indicates the medians (50th percentile). The left end of the box is the 25th percentile and the right end of the box is the 75th percentile. The horizontal line on the left end of each box is the bottom 25% of participants.

Figure 13-9 Box plot of adherence to frequency for participants with at least one follow-up questionnaire or end of pregnancy form

Table 13-1 Hazard ratio (HR) estimates of not completing the study by interactions between study sites, trimester at recruitment and chosen frequency from analysis in Section 4.2.1

	Denmark	Netherlands	Poland	United Kingdom
First trimester	1.00	1.00	1.00	1.00
Second trimester	1.00	0.47 (0.20,1.09)	0.85 (0.09,8.44)	0.70 (0.36,1.38)
Third trimester	1.00	1.06 (0.43,2.58)	2.80 (0.33,23.38)	0.64 (0.30,1.35)
4-weekly				
First trimester	1.00	0.64 (0.25,1.68)	2.45 (0.27,22.16)	0.70 (0.30,1.66)
Second trimester	0.92 (0.55,1.52)	1.35 (0.79,2.31)	1.71 (0.50,5.86)	0.73 (0.47,1.14)
Third trimester	1.19 (0.64,2.20)	0.99 (0.54,1.80)	1.45 (0.71,2.95)	1.27 (0.73,2.20)

Table 13-2 Table of interactions between study sites, trimester at recruitment and chosen frequency from analysis in Section 4.2.2

	Denmark	Netherlands	Poland	United Kingdom
First trimester	1.00	1.00	1.00	1.00
Second trimester	1.00	1.63 (0.87,3.06)	2.17 (1.21,3.92)	1.60 (1.02,2.53)
Third trimester	1.00	1.56 (0.77,3.19)	2.34 (1.30,4.22)	2.33 (1.41,3.84)
4-weekly				
First trimester	1.00	1.25 (0.62,2.49)	1.46 (0.65,3.30)	1.94 (1.20,3.13)
Second trimester	1.37 (1.06,1.79)	1.04 (0.80,1.35)	0.85 (0.53,1.36)	1.31 (1.04,1.66)

Third trimester	0.96 (0.62,1.49)	0.94 (0.56,1.60)	1.11 (0.74,1.66)	0.99 (0.70,1.40)

Table 13-3 Odds ratio of being certain not to return a follow-up questionnaire from analysis in Section 4.2.2

	Log(odds)	Odds ratio
4-weekly	0.45 (0.25,0.65)	1.56 (1.28, 1.91)
Joined too close to due date	0.82 (0.21,1.43)	2.26 (1.23,4.16)
2-weekly and sufficient time to provide a follow-up (constant)	-0.60 (-0.75,-0.45)	0.55 (0.47, 0.64)

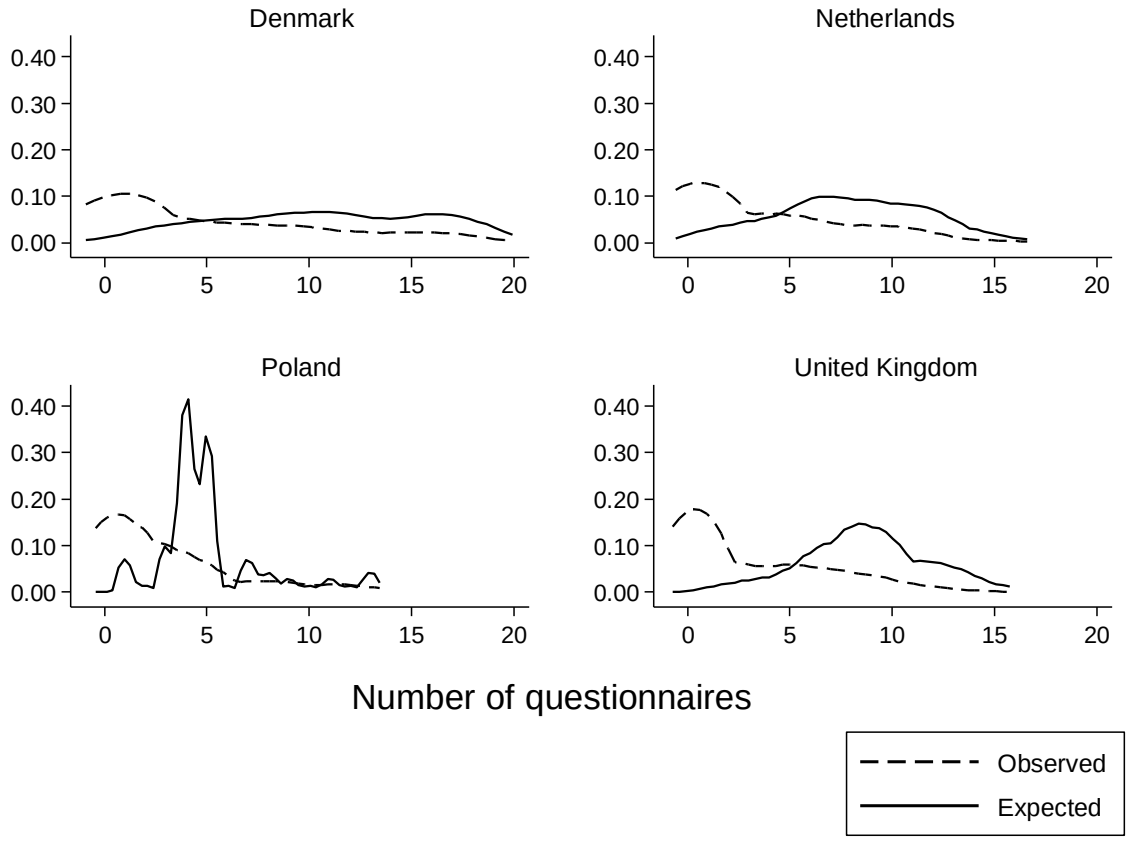


Figure 13-10 Density plots of actual versus expected number of follow-up questionnaires (including end of pregnancy) for participants who chose 2-weekly frequency

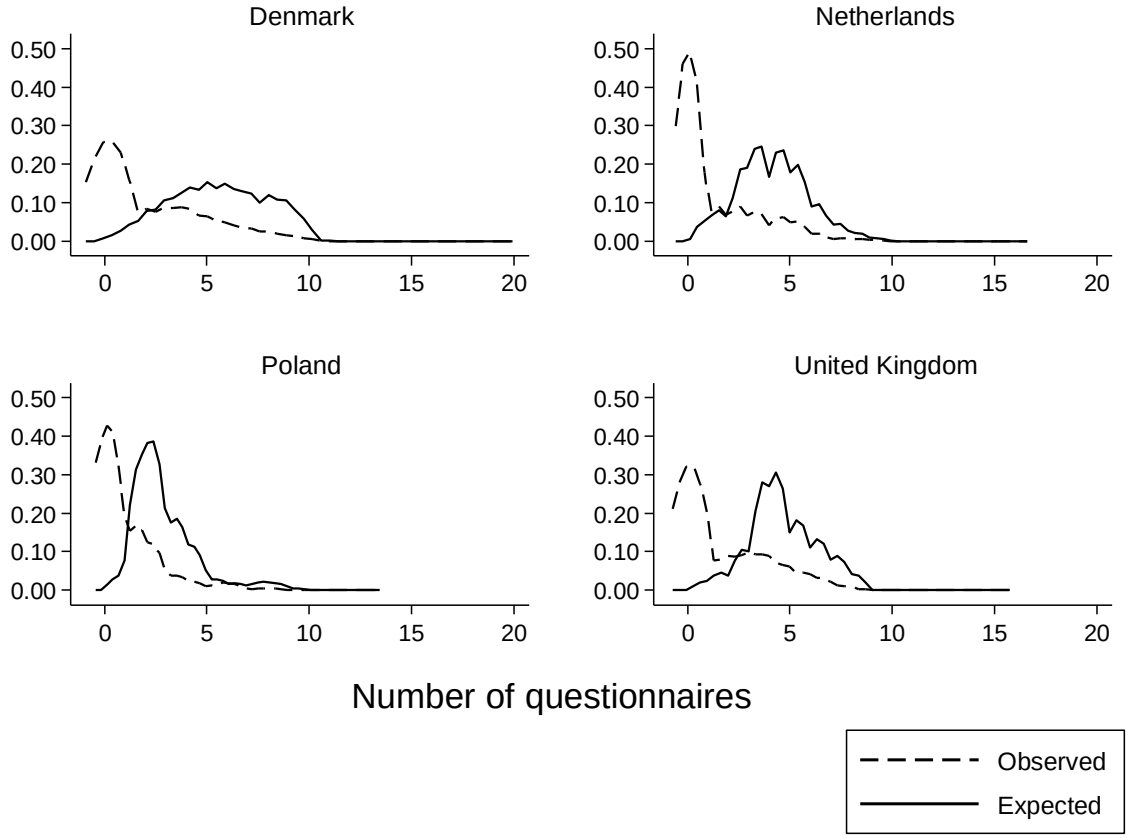


Figure 13-11 Density plots of actual versus expected number of follow-up questionnaires (including end of pregnancy) for participants who chose 4-weekly frequency

Table 13-4 Subgroup adherence, by interactions between study sites, trimester at recruitment and chosen frequency from analysis in Section 4.2.3

	Denmark	Netherlands	Poland	United Kingdom
First trimester	1.00	1.00	1.00	1.00
Second trimester	1.00	0.72 (0.54,0.97)	0.66 (0.44,1.00)	0.79 (0.64,0.97)
Third trimester	1.00	0.94 (0.65,1.37)	0.89 (0.58,1.38)	0.79 (0.58,1.07)
4-weekly				
First trimester	1.00	0.76 (0.56,1.04)	0.87 (0.60,1.25)	0.68 (0.54,0.86)
Second trimester	0.80 (0.66,0.97)	0.92 (0.76,1.11)	1.10 (0.81,1.49)	0.75 (0.64,0.87)
Third trimester	0.92 (0.69,1.23)	0.84 (0.66,1.08)	0.76 (0.56,1.04)	0.91 (0.72,1.16)

13.3 Demographics

13.3.1 Age of participants

Women were asked to provide their age at screening, and also to provide their date of birth in the baseline questionnaire. There are some discrepancies in the age calculated from the date of birth and the one provided at screening (Figure 13-12). This was as large as 7.9 years. For the purpose of analysis, we assumed that the calculated

age is more accurate. This assumption is based on the rationales that women would better provide the date of birth than stating their age, and that those who completed the baseline questionnaires would become more determine to provide better responses.

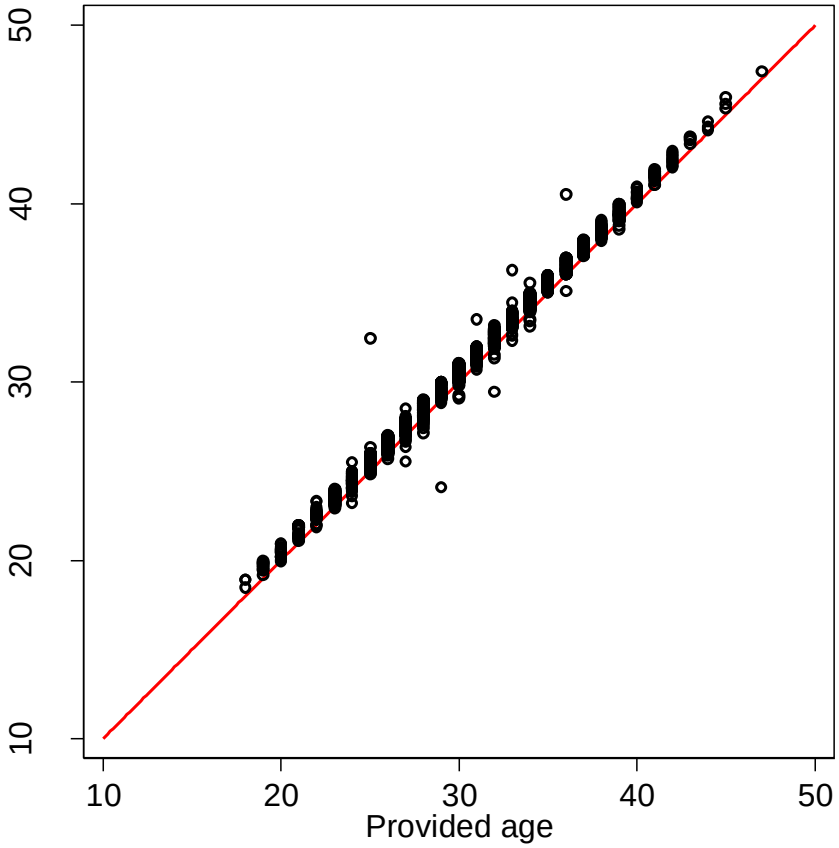


Figure 13-12 Discrepancy in age

13.3.2 Birth defects in blood relatives

Table 13-5 Birth defects in family at level 1

Birth defects in blood relatives Baseline_XX1:brthdeft] Baseline_XX1:deftdetl]	Denmark	Netherlands	Poland	United Kingdom
Relatives have known birth defects*	5.0% (32)	9.2% (44)	8.3% (20)	7.8% (55)
D66: Hereditary factor VIII deficiency			0.4% (1)	
E75: Disorders of sphingolipid metabolism and other lipid storage disorders				
E84: Cystic fibrosis				
F79: Unspecified intellectual disabilities	0.2% (1)			
F84: Pervasive developmental disorders	0.2% (1)			
H52: Disorders of refraction and accommodation			0.4% (1)	
I34: Nonrheumatic mitral valve disorders			0.4% (1)	
I42: Cardiomyopathy				0.1% (1)
I45: Other conduction disorders				0.3% (2)
I49: Other cardiac arrhythmias		0.2% (1)	0.4% (1)	
K40: Inguinal hernia	0.2% (1)			
P22: Respiratory distress of newborn		0.2% (1)		
Q00: Anencephaly and similar malformations				0.1% (1)
Q01: Encephalocele	0.2% (1)			
Q04: Other congenital malformations of brain	0.2% (1)			
Q05: Spina bifida		1.5% (7)	0.4% (1)	0.7% (5)
Q12: Congenital lens malformations	0.2% (1)			
Q16: Congenital malformations of ear causing impairment of hearing	0.2% (1)			
Q20: Congenital malformations of cardiac chambers and connections		0.2% (1)		
Q21: Congenital malformations of cardiac septa	0.5% (3)	1.5% (7)	1.7% (4)	1.3% (9)
Q22: Congenital malformations of pulmonary and tricuspid valves			0.4% (1)	0.3% (2)
Q24: Other congenital malformations of heart	0.6% (4)	0.8% (4)	2.5% (6)	1.1% (8)
Q25: Congenital malformations of great arteries		0.4% (2)		0.1% (1)
Q35: Cleft palate	0.3% (2)	1.9% (9)	0.8% (2)	0.4% (3)
Q36: Cleft lip				0.1% (1)
Q37: Cleft palate with cleft lip	0.3% (2)			0.3% (2)
Q40: Other congenital malformations of upper alimentary tract				0.4% (3)
Q43: Other congenital malformations of intestine	0.2% (1)			0.1% (1)
Q53: Undescended and ectopic testicle				0.1% (1)
Q54: Hypospadias		0.4% (2)		
Q55: Other congenital malformations of male genital organs				0.1% (1)
Q60: Renal agenesis and other reduction defects of kidney		0.2% (1)		
Q63: Other congenital malformations of kidney	0.2% (1)	0.2% (1)		0.3% (2)
Q65: Congenital deformities of hip	0.3% (2)	1.0% (5)		0.6% (4)
Q66: Congenital deformities of feet		0.4% (2)		0.1% (1)
Q68: Other congenital musculoskeletal deformities	0.2% (1)			0.3% (2)
Q69: Polydactyly			0.4% (1)	0.4% (3)
Q70: Syndactyly	0.2% (1)			
Q71: Reduction defects of upper limb	0.5% (3)			
Q75: Other congenital malformations of skull and face bones	0.2% (1)			
Q76: Congenital malformations of spine and bony thorax		0.2% (1)		0.1% (1)
Q78: Other osteochondrodysplasias				0.1% (1)
Q82: Other congenital malformations of skin				0.1% (1)

Q87: Other specified congenital malformation syndromes affecting multiple systems			0.4% (1)	
Q89: Other congenital malformations, not elsewhere classified	0.5% (3)	0.2% (1)		
Q90: Down syndrome	0.2% (1)			0.6% (4)
Q95: Balanced rearrangements and structural markers, not elsewhere classified	0.2% (1)			
Q96: Turner's syndrome	0.2% (1)			
Q99: Other chromosome abnormalities, not elsewhere classified	0.2% (1)			

Note: The total number represents number of participants (women). The ICD10 codes represent blood relatives with birth defects, and may be greater than the number of the number of participants.

Birth defects in blood relatives Baseline_XX1:brthdeft] Baseline_XX1:deftdetl]	Denmark	Netherlands	Poland	United Kingdom
Relatives have known birth defects*	5.0% (32)	9.2% (44)	8.3% (20)	7.8% (55)
D66: Hereditary factor VIII deficiency			**0.4% (1)**	
D66: Hereditary factor VIII deficiency			0.4% (1)	
E75: Disorders of sphingolipid metabolism and other lipid storage disorders		**0.2% (1)**		
E75.3: Sphingolipidosis, unspecified		0.2% (1)		
E84: Cystic fibrosis	**0.2% (1)**			**0.1% (1)**
E84.9: Cystic fibrosis, unspecified	0.2% (1)			0.1% (1)
F79: Unspecified intellectual disabilities	**0.2% (1)**			
F79: Unspecified intellectual disabilities	0.2% (1)			
F84: Pervasive developmental disorders	**0.2% (1)**			
F84.0: Autistic disorder	0.2% (1)			
H52: Disorders of refraction and accommodation			**0.4% (1)**	
H52.2: Astigmatism			0.4% (1)	
I34: Nonrheumatic mitral valve disorders			**0.4% (1)**	
I34.1: Nonrheumatic mitral (valve) prolapse			0.4% (1)	
I42: Cardiomyopathy				**0.1% (1)**
I42.9: Cardiomyopathy, unspecified				0.1% (1)
I45: Other conduction disorders				**0.3% (2)**
I45.8: Other specified conduction disorders				0.3% (2)
I49: Other cardiac arrhythmias		**0.2% (1)**	**0.4% (1)**	
I49.9: Cardiac arrhythmia, unspecified		0.2% (1)	0.4% (1)	
K40: Inguinal hernia	**0.2% (1)**			
K40: Inguinal hernia	0.2% (1)			
P22: Respiratory distress of newborn		**0.2% (1)**		
P22.9: Respiratory distress of newborn, unspecified		0.2% (1)		
Q00: Anencephaly and similar malformations				**0.1% (1)**
Q00.0: Anencephaly				0.1% (1)
Q01: Encephalocele	**0.2% (1)**			
Q01.9: Encephalocele, unspecified	0.2% (1)			
Q04: Other congenital malformations of brain	**0.2% (1)**			
Q04.0: Congenital malformations of corpus callosum	0.2% (1)			
Q05: Spina bifida		**1.5% (7)**	**0.4% (1)**	**0.7% (5)**
Q05.9: Spina bifida, unspecified		1.5% (7)	0.4% (1)	0.7% (5)
Q12: Congenital lens malformations	**0.2% (1)**			
Q12.0: Congenital cataract	0.2% (1)			
Q16: Congenital malformations of ear causing impairment of hearing	**0.2% (1)**			
Q16.9: Congenital malformation of ear causing impairment of hearing, unspecified	0.2% (1)			

Q20: Congenital malformations of cardiac chambers and connections		**0.2% (1)**		
Q20.9: Congenital malformation of cardiac chambers and connections, unspecified		0.2% (1)		
Q21: Congenital malformations of cardiac septa	**0.5% (3)**	**1.5% (7)**	**1.7% (4)**	**1.3% (9)**
Q21.0: Ventricular septal defect		0.6% (3)	0.4% (1)	0.1% (1)
Q21.1: Atrial septal defect		0.2% (1)	1.2% (3)	
Q21.3: Tetralogy of Fallot		0.4% (2)		0.1% (1)
Q21.9: Congenital malformation of cardiac septum, unspecified	0.5% (3)	0.2% (1)		1.0% (7)
Q22: Congenital malformations of pulmonary and tricuspid valves			**0.4% (1)**	**0.3% (2)**
Q22.0: Pulmonary valve atresia				0.3% (2)
Q22.8: Other congenital malformations of tricuspid valve			0.4% (1)	
Q24: Other congenital malformations of heart	**0.6% (4)**	**0.8% (4)**	**2.5% (6)**	**1.1% (8)**
Q24.6: Congenital heart block				0.1% (1)
Q24.8: Other specified congenital malformations of heart	0.3% (2)		2.1% (5)	
Q24.9: Congenital malformation of heart, unspecified	0.3% (2)	0.8% (4)	0.4% (1)	1.0% (7)
Q25: Congenital malformations of great arteries		**0.4% (2)**		**0.1% (1)**
Q25.1: Coarctation of aorta		0.2% (1)		0.1% (1)
Q25.6: Stenosis of pulmonary artery		0.2% (1)		
Q35: Cleft palate	**0.3% (2)**	**1.9% (9)**	**0.8% (2)**	**0.4% (3)**
Q35.9: Cleft palate, unspecified	0.3% (2)	0.8% (4)	0.8% (2)	0.4% (3)
Q35-Q37: Cleft palate		1.0% (5)		
Q36: Cleft lip				**0.1% (1)**
Q36: Cleft lip				0.1% (1)
Q37: Cleft palate with cleft lip	**0.3% (2)**			**0.3% (2)**
Q37: Cleft palate with cleft lip	0.3% (2)			0.3% (2)
Q40: Other congenital malformations of upper alimentary tract				**0.4% (3)**
Q40.0: Congenital hypertrophic pyloric stenosis				0.4% (3)
Q43: Other congenital malformations of intestine	**0.2% (1)**			**0.1% (1)**
Q43.1: Hirschsprung's disease				0.1% (1)
Q43.9: Congenital malformation of intestine, unspecified	0.2% (1)			
Q53: Undescended and ectopic testicle				**0.1% (1)**
Q53.2: Undescended testicle, bilateral				0.1% (1)
Q54: Hypospadias		**0.4% (2)**		
Q54.9: Hypospadias, unspecified		0.4% (2)		
Q55: Other congenital malformations of male genital organs				**0.1% (1)**
Q55.9: Congenital malformation of male genital organ, unspecified				0.1% (1)
Q60: Renal agenesis and other reduction defects of kidney		**0.2% (1)**		
Q60.0: Renal agenesis, unilateral		0.2% (1)		
Q63: Other congenital malformations of kidney	**0.2% (1)**	**0.2% (1)**		**0.3% (2)**
Q63.1: Lobulated, fused and horseshoe kidney		0.2% (1)		
Q63.9: Congenital malformation of kidney, unspecified	0.2% (1)			0.3% (2)
Q65: Congenital deformities of hip	**0.3% (2)**	**1.0% (5)**		**0.6% (4)**
Q65.9: Congenital deformity of hip, unspecified	0.3% (2)	1.0% (5)		0.6% (4)
Q66: Congenital deformities of feet		**0.4% (2)**		**0.1% (1)**
Q66.0: Congenital talipes equinovarus		0.4% (2)		0.1% (1)
Q68: Other congenital musculoskeletal deformities	**0.2% (1)**			**0.3% (2)**
Q68.1: Congenital deformity of finger(s) and hand	0.2% (1)			0.1% (1)
Q68.8: Other specified congenital musculoskeletal deformities				0.1% (1)

Q69: Polydactyly			**0.4% (1)**	**0.4% (3)**
Q69.0: Accessory finger(s)			0.4% (1)	0.1% (1)
Q69.2: Accessory toe(s)				0.1% (1)
Q69.9: Polydactyly, unspecified				0.1% (1)
Q70: Syndactyly	**0.2% (1)**			
Q70.9: Syndactyly, unspecified	0.2% (1)			
Q71.2: Congenital absence of both forearm and hand	0.2% (1)			
Q71: Reduction defects of upper limb	**0.5% (3)**			
Q71.3: Congenital absence of hand and finger	0.3% (2)			
Q75: Other congenital malformations of skull and face bones	**0.2% (1)**			
Q75.4: Mandibulofacial dysostosis	0.2% (1)			
Q76: Congenital malformations of spine and bony thorax		**0.2% (1)**		**0.1% (1)**
Q76.0: Spina bifida occulta		0.2% (1)		0.1% (1)
Q78: Other osteochondrodysplasias				**0.1% (1)**
Q78.8: Other specified osteochondrodysplasias				0.1% (1)
Q82: Other congenital malformations of skin				**0.1% (1)**
Q82.0: Hereditary lymphedema				0.1% (1)
Q87: Other specified congenital malformation syndromes affecting multiple systems			**0.4% (1)**	
Q87.4: Marfan's syndrome			0.4% (1)	
Q89: Other congenital malformations, not elsewhere classified	**0.5% (3)**	**0.2% (1)**		
Q89.2: Congenital malformations of other endocrine glands		0.2% (1)		
Q89.4: Conjoined twins	0.2% (1)			
Q89.9: Congenital malformation, unspecified	0.3% (2)			
Q90: Down syndrome	**0.2% (1)**			**0.6% (4)**
Q90.9: Down syndrome, unspecified	0.2% (1)			0.6% (4)
Q95: Balanced rearrangements and structural markers, not elsewhere classified	**0.2% (1)**			
Q95.9: Balanced rearrangement and structural marker, unspecified	0.2% (1)			
Q96: Turner's syndrome	**0.2% (1)**			
Q96.3: Mosaicism, 45, X/46, XX or XY	0.2% (1)			
Q99: Other chromosome abnormalities, not elsewhere classified	**0.2% (1)**			
Q99.9: Chromosomal abnormality, unspecified	0.2% (1)			

13.4 Chronic medical conditions

Table 13-6 Percentage (number) of mothers by chronic medical conditions that required or not required medications

	DK	NL	PL	UK	All
Depression, anxiety or other mental illnesses (any)	6.9% (44)	3.8% (18)	1.7% (4)	5.5% (39)	5.1% (105)
Stomach and bowel problems (any)	3.9% (25)	6.1% (29)	5.4% (13)	7.9% (56)	6.0% (123)
Diabetes (Type I/II)	0.6% (4)	1.1% (5)	0.8% (2)	1.4% (10)	1.0% (21)
Arthritis, other disorders associated with immune dysfunction or immunosuppression (any)	2.0% (13)	0.8% (4)	1.7% (4)	3.0% (21)	2.0% (42)
High blood pressure or other conditions related to the heart (any)	1.3% (8)	1.3% (6)	2.1% (5)	2.5% (18)	1.8% (37)
Breathing or respiratory/chest disorders	5.8% (37)	5.7% (27)	2.9% (7)	9.6% (68)	6.7% (139)
Migraines	6.4% (41)	3.6% (17)	2.5% (6)	3.0% (21)	4.1% (85)

Epilepsy	0.8% (5)	0.4% (2)	0.4% (1)	0.4% (3)	0.5% (11)
HIV or AIDS	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Hepatitis	0.0% (0)	0.0% (0)	0.4% (1)	0.1% (1)	0.1% (2)
Any other diseases or conditions not listed above	6.7% (43)	5.3% (25)	5.0% (12)	5.2% (37)	5.7% (117)
None	70.3% (449)	77.9% (371)	77.6% (187)	72.6% (515)	73.7% (1522)
No information (Missing)	0.2% (1)	0.0% (0)	0.4% (1)	0.0% (0)	0.1% (2)

13.5 All medications

Table 13-7 Rates per 1000 women for each medication reported by ATC codes

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	559	460	523	838	628
A01 - Stomatological preparations	3	0	4	1	2
A01A - Stomatological preparations	3	0	4	1	2
A01AB - Antiinfectives for local oral treatment	2	0	0	0	0
A01AB03 - Chlorhexidine	2	0	0	0	0
A01AD - Other agents for local oral treatment	2	0	4	1	1
A01AD02 - Benzydamine	2	0	4	1	1
A02 - Drugs for acid related disorders	266	261	141	433	308
A02A - Antacids	183	176	79	42	121
A02AA - Magnesium compounds	59	15	0	18	28
A02AA04 - Magnesium hydroxide	59	13	0	0	21
A02AB - Aluminium compounds	0	11	21	0	5
A02AB01 - Aluminium oxide	0	0	21	0	2
A02AB02 - Aluminium hydroxide	0	11	0	0	2
A02AC - Calcium compounds	0	0	46	3	6
A02AC01 - Calcium carbonate	0	0	46	3	6
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	116	147	8	11	75
A02AD01 - Ordinary salt combinations	116	147	8	3	72
A02AD02 - Magaldrate	0	0	0	1	0
A02AF - Antacids with antiflatulents	0	0	0	1	0
A02AF01 - Magaldrate and antiflatulents	0	0	0	1	0
A02AH - Antacids with sodium bicarbonate	6	0	0	1	2
A02AX - Antacids, other combinations	0	2	0	7	3
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	83	84	62	391	186
A02BA - H2-receptor antagonists	2	2	46	39	20
A02BA02 - Ranitidine	2	2	46	39	20
A02BC - Proton pump inhibitors	45	46	8	51	43
A02BC01 - Omeprazole	23	42	0	38	30
A02BC02 - Pantoprazole	8	4	8	0	4
A02BC03 - Lansoprazole	13	0	0	10	7
A02BC04 - Rabeprazole	0	0	0	1	0
A02BC05 - Esomeprazole	2	0	0	1	1
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	36	36	8	300	123
A02BX02 - Sucralfate	0	2	0	0	0
A02BX13 - Alginic acid	36	34	4	300	123
A03 - Drugs for functional gastrointestinal disorders	25	25	79	44	38

A03A - Drugs for functional gastrointestinal disorders	3	4	71	8	13
A03AA - Synt anticholin,esters with tertiary amino group	0	2	0	8	3
A03AA04 - Mebeverine	0	2	0	7	3
A03AA07 - Dicycloverine	0	0	0	1	0
A03AD - Papaverine and derivatives	0	0	66	0	8
A03AD02 - Drotaverine	0	0	66	0	8
A03AX - Other drugs for functional gastrointestinal disorders	3	2	4	0	2
A03AX13 - Silicones	3	0	4	0	1
A03B - Belladonna and derivatives, plain	0	4	0	4	2
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	0	4	0	4	2
A03BB01 - Butylscopolamine	0	4	0	4	2
A03F - Propulsives	22	17	8	31	22
A03FA - Propulsives	22	17	8	31	22
A03FA01 - Metoclopramide	22	15	8	27	20
A03FA03 - Domperidone	0	2	0	4	2
A04 - Antiemetics and antinauseants	19	2	8	18	14
A04A - Antiemetics and antinauseants	19	2	8	18	14
A04AA - Serotonin (5ht3) antagonists	16	0	0	13	9
A04AA01 - Ondansetron	16	0	0	13	9
A04AD - Other antiemetics	0	0	4	0	0
A05 - Bile and liver therapy	0	2	8	1	2
A05A - Bile therapy	0	2	4	1	1
A05AA - Bile acid preparations	0	2	4	1	1
A05AA02 - Ursodeoxycholic acid	0	2	4	1	1
A06 - Drugs for constipation	95	111	58	154	115
A06A - Drugs for constipation	95	111	58	154	115
A06AA - Softeners, emollients	2	0	0	0	0
A06AA02 - Docusate sodium	2	0	0	0	0
A06AB - Contact laxatives	6	4	8	23	12
A06AB02 - Bisacodyl	3	4	4	6	4
A06AB06 - Senna glycosides	0	0	4	16	6
A06AB08 - Sodium picosulfate	3	0	0	1	1
A06AC - Bulk-forming laxatives	53	19	0	44	36
A06AC01 - Ispaghula (psylla seeds)	53	19	0	44	36
A06AD - Osmotically acting laxatives	30	78	37	85	61
A06AD11 - Lactulose	16	36	37	73	43
A06AD15 - Macrogol	0	0	0	8	3
A06AD19 - Magnesium citrate	0	0	0	1	0
A06AD61 - Lactulose, combinations	0	0	0	1	0
A06AD65 - Macrogol, combinations	14	42	0	0	14
A06AG - Enemas	5	6	0	0	3
A06AG11 - Laurilsulfate, incl combinations	5	6	0	0	3
A06AX - Other drugs for constipation	0	0	8	3	2
A06AX01 - Glycerol	0	0	8	3	2
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	31	11	83	34	33
A07A - Intestinal antiinfectives	0	4	8	0	2
A07AA - Antibiotics	0	4	8	0	2
A07AA02 - Nystatin	0	4	8	0	2
A07B - Intestinal adsorbents	0	0	4	1	1

A07BA - Charcoal preparations	0	0	4	0	0
A07BC - Other intestinal adsorbents	0	0	0	1	0
A07BC02 - Kaolin	0	0	0	1	0
A07C - Electrolytes with carbohydrates	0	2	4	3	2
A07CA - Oral rehydration salt formulations	0	2	4	3	2
A07D - Antipropulsives	6	2	8	17	9
A07DA - Antipropulsives	6	2	8	17	9
A07DA03 - Loperamide	5	2	8	17	9
A07DA53 - Loperamide, combinations	2	0	0	0	0
A07E - Intestinal antiinflammatory agents	11	2	4	13	9
A07EA - Corticosteroids acting locally	2	0	0	1	1
A07EA01 - Prednisolone	2	0	0	0	0
A07EA06 - Budesonide	0	0	0	1	0
A07EC - Aminosalicylic acid and similar agents	9	2	4	11	8
A07EC01 - Sulfasalazine	3	0	0	0	1
A07EC02 - Mesalazine	6	2	4	11	7
A07F - Antidiarrheal microorganisms	13	0	41	0	9
A07FA - Antidiarrheal microorganisms	13	0	41	0	9
A07FA01 - Lactic acid producing organisms	11	0	17	0	5
A07FA02 - Saccharomyces boulardii	0	0	4	0	0
A07X - Other antidiarrheals	0	0	12	0	1
A07XA - Other antidiarrheals	0	0	12	0	1
A09 - Digestives, incl enzymes	2	0	0	1	1
A09A - Digestives, incl enzymes	2	0	0	1	1
A09AA - Enzyme preparations	2	0	0	1	1
A09AA02 - Multienzymes (lipase, protease etc)	2	0	0	1	1
A10 - Drugs used in diabetes	28	19	37	78	44
A10A - Insulins and analogues	6	19	25	39	23
A10AB - Insulins and analogues for injection, fast-acting	3	15	25	25	16
A10AB01 - Insulin (human)	0	0	0	3	1
A10AB04 - Insulin lispro	0	4	4	3	2
A10AB05 - Insulin aspart	3	11	21	20	13
A10AC - Insulins and analogues for injection, intermediate-acting	2	2	0	4	2
A10AC01 - Insulin (human)	2	2	0	4	2
A10AD - Insulins and analogues for injection, intermed.act. comb. w. fast-act.	0	0	0	3	1
A10AD01 - Insulin (human)	0	0	0	1	0
A10AD05 - Insulin aspart	0	0	0	1	0
A10AE - Onsulins and analogues for injection, long-acting	2	0	0	7	3
A10AE04 - Insulin glargine	0	0	0	6	2
A10AE05 - Insulin detemir	2	0	0	1	1
A10B - Blood glucose lowering drugs, excl. insulins	22	0	12	38	21
A10BA - Biguanides	22	0	12	38	21
A10BA02 - Metformin	22	0	12	38	21
A12 - Mineral supplements	89	29	104	73	72
A12A - Calcium	56	8	17	69	45
A12AA - Calcium	33	4	4	63	33
A12AA04 - Calcium carbonate	0	0	4	56	20
A12AX - Calcium, combinations with vitamin d and/or other drugs	23	4	8	6	11

A12B - Potassium	0	0	4	0	0
A12BA - Potassium	0	0	4	0	0
A12BA01 - Potassium chloride	0	0	4	0	0
A12C - Other mineral supplements	25	21	58	4	21
A12CA - Sodium	0	2	0	0	0
A12CA01 - Sodium chloride	0	2	0	0	0
A12CB - Zinc	9	2	0	4	5
A12CB01 - Zinc sulphate	0	0	0	1	0
A12CC - Magnesium	3	11	50	0	9
A12CC05 - Magnesium aspartate	0	0	8	0	1
A12CE - Selenium	5	2	0	0	2
A12CX - Other mineral products	6	0	8	0	3
B - Blood and blood forming organs	27	23	50	58	39
B01 - Antithrombotic agents	23	23	41	55	36
B01A - Antithrombotic agents	23	23	41	55	36
B01AA - Vitamin k antagonists	0	2	0	0	0
B01AA07 - Acenocoumarol	0	2	0	0	0
B01AB - Heparin group	5	13	21	24	15
B01AB01 - Heparin	0	0	0	1	0
B01AB04 - Dalteparin	0	0	0	4	1
B01AB05 - Enoxaparin	2	0	17	14	7
B01AB06 - Nadroparin	0	13	4	0	3
B01AB10 - Tinzaparin	3	0	0	4	2
B01AC - Platelet aggregation inhibitors excl. heparin	19	8	21	31	21
B01AC06 - Acetylsalicylic acid	17	8	21	31	20
B01AC30 - Combinations	2	0	0	0	0
B02 - Antihemorrhagics	2	0	4	1	1
B02A - Antifibrinolytics	2	0	0	0	0
B02AA - Amino acids	2	0	0	0	0
B02AA02 - Tranexamic acid	2	0	0	0	0
B02B - Vitamin k and other hemostatics	0	0	4	1	1
B02BA - Vitamin k	0	0	0	1	0
B02BX - Other systemic hemostatics	0	0	4	0	0
B02BX01 - Etamsylate	0	0	4	0	0
B05 - Blood substitutes and perfusion solutions	2	0	0	1	1
B05B - I.v. solutions	2	0	0	0	0
B05BA - Solutions for parenteral nutrition	2	0	0	0	0
B05BA02 - Fat emulsions	2	0	0	0	0
B05X - I.v. solution additives	0	0	0	1	0
B05XB - Amino acids	0	0	0	1	0
B05XB03 - Lysine	0	0	0	1	0
C - Cardiovascular system	47	40	129	45	54
C01 - Cardiac therapy	0	0	0	1	0
C01C - Cardiac stimulants excl. cardiac glycosides	0	0	0	1	0
C01CA - Adrenergic and dopaminergic agents	0	0	0	1	0
C01CA24 - Epinephrine	0	0	0	1	0
C02 - Antihypertensives	3	6	37	3	8
C02A - Antiadrenergic agents, centrally acting	3	6	37	3	8
C02AA - Rauwolfia alkaloids	0	0	4	0	0

C02AA05 - Deserpidine	0	0	4	0	0
C02AB - Methyldopa	3	6	33	3	7
C02AB01 - Methyldopa (levorotatory)	3	6	33	3	7
C03 - Diuretics	2	0	0	3	1
C03A - Low-ceiling diuretics, thiazides	0	0	0	1	0
C03AA - Thiazides, plain	0	0	0	1	0
C03AA01 - Bendroflumethiazide	0	0	0	1	0
C03C - High-ceiling diuretics	2	0	0	0	0
C03CA - Sulfonamides, plain	2	0	0	0	0
C03CA01 - Furosemide	2	0	0	0	0
C03D - Potassium-sparing agents	0	0	0	1	0
C03DA - Aldosterone antagonists	0	0	0	1	0
C03DA01 - Spironolactone	0	0	0	1	0
C05 - Vasoprotectives	27	17	75	8	24
C05A - Agents for treatment of hemorrhoids and anal fissures for topical use	27	17	4	8	15
C05AA - Corticosteroids	25	4	0	0	9
C05AA01 - Hydrocortisone	8	0	0	0	2
C05AA08 - Fluocortolone	17	0	0	0	5
C05AA12 - Triamcinolone	0	2	0	0	0
C05AD - Local anesthetics	0	2	0	0	0
C05AD01 - Lidocaine	0	2	0	0	0
C05AE - Musclerelaxants	0	0	0	1	0
C05AE01 - Glyceryl trinitrate	0	0	0	1	0
C05AX - Other agents for treatment of hemorrhoids and anal fissures for topical use	0	6	4	7	4
C05AX04 - Zinc preparations	0	6	0	7	4
C05AX05 - Tribenoside	0	0	4	0	0
C05C - Capillary stabilizing agents	0	0	71	0	8
C05CA - Bioflavonoids	0	0	71	0	8
C05CA04 - Troxerutin	0	0	4	0	0
C05CA51 - Rutoside, combinations	0	0	66	0	8
C07 - Beta blocking agents	9	8	4	17	11
C07A - Beta blocking agents, plain	9	8	4	17	11
C07AA - Beta blocking agents, plain, non-selective	0	0	0	8	3
C07AA05 - Propranolol	0	0	0	8	3
C07AB - Beta blocking agents, plain, selective	2	2	4	4	3
C07AB02 - Metoprolol	2	2	4	0	1
C07AB03 - Atenolol	0	0	0	1	0
C07AB07 - Bisoprolol	0	0	0	3	1
C07AG - Alpha- and beta blocking agents	8	6	0	4	5
C07AG01 - Labetalol	8	6	0	4	5
C08 - Calcium channel blockers	0	6	4	6	4
C08C - Selective calcium channel blockers with mainly vascular effects	0	6	0	3	2
C08CA - Dihydropyridine derivatives	0	6	0	3	2
C08CA05 - Nifedipine	0	6	0	3	2
C08D - Selective calcium channel blockers with direct cardiac effects	0	0	4	3	1
C08DA - Phenylalkylamine derivatives	0	0	4	1	1
C08DA01 - Verapamil	0	0	4	1	1
C08DB - Benzothiazepine derivatives	0	0	0	1	0

C08DB01 - Diltiazem	0	0	0	1	0
C09 - Agents acting on the renin-angiotensin system	3	0	4	3	2
C09A - Ace-inhibitors, plain	2	0	0	3	1
C09AA - Ace-inhibitors, plain	2	0	0	3	1
C09AA04 - Perindopril	0	0	0	3	1
C09AA05 - Ramipril	2	0	0	0	0
C09C - Angiotensin ii antagonists	2	0	4	0	1
C09CA - Angiotensin ii antagonists, plain	2	0	4	0	1
C09CA01 - Losartan	2	0	4	0	1
C10 - Lipid modifying agents	2	2	4	4	3
C10A - Lipid modifying agents, plain	2	2	4	4	3
C10AA - Hmg coa reductase inhibitors	2	2	4	0	1
C10AA01 - Simvastatin	2	2	0	0	1
C10AA07 - Rosuvastatin	0	0	4	0	0
C10AC - Bile acid sequestrants	0	0	0	1	0
C10AC01 - Colestyramine	0	0	0	1	0
C10AX - Other lipid modifying agents	0	0	0	3	1
C10AX06 - Omega-3-triglycerides incl. other esters and acids	0	0	0	3	1
D - Dermatologicals	139	134	141	89	121
D01 - Antifungals for dermatological use	49	38	120	49	55
D01A - Antifungals for topical use	49	38	120	49	55
D01AA - Antibiotics	0	0	108	0	13
D01AA01 - Nystatin	0	0	54	0	6
D01AA02 - Natamycin	0	0	54	0	6
D01AC - Imidazole and triazole derivatives	44	32	12	49	39
D01AC01 - Clotrimazole	27	8	0	44	25
D01AC02 - Miconazole	6	23	0	1	8
D01AC15 - Fluconazole	0	0	0	1	0
D01AC20 - Combinations	11	0	0	1	4
D01AC52 - Miconazole, combinations	0	0	0	1	0
D01AE - Other antifungals for topical use	5	6	0	0	3
D01AE12 - Salicylic acid	0	2	0	0	0
D01AE13 - Selenium sulfide	0	2	0	0	0
D01AE15 - Terbinafine	5	2	0	0	2
D02 - Emollients and protectives	0	6	0	1	2
D02A - Emollients and protectives	0	6	0	1	2
D02AC - Soft paraffin and fat products	0	2	0	0	0
D02AF - Salicylic acid preparations	0	0	0	1	0
D02AX - Other emollients and protectives	0	2	0	0	0
D04 - Antipruritics,incl antihist,anesthet,etc.	0	0	0	3	1
D04A - Antipruritics,incl antihist,anesthet,etc.	0	0	0	3	1
D04AA - Antihistamines for topical use	0	0	0	3	1
D04AA02 - Mepyramine	0	0	0	1	0
D05 - Antipsoriatics	2	0	0	3	1
D05A - Antipsoriatics for topical use	2	0	0	3	1
D05AX - Other antipsoriatics for topical use	2	0	0	3	1
D05AX05 - Tazarotene	0	0	0	1	0
D05AX52 - Calcipotriol, combinations	2	0	0	1	1
D06 - Antibiotics and chemother. for dermatological use	52	53	8	7	31

D06A - Antibiotics for topical use	8	2	0	3	4
D06AX - Other antibiotics for topical use	8	2	0	3	4
D06AX01 - Fusidic acid	6	2	0	3	3
D06AX09 - Mupirocin	2	0	0	0	0
D06B - Chemotherapeutics for topical use	44	48	8	4	27
D06BB - Antivirals	39	48	8	1	25
D06BB03 - Aciclovir	36	48	0	0	22
D06BB11 - Docosanol	0	0	4	1	1
D06BB53 - Aciclovir, combinations	3	0	0	0	1
D06BX - Other chemotherapeutics	5	0	0	3	2
D06BX01 - Metronidazole	5	0	0	3	2
D07 - Corticosteroids, dermatological preparations	30	29	8	18	23
D07A - Corticosteroids, plain	27	21	4	16	19
D07AA - Corticosteroids, weak (group i)	8	4	0	7	6
D07AA02 - Hydrocortisone	8	4	0	6	5
D07AB - Corticosteroids, moderately potent (group ii)	11	13	4	3	8
D07AB01 - Clobetasone	0	4	0	1	1
D07AB02 - Hydrocortisone butyrate	11	0	0	1	4
D07AB09 - Triamcinolone	0	8	0	0	2
D07AB10 - Alclometasone	0	0	4	0	0
D07AC - Corticosteroids, potent (group iii)	8	2	0	6	5
D07AC01 - Betamethasone	3	0	0	4	2
D07AC03 - Desoximetasone	0	2	0	0	0
D07AC13 - Mometasone	5	0	0	0	1
D07B - Corticosteroids, comb with antiseptics	0	0	0	1	0
D07BC - Corticosteroids, potent, comb with antiseptics	0	0	0	1	0
D07BC01 - Betamethasone and antiseptics	0	0	0	1	0
D07C - Corticosteroids, comb with antibiotics	3	0	4	0	1
D07CA - Corticosteroids, weak, comb with antibiotics	0	0	4	0	0
D07CC - Corticosteroids, potent, comb with antibiotics	3	0	0	0	1
D07CC01 - Betamethasone and antibiotics	3	0	0	0	1
D07X - Corticosteroids, other combinations	0	6	0	0	1
D07XA - Corticosteroids, weak, other combinations	0	4	0	0	1
D07XA01 - Hydrocortisone	0	4	0	0	1
D08 - Antiseptics and disinfectants	0	0	0	1	0
D08A - Antiseptics and disinfectants	0	0	0	1	0
D08AC - Biguanides and amidines	0	0	0	1	0
D08AC02 - Chlorhexidine	0	0	0	1	0
D09 - Medicated dressings	0	0	0	1	0
D09A - Medicated dressings	0	0	0	1	0
D09AA - Ointment dressings with antiinfectives	0	0	0	1	0
D09AA12 - Chlorhexidine	0	0	0	1	0
D10 - Anti-acne preparations	5	4	4	3	4
D10A - Anti-acne preparations for topical use	5	4	4	3	4
D10AD - Retinoids for topical use in acne	0	4	0	0	1
D10AD03 - Adapalene	0	4	0	0	1
D10AE - Peroxides	2	0	4	0	1
D10AE01 - Benzoyl peroxide	2	0	4	0	1
D10AF - Antiinfectives for treatment of acne	2	0	0	1	1

D10AF02 - Erythromycin	0	0	0	1	0
D10AF51 - Clindamycin, comb.	2	0	0	0	0
D10AX - Other anti-acne preparations for topical use	2	0	0	1	1
D10AX03 - Azelaic acid	2	0	0	1	1
D11 - Other dermatological preparations	3	0	0	1	1
D11A - Other dermatological preparations	3	0	0	1	1
D11AF - Wart and anti-corn preparations	2	0	0	0	0
D11AH - Agents for dermatitis, excluding corticosteroids	2	0	0	1	1
D11AH01 - Tacrolimus	2	0	0	1	1
G - Genito urinary system and sex hormones	380	319	402	206	309
G01 - Gynecological antiinfectives and antiseptics	131	50	129	25	76
G01A - Antiinfectives/antisept.,excl comb with corticost.	131	50	129	25	76
G01AA - Antibiotics	0	0	25	0	3
G01AA01 - Nystatin	0	0	8	0	1
G01AA02 - Natamycin	0	0	4	0	0
G01AA10 - Clindamycin	0	0	4	0	0
G01AA51 - Nystatin, combinations	0	0	4	0	0
G01AF - Imidazole derivatives	131	50	79	25	70
G01AF01 - Metronidazole	6	0	0	0	2
G01AF02 - Clotrimazole	99	21	50	25	50
G01AF04 - Miconazole	27	2	0	0	9
G01AF05 - Econazole	0	0	8	0	1
G01AF15 - Butoconazole	0	0	8	0	1
G01AX - Other antiinfectives and antiseptics	0	0	25	0	3
G01AX05 - Nifuratel	0	0	8	0	1
G01AX14 - Lactobacillus fermentum	0	0	17	0	2
G02 - Other gynecologicals	5	19	33	3	11
G02B - Contraceptives for topical use	5	13	0	3	5
G02BA - Intrauterine contraceptives	3	6	0	3	3
G02BA02 - Plastic iud with copper	2	6	0	0	2
G02BA03 - Plastic iud with progesterone	2	0	0	3	1
G02BB - Intravaginal contraceptives	2	6	0	0	2
G02BB01 - Vaginal ring with progestogen and estrogen	2	6	0	0	2
G02C - Other gynecologicals	0	6	33	0	5
G02CA - Sympathomimetics, labour repressants	0	0	4	0	0
G02CA03 - Fenoterol	0	0	4	0	0
G02CB - Prolactine inhibitors	0	0	29	0	3
G02CB01 - Bromocriptine	0	0	29	0	3
G02CX - Other gynecologicals	0	6	0	0	1
G02CX01 - Atosiban	0	6	0	0	1
G03 - Sex hormones and modulators of the genital system	244	250	232	176	221
G03A - Hormonal contraceptives for systemic use	36	55	33	104	63
G03AA - Progestogens and estrogens, fixed combinations	11	8	0	27	15
G03AA07 - Levonorgestrel and ethinylestradiol	2	2	0	4	2
G03AA09 - Desogestrel and ethinylestradiol	0	0	0	1	0
G03AA11 - Norgestimate and ethinylestradiol	2	0	0	0	0
G03AC - Progestogens	3	6	4	23	11
G03AC01 - Norethisterone	0	0	0	1	0
G03AC09 - Desogestrel	0	0	0	3	1

G03AD - Emergency contraceptives	3	21	8	13	11
G03B - Androgens	0	0	0	1	0
G03BA - 3-oxoandrosten (4) derivatives	0	0	0	1	0
G03BA03 - Testosterone	0	0	0	1	0
G03C - Estrogens	6	2	0	4	4
G03CA - Natural and semisynthetic estrogens, plain	6	2	0	4	4
G03CA03 - Estradiol	6	2	0	4	4
G03D - Progestogens	50	17	129	7	37
G03DA - Pregnen (4) derivatives	50	15	75	7	30
G03DA02 - Medroxyprogesterone	8	2	0	0	3
G03DA04 - Progesterone	42	13	75	7	27
G03DB - Pregnadien derivatives	0	0	54	0	6
G03DB01 - Dydrogesterone	0	0	54	0	6
G03DC - Estren derivatives	0	2	0	0	0
G03DC02 - Norethisterone	0	2	0	0	0
G03G - Gonadotropins and other ovulation stimulants	152	176	71	58	116
G03GA - Gonadotropins	124	134	21	37	84
G03GA01 - Chorionic gonadotropine	9	65	21	4	22
G03GA02 - Human menopausal gonadotrophin	17	8	0	14	12
G03GA04 - Urofollitrophin	0	4	0	0	1
G03GA05 - Follitropin alfa	19	19	0	0	10
G03GA06 - Follitropin beta	20	36	0	0	15
G03GA08 - Choriogonadotropin alfa	58	2	0	8	21
G03GB - Ovulation stimulants, synthetic	28	42	50	21	31
G03GB02 - Clomifene	28	42	50	21	31
G04 - Urologicals	0	0	8	1	1
G04B - Urologicals	0	0	8	1	1
G04BD - Drugs for urinary frequency and incontinence	0	0	0	1	0
G04BD04 - Oxybutynin	0	0	0	1	0
G04BX - Other urologicals	0	0	8	0	1
H - Systemic hormonal prep, excl sex hormones	44	69	112	44	58
H01 - Pituitary, hypothalamic hormones and analogues	5	6	0	4	4
H01B - Posterior pituitary lobe hormones	0	2	0	0	0
H01BB - Oxytocin and analogues	0	2	0	0	0
H01BB02 - Oxytocin	0	2	0	0	0
H01C - Hypothalamic hormones	5	4	0	4	4
H01CA - Gonadotrophin-releasing hormones	0	4	0	3	2
H01CA01 - Gonadorelin	0	4	0	1	1
H01CA02 - Nafarelin	0	0	0	1	0
H01CC - Anti gonadotropin releasing hormones	5	0	0	1	2
H01CC01 - Ganirelix	3	0	0	0	1
H01CC02 - Cetrorelix	2	0	0	1	1
H02 - Corticosteroids for systemic use	11	19	21	7	13
H02A - Corticosteroids for systemic use, plain	9	19	21	7	12
H02AB - Glucocorticoids	9	19	21	7	12
H02AB01 - Betamethasone	0	4	8	0	2
H02AB04 - Methylprednisolone	0	0	4	0	0
H02AB06 - Prednisolone	5	13	0	4	6
H02AB07 - Prednisone	5	0	8	1	3

H02AB08 - Triamcinolone	0	2	0	0	0
H02AB09 - Hydrocortisone	0	0	0	1	0
H03 - Thyroid therapy	28	44	91	32	41
H03A - Thyroid preparations	28	38	87	31	38
H03AA - Thyroid hormones	28	38	87	31	38
H03AA01 - Levothyroxine sodium	28	38	87	30	38
H03AA03 - Comb of levothyroxine and liothyronine	0	0	0	1	0
H03B - Antithyroid preparations	0	6	4	1	2
H03BA - Thiouracils	0	4	4	0	1
H03BA02 - Propylthiouracil	0	4	4	0	1
H03BB - Sulphur-containing imidazole derivatives	0	2	0	1	1
H03BB01 - Carbimazole	0	0	0	1	0
H03BB02 - Thiamazole	0	2	0	0	0
J - General antiinfectives for systemic use	235	103	241	385	257
J01 - Antibacterials for systemic use	197	95	183	291	204
J01A - Tetracyclines	3	2	4	0	2
J01AA - Tetracyclines	3	2	4	0	2
J01AA02 - Doxycycline	2	2	0	0	1
J01AA04 - Lymecycline	0	0	4	0	0
J01AA07 - Tetracycline	2	0	0	0	0
J01C - Beta-lactam antibacterials, penicillins	161	36	95	188	134
J01CA - Penicillins with extended spectrum	113	23	79	159	104
J01CA01 - Ampicillin	6	0	4	0	2
J01CA02 - Pivampicillin	6	0	0	0	2
J01CA04 - Amoxicillin	5	23	75	158	70
J01CA08 - Pivmecillinam	95	0	0	0	30
J01CA51 - Ampicillin, combinations	0	0	0	1	0
J01CE - Beta-lactamase sensitive penicillins	44	2	0	6	16
J01CE01 - Benzylpenicillin	0	0	0	4	1
J01CE02 - Phenoxymethylpenicillin	44	0	0	1	14
J01CE05 - Pheneticillin	0	2	0	0	0
J01CF - Beta-lactamase resistant penicillins	3	0	0	11	5
J01CF01 - Dicloxacillin	2	0	0	0	0
J01CF05 - Flucloxacillin	2	0	0	11	4
J01CR - Comb of penicillins, incl. beta-lactamase inhib.	0	11	17	10	8
J01CR02 - Amoxicillin and enzyme inhibitor	0	4	17	10	6
J01CR05 - Piperacillin and enzyme inhibitor	0	6	0	0	1
J01D - Other beta-lactam antibacterials	0	0	17	34	14
J01DB - First-generation cephalosporins	0	0	0	32	11
J01DB01 - Cefalexin	0	0	0	30	10
J01DB09 - Cefradine	0	0	0	3	1
J01DC - Second-generation cephalosporins	0	0	17	0	2
J01DC02 - Cefuroxime	0	0	17	0	2
J01DF - Monobactams	0	0	0	1	0
J01DF01 - Aztreonam	0	0	0	1	0
J01E - Sulfonamides and trimethoprim	14	2	0	7	7
J01EA - Trimethoprim and derivatives	0	2	0	7	3
J01EA01 - Trimethoprim	0	2	0	7	3
J01EB - Short-acting sulfonamides	14	0	0	0	4

J01EB02 - Sulfamethizole	14	0	0	0	4
J01F - Macrolides, lincosamides and streptogramins	6	2	29	25	15
J01FA - Macrolides	6	2	25	25	14
J01FA01 - Erythromycin	3	0	8	21	9
J01FA02 - Spiramycin	0	0	12	0	1
J01FA09 - Clarithromycin	2	0	4	0	1
J01FA10 - Azithromycin	2	2	0	4	2
J01FF - Lincosamides	0	0	4	0	0
J01FF01 - Clindamycin	0	0	4	0	0
J01X - Other antibacterials	3	36	33	21	20
J01XD - Imidazole derivatives	0	0	0	1	0
J01XD01 - Metronidazole	0	0	0	1	0
J01XE - Nitrofuran derivatives	3	36	17	20	18
J01XE01 - Nitrofurantoin	3	36	4	20	16
J01XX - Other antibacterials	0	0	17	0	2
J01XX01 - Fosfomycin	0	0	17	0	2
J02 - Antimycotics for systemic use	22	2	4	66	31
J02A - Antimycotics for systemic use	22	2	4	66	31
J02AB - Imidazole derivatives	0	0	0	3	1
J02AB02 - Ketoconazole	0	0	0	3	1
J02AC - Triazole derivatives	22	2	4	61	29
J02AC01 - Fluconazole	22	2	4	61	29
J02AX - Other antimycotics for systemic use	0	0	0	3	1
J02AX04 - Caspofungin	0	0	0	3	1
J05 - Antivirals for systemic use	14	4	54	27	21
J05A - Direct acting antivirals	14	4	54	27	21
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	13	0	54	27	19
J05AB01 - Aciclovir	11	0	54	27	19
J05AB11 - Valaciclovir	2	0	0	0	0
J05AH - Neuraminidase inhibitors	2	0	0	0	0
J05AH02 - Oseltamivir	2	0	0	0	0
J05AR - Antivirals for treatment of hiv infections, comb.	0	2	0	0	0
J05AR03 - Tenofovir disoproxil and emtricitabine	0	2	0	0	0
J05AX - Other antivirals	0	2	0	0	0
J05AX08 - Raltegravir	0	2	0	0	0
J06 - Immune sera and immunoglobulins	2	2	0	1	1
J06B - Immunoglobulins	2	2	0	1	1
J06BB - Specific immunoglobulins	2	2	0	1	1
J06BB01 - Anti-d (rh) immunoglobulin	2	2	0	1	1
L - Antineoplastic and immunomodulating agents	11	34	4	16	17
L02 - Endocrine therapy	6	27	0	7	11
L02A - Hormones and related agents	6	27	0	3	9
L02AE - Gonadotrophin releasing hormone analogues	6	27	0	3	9
L02AE01 - Buserelin	3	0	0	3	2
L02AE02 - Leuprorelin	0	2	0	0	0
L02AE03 - Goserelin	2	0	0	0	0
L02AE04 - Triptorelin	2	25	0	0	6
L02B - Hormone antagonists and related agents	0	0	0	4	1
L02BA - Anti-estrogens	0	0	0	3	1

L02BA01 - Tamoxifen	0	0	0	3	1
L02BG - Aromatase inhibitors	0	0	0	1	0
L02BG04 - Letrozole	0	0	0	1	0
L03 - Immunostimulants	0	0	4	0	0
L03A - Immunostimulants	0	0	4	0	0
L03AX - Other immunostimulants	0	0	4	0	0
L04 - Immunosuppressants	5	6	0	8	6
L04A - Immunosuppressants	5	6	0	8	6
L04AB - Tumor necrosis factor alpha (tnf-alpha) inhibitors	2	2	0	1	1
L04AB02 - Infliximab	2	2	0	1	1
L04AD - Calcineurin inhibitors	2	0	0	0	0
L04AD02 - Tacrolimus	2	0	0	0	0
L04AX - Other immunosuppressants	2	4	0	7	4
L04AX01 - Azathioprine	2	4	0	6	3
L04AX03 - Methotrexate	0	0	0	1	0
M - Musculo-skeletal system	113	29	66	76	76
M01 - Antiinflammatory and antirheumatic products	111	29	54	72	72
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	111	29	54	72	72
M01AB - Acetic acid derivatives and related substances	9	0	0	11	7
M01AB01 - Indometacin	2	0	0	0	0
M01AB05 - Diclofenac	8	0	0	11	6
M01AC - Oxicams	0	0	4	0	0
M01AC01 - Piroxicam	0	0	4	0	0
M01AE - Propionic acid derivatives	97	29	50	56	62
M01AE01 - Ibuprofen	95	29	46	44	57
M01AE02 - Naproxen	2	0	0	11	4
M01AE03 - Ketoprofen	0	0	4	0	0
M01AE14 - Dexibuprofen	0	0	0	1	0
M01AG - Fenamates	5	0	0	1	2
M01AG01 - Mefenamic acid	0	0	0	1	0
M01AG02 - Tolfenamic acid	5	0	0	0	1
M01AH - Coxibs	0	0	0	1	0
M01AH01 - Celecoxib	0	0	0	1	0
M01AX - Other antiinfl./antirheumatic agents, non-steroids	0	0	0	1	0
M01AX05 - Glucosamine	0	0	0	1	0
M02 - Topical products for joint and muscular pain	2	0	12	1	2
M02A - Topical products for joint and muscular pain	2	0	12	1	2
M02AA - Antiinfl. prep., non-steroids for topical use	2	0	8	1	2
M02AA05 - Benzydamine	0	0	8	0	1
M02AA07 - Piroxicam	0	0	0	1	0
M02AA15 - Diclofenac	2	0	0	0	0
M02AX - Other topical products for joint and muscular pain	0	0	4	0	0
M04 - Antigout preparations	0	0	0	1	0
M04A - Antigout preparations	0	0	0	1	0
M04AA - Preparations inhibiting uric acid production	0	0	0	1	0
M04AA01 - Allopurinol	0	0	0	1	0
M09 - Other drugs for disorders of musculo-skeletal syst	0	0	0	1	0
M09A - Other drugs for disorders of musculo-skeletal syst	0	0	0	1	0
M09AA - Quinine and derivatives	0	0	0	1	0

M09AA01 - Hydroquinine	0	0	0	1	0
N - Nervous system	695	626	452	893	719
N01 - Anesthetics	0	0	4	4	2
N01A - Anesthetics, general	0	0	0	1	0
N01AX - Other general anesthetics	0	0	0	1	0
N01AX63 - Nitrous oxide, combinations	0	0	0	1	0
N01B - Anesthetics, local	0	0	4	3	1
N01BB - Amides	0	0	4	3	1
N01BB02 - Lidocaine	0	0	4	0	0
N01BB52 - Lidocaine, combinations	0	0	0	3	1
N02 - Analgesics	579	544	382	739	603
N02A - Opioids	30	19	0	25	22
N02AA - Natural opium alkaloids	13	8	0	16	11
N02AA01 - Morphine	2	6	0	4	3
N02AA05 - Oxycodone	2	2	0	0	1
N02AA08 - Dihydrocodeine	0	0	0	3	1
N02AA59 - Codeine, combinations excl. psycholeptics	9	0	0	8	6
N02AB - Phenylpiperidine derivatives	2	0	0	0	0
N02AB02 - Pethidine	2	0	0	0	0
N02AX - Other opioids	16	11	0	10	11
N02AX02 - Tramadol	16	11	0	10	11
N02B - Other analgesics and antipyretics	507	504	373	708	560
N02BA - Salicylic acid derivatives	27	6	21	49	29
N02BA01 - Acetylsalicylic acid	2	6	21	48	21
N02BA03 - Choline salicylate	0	0	0	1	0
N02BA51 - Acetylsalicylic acid, comb excl psycholeptics	25	0	0	0	8
N02BB - Pyrazolones	0	0	12	0	1
N02BB02 - Metamizole sodium	0	0	12	0	1
N02BE - Anilides	480	498	340	657	529
N02BE01 - Paracetamol	479	464	336	584	495
N02BE02 - Tolfenamic acid	2	0	0	0	0
N02BE51 - Paracetamol, combinations excl psycholeptics	0	34	0	73	33
N02C - Antimigraine preparations	41	19	8	6	20
N02CA - Ergot alkaloids	0	0	4	0	0
N02CC - Selective 5ht(1)-receptor agonists	39	19	4	6	19
N02CC01 - Sumatriptan	28	13	4	4	14
N02CC02 - Naratriptan	2	0	0	0	0
N02CC03 - Zolmitriptan	2	0	0	0	0
N02CC04 - Rizatriptan	6	4	0	1	3
N02CC06 - Eletriptan	2	0	0	0	0
N03 - Antiepileptics	14	6	8	11	11
N03A - Antiepileptics	14	6	8	11	11
N03AA - Barbiturates and derivatives	0	0	4	0	0
N03AA02 - Phenobarbital	0	0	4	0	0
N03AB - Hydantoin derivatives	0	2	0	0	0
N03AB03 - Amino(diphenylhydantoin) valeric acid	0	2	0	0	0
N03AF - Carboxamide derivatives	2	0	0	1	1
N03AF01 - Carbamazepine	0	0	0	1	0
N03AF02 - Oxcarbazepine	2	0	0	0	0

N03AG - Fatty acid derivatives	2	0	4	0	1
N03AG01 - Valproic acid	2	0	4	0	1
N03AX - Other antiepileptics	11	4	0	10	8
N03AX09 - Lamotrigine	9	4	0	3	5
N03AX12 - Gabapentin	0	0	0	4	1
N03AX14 - Levetiracetam	0	0	0	3	1
N03AX16 - Pregabalin	2	0	0	0	0
N04 - Anti-parkinson drugs	0	2	0	0	0
N04B - Dopaminergic agents	0	2	0	0	0
N04BC - Dopamine agonists	0	2	0	0	0
N04BC05 - Pramipexole	0	2	0	0	0
N05 - Psycholeptics	14	27	29	39	28
N05A - Antipsychotics	8	6	0	34	15
N05AB - Phenothiazine with piperazine structure	2	0	0	27	10
N05AB03 - Perphenazine	2	0	0	0	0
N05AB04 - Prochlorperazine	0	0	0	27	9
N05AH - Diazepines, oxazepines, thiazepines and oxepines	5	6	0	6	5
N05AH04 - Quetiapine	5	6	0	6	5
N05AN - Lithium	2	0	0	1	1
N05AN01 - Lithium	2	0	0	1	1
N05B - Anxiolytics	3	4	25	3	6
N05BA - Benzodiazepine derivatives	3	4	21	3	5
N05BA01 - Diazepam	0	0	17	3	3
N05BA04 - Oxazepam	3	2	0	0	1
N05BA05 - Clorazepate potassium	0	0	4	0	0
N05BA06 - Lorazepam	0	2	0	0	0
N05BB - Diphenylmethane derivatives	0	0	4	0	0
N05BB01 - Hydroxyzine	0	0	4	0	0
N05C - Hypnotics and sedatives	3	17	4	3	6
N05CD - Benzodiazepine derivatives	2	11	0	0	3
N05CD05 - Triazolam	2	0	0	0	0
N05CD07 - Temazepam	0	11	0	0	2
N05CF - Benzodiazepine related drugs	0	0	0	3	1
N05CF01 - Zopiclone	0	0	0	1	0
N05CF02 - Zolpidem	0	0	0	1	0
N05CH - Melatonin receptor agonists	2	4	4	0	2
N05CH01 - Melatonin	2	4	4	0	2
N05CM - Other hypnotics and sedatives	0	2	0	0	0
N05CM09 - Valerianae radix	0	2	0	0	0
N06 - Psychoanaleptics	85	42	17	85	67
N06A - Antidepressants	81	40	17	83	65
N06AA - Non selective monoamine reuptake inhibitors	2	2	4	11	5
N06AA02 - Imipramine	0	0	0	1	0
N06AA04 - Clomipramine	0	0	4	0	0
N06AA09 - Amitriptyline	2	2	0	8	4
N06AA10 - Nortriptyline	0	0	0	1	0
N06AB - Selective serotonin reuptake inhibitors	56	29	4	55	44
N06AB03 - Fluoxetine	6	4	0	21	10
N06AB04 - Citalopram	25	6	0	14	14

N06AB05 - Paroxetine	0	6	0	0	1
N06AB06 - Sertraline	20	8	4	18	15
N06AB08 - Fluvoxamine	0	2	0	0	0
N06AB10 - Escitalopram	3	2	0	1	2
N06AX - Other antidepressants	23	8	8	14	15
N06AX05 - Trazodone	0	0	4	0	0
N06AX11 - Mirtazapine	2	2	0	6	3
N06AX12 - Bupropion	0	2	0	0	0
N06AX16 - Venlafaxine	19	4	4	6	9
N06AX21 - Duloxetine	3	0	0	1	1
N06AX22 - Agomelatine	0	0	0	1	0
N06B - Psychostimulants, agents used for adhd and nootropics	3	2	0	0	1
N06BA - Centrally acting sympathomimetics	3	2	0	0	1
N06BA04 - Methylphenidate	3	2	0	0	1
N06C - Psycholeptics and psychoanaleptics in combination	0	0	0	1	0
N06CA - Antidepressants in combination with psycholeptics	0	0	0	1	0
N06CA01 - Amitriptyline and psycholeptics	0	0	0	1	0
N07 - Other nervous system drugs	3	4	12	14	8
N07A - Parasympathomimetics	0	0	0	1	0
N07AX - Other parasympathomimetics	0	0	0	1	0
N07AX02 - Choline alfoscerate	0	0	0	1	0
N07B - Drugs used in addictive disorders	3	0	8	11	6
N07BA - Drugs used in nicotine dependence	3	0	4	7	4
N07BA01 - Nicotine	2	0	4	7	3
N07BA03 - Varenicline	2	0	0	0	0
N07BB - Drugs used in alcohol dependence	0	0	4	0	0
N07BB04 - Naltrexone	0	0	4	0	0
N07BC - Drugs used in opioid dependence	0	0	0	4	1
N07BC01 - Buprenorphine	0	0	0	1	0
N07BC02 - Methadone	0	0	0	1	0
N07BC06 - Diamorphine	0	0	0	1	0
N07C - Antivertigo preparations	0	4	4	1	2
N07CA - Antivertigo preparations	0	4	4	1	2
N07CA01 - Betahistine	0	0	0	1	0
N07CA02 - Cinnarizine	0	2	0	0	0
N07CA52 - Cinnarizine, combinations	0	2	0	0	0
P - Antiparasitic products, insecticides and repellants	5	2	0	11	6
P01 - Antiprotozoals	3	2	0	8	4
P01A - Agents against amoebiasis and other proto.diseases	2	2	0	4	2
P01AB - Nitroimidazole derivatives	2	2	0	4	2
P01AB01 - Metronidazole	2	2	0	4	2
P01B - Antimalarials	2	0	0	4	2
P01BA - Aminoquinolines	0	0	0	4	1
P01BA02 - Hydroxychloroquine	0	0	0	4	1
P01BC - Methanolquinolines	2	0	0	0	0
P01BC01 - Quinine	2	0	0	0	0
P02 - Anthelmintics	2	0	0	0	0
P02C - Antinematodal agents	2	0	0	0	0
P02CA - Benzimidazole derivatives	2	0	0	0	0

P02CA01 - Mebendazole	2	0	0	0	0
P03 - Ectoparasiticides, incl scabicides, insecticides and repellants	0	0	0	3	1
P03A - Ectoparasiticides, incl scabicides	0	0	0	3	1
P03AC - Pyrethrines, incl synthetic compounds	0	0	0	1	0
P03AC03 - Phenothrin	0	0	0	1	0
P03AX - Other ectoparasiticides, incl scabicides	0	0	0	1	0
P03AX05 - Dimeticone	0	0	0	1	0
R - Respiratory system	330	414	249	447	380
R01 - Nasal preparations	83	132	62	85	92
R01A - Decongestants and other nasal preparations for topical use	81	128	58	83	90
R01AA - Sympathomimetics, plain	52	63	25	21	41
R01AA04 - Phenylephrine	0	0	0	1	0
R01AA05 - Oxymetazoline	0	0	21	7	5
R01AA07 - Xylometazoline	52	63	4	13	35
R01AB - Sympathomimetics,combinations excl corticosteroids	0	0	4	0	0
R01AB02 - Naphazoline	0	0	4	0	0
R01AC - Antiallergic agents, excl corticosteroids	0	13	4	8	6
R01AC01 - Cromoglicic acid	0	8	0	8	5
R01AC02 - Levocabastine	0	2	4	0	1
R01AC03 - Azelastine	0	2	0	0	0
R01AD - Corticosteroids	30	38	17	48	36
R01AD01 - Beclomethasone	0	13	0	31	14
R01AD05 - Budesonide	5	4	4	0	3
R01AD08 - Fluticasone	8	17	0	11	10
R01AD09 - Mometasone	13	4	12	1	7
R01AD12 - Fluticasone furoate	5	0	0	0	1
R01AD60 - Hydrocortisone, combinations	0	0	0	3	1
R01AX - Other nasal preparations	0	15	8	6	6
R01AX10 - Various	0	15	4	0	4
R01AX30 - Combinations	0	0	0	1	0
R01B - Nasal decongestants for systemic use	0	0	4	1	1
R01BA - Sympathomimetics	0	0	4	1	1
R01BA02 - Pseudoephedrine	0	0	0	1	0
R01BA53 - Phenylephrine, combinations	0	0	4	0	0
R02 - Throat preparations	13	4	25	3	9
R02A - Throat preparations	13	4	25	3	9
R02AA - Antiseptics	13	0	25	3	8
R02AA03 - Dichlorobenzyl alcohol	11	0	0	1	4
R02AA05 - Chlorhexidine	2	0	0	0	0
R02AA20 - Various	0	0	0	1	0
R02AD - Anesthetics, local	0	4	0	0	1
R02AD02 - Lidocaine	0	4	0	0	1
R03 - Drugs for obstructive airway diseases	95	105	50	165	116
R03A - Adrenergics, inhalants	72	67	25	111	79
R03AC - Selective beta-2-adrenoceptor agonists	50	50	21	100	64
R03AC02 - Salbutamol	11	46	12	83	44
R03AC03 - Terbutaline	38	0	0	11	15
R03AC12 - Salmeterol	0	0	4	6	2
R03AC13 - Formoterol	2	0	4	0	1

R03AK - Adrenergics and other drugs for obstructive airway diseases	22	17	4	11	15
R03AK06 - Salmeterol and other drugs for obstructive airway diseases	5	15	4	1	6
R03AK07 - Formoterol and other drugs for obstructive airway diseases	17	2	0	8	9
R03AK08 - Formoterol and beclometasone	0	0	0	1	0
R03B - Other drugs for obstructive airway diseases, inhalants	20	29	21	48	32
R03BA - Glucocorticoids	20	27	21	44	30
R03BA01 - Beclomethasone	0	13	0	27	12
R03BA02 - Budesonide	20	15	17	8	15
R03BA05 - Fluticasone	0	0	0	8	3
R03BA08 - Ciclesonide	0	0	4	0	0
R03BB - Anticholinergics	0	2	0	1	1
R03BB01 - Ipratropium bromide	0	2	0	1	1
R03BC - Antiallergic agents, excl corticosteroids	0	0	0	3	1
R03BC01 - Cromoglicic acid	0	0	0	1	0
R03BC03 - Nedocromil	0	0	0	1	0
R03D - Other systemic drugs for obstructive airway diseases	0	4	4	6	3
R03DA - Xanthines	0	0	0	1	0
R03DA05 - Aminophylline	0	0	0	1	0
R03DC - Leukotriene receptor antagonists	0	2	4	4	2
R03DC03 - Montelukast	0	2	4	4	2
R03DX - Other systemic drugs for obstructive airway diseases	0	2	0	0	0
R03DX05 - Omalizumab	0	2	0	0	0
R05 - Cough and cold preparations	16	19	62	28	26
R05C - Expectorants,excl combinations with antitussives	3	8	54	1	10
R05CA - Expectorants	0	0	41	0	5
R05CB - Mucolytics	3	8	12	1	5
R05CB01 - Acetylcysteine	3	2	0	1	2
R05CB02 - Bromhexine	0	6	0	0	1
R05CB06 - Ambroxol	0	0	12	0	1
R05D - Cough suppressants, excl. combinations with expectorants	11	6	0	25	14
R05DA - Opium alkaloids and derivatives	11	6	0	25	14
R05DA04 - Codeine	5	4	0	25	11
R05DA07 - Noscapine	6	0	0	0	2
R05F - Antitussives and expectorants, combinations	2	0	0	0	0
R05FA - Opium derivatives and expectorants	2	0	0	0	0
R05FA02 - Opium derivatives and expectorants	2	0	0	0	0
R05X - Other cold preparations	0	0	8	1	1
R06 - Antihistamines for systemic use	122	153	46	166	136
R06A - Antihistamines for systemic use	122	151	46	166	135
R06AA - Aminoalkyl ethers	3	2	4	6	4
R06AA02 - Diphenhydramine	2	0	0	4	2
R06AA04 - Clemastine	2	2	0	0	1
R06AA09 - Doxylamine	0	0	4	0	0
R06AA59 - Doxylamine, combinations	0	0	0	1	0
R06AB - Substituted alkylamines	0	0	0	21	7
R06AB04 - Chlorpheniramine	0	0	0	21	7
R06AD - Phenothiazine derivatives	9	0	21	32	16
R06AD02 - Promethazine	9	0	4	6	5
R06AD03 - Thiethylperazine	0	0	17	0	2

R06AD52 - Promethazine, combinations	0	0	0	27	9
R06AE - Piperazine derivatives	77	109	8	75	76
R06AE03 - Cyclizine	8	2	0	61	24
R06AE05 - Meclozine	11	8	0	0	5
R06AE07 - Cetirizine	58	17	8	13	27
R06AE09 - Levocetirizine	0	11	0	1	3
R06AE55 - Meclozine, combinations	0	71	0	0	16
R06AX - Other antihistamines for systemic use	30	36	12	25	28
R06AX13 - Loratadine	8	25	4	17	15
R06AX18 - Acrivastine	8	0	0	1	3
R06AX25 - Mizolastine	0	2	0	1	1
R06AX26 - Fexofenadine	11	4	4	4	6
R06AX27 - Desloratadine	3	4	4	1	3
R07 - Other respiratory system products	0	0	4	0	0
R07A - Other respiratory system products	0	0	4	0	0
R07AX - Other respiratory system products	0	0	4	0	0
S - Sensory organs	23	27	12	11	19
S01 - Ophthalmologicals	23	25	12	10	18
S01A - Antiinfectives	6	2	0	4	4
S01AA - Antibiotics	6	2	0	4	4
S01AA01 - Chloramphenicol	2	2	0	1	1
S01AA13 - Fusidic acid	5	0	0	3	2
S01B - Antiinflammatory agents	2	6	0	1	2
S01BA - Corticosteroids, plain	2	4	0	1	2
S01BA01 - Dexamethasone	0	2	0	0	0
S01BA04 - Prednisolone	0	2	0	0	0
S01BA07 - Fluorometholone	0	0	0	1	0
S01C - Antiinflammatory agents and antiinfectives in comb	2	0	8	0	1
S01CA - Corticosteroids and antiinfectives in combination	2	0	8	0	1
S01CA01 - Dexamethasone and antiinfectives	2	0	0	0	0
S01CA06 - Fludrocortisone and antiinfectives	0	0	8	0	1
S01G - Decongestants and antiallergics	14	11	4	3	8
S01GX - Other antiallergics	11	11	4	3	7
S01GX01 - Cromoglicic acid	0	6	0	1	2
S01GX02 - Levocabastine	5	0	4	0	2
S01GX04 - Nedocromil	0	0	0	1	0
S01GX06 - Emedastine	0	2	0	0	0
S01GX08 - Ketotifen	0	2	0	0	0
S01GX09 - Olopatadine	6	0	0	0	2
S01K - Surgical aids	0	0	0	1	0
S01KA - Viscoelastic substances	0	0	0	1	0
S01KA01 - Hyaluronic acid	0	0	0	1	0
S01X - Other ophthalmologicals	0	4	0	0	1
S01XA - Other ophthalmologicals	0	4	0	0	1
S01XA20 - Artificial tears and other indifferent prep.	0	4	0	0	1
S02 - Otologicals	0	2	0	1	1
S02C - Corticosteroids and antiinfectives in combination	0	0	0	1	0
S02CA - Corticosteroids and antiinfectives in combination	0	0	0	1	0
S02CA06 - Dexamethasone and antiinfectives	0	0	0	1	0

V - Various	5	0	29	0	5
V01 - Allergens	5	0	0	0	1
V01A - Allergens	5	0	0	0	1
V01AA - Allergen extracts	5	0	0	0	1
V01AA02 - Grass pollen	3	0	0	0	1
V03 - All other therapeutic products	0	0	21	0	2
V03A - All other therapeutic products	0	0	21	0	2
V03AB - Antidotes	0	0	17	0	2
V03AB21 - Potassium iodide	0	0	17	0	2
V03AX - Other therapeutic products	0	0	4	0	0
V06 - General nutrients	0	0	4	0	0
V06D - Other nutrients	0	0	4	0	0
V07 - All other non-therapeutic products	0	0	4	0	0
V07A - All other non-therapeutic products	0	0	4	0	0
V07AT - Cosmetics	0	0	4	0	0

13.6 All medications by trimesters

Table 13-8 Proportional reporting ratios (PRR) of disproportional medications use in the first trimester using the best available information of ATC codes

Medications	PRR
C07AA05 - Propranolol	2.57 (2.48,2.66)
G03AA07 - Levonorgestrel and ethinylestradiol	2.57 (2.49,2.66)
G03CA03 - Estradiol	2.29 (1.81,2.89)
G03DA02 - Medroxyprogesterone	2.57 (2.48,2.66)
G03GA - Gonadotropins	2.57 (2.49,2.66)
G03GA01 - Chorionic gonadotropine	2.50 (2.31,2.70)
G03GA02 - Human menopausal gonadotrophin	2.31 (1.97,2.70)
G03GA05 - Follitropin alfa	2.58 (2.49,2.67)
G03GA06 - Follitropin beta	2.24 (1.91,2.64)
G03GA08 - Choriogonadotropin alfa	2.33 (2.08,2.60)
G03GB02 - Clomifene	2.37 (2.16,2.61)
H01CA01 - Gonadorelin	2.57 (2.48,2.66)
L02AE01 - Buserelin	2.57 (2.48,2.66)
L02AE04 - Triptorelin	2.57 (2.49,2.66)
M01AB05 - Diclofenac	2.20 (1.63,2.99)
M01AE02 - Naproxen	2.11 (1.59,2.79)
N02CC01 - Sumatriptan	2.57 (2.49,2.66)
N02CC04 - Rizatriptan	2.14 (1.50,3.07)
N05AH04 - Quetiapine	2.57 (2.49,2.66)
N05CH01 - Melatonin	2.14 (1.50,3.07)
N06AA09 - Amitriptyline	2.14 (1.50,3.07)

N06AB03 - Fluoxetine	2.32 (1.88,2.86)
N06AB04 - Citalopram	2.32 (1.88,2.86)
N06AB06 - Sertraline	2.20 (1.63,2.99)
N06AX16 - Venlafaxine	2.57 (2.48,2.66)
N06BA04 - Methylphenidate	2.57 (2.48,2.66)
R03DC03 - Montelukast	2.57 (2.48,2.66)
R06AD03 - Thiethylperazine	2.57 (2.48,2.66)
R06AX18 - Acrivastine	2.57 (2.48,2.66)
R06AX27 - Desloratadine	2.57 (2.48,2.66)

Note: MHRA's criteria for signal detection were used: PRR ≥ 2, $\chi^2 \geq 4$, and number of cases (use of medication in the first trimester) ≥ 3.

Table 13-9 Proportional reporting ratios (PRR) of disproportional medications use in the first trimester using the best available information of ATC codes, excluding G03, H01C and L02A codes

Medications	PRR
A07DA03 - Loperamide	2.13 (1.58,2.87)
C07AA05 - Propranolol	2.76 (2.66,2.87)
G02CB01 - Bromocriptine	2.15 (1.51,3.06)
M01AB05 - Diclofenac	2.37 (1.75,3.21)
M01AE01 - Ibuprofen	2.14 (1.91,2.40)
M01AE02 - Naproxen	2.26 (1.71,3.00)
N02CC01 - Sumatriptan	2.77 (2.67,2.87)
N02CC04 - Rizatriptan	2.30 (1.61,3.30)
N05AH04 - Quetiapine	2.77 (2.67,2.87)
N05CH01 - Melatonin	2.30 (1.61,3.30)
N06AA09 - Amitriptyline	2.30 (1.61,3.30)
N06AB03 - Fluoxetine	2.49 (2.02,3.07)
N06AB04 - Citalopram	2.49 (2.02,3.07)
N06AB06 - Sertraline	2.37 (1.75,3.21)
N06AX16 - Venlafaxine	2.76 (2.66,2.87)
N06BA04 - Methylphenidate	2.76 (2.66,2.87)
R03DC03 - Montelukast	2.76 (2.66,2.87)
R06AD03 - Thiethylperazine	2.76 (2.66,2.87)
R06AX18 - Acrivastine	2.76 (2.66,2.87)
R06AX27 - Desloratadine	2.76 (2.66,2.87)

Note: MHRA's criteria for signal detection were used: PRR ≥ 2, $\chi^2 \geq 4$, and number of cases (use of medication in the first trimester) ≥ 3.

Table 13-10 Proportional reporting ratios (PRR) of disproportional medications use in the first trimester using level 3 of ATC codes (pharmacological subgroup), excluding G03, H01C and L02A codes

Medications	PRR
A07D - Antipropulsives	2.18 (1.65,2.87)
C07A - Beta blocking agents, plain	2.30 (1.61,3.30)
D10A - Anti-acne preparations for topical use	2.30 (1.61,3.30)

M01A - Antiinflammatory/antirheumatic prod.,non-steroids	2.15 (1.94,2.39)
N02C - Antimigraine preparations	2.65 (2.39,2.93)
N03A - Antiepileptics	2.76 (2.66,2.87)
N06A - Antidepressants	2.50 (2.25,2.78)
N06B - Psychostimulants, agents used for ADHD and nootropics	2.76 (2.66,2.87)
R03D - Other systemic drugs for obstructive airway diseases	2.76 (2.66,2.87)

Note: MHRA's criteria for signal detection were used: PRR ≥ 2, $\chi^2 \geq 4$, and number of cases (use of medication in the first trimester) ≥ 3.

Table 13-11 Rates per 1000 women among those who provided information within the trimester

Medications	First	Second	Third
A - Alimentary tract and metabolism	172	283	330
A01 - Stomatological preparations	<1	1	1
A01A - Stomatological preparations	<1	1	1
A01AB - Antiinfectives for local oral treatment	0	0	1
A01AD - Other agents for local oral treatment	<1	1	0
A02 - Drugs for acid related disorders	62	151	214
A02A - Antacids	26	58	90
A02AA - Magnesium compounds	8	14	23
A02AB - Aluminium compounds	1	2	6
A02AC - Calcium compounds	1	3	7
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	15	37	51
A02AH - Antacids with sodium bicarbonate	<1	1	1
A02AX - Antacids, other combinations	0	1	2
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	36	93	124
A02BA - H2-receptor antagonists	3	10	12
A02BC - Proton pump inhibitors	11	14	13
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	22	69	98
A03 - Drugs for functional gastrointestinal disorders	18	14	12
A03A - Drugs for functional gastrointestinal disorders	3	5	8
A03AA - Synt anticholin,esters with tertiary amino group	1	1	0
A03AD - Papaverine and derivatives	2	4	6
A03AX - Other drugs for functional gastrointestinal disorders	<1	1	2
A03B - Belladonna and derivatives, plain	1	0	1
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	1	0	1
A03F - Propulsives	13	8	3
A03FA - Propulsives	13	8	3
A04 - Antiemetics and antinauseants	6	7	3
A04A - Antiemetics and antinauseants	6	7	3
A04AA - Serotonin (5ht3) antagonists	5	6	3
A04AD - Other antiemetics	0	1	0
A05 - Bile and liver therapy	0	0	3
A05A - Bile therapy	0	0	2
A05AA - Bile acid preparations	0	0	2
A06 - Drugs for constipation	42	62	40

A06A - Drugs for constipation	42	62	40
A06AA - Softeners, emollients	<1	0	0
A06AB - Contact laxatives	4	8	5
A06AC - Bulk-forming laxatives	13	20	9
A06AD - Osmotically acting laxatives	22	32	24
A06AG - Enemas	1	2	1
A06AX - Other drugs for constipation	1	1	1
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	10	11	6
A07A - Intestinal antiinfectives	0	1	2
A07AA - Antibiotics	0	1	2
A07B - Intestinal adsorbents	<1	1	0
A07BA - Charcoal preparations	0	1	0
A07BC - Other intestinal adsorbents	<1	0	0
A07C - Electrolytes with carbohydrates	<1	2	1
A07CA - Oral rehydration salt formulations	<1	2	1
A07D - Antipropulsives	5	1	1
A07DA - Antipropulsives	5	1	1
A07E - Intestinal antiinflammatory agents	<1	1	0
A07EA - Corticosteroids acting locally	0	1	0
A07EC - Aminosalicylic acid and similar agents	<1	0	0
A07F - Antidiarrheal microorganisms	2	5	2
A07FA - Antidiarrheal microorganisms	2	5	2
A07X - Other antidiarrheals	0	1	1
A07XA - Other antidiarrheals	0	1	1
A09 - Digestives, incl enzymes	0	0	1
A09A - Digestives, incl enzymes	0	0	1
A09AA - Enzyme preparations	0	0	1
A10 - Drugs used in diabetes	8	3	14
A10A - Insulins and analogues	0	1	8
A10AB - Insulins and analogues for injection, fast-acting	0	1	7
A10AC - Insulins and analogues for injection, intermediate-acting	0	0	1
A10B - Blood glucose lowering drugs, excl. insulins	8	3	6
A10BA - Biguanides	8	3	6
A12 - Mineral supplements	26	34	37
A12A - Calcium	18	23	19
A12AA - Calcium	12	19	17
A12AX - Calcium, combinations with vitamin d and/or other drugs	6	4	2
A12B - Potassium	0	0	1
A12BA - Potassium	0	0	1
A12C - Other mineral supplements	7	9	12
A12CA - Sodium	0	0	1
A12CB - Zinc	2	2	3
A12CC - Magnesium	2	4	7
A12CE - Selenium	1	1	0
A12CX - Other mineral products	1	2	1
B - Blood and blood forming organs	13	22	14
B01 - Antithrombotic agents	12	22	12
B01A - Antithrombotic agents	12	22	12
B01AA - Vitamin k antagonists	<1	0	0

B01AB - Heparin group	6	11	7
B01AC - Platelet aggregation inhibitors excl. heparin	5	11	4
B02 - Antihemorrhagics	0	0	2
B02A - Antifibrinolytics	0	0	1
B02AA - Amino acids	0	0	1
B02B - Vitamin k and other hemostatics	0	0	1
B02BA - Vitamin k	0	0	1
B05 - Blood substitutes and perfusion solutions	<1	1	0
B05B - I.v. solutions	<1	1	0
B05BA - Solutions for parenteral nutrition	<1	1	0
C - Cardiovascular system	10	13	35
C02 - Antihypertensives	<1	1	6
C02A - Antiadrenergic agents, centrally acting	<1	1	6
C02AA - Rauwolfia alkaloids	<1	0	0
C02AB - Methyldopa	0	1	6
C03 - Diuretics	1	0	0
C03A - Low-ceiling diuretics, thiazides	<1	0	0
C03AA - Thiazides, plain	<1	0	0
C03D - Potassium-sparing agents	<1	0	0
C03DA - Aldosterone antagonists	<1	0	0
C05 - Vasoprotectives	3	9	25
C05A - Agents for treatment of hemorrhoids and anal fissures for topical use	1	6	17
C05AA - Corticosteroids	<1	3	11
C05AD - Local anesthetics	0	0	1
C05AE - Musclerelaxants	0	1	0
C05AX - Other agents for treatment of hemorrhoids and anal fissures for topical use	<1	2	5
C05C - Capillary stabilizing agents	2	3	8
C05CA - Bioflavonoids	2	3	8
C07 - Beta blocking agents	2	1	0
C07A - Beta blocking agents, plain	2	1	0
C07AA - Beta blocking agents, plain, non-selective	1	0	0
C07AB - Beta blocking agents, plain, selective	1	0	0
C07AG - Alpha- and beta blocking agents	0	1	0
C08 - Calcium channel blockers	0	2	3
C08C - Selective calcium channel blockers with mainly vascular effects	0	2	3
C08CA - Dihydropyridine derivatives	0	2	3
C09 - Agents acting on the renin-angiotensin system	2	0	0
C09A - Ace-inhibitors, plain	1	0	0
C09AA - Ace-inhibitors, plain	1	0	0
C09C - Angiotensin ii antagonists	1	0	0
C09CA - Angiotensin ii antagonists, plain	1	0	0
C10 - Lipid modifying agents	1	1	1
C10A - Lipid modifying agents, plain	1	1	1
C10AA - Hmg coa reductase inhibitors	1	0	0
C10AX - Other lipid modifying agents	0	1	1
D - Dermatologicals	36	61	54
D01 - Antifungals for dermatological use	15	29	35
D01A - Antifungals for topical use	15	29	35

D01AA - Antibiotics	6	7	7
D01AC - Imidazole and triazole derivatives	9	21	25
D01AE - Other antifungals for topical use	<1	1	3
D02 - Emollients and protectives	<1	0	1
D02A - Emollients and protectives	<1	0	1
D02AF - Salicylic acid preparations	<1	0	0
D02AX - Other emollients and protectives	0	0	1
D04 - Antipruritics,incl antihist,anesthet,etc.	0	0	2
D04A - Antipruritics,incl antihist,anesthet,etc.	0	0	2
D04AA - Antihistamines for topical use	0	0	2
D05 - Antipsoriatics	<1	1	0
D05A - Antipsoriatics for topical use	<1	1	0
D05AX - Other antipsoriatics for topical use	<1	1	0
D06 - Antibiotics and chemother. for dermatological use	8	18	11
D06A - Antibiotics for topical use	0	3	3
D06AX - Other antibiotics for topical use	0	3	3
D06B - Chemotherapeutics for topical use	8	15	8
D06BB - Antivirals	7	13	7
D06BX - Other chemotherapeutics	1	2	1
D07 - Corticosteroids, dermatological preparations	9	11	6
D07A - Corticosteroids, plain	8	9	3
D07AA - Corticosteroids, weak (group i)	3	3	1
D07AB - Corticosteroids, moderately potent (group ii)	3	4	1
D07AC - Corticosteroids, potent (group iii)	1	3	1
D07B - Corticosteroids, comb with antiseptics	<1	0	0
D07BC - Corticosteroids, potent, comb with antiseptics	<1	0	0
D07C - Corticosteroids, comb with antibiotics	<1	1	2
D07CA - Corticosteroids, weak, comb with antibiotics	<1	0	1
D07CC - Corticosteroids, potent, comb with antibiotics	0	1	1
D07X - Corticosteroids, other combinations	0	1	1
D07XA - Corticosteroids, weak, other combinations	0	1	0
D08 - Antiseptics and disinfectants	<1	0	0
D08A - Antiseptics and disinfectants	<1	0	0
D08AC - Biguanides and amidines	<1	0	0
D09 - Medicated dressings	0	1	0
D09A - Medicated dressings	0	1	0
D09AA - Ointment dressings with antiinfectives	0	1	0
D10 - Anti-acne preparations	2	1	0
D10A - Anti-acne preparations for topical use	2	1	0
D10AD - Retinoids for topical use in acne	1	0	0
D10AE - Peroxides	1	0	0
D10AF - Antiinfectives for treatment of acne	<1	0	0
D10AX - Other anti-acne preparations for topical use	0	1	0
D11 - Other dermatological preparations	<1	1	0
D11A - Other dermatological preparations	<1	1	0
D11AF - Wart and anti-corn preparations	0	1	0
D11AH - Agents for dermatitis, excluding corticosteroids	<1	1	0
G - Genito urinary system and sex hormones	142	58	59
G01 - Gynecological antiinfectives and antiseptics	28	38	39

G01A - Antiinfectives/antisept.,excl comb with corticost.	28	38	39
G01AA - Antibiotics	1	0	4
G01AF - Imidazole derivatives	25	36	32
G01AX - Other antiinfectives and antiseptics	1	2	3
G02 - Other gynecologicals	2	1	4
G02C - Other gynecologicals	2	1	4
G02CA - Sympathomimetics, labour repressants	0	0	1
G02CB - Prolactine inhibitors	2	1	1
G02CX - Other gynecologicals	0	0	3
G03 - Sex hormones and modulators of the genital system	111	19	15
G03A - Hormonal contraceptives for systemic use	6	0	0
G03AA - Progestogens and estrogens, fixed combinations	3	0	0
G03AC - Progestogens	2	0	0
G03B - Androgens	0	0	1
G03BA - 3-oxoandrosten (4) derivatives	0	0	1
G03C - Estrogens	4	1	0
G03CA - Natural and semisynthetic estrogens, plain	4	1	0
G03D - Progestogens	23	14	9
G03DA - Pregnen (4) derivatives	19	11	6
G03DB - Pregnadien derivatives	3	2	3
G03DC - Estren derivatives	<1	0	0
G03G - Gonadotropins and other ovulation stimulants	78	4	5
G03GA - Gonadotropins	59	3	4
G03GB - Ovulation stimulants, synthetic	19	1	2
G04 - Urologicals	<1	1	0
G04B - Urologicals	<1	1	0
G04BD - Drugs for urinary frequency and incontinence	0	1	0
G04BX - Other urologicals	<1	1	0
H - Systemic hormonal prep, excl sex hormones	13	15	11
H01 - Pituitary, hypothalamic hormones and analogues	4	0	0
H01C - Hypothalamic hormones	4	0	0
H01CA - Gonadotrophin-releasing hormones	2	0	0
H01CC - Anti gonadotropin releasing hormones	2	0	0
H02 - Corticosteroids for systemic use	5	3	3
H02A - Corticosteroids for systemic use, plain	5	3	3
H02AB - Glucocorticoids	5	3	3
H03 - Thyroid therapy	4	11	8
H03A - Thyroid preparations	3	11	8
H03AA - Thyroid hormones	3	11	8
H03B - Antithyroid preparations	1	1	0
H03BA - Thiouracils	<1	1	0
H03BB - Sulphur-containing imidazole derivatives	<1	0	0
J - General antiinfectives for systemic use	81	118	103
J01 - Antibacterials for systemic use	66	94	84
J01A - Tetracyclines	1	1	0
J01AA - Tetracyclines	1	1	0
J01C - Beta-lactam antibacterials, penicillins	45	64	57
J01CA - Penicillins with extended spectrum	34	53	45
J01CE - Beta-lactamase sensitive penicillins	5	7	6

J01CF - Beta-lactamase resistant penicillins	2	1	3
J01CR - Comb of penicillins, incl. beta-lactamase inhib.	3	4	4
J01D - Other beta-lactam antibacterials	5	4	8
J01DB - First-generation cephalosporins	4	4	6
J01DC - Second-generation cephalosporins	1	0	2
J01DF - Monobactams	<1	0	0
J01E - Sulfonamides and trimethoprim	2	3	3
J01EA - Trimethoprim and derivatives	1	1	1
J01EB - Short-acting sulfonamides	1	2	2
J01F - Macrolides, lincosamides and streptogramins	4	6	10
J01FA - Macrolides	4	6	9
J01FF - Lincosamides	0	0	1
J01X - Other antibacterials	6	13	5
J01XD - Imidazole derivatives	0	1	0
J01XE - Nitrofuran derivatives	4	11	5
J01XX - Other antibacterials	1	1	0
J02 - Antimycotics for systemic use	10	13	11
J02A - Antimycotics for systemic use	10	13	11
J02AB - Imidazole derivatives	0	1	0
J02AC - Triazole derivatives	10	12	10
J02AX - Other antimycotics for systemic use	<1	1	1
J05 - Antivirals for systemic use	5	11	7
J05A - Direct acting antivirals	5	11	7
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	5	11	5
J05AR - Antivirals for treatment of hiv infections, comb.	0	0	1
J05AX - Other antivirals	0	0	1
J06 - Immune sera and immunoglobulins	0	0	2
J06B - Immunoglobulins	0	0	2
J06BB - Specific immunoglobulins	0	0	2
L - Antineoplastic and immunomodulating agents	7	1	0
L02 - Endocrine therapy	7	0	0
L02A - Hormones and related agents	6	0	0
L02AE - Gonadotrophin releasing hormone analogues	6	0	0
L02B - Hormone antagonists and related agents	<1	0	0
L02BA - Anti-estrogens	<1	0	0
L03 - Immunostimulants	0	1	0
L03A - Immunostimulants	0	1	0
L03AX - Other immunostimulants	0	1	0
L04 - Immunosuppressants	<1	1	0
L04A - Immunosuppressants	<1	1	0
L04AB - Tumor necrosis factor alpha (tnf-alpha) inhibitors	<1	1	0
M - Musculo-skeletal system	45	14	8
M01 - Antiinflammatory and antirheumatic products	45	13	5
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	45	13	5
M01AB - Acetic acid derivatives and related substances	2	1	1
M01AC - Oxicams	<1	0	0
M01AE - Propionic acid derivatives	40	11	4
M01AG - Fenamates	<1	0	0
M01AH - Coxibs	<1	0	0

M01AX - Other antiinfl./antirheumatic agents, non-steroids	<1	1	0
M02 - Topical products for joint and muscular pain	0	1	3
M02A - Topical products for joint and muscular pain	0	1	3
M02AA - Antiinfl. prep., non-steroids for topical use	0	1	2
M02AX - Other topical products for joint and muscular pain	0	0	1
M09 - Other drugs for disorders of musculo-skeletal syst	<1	0	0
M09A - Other drugs for disorders of musculo-skeletal syst	<1	0	0
M09AA - Quinine and derivatives	<1	0	0
N - Nervous system	279	307	214
N01 - Anesthetics	0	1	2
N01A - Anesthetics, general	0	1	0
N01AX - Other general anesthetics	0	1	0
N01B - Anesthetics, local	0	1	2
N01BB - Amides	0	1	2
N02 - Analgesics	237	294	200
N02A - Opioids	9	6	10
N02AA - Natural opium alkaloids	4	4	6
N02AB - Phenylpiperidine derivatives	0	0	1
N02AX - Other opioids	5	2	3
N02B - Other analgesics and antipyretics	218	287	190
N02BA - Salicylic acid derivatives	12	18	5
N02BB - Pyrazolones	<1	1	0
N02BE - Anilides	206	269	184
N02C - Antimigraine preparations	9	1	0
N02CA - Ergot alkaloids	<1	0	0
N02CC - Selective 5ht(1)-receptor agonists	8	1	0
N03 - Antiepileptics	2	0	0
N03A - Antiepileptics	2	0	0
N03AF - Carboxamide derivatives	<1	0	0
N03AX - Other antiepileptics	1	0	0
N04 - Anti-parkinson drugs	0	0	1
N04B - Dopaminergic agents	0	0	1
N04BC - Dopamine agonists	0	0	1
N05 - Psycholeptics	15	7	9
N05A - Antipsychotics	10	5	0
N05AB - Phenothiazine with piperazine structure	7	5	0
N05AH - Diazepines, oxazepines, thiazepines and oxepines	2	0	0
N05AN - Lithium	<1	0	0
N05B - Anxiolytics	2	1	4
N05BA - Benzodiazepine derivatives	2	1	4
N05C - Hypnotics and sedatives	3	1	5
N05CD - Benzodiazepine derivatives	1	1	4
N05CF - Benzodiazepine related drugs	<1	1	1
N05CH - Melatonin receptor agonists	2	0	1
N06 - Psychoanaleptics	21	3	0
N06A - Antidepressants	19	3	0
N06AA - Non selective monoamine reuptake inhibitors	2	1	0
N06AB - Selective serotonin reuptake inhibitors	13	2	0
N06AX - Other antidepressants	4	1	0

N06B - Psychostimulants, agents used for adhd and nootropics	1	0	0
N06BA - Centrally acting sympathomimetics	1	0	0
N07 - Other nervous system drugs	4	2	3
N07A - Parasympathomimetics	<1	0	0
N07AX - Other parasympathomimetics	<1	0	0
N07B - Drugs used in addictive disorders	3	2	3
N07BA - Drugs used in nicotine dependence	2	1	2
N07BB - Drugs used in alcohol dependence	<1	0	0
N07BC - Drugs used in opioid dependence	<1	1	1
N07C - Antivertigo preparations	0	1	0
N07CA - Antivertigo preparations	0	1	0
P - Antiparasitic products, insecticides and repellants	1	2	1
P01 - Antiprotozoals	1	1	0
P01A - Agents against amoebiasis and other proto.diseases	1	1	0
P01AB - Nitroimidazole derivatives	1	1	0
P02 - Anthelmintics	0	1	0
P02C - Antinematodal agents	0	1	0
P02CA - Benzimidazole derivatives	0	1	0
P03 - Ectoparasiticides, incl scabicides, insecticides and repellants	0	0	1
P03A - Ectoparasiticides, incl scabicides	0	0	1
P03AC - Pyrethrines, incl synthetic compounds	0	0	1
R - Respiratory system	120	115	110
R01 - Nasal preparations	26	46	47
R01A - Decongestants and other nasal preparations for topical use	26	46	46
R01AA - Sympathomimetics, plain	12	23	22
R01AC - Antiallergic agents, excl corticosteroids	2	4	5
R01AD - Corticosteroids	12	14	14
R01AX - Other nasal preparations	0	5	4
R01B - Nasal decongestants for systemic use	<1	0	0
R01BA - Sympathomimetics	<1	0	0
R02 - Throat preparations	2	6	5
R02A - Throat preparations	2	6	5
R02AA - Antiseptics	2	5	4
R02AD - Anesthetics, local	0	1	1
R03 - Drugs for obstructive airway diseases	9	5	5
R03A - Adrenergics, inhalants	5	4	4
R03AC - Selective beta-2-adrenoceptor agonists	3	3	4
R03AK - Adrenergics and other drugs for obstructive airway diseases	2	1	0
R03B - Other drugs for obstructive airway diseases, inhalants	2	1	2
R03BA - Glucocorticoids	2	1	2
R03D - Other systemic drugs for obstructive airway diseases	2	0	0
R03DC - Leukotriene receptor antagonists	1	0	0
R03DX - Other systemic drugs for obstructive airway diseases	<1	0	0
R05 - Cough and cold preparations	10	11	10
R05C - Expectorants,excl combinations with antitussives	3	5	3
R05CA - Expectorants	1	4	1
R05CB - Mucolytics	1	2	2
R05D - Cough suppressants, excl. combinations with expectorants	5	4	6
R05DA - Opium alkaloids and derivatives	5	4	6

R05F - Antitussives and expectorants, combinations	<1	0	0
R05FA - Opium derivatives and expectorants	<1	0	0
R05X - Other cold preparations	<1	1	0
R06 - Antihistamines for systemic use	73	46	41
R06A - Antihistamines for systemic use	72	46	41
R06AA - Aminoalkyl ethers	1	3	2
R06AB - Substituted alkylamines	3	2	4
R06AD - Phenothiazine derivatives	12	7	1
R06AE - Piperazine derivatives	42	27	24
R06AX - Other antihistamines for systemic use	14	8	9
R07 - Other respiratory system products	0	0	1
R07A - Other respiratory system products	0	0	1
R07AX - Other respiratory system products	0	0	1
S - Sensory organs	5	7	6
S01 - Ophthalmologicals	5	7	5
S01A - Antiinfectives	1	1	4
S01AA - Antibiotics	1	1	4
S01B - Antiinflammatory agents	<1	1	0
S01BA - Corticosteroids, plain	<1	1	0
S01C - Antiinflammatory agents and antiinfectives in comb	<1	1	0
S01CA - Corticosteroids and antiinfectives in combination	<1	1	0
S01G - Decongestants and antiallergics	3	3	2
S01GX - Other antiallergics	3	3	2
S01K - Surgical aids	0	1	0
S01KA - Viscoelastic substances	0	1	0
S01X - Other ophthalmologicals	0	1	0
S01XA - Other ophthalmologicals	0	1	0
S02 - Otologicals	0	0	1
S02C - Corticosteroids and antiinfectives in combination	0	0	1
S02CA - Corticosteroids and antiinfectives in combination	0	0	1
V - Various	1	2	3
V01 - Allergens	<1	0	1
V01A - Allergens	<1	0	1
V01AA - Allergen extracts	<1	0	1
V03 - All other therapeutic products	1	2	1
V03A - All other therapeutic products	1	2	1
V03AB - Antidotes	1	1	0
V03AX - Other therapeutic products	0	1	1
V07 - All other non-therapeutic products	0	0	1
V07A - All other non-therapeutic products	0	0	1
V07AT - Cosmetics	0	0	1

13.7 Over-the-counter (OTC) medications

Table 13-12 Rates per 1000 women who reported use of OTC medications (including those available through both OTC and prescription)

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	397	357	162	543	411
A01 - Stomatological preparations	2	0	4	1	1

A01A - Stomatological preparations	2	0	4	1	1
A01AD - Other agents for local oral treatment	2	0	4	1	1
A02 - Drugs for acid related disorders	257	244	66	391	277
A02A - Antacids	175	160	8	3	93
A02AA - Magnesium compounds	59	13	0	0	21
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	116	147	8	3	72
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	81	84	58	388	185
A02BA - H2-receptor antagonists	2	2	46	39	20
A02BC - Proton pump inhibitors	44	46	8	48	42
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	36	36	4	300	123
A03 - Drugs for functional gastrointestinal disorders	3	0	4	0	1
A03A - Drugs for functional gastrointestinal disorders	3	0	4	0	1
A03AX - Other drugs for functional gastrointestinal disorders	3	0	4	0	1
A06 - Drugs for constipation	94	107	50	127	103
A06A - Drugs for constipation	94	107	50	127	103
A06AB - Contact laxatives	6	4	4	7	6
A06AC - Bulk-forming laxatives	53	19	0	44	36
A06AD - Osmotically acting laxatives	30	78	37	73	57
A06AG - Enemas	5	6	0	0	3
A06AX - Other drugs for constipation	0	0	8	3	2
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	17	2	25	17	15
A07D - Antipropulsives	6	2	8	17	9
A07DA - Antipropulsives	6	2	8	17	9
A07F - Antidiarrheal microorganisms	11	0	17	0	5
A07FA - Antidiarrheal microorganisms	11	0	17	0	5
A09 - Digestives, incl enzymes	2	0	0	1	1
A09A - Digestives, incl enzymes	2	0	0	1	1
A09AA - Enzyme preparations	2	0	0	1	1
A12 - Mineral supplements	23	4	12	6	12
A12A - Calcium	23	4	8	6	11
A12AX - Calcium, combinations with vitamin d and/or other drugs	23	4	8	6	11
A12B - Potassium	0	0	4	0	0
A12BA - Potassium	0	0	4	0	0
B - Blood and blood forming organs	17	8	21	31	20
B01 - Antithrombotic agents	17	8	21	31	20
B01A - Antithrombotic agents	17	8	21	31	20
B01AC - Platelet aggregation inhibitors excl. heparin	17	8	21	31	20
D - Dermatologicals	86	90	4	52	66
D01 - Antifungals for dermatological use	36	34	0	45	34
D01A - Antifungals for topical use	36	34	0	45	34
D01AC - Imidazole and triazole derivatives	31	32	0	45	32
D01AE - Other antifungals for topical use	5	2	0	0	2
D02 - Emollients and protectives	0	4	0	0	1
D02A - Emollients and protectives	0	4	0	0	1
D02AC - Soft paraffin and fat products	0	2	0	0	0
D02AX - Other emollients and protectives	0	2	0	0	0
D06 - Antibiotics and chemother. for dermatological use	39	48	0	0	23

D06B - Chemotherapeutics for topical use	39	48	0	0	23
D06BB - Antivirals	39	48	0	0	23
D07 - Corticosteroids, dermatological preparations	8	4	0	6	5
D07A - Corticosteroids, plain	8	4	0	6	5
D07AA - Corticosteroids, weak (group i)	8	4	0	6	5
D08 - Antiseptics and disinfectants	0	0	0	1	0
D08A - Antiseptics and disinfectants	0	0	0	1	0
D08AC - Biguanides and amidines	0	0	0	1	0
D10 - Anti-acne preparations	2	0	4	0	1
D10A - Anti-acne preparations for topical use	2	0	4	0	1
D10AE - Peroxides	2	0	4	0	1
D11 - Other dermatological preparations	2	0	0	0	0
D11A - Other dermatological preparations	2	0	0	0	0
D11AF - Wart and anti-corn preparations	2	0	0	0	0
G - Genito urinary system and sex hormones	99	21	50	25	50
G01 - Gynecological antiinfectives and antiseptics	99	21	50	25	50
G01A - Antiinfectives/antisept.,excl comb with corticost.	99	21	50	25	50
G01AF - Imidazole derivatives	99	21	50	25	50
M - Musculo-skeletal system	97	29	46	47	58
M01 - Antiinflammatory and antirheumatic products	95	29	46	45	57
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	95	29	46	45	57
M01AE - Propionic acid derivatives	95	29	46	44	57
M01AX - Other antiinfl./antirheumatic agents, non-steroids	0	0	0	1	0
M02 - Topical products for joint and muscular pain	2	0	0	1	1
M02A - Topical products for joint and muscular pain	2	0	0	1	1
M02AA - Antiinfl. prep., non-steroids for topical use	2	0	0	1	1
N - Nervous system	507	506	365	715	562
N01 - Anesthetics	0	0	4	3	1
N01B - Anesthetics, local	0	0	4	3	1
N01BB - Amides	0	0	4	3	1
N02 - Analgesics	505	504	357	705	556
N02B - Other analgesics and antipyretics	505	504	357	705	556
N02BA - Salicylic acid derivatives	27	6	21	48	29
N02BE - Anilides	479	498	336	657	528
N07 - Other nervous system drugs	2	2	4	7	4
N07B - Drugs used in addictive disorders	2	0	4	7	3
N07BA - Drugs used in nicotine dependence	2	0	4	7	3
N07C - Antivertigo preparations	0	2	0	0	0
N07CA - Antivertigo preparations	0	2	0	0	0
P - Antiparasitic products, insecticides and repellants	2	0	0	0	0
P01 - Antiprotozoals	2	0	0	0	0
P01B - Antimalarials	2	0	0	0	0
P01BC - Methanolquinolines	2	0	0	0	0
R - Respiratory system	205	181	50	173	170
R01 - Nasal preparations	64	109	12	63	68
R01A - Decongestants and other nasal preparations for topical use	64	109	12	63	68
R01AA - Sympathomimetics, plain	52	63	4	13	35

R01AC - Antiallergic agents, excl corticosteroids	0	13	4	8	6
R01AD - Corticosteroids	13	34	4	42	27
R02 - Throat preparations	13	0	0	1	4
R02A - Throat preparations	13	0	0	1	4
R02AA - Antiseptics	13	0	0	1	4
R05 - Cough and cold preparations	9	8	12	1	7
R05C - Expectorants,excl combinations with antitussives	3	8	12	1	5
R05CB - Mucolytics	3	8	12	1	5
R05D - Cough suppressants, excl. combinations with expectorants	6	0	0	0	2
R05DA - Opium alkaloids and derivatives	6	0	0	0	2
R06 - Antihistamines for systemic use	119	63	25	107	91
R06A - Antihistamines for systemic use	119	63	25	107	91
R06AA - Aminoalkyl ethers	3	2	0	4	3
R06AD - Phenothiazine derivatives	9	0	4	6	5
R06AE - Piperazine derivatives	77	27	8	73	56
R06AX - Other antihistamines for systemic use	30	34	12	24	27
S - Sensory organs	5	13	4	1	5
S01 - Ophthalmologicals	5	13	4	1	5
S01G - Decongestants and antiallergics	5	8	4	1	4
S01GX - Other antiallergics	5	8	4	1	4
S01X - Other ophthalmologicals	0	4	0	0	1
S01XA - Other ophthalmologicals	0	4	0	0	1

13.8 Prescription-only medications

Table 13-13 Rates per 1000 women who reported use of medications available only through prescriptions

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	161	103	357	295	216
A01 - Stomatological preparations	2	0	0	0	0
A01A - Stomatological preparations	2	0	0	0	0
A01AB - Antiinfectives for local oral treatment	2	0	0	0	0
A02 - Drugs for acid related disorders	9	17	75	42	30
A02A - Antacids	8	17	71	39	28
A02AA - Magnesium compounds	0	2	0	18	7
A02AB - Aluminium compounds	0	11	21	0	5
A02AC - Calcium compounds	0	0	46	3	6
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	0	0	0	8	3
A02AF - Antacids with antiflatulents	0	0	0	1	0
A02AH - Antacids with sodium bicarbonate	6	0	0	1	2
A02AX - Antacids, other combinations	0	2	0	7	3
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	2	0	4	3	2
A02BC - Proton pump inhibitors	2	0	0	3	1
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	0	0	4	0	0

A03 - Drugs for functional gastrointestinal disorders	22	25	75	44	36
A03A - Drugs for functional gastrointestinal disorders	0	4	66	8	12
A03AA - Synt anticholin,esters with tertiary amino group	0	2	0	8	3
A03AD - Papaverine and derivatives	0	0	66	0	8
A03AX - Other drugs for functional gastrointestinal disorders	0	2	0	0	0
A03B - Belladonna and derivatives, plain	0	4	0	4	2
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	0	4	0	4	2
A03F - Propulsives	22	17	8	31	22
A03FA - Propulsives	22	17	8	31	22
A04 - Antiemetics and antinauseants	19	2	8	18	14
A04A - Antiemetics and antinauseants	19	2	8	18	14
A04AA - Serotonin (5ht3) antagonists	16	0	0	13	9
A04AD - Other antiemetics	0	0	4	0	0
A05 - Bile and liver therapy	0	2	8	1	2
A05A - Bile therapy	0	2	4	1	1
A05AA - Bile acid preparations	0	2	4	1	1
A06 - Drugs for constipation	2	4	8	27	12
A06A - Drugs for constipation	2	4	8	27	12
A06AA - Softeners, emollients	2	0	0	0	0
A06AB - Contact laxatives	0	0	4	16	6
A06AD - Osmotically acting laxatives	0	0	0	11	4
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	14	8	58	17	19
A07A - Intestinal antiinfectives	0	4	8	0	2
A07AA - Antibiotics	0	4	8	0	2
A07B - Intestinal adsorbents	0	0	4	1	1
A07BA - Charcoal preparations	0	0	4	0	0
A07BC - Other intestinal adsorbents	0	0	0	1	0
A07C - Electrolytes with carbohydrates	0	2	4	3	2
A07CA - Oral rehydration salt formulations	0	2	4	3	2
A07E - Intestinal antiinflammatory agents	11	2	4	13	9
A07EA - Corticosteroids acting locally	2	0	0	1	1
A07EC - Aminosalicylic acid and similar agents	9	2	4	11	8
A07F - Antidiarrheal microorganisms	2	0	25	0	3
A07FA - Antidiarrheal microorganisms	2	0	25	0	3
A07X - Other antidiarrheals	0	0	12	0	1
A07XA - Other antidiarrheals	0	0	12	0	1
A10 - Drugs used in diabetes	28	19	37	78	44
A10A - Insulins and analogues	6	19	25	39	23
A10AB - Insulins and analogues for injection, fast-acting	3	15	25	25	16
A10AC - Insulins and analogues for injection, intermediate-acting	2	2	0	4	2
A10AD - Insulins and analogues for injection, intermed.act. comb. w. fast-act.	0	0	0	3	1
A10AE - Onsulins and analogues for injection, long-acting	2	0	0	7	3
A10B - Blood glucose lowering drugs, excl. insulins	22	0	12	38	21
A10BA - Biguanides	22	0	12	38	21
A12 - Mineral supplements	66	25	87	68	60
A12A - Calcium	33	4	8	63	34

A12AA - Calcium	33	4	4	63	33
A12C - Other mineral supplements	25	21	54	4	20
A12CA - Sodium	0	2	0	0	0
A12CB - Zinc	9	2	0	4	5
A12CC - Magnesium	3	11	46	0	9
A12CE - Selenium	5	2	0	0	2
A12CX - Other mineral products	6	0	8	0	3
B - Blood and blood forming organs	9	15	29	27	19
B01 - Antithrombotic agents	6	15	21	24	16
B01A - Antithrombotic agents	6	15	21	24	16
B01AA - Vitamin k antagonists	0	2	0	0	0
B01AB - Heparin group	5	13	21	24	15
B01AC - Platelet aggregation inhibitors excl. heparin	2	0	0	0	0
B02 - Antihemorrhagics	2	0	4	1	1
B02A - Antifibrinolytics	2	0	0	0	0
B02AA - Amino acids	2	0	0	0	0
B02B - Vitamin k and other hemostatics	0	0	4	1	1
B02BA - Vitamin k	0	0	0	1	0
B02BX - Other systemic hemostatics	0	0	4	0	0
B05 - Blood substitutes and perfusion solutions	2	0	0	1	1
B05B - I.v. solutions	2	0	0	0	0
B05BA - Solutions for parenteral nutrition	2	0	0	0	0
B05X - I.v. solution additives	0	0	0	1	0
B05XB - Amino acids	0	0	0	1	0
C - Cardiovascular system	47	40	124	45	54
C01 - Cardiac therapy	0	0	0	1	0
C01C - Cardiac stimulants excl. cardiac glycosides	0	0	0	1	0
C01CA - Adrenergic and dopaminergic agents	0	0	0	1	0
C02 - Antihypertensives	3	6	37	3	8
C02A - Antiadrenergic agents, centrally acting	3	6	37	3	8
C02AA - Rauwolfia alkaloids	0	0	4	0	0
C02AB - Methyldopa	3	6	33	3	7
C03 - Diuretics	2	0	0	3	1
C03A - Low-ceiling diuretics, thiazides	0	0	0	1	0
C03AA - Thiazides, plain	0	0	0	1	0
C03C - High-ceiling diuretics	2	0	0	0	0
C03CA - Sulfonamides, plain	2	0	0	0	0
C03D - Potassium-sparing agents	0	0	0	1	0
C03DA - Aldosterone antagonists	0	0	0	1	0
C05 - Vasoprotectives	27	17	71	8	23
C05A - Agents for treatment of hemorrhoids and anal fissures for topical use	27	17	4	8	15
C05AA - Corticosteroids	25	4	0	0	9
C05AD - Local anesthetics	0	2	0	0	0
C05AE - Musclerelaxants	0	0	0	1	0
C05AX - Other agents for treatment of hemorrhoids and anal fissures for topical use	0	6	4	7	4
C05C - Capillary stabilizing agents	0	0	66	0	8

C05CA - Bioflavonoids	0	0	66	0	8
C07 - Beta blocking agents	9	8	4	17	11
C07A - Beta blocking agents, plain	9	8	4	17	11
C07AA - Beta blocking agents, plain, non-selective	0	0	0	8	3
C07AB - Beta blocking agents, plain, selective	2	2	4	4	3
C07AG - Alpha- and beta blocking agents	8	6	0	4	5
C08 - Calcium channel blockers	0	6	4	6	4
C08C - Selective calcium channel blockers with mainly vascular effects	0	6	0	3	2
C08CA - Dihydropyridine derivatives	0	6	0	3	2
C08D - Selective calcium channel blockers with direct cardiac effects	0	0	4	3	1
C08DA - Phenylalkylamine derivatives	0	0	4	1	1
C08DB - Benzothiazepine derivatives	0	0	0	1	0
C09 - Agents acting on the renin-angiotensin system	3	0	4	3	2
C09A - Ace-inhibitors, plain	2	0	0	3	1
C09AA - Ace-inhibitors, plain	2	0	0	3	1
C09C - Angiotensin ii antagonists	2	0	4	0	1
C09CA - Angiotensin ii antagonists, plain	2	0	4	0	1
C10 - Lipid modifying agents	2	2	4	4	3
C10A - Lipid modifying agents, plain	2	2	4	4	3
C10AA - Hmg coa reductase inhibitors	2	2	4	0	1
C10AC - Bile acid sequestrants	0	0	0	1	0
C10AX - Other lipid modifying agents	0	0	0	3	1
D - Dermatologicals	52	44	137	37	55
D01 - Antifungals for dermatological use	11	4	120	4	20
D01A - Antifungals for topical use	11	4	120	4	20
D01AA - Antibiotics	0	0	108	0	13
D01AC - Imidazole and triazole derivatives	11	0	12	4	6
D01AE - Other antifungals for topical use	0	4	0	0	1
D02 - Emollients and protectives	0	2	0	1	1
D02A - Emollients and protectives	0	2	0	1	1
D02AF - Salicylic acid preparations	0	0	0	1	0
D04 - Antipruritics,incl antihist,anesthet,etc.	0	0	0	3	1
D04A - Antipruritics,incl antihist,anesthet,etc.	0	0	0	3	1
D04AA - Antihistamines for topical use	0	0	0	3	1
D05 - Antipsoriatics	2	0	0	3	1
D05A - Antipsoriatics for topical use	2	0	0	3	1
D05AX - Other antipsoriatics for topical use	2	0	0	3	1
D06 - Antibiotics and chemother. for dermatological use	13	4	8	7	8
D06A - Antibiotics for topical use	8	2	0	3	4
D06AX - Other antibiotics for topical use	8	2	0	3	4
D06B - Chemotherapeutics for topical use	5	0	8	4	4
D06BB - Antivirals	0	0	8	1	1
D06BX - Other chemotherapeutics	5	0	0	3	2
D07 - Corticosteroids, dermatological preparations	22	25	8	13	18
D07A - Corticosteroids, plain	19	17	4	10	14
D07AA - Corticosteroids, weak (group i)	0	0	0	1	0

D07AB - Corticosteroids, moderately potent (group ii)	11	13	4	3	8
D07AC - Corticosteroids, potent (group iii)	8	2	0	6	5
D07B - Corticosteroids, comb with antiseptics	0	0	0	1	0
D07BC - Corticosteroids, potent, comb with antiseptics	0	0	0	1	0
D07C - Corticosteroids, comb with antibiotics	3	0	4	0	1
D07CA - Corticosteroids, weak, comb with antibiotics	0	0	4	0	0
D07CC - Corticosteroids, potent, comb with antibiotics	3	0	0	0	1
D07X - Corticosteroids, other combinations	0	6	0	0	1
D07XA - Corticosteroids, weak, other combinations	0	4	0	0	1
D09 - Medicated dressings	0	0	0	1	0
D09A - Medicated dressings	0	0	0	1	0
D09AA - Ointment dressings with antiinfectives	0	0	0	1	0
D10 - Anti-acne preparations	3	4	0	3	3
D10A - Anti-acne preparations for topical use	3	4	0	3	3
D10AD - Retinoids for topical use in acne	0	4	0	0	1
D10AF - Antiinfectives for treatment of acne	2	0	0	1	1
D10AX - Other anti-acne preparations for topical use	2	0	0	1	1
D11 - Other dermatological preparations	2	0	0	1	1
D11A - Other dermatological preparations	2	0	0	1	1
D11AH - Agents for dermatitis, excluding corticosteroids	2	0	0	1	1
G - Genito urinary system and sex hormones	275	282	336	176	250
G01 - Gynecological antiinfectives and antiseptics	33	29	79	0	26
G01A - Antiinfectives/antisept.,excl comb with corticost.	33	29	79	0	26
G01AA - Antibiotics	0	0	25	0	3
G01AF - Imidazole derivatives	33	29	29	0	20
G01AX - Other antiinfectives and antiseptics	0	0	25	0	3
G02 - Other gynecologicals	5	19	33	3	11
G02B - Contraceptives for topical use	5	13	0	3	5
G02BA - Intrauterine contraceptives	3	6	0	3	3
G02BB - Intravaginal contraceptives	2	6	0	0	2
G02C - Other gynecologicals	0	6	33	0	5
G02CA - Sympathomimetics, labour repressants	0	0	4	0	0
G02CB - Prolactine inhibitors	0	0	29	0	3
G02CX - Other gynecologicals	0	6	0	0	1
G03 - Sex hormones and modulators of the genital system	238	233	216	172	212
G03A - Hormonal contraceptives for systemic use	36	55	33	104	63
G03AA - Progestogens and estrogens, fixed combinations	11	8	0	27	15
G03AC - Progestogens	3	6	4	23	11
G03AD - Emergency contraceptives	3	21	8	13	11
G03B - Androgens	0	0	0	1	0
G03BA - 3-oxoandrosten (4) derivatives	0	0	0	1	0
G03C - Estrogens	6	2	0	4	4
G03CA - Natural and semisynthetic estrogens, plain	6	2	0	4	4
G03D - Progestogens	49	17	124	7	36
G03DA - Pregnen (4) derivatives	49	15	75	7	30
G03DB - Pregnadien derivatives	0	0	50	0	6
G03DC - Estren derivatives	0	2	0	0	0

G03G - Gonadotropins and other ovulation stimulants	147	160	58	54	108
G03GA - Gonadotropins	122	126	17	35	81
G03GB - Ovulation stimulants, synthetic	25	34	41	18	27
G04 - Urologicals	0	0	8	1	1
G04B - Urologicals	0	0	8	1	1
G04BD - Drugs for urinary frequency and incontinence	0	0	0	1	0
G04BX - Other urologicals	0	0	8	0	1
H - Systemic hormonal prep, excl sex hormones	44	69	112	44	58
H01 - Pituitary, hypothalamic hormones and analogues	5	6	0	4	4
H01B - Posterior pituitary lobe hormones	0	2	0	0	0
H01BB - Oxytocin and analogues	0	2	0	0	0
H01C - Hypothalamic hormones	5	4	0	4	4
H01CA - Gonadotrophin-releasing hormones	0	4	0	3	2
H01CC - Anti gonadotropin releasing hormones	5	0	0	1	2
H02 - Corticosteroids for systemic use	11	19	21	7	13
H02A - Corticosteroids for systemic use, plain	9	19	21	7	12
H02AB - Glucocorticoids	9	19	21	7	12
H03 - Thyroid therapy	28	44	91	32	41
H03A - Thyroid preparations	28	38	87	31	38
H03AA - Thyroid hormones	28	38	87	31	38
H03B - Antithyroid preparations	0	6	4	1	2
H03BA - Thiouracils	0	4	4	0	1
H03BB - Sulphur-containing imidazole derivatives	0	2	0	1	1
J - General antiinfectives for systemic use	235	103	241	385	257
J01 - Antibacterials for systemic use	197	95	183	291	204
J01A - Tetracyclines	3	2	4	0	2
J01AA - Tetracyclines	3	2	4	0	2
J01C - Beta-lactam antibacterials, penicillins	161	36	95	188	134
J01CA - Penicillins with extended spectrum	113	23	79	159	104
J01CE - Beta-lactamase sensitive penicillins	44	2	0	6	16
J01CF - Beta-lactamase resistant penicillins	3	0	0	11	5
J01CR - Comb of penicillins, incl. beta-lactamase inhib.	0	11	17	10	8
J01D - Other beta-lactam antibacterials	0	0	17	34	14
J01DB - First-generation cephalosporins	0	0	0	32	11
J01DC - Second-generation cephalosporins	0	0	17	0	2
J01DF - Monobactams	0	0	0	1	0
J01E - Sulfonamides and trimethoprim	14	2	0	7	7
J01EA - Trimethoprim and derivatives	0	2	0	7	3
J01EB - Short-acting sulfonamides	14	0	0	0	4
J01F - Macrolides, lincosamides and streptogramins	6	2	29	25	15
J01FA - Macrolides	6	2	25	25	14
J01FF - Lincosamides	0	0	4	0	0
J01X - Other antibacterials	3	36	33	21	20
J01XD - Imidazole derivatives	0	0	0	1	0
J01XE - Nitrofuran derivatives	3	36	17	20	18
J01XX - Other antibacterials	0	0	17	0	2
J02 - Antimycotics for systemic use	22	2	4	66	31

J02A - Antimycotics for systemic use	22	2	4	66	31
J02AB - Imidazole derivatives	0	0	0	3	1
J02AC - Triazole derivatives	22	2	4	61	29
J02AX - Other antimycotics for systemic use	0	0	0	3	1
J05 - Antivirals for systemic use	14	4	54	27	21
J05A - Direct acting antivirals	14	4	54	27	21
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	13	0	54	27	19
J05AH - Neuraminidase inhibitors	2	0	0	0	0
J05AR - Antivirals for treatment of hiv infections, comb.	0	2	0	0	0
J05AX - Other antivirals	0	2	0	0	0
J06 - Immune sera and immunoglobulins	2	2	0	1	1
J06B - Immunoglobulins	2	2	0	1	1
J06BB - Specific immunoglobulins	2	2	0	1	1
L - Antineoplastic and immunomodulating agents	9	34	4	14	16
L02 - Endocrine therapy	5	27	0	6	10
L02A - Hormones and related agents	5	27	0	3	9
L02AE - Gonadotrophin releasing hormone analogues	5	27	0	3	9
L02B - Hormone antagonists and related agents	0	0	0	3	1
L02BA - Anti-estrogens	0	0	0	3	1
L03 - Immunostimulants	0	0	4	0	0
L03A - Immunostimulants	0	0	4	0	0
L03AX - Other immunostimulants	0	0	4	0	0
L04 - Immunosuppressants	5	6	0	8	6
L04A - Immunosuppressants	5	6	0	8	6
L04AB - Tumor necrosis factor alpha (tnf-alpha) inhibitors	2	2	0	1	1
L04AD - Calcineurin inhibitors	2	0	0	0	0
L04AX - Other immunosuppressants	2	4	0	7	4
M - Musculo-skeletal system	14	0	21	30	17
M01 - Antiinflammatory and antirheumatic products	14	0	8	27	15
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	14	0	8	27	15
M01AB - Acetic acid derivatives and related substances	8	0	0	11	6
M01AC - Oxicams	0	0	4	0	0
M01AE - Propionic acid derivatives	2	0	4	13	5
M01AG - Fenamates	5	0	0	1	2
M01AH - Coxibs	0	0	0	1	0
M02 - Topical products for joint and muscular pain	0	0	12	0	1
M02A - Topical products for joint and muscular pain	0	0	12	0	1
M02AA - Antiinfl. prep., non-steroids for topical use	0	0	8	0	1
M02AX - Other topical products for joint and muscular pain	0	0	4	0	0
M04 - Antigout preparations	0	0	0	1	0
M04A - Antigout preparations	0	0	0	1	0
M04AA - Preparations inhibiting uric acid production	0	0	0	1	0
M09 - Other drugs for disorders of musculo-skeletal syst	0	0	0	1	0
M09A - Other drugs for disorders of musculo-skeletal syst	0	0	0	1	0
M09AA - Quinine and derivatives	0	0	0	1	0
N - Nervous system	185	120	87	178	156

N01 - Anesthetics	0	0	0	1	0
N01A - Anesthetics, general	0	0	0	1	0
N01AX - Other general anesthetics	0	0	0	1	0
N02 - Analgesics	70	40	25	34	46
N02A - Opioids	30	19	0	25	22
N02AA - Natural opium alkaloids	13	8	0	16	11
N02AB - Phenylpiperidine derivatives	2	0	0	0	0
N02AX - Other opioids	16	11	0	10	11
N02B - Other analgesics and antipyretics	2	0	17	3	3
N02BA - Salicylic acid derivatives	0	0	0	1	0
N02BB - Pyrazolones	0	0	12	0	1
N02BE - Anilides	2	0	4	0	1
N02C - Antimigraine preparations	39	19	8	6	19
N02CA - Ergot alkaloids	0	0	4	0	0
N02CC - Selective 5ht(1)-receptor agonists	38	19	4	6	18
N03 - Antiepileptics	14	6	8	11	11
N03A - Antiepileptics	14	6	8	11	11
N03AA - Barbiturates and derivatives	0	0	4	0	0
N03AB - Hydantoin derivatives	0	2	0	0	0
N03AF - Carboxamide derivatives	2	0	0	1	1
N03AG - Fatty acid derivatives	2	0	4	0	1
N03AX - Other antiepileptics	11	4	0	10	8
N04 - Anti-parkinson drugs	0	2	0	0	0
N04B - Dopaminergic agents	0	2	0	0	0
N04BC - Dopamine agonists	0	2	0	0	0
N05 - Psycholeptics	14	27	29	39	28
N05A - Antipsychotics	8	6	0	34	15
N05AB - Phenothiazine with piperazine structure	2	0	0	27	10
N05AH - Diazepines, oxazepines, thiazepines and oxepines	5	6	0	6	5
N05AN - Lithium	2	0	0	1	1
N05B - Anxiolytics	3	4	25	3	6
N05BA - Benzodiazepine derivatives	3	4	21	3	5
N05BB - Diphenylmethane derivatives	0	0	4	0	0
N05C - Hypnotics and sedatives	3	17	4	3	6
N05CD - Benzodiazepine derivatives	2	11	0	0	3
N05CF - Benzodiazepine related drugs	0	0	0	3	1
N05CH - Melatonin receptor agonists	2	4	4	0	2
N05CM - Other hypnotics and sedatives	0	2	0	0	0
N06 - Psychoanaleptics	85	42	17	85	67
N06A - Antidepressants	81	40	17	83	65
N06AA - Non selective monoamine reuptake inhibitors	2	2	4	11	5
N06AB - Selective serotonin reuptake inhibitors	56	29	4	55	44
N06AX - Other antidepressants	23	8	8	14	15
N06B - Psychostimulants, agents used for adhd and nootropics	3	2	0	0	1
N06BA - Centrally acting sympathomimetics	3	2	0	0	1
N06C - Psycholeptics and psychoanaleptics in combination	0	0	0	1	0
N06CA - Antidepressants in combination with psycholeptics	0	0	0	1	0

N07 - Other nervous system drugs	2	2	8	7	4
N07A - Parasympathomimetics	0	0	0	1	0
N07AX - Other parasympathomimetics	0	0	0	1	0
N07B - Drugs used in addictive disorders	2	0	4	4	2
N07BA - Drugs used in nicotine dependence	2	0	0	0	0
N07BB - Drugs used in alcohol dependence	0	0	4	0	0
N07BC - Drugs used in opioid dependence	0	0	0	4	1
N07C - Antivertigo preparations	0	2	4	1	1
N07CA - Antivertigo preparations	0	2	4	1	1
P - Antiparasitic products, insecticides and repellants	3	2	0	11	5
P01 - Antiprotozoals	2	2	0	8	4
P01A - Agents against amoebiasis and other proto.diseases	2	2	0	4	2
P01AB - Nitroimidazole derivatives	2	2	0	4	2
P01B - Antimalarials	0	0	0	4	1
P01BA - Aminoquinolines	0	0	0	4	1
P02 - Anthelmintics	2	0	0	0	0
P02C - Antinematodal agents	2	0	0	0	0
P02CA - Benzimidazole derivatives	2	0	0	0	0
P03 - Ectoparasiticides, incl scabicides, insecticides and repellants	0	0	0	3	1
P03A - Ectoparasiticides, incl scabicides	0	0	0	3	1
P03AC - Pyrethrines, incl synthetic compounds	0	0	0	1	0
P03AX - Other ectoparasiticides, incl scabicides	0	0	0	1	0
R - Respiratory system	125	233	199	272	209
R01 - Nasal preparations	19	23	50	21	24
R01A - Decongestants and other nasal preparations for topical use	17	19	46	20	22
R01AA - Sympathomimetics, plain	0	0	21	8	5
R01AB - Sympathomimetics,combinations excl corticosteroids	0	0	4	0	0
R01AD - Corticosteroids	17	4	12	6	10
R01AX - Other nasal preparations	0	15	8	6	6
R01B - Nasal decongestants for systemic use	0	0	4	1	1
R01BA - Sympathomimetics	0	0	4	1	1
R02 - Throat preparations	0	4	25	1	4
R02A - Throat preparations	0	4	25	1	4
R02AA - Antiseptics	0	0	25	1	3
R02AD - Anesthetics, local	0	4	0	0	1
R03 - Drugs for obstructive airway diseases	95	105	50	165	116
R03A - Adrenergics, inhalants	72	67	25	111	79
R03AC - Selective beta-2-adrenoceptor agonists	50	50	21	100	64
R03AK - Adrenergics and other drugs for obstructive airway diseases	22	17	4	11	15
R03B - Other drugs for obstructive airway diseases, inhalants	20	29	21	48	32
R03BA - Glucocorticoids	20	27	21	44	30
R03BB - Anticholinergics	0	2	0	1	1
R03BC - Antiallergic agents, excl corticosteroids	0	0	0	3	1
R03D - Other systemic drugs for obstructive airway diseases	0	4	4	6	3
R03DA - Xanthines	0	0	0	1	0
R03DC - Leukotriene receptor antagonists	0	2	4	4	2

R03DX - Other systemic drugs for obstructive airway diseases	0	2	0	0	0
R05 - Cough and cold preparations	6	11	50	25	19
R05C - Expectorants,excl combinations with antitussives	0	0	41	0	5
R05CA - Expectorants	0	0	41	0	5
R05D - Cough suppressants, excl. combinations with expectorants	5	6	0	24	11
R05DA - Opium alkaloids and derivatives	5	6	0	24	11
R05F - Antitussives and expectorants, combinations	2	0	0	0	0
R05FA - Opium derivatives and expectorants	2	0	0	0	0
R05X - Other cold preparations	0	0	8	1	1
R06 - Antihistamines for systemic use	3	90	21	59	45
R06A - Antihistamines for systemic use	3	88	21	59	44
R06AA - Aminoalkyl ethers	0	0	4	1	1
R06AB - Substituted alkylamines	0	0	0	21	7
R06AD - Phenothiazine derivatives	0	0	17	27	11
R06AE - Piperazine derivatives	0	82	0	1	19
R06AX - Other antihistamines for systemic use	0	2	0	1	1
R07 - Other respiratory system products	0	0	4	0	0
R07A - Other respiratory system products	0	0	4	0	0
R07AX - Other respiratory system products	0	0	4	0	0
S - Sensory organs	19	15	8	10	14
S01 - Ophthalmologicals	19	13	8	8	13
S01A - Antiinfectives	6	2	0	4	4
S01AA - Antibiotics	6	2	0	4	4
S01B - Antiinflammatory agents	2	6	0	1	2
S01BA - Corticosteroids, plain	2	4	0	1	2
S01C - Antiinflammatory agents and antiinfectives in comb	2	0	8	0	1
S01CA - Corticosteroids and antiinfectives in combination	2	0	8	0	1
S01G - Decongestants and antiallergics	9	2	0	1	4
S01GX - Other antiallergics	6	2	0	1	3
S01K - Surgical aids	0	0	0	1	0
S01KA - Viscoelastic substances	0	0	0	1	0
S02 - Otologicals	0	2	0	1	1
S02C - Corticosteroids and antiinfectives in combination	0	0	0	1	0
S02CA - Corticosteroids and antiinfectives in combination	0	0	0	1	0
V - Various	5	0	29	0	5
V01 - Allergens	5	0	0	0	1
V01A - Allergens	5	0	0	0	1
V01AA - Allergen extracts	5	0	0	0	1
V03 - All other therapeutic products	0	0	21	0	2
V03A - All other therapeutic products	0	0	21	0	2
V03AB - Antidotes	0	0	17	0	2
V03AX - Other therapeutic products	0	0	4	0	0
V06 - General nutrients	0	0	4	0	0
V06D - Other nutrients	0	0	4	0	0
V07 - All other non-therapeutic products	0	0	4	0	0
V07A - All other non-therapeutic products	0	0	4	0	0
V07AT - Cosmetics	0	0	4	0	0

13.9 Medications for chronic medical conditions

Table 13-14 Rates per 1000 women taking medication for chronic medical conditions up to a month before and during pregnancy

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	63	67	83	161	100
A02 - Drugs for acid related disorders	30	29	46	68	45
A02A - Antacids	9	11	8	3	7
A02AA - Magnesium compounds	8	2	0	0	3
A02AA04 - Magnesium hydroxide	8	2	0	0	3
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	2	8	4	0	3
A02AD01 - Ordinary salt combinations	2	8	4	0	3
A02AF - Antacids with antiflatulents	0	0	0	1	0
A02AF01 - Magaldrate and antiflatulents	0	0	0	1	0
A02AX - Antacids, other combinations	0	0	0	1	0
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	20	19	37	65	37
A02BA - H2-receptor antagonists	0	2	29	10	7
A02BA02 - Ranitidine	0	2	29	10	7
A02BC - Proton pump inhibitors	20	17	8	24	19
A02BC01 - Omeprazole	8	17	0	20	13
A02BC02 - Pantoprazole	2	0	8	0	1
A02BC03 - Lansoprazole	11	0	0	3	4
A02BC05 - Esomeprazole	0	0	0	1	0
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	0	0	0	31	11
A02BX13 - Alginic acid	0	0	0	31	11
A03 - Drugs for functional gastrointestinal disorders	0	6	4	10	5
A03A - Drugs for functional gastrointestinal disorders	0	4	4	6	3
A03AA - Synt anticholin,esters with tertiary amino group	0	2	0	6	2
A03AA04 - Mebeverine	0	2	0	6	2
A03AD - Papaverine and derivatives	0	0	4	0	0
A03AD02 - Drotaverine	0	0	4	0	0
A03AX - Other drugs for functional gastrointestinal disorders	0	2	0	0	0
A03B - Belladonna and derivatives, plain	0	2	0	1	1
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	0	2	0	1	1
A03BB01 - Butylscopolamine	0	2	0	1	1
A03F - Propulsives	0	0	0	3	1
A03FA - Propulsives	0	0	0	3	1
A03FA01 - Metoclopramide	0	0	0	1	0
A03FA03 - Domperidone	0	0	0	1	0
A04 - Antiemetics and antinauseants	2	0	0	0	0
A04A - Antiemetics and antinauseants	2	0	0	0	0
A04AA - Serotonin (5ht3) antagonists	2	0	0	0	0

A04AA01 - Ondansetron	2	0	0	0	0
A05 - Bile and liver therapy	0	0	4	0	0
A05A - Bile therapy	0	0	4	0	0
A05AA - Bile acid preparations	0	0	4	0	0
A05AA02 - Ursodeoxycholic acid	0	0	4	0	0
A06 - Drugs for constipation	5	17	0	16	11
A06A - Drugs for constipation	5	17	0	16	11
A06AC - Bulk-forming laxatives	3	4	0	6	4
A06AC01 - Ispaghula (psylla seeds)	3	4	0	6	4
A06AD - Osmotically acting laxatives	2	13	0	10	7
A06AD11 - Lactulose	0	0	0	7	2
A06AD15 - Macrogol	0	0	0	3	1
A06AD65 - Macrogol, combinations	2	13	0	0	3
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	11	2	8	16	10
A07D - Antipropulsives	0	0	4	4	2
A07DA - Antipropulsives	0	0	4	4	2
A07DA03 - Loperamide	0	0	4	4	2
A07E - Intestinal antiinflammatory agents	11	2	4	11	8
A07EA - Corticosteroids acting locally	2	0	0	1	1
A07EA01 - Prednisolone	2	0	0	0	0
A07EA06 - Budesonide	0	0	0	1	0
A07EC - Aminosalicylic acid and similar agents	9	2	4	10	7
A07EC01 - Sulfasalazine	3	0	0	0	1
A07EC02 - Mesalazine	6	2	4	10	6
A09 - Digestives, incl enzymes	0	0	0	1	0
A09A - Digestives, incl enzymes	0	0	0	1	0
A09AA - Enzyme preparations	0	0	0	1	0
A09AA02 - Multienzymes (lipase, protease etc)	0	0	0	1	0
A10 - Drugs used in diabetes	14	13	21	47	26
A10A - Insulins and analogues	6	13	17	32	18
A10AB - Insulins and analogues for injection, fast-acting	3	11	17	18	12
A10AB01 - Insulin (human)	0	0	0	3	1
A10AB04 - Insulin lispro	0	4	4	3	2
A10AB05 - Insulin aspart	3	6	12	13	8
A10AC - Insulins and analogues for injection, intermediate-acting	2	0	0	4	2
A10AC01 - Insulin (human)	2	0	0	4	2
A10AD - Insulins and analogues for injection, intermed.act. comb. w. fast-act.	0	0	0	3	1
A10AD01 - Insulin (human)	0	0	0	1	0
A10AD05 - Insulin aspart	0	0	0	1	0
A10AE - Onsulins and analogues for injection, long-acting	2	0	0	7	3
A10AE04 - Insulin glargine	0	0	0	6	2
A10AE05 - Insulin detemir	2	0	0	1	1
A10B - Blood glucose lowering drugs, excl. insulins	8	0	4	14	8
A10BA - Biguanides	8	0	4	14	8
A10BA02 - Metformin	8	0	4	14	8
A12 - Mineral supplements	2	0	0	4	2
A12A - Calcium	2	0	0	4	2

A12AA - Calcium	2	0	0	1	1
A12AA04 - Calcium carbonate	0	0	0	1	0
A12AX - Calcium, combinations with vitamin d and/or other drugs	0	0	0	3	1
B - Blood and blood forming organs	5	6	8	16	9
B01 - Antithrombotic agents	5	6	8	16	9
B01A - Antithrombotic agents	5	6	8	16	9
B01AB - Heparin group	0	2	4	4	2
B01AB01 - Heparin	0	0	0	1	0
B01AB05 - Enoxaparin	0	0	4	3	1
B01AB06 - Nadroparin	0	2	0	0	0
B01AC - Platelet aggregation inhibitors excl. heparin	5	4	4	11	7
B01AC06 - Acetylsalicylic acid	3	4	4	11	6
B01AC30 - Combinations	2	0	0	0	0
C - Cardiovascular system	14	17	21	17	16
C02 - Antihypertensives	2	4	12	0	3
C02A - Antiadrenergic agents, centrally acting	2	4	12	0	3
C02AB - Methyldopa	2	4	12	0	3
C02AB01 - Methyldopa (levorotatory)	2	4	12	0	3
C03 - Diuretics	2	0	0	1	1
C03A - Low-ceiling diuretics, thiazides	0	0	0	1	0
C03AA - Thiazides, plain	0	0	0	1	0
C03AA01 - Bendroflumethiazide	0	0	0	1	0
C03C - High-ceiling diuretics	2	0	0	0	0
C03CA - Sulfonamides, plain	2	0	0	0	0
C03CA01 - Furosemide	2	0	0	0	0
C07 - Beta blocking agents	8	8	4	10	8
C07A - Beta blocking agents, plain	8	8	4	10	8
C07AA - Beta blocking agents, plain, non-selective	0	0	0	3	1
C07AA05 - Propranolol	0	0	0	3	1
C07AB - Beta blocking agents, plain, selective	2	2	4	3	2
C07AB02 - Metoprolol	2	2	4	0	1
C07AB03 - Atenolol	0	0	0	1	0
C07AB07 - Bisoprolol	0	0	0	1	0
C07AG - Alpha- and beta blocking agents	6	6	0	4	5
C07AG01 - Labetalol	6	6	0	4	5
C08 - Calcium channel blockers	0	2	4	1	1
C08C - Selective calcium channel blockers with mainly vascular effects	0	2	0	0	0
C08CA - Dihydropyridine derivatives	0	2	0	0	0
C08CA05 - Nifedipine	0	2	0	0	0
C08D - Selective calcium channel blockers with direct cardiac effects	0	0	4	1	1
C08DA - Phenylalkylamine derivatives	0	0	4	0	0
C08DA01 - Verapamil	0	0	4	0	0
C08DB - Benzothiazepine derivatives	0	0	0	1	0
C08DB01 - Diltiazem	0	0	0	1	0
C09 - Agents acting on the renin-angiotensin system	2	0	0	3	1
C09A - Ace-inhibitors, plain	0	0	0	3	1
C09AA - Ace-inhibitors, plain	0	0	0	3	1

C09AA04 - Perindopril	0	0	0	3	1
C09C - Angiotensin ii antagonists	2	0	0	0	0
C09CA - Angiotensin ii antagonists, plain	2	0	0	0	0
C09CA01 - Losartan	2	0	0	0	0
C10 - Lipid modifying agents	2	2	0	1	1
C10A - Lipid modifying agents, plain	2	2	0	1	1
C10AA - Hmg coa reductase inhibitors	2	2	0	0	1
C10AA01 - Simvastatin	2	2	0	0	1
C10AC - Bile acid sequestrants	0	0	0	1	0
C10AC01 - Colestyramine	0	0	0	1	0
D - Dermatologicals	6	15	0	7	8
D02 - Emollients and protectives	0	2	0	0	0
D02A - Emollients and protectives	0	2	0	0	0
D02AC - Soft paraffin and fat products	0	2	0	0	0
D05 - Antipsoriatics	2	0	0	0	0
D05A - Antipsoriatics for topical use	2	0	0	0	0
D05AX - Other antipsoriatics for topical use	2	0	0	0	0
D05AX52 - Calcipotriol, combinations	2	0	0	0	0
D06 - Antibiotics and chemother. for dermatological use	2	0	0	0	0
D06B - Chemotherapeutics for topical use	2	0	0	0	0
D06BB - Antivirals	2	0	0	0	0
D06BB03 - Aciclovir	2	0	0	0	0
D07 - Corticosteroids, dermatological preparations	2	13	0	6	5
D07A - Corticosteroids, plain	2	8	0	6	4
D07AA - Corticosteroids, weak (group i)	0	2	0	1	1
D07AA02 - Hydrocortisone	0	2	0	1	1
D07AB - Corticosteroids, moderately potent (group ii)	2	4	0	1	2
D07AB01 - Clobetasone	0	2	0	0	0
D07AB02 - Hydrocortisone butyrate	2	0	0	1	1
D07AB09 - Triamcinolone	0	2	0	0	0
D07AC - Corticosteroids, potent (group iii)	0	2	0	3	1
D07AC01 - Betamethasone	0	0	0	1	0
D07AC03 - Desoximetasone	0	2	0	0	0
D07X - Corticosteroids, other combinations	0	2	0	0	0
D07XA - Corticosteroids, weak, other combinations	0	2	0	0	0
D07XA01 - Hydrocortisone	0	2	0	0	0
D10 - Anti-acne preparations	2	0	0	0	0
D10A - Anti-acne preparations for topical use	2	0	0	0	0
D10AX - Other anti-acne preparations for topical use	2	0	0	0	0
D10AX03 - Azelaic acid	2	0	0	0	0
D11 - Other dermatological preparations	0	0	0	1	0
D11A - Other dermatological preparations	0	0	0	1	0
D11AH - Agents for dermatitis, excluding corticosteroids	0	0	0	1	0
D11AH01 - Tacrolimus	0	0	0	1	0
H - Systemic hormonal prep, excl sex hormones	22	34	54	25	30
H02 - Corticosteroids for systemic use	3	4	4	6	4
H02A - Corticosteroids for systemic use, plain	3	4	4	6	4
H02AB - Glucocorticoids	3	4	4	6	4
H02AB04 - Methylprednisolone	0	0	4	0	0

H02AB06 - Prednisolone	2	4	0	4	3
H02AB07 - Prednisone	2	0	0	0	0
H02AB09 - Hydrocortisone	0	0	0	1	0
H03 - Thyroid therapy	19	29	50	20	25
H03A - Thyroid preparations	19	25	50	18	24
H03AA - Thyroid hormones	19	25	50	18	24
H03AA01 - Levothyroxine sodium	19	25	50	18	24
H03B - Antithyroid preparations	0	4	0	1	1
H03BA - Thiouracils	0	4	0	0	1
H03BA02 - Propylthiouracil	0	4	0	0	1
H03BB - Sulphur-containing imidazole derivatives	0	0	0	1	0
H03BB01 - Carbimazole	0	0	0	1	0
J - General antiinfectives for systemic use	3	0	8	3	3
J01 - Antibacterials for systemic use	2	0	8	3	2
J01A - Tetracyclines	2	0	0	0	0
J01AA - Tetracyclines	2	0	0	0	0
J01AA02 - Doxycycline	2	0	0	0	0
J01C - Beta-lactam antibacterials, penicillins	0	0	0	1	0
J01CE - Beta-lactamase sensitive penicillins	0	0	0	1	0
J01CE01 - Benzylpenicillin	0	0	0	1	0
J01F - Macrolides, lincosamides and streptogramins	0	0	8	1	1
J01FA - Macrolides	0	0	8	1	1
J01FA02 - Spiramycin	0	0	4	0	0
J01FA09 - Clarithromycin	0	0	4	0	0
J01FA10 - Azithromycin	0	0	0	1	0
J05 - Antivirals for systemic use	2	0	0	0	0
J05A - Direct acting antivirals	2	0	0	0	0
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	2	0	0	0	0
J05AB11 - Valaciclovir	2	0	0	0	0
L - Antineoplastic and immunomodulating agents	5	6	0	7	5
L04 - Immunosuppressants	5	6	0	7	5
L04A - Immunosuppressants	5	6	0	7	5
L04AB - Tumor necrosis factor alpha (tnf-alpha) inhibitors	2	2	0	0	1
L04AB02 - Infliximab	2	2	0	0	1
L04AD - Calcineurin inhibitors	2	0	0	0	0
L04AD02 - Tacrolimus	2	0	0	0	0
L04AX - Other immunosuppressants	2	4	0	7	4
L04AX01 - Azathioprine	2	4	0	6	3
L04AX03 - Methotrexate	0	0	0	1	0
M - Musculo-skeletal system	39	11	4	17	21
M01 - Antiinflammatory and antirheumatic products	39	11	4	16	20
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	39	11	4	16	20
M01AB - Acetic acid derivatives and related substances	6	0	0	8	5
M01AB05 - Diclofenac	6	0	0	8	5
M01AE - Propionic acid derivatives	28	11	4	6	14
M01AE01 - Ibuprofen	28	11	4	4	13
M01AE02 - Naproxen	0	0	0	1	0
M01AG - Fenamates	5	0	0	1	2

M01AG01 - Mefenamic acid	0	0	0	1	0
M01AG02 - Tolfenamic acid	5	0	0	0	1
M04 - Antigout preparations	0	0	0	1	0
M04A - Antigout preparations	0	0	0	1	0
M04AA - Preparations inhibiting uric acid production	0	0	0	1	0
M04AA01 - Allopurinol	0	0	0	1	0
N - Nervous system	192	95	50	110	125
N02 - Analgesics	102	50	17	35	57
N02A - Opioids	11	6	0	4	6
N02AA - Natural opium alkaloids	3	0	0	3	2
N02AA01 - Morphine	2	0	0	0	0
N02AA08 - Dihydrocodeine	0	0	0	1	0
N02AA59 - Codeine, combinations excl. psycholeptics	2	0	0	1	1
N02AX - Other opioids	8	6	0	1	4
N02AX02 - Tramadol	8	6	0	1	4
N02B - Other analgesics and antipyretics	55	27	12	30	35
N02BA - Salicylic acid derivatives	11	0	0	4	5
N02BA01 - Acetylsalicylic acid	0	0	0	4	1
N02BA51 - Acetylsalicylic acid, comb excl psycholeptics	11	0	0	0	3
N02BB - Pyrazolones	0	0	4	0	0
N02BB02 - Metamizole sodium	0	0	4	0	0
N02BE - Anilides	44	27	8	25	30
N02BE01 - Paracetamol	42	6	8	17	21
N02BE02 - Tolfenamic acid	2	0	0	0	0
N02BE51 - Paracetamol, combinations excl psycholeptics	0	21	0	8	8
N02C - Antimigraine preparations	36	17	4	1	16
N02CC - Selective 5ht(1)-receptor agonists	36	17	4	1	16
N02CC01 - Sumatriptan	27	11	4	1	12
N02CC03 - Zolmitriptan	2	0	0	0	0
N02CC04 - Rizatriptan	6	4	0	0	3
N02CC06 - Eletriptan	2	0	0	0	0
N03 - Antiepileptics	14	4	8	8	9
N03A - Antiepileptics	14	4	8	8	9
N03AA - Barbiturates and derivatives	0	0	4	0	0
N03AA02 - Phenobarbital	0	0	4	0	0
N03AF - Carboxamide derivatives	2	0	0	0	0
N03AF02 - Oxcarbazepine	2	0	0	0	0
N03AG - Fatty acid derivatives	2	0	4	0	1
N03AG01 - Valproic acid	2	0	4	0	1
N03AX - Other antiepileptics	11	4	0	8	7
N03AX09 - Lamotrigine	9	4	0	3	5
N03AX12 - Gabapentin	0	0	0	3	1
N03AX14 - Levetiracetam	0	0	0	3	1
N03AX16 - Pregabalin	2	0	0	0	0
N05 - Psycholeptics	8	6	8	8	8
N05A - Antipsychotics	6	4	0	6	5
N05AB - Phenothiazine with piperazine structure	2	0	0	1	1
N05AB03 - Perphenazine	2	0	0	0	0
N05AB04 - Prochlorperazine	0	0	0	1	0

N05AH - Diazepines, oxazepines, thiazepines and oxepines	3	4	0	4	3
N05AH04 - Quetiapine	3	4	0	4	3
N05AN - Lithium	2	0	0	0	0
N05AN01 - Lithium	2	0	0	0	0
N05B - Anxiolytics	2	2	8	1	2
N05BA - Benzodiazepine derivatives	2	2	8	1	2
N05BA01 - Diazepam	0	0	4	1	1
N05BA04 - Oxazepam	2	2	0	0	1
N05BA05 - Clorazepate potassium	0	0	4	0	0
N05C - Hypnotics and sedatives	0	0	0	1	0
N05CF - Benzodiazepine related drugs	0	0	0	1	0
N05CF01 - Zopiclone	0	0	0	1	0
N06 - Psychoanaleptics	69	32	17	55	49
N06A - Antidepressants	66	32	17	54	48
N06AA - Non selective monoamine reuptake inhibitors	2	0	4	7	3
N06AA02 - Imipramine	0	0	0	1	0
N06AA04 - Clomipramine	0	0	4	0	0
N06AA09 - Amitriptyline	2	0	0	4	2
N06AA10 - Nortriptyline	0	0	0	1	0
N06AB - Selective serotonin reuptake inhibitors	45	25	4	39	34
N06AB03 - Fluoxetine	5	4	0	14	7
N06AB04 - Citalopram	20	4	0	11	11
N06AB05 - Paroxetine	0	6	0	0	1
N06AB06 - Sertraline	17	8	4	14	13
N06AB08 - Fluvoxamine	0	2	0	0	0
N06AB10 - Escitalopram	3	0	0	0	1
N06AX - Other antidepressants	19	6	8	7	11
N06AX05 - Trazodone	0	0	4	0	0
N06AX11 - Mirtazapine	2	0	0	3	1
N06AX12 - Bupropion	0	2	0	0	0
N06AX16 - Venlafaxine	14	4	4	4	7
N06AX21 - Duloxetine	3	0	0	0	1
N06B - Psychostimulants, agents used for adhd and nootropics	3	0	0	0	1
N06BA - Centrally acting sympathomimetics	3	0	0	0	1
N06BA04 - Methylphenidate	3	0	0	0	1
N06C - Psycholeptics and psychoanaleptics in combination	0	0	0	1	0
N06CA - Antidepressants in combination with psycholeptics	0	0	0	1	0
N06CA01 - Amitriptyline and psycholeptics	0	0	0	1	0
N07 - Other nervous system drugs	0	2	0	3	1
N07B - Drugs used in addictive disorders	0	0	0	1	0
N07BC - Drugs used in opioid dependence	0	0	0	1	0
N07BC01 - Buprenorphine	0	0	0	1	0
N07C - Antivertigo preparations	0	2	0	1	1
N07CA - Antivertigo preparations	0	2	0	1	1
N07CA01 - Betahistine	0	0	0	1	0
N07CA02 - Cinnarizine	0	2	0	0	0
P - Antiparasitic products, insecticides and repellants	3	2	0	4	3
P01 - Antiprotozoals	3	2	0	4	3
P01A - Agents against amoebiasis and other proto.diseases	2	2	0	0	1

P01AB - Nitroimidazole derivatives	2	2	0	0	1
P01AB01 - Metronidazole	2	2	0	0	1
P01B - Antimalarials	2	0	0	4	2
P01BA - Aminoquinolines	0	0	0	4	1
P01BA02 - Hydroxychloroquine	0	0	0	4	1
P01BC - Methanolquinolines	2	0	0	0	0
P01BC01 - Quinine	2	0	0	0	0
R - Respiratory system	114	124	46	181	131
R01 - Nasal preparations	8	15	4	4	8
R01A - Decongestants and other nasal preparations for topical use	8	15	4	3	7
R01AA - Sympathomimetics, plain	2	0	0	0	0
R01AA07 - Xylometazoline	2	0	0	0	0
R01AD - Corticosteroids	6	15	4	3	7
R01AD01 - Beclomethasone	0	0	0	1	0
R01AD08 - Fluticasone	2	15	0	0	4
R01AD09 - Mometasone	3	0	4	1	2
R01AD12 - Fluticasone furoate	2	0	0	0	0
R01B - Nasal decongestants for systemic use	0	0	0	1	0
R01BA - Sympathomimetics	0	0	0	1	0
R01BA02 - Pseudoephedrine	0	0	0	1	0
R03 - Drugs for obstructive airway diseases	85	95	33	161	107
R03A - Adrenergics, inhalants	66	63	21	107	74
R03AC - Selective beta-2-adrenoceptor agonists	44	46	21	97	60
R03AC02 - Salbutamol	9	42	12	80	42
R03AC03 - Terbutaline	33	0	0	11	14
R03AC12 - Salmeterol	0	0	4	6	2
R03AC13 - Formoterol	2	0	4	0	1
R03AK - Adrenergics and other drugs for obstructive airway diseases	22	17	0	10	14
R03AK06 - Salmeterol and other drugs for obstructive airway diseases	5	15	0	1	5
R03AK07 - Formoterol and other drugs for obstructive airway diseases	17	2	0	8	9
R03B - Other drugs for obstructive airway diseases, inhalants	19	27	12	48	30
R03BA - Glucocorticoids	19	25	12	44	28
R03BA01 - Beclomethasone	0	11	0	27	12
R03BA02 - Budesonide	19	15	8	8	13
R03BA05 - Fluticasone	0	0	0	8	3
R03BA08 - Ciclesonide	0	0	4	0	0
R03BB - Anticholinergics	0	2	0	1	1
R03BB01 - Ipratropium bromide	0	2	0	1	1
R03BC - Antiallergic agents, excl corticosteroids	0	0	0	3	1
R03BC01 - Cromoglicic acid	0	0	0	1	0
R03BC03 - Nedocromil	0	0	0	1	0
R03D - Other systemic drugs for obstructive airway diseases	0	2	0	6	2
R03DA - Xanthines	0	0	0	1	0
R03DA05 - Aminophylline	0	0	0	1	0
R03DC - Leukotriene receptor antagonists	0	2	0	4	2
R03DC03 - Montelukast	0	2	0	4	2

R05 - Cough and cold preparations	2	0	0	7	3
R05C - Expectorants,excl combinations with antitussives	0	0	0	1	0
R05CB - Mucolytics	0	0	0	1	0
R05CB01 - Acetylcysteine	0	0	0	1	0
R05D - Cough suppressants, excl. combinations with expectorants	2	0	0	6	2
R05DA - Opium alkaloids and derivatives	2	0	0	6	2
R05DA04 - Codeine	2	0	0	6	2
R06 - Antihistamines for systemic use	20	15	8	8	14
R06A - Antihistamines for systemic use	20	13	8	8	13
R06AA - Aminoalkyl ethers	2	0	0	0	0
R06AA04 - Clemastine	2	0	0	0	0
R06AB - Substituted alkylamines	0	0	0	1	0
R06AB04 - Chlorpheniramine	0	0	0	1	0
R06AD - Phenothiazine derivatives	3	0	0	0	1
R06AD02 - Promethazine	3	0	0	0	1
R06AE - Piperazine derivatives	5	4	4	4	4
R06AE03 - Cyclizine	0	0	0	1	0
R06AE07 - Cetirizine	5	2	4	3	3
R06AE09 - Levocetirizine	0	2	0	0	0
R06AX - Other antihistamines for systemic use	11	8	4	3	7
R06AX13 - Loratadine	2	8	0	1	3
R06AX18 - Acrivastine	5	0	0	0	1
R06AX26 - Fexofenadine	5	0	0	1	2
R06AX27 - Desloratadine	0	0	4	0	0
S - Sensory organs	2	4	4	1	2
S01 - Ophthalmologicals	2	4	4	1	2
S01G - Decongestants and antiallergics	2	2	4	1	2
S01GX - Other antiallergics	2	2	4	1	2
S01GX01 - Cromoglicic acid	0	2	0	1	1
S01GX02 - Levocabastine	0	0	4	0	0
S01GX09 - Olopatadine	2	0	0	0	0
S01X - Other ophthalmologicals	0	2	0	0	0
S01XA - Other ophthalmologicals	0	2	0	0	0
S01XA20 - Artificial tears and other indifferent prep.	0	2	0	0	0
V - Various	3	0	4	0	1
V01 - Allergens	3	0	0	0	1
V01A - Allergens	3	0	0	0	1
V01AA - Allergen extracts	3	0	0	0	1
V01AA02 - Grass pollen	2	0	0	0	0
V06 - General nutrients	0	0	4	0	0
V06D - Other nutrients	0	0	4	0	0

13.10 Short-term illnesses-related medications

Table 13-15 Rates per 1000 women who took medications for short-term illnesses during pregnancy

Medications	DK	NL	PL	UK	All

A - Alimentary tract and metabolism	358	361	270	635	444
A01 - Stomatological preparations	0	0	4	0	0
A01A - Stomatological preparations	0	0	4	0	0
A01AD - Other agents for local oral treatment	0	0	4	0	0
A01AD02 - Benzydamine	0	0	4	0	0
A02 - Drugs for acid related disorders	230	229	100	367	262
A02A - Antacids	172	162	71	30	109
A02AA - Magnesium compounds	52	11	0	18	25
A02AA04 - Magnesium hydroxide	52	11	0	0	18
A02AB - Aluminium compounds	0	11	21	0	5
A02AB01 - Aluminium oxide	0	0	21	0	2
A02AB02 - Aluminium hydroxide	0	11	0	0	2
A02AC - Calcium compounds	0	0	46	3	6
A02AC01 - Calcium carbonate	0	0	46	3	6
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	114	141	4	6	70
A02AD01 - Ordinary salt combinations	114	141	4	3	69
A02AD02 - Magaldrate	0	0	0	1	0
A02AH - Antacids with sodium bicarbonate	6	0	0	0	2
A02AX - Antacids, other combinations	0	0	0	3	1
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	58	67	29	337	153
A02BA - H2-receptor antagonists	0	0	21	31	13
A02BA02 - Ranitidine	0	0	21	31	13
A02BC - Proton pump inhibitors	25	32	0	24	23
A02BC01 - Omeprazole	14	32	0	21	19
A02BC02 - Pantoprazole	6	0	0	0	2
A02BC03 - Lansoprazole	3	0	0	3	2
A02BC05 - Esomeprazole	2	0	0	0	0
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	33	36	8	282	116
A02BX02 - Sucralfate	0	2	0	0	0
A02BX13 - Alginic acid	33	34	4	282	115
A03 - Drugs for functional gastrointestinal disorders	17	21	29	32	25
A03A - Drugs for functional gastrointestinal disorders	2	2	21	1	4
A03AA - Synt anticholin,esters with tertiary amino group	0	0	0	1	0
A03AA07 - Dicycloverine	0	0	0	1	0
A03AD - Papaverine and derivatives	0	0	21	0	2
A03AD02 - Drotaverine	0	0	21	0	2
A03AX - Other drugs for functional gastrointestinal disorders	2	2	0	0	1
A03AX13 - Silicones	2	0	0	0	0
A03B - Belladonna and derivatives, plain	0	2	0	1	1
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	0	2	0	1	1
A03BB01 - Butylscopolamine	0	2	0	1	1
A03F - Propulsives	16	17	8	30	20
A03FA - Propulsives	16	17	8	30	20
A03FA01 - Metoclopramide	16	15	8	27	18
A03FA03 - Domperidone	0	2	0	3	1
A04 - Antiemetics and antinauseants	13	0	4	14	9

A04A - Antiemetics and antinauseants	13	0	4	14	9
A04AA - Serotonin (5ht3) antagonists	13	0	0	13	8
A04AA01 - Ondansetron	13	0	0	13	8
A04AD - Other antiemetics	0	0	4	0	0
A05 - Bile and liver therapy	0	2	4	1	1
A05A - Bile therapy	0	2	0	1	1
A05AA - Bile acid preparations	0	2	0	1	1
A05AA02 - Ursodeoxycholic acid	0	2	0	1	1
A06 - Drugs for constipation	77	92	58	135	98
A06A - Drugs for constipation	77	92	58	135	98
A06AA - Softeners, emollients	2	0	0	0	0
A06AA02 - Docusate sodium	2	0	0	0	0
A06AB - Contact laxatives	5	4	8	23	11
A06AB02 - Bisacodyl	3	4	4	6	4
A06AB06 - Senna glycosides	0	0	4	16	6
A06AB08 - Sodium picosulfate	2	0	0	1	1
A06AC - Bulk-forming laxatives	38	15	0	41	29
A06AC01 - Ispaghula (psylla seeds)	38	15	0	41	29
A06AD - Osmotically acting laxatives	28	67	37	69	52
A06AD11 - Lactulose	16	36	37	62	39
A06AD15 - Macrogol	0	0	0	6	2
A06AD19 - Magnesium citrate	0	0	0	1	0
A06AD65 - Macrogol, combinations	13	32	0	0	11
A06AG - Enemas	5	6	0	0	3
A06AG11 - Laurilsulfate, incl combinations	5	6	0	0	3
A06AX - Other drugs for constipation	0	0	8	3	2
A06AX01 - Glycerol	0	0	8	3	2
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	17	8	37	16	17
A07A - Intestinal antiinfectives	0	4	0	0	1
A07AA - Antibiotics	0	4	0	0	1
A07AA02 - Nystatin	0	4	0	0	1
A07B - Intestinal adsorbents	0	0	4	1	1
A07BA - Charcoal preparations	0	0	4	0	0
A07BC - Other intestinal adsorbents	0	0	0	1	0
A07BC02 - Kaolin	0	0	0	1	0
A07C - Electrolytes with carbohydrates	0	2	4	3	2
A07CA - Oral rehydration salt formulations	0	2	4	3	2
A07D - Antipropulsives	6	2	4	11	7
A07DA - Antipropulsives	6	2	4	11	7
A07DA03 - Loperamide	5	2	4	11	6
A07DA53 - Loperamide, combinations	2	0	0	0	0
A07F - Antidiarrheal microorganisms	11	0	12	0	5
A07FA - Antidiarrheal microorganisms	11	0	12	0	5
A07FA01 - Lactic acid producing organisms	11	0	0	0	3
A07X - Other antidiarrheals	0	0	12	0	1
A07XA - Other antidiarrheals	0	0	12	0	1
A10 - Drugs used in diabetes	0	6	4	14	7
A10A - Insulins and analogues	0	6	4	7	4
A10AB - Insulins and analogues for injection, fast-acting	0	4	4	7	4

A10AB05 - Insulin aspart	0	4	4	7	4
A10AC - Insulins and analogues for injection, intermediate-acting	0	2	0	0	0
A10AC01 - Insulin (human)	0	2	0	0	0
A10B - Blood glucose lowering drugs, excl. insulins	0	0	0	7	2
A10BA - Biguanides	0	0	0	7	2
A10BA02 - Metformin	0	0	0	7	2
A12 - Mineral supplements	5	2	29	55	24
A12A - Calcium	2	0	12	54	20
A12AA - Calcium	2	0	4	54	19
A12AA04 - Calcium carbonate	0	0	4	54	19
A12AX - Calcium, combinations with vitamin d and/or other drugs	0	0	4	0	0
A12C - Other mineral supplements	0	2	12	1	2
A12CB - Zinc	0	0	0	1	0
A12CB01 - Zinc sulphate	0	0	0	1	0
A12CC - Magnesium	0	2	8	0	1
A12CX - Other mineral products	0	0	4	0	0
B - Blood and blood forming organs	9	0	4	11	7
B01 - Antithrombotic agents	6	0	4	8	5
B01A - Antithrombotic agents	6	0	4	8	5
B01AB - Heparin group	2	0	0	4	2
B01AB04 - Dalteparin	0	0	0	3	1
B01AB05 - Enoxaparin	2	0	0	1	1
B01AC - Platelet aggregation inhibitors excl. heparin	5	0	4	4	3
B01AC06 - Acetylsalicylic acid	5	0	4	4	3
B02 - Antihemorrhagics	2	0	0	1	1
B02A - Antifibrinolytics	2	0	0	0	0
B02AA - Amino acids	2	0	0	0	0
B02AA02 - Tranexamic acid	2	0	0	0	0
B02B - Vitamin k and other hemostatics	0	0	0	1	0
B02BA - Vitamin k	0	0	0	1	0
B05 - Blood substitutes and perfusion solutions	2	0	0	1	1
B05B - I.v. solutions	2	0	0	0	0
B05BA - Solutions for parenteral nutrition	2	0	0	0	0
B05BA02 - Fat emulsions	2	0	0	0	0
B05X - I.v. solution additives	0	0	0	1	0
B05XB - Amino acids	0	0	0	1	0
B05XB03 - Lysine	0	0	0	1	0
C - Cardiovascular system	23	17	71	10	23
C02 - Antihypertensives	2	2	21	3	4
C02A - Antiadrenergic agents, centrally acting	2	2	21	3	4
C02AB - Methyldopa	2	2	21	3	4
C02AB01 - Methyldopa (levorotatory)	2	2	21	3	4
C05 - Vasoprotectives	20	13	50	3	16
C05A - Agents for treatment of hemorrhoids and anal fissures for topical use	20	13	4	3	11
C05AA - Corticosteroids	20	4	0	0	7
C05AA01 - Hydrocortisone	6	0	0	0	2
C05AA08 - Fluocortolone	14	0	0	0	4

C05AA12 - Triamcinolone	0	2	0	0	0
C05AD - Local anesthetics	0	2	0	0	0
C05AD01 - Lidocaine	0	2	0	0	0
C05AE - Musclerelaxants	0	0	0	1	0
C05AE01 - Glyceryl trinitrate	0	0	0	1	0
C05AX - Other agents for treatment of hemorrhoids and anal fissures for topical use	0	4	4	1	2
C05AX04 - Zinc preparations	0	4	0	1	1
C05AX05 - Tribenoside	0	0	4	0	0
C05C - Capillary stabilizing agents	0	0	46	0	5
C05CA - Bioflavonoids	0	0	46	0	5
C05CA51 - Rutoside, combinations	0	0	46	0	5
C07 - Beta blocking agents	2	0	0	0	0
C07A - Beta blocking agents, plain	2	0	0	0	0
C07AG - Alpha- and beta blocking agents	2	0	0	0	0
C07AG01 - Labetalol	2	0	0	0	0
C08 - Calcium channel blockers	0	2	0	4	2
C08C - Selective calcium channel blockers with mainly vascular effects	0	2	0	3	1
C08CA - Dihydropyridine derivatives	0	2	0	3	1
C08CA05 - Nifedipine	0	2	0	3	1
C08D - Selective calcium channel blockers with direct cardiac effects	0	0	0	1	0
C08DA - Phenylalkylamine derivatives	0	0	0	1	0
C08DA01 - Verapamil	0	0	0	1	0
D - Dermatologicals	103	92	133	63	91
D01 - Antifungals for dermatological use	44	32	120	49	52
D01A - Antifungals for topical use	44	32	120	49	52
D01AA - Antibiotics	0	0	108	0	13
D01AA01 - Nystatin	0	0	54	0	6
D01AA02 - Natamycin	0	0	54	0	6
D01AC - Imidazole and triazole derivatives	39	32	12	49	38
D01AC01 - Clotrimazole	25	8	0	44	25
D01AC02 - Miconazole	5	23	0	1	7
D01AC15 - Fluconazole	0	0	0	1	0
D01AC20 - Combinations	9	0	0	1	3
D01AC52 - Miconazole, combinations	0	0	0	1	0
D01AE - Other antifungals for topical use	5	0	0	0	1
D01AE15 - Terbinafine	5	0	0	0	1
D02 - Emollients and protectives	0	2	0	0	0
D02A - Emollients and protectives	0	2	0	0	0
D04 - Antipruritics,incl antihist,anesthet,etc.	0	0	0	1	0
D04A - Antipruritics,incl antihist,anesthet,etc.	0	0	0	1	0
D04AA - Antihistamines for topical use	0	0	0	1	0
D04AA02 - Mepyramine	0	0	0	1	0
D06 - Antibiotics and chemother. for dermatological use	44	53	8	4	28
D06A - Antibiotics for topical use	5	2	0	1	2
D06AX - Other antibiotics for topical use	5	2	0	1	2
D06AX01 - Fusidic acid	5	2	0	1	2
D06B - Chemotherapeutics for topical use	39	48	8	3	25

D06BB - Antivirals	38	48	8	1	24
D06BB03 - Aciclovir	34	48	0	0	22
D06BB11 - Docosanol	0	0	4	1	1
D06BB53 - Aciclovir, combinations	3	0	0	0	1
D06BX - Other chemotherapeutics	2	0	0	1	1
D06BX01 - Metronidazole	2	0	0	1	1
D07 - Corticosteroids, dermatological preparations	14	6	4	6	8
D07A - Corticosteroids, plain	13	4	0	6	7
D07AA - Corticosteroids, weak (group i)	6	0	0	3	3
D07AA02 - Hydrocortisone	6	0	0	3	3
D07AB - Corticosteroids, moderately potent (group ii)	5	4	0	1	3
D07AB01 - Clobetasone	0	0	0	1	0
D07AB02 - Hydrocortisone butyrate	5	0	0	0	1
D07AB09 - Triamcinolone	0	4	0	0	1
D07AC - Corticosteroids, potent (group iii)	2	0	0	1	1
D07AC01 - Betamethasone	2	0	0	1	1
D07C - Corticosteroids, comb with antibiotics	2	0	4	0	1
D07CA - Corticosteroids, weak, comb with antibiotics	0	0	4	0	0
D07CC - Corticosteroids, potent, comb with antibiotics	2	0	0	0	0
D07CC01 - Betamethasone and antibiotics	2	0	0	0	0
D07X - Corticosteroids, other combinations	0	2	0	0	0
D08 - Antiseptics and disinfectants	0	0	0	1	0
D08A - Antiseptics and disinfectants	0	0	0	1	0
D08AC - Biguanides and amidines	0	0	0	1	0
D08AC02 - Chlorhexidine	0	0	0	1	0
D09 - Medicated dressings	0	0	0	1	0
D09A - Medicated dressings	0	0	0	1	0
D09AA - Ointment dressings with antiinfectives	0	0	0	1	0
D09AA12 - Chlorhexidine	0	0	0	1	0
D11 - Other dermatological preparations	2	0	0	0	0
D11A - Other dermatological preparations	2	0	0	0	0
D11AH - Agents for dermatitis, excluding corticosteroids	2	0	0	0	0
D11AH01 - Tacrolimus	2	0	0	0	0
G - Genito urinary system and sex hormones	133	53	158	24	80
G01 - Gynecological antiinfectives and antiseptics	130	50	104	24	72
G01A - Antiinfectives/antisept.,excl comb with corticost.	130	50	104	24	72
G01AA - Antibiotics	0	0	21	0	2
G01AA01 - Nystatin	0	0	4	0	0
G01AA02 - Natamycin	0	0	4	0	0
G01AA10 - Clindamycin	0	0	4	0	0
G01AA51 - Nystatin, combinations	0	0	4	0	0
G01AF - Imidazole derivatives	130	50	71	24	68
G01AF01 - Metronidazole	6	0	0	0	2
G01AF02 - Clotrimazole	99	21	46	24	49
G01AF04 - Miconazole	25	2	0	0	8
G01AF05 - Econazole	0	0	8	0	1
G01AF15 - Butoconazole	0	0	8	0	1
G01AX - Other antiinfectives and antiseptics	0	0	12	0	1
G01AX05 - Nifuratel	0	0	4	0	0

G01AX14 - Lactobacillus fermentum	0	0	8	0	1
G02 - Other gynecologicals	0	2	4	0	1
G02C - Other gynecologicals	0	2	4	0	1
G02CA - Sympathomimetics, labour repressants	0	0	4	0	0
G02CA03 - Fenoterol	0	0	4	0	0
G02CX - Other gynecologicals	0	2	0	0	0
G02CX01 - Atosiban	0	2	0	0	0
G03 - Sex hormones and modulators of the genital system	3	0	46	0	6
G03D - Progestogens	3	0	46	0	6
G03DA - Pregnen (4) derivatives	3	0	25	0	4
G03DA04 - Progesterone	3	0	25	0	4
G03DB - Pregnadien derivatives	0	0	21	0	2
G03DB01 - Dydrogesterone	0	0	21	0	2
G04 - Urologicals	0	0	4	0	0
G04B - Urologicals	0	0	4	0	0
G04BX - Other urologicals	0	0	4	0	0
H - Systemic hormonal prep, excl sex hormones	2	8	21	0	5
H02 - Corticosteroids for systemic use	2	4	4	0	2
H02A - Corticosteroids for systemic use, plain	2	4	4	0	2
H02AB - Glucocorticoids	2	4	4	0	2
H02AB01 - Betamethasone	0	2	4	0	1
H02AB06 - Prednisolone	2	2	0	0	1
H03 - Thyroid therapy	0	4	17	0	3
H03A - Thyroid preparations	0	4	17	0	3
H03AA - Thyroid hormones	0	4	17	0	3
H03AA01 - Levothyroxine sodium	0	4	17	0	3
J - General antiinfectives for systemic use	199	90	195	355	227
J01 - Antibacterials for systemic use	166	88	145	262	179
J01A - Tetracyclines	0	2	0	0	0
J01AA - Tetracyclines	0	2	0	0	0
J01AA02 - Doxycycline	0	2	0	0	0
J01C - Beta-lactam antibacterials, penicillins	141	34	87	178	123
J01CA - Penicillins with extended spectrum	100	23	71	152	97
J01CA01 - Ampicillin	5	0	4	0	2
J01CA02 - Pivampicillin	5	0	0	0	1
J01CA04 - Amoxicillin	3	23	66	151	66
J01CA08 - Pivmecillinam	88	0	0	0	27
J01CA51 - Ampicillin, combinations	0	0	0	1	0
J01CE - Beta-lactamase sensitive penicillins	39	2	0	4	14
J01CE01 - Benzylpenicillin	0	0	0	3	1
J01CE02 - Phenoxymethylpenicillin	39	0	0	1	13
J01CE05 - Pheneticillin	0	2	0	0	0
J01CF - Beta-lactamase resistant penicillins	2	0	0	10	4
J01CF05 - Flucloxacillin	2	0	0	10	4
J01CR - Comb of penicillins, incl. beta-lactamase inhib.	0	8	17	10	7
J01CR02 - Amoxicillin and enzyme inhibitor	0	2	17	10	6
J01CR05 - Piperacillin and enzyme inhibitor	0	6	0	0	1
J01D - Other beta-lactam antibacterials	0	0	17	31	13
J01DB - First-generation cephalosporins	0	0	0	30	10

J01DB01 - Cefalexin	0	0	0	27	9
J01DB09 - Cefradine	0	0	0	3	1
J01DC - Second-generation cephalosporins	0	0	17	0	2
J01DC02 - Cefuroxime	0	0	17	0	2
J01DF - Monobactams	0	0	0	1	0
J01DF01 - Aztreonam	0	0	0	1	0
J01E - Sulfonamides and trimethoprim	14	2	0	7	7
J01EA - Trimethoprim and derivatives	0	2	0	7	3
J01EA01 - Trimethoprim	0	2	0	7	3
J01EB - Short-acting sulfonamides	14	0	0	0	4
J01EB02 - Sulfamethizole	14	0	0	0	4
J01F - Macrolides, lincosamides and streptogramins	5	2	12	20	10
J01FA - Macrolides	5	2	8	20	10
J01FA01 - Erythromycin	3	0	8	18	8
J01FA10 - Azithromycin	2	2	0	1	1
J01FF - Lincosamides	0	0	4	0	0
J01FF01 - Clindamycin	0	0	4	0	0
J01X - Other antibacterials	3	36	29	18	19
J01XD - Imidazole derivatives	0	0	0	1	0
J01XD01 - Metronidazole	0	0	0	1	0
J01XE - Nitrofuran derivatives	3	36	17	17	17
J01XE01 - Nitrofurantoin	3	36	4	17	15
J01XX - Other antibacterials	0	0	12	0	1
J01XX01 - Fosfomycin	0	0	12	0	1
J02 - Antimycotics for systemic use	19	2	4	66	30
J02A - Antimycotics for systemic use	19	2	4	66	30
J02AB - Imidazole derivatives	0	0	0	3	1
J02AB02 - Ketoconazole	0	0	0	3	1
J02AC - Triazole derivatives	19	2	4	61	28
J02AC01 - Fluconazole	19	2	4	61	28
J02AX - Other antimycotics for systemic use	0	0	0	3	1
J02AX04 - Caspofungin	0	0	0	3	1
J05 - Antivirals for systemic use	13	0	46	27	18
J05A - Direct acting antivirals	13	0	46	27	18
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	13	0	46	27	18
J05AB01 - Aciclovir	11	0	46	27	18
J05AB11 - Valaciclovir	2	0	0	0	0
J06 - Immune sera and immunoglobulins	2	0	0	0	0
J06B - Immunoglobulins	2	0	0	0	0
J06BB - Specific immunoglobulins	2	0	0	0	0
J06BB01 - Anti-d (rh) immunoglobulin	2	0	0	0	0
L - Antineoplastic and immunomodulating agents	0	0	4	0	0
L03 - Immunostimulants	0	0	4	0	0
L03A - Immunostimulants	0	0	4	0	0
L03AX - Other immunostimulants	0	0	4	0	0
M - Musculo-skeletal system	61	13	46	30	37
M01 - Antiinflammatory and antirheumatic products	59	13	37	28	35
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	59	13	37	28	35

M01AB - Acetic acid derivatives and related substances	3	0	0	3	2
M01AB01 - Indometacin	2	0	0	0	0
M01AB05 - Diclofenac	2	0	0	3	1
M01AE - Propionic acid derivatives	56	13	37	25	33
M01AE01 - Ibuprofen	56	13	33	24	32
M01AE02 - Naproxen	0	0	0	1	0
M01AE03 - Ketoprofen	0	0	4	0	0
M02 - Topical products for joint and muscular pain	2	0	8	1	2
M02A - Topical products for joint and muscular pain	2	0	8	1	2
M02AA - Antiinfl. prep., non-steroids for topical use	2	0	4	1	1
M02AA05 - Benzydamine	0	0	4	0	0
M02AA07 - Piroxicam	0	0	0	1	0
M02AA15 - Diclofenac	2	0	0	0	0
M02AX - Other topical products for joint and muscular pain	0	0	4	0	0
N - Nervous system	502	502	373	676	547
N01 - Anesthetics	0	0	0	4	1
N01A - Anesthetics, general	0	0	0	1	0
N01AX - Other general anesthetics	0	0	0	1	0
N01AX63 - Nitrous oxide, combinations	0	0	0	1	0
N01B - Anesthetics, local	0	0	0	3	1
N01BB - Amides	0	0	0	3	1
N01BB52 - Lidocaine, combinations	0	0	0	3	1
N02 - Analgesics	495	481	357	643	526
N02A - Opioids	14	6	0	8	9
N02AA - Natural opium alkaloids	9	4	0	7	6
N02AA01 - Morphine	0	4	0	3	2
N02AA08 - Dihydrocodeine	0	0	0	3	1
N02AA59 - Codeine, combinations excl. psycholeptics	9	0	0	1	3
N02AB - Phenylpiperidine derivatives	2	0	0	0	0
N02AB02 - Pethidine	2	0	0	0	0
N02AX - Other opioids	3	2	0	1	2
N02AX02 - Tramadol	3	2	0	1	2
N02B - Other analgesics and antipyretics	477	475	357	635	517
N02BA - Salicylic acid derivatives	16	4	17	16	13
N02BA01 - Acetylsalicylic acid	0	4	17	14	8
N02BA03 - Choline salicylate	0	0	0	1	0
N02BA51 - Acetylsalicylic acid, comb excl psycholeptics	16	0	0	0	5
N02BB - Pyrazolones	0	0	4	0	0
N02BB02 - Metamizole sodium	0	0	4	0	0
N02BE - Anilides	462	471	336	619	503
N02BE01 - Paracetamol	462	458	332	566	481
N02BE51 - Paracetamol, combinations excl psycholeptics	0	13	0	54	21
N02C - Antimigraine preparations	3	0	0	0	1
N02CC - Selective 5ht(1)-receptor agonists	3	0	0	0	1
N02CC01 - Sumatriptan	2	0	0	0	0
N02CC03 - Zolmitriptan	2	0	0	0	0
N04 - Anti-parkinson drugs	0	2	0	0	0
N04B - Dopaminergic agents	0	2	0	0	0
N04BC - Dopamine agonists	0	2	0	0	0

N04BC05 - Pramipexole	0	2	0	0	0
N05 - Psycholeptics	5	15	12	25	15
N05A - Antipsychotics	2	0	0	24	9
N05AB - Phenothiazine with piperazine structure	0	0	0	24	8
N05AB04 - Prochlorperazine	0	0	0	24	8
N05AH - Diazepines, oxazepines, thiazepines and oxepines	2	0	0	0	0
N05AH04 - Quetiapine	2	0	0	0	0
N05B - Anxiolytics	2	2	12	0	2
N05BA - Benzodiazepine derivatives	2	2	12	0	2
N05BA01 - Diazepam	0	0	12	0	1
N05BA04 - Oxazepam	2	0	0	0	0
N05BA06 - Lorazepam	0	2	0	0	0
N05C - Hypnotics and sedatives	2	13	0	1	4
N05CD - Benzodiazepine derivatives	2	8	0	0	2
N05CD05 - Triazolam	2	0	0	0	0
N05CD07 - Temazepam	0	8	0	0	2
N05CF - Benzodiazepine related drugs	0	0	0	1	0
N05CF01 - Zopiclone	0	0	0	1	0
N05CH - Melatonin receptor agonists	0	2	0	0	0
N05CH01 - Melatonin	0	2	0	0	0
N05CM - Other hypnotics and sedatives	0	2	0	0	0
N05CM09 - Valerianae radix	0	2	0	0	0
N06 - Psychoanaleptics	3	2	0	1	2
N06A - Antidepressants	3	2	0	1	2
N06AB - Selective serotonin reuptake inhibitors	3	0	0	1	1
N06AB03 - Fluoxetine	2	0	0	1	1
N06AB04 - Citalopram	2	0	0	0	0
N06AX - Other antidepressants	0	2	0	0	0
N06AX11 - Mirtazapine	0	2	0	0	0
N07 - Other nervous system drugs	0	2	4	1	1
N07B - Drugs used in addictive disorders	0	0	0	1	0
N07BC - Drugs used in opioid dependence	0	0	0	1	0
N07BC06 - Diamorphine	0	0	0	1	0
N07C - Antivertigo preparations	0	2	4	0	1
N07CA - Antivertigo preparations	0	2	4	0	1
N07CA52 - Cinnarizine, combinations	0	2	0	0	0
P - Antiparasitic products, insecticides and repellants	2	0	0	4	2
P01 - Antiprotozoals	2	0	0	3	1
P01A - Agents against amoebiasis and other proto.diseases	2	0	0	3	1
P01AB - Nitroimidazole derivatives	2	0	0	3	1
P01AB01 - Metronidazole	2	0	0	3	1
P03 - Ectoparasiticides, incl scabicides, insecticides and repellants	0	0	0	1	0
P03A - Ectoparasiticides, incl scabicides	0	0	0	1	0
P03AC - Pyrethrines, incl synthetic compounds	0	0	0	1	0
P03AC03 - Phenothrin	0	0	0	1	0
R - Respiratory system	188	239	154	245	215
R01 - Nasal preparations	66	109	46	79	78
R01A - Decongestants and other nasal preparations for topical use	64	107	46	79	77

R01AA - Sympathomimetics, plain	41	61	25	21	37
R01AA04 - Phenylephrine	0	0	0	1	0
R01AA05 - Oxymetazoline	0	0	21	7	5
R01AA07 - Xylometazoline	41	61	4	13	31
R01AC - Antiallergic agents, excl corticosteroids	0	13	4	8	6
R01AC01 - Cromoglicic acid	0	8	0	8	5
R01AC02 - Levocabastine	0	2	4	0	1
R01AC03 - Azelastine	0	2	0	0	0
R01AD - Corticosteroids	23	25	12	44	30
R01AD01 - Beclomethasone	0	13	0	30	13
R01AD05 - Budesonide	5	4	4	0	3
R01AD08 - Fluticasone	8	4	0	11	7
R01AD09 - Mometasone	8	4	8	0	4
R01AD12 - Fluticasone furoate	3	0	0	0	1
R01AD60 - Hydrocortisone, combinations	0	0	0	3	1
R01AX - Other nasal preparations	0	8	4	6	4
R01AX10 - Various	0	8	4	0	2
R01AX30 - Combinations	0	0	0	1	0
R02 - Throat preparations	8	2	25	3	7
R02A - Throat preparations	8	2	25	3	7
R02AA - Antiseptics	8	0	25	3	6
R02AA03 - Dichlorobenzyl alcohol	6	0	0	1	2
R02AA05 - Chlorhexidine	2	0	0	0	0
R02AA20 - Various	0	0	0	1	0
R02AD - Anesthetics, local	0	2	0	0	0
R02AD02 - Lidocaine	0	2	0	0	0
R03 - Drugs for obstructive airway diseases	2	2	8	3	3
R03A - Adrenergics, inhalants	2	0	0	3	1
R03AC - Selective beta-2-adrenoceptor agonists	2	0	0	3	1
R03AC02 - Salbutamol	2	0	0	3	1
R03B - Other drugs for obstructive airway diseases, inhalants	0	2	8	0	1
R03BA - Glucocorticoids	0	2	8	0	1
R03BA01 - Beclomethasone	0	2	0	0	0
R03BA02 - Budesonide	0	0	8	0	1
R05 - Cough and cold preparations	11	8	46	20	17
R05C - Expectorants,excl combinations with antitussives	3	6	46	0	8
R05CA - Expectorants	0	0	37	0	4
R05CB - Mucolytics	3	6	8	0	3
R05CB01 - Acetylcysteine	3	2	0	0	1
R05CB02 - Bromhexine	0	4	0	0	1
R05CB06 - Ambroxol	0	0	8	0	1
R05D - Cough suppressants, excl. combinations with expectorants	8	2	0	18	9
R05DA - Opium alkaloids and derivatives	8	2	0	18	9
R05DA04 - Codeine	2	0	0	18	7
R05DA07 - Noscapine	6	0	0	0	2
R05X - Other cold preparations	0	0	0	1	0
R06 - Antihistamines for systemic use	102	118	25	141	110
R06A - Antihistamines for systemic use	102	118	25	141	110

R06AA - Aminoalkyl ethers	2	2	4	6	3
R06AA02 - Diphenhydramine	2	0	0	4	2
R06AA04 - Clemastine	0	2	0	0	0
R06AA09 - Doxylamine	0	0	4	0	0
R06AA59 - Doxylamine, combinations	0	0	0	1	0
R06AB - Substituted alkylamines	0	0	0	17	6
R06AB04 - Chlorpheniramine	0	0	0	17	6
R06AD - Phenothiazine derivatives	8	0	12	30	14
R06AD02 - Promethazine	8	0	0	3	3
R06AD03 - Thiethylperazine	0	0	12	0	1
R06AD52 - Promethazine, combinations	0	0	0	27	9
R06AE - Piperazine derivatives	69	95	8	71	68
R06AE03 - Cyclizine	6	2	0	61	23
R06AE05 - Meclozine	11	8	0	0	5
R06AE07 - Cetirizine	52	8	8	10	22
R06AE09 - Levocetirizine	0	4	0	0	1
R06AE55 - Meclozine, combinations	0	71	0	0	16
R06AX - Other antihistamines for systemic use	23	21	0	16	17
R06AX13 - Loratadine	6	19	0	13	11
R06AX18 - Acrivastine	3	0	0	0	1
R06AX25 - Mizolastine	0	2	0	0	0
R06AX26 - Fexofenadine	11	0	0	3	4
R06AX27 - Desloratadine	3	0	0	0	1
R07 - Other respiratory system products	0	0	4	0	0
R07A - Other respiratory system products	0	0	4	0	0
R07AX - Other respiratory system products	0	0	4	0	0
S - Sensory organs	17	13	4	6	11
S01 - Ophthalmologicals	17	13	4	4	10
S01A - Antiinfectives	5	2	0	3	3
S01AA - Antibiotics	5	2	0	3	3
S01AA01 - Chloramphenicol	2	2	0	0	1
S01AA13 - Fusidic acid	3	0	0	3	2
S01B - Antiinflammatory agents	0	2	0	0	0
S01BA - Corticosteroids, plain	0	2	0	0	0
S01BA04 - Prednisolone	0	2	0	0	0
S01C - Antiinflammatory agents and antiinfectives in comb	2	0	4	0	1
S01CA - Corticosteroids and antiinfectives in combination	2	0	4	0	1
S01CA01 - Dexamethasone and antiinfectives	2	0	0	0	0
S01CA06 - Fludrocortisone and antiinfectives	0	0	4	0	0
S01G - Decongestants and antiallergics	11	6	0	1	5
S01GX - Other antiallergics	11	6	0	1	5
S01GX01 - Cromoglicic acid	0	4	0	0	1
S01GX02 - Levocabastine	5	0	0	0	1
S01GX04 - Nedocromil	0	0	0	1	0
S01GX06 - Emedastine	0	2	0	0	0
S01GX09 - Olopatadine	6	0	0	0	2
S02 - Otologicals	0	0	0	1	0
S02C - Corticosteroids and antiinfectives in combination	0	0	0	1	0
S02CA - Corticosteroids and antiinfectives in combination	0	0	0	1	0

S02CA06 - Dexamethasone and antiinfectives	0	0	0	1	0
V - Various	3	0	4	0	1
V01 - Allergens	3	0	0	0	1
V01A - Allergens	3	0	0	0	1
V01AA - Allergen extracts	3	0	0	0	1
V01AA02 - Grass pollen	2	0	0	0	0
V03 - All other therapeutic products	0	0	4	0	0
V03A - All other therapeutic products	0	0	4	0	0
V03AX - Other therapeutic products	0	0	4	0	0

13.11 Influence of pregnancy on medications use

13.11.1 Impact on medications use when planning pregnancy

Table 13-16 Rates per 1000 who stopped specified medications while trying to get pregnant

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	6	17	25	15	14
A01 - Stomatological preparations	0	0	0	2	1
A01A - Stomatological preparations	0	0	0	2	1
A01AB - Antiinfectives for local oral treatment	0	0	0	2	1
A01AB09 - Miconazole	0	0	0	2	1
A02 - Drugs for acid related disorders	2	7	6	6	5
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	2	7	6	6	5
A02BC - Proton pump inhibitors	2	7	6	6	5
A02BC01 - Omeprazole	0	5	0	6	3
A02BC02 - Pantoprazole	0	2	0	0	1
A02BC03 - Lansoprazole	2	0	0	0	1
A03 - Drugs for functional gastrointestinal disorders	2	7	6	4	4
A03A - Drugs for functional gastrointestinal disorders	2	7	6	0	3
A03AA - Synt anticholin,esters with tertiary amino group	0	7	0	0	2
A03AA04 - Mebeverine	0	7	0	0	2
A03AB - Synth. anticholinergics, quatern. ammonium comp.	2	0	0	0	1
A03AB05 - Propantheline	2	0	0	0	1
A03AD - Papaverine and derivatives	0	0	6	0	1
A03AD02 - Drotaverine	0	0	6	0	1
A03B - Belladonna and derivatives, plain	0	0	0	4	1
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	0	0	0	4	1
A03BB01 - Butylscopolamine	0	0	0	4	1
A06 - Drugs for constipation	0	2	0	2	1
A06A - Drugs for constipation	0	2	0	2	1
A06AD - Osmotically acting laxatives	0	2	0	0	1
A06AD15 - Macrogol	0	2	0	0	1
A06AX - Other drugs for constipation	0	0	0	2	1
A06AX05 - Prucalopride	0	0	0	2	1
A10 - Drugs used in diabetes	2	0	6	2	2

A10B - Blood glucose lowering drugs, excl. insulins	2	0	6	2	2
A10BA - Biguanides	2	0	6	2	2
A10BA02 - Metformin	2	0	6	2	2
A16 - Other alimentary tract and metabolism products	0	0	6	0	1
A16A - Other alimentary tract and metabolism products	0	0	6	0	1
A16AA - Amino acids and derivatives	0	0	6	0	1
A16AA01 - Levocarnitine	0	0	6	0	1
B - Blood and blood forming organs	2	0	0	0	1
B01 - Antithrombotic agents	2	0	0	0	1
B01A - Antithrombotic agents	2	0	0	0	1
B01AC - Platelet aggregation inhibitors excl. heparin	2	0	0	0	1
B01AC06 - Acetylsalicylic acid	2	0	0	0	1
C - Cardiovascular system	14	5	19	11	11
C03 - Diuretics	2	0	0	4	2
C03C - High-ceiling diuretics	2	0	0	2	1
C03CA - Sulfonamides, plain	2	0	0	2	1
C03CA01 - Furosemide	2	0	0	2	1
C03D - Potassium-sparing agents	0	0	0	2	1
C03DA - Aldosterone antagonists	0	0	0	2	1
C03DA01 - Spironolactone	0	0	0	2	1
C07 - Beta blocking agents	2	2	6	6	4
C07A - Beta blocking agents, plain	2	2	6	6	4
C07AA - Beta blocking agents, plain, non-selective	0	2	0	4	2
C07AA05 - Propranolol	0	2	0	4	2
C07AB - Beta blocking agents, plain, selective	2	0	6	0	1
C07AB02 - Metoprolol	2	0	0	0	1
C07AB07 - Bisoprolol	0	0	6	0	1
C08 - Calcium channel blockers	4	0	6	0	2
C08C - Selective calcium channel blockers with mainly vascular effects	2	0	0	0	1
C08CA - Dihydropyridine derivatives	2	0	0	0	1
C08CA01 - Amlodipine	2	0	0	0	1
C08D - Selective calcium channel blockers with direct cardiac effects	2	0	6	0	1
C08DA - Phenylalkylamine derivatives	2	0	6	0	1
C08DA01 - Verapamil	2	0	6	0	1
C09 - Agents acting on the renin-angiotensin system	6	0	6	0	3
C09A - Ace-inhibitors, plain	2	0	0	0	1
C09AA - Ace-inhibitors, plain	2	0	0	0	1
C09AA02 - Enalapril	2	0	0	0	1
C09C - Angiotensin ii antagonists	2	0	6	0	1
C09CA - Angiotensin ii antagonists, plain	2	0	6	0	1
C09CA01 - Losartan	0	0	6	0	1
C09CA06 - Candesartan	2	0	0	0	1
C09D - Angiotensin ii antagonists, combinations	2	0	0	0	1
C09DA - Angiotensin ii antagonists and diuretics	2	0	0	0	1
C09DA01 - Losartan and diuretics	2	0	0	0	1
C10 - Lipid modifying agents	0	2	0	2	1
C10A - Lipid modifying agents, plain	0	2	0	2	1

C10AA - Hmg coa reductase inhibitors	0	2	0	2	1
C10AA01 - Simvastatin	0	2	0	0	1
C10AA05 - Atorvastatin	0	0	0	2	1
D - Dermatologicals	2	10	0	0	3
D07 - Corticosteroids, dermatological preparations	0	2	0	0	1
D07A - Corticosteroids, plain	0	2	0	0	1
D07AC - Corticosteroids, potent (group iii)	0	2	0	0	1
D07AC01 - Betamethasone	0	2	0	0	1
D10 - Anti-acne preparations	2	7	0	0	3
D10A - Anti-acne preparations for topical use	0	7	0	0	2
D10AD - Retinoids for topical use in acne	0	5	0	0	1
D10AD03 - Adapalene	0	5	0	0	1
D10AF - Antiinfectives for treatment of acne	0	2	0	0	1
D10AF02 - Erythromycin	0	2	0	0	1
D10B - Anti-acne preparations for systemic use	2	0	0	0	1
D10BA - Retinoids for treatment of acne	2	0	0	0	1
D10BA01 - Isotretinoin	2	0	0	0	1
G - Genito urinary system and sex hormones	23	12	89	47	35
G02 - Other gynecologicals	4	2	6	0	3
G02B - Contraceptives for topical use	2	2	0	0	1
G02BB - Intravaginal contraceptives	2	2	0	0	1
G02BB01 - Vaginal ring with progestogen and estrogen	2	2	0	0	1
G02C - Other gynecologicals	2	0	6	0	1
G02CB - Prolactine inhibitors	2	0	6	0	1
G02CB01 - Bromocriptine	0	0	6	0	1
G02CB04 - Quinagolide	2	0	0	0	1
G03 - Sex hormones and modulators of the genital system	19	10	82	47	32
G03A - Hormonal contraceptives for systemic use	16	5	51	43	26
G03AA - Progestogens and estrogens, fixed combinations	12	2	51	38	22
G03AA03 - Lynestrenol and ethinylestradiol	0	0	0	2	1
G03AA05 - Norethisterone and ethinylestradiol	0	0	0	6	2
G03AA07 - Levonorgestrel and ethinylestradiol	0	2	0	15	6
G03AA08 - Medroxyprogesterone and ethinylestradiol	2	0	0	0	1
G03AA09 - Desogestrel and ethinylestradiol	0	0	19	4	3
G03AA10 - Gestodene and ethinylestradiol	8	0	0	2	3
G03AA11 - Norgestimate and ethinylestradiol	0	0	6	6	3
G03AA12 - Drospirenone and ethinylestradiol	2	0	25	4	4
G03AC - Progestogens	0	0	0	4	1
G03AC09 - Desogestrel	0	0	0	4	1
G03B - Androgens	0	2	0	0	1
G03D - Progestogens	0	0	6	0	1
G03DB - Pregnadien derivatives	0	0	6	0	1
G03DB01 - Dydrogesterone	0	0	6	0	1
G03G - Gonadotropins and other ovulation stimulants	0	0	13	0	1
G03GB - Ovulation stimulants, synthetic	0	0	13	0	1
G03H - Antiandrogens	0	2	13	4	3
G03HB - Antiandrogens and estrogens	0	2	13	4	3
G03HB01 - Cyproterone and estrogen	0	2	13	4	3
H - Systemic hormonal prep, excl sex hormones	0	2	0	2	1

H02 - Corticosteroids for systemic use	0	2	0	0	1
H02A - Corticosteroids for systemic use, plain	0	2	0	0	1
H02AB - Glucocorticoids	0	2	0	0	1
H02AB07 - Prednisone	0	2	0	0	1
H03 - Thyroid therapy	0	0	0	2	1
H03A - Thyroid preparations	0	0	0	2	1
H03AA - Thyroid hormones	0	0	0	2	1
H03AA01 - Levothyroxine sodium	0	0	0	2	1
J - General antiinfectives for systemic use	2	0	0	4	2
J01 - Antibacterials for systemic use	2	0	0	2	1
J01A - Tetracyclines	2	0	0	2	1
J01AA - Tetracyclines	2	0	0	2	1
J01AA02 - Doxycycline	2	0	0	0	1
J01AA06 - Oxytetracycline	0	0	0	2	1
J05 - Antivirals for systemic use	0	0	0	2	1
J05A - Direct acting antivirals	0	0	0	2	1
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0	0	0	2	1
J05AB01 - Aciclovir	0	0	0	2	1
L - Antineoplastic and immunomodulating agents	6	0	0	4	3
L03 - Immunostimulants	2	0	0	0	1
L03A - Immunostimulants	2	0	0	0	1
L03AB - Interferons	2	0	0	0	1
L03AB07 - Interferon beta-1a	2	0	0	0	1
L04 - Immunosuppressants	4	0	0	4	3
L04A - Immunosuppressants	4	0	0	4	3
L04AA - Selective immunosuppressants	2	0	0	0	1
L04AA06 - Mycophenolic acid	2	0	0	0	1
L04AX - Other immunosuppressants	2	0	0	4	2
L04AX03 - Methotrexate	2	0	0	4	2
M - Musculo-skeletal system	33	22	13	17	23
M01 - Antiinflammatory and antirheumatic products	33	20	6	11	20
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	33	20	6	11	20
M01AB - Acetic acid derivatives and related substances	8	2	0	6	5
M01AB05 - Diclofenac	8	2	0	6	5
M01AC - Oxicams	2	0	0	0	1
M01AC01 - Piroxicam	2	0	0	0	1
M01AE - Propionic acid derivatives	21	15	6	2	11
M01AE01 - Ibuprofen	19	12	6	2	10
M01AE02 - Naproxen	2	2	0	0	1
M01AH - Coxibs	0	2	0	4	2
M01AH01 - Celecoxib	0	2	0	2	1
M01AH05 - Etoricoxib	0	0	0	2	1
M01AX - Other antiinfl./antirheumatic agents, non-steroids	2	0	0	0	1
M01AX05 - Glucosamine	2	0	0	0	1
M02 - Topical products for joint and muscular pain	0	2	0	4	2
M02A - Topical products for joint and muscular pain	0	2	0	4	2
M02AA - Antiinfl. prep., non-steroids for topical use	0	2	0	4	2
M02AA12 - Naproxen	0	0	0	2	1

M02AA15 - Diclofenac	0	2	0	2	1
M03 - Muscle relaxants	0	0	6	0	1
M03B - Muscle relaxants, centrally acting agents	0	0	6	0	1
M03BX - Other centrally acting agents	0	0	6	0	1
M04 - Antigout preparations	0	0	0	2	1
M04A - Antigout preparations	0	0	0	2	1
M04AC - Preparations w. no effect on uric acid metabolism	0	0	0	2	1
M04AC01 - Colchicine	0	0	0	2	1
N - Nervous system	93	42	19	88	71
N02 - Analgesics	45	25	13	13	26
N02A - Opioids	8	2	0	9	6
N02AA - Natural opium alkaloids	2	0	0	6	3
N02AA58 - Dihydrocodeine, combinations	0	0	0	2	1
N02AA59 - Codeine, combinations excl. psycholeptics	2	0	0	2	1
N02AX - Other opioids	6	2	0	4	4
N02AX01 - Tilidine	0	2	0	0	1
N02AX02 - Tramadol	6	0	0	4	3
N02B - Other analgesics and antipyretics	23	2	6	2	9
N02BA - Salicylic acid derivatives	10	0	0	0	3
N02BA51 - Acetylsalicylic acid, comb excl psycholeptics	10	0	0	0	3
N02BE - Anilides	12	2	6	2	6
N02BE01 - Paracetamol	12	0	0	0	4
N02BE51 - Paracetamol, combinations excl psycholeptics	0	2	6	2	2
N02C - Antimigraine preparations	14	20	6	2	11
N02CC - Selective 5ht(1)-receptor agonists	14	20	6	2	11
N02CC01 - Sumatriptan	12	12	6	0	8
N02CC03 - Zolmitriptan	0	0	0	2	1
N02CC04 - Rizatriptan	2	7	0	0	3
N03 - Antiepileptics	8	2	0	8	6
N03A - Antiepileptics	8	2	0	8	6
N03AX - Other antiepileptics	8	2	0	8	6
N03AX09 - Lamotrigine	4	0	0	0	1
N03AX11 - Topiramate	4	2	0	0	2
N03AX12 - Gabapentin	0	0	0	6	2
N03AX16 - Pregabalin	0	0	0	2	1
N05 - Psycholeptics	6	2	0	6	4
N05A - Antipsychotics	4	2	0	4	3
N05AA - Phenothiazine with aliphatic side chain	0	0	0	2	1
N05AA03 - Promazine	0	0	0	2	1
N05AF - Thioxanthene derivatives	2	0	0	0	1
N05AF03 - Chlorprothixene	2	0	0	0	1
N05AH - Diazepines, oxazepines, thiazepines and oxepines	2	2	0	2	2
N05AH03 - Olanzapine	0	0	0	2	1
N05AH04 - Quetiapine	2	2	0	0	1
N05B - Anxiolytics	0	0	0	2	1
N05BA - Benzodiazepine derivatives	0	0	0	2	1
N05BA01 - Diazepam	0	0	0	2	1
N05C - Hypnotics and sedatives	2	0	0	0	1
N05CH - Melatonin receptor agonists	2	0	0	0	1

N05CH01 - Melatonin	2	0	0	0	1
N06 - Psychoanaleptics	33	12	6	60	34
N06A - Antidepressants	27	10	6	60	32
N06AA - Non selective monoamine reuptake inhibitors	2	2	0	11	5
N06AA09 - Amitriptyline	2	0	0	9	4
N06AA10 - Nortriptyline	0	2	0	2	1
N06AB - Selective serotonin reuptake inhibitors	23	5	6	41	23
N06AB03 - Fluoxetine	0	2	6	8	4
N06AB04 - Citalopram	14	0	0	19	11
N06AB05 - Paroxetine	4	2	0	0	2
N06AB06 - Sertraline	4	0	0	11	5
N06AB10 - Escitalopram	0	0	0	4	1
N06AX - Other antidepressants	2	2	0	8	4
N06AX05 - Trazodone	0	0	0	2	1
N06AX12 - Bupropion	0	2	0	0	1
N06AX16 - Venlafaxine	2	0	0	4	2
N06AX18 - Reboxetine	0	0	0	2	1
N06B - Psychostimulants, agents used for adhd and nootropics	6	2	0	0	3
N06BA - Centrally acting sympathomimetics	6	2	0	0	3
N06BA04 - Methylphenidate	6	2	0	0	3
N07 - Other nervous system drugs	0	0	0	2	1
N07C - Antivertigo preparations	0	0	0	2	1
N07CA - Antivertigo preparations	0	0	0	2	1
N07CA01 - Betahistine	0	0	0	2	1
P - Antiparasitic products, insecticides and repellants	0	2	0	2	1
P01 - Antiprotozoals	0	2	0	2	1
P01B - Antimalarials	0	2	0	2	1
P01BA - Aminoquinolines	0	2	0	2	1
P01BA02 - Hydroxychloroquine	0	2	0	2	1
R - Respiratory system	12	65	6	9	24
R01 - Nasal preparations	4	7	0	0	3
R01A - Decongestants and other nasal preparations for topical use	4	7	0	0	3
R01AD - Corticosteroids	4	5	0	0	3
R01AD09 - Mometasone	2	2	0	0	1
R01AD12 - Fluticasone furoate	2	0	0	0	1
R03 - Drugs for obstructive airway diseases	2	22	0	0	6
R03A - Adrenergics, inhalants	2	15	0	0	4
R03AC - Selective beta-2-adrenoceptor agonists	0	5	0	0	1
R03AC02 - Salbutamol	0	2	0	0	1
R03AC13 - Formoterol	0	2	0	0	1
R03AK - Adrenergics and other drugs for obstructive airway diseases	2	10	0	0	3
R03AK06 - Salmeterol and other drugs for obstructive airway diseases	0	5	0	0	1
R03AK07 - Formoterol and other drugs for obstructive airway diseases	2	5	0	0	2
R03B - Other drugs for obstructive airway diseases, inhalants	0	5	0	0	1
R03BA - Glucocorticoids	0	5	0	0	1

R03BA08 - Ciclesonide	0	5	0	0	1
R03D - Other systemic drugs for obstructive airway diseases	0	2	0	0	1
R03DC - Leukotriene receptor antagonists	0	2	0	0	1
R03DC03 - Montelukast	0	2	0	0	1
R05 - Cough and cold preparations	2	2	0	0	1
R05D - Cough suppressants, excl. combinations with expectorants	2	0	0	0	1
R05DA - Opium alkaloids and derivatives	2	0	0	0	1
R05DA04 - Codeine	2	0	0	0	1
R05X - Other cold preparations	0	2	0	0	1
R06 - Antihistamines for systemic use	4	32	6	9	13
R06A - Antihistamines for systemic use	4	30	6	9	13
R06AE - Piperazine derivatives	4	20	0	0	6
R06AE07 - Cetirizine	4	0	0	0	1
R06AE09 - Levocetirizine	0	20	0	0	5
R06AX - Other antihistamines for systemic use	0	10	6	9	6
R06AX13 - Loratadine	0	2	6	4	3
R06AX26 - Fexofenadine	0	5	0	4	3
R06AX27 - Desloratadine	0	2	0	2	1
V - Various	0	0	6	0	1
V10 - Therapeutic radiopharmaceuticals	0	0	6	0	1

13.11.2 Impact on medications use when finding out being pregnant

Table 13-17 Rates per 1000 women who stopped medications when found out being pregnant

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	16	2	4	30	16
A02 - Drugs for acid related disorders	3	2	0	8	4
A02A - Antacids	2	0	0	0	0
A02AA - Magnesium compounds	2	0	0	0	0
A02AA04 - Magnesium hydroxide	2	0	0	0	0
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	2	2	0	8	4
A02BA - H2-receptor antagonists	0	0	0	1	0
A02BA02 - Ranitidine	0	0	0	1	0
A02BC - Proton pump inhibitors	2	2	0	7	3
A02BC02 - Pantoprazole	0	2	0	0	0
A02BC03 - Lansoprazole	2	0	0	6	2
A02BC04 - Rabeprazole	0	0	0	1	0
A03 - Drugs for functional gastrointestinal disorders	0	0	0	7	2
A03A - Drugs for functional gastrointestinal disorders	0	0	0	3	1
A03AA - Synt anticholin,esters with tertiary amino group	0	0	0	3	1
A03AA04 - Mebeverine	0	0	0	3	1
A03B - Belladonna and derivatives, plain	0	0	0	3	1
A03BB - Belladonna alkaloids semisynt,quater ammonium comp	0	0	0	3	1
A03BB01 - Butylscopolamine	0	0	0	3	1
A03F - Propulsives	0	0	0	1	0
A03FA - Propulsives	0	0	0	1	0

A03FA03 - Domperidone	0	0	0	1	0
A06 - Drugs for constipation	2	0	0	4	2
A06A - Drugs for constipation	2	0	0	4	2
A06AB - Contact laxatives	2	0	0	0	0
A06AB08 - Sodium picosulfate	2	0	0	0	0
A06AD - Osmotically acting laxatives	0	0	0	4	1
A06AD11 - Lactulose	0	0	0	1	0
A06AD15 - Macrogol	0	0	0	3	1
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	0	0	0	6	2
A07D - Antipropulsives	0	0	0	4	1
A07DA - Antipropulsives	0	0	0	4	1
A07DA03 - Loperamide	0	0	0	4	1
A07E - Intestinal antiinflammatory agents	0	0	0	1	0
A07EC - Aminosalicylic acid and similar agents	0	0	0	1	0
A07EC02 - Mesalazine	0	0	0	1	0
A10 - Drugs used in diabetes	11	0	4	4	5
A10B - Blood glucose lowering drugs, excl. insulins	11	0	4	4	5
A10BA - Biguanides	11	0	4	4	5
A10BA02 - Metformin	11	0	4	4	5
B - Blood and blood forming organs	0	4	0	0	1
B01 - Antithrombotic agents	0	4	0	0	1
B01A - Antithrombotic agents	0	4	0	0	1
B01AA - Vitamin k antagonists	0	2	0	0	0
B01AA07 - Acenocoumarol	0	2	0	0	0
B01AB - Heparin group	0	2	0	0	0
B01AB06 - Nadroparin	0	2	0	0	0
C - Cardiovascular system	5	0	12	7	5
C02 - Antihypertensives	0	0	4	0	0
C02A - Antiadrenergic agents, centrally acting	0	0	4	0	0
C02AA - Rauwolfia alkaloids	0	0	4	0	0
C02AA05 - Deserpidine	0	0	4	0	0
C03 - Diuretics	0	0	0	1	0
C03D - Potassium-sparing agents	0	0	0	1	0
C03DA - Aldosterone antagonists	0	0	0	1	0
C03DA01 - Spironolactone	0	0	0	1	0
C07 - Beta blocking agents	0	0	0	6	2
C07A - Beta blocking agents, plain	0	0	0	6	2
C07AA - Beta blocking agents, plain, non-selective	0	0	0	4	1
C07AA05 - Propranolol	0	0	0	4	1
C07AB - Beta blocking agents, plain, selective	0	0	0	1	0
C07AB07 - Bisoprolol	0	0	0	1	0
C09 - Agents acting on the renin-angiotensin system	3	0	4	0	1
C09A - Ace-inhibitors, plain	2	0	0	0	0
C09AA - Ace-inhibitors, plain	2	0	0	0	0
C09AA05 - Ramipril	2	0	0	0	0
C09C - Angiotensin ii antagonists	2	0	4	0	1
C09CA - Angiotensin ii antagonists, plain	2	0	4	0	1
C09CA01 - Losartan	2	0	4	0	1
C10 - Lipid modifying agents	2	0	4	0	1

C10A - Lipid modifying agents, plain	2	0	4	0	1
C10AA - Hmg coa reductase inhibitors	2	0	4	0	1
C10AA01 - Simvastatin	2	0	0	0	0
C10AA07 - Rosuvastatin	0	0	4	0	0
D - Dermatologicals	2	11	4	8	6
D01 - Antifungals for dermatological use	0	2	0	0	0
D01A - Antifungals for topical use	0	2	0	0	0
D01AE - Other antifungals for topical use	0	2	0	0	0
D01AE12 - Salicylic acid	0	2	0	0	0
D05 - Antipsoriatics	0	0	0	1	0
D05A - Antipsoriatics for topical use	0	0	0	1	0
D05AX - Other antipsoriatics for topical use	0	0	0	1	0
D05AX05 - Tazarotene	0	0	0	1	0
D06 - Antibiotics and chemother. for dermatological use	2	0	0	1	1
D06B - Chemotherapeutics for topical use	2	0	0	1	1
D06BX - Other chemotherapeutics	2	0	0	1	1
D06BX01 - Metronidazole	2	0	0	1	1
D07 - Corticosteroids, dermatological preparations	0	6	0	3	2
D07A - Corticosteroids, plain	0	6	0	1	2
D07AA - Corticosteroids, weak (group i)	0	2	0	1	1
D07AA02 - Hydrocortisone	0	2	0	1	1
D07AB - Corticosteroids, moderately potent (group ii)	0	2	0	0	0
D07AB01 - Clobetasone	0	2	0	0	0
D07B - Corticosteroids, comb with antiseptics	0	0	0	1	0
D07BC - Corticosteroids, potent, comb with antiseptics	0	0	0	1	0
D07BC01 - Betamethasone and antiseptics	0	0	0	1	0
D10 - Anti-acne preparations	0	2	4	1	1
D10A - Anti-acne preparations for topical use	0	2	4	1	1
D10AD - Retinoids for topical use in acne	0	2	0	0	0
D10AD03 - Adapalene	0	2	0	0	0
D10AE - Peroxides	0	0	4	0	0
D10AE01 - Benzoyl peroxide	0	0	4	0	0
D10AF - Antiinfectives for treatment of acne	0	0	0	1	0
D10AF02 - Erythromycin	0	0	0	1	0
D11 - Other dermatological preparations	0	0	0	1	0
D11A - Other dermatological preparations	0	0	0	1	0
D11AH - Agents for dermatitis, excluding corticosteroids	0	0	0	1	0
D11AH01 - Tacrolimus	0	0	0	1	0
G - Genito urinary system and sex hormones	3	4	12	16	9
G02 - Other gynecologicals	0	0	12	0	1
G02C - Other gynecologicals	0	0	12	0	1
G02CB - Prolactine inhibitors	0	0	12	0	1
G02CB01 - Bromocriptine	0	0	12	0	1
G03 - Sex hormones and modulators of the genital system	3	4	0	16	7
G03A - Hormonal contraceptives for systemic use	3	2	0	13	6
G03AA - Progestogens and estrogens, fixed combinations	3	2	0	6	3
G03AA07 - Levonorgestrel and ethinylestradiol	2	2	0	4	2
G03AA09 - Desogestrel and ethinylestradiol	0	0	0	1	0
G03AA11 - Norgestimate and ethinylestradiol	2	0	0	0	0

G03AC - Progestogens	0	0	0	6	2
G03AC01 - Norethisterone	0	0	0	1	0
G03AC09 - Desogestrel	0	0	0	3	1
G03G - Gonadotropins and other ovulation stimulants	0	2	0	3	1
G03GB - Ovulation stimulants, synthetic	0	2	0	3	1
G03GB02 - Clomifene	0	2	0	3	1
H - Systemic hormonal prep, excl sex hormones	0	4	0	1	1
H01 - Pituitary, hypothalamic hormones and analogues	0	0	0	1	0
H01C - Hypothalamic hormones	0	0	0	1	0
H01CA - Gonadotrophin-releasing hormones	0	0	0	1	0
H01CA02 - Nafarelin	0	0	0	1	0
H02 - Corticosteroids for systemic use	0	2	0	0	0
H02A - Corticosteroids for systemic use, plain	0	2	0	0	0
H02AB - Glucocorticoids	0	2	0	0	0
H02AB01 - Betamethasone	0	2	0	0	0
H03 - Thyroid therapy	0	2	0	0	0
H03B - Antithyroid preparations	0	2	0	0	0
H03BB - Sulphur-containing imidazole derivatives	0	2	0	0	0
H03BB02 - Thiamazole	0	2	0	0	0
J - General antiinfectives for systemic use	3	0	8	0	2
J01 - Antibacterials for systemic use	3	0	4	0	1
J01A - Tetracyclines	2	0	4	0	1
J01AA - Tetracyclines	2	0	4	0	1
J01AA04 - Lymecycline	0	0	4	0	0
J01AA07 - Tetracycline	2	0	0	0	0
J01C - Beta-lactam antibacterials, penicillins	2	0	0	0	0
J01CF - Beta-lactamase resistant penicillins	2	0	0	0	0
J01CF01 - Dicloxacillin	2	0	0	0	0
J05 - Antivirals for systemic use	0	0	4	0	0
J05A - Direct acting antivirals	0	0	4	0	0
J05AB - Nucleosides and nucleotides excl. reverse transcriptase inhibitors	0	0	4	0	0
J05AB01 - Aciclovir	0	0	4	0	0
L - Antineoplastic and immunomodulating agents	0	0	0	3	1
L02 - Endocrine therapy	0	0	0	1	0
L02B - Hormone antagonists and related agents	0	0	0	1	0
L02BA - Anti-estrogens	0	0	0	1	0
L02BA01 - Tamoxifen	0	0	0	1	0
L04 - Immunosuppressants	0	0	0	1	0
L04A - Immunosuppressants	0	0	0	1	0
L04AB - Tumor necrosis factor alpha (tnf-alpha) inhibitors	0	0	0	1	0
L04AB02 - Infliximab	0	0	0	1	0
M - Musculo-skeletal system	34	15	12	39	29
M01 - Antiinflammatory and antirheumatic products	34	15	12	38	29
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	34	15	12	38	29
M01AB - Acetic acid derivatives and related substances	2	0	0	4	2
M01AB05 - Diclofenac	2	0	0	4	2
M01AC - Oxicams	0	0	4	0	0
M01AC01 - Piroxicam	0	0	4	0	0

M01AE - Propionic acid derivatives	33	15	8	31	25
M01AE01 - Ibuprofen	31	15	8	21	21
M01AE02 - Naproxen	2	0	0	10	4
M01AG - Fenamates	0	0	0	1	0
M01AG01 - Mefenamic acid	0	0	0	1	0
M01AH - Coxibs	0	0	0	1	0
M01AH01 - Celecoxib	0	0	0	1	0
M09 - Other drugs for disorders of musculo-skeletal syst	0	0	0	1	0
M09A - Other drugs for disorders of musculo-skeletal syst	0	0	0	1	0
M09AA - Quinine and derivatives	0	0	0	1	0
M09AA01 - Hydroquinine	0	0	0	1	0
N - Nervous system	58	25	25	69	50
N02 - Analgesics	34	15	12	23	23
N02A - Opioids	8	2	0	7	5
N02AA - Natural opium alkaloids	0	2	0	0	0
N02AA05 - Oxycodone	0	2	0	0	0
N02AX - Other opioids	8	0	0	7	5
N02AX02 - Tramadol	8	0	0	7	5
N02B - Other analgesics and antipyretics	16	6	8	13	12
N02BA - Salicylic acid derivatives	3	0	4	3	2
N02BA01 - Acetylsalicylic acid	0	0	4	3	1
N02BA51 - Acetylsalicylic acid, comb excl psycholeptics	3	0	0	0	1
N02BB - Pyrazolones	0	0	4	0	0
N02BB02 - Metamizole sodium	0	0	4	0	0
N02BE - Anilides	13	6	0	10	9
N02BE01 - Paracetamol	13	2	0	0	4
N02BE51 - Paracetamol, combinations excl psycholeptics	0	4	0	10	4
N02C - Antimigraine preparations	11	4	4	3	6
N02CA - Ergot alkaloids	0	0	4	0	0
N02CC - Selective 5ht(1)-receptor agonists	9	4	0	3	5
N02CC01 - Sumatriptan	3	4	0	1	2
N02CC02 - Naratriptan	2	0	0	0	0
N02CC04 - Rizatriptan	3	0	0	1	1
N02CC06 - Eletriptan	2	0	0	0	0
N03 - Antiepileptics	2	0	0	4	2
N03A - Antiepileptics	2	0	0	4	2
N03AF - Carboxamide derivatives	0	0	0	1	0
N03AF01 - Carbamazepine	0	0	0	1	0
N03AX - Other antiepileptics	2	0	0	3	1
N03AX12 - Gabapentin	0	0	0	3	1
N03AX16 - Pregabalin	2	0	0	0	0
N05 - Psycholeptics	3	4	4	7	5
N05A - Antipsychotics	2	2	0	4	2
N05AH - Diazepines, oxazepines, thiazepines and oxepines	2	2	0	3	2
N05AH04 - Quetiapine	2	2	0	3	2
N05AN - Lithium	0	0	0	1	0
N05AN01 - Lithium	0	0	0	1	0
N05B - Anxiolytics	2	0	0	1	1
N05BA - Benzodiazepine derivatives	2	0	0	1	1

N05BA01 - Diazepam	0	0	0	1	0
N05BA04 - Oxazepam	2	0	0	0	0
N05C - Hypnotics and sedatives	0	2	4	1	1
N05CD - Benzodiazepine derivatives	0	2	0	0	0
N05CD07 - Temazepam	0	2	0	0	0
N05CF - Benzodiazepine related drugs	0	0	0	1	0
N05CF02 - Zolpidem	0	0	0	1	0
N05CH - Melatonin receptor agonists	0	0	4	0	0
N05CH01 - Melatonin	0	0	4	0	0
N06 - Psychoanaleptics	19	6	8	35	20
N06A - Antidepressants	16	4	8	35	19
N06AA - Non selective monoamine reuptake inhibitors	2	0	4	4	2
N06AA04 - Clomipramine	0	0	4	0	0
N06AA09 - Amitriptyline	2	0	0	4	2
N06AB - Selective serotonin reuptake inhibitors	9	4	4	23	12
N06AB03 - Fluoxetine	0	0	0	11	4
N06AB04 - Citalopram	5	2	0	6	4
N06AB06 - Sertraline	3	0	4	4	3
N06AB10 - Escitalopram	0	2	0	1	1
N06AX - Other antidepressants	5	0	0	8	4
N06AX11 - Mirtazapine	0	0	0	3	1
N06AX16 - Venlafaxine	3	0	0	3	2
N06AX21 - Duloxetine	2	0	0	1	1
N06AX22 - Agomelatine	0	0	0	1	0
N06B - Psychostimulants, agents used for adhd and nootropics	3	2	0	0	1
N06BA - Centrally acting sympathomimetics	3	2	0	0	1
N06BA04 - Methylphenidate	3	2	0	0	1
R - Respiratory system	28	34	25	31	30
R01 - Nasal preparations	8	4	0	3	4
R01A - Decongestants and other nasal preparations for topical use	8	4	0	3	4
R01AA - Sympathomimetics, plain	3	0	0	1	1
R01AA05 - Oxymetazoline	0	0	0	1	0
R01AA07 - Xylometazoline	3	0	0	0	1
R01AD - Corticosteroids	5	4	0	1	3
R01AD01 - Beclomethasone	0	0	0	1	0
R01AD08 - Fluticasone	0	2	0	0	0
R01AD09 - Mometasone	5	2	0	0	2
R03 - Drugs for obstructive airway diseases	8	8	17	4	8
R03A - Adrenergics, inhalants	5	6	8	1	4
R03AC - Selective beta-2-adrenoceptor agonists	3	2	4	1	2
R03AC02 - Salbutamol	2	2	4	1	2
R03AC03 - Terbutaline	2	0	0	0	0
R03AK - Adrenergics and other drugs for obstructive airway diseases	2	4	4	0	2
R03AK06 - Salmeterol and other drugs for obstructive airway diseases	0	2	4	0	1
R03AK07 - Formoterol and other drugs for obstructive airway diseases	2	2	0	0	1

R03B - Other drugs for obstructive airway diseases, inhalants	3	0	4	0	1
R03BA - Glucocorticoids	3	0	4	0	1
R03BA02 - Budesonide	3	0	0	0	1
R03BA08 - Ciclesonide	0	0	4	0	0
R03D - Other systemic drugs for obstructive airway diseases	0	2	4	3	2
R03DC - Leukotriene receptor antagonists	0	0	4	3	1
R03DC03 - Montelukast	0	0	4	3	1
R03DX - Other systemic drugs for obstructive airway diseases	0	2	0	0	0
R03DX05 - Omalizumab	0	2	0	0	0
R05 - Cough and cold preparations	3	2	0	3	2
R05C - Expectorants,excl combinations with antitussives	0	2	0	0	0
R05CB - Mucolytics	0	2	0	0	0
R05CB02 - Bromhexine	0	2	0	0	0
R05D - Cough suppressants, excl. combinations with expectorants	2	0	0	3	1
R05DA - Opium alkaloids and derivatives	2	0	0	3	1
R05DA04 - Codeine	2	0	0	3	1
R05F - Antitussives and expectorants, combinations	2	0	0	0	0
R05FA - Opium derivatives and expectorants	2	0	0	0	0
R05FA02 - Opium derivatives and expectorants	2	0	0	0	0
R06 - Antihistamines for systemic use	9	19	8	21	15
R06A - Antihistamines for systemic use	9	17	8	21	15
R06AB - Substituted alkylamines	0	0	0	3	1
R06AB04 - Chlorpheniramine	0	0	0	3	1
R06AD - Phenothiazine derivatives	0	0	0	1	0
R06AD02 - Promethazine	0	0	0	1	0
R06AE - Piperazine derivatives	6	6	0	4	5
R06AE03 - Cyclizine	2	0	0	0	0
R06AE07 - Cetirizine	5	2	0	3	3
R06AE09 - Levocetirizine	0	4	0	1	1
R06AX - Other antihistamines for systemic use	3	11	8	10	8
R06AX13 - Loratadine	0	2	4	3	2
R06AX18 - Acrivastine	2	0	0	1	1
R06AX25 - Mizolastine	0	0	0	1	0
R06AX26 - Fexofenadine	2	4	4	3	3
R06AX27 - Desloratadine	0	4	0	1	1
S - Sensory organs	0	4	0	1	1
S01 - Ophthalmologicals	0	4	0	1	1
S01B - Antiinflammatory agents	0	2	0	0	0
S01BA - Corticosteroids, plain	0	2	0	0	0
S01BA01 - Dexamethasone	0	2	0	0	0
S01G - Decongestants and antiallergics	0	2	0	1	1
S01GX - Other antiallergics	0	2	0	1	1
S01GX01 - Cromoglicic acid	0	0	0	1	0
S01GX08 - Ketotifen	0	2	0	0	0
V - Various	0	0	4	0	0
V03 - All other therapeutic products	0	0	4	0	0
V03A - All other therapeutic products	0	0	4	0	0

V03AB - Antidotes	0	0	4	0	0
V03AB21 - Potassium iodide	0	0	4	0	0

13.12 Medications from other people

Table 13-18 Rates per 1000 women who reported use of medications from other people

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	6	2	0	6	4
A02 - Drugs for acid related disorders	6	0	0	6	4
A02A - Antacids	3	0	0	4	2
A02AA - Magnesium compounds	2	0	0	0	0
A02AA04 - Magnesium hydroxide	2	0	0	0	0
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	2	0	0	0	0
A02AD01 - Ordinary salt combinations	2	0	0	0	0
A02AH - Antacids with sodium bicarbonate	0	0	0	1	0
A02AX - Antacids, other combinations	0	0	0	3	1
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	3	0	0	1	1
A02BA - H2-receptor antagonists	2	0	0	0	0
A02BA02 - Ranitidine	2	0	0	0	0
A02BC - Proton pump inhibitors	0	0	0	1	0
A02BC01 - Omeprazole	0	0	0	1	0
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	2	0	0	0	0
A02BX13 - Alginic acid	2	0	0	0	0
A06 - Drugs for constipation	0	2	0	0	0
A06A - Drugs for constipation	0	2	0	0	0
A06AD - Osmotically acting laxatives	0	2	0	0	0
A06AD65 - Macrogol, combinations	0	2	0	0	0
D - Dermatologicals	5	2	0	1	2
D02 - Emollients and protectives	0	0	0	1	0
D02A - Emollients and protectives	0	0	0	1	0
D02AF - Salicylic acid preparations	0	0	0	1	0
D07 - Corticosteroids, dermatological preparations	3	2	0	0	1
D07A - Corticosteroids, plain	3	0	0	0	1
D07AB - Corticosteroids, moderately potent (group ii)	2	0	0	0	0
D07AB02 - Hydrocortisone butyrate	2	0	0	0	0
D07AC - Corticosteroids, potent (group iii)	2	0	0	0	0
D07AC13 - Mometasone	2	0	0	0	0
D07X - Corticosteroids, other combinations	0	2	0	0	0
D07XA - Corticosteroids, weak, other combinations	0	2	0	0	0
D07XA01 - Hydrocortisone	0	2	0	0	0
D11 - Other dermatological preparations	2	0	0	0	0
D11A - Other dermatological preparations	2	0	0	0	0
D11AH - Agents for dermatitis, excluding corticosteroids	2	0	0	0	0
D11AH01 - Tacrolimus	2	0	0	0	0
G - Genito urinary system and sex hormones	0	2	0	0	0
G03 - Sex hormones and modulators of the genital system	0	2	0	0	0

G03D - Progestogens	0	2	0	0	0
G03DA - Pregnen (4) derivatives	0	2	0	0	0
G03DA04 - Progesterone	0	2	0	0	0
H - Systemic hormonal prep, excl sex hormones	0	0	0	1	0
H03 - Thyroid therapy	0	0	0	1	0
H03A - Thyroid preparations	0	0	0	1	0
H03AA - Thyroid hormones	0	0	0	1	0
H03AA01 - Levothyroxine sodium	0	0	0	1	0
N - Nervous system	3	0	0	3	2
N02 - Analgesics	3	0	0	3	2
N02A - Opioids	2	0	0	0	0
N02AA - Natural opium alkaloids	2	0	0	0	0
N02AA05 - Oxycodone	2	0	0	0	0
N02B - Other analgesics and antipyretics	2	0	0	3	1
N02BE - Anilides	2	0	0	3	1
N02BE01 - Paracetamol	2	0	0	1	1
N02BE51 - Paracetamol, combinations excl psycholeptics	0	0	0	1	0
R - Respiratory system	0	0	0	1	0
R03 - Drugs for obstructive airway diseases	0	0	0	1	0
R03B - Other drugs for obstructive airway diseases, inhalants	0	0	0	1	0
R03BA - Glucocorticoids	0	0	0	1	0
R03BA02 - Budesonide	0	0	0	1	0

13.13 Decided not to take doctor's prescribed medications

Table 13-19 Rates per 1000 women who stopped or did not take doctor's prescribed medications during and up to 1 month before pregnancy

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	20	19	25	25	22
A02 - Drugs for acid related disorders	6	6	0	8	6
A02A - Antacids	2	4	0	6	3
A02AD - Combinations and complexes of aluminium, calcium and magnesium compounds	0	0	0	6	2
A02AX - Antacids, other combinations	0	2	0	0	0
A02B - Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	5	2	0	3	3
A02BC - Proton pump inhibitors	5	2	0	1	2
A02BC01 - Omeprazole	5	2	0	1	2
A02BX - Other drugs peptic ulcer and gastro-oesophageal reflux disease (gord)	0	0	0	1	0
A02BX13 - Alginic acid	0	0	0	1	0
A03 - Drugs for functional gastrointestinal disorders	6	0	8	0	3
A03A - Drugs for functional gastrointestinal disorders	0	0	8	0	1
A03AD - Papaverine and derivatives	0	0	8	0	1
A03AD02 - Drotaverine	0	0	8	0	1
A03F - Propulsives	6	0	0	0	2
A03FA - Propulsives	6	0	0	0	2
A03FA01 - Metoclopramide	6	0	0	0	2

A04 - Antiemetics and antinauseants	6	2	4	4	4
A04A - Antiemetics and antinauseants	6	2	4	4	4
A04AA - Serotonin (5ht3) antagonists	3	0	0	0	1
A04AA01 - Ondansetron	3	0	0	0	1
A06 - Drugs for constipation	0	11	0	10	6
A06A - Drugs for constipation	0	11	0	10	6
A06AC - Bulk-forming laxatives	0	4	0	0	1
A06AC01 - Ispaghula (psylla seeds)	0	4	0	0	1
A06AD - Osmotically acting laxatives	0	2	0	10	4
A06AD11 - Lactulose	0	0	0	8	3
A06AD61 - Lactulose, combinations	0	0	0	1	0
A06AD65 - Macrogol, combinations	0	2	0	0	0
A07 - Antidiarr.,intest. antiinfl./antiinfect. agents	0	0	12	0	1
A07A - Intestinal antiinfectives	0	0	4	0	0
A07AA - Antibiotics	0	0	4	0	0
A07AA02 - Nystatin	0	0	4	0	0
A07F - Antidiarrheal microorganisms	0	0	8	0	1
A07FA - Antidiarrheal microorganisms	0	0	8	0	1
A07FA01 - Lactic acid producing organisms	0	0	4	0	0
A07FA02 - Saccharomyces boulardii	0	0	4	0	0
A10 - Drugs used in diabetes	2	0	0	3	1
A10B - Blood glucose lowering drugs, excl. insulins	2	0	0	3	1
A10BA - Biguanides	2	0	0	3	1
A10BA02 - Metformin	2	0	0	3	1
B - Blood and blood forming organs	2	0	8	6	3
B01 - Antithrombotic agents	2	0	4	6	3
B01A - Antithrombotic agents	2	0	4	6	3
B01AC - Platelet aggregation inhibitors excl. heparin	2	0	4	6	3
B01AC06 - Acetylsalicylic acid	2	0	4	6	3
B02 - Antihemorrhagics	0	0	4	0	0
B02B - Vitamin k and other hemostatics	0	0	4	0	0
B02BX - Other systemic hemostatics	0	0	4	0	0
B02BX01 - Etamsylate	0	0	4	0	0
C - Cardiovascular system	3	0	0	4	2
C01 - Cardiac therapy	0	0	0	1	0
C01C - Cardiac stimulants excl. cardiac glycosides	0	0	0	1	0
C01CA - Adrenergic and dopaminergic agents	0	0	0	1	0
C01CA24 - Epinephrine	0	0	0	1	0
C05 - Vasoprotectives	2	0	0	1	1
C05A - Agents for treatment of hemorrhoids and anal fissures for topical use	2	0	0	1	1
C05AE - Musclerelaxants	0	0	0	1	0
C05AE01 - Glyceryl trinitrate	0	0	0	1	0
C07 - Beta blocking agents	0	0	0	1	0
C07A - Beta blocking agents, plain	0	0	0	1	0
C07AA - Beta blocking agents, plain, non-selective	0	0	0	1	0
C07AA05 - Propranolol	0	0	0	1	0
D - Dermatologicals	3	6	0	3	3
D01 - Antifungals for dermatological use	0	0	0	1	0

D01A - Antifungals for topical use	0	0	0	1	0
D01AC - Imidazole and triazole derivatives	0	0	0	1	0
D01AC20 - Combinations	0	0	0	1	0
D07 - Corticosteroids, dermatological preparations	2	0	0	1	1
D07A - Corticosteroids, plain	0	0	0	1	0
D07AA - Corticosteroids, weak (group i)	0	0	0	1	0
D07C - Corticosteroids, comb with antibiotics	2	0	0	0	0
D07CC - Corticosteroids, potent, comb with antibiotics	2	0	0	0	0
D07CC01 - Betamethasone and antibiotics	2	0	0	0	0
D10 - Anti-acne preparations	2	2	0	0	1
D10A - Anti-acne preparations for topical use	2	2	0	0	1
D10AD - Retinoids for topical use in acne	0	2	0	0	0
D10AD03 - Adapalene	0	2	0	0	0
D10AF - Antiinfectives for treatment of acne	2	0	0	0	0
D10AF51 - Clindamycin, comb.	2	0	0	0	0
G - Genito urinary system and sex hormones	0	0	12	1	2
G01 - Gynecological antiinfectives and antiseptics	0	0	4	1	1
G01A - Antiinfectives/antisept.,excl comb with corticost.	0	0	4	1	1
G01AA - Antibiotics	0	0	4	0	0
G01AA01 - Nystatin	0	0	4	0	0
G01AF - Imidazole derivatives	0	0	0	1	0
G01AF02 - Clotrimazole	0	0	0	1	0
G03 - Sex hormones and modulators of the genital system	0	0	8	0	1
G03D - Progestogens	0	0	8	0	1
G03DB - Pregnadien derivatives	0	0	8	0	1
G03DB01 - Dydrogesterone	0	0	8	0	1
H - Systemic hormonal prep, excl sex hormones	2	2	0	1	1
H01 - Pituitary, hypothalamic hormones and analogues	0	2	0	0	0
H01B - Posterior pituitary lobe hormones	0	2	0	0	0
H01BB - Oxytocin and analogues	0	2	0	0	0
H01BB02 - Oxytocin	0	2	0	0	0
H02 - Corticosteroids for systemic use	2	0	0	0	0
H03 - Thyroid therapy	0	0	0	1	0
H03A - Thyroid preparations	0	0	0	1	0
H03AA - Thyroid hormones	0	0	0	1	0
H03AA01 - Levothyroxine sodium	0	0	0	1	0
J - General antiinfectives for systemic use	17	4	8	17	13
J01 - Antibacterials for systemic use	13	4	8	17	12
J01C - Beta-lactam antibacterials, penicillins	3	0	4	3	2
J01CA - Penicillins with extended spectrum	2	0	4	3	2
J01CA04 - Amoxicillin	0	0	4	3	1
J01CA08 - Pivmecillinam	2	0	0	0	0
J01CE - Beta-lactamase sensitive penicillins	2	0	0	0	0
J01CE02 - Phenoxymethylpenicillin	2	0	0	0	0
J01D - Other beta-lactam antibacterials	0	0	0	3	1
J01DB - First-generation cephalosporins	0	0	0	3	1
J01DB01 - Cefalexin	0	0	0	3	1
J01E - Sulfonamides and trimethoprim	2	0	0	0	0
J01EB - Short-acting sulfonamides	2	0	0	0	0

J01EB02 - Sulfamethizole	2	0	0	0	0
J01F - Macrolides, lincosamides and streptogramins	2	0	0	3	1
J01FA - Macrolides	2	0	0	3	1
J01FA01 - Erythromycin	2	0	0	1	1
J01FA10 - Azithromycin	0	0	0	1	0
J01X - Other antibacterials	0	0	0	1	0
J01XE - Nitrofuran derivatives	0	0	0	1	0
J01XE01 - Nitrofurantoin	0	0	0	1	0
J02 - Antimycotics for systemic use	3	0	0	0	1
J02A - Antimycotics for systemic use	3	0	0	0	1
J02AC - Triazole derivatives	3	0	0	0	1
J02AC01 - Fluconazole	3	0	0	0	1
J05 - Antivirals for systemic use	2	0	0	0	0
J05A - Direct acting antivirals	2	0	0	0	0
J05AH - Neuraminidase inhibitors	2	0	0	0	0
J05AH02 - Oseltamivir	2	0	0	0	0
M - Musculo-skeletal system	2	0	0	3	1
M01 - Antiinflammatory and antirheumatic products	2	0	0	3	1
M01A - Antiinflammatory/antirheumatic prod.,non-steroids	2	0	0	3	1
M01AE - Propionic acid derivatives	2	0	0	3	1
M01AE01 - Ibuprofen	2	0	0	1	1
M01AE14 - Dexibuprofen	0	0	0	1	0
N - Nervous system	8	4	8	25	13
N02 - Analgesics	2	0	0	17	6
N02A - Opioids	0	0	0	3	1
N02AA - Natural opium alkaloids	0	0	0	3	1
N02AA59 - Codeine, combinations excl. psycholeptics	0	0	0	3	1
N02B - Other analgesics and antipyretics	2	0	0	13	5
N02BE - Anilides	2	0	0	11	4
N02BE01 - Paracetamol	2	0	0	6	2
N02BE51 - Paracetamol, combinations excl psycholeptics	0	0	0	6	2
N02C - Antimigraine preparations	0	0	0	1	0
N02CC - Selective 5ht(1)-receptor agonists	0	0	0	1	0
N02CC01 - Sumatriptan	0	0	0	1	0
N03 - Antiepileptics	0	2	0	0	0
N03A - Antiepileptics	0	2	0	0	0
N03AB - Hydantoin derivatives	0	2	0	0	0
N03AB03 - Amino(diphenylhydantoin) valeric acid	0	2	0	0	0
N05 - Psycholeptics	0	0	8	3	2
N05A - Antipsychotics	0	0	0	3	1
N05AB - Phenothiazine with piperazine structure	0	0	0	3	1
N05AB04 - Prochlorperazine	0	0	0	3	1
N05B - Anxiolytics	0	0	8	0	1
N05BA - Benzodiazepine derivatives	0	0	4	0	0
N05BA01 - Diazepam	0	0	4	0	0
N05BB - Diphenylmethane derivatives	0	0	4	0	0
N05BB01 - Hydroxyzine	0	0	4	0	0
N06 - Psychoanaleptics	6	2	0	4	4
N06A - Antidepressants	6	2	0	4	4

N06AA - Non selective monoamine reuptake inhibitors	0	2	0	0	0
N06AA09 - Amitriptyline	0	2	0	0	0
N06AB - Selective serotonin reuptake inhibitors	3	0	0	1	1
N06AB03 - Fluoxetine	0	0	0	1	0
N06AB06 - Sertraline	3	0	0	0	1
N06AX - Other antidepressants	3	0	0	0	1
N06AX16 - Venlafaxine	2	0	0	0	0
N06AX21 - Duloxetine	2	0	0	0	0
N07 - Other nervous system drugs	0	0	0	1	0
N07B - Drugs used in addictive disorders	0	0	0	1	0
N07BA - Drugs used in nicotine dependence	0	0	0	1	0
N07BA01 - Nicotine	0	0	0	1	0
P - Antiparasitic products, insecticides and repellants	0	0	0	1	0
P03 - Ectoparasiticides, incl scabicides, insecticides and repellants	0	0	0	1	0
P03A - Ectoparasiticides, incl scabicides	0	0	0	1	0
P03AX - Other ectoparasiticides, incl scabicides	0	0	0	1	0
P03AX05 - Dimeticone	0	0	0	1	0
R - Respiratory system	9	13	8	7	9
R01 - Nasal preparations	2	2	4	1	2
R01A - Decongestants and other nasal preparations for topical use	2	0	4	1	1
R01AB - Sympathomimetics,combinations excl corticosteroids	0	0	4	0	0
R01AB02 - Naphazoline	0	0	4	0	0
R01AD - Corticosteroids	2	0	0	1	1
R01AD09 - Mometasone	2	0	0	0	0
R03 - Drugs for obstructive airway diseases	3	2	0	0	1
R06 - Antihistamines for systemic use	3	8	4	6	5
R06A - Antihistamines for systemic use	3	8	4	6	5
R06AA - Aminoalkyl ethers	0	2	0	0	0
R06AA04 - Clemastine	0	2	0	0	0
R06AD - Phenothiazine derivatives	0	0	4	1	1
R06AD02 - Promethazine	0	0	4	1	1
R06AE - Piperazine derivatives	0	2	0	1	1
R06AE03 - Cyclizine	0	0	0	1	0
R06AE09 - Levocetirizine	0	2	0	0	0
R06AX - Other antihistamines for systemic use	0	0	0	1	0
R06AX13 - Loratadine	0	0	0	1	0
S - Sensory organs	5	4	4	0	3
S01 - Ophthalmologicals	5	2	4	0	2
S01B - Antiinflammatory agents	2	2	0	0	1
S01BA - Corticosteroids, plain	2	0	0	0	0
S01C - Antiinflammatory agents and antiinfectives in comb	0	0	4	0	0
S01CA - Corticosteroids and antiinfectives in combination	0	0	4	0	0
S01CA06 - Fludrocortisone and antiinfectives	0	0	4	0	0
S01G - Decongestants and antiallergics	3	0	0	0	1
S02 - Otologicals	0	2	0	0	0

13.14 List of pregnancy-related medicinal products, excluding iron and multivitamin

Table 13-20 Rates per 1000 women who took pregnancy-related medications during and up to 1 month before pregnancy

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	6	0	0	3	3
A10 - Drugs used in diabetes	6	0	0	3	3
A10B - Blood glucose lowering drugs, excl. insulins	6	0	0	3	3
A10BA - Biguanides	6	0	0	3	3
A10BA02 - Metformin	6	0	0	3	3
G - Genito urinary system and sex hormones	199	189	112	62	139
G02 - Other gynecologicals	0	0	25	0	3
G02C - Other gynecologicals	0	0	25	0	3
G02CB - Prolactine inhibitors	0	0	25	0	3
G02CB01 - Bromocriptine	0	0	25	0	3
G03 - Sex hormones and modulators of the genital system	199	189	87	62	137
G03C - Estrogens	6	2	0	3	3
G03CA - Natural and semisynthetic estrogens, plain	6	2	0	3	3
G03CA03 - Estradiol	6	2	0	3	3
G03D - Progestogens	42	11	17	0	17
G03DA - Pregnen (4) derivatives	42	8	8	0	16
G03DA02 - Medroxyprogesterone	8	2	0	0	3
G03DA04 - Progesterone	34	6	8	0	13
G03DB - Pregnadien derivatives	0	0	8	0	1
G03DB01 - Dydrogesterone	0	0	8	0	1
G03DC - Estren derivatives	0	2	0	0	0
G03DC02 - Norethisterone	0	2	0	0	0
G03G - Gonadotropins and other ovulation stimulants	150	176	71	58	115
G03GA - Gonadotropins	124	134	21	37	84
G03GA01 - Chorionic gonadotropine	9	65	21	4	22
G03GA02 - Human menopausal gonadotrophin	17	8	0	14	12
G03GA04 - Urofollitrophin	0	4	0	0	1
G03GA05 - Follitropin alfa	19	19	0	0	10
G03GA06 - Follitropin beta	20	36	0	0	15
G03GA08 - Choriogonadotropin alfa	58	2	0	8	21
G03GB - Ovulation stimulants, synthetic	27	42	50	21	31
G03GB02 - Clomifene	27	42	50	21	31
H - Systemic hormonal prep, excl sex hormones	8	6	0	3	5
H01 - Pituitary, hypothalamic hormones and analogues	5	4	0	3	3
H01C - Hypothalamic hormones	5	4	0	3	3
H01CA - Gonadotrophin-releasing hormones	0	4	0	1	1
H01CA01 - Gonadorelin	0	4	0	1	1
H01CC - Anti gonadotropin releasing hormones	5	0	0	1	2
H01CC01 - Ganirelix	3	0	0	0	1
H01CC02 - Cetrorelix	2	0	0	1	1
H02 - Corticosteroids for systemic use	3	2	0	0	1
H02A - Corticosteroids for systemic use, plain	3	2	0	0	1
H02AB - Glucocorticoids	3	2	0	0	1
H02AB06 - Prednisolone	2	2	0	0	1

H02AB07 - Prednisone	2	0	0	0	0
L - Antineoplastic and immunomodulating agents	6	27	0	7	11
L02 - Endocrine therapy	6	27	0	7	11
L02A - Hormones and related agents	6	27	0	3	9
L02AE - Gonadotrophin releasing hormone analogues	6	27	0	3	9
L02AE01 - Buserelin	3	0	0	3	2
L02AE02 - Leuprorelin	0	2	0	0	0
L02AE03 - Goserelin	2	0	0	0	0
L02AE04 - Triptorelin	2	25	0	0	6
L02B - Hormone antagonists and related agents	0	0	0	4	1
L02BA - Anti-estrogens	0	0	0	3	1
L02BA01 - Tamoxifen	0	0	0	3	1
L02BG - Aromatase inhibitors	0	0	0	1	0
L02BG04 - Letrozole	0	0	0	1	0

13.15 List of multivitamins and iron supplements

Table 13-21 Rates per 1000 women who used multivitamins and iron supplements during pregnancy

Medications	DK	NL	PL	UK	All
A - Alimentary tract and metabolism	926	794	560	708	778
A11 - Vitamins	926	794	560	708	778
A11A - Multivitamins, combinations	858	737	519	671	726
A11AA - Multivitamins with minerals	5	36	104	24	30
A11AA01 - Multivitamins and iron	0	17	0	3	5
A11AA03 - Multivit and other minerals, incl combinations	0	0	95	3	12
A11AB - Multivitamins, other combinations	2	0	4	0	1
A11C - Vit a and d, incl combinations of the two	27	40	12	21	26
A11CC - Vitamin d and analogues	25	40	12	21	26
A11CC05 - Colecalciferol	9	2	12	0	5
A11D - Vit b1,plain and in comb with vitamin b6 and b12	6	0	0	0	2
A11E - Vitamin b-complex, incl combinations	19	4	4	3	8
A11EA - Vitamin b-complex, plain	6	0	0	1	2
A11G - Ascorbic acid (vit c), incl combinations	9	11	8	6	8
A11GA - Ascorbic acid (vit c), plain	8	4	4	6	6
A11GA01 - Ascorbic acid (vit c)	0	2	4	1	1
A11GB - Ascorbic acid (vit c), combinations	0	0	4	0	0
A11H - Other plain vitamin preparations	8	2	0	4	4
A11HA - Other plain vitamin preparations	8	2	0	4	4
A11HA02 - Pyridoxine (vit b6)	5	0	0	3	2
A11HA03 - Tocopherol (vit e)	2	0	0	0	0
A11HA04 - Riboflavin (vit b2)	0	0	0	1	0
A11HA06 - Pyridoxal phosphate	2	0	0	0	0
B - Blood and blood forming organs	1329	893	996	962	1063
B03 - Antianemic preparations	1329	893	996	962	1063

B03A - Iron preparations	659	101	290	179	323
B03AA - Iron bivalent, oral preparations	3	8	41	10	11
B03AA02 - Ferrous fumarate	0	6	0	3	2
B03AA07 - Ferrous sulphate	0	2	41	6	7
B03AC - Iron trivalent, parenteral preparations	0	2	0	0	0
B03AC01 - Ferric oxide polymaltose complexes	0	2	0	0	0
B03AD - Iron in combination with folic acid	0	0	12	0	1
B03AD03 - Ferrous sulphate	0	0	12	0	1
B03AE - Iron in other combinations	9	0	12	7	7
B03B - Vitamin b12 and folic acid	670	792	705	783	741
B03BA - Vitamin b12 (cyanocobalamin and derivatives)	13	6	4	8	9
B03BA02 - Cyanocobalamin tannin complex	5	0	0	0	1
B03BA03 - Hydroxocobalamin	0	6	0	7	4
B03BA05 - Mecobalamin	0	0	0	1	0
B03BB - Folic acid and derivatives	657	786	701	774	732
B03BB01 - Folic acid	657	786	697	774	732

13.16 Vaccines and antimalarials used during pregnancy

Table 13-22 Rates per 1000 women who had vaccinations and/or had antimalarials during pregnancy

Medications	DK	NL	PL	UK	All
J - General antiinfectives for systemic use	244	78	25	1051	457
J01 - Antibacterials for systemic use	2	0	0	0	0
J01A - Tetracyclines	2	0	0	0	0
J01AA - Tetracyclines	2	0	0	0	0
J01AA02 - Doxycycline	2	0	0	0	0
J06 - Immune sera and immunoglobulins	16	8	4	20	14
J06B - Immunoglobulins	16	8	4	20	14
J06BB - Specific immunoglobulins	16	8	4	20	14
J06BB01 - Anti-D (rh) immunoglobulin	16	8	4	18	14
J06BB03 - Varicella/zoster immunoglobulin	0	0	0	1	0
J07 - Vaccines	227	69	21	1031	443
J07A - Bacterial vaccines	9	15	0	118	47
J07AF - Diphtheria vaccines	0	4	0	55	20
J07AL - Pneumococcal vaccines	0	0	0	1	0
J07AM - Tetanus vaccines	8	6	0	61	25
J07AP - Typhoid vaccines	2	4	0	1	2
J07B - Viral vaccines	218	55	17	592	285
J07BB - Influenza vaccines	149	38	8	518	233
J07BB02 - Influenza, purified antigen	146	36	8	475	217
J07BC - Hepatitis vaccines	5	6	4	4	5
J07BC01 - Hepatitis B, purified antigen	2	2	4	1	2
J07BC02 - Hepatitis A, inactivated, whole virus	3	4	0	3	3
J07BD - Measles vaccines	0	2	4	6	3
J07BD52 - Measles, comb. w. mumps and rubella, live	0	0	4	0	0

attenuated					
J07BE - Mumps vaccines	0	2	0	6	2
J07BF - Poliomyelitis vaccines	0	4	0	51	18
J07BJ - Rubella, vaccines	0	2	0	6	2
J07BK - Varicella zoster vaccines	0	0	0	1	0
J07BM - Papillomavirus vaccines	64	0	0	1	20
J07C - Bacterial and viral vaccines, combined	0	0	0	320	110
J07CA - Bacterial and viral vaccines, combined	0	0	0	320	110
J07CA02 - Diphtheria-pertussis-poliomyelitis-tetanus	0	0	0	1	0
J07CA05 - Diphteria-hepatitis b-pertussis-tetanus	0	0	0	319	109
J07X - Other vaccines	0	0	4	0	0
L - Antineoplastic and immunomodulating agents	0	0	0	3	1
L03 - Immunostimulants	0	0	0	3	1
L03A - Immunostimulants	0	0	0	3	1
L03AX - Other immunostimulants	0	0	0	3	1
L03AX03 - Bcg vaccine	0	0	0	3	1
P - Antiparasitic products, insecticides and repellants	3	0	4	1	2
P01 - Antiprotozoals	3	0	4	1	2
P01B - Antimalarials	3	0	4	1	2
P01BA - Aminoquinolines	2	0	0	0	0
P01BA01 - Chloroquine	2	0	0	0	0
P01BB - Biguanides	0	0	4	1	1
P01BB51 - Proguanil, combinations	0	0	4	1	1
P01BC - Methanolquinolines	2	0	0	0	0
P01BC02 - Mefloquine	2	0	0	0	0
V - Various	5	0	0	0	1
V01 - Allergens	5	0	0	0	1
V01A - Allergens	5	0	0	0	1
V01AA - Allergen extracts	5	0	0	0	1
V01AA02 - Grass pollen	2	0	0	0	0

13.17 THIN SRC approval letter

SRC Feedback

Researcher Name: Shahrul Mt-Isa
Organisation: Imperial College London
SRC Reference Number: 14-037R
Date: 16th September 2014
Study title: Pregnancy Study: Comparison and validation of THIN data to self-reported medications and birth outcomes.
Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

I am happy with it, they have address all our previous concerns and it is in general much clear what their intent is and that it will be carried out to an acceptable standard. I will be happy to approve.

We are pleased to inform that you can proceed with the study as this is now approved. CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform CSD Medical Research in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Research Associate

SRC
Scientific Review Committee

13.18 Comparison of pregnancy outcome to EHRs in the UK

Table 13-23 End of pregnancy information from THIN (women with postnatal codes only are displayed in italic)

	ID	Event date	Date recruitment	Due date	Description of code
1	277	10/10/2013	01/03/2013	01/08/2013	Postnatal exam. - maternal
	277	11/08/2013	01/03/2013	01/08/2013	Spontaneous vaginal delivery
2*	292	03/10/2013	04/03/2013	26/08/2013	Postnatal examination
	292	16/09/2013	04/03/2013	26/08/2013	Maternity infant details
	292	18/08/2013	04/03/2013	26/08/2013	Maternity outcome
	292	18/08/2013	04/03/2013	26/08/2013	Maternity delivery details baby
	292	18/08/2013	04/03/2013	26/08/2013	Maternity perineum
3	*301*	*16/07/2013*	*04/03/2013*	*25/05/2013*	*Postnatal exam. - maternal*
4*	322	05/08/2013	17/03/2013	05/08/2013	Outcome of delivery
5	370	05/06/2013	03/04/2013	10/04/2013	Postnatal examination
	370	05/06/2013	03/04/2013	10/04/2013	Postnatal examination observations
	370	26/04/2013	03/04/2013	10/04/2013	Post partum care
	370	24/04/2013	03/04/2013	10/04/2013	Spontaneous vertex delivery
6	386	12/10/2013	05/04/2013	30/09/2013	Normal delivery
	386	12/10/2013	05/04/2013	30/09/2013	ND - Normal delivery
7	432	11/06/2013	18/05/2013	04/07/2013	Caesarean delivery
8	*448*	*13/11/2013*	*20/05/2013*	*20/09/2013*	*Postnatal examination*
9	523	20/11/2013	01/08/2013	25/09/2013	Postnatal exam. - maternal
	523	29/09/2013	01/08/2013	25/09/2013	Normal delivery
10	597	09/01/2014	26/09/2013	12/12/2013	Postnatal visit
	597	14/10/2013	26/09/2013	12/12/2013	Sublux of symphysis pubis in preg childbirth and puerp

* Both reported live births in PROTECT

13.19 Validation of medications use in the UK for linked women

Table 13-24 The agreement between electronic health records (THIN) and self-reported data (PROTECT) within therapeutic group

ATC	P∩T	P	T	(P ∪ T)′	J[1]	S_+[2]	κ[3]	S_-[4]
A02-Drugs for acid related disorders								
A02AA-Magnesium compounds	0	1	0	17	0.00	0.00	0.00	0.97
A02BA02-Ranitidine	1	0	1	16	0.50	0.67	0.64	0.97
A02BC01-Omeprazole	1	0	0	17	1.00	1.00	1.00	1.00
A02BX13-Alginic acid	2	4	2	10	0.25	0.40	0.18	0.77
A02EA-Antiregurgitants	0	0	1	17	0.00	0.00	0.00	0.97
A06-Drugs for constipation								
A06-Drugs for constipation	0	0	1	17	0.00	0.00	0.00	0.97
A06AC01-Ispaghula (psylla seeds)	1	0	0	17	1.00	1.00	1.00	1.00
A10-Drugs used in diabetes								
A10BA02-Metformin	0	1	0	17	0.00	0.00	0.00	0.97
A11-Vitamins								
A11-Vitamins	0	1	0	17	0.00	0.00	0.00	0.97
A11A-Multivitamins, combinations	0	12	0	6	0.00	0.00	0.00	0.50
A11CC-Vitamin d and analogues	0	1	0	17	0.00	0.00	0.00	0.97
A12-Mineral supplements								
A12AA04-Calcium carbonate	0	1	0	17	0.00	0.00	0.00	0.97
A12AX01-Calcium carbonate and cholecalciferol	0	0	1	17	0.00	0.00	0.00	0.97
B01-Antithrombotic agents								
B01AB05-Enoxaparin	1	0	0	17	1.00	1.00	1.00	1.00
B02-Antihemorrhagics								
B02AA02-Tranexamic acid	0	0	1	17	0.00	0.00	0.00	0.97
B03-Antianemic preparations								
B03A-Iron preparations	0	2	0	16	0.00	0.00	0.00	0.94
B03AA02-Ferrous fumarate	0	0	1	17	0.00	0.00	0.00	0.97
B03AA07-Ferrous sulphate	0	0	1	17	0.00	0.00	0.00	0.97
B03AD02-Ferrous fumarate	0	0	1	17	0.00	0.00	0.00	0.97
B03BB01-Folic acid	1	14	0	3	0.07	0.13	0.02	0.30
C03-Diuretics								
C03AA01-Bendroflumethiazide	1	0	0	17	1.00	1.00	1.00	1.00
C09-Agents acting on the renin-angiotensin system								
C09AA04-Perindopril	1	0	0	17	1.00	1.00	1.00	1.00
D01-Antifungals for dermatological use								
D01AC01-Clotrimazole	1	1	0	16	0.50	0.67	0.64	0.97
D02-Emollients and protectives								
D02AC-Soft paraffin and fat products	0	0	2	16	0.00	0.00	0.00	0.94
D07-Corticosteroids, dermatological preparations								
D07CA01-Hydrocortisone and antibiotics	0	0	1	17	0.00	0.00	0.00	0.97
D07CC01-Betamethasone and antibiotics	0	0	1	17	0.00	0.00	0.00	0.97
D10-Anti-acne preparations								
D10AF52-Erythromycin,combinations	0	0	1	17	0.00	0.00	0.00	0.97
D99								
D99-Dermatologicals: Sublevel unknown	0	0	1	17	0.00	0.00	0.00	0.97
F99								
F99-Fish oil: Sublevel unknown	0	2	0	16	0.00	0.00	0.00	0.94

G01-Gynecological antiinfectives and antiseptics								
G01AF02-Clotrimazole	1	1	1	15	0.33	0.50	0.44	0.94
G03-Sex hormones and modulators of the genital system								
G03A-Hormonal contraceptives for systemic use	0	1	0	17	0.00	0.00	0.00	0.97
G03AC-Progestogens	0	1	0	17	0.00	0.00	0.00	0.97
G03AC01-Norethisterone	1	0	0	17	1.00	1.00	1.00	1.00
G03AC09-Desogestrel	0	0	1	17	0.00	0.00	0.00	0.97
G03DC02-Norethisterone	0	0	1	17	0.00	0.00	0.00	0.97
G03GB02-Clomifene	0	0	1	17	0.00	0.00	0.00	0.97
H03-Thyroid therapy								
H03AA01-Levothyroxine sodium	2	0	0	16	1.00	1.00	1.00	1.00
J01-Antibacterials for systemic use								
J01-Antibacterials for systemic use	0	1	0	17	0.00	0.00	0.00	0.97
J01CA04-Amoxicillin	3	0	3	12	0.50	0.67	0.57	0.89
J01DB01-Cefalexin	0	0	1	17	0.00	0.00	0.00	0.97
J01EA01-Trimethoprim	1	0	1	16	0.50	0.67	0.64	0.97
J02-Antimycotics for systemic use								
J02AC01-Fluconazole	0	1	0	17	0.00	0.00	0.00	0.97
M01-Antiinflammatory and antirheumatic products								
M01AE01-Ibuprofen	0	1	0	17	0.00	0.00	0.00	0.97
M02-Topical products for joint and muscular pain								
M02AA13-Ibuprofen	0	0	1	17	0.00	0.00	0.00	0.97
N02-Analgesics								
N02AX02-Tramadol	0	0	1	17	0.00	0.00	0.00	0.97
N02BA01-Acetylsalicylic acid	0	1	0	17	0.00	0.00	0.00	0.97
N02BE01-Paracetamol	0	4	0	14	0.00	0.00	0.00	0.88
N02BE51-Paracetamol, combinations excl psycholeptics	1	0	1	16	0.50	0.67	0.64	0.97
N03-Antiepileptics								
N03AX16-Pregabalin	0	0	1	17	0.00	0.00	0.00	0.97
N04-Anti-parkinson drugs								
N04BC04-Ropinirole	0	0	1	17	0.00	0.00	0.00	0.97
N05-Psycholeptics								
N05BA01-Diazepam	0	0	1	17	0.00	0.00	0.00	0.97
N05CF01-Zopiclone	1	0	0	17	1.00	1.00	1.00	1.00
N06-Psychoanaleptics								
N06AB03-Fluoxetine	0	0	1	17	0.00	0.00	0.00	0.97
N06AB06-Sertraline	0	0	1	17	0.00	0.00	0.00	0.97
N06AX16-Venlafaxine	1	0	0	17	1.00	1.00	1.00	1.00
R01-Nasal preparations								
R01AC01-Cromoglicic acid	0	1	0	17	0.00	0.00	0.00	0.97
R01AD01-Beclomethasone	0	1	0	17	0.00	0.00	0.00	0.97
R01AX30-Combinations	0	0	1	17	0.00	0.00	0.00	0.97
R03-Drugs for obstructive airway diseases								
R03AC02-Salbutamol	0	1	0	17	0.00	0.00	0.00	0.97
R05-Cough and cold preparations								
R05DA04-Codeine	0	0	1	17	0.00	0.00	0.00	0.97
R06-Antihistamines for systemic use								
R06A-Antihistamines for systemic use	0	1	0	17	0.00	0.00	0.00	0.97
R06AB04-Chlorpheniramine	1	0	0	17	1.00	1.00	1.00	1.00

R06AE07-Cetirizine	1	0	0	17	1.00	1.00	1.00	1.00
S01-Ophthalmologicals								
S01GX01-Cromoglicic acid	0	0	1	17	0.00	0.00	0.00	0.97
S01XA20-Artificial tears and other indifferent prep.	0	0	1	17	0.00	0.00	0.00	0.97
S02-Otologicals								
S02AA14-Gentamicin	0	0	1	17	0.00	0.00	0.00	0.97
S02AA30-Antiinfectives, combinations	0	0	1	17	0.00	0.00	0.00	0.97
S02CA02-Flumetasone and antiinfectives	0	0	1	17	0.00	0.00	0.00	0.97
S03-Ophthalmological and otological preparations								
S03CA01-Dexamethasone and antiinfectives	0	0	1	17	0.00	0.00	0.00	0.97
V07-All other non-therapeutic products								
V07-All other non-therapeutic products	0	0	1	17	0.00	0.00	0.00	0.97
V07AD-Blood tests, auxiliary products	0	0	1	17	0.00	0.00	0.00	0.97
V07AY-Other non-therapeutic auxiliary products	0	0	2	16	0.00	0.00	0.00	0.94

[1] Jaccard Index Positive agreement where the medication is found in either or both sources[28]

[2] Positive agreement[29-31]

[3] Cohen's κ(Kappa)[32]

[4] Negative agreement[29-31]