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DEFINITIONS

- Participants in this tender are referred to herein according to the following codes:

  - **EMC**. Erasmus University Medical Center (Netherlands). Contractor
  - **PHARMO.** PHARMO Coöperation UA (Netherlands). Subcontractor
  - **ARS.** Agenzia regionale di sanità della Toscana (Italy). Subcontractor
  - **SYNAPSE.** Synapse Research Management Partners S.L. (Spain). Subcontractor

- **Contract**: Legal document signed between the Contractors and the European Medicines Agency for the undertaking of the tender.
- **Contractor**: A tenderer to which a framework contract has been awarded and signed with the EMA. It is responsible before the EMA of the right execution of the tender and of the delivery of the results in due time and form according to the Contract.
- **EMA.** European Medicines Agency.
- **Subcontractor**: Organisation supporting the Contractor in the fulfilment of the tender objectives and technical execution.
- **Technical specifications**. Official document generated by the EMA for the tender that includes a detailed description of all technical requirements, contractual arrangements, and price, that enables the EMA to specify and acquire services provided by resources not employed directly by the EMA.
- **Tender**: Public (or restrictive) offer made by the EMA to specific providers to enter into the contract of transaction of services at certain specified cost.
- **Work plan**: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in the Contract.

1. BACKGROUND

Since ages, attempts have been made to control contraception with various substances and devices. The first experiments with hormonal contraception took place in the 1920s. It was discovered that temporary sterility could be induced when the ovaries of pregnant animals were transplanted into non-pregnant animals[1]. The reason for infertility was the anti-ovulatory effect of progesterone. During pregnancy, progesterone levels are high and prevent maturation of any additional eggs in favour of the developing foetus. Progestin, a synthetic progestogen with effects similar to progesterone, but with improved oral bioavailability, was developed in the 1950s and was the first agent used in clinical trials of oral contraception. The addition of oestrogen was found to be necessary to minimize spotting and breakthrough bleeding[2]. In 1960, Enovid (US) / Enavid (UK), which contained 150 ug of mestranol (estrogen) and 9.58 mg of norethynodrel (progestin), was the first drug approved for contraception.

Hormonal contraceptives are among the most effective drugs available - actual effectiveness is almost 100% but it relies on correct usage[3]. However, high effectiveness came with side effects and an association with venous and cerebral thrombosis was established shortly after introduction[4]. In addition, oral contraceptive use has been associated with increased risk of stroke and myocardial infarction among women who smoke, have high blood pressure, or other cardiovascular or cerebrovascular risk factors[1].
The risk of cardiovascular disease has been related to the effect of estrogens on synthesis of procoagulant proteins and angiotensinogen in the liver. Reducing the estrogen dose in oral contraceptives over the years has resulted in a reduction of the associated thrombotic risk and the early formulations have made place for newer, safer formulations. Along with lowering the dose of estrogen, the progestogen content has also evolved. New types of progestogen were introduced in order to allow lower doses of estrogen (first- to second generation) and, later, to reduce metabolic and vascular impact of progestogens (second-to third generation)[5]. After introduction of the third generation pill, however, studies were published on an increased risk of venous thrombosis despite it being designed to further reduce the risk. Until today, there has been much debate about the safety profiles of second and third generation oral contraceptives[6-8].

Another area of debate is the association of oral contraceptives with various types of cancer. On one hand, combined oral contraceptive use protects against endometrial and ovarian cancer, and there may also be some protection against colorectal cancer[5]. On the other hand, combined oral contraceptive use may be associated with an increased risk of breast and cervical cancer. Many studies, meta-analyses and reviews have elaborated on the association with breast cancer - current beliefs are that the risk may be increased but the magnitude of the risk increase, the role of confounding and the applicability to use of the most recent formulations remains unclear[9].

Milder side effects exist that may influence adherence, and thus actual effectiveness of oral contraceptives. These effects include breakthrough bleeding, weight gain, loss of libido and depression. Positive side effects, among which alternative indications for oral contraceptive pills, are menstrual cycle regulation and treatment of acne[10].

Fifty years after market introduction, the pill has become one of the most widely and frequently used drugs in the world. The pill is available in various formulations and the user population is even more diverse.

The current challenge in safety monitoring of oral contraceptive use therefore is to determine the optimal balance between effectiveness, both for contraception and other positive effects, and the risk of adverse effects. The aspects of risk and benefit will have different weights, depending on for example age, family and personal medical history, lifestyle factors and medical conditions. For oral contraceptives, the impact of oral contraceptive use among women with elevated cardiovascular risk remains of particular interest.

The study aimed to set the basis for future safety evaluations of oral contraceptive use in Europe, by assessing current user and treatment characteristics in daily practice.

2. STUDY OBJECTIVES

Specific study objectives were to assess among women using oral contraceptive in 2009 and 2010 in three different countries in Europe:

- prevalence estimates (users on January 1, 2010)
- start rates (starters per year)
- demographics
- health indicators and morbidity
- treatment characteristics

3. METHODS

3.1. STUDY DESIGN

The user and treatment characteristics of oral contraceptives were studied in a retrospective database study over the years 2009 and 2010. In order to capture patterns of use across Europe, the study included the following countries and databases:

DATABASE	PARTNER	COUNTRY	INDIVIDUALS
IPCI	Erasmus University Medical Center Rotterdam (EMC)	NL	1 Million
PHARMO	PHARMO Institute (PHARMO)	NL	4 Million
THIN	The Health Improvement Network (THIN)	UK	7.5 Million
HSD	Agenzia Regionale di Sanità della Toscana (ARS)	IT	1 Million
			13.5 Million

3.1.1. IPCI

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical Center. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout The Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout The Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender.
The database contains information on about 1.2 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity prescribed, dosage regimens, strength and indication are entered into the computer. The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO.

3.1.2. PHARMO

The PHARMO Record Linkage System (PHARMO RLS) includes several linked databases, among which are drug dispensing records and hospital records from about four million individuals in defined areas in the Netherlands. The different databases are linked through probabilistic linkage methods. The drug dispensing histories contain data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens and the duration of use of the drug. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital records include detailed information concerning primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).For a detailed description of the PHARMO database, we refer to earlier work[11].

3.1.3. THIN

The Health Improvement Network (THIN) is a database of primary care medical records from the United Kingdom. General practitioners are trained to complete their medical records using the Vision general practice computer system (InPractice Systems, London, UK). This electronic record serves as the primary medical records for the practice.
Data recorded in THIN include demographics, details from general practitioners' visits such as medical diagnoses and prescriptions written by the general practitioners, diagnoses from specialist referrals and hospital admissions, some results of laboratory tests, some lifestyle characteristics and other measurements as taken in the practice. Within the database, diagnoses are recorded using READ codes. Prospective data collection for THIN began in September 2002, with electronic medical records that date back to 1985. In addition, practices may retrospectively enter significant medical events into the electronic medical record. Currently, the database has 2.7 million active patients registered. Recently a validation study was conducted by Lewis et al which concluded that "THIN data that are collected outside of

the General Practice Research Database (GPRD) appear as valid as the data collected as part of the GPRD[12]

3.1.4. HSD

The Health Search/Longitudinal Patients Database (HSD) is a longitudinal observational database that is representative of the general Italian population. It was established in 1998 by the Italian College of General Practitioners. The HSD contains data from computer-based patient records from a select group of GPs (covering a total of 1.2 million active patients) located throughout Italy who voluntarily agreed to collect data for the database and attend specified training courses. Turnover occurs as patients move and transfer to new practices. The records of 'transferred out' patients remain in the database and are available for retrospective studies with the appropriate time periods.
The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, free text patients diary, hospital admission, and death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug names are coded according to the ATC classification system. To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates. The HSD complies with European Union, guidelines on the use of medical data for research. Approval for use of data is obtained from the Italian College of Primary Care Physicians. Data are in house, no ethical approval needed.

3.2. DATA CAPTURE

The databases included in the study extract their data from different countries and healthcare settings. In the Netherlands, oral contraceptives are primarily prescribed by general practitioners and dispensed through outpatient pharmacies. A prescription is mandatory, but for refills a user may go directly to the pharmacy and the prescription does not need to be renewed for each specific dispensing. Reimbursement depends on the insurance company a women is affiliated with but does not influence registration in the databases. IPCI captures prescriptions and PHARMO captures dispensing of oral contraceptives.

In the UK, oral contraceptives are only dispensed in case of a prescription (also for refills). Currently, there are some pilot studies where oral contraceptives are available at the pharmacy without a GP prescription.
For the THIN database, oral contraceptives were captured from the therapy file. In the UK, patients can also obtain their contraceptive medications from community contraception clinics, some genitourinary medicine (GUM) clinics, sexual health clinics and some young persons services. Where the prescription is not issued by the GP, there will be an additional health code – these prescriptions were not taken into account for this report, as these additional health records do not contain the required detail of information

In Italy, reimbursement depends on which oral contraceptive is used, but prescription is mandatory. HSD captures all oral contraceptive drugs prescribed by general practitioners. These include reimbursed as well as non-reimbursed oral contraceptives.

3.3. MAPPING

Drug prescription and/or dispensing data were used to evaluate the drug exposure to oral contraceptives and co-medication. Drug prescriptions and dispensings in the databases are locally coded using the national product codes, which differ among countries but these product codes are linked to the World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system[13]. Only THIN uses different coding scheme for drugs (British National Formulary/Multilex codes) which may be however mapped to ATC.

Health indicators and morbidity were assessed using different disease coding terminologies, depending on the database: (1) International Classification of Primary Care (ICPC) for IPCI (2) International Classification of Diseases 9th revision-Clinical Modification (ICD-9CM) for HSD, THIN, and PHARMO. The process of mapping of event data extraction from the different databases was based on medical concepts derived from the Unified Medical Language System (UMLS) and was adopted from the process previously described in other publications[14-15].

3.4. STUDY PERIOD

The study period runs from 1st January 2009 until 31st December 2010. User characteristics were assessed at the index date (see below) and cover all available history. Treatment characteristics were assessed during 2009-2010.

3.5. EXPOSURE DEFINITION

Oral contraceptives in the study include all preparations under ATC code G03AA (progestogens and estrogens, fixed combinations) except G03AA13 (norelgestromin and estrogen transdermal preparation), G03AB (progestogens and estrogens, sequential preparations) and G03AC (progestogens), except G03AC03 in PHARMO and IPCI (levonorgestrel intra-uterine device in the Netherlands but oral in UK and Italy), G03AC06 (medroxyprogesterone injection) and G03AC08 (etonogestrel subcutaneous implant). See for the list of oral contraceptives the Annex 1 in spreadsheet format (*Codes for OC Comedication& Morbidity*).

From consecutive oral contraceptive prescription/dispensing records in the entire database, episodes of uninterrupted use were constructed. Uninterrupted use was defined as no gap between expiry of a prescription/dispensing and a refill. In case of a refill with any oral contraceptive before expiry of the preceding prescription/dispensing, the assumed starting date of the refill was the day after the expiry date of the previous. Switching between formulations was allowed within an episode, i.e. an episode of oral contraceptive use can contain multiple subsequent formulations.

3.6. STUDY POPULATION

The source population for the study were all women in the database any time in 2009 or 2010, and who had at least one year follow-up in the database.

Study follow-up started one year after database entry or January 1, 2009, whichever came latest. Follow-up ended at database exit (death, transferring out of the database or end of data collection) or at the end of the study period (December 31, 2010), whichever came first.

From the source population, all women with a prescription (IPCI, THIN, HSD) or dispensing (PHARMO, hereafter also referred to as 'prescription') of an oral contraceptive during study follow-up were selected as users. The index date was defined as the date of first prescription *during study follow-up*.
Users were classified as starters or existing user based on use of oral contraceptives in the year preceding the index date. Starters had a first prescription after at least one year non-exposure. Note that these starters will include first-time users as well as re-starters after for example pregnancy and delivery. Existing users had a previous prescription of oral contraceptives within a year before the index prescription.

Non-users had no prescription of oral contraceptives during study follow-up. For non-users start of follow-up was the index date.

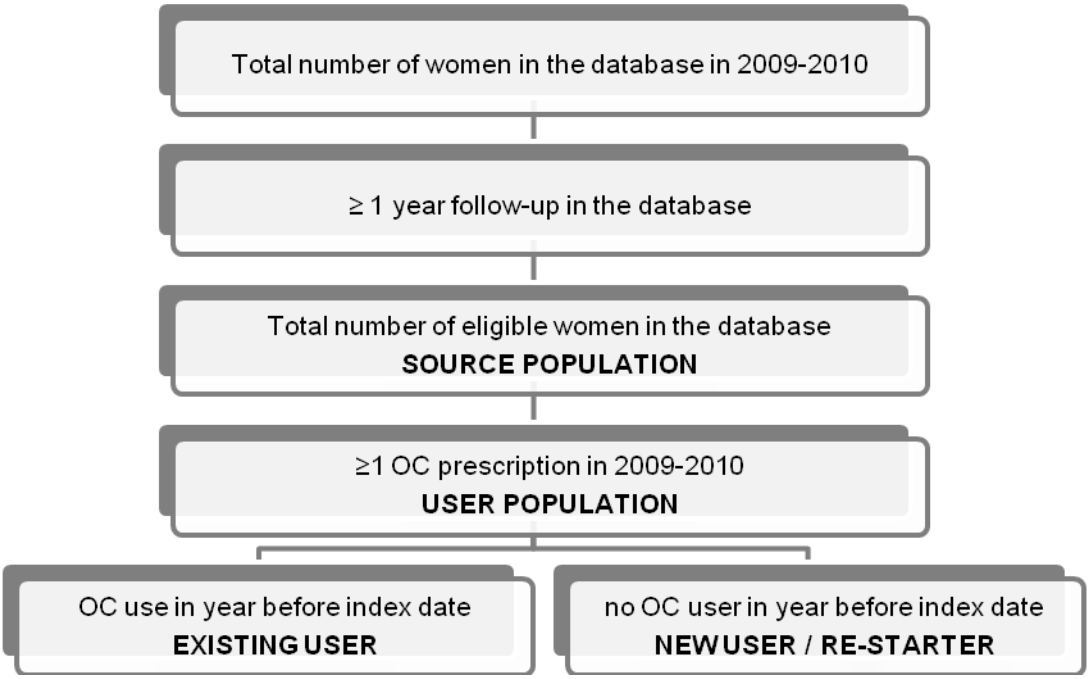

Figure 3.6-1 Study population

3.7. PREVALENCE OF ORAL CONTRACEPTIVE USE

A point prevalence of oral contraceptive use was calculated on January 1, 2010. From among all women in the source population on January 1, 2010 (denominator), prevalent users were all who were exposed on that day (numerator).

3.8. ORAL CONTRACEPTIVE (RE-)START RATE

The start rate was calculated as the number of starters during the study period, 2009-2010, (numerator) per 1,000 person-years. Note that these starters include first-time starters as well as re-starters, see above. The denominator was the number of accumulated person-years 'at risk' (unexposed), i.e. between start of follow-up and the index date ((re-)starters) or start and end of follow-up (non-users). Note that existing user person-time was not included in the denominator as existing users are not at 'risk' of initiating oral contraceptive use.

3.9. POPULATION CHARACTERISTICS

Demographic characteristics for oral contraceptive starters and existing users and for non-users were assessed on the index date and include the following:

- Age: by 5-year category: younger than 15, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54 and 55 or older, and mean (standard deviation (±sd)) and median (interquartile range (IQR)) age in years
- History in database (in person years), preceding index date: mean ±sd and median (IQR)
- Follow-up in database (in person years), after index date: mean ±sd and median (IQR)

Health indicators for oral contraceptive users and for non-users were assessed on the index date and include the following:

- Body mass index: number (%) measured within three months of the index date (either before or after), and median (IQR)

- Previous GP diagnosis, number (%):
  - Hypertension
  - Lipid disorders
  - Diabetes mellitus
  - Asthma or chronic obstructive pulmonary disease (COPD)
  - Systemic lupus erythematosus (SLE)
  - Rheumatoid arthritis
  - Multiple sclerosis (MS)

  These diagnoses were only assessed in the GP databases (IPCI, THIN, HSD) as hospital admission is not required. Diagnoses were identified in the entire available history.

- Use of drugs for chronic conditions, number (%):
  - antihypertensive drugs
  - diuretics
  - beta blocking agents
  - calcium channel blockers
  - agents acting on the renin-angiotensin system
  - lipid-modifying agents
  - diabetes drugs
  - drugs for obstructive airway diseases

A women was considered using the drug when ≥2 prescriptions in the year before the index date were identified.

Other variables of interest were parity and smoking. However, the availability of this information was limited. Some smoking status information was available in IPCI and THIN and some parity information was available in THIN, but for less than 5% of the population. Recording of smoking status and definitely parity status by the GP is not systematically done and likely selective. Therefore these variables could not be analyzed.

Also, the number (%) of women with a previous diagnosis of disease associated with the use of oral contraceptives were assessed on the index date. These events could be regarded as contra-indications and include the following:

- Deep vein thrombosis
- Pulmonary embolism
- Cerebrovascular disease
- Myocardial infarction
- Breast cancer
- Cervical cancer

These diagnoses were assessed in the PHARMO (hospital admissions) and GP databases (IPCI, THIN, HSD). Diagnoses were identified in the entire available history.

As the use of oral contraceptives and diagnosis of or use of drugs for the different diseases are all related to age, the proportions were presented overall as well as by 10-year age group.

See Annex 1 for the variable definitions in the different coding systems.

3.10.TREATMENT CHARACTERISTICS

Treatment characteristics are presented separately for oral contraceptive starters and existing users and include:

- History of oral contraceptive use, at the time of index date:
  - number (%) of users with previous exposure in database
  - mean ±sd and median (IQR) accumulated person-time of exposure (may include interruptions)
- Duration of uninterrupted use preceding the index date:
  - ever since database entry (actual duration not known if start was before database entry), or when started during database follow-up: < 1 year, 1-2 years, 3-4 years, 5-6 years, 7-8 years, ≥ 9 years, mean ±sd and median (IQR).
- Formulations used in 2009-2010: number (%) of users with a) combined, fixed hormone doses, b) combined, varying (sequential) hormone doses or c) progestogen only preparations.
- Type of oral contraceptives used in 2009-2010 at the chemical substance level, n (%).

Note that starters, defined as one year free of exposure preceding the index date, may have an earlier history of oral contraceptive use (re-starters). The duration of uninterrupted use at the index date, which can only be assessed for existing users, was defined as the duration of the exposed episode (section 3.4) preceding the index date. This is a fraction of the total

(accumulated) exposed person-time at index, which is calculated by summing all exposed person-time between database entry and index date regardless of episode interruptions.

Treatment pattern was assessed for all oral contraceptive users during 2009 and 2010 and included:

- Changes in oral contraceptive use on the level of chemical substance:
  - No change
  - Switch or discontinuation
- Most frequent switches on the level of chemical substance
- Types of switch on the level of formulation (fixed, sequential, progestogen-only)

Switches were analyzed on the switch level, i.e. a user who switches twice within the study period was counted twice. Between switches, gaps were allowed.

3.11.ANALYSIS

A distributed network approach was adopted for the database study. Due to lack of common statistical software and large differences in analytical capabilities across sites, we used a standardized common software called JERBOA. Jerboa is a JAVA based software that can elaborate the databases locally and produce aggregated output datasets that was shared centrally for further analyses. This software was developed within the EU-ADR project and it has been used in other EU funded projects (i.e. SOS: www.sos-nsaids-project.org; VAESCO: www.vaesco.net).

In these projects Jerboa software has been tested by comparing the Jerboa outputs for drug utilization and case control study with the output generated by expert epidemiologists using SAS. The results obtained through Jerboa corresponded exactly to the results generated through the use of software for data management and analyses.

Descriptive statistics include proportions, mean and standard deviations (sd), median and interquartile ranges (IQR) of the aggregated datasets. Start rate and prevalence were calculated for the pooled dataset as well as for the individual datasets. Population and treatment characteristics were assessed for the individual datasets. Stratified analysis were performed per database and separately for users and non-users, for starters and existing users, and stratified by age where applicable.

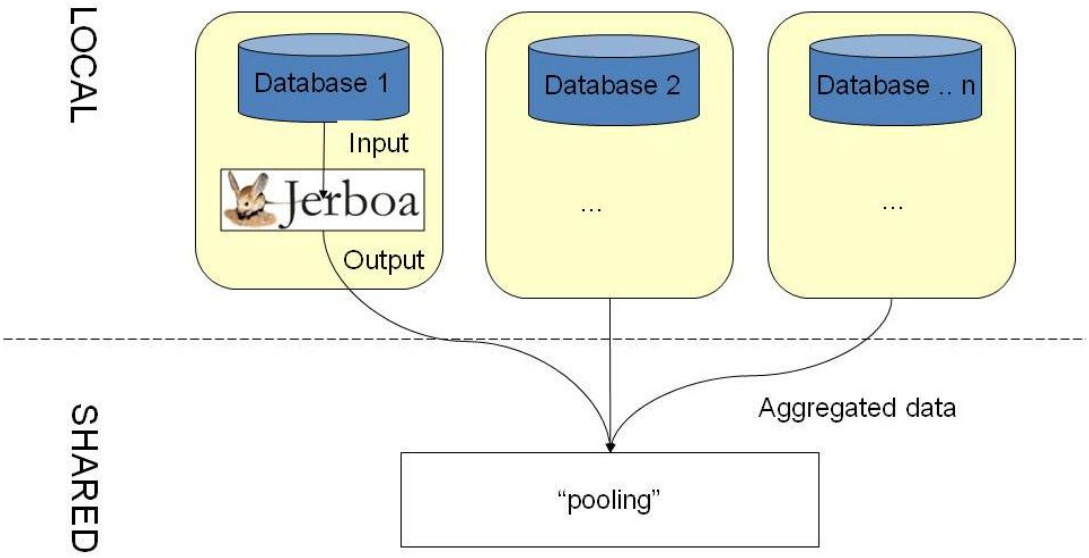

Figure 3.11-1 JERBOA model for distributed computing on databases

4. RESULTS

4.1. PREVALENCE AND (RE-)START RATE OF ORAL CONTRACEPTIVE USE

Table 4.1-1. Prevalence and (re-)start rate of oral contraceptive use in 2009-2010

	TOTAL	PHARMO	IPCI	THIN	HSD
TOTAL POPULATION, N (%)					
Number of women	4,888,681 (100)	1,887,818 (100)	368,449 (100)	2,066,576 (100)	565,838 (100)
Number of users	664,314 (14)	295,984 (16)	45,747 (12)	291,139 (14)	31,444 (6)
Prevalence					
Population size at Jan 1, 2010	4,484,080	1,800,278	313,067	1,830,324	540,411
Number of users at Jan 1, 2010	361,064	187,116	15,502	151,182	7,264
Prevalence per 1000	81	104	50	83	13
Start rate					
Unexposed person-years 2009-2010	7,813,650	3,038,845	518,511	3,222,213	1,034,081
Oral contraceptive starters in 2009-2010*	206,593	79,797	23,305	88,258	15,233
Start rate per 1000 person-years	26	26	45	27	15

**no use in year before first prescription/dispensing in 2009-2010*

In total, 4.9 million women were included in the study, from four healthcare databases in three countries (the Netherlands, UK and Italy). Overall, 14% has been using an oral contraceptive during the study period. In the Netherlands (PHARMO, IPCI) and UK (THIN), 12-16% had used oral contraceptives and in Italy (HSD) 6% had used oral contraceptives according to the databases.

The overall prevalence of oral contraceptive use at January 1, 2010 was 81 per 1,000 women. Prevalence estimates in the different databases ranged from 13 per 1,000 in HSD to 104 per 1,000 in PHARMO. The overall start rate of oral contraceptive use was 26 per 1,000 person-years among women. Estimates in the different databases ranged from 15 per 1,000 person-years in HSD to 45 per 1,000 person-years in IPCI.

The differences in prevalence and start rates, notably between the two Dutch databases, is likely due to the fact that the PHARMO database captures dispensing of oral contraceptives at the outpatient pharmacy while IPCI captures prescriptions of oral contraceptives at the general practitioner's office. In the Netherlands, a refill can be picked up at the pharmacy without a new prescription from the general practitioner. In IPCI, a woman might thus be classified as non-user when she directly picks up a refill after expiry of the previous prescription. Upon a new prescription from the general practitioner (e.g. when switching), she was classified as starter by the lack of prescriptions in the previous year. From the overall user proportions, 16% in PHARMO and 12% in IPCI during 2009-2010, we can conclude that most users were identified through both settings.

In the UK, a prescription is needed also for refills. Therefore the overlap between THIN and PHARMO was high. The start rate in THIN was similar to PHARMO and the prevalence and user proportion in between the Dutch databases.

In Italy a single prescription is valid for 6 months. In Italy, all estimates were lower than in the other databases. It has been shown that the proportion of women using oral contraceptives in Italy is lower than in NL and UK[16].

The highest user prevalence was observed at 15-19 years in PHARMO and IPCI and 20-24 in THIN and HSD (Figure 4.1-1). In between the ages 15 and 49 (reproductive age), 20% of women in PHARMO, 17% of women in THIN, 10% of women in IPCI and 3% of women in HSD was using oral contraceptives.

The highest start rate was observed at 15-19 years in PHARMO, IPCI and THIN (Figure 4.1-2). Per 1,000 person-years, up to 229 women (IPCI) started using oral contraceptives. In HSD the start rate was highest at 20-24 when 59 women per 1,000 person-years started using oral contraceptives. At these ages women were likely first-time starters, and re-starting likely contributes more and more to the start rate at higher ages. After the age of 25, the start rate gradually declined and at the age of 55 the start rate fell below 1 per 1,000 person years except in PHARMO where the start rate after 55 years was 4 per 1,000 person years.

The patterns of oral contraceptive use in HSD were different from the other databases. The peak in start rate as well as prevalence observed in PHARMO, IPCI and THIN at the younger ages was not as pronounced and use was more evenly distributed across age groups.

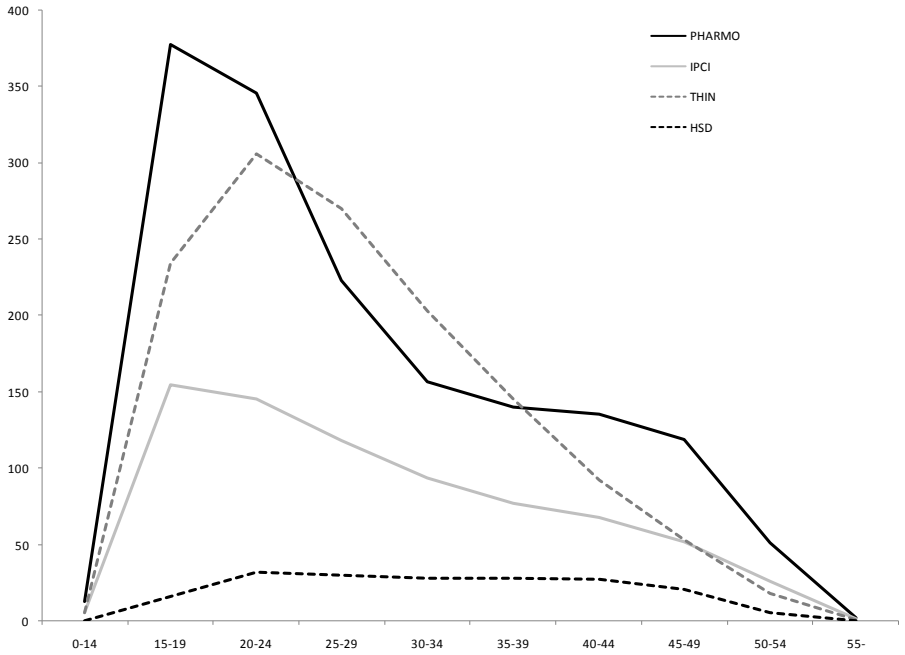

Figure 4.1-1. Prevalence of oral contraceptive use per 1,000 women by 5-year age group in 2009-2010

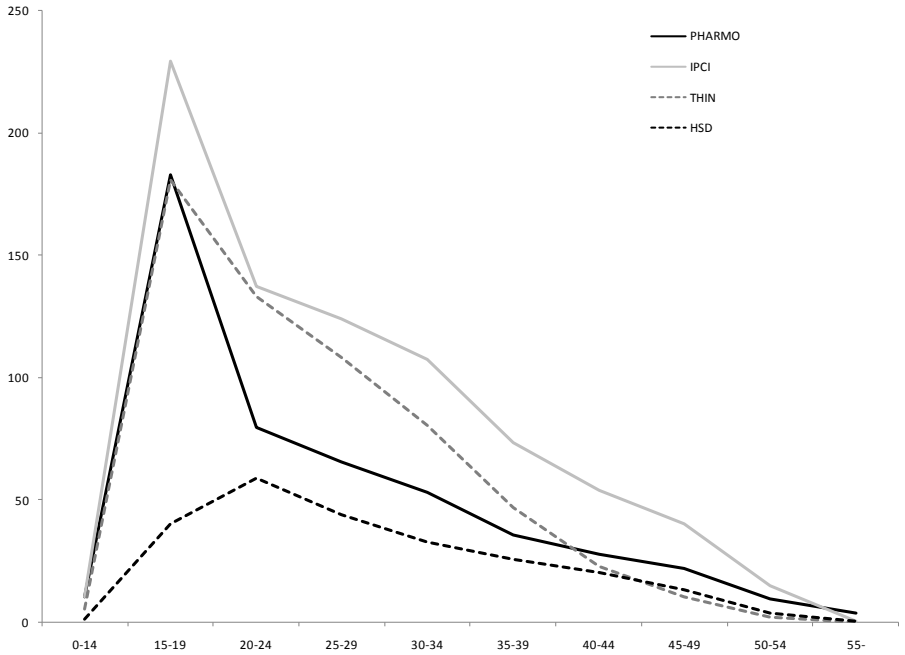

Figure 4.1-2. Oral contraceptive (re-)start rate per 1,000 person years among women, by 5-year age group in 2009-2010

4.2. POPULATION CHARACTERISTICS

*Table 4.2-1. Demographic characteristics of oral contraceptive **(re-)starters** in 2009-2010*

	PHARMO	IPCI	THIN	HSD
TOTAL, N (%)	79,797 (100)	23,305 (100)	88,258 (100)	15,233 (100)
AGE (in years)				
<15	4,615 (6)	1,016 (4)	3,145 (4)	24 (<0.5)
15-19	18,581 (23)	5,366 (23)	24,290 (28)	1,757 (12)
20-24	8,850 (11)	3,376 (14)	14,859 (17)	2,863 (19)
25-29	9,998 (13)	3,382 (15)	14,393 (16)	2,505 (16)
30-34	10,398 (13)	3,084 (13)	12,489 (14)	2,424 (16)
35-39	8,928 (11)	2,659 (11)	9,956 (11)	2,236 (15)
40-44	7,014 (9)	2,127 (9)	5,827 (7)	1,877 (12)
45-49	5,210 (7)	1,624 (7)	2,711 (3)	1,172 (8)
50-54	2,180 (3)	583 (3)	541 (1)	276 (2)
≥55	4,023 (5)	88 (<0.5)	47 (<0.5)	99 (1)
History in database (months)				
Mean ±sd	98 ± 46	32 ± 15	115 ± 66	126 ± 77
Median (IQR)	105 (63-140)	29 (21-40)	122 (47-180)	114 (75-164)
Follow-up in database (months)				
Mean ±sd	12 ± 7	11 ± 7	12 ± 7	13 ± 7
Median (IQR)	12 (6-18)	11 (6-17)	12 (6-18)	13 (7-19)

NOTE: Status on index: date of first prescription of oral contraceptives during 2009-2010

*Table 4.2-2. Demographic characteristics of **existing** oral contraceptive users in 2009-2010*

	PHARMO	IPCI	THIN	HSD
TOTAL, N (%)	216,187 (100)	22,442 (100)	202,881 (100)	16,211 (100)
AGE (in years)				
<15	1,589 (1)	279 (1)	914 (<0.5)	2 (<0.5)
15-19	33,726 (16)	3,867 (17)	26,068 (13)	806 (5)
20-24	42,422 (20)	4,316 (19)	46,232 (23)	2,410 (15)
25-29	32,796 (15)	3,660 (16)	44,799 (22)	2,598 (16)
30-34	24,854 (11)	2,762 (12)	32,284 (16)	2,556 (16)
35-39	25,923 (12)	2,570 (11)	24,978 (12)	2,623 (16)
40-44	24,151 (11)	2,243 (10)	16,088 (8)	2,688 (17)
45-49	20,278 (9)	1,719 (8)	8,518 (4)	1,957 (12)
50-54	8,755 (4)	863 (4)	2,660 (1)	494 (3)
≥55	1,693 (1)	163 (1)	340 (<0.5)	77 (<0.5)
History in database (months)				
Mean ±sd	88 ± 44	22 ± 12	95 ± 68	128 ± 81
Median (IQR)	96 (56-132)	17 (12-28)	85 (23-174)	116 (79-166)
Follow-up in database (months)				
Mean ±sd	22 ± 4	18 ± 7	20 ± 7	22 ± 4
Median (IQR)	24 (24-24)	20 (13-24)	24 (19-24)	24 (21-24)

NOTE: Status on index: date of first prescription of oral contraceptives during 2009-2010

*Table 4.2-3. Demographic characteristics of **non-users** of oral contraceptives in 2009-2010*

	PHARMO	IPCI	THIN	HSD
TOTAL, N (%)	1,591,834 (100)	322,702 (100)	1,775,437 (100)	534,394 (100)
AGE (in years)				
<15	237,876 (15)	63,551 (20)	345,591 (19)	13,519 (3)
15-19	45,107 (3)	12,265 (4)	66,602 (4)	23,551 (4)
20-24	55,850 (4)	16,025 (5)	70,349 (4)	24,189 (5)
25-29	78,002 (5)	18,238 (6)	81,524 (5)	29,139 (5)
30-34	99,431 (6)	17,921 (6)	89,233 (5)	38,170 (7)
35-39	128,355 (8)	21,875 (7)	115,056 (6)	44,421 (8)
40-44	129,113 (8)	23,538 (7)	135,581 (8)	47,138 (9)
45-49	123,653 (8)	23,994 (7)	135,950 (8)	45,035 (8)
50-54	118,366 (7)	23,384 (7)	125,362 (7)	41,674 (8)
≥55	576,081 (36)	101,911 (32)	610,189 (34)	227,558 (43)
History in database (months)				
Mean ±sd	91 ± 44	21 ± 12	107 ± 65	137 ± 109
Median (IQR)	108 (60-132)	16 (12-26)	121 (39-174)	115 (77-173)
Follow-up in database (months)				
Mean ±sd	22 ± 5	19 ± 7	21 ± 6	23 ± 4
Median (IQR)	24 (24-24)	22 (14-24)	24 (24-24)	24 (24-24)

NOTE: Status on index: January 1, 2009 or date of database entry, whichever came latest

The age distributions in the different user groups were as observed in Figures 4.1-1 and 4.1-2: women aged 15-25 contributed mainly to the group of (re-)starters, existing users were slightly older and oral contraceptive use was more distributed over age groups in HSD than in PHARMO, IPCI and THIN. Non-users were mainly younger than 15 or older than 55 years. Therefore, when comparing morbidity and previous disease, the difference in age was taken into account. The available history in the database, where previous disease was identified, is a function of age as well as start of data collection. The available history was only slightly shorter among (new) users and thus seems mainly determined by start of data collection.

*Table 4.2-4. Health indicators and morbidity among **users** of oral contraceptives in 2009-2010*

	PHARMO	IPCI	THIN	HSD
TOTAL, N (%)	295,984 (100.0)	45,747 (100.0)	291,139 (100.0)	31,444 (100.0)
Body mass index				
Number with value (%)		1,124 (2.5)	94,588 (32.5)	
Median (IQR)		27 (22-32)	25 (22-29)	
Diagnosis of chronic conditions, N (%)*				
Hypertension	NA	1,752 (3.8)	4,086 (1.4)	1,637 (5.2)
Lipid disorder	NA			
Diabetes mellitus	NA	556 (1.2)	2,186 (0.8)	240 (0.8)
Asthma or chronic obstructive pulmonary disease (COPD)	NA	5,313 (11.6)	47,874 (16.4)	2,069 (6.6)
Diagnosis of systemic lupus erythematosus (SLE)	NA	265 (0.6)	250 (<0.1)	17 (<0.1)
Diagnosis of rheumatoid arthritis	NA	349 (0.8)	1,076 (0.4)	81 (0.3)
Diagnosis of multiple sclerosis (MS)	NA	87 (0.2)	472 (0.2)	85 (0.3)
Use of drugs for chronic conditions, N (%)				
Antihypertensive drugs	252 (<0.1)	50 (0.1)	111 (<0.1)	38 (0.1)
Diuretics	1,984 (0.7)	373 (0.8)	764 (0.3)	167 (0.5)
Beta blocking agents	3,746 (1.3)	1,073 (2.3)	1,877 (0.6)	424 (1.3)
Calcium channel blockers	866 (0.3)	126 (0.3)	515 (0.2)	84 (0.3)
Agents acting on the renin-angiotensin system	3,214 (1.1)	407 (0.9)	1,266 (0.4)	429 (1.4)
Lipid-modifying agents	2,008 (0.7)	275 (0.6)	842 (0.3)	95 (0.3)
Diabetes drugs	2,124 (0.7)	221 (0.5)	2,032 (0.7)	149 (0.5)
Drugs for obstructive airway diseases	13,182 (4.5)	2,317 (5.1)	19,467 (6.7)	1,378 (4.4)

NOTE: Status on index: date of first prescription of oral contraceptives during 2009-2010. BMI measurements were included when measured within three months of the index date (either before or after). Diagnoses were identified in the entire available history of the GP databases. PHARMO captures hospital admissions, which are insensitive for the selected conditions. "Use" was defined as at least two prescriptions in the year preceding the index date.

*Table 4.2-5. Health indicators and morbidity among **non-users** of oral contraceptives in 2009-2010*

	PHARMO	IPCI	THIN	HSD
TOTAL, N (%)	1,591,834 (100.0)	322,702 (100.0)	1,775,437 (100.0)	534,394 (100.0)
Body mass index				
Number with value (%)		16,194 (5.0)	252,267 (14.2)	
Median (IQR)		28 (25-32)	27 (24-32)	
Diagnosis of chronic conditions, N (%)*				
Hypertension	NA	48,374 (15.0)	292,068 (16.5)	116,420 (21.8)
Lipid disorder	NA			
Diabetes mellitus	NA	17,163 (5.3)	70,867 (4.0)	29,200 (5.5)
Asthma or chronic obstructive pulmonary disease (COPD)	NA	34,623 (10.7)	222,513 (12.5)	30,299 (5.7)
Diagnosis of systemic lupus erythematosus (SLE)	NA	1,750 (0.5)	3,512 (0.2)	519 (<0.1)
Diagnosis of rheumatoid arthritis	NA	5,673 (1.8)	21,682 (1.2)	3,859 (0.7)
Diagnosis of multiple sclerosis (MS)	NA	676 (0.2)	5,413 (0.3)	705 (0.1)
Use of drugs for chronic conditions, N (%)				
Antihypertensive drugs	1428 (<0.1)	421 (0.1)	7,372 (0.4)	7,145 (1.3)
Diuretics	40,126 (2.5)	15,217 (4.7)	78,065 (4.4)	27,456 (5.1)
Beta blocking agents	38,900 (2.4)	23,044 (7.1)	40,113 (2.3)	34,337 (6.4)
Calcium channel blockers	15,594 (1.0)	4,480 (1.4)	43,779 (2.5)	19,179 (3.6)
Agents acting on the renin-angiotensin system	48,384 (3.0)	13,386 (4.1)	74,536 (4.2)	56,858 (10.6)
Lipid-modifying agents	46,670 (2.9)	14,714 (4.6)	102,175 (5.8)	31,579 (5.9)
Diabetes drugs	33,164 (2.1)	9,466 (2.9)	39,203 (2.2)	20,391 (3.8)
Drugs for obstructive airway diseases	61,055 (3.8)	17,570 (5.4)	141,111 (7.9)	23,896 (4.5)

NOTE: Status on index: January 1, 2009 or date of database entry, whichever came latest. BMI measurements were included when measured within three months of the index date (either before or after). Diagnoses were identified in the entire available history of the GP databases. PHARMO captures hospital admissions, which are insensitive for the selected conditions. "Use" was defined as at least two prescriptions in the year preceding the index date.

Health indicators and morbidity included diagnoses for chronic diseases and drugs used to treat chronic conditions. Tables 4.2-4 & 4.2-5 present the overall, crude proportions of health indicators among oral contraceptive users and non-users.

As the use of oral contraceptives and diagnosis of or use of drugs for the different diseases were all related to age, the proportions were also presented by 10-year age group in Figures 4.2-1 and 4.2-2.

Diagnoses of hypertension, diabetes and respiratory disease and the more rare diseases systemic lupus erythematosus (SLE), rheumatoid arthritis and multiple sclerosis were identified in the GP databases IPCI, THIN and HSD. The PHARMO databases used in this study only capture diagnoses from hospital admissions, and thus are insufficiently sensitive for these conditions.

The proportion of women diagnosed with hypertension in the GP databases as well as the proportion of women on anti-hypertensive and other cardiovascular drugs clearly increased with age. The proportion of women diagnosed with hypertension increased up to about 45% among women older than 50 years, but was below 2% among women up to 30 years old. In IPCI and HSD, the prevalence of hypertensive disease may be somewhat higher among oral contraceptive users than among non-users in the younger age groups, although no formal statistical comparison was performed. The same might be true for the use of diuretics, beta blocking agents, calcium channel blockers and agents acting on the renin-angiotensin system in PHARMO, IPCI and HSD. In THIN, all proportions were lower among users of oral contraceptives than among non-users.

The proportions of women diagnosed with or treated for diabetes, or treated with lipid-modifying agents were similar across databases: up to about 15% was diagnosed or treated and prevalence clearly increased with age. Like for hypertension and treatment, the proportions may be higher among oral contraceptive users than among non-users in the younger age groups in PHARMO and IPCI. Among women under 35, where oral contraceptive use was most prevalent, proportions were lower than 1%.

The proportions of women diagnosed with or treated for obstructive airway disease were more constant across age groups in all databases. In all databases and in most age groups, proportions of women with obstructive airway disease appeared higher among oral contraceptive users than among non-users.

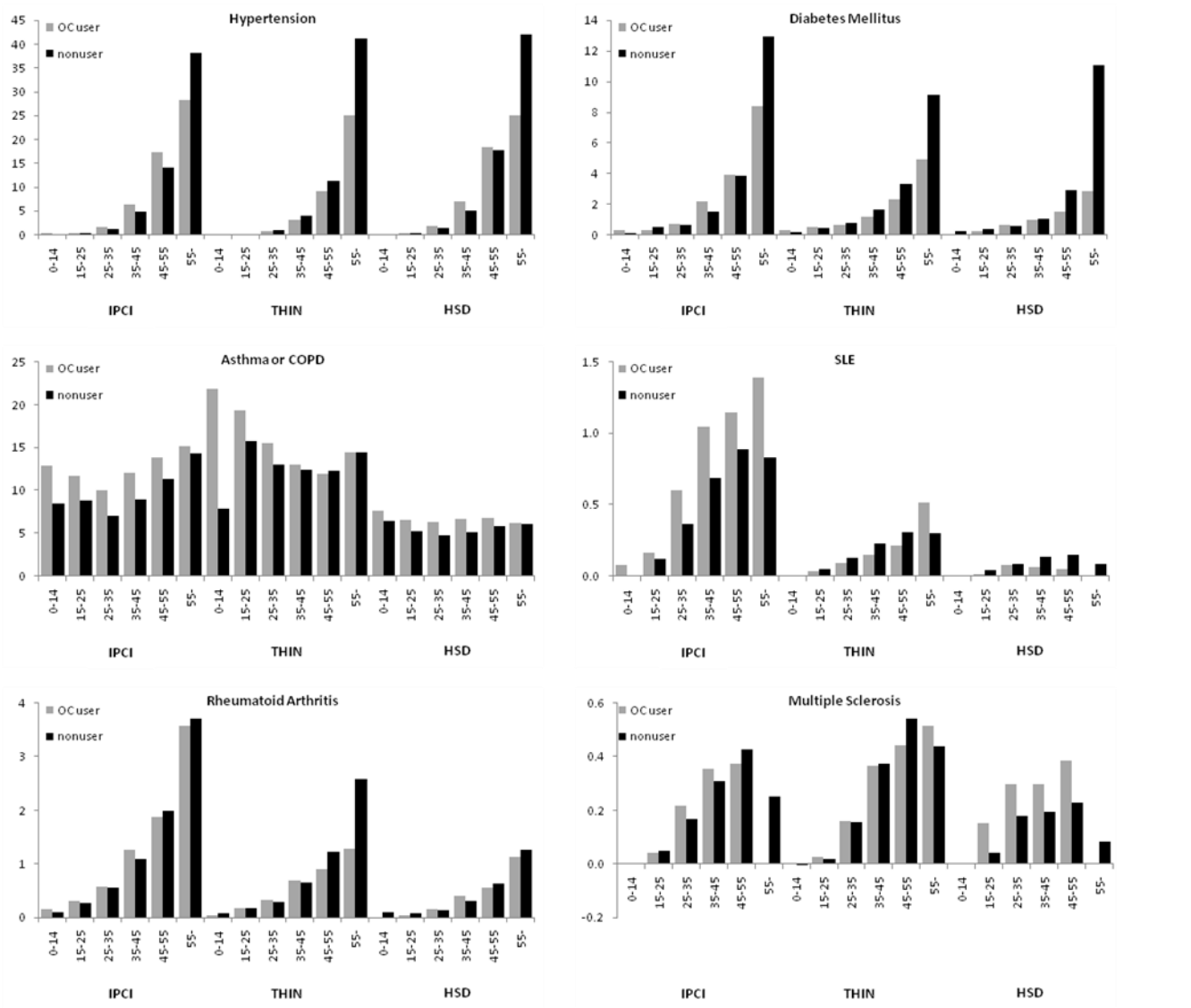

Figure 4.2-1. Percentage of oral contraceptive users and non-users with a previous diagnosis of different chronic conditions, by age. Diagnoses were identified from the GP databases only. Note that graphs are scaled individually.

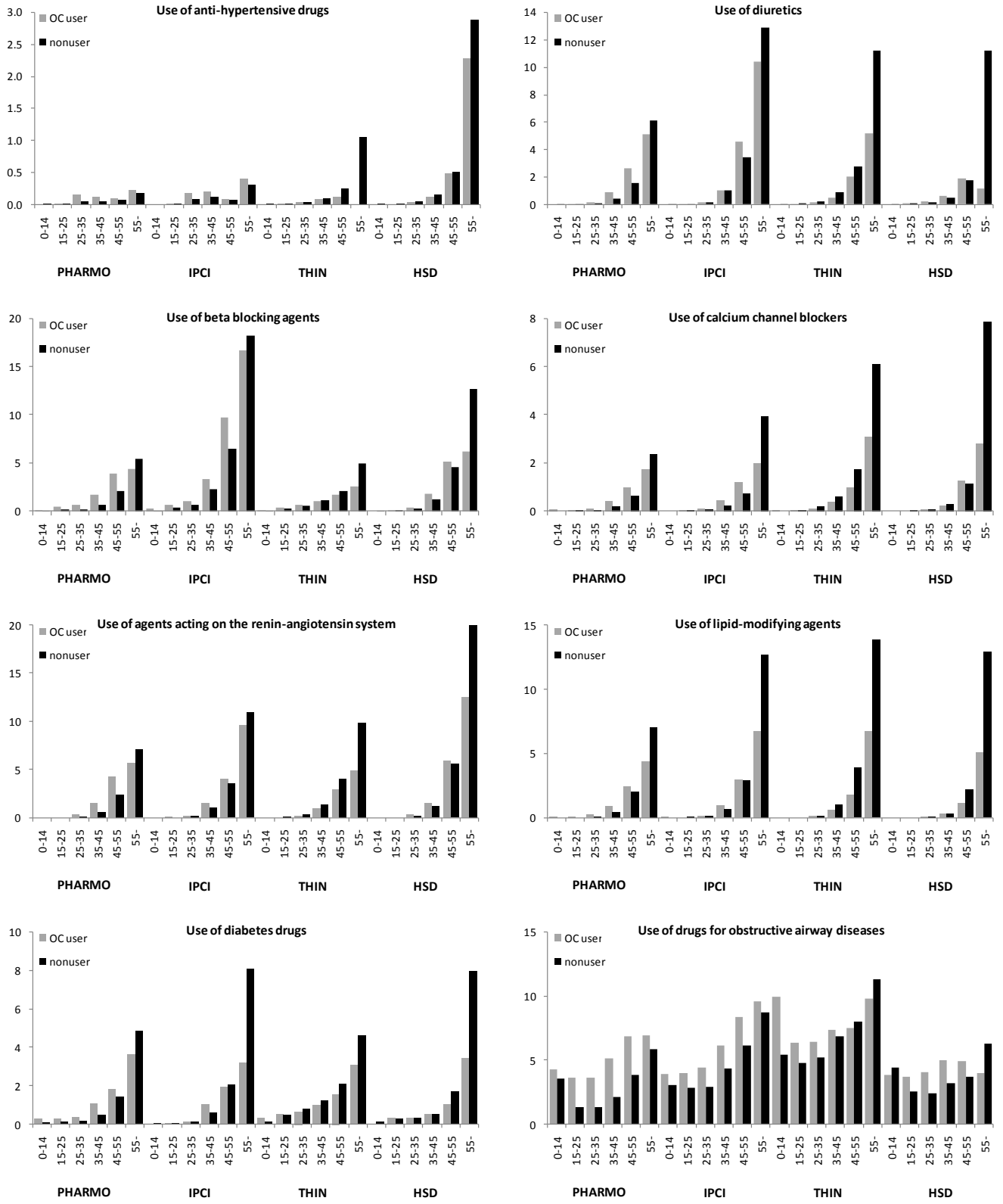

Figure 4.2-2. Percentage of oral contraceptive users and non-users who were using drugs for different chronic conditions, by age. "Use" was defined as at least two prescriptions in the year preceding the index date.

Table 4.2-6. Previous diagnosis of disease associated with the use of oral contraceptives among users and non-users of oral contraceptives in 2009-2010

	PHARMO	IPCI	THIN	HSD
USERS, N (%)	295,984 (100.0)	45,747 (100.0)	291,139 (100.0)	31,444 (100.0)
History of deep vein thrombosis	33 (<0.1)	259 (0.6)	898 (0.3)	200 (0.6)
History of pulmonary embolism	197 (<0.1)	73 (0.2)	282 (<0.1)	7 (<0.1)
History of cerebrovascular disease	617 (0.2)	121 (0.3)	210 (<0.1)	40 (0.1)
History of myocardial infarction	274 (<0.1)	51 (0.1)	30 (<0.1)	1 (<0.1)
History of breast cancer	388 (0.1)	51 (0.1)	95 (<0.1)	32 (0.1)
History of cervical cancer	65 (<0.1)	67 (0.1)	69 (<0.1)	31 (<0.1)
NON-USERS, N (%)	1,591,834 (100.0)	322,702 (100.0)	1,775,437 (100.0)	534,394 (100.0)
History of deep vein thrombosis	467 (<0.1)	5,369 (1.7)	20,762 (1.2)	11,591 (2.2)
History of pulmonary embolism	3,209 (0.2)	1,627 (0.5)	10,251 (0.6)	693 (0.1)
History of cerebrovascular disease	15,893 (1.0)	7,607 (2.4)	37,490 (2.1)	15,583 (2.9)
History of myocardial infarction	7,915 (0.5)	2,576 (0.8)	16,611 (0.9)	1,661 (0.3)
History of breast cancer	14,847 (0.9)	5,920 (1.8)	23,790 (1.3)	9,849 (1.8)
History of cervical cancer	820 (<0.1)	908 (0.3)	2,532 (0.1)	554 (0.1)

NOTE: Status on index: date of first prescription of oral contraceptives during 2009-2010, or start of study for non-users.
Diagnoses were identified in the entire available history before the index date. The PHARMO database identifies hospital admissions; IPCI, THIN and HSD identify diagnoses from the GP records (GP diagnoses and communications from medical specialists and admissions)

Historical events of diseases associated with the use of oral contraceptives were assessed by diagnosis codes. Overall, events were more frequent among non-users. However, the proportion of individuals who have experienced one of these events depends on age, not only because the risk increases but also because of the accumulated history. The use of oral contraceptives varies by age as well and therefore the proportions were stratified by age.

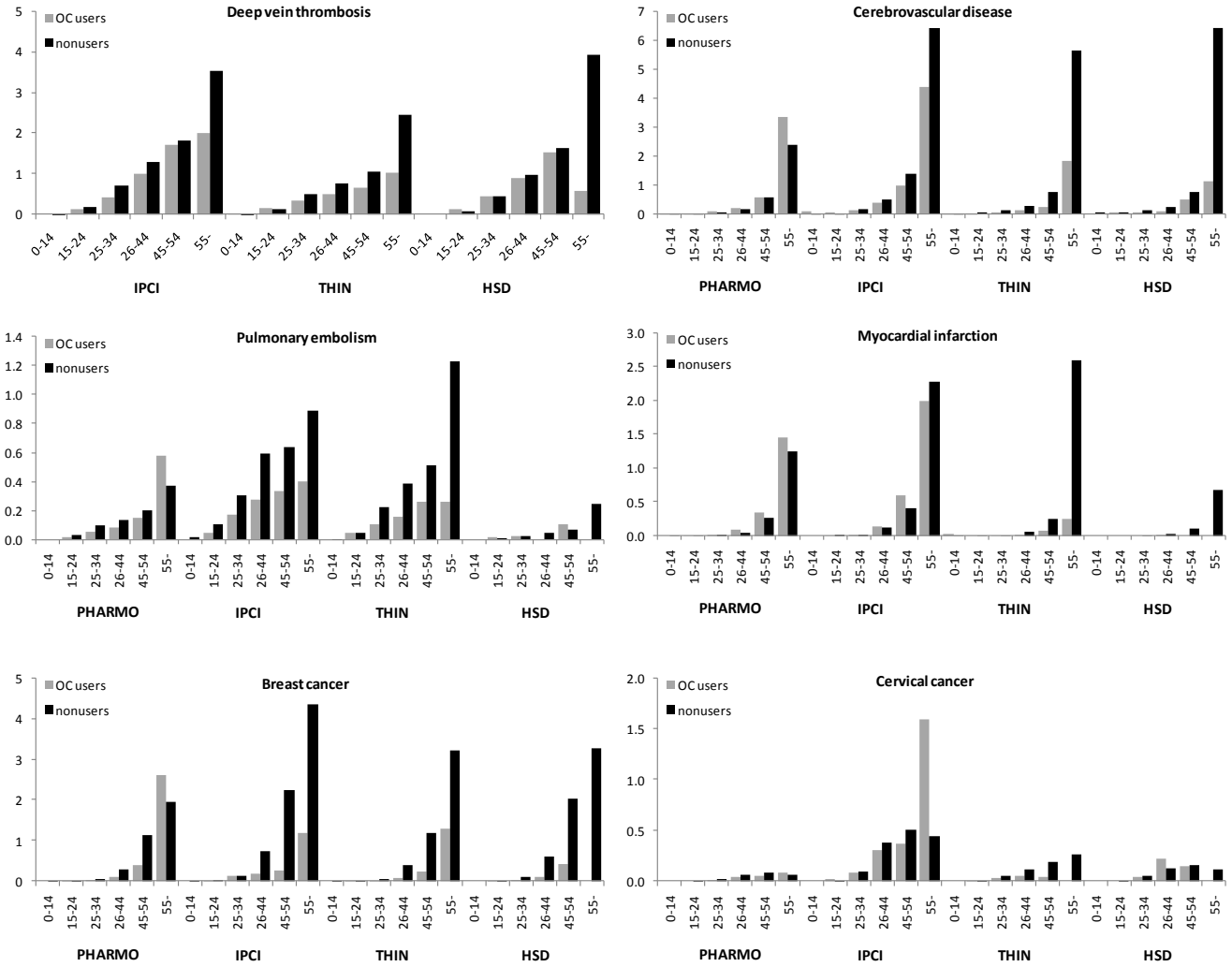

Figure 4.2-1. Percentage of oral contraceptive users and non-users with previous diagnosis of diseases associated with the use of oral contraceptives, by age group

Deep vein thrombosis was hardly captured by the PHARMO hospital admission database as these patients do not necessarily require inpatient care. Pulmonary embolism, cerebrovascular disease and myocardial infarction patients are more likely to be admitted and therefore were captured in the PHARMO hospital admissions. A clear association was

observed between age and the proportion of women with a previous deep vein thrombosis and pulmonary embolism. In particular for pulmonary embolism, proportions were lower among oral contraceptive users as these are clear contra-indications. The seemingly large difference between users and non-user over age 55 for pulmonary embolism as well as cerebrovascular disease and myocardial infarction in PHARMO may be an outlier due to low numbers and requires more formal comparison.
Among women up to 30 years old, the proportion of women with previous deep vein thrombosis was below 1%, the proportion with previous pulmonary embolism below 0.3% and the proportion with previous cerebrovascular disease below 0.2% and the proportion with previous myocardial infarction below 0.05%.

Previous diagnosis of breast and cervical cancer was rare especially among women below 30 years (0.1% of women).

4.3. TREATMENT CHARACTERISTICS

Among starters, defined by no use in the previous year, 39-51% had actually used oral contraceptives before and were thus re-starters. In other words, 49-61% of starters in the databases were first time starters in the database and the incidence of oral contraceptive use is about half the start rate presented in Table 4.1-1.

The assessment of accumulated exposed person-time before the index date is limited by the start of data collection; either start of the database in general or database entry of an individual. This accumulated person-time includes all periods of use during database history, regardless of discontinuations in between episodes of oral contraceptive use. Among starters, the median accumulated previous exposure ranged from six months (IPCI, HSD) to over two years in PHARMO.

Among existing users, who by definition were exposed to oral contraceptives before the study period, the median accumulated exposed person-time ranged from 11 to 44 months. At the index date, most users had been continuously using oral contraceptives for not more than 2 years. For users who were already using oral contraceptives at database entry, the duration of use could not be determined. In IPCI this proportion was 51%, the highest among the databases because IPCI had the shortest mean database history before the study period.

Note that also some non-users had a history of oral contraceptive use. Proportions of non-users with previous exposure in the database were 22% in PHARMO, 18% in IPCI, 16% in THIN and 12% in HSD.

Table 4.3-1. History and duration of oral contraceptive use

	PHARMO	IPCI	THIN	HSD
STARTERS, N (%)	79,797 (100)	23,305 (100)	88,258 (100)	15,233 (100)
History of oral contraceptive use				
Previous use in database	32,281 (40)	9,130 (39)	40,315 (46)	7,714 (51)
No previous use in database	47,516 (60)	14,175 (61)	47,943 (54)	7,519 (49)
Previous use: accumulated person-months of exposure				
Mean ±sd	37 ± 34	18 ± 26	27 ± 28	14 ± 20
Median (IQR)	27 (9-55)	6 (3-19)	17 (6-39)	6 (2-18)
EXISTING USERS, N (%)	216,187 (100)	22,442 (100)	202,881 (100)	16,211 (100)
Previous use: accumulated person-months of exposure				
Mean ±sd	53 ± 43	25 ± 34	42 ± 38	31 ± 34
Median (IQR)	44 (16-79)	11 (5-28)	29 (11-62)	17 (6-46)
Duration of uninterrupted use before index date				
No use exposure preceding index date	14,440 (7)	4,452 (20)	20,204 (10)	8,030 (50)
Since database entry (duration not known)	6,980 (3)	11,532 (51)	4,763 (2)	156 (1)
Start during database follow-up				
< 1 year	83,123 (38)	5,663 (25)	100,361 (49)	5,849 (36)
1-2 years	51,248 (24)	745 (3)	44,169 (22)	1,268 (8)
3-4 years	26,471 (12)	50 (<0.5)	16,709 (8)	520 (3)
5-6 years	17,903 (8)		8,334 (4)	224 (1)
7-8 years	8,492 (4)		4,626 (2)	86 (1)
≥ 9 years	7,530 (3)		3,715 (2)	78 (<0.5)
Mean ±sd, months	30 ± 32	6 ± 7	21 ± 27	13 ± 22
Median (IQR) , months	17 (5-45)	3 (1-7)	10 (4-27)	3 (1-14)

NOTE: Status on index: date of first prescription of oral contraceptives during 2009-2010

Table 4.3-2. Oral contraceptive preparations used in 2009-2010

	PHARMO	IPCI	THIN	HSD
USERS, N (%)	295,984 (100.0)	45,747 (100.0)	291,139 (100.0)	31,444 (100.0)
Fixed combination preparations (ATC, generation)	275,829 (93.2)	42,708 (93.4)	214,826 (73.8)	25,991 (82.7)
Lynesterol & estrogen (G03AA03, II)	4,749 (1.6)	672 (1.5)		
Norethisterone & estrogen (G03AA05, II)	2,971 (1.0)	461 (1.0)	16,885 (5.8)	
Levonorgestrel & estrogen (G03AA07, II)	211,650 (71.5)	33,242 (72.7)	123,306 (42.4)	2,106 (6.7)
Desogestrel & estrogen (G03AA09, III)	29,688 (10.0)	4,067 (8.9)	22,623 (7.8)	2,619 (8.3)
Gestodene & estrogen (G03AA10, III)	14,126 (4.8)	2,005 (4.4)	10,074 (3.5)	12,374 (39.4)
Norgestimate & estrogen (G03AA11, III)	1,467 (0.5)	308 (0.7)	32,116 (11.0)	
Drospirenone & estrogen (G03AA12,other))	23,152 (7.8)	4,090 (8.9)	31,354 (10.8)	9,950 (31.6)
Sequential combination preparations	20,138 (6.8)	2,442 (5.3)	9,856 (3.4)	4,641 (14.8)
Levonorgestrel & estrogen (G03AB03, II)	19,287 (6.5)	2,233 (4.9)	7,187 (2.5)	
Norethisterone & estrogen (G03AB04, II)	712 (0.2)	87 (0.2)	2,271 (0.8)	
Desogestrel & estrogen (G03AB05, III)	24 (<0.1)	1 (<0.1)		796 (2.5)
Gestodene & estrogen (G03AB06, III)	134 (<0.1)	25 (<0.1)	237 (<0.1)	3,851 (12.2)
Dienogest & estrogen (G03AB08, other)	72 (<0.1)	107 (0.2)	237 (<0.1)	
Progestogen-only preparations	7,303 (2.5)	1,877 (4.1)	91,018 (31.3)	1,802 (5.7)
Norethisterone (G03AC01, II)			25,349 (8.7)	
Lynesterol (G03AC02, II)	1 (<0.1)	2 (<0.1)		
Levonorgestrel (G03AC03, II)			2,210 (0.8)	1,378 (4.4)
Desogestrel (G03AC09, III)	7,302 (2.5)	1,875 (4.1)	68,890 (23.7)	427 (1.4)

All preparations used in 2009-2010 were included, i.e. a woman using two different preparations in the study period will appear twice.

The types of oral contraceptive used in 2009 and 2010 are listed in Table 4.3-2. The assessment was done on ATC/prescription level, so if a women used two different oral contraceptives during the study period she was counted twice.

in all databases, use of fixed combination oral contraceptives was most prevalent. In the Netherlands (PHARMO and IPCI), levonorgestrel containing preparations (G03AA07) dominated this oral contraceptive class: more than 70% of users had been using such preparation in the study period. Second most prevalent were drospirenone containing preparations (G03AA12), used by 8-9% of users. In THIN levonorgestrel containing preparations were most prevalent as well but used by 42% of users, followed by norgestimate containing preparations (G03AA11) and drospirenone containing preparations (G03AA12), each used by 11% of users. In HSD, most women had used gestodene containing preparations (G03AA10) or drospirenone containing preparations (G03AA12), used by 39% and 32%, respectively.

Sequential combinations were most prevalent in HSD, where mainly gestodene containing preparations (G03AB06) were used (12%). In the Netherlands and THIN, levonorgestrel containing preparations (G03AB03) were most prevalent among sequential combination oral contraceptives.

Progestogen-only preparations were most prevalent in THIN, where 31% of users had used such a preparation and 24% had used desogestrel (G03AC09).

Classifying the progestogens by generation leads to the observation that in the Netherlands mainly second generation progestogens (levonorgestrel) were used, in the UK second generation was also more frequent but the third generation progestogens (norgestimate) constitute a larger proportion of prescriptions and in Italy, third generation progestogens (gestodene) were most frequently used.

During 2009 and 2010, up to about 10% of users either discontinued using oral contraceptives or switched to another type in the PHARMO, IPCI and HSD databases (Table 4.3-3). In THIN a larger proportion of users changing their oral contraceptive use was observed (19%). These changes were primarily switches: about 15% switched oral contraceptive preparation in THIN. Only in HSD discontinuations were more frequent than switches.

The specific switches that were most frequent were among the most frequently observed oral contraceptives. In PHARMO and IPCI the most frequent switch was from levonorgestrel to drospirenone containing preparations, both fixed combinations ('AA07 to AA12'). In HSD women also switched most frequently to drospirenone but from gestodene containing preparations which were most prevalent ('AA10 to AA12'). Only in THIN, the most frequently observed switch was between types of formulation: from the fixed combination levonorgestrel and estrogen to desogestrel only ('AA07 to AC09').

Table 4.3-3. Discontinuations and preparation switches among oral contraceptive users during 2009-2010

	PHARMO		IPCI		THIN		HSD
TOTAL NUMBER OF USERS (%)	295,984 (100.0)		45,747 (100.0)		291,139 (100.0)		31,444 (100.0)
Changes in oral contraceptive use							
No changes	271,632 (91.8)		40,852 (89.3)		236,766 (81.3)		27,772 (88.3)
Change							
≥1 switch	17,406 (5.9)		3,043 (6.7)		43,208 (14.8)		1,802 (5.7)
≥1 discontinuation	7,313 (2.5)		1,928 (4.2)		12,208 (4.2)		1,943 (6.2)
Most frequent switches							
AA07 to AA12	3,291 (22.5)	AA07 to AA12	524 (20.2)	AA07 to AC09	4,829 (13.9)	AA10 to AA12	272 (18.4)
AC09 to AA07	1,492 (10.2)	AC09 to AA07	387 (14.9)	AA07 to AA12	2,206 (6.3)	AA12 to AA10	168 (11.3)
AA12 to AA07	1,268 (8.7)	AA12 to AA07	223 (8.6)	AC09 to AC01	2,174 (6.3)	AA10 to AB06	82 (5.5)
AA07 to AA09	954 (6.5)	AA07 to AA09	194 (7.5)	AA07 to AA11	2,039 (5.9)	AB06 to AA12	79 (5.3)
AA07 to AB03	954 (6.5)	AA07 to AB03	150 (5.8)	AC09 to AA07	1,962 (5.6)	AB06 to AA10	74 (5.0)

As observed in Table 4.3-4-7, most switches in the PHARMO (60%), IPCI (61%) and HSD (49%) occurred between fixed combination oral contraceptives. In the Netherlands 13-17% of switches were from progestogen only to fixed combinations. In HSD switches from sequential combinations were more frequent than switches to progestogen only.
In THIN the proportion of switches within fixed combinations was lower (40%) and 28% switched from fixed combinations to progestogen only.

*Table 4.3-4. Types of switch between formulations in 2009-2010 - **PHARMO** database*

SECOND	Combined, fixed	Combined, sequential	Progestogen only
FIRST			
Combined, fixed	12455(60)	1834(9)	1446(7)
Combined, sequential	1967(10)	74(<1)	76(<1)
Progestogen only	2610(13)	139(1)	0(<1)

*Table 4.3-5. Types of switch between formulations in 2009-2010 - **IPCI** database*

SECOND	Combined, fixed	Combined, sequential	Progestogen only
FIRST			
Combined, fixed	2179(61)	297(8)	212(6)
Combined, sequential	224(6)	8(<1)	11(<1)
Progestogen only	595(17)	23(1)	0(-)

*Table 4.3-6. Types of switch between formulations in 2009-2010 - **THIN** database*

SECOND	Combined, fixed	Combined, sequential	Progestogen only
FIRST			
Combined, fixed	21434(40)	1440(3)	14681(28)
Combined, sequential	1020(2)	61(<1)	812(2)
Progestogen only	8265(15)	328(1)	5290(10)

*Table 4.3-7. Types of switch between formulations in 2009-2010 - **HSD** database*

SECOND	Combined, fixed	Combined, sequential	Progestogen only
FIRST			
Combined, fixed	1077(49)	277(13)	170(8)
Combined, sequential	339(16)	5(<1)	39(2)
Progestogen only	245(11)	22(1)	2(<1)

5. DISCUSSION

This descriptive study on oral contraceptives in Europe assessed the prevalence and patterns of use and user characteristics in four databases from the Netherlands, United Kingdom and Italy.

Finding a healthcare database that captures oral contraceptive use is a challenge as oral contraceptives are only partly reimbursed (claims/reimbursement databases), the GP is not involved in every single dispensing/refill (GP databases) and women may obtain their refills from internet pharmacies instead of the outpatient pharmacy, especially healthy women who do not need to attend the pharmacy for other reasons (dispensing databases). In fact, higher prevalence of use was reported in the UN's World Contraceptive Use 2009 than in this study: 41% of Dutch women, 29% of UK women and 14% of Italian women use the pill according to the UN report[16]. The databases included in this study show differences that are explained by their different nature but also similarities that provide a picture of oral contraceptive use and users in Europe. However, this is only assuming that the use captured by the databases is representative for the actual use in the different countries. As user characteristics were similar between the databases, selection seems indeed limited.

About 1 or 2 among every 10 women of reproductive age in the Dutch and UK databases used an oral contraceptive during the study period. The proportion of women ever exposed to oral contraceptives is much higher as women switch between use and non-use because of pregnancy, delivery or other health-related reason. Among the non-users in this study, i.e. non-users in 2009-2010, up to 22% of non-users (PHARMO) was previously exposed to oral contraceptives.

The health indicators assessed in this study were diagnosis of and use of drugs for chronic conditions. The selection of conditions was driven by those proposed in the technical specifications of the tender. The rarer autoimmune diseases systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis were also rare among oral contraceptive users and rates did not seem to differ from non-users. More common were diabetes and cardiovascular and respiratory disease, although mainly at the older ages when women are no longer using contraceptives. Statistical comparisons were outside the scope of this study, but the results do not indicate that oral contraceptive users were any healthier than non-users. Increasing prevalence of cardiovascular disease will thus also apply to young women using oral contraceptives. It should be noted that prevalence of morbidity tends to be underestimated for some conditions in GP databases and hospital admission data only capture severe events, but this applies to both oral contraceptive users and non-users.

Previous diagnosis of deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular disease and breast and cervical cancers were rare. The low numbers limited interpretation of the trends among oral contraceptive users and non-users at different ages, but overall, fewer users than non-users had previously experienced such an event.

Each country and database included in the study demonstrated different habits regarding the type of oral contraceptives used. In the Netherlands, fixed combinations of estrogen and

levonorgestrel (second-generation progestogen) were used by the majority of women. In the UK, levonorgestrel containing preparations were used by many women as well but also many users of fixed combinations of estrogen with norgestimate (third generation progestogen) or drospirenone were observed. In Italy women mainly used fixed combinations of estrogen with gestodene (third-generation progestogen) or drospirenone. Third-generation progestogens have been associated with a higher risk of venous thrombosis than second-generation progestogens[6-8]. Apart from different prescribing habits, the type of oral contraceptives observed in the databases is also influenced by local availability (less choice for prescribers) and distribution channels (whether a preparation is captured by database).

For safety monitoring of oral contraceptive use, this study provides the following conclusions, keeping in mind its limitations. First, users of oral contraceptives do not differ from non-users and trends in health among European women also apply to oral contraceptive users. Second, use is not registered very well in Europe which limits the possibilities of pharmacovigilance, due to the different distribution channels and because oral contraceptives are for a large part not reimbursed. In surveys, the proportion of users is structurally higher than in healthcare databases. In the GP systems, oral contraceptive users can be identified but the actual use is not captured well.

6. REFERENCES

1. Chadwick KD, Burkman RT, Tornesi BM, Mahadevan B. Fifty years of "the pill": risk reduction and discovery of benefits beyond contraception, reflections, and forecast. Toxicological sciences : an official journal of the Society of Toxicology 2012;125(1):2-9.
2. Mears E. Clinical trials of oral contraceptives. British medical journal 1961;2(5261):1179-83.
3. Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception 2010;15 Suppl 2:S19-31.
4. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. British medical journal 1969;2(5658):651-7.
5. Burkman R, Bell C, Serfaty D. The evolution of combined oral contraception: improving the risk-to-benefit ratio. Contraception 2011;84(1):19-34.
6. Dunn N. The risk of deep venous thrombosis with oral contraceptives containing drospirenone. BMJ 2011;342:d2519.
7. Hannaford PC. Epidemiology of the contraceptive pill and venous thromboembolism. Thrombosis research 2011;127 Suppl 3:S30-4.
8. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921.
9. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, et al. Hormonal contraception and risk of cancer. Human reproduction update 2010;16(6):631-50.
10. Kaunitz AM. Oral contraceptive health benefits: perception versus reality. Contraception 1999;59(1 Suppl):29S-33S.
11. Herings RMC. PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in The Netherlands. Utrecht University, 1993.
12. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiology and drug safety 2007;16(4):393-401.
13. WHO ATC Classification system. http://www.whocc.no/atc/structure_and_principles/.
14. Avillach P, Joubert M, Thiessard F, Trifiro G, Dufour JC, Pariente A, et al. Design and evaluation of a semantic approach for the homogeneous identification of events in eight patient databases: a contribution to the European EU-ADR project. Studies in health technology and informatics 2010;160(Pt 2):1085-9.
15. Avillach P, Mougin F, Joubert M, Thiessard F, Pariente A, Dufour JC, et al. A semantic approach for the homogeneous identification of events in eight patient databases: a contribution to the European eu-ADR project. Studies in health technology and informatics 2009;150:190-4.
16. United Nations, Department of Economic and Social Affairs, Population Division (2009). World Contraceptive Use 2009 (POP/DB/CP/Rev2009).