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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
  - **UNIMIB.** Università di Milano-Bicocca (Italy). 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 aims 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 are to assess among women using oral contraceptive in 2009 and 2010 in different countries in Europe:

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

3. METHODS

3.1. STUDY DESIGN

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

DATABASE	MANAGING ORGANISATION	COUNTRY	INDIVIDUALS
IPCI	Erasmus University Medical Center Rotterdam (EMC)	NL	1 Million
PHARMO	PHARMO Coöperatie U.A. (PHARMO)	NL	4 Million
THIN	The Health Improvement Network (THIN)	UK	7.5 Million
SISR Toscana	Agenzia Regionale di Sanità della Toscana (ARS)	IT	3.5 Million
SISR Lombardia	Università degli Studi di Milano-Bicocca (UNIMIB)	IT	9 Million
			25.1 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]. Currently, data are available from 1998 up to 2010.

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. SISR Toscana

The SISR Toscana database includes several linked databases, referring to health conditions and health services provided to the whole stable population of Tuscany (both Italian and legal immigrant population), which comprises about 3.5 million individuals. Databases comprise all of the Italian administrative databases (IAD): population registry (birth/entry date, death/exit date, gender, citizenship, municipality of residence); hospitalizations (primary diagnosis, five secondary diagnoses and procedures in ICD9CM, dates of hospital admission and discharge, ward specialty of admission and discharge coded with a national coding system); drug dispensing (ATC classification, dispensing date, amount dispensed, DDD) both from direct dispensing from the health system and from commercial distribution; outpatient activity (national coding system of diagnostic and specialist activities such as laboratory tests, imaging or specialist visits); disease-specific exemptions from co-payment to healthcare (diagnosis coded in ICD9CM); birth registry (detailed information on mother, child, pregnancy and birth). Moreover a death registry is available with causes of death coded in ICD9CM. Record linkage is deterministic on a personal de-identified code. Currently, data are available from 2003 up to 2011.

3.1.5. SISR Lombardia

Since 1997, Lombardia, a region of Italy which accounts for about 16% (9 million) of its population, collects data on the access to health services of the beneficiaries of the National Health Service (NHS) residing in the Region using an automated system of databases. In particular: (i) a database of residents who receive NHS assistance (practically the whole resident population), including demographic and administrative data; (ii) a hospital discharge database providing data on diagnoses (coded as ICD-9 CM) recorded for each admission in a public or private hospital of the Region; and (iii) a database on outpatient drug prescriptions reimbursable by the NHS providing data on the ATC (Anatomical Therapeutic Chemical) code, and the corresponding amount of active drug, for each prescription collected in a pharmacy of the Region. For each patient, the information contained in the three database can be linked using a unique encrypted identification code which discard the possibility of indentify the subject according in order to preserve privacy.

3.2. MAPPING

Drug prescription and/or dispensing data will be 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 will be 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 SISR Lombardia, SISR Toscana, THIN, and PHARMO. The process of mapping of event data

extraction from the different databases will be based on medical concepts derived from the Unified Medical Language System (UMLS) and will be adopted from the process previously described in other publications[14-15].

3.3. STUDY PERIOD

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

3.4. STUDY POPULATION

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

Study follow-up starts one year after database entry or January 1, 2009, whichever comes latest. Follow-up ends 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 comes first.

From the source population, all women with a prescription (IPCI, THIN) or dispensing (PHARMO, SISR-T, SISR-L) of oral contraceptives during study follow-up will be selected as users. The index date will be defined as the date of first prescription or dispensing during study follow-up. See for the definition of 'oral contraceptive' the Annex 1 in spreadsheet format (*Codes for OC Comedication & Morbidity*).
Non-users are women who have no prescription or dispensing of oral contraceptives during study follow-up. For non-users, the index date will be defined as start of follow-up.

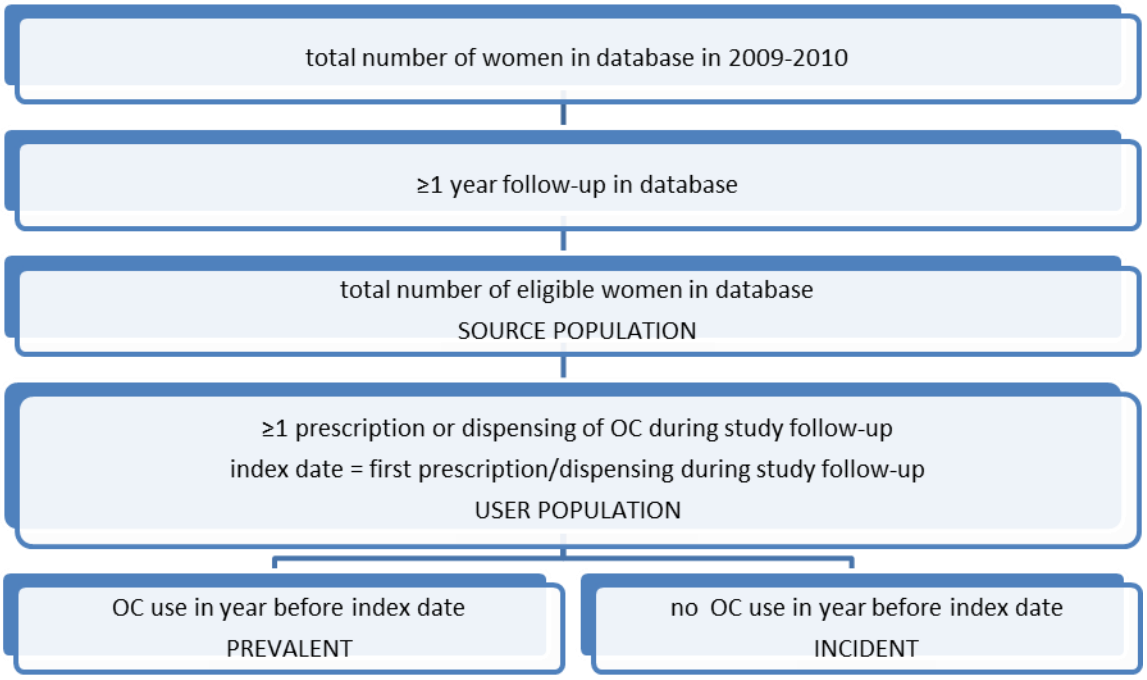

Figure 3.1 Study population

3.5. EXPOSURE DEFINITION

From consecutive prescription/dispensing records in the entire database history of a user, episodes of uninterrupted use will be constructed. Uninterrupted use is 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 is the day after the expiry date of the previous. Switching between formulations is allowed within an episode, i.e. an episode of oral contraceptive use can contain multiple subsequent formulations.

3.6. PREVALENCE AND INCIDENCE OF ORAL CONTRACEPTIVE USE

The prevalence of oral contraceptive use will be calculated on January 1, 2010. From among all women in the source population on January 1, 2010 (denominator), prevalent users are all who are exposed on that day (numerator).

The incidence of oral contraceptive use will be calculated as the number of new users during the study period, 2009-2010, (numerator) per 100,000 person-years. New users are defined as users who were not exposed to oral contraceptives during the year preceding the index date. . The denominator is the number of accumulated person-years 'at risk' (unexposed), i.e. between start of follow-up and the index date (new users) or start and end of follow-up (non-users). Note that prevalent user person-time is not included in the denominator as prevalent users are not at 'risk' of initiating oral contraceptive use.

3.7. POPULATION CHARACTERISTICS

Characteristics for both prevalent and incident users and for non-users will be assessed on the index date and include the following:

Demographic characteristics:

- 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
- Parity: no children, 1 child, 2-3 children, 4-5 children, 6 or more children
- 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 at index:

- Body mass index: mean ±sd and median (IQR)
- Smoking: number (%) of smokers
- Previous diagnosis of or use of drugs for chronic conditions, number (%):
  - Hypertension: diagnosis or use of antihypertensive drugs
  - Use of diuretics
  - Use of beta blocking agents
  - Use of calcium channel blockers

- Use of agents acting on the renin-angiotensin system
- Lipid disorders: diagnosis or use of lipid-modifying agents
- Diabetes mellitus: diagnosis or use of diabetes drugs
- Asthma or chronic obstructive pulmonary disease (COPD): diagnosis or use of drugs for obstructive airway diseases
- Diagnosis of systemic lupus erythematosus (SLE)
- Diagnosis of rheumatoid arthritis
- Diagnosis of multiple sclerosis (MS)

Parity is not available in PHARMO and only partly available in other databases. Smoking status is only partly available in IPCI and THIN, and body mass index is only partly available in THIN. For body mass index and smoking status, the recording closest to the index date will be included, if within three months of the index date (either before or after).
Diagnoses of chronic conditions will be identified in the entire available history before the index date. Note that the sensitivity of identifying diagnosis depends on the data source: as some conditions do not require hospital admission, sensitivity will be lower in hospital admission data sources (PHARMO, SISR-T, SISR-L) than in primary care data sources (IPCI, THIN).
Use of drugs for chronic conditions will be considered as proxy for underlying disease if the patient uses at least two prescriptions or dispensings in the year preceding the index date.

Previous diagnosis of disease associated with the use of oral contraceptives, n (%):

- History of deep vein thrombosis
- History of pulmonary embolism
- History of cerebrovascular disease
- History of myocardial infarction
- History of breast cancer
- History of cervical cancer

Diagnoses will be identified in the entire available history before the index date. Note that the sensitivity of identifying diagnosis depends on the condition and data source: as some conditions do not require hospital admission, sensitivity will be lower in hospital admission data sources (PHARMO, SISR-T, SISR-L) than in primary care data sources (IPCI, THIN).

See section 6 for the variable definitions in the different coding systems.

3.8. TREATMENT CHARACTERISTICS

Treatment characteristics will be stratified by incident and prevalent use 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).

- Formulation used on index date: number (%) of users with combined, fixed hormone doses, combined, varying (sequential) hormone doses or progestin only preparations.
- Type of oral contraceptive used on index date at the chemical substance level and stratified by estrogen and progestogen dose, n (%).

Note that incident users, defined as one year free of exposure preceding the index date, may have an earlier history of oral contraceptive use. The duration of uninterrupted use at the index date, which can only be assessed for prevalent users, is 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 will be assessed during 2009 and 2010 and includes:

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

Switches will be analyzed on the switch level, i.e. a user who switches twice within the study period is counted twice. Between switches, gaps are allowed.

3.9. ANALYSIS

A distributed network approach will be adopted for the database study. Due to lack of common statistical software and large differences in analytical capabilities across sites, we will use a standardized common software called JERBOA. Jerboa is a JAVA based software that can elaborate the databases locally and produce aggregated output datasets that will be 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 will include proportions, mean and standard deviations (sd), median and interquartile ranges (IQR) of the aggregated datasets. Incidence and prevalence will be presented for the pooled dataset as well as for the individual datasets. Population and treatment characteristics will be presented for the individual datasets. Stratified analysis will be performed per database and separately for incident and prevalent users. In addition, analysis will be performed by age category and presented in strata if needed.

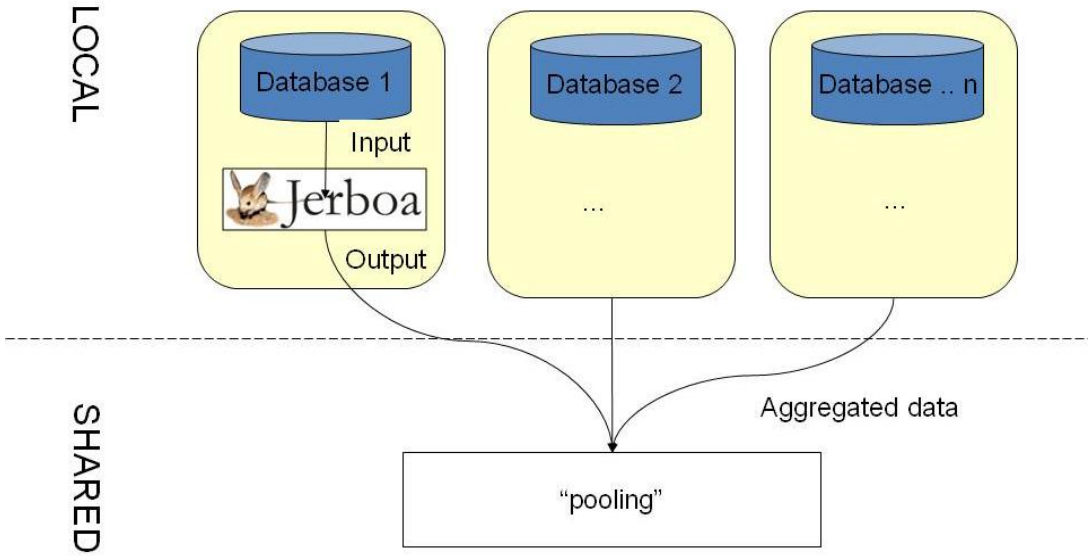

Figure 3.2 JERBOA model for distributed computing on databases

4. TABLE AND FIGURE SHELLS

Below are proposed table and figure shells. As described in section 3.8, the final choice of tables, in particular whether or not results will be presented in strata, will depend on the study results. When results differ clearly between strata this will be presented in the table or at least in the text.

4.1 PREVALENCE AND INCIDENCE OF ORAL CONTRACEPTIVE USE

Table 4.1. Prevalence and incidence of oral contraceptive use in 2009-2010

	TOTAL	IPCI	PHARMO	THIN	SISR-T	SISR-L
TOTAL POPULATION, N (%)						
Number of women						
Number of users						
Prevalence						
Population size at Jan 1, 2010						
Number of users at Jan 1, 2010						
Prevalence per 100,000						
Incidence						
Unexposed person-years 2009-2010						
New users in 2009-2010*						
Incidence per 100,000 person-years						

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

4.2 POPULATION CHARACTERISTICS

Table 4.2. Demographic characteristics of oral contraceptive users and non-users in 2009-2010

	INCIDENT USERS	PREVALENT USERS	NON-USERS
TOTAL, N (%)			
AGE (in years)			
<15			
15-19			
20-24			
25-29			
30-34			
35-39			
40-44			
45-49			
50-54			
≥55			
Mean ±sd			
Median (IQR)			
Parity			
None			
1 child			
2-3 children			
4-5 children			
6 or more			
History in database			
Mean ±sd			
Median (IQR)			
Follow-up in database			
Mean ±sd			
Median (IQR)			

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

This table will be presented for each database separately, unless heterogeneity is negligible.

Table 4.3. Health indicators and morbidity among oral contraceptive users and non-users in 2009-2010

	INCIDENT USERS	PREVALENT USERS	NON-USERS
TOTAL, N (%)			
Body mass index			
Mean ±sd			
Median (IQR)			
Smoker, N (%)			
Previous diagnosis of or use of drugs for chronic conditions, N (%)			
Diagnosis of hypertension or use of antihypertensive drugs			
Use of diuretics			
Use of beta blocking agents			
Use of calcium channel blockers			
Use of agents acting on the renin-angiotensin system			
Diagnosis of lipid disorder or use of lipid-modifying agents			
Diagnosis or diabetes mellitus or use of diabetes drugs			
Diagnosis or Asthma or chronic obstructive pulmonary disease (COPD) or use of drugs for obstructive airway diseases			
Diagnosis of systemic lupus erythematosus (SLE)			
Diagnosis of rheumatoid arthritis			
Diagnosis of multiple sclerosis (MS)			

NOTE: Status on index: date of first prescription or dispensing of oral contraceptives during 2009-2010
For weight, body mass index and smoking status, the recording closest to the index date will be included (either before or after). Diagnoses of chronic conditions will be identified in the entire available history before the index date. Note that the sensitivity of identifying diagnosis depends on the data source.
Use of drugs is defined as at least two prescriptions or dispensings in the year preceding the index date.

This table will be presented for each database separately, unless heterogeneity is negligible.

Table 4.4. Previous diagnosis of disease associated with the use of oral contraceptives among users and non-users of oral contraceptives in 2009-2010

	INCIDENT USERS	PREVALENT USERS	NON-USERS
TOTAL, N (%)			
History of deep vein thrombosis			
History of pulmonary embolism			
History of cerebrovascular disease			
History of myocardial infarction			
History of breast cancer			
History of cervical cancer			

NOTE: Status on index: date of first prescription or dispensing of oral contraceptives during 2009-2010
Diagnoses will be identified in the entire available history before the index date. Note that the sensitivity of identifying diagnosis depends on the data source.

This table will be presented for each database separately, unless heterogeneity is negligible.

4.3 TREATMENT CHARACTERISTICS

Table 4.2.1. History and duration of oral contraceptive use

	INCIDENT USERS	PREVALENT USERS
TOTAL, N (%)		
History of oral contraceptive use		
Previous use in database		
No previous use in database		
Person-time exposed in database before index date		
Mean ±sd		
Median (IQR)		
Duration of uninterrupted use before index date		
Since database entry (duration not known)	NA	
Start during database follow-up	NA	
< 1 year	NA	
1-2 years	NA	
3-4 years	NA	
5-6 years	NA	
7-8 years	NA	
≥ 9 years	NA	
Mean ±sd	NA	
Median (IQR)	NA	

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

This table will be presented for each database separately, unless heterogeneity is negligible.

Table 1.1.2. Fixed combination oral contraceptive preparations among women in 2009-2010

	ALL	INCIDENT USERS	PREVALENT USERS
TOTAL NUMBER OF USERS (%)			
Etynodiol and estrogen			
Quingestanol and estrogen			
Lynestrenol and estrogen			
Megestrol and estrogen			
Norethisterone and estrogen			
Norgestrel and estrogen			
Levonorgestrel and estrogen			
100 mcg levonorgestrel / 20 mcg estrogen			
150 mcg levonorgestrel / 30 mcg estrogen			
125 mcg levonorgestrel / 50 mcg estrogen			
Medroxyprogesterone and estrogen			
Desogestrel and estrogen			
Gestodene and estrogen			
Norgestimate and estrogen			
Drospirenone and estrogen			
Norelgestromin and estrogen			
Nomegestrol and estrogen			
Chlormadinone and estrogen			

NOTE: This table will also list the different estrogen and progestogen doses within preparations, Levonorgestrel and estrogen doses are presented as example.
All preparations used in 2009-2010 are included, i.e. a women using two different preparations in the study period will appear twice.

This table will be presented for each database separately, unless heterogeneity is negligible. This table will also be presented for sequential combination oral contraceptive preparations and for progestogen-only oral contraceptive preparations.

Table 1.1.3. Discontinuations and preparation switches of oral contraceptives during 2009-2010

	ALL	INCIDENT USERS	PREVALENT USERS
TOTAL NUMBER OF USERS (%)			
Changes in oral contraceptive use			
No changes			
Change			
≥1 switch			
≥1 discontinuation			
Most frequent switches			
OC#1 to OC#2			
OC#1 to OC#2			
OC#1 to OC#2			
OC#1 to OC#2			
OC#1 to OC#2			

Table 1.1.4. Types of switch between formulations in 2009-2010

SECOND	Combined, fixed	Combined, sequential	Progestin only
FIRST			
Combined, fixed	NA		
Combined, sequential		NA	
Progestin only			NA

These tables will be presented for each database separately, unless heterogeneity is negligible.

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