Study Report

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DARWIN EU® - Treatment patterns in postmenopausal women in European countries: A real-world observational study

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Authors: Ellen Gerritsen, Dina Vojinovic

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Study title	DARWIN EU® - Treatment patterns in postmenopausal women in European countries: A real-world observational study
Study report version	V5.0
Date	21/09/2026
EUPAS number	EUPAS1000000821
Active substance	Hormone replacement therapy (HRT) including oestrogen, progestogen, and combination products.
Medicinal product	Medicinal products mapped to the pre-specified hormone replacement therapy (HRT). A list is provided in **ANNEX III**.
Research question and objectives	Research question: What are the patterns and trends in HRT utilisation among postmenopausal women in European countries over the past three decades? Study objectives: 1. To describe the demographic and clinical characteristics of postmenopausal women, including age, body mass index (BMI), smoking status, concomitant conditions, and HRT used at treatment initiation, where applicable. Estimates were stratified by HRT status and presented for selected calendar years. 2. To estimate annual prevalence of HRT use among postmenopausal women, overall and stratified by HRT formulation, route of administration (systemic or local), and HRT type (natural or synthetic) (if feasible). Estimates were additionally stratified by age group at treatment initiation. 3. To estimate the duration of HRT use among postmenopausal women initiating HRT, overall and by age group. 4. To describe HRT treatment patterns among postmenopausal women over ten years following HRT initiation, including **a)** treatment grouped by HRT formulation, type, and route of administration and **b)** treatment grouped by HRT formulation and route of administration, stratified by prespecified calendar periods.
Countries of study	Denmark, Germany, Spain, the United Kingdom
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público
BMI	Body mass index
CC	Coordination Centre
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
ETL	Extract, Transform, Load
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
GDPR	General Data Protection Regulation
GP	General Practitioner
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
IQVIA DA Germany	IQVIA Disease Analyzer Germany
IQR	Interquartile range
IRB	Institutional Review Board
IUD	Intrauterine Device
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
SIDIAP	The Information System for Research in Primary Care
SmPC	Summary of Product Characteristics
SNOMED	Systematized Nomenclature of Medicine
VMS	Vasomotor symptoms
WHI	Women's Health Initiative

1. TITLE

DARWIN EU® - Treatment patterns in postmenopausal women in European countries: A real-world observational study

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigators	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientists	Akram Mendez Gargi Jadhav	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
IQVIA DA Germany	Isabella Kaczmarczyk James Brash	IQVIA
BIFAP	Ana LIorente-Garcia Miguel Angel Macia Martinez Marta Monreal Di Bello Cristina Justo Astorgano	Agencia Española de Medicamentos y Productos Sanitarios
SIDIAP	Anna Palomar Cros Agustina Giuliodori Picco Irene López Sánchez Laura Granés González (Invitado) Elena Roel Herranz	Institute for Primary Health Care Research Jordi Gol i Gurina
CPRD GOLD	Antonella Delmestri Marta Pineda Moncusí Mandickel Kamtengeni Hezekiah Omulo	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Treatment patterns in postmenopausal women in European countries: A real-world observational study

Rationale and background

Vasomotor symptoms (VMS), including hot flashes and night sweats, affect up to 80% of menopausal women and significantly impair quality of life. Hormone replacement therapy (HRT) remains the primary treatment for VMS, with various formulations and regimens available depending on clinical factors. Despite its widespread use, there are risks associated with HRT, which vary by age, timing, and treatment type. However, contemporary data on HRT utilisation patterns in Europe are limited, highlighting the need for real-world evidence to inform regulatory decisions.

Research question and objectives

Research question

What are the patterns and trends in hormone replacement therapy (HRT) utilisation among postmenopausal women in European countries over the past three decades?

Objectives

The specific objectives of this study were:

1. To describe the demographic and clinical characteristics of postmenopausal women, including age, body mass index (BMI), smoking status, concomitant conditions, and HRT used at treatment initiation, where applicable. Estimates were stratified by HRT status and presented for selected calendar years.
2. To estimate annual prevalence of HRT use among postmenopausal women, overall and stratified by HRT formulation, route of administration (systemic or local), and HRT type (natural or synthetic) (if feasible). Estimates were additionally stratified by age group at treatment initiation.
3. To estimate the duration of HRT use among postmenopausal women initiating HRT, overall and by age group.
4. To describe HRT treatment patterns among postmenopausal women over ten years following HRT initiation, including **a)** treatment grouped by HRT formulation, type, and route of administration and **b)** treatment grouped by HRT formulation and route of administration, stratified by prespecified calendar periods.

Methods

Study design

A descriptive retrospective cohort study was conducted in postmenopausal women defined as **i)** women aged 50 to 65 years and **ii)** women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause. The study population included all postmenopausal women who met the criteria defined above during the study period (*objective 2*), which was further divided into new HRT users and non-HRT users (*objective 1*). For *objectives 3 and 4*, only postmenopausal women initiating HRT during the study period were included.

Variables

Exposure: HRT treatment with prespecified plain and combinations products of oestrogen, progestogen, and/or androgen.

Indication: Postmenopausal symptoms/disorders

Data sources: One population-based data source (Danish Data Health Registries (DK-DHR) from Denmark), three primary care data sources (Clinical Practice Research Datalink GOLD (CPRD GOLD) from the United Kingdom, IQVIA Disease Analyzer Germany (IQVIA DA Germany) from Germany, and The Information System for Research in Primary Care (SIDIAP) from Spain), and one primary care data source linked to hospital care (Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP) from Spain) were used in the study.

Statistical analysis

Clinical characteristics of interest were reported as counts and proportions for categorical variables, and as medians with interquartile ranges (IQR) for continuous variables. Annual prevalence of HRT use was estimated and expressed as a proportion of women using HRT among postmenopausal women. The annual prevalence was also estimated for HRT formulation (e.g. oestrogen only products; combination products including: oestrogen and progestogen / oestrogen and androgen / oestrogen, progestogen, and androgen, or other), route of administration (systemic or local), and HRT type (natural or synthetic) (if feasible). All prevalence estimates were reported overall and stratified by age group at treatment initiation (<50 years, 50–60 years, and >60 years). Treatment duration was estimated, and the minimum, Q25, median, Q75, and maximum were provided. The treatment patterns were described based on the sequence of HRT treatment over ten years following HRT initiation. These analyses were performed overall, and results for *objective 3* were also stratified by age group (<50 years, 50–60 years, and >60 years).

Results

A total of 1,370,059 new HRT users (DK-DHR: 448,956; IQVIA DA Germany: 146,740; BIFAP: 328,352, SIDIAP: 105,950, CPRD GOLD: 340,061) and 12,100,035 non-HRT users (DK-DHR: 1,248,826; IQVIA DA Germany: 3,542,357; BIFAP: 4,550,113, SIDIAP: 1,179,632, CPRD GOLD: 1,579,107) met inclusion criteria during the study period.

Demographic and clinical characteristics

Across all data sources, the number of women included in each selected calendar year generally increased over time, as women could contribute to multiple years while under observation. The study population was predominantly comprised of women aged ≥50 years, with limited representation of women aged <50 years.

HRT products used at initiation varied across data sources and calendar years, with results reflecting the product recorded at HRT initiation and not accounting for concomitant use of separately prescribed progestogens or other HRT products. In DK-DHR, oestradiol-containing products accounted for 40.5% in 2000 and 75.5% in 2024, while in IQVIA DA Germany, oestriol-containing products accounted for >50% in 2020–2024. In BIFAP and SIDIAP, promestriene predominated up to 2015, accounting for 59.9% to 65.1% in BIFAP and 78.4% to 87.0% in SIDIAP, while oestriol products became the most frequent product in BIFAP in 2024 (43.3%). In CPRD GOLD, oestradiol-containing products were most frequent from 2005 onwards, accounting for 20.0% in 2005 to 38.0% in 2020 and 2024. Testosterone-containing therapies were not observed in any data source.

Among women included in each selected calendar year, the frequency of recorded menopause diagnoses varied by data source. In DK-DHR, frequencies ranged from 0.9% in 2010 to 1.3% in 2024 for HRT users, while remaining stable at 0.5% for non-HRT. In IQVIA DA Germany, the frequency among HRT users remained stable around 6.3%–14.3% across calendar years, compared with consistently low proportions (<1%) among non-HRT users. In the Spanish data sources, the frequency ranged from 2.2% to 13.5% (BIFAP)

and from 4.0% to 8.0% (SIDIAP) in HRT users, and below 4.0% (BIFAP and SIDIAP) in non-HRT users. In CPRD GOLD, proportions ranged from 2.8% to 30.3% in HRT users, and from 0.6% to 2.2% in non-HRT users.

Concomitant conditions and top 10 comedications and comorbidities

Among women included in each selected calendar year, the frequency of recorded concomitant conditions increased over time in both HRT users and non-HRT users. HRT users generally had a higher burden of recorded comorbidities than non-HRT users, particularly anxiety, sleep disorders, osteoporosis, hypertension, and dyslipidaemia, although the magnitude of differences varied across data sources. For example, in DK-DHR in 2024, osteoporosis was recorded in 20.7% of HRT users versus 10.6% of non-HRT users, and sleep disorders in 34.8% versus 22.5%, respectively. A record of hysterectomy was uncommon across all data sources, and more than 88% of women were classified as having an intact uterus in both HRT users and non-HRT users throughout calendar years.

Analgesics, gastroprotective agents, cardiometabolic medications, endocrine therapies, and vaccinations were the most frequently recorded comedications in both HRT users and non-HRT users, while pain-related, cardiometabolic, musculoskeletal, infectious, and mental health conditions were the most frequent comorbidities.

Prevalence of HRT use among postmenopausal women

Annual prevalence of HRT use varied substantially across data sources and over time. Prevalence was consistently highest in DK-DHR, remaining around 26.6% between 1996 and 2002, declining to 18.6% in 2005, and stabilising thereafter. In IQVIA DA Germany, prevalence declined from 11.8% in 1993 to 2.2% in 2020, with a modest increase to 3.6% in 2024. In BIFAP, prevalence decreased from 6.5% in 2005 to 0.7% in 2015, remained stable until 2022, and increased to 5.3% in 2024, while in SIDIAP, it decreased from approximately 6.0% in 2010–2013 to 1.2% in 2015, followed by an increase to 3.5% in 2024. In CPRD GOLD, prevalence increased from 2.1% in 1988 to a peak of 26.8% in 2001, decreased thereafter, and increased again to 17.7% in 2024.

Annual prevalence patterns differed by HRT formulation, route of administration, and HRT type. Oestrogen-containing products were the most frequently used HRT formulation, particularly in recent years, while the annual prevalence of fixed combination products containing oestrogen and progestogen decreased markedly across data sources. When stratified by route of administration, systemic HRT use generally decreased over time, whereas local HRT use increased or remained stable in several data sources, with DK-DHR showing the most pronounced shift from systemic to local HRT. When stratified by HRT type, natural HRT was the predominant HRT type across most data sources and broadly followed overall prevalence trends, whereas synthetic HRT was more prominent in earlier years in SIDIAP and BIFAP. Sensitivity analyses yielded higher absolute estimates but consistent temporal patterns.

Duration of HRT use among postmenopausal women

Treatment duration varied across HRT products and data sources. Across HRT products, the median treatment duration ranged from 11 days for ethinylestradiol-containing products in IQVIA DA Germany to 534 days for fixed combination product containing oestradiol and norethisterone in DK-DHR and 1,826 days for levonorgestrel intrauterine devices (IUD) in CPRD GOLD, DK-DHR, and IQVIA DA Germany. A higher number of prescription records/dispensings was generally observed for HRT with longer duration of use. Age-stratified analyses indicated substantial heterogeneity across data sources, with generally longer duration of use among women aged <50 years. Sensitivity analyses without application of a maximum allowed treatment gap between consecutive prescriptions resulted in longer total treatment durations but showed patterns consistent with the main analysis.

HRT treatment patterns

Treatment patterns following HRT initiation were characterised by the predominant use of single products and limited switching between HRT treatments across data sources. First-line treatments varied across data sources, with natural vaginal and oral oestrogen products predominating in DK-DHR and oral, vaginal, topical, and other natural oestrogen formulations contributing substantially in CPRD GOLD. Combination therapies accounted for only a small proportion of first-line treatments across all data sources.

The majority of postmenopausal women followed a single-step treatment pathway, indicating no treatment changes during follow-up. Among women who changed treatment, switches most commonly involved alternative oestrogen-containing or progestogen-containing products. When stratified by prespecified calendar periods, treatment patterns shifted over time, with increasing use of vaginal oestrogen in some data sources and greater diversification of HRT formulations in more recent years, while transitions between oestrogen-containing products remained the most common treatment change.

Discussion

This multi-country study characterised HRT use, treatment duration, and treatment patterns among postmenopausal women across five European healthcare data sources, including 1.37 million new HRT users and 12.1 million postmenopausal women not using HRT. Across data sources, the overall annual prevalence of HRT use declined after 2002 and increased modestly in more recent years. A higher prevalence among women aged <50 years likely reflects treatment of premature or early menopause. Oestrogen-containing products were the most frequently recorded HRT products, although concomitant use of separately prescribed progestogens was not assessed in the prevalence analyses, and the use of oestrogen-only products should not be interpreted as the absence of concurrent progestogen treatment. A clear shift from systemic to local HRT products, particularly vaginal oestrogens, was observed over time, and natural HRT products predominated across most data sources.

Treatment duration varied across HRT products and data sources and was generally longer among women aged <50 years in several data sources. Treatment patterns over up to 10 years following initiation were largely characterised by single products and a high proportion of single-step treatment pathways. When treatment changes were identified, they primarily involved switching between different oestrogen-containing products, while concomitant use of oestrogen and progestogen remained uncommon.

Together, these results provide a quantitative and population-based overview of contemporary HRT utilisation across Europe and define a clear exposure context for subsequent comparative safety and effectiveness analyses.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study deliverable	Timelines (planned*)	Timelines (actual)
Final Study Protocol	January 2026	23 January 2026
Creation of Analytical code	December 2025/January 2026	January 2026/March 2026
Execution of Analytical Code on the data	January 2026	March 2026
Draft Study Report	February 2026	31 March 2026
Final Study Report	March 2026	5 May 2026

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources and deliverables review rounds.

6. RATIONALE AND BACKGROUND

Menopausal symptoms induce significant burden on the health and quality of life of women. Central among these are vasomotor symptoms (VMS; also referred to as hot flashes), typically accompanied by sweating and flushing.[1-3] Up to 80% of menopausal women experience VMS to some degree, with 20–30% reporting severe symptoms.[1-4] These vasomotor symptoms cause anxiety and sleep disruption and tend to be the most lifestyle limiting symptom in many women.[4]

Currently, there are several treatment options for oestrogen deficiency symptoms in postmenopausal women. Hormone replacement therapy (HRT) is the treatment of choice for vasomotor and genitourinary syndrome of menopause.[4] Other commonly used therapies for the relief of oestrogen deficiency symptoms are non-hormonal treatments requiring a prescription (selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, venlafaxine, paroxetine, citalopram), over the counter treatments (calcium/vitamin D, soy products), and lifestyle changes (exercise, diet).[2, 4] Treatment options are often combined to relieve symptoms.[2, 4]

HRT may contain oestrogen alone or an oestrogen and a progestogen combination, which can be taken continuously or sequentially for 14 days. The choice of combining therapy with a progestogen is dependent on the presence of an intact uterus.[5-7] Oestrogens in HRT are available as oral conjugated equine oestrogens, synthetic ethinyl oestradiol, micronized oestradiol, and oestradiol valerate.[6] It is worth noting that the availability of the different forms varies between countries. In some countries the most widely prescribed oestrogen formulations might be oral preparations and, in others, transdermal oestradiol.[8] In some cases, testosterone is added to oestrogen and progestogen therapy to address symptoms, such as reduced libido and sexual dysfunction, in postmenopausal women.[9]

Some studies have suggested that the absolute risks of adverse events in postmenopausal women receiving HRT depend on several factors, including age at initiation and timing in relation to menopause, HRT type, dosage, duration, and route of administration.[4, 10-13]

To our knowledge, studies describing contemporary patterns and trends of HRT utilisation in European countries are very scarce. A better understanding of the use of these medicines in real-world settings can help inform regulatory decision making.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What are the patterns and trends in hormone replacement therapy (HRT) utilisation among postmenopausal women in European countries over the past three decades?

Objectives

The specific objectives of this study were:

1. To describe the demographic and clinical characteristics of postmenopausal women, including age, body mass index (BMI), smoking status, concomitant conditions, and HRT used at treatment initiation, where applicable. Estimates were stratified by HRT status and presented for selected calendar years.
2. To estimate annual prevalence of HRT use among postmenopausal women, overall and stratified by HRT formulation, route of administration (systemic or local), and HRT type (natural or synthetic) (if feasible). Estimates were additionally stratified by age group at treatment initiation.
3. To estimate the duration of HRT use among postmenopausal women initiating HRT, overall and by age group.
4. To describe HRT treatment patterns among postmenopausal women over ten years following HRT initiation, including **a)** treatment grouped by HRT formulation, type, and route of administration and **b)** treatment grouped by HRT formulation and route of administration, stratified by prespecified calendar periods.

8. RESEARCH METHODS

8.1. Study design

A cohort study was conducted using routinely collected health data from 5 data sources from 4 countries across Europe.

The study comprised:

- A patient-level characterisation was conducted to address *objective 1*, describing the demographic and clinical characteristics of postmenopausal women, stratified into two cohorts: new HRT users and non-HRT users (**Figure 1a**). For new HRT users, the type of HRT used at treatment initiation was also described.
- A population-level drug utilisation study was conducted to address *objective 2*, to estimate the annual prevalence of HRT use among postmenopausal women, overall and stratified by formulations, route of administration, and type of HRT (if feasible) (**Figure 1b**).
- A patient-level drug utilisation study was conducted to address *objectives 3* and *4*, estimating HRT duration among postmenopausal women and describing treatment patterns (**Figure 1c**).

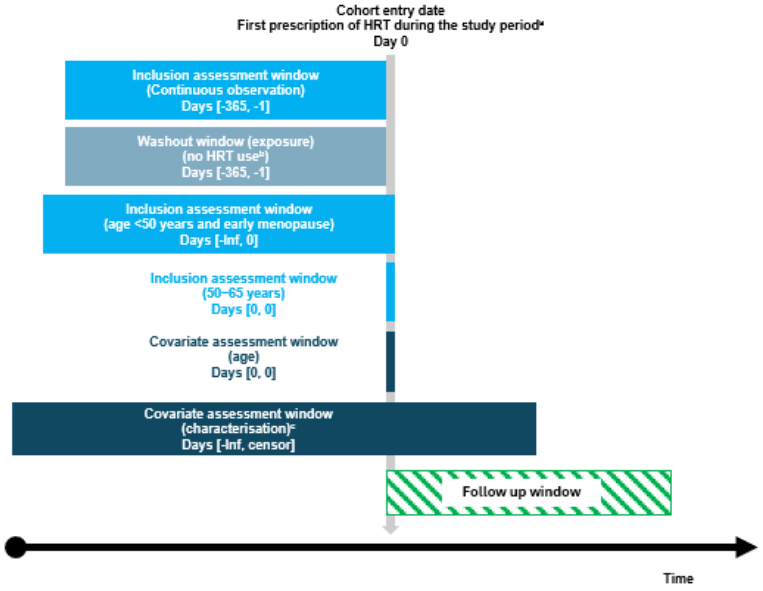


Figure 1a. Graphical depiction of the study design for *objective 1*.

a. Characterisation was done for non-HRT users as well. Non-HRT users: i) women aged 50 to 65 years and ii) women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause with no record of HRT prescription prior to the cohort entry date [-Inf, 0]. These women were followed up until the earliest of HRT prescription record, loss to follow-up, death, end of observation period (the latest available data). They may have contributed to both cohorts (HRT user and non-users). Their person-time was attributed accordingly. Characterisation for HRT users and non-HRT users was reported for selected calendar years.
b. Applied to women aged 50 to 65 years, and to women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause initiating HRT.
c. Clinical characteristics were described, including body mass index (BMI), smoking status, menopause, and concomitant conditions. For new HRT users, the type of HRT used at treatment initiation was also described.

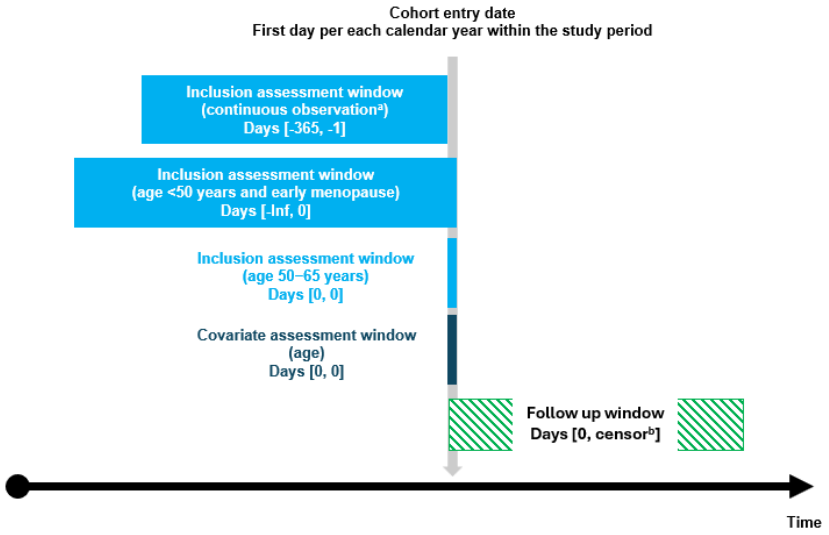


Figure 1b. Graphical depiction of the study design for *objective 2*.

a. Applied to women aged 50 to 65 years, and to women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause.
b. Death, loss to follow-up, end of data source availability, end of each calendar year (i.e. 31 December), or end of the study period (31/12/2024).

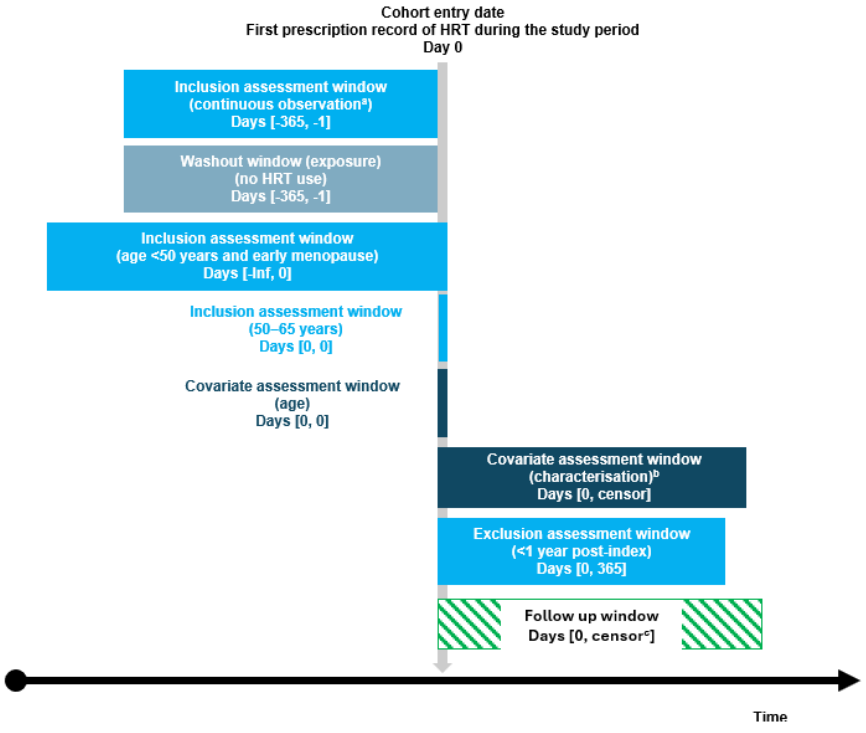


Figure 1c. Graphical depiction of the study design for *objectives 3* and *4*.

a. Applied to women aged 50 to 65 years, and women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause.
b. Characterisation of HRT treatment pattern overall and stratified by prespecified calendar periods.
c. Death, loss to follow-up, end of data source availability, or end of the study period (31/12/2024).

8.2. Follow-up

For the characterisation of postmenopausal HRT users *(objective 1)*, patient-level drug utilisation of treatment duration *(objective 3)*, and the description of treatment patterns *(objective 4),* follow-up started on the date of the first recorded prescription of HRT during the study period, provided the woman met the postmenopausal definition (either by age 50–65 or <50 with a history of premature/early menopause), had no prior HRT exposure in 365 days before this date, and had at least 365 days of data visibility prior to this date. For *objectives 1* and *3*, the end of follow-up was defined as the earliest of loss to follow-up, death, or the end of the observation period (the latest available data). For *objective 4,* follow-up was additionally censored at 10 years after the date of HRT initiation.

For the characterisation of postmenopausal non-HRT users *(objective 1)*, follow-up started once women met the inclusion criteria (either age 50–65 years or <50 years with a history of premature/early menopause with no record of prior HRT prescription at any time prior to the cohort entry and at least 365 days of data visibility). The end of follow-up was defined as the earliest of a HRT prescription record, loss to follow-up, death, or the end of the observation period (the latest available data). Women entered the HRT user cohort upon initiation of HRT and could subsequently contribute person-time to the HRT user cohort. As a result, women may have contributed person-time to both the HRT user and non-HRT user cohorts.

For the calculation of population-level drug utilisation *(objective 2),* follow-up started on the respective date of the latest of the following: i) the date from which data quality was considered sufficient, or ii) date at which they had 365 days of prior history, provided that women met the postmenopausal definition (either by age 50–65 or <50 with a history of premature/early menopause). The end of follow-up was defined as the earliest of loss to follow-up, death, or the end of the observation period (the latest available data), whichever occurred first.

An example of entry and exit into the denominator population is shown in **Figure 2**. In this example, person ID 1 already had sufficient prior history before the study start date, and the observation period ended after the study end date, so this individual contributed during the entire study period. Person IDs 2 and 4 only entered the study when they had sufficient prior history. Person ID 3 left when exiting the data source (the end of the observation period). Lastly, person ID 5 had two observation periods in the data source. The first period contributed time from the study start until the end of the observation period, the second started contributing time again once sufficient prior history was reached and exited at the study end date.

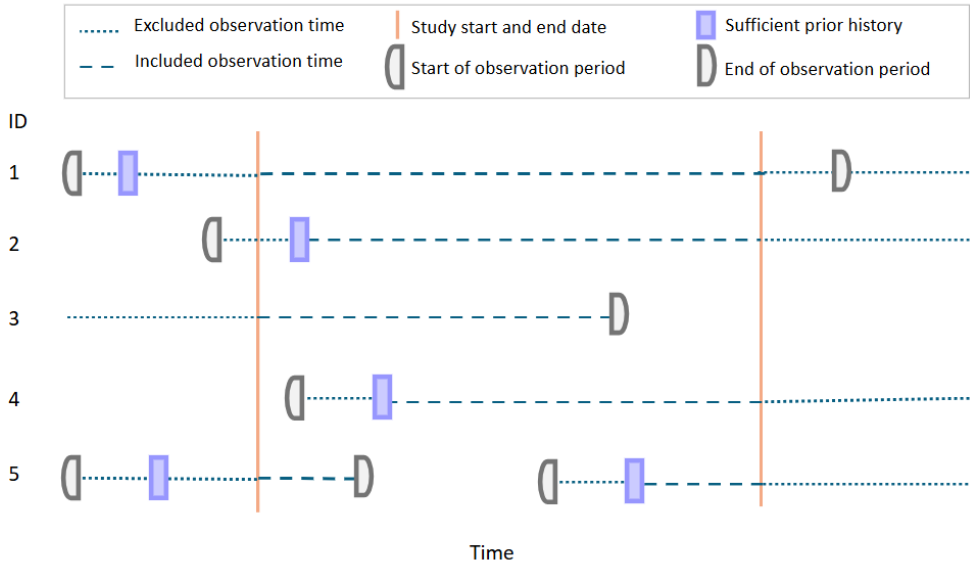


Figure 2. Included observation time for the denominator population.

8.3. Study population with inclusion and exclusion criteria

For the characterisation of postmenopausal HRT users *(objective 1)*, patient-level drug utilisation to estimate treatment duration *(objective 3)*, and the description of treatment patterns *(objective 4),* the study population included postmenopausal women initiating HRT during the study period.

Inclusion criteria:

- Postmenopausal women, defined as i) women aged 50 to 65 years and ii) women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause (primary ovarian insufficiency/failure, premature menopause, early menopause, bilateral oophorectomy, or hysterectomy with ovarian removal).
- First record of HRT prescription between the earliest available date at which the data was of sufficient quality until 31 December 2024 (or the most recent data available).
- No prior HRT exposure in the 365 days prior to HRT initiation.
- At least 365 days of data visibility prior to HRT initiation.

Exclusion criteria:

- Postmenopausal women initiating HRT <365 days before the end of data availability in the respective data source (to ensure sufficient follow-up) *(objectives 3* and *4).*

The final concept sets used for the identification of premature or early menopause are described in **Table S2** (**ANNEX IV**).

For the characterisation of postmenopausal non-HRT users *(objective 1),* the study population included:

Inclusion criteria:

- Postmenopausal women, defined as i) women aged 50 to 65 years and ii) women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause (primary ovarian insufficiency/failure, premature menopause, early menopause, bilateral oophorectomy, or hysterectomy with ovarian removal).
- No record of HRT prescription prior to or at the cohort entry date [-Inf, 0].

- At least 365 days of data visibility prior to the cohort entry date.

Exclusion criteria:

- No formal exclusion criteria were applied beyond the inclusion criteria.

For the calculation of the prevalence of HRT use *(objective 2)*, the study population included postmenopausal women.

Inclusion criteria:

- Postmenopausal women, defined as i) women aged 50 to 65 years and ii) women aged <50 years with a prior history of conditions or procedures indicating premature or early menopause (primary ovarian insufficiency/failure, premature menopause, early menopause, bilateral oophorectomy, or hysterectomy with ovarian removal).
- At least 365 days of data visibility prior to the index date.

Exclusion criteria:

- No formal exclusion criteria were applied beyond the inclusion criteria.

8.4. Study setting and data sources

This study was conducted using routinely collected data from 1 registry and 4 primary care data sources of the DARWIN EU® Data Network from 4 European countries. All data were *a priori* mapped to the Observational Medical Outcomes Partnership (OMOP) Common data Model (CDM).

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
3. Spain: Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP)
4. Spain: The Information System for Research in Primary Care (SIDIAP)
5. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Information on the data sources included in this study is provided in **Table 1** and **ANNEX I**.

Data sources selection

These data sources fulfilled the criteria required in terms of data quality, completeness, timeliness, and representativeness for drug utilisation study while covering different regions of Europe (**ANNEX II**).

Table 1. Data source justification and key characteristics.

Country	Data source acronym	Type of data	Oestrogens (n)[a]	Oestrogens + progesterone (n)[a]	Data collection start year	Source release date	Last observation period month	Follow-up duration (days), median (IQR)[b]	IRB approval
Denmark	DK-DHR	Registry	2,700	254,800	1995	10/04/2025	11/2024	7,920 (2,610–10,900)	Umbrella protocol
Germany	IQVIA DA Germany	Outpatient GP Care	29,400	36,500	1992	17/10/2025	06/2025	116 (0–1,610)	Not needed
Spain	BIFAP	GP and hospital care	3,800	–	2001 (good quality 2005)	31/12/2024	12/2024	2,550 (2,050–5,430)	1–3 months
Spain	SIDIAP	Outpatient GP Care	2,100	33,000	2006 (good quality from 2010)	26/11/2025	12/2024	5,670 (2,220–6,390)	1–3 months
The United Kingdom	CPRD GOLD	Outpatient GP Care	251,800	800	1987	01/01/2025	07/2025	2,150 (727–4,930)	Umbrella protocol

Abbreviations: DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; GP = general practitioner; IQR = interquartile range.
[a] = person counts at drug era (as generated from drug era).
[b] = median follow-up of the first observation period.
– = not available.

8.5. Study period

The study period was from the earliest available date at which the data was of sufficient quality until 31 December 2024 (or the most recent data available) for each contributing data source. The start of data availability varied across the contributing data sources, with the earliest available data dating back to 1987. Detailed information about the study period per data source can be found in **Section 8.4**.

8.6. Variables

8.6.1. Exposure

The primary exposure was defined as a prescription or dispensing record of HRT, representing the first recorded prescription in the study period with no prior HRT use in the 365 days prior to the index date.

To define treatment episodes, sequential prescriptions were grouped, allowing for a maximum gap of 90 days between the end of one prescription and the start of the next.

The final concept sets used for the identification of exposures are described in **ANNEX IV.** These codes were refined during study execution, following the standard DARWIN EU® phenotyping processes, which involve the review of code lists and the review of phenotypes after their execution in the participating data sources. Phenotypes were defined following input from the European Medicines Agency (EMA).

8.6.2. Outcome

The outcomes were as follows:

- Characterisation of postmenopausal HRT users and non-HRT users *(objective 1).*
- Annual prevalence of HRT use among postmenopausal women, including formulations, route of administration, and type of HRT (if feasible) (*objective 2).*
- Duration of HRT treatment among postmenopausal women *(objective 3).*
- Treatment patterns following HRT treatment initiation *(objective 4).*

8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

The variables for characterisation of postmenopausal HRT users or non-HRT users *(objective 1)* were as follows:

- Demographic and clinical characteristics:
  - Age groups (<50 years, 50–60 years, and >60 years)
  - BMI (reported as median with interquartile ranges)
  - Smoking status (reported as smoker/non-smoker/missing, if feasible)
  - Received menopause diagnosis (yes/no)
  - Type of HRT used at treatment initiation (where applicable):
    - G03CA Natural and semisynthetic oestrogens, plain
      - Oestradiol
      - Oestriol
      - Conjugated equine oestrogens
      - Esterified oestrogens
      - Chlorotrianisene

- Ethinylestradiol
- Oestrone
- Promestriene

- G03CB Synthetic oestrogens, plain
  - Dienestrol
  - Methallenestril
  - Moxestrol
  - Diethylstilbestrol
- G03CC Oestrogen combinations
  - Conjugated oestrogens and bazedoxifene
- G03CX Other oestrogens
  - Tibolone
- G03D Progestogens, plain
  - Micronised progesterone
  - Hydroxyprogesterone
  - Dydrogesterone
  - Norethisterone
  - Levonorgestrel (intrauterine device (IUD))
  - Medroxyprogesterone acetate
  - Lynestrenol
  - Megestrol/Medrogestone
  - Nomegestrol
- G03EA Oestrogen and androgen, fixed combination
  - Oestradiol; Testosterone
  - Esterified oestrogens; methyltestosterone
  - Conjugated oestrogens; methyltestosterone
  - Testosterone; oestrogen
  - Prasterone; oestrogen
- G03F Progestogen and oestrogens, fixed combinations
  - Oestradiol; Levonorgestrel
  - Oestradiol; Medroxyprogesterone
  - Oestradiol; Norethisterone
  - Oestradiol; Dydrogesterone
  - Oestradiol; Progesterone

        - Oestradiol; Drospirenone
        - Conjugated oestrogens; Medroxyprogesterone
    - Androgen, progestogens, and oestrogens, fixed combinations
        - Oestradiol; Norethindone; Testosterone
- Concomitant conditions (reported as N (%)):
    - Cardiovascular disease
    - Hypertension
    - Diabetes mellitus
    - Dyslipidaemia
    - Metabolic syndrome
    - Osteoporosis
    - Depression
    - Anxiety
    - Sleep disorders
    - Uterus status:
        - Hysterectomised
        - Intact uterus*

*In Real-World Data, an intact uterus is rarely explicitly recorded. Unless a hysterectomy procedure or a diagnosis code indicating the absence of the uterus is present in the patient's history, the uterus is assumed to be intact.

Characterisation was performed on 1 July for the following calendar years: 1990, 1995, 2000, 2005, 2010, 2015, 2020, and 2024.

Assessment windows:

- Demographic characteristics (age): on calendar date [0, 0]
- Clinical characteristics: 1 year prior to the calendar date [-365, 0]
- Concomitant conditions: any time prior to the calendar date [-Inf, 0] and 1 year post the calendar date [1, 365]

Large-scale characterisation: the top 10 most frequent diagnostic codes (comorbidities) or prescribed medications (comedication) were assessed at the pre-selected mid-year calendar date [0,0], 1 year prior to this calendar date [-365, 0] and 1 year post this date [1, 365].

The covariates considered in the analyses estimating prevalence of HRT *(objective 2)* were as follows:

- Calendar year
- Age groups: <50 years, 50–60 years, and >60 years
- HRT formulation: oestrogen product; combination product oestrogen and progestogen; combination product oestrogen and androgen; combination product oestrogen, progestogen, and androgen; or other
- Route of administration (based on the effect): systemic (oral tablets, transdermal patches,

subcutaneous implants, topical sprays, gels, and creams), local (vaginal creams, tablets, rings), unspecified

- HRT type: natural, synthetic (if feasible)

The covariates for calculation of treatment duration of HRT *(objective 3)* included:

- Age groups (<50 years, 50–60 years, and >60 years)

The variables for the characterisation of treatment patterns *(objective 4)* included current and historical HRT, capturing changes over the past three decades. These variables included:

- Treatment grouped by HRT formulation, type, and route of administration:
  - Natural oestrogen, oral
  - Natural oestrogen, topical
  - Natural oestrogen, vaginal
  - Natural oestrogen, other/missing
  - Synthetic oestrogen, oral
  - Synthetic oestrogen, topical
  - Synthetic oestrogen, vaginal
  - Synthetic oestrogen, other/missing
  - Progestogens (no combinations)
  - Testosterone (no combinations)
- Treatment grouped by HRT formulation and route of administration, stratified by prespecified calendar periods:
  - Oestrogen, oral
  - Oestrogen, topical
  - Oestrogen, vaginal
  - Oestrogen, other
  - Progestogens (no combinations)
  - Testosterone (no combinations)
  - Treatment patterns of HRT initiators were stratified into the following calendar periods, depending on when treatment was initiated: i) 1995–2002, ii) 2003–2015, iii) 2016–2024.

The final concept sets used for the identification of covariates are described in **ANNEX IV**. These codes were refined during study execution, following the standard DARWIN EU® phenotyping processes, which involve the review of code lists and the review of phenotypes after their execution in the participating data sources. Phenotypes were defined following input from the European Medicines Agency (EMA).

8.7. Study size

No sample size was calculated, as this was a drug utilisation study with a descriptive design, and no formal hypothesis testing was performed. The study relied on existing routinely collected data to estimate the prevalence of HRT use and to describe treatment patterns. Thus, the sample size was driven by the availability of data for eligible individuals within the included data sources.

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources, and quality control checks were performed. Once all the tests passed (see **ANNEX III**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the results, aggregated by default.

The study results of all data sources were checked, after which they were made available to the study team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Main statistical methods

R-packages

The patient-level characterisation of postmenopausal HRT users and non-HRT users *(objective 1)* was estimated based on OMOP CDM mapped data using the *CohortCharacteristics* R package (https://darwin-eu.github.io/CohortCharacteristics/). The population-level utilisation of HRT in postmenopausal women *(objective 2)* was assessed using the *IncidencePrevalence* R package (https://darwin-eu.github.io/IncidencePrevalence/), the patient-level utilisation including treatment duration *(objective 3)* was estimated using the *DrugUtilisation* R package (https://github.com/darwin-eu/DrugUtilisation), and the patient-level characterisation of treatment patterns *(objective 4)* was described using the *TreatmentPatterns* R package (https://github.com/darwin-eu-dev/TreatmentPatterns). All packages are publicly available and developed by DARWIN EU®.

Characterisation of postmenopausal women *(objective 1)*

Postmenopausal women, including HRT users and non-HRT users, were characterised in terms of age, clinical characteristics (BMI, smoking status, code for menopause), and concomitant conditions. Clinical characteristics were reported as counts and proportions for categorical variables and as medians with interquartile ranges (IQR) for continuous variables. For clinical characteristics, the percentage of unknowns was also reported. Among HRT users, the type of treatment used at initiation was also described using counts and proportions.

Prevalence of HRT use in postmenopausal women *(objective 2)*

Prevalence was calculated as the annual period prevalence, which summarised the total number of postmenopausal women who are using HRT (*objective 2*) during a given calendar year divided by the total number of postmenopausal women at risk of initiating HRT in that year. This measure reflected the proportion of individuals exposed to HRT during a specified time interval. Binomial 95% confidence intervals were computed to quantify statistical uncertainty around the prevalence estimates.

An illustration of the calculation of period prevalence is shown below in **Figure 3**. Between time t+2 and t+3, two of the five study participants were users of the pre-selected drug of interest, giving a prevalence of 40%. Meanwhile, for the period t to t+1, all five participants also had some observation time during the year, with one of the five study participants being a user of the pre-selected drug of interest.

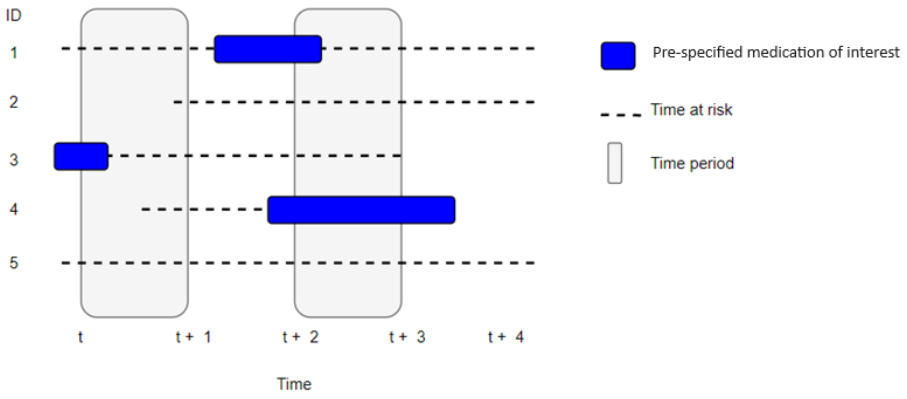


Figure 3. Period prevalence example.

Annual prevalence estimates were presented overall, and by age group (<50 years, 50–60 years, >60 years). If applicable, age at the index date was calculated using January 1 of the year of birth as proxy for the actual date of birth. Date/month is either not present or cannot be made available for governance reasons. If available, date is often set to first of the month for patient's privacy.

Drug exposure calculations

Drug eras were defined as follows: HRT exposure started at the date of the new prescription within the study period after a washout interval of 365 days. For each prescription record, the estimated duration of use was retrieved from the drug exposure table in the data source, using both the start and end dates. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) when the gap between the end of one prescription record and the start of the next prescription was ≤90 days.

Figure 4 provides an illustrative example of how different gap era values affect the construction of drug episodes. Setting the gap era to 0 resulted in three distinct episodes, only joining overlapping records. When the gap era was set to any value between 1 and 28 days, consecutive episodes separated by gaps within this range were merged, resulting in two episodes. If the gap era exceeded 29 days, all records were collapsed into a single continuous episode. For the purpose of this study, the gap era was set to ≤90 days. Therefore, in the illustrative example shown in **Figure 4**, prescription records corresponding to drug exposures 1, 2, 3, and 4 would be aggregated into a single continuous episode.

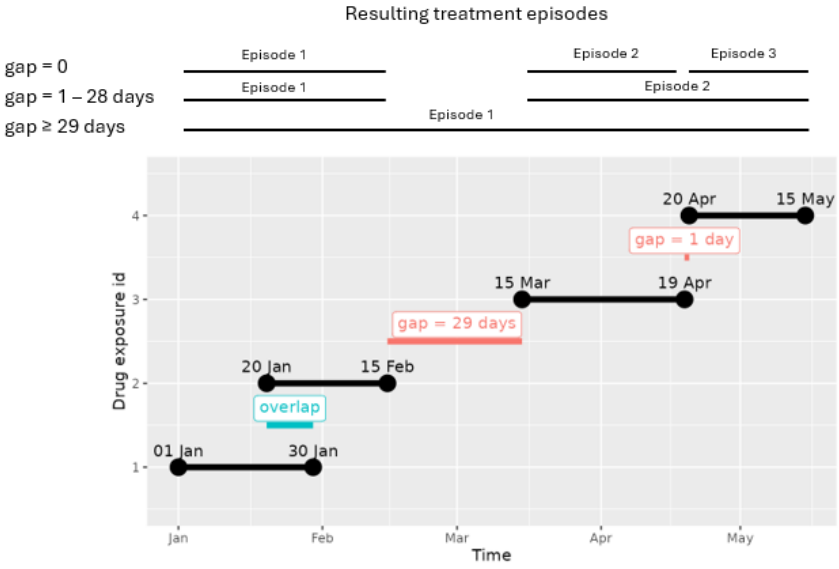


Figure 4. Gap era joint mode.

Bold horizontal black lines in the lower panel represent drug episodes recorded at different times. Prescribing/dispensing records of the same drug are illustrated on the Y-axis and time in months on the X-axis. The upper panel shows the resulting treatment episodes derived from the same exposure history using different gap era definitions (gap = 0 days, gap = 1–28 days, and gap ≥ 29 days). The figure illustrates how the same exposure records merge into three, two, or one treatment episode(s), depending on the applied gap era, respectively. The gap era of ≤90 days used in this study corresponds to the bottom scenario.

If two exposures overlapped, the overlap time was considered exposed to the first exposure. No time was added at the end of the combined drug era to account for the overlap. If two exposures started at the same date, the overlapping period was considered exposed to both.

Treatment duration *(objective 3)*

Treatment duration was calculated as the total number of days an individual was continuously exposed to HRT among postmenopausal women. Exposure periods were constructed by merging consecutive prescription records, allowing for treatment gaps of up to 90 days between prescriptions. The duration was calculated from the start date of the first prescription to the end date of the last prescription within the merged sequence. In accordance with OMOP CDM conventions, treatment duration was derived from drug_exposure_start_date and drug_exposure_end_date, with an additional day included to account for both the start and end dates in the exposure period (https://ohdsi.github.io/CommonDataModel/cdm54.html#drug_exposure/). This calculation assumed accurate recording of both dates, as discrepancies could affect the estimated duration of exposure time. Continuous exposure is assumed throughout the interval between the start and end dates, allowing for a maximum interruption of 90 days. Periods of drug exposure before the cohort start or after the cohort end date were excluded. Missing exposure data was treated as zero, indicating no exposure during periods with missing information.

End-date availability and derivation varied across data sources. In CPRD GOLD, prescription end dates are not explicitly recorded and are derived during the Extract, Transform, Load (ETL) process using source prescription information on quantity and treatment duration (qty and numdays). Where these data are missing or incomplete, treatment duration is assigned based on the most frequently observed duration for the corresponding product formulation. In the remaining data sources, end dates were derived according to source-specific ETL specifications and available prescription information. End-date inference was applied only where necessary, and the applied method varied by data sources according to source data availability and ETL specifications.

Treatment duration was summarised using descriptive statistics, including minimum, quartiles, and maximum values. Where duration could not be reliably calculated, it was not reported.

Treatment patterns (*objective 4*)

The number and percentage of patients receiving each of the treatment options (**Section 8.6.3.**), as well as treatment combinations, were described in the study population (*objective 4*). Treatment combinations were defined algorithmically based on the drug input cohorts (**Section 8.6.3.**) and prespecified parameters (**Figure 5**). Additionally, Sunburst plots and Sankey diagrams were used to visualise treatment patterns and sequences over time. Sankey diagrams were censored, as described in **Section 8.2**.

To construct treatment pathways, various parameters can be defined in the *TreatmentPatterns* package (**Figure 5**). A summary of decisions to construct individual treatment pathways is provided below. In this context, events labelled A, B, and C refer to the treatments of interest. For a comprehensive description of the steps involved, from extracting information from medical records to generating treatment pathways, please refer to the full methodology in the referenced publication.[14]

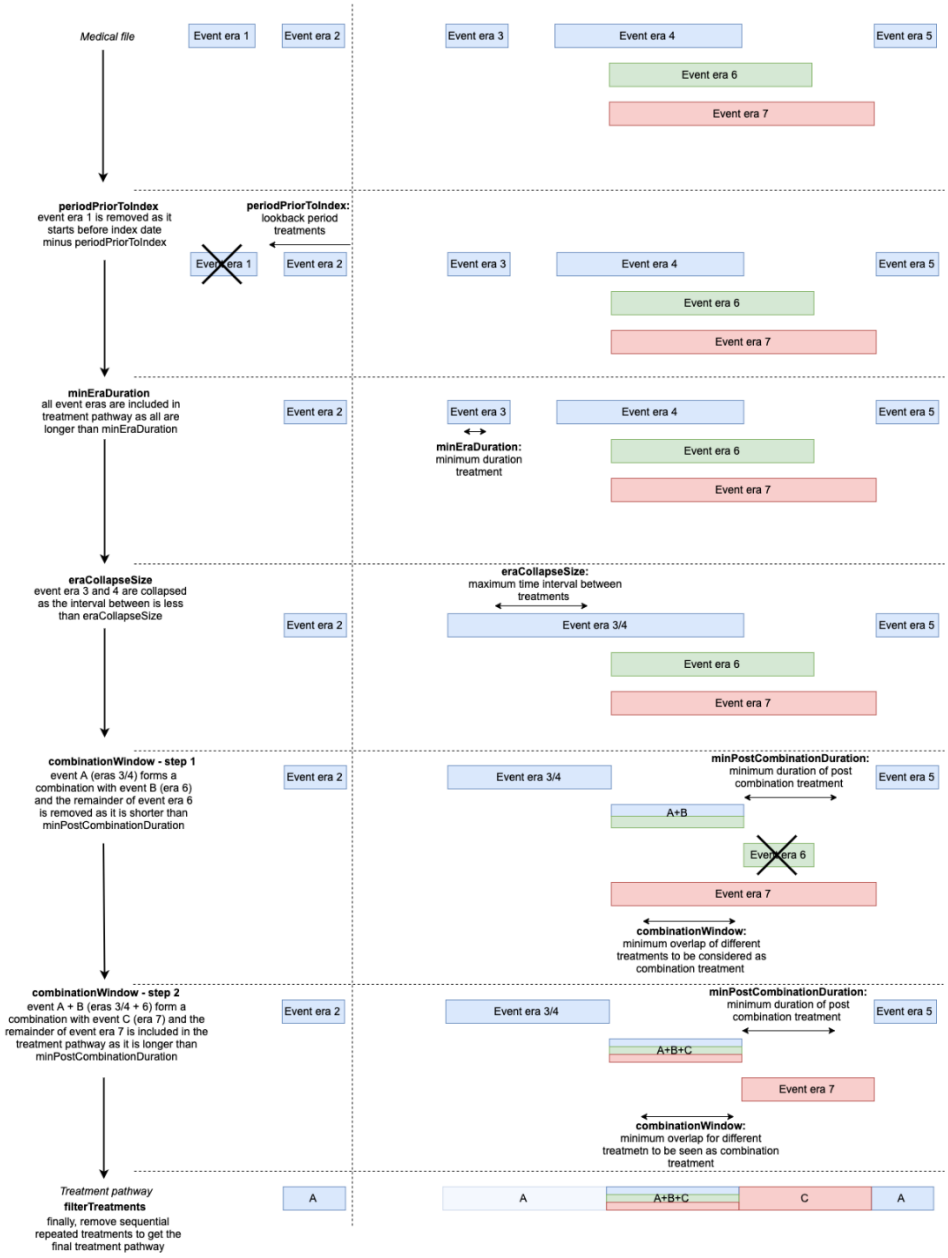


Figure 5. Parameters in the *TreatmentPatterns* package.

The parameters outlined in this study are described in **Table 2**. Treatment pattern parameters were defined based on existing knowledge and were refined following drug exposure diagnostics assessing episode length distributions. HRT is a chronic therapy typically prescribed in monthly or multi-month cycles; therefore, an era collapse size of 90 days accommodated realistic refill gaps without misclassifying temporary interruptions. Based on cohort diagnostics results and in line with clinical practical guidelines, treatment duration for long-acting HRT products was modelled. Specifically, treatment duration was set to 90 days for oestradiol vaginal rings, 6 months for oestradiol implants, and 5 years for intrauterine devices (IUDs).

Table 1. List of pathway settings with description and expected input.

Individual pathway settings		
periodPriorToIndex	The period (number of days) prior to the index date of the target cohort from which treatments should be included	0
minEraDuration	Minimum time an event era should last to be included in the analysis	30
eraCollapseSize	Maximum gap within two eras of the same event cohort which would still allow the eras to be collapsed into one era	90
combinationWindow	Time that two event eras need to overlap to be considered a combination treatment	30
minPostCombinationDuration	Minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	30
filterTreatments	Select which treatments should be included in pathway: first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	Changes
maxPathLength	Maximum number of treatments included in pathway	5
Aggregate pathway settings (post-processing)*		
minCellCount	Minimum number of persons with a specific treatment pathway for the pathway to be included in analysis	5
minCellMethod	Select to completely remove / sequentially adjust (by removing last step as often as necessary) treatment pathways below minCellCount	Adjust
groupCombinations	Select to group all non-fixed combinations in one category 'other' in the sunburst plot	TRUE
addNoPaths	Select to include untreated persons without treatment pathway in the sunburst plot	TRUE

*Aggregate pathway settings are post-processing parameters applied after individual patient-level pathways have been generated. They do not affect the underlying treatment episodes or sequence construction. Instead, they control how pathways are summarised, filtered, and visualised in aggregate outputs.

8.9.2. Missing values

We assumed that the absence of a prescription record in the data source meant that the individual did not receive the respective treatment. Similarly, for assessment of comorbidities, the absence of a diagnostic code for a given condition was interpreted as the absence of recorded evidence of the condition in the data source.

8.9.3. Sensitivity analysis

Sensitivity analyses are presented by means of **Table 3**. To assess the robustness of prevalence findings (*objective 2)* and treatment patterns (*objective 4)*, study objectives were reevaluated using a narrower population definition, which included: 1) women aged 50 to 65 years with a diagnosis of menopause or menopause-specific symptoms and 2) women under 50 years with a history of conditions or procedures indicating premature or early menopause.

Table 2. Sensitivity analyses – rationale, strengths, and limitations.

Sensitivity analysis	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Assessment of narrow study population definition	The definition of the study population varied. The sensitivity population added a clinical confirmation layer by requiring a diagnosis of menopause or menopause-specific symptoms for women aged 50–65.	To test the robustness of findings.	Greater specificity in identifying true postmenopausal women.	Women with documented menopause diagnoses or symptoms may differ from others in healthcare use or comorbidities, which could introduce bias. This analysis relied heavily on the accuracy and completeness of diagnostic coding. If menopause-related conditions are under-recorded or inconsistently coded across data sources, the sensitivity population may not fully represent the intended subgroup.

8.10. Deviations from the protocol

Deviation number	Protocol version	Date	Section of study protocol	Deviation	Reason
1	V5.0	05/03/2026	Methods	Definition of postmenopausal women not on HRT extended to include women aged <50 years with a prior history of conditions or procedures indicating early menopause.	To align with the definition of postmenopausal women on HRT.
2	V5.0	04/03/2026	Methods, results	Progestogen only formulations removed from the list of prespecified HRT formulations (*objective 2*).	Progestogen-only products are commonly used for indications other than menopause.
3	V5.0	05/03/2026	Methods, results	Additional objective added to treatment patterns analyses (*objective 4*). Treatment patterns were assessed using i) HRT grouped by formulation, type, and route, and ii) HRT grouped by formulation and route of administration, stratified by prespecified calendar periods: i) 1995–2002, ii) 2003–2015, iii) 2016–2024. Age stratified analyses were removed.	To improve the clinical and regulatory interpretability of treatment pattern analyses following a change in the study requestor.
4	V5.0	29/05/2026	Methods, results	Results from IQVIA DA Germany for the treatment patterns analysis (*objective 4*) were excluded.	The treatment patterns analysis in IQVIA DA Germany captured 44% of the HRT users based on the prespecified parameters. In line with EMA guidance, these results were excluded due to limited population coverage.
5	V5.0	29/05/2026	Methods, results	Additional descriptive analyses were conducted to contextualise the treatment duration results, including assessment of follow-up time, the number of prescriptions contributing to	These post hoc analyses were performed to support interpretation of the treatment duration findings and to evaluate the impact of

Deviation number	Protocol version	Date	Section of study protocol	Deviation	Reason
				treatment duration estimates, and estimation of total treatment duration without applying the prespecified treatment gap used for treatment era construction.	methodological assumptions, particularly the prespecified treatment gap.

9. RESULTS

The full set of results for this study is available through an interactive web-application Shiny app at EUPAS1000000821.

Characterisation of postmenopausal women

9.1.1. Participants

A total of 1,370,059 postmenopausal women met the inclusion criteria and were retained in the final population of new HRT users (DK-DHR: 448,956; IQVIA DA Germany: 146,740; BIFAP: 328,352, SIDIAP: 105,950; CPRD GOLD: 340,061), while 12,100,035 postmenopausal women met the inclusion criteria and were included in the final study population of non-HRT users (DK-DHR: 1,248,826; IQVIA DA Germany: 3,542,357; BIFAP: 4,550,113; SIDIAP: 1,179,632; CPRD GOLD: 1,579,107) during the study period (**Table 4**).

Table 3. Attrition table for HRT initiators and non-HRT users.

Variable	DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
HRT users					
Postmenopausal women: i) women aged 50 to 65 years, or ii) women aged <50 years with prior premature/early menopause	1,616,103	3,658,173	4,686,792	1,277,193	1,953,858
Postmenopausal women with at least one HRT prescription record	820,647	260,657	459,135	182,730	712,674
At least 365 days of data visibility prior to HRT initiation	739,989	209,068	407,430	161,284	533,410
Cohort start during the pre-specified study period per data source	739,989	209,068	405,749	126,872	533,410
At least one HRT prescription on or after postmenopausal women cohort entry	614,389	192,352	351,776	110,670	439,007
First recorded HRT prescription is the index date	448,956	146,740	328,352	105,950	340,061
Non-HRT users					
Postmenopausal women: i) women aged 50 to 65 years, or ii) women aged <50 years with prior premature/early menopause	1,616,103	3,658,173	4,686,792	1,277,193	1,953,858
No record of HRT prescription prior to or at the cohort entry date	1,248,826	3,542,357	4,550,113	1,179,632	1,579,107

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD.

9.1.2. Demographic and clinical characteristics

In general, the number of postmenopausal women classified as HRT users and non-HRT users included in each selected calendar year increased over time across all data sources, as women could contribute to multiple years while under observation (**Table 5**). In both cohorts, women aged 50 to 60 years and above 60 years predominately contributed to cohort composition, while women aged below 50 years represented a small proportion of the study population.

The proportion of postmenopausal women with a recorded diagnosis of menopause varied across data sources and cohorts of HRT users and non-HRT users over time (**Table S5**). Overall, across all data sources and selected calendar years, menopause diagnoses were more frequently recorded among HRT users than non-HRT users. In DK-DHR, recorded menopause diagnoses were uncommon, typically below 0.5% in non-HRT users and ranging from 0.9% in 2010 to 1.3% in 2024 in HRT users. In contrast, IQVIA DA Germany showed substantially higher recording of menopause diagnoses among HRT users, ranging from 6.3% to 14.3% across calendar years, compared with consistently low proportions (<1%) among non-HRT users. In BIFAP, higher recording of menopause diagnoses was observed among HRT users, ranging from 2.2% to 13.5%, while menopause diagnoses were recorded in 1.2% to 3.4% of non-HRT users. SIDIAP showed higher recording of menopause diagnoses among HRT users, ranging from 4% to 8%, compared to proportions in non-HRT users, typically below 4%. CPRD GOLD showed substantially higher recording of menopause diagnoses among HRT users, ranging from 2.8% to 30.3% across calendar years, compared with consistently lower proportions between 0.6% and 2.2% in non-HRT users. In IQVIA DA Germany, BIFAP, and CPRD GOLD, higher recordings of menopause diagnoses among HRT users were observed before 2010 than in more recent years.

BMI was assessed in the year prior to prespecified calendar years, and information was available for very few women, with missingness exceeding 90% in DK-DHR and IQVIA DA Germany across most calendar years and remaining substantial in BIFAP (78–88%), SIDIAP (56–75%), and CPRD GOLD (60–86%), irrespective of HRT use. Median BMI values were broadly comparable between HRT users and non-HRT users over time across the data sources (**Table S5**). In DK-DHR, median BMI generally ranged between approximately 24–26 kg/m^2 among HRT users and 24–27 kg/m^2 among non-HRT users. In IQVIA DA Germany, median BMI was approximately 26 kg/m^2 among HRT users and ranged between 26–29 kg/m^2 among non-HRT users whereas in BIFAP and SIDIAP, median values were approximately 28–29 kg/m^2 in both cohorts. In CPRD GOLD, median BMI was approximately 25–28 kg/m^2 among HRT users and ranged between approximately 26–29 kg/m^2 among non-HRT users.

Similarly, data on smoking status were sparsely recorded across all data sources and calendar years, with majority of records classified as missing (exceeding 99% in DK-DHR, IQVIA DA Germany, and BIFAP, and 91% in SIDIAP, irrespective of HRT status), except in CPRD GOLD where smoking status was recorded among approximately 30% to 50% of both HRT users and non-HRT users between 2005 and 2024 (**Table S5**). In CPRD GOLD, the proportion of current smokers ranged between approximately 3% and 11% of postmenopausal women, without substantial differences between HRT users and non-HRT users.

Treatment at HRT initiation was characterised by substantial variation in the specific products used across data sources and calendar years (**Table 6**). Among HRT users still under observation on 1 July of each selected year, treatments were described using the product category recorded at the HRT initiation date. Results describe the specific HRT product and do not account for concomitant use of separately prescribed progestogens or other HRT products. Therefore, initiation with an oestrogen-containing product should not be interpreted as evidence of oestrogen monotherapy. In DK-DHR, initiation patterns shifted over time, with early calendar years characterised by a mix of fixed oestrogen and progestogen combination products and a substantial contribution of older formulations (e.g. dienestrol). The most frequently prescribed products characterised in 2000 included oestradiol-containing products (40.5%), fixed combination products containing oestradiol and norethisterone (22.5%), and dienestrol-containing products (19.1%).

Other treatments, such as oestriol-containing products (8.7%) and fixed combination products containing oestradiol and medroxyprogesterone (4.6%), were less frequent. The frequency of oestradiol-containing products was 75.5% in 2024, accompanied by a decline in dienestrol-based products and fixed combination products containing oestrogen and progestogen. Fixed combination products containing oestradiol and norethisterone declined from 22.5% in 2000 to 11.7% in 2024, and fixed combinations products containing oestradiol and medroxyprogesterone from 4.6% to 1.7% over the same period. In IQVIA DA Germany, treatment at initiation showed a distinct pattern in 1995, with most frequently prescribed products including conjugated oestrogens (20.7%), oestradiol (25.1%), oestriol (17.3%), and fixed combination products containing oestradiol and norethisterone (22.3%). Over time, oestriol-containing products became increasingly dominant, exceeding 50% by 2020 and 2024, while oestradiol-containing products slightly increased but remained relatively stable. Fixed combination products containing oestradiol and norethisterone or oestradiol and levonorgestrel, declined over time, with each accounting for <6% by 2024. In BIFAP, promestriene (59.9%), oestriol (19.8%), tibolone (8.1%), and oestradiol-containing products (6.5%) were most evident in 2005. These frequencies slightly fluctuated over time, and, while the use of promestriene-containing products increased to 65.1% in 2015 before decreasing to 29.3% in 2024, the use of oestriol-containing products increased to 43.3% in 2024. Tibolone-containing products were recorded among 9.1% and oestradiol-containing products among 12.6% in 2024. In SIDIAP, promestriene-containing products, a local oestrogen therapy, were the most frequently characterised in 2010 and 2015 (78.3%–87.0%), with a gradual decline thereafter to 60.4% in 2024. From 2010 onwards, oestradiol-containing products increased from 1.9% to 6.1% in 2024, while oestriol-containing products showed an increase from 12.6% to 22.0% in 2024. Fixed combination products containing oestrogen and progestogen remained uncommon in SIDIAP, each contributing ≤3.6% across all observed calendar years. In CPRD GOLD, dienestrol (23.3%), conjugated oestrogens (15.7%), and oestradiol-containing products (12.0%) were most frequently prescribed in 1990, while reported use of oestradiol (38.0%), oestradiol and norethisterone (28.3%), and oestriol-containing products (24.1%) were most frequent in 2024. Across all data sources and calendar years, initiation with therapies containing androgen or fixed oestrogen and androgen combination products was absent, with most such categories consistently recording zero or suppressed counts (<5). These products include conjugated oestrogens and testosterone, oestradiol and testosterone, and related combination products. Similarly, several historically used oestrogen formulations (e.g. diethylstilbestrol, methallenestril, moxestrol products) were either not prescribed or contributed negligibly to initiation patterns throughout follow-up.

Table **4**. Distribution of age among postmenopausal women stratified by HRT use across selected calendar years by data source.

	HRT users				non-HRT users			
	N	<50	50–60	>60	N	<50	50-60	>60
DK-DHR								
2000	80,548	954	56,239	23,355	390,142	336	242,177	147,629
2005	146,478	1,408	74,906	70,164	438,166	737	242,568	194,861
2010	205,892	1,520	57,726	146,646	493,412	1,130	252,545	239,737
2015	265,727	1,647	58,022	206,058	548,428	1,153	276,399	270,876
2020	321,499	1,705	59,979	259,815	587,167	1,020	284,388	301,759
2024	359,799	1,646	61,452	296,701	604,738	926	279,170	324,642
IQVIA DA Germany								
1995	1,231	12	911	308	33,434	184	23,591	9,659
2000	3,572	77	1,973	1,522	104,177	446	59,450	44,281

	HRT users				non-HRT users			
	N	<50	50–60	>60	N	<50	50-60	>60
2005	7,966	83	3,571	4,312	287,476	530	151,149	135,797
2010	21,104	306	9,495	11,303	720,453	1,494	407,021	311,938
2015	40,371	590	17,143	22,638	1,274,729	2,042	697,69	574,997
2020	62,329	905	24,580	36,844	1,675,662	2,374	862,518	810,770
2024	63,520	1,005	24,537	37,978	1,226,648	1,877	551,816	672,955
BIFAP								
2005	1,730	8	1,259	463	148,805	85	105,429	43,291
2010	33,176	306	17,933	14,937	954,968	1,266	565,203	388,499
2015	65,119	931	24,988	39,200	1,665,167	2,435	914,976	747,756
2020	91,028	1,379	24,459	65,190	3,214,794	4,522	1,794,129	1,416,143
2024	260,535	2,659	103,563	154,313	3,674,126	7,972	1,836,609	1,829,545
SIDIAP								
2010	8,705	48	5,609	3,048	489,098	1,076	342,934	145,088
2015	48,929	435	20,122	28,372	625,071	2,592	370,239	252,240
2020	64,116	889	13,774	49,453	803,515	3,010	421,317	379,188
2024	95,546	1,233	20,232	74,081	927,930	3,424	448,536	475,970
CPRD GOLD								
1990	459	5	368	86	14,113	10	9,260	4,843
1995	19,291	893	12,801	5,597	96,634	335	50,765	45,534
2000	47,086	1,908	26,834	18,344	193,120	510	103,327	89,283
2005	85,190	3,138	41,831	40,221	471,461	1,343	268,821	201,297
2010	118,207	4,088	46,311	67,808	597,586	2,070	315,172	280,344
2015	118,990	3,017	43,643	72,330	556,404	1,670	289,375	265,359
2020	104,750	1,611	40,110	63,029	404,105	989	196,128	206,988
2024	121,006	1,144	51,924	67,938	299,425	552	117,458	181,415

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; N = number of individuals.
Values are reported as N.
Age categories are not mutually exclusive; individuals may contribute to different age categories across calendar years as they age.

Table 6. HRT used at treatment initiation in postmenopausal women across selected calendar years by data source.

Variable	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
DK-DHR								
HRT users	–	–	80,548	146,478	205,892	265,727	321,499	359,799
conjugated_oestrogens_and_bazedoxifene	–	–	0	0	0	0	<5	<5
conjugated_oestrogens_plain	–	–	182 (0.23)	182 (0.12)	166 (0.08)	156 (0.06)	130 (0.04)	108 (0.03)
dienestrol_plain	–	–	15,344 (19.05)	23,057 (15.74)	21,558 (10.47)	19,565 (7.36)	17,003 (5.29)	14,287 (3.97)
diethylstilbestrol_plain	–	–	0	<5	0	0	0	0
ethinylestradiol_plain	–	–	353 (0.44)	522 (0.36)	606 (0.29)	667 (0.25)	661 (0.21)	640 (0.18)
levonorgestrel_iud	–	–	17 (0.02)	47 (0.03)	85 (0.04)	135 (0.05)	285 (0.09)	454 (0.13)
lynestrenol_plain	–	–	34 (0.04)	70 (0.05)	90 (0.04)	85 (0.03)	78 (0.02)	71 (0.02)
medroxyprogesterone_acetate_plain	–	–	1,092 (1.36)	1,498 (1.02)	1,603 (0.78)	1,682 (0.63)	1,942 (0.6)	2,417 (0.67)
norethisterone_plain	–	–	1,281 (1.59)	2,007 (1.37)	1,936 (0.94)	1,858 (0.70)	1,864 (0.58)	1,953 (0.54)
oestradiol_drospirenone	–	–	0	26 (0.02)	199 (0.10)	275 (0.10)	316 (0.10)	315 (0.09)
oestradiol_levonorgestrel	–	–	3,167 (3.93)	5,092 (3.48)	5,328 (2.59)	5,135 (1.93)	4,855 (1.51)	4,516 (1.26)
oestradiol_medroxyprogesterone	–	–	3,720 (4.62)	5,761 (3.93)	6,107 (2.97)	6,318 (2.38)	6,319 (1.97)	6,036 (1.68)
oestradiol_plain	–	–	32,624 (40.50)	68,910 (47.04)	119,009 (57.8)	175,193 (65.93)	230,121 (71.58)	271,802 (75.54)
oestriol_plain	–	–	7,034 (8.73)	13,090 (8.94)	18,580 (9.02)	20,442 (7.69)	20,753 (6.46)	20,177 (5.61)
oestradiol_norethisterone	–	–	18,087 (22.45)	29,363 (20.05)	33,839 (16.44)	37,518 (14.12)	41,213 (12.82)	42,035 (11.68)
progesterone_plain	–	–	0	<5	6 (0.00)	10 (0.00)	21 (0.01)	749 (0.21)
tibolone_plain	–	–	690 (0.86)	1,475 (1.01)	1,637 (0.8)	1,709 (0.64)	1,769 (0.55)	1,719 (0.48)
IQVIA DA Germany								

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HRT users	–	1,231	3,572	7,966	21,104	40,371	62,329	63,520
conjugated_oestrogens_medroxyprogesterone	–	0	125 (3.50)	237 (2.98)	256 (1.21)	265 (0.66)	212 (0.34)	129 (0.20)
conjugated_oestrogens_plain	–	255 (20.71)	477 (13.35)	738 (9.26)	1,000 (4.74)	1,076 (2.67)	948 (1.52)	604 (0.95)
dydrogesterone_plain	–	<5	<5	<5	13 (0.06)	78 (0.19)	179 (0.29)	171 (0.27)
ethinylestradiol_plain	–	<5	<5	13 (0.16)	75 (0.36)	74 (0.18)	56 (0.09)	26 (0.04)
hydroxyprogesterone_plain	–	0	0	<5	<5	<5	<5	<5
levonorgestrel_iud	–	0	0	0	0	<5	7 (0.01)	7 (0.01)
lynestrenol_plain	–	<5	<5	<5	7 (0.03)	<5	<5	<5
medrogestone_plain	–	10 (0.81)	17 (0.48)	16 (0.20)	13 (0.06)	6 (0.01)	<5	<5
medroxyprogesterone_acetate_plain	–	21 (1.71)	35 (0.98)	26 (0.33)	18 (0.09)	37 (0.09)	56 (0.09)	42 (0.07)
nomegestrol_plain	–	0	0	0	0	0	0	8 (0.01)
norethisterone_plain	–	23 (1.87)	97 (2.72)	146 (1.83)	219 (1.04)	167 (0.41)	126 (0.20)	65 (0.10)
oestradiol_drospirenone	–	0	0	51 (0.64)	341 (1.62)	504 (1.25)	559 (0.90)	396 (0.62)
oestradiol_dydrogesterone	–	0	27 (0.76)	246 (3.09)	715 (3.39)	1,660 (4.11)	2,610 (4.19)	2,571 (4.05)
oestradiol_levonorgestrel	–	92 (7.47)	227 (6.35)	309 (3.88)	892 (4.23)	2,130 (5.28)	2,934 (4.71)	2,110 (3.32)
oestradiol_medroxyprogesterone	–	31 (2.52)	179 (5.01)	323 (4.05)	404 (1.91)	435 (1.08)	416 (0.67)	253 (0.40)
oestradiol_plain	–	309 (25.10)	980 (27.44)	2,210 (27.74)	6,262 (29.67)	11,302 (28.00)	17,825 (28.60)	21,191 (33.36)
oestradiol_prasterone	–	61 (4.96)	100 (2.80)	165 (2.07)	310 (1.47)	301 (0.75)	220 (0.35)	140 (0.22)
oestradiol_progesterone	–	<5	<5	<5	0	0	0	434 (0.68)
oestriol_plain	–	213 (17.30)	550 (15.4)	1,578 (19.81)	7,335 (34.76)	18,160 (44.98)	31,637 (50.76)	32,476 (51.13)
oestradiol_norethisterone	–	274 (22.26)	894 (25.03)	1,985 (24.92)	3,330 (15.78)	4,379 (10.85)	4,946 (7.94)	3,575 (5.63)
progesterone_plain	–	<5	14 (0.39)	77 (0.97)	278 (1.32)	1,015 (2.51)	3,938 (6.32)	8,552 (13.46)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
tibolone_plain	–	0	40 (1.12)	165 (2.07)	327 (1.55)	401 (0.99)	442 (0.71)	320 (0.50)
BIFAP								
HRT users	**–**	**–**	**–**	**1,730**	**33,176**	**65,119**	**91,028**	**260,535**
conjugated_oestrogens_plain	–	–	–	5 (0.29)	207 (0.62)	251 (0.39)	246 (0.27)	223 (0.09)
ethinylestradiol_plain	–	–	–	41 (2.37)	898 (2.71)	2,080 (3.19)	3,849 (4.23)	7,635 (2.93)
lynestrenol_plain	–	–	–	0	0	<5	<5	<5
medrogestone_plain	–	–	–	<5	6 (0.02)	6 (0.01)	6 (0.01)	<5
medroxyprogesterone_acetate_plain	–	–	–	10 (0.58)	93 (0.28)	212 (0.33)	330 (0.36)	419 (0.16)
megesterol_plain	–	–	–	0	0	<5	<5	8 (0.00)
nomegestrol_plain	–	–	–	0	0	<5	72 (0.08)	186 (0.07)
norethisterone_plain	–	–	–	21 (1.21)	436 (1.31)	997 (1.53)	1,653 (1.82)	4,645 (1.78)
oestradiol_plain	–	–	–	113 (6.53)	1,475 (4.45)	3,136 (4.82)	5,730 (6.29)	32,724 (12.56)
oestriol_plain	–	–	–	343 (19.83)	5,729 (17.27)	5,888 (9.04)	13,382 (14.70)	112,718 (43.26)
oestradiol_norethisterone	–	–	–	63 (3.64)	1,020 (3.07)	2,364 (3.63)	4,091 (4.49)	8,726 (3.35)
progesterone_plain	–	–	–	18 (1.04)	192 (0.58)	512 (0.79)	1,049 (1.15)	3,587 (1.38)
promestriene_plain	–	–	–	1,037 (59.94)	19,857 (59.85)	42,387 (65.09)	49,934 (54.86)	76,266 (29.27)
tibolone_plain	–	–	–	140 (8.09)	4,197 (12.65)	9,323 (14.32)	14,165 (15.56)	23,581 (9.05)
SIDIAP								
HRT users	**–**	**–**	**–**	**–**	**8,705**	**48,929**	**64,116**	**95,546**
conjugated_oestrogens_and_bazedoxifene	–	–	–	–	0	0	500 (0.78)	532 (0.56)
conjugated_oestrogens_plain	–	–	–	–	22 (0.25)	58 (0.12)	55 (0.09)	51 (0.05)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
lynestrenol_plain	–	–	–	–	<5	<5	<5	<5
medroxyprogesterone_acetate_plain	–	–	–	–	8 (0.09)	44 (0.09)	60 (0.09)	81 (0.08)
megesterol_plain	–	–	–	–	0	<5	<5	<5
norethisterone_plain	–	–	–	–	9 (0.10)	27 (0.06)	35 (0.05)	44 (0.05)
oestradiol_medroxyprogesterone	–	–	–	–	9 (0.10)	61 (0.12)	98 (0.15)	108 (0.11)
oestradiol_plain	–	–	–	–	166 (1.91)	985 (2.01)	2,081 (3.25)	5,819 (6.09)
oestriol_plain	–	–	–	–	1,099 (12.62)	1,100 (2.25)	5,643 (8.8)	21,012 (21.99)
oestradiol_norethisterone	–	–	–	–	158 (1.82)	980 (2.00)	1,819 (2.84)	3,388 (3.55)
progesterone_plain	–	–	–	–	20 (0.23)	133 (0.27)	388 (0.61)	1,004 (1.05)
promestriene_plain	–	–	–	–	6,824 (78.39)	42,553 (86.97)	48,900 (76.27)	57,724 (60.41)
tibolone_plain	–	–	–	–	484 (5.56)	3,331 (6.81)	5,191 (8.10)	7,239 (7.58)
CPRD GOLD								
HRT users	**459**	**19,291**	**47,086**	**85,190**	**118,207**	**118,990**	**104,750**	**121,006**
conjugated_oestrogens_and_bazedoxifene	0	0	0	0	0	0	<5	<5
conjugated_oestrogens_medroxyprogesterone	0	0	2,680 (5.69)	4,963 (5.83)	5,893 (4.99)	5,065 (4.26)	2,967 (2.83)	2,013 (1.66)
conjugated_oestrogens_plain	72 (15.69)	3,191 (16.54)	6,180 (13.12)	9,661 (11.34)	10,359 (8.76)	6,662 (5.60)	2,694 (2.57)	1,614 (1.33)
dienestrol_plain	107 (23.31)	3,188 (16.53)	6,088 (12.93)	5,630 (6.61)	3,978 (3.37)	1,675 (1.41)	419 (0.40)	188 (0.16)
diethylstilbestrol_plain	0	<5	10 (0.02)	11 (0.01)	6 (0.01)	<5	<5	0
dydrogesterone_plain	<5	53 (0.27)	83 (0.18)	105 (0.12)	101 (0.09)	57 (0.05)	11 (0.01)	7 (0.01)
ethinylestradiol_plain	<5	127 (0.66)	130 (0.28)	139 (0.16)	95 (0.08)	52 (0.04)	20 (0.02)	16 (0.01)
levonorgestrel_iud	0	0	<5	9 (0.01)	26 (0.02)	65 (0.05)	160 (0.15)	320 (0.26)
medroxyprogesterone_acetate_plain	<5	57 (0.30)	114 (0.24)	125 (0.15)	131 (0.11)	101 (0.08)	90 (0.09)	260 (0.21)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
megesterol_plain	0	0	0	<5	<5	<5	<5	<5
norethisterone_plain	<5	82 (0.43)	246 (0.52)	340 (0.40)	366 (0.31)	266 (0.22)	155 (0.15)	138 (0.11)
oestradiol_drospirenone	0	0	0	0	46 (0.04)	73 (0.06)	84 (0.08)	49 (0.04)
oestradiol_dydrogesterone	0	0	538 (1.14)	1,977 (2.32)	2,625 (2.22)	2,540 (2.13)	3,262 (3.11)	3,205 (2.65)
oestradiol_levonorgestrel	14 (3.05)	791 (4.10)	1,622 (3.44)	2,214 (2.60)	2,367 (2.00)	1,729 (1.45)	1,520 (1.45)	1,559 (1.29)
oestradiol_medroxyprogesterone	0	0	487 (1.03)	1,002 (1.18)	1,053 (0.89)	851 (0.72)	599 (0.57)	469 (0.39)
oestradiol_plain	55 (11.98)	2,619 (13.58)	7,837 (16.64)	17,006 (19.96)	30,255 (25.59)	38,784 (32.59)	39,747 (37.94)	45,993 (38.01)
oestriol_plain	20 (4.36)	1,311 (6.80)	3,331 (7.07)	13,000 (15.26)	27,048 (22.88)	30,673 (25.78)	25,913 (24.74)	29,184 (24.12)
oestradiol_norethisterone	16 (3.49)	1,375 (7.13)	7,090 (15.06)	14,613 (17.15)	19,482 (16.48)	20,569 (17.29)	22,632 (21.61)	34,243 (28.30)
progesterone_plain	0	0	8 (0.02)	11 (0.01)	30 (0.03)	73 (0.06)	519 (0.50)	7,349 (6.07)
tibolone_plain	0	1,540 (7.98)	2,775 (5.89)	4,792 (5.63)	5,477 (4.63)	4,342 (3.65)	2,772 (2.65)	2,130 (1.76)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = hormonal replacement therapy; N = number of individuals; – = no data available; <5 = cell counts <5.
Values are reported as N (%).
HRT with zero counts across all calendar years were excluded from the table.

9.1.3. Concomitant conditions

Across all data sources, the frequency of prespecified concomitant conditions, recorded **any time prior to the prespecified mid-year characterisation date in each selected calendar year**, increased over time in both HRT users and non-HRT users (**Table 7**). In DK-DHR and BIFAP, HRT users consistently showed higher frequencies than non-HRT users for several conditions, particularly hypertension, dyslipidaemia, osteoporosis, depression, and sleep disorders, with differences becoming more pronounced in later years. In DK-DHR, hypertension and dyslipidaemia were recorded in over 40% of HRT users based on characterisation in 2024 compared with approximately 30% among non-HRT users in 2024, while osteoporosis and sleep disorders were roughly two-fold more common in HRT users (20.7% vs 10.6% and 34.9% vs 22.5%, respectively). In BIFAP, dyslipidaemia was recorded in 45.7% of HRT users compared to 36.8% of non-HRT users and osteoporosis in 14.3% of HRT users compared to 8.4% of non-HRT users for example. In IQVIA DA Germany, records of cardiometabolic conditions were common in both cohorts, with hypertension remaining stable over time at around 20–29%. Differences between HRT users and non-HRT users were generally modest. Records of dyslipidaemia and osteoporosis were more frequent among HRT users in earlier calendar years, while in later years it converged across cohorts. Recorded frequencies of anxiety and sleep disorders increased over time in both cohorts and were consistently more prevalent among HRT users. In SIDIAP, the frequency of several conditions was higher among HRT users compared with non-HRT users, especially in later years. HRT users had higher recorded prevalence of anxiety (44.5% vs 35.8%), hypertension (32.0% vs 25.8%), dyslipidaemia (26.9% vs 19.6%), osteoporosis (19.6% vs 9.5%), and sleep disorders (30.7% vs 19.2%) based on characterisation in 2024. Although both BIFAP and SIDIAP are Spanish data sources, they cover different populations, with BIFAP including multiple Spanish regions and SIDIAP restricted to Catalonia. Similarly, in CPRD GOLD, frequency of several conditions was higher among HRT users compared with non-HRT users. For example, HRT users had higher recorded prevalence of anxiety (16.7% vs 10.7%), depression (24.0% vs 15.7%), hypertension (23.9% vs 22.7%), dyslipidaemia (7.8% vs 6.3%), osteoporosis (6.3% vs 5.3%), and sleep disorders (13.0% vs 7.9%) based on characterisation in 2024. Across all data sources, a record of hysterectomy was uncommon, and more than 88% of women were classified as having an intact uterus in both HRT initiators and non-HRT users throughout calendar years.

The frequency of prespecified concomitant conditions recorded within one year after the prespecified mid-year characterisation date was lower than that observed when considering any time prior time window (**Table S6**). This pattern was consistent for both HRT users and non-HRT users and across calendar years, reflecting the shorter observation window. Nevertheless, differences between cohorts remained broadly similar to those observed before the characterisation date.

Table 7. Concomitant conditions of postmenopausal women recorded any time prior to the prespecified calendar date, stratified by HRT use across selected calendar years by data source.

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR								
HRT users								
Concomitant conditions								
· Anxiety	–	–	740 (0.92)	2,396 (1.64)	5,200 (2.53)	9,680 (3.64)	15,454 (4.81)	20,488 (5.69)
· Cardiovascular disease	–	–	1,688 (2.10)	5,788 (3.95)	11,619 (5.64)	18,842 (7.09)	25,800 (8.02)	30,110 (8.37)
· Depression	–	–	1,417 (1.76)	14,622 (9.98)	38,410 (18.66)	59,666 (22.45)	78,008 (24.26)	92,140 (25.61)
· Diabetes mellitus	–	–	1,599 (1.99)	6,694 (4.57)	14,579 (7.08)	24,566 (9.24)	32,570 (10.13)	41,100 (11.42)
· Diabetes mellitus type 2	–	–	1,198 (1.49)	4,232 (2.89)	10,667 (5.18)	20,043 (7.54)	27,315 (8.50)	35,699 (9.92)
· Dyslipidaemia	–	–	913 (1.13)	16,540 (11.29)	59,870 (29.08)	94,557 (35.58)	122,535 (38.11)	153,518 (42.67)
· Hypertension	–	–	2,679 (3.33)	18,831 (12.86)	52,313 (25.41)	90,031 (33.88)	128,361 (39.93)	155,770 (43.29)
· Metabolic syndrome	–	–	0	0	0	0	0	0
· Osteoporosis	–	–	1,347 (1.67)	7,870 (5.37)	21,379 (10.38)	39,742 (14.96)	57,469 (17.88)	74,360 (20.67)
· Sleep disorders	–	–	101 (0.13)	13,282 (9.07)	42,601 (20.69)	70,401 (26.49)	100,887 (31.38)	125,406 (34.85)
Uterus status:								
· Hysterectomised	–	–	59 (0.07)	303 (0.21)	750 (0.36)	1,504 (0.57)	2,226 (0.69)	2,639 (0.73)
· Intact uterus*	–	–	80,489 (99.93)	146,175 (99.79)	205,142 (99.64)	264,223 (99.43)	319,273 (99.31)	357,160 (99.27)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	–	2,347 (0.60)	5,564 (1.27)	11,113 (2.25)	19,882 (3.63)	30,281 (5.16)	37,690 (6.23)
· Cardiovascular disease	–	–	8,507 (2.18)	16,092 (3.67)	23,262 (4.71)	28,855 (5.26)	32,060 (5.46)	32,621 (5.39)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Depression	–	–	4,755 (1.22)	29,884 (6.82)	67,645 (13.71)	96,308 (17.56)	114,194 (19.45)	124,728 (20.63)
· Diabetes mellitus	–	–	9,084 (2.33)	21,861 (4.99)	34,086 (6.91)	45,851 (8.36)	54,042 (9.20)	64,584 (10.68)
· Diabetes mellitus type 2	–	–	6,658 (1.71)	13,230 (3.02)	23,752 (4.81)	36,306 (6.62)	43,592 (7.42)	53,693 (8.88)
· Dyslipidaemia	–	–	3,748 (0.96)	41,853 (9.55)	110,010 (22.3)	139,736 (25.48)	154,004 (26.23)	178,818 (29.57)
· Hypertension	–	–	11,518 (2.95)	47,189 (10.77)	99,818 (20.23)	138,371 (25.23)	171,131 (29.15)	190,724 (31.54)
· Metabolic syndrome	–	–	0	0	0	0	0	0
· Osteoporosis	–	–	3,103 (0.80)	14,201 (3.24)	30,139 (6.11)	45,906 (8.37)	55,491 (9.45)	64,327 (10.64)
· Sleep disorders	–	–	321 (0.08)	24,846 (5.67)	62,532 (12.67)	91,011 (16.59)	117,367 (19.99)	136,206 (22.52)
Uterus status:								
· Hysterectomised	–	–	43 (0.01)	102 (0.02)	146 (0.03)	206 (0.04)	222 (0.04)	219 (0.04)
· Intact uterus*	–	–	390,099 (99.99)	438,064 (99.98)	493,266 (99.97)	548,222 (99.96)	586,945 (99.96)	604,519 (99.96)
IQVIA DA Germany								
HRT users								
Concomitant conditions								
· Anxiety	–	67 (5.44)	381 (10.67)	899 (11.29)	2,117 (10.03)	4,992 (12.37)	9,478 (15.21)	11,967 (18.84)
· Cardiovascular disease	–	58 (4.71)	172 (4.82)	378 (4.75)	793 (3.76)	1,420 (3.52)	2,247 (3.61)	2,673 (4.21)
· Depression	–	62 (5.04)	291 (8.15)	680 (8.54)	1,581 (7.49)	3,279 (8.12)	5,724 (9.18)	6,654 (10.48)
· Diabetes mellitus	–	71 (5.77)	284 (7.95)	684 (8.59)	1,619 (7.67)	3,132 (7.76)	4,837 (7.76)	5,434 (8.55)
· Diabetes mellitus type 2	–	13 (1.06)	56 (1.57)	265 (3.33)	802 (3.80)	1,734 (4.30)	2,897 (4.65)	3,266 (5.14)
· Dyslipidaemia	–	229 (18.60)	680 (19.04)	1,378 (17.30)	2,653 (12.57)	4,235 (10.49)	5,949 (9.54)	6,974 (10.98)
· Hypertension	–	250 (20.31)	842 (23.57)	1,955 (24.54)	5,431 (25.73)	10,388 (25.73)	15,713 (25.21)	16,496 (25.97)
· Metabolic syndrome	–	0	0	0	0	0	0	0

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Osteoporosis	–	180 (14.62)	582 (16.29)	1,050 (13.18)	2,110 (10.00)	3,359 (8.32)	4,541 (7.29)	4,925 (7.75)
· Sleep disorders	–	101 (8.20)	349 (9.77)	801 (10.06)	2,161 (10.24)	4,533 (11.23)	8,151 (13.08)	10,370 (16.33)
Uterus status:								
· Hysterectomised	–	0	<5	42 (0.53)	108 (0.51)	178 (0.44)	234 (0.38)	230 (0.36)
· Intact uterus*	–	1,231 (100)	3,571 (99.97)	7,924 (99.47)	20,996 (99.49)	40,193 (99.56)	62,095 (99.62)	63,290 (99.64)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	764 (2.29)	2,908 (2.79)	9,430 (3.28)	32,212 (4.47)	78,525 (6.16)	149,273 (8.91)	181,219 (14.77)
· Cardiovascular disease	–	1,065 (3.19)	3,080 (2.96)	8,166 (2.84)	20,566 (2.85)	39,579 (3.10)	61,112 (3.65)	67,220 (5.48)
· Depression	–	904 (2.70)	2,882 (2.77)	9,319 (3.24)	32,188 (4.47)	75,594 (5.93)	138,442 (8.26)	156,001 (12.72)
· Diabetes mellitus	–	1,925 (5.76)	5,909 (5.67)	18,451 (6.42)	48,587 (6.74)	97,516 (7.65)	140,989 (8.41)	142,414 (11.61)
· Diabetes mellitus type 2	–	532 (1.59)	2,183 (2.10)	9,313 (3.24)	28,415 (3.94)	64,141 (5.03)	97,234 (5.80)	103,366 (8.43)
· Dyslipidaemia	–	4,602 (13.76)	12,573 (12.07)	32,844 (11.42)	77,835 (10.80)	136,893 (10.74)	193,376 (11.54)	207,676 (16.93)
· Hypertension	–	6,897 (20.63)	20,325 (19.51)	59,144 (20.57)	149,017 (20.68)	275,269 (21.59)	379,841 (22.67)	356,685 (29.08)
· Metabolic syndrome	–	0	0	0	0	0	0	0
· Osteoporosis	–	2,113 (6.32)	5,668 (5.44)	13,881 (4.83)	34,083 (4.73)	62,390 (4.89)	90,533 (5.40)	92,455 (7.54)
· Sleep disorders	–	1,268 (3.79)	3,322 (3.19)	9,349 (3.25)	27,367 (3.80)	62,796 (4.93)	115,270 (6.88)	136,987 (11.17)
Uterus status:								
· Hysterectomised	–	32 (0.10)	133 (0.13)	404 (0.14)	746 (0.10)	1,055 (0.08)	1,091 (0.07)	889 (0.07)
· Intact uterus*	–	33,402 (99.9)	104,044 (99.87)	287,072 (99.86)	719,707 (99.90)	1,273,674 (99.92)	1,674,571 (99.93)	1,225,759 (99.93)
BIFAP								

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HRT users								
Concomitant conditions								
· Anxiety	–	–	–	28 (1.62)	1,286 (3.88)	3,358 (5.16)	7,146 (7.85)	32,429 (12.45)
· Cardiovascular disease	–	–	–	13 (0.75)	647 (1.95)	2,078 (3.19)	4,168 (4.58)	10,656 (4.09)
· Depression	–	–	–	136 (7.86)	5,372 (16.19)	13,138 (20.18)	20,781 (22.83)	52,658 (20.21)
· Diabetes mellitus	–	–	–	39 (2.25)	2,000 (6.03)	5,569 (8.55)	9,873 (10.85)	28,032 (10.76)
· Diabetes mellitus type 2	–	–	–	29 (1.68)	1,604 (4.83)	4,645 (7.13)	8,735 (9.60)	24,955 (9.58)
· Dyslipidaemia	–	–	–	203 (11.73)	9,154 (27.59)	25,140 (38.61)	41,365 (45.44)	119,126 (45.72)
· Hypertension	–	–	–	149 (8.61)	6,081 (18.33)	16,116 (24.75)	27,678 (30.41)	75,425 (28.95)
· Metabolic syndrome	–	–	–	0	39 (0.12)	90 (0.14)	160 (0.18)	627 (0.24)
· Osteoporosis	–	–	–	108 (6.24)	5,103 (15.38)	11,582 (17.79)	16,939 (18.61)	37,224 (14.29)
· Sleep disorders	–	–	–	94 (5.43)	4,596 (13.85)	13,560 (20.82)	23,932 (26.29)	66,414 (25.49)
Uterus status:								
· Hysterectomised	–	–	–	5 (0.29)	296 (0.89)	950 (1.46)	2,383 (2.62)	8,761 (3.36)
· Intact uterus*	–	–	–	1,725 (99.71)	32,880 (99.11)	64,169 (98.54)	88,645 (97.38)	251,774 (96.64)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	–	–	2,129 (1.43)	17,292 (1.81)	47,038 (2.82)	165,013 (5.13)	337,432 (9.18)
· Cardiovascular disease	–	–	–	1,078 (0.72)	14,093 (1.48)	35,607 (2.14)	76,793 (2.39)	116,812 (3.18)
· Depression	–	–	–	10,133 (6.81)	95,520 (10.00)	198,704 (11.93)	359,924 (11.20)	504,804 (13.74)
· Diabetes mellitus	–	–	–	4,625 (3.11)	55,388 (5.80)	115,536 (6.94)	234,894 (7.31)	334,633 (9.11)
· Diabetes mellitus type 2	–	–	–	3,722 (2.50)	45,954 (4.81)	99,003 (5.95)	198,841 (6.19)	285,605 (7.77)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Dyslipidaemia	–	–	–	16,490 (11.08)	204,096 (21.37)	463,579 (27.84)	867,161 (26.97)	1,350,961 (36.77)
· Hypertension	–	–	–	14,089 (9.47)	155,213 (16.25)	304,407 (18.28)	627,766 (19.53)	906,205 (24.66)
· Metabolic syndrome	–	–	–	45 (0.03)	693 (0.07)	1,433 (0.09)	4,490 (0.14)	7,693 (0.21)
· Osteoporosis	–	–	–	8,010 (5.38)	94,005 (9.84)	159,737 (9.59)	234,972 (7.31)	307,171 (8.36)
· Sleep disorders	–	–	–	6,365 (4.28)	91,550 (9.59)	218,803 (13.14)	416,485 (12.96)	621,006 (16.90)
Uterus status:								
· Hysterectomised	–	–	–	180 (0.12)	2,554 (0.27)	9,425 (0.57)	35,401 (1.10)	60,247 (1.64)
· Intact uterus*	–	–	–	148,625 (99.88)	952,414 (99.73)	1,655,742 (99.43)	3,179,393 (98.9)	3,613,879 (98.36)
SIDIAP								
HRT users								
Concomitant conditions								
· Anxiety	–	–	–	–	1,236 (14.20)	13,233 (27.05)	23,906 (37.29)	42,517 (44.50)
· Cardiovascular disease	–	–	–	–	49 (0.56)	788 (1.61)	1,802 (2.81)	3,743 (3.92)
· Depression	–	–	–	–	704 (8.09)	7,947 (16.24)	13,641 (21.28)	23,259 (24.34)
· Diabetes mellitus	–	–	–	–	294 (3.38)	3,806 (7.78)	6,848 (10.68)	12,332 (12.91)
· Diabetes mellitus type 2	–	–	–	–	289 (3.32)	3,731 (7.63)	6,696 (10.44)	11,920 (12.48)
· Dyslipidaemia	–	–	–	–	942 (10.82)	10,174 (20.79)	15,532 (24.22)	25,734 (26.93)
· Hypertension	–	–	–	–	978 (11.23)	10,471 (21.40)	17,728 (27.65)	30,526 (31.95)
· Metabolic syndrome	–	–	–	–	0	15 (0.03)	58 (0.09)	151 (0.16)
· Osteoporosis	–	–	–	–	803 (9.22)	7,053 (14.41)	11,199 (17.47)	18,719 (19.59)
· Sleep disorders	–	–	–	–	407 (4.68)	7,218 (14.75)	15,329 (23.91)	29,297 (30.66)

Variable	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
Uterus status:								
· Hysterectomised	–	–	–	–	<5	16 (0.03)	27 (0.04)	75 (0.08)
· Intact uterus*	–	–	–	–	8,702 (99.97)	48,913 (99.97)	64,089 (99.96)	95,471 (99.92)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	–	–	–	52,262 (10.69)	132,173 (21.15)	238,311 (29.66)	332,580 (35.84)
· Cardiovascular disease	–	–	–	–	2,580 (0.53)	7,573 (1.21)	14,759 (1.84)	22,514 (2.43)
· Depression	–	–	–	–	29,077 (5.95)	72,346 (11.57)	116,975 (14.56)	154,433 (16.64)
· Diabetes mellitus	–	–	–	–	20,087 (4.11)	47,010 (7.52)	74,520 (9.27)	101,466 (10.93)
· Diabetes mellitus type 2	–	–	–	–	19,458 (3.98)	45,679 (7.31)	70,610 (8.79)	92,682 (9.99)
· Dyslipidaemia	–	–	–	–	43,919 (8.98)	100,610 (16.10)	143,143 (17.81)	181,962 (19.61)
· Hypertension	–	–	–	–	54,418 (11.13)	120,305 (19.25)	182,894 (22.76)	239,365 (25.80)
· Metabolic syndrome	–	–	–	–	11 (0.00)	182 (0.03)	531 (0.07)	1,250 (0.13)
· Osteoporosis	–	–	–	–	24,981 (5.11)	46,273 (7.40)	66,838 (8.32)	88,404 (9.53)
· Sleep disorders	–	–	–	–	15,171 (3.10)	58,159 (9.30)	117,818 (14.66)	178,118 (19.20)
Uterus status:								
· Hysterectomised	–	–	–	–	18 (0.00)	33 (0.01)	64 (0.01)	121 (0.01)
· Intact uterus*	–	–	–	–	489,080 (100)	625,038 (99.99)	803,451 (99.99)	927,809 (99.99)
CPRD GOLD								
HRT users								
Concomitant conditions								
· Anxiety	35 (7.63)	2,247 (11.65)	6,888 (14.63)	13,072 (15.34)	18,579 (15.72)	19,443 (16.34)	16,979 (16.21)	20,165 (16.66)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Cardiovascular disease	5 (1.09)	335 (1.74)	1,261 (2.68)	2,685 (3.15)	4,069 (3.44)	4,658 (3.91)	4,685 (4.47)	5,728 (4.73)
· Depression	40 (8.71)	3,414 (17.70)	9,827 (20.87)	18,009 (21.14)	26,575 (22.48)	28,729 (24.14)	25,620 (24.46)	29,057 (24.01)
· Diabetes mellitus	<5	418 (2.17)	1,506 (3.20)	4,159 (4.88)	7,563 (6.40)	9,003 (7.57)	8,772 (8.37)	10,897 (9.01)
· Diabetes mellitus type 2	<5	200 (1.04)	972 (2.06)	3,404 (4.00)	6,773 (5.73)	8,034 (6.75)	7,651 (7.30)	9,435 (7.80)
· Dyslipidaemia	<5	773 (4.01)	2,723 (5.78)	7,630 (8.96)	14,082 (11.91)	14,064 (11.82)	9,660 (9.22)	9,376 (7.75)
· Hypertension	33 (7.19)	2,730 (14.15)	8,626 (18.32)	19,826 (23.27)	29,549 (25.00)	29,509 (24.80)	24,733 (23.61)	28,884 (23.87)
· Metabolic syndrome	0	0	0	<5	78 (0.07)	76 (0.06)	46 (0.04)	51 (0.04)
· Osteoporosis	<5	608 (3.15)	2,341 (4.97)	4,636 (5.44)	7,447 (6.30)	8,330 (7.00)	7,267 (6.94)	7,598 (6.28)
· Sleep disorders	29 (6.32)	2,091 (10.84)	5,658 (12.02)	11,332 (13.30)	18,180 (15.38)	19,504 (16.39)	15,309 (14.61)	15,737 (13.01)
Uterus status:								
· Hysterectomised	39 (8.50)	2,105 (10.91)	5,603 (11.90)	9,338 (10.96)	12,559 (10.62)	11,529 (9.69)	8,513 (8.13)	8,021 (6.63)
· Intact uterus*	420 (91.50)	17,186 (89.09)	41,483 (88.10)	75,852 (89.04)	105,648 (89.38)	107,461 (90.31)	96,237 (91.87)	112,985 (93.37)
Non-HRT users								
Concomitant conditions								
· Anxiety	423 (3.00)	6,334 (6.55)	14,189 (7.35)	32,026 (6.79)	51,067 (8.55)	55,401 (9.96)	42,680 (10.56)	32,005 (10.69)
· Cardiovascular disease	114 (0.81)	1,966 (2.03)	4,590 (2.38)	10,238 (2.17)	15,961 (2.67)	17,589 (3.16)	15,594 (3.86)	14,087 (4.70)
· Depression	686 (4.86)	8,913 (9.22)	19,223 (9.95)	44,578 (9.46)	78,462 (13.13)	88,315 (15.87)	66,293 (16.40)	47,124 (15.74)
· Diabetes mellitus	181 (1.28)	2,739 (2.83)	6,874 (3.56)	23,604 (5.01)	40,625 (6.80)	43,997 (7.91)	35,402 (8.76)	30,314 (10.12)
· Diabetes mellitus type 2	54 (0.38)	1,256 (1.30)	4,013 (2.08)	18,682 (3.96)	35,195 (5.89)	38,046 (6.84)	30,499 (7.55)	26,395 (8.82)
· Dyslipidaemia	125 (0.89)	2,944 (3.05)	8,115 (4.20)	26,766 (5.68)	47,831 (8.00)	44,245 (7.95)	26,440 (6.54)	18,767 (6.27)
· Hypertension	918 (6.50)	12,634 (13.07)	27,339 (14.16)	79,769 (16.92)	121,317 (20.30)	113,317 (20.37)	82,709 (20.47)	67,820 (22.65)
· Metabolic syndrome	0	0	0	9 (0)	267 (0.04)	256 (0.05)	146 (0.04)	124 (0.04)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Osteoporosis	28 (0.20)	965 (1.00)	3,319 (1.72)	10,248 (2.17)	19,982 (3.34)	22,638 (4.07)	18,386 (4.55)	15,726 (5.25)
· Sleep disorders	433 (3.07)	5,875 (6.08)	11,012 (5.70)	25,174 (5.34)	45,348 (7.59)	49,435 (8.88)	34,076 (8.43)	23,706 (7.92)
Uterus status:								
· Hysterectomised	285 (2.02)	2,033 (2.10)	3,641 (1.89)	7,487 (1.59)	12,898 (2.16)	14,179 (2.55)	10,584 (2.62)	7,990 (2.67)
· Intact uterus*	13,828 (97.98)	94,601 (97.90)	189,479 (98.11)	463,974 (98.41)	584,688 (97.84)	542,225 (97.45)	393,521 (97.38)	291,435 (97.33)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = hormonal replacement therapy; N = number of individuals; – = no data available.
*In Real-World Data, an intact uterus is rarely explicitly recorded. Unless a hysterectomy procedure or a diagnosis code indicating the absence of the uterus is present in the patient's history, the uterus is assumed to be intact.

9.1.4. Comedication

Across all data sources and calendar years, comedication patterns were dominated by cardiovascular, gastroprotective, analgesic, endocrine, and bone-related therapies, with broadly similar therapeutic classes observed among HRT users and non-HRT users characterised at the prespecified mid-year date in each selected calendar year (**Table S7**). For example, in DK-DHR, acetaminophen became the most frequent comedication in both cohorts from 2015 onwards, recorded among 11.2% of HRT users and 7.9% of non-HRT users in 2024. In IQVIA DA Germany, cholecalciferol was one of the most frequently described drugs in both cohorts, recorded among 2.0% of HRT users and 2.1% of non-HRT users in 2024. In BIFAP, the top 10 of most frequently recorded comedications over time was largely comparable between cohorts. For example, calcifediol was recorded in 15.5% of HRT users and 12.1% of non-HRT users. In SIDIAP, acetaminophen and omeprazole were the most frequently recorded drug in both cohorts during later years. In CPRD GOLD, omeprazole and atorvastatin were frequently recorded among both cohorts during recent years, for example, omeprazole was recorded among 12.7% of HRT users and 10.1% non-HRT users in 2024.

Across data sources and calendar years, comedication patterns assessed in the one-year period prior to the prespecified mid-year characterisation date in each selected calendar year were broadly comparable to those observed in the one year postdate period, with consistently high use of analgesics, gastrointestinal therapies, cardiometabolic medications, and vaccinations in later years (**Table S8–S9**).

9.1.5. Comorbidities

Across all data sources, the frequency of recorded comorbidities increased over calendar time in both HRT users and non-HRT users. During the year preceding the mid-year characterisation date in each selected calendar year, pain was most commonly reported among both cohorts in DK-DHR, affecting around 49.1% of HRT users and 36.6% of non-HRT users in 2024 (**Table S10**). In IQVIA DA Germany, perimenopausal disorder was most frequent in the early years, recorded among 41.4% of HRT users in 1995, followed by a decrease to 16.5% in 2024, while atrophic vaginitis was most frequent in later calendar years, affecting 17.2% in 2024. Among non-HRT users, essential hypertension was most common, affecting up to 10.4%. of postmenopausal women in 2024. In BIFAP, common cold and viral upper respiratory tract infections were the most frequently recorded comorbidities in both cohorts throughout the pre-specified calendar years, with frequencies up to 12.2% among HRT users and 8.7% among non-HRT users. In SIDIAP, common cold and urinary tract infectious disease were most common in both cohorts, with urinary tract infectious disease reported among 14.0% of HRT users and 6.6% of non-HRT users in 2024, and common cold reported among 12.7% of HRT users and 8.8% of non-HRT users in 2024. Cough was consistently reported in up to 10.9% of HRT users and 8.1% of non-HRT users in CPRD GOLD (**Table S10**).

Comorbidity patterns were broadly consistent across the different assessment windows, with higher prevalence observed in more recent calendar years (**Table S11–12**).

9.2. Prevalence of HRT use among postmenopausal women

9.2.1. Overall annual prevalence of HRT use

Annual prevalence of HRT use among postmenopausal women showed distinct temporal trends across the data sources during the study period (**Figure 6**).

DK-DHR reported the highest annual prevalence of overall HRT use during the study period. In DK-DHR, annual prevalence was 26.6% in 1996 and remained relatively stable until 2002, followed by a decline, reaching 18.6% in 2005. Thereafter, annual prevalence estimates remained relatively stable for the remainder of the study period. In IQVIA DA Germany, annual prevalence of overall HRT use was 11.8% in 1993, followed by gradual decline to 4.3% in 2001 and a further decrease to 2.2% in 2020, with a subsequent increase to 3.6% in 2024. In BIFAP, annual prevalence of overall HRT use decreased from

6.5% in 2005 to 0.7% in 2015, remained relatively stable until 2022, and subsequently increased to 5.3% in 2024. In SIDIAP, annual prevalence remained stable between 2010 and 2013, with estimates of approximately 6.0%, followed by a steep decline to 1.2% in 2015, after which prevalence remained stable until 2022, followed by gradual increase reaching 3.5% in 2024. Annual prevalence in CPRD GOLD increased from 2.1% in 1988 to a peak of 26.8% in 2001, followed by steep decrease to 14.2% in 2005 and a more gradual decline to 8.9% in 2015. Thereafter, annual prevalence increased again, reaching 17.7% in 2024.

When stratified by age, the temporal patterns in annual prevalence of overall HRT use among women aged 50 to 60 years and above 60 years of age were broadly consistent with the trends observed in the overall analysis. In contrast, a distinct pattern with highest annual prevalence estimates during the study period was observed among women aged below 50 years with premature menopause across all data sources (**Figure 7**). In DK-DHR, the annual prevalence of HRT use among women aged below 50 years of age was approximately 70.0% during the 1990s, followed by a steep decline from 71.2% in 2002 to 52.9% in 2005 and a further decrease to 46.7% in 2013, after which annual prevalence subsequently increased to 54.1% in 2024. In IQVIA DA Germany, annual prevalence among women aged below 50 years declined from 14.5% in 1993 to 8.4% in 1997, followed by a gradual increase over time, reaching 25.8% in 2024. A similar pattern was observed in SIDIAP, where annual prevalence gradually increased over time from 14.2% in 2010 to 24.1% in 2024. In BIFAP, annual prevalence decreased from 21.7% in 2005 to 16.3% in 2009, followed by an increase to 19.9% in 2013 and stable estimates until 2022, and a further increase to 23.7% in 2024. In CPRD GOLD, annual prevalence was censored due to low counts in 1989 and increased from 36.5% in 1990 to 75.2% in 1996, remained relatively stable until 2002, after which it decreased to 59.8% in 2005 and further to 52.4% in 2020, followed by an increase to 62.8% in 2024.

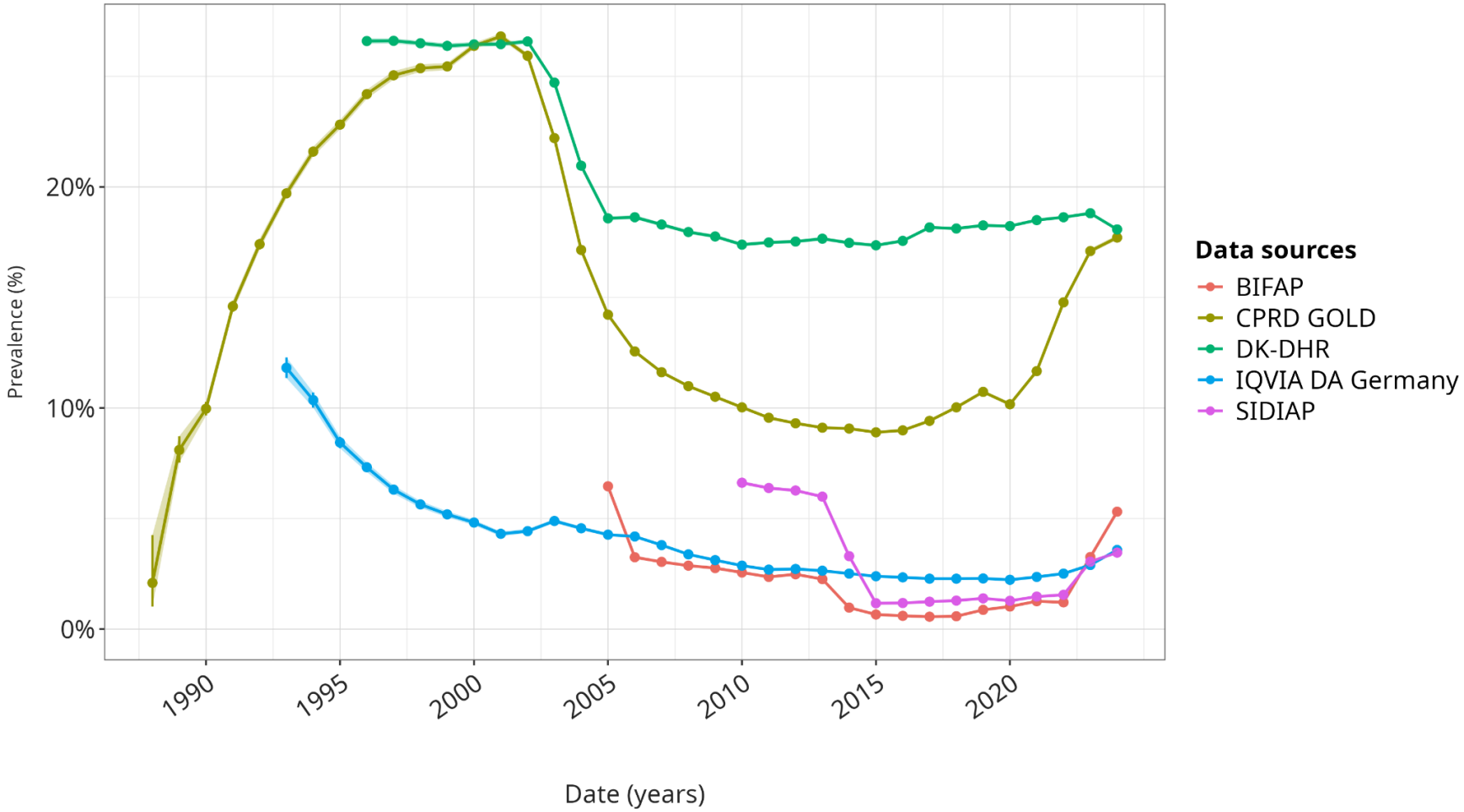


Figure 6. Annual prevalence of HRT use among postmenopausal women.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

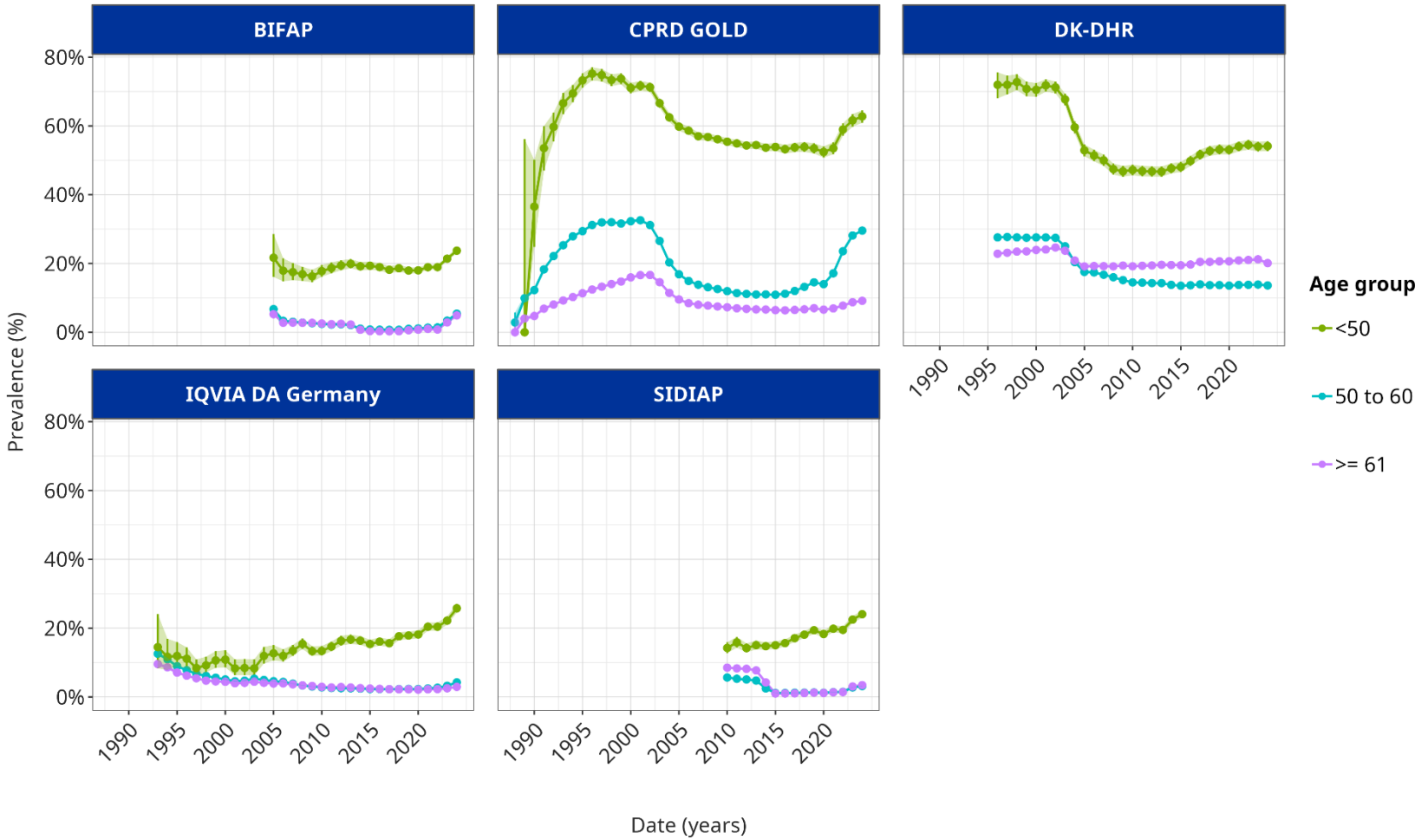


Figure 7. Annual prevalence of HRT use among postmenopausal women, stratified by age group.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

9.2.2. Annual prevalence of HRT use stratified by formulation

The annual prevalence of HRT use stratified by formulation showed a broadly similar pattern across data sources (**Figure 8**). Oestrogen-containing HRT products represented the majority of prevalent HRT use, particularly in more recent years. Fixed oestrogen and progestogen combination products were more prevalent at the beginning of the study period, but their use decreased over time, while combination products containing androgens and other HRT products remained uncommon throughout the study period.

In DK-DHR, the annual prevalence of oestrogen-containing products was stable during the 1990s, with estimates of approximately 15%, followed by decrease from 16.3% in 2002 to 13.7% in 2005, and subsequent gradual increase to 17.8% in 2023 and 17.1% in 2024. In contrast, the annual prevalence of fixed combination products containing oestrogen and progestogen decreased from 13.5% in 1996 to 1.2% in 2024, with a pronounced decline from 12.1% in 2002 to 5.0% in 2005. In IQVIA DA Germany, the annual prevalence of oestrogen-containing products decreased from 8.4% in 1993 to 2.3% in 2001, followed by a period of low and relatively stable prevalence around 2%. In the more recent years, the annual prevalence increased from 1.9% in 2020 to 3.2% in 2024. The annual prevalence of fixed combination products containing oestrogen and progestogen decreased during the study period from 3.2% in 1993 to 0.4% in 2024. In BIFAP, the annual prevalence of oestrogen-containing products decreased from 4.8% in 2005 to 0.3% in 2015, remained stable at this level until 2022, and subsequently increased to 4.9% in 2024, while the prevalence of fixed combination products containing oestrogen and progestogen remained stable over time, with estimates below 0.5%. In SIDIAP, oestrogen-containing products represented the majority of prevalent HRT use. Estimates were relatively stable at approximately 5.7% from 2010 to 2013, followed by a sharp decline to 0.7% in 2015 and stabilisation at this level before increasing from 1.1% in 2022 to 3.0% in 2024. In CPRD GOLD, the annual prevalence of oestrogen-containing products increased from 4.1% in 1989 to 12.2% in 2001, followed by decrease to 6.8% in 2007 and stable estimates until 2020, after which estimates increased reaching 12.8% in 2024. Estimates for fixed combination products containing oestrogen and progestogen followed similar pattern to that observed for oestrogen-containing products.

Fixed combination products containing androgens and other products contributed minimally to overall HRT prevalence across all data sources.

The annual prevalence of HRT formulation use stratified by age showed consistently higher estimates among postmenopausal women aged below 50 years across data sources for both oestrogen-containing products and fixed combination products containing oestrogen and progestogen (**Figure 9**). Age differences were observed for other products in some data sources, whereas no differences were observed for androgen containing HRT products. In DK-DHR, annual prevalence of oestrogen-containing products in women aged below 50 years was stable at around 64% from 1996 to 2002, followed by a decrease to 41.5% in 2005, subsequent stabilisation, and a gradual increase from 34.9% in 2015 to 44.1% in 2024. In contrast, a slight decrease in prevalence over time was observed among women aged 50 to 60 years, while an increase was seen among aged above 60 years. For fixed combination products containing oestrogen and progestogen, the annual prevalence among women aged below 50 years remained relatively stable at around 15.0% during the study period, whereas a decrease was observed between 2002 and 2005 among women aged 50 to 60 years and above 60 years, from 14.1% to 5.7% and 9.1% to 4.1%, respectively. Similarly, in IQVIA DA Germany, BIFAP, and SIDIAP, the annual prevalence estimates were slightly higher for women aged under 50 years for both oestrogen-containing products and fixed combination products containing oestrogen and progestogen, while the annual prevalence estimates were comparable across the two older age groups. In CPRD GOLD, the annual prevalence of oestrogen-containing products among women aged below 50 years increased from 34.6% in 1990 to a peak of 70.3% in 1996, followed by a decrease to 35.0% in 2018, and a subsequent increase to 49.4% in 2024. The annual prevalence of fixed combination products containing oestrogen and progestogen in CPRD GOLD was highest among

postmenopausal women aged between 50 and 60 years, increasing from 0.7% in 1989 to 14.5% in 2001, followed by a decrease to 4.2% in 2013, and a subsequent increase to 13.9% in 2023, while the annual prevalence in postmenopausal women below 50 years increased from 1.5% in 1992 to 20.1% in 2023 and 18.3% in 2024.

For other available formulations, slightly higher annual prevalence estimates among postmenopausal women below 50 years were observed in BIFAP, SIDIAP, and CPRD GOLD.

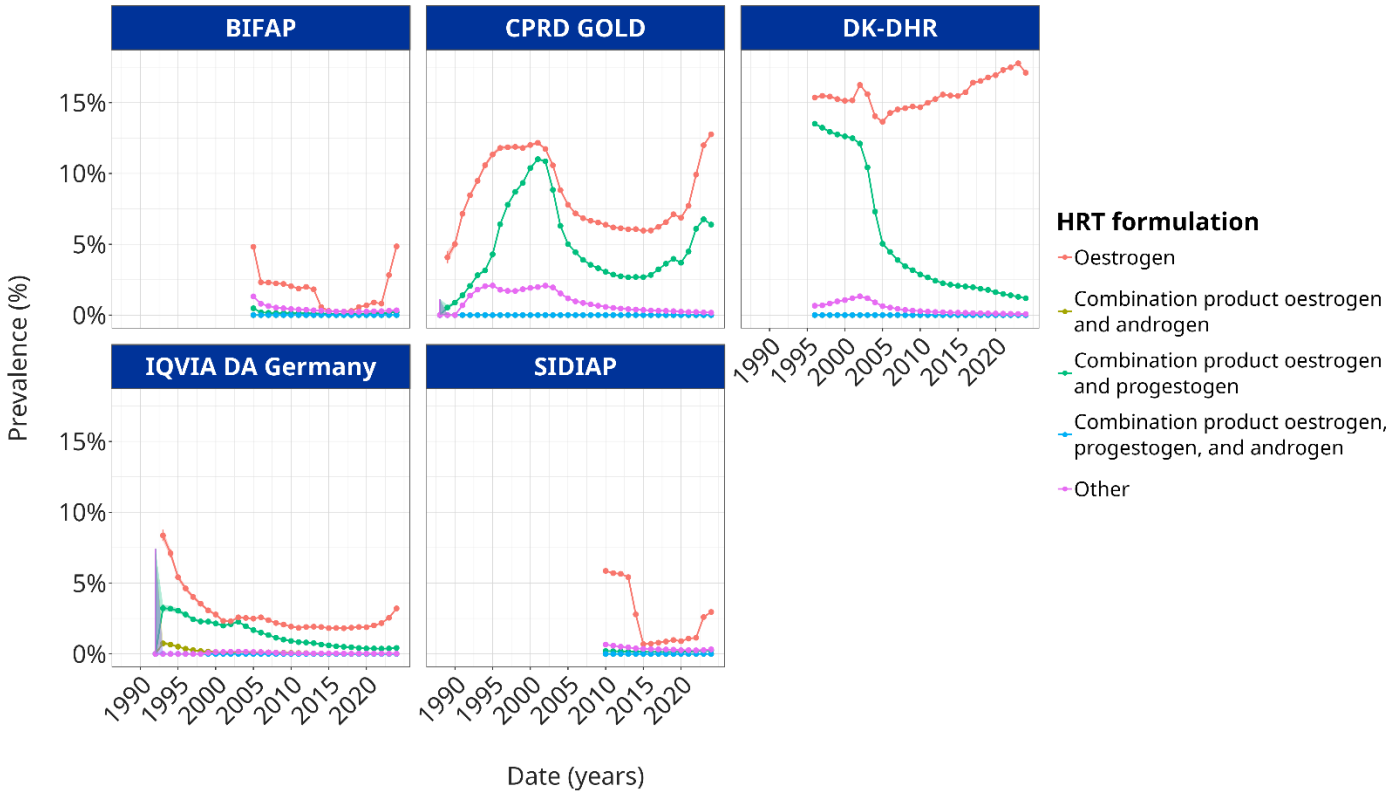


Figure 8. Annual prevalence of HRT use among postmenopausal women, by HRT formulation.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

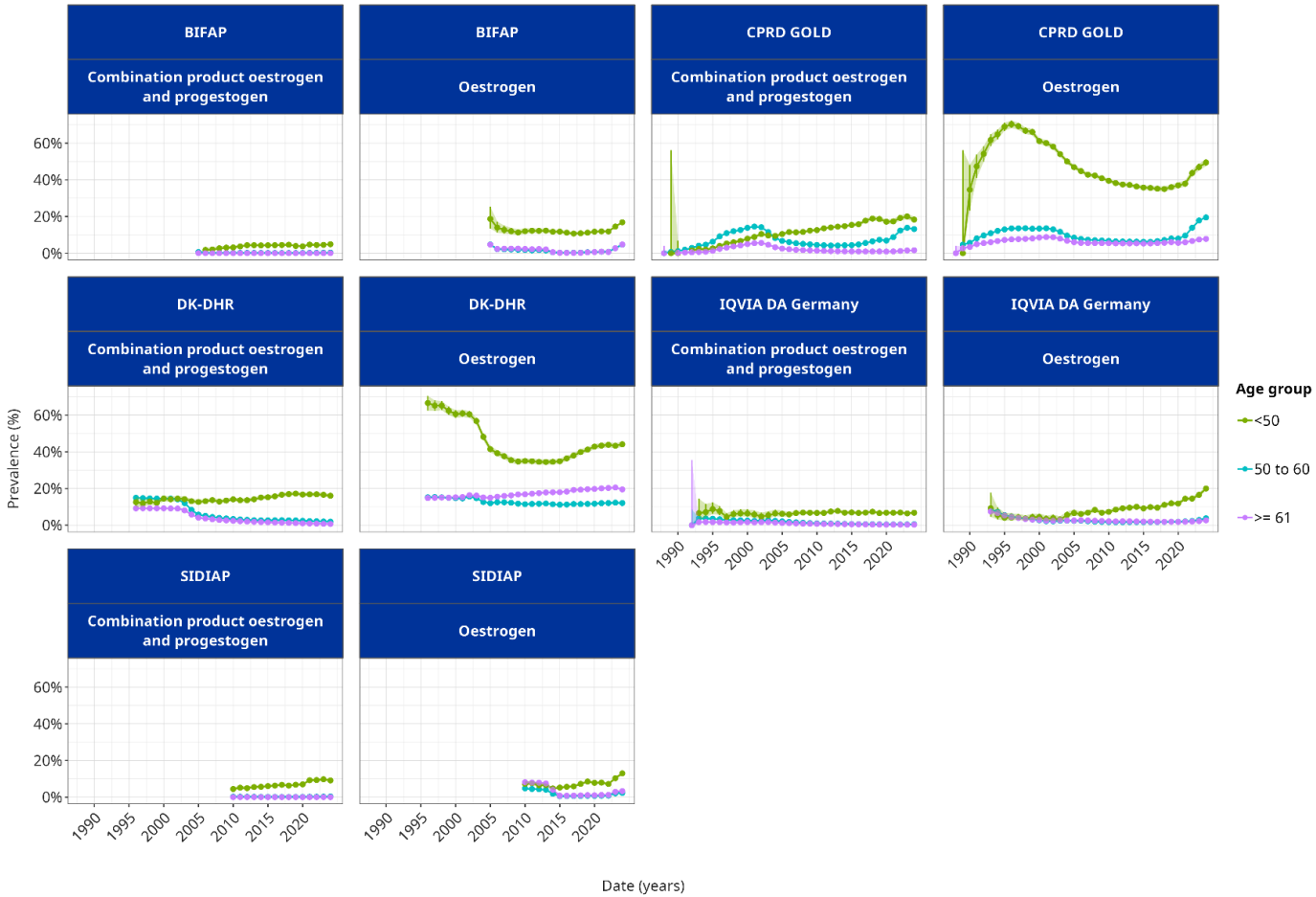


Figure 9. Annual prevalence by HRT formulation, stratified by age group.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.
Formulations classified as other and androgen-containing combinations are not shown, as no age-related differences were identified for these formulations; full results are available in the Shiny app.

9.2.3. Annual prevalence of HRT use stratified by route of administration

The annual prevalence of HRT use, stratified by route of administration, showed predominantly systemic use in earlier years and increasing use of HRT products with local effect during the study period in most data sources, while HRT products with an unspecified route remained limited across all data sources, with the exception of BIFAP and SIDIAP (**Figure 10**).

In DK-DHR, the annual prevalence of systemic HRT products was stable from 1996 to 2002 with estimates of approximately 21%, followed by a decrease from 20.1% in 2002 to 9.6% in 2005, and a further gradual decrease to 3.1% in 2024. The annual prevalence of HRT products with a local effect increased gradually from 3.4% in 1996 to 16.1% in 2023. Similarly, in IQVIA DA Germany, the annual prevalence of systemic HRT products decreased from 10.8% in 1993 to 1.3% in 2020, followed by a slight increase to 2.1% in 2024. The annual prevalence of products with a local or unspecified route of administration remained consistently low (<1.8% and <0.05%, respectively) during the study period. In BIFAP, the annual prevalence of systemic HRT products was 2.7% in 2005, and was 1.1% in 2005 for HRT products with a local effect, and estimates remained below 1.5% during the subsequent years, while HRT products with an unspecified route of administration showed stable estimates of approximately 1.6% until 2013, followed by a decrease to a 0.5% in 2014, and subsequently stable estimates until 2022. Thereafter, annual prevalence increased from 0.7% in 2022 to 4.7% in 2024. In SIDIAP, the annual prevalence of systemic HRT products remained low during the study period, while HRT products with a local effect showed a slight increase over time. HRT products with an unspecified route of administration showed estimates of approximately 5% from 2010 to 2013, followed by a decrease to 0.6% in 2015 and stable estimates in the following years, with an increase from 0.7% in 2023 to 1.4% in 2024. In CPRD GOLD, the annual prevalence of systemic HRT products was comparable to overall annual estimates of HRT use, while the annual prevalence of HRT products with a local effect increased from 0.5% in 1989 to 2.8% in 2019, followed by a slight decrease to 2.0% in 2024. The annual prevalence of HRT products with an unspecified route of administration remained consistently low (<0.2%).

The annual prevalence of HRT use based on route of administration stratified by age showed distinct patterns across data sources (**Figure 11**). In DK-DHR, among postmenopausal women using HRT products with a local effect, trends over time were broadly comparable across age groups, with the highest annual prevalence consistently observed among women older than 60 years. For systemic HRT products, the highest prevalence was observed among women aged below 50 years, with similar temporal trends across all age groups. In IQVIA DA Germany, BIFAP, SIDIAP, and CPRD GOLD, systemic HRT products were more prevalent among women aged below 50 years compared to older age groups. In BIFAP, HRT products with an unspecified route of administration were more prevalent among women aged below 50 years compared with older age groups, while in SIDIAP, HRT products with an unspecified route of administration were more prevalent among women older than 60 years until 2013 and among women aged below 50 years from 2015 onwards. These findings should be interpreted with caution, as the route of administration could not be identified for these products. There were no age-related differences reported for HRT products with local or unspecified route of administration in other data sources.

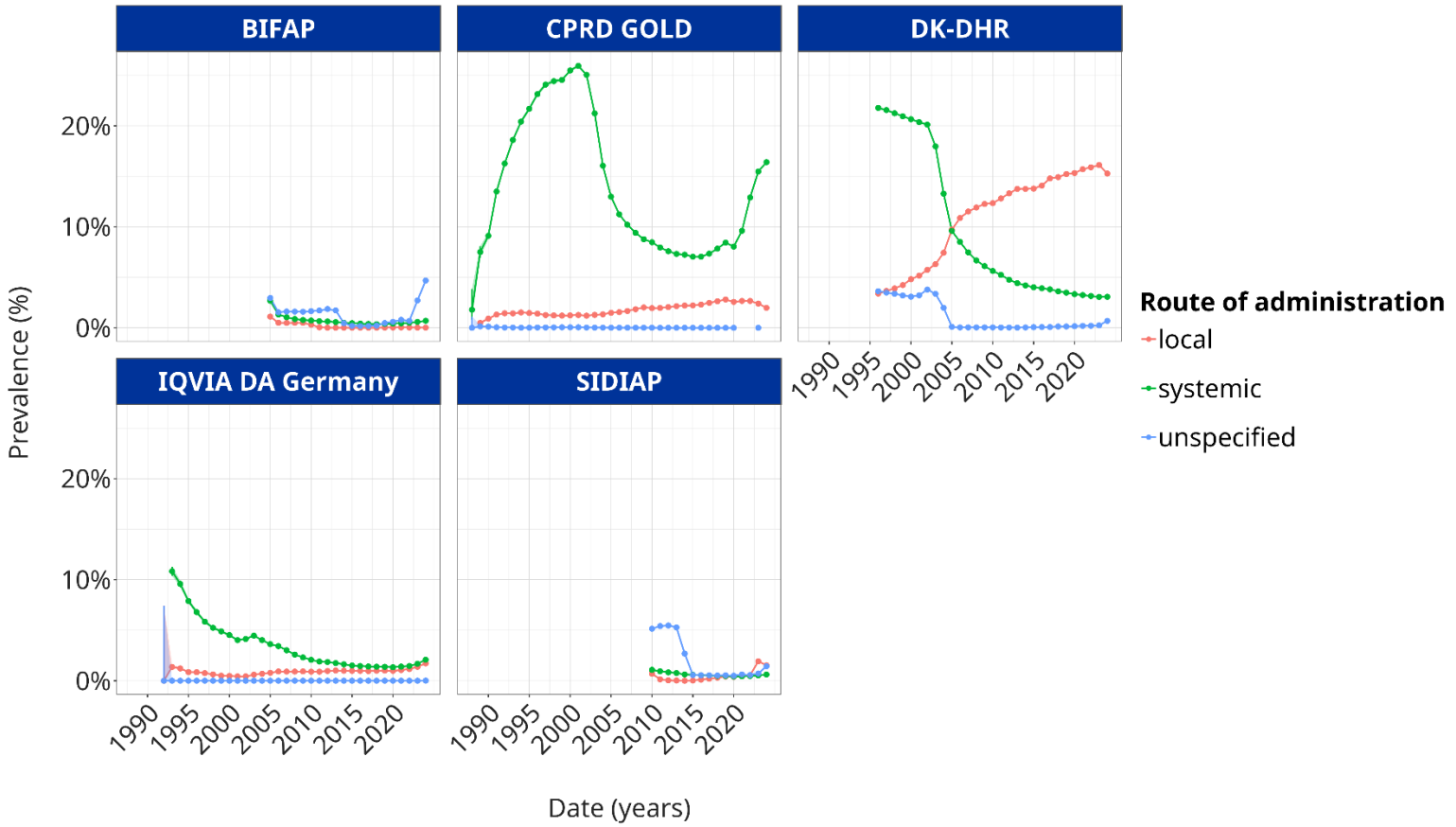


Figure 10. Annual prevalence of HRT use among postmenopausal women, by route of administration.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.
Unspecified route of administration: HRT products for which information on the route of administration was unavailable.



Figure 11. Annual prevalence of HRT route of administration, stratified by age group.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.
Unspecified route of administration: HRT products for which information on the route of administration was unavailable.

9.2.4. Annual prevalence of HRT use stratified by HRT type

Finally, the annual prevalence of HRT use stratified by type showed broadly consistent pattern across data sources, with natural HRT products representing the majority of prevalent use during the study period, while synthetic HRT products were less prevalent (**Figure 12**).

In DK-DHR, the annual prevalence of natural HRT products was stable from 1996 to 2002 with estimates of approximately 24%, followed by a decrease from 24.4% in 2002 to 18.0% in 2005 and subsequent stabilisation. In contrast, the annual prevalence of synthetic HRT products was around 3% until 2004, followed by a decrease from 2.6% in 2004 to 0.7% in 2005 with subsequent stabilisation at that low level. In IQVIA DA Germany, the annual prevalence of natural HRT products declined from 11.8% in 1993 to 4.2% in 2001, followed by a further gradual decline to 2.2% in 2020, and a slight increase to 3.6% in 2024. In SIDIAP, synthetic HRT products accounted for the majority of prevalent use from 2010 to 2013, with estimates around 6%, while natural HRT products remained limited during the study period, with a slight increase to 2.0% in 2024 towards the end of study period. A similar pattern was observed in BIFAP, with synthetic HRT products representing the majority of prevalent use from 2005 to 2013, with estimates of around 2%, while natural HRT products remained limited (<1% during the majority of the study period) with an increase to 4.1% in 2024. In CPRD GOLD, natural HRT products accounted for the majority of prevalent use, with estimates increasing from 1.8% in 1988 to 25.1% in 2001, followed by a steep decline to 13.2% in 2005, and a more gradual decrease to 8.6% in 2015, with a subsequent increase to 17.6% in 2024. Synthetic HRT products increased from 1.1% in 1989 to 3.8% in 1994, followed by a decrease over time to 0.2% in 2024.

The annual prevalence of HRT product type stratified by age showed consistently higher estimates among postmenopausal women aged below 50 years across data sources for natural HRT products, while the annual prevalence estimates were comparable across the two older age groups. (**Figure 13**). In DK-DHR, for example, the annual prevalence of natural HRT products in women aged below 50 years was stable at around 70% from 1996 to 2002, followed by a decrease to 51.5% in 2005, subsequent stabilisation, and a gradual increase from 47.6% in 2015 to 53.9% in 2024. In contrast, a slight decrease in prevalence over time was observed for women aged 50 to 60 years and among women aged above 60 years. No age differences were observed for synthetic HRT products, except in BIFAP.

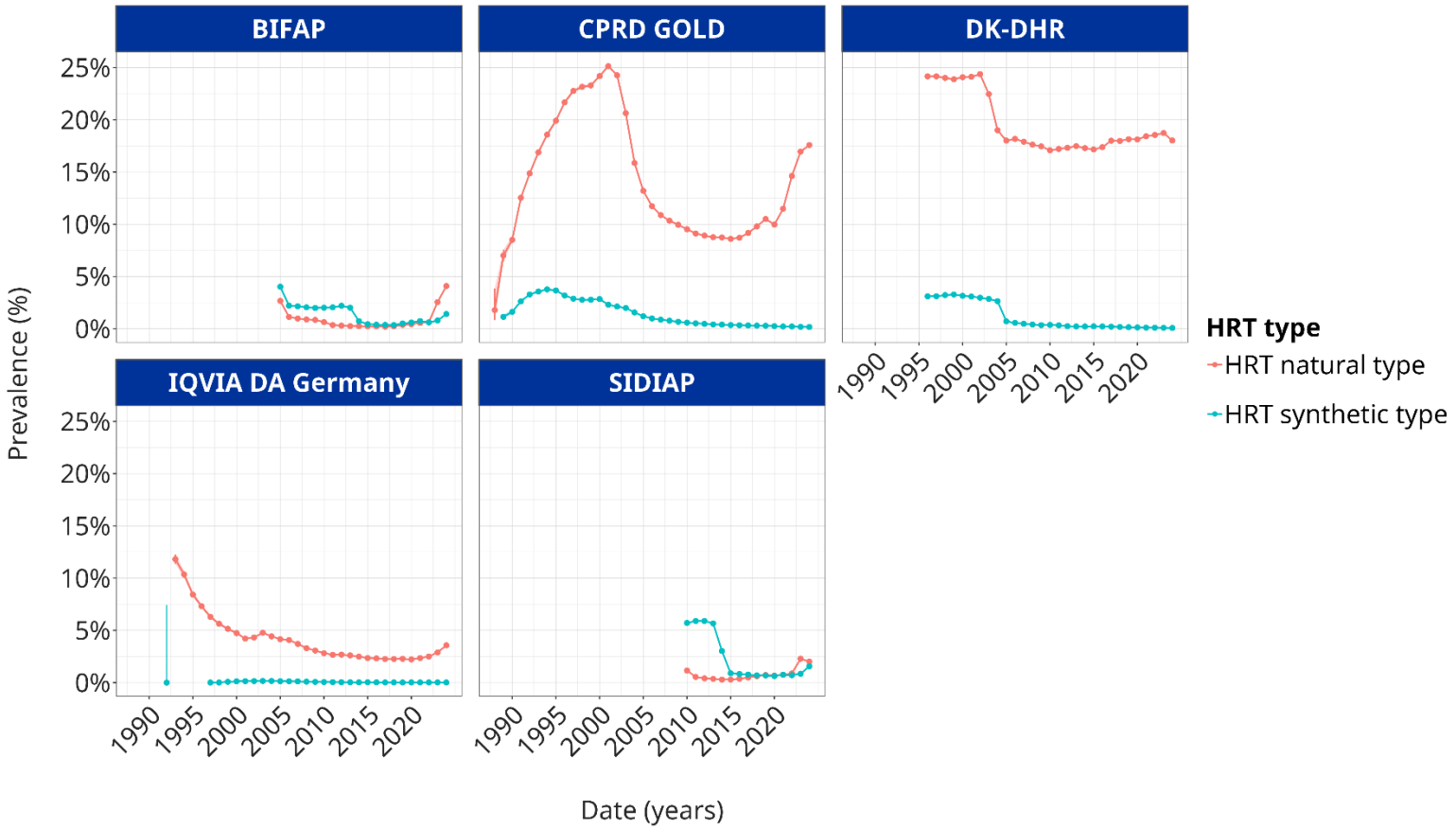


Figure 12. Annual prevalence of HRT use among postmenopausal women, by HRT type.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

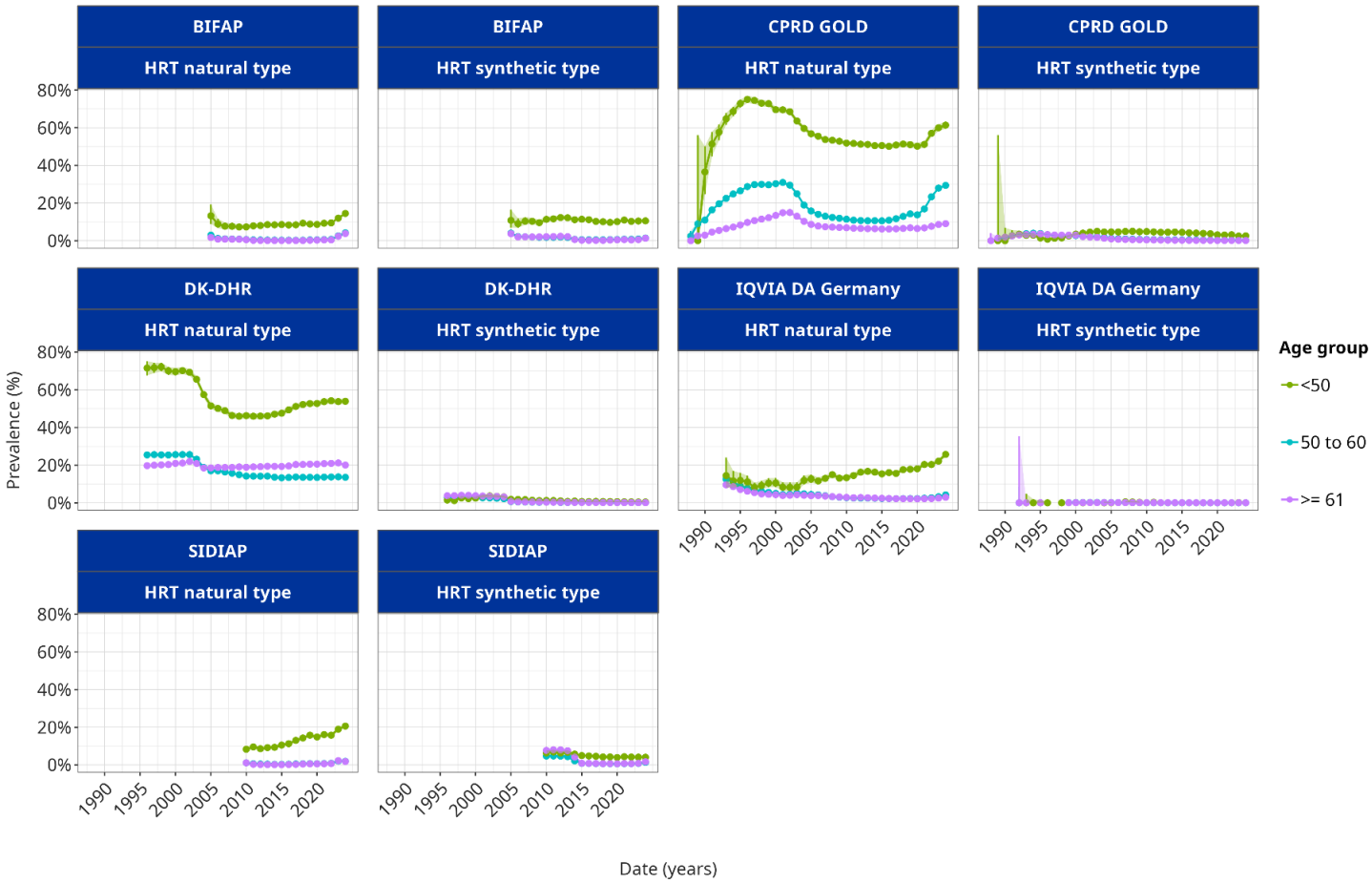


Figure 13. Annual prevalence by HRT type, stratified by age group.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

9.2.5. Sensitivity analysis: narrow definition of study population

In the sensitivity analyses using a narrower definition of postmenopausal women, annual prevalence estimates of HRT use were broadly consistent with the trends observed in the main analysis across all data sources (**Figures S1–S4** in **ANNEX V**). Absolute prevalence estimates were higher in the narrower population definition than in the main analysis, but the overall temporal trend remained comparable, confirming robustness of findings.

9.3. Duration of HRT use among postmenopausal women initiating HRT

Treatment duration, estimated by combining consecutive prescription records/dispensings separated by gaps of up to 90 days, varied substantially across HRT products and data sources (**Table 8**). Across HRT products, the median treatment duration ranged from 11 days for ethinylestradiol-containing products in IQVIA DA Germany to 534 days for fixed combination products containing oestradiol and norethisterone in DK-DHR and 1,826 days for IUD in CPRD GOLD, DK-DHR, and IQVIA DA Germany, reflecting the imputed duration of clinical use. Longer treatment durations were generally accompanied by a higher number of prescription or dispensing records.

The median treatment duration for oestradiol-containing products ranged from 30 days in IQVIA DA Germany to 324 days in DK-DHR, based on a median of 2 and 8 prescription records/dispensings, respectively, while the corresponding duration for oestriol-containing products ranged from 31 days in IQVIA DA Germany to 306 days in SIDIAP, based on a median of 1 and 2 prescription records/dispensings, respectively. For conjugated oestrogen-containing products, the median treatment duration of use ranged from 34 days in SIDIAP and 42 days in DK-DHR to 227 days in IQVIA DA Germany and 235 days in CPRD GOLD, corresponding to a median of 1 to 3 prescription records/dispensings. Treatment duration for tibolone was generally longer, ranging from 175 days in IQVIA DA Germany to 377 days in SIDIAP, based on a median of 2 and 6 prescription records/dispensings, respectively. Several historically used products, including dienestrol and diethylstilbestrol-containing products, showed short median treatment durations and limited use, and should therefore be interpreted with caution. The median treatment duration for dienestrol-containing products was 36 days in DK-DHR and 30 days in CPRD GOLD and was 28 days in CPRD GOLD for diethylstilbestrol-containing products. Among fixed combination products containing oestrogen and progestogen, the median treatment duration varied across data sources. For fixed combination products containing oestradiol and norethisterone, the median treatment duration ranged from 168 days in IQVIA DA Germany to 534 days in DK-DHR, based on a median of 2 and 7 prescription records/dispensings, respectively. For fixed combination products containing oestradiol and medroxyprogesterone, the median treatment duration ranged from 224 days in IQVIA DA Germany and 253 days in CPRD GOLD (both with a median of 3 prescription records/dispensings) to 396 days in DK-DHR (median of 5 prescription records/dispensings), while for fixed combination products containing oestradiol and drospirenone, it ranged from 164 days in CPRD GOLD to 326 days in DK-DHR, corresponding to a median number of 2 prescription records/dispensings in CPRD GOLD and 4 in DK-DHR. For fixed combination products containing oestradiol and levonorgestrel, the median treatment duration ranged from 84 days in IQVIA DA Germany to 425 days in DK-DHR, corresponding to a median of 2 and 5 prescription records/dispensings, respectively. The median treatment duration for levonorgestrel IUD was imputed and aligned with expected clinical use of 1,826 days (5 years) in DK-DHR, IQVIA DA Germany, and SIDIAP.

When stratified by age groups, the median treatment duration varied across data sources and demonstrated heterogeneity in an age-specific pattern (**Table 9**). For oestradiol-containing products, the median treatment duration was longest among women aged below 50 years, ranging from 391 days in BIFAP to 1,488 days in DK-DHR, corresponding to a median of 8 and 21 prescription records/dispensings, respectively. The shortest treatment durations were observed among women aged >60 years, ranging from 107 days in CPRD GOLD to 243 days in DK-DHR, corresponding to a median of 2 and 7 prescription records/dispensings, respectively. IQVIA DA Germany was an exception, with consistently short treatment

durations across all age groups (30–60 days) and a median of 2 prescription records/dispensings. For oestriol-containing products, age-related variation was limited. The median treatment duration remained relatively stable across age groups within each data source, including approximately 96 days in DK-DHR (median 2 prescription records/dispensings), around 30 days in IQVIA DA Germany, and approximately 65 days in CPRD GOLD. Longer treatment durations were observed in BIFAP (181–203 days) and SIDIAP (306–348 days).

In most data sources, the longest treatment duration of tibolone-containing products was in the <50 years age group, ranging from 336 days in CPRD GOLD to 607 days in SIDIAP, and shortest in the >60 years age group, ranging from 182 days in BIFAP to 236 days in DK-DHR. In IQVIA DA Germany, the longest duration of 336 days was seen in the >60 years age group, while the shortest duration (84 days) was observed in the <50 years age group.

As an additional analysis, the total treatment duration was estimated using all prescription records/dispensings received throughout the complete follow up period, without applying the prespecified treatment gap between prescriptions. Total treatment durations were generally longer across HRT products and data sources (**Table S13**). Similarly, the overall patterns observed in the main analysis were generally maintained across age strata and data sources, with generally longer treatment durations (**Table S14**).

The observed treatment durations may have been affected by the median follow-up time of HRT initiators, which ranged from 592 days in BIFAP to 4,374 days in DK-DHR. Detailed information is available in the Shiny app (EUPAS1000000821).

Table 8. Duration of HRT treatment among postmenopausal women, overall.

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
Conjugated oestrogens plain	number records	N	206	1,947	270	65	17,144
	number subjects	N	206	1,947	270	65	17,144
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	3 (1 – 10)	4 (1 – 13)	2 (1 – 3)	3 (1 – 11)
	days exposed	Median (Q25 – Q75)	42 (42 – 84)	227 (84 – 882)	190 (54 – 542)	34 (31 – 154)	235 (74 – 1,032)
Ethinylestradiol plain	number records	N	1,148	125	7,501	–	222
	number subjects	N	1,148	125	7,501	–	222
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (2 – 6)	1 (1 – 1)	5 (1 – 16)	–	3 (1 – 9)
	days exposed	Median (Q25 – Q75)	157 (84 – 295)	11 (11 – 22)	199 (58 – 581)	–	199 (90 – 601)
Lynestrenol plain	number records	N	93	7	<5	<5	–
	number subjects	N	93	7	<5	<5	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	3 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	63 (30 – 276)	105 (60 – 284)	–	–	–
Medrogestone plain	number records	N	–	24	6	–	–
	number subjects	N	–	24	6	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 3)	2 (1 – 3)	–	–
	days exposed	Median (Q25 – Q75)	–	87 (41 – 204)	58 (38 – 89)	–	–
Medroxyprogesterone acetate plain	number records	N	2,713	136	437	84	531

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number subjects	N	2,713	136	437	84	531
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 5)	3 (1 – 11)	2 (1 – 3)	3 (1 – 7)
	days exposed	Median (Q25 – Q75)	82 (40 – 280)	50 (15 – 325)	125 (31 – 425)	43 (31 – 166)	136 (56 – 434)
Megesterol plain	number records	N	–	–	9	<5	10
	number subjects	N	–	–	9	<5	10
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	4 (1 – 10)	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	–	–	126 (31 – 354)	–	85 (28 – 309)
Nomegestrol plain	number records	N	–	9	185	–	–
	number subjects	N	–	9	185	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 3)	2 (1 – 5)	–	–
	days exposed	Median (Q25 – Q75)	–	168 (144 – 355)	116 (85 – 355)	–	–
Norethisterone plain	number records	N	2,427	342	4,064	42	751
	number subjects	N	2,427	342	4,064	42	751
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 3)	8 (2 – 18)	2 (1 – 2)	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	136 (84 – 409)	36 (12 – 131)	273 (79 – 575)	31 (31 – 61)	84 (28 – 312)
Oestradiol plain	number records	N	315,076	40,480	25,954	4,576	106,798
	number subjects	N	315,076	40,480	25,954	4,576	106,798

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number of prescription records/dispensings**	Median (Q25 – Q75)	8 (2 – 25)	2 (1 – 7)	4 (1 – 9)	2 (1 – 8)	3 (1 – 11)
	days exposed	Median (Q25 – Q75)	324 (50 – 1,233)	30 (3 – 168)	192 (56 – 426)	286 (81 – 533)	218 (84 – 756)
Oestriol plain	number records	N	28,269	69,919	84,556	21,369	77,439
	number subjects	N	28,269	69,919	84,556	21,369	77,439
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 3)	4 (1 – 10)	2 (1 – 4)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	95 (61 – 328)	31 (30 – 100)	191 (51 – 399)	306 (85 – 412)	67 (30 – 189)
Oestradiol norethisterone	number records	N	51,179	9,258	8,408	3,193	71,702
	number subjects	N	51,179	9,258	8,408	3,193	71,702
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 19)	2 (1 – 8)	12 (3 – 29)	7 (2 – 22)	4 (2 – 10)
	days exposed	Median (Q25 – Q75)	534 (93 – 1,514)	168 (84 – 657)	411 (96 – 939)	448 (181 – 974)	342 (88 – 890)
Progesterone plain	number records	N	459	13,080	3,045	831	8,847
	number subjects	N	459	13,080	3,045	831	8,847
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 9)	3 (1 – 8)	6 (2 – 15)	5 (2 – 13)	6 (2 – 11)
	days exposed	Median (Q25 – Q75)	295 (69 – 502)	182 (3 – 620)	283 (72 – 618)	379 (151 – 704)	359 (115 – 718)
Promestriene plain	number records	N	–	–	75,254	59,090	–
	number subjects	N	–	–	75,254	59,090	–
	Number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 4)	2 (1 – 5)	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	days exposed	Median (Q25 – Q75)	–	–	62 (31 – 212)	122 (38 – 469)	–
Tibolone plain	number records	N	2,204	827	23,807	7,217	9,942
	number subjects	N	2,204	827	23,807	7,217	9,942
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 15)	2 (1 – 7)	7 (2 – 22)	6 (2 – 19)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	342 (84 – 1,214)	175 (84 – 689)	255 (57 – 758)	377 (108 – 887)	220 (84 – 776)
Conjugated oestrogens and bazedoxifene	number records	N	<5	–	–	528	<5
	number subjects	N	<5	–	–	528	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	5 (2 – 17)	–
	days exposed	Median (Q25 – Q75)	–	–	–	366 (102 – 775)	–
Conjugated oestrogens medroxyprogesterone	number records	N	–	481	–	–	10,887
	number subjects	N	–	481	–	–	10,887
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 8)	–	–	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	206 (84 – 687)	–	–	245 (84 – 741)
Dienestrol plain	number records	N	24,520	–	–	–	7,496
	number subjects	N	24,520	–	–	–	7,496
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	–	–	1 (1 – 2)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	days exposed	Median (Q25 – Q75)	36 (7 – 138)	–	–	–	30 (28 – 82)
Diethylstilbestrol plain	number records	N	<5	–	–	–	23
	number subjects	N	<5	–	–	–	23
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	–	–	–	28 (10 – 43)
Dydrogesterone plain	number records	N	–	373	–	–	171
	number subjects	N	–	373	–	–	171
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 4)	–	–	2 (1 – 7)
	days exposed	Median (Q25 – Q75)	–	84 (14 – 267)	–	–	110 (30 – 372)
Levonorgestrel IUD***	number records	N	434	11	–	–	506
	number subjects	N	434	11	–	–	506
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	1 (1 – 1)	–	–	1 (1 – 1)
	days exposed	Median (Q25 – Q75)	1,826 (1,826 – 1,826)	1,826 (1,826– 1,826)	–	–	1,826 (1,826 – 1,826)
Oestradiol drospirenone	number records	N	349	933	–	–	172
	number subjects	N	349	933	–	–	172
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (1 – 13)	2 (1 – 8)	–	–	2 (1 – 7)
	days exposed	Median (Q25 – Q75)	326 (84 – 1,110)	175 (84 – 689)	–	–	164 (84 – 596)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
Oestradiol dydrogesterone	number records	N	–	5,081	–	–	8,410
	number subjects	N	–	5,081	–	–	8,410
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 9)	–	–	4 (1 – 9)
	days exposed	Median (Q25 – Q75)	–	169 (84 – 760)	–	–	315 (84 – 859)
Oestradiol levonorgestrel	number records	N	5,623	4,902	–	–	5,338
	number subjects	N	5,623	4,902	–	–	5,338
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 12)	2 (1 – 5)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	425 (84 – 1,064)	84 (30 – 330)	–	–	150 (84 – 416)
Oestradiol medroxyprogesterone	number records	N	7,525	808	–	117	1,920
	number subjects	N	7,525	808	–	117	1,920
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 13)	3 (1 – 8)	–	3 (2 – 10)	3 (1 – 6)
	days exposed	Median (Q25 – Q75)	396 (91 – 1,088)	224 (84 – 697)	–	299 (71 – 653)	253 (91 – 665)
Chlorotrianisene plain	number records	N	–	<5	–	–	–
	number subjects	N	–	<5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Hydroxyprogesterone plain	number records	N	–	5	–	–	–
	number subjects	N	–	5	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 1)	–	–	–
	days exposed	Median (Q25 – Q75)	–	25 (25 – 25)	–	–	–
Oestradiol prasterone	number records	N	–	527	–	–	–
	number subjects	N	–	527	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 9)	–	–	–
	days exposed	Median (Q25 – Q75)	–	95 (30 – 476)	–	–	–
Oestradiol progesterone	number records	N	–	561	–	–	–
	number subjects	N	–	561	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	–	109 (84 – 406)	–	–	–

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; days exposed = time in days a person has been exposed to the drug of interest; N = number of individuals; Q25 = 25th percentile; Q75 = 75th percentile; – = no data available.
*Plain refers to products containing only the specified active substance (e.g. oestradiol plain = oestradiol-only product)
**Number of prescription records/dispensings = number of prescription records/dispensings contributing to treatment duration.
***Median treatment duration is imputed and aligned with expected clinical use.

Table 9. Duration of HRT treatment among postmenopausal women, stratified by age group.

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Age group <50 years							
Conjugated oestrogens plain	number records	N	<5	28	9	<5	2,765
	number subjects	N	<5	28	9	<5	2,765
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5.25)	7 (3 – 16)	–	8 (3 – 19)
	days exposed	Median (Q25 – Q75)	–	118 (84 – 377)	325 (277 – 658)	–	660 (190 – 1,883)
Ethinylestradiol plain	number records	N	10	10	1,336	–	43
	number subjects	N	10	10	1,336	–	43
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (1 – 4)	1 (1 – 2)	13 (4 – 33)	–	5 (2 – 10)
	days exposed	Median (Q25 – Q75)	171 (105 – 238)	22 (21 – 53)	523 (156 – 1,195)	–	324 (104 – 576)
Medroxyprogesterone acetate plain	number records	N	116	8	61	10	26
	number subjects	N	116	8	61	10	26
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (2 – 8)	1 (1 – 11.25)	8 (3 – 37)	2 (2 – 6)	3 (1 – 7)
	days exposed	Median (Q25 – Q75)	214 (80 – 434)	23 (12 – 748)	387 (125 – 1,128)	210 (88 – 485)	199 (90 – 332)
Megesterol plain	number records	N	–	–	<5	–	–
	number subjects	N	–	–	<5	–	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Nomegestrol plain	number records	N	–	<5	28	–	–
	number subjects	N	–	<5	28	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 6)	–	–
	days exposed	Median (Q25 – Q75)	–	–	206 (85 – 402)	–	–
Norethisterone plain	number records	N	63	17	537	<5	19
	number subjects	N	63	17	537	<5	19
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (1 – 6)	1 (1 – 2)	15 (4 – 33)	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	300 (84 – 616)	36 (12 – 48)	509 (160 – 1,032)	–	84 (34 – 164)
Oestradiol plain	number records	N	5,852	1,463	1,019	575	9,001
	number subjects	N	5,852	1,463	1,019	575	9,001
	number of prescription records/dispensings**	Median (Q25 – Q75)	21 (7 – 43)	2 (1 – 7)	8 (2 – 22)	7 (2 – 19)	13 (5 – 26)
	days exposed	Median (Q25 – Q75)	1,488 (441 – 3,093)	36 (3 – 168)	391 (114 – 886)	493 (224 – 1,074)	900 (315 – 1,958)
Oestriol plain	number records	N	110	879	187	124	285

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number subjects	N	110	879	187	124	285
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 2)	3 (1 – 8)	2 (1 – 3)	1 (1 – 3)
	days exposed	Median (Q25 – Q75)	100 (37 – 382)	30 (30 – 60)	181 (42 – 365)	348 (91 – 438)	57 (28 – 165)
Oestradiol norethisterone	number records	N	1,328	261	740	692	2,440
	number subjects	N	1,328	261	740	692	2,440
	number of prescription records/dispensings**	Median (Q25 – Q75)	11 (3 – 25)	2 (1 – 5)	17 (5 – 40)	6 (2 – 24)	6 (2 – 14)
	days exposed	Median (Q25 – Q75)	962 (256 – 2,144)	84 (60 – 363)	566 (180 – 1,323)	521 (251 – 1,091)	444 (142 – 1,254)
Progesterone plain	number records	N	28	582	335	160	141
	number subjects	N	28	582	335	160	141
	number of prescription records/dispensings**	Median (Q25 – Q75)	6 (2 – 11)	3 (1 – 8)	7 (2 – 18)	4 (2 – 15)	5 (2 – 11)
	days exposed	Median (Q25 – Q75)	286 (103 – 373)	178 (30 – 619)	401 (99 – 868)	374 (136 – 825)	272 (90 – 659)
Promestriene plain	number records	N	–	–	122	179	–
	number subjects	N	–	–	122	179	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	1 (1 – 3)	2 (1 – 3)	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	–	–	59 (31 – 179)	96 (40 – 366)	–
Tibolone plain	number records	N	64	8	664	341	815
	number subjects	N	64	8	664	341	815
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 16)	1 (1 – 2)	10 (3 – 32)	10 (2 – 29)	5 (2 – 15)
	days exposed	Median (Q25 – Q75)	462 (111 – 1,339)	84 (84 – 126)	368 (98 – 1,011)	607 (246 – 1,237)	336 (109 – 1,194)
Conjugated oestrogens medroxyprogesterone	number records	N	–	8	–	–	319
	number subjects	N	–	8	–	–	319
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (2 – 5)	–	–	3 (1 – 7)
	days exposed	Median (Q25 – Q75)	–	277 (162 – 455)	–	–	197 (84 – 705)
Dienestrol plain	number records	N	35	–	–	–	15
	number subjects	N	35	–	–	–	15
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	–	–	–	1 (1 – 4)
	days exposed	Median (Q25 – Q75)	14 (7 – 56)	–	–	–	28 (28 – 122)
Dydrogesterone plain	number records	N	–	27	–	–	8
	number subjects	N	–	27	–	–	8

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 3)	–	–	2 (2 – 3)
	days exposed	Median (Q25 – Q75)	–	30 (14 – 227)	–	–	99 (59 – 185)
Levonorgestrel IUD***	number records	N	20	–	–	–	15
	number subjects	N	20	–	–	–	15
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	–	–	–	1 (1 – 1)
	days exposed	Median (Q25 – Q75)	1,826 (1,826 – 1,826)	–	–	–	1,826 (1,826 – 1,826)
Oestradiol drospirenone	number records	N	8	30	–	–	11
	number subjects	N	8	30	–	–	11
	number of prescription records/dispensings**	Median (Q25 – Q75)	6 (4 – 13)	2.50 (1 – 16)	–	–	10 (2 – 16)
	days exposed	Median (Q25 – Q75)	363 (226 – 974)	249 (84 – 1,500)	–	–	820 (84 – 1,240)
Oestradiol dydrogesterone	number records	N	–	348	–	–	387
	number subjects	N	–	348	–	–	387
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 9)	–	–	5 (2 – 12)
	days exposed	Median (Q25 – Q75)	–	172 (84 – 731)	–	–	504 (154 – 1,202)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestradiol levonorgestrel	number records	N	26	498	–	–	163
	number subjects	N	26	498	–	–	163
	number of prescription records/dispensings**	Median (Q25 – Q75)	6 (2 – 12)	2 (1 – 4)	–	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	458 (161 – 799)	84 (63 – 294)	–	–	152 (84 – 492)
Oestradiol medroxyprogesterone	number records	N	50	38	–	44	53
	number subjects	N	50	38	–	44	53
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (2 – 13)	3 (1 – 4)	–	3 (1 – 15)	3 (1 – 9)
	days exposed	Median (Q25 – Q75)	294 (164 – 1,072)	203 (78 – 299)	–	334 (119 – 768)	343 (119 – 837)
Lynestrenol plain	number records	N	<5	–	–	–	–
	number subjects	N	<5	–	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Oestradiol prasterone	number records	N	–	10	–	–	–
	number subjects	N	–	10	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 1)	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	–	30 (30 – 30)	–	–	–
Oestradiol progesterone	number records	N	–	13	–	–	–
	number subjects	N	–	13	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	–	168 (84 – 433)	–	–	–
Conjugated oestrogens and bazedoxifene	number records	N	–	–	–	74	–
	number subjects	N	–	–	–	74	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	5 (2 – 16)	–
	days exposed	Median (Q25 – Q75)	–	–	–	354 (125 – 752)	–
Age group 50–60 years							
Conjugated oestrogens plain	number records	N	127	1,110	221	57	11,027
	number subjects	N	127	1,110	221	57	11,027
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	3 (1 – 10)	4 (1 – 13)	2 (1 – 3)	3 (1 – 11)
	days exposed	Median (Q25 – Q75)	42 (42 – 120)	213 (84 – 865)	190 (57 – 579)	33 (31 – 146)	249 (84 – 1,048)
Ethinylestradiol plain	number records	N	1,112	113	5,974	–	154
	number subjects	N	1,112	113	5,974	–	154

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (2 – 6)	1 (1 – 1)	4 (1 – 13)	–	3 (1 – 9)
	days exposed	Median (Q25 – Q75)	155 (84 – 296)	11 (11 – 22)	171 (51 – 492)	–	188 (90 – 601)
Lynestrenol plain	number records	N	86	5	<5	<5	–
	number subjects	N	86	5	<5	<5	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 3)	–	–	–
	days exposed	Median (Q25 – Q75)	74 (30 – 285)	60 (60 – 218)	–	–	–
Medrogestone plain	number records	N	–	18	5	–	–
	number subjects	N	–	18	5	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 3)	1 (1 – 3)	–	–
	days exposed	Median (Q25 – Q75)	–	105 (50 – 200)	57 (31 – 99)	–	–
Medroxyprogesterone acetate plain	number records	N	2,487	109	360	67	458
	number subjects	N	2,487	109	360	67	458
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 4)	3 (1 – 9)	2 (1 – 2)	2 (1 – 7)
	days exposed	Median (Q25 – Q75)	80 (40 – 274)	51 (15 – 303)	98 (29 – 367)	31 (31 – 108)	126 (52 – 434)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Megesterol plain	number records	N	–	–	5	<5	7
	number subjects	N	–	–	5	<5	7
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	4 (1 – 5)	–	2 (2 – 5)
	days exposed	Median (Q25 – Q75)	–	–	126 (31 – 156)	–	86 (28 – 246)
Nomegestrol plain	number records	N	–	7	156	–	–
	number subjects	N	–	7	156	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 2)	2 (1 – 5)	–	–
	days exposed	Median (Q25 – Q75)	–	168 (114 – 262)	113 (58 – 318)	–	–
Norethisterone plain	number records	N	2,286	285	3,467	40	665
	number subjects	N	2,286	285	3,467	40	665
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 3)	7 (2 – 17)	2 (1 – 2)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	134 (84 – 405)	36 (11 – 133)	245 (66 – 531)	32 (31 – 70)	84 (28 – 301)
Oestradiol plain	number records	N	194,602	31,998	17,826	3,021	71,129
	number subjects	N	194,602	31,998	17,826	3,021	71,129
	number of prescription records/dispensings**	Median (Q25 – Q75)	9 (2 – 27)	2 (1 – 7)	4 (1 – 9)	2 (1 – 7)	4 (1 – 11)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	364 (60 – 1,346)	30 (3 – 158)	198 (57 – 438)	267 (81 – 518)	249 (84 – 771)
Oestriol plain	number records	N	16,738	39,850	43,995	10,060	40,880
	number subjects	N	16,738	39,850	43,995	10,060	40,880
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	2 (1 – 3)	4 (1 – 9)	2 (1 – 4)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	96 (60 – 325)	34 (30 – 100)	181 (51 – 391)	306 (85 – 402)	65 (30 – 189)
Oestradiol norethisterone	number records	N	47,185	7,094	7,340	2,394	66,460
	number subjects	N	47,185	7,094	7,340	2,394	66,460
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 19)	2 (1 – 8)	12 (3 – 28)	7 (2 – 22)	4 (2 – 10)
	days exposed	Median (Q25 – Q75)	551 (108 – 1,517)	162 (84 – 623)	404 (91 – 918)	436 (171 – 951)	345 (90 – 888)
Progesterone plain	number records	N	424	11,727	2,568	646	8,360
	number subjects	N	424	11,727	2,568	646	8,360
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 9)	3 (1 – 8)	6 (2 – 15)	5 (2 – 13)	6 (2 – 11)
	days exposed	Median (Q25 – Q75)	302 (70 – 512)	186 (10 – 633)	280 (68 – 603)	380 (156 – 700)	361 (116 – 724)
Promestriene plain	number records	N	–	–	40,208	32,604	–
	number subjects	N	–	–	40,208	32,604	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 4)	2 (1 – 5)	–
	days exposed	Median (Q25 – Q75)	–	–	62 (31 – 192)	121 (38 – 478)	–
Tibolone plain	number records	N	1,926	589	21,403	6,313	7,767
	number subjects	N	1,926	589	21,403	6,313	7,767
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 16)	2 (1 – 7)	7 (2 – 22)	6 (2 – 20)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	346 (84 – 1,218)	168 (84 – 597)	260 (57 – 758)	380 (110 – 896)	202 (84 – 741)
Conjugated oestrogens and bazedoxifene	number records	N	<5	–	–	422	<5
	number subjects	N	<5	–	–	422	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	5 (2 – 17)	–
	days exposed	Median (Q25 – Q75)	–	–	–	368 (100 – 773)	–
Conjugated oestrogens medroxyprogesterone	number records	N	–	347	–	–	9,590
	number subjects	N	–	347	–	–	9,590
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 8)	–	–	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	207 (84 – 723)	–	–	245 (84 – 748)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Dienestrol plain	number records	N	15,866	–	–	–	3,807
	number subjects	N	15,866	–	–	–	3,807
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	35 (7 – 134)	–	–	–	30 (28 – 72)
Diethylstilbestrol plain	number records	N	–	–	–	–	11
	number subjects	N	–	–	–	–	11
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	–	–	–	28 (10 – 57)
Dydrogesterone plain	number records	N	–	330	–	–	146
	number subjects	N	–	330	–	–	146
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 4)	–	–	2 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	84 (14 – 252)	–	–	121 (30 – 391)
Levonorgestrel IUD***	number records	N	414	11	–	–	489
	number subjects	N	414	11	–	–	489
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	1 (1 – 1)	–	–	1 (1 – 1)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	1,826 (1,826 – 1,826)	1,826 (1,826 – 1,826)	–	–	1,826 (1,826 – 1,826)
Oestradiol drospirenone	number records	N	331	751	–	–	152
	number subjects	N	331	751	–	–	152
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 13)	2 (1 – 8)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	359 (84 – 1,122)	193 (84 – 730)	–	–	156 (84 – 451)
Oestradiol dydrogesterone	number records	N	–	4,110	–	–	7,827
	number subjects	N	–	4,110	–	–	7,827
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 9)	–	–	4 (1 – 9)
	days exposed	Median (Q25 – Q75)	–	168 (84 – 720)	–	–	314 (84 – 847)
Oestradiol levonorgestrel	number records	N	5,540	3,967	–	–	5,011
	number subjects	N	5,540	3,967	–	–	5,011
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 12)	1 (1 – 5)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	427 (86 – 1,067)	84 (30 – 316)	–	–	151 (84 – 415)
Oestradiol medroxyprogesterone	number records	N	7,243	633	–	71	1,810
	number subjects	N	7,243	633	–	71	1,810

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 13)	3 (1 – 8)	–	4 (2 – 10)	3 (1 – 6)
	days exposed	Median (Q25 – Q75)	399 (91 – 1,090)	192 (84 – 675)	–	288 (65 – 474)	252 (91 – 662)
Hydroxyprogesterone plain	number records	N	–	5	–	–	–
	number subjects	N	–	5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 1)	–	–	–
	days exposed	Median (Q25 – Q75)	–	25 (25 – 25)	–	–	–
Oestradiol prasterone	number records	N	–	337	–	–	–
	number subjects	N	–	337	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 7)	–	–	–
	days exposed	Median (Q25 – Q75)	–	90 (30 – 427)	–	–	–
Oestradiol progesterone	number records	N	–	518	–	–	–
	number subjects	N	–	518	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	–	127 (84 – 415)	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Age group >60 years							
Conjugated oestrogens plain	number records	N	78	809	40	5	3,352
	number subjects	N	78	809	40	5	3,352
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	3 (1 – 10)	3 (1 – 10)	1 (1 – 2)	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	42 (42 – 84)	248 (84 – 918)	150 (29 – 430)	69 (65 – 300)	77 (30 – 301)
Ethinylestradiol plain	number records	N	26	<5	191	–	25
	number subjects	N	26	<5	191	–	25
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	1 (1 – 4)	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	114 (84 – 339)	–	57 (29 – 180)	–	136 (30 – 713)
Medrogestone plain	number records	N	–	6	<5	–	–
	number subjects	N	–	6	<5	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 2)	–	–	–
	days exposed	Median (Q25 – Q75)	–	54 (30 – 165)	–	–	–
Medroxyprogesterone acetate plain	number records	N	110	19	16	7	47
	number subjects	N	110	19	16	7	47

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 4)	1 (1 – 6)	4 (1 – 10)	3 (2 – 4)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	50 (30 – 200)	50 (30 – 287)	148 (43 – 372)	188 (94 – 748)	198 (68 – 596)
Megesterol plain	number records	N	–	–	<5	–	<5
	number subjects	N	–	–	<5	–	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Nomegestrol plain	number records	N	–	–	<5	–	–
	number subjects	N	–	–	<5	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Norethisterone plain	number records	N	78	40	60	–	67
	number subjects	N	78	40	60	–	67
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 8)	2 (1 – 4)	3 (1 – 6)	–	2 (1 – 10)
	days exposed	Median (Q25 – Q75)	84 (20 – 300)	50 (24 – 157)	92 (29 – 272)	–	114 (58 – 674)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestradiol plain	number records	N	114,622	7,019	7,109	980	26,668
	number subjects	N	114,622	7,019	7,109	980	26,668
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 20)	2 (1 – 6)	3 (1 – 7)	2 (1 – 5)	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	243 (34 – 954)	60 (18 – 274)	172 (53 – 375)	181 (47 – 383)	107 (80 – 337)
Oestriol plain	number records	N	11,421	29,190	40,374	11,185	36,274
	number subjects	N	11,421	29,190	40,374	11,185	36,274
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 3)	4 (1 – 10)	2 (1 – 4)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	93 (67 – 334)	30 (30 – 97)	203 (55 – 407)	306 (85 – 420)	68 (30 – 189)
Oestradiol norethisterone	number records	N	2,666	1,903	328	107	2,802
	number subjects	N	2,666	1,903	328	107	2,802
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (1 – 12)	3 (1 – 10)	7 (2 – 23)	3 (1 – 14)	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	203 (84 – 1,024)	182 (84 – 800)	290 (57 – 802)	338 (58 – 773)	221 (84 – 661)
Progesterone plain	number records	N	7	771	142	25	346
	number subjects	N	7	771	142	25	346
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	1 (1 – 5)	4 (1 – 15)	2 (2 – 10)	5 (2 – 10)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	15 (8 – 30)	90 (2 – 387)	182 (44 – 504)	366 (112 – 552)	312 (90 – 617)
Promestriene plain	number records	N	–	–	34,924	26,307	–
	number subjects	N	–	–	34,924	26,307	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 4)	2 (1 – 5)	–
	days exposed	Median (Q25 – Q75)	–	–	83 (31 – 234)	133 (38 – 461)	–
Tibolone plain	number records	N	214	230	1,740	563	1,360
	number subjects	N	214	230	1,740	563	1,360
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (1 – 14)	4 (1 – 10)	4 (1 – 18)	4 (2 – 14)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	236 (84 – 1,082)	336 (84 – 900)	182 (48 – 643)	218 (61 – 580)	221 (84 – 717)
Conjugated oestrogens medroxyprogesterone	number records	N	–	126	–	–	978
	number subjects	N	–	126	–	–	978
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 6)	–	–	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	177 (84 – 550)	–	–	233 (84 – 701)
Dienestrol plain	number records	N	8,619	–	–	–	3,674
	number subjects	N	8,619	–	–	–	3,674

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	–	–	1 (1 – 3)
	days exposed	Median (Q25 – Q75)	37 (7 – 144)	–	–	–	30 (28 – 84)
Diethylstilbestrol plain	number records	N	<5	–	–	–	12
	number subjects	N	<5	–	–	–	12
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	–	–	–	28 (13 – 38)
Dydrogesterone plain	number records	N	–	16	–	–	17
	number subjects	N	–	16	–	–	17
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 7)	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	208 (84 – 608)	–	–	30 (28 – 140)
Levonorgestrel IUD***	number records	N	–	–	–	–	<5
	number subjects	N	–	–	–	–	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestradiol drospirenone	number records	N	10	152	–	–	9
	number subjects	N	10	152	–	–	9
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	2 (1 – 6)	–	–	6 (3 – 10)
	days exposed	Median (Q25 – Q75)	45 (30 – 84)	136 (84 – 509)	–	–	548 (296 – 700)
Oestradiol dydrogesterone	number records	N	–	623	–	–	196
	number subjects	N	–	623	–	–	196
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 10)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	–	207 (84 – 971)	–	–	170 (84 – 586)
Oestradiol levonorgestrel	number records	N	57	437	–	–	164
	number subjects	N	57	437	–	–	164
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	2 (1 – 7)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	168 (84 – 459)	120 (30 – 515)	–	–	110 (82 – 386)
Oestradiol medroxyprogesterone	number records	N	232	137	–	<5	57
	number subjects	N	232	137	–	<5	57
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (1 – 12)	4 (1 – 9)	–	–	2 (1 – 7)

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	334 (84 – 1,052)	291 (84 – 792)	–	–	306 (91 – 661)
Lynestrenol plain	number records	N	6	<5	–	–	–
	number subjects	N	6	<5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	–	–	–	–
	days exposed	Median (Q25 – Q75)	30 (30 – 70)	–	–	–	–
Chlorotrianisene plain	number records	N	–	<5	–	–	–
	number subjects	N	–	<5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Oestradiol prasterone	number records	N	–	180	–	–	–
	number subjects	N	–	180	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 10)	–	–	–
	days exposed	Median (Q25 – Q75)	–	128 (30 – 625)	–	–	–
Oestradiol progesterone	number records	N	–	30	–	–	–
	number subjects	N	–	30	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK-DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number exposures	Median (Q25 – Q75)	–	1 (1 – 3)	–	–	–
	days exposed	Median (Q25 – Q75)	–	84 (84 – 230)	–	–	–
Conjugated oestrogens and bazedoxifene	number records	N	–	–	–	32	–
	number subjects	N	–	–	–	32	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	2 (2 – 21)	–
	days exposed	Median (Q25 – Q75)	–	–	–	348 (84 – 806)	–

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; days exposed = time in days a person has been exposed to the drug of interest; N = number of individuals; Q25 = 25th percentile; Q75 = 75th percentile; – = no data available.
*Plain refers to products containing only the specified active substance (e.g. oestradiol plain = oestradiol-only product)
**Number of prescription records/dispensings = number of prescription records dispensings contributing to treatment duration.
***Median treatment duration is imputed and aligned with expected clinical use.

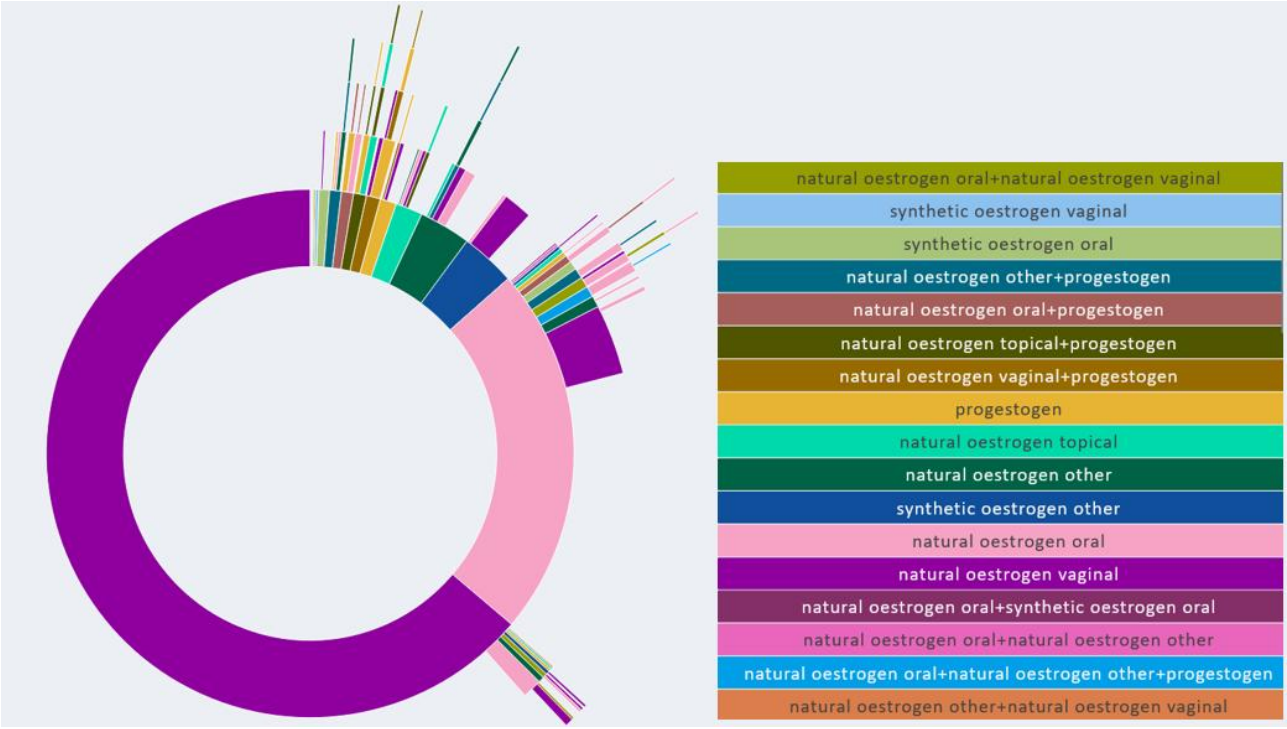
9.4. HRT treatment patterns among postmenopausal women

9.4.1. HRT treatment patterns overall

Treatment patterns over up to 10 years following HRT initiation in postmenopausal women varied across DK-DHR, BIFAP, SIDIAP, and CPRD GOLD, both in terms of first-line therapy and subsequent treatment pathways (**Figures 14–17**). IQVIA DA Germany was excluded from this analysis due to limited population coverage under the prespecified criteria. Across all included data sources, the majority of postmenopausal women initiated HRT with a single product. In DK-DHR, the most common first-line treatments were natural oestrogen vaginal (63.8%) and natural oestrogen oral products (22.7%). In CPRD GOLD, first-line treatment was distributed across natural oestrogen oral products (36.4%), natural oestrogen vaginal products (20.5%), natural oestrogen topical products (18.0%), and natural oestrogen products with other routes of administration (14.7%). Natural oestrogen products with other routes of administration included products with unknown routes and routes other than oral, topical, or vaginal administration. In BIFAP, first-line treatment was predominately natural oestrogen products with other routes of administration (44.6%) and synthetic oestrogen products with other routes of administration (31.8%), while in SIDIAP first-line use was dominated by synthetic oestrogen products with other routes of administration (62.3%) and natural vaginal oestrogen products (22.7%). Concomitant use of oestrogen and progestogen as separate products accounted for only a small proportion of the first-line treatment. Among these, use of natural oestrogen vaginal and progestogen products (0.9%) was most common in DK-DHR; natural oestrogen vaginal and progestogen products (1.8%) in CPRD GOLD; synthetic oestrogen, other, and progestogen products (1.6%) in BIFAP; and natural oestrogen, other, and progestogen products (0.7%) in SIDIAP.

The majority of postmenopausal women followed a single-step treatment pathway, indicating no treatment changes during follow-up (**Figures 14–17**). Among postmenopausal women who changed treatment, switches most frequently involved alternative oestrogen products or progestogen-containing therapies.

Comprehensive details of treatment pathways are available for further exploration in the interactive Shiny application (EUPAS1000000821). Sankey plots are also available in the Shiny app.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	natural oestrogen vaginal	63.81%	212,150
2	1	natural oestrogen oral	22.69%	75,449
3	1	synthetic oestrogen other	3.37%	11,189
4	1	natural oestrogen other	3.18%	10,568
5	1	natural oestrogen topical	1.66%	5,517
6	1	progestogen	1.00%	3,321
7	1	natural oestrogen vaginal+progestogen	0.87%	2,880
8	1	natural oestrogen topical+progestogen	0.79%	2,623
9	1	natural oestrogen oral+progestogen	0.74%	2,472
10	1	synthetic oestrogen oral	0.64%	2,137

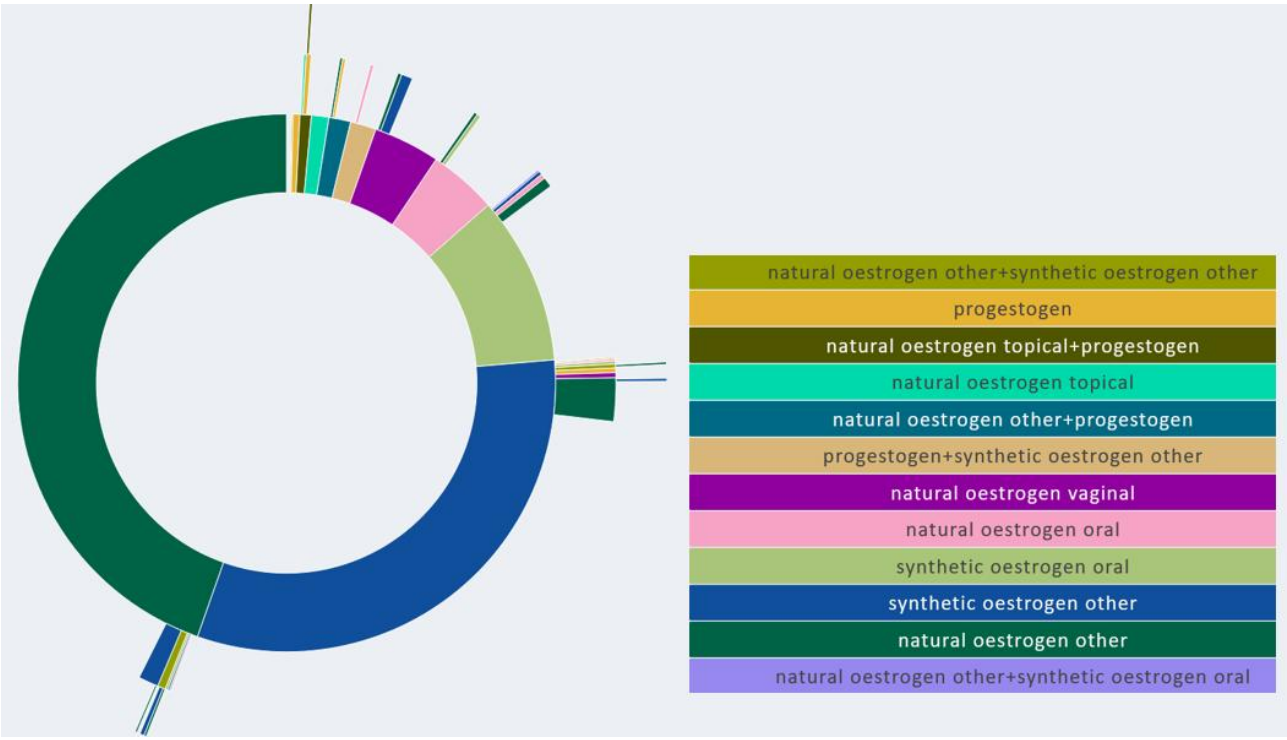
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	natural oestrogen vaginal	61.56%	204,679
2	natural oestrogen oral	15.18%	50,483
3	natural oestrogen oral-natural oestrogen vaginal	3.21%	10,658
4	synthetic oestrogen other	1.66%	5,523
5	natural oestrogen other	1.58%	5,254
6	synthetic oestrogen other-natural oestrogen vaginal	1.40%	4,665
7	natural oestrogen topical	0.89%	2,971
8	progestogen	0.58%	1,928
9	natural oestrogen vaginal-natural oestrogen oral	0.47%	1,562
10	synthetic oestrogen oral	0.42%	1,412

Figure 34. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall, in DK-DHR.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another.
DK-DHR = Danish Data Health Registries; HRT = Hormone replacement therapy.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	natural oestrogen other	44.62%	80,502
2	1	synthetic oestrogen other	31.75%	57,295
3	1	synthetic oestrogen oral	10.14%	18,291
4	1	natural oestrogen oral	4.11%	7,410
5	1	natural oestrogen vaginal	4.00%	7,220
6	1	progestogen+synthetic oestrogen other	1.55%	2,796
7	1	natural oestrogen other+progestogen	1.31%	2,369
8	1	natural oestrogen topical	1.04%	1,884
9	1	natural oestrogen topical+progestogen	0.69%	1,237
10	1	progestogen	0.42%	750

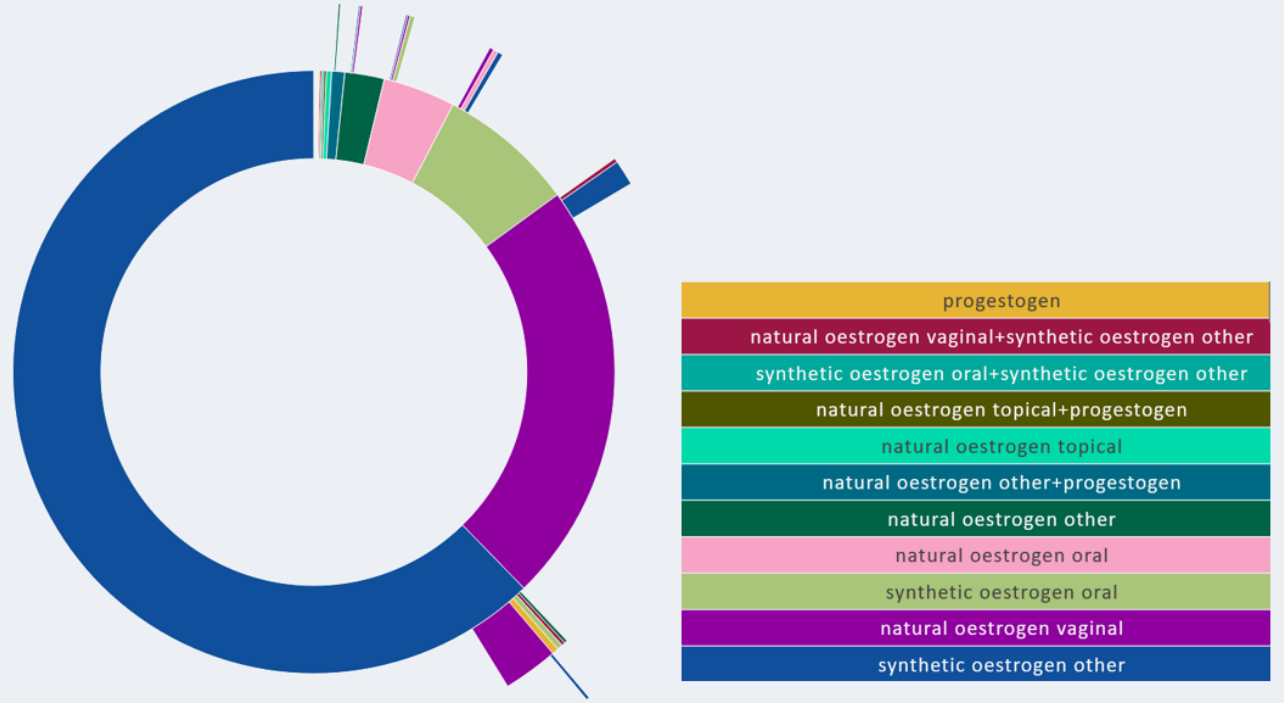
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	natural oestrogen other	42.61%	76,878
2	synthetic oestrogen other	28.50%	51,431
3	synthetic oestrogen oral	8.82%	15,912
4	natural oestrogen oral	3.47%	6,269
5	natural oestrogen vaginal	3.15%	5,678
6	synthetic oestrogen other-natural oestrogen other	1.95%	3,519
7	progestogen+synthetic oestrogen other	1.12%	2,012
8	natural oestrogen other+progestogen	0.96%	1,734
9	natural oestrogen other-synthetic oestrogen other	0.87%	1,563
10	natural oestrogen topical	0.83%	1,499

Figure 45. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall, in BIFAP.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line).

Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another.
BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; HRT = Hormone replacement therapy.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	synthetic oestrogen other	62.28%	56,082
2	1	natural oestrogen vaginal	22.72%	20,460
3	1	synthetic oestrogen oral	7.35%	6,618
4	1	natural oestrogen oral	3.88%	3,496
5	1	natural oestrogen other	2.12%	1,911
6	1	natural oestrogen other+progestogen	0.70%	627
7	1	natural oestrogen topical	0.28%	250
8	1	natural oestrogen topical+progestogen	0.13%	121
9	1	synthetic oestrogen oral+synthetic oestrogen other	0.11%	102
10	1	progestogen	0.08%	72

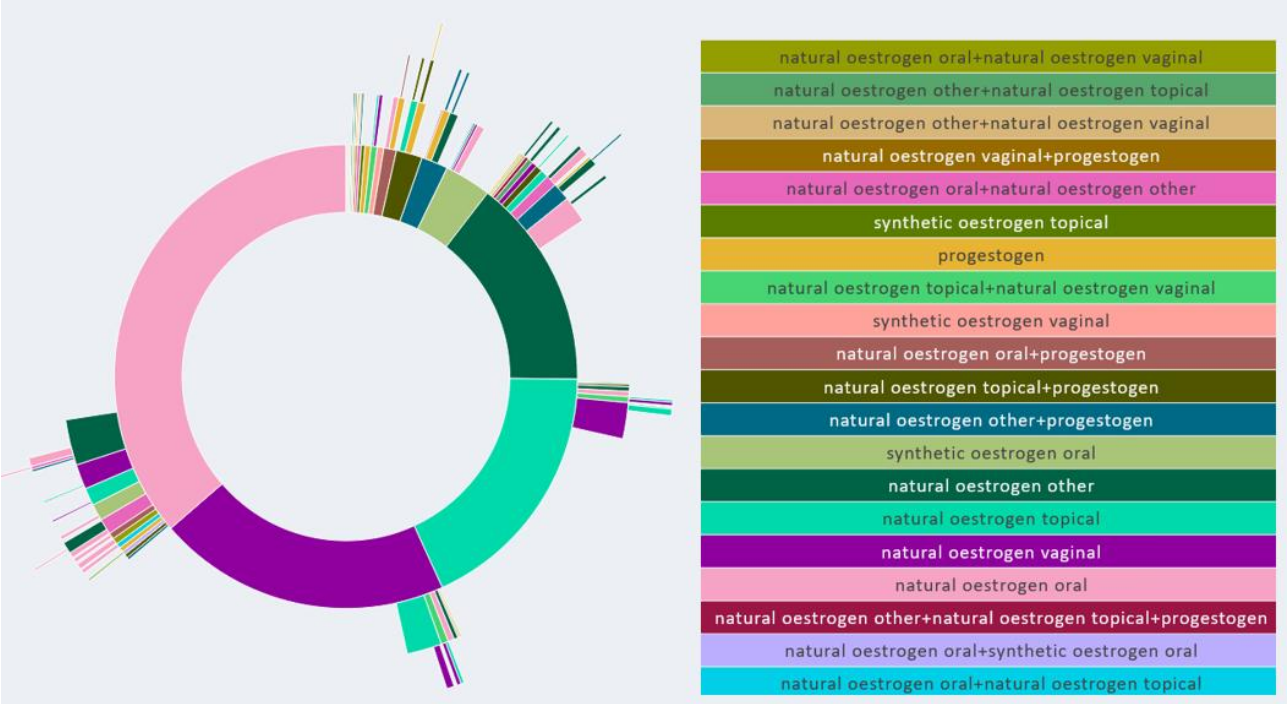
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	synthetic oestrogen other	58.80%	52,950
2	natural oestrogen vaginal	21.24%	19,123
3	synthetic oestrogen oral	6.44%	5,799
4	natural oestrogen oral	3.22%	2,898
5	synthetic oestrogen other-natural oestrogen vaginal	2.26%	2,037
6	natural oestrogen other	1.64%	1,481
7	natural oestrogen vaginal-synthetic oestrogen other	1.06%	956
8	natural oestrogen other+progestogen	0.49%	438
9	synthetic oestrogen other-progestogen	0.27%	240
10	natural oestrogen topical	0.23%	209

Figure 56. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall, in SIDIAP.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
HRT = Hormone replacement therapy; SIDIAP = The Information System for Research in Primary Care.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	natural oestrogen oral	36.35%	100,651
2	1	natural oestrogen vaginal	20.48%	56,700
3	1	natural oestrogen topical	17.99%	49,816
4	1	natural oestrogen other	14.71%	40,734
5	1	synthetic oestrogen oral	3.27%	9,064
6	1	natural oestrogen other+progestogen	1.86%	5,163
7	1	natural oestrogen vaginal+progestogen	1.83%	5,058
8	1	natural oestrogen oral+progestogen	0.88%	2,428
9	1	synthetic oestrogen vaginal	0.45%	1,251
10	1	progestogen	0.42%	1,154

b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	natural oestrogen oral	27.44%	75,966
2	natural oestrogen vaginal	17.12%	47,400
3	natural oestrogen topical	14.65%	40,574
4	natural oestrogen other	9.45%	26,163
5	synthetic oestrogen oral	2.35%	6,501
6	natural oestrogen topical-natural oestrogen vaginal	1.61%	4,460
7	natural oestrogen oral-natural oestrogen other	1.56%	4,333
8	natural oestrogen vaginal-natural oestrogen topical	1.52%	4,196
9	natural oestrogen oral-natural oestrogen vaginal	1.17%	3,252
10	natural oestrogen other-natural oestrogen oral	1.08%	2,982

Figure 67. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall, in CPRD GOLD.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another.
CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

9.4.2. HRT treatment pattern stratified by prespecified calendar periods

Treatment patterns stratified by prespecified calendar periods demonstrated distinct patterns across time periods and data sources.

In DK-DHR, treatment patterns following initiation of HRT evolved across calendar periods (**Figure 18**). During 1995–2002, postmenopausal women initiated HRT therapy with oral oestrogen (47.5%), vaginal (32.4%), and other oestrogen products (14.9%). Concomitant use of oestrogen and progestogen as separate products was uncommon, with other oestrogen plus progestogen combinations accounting for 1.1% of initiations. Treatment pathways reflected diversity, with oral (32.2%) and vaginal oestrogen products (29.4%) as the most frequent single-line treatments, and a range of switching patterns between oral and vaginal or other oestrogen products. In 2003–2015, there was a clear shift towards vaginal oestrogen products, which became the predominant first-line therapy (79.5%), while use of oral oestrogen (14.1%) and other oestrogen products (2.6%) declined substantially. All other treatment categories each accounted for less than 1% of initiations. Concomitant use of oestrogen and progestogen products remained infrequent, with vaginal oestrogen plus progestogen combinations representing the most common combination (0.8%). Treatment pathways during this period were largely characterised by persistence on vaginal oestrogen products (77.6%), with limited switching, most commonly between vaginal and oral products. In 2016–2024, vaginal oestrogen products continued to dominate first-line treatment (77.6%), with further reductions in oral oestrogen use (9.7%). Other oestrogen and topical products each accounted for approximately 2–3% of initiations, while treatments involving progestogen remained relatively uncommon (≤2% individually). Treatment pathways remained stable compared with the previous period, with the majority of women continuing on a single treatment line, most frequently vaginal oestrogen products (75.7%). Among those with treatment changes, transitions most often involved oral oestrogen or addition of progestogen to vaginal products, although these patterns occurred in a small proportion of patients.

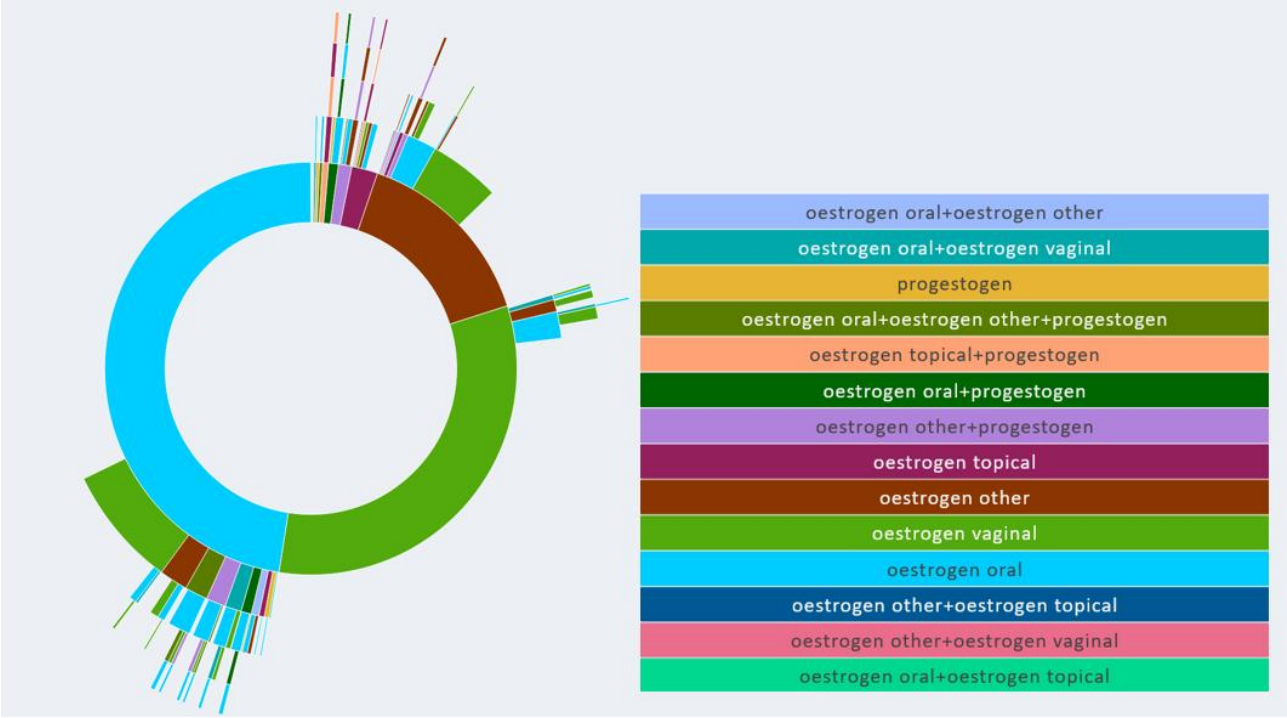
In BIFAP, treatment patterns also changed substantially over time (**Figure 19**). During 2003–2015, the vast majority of postmenopausal women initiated HRT with other oestrogen products (64.4%), followed by oral oestrogen (20.6%), and vaginal oestrogen products (10.4%). Oestrogen products with other routes of administration included products with unknown routes and routes other than oral, topical, or vaginal administration. Concomitant use of oestrogen and progestogen as separate products was infrequent, with other oestrogen plus progestogen (2.6%) being the most commonly observed first-line combination. Most women remained on a single line of treatment; among those who switched, the most common transitions were between different oestrogen products, including vaginal to other oestrogen (1.8%) and oral to other oestrogen (1.1%). In 2016–2024, single-product therapy remained predominant in BIFAP but with increasing use of other oestrogen products, accounting for 80.6% of first-line treatments, followed by oral oestrogen (12.1%). Concomitant use of oestrogen and progestogen as separate products was still uncommon, with other oestrogen plus progestogen (3.1%) and topical oestrogen plus progestogen (0.9%) representing the most frequent combinations. Treatment pathways during this period continued to be dominated by single-line therapy, while among women with treatment changes, switching most commonly occurred between other and oral oestrogen formulations or involved the addition of progestogen.

In SIDIAP, the majority of postmenopausal women initiated HRT with single product from 2003 to 2015, including other oestrogen (88.2%), oral oestrogen (8.6%), and vaginal oestrogen (2.1%) (**Figure 20**). Concomitant use of oestrogen and progestogen as separate products was observed in a small proportion of postmenopausal women with other oestrogen and progestogen being most frequent combination (0.3%).

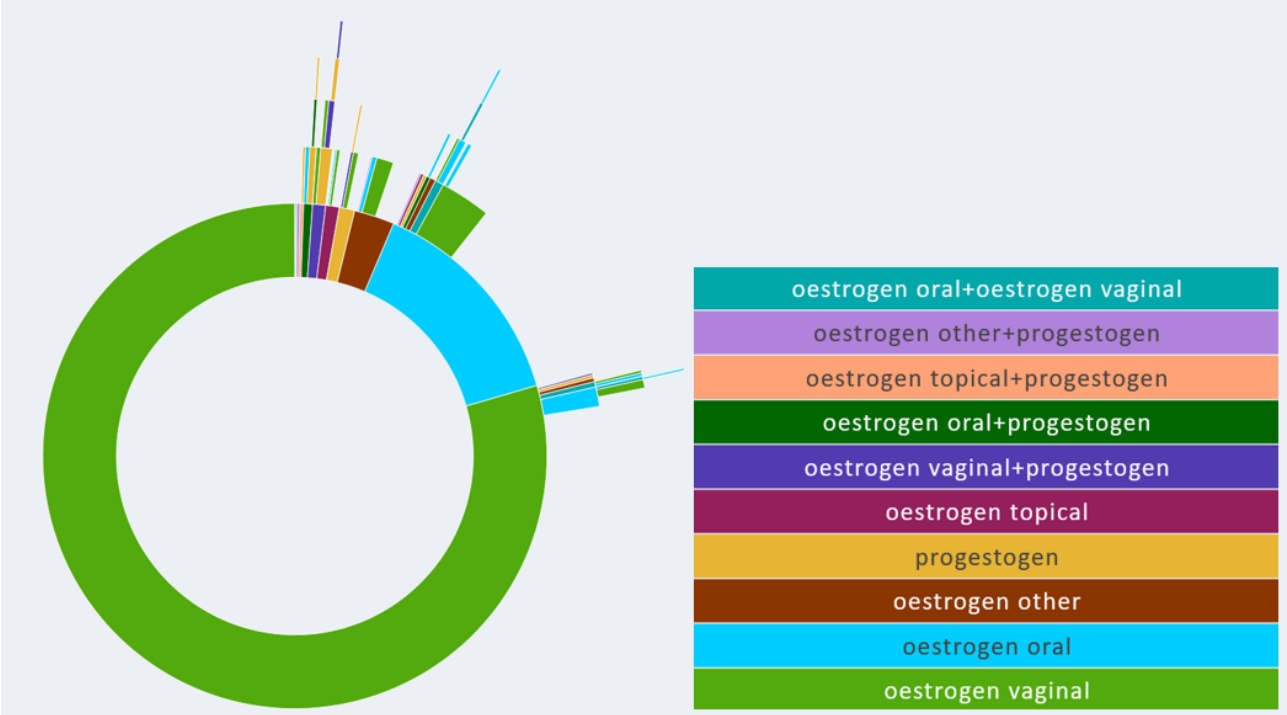
Most postmenopausal women stayed on single line HRT, while among women that switched treatments, most common was a switch from other oestrogen to vaginal oestrogen (2.4%) and vaginal to other oestrogen products (0.6%). For the subsequent period from 2016 to 2024, single product treatment remained predominant with greater diversity across treatment categories (**Figure 20**). In addition to other oestrogen products (34.5%), vaginal oestrogen (48.3%), and oral oestrogen (14.8%), other oestrogen and progestogen combinations (1.4%) were also observed. Among pathways involving sequential HRT therapies, switches occurred between oestrogen products, from other to vaginal oestrogen (2.3%), vaginal to other oestrogen (1.7%), oral to vaginal oestrogen (0.4%), oral to other oestrogen (0.3%), or other to oral oestrogen (0.2%).

In CPRD GOLD, treatment patterns following HRT initiation also changed over time (**Figure 21**). During 1995–2002, first-line therapy was predominantly oral oestrogen (69.4%), with substantially lower use of other (12.9%), topical (8.1%), and vaginal oestrogen products (8.0%). Concomitant use of oestrogen and progestogen as separate products was uncommon, with each combination accounting for less than 1% of initiations. Treatment pathways were largely characterised by persistence on oral oestrogen (58.6%), although a range of switches between oral, vaginal, and other oestrogen products was observed. In 2003–2015, the distribution of first-line treatments became more balanced, with oral oestrogen products remaining the most common (40.6%), followed by vaginal (28.0%), and topical oestrogen (21.1%), while use of other oestrogen products declined (7.1%). Oral oestrogen plus progestogen represented the most frequent combination (1.2%). Treatment pathways reflected a reduction in dominance of single oral oestrogen, with greater representation of vaginal and topical oestrogen as single-line therapies, and switching most commonly occurring between these products. In 2016–2024, no single first-line therapy predominated, with use distributed across other (25.3%), topical (21.7%), vaginal (20.6%), and oral oestrogen products (19.0%). Compared with earlier periods, concomitant use of oestrogen and progestogen was more frequently observed, particularly topical oestrogen plus progestogen (5.2%) and other oestrogen plus progestogen (5.0%), although all other combinations remained uncommon. Treatment pathways in this period were more heterogeneous, with topical (18.3%), vaginal (17.1%), other (16.2%), and oral oestrogen products (12.2%) contributing similarly among the most common single-line treatments. Switching patterns most frequently involved transitions between oestrogen products or addition of progestogen, each representing a relatively small proportion of women.

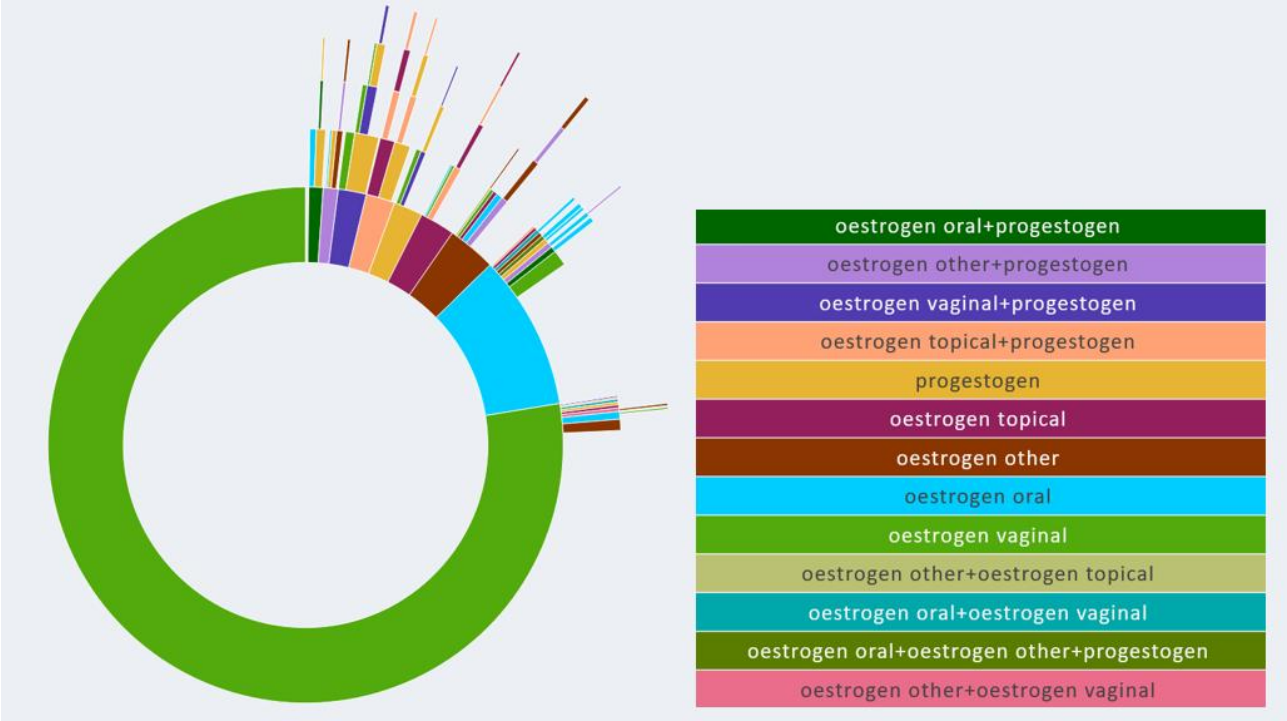
Calendar period 1995–2002



Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1995–2002				
1	1	oestrogen oral	47.52%	49,637
2	1	oestrogen vaginal	32.39%	33,836
3	1	oestrogen other	14.85%	15,510
4	1	oestrogen topical	2.04%	2,128
5	1	oestrogen other+progestogen	1.05%	1,099
6	1	oestrogen oral+progestogen	0.76%	796
7	1	oestrogen topical+progestogen	0.47%	494
8	1	oestrogen oral+oestrogen other+progestogen	0.25%	259
9	1	progestogen	0.24%	248
10	1	oestrogen oral+oestrogen vaginal	0.18%	186
2003–2015				
1	1	oestrogen vaginal	79.51%	108,303
2	1	oestrogen oral	14.09%	19,187
3	1	oestrogen other	2.59%	3,531
4	1	progestogen	0.99%	1,342
5	1	oestrogen topical	0.87%	1,188
6	1	oestrogen vaginal+progestogen	0.84%	1,138
7	1	oestrogen oral+progestogen	0.57%	779
8	1	oestrogen topical+progestogen	0.22%	299
9	1	oestrogen other+progestogen	0.20%	273
10	1	oestrogen oral+oestrogen vaginal	0.09%	128
2016–2024				
1	1	oestrogen vaginal	77.58%	70,642
2	1	oestrogen oral	9.72%	8,850
3	1	oestrogen other	3.05%	2,781
4	1	oestrogen topical	2.20%	2,007
5	1	progestogen	1.83%	1,668
6	1	oestrogen topical+progestogen	1.81%	1,652
7	1	oestrogen vaginal+progestogen	1.77%	1,610

ID	Line	Drug combination	Percentage	Frequency
8	1	oestrogen other+progestogen	0.93%	850
9	1	oestrogen oral+progestogen	0.90%	820
10	1	oestrogen other+oestrogen vaginal	0.06%	52

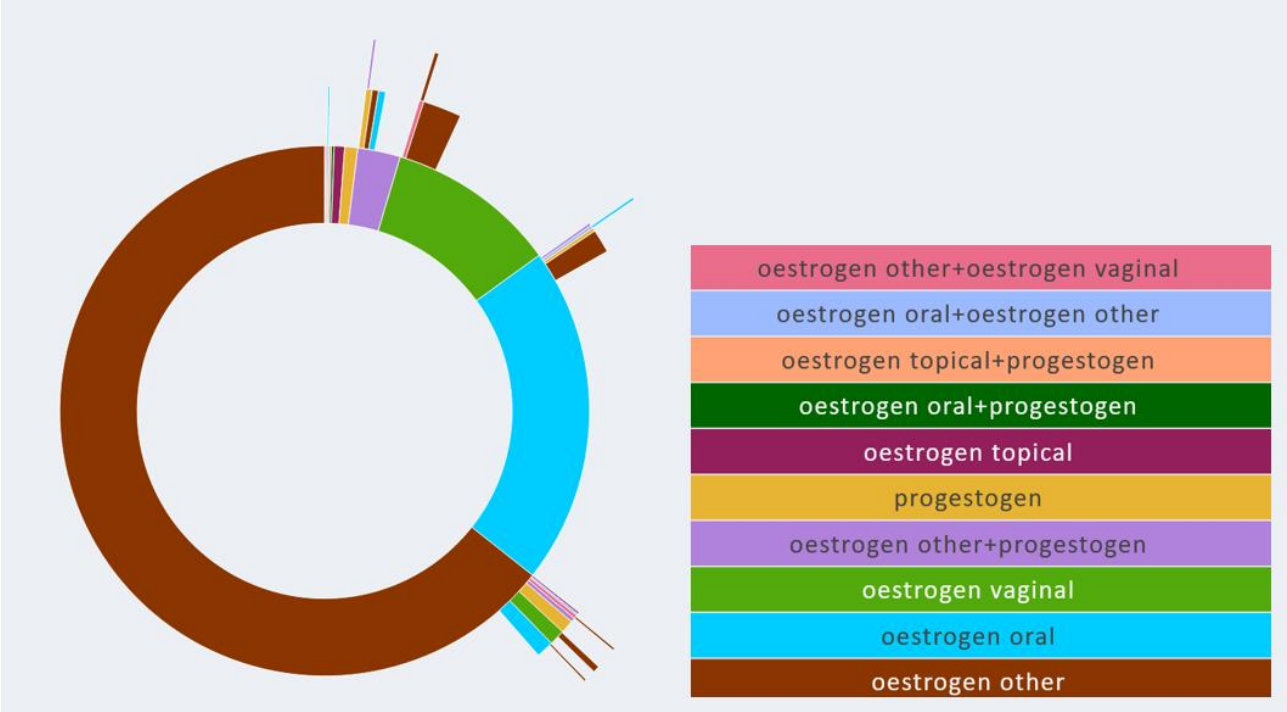
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1995–2002			
1	oestrogen oral	32.18%	33,615
2	oestrogen vaginal	29.40%	30,706
3	oestrogen other	7.32%	7,651
4	oestrogen oral-oestrogen vaginal	7.15%	7,472
5	oestrogen other-oestrogen vaginal	4.32%	4,515
6	oestrogen other-oestrogen oral	1.19%	1,238
7	oestrogen topical	0.94%	980
8	oestrogen vaginal-oestrogen oral	0.82%	856
9	oestrogen oral-oestrogen other	0.80%	836
10	oestrogen oral-oestrogen oral+oestrogen other+progestogen-oestrogen oral	0.67%	701
2003–2015			
1	oestrogen vaginal	77.57%	105,662
2	oestrogen oral	9.86%	13,426
3	oestrogen oral-oestrogen vaginal	2.37%	3,232
4	oestrogen other	1.23%	1,679
5	oestrogen other-oestrogen vaginal	0.86%	1,176
6	progestogen	0.50%	686
7	oestrogen vaginal-oestrogen oral	0.49%	663
8	oestrogen topical	0.49%	662
9	oestrogen vaginal-oestrogen oral-oestrogen vaginal	0.34%	457
10	progestogen-oestrogen vaginal	0.27%	366
2016–2024			
1	oestrogen vaginal	75.74%	6,8964
2	oestrogen oral	7.11%	6,470
3	oestrogen other	1.66%	1,513
4	oestrogen topical	1.46%	1,329
5	progestogen	1.22%	1,108
6	oestrogen oral-oestrogen vaginal	0.76%	689
7	oestrogen vaginal+progesterone-progestogen	0.58%	527
8	oestrogen vaginal+progestogen-oestrogen vaginal	0.46%	421
10	oestrogen vaginal-oestrogen other	0.44%	405
9	oestrogen topical+progestogen-progestogen	0.44%	405

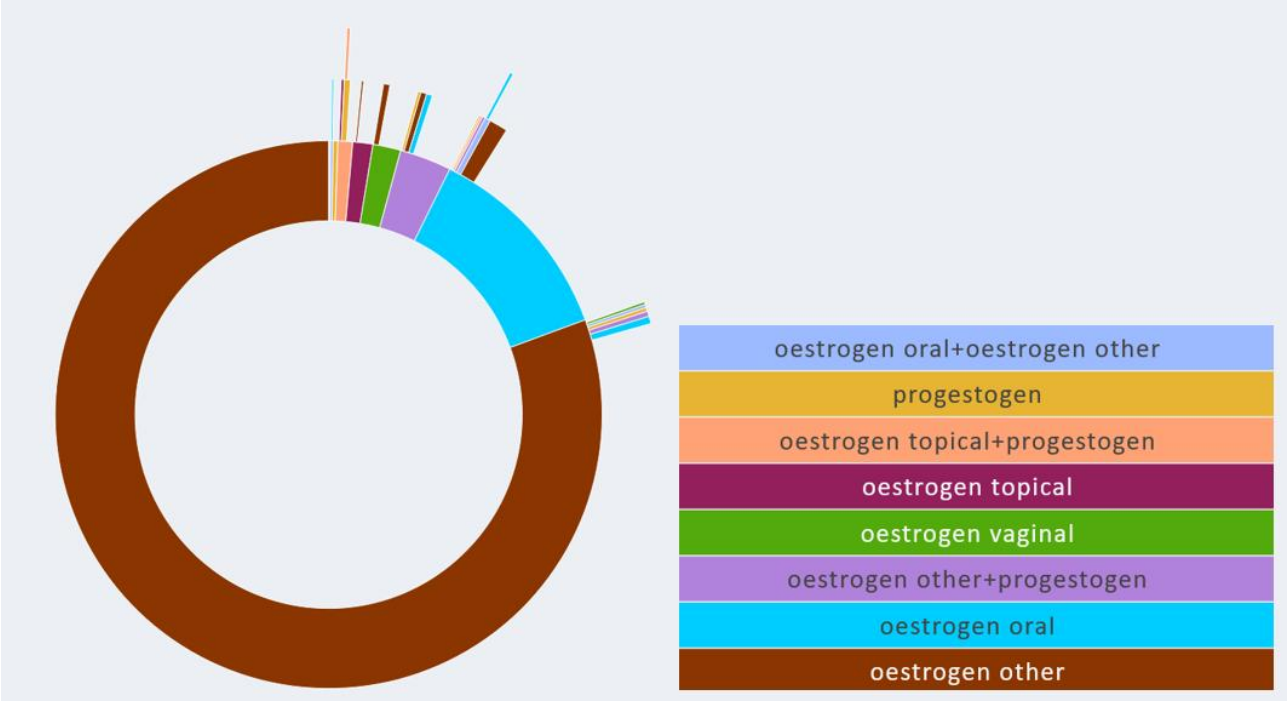
Figure 18. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in DK-DHR.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 1995–2002, 2003–2015, 2016–2024.
DK-DHR = Danish Data Health Registries.

Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
2003–2015				
1	1	oestrogen other	64.36%	31,035
2	1	oestrogen oral	20.62%	9,944
3	1	oestrogen vaginal	10.41%	5,021
4	1	oestrogen other+progestogen	2.60%	1,255

ID	Line	Drug combination	Percentage	Frequency
5	1	progestogen	0.79%	381
6	1	oestrogen topical	0.64%	309
7	1	oestrogen oral+progestogen	0.16%	79
8	1	oestrogen topical+progestogen	0.15%	70
9	1	oestrogen oral+oestrogen other	0.13%	64
10	1	oestrogen other+oestrogen vaginal	0.11%	51
2016–2024				
1	1	oestrogen other	80.63%	107,262
2	1	oestrogen oral	12.07%	16,059
3	1	oestrogen other+progestogen	3.06%	4,068
4	1	oestrogen vaginal	1.65%	2,199
5	1	oestrogen topical	1.18%	1,575
6	1	oestrogen topical+progestogen	0.87%	1,162
7	1	progestogen	0.27%	359
8	1	oestrogen oral+oestrogen other	0.16%	211
9	1	oestrogen other+oestrogen vaginal	0.03%	41
10	1	oestrogen oral+progestogen	0.03%	37

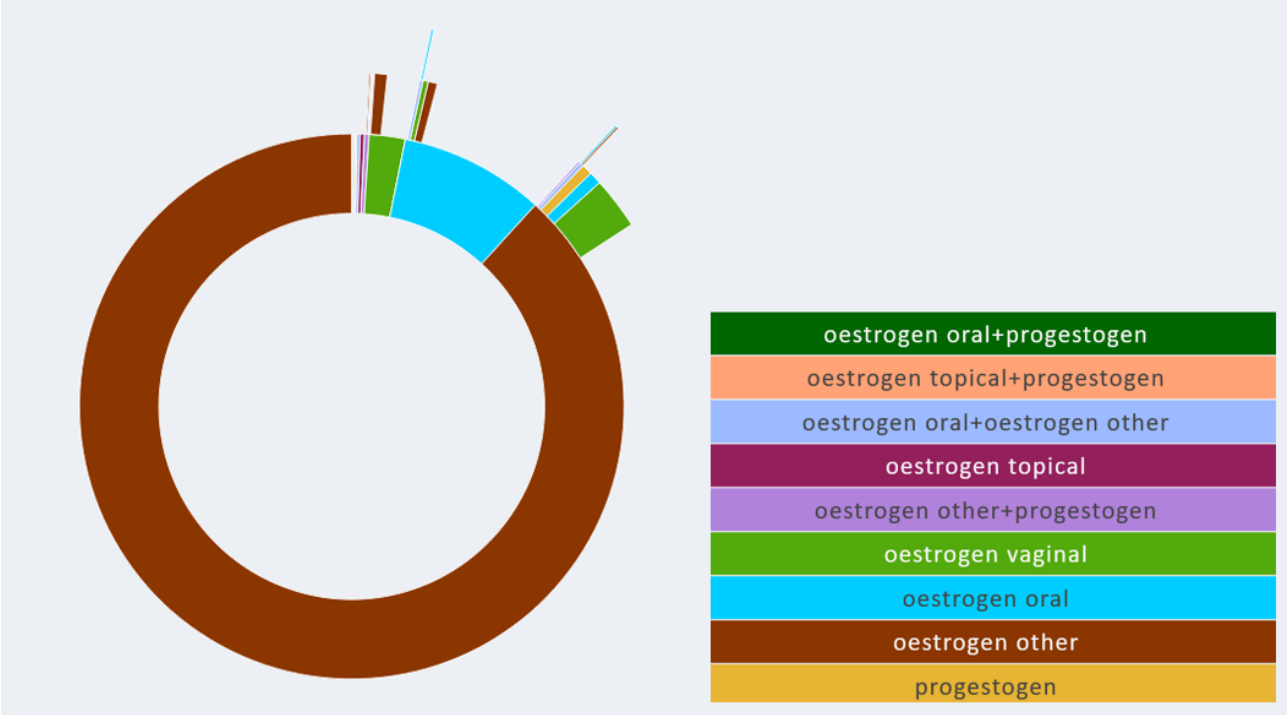
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
2003–2015			
1	oestrogen other	61.44%	29,628
2	oestrogen oral	18.81%	9,071
3	oestrogen vaginal	8.15%	3,928
4	oestrogen vaginal-oestrogen other	1.84%	888
5	oestrogen other+progestogen	1.58%	763
6	oestrogen oral-oestrogen other	1.09%	527
7	oestrogen other-oestrogen oral	0.75%	362
8	progestogen	0.68%	328
9	oestrogen other-progestogen	0.61%	295
10	oestrogen topical	0.55%	267
2016–2024			
1	oestrogen other	79.38%	105,603
2	oestrogen oral	10.47%	13,931
3	oestrogen other+progestogen	2.29%	3,050
4	oestrogen vaginal	1.31%	1,749
5	oestrogen topical	0.92%	1,230
6	oestrogen oral-oestrogen other	0.84%	1,115
7	oestrogen topical+progestogen	0.37%	494
8	oestrogen vaginal-oestrogen other	0.31%	411
9	oestrogen other-oestrogen oral	0.29%	380
10	oestrogen other+progestogen-oestrogen oral	0.25%	339

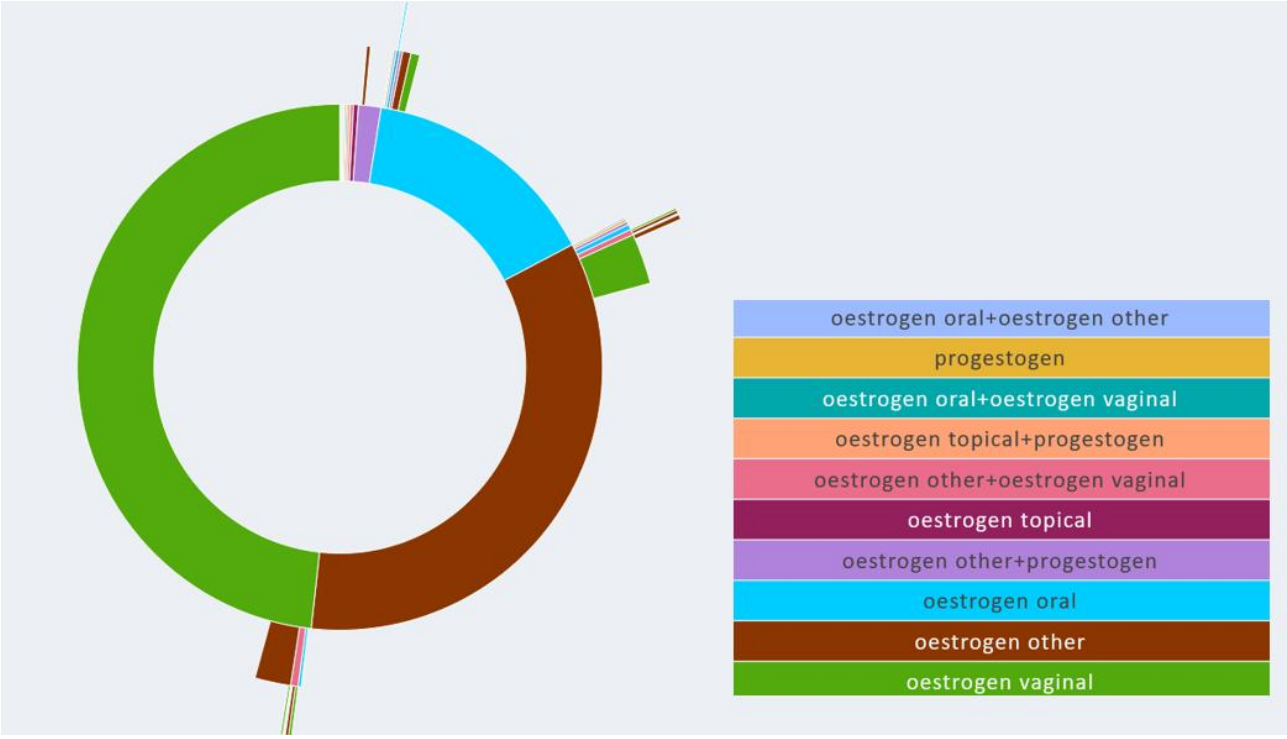
Figure 19. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in BIFAP.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 2003–2015, 2016–2024.
BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público.

Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
2003–2015				
1	1	oestrogen other	88.23%	44,236
2	1	oestrogen oral	8.61%	4,317
3	1	oestrogen vaginal	2.14%	1,074

ID	Line	Drug combination	Percentage	Frequency
4	1	oestrogen other+progestogen	0.27%	134
5	1	oestrogen topical	0.26%	129
6	1	oestrogen oral+oestrogen other	0.19%	96
7	1	oestrogen topical+progestogen	0.10%	48
8	1	oestrogen oral+progestogen	0.09%	43
9	1	progesterone	0.06%	29
10	1	oestrogen other+oestrogen vaginal	0.06%	29
2016–2024				
1	1	oestrogen vaginal	48.25%	19,407
2	1	oestrogen other	34.45%	13,857
3	1	oestrogen oral	14.77%	5,941
4	1	oestrogen other+progestogen	1.38%	556
5	1	oestrogen topical	0.30%	122
6	1	oestrogen topical+progestogen	0.18%	73
7	1	oestrogen other+oestrogen vaginal	0.18%	74
8	1	progestogen	0.11%	43
9	1	oestrogen oral+oestrogen vaginal	0.11%	43
10	1	oestrogen oral+oestrogen other	0.09%	35

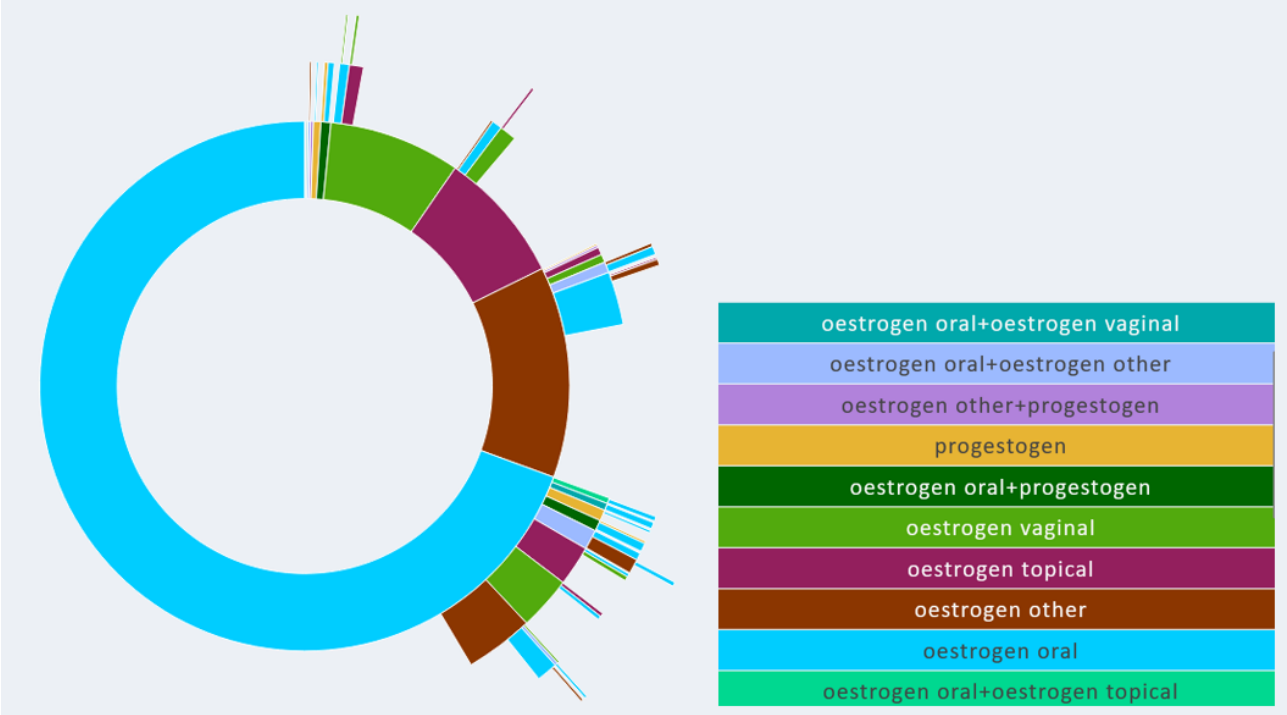
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
2003–2015			
1	oestrogen other	84.16%	42195
2	oestrogen oral	7.63%	3824
3	oestrogen other-oestrogen vaginal	2.43%	1219
4	oestrogen vaginal	1.45%	725
5	oestrogen vaginal-oestrogen other	0.61%	306
6	oestrogen other-oestrogen oral	0.52%	260
7	oestrogen other-progestogen	0.48%	240
8	oestrogen oral-oestrogen other	0.42%	210
9	oestrogen oral-oestrogen vaginal	0.24%	121
10	oestrogen topical	0.22%	109
2016–2024			
1	oestrogen vaginal	45.75%	18398
2	oestrogen other	30.95%	12446
3	oestrogen oral	13.29%	5344
4	oestrogen other-oestrogen vaginal	2.31%	930
5	oestrogen vaginal-oestrogen other	1.70%	682
6	oestrogen other+progestogen	1.00%	401
7	oestrogen oral-oestrogen vaginal	0.42%	169
8	oestrogen oral-oestrogen other	0.32%	129
9	oestrogen topical	0.25%	100
10	oestrogen other-oestrogen oral	0.24%	97

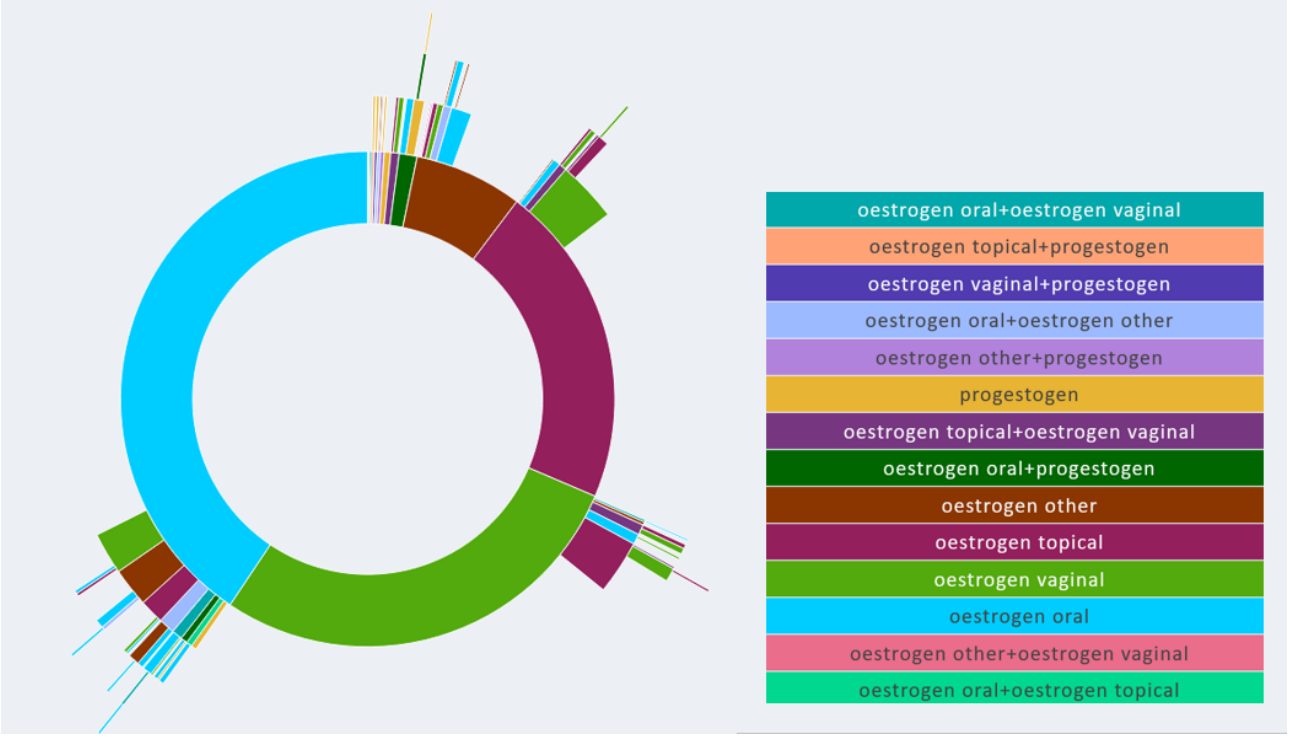
Figure 20. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in SIDIAP.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 2003–2015, 2016–2024. SIDIAP = The Information System for Research in Primary Care.

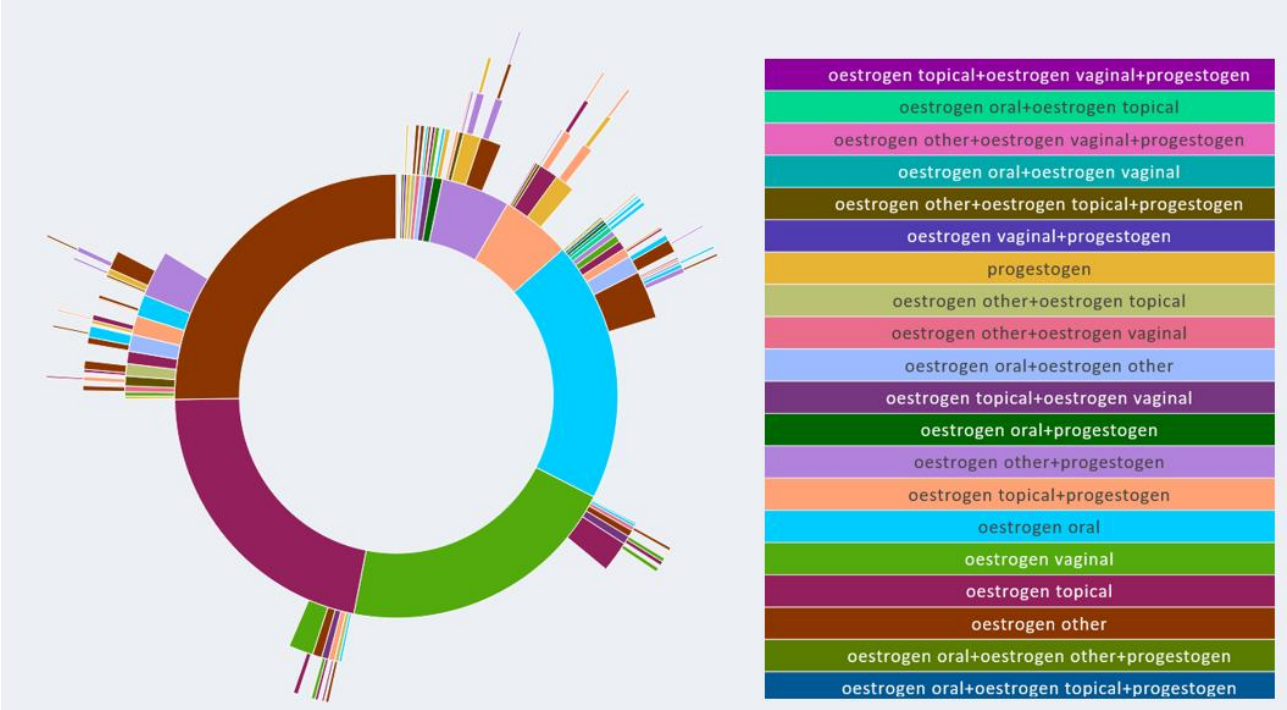
Calendar period 1995–2002



Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1995–2002				
1	1	oestrogen oral	69.42%	34,041
2	1	oestrogen other	12.90%	6,325
3	1	oestrogen topical	8.08%	3,961
4	1	oestrogen vaginal	8.03%	3,937
5	1	oestrogen oral+progestogen	0.61%	298
6	1	progestogen	0.45%	221
7	1	oestrogen other+progestogen	0.17%	85
8	1	oestrogen oral+oestrogen other	0.15%	72
9	1	oestrogen oral+oestrogen vaginal	0.10%	47
10	1	oestrogen oral+oestrogen topical	0.05%	26
2003–2015				
1	1	oestrogen oral	40.60%	49,082
2	1	oestrogen vaginal	27.98%	33,830
3	1	oestrogen topical	21.10%	25,513
4	1	oestrogen other	7.10%	8,581
5	1	oestrogen oral+progestogen	1.17%	1,418
6	1	oestrogen topical+oestrogen vaginal	0.54%	658
7	1	progestogen	0.42%	506
8	1	oestrogen other+progestogen	0.26%	316
9	1	oestrogen vaginal+progestogen	0.18%	217
10	1	oestrogen topical+progestogen	0.17%	207
2016–2024				
1	1	oestrogen other	25.25%	23,328
2	1	oestrogen topical	21.68%	20,030
3	1	oestrogen vaginal	20.57%	19,004
4	1	oestrogen oral	18.99%	17,543
5	1	oestrogen topical+progestogen	5.15%	4,761
6	1	oestrogen other+progestogen	5.01%	4,632
7	1	oestrogen oral+progestogen	0.67%	623
8	1	oestrogen topical+oestrogen vaginal	0.56%	514

ID	Line	Drug combination	Percentage	Frequency
9	1	oestrogen other+oestrogen vaginal	0.34%	313
10	1	progestogen	0.31%	290

b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1995–2002			
1	oestrogen oral	58.56%	28,718
2	oestrogen other	8.63%	4,231
3	oestrogen vaginal	6.70%	3,286
4	oestrogen topical	6.49%	3,184
5	oestrogen oral-oestrogen vaginal	2.34%	1,147
6	oestrogen other-oestrogen oral	2.19%	1,072
7	oestrogen oral-oestrogen other	2.17%	1,066
8	oestrogen oral-oestrogen topical	1.66%	814
9	oestrogen topical-oestrogen vaginal	0.73%	356
10	oestrogen oral-oestrogen other-oestrogen oral	0.72%	354
2003–2015			
1	oestrogen oral	32.39%	39,150
2	oestrogen vaginal	23.59%	28,512
3	oestrogen topical	16.82%	20,337
4	oestrogen other	4.73%	5,715
5	oestrogen topical-oestrogen vaginal	2.58%	3,113
6	oestrogen vaginal-oestrogen topical	2.13%	2,580
7	oestrogen oral-oestrogen vaginal	1.83%	2,209
8	oestrogen oral-oestrogen other	1.26%	1,522
9	oestrogen oral-oestrogen topical	1.02%	1,235
10	oestrogen other-oestrogen oral	0.86%	1,037
2016–2024			
1	oestrogen topical	18.30%	16,907
2	oestrogen vaginal	17.10%	15,798
3	oestrogen other	16.16%	14,935
4	oestrogen oral	12.18%	11,251
5	oestrogen topical+progestogen	2.26%	2,086
6	oestrogen other+progestogen	2.05%	1,895
7	oestrogen oral-oestrogen other	1.77%	1,633
8	oestrogen vaginal-oestrogen topical	1.53%	1,411
9	oestrogen other-oestrogen other+progestogen	1.22%	1,125
10	oestrogen topical-oestrogen vaginal	1.13%	1,041

Figure 21. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in CPRD GOLD.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 1995–2002, 2003–2015, 2016–2024.
CPRD GOLD = Clinical Practice Research Datalink GOLD.

9.4.3. Sensitivity analysis: narrow definition of the study population

In the sensitivity analysis based on a narrow definition of the study population, treatment pattern results were broadly consistent with the trend observed in both the main analysis and the analysis stratified by prespecified calendar period across all data sources (**Figures S5–S12** in **ANNEX V**). The overall trend remained comparable.

10. DISCUSSION

10.1. Key results

A total of 1,370,059 new HRT users (DK-DHR: 448,956; IQVIA DA Germany: 146,740; BIFAP: 328,352, SIDIAP: 105,950, CPRD GOLD: 340,061) and 12,100,035 non-HRT users (DK-DHR: 1,248,826; IQVIA DA Germany: 3,542,357; BIFAP: 4,550,113; SIDIAP: 1,179,632; CPRD GOLD: 1,579,107) met inclusion criteria and were included in the final study population during the study period.

Demographic and clinical characteristics of postmenopausal women

The size of both HRT user and non-HRT user cohorts included in each selected calendar year increased over time across all data sources, as women could contribute to multiple years while under observation. Across cohorts, the study population was predominantly composed of women aged ≥50 years, with limited representation of women aged <50 years.

The proportion of postmenopausal women with a recorded menopause diagnosis varied across data sources: up to 1.3% of the HRT users and <0.5% of non-HRT users in DK-DHR; in 6.3–14.3% of HRT users compared with <1% of non-HRT users in IQVIA DA Germany; in 2.2–13.5% of HRT users compared to 1.2–3.4% of non-HRT users in BIFAP; <8% of HRT users and <4% of non-HRT users in SIDIAP; and in 2.8–30.3% of HRT users compared with <2.2% of non-HRT users in CPRD GOLD.

Availability of BMI and smoking status variables was limited across most data sources. The use of a one year assessment window identified recent recordings but may have underestimated the availability of these characteristics in data sources where measurements and lifestyle factors were recorded less frequently.

HRT products used at initiation varied substantially across data sources and calendar years, with results reflecting the product recorded at HRT initiation and not accounting for concomitant use of separately prescribed progestogens or other HRT products. In DK-DHR, oestradiol-containing plain products accounted for 40.5% in 2000 and 75.5% in 2024, while fixed combination products containing both oestrogen and progestogen were less frequent (e.g. fixed oestradiol norethisterone combination products: 22.5% in 2000 and 11.7% in 2024; fixed oestradiol medroxyprogesterone combination products: 4.6% in 2000 to 1.7% in 2024). In IQVIA DA Germany, the frequency of oestriol-containing products increased to >50% based on characterisation between 2020 and 2024, while fixed combination products decreased to <6%. In BIFAP, promestriene plain (59.9%) was most evident in 2005, while the use of promestriene plain decreased to 29.3% and use of oestriol plain increased to 43.3% in 2024. In SIDIAP, promestriene plain products were the most frequently recorded HRT between 2010 and 2015 (78.3%–87.0%), declining to 60.4% in 2024, while the use of oestradiol plain products increased to 6.1% in 2024, and oestriol plain products to 22.0% in 2024. In CPRD GOLD, dienestrol plain products (23.3%) were most frequently prescribed in 1990, while reported use of oestradiol plain (38.0%), oestradiol norethisterone (28.3%), and oestriol plain (24.1%) was most frequent in 2024.

Concomitant conditions

The frequency of prespecified concomitant conditions (assessed any time prior to the prespecified mid-year characterisation date in each selected calendar year) increased over calendar time in both HRT users and non-HRT users. HRT users generally showed a higher comorbidity burden, although differences varied by data source. In DK-DHR, hypertension and dyslipidaemia were each recorded in >40% of the HRT users

based on characterisation in 2024 versus 30% of non-HRT users in 2024, while osteoporosis (20.7% vs 10.6%) and sleep disorders (34.9% vs 22.5%) were approximately two-fold more frequent among HRT users. In IQVIA DA Germany, cardiometabolic conditions were common in both cohorts, with hypertension remaining stable over time at around 20–29%. Differences between cohorts were modest overall, although anxiety and sleep disorders remained consistently more frequent among HRT users. In BIFAP, dyslipidaemia was recorded in 45.7% of HRT users compared to 36.8% of non-HRT users and osteoporosis in 14.3% of HRT users compared to 8.4% of non-HRT users for example. In SIDIAP, higher frequency was observed among HRT users in 2024 for anxiety (44.5% vs 35.8%), hypertension (32.0% vs 25.8%), dyslipidaemia (26.9% vs 19.6%), osteoporosis (19.6% vs 9.5%), and sleep disorders (30.7% vs 19.2%) based on characterisation in 2024. Although both BIFAP and SIDIAP are Spanish data sources, they cover different populations, with BIFAP including multiple Spanish regions and SIDIAP restricted to Catalonia. Similarly, in CPRD GOLD, frequency of several conditions was higher among HRT users compared with non-HRT users for anxiety (16.7% vs 10.7%), depression (24.0% vs 15.7%), hypertension (23.9% vs 22.7%), dyslipidaemia (7.8% vs 6.3%), osteoporosis (6.3% vs 5.3%), and sleep disorders (13.0% vs 7.9%) based on characterisation in 2024. A record of hysterectomy was uncommon across all data sources, with more than 88% of women being classified as having an intact uterus in both HRT users and non-HRT users throughout selected calendar years.

Top 10 comedications and comorbidities

Analgesics, gastroprotective agents, cardiovascular medications, bone-related therapies, and endocrine therapies were among the most frequently recorded concomitant treatments in both HRT users and non-HRT users. The most frequently recorded comorbidities increased over time and were dominated by pain-related, cardiovascular, and infectious conditions. Compared with non-HRT users, HRT users consistently showed higher prevalence of pain-related, urogenital, and menopause-associated comorbidities, while non-HRT users more frequently presented with chronic systemic diseases. These patterns were consistent across data sources and over time.

Annual prevalence of HRT use among postmenopausal women

The annual prevalence of HRT use among postmenopausal women showed distinct temporal trends across data sources during the study period. In DK-DHR, the annual prevalence of overall HRT use remained stable at approximately 26.6% in 1996 until 2002, followed by a decline to 18.6% in 2005 and subsequent stabilisation. In IQVIA DA Germany, the annual prevalence decreased from 11.8% in 1993 to 2.2% in 2020, with a subsequent increase to 3.6% in 2024. In BIFAP, the annual prevalence decreased from 6.5% in 2005 to 0.7% in 2015, remained relatively stable until 2022, and increased to 5.3% in 2024. In SIDIAP, the annual prevalence was around 6.0% between 2010 and 2013, decreased sharply to 1.2% in 2015, and increased to 3.5% by 2024. In CPRD GOLD, the annual prevalence increased from 2.1% in 1988 to a peak of 26.8% in 2001, followed by a decrease to 14.2% in 2005, and a more gradual decline to 8.9% in 2015, with a subsequent increase to 17.7% in 2024.

Across all data sources, temporal trends were broadly consistent across women aged 50 to 60 years and above 60 years of age, while substantially higher annual HRT prevalence estimates were observed among women aged below 50 years with premature menopause. In DK-DHR, prevalence of HRT use in this latter group decreased from approximately 70% in the 1990s to 46.7% in 2013, followed by an increase to 54.1% in 2024. In IQVIA DA Germany and SIDIAP, prevalence of HRT use in women aged below 50 years increased over time, reaching 25.8% and 24.1% in 2024, respectively. In BIFAP, prevalence of HRT use decreased from 21.7% in 2005 to 16.3% in 2009, before increasing to 23.7% in 2024. In CPRD GOLD, prevalence of HRT use was censored due to low counts in 1989 and increased from 36.5% in 1990 to 75.2% in 1996, remained relatively stable until 2002, fluctuated thereafter, and reached 62.8% in 2024.

The annual prevalence of HRT use stratified by formulation showed distinct trends. In DK-DHR, the annual prevalence of oestrogen-containing products was approximately 15% in the 1990s, decreased to 13.7% in

2005, and increased to 17.1% in 2024. In IQVIA DA Germany, the annual prevalence of oestrogen-containing products decreased from 8.4% in 1993 to around 2% in the 2000s, followed by a modest increase to 3.2% in 2024. In BIFAP, the annual prevalence of oestrogen-containing products was 4.8% in 2005 and 4.9% 2024, with fluctuation in estimates over time, and in SIDIAP, it was around 5.7% in 2010 to 2013, decreased to 0.7% in 2015, and subsequently increased to 3.0% in 2024. In CPRD GOLD, the annual prevalence of oestrogen-containing products was 4.1% in 1989, fluctuated over time, reaching 12.8% in 2024. The annual prevalence of fixed combination products containing oestrogen and progestogen decreased from 13.5% in 1996 to 1.2% in 2024 in DK-DHR, from 3.2% in 1993 to 0.4% in 2024 in IQVIA DA Germany, while remaining below 0.5% in BIFAP and SIDIAP. In CPRD GOLD, the annual prevalence followed a similar pattern as observed for oestrogen-containing products. Fixed combination products containing androgens and other products did not contribute or contributed minimally to overall HRT prevalence across all data sources. When stratified by age, the annual prevalence of HRT formulation was consistently higher among postmenopausal women aged below 50 years across data sources for both oestrogen-containing products and combination products containing oestrogen and progestogen, while there was no observed age differences for other HRT products.

A shift in route of administration was observed, with decreasing use of systemic HRT products and increasing use of products with local effect over time. In DK-DHR, the annual prevalence of systemic HRT products decreased from approximately 21% in 1996 to 2002 to 3.1% in 2024, whereas the annual prevalence of HRT products with a local effect increased from 3.4% in 1996 to 16.1% in 2023. Similar patterns were observed in IQVIA DA Germany, where the annual prevalence of systemic HRT products decreased from 10.8% in 1993 to 2.1% in 2024, while HRT products with a local effect remained below 1.8%. In SIDIAP, the annual prevalence of systemic HRT products remained low, whereas HRT products with a local effect slightly increased over the time. In CPRD GOLD, systemic HRT products followed a similar trend as for overall annual HRT prevalence, while products with a local effect increased from 0.5% in 1989 to 2.0% in 2024. In BIFAP, the annual prevalence of systemic HRT products was 2.7% in 2005 and 1.1% of HRT products with a local effect in 2005, and estimates remained below 1.5% during the subsequent years. When stratified by age, distinct patterns were observed among data sources.

Finally, natural HRT products represented the majority of HRT use across data sources and followed overall temporal trends. In DK-DHR, the annual prevalence of natural HRT products was around 24% in 1996 to 2002, declining to 18.0% in 2005, and subsequent stabilisation. In IQVIA DA Germany, the annual prevalence of natural HRT products decreased from 11.8% in 1993 to 2.2% in 2020, followed by an increase to 3.6% in 2024. In SIDIAP, synthetic HRT products predominated in earlier years (around 6% in 2010–2013), whereas natural HRT products remained limited. In BIFAP, synthetic HRT products represented the majority of prevalent use in 2005–2013 (around 2%), while natural HRT products remained limited (<1% during majority of study period), with an increase to 4.1% in 2024. In CPRD GOLD, natural HRT products predominated and increased from 1.8% in 1988 to 25.1% in 2001, followed by a decrease to 8.6% in 2015, and a subsequent increase to 17.6% in 2024, while synthetic HRT products increased from 1.1% in 1989 to 3.8% in 1994, followed by a decrease over time to 0.2% in 2024.

Sensitivity analyses using a narrower population definition yielded higher absolute prevalence estimates but showed consistent temporal trends, supporting robustness of the findings.

Duration of HRT use among postmenopausal women initiating HRT

Treatment duration, estimated by combining consecutive prescription records/dispensings separated by gaps of up to 90 days, varied substantially across HRT products and data sources. The median treatment duration ranged from 11 days for ethinylestradiol-containing products in IQVIA DA Germany to 534 days for fixed combination products containing oestradiol and norethisterone in DK-DHR and 1,826 days for IUD in CPRD GOLD, DK-DHR, and IQVIA DA Germany, reflecting the imputed duration of clinical use. Longer treatment durations were generally accompanied by a higher number of prescription or dispensing records.

The median treatment duration of oestradiol-containing products ranged from 30 days in IQVIA DA Germany to 324 days in DK-DHR, while it ranged from 31 days in IQVIA DA Germany to 306 days in SIDIAP for oestriol-containing products. Use of tibolone was generally associated with longer treatment durations, ranging from 175 days in IQVIA DA Germany to 377 days in SIDIAP. Very short treatment durations were observed for historically used products, such as dienestrol and diethylstilbestrol. However, these estimates should be interpreted with caution given historical context and potential limitations in exposure recording. Fixed combination products containing oestrogen and progestogen were generally associated with longer treatment durations (oestradiol and norethisterone: from 168 days in IQVIA DA Germany to 534 days in DK-DHR; oestradiol and medroxyprogesterone: from 224 days in IQVIA DA Germany to 396 days in DK-DHR; oestradiol and levonorgestrel: from 84 days in IQVIA DA Germany to 425 days in DK-DHR). The median treatment duration for levonorgestrel IUD was imputed and aligned with expected clinical use in DK-DHR, IQVIA DA Germany, and SIDIAP.

Age-stratified analyses showed heterogeneity across data sources, with treatment durations generally longer among women aged <50 years than among those aged 50–60 years or >60 years. Treatment durations were also generally longer when estimated using all prescription records/dispensings throughout follow-up, without applying the prespecified gap. The overall patterns remained consistent across HRT types and data sources.

HRT treatment patterns among postmenopausal women

Treatment patterns up to 10 years following HRT initiation in postmenopausal women varied across data sources but were consistently characterised by predominant use of a single product and limited treatment switching. In DK-DHR, the most common first-line treatments were natural oestrogen vaginal (63.8%) and natural oestrogen oral products (22.7%), while in CPRD GOLD natural oestrogen oral products (36.4%), natural oestrogen vaginal products (20.5%), natural oestrogen topical products (18.0%), and natural oestrogen with other routes of administration (14.7%) were most common. In BIFAP, natural oestrogen products with other routes of administration (44.6%) and synthetic oestrogen products with other routes of administration (31.8%) were the most frequent first-line treatments. In SIDIAP, first-line treatment was dominated by synthetic oestrogen products with other routes of administration (62.3%) and natural vaginal oestrogen products (22.7%). Concomitant use of oestrogen and progestogen as separate products was uncommon. The majority of women contributed to single-step treatment pathways, indicating that no treatment changes were identified according to the predefined pathway algorithm. Among those who changed treatment, transitions most commonly occurred between different oestrogen products.

Treatment patterns stratified by prespecified calendar periods demonstrated distinct temporal trends across data sources. In DK-DHR, a shift from oral to vaginal oestrogen products occurred over time, with vaginal oestrogen products becoming the dominant first-line treatment from 2003 onwards. In CPRD GOLD, treatment patterns became more evenly distributed across oestrogen-containing products in later years, accompanied by a modest increase in concomitant use of oestrogen and progestogen. In BIFAP, oestrogen products with other routes of administration remained the predominant first-line treatment throughout the study period, increasing from 64.4% in 2003–2015 to 80.6% in 2016–2024. In SIDIAP, the initial predominance of oestrogen products with other routes of administration (88.2%) shifted towards greater use of vaginal oestrogen products (48.3%) in 2016–2024. Across all periods and data sources, most women remained on a single line of treatment, while treatment changes primarily involved switching between oestrogen products or the addition of progestogen.

10.2. Strengths and limitations of the research methods

Strengths

This study leveraged a large and diverse set of Real-World Data sources from four European countries (Denmark, Germany, Spain, and the United Kingdom), covering both registry-based and outpatient general

practitioner care. The geographic coverage and longitudinal nature of these data sources enabled assessment of treatment patterns over time in Europe. Use of the OMOP CDM ensured standardised data structuring, harmonised variables, and consistent cohort definitions, facilitating reproducible analyses across sources.

Limitations

This study was informed by routinely collected healthcare data, which introduced several important considerations that may have influenced the interpretation of the findings. The results reflect only the populations captured within the five data sources included in this study and may not be generalisable to other countries or healthcare systems.

Routinely collected electronic health records are primarily designed for clinical purposes rather than research, and as such, may contain incomplete, inconsistent, or variably recorded information. This affects the documentation of key variables such as comorbidities, symptoms, and clinical indications, which are essential for accurate patient-level characterisation. Consequently, the study can only capture information that has been recorded in the source data, and incomplete documentation may lead to under-ascertainment. For example, in Germany, hysterectomy procedures are typically performed in hospitals and may only be captured if subsequently documented by office-based gynaecologists in IQVIA DA Germany. The recording of prior hysterectomy therefore depends on how this information is documented in the practice system. Furthermore, historical hysterectomies may be recorded using broad diagnosis codes indicating the absence of reproductive organs or follow-up after surgery rather than specific hysterectomy-related codes. Consequently, hysterectomy may not always be identified through the procedure and diagnosis codes used in the OMOP CDM. As a result, estimates reflect recorded histories of hysterectomy rather than all hysterectomies performed, potentially contributing to under-ascertainment of hysterectomy in this data source.

Identification of postmenopausal women was based on an age-based proxy across all data sources, due to inconsistent or absent documentation of menopause diagnoses. For early menopause, additional diagnostic codes and conditions compatible with menopause were used. While commonly used in observational research, this may have led to misclassification, particularly in cases of early menopause.

Data sources have information on the prescribing of medications, but information on whether prescriptions were redeemed or consumed was not available. Furthermore, some women may be treated in specialist centres, and prescriptions issued outside primary care practices may have not been recorded in data sources that include only information on prescribing in primary care (e.g. CPRD and BIFAP), potentially resulting in underestimation of HRT use.

Indications for medication use were not recorded as such in the data sources. Therefore, medicines such as progesterones may have been prescribed for conditions other than menopause management. Additionally, classification of HRT included both medications specifically indicated for HRT and those that may have served as contraceptives. In postmenopausal women, such medications are considered HRT.

Estimation of treatment duration was also subject to limitations inherent to real-world data. Due to documentation gaps as well as complexities related to registration of heterogeneous administrative form use durations, end-of-treatment dates may have been incomplete or lacked precise end dates, requiring methods aligned with OMOP CDM conventions. While this promotes consistency across sources, it may not have fully captured true treatment variability and should be interpreted with caution.

The COVID-19 pandemic may have influenced healthcare access and prescribing practices, potentially affecting prevalence estimates of HRT use during the pandemic period. However, the study period extended until 31 December 2024, allowing assessment of more recent prescribing practices after the pandemic period.

10.3. Interpretation

Overall, this multi-country study provides a description of HRT use among postmenopausal women across several European healthcare settings, including more than 1.3 million HRT initiators during the study period. The clinical characteristics of women initiating HRT were broadly comparable across data sources and aligned with expectations for postmenopausal populations captured in routine healthcare data. Limited recording of menopause diagnoses and lifestyle-related variables, such as smoking and BMI, reflects known limitations of routinely collected data. These characteristics were assessed within the year preceding each pre-specified calendar date to provide a description of the study population. However, BMI measurements and smoking status are not necessarily recorded on a yearly basis in routine clinical practice and may remain unchanged for extended periods. As a result, restricting ascertainment to a one year window may have underestimated the availability of these variables, particularly in data sources where measurements are recorded intermittently or only during specific clinical encounters. Consequently, the observed high proportion of missing values likely reflects both limitations in routine data capture and the selected assessment window. These limitations primarily affect patient characterisation rather than exposure definition.

The frequency of recorded concomitant conditions should be interpreted in the context of the descriptive study design. These analyses characterised conditions recorded among women contributing to the HRT user cohort at prespecified calendar dates and were not intended to assess prescribing appropriateness or adherence to treatment recommendations. Consequently, the presence of cardiovascular risk factors or other comorbidities among HRT users should not be interpreted as evidence of non-alignment with Summary of Product Characteristics (SmPC) recommendations.[15]

Annual prevalence of HRT use showed substantial variation between data sources but consistent temporal patterns with sharp declines in the early 2000s, and stabilisation or modest increases in more recent years. The use of HRT decreased in the early 2000s with the initial publication of the Women's Health Initiative (WHI) results in 2002 and subsequent changes in clinical guidance, followed by later re-evaluation of risk profiles by age, formulation, route of administration, and timing of initiation.[16-18] The observed trends are broadly consistent with the evolution of clinical recommendations and product information, which emphasised individualised prescribing, use of the lowest effective dose for the shortest duration necessary, and careful consideration of route of administration and the need for progestogen in women with an intact uterus receiving systemic oestrogen therapy. The decline in HRT use following the WHI has been attributed to concerns regarding the benefit-risk balance of combined oestrogen-progestin therapy, which subsequently led to more cautious prescribing practices and revision of treatment recommendations. The EMA HRT clinical investigation guideline similarly notes that HRT generally consists of oestrogen alone or in combination with progestogen, with progestogen added to mitigate the increased risk of endometrial cancer associated with systemic oestrogen therapy in women with a uterus. The recent modest increase in HRT prevalence observed in several data sources is also consistent with emerging European utilisation data. A recent French national study by EPI-PHARE, a scientific group in pharmaco-epidemiology, reported a continuous decrease in menopausal hormone therapy use between 2012 and 2022, followed by an increase from 2022 onwards, with prescribing practices increasingly characterised by transdermal oestradiol and micronised progesterone.[19] Similarly, recent Danish nationwide evidence reported declines in menopausal hormone therapy use over time, supporting the temporal patterns observed in the present study. Direct comparison of prevalence estimates should, however, be interpreted with caution, as the Danish study focused on systemic menopausal hormone therapy, whereas the present study additionally included local oestrogen products.[20]

Higher prevalence observed among women aged <50 years across all data sources should be interpreted as reflecting use in women with premature or early menopause and does not represent general HRT use below the age of 50. This pattern is expected and consistent with guidelines recommending HRT in this subgroup.

Differences in absolute prevalence across data sources are likely driven by healthcare system factors, including national guidelines, reimbursement policies, prescribing practices, and data capture mechanisms, rather than true differences in underlying clinical need. Differences in data capture may also contribute to the observed variation. For example, DK-DHR is a nationwide registry, whereas other participating data sources are primarily based on primary care records. Consequently, HRT prescribed by gynaecologists and other specialists may be captured differently across data sources. As this study was designed to characterise HRT utilisation within individual data sources, observed differences between data sources should be interpreted with caution.

The results from SIDIAP warrant specific contextualisation. The decline in HRT prevalence after 2014 coincides with the removal of promestriene from public reimbursement in Spain, while the subsequent increase aligns with its re-introduction in 2023. During periods without public funding, prescriptions may have been issued privately and under recorded in electronic health records, suggesting that observed changes partly reflect reimbursement and data capture rather than abrupt shifts in clinical practice. Sensitivity analyses further support the robustness of prevalence findings, demonstrating that alternative postmenopausal population definitions affected the magnitude of estimates but not the direction or timing of observed trends.

Interpretation of the prevalence analyses should consider that these analyses were based on a pre-specified set of HRT products, including oestrogen-containing products and fixed oestrogen-progestogen combination products. Current recommendations distinguish between local oestrogen products and systemic oestrogen therapy, as the requirement for concomitant progestogen is particularly relevant for systemic oestrogen use in women with an intact uterus. As prevalence analyses did not assess concomitant use of separately prescribed progestogens, some women using oestrogen-containing products may have also received progestogen, in line with treatment recommendations. Therefore, these findings should not be interpreted as evidence of non-alignment with SmPC recommendations or as evidence of unopposed systemic oestrogen use. Rather, they indicate that product-level utilisation patterns need to be interpreted together with route of administration, hysterectomy status, and concomitant prescriptions.[15]

Treatment duration varied substantially across HRT products and data sources. These differences were generally accompanied by corresponding variation in the number of prescription records/dispensings, suggesting that treatment duration estimates were influenced by differences in prescribing patterns and exposure recording practices across data sources. Differences in follow-up time may also have contributed to some of the observed variation (EUPAS1000000821).

Treatment patterns following HRT initiation were characterised by predominant use of single products and limited switching between HRT treatments across data sources. Across prespecified calendar periods, treatment patterns changed over time in a manner consistent with major developments in clinical recommendations. During 1995–2002, initiation was largely dominated by systemic oral oestrogen products with limited switching, reflecting prescribing practice prior to publication of the WHI trial results in 2002. In the subsequent period (2003–2015), declining HRT use and greater diversity in formulations and routes of administration were observed, consistent with recommendations regarding the benefit-risk profile of systemic HRT. In the most recent period (2016–2024), treatment patterns became more heterogeneous, with increased use of local oestrogen products and treatment pathways involving progestogens, which may reflect further refinement of clinical guidance according to formulation, route of administration, age, and timing of treatment initiation.

The evolution of treatment at initiation, towards greater use of oestradiol-containing products in DK-DHR, oestriol-containing products in IQVIA DA Germany, and local oestrogen products in SIDIAP, alongside declining use of combination products, is consistent with changes in the evidence base and guideline recommendations following the WHI publications and subsequent European guidance emphasising more cautious and individualised use of systemic HRT products. Across calendar periods, shifts in formulation

choice and route of administration broadly correspond with major clinical and regulatory milestones, supporting the external validity of the findings. Although some heterogeneity in treatment pathways was observed in more recent years, most women remained on their initial therapy or followed a small number of simple switches, with complex multi-step pathways occurring infrequently. Observed transitions involving progestogen products and recurrent switches between progestogen and combined topical oestrogen-progestogen products, should be interpreted cautiously, as they may reflect component-based prescribing and dispensing practices rather than true clinical switching. Unlike prevalence analyses, treatment pattern analyses could also identify combinations arising from separate oestrogen and progestogen prescriptions when these met the predefined pathway criteria. Treatment pattern results should also be interpreted in light of the pre-specified parameters, as assumptions regarding prescription duration and allowable treatment gaps may have influenced the identification of treatment discontinuation, switching, and combination therapy across data sources.

Taken together, these findings are broadly consistent with existing evidence on temporal trends in HRT use and treatment practices in Europe. These findings contribute to a better understanding of real-world HRT initiation, utilisation, and treatment patterns across multiple healthcare settings and time periods.

10.4. Generalisability

While our study comprised data from five data sources across European countries, and covered inpatient hospital care, registry, and outpatient general practitioner care, findings from this study are not to be generalised to other countries or data sources and only reflect the situation in the specific region and setting covered by the respective data source.

11. CONCLUSION

This multi-country study provides a description of HRT use and treatment patterns among postmenopausal women across European healthcare settings. Temporal trends in HRT use were broadly consistent across data sources, with declines in HRT use during the early 2000s followed by stabilisation or modest increases in more recent years. HRT use was predominantly characterised by oestrogen-containing products, with decreasing use of fixed oestrogen and progestogen combination products and a shift from systemic to local routes of administration over time. Treatment patterns were characterised by predominant use of single products, with relatively limited treatment changes identified. These findings provide important contextual information on contemporary HRT utilisation across Europe and inform interpretation of future safety and effectiveness analyses.

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13. ANNEXES

ANNEX I. Description of data sources

Danish Data Health Registries (DK-DHR), Denmark

Denmark Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority and covers the entire population, which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from birth to death in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so it captures data on all Danes throughout their lives, regardless of whether they have moved around the country. The high quality of Danish health data is attributed to standardisation, digitisation, and comprehensive documentation, which together enhance accuracy, consistency, and reliability, minimising potential for interpretation errors. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. The current data release includes data on the entire Danish population of 5.9 million persons from 1995. It includes data from the following registries: The central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, the Laboratory Database (including coronavirus disease 2019 test results), and the Vaccination Registry (including COVID-19 vaccinations).

IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992.[21] This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, were instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within the IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnoses according to the International Classification of Diseases, 10th revision (ICD-10), and prescription records. While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources, and therefore, information on mortality is incomplete. Routine updates are conducted at regular intervals. Data quality is assessed based on several criteria, including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies.[22, 23]

Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP), Spain

BIFAP (http://www.bifap.org/index_EN.html) is a longitudinal population-based data source of medical patient records of the Spanish National Health Service (SNS) from 9 participating Regions throughout Spain out of the 17 Spanish Regions. The population currently included represents 36% of the total Spanish population. Spain has a SNS that provides universal access to health services through the Regional Healthcare Services. Primary care physicians (PCPs), both general practitioners and paediatricians, have a central role. They act as gatekeepers of the system and also exchange information with other levels of care to ensure the continuity of care. Most (98.9%) of the population is registered with a PCP, and, in addition, most drug prescriptions are written at the primary care level. BIFAP includes a collection of databases linked at the individual patient level. The main one is the Primary care Database given the central role of

PCPs in the SNS. Linked, there are additional important structural databases like the medicines dispensed at community pharmacies and the patients' hospital diagnosis at discharge. 7 out of the 9 regions have linkage to hospital data. However, hospital data is available for different time periods for each region. From 2014 onwards, linkage to hospital data is available for >68% of patients. Linkage to SARS-CoV-2 diagnostics tests and COVID-19 vaccination registries are also included. Additional databases are also linked for a subset of patients (hospital pharmacy, cause of death registry). BIFAP program is a non-profit program financed by the Spanish Agency of Medicines and Medical Devices (AEMPS), a government agency belonging to the ministry of Health in collaboration with the regional health authorities.

The Information System for Research in Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymised patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymised patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic, and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

Clinical Practice Research Datalink GOLD (CPRD GOLD), The United Kingdom

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.[24] The source population registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. GOLD contains data from all four UK constituent countries, and the current regional distribution of its GP practices is 0.89% in England, 61.13% in Scotland, 26.41% in Wales, and 11.57% in Northern Ireland (January 2025).[24]

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialists/hospitals and their outcomes, laboratory tests/results, and prescribed medications. GPs receive information about patient contacts with secondary care, but this information must be manually entered into the patient record and therefore, may be incomplete. GOLD has been assessed and found broadly representative of the UK general population in terms of age and sex.[24] GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far.[25-27]

In terms of quality checks, the integrity, structure, and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length, and format. Duplicate records are identified and removed. Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the database (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a

patient-level data quality metric in the form of a binary ‘acceptability’ flag. This is based on recording and internal consistency of key variables, including date of birth, practice registration date and transfer out date.

ANNEX II. Fitness for use assessment

Data source justification and key characteristics

Multiple data sources were included in this study, as they represented registry-based and outpatient general practitioner care databases that provided relevant information on HRT use in postmenopausal women. Based on preliminary feasibility assessments, the expected number of individuals with oestrogen use ranged from approximately 2,100 (SIDIAP) to 251,800 (CPRD GOLD), while the number of individuals with oestrogen + progesterone product use ranged from 800 (CPRD GOLD) to 254,800 (DK-DHR). Data availability and follow-up were sufficient to support the study objectives, with data collection start years ranging from 1987 (CPRD GOLD) to 2006 (SIDIAP), and the most recent data releases occurring between November 2024 (DK-DHR) and July 2025 (CPRD GOLD). Median follow-up duration varied across sources, ranging from 116 days (IQVIA DA Germany) to 7,920 days (DK-DHR), ensuring adequate longitudinal coverage. While IQVIA DA Germany and CPRD GOLD aligned with the intended study period (1 January 1994 to 31 December 2024), for these data sources we used the earliest date available. The actual study period for other data sources was adjusted based on data quality considerations, specifically regarding the earliest reliable data availability and the last observation period available. Subsequently, the actual study period was from 1995 until November 2024 in DK-DHR (the last date of prescription data is 30 September 2024), from 2005 until December 2024 in BIFAP, and from 2010 until December 2024 in SIDIAP. Institutional Review Board (IRB) approvals were either covered under existing umbrella protocols or expected to be obtained within 1 to 3 months (BIFAP, SIDIAP), supporting timely execution of the study within the established timelines.

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

The analytic code for this study was written in R and used standardised analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

Data source quality control

When defining cohorts for indications, a systematic search of possible codes for inclusion was identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and uses this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *PhenotypeR* (https://github.com/OHDSI/phenotypeR) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages were run to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluated ingredient-specific attributes and patterns in drug exposure records.

The study code was based on DARWIN EU® R packages: *CohortCharacteristics* to characterise postmenopausal women, initiating HRT treatment or not on HRT, *IncidencePrevalence* to estimate prevalence, *DrugUtilisation* to characterise the drug use, and *TreatmentPatterns* to characterise HRT treatment patterns. These packages included numerous automated unit tests to ensure the validity of the

codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

ANNEX IV. Concept lists

Table S1. List of conditions definitions indicating menopause.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Menopause	Climacteric arthritis	79109	-	SNOMED
Menopause	Climacteric flushing	4144760	-	SNOMED
Menopause	Female climacteric state	4113665	-	SNOMED
Menopause	Genitourinary syndrome of menopause	37209648	-	SNOMED
Menopause	Menopausal concentration lack	4112942	-	SNOMED
Menopause	Menopausal depression	4223090	-	SNOMED
Menopause	Menopausal headache	4113841	-	SNOMED
Menopause	Menopausal osteoporosis	4136988	-	SNOMED
Menopause	Menopausal profile	4135533	-	SNOMED
Menopause	Menopausal sleeplessness	4113205	-	SNOMED
Menopause	Menopausal syndrome	439082	-	SNOMED
Menopause	Menopause	4059477	-	OMOP Extension
Menopause	Menopause finding	4172857	-	SNOMED
Menopause	Menopause ovarian failure	4129547	-	SNOMED
Menopause	Postmenopausal androgenetic alopecia	4296346	-	SNOMED
Menopause	Postmenopausal atrophy of vocal cord	4048499	-	SNOMED
Menopause	Postmenopausal depression	37166876	-	SNOMED
Menopause	Postmenopausal frontal fibrosing alopecia	4296347	-	SNOMED
Menopause	Postmenopausal hormone replacement therapy	37110086	-	SNOMED
Menopause	Postmenopausal osteopenia	42536667	-	SNOMED
Menopause	Postmenopausal osteoporosis	4010333	-	SNOMED
Menopause	Postmenopausal urethral atrophy	4054881	-	SNOMED
Menopause	Abnormal perimenopausal bleeding	4201098	Yes	SNOMED
Menopause	H/O: postmenopausal bleeding	4058559	Yes	SNOMED
Menopause	Menopause absent	4128330	Yes	SNOMED
Menopause	Perimenopausal atrophic vaginitis	4255393	Yes	SNOMED
Menopause	Perimenopausal state	45757505	Yes	SNOMED
Menopause	Premenopausal state	4331463	Yes	SNOMED

Table S2. List of conditions definitions indicating early menopause.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Premature menopause	Premature menopause	198715	-	SNOMED
Premature menopause	Postsurgical menopause	4154697	-	SNOMED
Premature menopause	Primary ovarian failure	4279913	-	SNOMED
Premature menopause	Excision of bilateral ovaries	4297990	-	SNOMED
Premature menopause	Bilateral acquired absence of ovary	36716936	-	SNOMED
Premature menopause	46,XX ovarian dysgenesis, short stature syndrome	37165047	Yes	SNOMED
Premature menopause	Laparoscopic excision of bilateral ovarian cysts	43531188	Yes	SNOMED
Premature menopause	Lung fibrosis, immunodeficiency, 46,XX gonadal dysgenesis syndrome	36716112	Yes	SNOMED
Premature menopause	Ovarian dysgenesis	4004647	Yes	SNOMED
Premature menopause	Ovarioleukodystrophy	608037	Yes	SNOMED
Premature menopause	Pure gonadal dysgenesis 46,XX	4317840	Yes	SNOMED
Premature menopause	Bilateral salpingo-oophorectomy with omentectomy, total abdominal hysterectomy and radical dissection for debulking	2110268	Yes	CPT4
Premature menopause	Bilateral salpingo-oophorectomy with omentectomy, total abdominal hysterectomy and radical dissection for debulking; with pelvic lymphadenectomy and limited para-aortic lymphadenectomy	2110269	Yes	CPT4
Premature menopause	Bilateral salpingo-oophorectomy with total omentectomy, total abdominal hysterectomy for malignancy	2110270	Yes	CPT4
Premature menopause	Laparoscopic removal of remaining ovary	2004251	Yes	ICD9Proc
Premature menopause	Laparoscopic removal of remaining ovary and tube	2004266	Yes	ICD9Proc
Premature menopause	Laparoscopy, surgical, supracervical hysterectomy, for uterus 250 g or less	2110210	Yes	CPT4
Premature menopause	Laparoscopy, surgical, supracervical hysterectomy, for uterus greater than 250 g	2110212	Yes	CPT4
Premature menopause	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less	2110230	Yes	CPT4

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Premature menopause	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g	2110232	Yes	CPT4
Premature menopause	Laparoscopy, surgical, with vaginal hysterectomy, for uterus 250 g or less	2110218	Yes	CPT4
Premature menopause	Laparoscopy, surgical, with vaginal hysterectomy, for uterus greater than 250 g	2110220	Yes	CPT4
Premature menopause	Oophorectomy, partial or total, unilateral or bilateral	2110264	Yes	CPT4
Premature menopause	Other removal of both ovaries and tubes at same operative episode	2004263	Yes	ICD9Proc
Premature menopause	Other removal of both ovaries at same operative episode	2004248	Yes	ICD9Proc
Premature menopause	Other removal of remaining ovary and tube	2004264	Yes	ICD9Proc
Premature menopause	Resection (initial) of ovarian, tubal or primary peritoneal malignancy with bilateral salpingo-oophorectomy and omentectomy	2110265	Yes	CPT4
Premature menopause	Resection (initial) of ovarian, tubal or primary peritoneal malignancy with bilateral salpingo-oophorectomy and omentectomy; with radical dissection for debulking (ie, radical excision or destruction, intra-abdominal or retroperitoneal tumors)	2110267	Yes	CPT4
Premature menopause	Resection (initial) of ovarian, tubal or primary peritoneal malignancy with bilateral salpingo-oophorectomy and omentectomy; with total abdominal hysterectomy, pelvic and limited para-aortic lymphadenectomy	2110266	Yes	CPT4
Premature menopause	Other removal of remaining ovary	2004249	Yes	ICD9Proc
Premature menopause	Wedge resection of bilateral ovaries	4195462	Yes	SNOMED

Table S3. List of measurements/conditions/procedures.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
BMI	Body mass index	4245997	-	SNOMED
BMI	Measurement of body mass index	44783982	-	SNOMED
BMI	Body mass index (BMI) [Ratio]	3038553	-	LOINC
Smoking	Tobacco or its derivatives user	903654	-	OMOP Extension
Smoking	Current smoker	40766945	-	LOINC
Smoking	Passive smoker	903656	Yes	OMOP Extension
Smoking	Moist tobacco user	903669	Yes	OMOP Extension

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Smoking	Smokeless tobacco user	903666	Yes	OMOP Extension
Smoking	Snuff user	903668	Yes	OMOP Extension
Non-smoker	Currently doesn't use tobacco or its derivatives	903651	-	OMOP Extension
Non-smoker	Never smoker	45879404	-	LOINC
Non-smoker	Never smoked cigarettes	1450767	-	SNOMED
Non-smoker	Never smoked	35821355	-	UK Biobank
Non-smoker	Never smoked	45883537	-	LOINC
Non-smoker	Former smoker	45883458	-	LOINC
Non-smoker	Passive smoker	903656	-	OMOP Extension
Smoking categories	On the average, when you smoke, or on the last day you smoked every day, about how many cigarettes do, or did, you smoke [PhenX]	40766579	-	LOINC
Smoking categories	Tobacco smoking status	43054909	-	LOINC
Cardiovascular disease	Cerebrovascular disease	381591	-	SNOMED
Cardiovascular disease	Myocardial infarction	4329847	-	SNOMED
Hypertension	Hypertensive disorder	316866	-	SNOMED
Hypertension	Hypertensive complication	42709887	-	SNOMED
Hypertension	Transient hypertension	4199306	Yes	SNOMED
Hypertension	Transient hypertension of pregnancy	441922	Yes	SNOMED
Hypertension	Exacerbation of pre-eclampsia	1340440	Yes	OMOP Extension
Hypertension	Fetal disorder due to maternal pre-eclampsia	604804	Yes	SNOMED
Hypertension	Impending eclampsia	4034095	Yes	SNOMED
Hypertension	Mild pre-eclampsia	314090	Yes	SNOMED
Hypertension	Nephropathy following pre-eclampsia	42537547	Yes	SNOMED
Hypertension	Postpartum pre-eclampsia	35622939	Yes	SNOMED
Hypertension	Pre-eclampsia	439393	Yes	SNOMED
Hypertension	Severe pre-eclampsia	433536	Yes	SNOMED
Hypertension	Postpartum pregnancy-induced hypertension	45757788	Yes	SNOMED
Hypertension	Pregnancy induced hypertension with pulmonary edema	44784483	Yes	SNOMED
Hypertension	Pregnancy-induced hypertension	4167493	Yes	SNOMED
Hypertension	Perioperative hypertension	762994	Yes	SNOMED
Hypertension	Postoperative hypertension	43021830	Yes	SNOMED
Hypertension	Neonatal hypertension	4071202	Yes	SNOMED
Anxiety disorder	Anxiety disorder	442077	-	SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Depressive disorder	Depressive disorder	440383	-	SNOMED
Sleep disorders	Sleep disorder	435524	-	SNOMED
Osteoporosis	Osteoporosis	80502	-	SNOMED
Metabolic syndrome	Metabolic syndrome X	436940	-	SNOMED
Diabetes mellitus	Diabetes mellitus	201820	-	SNOMED
Diabetes mellitus	Complication due to diabetes mellitus	442793	-	SNOMED
Diabetes mellitus type 2	Type 2 diabetes mellitus	201826	-	SNOMED
Diabetes mellitus type 2	Disorder due to type 2 diabetes mellitus	443732	-	SNOMED
Dyslipidaemia	Hyperlipidemia	432867	-	SNOMED
Dyslipidaemia	Dyslipidemia	4159131	-	SNOMED
Hysterectomy	Prolapse of vaginal vault after hysterectomy	195599	-	SNOMED
Hysterectomy	Postpartum hysterectomy	3655186	-	SNOMED
Hysterectomy	Abdominal hysterectomy	4021529	-	SNOMED
Hysterectomy	Total hysterectomy	4023403	-	SNOMED
Hysterectomy	Laparoscopic hysterectomy	4127887	-	SNOMED
Hysterectomy	Vaginal hysterectomy with conservation of ovaries	4136878	-	SNOMED
Hysterectomy	Post-hysterectomy menopause	4175534	-	SNOMED
Hysterectomy	Vaginal hysterectomy with partial colpectomy	4299781	-	SNOMED
Hysterectomy	Total hysterectomy	36307836	-	LOINC
Hysterectomy	Vaginal hysterectomy and excision of periuterine tissue	40490442	-	SNOMED
Hysterectomy	Sampling of vagina for Papanicolaou smear after hysterectomy for malignant disease	45765724	-	SNOMED
Hysterectomy	Sampling of vagina for Papanicolaou smear after hysterectomy for dysplasia of cervix	45765725	-	SNOMED
Hysterectomy	Sampling of vagina for Papanicolaou smear after benign hysterectomy	45765726	-	SNOMED
Hysterectomy	Vaginal hysterectomy and right salpingo-oophorectomy	45769915	-	SNOMED
Hysterectomy	Vaginal hysterectomy and left salpingo-oophorectomy	45769916	-	SNOMED
Hysterectomy	Laparoscopy, surgical, ablation of uterine fibroid(s), including intraoperative ultrasound guidance and monitoring, radiofrequency (Deprecated)	44816468	Yes	CPT4
Hysterectomy	Laparoscopic adenomyomectomy	35624826	Yes	SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Hysterectomy	Laparoscopic laser myomectomy	44806664	Yes	SNOMED
Hysterectomy	Laparoscopic myomectomy	42872568	Yes	SNOMED

Table S4. List of medicines definitions.

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Oestriol plain	Estriol Vaginal Suppository	Natural and semisynthetic estrogens, plain	G03CA	994614	Yes
Oestriol plain	estriol Vaginal Mechanical Pessaries with Substance	Natural and semisynthetic estrogens, plain	G03CA	2913155	Yes
Oestriol plain	estriol 0.5 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	19109773	-
Oestriol plain	Estriol Vaginal Ring	Natural and semisynthetic estrogens, plain	G03CA	21096109	Yes
Oestriol plain	Estriol Topical Ointment	Natural and semisynthetic estrogens, plain	G03CA	21174698	Yes
Oestriol plain	Estriol Topical Cream	Natural and semisynthetic estrogens, plain	G03CA	36405712	Yes
Oestriol plain	estriol Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40037934	Yes
Oestriol plain	estriol Vaginal Cream	Natural and semisynthetic estrogens, plain	G03CA	40037935	Yes
Oestriol plain	estriol Vaginal Gel	Natural and semisynthetic estrogens, plain	G03CA	40037936	Yes
Oestriol plain	estriol Vaginal Ointment	Natural and semisynthetic estrogens, plain	G03CA	40037937	Yes
Oestriol plain	Estriol Injectable Solution	Natural and semisynthetic estrogens, plain	G03CA	40955256	Yes
Oestriol plain	estriol Vaginal Mechanical Pessaries with Substance	Natural and semisynthetic estrogens, plain	G03CA	42614841	Yes
Oestriol plain	estriol	Natural and semisynthetic estrogens, plain	G03CA	19049038	-
Oestradiol plain	Estradiol Vaginal delivery system	Natural and semisynthetic estrogens, plain	G03CA	21119327	Yes
Oestradiol plain	estradiol Medicated Patch	Natural and semisynthetic estrogens, plain	G03CA	35864607	Yes
Oestradiol plain	estradiol Topical Spray	Natural and semisynthetic estrogens, plain	G03CA	40142319	Yes
Oestradiol plain	estradiol Vaginal Suppository	Natural and semisynthetic estrogens, plain	G03CA	36063507	Yes
Oestradiol plain	estradiol Vaginal Mechanical Pessaries with Substance	Natural and semisynthetic estrogens, plain	G03CA	2919412	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Oestradiol plain	Estradiol Topical Solution	Natural and semisynthetic estrogens, plain	G03CA	36887539	Yes
Oestradiol plain	Estradiol Delayed Release Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	43214578	Yes
Oestradiol plain	Estradiol Vaginal Ointment	Natural and semisynthetic estrogens, plain	G03CA	40986439	Yes
Oestradiol plain	Estradiol Vaginal Gel	Natural and semisynthetic estrogens, plain	G03CA	21129128	Yes
Oestradiol plain	Estradiol Oral Solution	Natural and semisynthetic estrogens, plain	G03CA	41298438	Yes
Oestradiol plain	Estradiol Vaginal device	Natural and semisynthetic estrogens, plain	G03CA	21080172	Yes
Oestradiol plain	estradiol Vaginal System	Natural and semisynthetic estrogens, plain	G03CA	37496964	Yes
Oestradiol plain	estradiol Nasal Spray	Natural and semisynthetic estrogens, plain	G03CA	40037551	Yes
Oestradiol plain	estradiol Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40037552	Yes
Oestradiol plain	estradiol Topical Lotion	Natural and semisynthetic estrogens, plain	G03CA	40037563	Yes
Oestradiol plain	estradiol Topical Gel	Natural and semisynthetic estrogens, plain	G03CA	40037560	Yes
Oestradiol plain	estradiol Vaginal Cream	Natural and semisynthetic estrogens, plain	G03CA	40037567	Yes
Oestradiol plain	estradiol Topical Ointment	Natural and semisynthetic estrogens, plain	G03CA	40037565	Yes
Oestradiol plain	estradiol Injectable Solution	Natural and semisynthetic estrogens, plain	G03CA	40037531	Yes
Oestradiol plain	estradiol Drug Implant	Natural and semisynthetic estrogens, plain	G03CA	40037529	Yes
Oestradiol plain	Estradiol Injectable Suspension	Natural and semisynthetic estrogens, plain	G03CA	40923849	Yes
Oestradiol plain	estradiol Vaginal Insert	Natural and semisynthetic estrogens, plain	G03CA	1356401	Yes
Oestradiol plain	Estradiol Prefilled Syringe	Natural and semisynthetic estrogens, plain	G03CA	41267430	Yes
Oestradiol plain	Estradiol Vaginal Tablet	Natural and semisynthetic estrogens, plain	G03CA	783424	Yes
Oestradiol plain	Estradiol Oral Powder	Natural and semisynthetic estrogens, plain	G03CA	43283802	Yes
Oestradiol plain	Estradiol Topical Cream	Natural and semisynthetic estrogens, plain	G03CA	43858643	Yes
Oestradiol plain	estradiol Transdermal System	Natural and semisynthetic estrogens, plain	G03CA	40221070	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Oestradiol plain	estradiol Vaginal Mechanical Pessaries with Substance	Natural and semisynthetic estrogens, plain	G03CA	42614420	Yes
Oestradiol plain	Estradiol 17 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	36888209	Yes
Oestradiol plain	estradiol 0.0006 MG/MG	Natural and semisynthetic estrogens, plain	G03CA	1548737	Yes
Oestradiol plain	estradiol	Natural and semisynthetic estrogens, plain	G03CA	1548195	-
chlorotrianisene plain	chlorotrianisene Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40020734	Yes
chlorotrianisene plain	chlorotrianisene Oral Capsule	Natural and semisynthetic estrogens, plain	G03CA	40020732	Yes
chlorotrianisene plain	chlorotrianisene	Natural and semisynthetic estrogens, plain	G03CA	19092684	-
conjugated oestrogens plain	estrogens, conjugated (USP) Injection	Natural and semisynthetic estrogens, plain	G03CA	35604992	Yes
conjugated oestrogens plain	Estrogens, Conjugated (USP) Topical Ointment	Natural and semisynthetic estrogens, plain	G03CA	21060458	Yes
conjugated oestrogens plain	Estrogens, Conjugated (USP) Topical Cream	Natural and semisynthetic estrogens, plain	G03CA	44068959	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Injectable Suspension	Natural and semisynthetic estrogens, plain	G03CA	40038307	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Extended Release Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40038304	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Injectable Solution	Natural and semisynthetic estrogens, plain	G03CA	40038305	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Vaginal Cream	Natural and semisynthetic estrogens, plain	G03CA	40038311	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Oral Capsule	Natural and semisynthetic estrogens, plain	G03CA	40038308	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40038309	Yes
conjugated oestrogens plain	estrogens, conjugated (USP) Delayed Release Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40038303	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
conjugated oestrogens plain	estrogens, conjugated (USP)	Natural and semisynthetic estrogens, plain	G03CA	1549080	-
Esterified oestrogens plain	estrogens, esterified (USP) Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40038634	Yes
Esterified oestrogens plain	estrogens, esterified (USP)	Natural and semisynthetic estrogens, plain	G03CA	1551673	-
Ethinylestradiol plain	Ethinyl Estradiol Delayed Release Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	36783982	Yes
Ethinylestradiol plain	Ethinyl Estradiol Oral Suspension	Natural and semisynthetic estrogens, plain	G03CA	21138927	Yes
Ethinylestradiol plain	Ethinyl Estradiol Vaginal Gel	Natural and semisynthetic estrogens, plain	G03CA	41298427	Yes
Ethinylestradiol plain	Ethinyl Estradiol Transdermal System	Natural and semisynthetic estrogens, plain	G03CA	43691622	Yes
Ethinylestradiol plain	Ethinyl Estradiol Sublingual Tablet	Natural and semisynthetic estrogens, plain	G03CA	40924035	Yes
Ethinylestradiol plain	Ethinyl Estradiol Oral Capsule	Natural and semisynthetic estrogens, plain	G03CA	21050573	Yes
Ethinylestradiol plain	ethinyl estradiol Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40040565	Yes
Ethinylestradiol plain	ethinyl estradiol	Natural and semisynthetic estrogens, plain	G03CA	1549786	-
Oestrone plain	estrone 5 MG/ML [Estragyn 5]	Natural and semisynthetic estrogens, plain	G03CA	19120339	-
Oestrone plain	estrone 5 MG/ML [Kestrone 5]	Natural and semisynthetic estrogens, plain	G03CA	19070676	-
Oestrone plain	estrone 0.625 MG	Natural and semisynthetic estrogens, plain	G03CA	1549294	-
Oestrone plain	estrone 5 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	1549293	-
Oestrone plain	estrone 2.5 MG	Natural and semisynthetic estrogens, plain	G03CA	1549292	-
Oestrone plain	estrone 2 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	1549291	-
Oestrone plain	estrone 1.5 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	1549290	-
Oestrone plain	estrone	Natural and semisynthetic estrogens, plain	G03CA	1549254	-
Oestrone plain	Estrone Oral Solution	Natural and semisynthetic estrogens, plain	G03CA	44042922	Yes
Oestrone plain	estrone Injectable Solution	Natural and semisynthetic estrogens, plain	G03CA	40038677	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Oestrone plain	estrone Injectable Suspension	Natural and semisynthetic estrogens, plain	G03CA	40038683	Yes
Oestrone plain	estrone Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	40038684	Yes
Oestrone plain	estrone Vaginal Cream	Natural and semisynthetic estrogens, plain	G03CA	40038685	Yes
Oestrone plain	Estrone 12 X	Natural and semisynthetic estrogens, plain	G03CA	44053161	-
Oestrone plain	Estrone 3 X [Folliculinum]	Natural and semisynthetic estrogens, plain	G03CA	44054713	-
Oestrone plain	estrone 15 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	19101968	-
Oestrone plain	estrone 5 MG/ML [Wehgen V]	Natural and semisynthetic estrogens, plain	G03CA	19085590	-
Oestrone plain	estrone 1.4 MG	Natural and semisynthetic estrogens, plain	G03CA	36051485	-
Oestrone plain	estrone 2 MG	Natural and semisynthetic estrogens, plain	G03CA	19082599	-
Oestrone plain	estrone 2 MG/ML [Aquest]	Natural and semisynthetic estrogens, plain	G03CA	19054955	-
Oestrone plain	Estrone 0.001 MG/ML [Estragyn 5]	Natural and semisynthetic estrogens, plain	G03CA	44106303	-
Oestrone plain	estrone 10 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	19109779	-
Oestrone plain	estrone 2 MG/ML [Estrogenic]	Natural and semisynthetic estrogens, plain	G03CA	19064805	-
Oestrone plain	estrone 1.5 MG	Natural and semisynthetic estrogens, plain	G03CA	19081206	-
Oestrone plain	Estrone 0.001 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	44066176	-
Oestrone plain	Estrone 3 X	Natural and semisynthetic estrogens, plain	G03CA	44040098	-
Oestrone plain	Estrone 0.2 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	40889609	-
Oestrone plain	Estrone 1.25 MG [Genoral]	Natural and semisynthetic estrogens, plain	G03CA	43295218	-
Oestrone plain	Estrone 1 MG/MG [Oestrilin]	Natural and semisynthetic estrogens, plain	G03CA	44119329	-
Oestrone plain	Estrone 1 MG/MG	Natural and semisynthetic estrogens, plain	G03CA	44078885	-
Oestrone plain	Estrone 1.25 MG	Natural and semisynthetic estrogens, plain	G03CA	36894132	-
Oestrone plain	Estrone 0.8 MG	Natural and semisynthetic estrogens, plain	G03CA	40822270	-

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Oestrone plain	estrone 2 MG/ML [Primestrin]	Natural and semisynthetic estrogens, plain	G03CA	19120783	-
Oestrone plain	estrone 2 MG/ML [Estro-A]	Natural and semisynthetic estrogens, plain	G03CA	19032800	-
Oestrone plain	Estrone 0.625 MG [Genoral]	Natural and semisynthetic estrogens, plain	G03CA	43273588	-
Oestrone plain	Estrone 0.625 MG [Ogen]	Natural and semisynthetic estrogens, plain	G03CA	43273589	-
Oestrone plain	estrone 1 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	1549297	-
Oestrone plain	estrone 2 MG/ML [Estra AQ]	Natural and semisynthetic estrogens, plain	G03CA	19073231	-
Oestrone plain	Estrone 1.25 MG [Ogen]	Natural and semisynthetic estrogens, plain	G03CA	43257208	-
Promestriene plain	promestriene Vaginal Insert	Natural and semisynthetic estrogens, plain	G03CA	43034867	Yes
Promestriene plain	promestriene Topical Cream	Natural and semisynthetic estrogens, plain	G03CA	43139090	Yes
Promestriene plain	promestriene Vaginal Cream	Natural and semisynthetic estrogens, plain	G03CA	40102379	Yes
Promestriene plain	promestriene Oral Capsule	Natural and semisynthetic estrogens, plain	G03CA	40102378	Yes
Promestriene plain	promestriene Oral Tablet	Natural and semisynthetic estrogens, plain	G03CA	35856270	Yes
Promestriene plain	promestriene Vaginal Tablet	Natural and semisynthetic estrogens, plain	G03CA	35856275	Yes
Promestriene plain	promestriene Topical Ointment	Natural and semisynthetic estrogens, plain	G03CA	35856272	Yes
Promestriene plain	promestriene Vaginal Suppository	Natural and semisynthetic estrogens, plain	G03CA	2045136	Yes
Promestriene plain	promestriene 100 MG	Natural and semisynthetic estrogens, plain	G03CA	35856269	-
Promestriene plain	promestriene 0.01 MG/MG [COLMEX]	Natural and semisynthetic estrogens, plain	G03CA	2045135	-
Promestriene plain	promestriene 10 MG [COLMEX]	Natural and semisynthetic estrogens, plain	G03CA	2045132	-
Promestriene plain	promestriene	Natural and semisynthetic estrogens, plain	G03CA	19029079	-
Promestriene plain	promestriene 0.01 MG/MG	Natural and semisynthetic estrogens, plain	G03CA	35411903	-
Promestriene plain	promestriene 10 MG [COLPOTROPHINE]	Natural and semisynthetic estrogens, plain	G03CA	43161234	-
Promestriene plain	promestriene 10 MG	Natural and semisynthetic estrogens, plain	G03CA	19090692	-

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Promestriene plain	promestriene 10 MG/ML [COLPOTROPHINE]	Natural and semisynthetic estrogens, plain	G03CA	43205075	-
Promestriene plain	promestriene 10 MG/ML	Natural and semisynthetic estrogens, plain	G03CA	19029103	-
Promestriene plain	promestriene 0.03 MG	Natural and semisynthetic estrogens, plain	G03CA	19111555	-
Promestriene plain	promestriene 0.01 MG/MG	Natural and semisynthetic estrogens, plain	G03CA	35411903	-
Promestriene plain	promestriene 0.01 MG/MG [COLPOTROPHINE]	Natural and semisynthetic estrogens, plain	G03CA	35408824	-
Promestriene plain	promestriene 10 MG [Gengbaofen]	Natural and semisynthetic estrogens, plain	G03CA	35856267	-
Promestriene plain	promestriene 10 MG [Kebaojing]	Natural and semisynthetic estrogens, plain	G03CA	35856266	-
Dienestrol plain	dienestrol Vaginal Cream	Synthetic estrogens, plain	G03CB	40032855	Yes
Dienestrol plain	Dienestrol Sublingual Tablet	Synthetic estrogens, plain	G03CB	41267482	Yes
Dienestrol plain	dienestrol Topical Cream	Synthetic estrogens, plain	G03CB	40111249	Yes
Dienestrol plain	Dienestrol 0.1 MG	Synthetic estrogens, plain	G03CB	41202144	-
Dienestrol plain	dienestrol	Synthetic estrogens, plain	G03CB	925102	-
Methallenestril	METHALLENESTRIL	Synthetic estrogens, plain	G03CB	36863204	Yes
Moxestrol	MOXESTROL	Synthetic estrogens, plain	G03CB	36852976	Yes
Diethylstilbestrol plain	diethylstilbestrol Vaginal Insert	Synthetic estrogens, plain	G03CB	1356398	Yes
Diethylstilbestrol plain	diethylstilbestrol Rectal Suppository	Synthetic estrogens, plain	G03CB	35865217	Yes
Diethylstilbestrol plain	Diethylstilbestrol Drug Implant	Synthetic estrogens, plain	G03CB	40986484	Yes
Diethylstilbestrol plain	Diethylstilbestrol Vaginal Ring	Synthetic estrogens, plain	G03CB	40727867	Yes
Diethylstilbestrol plain	diethylstilbestrol Delayed Release Oral Tablet	Synthetic estrogens, plain	G03CB	40033198	Yes
Diethylstilbestrol plain	diethylstilbestrol Injectable Solution	Synthetic estrogens, plain	G03CB	40033199	Yes
Diethylstilbestrol plain	diethylstilbestrol Oral Tablet	Synthetic estrogens, plain	G03CB	40033201	Yes
Diethylstilbestrol plain	diethylstilbestrol Vaginal Suppository	Synthetic estrogens, plain	G03CB	36063686	Yes
Diethylstilbestrol plain	diethylstilbestrol	Synthetic estrogens, plain	G03CB	1525866	-
Conjugated oestrogens and bazedoxifene	bazedoxifene / Estrogens, Conjugated (USP) Delayed Release Oral Capsule	Estrogens, combinations with other drugs	G03CC	36266937	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Conjugated oestrogens and bazedoxifene	bazedoxifene / Estrogens, Conjugated (USP) Extended Release Oral Tablet	Estrogens, combinations with other drugs	G03CC	44069197	Yes
Conjugated oestrogens and bazedoxifene	bazedoxifene / estrogens, conjugated (USP) Oral Tablet	Estrogens, combinations with other drugs	G03CC	44506576	Yes
Tibolone plain	tibolone Oral Tablet	Other estrogens	G03CX	40098482	Yes
Tibolone plain	tibolone 2.5 MG [Liviella]	Other estrogens	G03CX	43802767	-
Tibolone plain	tibolone 2.5 MG [Xyvion]	Other estrogens	G03CX	43280119	-
Tibolone plain	tibolone 2.5 MG [TIBOLAN]	Other estrogens	G03CX	2044009	-
Tibolone plain	tibolone 2.5 MG [LIVIEM]	Other estrogens	G03CX	2044008	-
Tibolone plain	tibolone 2.5 MG [LIBON]	Other estrogens	G03CX	2044007	-
Tibolone plain	tibolone 2.5 MG [Tibolinia]	Other estrogens	G03CX	36258996	-
Tibolone plain	tibolone 2.5 MG [Heria]	Other estrogens	G03CX	36266698	-
Tibolone plain	tibolone 2.5 MG [Livial]	Other estrogens	G03CX	19115463	-
Tibolone plain	tibolone 2.5 MG [TIBIOL]	Other estrogens	G03CX	42958948	-
Tibolone plain	tibolone 2.5 MG [LIBRON]	Other estrogens	G03CX	42958947	-
Tibolone plain	tibolone 2.5 MG [Tibolon Aristo]	Other estrogens	G03CX	43748737	-
Tibolone plain	tibolone 2.5 MG [Zizhuaiwei]	Other estrogens	G03CX	35855682	-
Tibolone plain	tibolone 2.5 MG [Liweiai]	Other estrogens	G03CX	35855681	-
Tibolone plain	tibolone 2.5 MG [Sempreluna]	Other estrogens	G03CX	42656736	-
Tibolone plain	tibolone 2.5 MG [Tibolone Gedeon Richter]	Other estrogens	G03CX	36787628	-
Tibolone plain	tibolone 2.5 MG	Other estrogens	G03CX	19041935	-
Tibolone plain	tibolone 2.5 MG [Livilan]	Other estrogens	G03CX	2913274	-
Tibolone plain	tibolone 2.5 MG [Shyla]	Other estrogens	G03CX	36507073	-
Tibolone plain	tibolone	Other estrogens	G03CX	19041933	-
Progesterone plain	progesterone Vaginal System	Progestogens	G03D	36026918	Yes
Progesterone plain	Progesterone Topical Ointment	Progestogens	G03D	42480364	Yes
Progesterone plain	Progesterone Vaginal Ring	Progestogens	G03D	21080372	Yes
Progesterone plain	Progesterone Oral Tablet	Progestogens	G03D	36277112	Yes
Progesterone plain	Progesterone Intramuscular Solution	Progestogens	G03D	44094421	Yes
Progesterone plain	progesterone Vaginal Insert	Progestogens	G03D	1356345	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Progesterone plain	progesterone Injectable Solution	Progestogens	G03D	40075410	Yes
Progesterone plain	progesterone Oral Capsule	Progestogens	G03D	40075413	Yes
Progesterone plain	progesterone Injectable Suspension	Progestogens	G03D	40075412	Yes
Progesterone plain	progesterone Topical Cream	Progestogens	G03D	40075417	Yes
Progesterone plain	progesterone Vaginal Gel	Progestogens	G03D	40075423	Yes
Progesterone plain	progesterone Vaginal Cream	Progestogens	G03D	40075422	Yes
Progesterone plain	progesterone Topical Lotion	Progestogens	G03D	40075421	Yes
Progesterone plain	progesterone Topical Gel	Progestogens	G03D	40075420	Yes
Progesterone plain	Progesterone Vaginal Spray	Progestogens	G03D	41298183	Yes
Progesterone plain	progesterone Vaginal Mechanical Pessaries with Substance	Progestogens	G03D	2919255	Yes
Progesterone plain	progesterone Vaginal Mechanical Pessaries with Substance	Progestogens	G03D	42614428	Yes
Progesterone plain	Progesterone Prefilled Syringe	Progestogens	G03D	42479195	Yes
Progesterone plain	Progesterone Vaginal Suppository	Progestogens	G03D	784044	Yes
Progesterone plain	progesterone 400 MG	Progestogens	G03D	19099976	Yes
Progesterone plain	progesterone 100 MG	Progestogens	G03D	1552387	Yes
Progesterone plain	Progesterone 200 MG Vaginal Suppository	Progestogens	G03D	590523	Yes
Progesterone plain	Progesterone 200 MG [Utrogestan]	Progestogens	G03D	21149084	Yes
Progesterone plain	Progesterone 200 MG [Utrogest]	Progestogens	G03D	36419357	Yes
Progesterone plain	progesterone	Progestogens	G03D	1552310	-
Hydroxyprogesterone plain	17-alpha-hydroxyprogesterone Injection	Progestogens	G03D	36249937	Yes
Hydroxyprogesterone plain	17-alpha-Hydroxyprogesterone Prefilled Syringe	Progestogens	G03D	42482504	Yes
Hydroxyprogesterone plain	17-alpha-hydroxyprogesterone Injectable Solution	Progestogens	G03D	40051622	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Hydroxyprogesterone plain	17-alpha-hydroxyprogesterone Oral Tablet	Progestogens	G03D	40051627	Yes
Hydroxyprogesterone plain	17-alpha-hydroxyprogesterone Auto-Injector	Progestogens	G03D	964063	Yes
Hydroxyprogesterone plain	17-alpha-hydroxyprogesterone	Progestogens	G03D	19077143	-
Dydrogesterone plain	dydrogesterone Oral Tablet	Progestogens	G03D	40033432	Yes
Dydrogesterone plain	Dydrogesterone Delayed Release Oral Tablet	Progestogens	G03D	43178242	Yes
Dydrogesterone plain	dydrogesterone	Progestogens	G03D	19040060	-
Norethisterone plain	Norethindrone Oral Suspension	Progestogens	G03D	21168557	Yes
Norethisterone plain	Norethindrone Delayed Release Oral Tablet	Progestogens	G03D	41173878	Yes
Norethisterone plain	norethindrone Oral Tablet	Progestogens	G03D	40072443	Yes
Norethisterone plain	norethindrone Injectable Solution	Progestogens	G03D	40072442	Yes
Norethisterone plain	Norethindrone Prefilled Syringe	Progestogens	G03D	42479131	Yes
Norethisterone plain	Norethindrone Transdermal System	Progestogens	G03D	43674653	Yes
Norethisterone plain	norethindrone	Progestogens	G03D	1521369	-
Levonorgestrel (IUD)	Levonorgestrel Intrauterine device	Progestogens	G03D	21119300	Yes
Levonorgestrel (IUD)	Levonorgestrel Intrauterine Drug Delivery System	Progestogens	G03D	43156616	Yes
Levonorgestrel (IUD)	levonorgestrel Intrauterine System	Progestogens	G03D	1718400	Yes
Levonorgestrel (IUD)	Levonorgestrel 13.5 MG Vaginal Ring [Jaydess] Box of 1	Progestogens	G03D	40875328	-
Levonorgestrel (IUD)	Levonorgestrel 13.5 MG Vaginal Ring [Jaydess] Box of 1 by Emra-Med	Progestogens	G03D	44182380	-
Levonorgestrel (IUD)	Levonorgestrel 13.5 MG Vaginal Ring [Jaydess] Box of 1 by European	Progestogens	G03D	44167396	-
Levonorgestrel (IUD)	Levonorgestrel 13.5 MG Vaginal Ring [Jaydess] Box of 1 by Jenapharm	Progestogens	G03D	40978608	-
Levonorgestrel (IUD)	Levonorgestrel 13.5 MG Vaginal Ring [Jaydess] Box of 1 by Kohlpharma	Progestogens	G03D	41197778	-
Levonorgestrel (IUD)	Levonorgestrel 13.5 MG Vaginal Ring [Jaydess] Box of 5 by Jenapharm	Progestogens	G03D	41322052	-

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Levonorgestrel (IUD)	Levonorgestrel 19.5 MG Vaginal Ring [Kyleena] Box of 1 by Jenapharm	Progestogens	G03D	44174885	-
Levonorgestrel (IUD)	Levonorgestrel 19.5 MG Vaginal Ring [Kyleena] Box of 5 by Jenapharm	Progestogens	G03D	44182381	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Levosert] Box of 1	Progestogens	G03D	36419581	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1	Progestogens	G03D	41218791	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Apothekamed	Progestogens	G03D	44167398	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Cc	Progestogens	G03D	41072263	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Docpharm	Progestogens	G03D	40854052	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Emra-Med	Progestogens	G03D	41259677	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Eurim-Pharm	Progestogens	G03D	41259676	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Gerke	Progestogens	G03D	44159861	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Jenapharm	Progestogens	G03D	40885330	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Kohlpharma	Progestogens	G03D	40947620	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 1 by Orifarm Leverkus	Progestogens	G03D	44171151	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 5 by Gerke	Progestogens	G03D	40916202	-
Levonorgestrel (IUD)	Levonorgestrel 52 MG Vaginal Ring [Mirena] Box of 5 by Jenapharm	Progestogens	G03D	40947619	-
Medroxyprogesterone acetate plain	Medroxyprogesterone Injectable Solution	Progestogens	G03D	40923915	Yes
Medroxyprogesterone acetate plain	medroxyprogesterone Prefilled Syringe	Progestogens	G03D	40141899	Yes
Medroxyprogesterone acetate plain	medroxyprogesterone Injectable Suspension	Progestogens	G03D	40065619	Yes
Medroxyprogesterone acetate plain	medroxyprogesterone Oral Capsule	Progestogens	G03D	40065623	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Medroxyprogesterone acetate plain	medroxyprogesterone Oral Tablet	Progestogens	G03D	40065626	Yes
Medroxyprogesterone acetate plain	medroxyprogesterone Oral Suspension	Progestogens	G03D	40065624	Yes
Medroxyprogesterone acetate plain	medroxyprogesterone Injection	Progestogens	G03D	35604745	Yes
Medroxyprogesterone acetate plain	Medroxyprogesterone Oral Solution	Progestogens	G03D	42479049	Yes
Medroxyprogesterone acetate plain	medroxyprogesterone	Progestogens	G03D	1500211	-
Lynestrenol plain	lynestrenol Oral Tablet	Progestogens	G03D	40065112	Yes
Lynestrenol plain	lynestrenol	Progestogens	G03D	19092358	-
Medrogestone plain	medrogestone Oral Tablet	Progestogens	G03D	40065265	Yes
Medrogestone plain	medrogestone	Progestogens	G03D	19000207	-
Megestrol plain	Megestrol Oral Capsule	Progestogens	G03D	21023165	Yes
Megestrol plain	megestrol Oral Tablet	Progestogens	G03D	40066018	Yes
Megestrol plain	megestrol Oral Suspension	Progestogens	G03D	40066015	Yes
Megestrol plain	megestrol	Progestogens	G03D	1300978	-
Nomegestrol plain	nomegestrol Oral Tablet	Progestogens	G03D	40058693	Yes
Nomegestrol plain	nomegestrol	Progestogens	G03D	19015533	-
Oestradiol; Testosterone	Estradiol / Testosterone Prefilled Syringe	Androgens and estrogens	G03EA	41143028	Yes
Oestradiol; Testosterone	Estradiol / Testosterone Intramuscular Solution	Androgens and estrogens	G03EA	44081627	Yes
Oestradiol; Testosterone	Estradiol / Testosterone Injection	Androgens and estrogens	G03EA	35131395	Yes
Oestradiol; Testosterone	estradiol / testosterone Injectable Suspension	Androgens and estrogens	G03EA	40042054	Yes
Oestradiol; Testosterone	estradiol / testosterone Injectable Solution	Androgens and estrogens	G03EA	40042044	Yes
Oestradiol; Testosterone	estradiol / testosterone Drug Implant	Androgens and estrogens	G03EA	1525700	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Esterified estrogens; methyltestosterone	estrogens, esterified (USP) / methyltestosterone Oral Tablet	Androgens and estrogens	G03EA	40038314	Yes
Conjugated oestrogens; Methyltestosterone	estrogens, conjugated (USP) / methyltestosterone Oral Tablet	Androgens and estrogens	G03EA	40037964	Yes
Ethinylestradiol; Methyltestosterone	ethinyl estradiol / methyltestosterone Oral Tablet	Androgens and estrogens	G03EA	40039776	Yes
Oestrone; Testosterone	estrone / testosterone Injectable Suspension	Androgens and estrogens	G03EA	40038640	Yes
Oestradiol; Prasterone	Estradiol / prasterone Prefilled Syringe	Androgens and estrogens	G03EA	41267426	Yes
Oestradiol; Prasterone	estradiol / prasterone Injectable Suspension	Androgens and estrogens	G03EA	40042040	Yes
Oestradiol; Prasterone	Estradiol / prasterone Injectable Solution	Androgens and estrogens	G03EA	40830590	Yes
Oestrogens; Testosterone	estrogens / testosterone Oral Tablet	Androgens and estrogens	G03EA	40037946	Yes
Oestradiol; Norethindone; Testosterone	Estradiol / Norethindrone / Testosterone Prefilled Syringe	Androgen, progestogen and estrogen in combination	G03EB	41267427	Yes
Oestradiol; Norethindone; Testosterone	Estradiol / Norethindrone / Testosterone Injection	Androgen, progestogen and estrogen in combination	G03EB	35159632	Yes
Oestradiol; Norethisterone	estradiol / norethindrone Transdermal System	Progestogens and estrogens in combination	G03F	40221101	Yes
Oestradiol; Norethisterone	estradiol / norethindrone Oral Tablet	Progestogens and estrogens in combination	G03F	40042037	Yes
Oestradiol; Norethisterone	estradiol / norethindrone Injectable Solution	Progestogens and estrogens in combination	G03F	40042036	Yes
Oestradiol; Norethisterone	Estradiol / Norethindrone Delayed Release Oral Tablet	Progestogens and estrogens in combination	G03F	43134206	Yes
Oestradiol; Drospirenone	drospirenone / estradiol Oral Tablet	Progestogens and estrogens in combination	G03F	44785026	Yes
Oestradiol; Drospirenone	drospirenone / Estradiol Delayed Release Oral Tablet	Progestogens and estrogens in combination	G03F	43189248	Yes
Oestradiol; Levonorgestrel	estradiol / levonorgestrel Transdermal System	Progestogens and estrogens in combination	G03F	40221097	Yes
Oestradiol; Levonorgestrel	Estradiol / Levonorgestrel Oral Tablet	Progestogens and estrogens in combination	G03F	21148852	Yes
Oestradiol; Levonorgestrel	Estradiol / Levonorgestrel Delayed Release Oral Tablet	Progestogens and estrogens in combination	G03F	43679562	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Oestradiol; Dydrogesterone	dydrogesterone / estradiol Oral Tablet	Progestogens and estrogens in combination	G03F	40033424	Yes
Oestradiol; Dydrogesterone	Dydrogesterone / Estradiol Oral Capsule	Progestogens and estrogens in combination	G03F	36261782	Yes
Oestradiol; Dydrogesterone	Dydrogesterone / Estradiol Extended Release Oral Capsule	Progestogens and estrogens in combination	G03F	36269491	Yes
Oestradiol; Dydrogesterone	Dydrogesterone / Estradiol Delayed Release Oral Tablet	Progestogens and estrogens in combination	G03F	43134116	Yes
Oestradiol; Medroxyprogesterone	estradiol / medroxyprogesterone Oral Tablet	Progestogens and estrogens in combination	G03F	40042032	Yes
Oestradiol; Medroxyprogesterone	Estradiol / Medroxyprogesterone Oral Capsule	Progestogens and estrogens in combination	G03F	41017482	Yes
Oestradiol; Medroxyprogesterone	estradiol / medroxyprogesterone Injectable Suspension	Progestogens and estrogens in combination	G03F	40042030	Yes
Oestradiol; Medroxyprogesterone	Estradiol / Medroxyprogesterone Extended Release Oral Capsule	Progestogens and estrogens in combination	G03F	41267428	Yes
Oestradiol; Progesterone	estradiol / progesterone Oral Capsule	Progestogens and estrogens in combination	G03F	1356326	Yes
Oestradiol; Progesterone	estradiol / progesterone Injectable Suspension	Progestogens and estrogens in combination	G03F	40042043	Yes
Oestradiol; Progesterone	estradiol / progesterone Injectable Solution	Progestogens and estrogens in combination	G03F	40042042	Yes
Oestradiol; Progesterone	estradiol / progesterone Drug Implant	Progestogens and estrogens in combination	G03F	46221385	Yes
Conjugated oestrogens; Medroxyprogesterone	estrogens, conjugated (USP) / medroxyprogesterone Oral Tablet	Progestogens and estrogens in combination	G03F	40037958	Yes
Conjugated oestrogens; Medroxyprogesterone	Estrogens, Conjugated (USP) / Medroxyprogesterone Oral Capsule	Progestogens and estrogens in combination	G03F	44094665	Yes
Conjugated oestrogens; Medroxyprogesterone	Estrogens, Conjugated (USP) / Medroxyprogesterone Extended Release Oral Tablet	Progestogens and estrogens in combination	G03F	42482220	Yes
Conjugated oestrogens; Medroxyprogesterone	Estrogens, Conjugated (USP) / Medroxyprogesterone Delayed Release Oral Tablet	Progestogens and estrogens in combination	G03F	36893485	Yes
Conjugated oestrogens;	estrogens, conjugated (USP) / estrogens, esterified (USP) / medroxyprogesterone Oral Tablet	Progestogens and estrogens in combination	G03F	40037955	Yes

HRT formulation*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
Medroxyprogesterone					

*Concept IDs of combination products were excluded from plain HRT types. Combination products were classified as natural or synthetic based on the oestrogen type. The route of administration was based on the effect of the product (local vs. systemic).

ANNEX V. Supplementary Figures

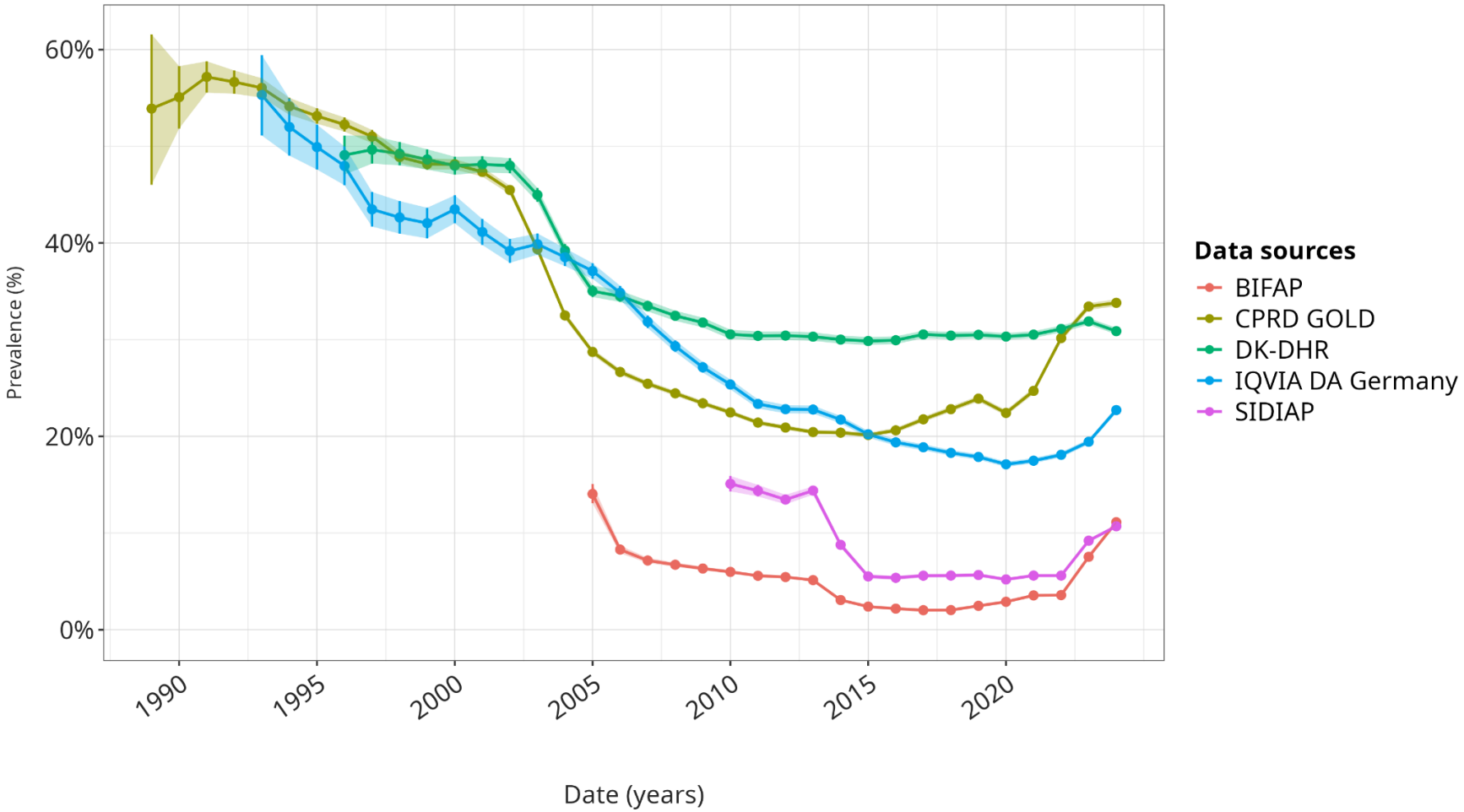


Figure S1. Annual prevalence of HRT use among postmenopausal women, sensitivity analysis.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

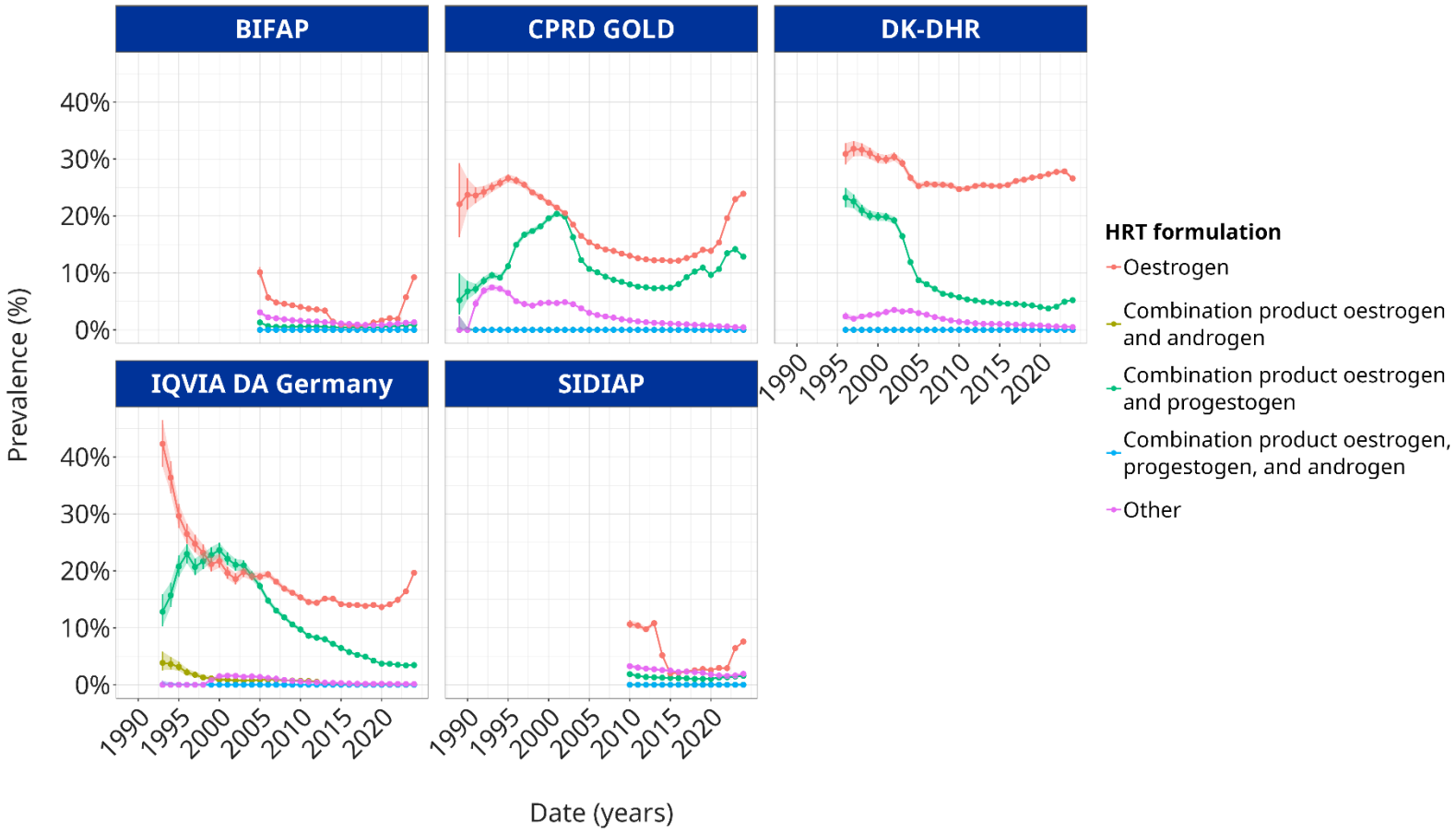


Figure S2. Annual prevalence of HRT use in postmenopausal women, by HRT formulation, sensitivity analysis.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.

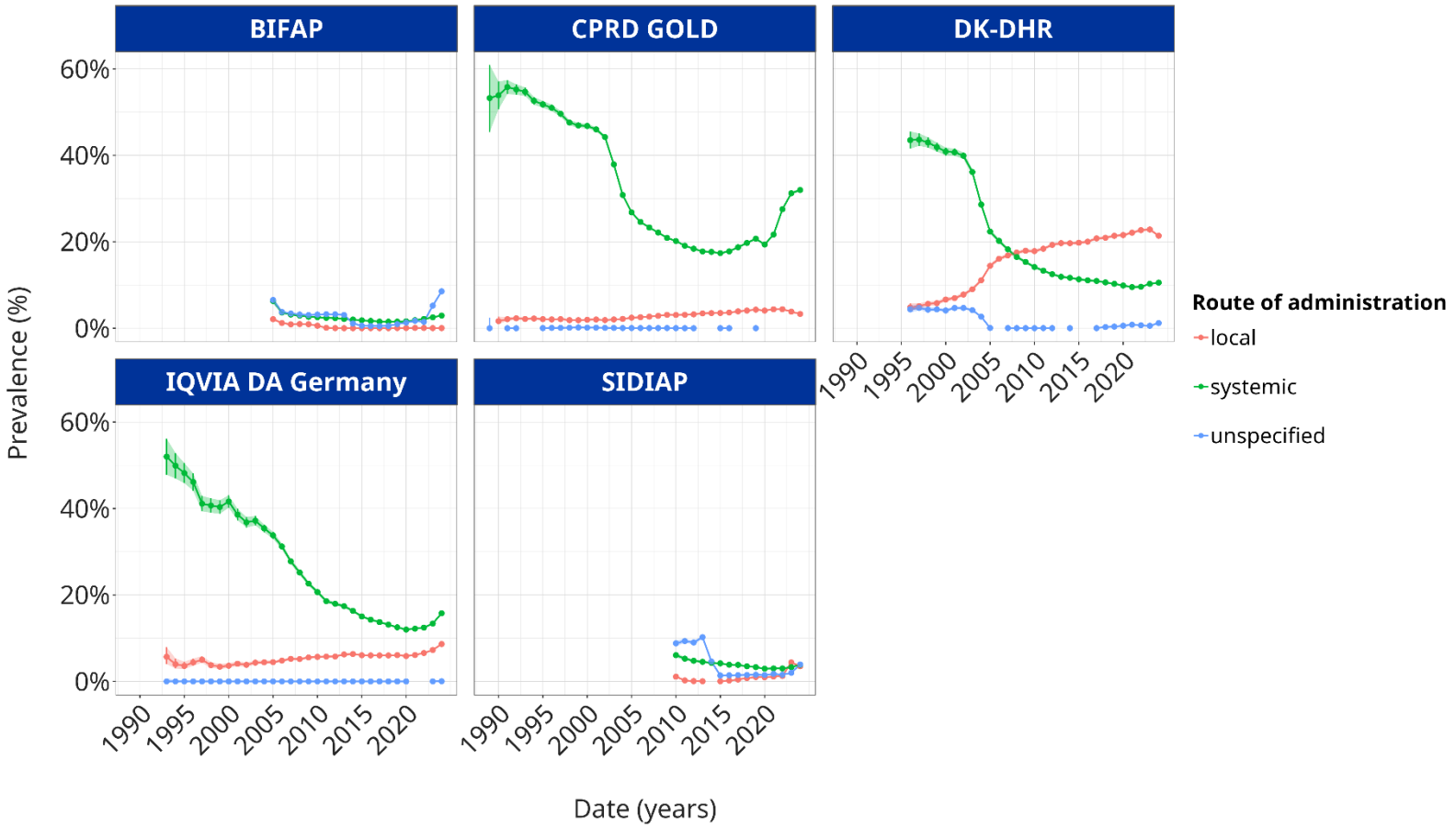


Figure S3. Annual prevalence of HRT use in postmenopausal women, by route of administration, sensitivity analysis.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy; Unspecified route of administration: HRT products for which information on the route of administration was unavailable.

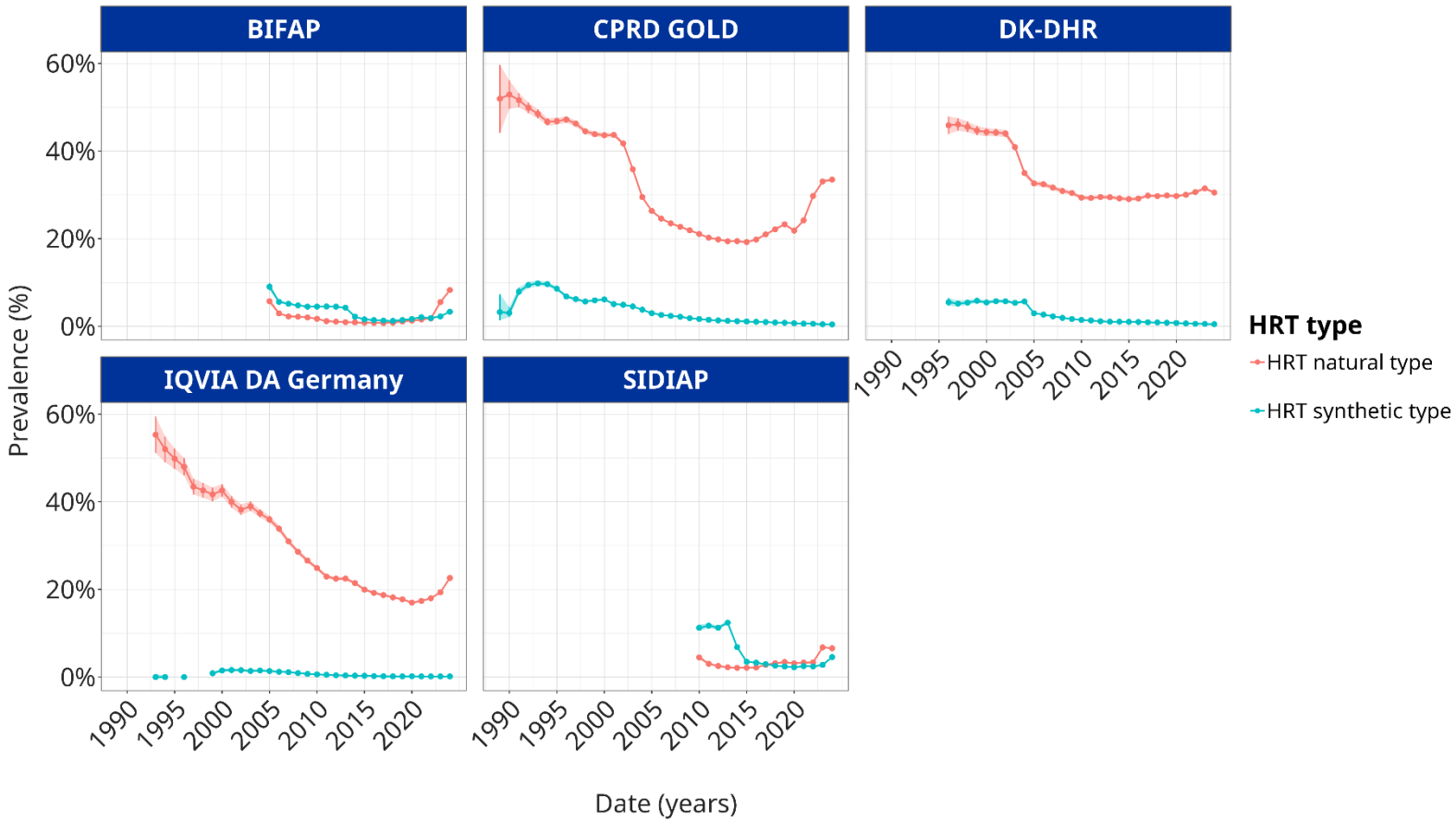
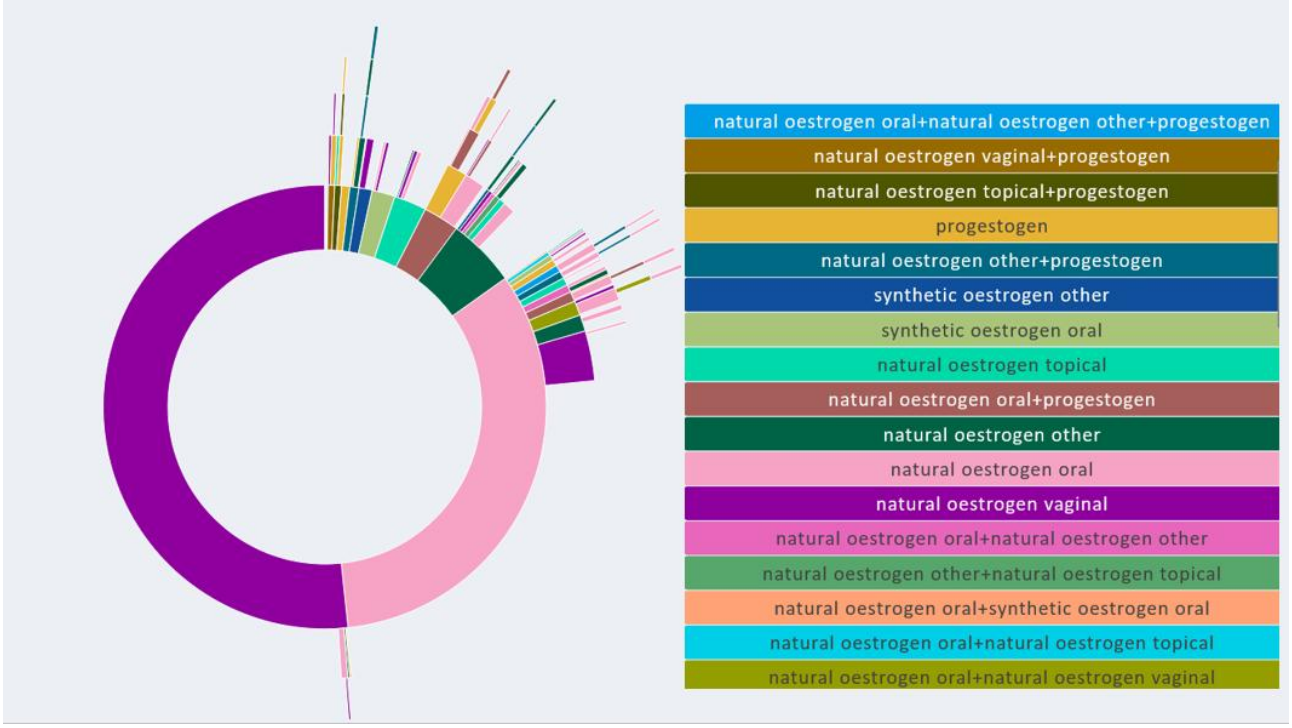


Figure S4. Annual prevalence of HRT use in postmenopausal women, by HRT type, sensitivity analysis.

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; HRT = Hormone replacement therapy.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	natural oestrogen vaginal	51.68%	8,058
2	1	natural oestrogen oral	33.16%	5,170
3	1	natural oestrogen other	5.04%	786
4	1	natural oestrogen oral+progestogen	2.61%	407
5	1	natural oestrogen topical	2.38%	371
6	1	synthetic oestrogen oral	1.69%	263
7	1	synthetic oestrogen other	0.96%	150
8	1	natural oestrogen other+progestogen	0.67%	104
9	1	progestogen	0.60%	94
10	1	natural oestrogen vaginal+progestogen	0.47%	74

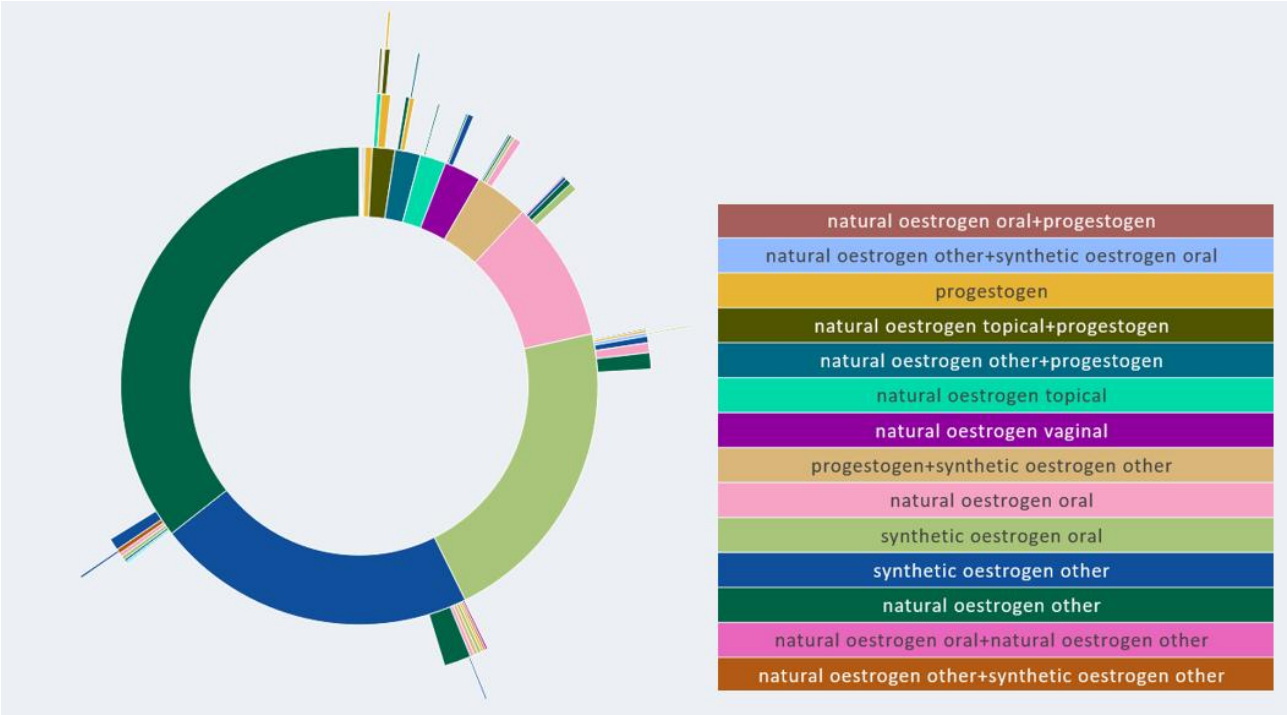
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	natural oestrogen vaginal	50.97%	7,948
2	natural oestrogen oral	24.87%	3,877
3	natural oestrogen other	2.91%	454
4	natural oestrogen oral-natural oestrogen vaginal	2.75%	429
5	natural oestrogen topical	1.68%	262
6	synthetic oestrogen oral	1.30%	203
7	natural oestrogen oral+progestogen-natural oestrogen oral	0.97%	152
8	natural oestrogen other-natural oestrogen oral	0.59%	92
9	synthetic oestrogen other	0.53%	82
10	natural oestrogen oral-natural oestrogen other	0.52%	81

Figure S5. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall in DK-DHR, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
DK-DHR = Danish Data Health Registries.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	natural oestrogen other	35.6%	12,592
2	1	synthetic oestrogen other	21.73%	7,686
3	1	synthetic oestrogen oral	21.18%	7,492
4	1	natural oestrogen oral	9.49%	3,356
5	1	progestogen+synthetic oestrogen other	3.62%	1,279
6	1	natural oestrogen vaginal	2.50%	885
7	1	natural oestrogen topical	1.76%	623
8	1	natural oestrogen other+progestogen	1.72%	610
9	1	natural oestrogen topical+progestogen	1.53%	540
10	1	progestogen	0.48%	171

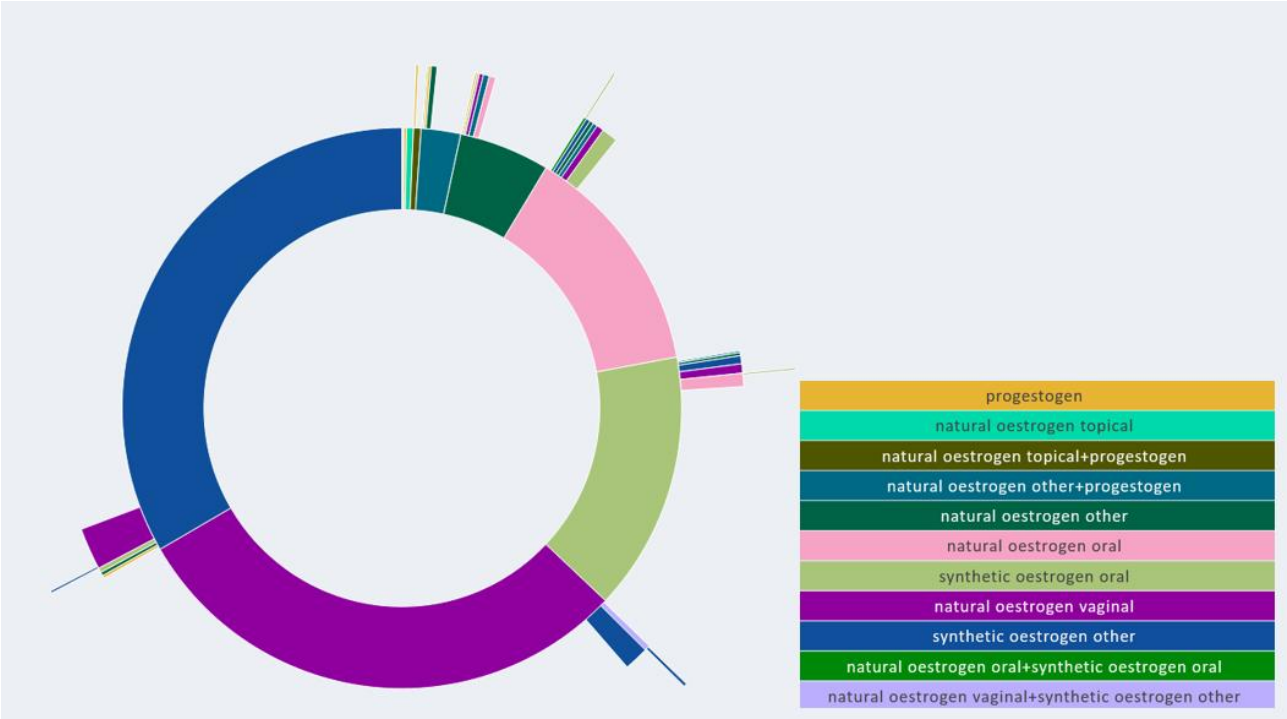
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	natural oestrogen other	33.78%	11,948
2	synthetic oestrogen other	19.12%	6,764
3	synthetic oestrogen oral	18.58%	6,573
4	natural oestrogen oral	8.20%	2,902
5	progestogen+synthetic oestrogen other	2.67%	945
6	natural oestrogen vaginal	1.99%	704
7	natural oestrogen topical	1.44%	511
8	synthetic oestrogen other-natural oestrogen other	1.37%	486
9	natural oestrogen other+progestogen	1.09%	387
10	synthetic oestrogen oral-natural oestrogen other	0.88%	313

Figure S6. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall in BIFAP, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Públicoer.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	synthetic oestrogen other	33.39%	3,434
2	1	natural oestrogen vaginal	29.58%	3,042
3	1	synthetic oestrogen oral	14.95%	1,538
4	1	natural oestrogen oral	13.46%	1,384
5	1	natural oestrogen other	5.24%	539
6	1	natural oestrogen other+progestogen	2.28%	235
7	1	natural oestrogen topical+progestogen	0.44%	45
8	1	natural oestrogen topical	0.39%	40
9	1	progestogen	0.16%	16
10	1	synthetic oestrogen oral+synthetic oestrogen other	0.07%	7

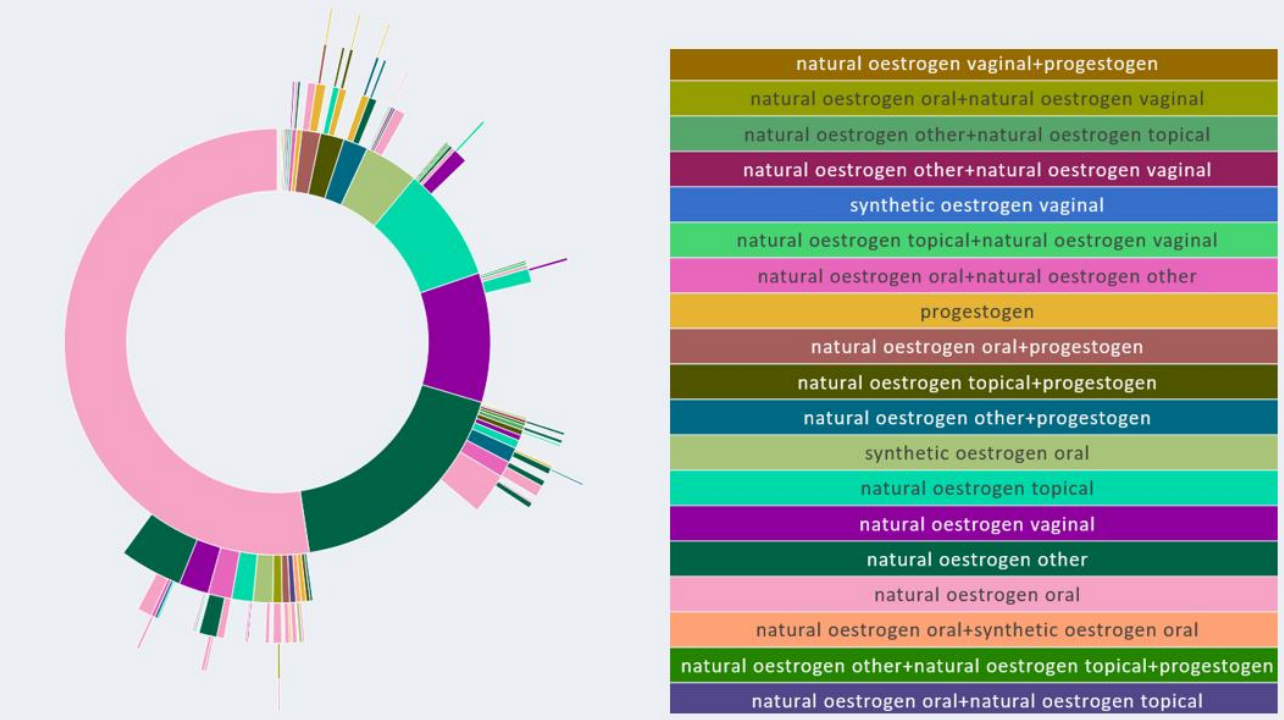
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1	synthetic oestrogen other	30.73%	3,161
2	natural oestrogen vaginal	28.03%	2,883
3	synthetic oestrogen oral	13.04%	1,341
4	natural oestrogen oral	11.33%	1,165
5	natural oestrogen other	4.20%	432
6	synthetic oestrogen other-natural oestrogen vaginal	1.89%	194
7	natural oestrogen other+progestogen	1.74%	179
8	natural oestrogen vaginal-synthetic oestrogen other	1.16%	119
9	natural oestrogen oral-synthetic oestrogen oral	0.68%	70
10	synthetic oestrogen oral-natural oestrogen oral	0.53%	55

Figure S7. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall in SIDIAP, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
SIDIAP = The Information System for Research in Primary Care.



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1	1	natural oestrogen oral	52.39%	37,851
2	1	natural oestrogen other	18.02%	13,019
3	1	natural oestrogen vaginal	9.83%	7,103
4	1	natural oestrogen topical	8.67%	6,267
5	1	synthetic oestrogen oral	4.15%	3,000
6	1	natural oestrogen other+progestogen	1.86%	1,347
7	1	natural oestrogen topical+progestogen	1.81%	1,307
8	1	natural oestrogen oral+progestogen	1.42%	1,026
9	1	progestogen	0.38%	275
10	1	natural oestrogen oral+natural oestrogen other	0.37%	264

b) Top 10 treatment pathways.

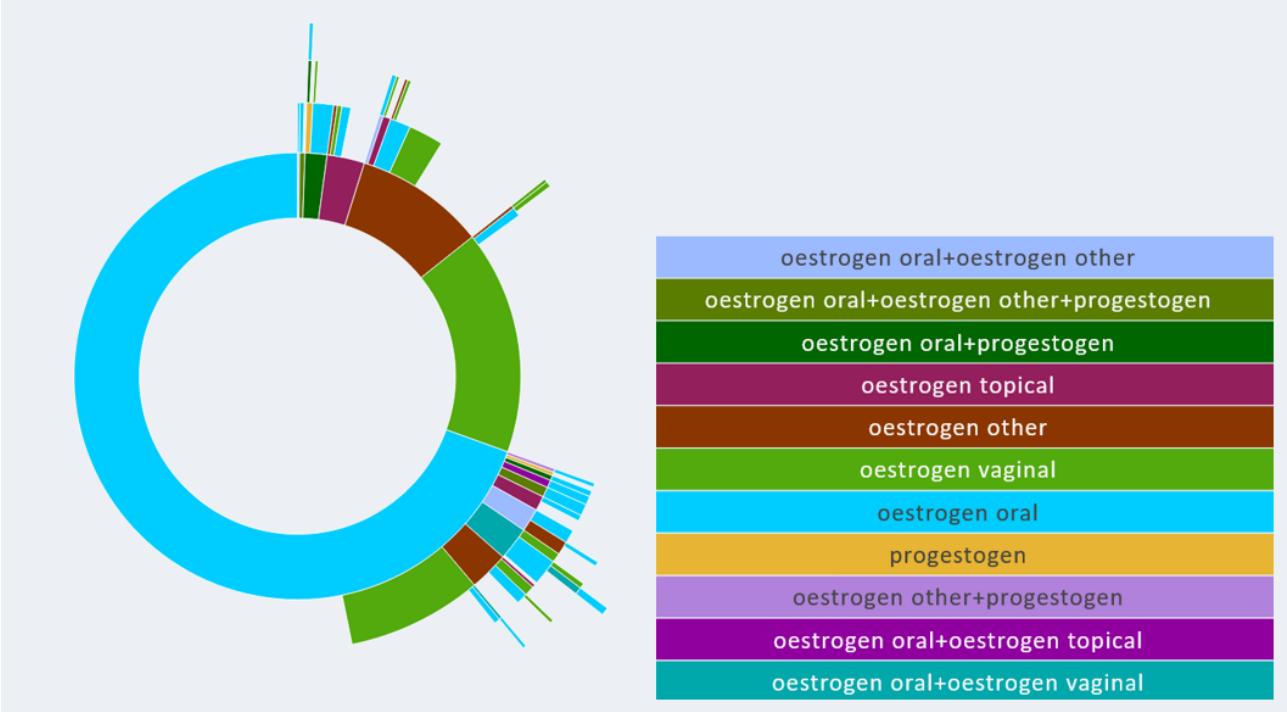
ID	Drug combination	Percentage	Frequency
1	natural oestrogen oral	39.97%	28,875
2	natural oestrogen other	11.46%	8,278
3	natural oestrogen vaginal	8.25%	5,958
4	natural oestrogen topical	6.95%	5,024
5	synthetic oestrogen oral	2.95%	2,128
6	natural oestrogen oral-natural oestrogen other	2.38%	1,716
7	natural oestrogen other-natural oestrogen oral	1.87%	1,352
8	natural oestrogen oral-natural oestrogen vaginal	1.56%	1,130
9	natural oestrogen oral-natural oestrogen topical	1.08%	777
10	natural oestrogen oral-synthetic oestrogen oral	0.85%	612

Figure S8. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women, overall in CPRD GOLD, sensitivity analysis.

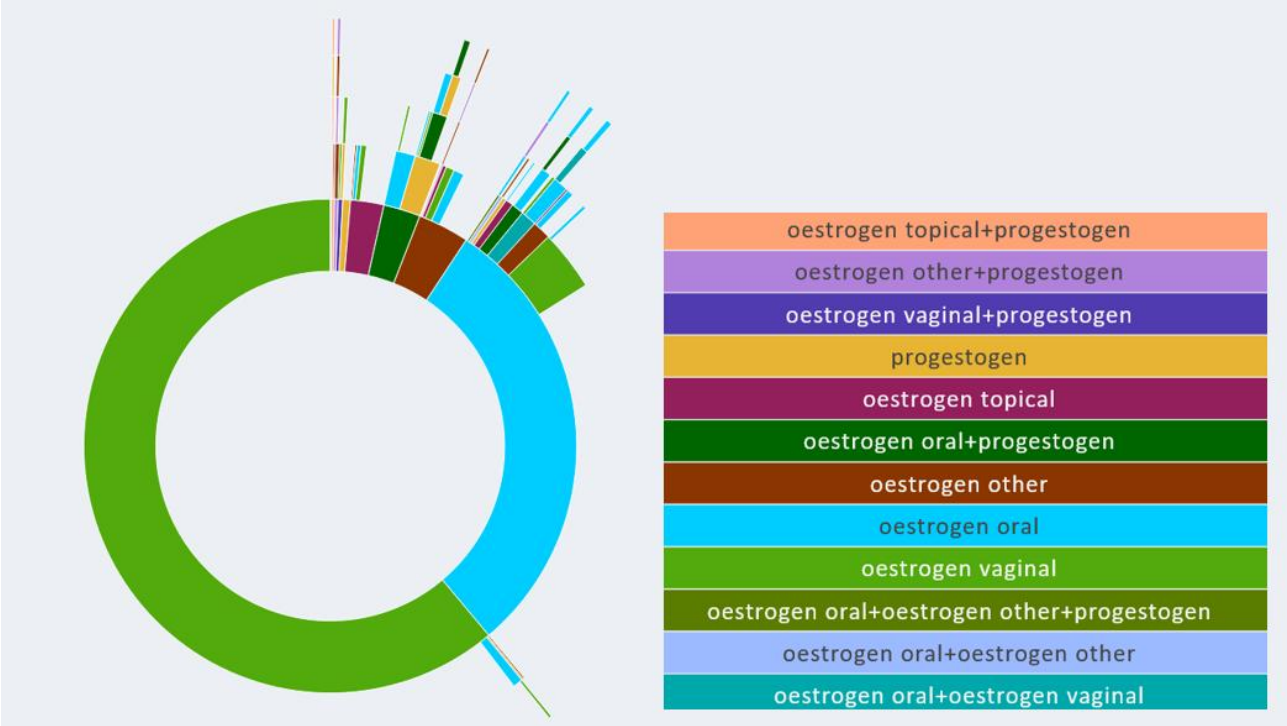
The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway

(b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another.
CPRD GOLD = Clinical Practice Research Datalink GOLD.

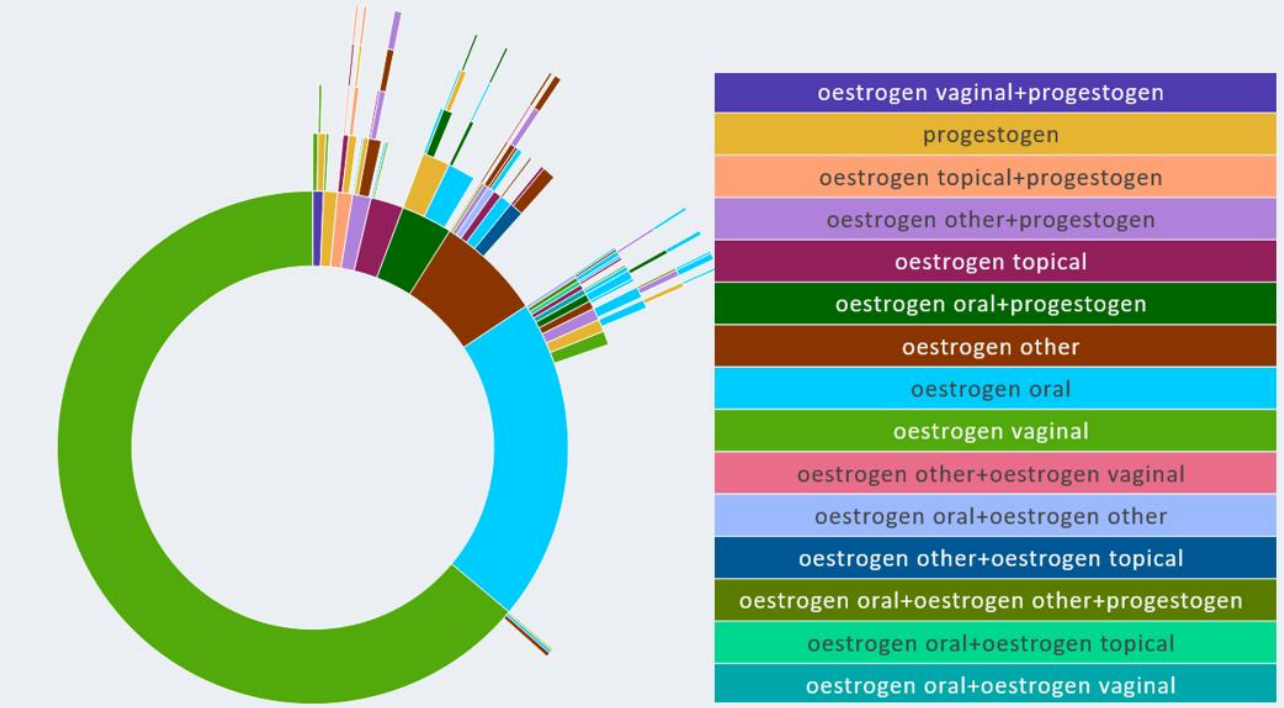
Calendar period 1995–2002



Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1995–2002				
1	1	oestrogen oral	47.52%	49,637
2	1	oestrogen vaginal	32.39%	33,836
3	1	oestrogen other	14.85%	15,510
4	1	oestrogen topical	2.04%	2,128
5	1	oestrogen other+progestogen	1.05%	1,099
6	1	oestrogen oral+progestogen	0.76%	796
7	1	oestrogen topical+progestogen	0.47%	494
8	1	oestrogen oral+oestrogen other+progestogen	0.25%	259
9	1	progestogen	0.24%	248
10	1	oestrogen oral+oestrogen vaginal	0.18%	186
2003–2015				
1	1	oestrogen vaginal	61.11%	4003
2	1	oestrogen oral	29.59%	1938
3	1	oestrogen other	3.37%	221
4	1	oestrogen oral+progestogen	2.43%	159
5	1	oestrogen topical	2.18%	143
6	1	progestogen	0.50%	33
7	1	oestrogen vaginal+progestogen	0.31%	20
8	1	oestrogen other+progestogen	0.23%	15
9	1	oestrogen topical+progestogen	0.20%	13
10	1	oestrogen oral+oestrogen other	0.08%	5
2016–2024				
1	1	oestrogen vaginal	63.93%	3,502
2	1	oestrogen oral	20.37%	1,116
3	1	oestrogen other	6.70%	367
4	1	oestrogen oral+progestogen	3.25%	178
5	1	oestrogen topical	2.08%	114
6	1	oestrogen other+progestogen	1.17%	64
7	1	oestrogen topical+progestogen	0.95%	52
8	1	progestogen	0.88%	48

ID	Line	Drug combination	Percentage	Frequency
9	1	oestrogen vaginal+progestogen	0.68%	37
10	2	oestrogen oral	2.45%	134

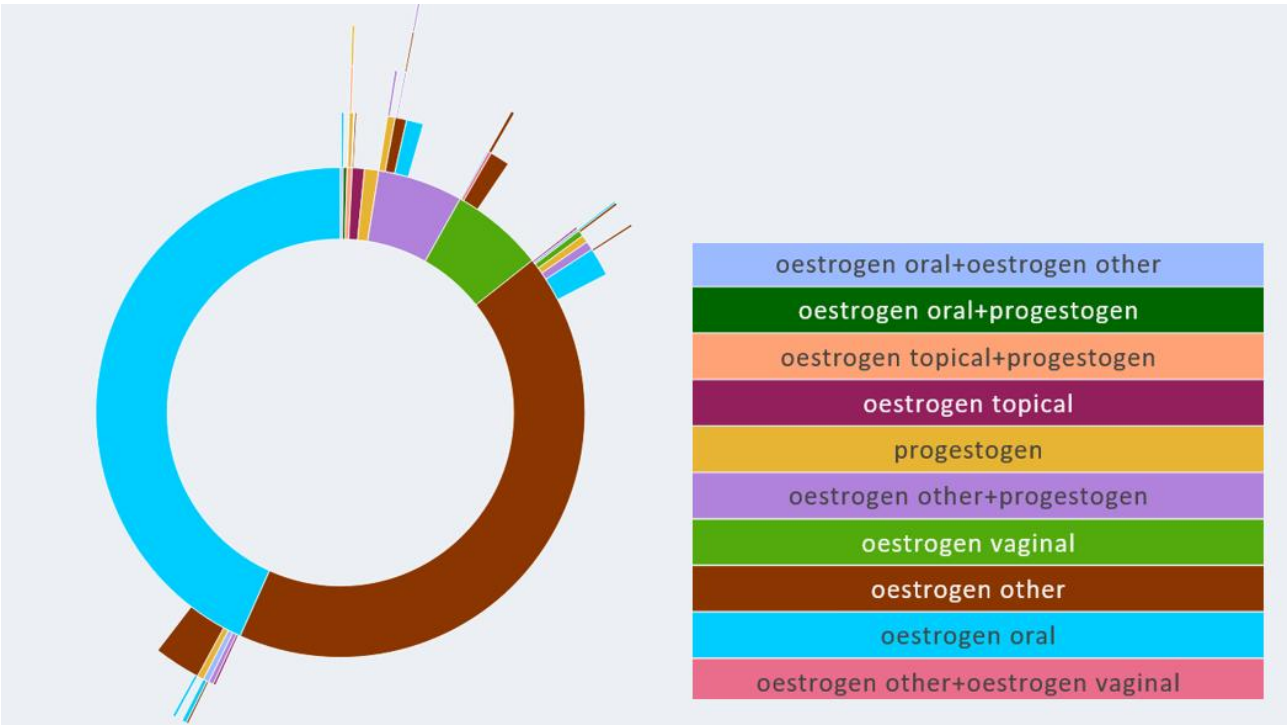
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1995–2002			
1	oestrogen oral	32.18%	33,615
2	oestrogen vaginal	29.40%	30,706
3	oestrogen other	7.32%	7,651
4	oestrogen oral-oestrogen vaginal	7.15%	7,472
5	oestrogen other-oestrogen vaginal	4.32%	4,515
6	oestrogen other-oestrogen oral	1.19%	1,238
7	oestrogen topical	0.94%	980
8	oestrogen vaginal-oestrogen oral	0.82%	856
9	oestrogen oral-oestrogen other	0.80%	836
10	oestrogen oral-oestrogen oral+oestrogen other+progestogen-oestrogen oral	0.67%	701
2003–2015			
1	oestrogen vaginal	60.41%	3957
2	oestrogen oral	22.81%	1494
3	oestrogen oral-oestrogen vaginal	2.99%	196
4	oestrogen other	2.00%	131
5	oestrogen topical	1.57%	103
6	oestrogen oral+progestogen-oestrogen oral	0.85%	56
7	oestrogen oral-oestrogen other	0.61%	40
8	oestrogen other-oestrogen oral	0.56%	37
9	progesterone	0.50%	33
10	oestrogen oral+progestogen-progesterone	0.47%	31
2016–2024			
1	oestrogen vaginal	63.44%	3,475
2	oestrogen oral	16.39%	898
3	oestrogen other	4.07%	223
4	oestrogen topical	1.86%	102
5	oestrogen oral+progestogen-oestrogen oral	1.26%	69
6	oestrogen oral+progestogen-progesterone	0.86%	47
7	progestogen	0.73%	40
8	oestrogen oral-oestrogen vaginal	0.71%	39
9	oestrogen other-oestrogen other+oestrogen topical-oestrogen other	0.58%	32
10	oestrogen other-oestrogen oral	0.55%	30

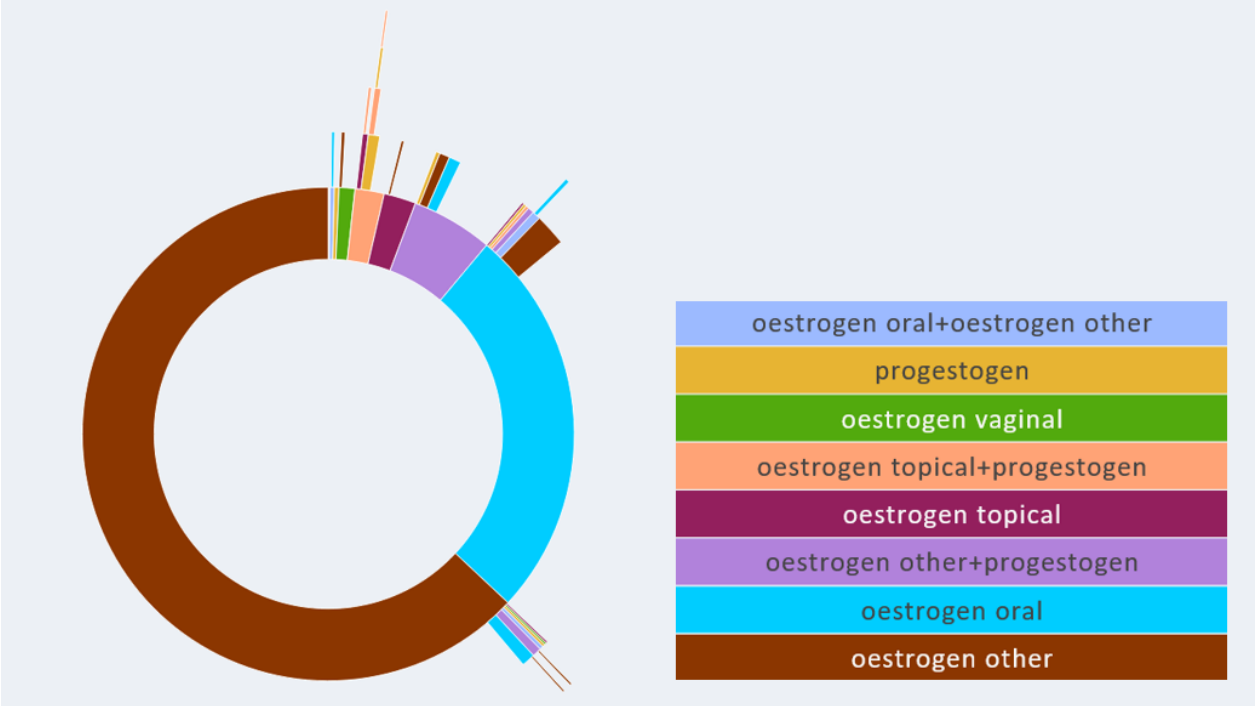
Figure S9. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in DK-DHR, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 1995–2002, 2003–2015, 2016–2024.
DK-DHR = Danish Data Health Registries.

Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
2003–2015				
1	1	oestrogen oral	43.28%	4,325
2	1	oestrogen other	42.39%	4,236
3	1	oestrogen vaginal	6.19%	619
4	1	oestrogen other+progestogen	5.63%	563

ID	Line	Drug combination	Percentage	Frequency
5	1	progestogen	0.93%	93
6	1	oestrogen topical	0.81%	81
7	1	oestrogen topical+progestogen	0.34%	34
8	1	oestrogen oral+progestogen	0.24%	24
9	1	oestrogen oral+oestrogen other	0.19%	19
10	2	oestrogen other	4.43%	443
2016–2024				
1	1	oestrogen other	63.03%	16,209
2	1	oestrogen oral	25.84%	6,646
3	1	oestrogen other+progestogen	5.37%	1,380
4	1	oestrogen topical	2.11%	543
5	1	oestrogen topical+progestogen	1.92%	493
6	1	oestrogen vaginal	1.04%	268
7	1	progestogen	0.30%	77
8	1	oestrogen oral+oestrogen other	0.29%	75
9	1	oestrogen oral+progestogen	0.08%	20
10	1	testosterone	0.02%	6

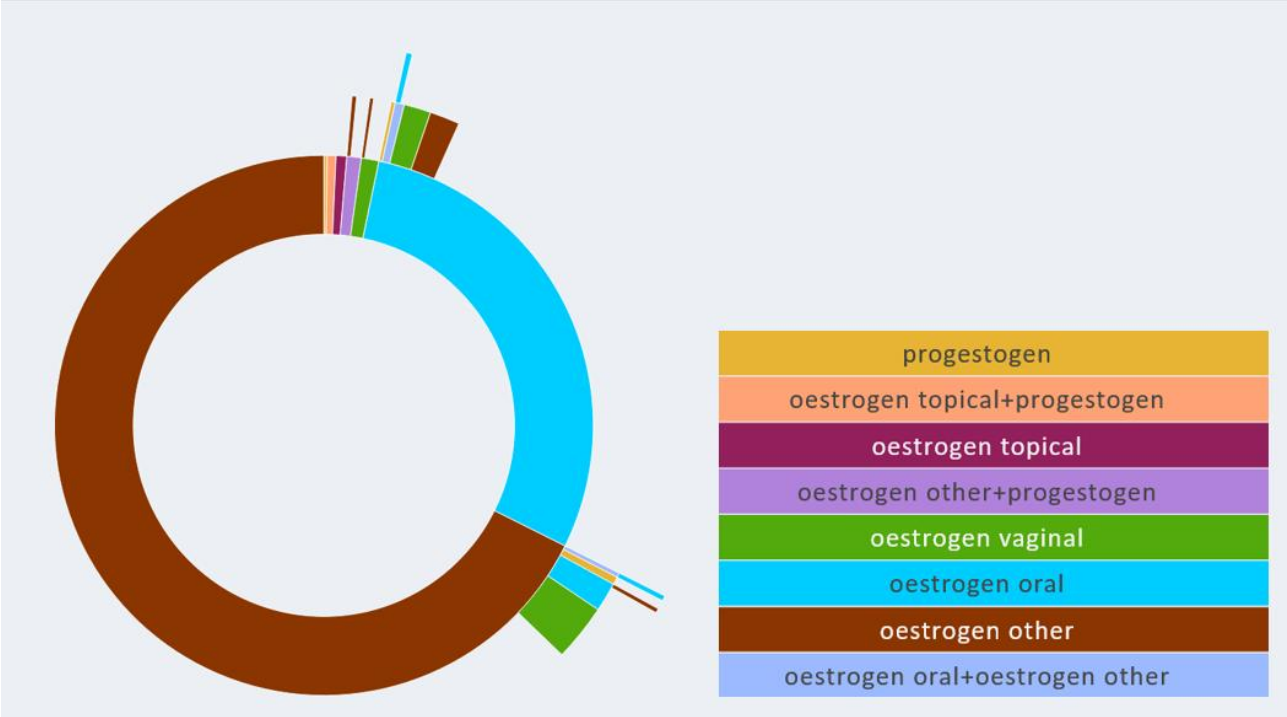
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
2003–2015			
1	oestrogen oral	39.56%	3,954
2	oestrogen other	39.33%	3,931
3	oestrogen vaginal	4.87%	487
4	oestrogen other+progestogen	3.67%	367
5	oestrogen oral-oestrogen other	2.38%	238
6	oestrogen other-oestrogen oral	1.42%	142
7	oestrogen vaginal-oestrogen other	1.07%	107
8	oestrogen other+progestogen-oestrogen oral	0.86%	86
9	progestogen	0.74%	74
10	oestrogen topical	0.71%	71
2016–2024			
1	oestrogen other	61.19%	15,737
2	oestrogen oral	22.92%	5,895
3	oestrogen other+progestogen	3.89%	1,001
4	oestrogen topical	1.71%	440
5	oestrogen oral-oestrogen other	1.59%	409
6	oestrogen topical+progestogen	0.91%	235
7	oestrogen vaginal	0.84%	217
8	oestrogen other+progestogen-oestrogen oral	0.59%	153
9	oestrogen other-oestrogen oral	0.58%	150
10	oestrogen other+progestogen-oestrogen other	0.42%	108

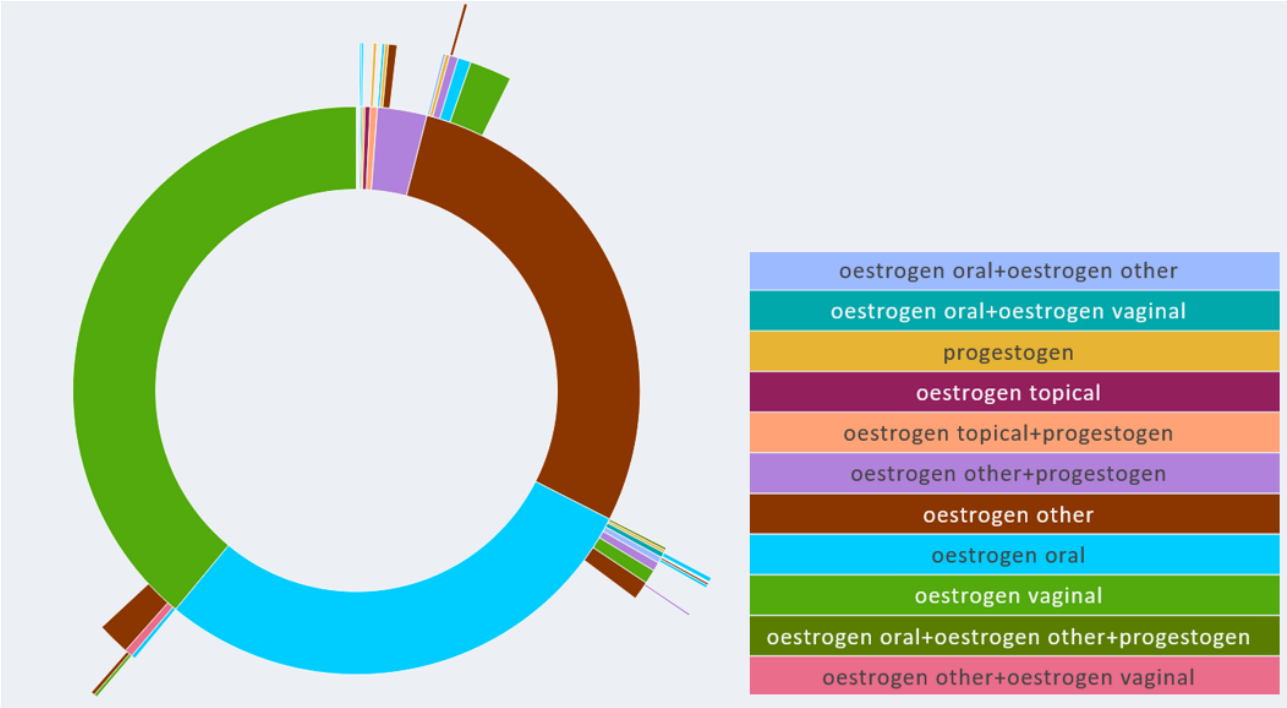
Figure S10. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in BIFAP, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 2003–2015, 2016–2024.
BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público.

Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
2003–2015				
1	1	oestrogen other	67.63%	1,795
2	1	oestrogen oral	29.09%	772
3	1	oestrogen vaginal	1.06%	28
4	1	oestrogen other+progestogen	0.87%	23

ID	Line	Drug combination	Percentage	Frequency
5	1	oestrogen topical	0.64%	17
6	1	oestrogen topical+progestogen	0.53%	14
7	1	progesterone	0.19%	5
8	2	oestrogen vaginal	4.11%	109
9	2	oestrogen other	1.88%	50
10	2	oestrogen oral	1.43%	38
2016–2024				
1	1	oestrogen vaginal	38.99%	3,022
2	1	oestrogen oral	28.53%	2,211
3	1	oestrogen other	28.48%	2,207
4	1	oestrogen other+progestogen	2.83%	219
5	1	oestrogen topical+progestogen	0.40%	31
6	1	oestrogen topical	0.30%	23
7	1	progestogen	0.14%	11
8	1	oestrogen oral+oestrogen vaginal	0.10%	8
9	1	oestrogen oral+oestrogen other	0.09%	7
10	1	oestrogen other+oestrogen vaginal	0.08%	6

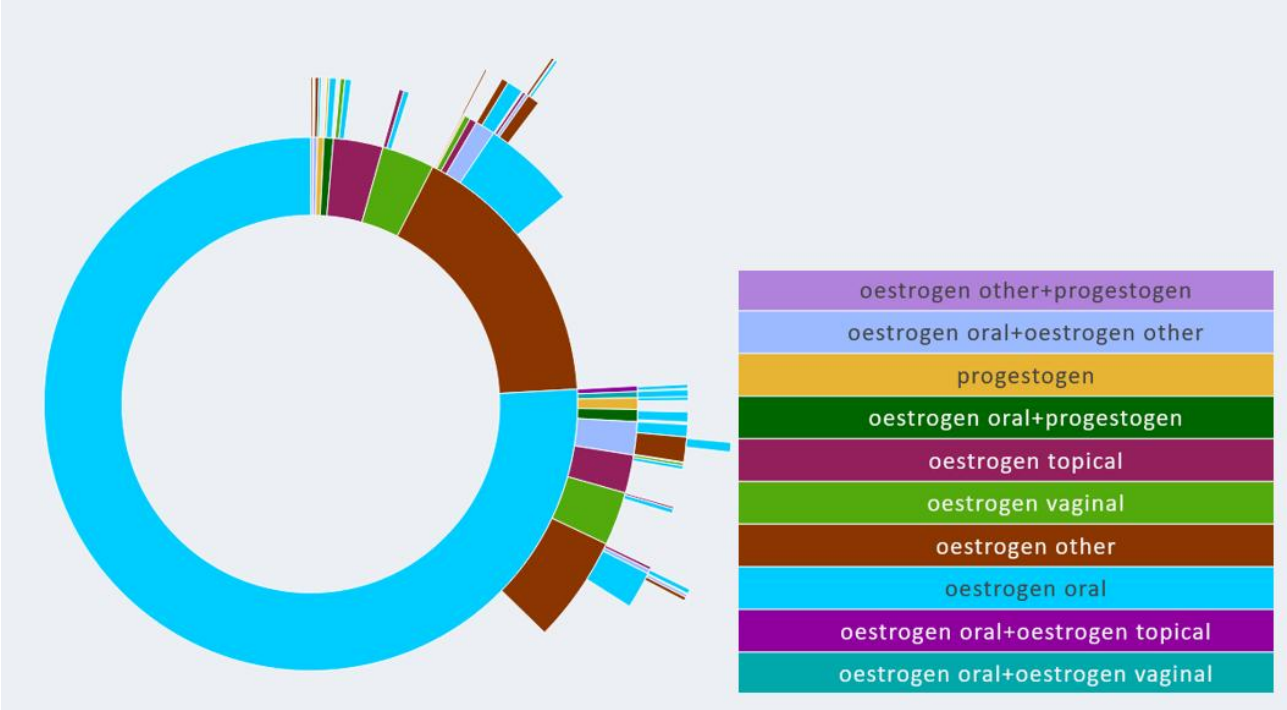
b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
2003–2015			
1	oestrogen other	62.81%	1,667
2	oestrogen oral	25.66%	681
3	oestrogen other-oestrogen vaginal	2.79%	74
4	oestrogen oral-oestrogen other	1.47%	39
5	oestrogen oral-oestrogen vaginal	1.32%	35
6	oestrogen other-oestrogen oral	1.24%	33
7	oestrogen vaginal	0.87%	23
8	oestrogen other+progestogen	0.64%	17
9	oestrogen topical	0.64%	17
10	oestrogen topical+progestogen	0.53%	14
2016–2024			
1	oestrogen vaginal	36.9%	2860
2	oestrogen oral	25.82%	2001
3	oestrogen other	25.17%	1951
4	oestrogen other+progestogen	2.13%	165
5	oestrogen other-oestrogen vaginal	1.88%	146
6	oestrogen vaginal-oestrogen other	1.52%	118
7	oestrogen oral-oestrogen other	0.71%	55
8	oestrogen oral-oestrogen vaginal	0.66%	51
9	oestrogen other-oestrogen oral	0.61%	47
10	oestrogen oral-oestrogen other+progestogen	0.41%	32

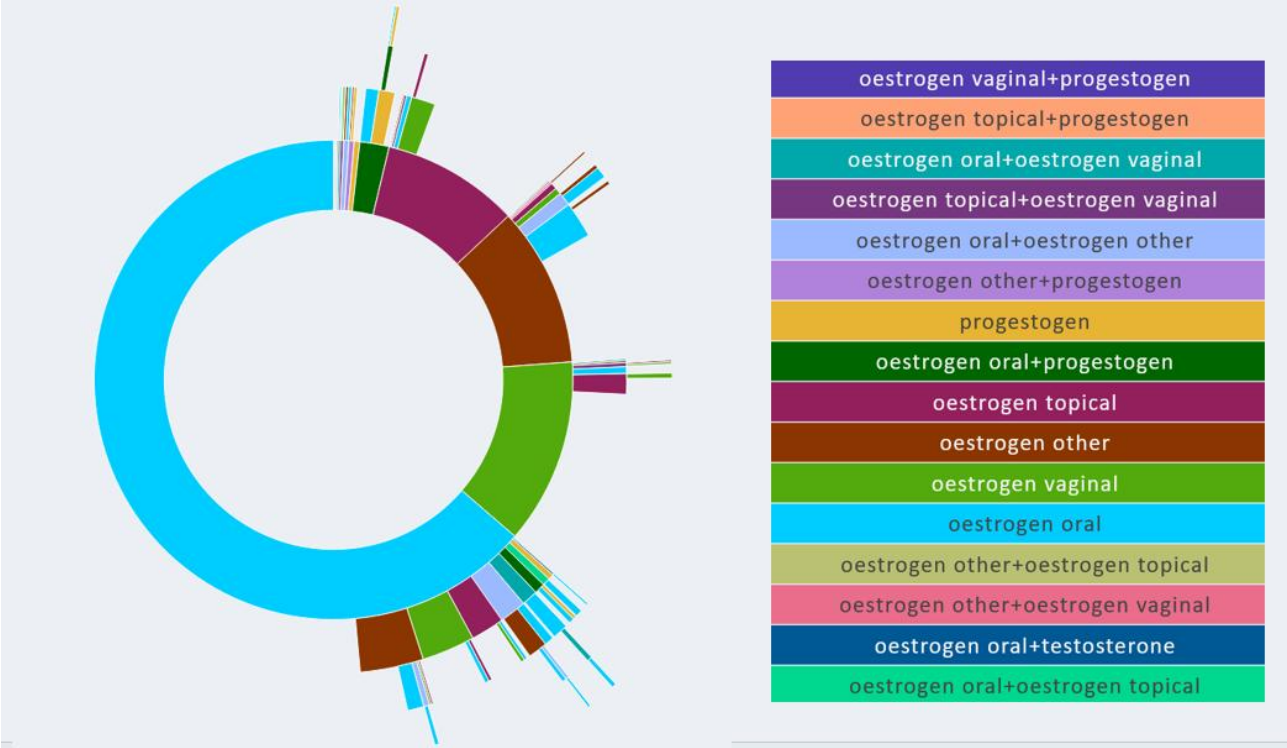
Figure S11. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in SIDIAP, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. "Line" refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another.
Calendar periods: 2003–2015, 2016–2024.
SIDIAP = The Information System for Research in Primary Care.

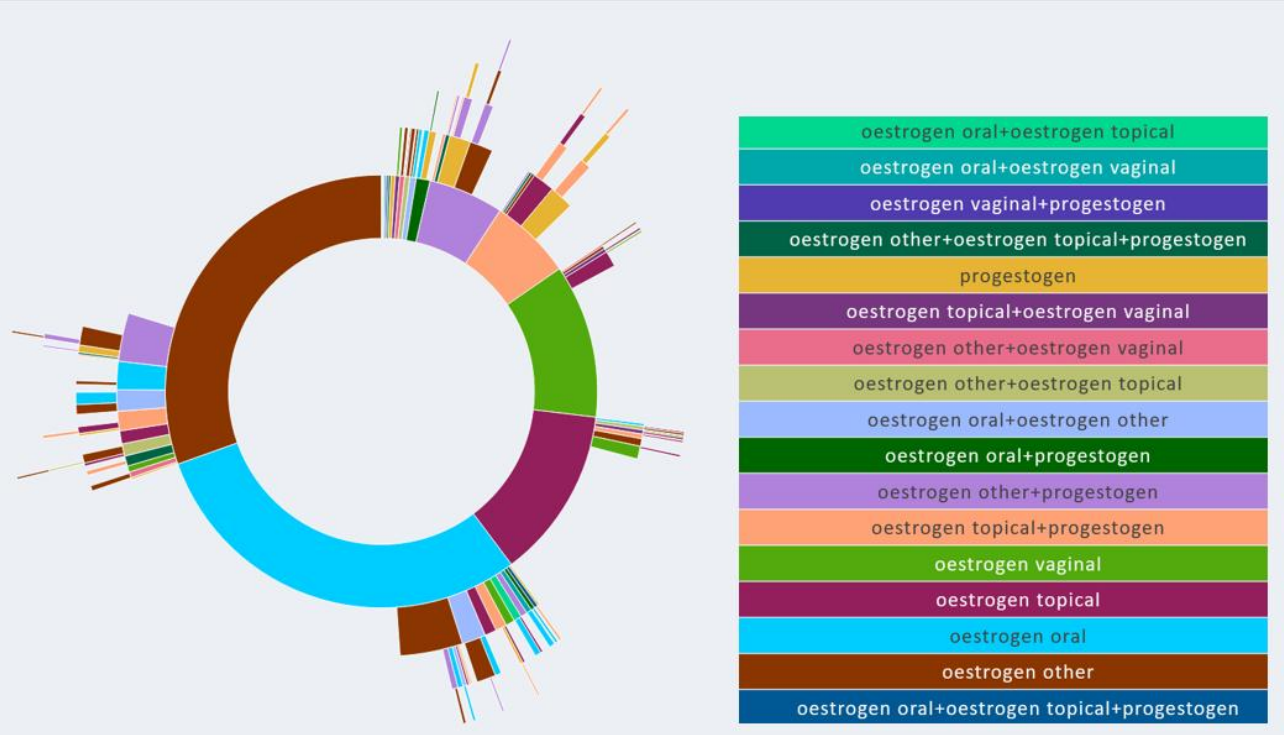
Calendar period 1995–2002



Calendar period 2003–2015



Calendar period 2016–2024



a) Top 10 drug combinations.

ID	Line	Drug combination	Percentage	Frequency
1995–2002				
1	1	oestrogen oral	75.89%	9,472
2	1	oestrogen other	16.55%	2,066
3	1	oestrogen vaginal	3.20%	400
4	1	oestrogen topical	3.00%	375
5	1	oestrogen oral+progestogen	0.57%	71
6	1	progestogen	0.38%	48
7	1	oestrogen oral+oestrogen other	0.26%	32
8	1	oestrogen other+progestogen	0.14%	18
9	2	oestrogen oral	5.73%	715
10	2	oestrogen other	5.62%	701
2003–2015				
1	1	oestrogen oral	63.68%	22,153
2	1	oestrogen vaginal	12.52%	4,355
3	1	oestrogen other	10.78%	3,749
4	1	oestrogen topical	9.28%	3,230
5	1	oestrogen oral+progestogen	1.98%	690
6	1	progestogen	0.38%	132
7	1	oestrogen oral+oestrogen other	0.35%	123
8	1	oestrogen other+progestogen	0.35%	123
9	1	oestrogen topical+oestrogen vaginal	0.20%	70
10	1	oestrogen oral+oestrogen vaginal	0.16%	54
2016–2024				
1	1	oestrogen other	30.45%	6,143
2	1	oestrogen oral	29.82%	6,015
3	1	oestrogen topical	12.83%	2,588
4	1	oestrogen vaginal	11.50%	2,320
5	1	oestrogen topical+progestogen	6.15%	1,241
6	1	oestrogen other+progestogen	5.63%	1,136
7	1	oestrogen oral+progestogen	1.04%	209

ID	Line	Drug combination	Percentage	Frequency
8	1	oestrogen oral+oestrogen other	0.47%	95
9	1	oestrogen other+oestrogen vaginal	0.38%	76
10	1	progestogen	0.32%	65

b) Top 10 treatment pathways.

ID	Drug combination	Percentage	Frequency
1995–2002			
1	oestrogen oral	62.67%	7,823
2	oestrogen other	10.04%	1,253
3	oestrogen other-oestrogen oral	3.77%	471
4	oestrogen oral-oestrogen other	3.32%	414
5	oestrogen vaginal	2.69%	336
6	oestrogen topical	2.37%	296
7	oestrogen oral-oestrogen vaginal	2.36%	295
8	oestrogen oral-oestrogen topical	1.62%	202
9	oestrogen oral-oestrogen other-oestrogen oral	1.29%	161
10	oestrogen oral-oestrogen oral+oestrogen other-oestrogen other	0.64%	80
2003–2015			
1	oestrogen oral	51.45%	17,899
2	oestrogen vaginal	10.53%	3,664
3	oestrogen topical	7.40%	2,573
4	oestrogen other	6.99%	2,433
5	oestrogen oral-oestrogen vaginal	2.45%	852
6	oestrogen oral-oestrogen other	2.06%	718
7	oestrogen other-oestrogen oral	1.62%	564
8	oestrogen oral-oestrogen topical	1.48%	515
9	oestrogen topical-oestrogen vaginal	1.11%	386
10	oestrogen vaginal-oestrogen topical	0.87%	301
2016–2024			
1	oestrogen oral	20.68%	4,171
2	oestrogen other	20.22%	4,080
3	oestrogen topical	10.63%	2,145
4	oestrogen vaginal	9.77%	1,971
5	oestrogen topical+progestogen	2.76%	557
6	oestrogen oral-oestrogen other	2.58%	521
7	oestrogen other+progestogen	2.37%	479
8	oestrogen other-oestrogen other+progestogen	1.36%	274
9	oestrogen other-oestrogen oral	1.27%	256
10	oestrogen other+progestogen-oestrogen other	0.91%	184

Figure S12. Sunburst plot depicting treatment patterns over 10 years following HRT initiation in postmenopausal women by calendar periods, in CPRD GOLD, sensitivity analysis.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provide detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the Shiny app. “Line” refers to the position in the treatment sequence (e.g. first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The “+” symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the “–” symbol represents a switch from one regimen to another.
Calendar periods: 1995–2002, 2003–2015, 2016–2024.
CPRD GOLD = Clinical Practice Research Datalink GOLD.

ANNEX VI. Supplementary Tables

Table S5. Clinical characteristics of postmenopausal women one year prior to the prespecified calendar date stratified by HRT use across selected calendar years by data source.

Variable	1990	1995	2000	2005	2010	2015	2020	2024
DK-DHR								
HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	–	–	–	24 (21–29)	25.3 (22.2–29.3)	25.6 (22.5–29.7)	26 (22.8–29.9)
· Missing	–	–	80,548 (100)	146,478 (100)	204,464 (99.31)	251,684 (94.72)	309,097 (96.14)	328,752 (91.37)
Smoking status								
· Current smoker	–	–	14 (0.02)	136 (0.09)	129 (0.06)	151 (0.06)	70 (0.02)	43 (0.01)
· Non smoker	–	–	–	–	–	–	–	–
· Missing	–	–	80,534 (99.98)	146,342 (99.91)	205,763 (99.94)	265,576 (99.94)	321,429 (99.98)	359,756 (99.99)
Menopause diagnosis	–	–						
· Yes	–	–	633 (0.79)	1,247 (0.84)	1,913 (0.93)	2,614 (0.98)	2,412 (0.75)	4,779 (1.33)
· No	–	–	79,915 (99.21)	145,243 (99.16)	203,979 (99.07)	263,113 (99.02)	319,087 (99.25)	355,020 (98.67))
· Missing	–	–	–	–	–	–	–	–
Non-HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	–	–	–	24 (20–28)	25.4 (22–29.8)	26 (22.4–30.9)	26.8 (23–31.6)
· Missing	–	–	390,142 (100)	438,166 (100)	490,668 (99.44)	526,704 (96.04)	570,830 (97.22)	568,028 (93.93)
Smoking status								
· Current smoker	–	–	51 (0.01)	365 (0.08)	253 (0.05)	371 (0.07)	165 (0.03)	67 (0.01)
· Non smoker	–	–	–	–	–	–	–	–

Variable	1990	1995	2000	2005	2010	2015	2020	2024
· Missing	–	–	390,091 (99.99)	437,801 (99.92)	493,159 (99.95)	548,057 (99.93)	587,002 (99.97)	604,671 (99.99)
Menopause diagnosis								
· Yes	–	–	1,160 (0.30)	1,616 (0.37)	2,321 (0.47)	2,791 (0.51)	2,255 (0.38)	3,035 (0.50)
· No	–	–	388,982 (99.70)	436,550 (99.63)	491,091 (99.53)	545,637 (99.49)	584,912 (99.62)	601,703 (99.50)
· Missing	–	–	–	–	–	–	–	–
IQVIA DA Germany								
HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	25.92 (24.42–29.82)	–	26.41 (24.02–29.71)	26.22 (23.42–30.05)	25.5 (22.86–29.34)	25.8 (23.05–29.72)	25.59 (22.84–29.27)
· Missing	–	1,219 (99.03)	3,572 (100)	7,396 (92.84)	20,076 (95.13)	38,493 (95.35)	59,650 (95.70)	60,469 (95.20)
Smoking status								
· Current smoker	–	<5	<5	68 (0.85)	151 (0.72)	283 (0.70)	465 (0.75)	395 (0.62)
· Non smoker	–	–	–	–	–	–	–	–
· Missing	–	1,227 (99.68)	3,568 (99.89)	7,898 (99.15)	20,953 (99.28)	40,088 (99.30)	61,864 (99.25)	63,125 (99.38)
Menopause diagnosis								
· Yes	–	176 (14.30)	510 (14.28)	1,121 (14.07)	1,899 (9.00)	3,321 (8.23)	3,925 (6.30)	5,403 (8.51)
· No	–	1,055 (85.70)	3,062 (85.72)	6,845 (85.93)	19,205 (91.00)	37,050 (91.77)	58,404 (93.70)	58,117 (91.49)
· Missing	–	–	–	–	–	–	–	–
Non-HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	26.19 (23.78–29.76)	28.55 (25.87–35.35)	26.77 (23.81–30.86)	27.47 (24.09–31.83)	27.44 (24.01–32.05)	27.86 (24.09–32.72)	27.58 (23.8–32.39)
· Missing	–	33,190 (99.27)	104,161 (99.98)	283,142 (98.49)	709,332 (98.46)	1,247,055 (97.83)	1,635,041 (97.58)	1,188,682 (96.90)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
Smoking status								
· Current smoker	–	43 (0.13)	54 (0.05)	571 (0.20)	3,261 (0.45)	6,449 (0.51)	8,036 (0.48)	7,306 (0.60)
· Non smoker	–	–	<5	5 (0.00)	<5	–	–	–
· Missing		33,391 (99.87)	104,122 (99.95)	286,900 (99.80)	717,191 (99.55)	1,268,280 (99.49)	1,667,626 (99.52)	1,219,342 (99.40)
Menopause diagnosis	–							
· Yes	–	322 (0.96)	537 (0.52)	2,332 (0.81)	3,805 (0.53)	7,219 (0.57)	9,180 (0.55)	10,653 (0.87)
· No	–	33,112 (99.04)	103,640 (99.48)	285,144 (99.19)	716,648 (99.47)	1,267,510 (99.43)	1,666,482 (99.45)	1,215,995 (99.13)
· Missing	–	–	–	–	–	–	–	–
BIFAP								
HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	–	–	27.97 (25.43-30.72)	28.85 (25.72-32.46)	28.38 (25.39-31.94)	28.40 (25.32-31.92)	27.73 (24.57-31.28)
· Missing	–	–	–	1,524 (88.09)	26,992 (81.36)	51,679 (79.36)	74,216 (81.53)	204,817 (78.61)
Smoking status								
· Current smoker	–	–	–	–	–	–	401 (0.44)	1,626 (0.62)
· Non smoker	–	–	–	–	–	–	<5	15 (0.01)
· Missing	–	–	–	1,730 (100)	33,176 (100)	65,119 (100)	90,625 (99.56)	258,894 (99.37)
Menopause diagnosis								
· Yes	–	–	–	233 (13.47)	1,766 (5.32)	1,873 (2.88)	1,994 (2.19)	10,908 (4.19)
· No	–	–	–	1,497 (86.53)	31,410 (94.68)	63,246 (97.12)	89,034 (97.81)	249,627 (95.81)
· Missing	–	–	–	–	–	–	–	–
Non-HRT users								

Variable	1990	1995	2000	2005	2010	2015	2020	2024
BMI (kg/m^2)								
· Median (IQR)	–	–	–	29.34 (26.16-33.22)	29.26 (26.01-33.13)	28.65 (25.41-32.53)	28.76 (25.35-32.81)	28.27 (24.75-32.43)
· Missing	–	–	–	126,112 (84.75)	760,299 (79.62)	1,305,759 (78.42)	2,753,870 (85.66)	3,045,072 (82.88)
Smoking status								
· Current smoker	–	–	–	–	–	<5	20,613 (0.64)	26,257 (0.71)
· Non smoker	–	–	–	–	–	<5	106 (0.00)	136 (0.00)
· Missing	–	–	–	148,805 (100)	954,968 (100)	1,665,163 (100)	3,194,075 (99.36)	3,647,733 (99.28)
Menopause diagnosis								
· Yes	–	–	–	5,068 (3.41)	21,915 (2.29)	23,725 (1.42)	37,035 (1.15)	53,426 (1.45)
· No	–	–	–	143,737 (96.59)	933,053 (97.71)	1,641,442 (98.58)	3,177,759 (98.85)	3,620,700 (98.55)
· Missing	–	–	–	–	–	–	–	–
SIDIAP								
HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	–	–	–	28.16 (25.32-31.65)	28.08 (25.09-31.64)	28.20 (25.09-31.80)	27.63 (24.44-31.24)
· Missing	–	–	–	–	5,672 (65.16)	27,573 (56.35)	38,942 (60.74)	53,876 (56.39)
Smoking status								
· Current smoker	–	–	–	–	147 (1.69)	641 (1.31)	485 (0.76)	825 (0.86)
· Non smoker	–	–	–	–	655 (7.52)	1,470 (3.00)	1,065 (1.66)	1,836 (1.92)
· Missing	–	–	–	–	7,903 (90.79)	46,818 (95.69)	62,566 (97.58)	92,885 (97.21)
Menopause diagnosis								
· Yes	–	–	–	–	613 (7.04)	3,907 (7.99)	2,562 (4.00)	4,931 (5.16)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
· No	–	–	–	–	8,092 (92.96)	45,022 (92.01)	61,554 (96.00)	90,615 (94.84)
· Missing	–	–	–	–	–	–	–	–
Non-HRT users								
BMI (kg/m^2)								
· Median (IQR)	–	–	–	–	29.05 (25.68–33.09)	28.67 (25.2–32.83)	28.71 (25.1–32.85)	28.26 (24.67–32.46)
· Missing	–	–	–	–	366,067 (74.85)	421,562 (67.44)	579,176 (72.08)	628,967 (67.78)
Smoking status								
· Current smoker	–	–	–	–	8,453 (1.73)	9,626 (1.54)	7,481 (0.93)	9,756 (1.05)
· Non smoker	–	–	–	–	31,238 (6.39)	21,125 (3.38)	16,613 (2.07)	22,113 (2.38)
· Missing	–	–	–	–	449,407 (91.88)	594,320 (95.08)	779,421 (97.00)	896,061 (96.57)
Menopause diagnosis								
· Yes	–	–	–	–	10,342 (2.11)	22,816 (3.65)	15,432 (1.92)	14,622 (1.58)
· No	–	–	–	–	478,756 (97.89)	602,255 (96.35)	788,083 (98.08)	913,308 (98.42)
· Missing	–	–	–	–	–	–	–	–
CPRD GOLD								
HRT users								
BMI (kg/m^2)								
· Median (IQR)	25.30 (23.30-28.20)	25.70 (23.20-29.20)	26.50 (23.50-30.40)	27.20 (23.90-31.20)	27.60 (24.20-31.90)	27.60 (24.00-32.00)	28.00 (24.30-32.50)	28.30 (24.50-33.20)
· Missing	298 (64.92)	14,280 (74.02)	36,814 (78.18)	59,422 (69.75)	73,684 (62.33)	75,616 (63.55)	73,280 (69.96)	73,295 (60.57)
Smoking status								

Variable	1990	1995	2000	2005	2010	2015	2020	2024
· Current smoker	45 (9.80)	878 (4.55)	1,889 (4.01)	8,373 (9.83)	10,855 (9.18)	8,525 (7.16)	4,811 (4.59)	5,175 (4.28)
· Non smoker	101 (22.00)	2,666 (13.82)	2,402 (5.10)	32,066 (37.64)	48,348 (40.90)	45,002 (37.82)	29,776 (28.43)	37,500 (30.99)
· Missing	313 (68.19)	15,747 (81.63)	42,795 (90.89)	44,751 (52.53)	59,004 (49.92)	65,463 (55.02)	70,163 (66.98)	78,331 (64.73)
Menopause diagnosis								
· Yes	139 (30.28)	1,594 (8.26)	2,556 (5.43)	4,287 (5.03)	4,793 (4.05)	4,177 (3.51)	2,975 (2.84)	4,204 (3.47)
· No	320 (69.72)	17,697 (91.74)	44,530 (94.57)	80,903 (94.97)	113,414 (95.95)	114,813 (96.49)	101,775 (97.16)	116,802 (96.53)
· Missing	–	–	–	–	–	–	–	–
Non-HRT users								
BMI (kg/m^2)								
· Median (IQR)	25.90 (23.18-29.2)	26.50 (23.60-30.40)	27.60 (24.20-32.00)	28.10 (24.40-32.80)	28.60 (24.80-33.50)	28.60 (24.60-33.70)	29.10 (24.80-34.30)	29.20 (24.90-34.60)
· Missing	11,577 (82.03)	79,175 (81.93)	165,146 (85.51)	349,176 (74.06)	403,901 (67.59)	382,608 (68.76)	305,938 (75.71)	210,420 (70.27)
Smoking status								
· Current smoker	759 (5.38)	3,885 (4.02)	6,102 (3.16)	48,343 (10.25)	63,487 (10.62)	48,401 (8.70)	21,748 (5.38)	14,807 (4.95)
· Non smoker	1,701 (12.05)	10,323 (10.68)	7,375 (3.82)	150,833 (31.99)	202,111 (33.82)	173,422 (31.17)	91,642 (22.68)	71,717 (23.95)
· Missing	11,653 (82.57)	82,426 (85.30)	179,643 (93.02)	272,285 (57.75)	331,988 (55.55)	334,581 (60.13)	290,715 (71.94)	212,901 (71.10)
Menopause diagnosis								

Variable	1990	1995	2000	2005	2010	2015	2020	2024
· Yes	315 (2.23)	1,304 (1.35)	2,690 (1.39)	6,799 (1.44)	8,623 (1.44)	7,204 (1.29)	3,119 (0.77)	1,717 (0.57)
· No	13,798 (97.77)	95,330 (98.65)	190,430 (98.61)	464,662 (98.56)	588,963 (98.56)	549,200 (98.71)	400,986 (99.23)	297,708 (99.43)
· Missing	–	–	–	–	–	–	–	–

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD, IQR = interquartile range; – = no data available.
Values are reported as N (%) unless otherwise specified.
BMI is presented as median (interquartile range).

Table S6. Concomitant conditions of postmenopausal women recorded one year post the prespecified calendar date, stratified by HRT use across selected calendar years by data source.

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR								
HRT users								
Concomitant conditions								
· Anxiety	–	–	171 (0.21)	421 (0.29)	751 (0.36)	1,362 (0.51)	1,447 (0.45)	769 (0.21)
· Cardiovascular disease	–	–	625 (0.78)	1,420 (0.97)	2,227 (1.08)	2,858 (1.08)	3,221 (1.00)	1,323 (0.37)
· Depression	–	–	530 (0.66)	14,625 (9.98)	23,933 (11.62)	27,023 (10.17)	31,762 (9.88)	26,513 (7.37)
· Diabetes mellitus	–	–	1,229 (1.53)	6,666 (4.55)	13,775 (6.69)	19,666 (7.40)	26,853 (8.35)	28,735 (7.99)
· Diabetes mellitus type 2	–	–	825 (1.02)	2,507 (1.71)	7,911 (3.84)	13,036 (4.91)	20,092 (6.25)	23,090 (6.42)
· Dyslipidaemia	–	–	486 (0.60)	20,994 (14.33)	52,966 (25.73)	62,753 (23.62)	84,457 (26.27)	82,811 (23.02)
· Hypertension	–	–	1,314 (1.63)	14,454 (9.87)	26,669 (12.95)	45,606 (17.16)	71,308 (22.18)	63,987 (17.79)
· Metabolic syndrome	–	–	0	0	0	0	0	0
· Osteoporosis	–	–	544 (0.68)	6,937 (4.74)	17,626 (8.56)	27,168 (10.22)	37,537 (11.68)	31,199 (8.67)
· Sleep disorders	–	–	55 (0.07)	14,248 (9.73)	19,832 (9.63)	26,237 (9.87)	32,329 (10.06)	20,302 (5.64)
Uterus status:								
· Hysterectomised	–	–	29 (0.04)	87 (0.06)	177 (0.09)	303 (0.11)	274 (0.09)	173 (0.05)
· Intact uterus	–	–	80,519 (99.96)	146,391 (99.94)	205,715 (99.91)	265,424 (99.89)	321,225 (99.91)	359,626 (99.95)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	–	634 (0.16)	1,124 (0.26)	1,725 (0.35)	3,031 (0.55)	2,994 (0.51)	1,483 (0.25)
· Cardiovascular disease	–	–	3,417 (0.88)	4,181 (0.95)	4,370 (0.89)	4,292 (0.78)	3,895 (0.66)	1,418 (0.23)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Depression	–	–	1,915 (0.49)	30,035 (6.86)	41,432 (8.40)	40,766 (7.43)	41,415 (7.05)	31,017 (5.13)
· Diabetes mellitus	–	–	7,073 (1.81)	22,162 (5.06)	32,799 (6.65)	37,839 (6.90)	45,597 (7.77)	44,814 (7.41)
· Diabetes mellitus type 2	–	–	4,690 (1.2)	7,528 (1.72)	17,800 (3.61)	24,479 (4.46)	33,908 (5.78)	35,884 (5.93)
· Dyslipidaemia	–	–	2,178 (0.56)	53,229 (12.15)	99,113 (20.09)	95,351 (17.39)	110,966 (18.9)	99,843 (16.51)
· Hypertension	–	–	5,993 (1.54)	38,186 (8.72)	52,397 (10.62)	72,717 (13.26)	99,364 (16.92)	82,487 (13.64)
· Metabolic syndrome	–	–	0	0	0	0	0	0
· Osteoporosis	–	–	1,901 (0.49)	13,928 (3.18)	26,240 (5.32)	33,078 (6.03)	37,562 (6.4)	28,115 (4.65)
· Sleep disorders	–	–	179 (0.05)	26,765 (6.11)	28,225 (5.72)	31,492 (5.74)	34,256 (5.83)	18,729 (3.10)
Uterus status:								
· Hysterectomised	–	–	25 (0.01)	32 (0.01)	76 (0.02)	98 (0.02)	61 (0.01)	18 (0)
· Intact uterus	–	–	390,117 (99.99)	438,134 (99.99)	493,336 (99.98)	548,330 (99.98)	587,106 (99.99)	604,720 (100)
IQVIA DA Germany								
HRT users								
Concomitant conditions								
· Anxiety	–	32 (2.60)	107 (3.00)	152 (1.91)	373 (1.77)	883 (2.19)	1,495 (2.40)	1,955 (3.08)
· Cardiovascular disease	–	30 (2.44)	52 (1.46)	117 (1.47)	219 (1.04)	323 (0.8)	514 (0.82)	625 (0.99)
· Depression	–	27 (2.19)	59 (1.65)	161 (2.02)	329 (1.56)	712 (1.76)	948 (1.52)	1,076 (1.7)
· Diabetes mellitus	–	38 (3.09)	117 (3.28)	270 (3.39)	621 (2.94)	930 (2.30)	1,374 (2.20)	1,575 (2.48)
· Diabetes mellitus type 2	–	10 (0.81)	41 (1.15)	132 (1.66)	374 (1.77)	644 (1.60)	1,009 (1.62)	1,145 (1.81)
· Dyslipidaemia	–	88 (7.15)	268 (7.50)	485 (6.09)	889 (4.21)	1,154 (2.86)	1,536 (2.46)	2,222 (3.51)
· Hypertension	–	185 (15.03)	521 (14.59)	1,107 (13.9)	2,241 (10.62)	3,246 (8.04)	4,310 (6.92)	5,045 (7.96)
· Metabolic syndrome	–	0	0	0	0	0	0	0

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Osteoporosis	–	76 (6.17)	178 (4.98)	282 (3.54)	399 (1.89)	578 (1.43)	775 (1.24)	1,115 (1.76)
· Sleep disorders	–	49 (3.98)	125 (3.50)	278 (3.49)	507 (2.40)	844 (2.09)	1,274 (2.04)	1,699 (2.68)
Uterus status:								
· Hysterectomised	–	0	6 (0.17)	7 (0.09)	13 (0.06)	17 (0.04)	22 (0.04)	34 (0.05)
· Intact uterus	–	1,231 (100)	3,566 (99.83)	7,959 (99.91)	21,091 (99.94)	40,354 (99.96)	62,307 (99.96)	63,486 (99.95)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	333 (1.00)	551 (0.53)	2,133 (0.74)	8,391 (1.16)	18,055 (1.42)	33,731 (2.01)	43,361 (3.54)
· Cardiovascular disease	–	390 (1.17)	595 (0.57)	2,040 (0.71)	5,331 (0.74)	9,306 (0.73)	14,266 (0.85)	21,139 (1.73)
· Depression	–	324 (0.97)	541 (0.52)	2,774 (0.97)	11,359 (1.58)	24,448 (1.92)	38,266 (2.28)	44,822 (3.66)
· Diabetes mellitus	–	841 (2.52)	1,822 (1.75)	6,150 (2.14)	17,834 (2.48)	32,125 (2.52)	44,310 (2.65)	54,097 (4.42)
· Diabetes mellitus type 2	–	214 (0.64)	805 (0.77)	3,465 (1.21)	11,711 (1.63)	22,516 (1.77)	31,712 (1.89)	39,120 (3.2)
· Dyslipidaemia	–	1,439 (4.3)	2,609 (2.5)	7,940 (2.76)	18,626 (2.59)	30,557 (2.40)	45,980 (2.74)	64,317 (5.26)
· Hypertension	–	3,143 (9.4)	5,549 (5.33)	19,036 (6.62)	46,466 (6.45)	81,186 (6.37)	115,538 (6.90)	131,133 (10.71)
· Metabolic syndrome	–	0	0	0	0	0	0	0
· Osteoporosis	–	518 (1.55)	946 (0.91)	3,463 (1.2)	8,924 (1.24)	15,831 (1.24)	23,328 (1.39)	33,284 (2.72)
· Sleep disorders	–	572 (1.71)	805 (0.77)	2,764 (0.96)	7,170 (1.00)	15,306 (1.20)	26,039 (1.55)	35,069 (2.87)
Uterus status:								
· Hysterectomised	–	0	11 (0.01)	25 (0.01)	59 (0.01)	80 (0.01)	89 (0.01)	106 (0.01)
· Intact uterus	–	33,434 (100)	104,166 (99.99)	287,451 (99.99)	720,394 (99.99)	1,274,649 (99.99)	1,675,573 (99.99)	1,226,542 (99.99)
BIFAP								

Variable	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
HRT users								
Concomitant conditions								
· Anxiety	–	–	–	18 (1.04)	297 (0.90)	636 (0.98)	1,315 (1.44)	2,925 (1.12)
· Cardiovascular disease	–	–	–	14 (0.81)	231 (0.70)	509 (0.78)	686 (0.75)	948 (0.36)
· Depression	–	–	–	74 (4.28)	1,336 (4.03)	2,026 (3.11)	2,117 (2.33)	2,778 (1.07)
· Diabetes mellitus	–	–	–	23 (1.33)	467 (1.41)	1,035 (1.59)	1,820 (2.00)	3,353 (1.29)
· Diabetes mellitus type 2	–	–	–	17 (0.98)	386 (1.16)	882 (1.35)	1,669 (1.83)	2,475 (0.95)
· Dyslipidaemia	–	–	–	90 (5.20)	1,862 (5.61)	3,107 (4.77)	4,705 (5.17)	10,155 (3.9)
· Hypertension	–	–	–	59 (3.41)	1,267 (3.82)	2,478 (3.81)	4,307 (4.73)	7,380 (2.83)
· Metabolic syndrome	–	–	–	0	14 (0.04)	8 (0.01)	25 (0.03)	192 (0.07)
· Osteoporosis	–	–	–	49 (2.83)	1,085 (3.27)	1,424 (2.19)	1,326 (1.46)	2,864 (1.10)
· Sleep disorders	–	–	–	57 (3.29)	1,580 (4.76)	2,710 (4.16)	2,712 (2.98)	4,473 (1.72)
Uterus status:								
· Hysterectomised	–	–	–	<5	27 (0.08)	94 (0.14)	201 (0.22)	320 (0.12)
· Intact uterus	–	–	–	1,726 (99.77)	33,149 (99.92)	65,025 (99.86)	90,827 (99.78)	260,215 (99.88)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	–	–	1,170 (0.79)	4,713 (0.49)	10,190 (0.61)	52,229 (1.62)	30,847 (0.84)
· Cardiovascular disease	–	–	–	742 (0.50)	4,724 (0.49)	8,653 (0.52)	18,140 (0.56)	11,496 (0.31)
· Depression	–	–	–	5,163 (3.47)	22,512 (2.36)	29,685 (1.78)	57,927 (1.8)	31,296 (0.85)
· Diabetes mellitus	–	–	–	2,282 (1.53)	12,830 (1.34)	22,557 (1.35)	65,967 (2.05)	46,739 (1.27)
· Diabetes mellitus type 2	–	–	–	1,756 (1.18)	10,306 (1.08)	19,276 (1.16)	50,846 (1.58)	30,710 (0.84)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Dyslipidaemia	–	–	–	7,070 (4.75)	44,201 (4.63)	65,849 (3.95)	171,632 (5.34)	134,696 (3.67)
· Hypertension	–	–	–	5,569 (3.74)	31,843 (3.33)	50,930 (3.06)	161,954 (5.04)	104,771 (2.85)
· Metabolic syndrome	–	–	–	31 (0.02)	196 (0.02)	297 (0.02)	1,828 (0.06)	1,903 (0.05)
· Osteoporosis	–	–	–	3,589 (2.41)	18,557 (1.94)	18,702 (1.12)	31,650 (0.98)	28,430 (0.77)
· Sleep disorders	–	–	–	4,287 (2.88)	28,919 (3.03)	41,394 (2.49)	71,503 (2.22)	47,388 (1.29)
Uterus status:								
· Hysterectomised	–	–	–	99 (0.07)	359 (0.04)	2,225 (0.13)	5,307 (0.17)	1,718 (0.05)
· Intact uterus	–	–	–	148,706 (99.93)	954,609 (99.96)	1,662,942 (99.87)	3,209,487 (99.83)	3,672,408 (99.95)
SIDIAP								
HRT users								
Concomitant conditions								
· Anxiety	–	–	–	–	478 (5.49)	2,961 (6.05)	3,110 (4.85)	2,355 (2.46)
· Cardiovascular disease	–	–	–	–	34 (0.39)	406 (0.83)	375 (0.58)	497 (0.52)
· Depression	–	–	–	–	328 (3.77)	1,750 (3.58)	1,500 (2.34)	1,227 (1.28)
· Diabetes mellitus	–	–	–	–	89 (1.02)	591 (1.21)	883 (1.38)	791 (0.83)
· Diabetes mellitus type 2	–	–	–	–	86 (0.99)	569 (1.16)	852 (1.33)	761 (0.80)
· Dyslipidaemia	–	–	–	–	306 (3.52)	1,533 (3.13)	1,237 (1.93)	1,121 (1.17)
· Hypertension	–	–	–	–	247 (2.84)	1,148 (2.35)	1,517 (2.37)	1,560 (1.63)
· Metabolic syndrome	–	–	–	–	0	8 (0.02)	8 (0.01)	20 (0.02)
· Osteoporosis	–	–	–	–	308 (3.54)	1,212 (2.48)	977 (1.52)	1,326 (1.39)
· Sleep disorders	–	–	–	–	189 (2.17)	1,641 (3.35)	1,664 (2.6)	3,771 (3.95)

Variable	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
Uterus status:								
· Hysterectomised	–	–	–	–	0	<5	<5	<5
· Intact uterus	–	–	–	–	8,705 (100)	48,927 (100)	64,112 (99.99)	95,542 (100)
Non-HRT users								
Concomitant conditions								
· Anxiety	–	–	–	–	19,954 (4.08)	28,995 (4.64)	32,736 (4.07)	19,241 (2.07)
· Cardiovascular disease	–	–	–	–	1,939 (0.40)	3,903 (0.62)	2,822 (0.35)	2,831 (0.31)
· Depression	–	–	–	–	12,973 (2.65)	16,899 (2.70)	14,326 (1.78)	8,127 (0.88)
· Diabetes mellitus	–	–	–	–	6,624 (1.35)	7,783 (1.25)	9,460 (1.18)	6,238 (0.67)
· Diabetes mellitus type 2	–	–	–	–	6,268 (1.28)	7,340 (1.17)	8,936 (1.11)	5,904 (0.64)
· Dyslipidaemia	–	–	–	–	14,682 (3.00)	16,495 (2.64)	12,922 (1.61)	8,688 (0.94)
· Hypertension	–	–	–	–	13,155 (2.69)	14,482 (2.32)	15,426 (1.92)	12,048 (1.30)
· Metabolic syndrome	–	–	–	–	<5	78 (0.01)	109 (0.01)	164 (0.02)
· Osteoporosis	–	–	–	–	9,700 (1.98)	8,657 (1.39)	6,950 (0.87)	6,827 (0.74)
· Sleep disorders	–	–	–	–	6,869 (1.4)	14,757 (2.36)	13,921 (1.73)	21,964 (2.37)
Uterus status:								
· Hysterectomised	–	–	–	–	9 (0)	9 (0)	12 (0)	11 (0)
· Intact uterus	–	–	–	–	489,089 (100)	625,062 (100)	803,503 (100)	927,919 (100)
CPRD GOLD **HRT users**								
Concomitant conditions								
· Anxiety	21 (4.58)	534 (2.77)	1,241 (2.64)	1,739 (2.04)	1,771 (1.50)	1,470 (1.24)	968 (0.92)	914 (0.76)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Cardiovascular disease	<5	136 (0.70)	330 (0.70)	463 (0.54)	611 (0.52)	667 (0.56)	609 (0.58)	548 (0.45)
· Depression	29 (6.32)	1,053 (5.46)	2,040 (4.33)	2,896 (3.40)	2,606 (2.21)	1,762 (1.48)	874 (0.83)	708 (0.59)
· Diabetes mellitus	<5	188 (0.97)	751 (1.6)	1,631 (1.91)	1,982 (1.68)	1,854 (1.56)	1,337 (1.28)	1,968 (1.63)
· Diabetes mellitus type 2	<5	52 (0.27)	348 (0.74)	1,054 (1.24)	996 (0.84)	879 (0.74)	729 (0.70)	854 (0.71)
· Dyslipidaemia	6 (1.31)	238 (1.23)	742 (1.58)	2,030 (2.38)	1,432 (1.21)	798 (0.67)	377 (0.36)	478 (0.40)
· Hypertension	20 (4.36)	855 (4.43)	2,193 (4.66)	3,175 (3.73)	2,093 (1.77)	1,672 (1.41)	1,351 (1.29)	1,815 (1.50)
· Metabolic syndrome	0	0	0	<5	<5	5 (0)	<5	<5
· Osteoporosis	<5	192 (1.00)	496 (1.05)	800 (0.94)	936 (0.79)	964 (0.81)	523 (0.50)	700 (0.58)
· Sleep disorders	24 (5.23)	480 (2.49)	1,059 (2.25)	2,126 (2.50)	2,610 (2.21)	1,676 (1.41)	700 (0.67)	820 (0.68)
Uterus status:								
· Hysterectomised	<5	104 (0.54)	144 (0.31)	201 (0.24)	194 (0.16)	199 (0.17)	131 (0.13)	175 (0.14)
· Intact uterus	455 (99.13)	19,187 (99.46)	46,942 (99.69)	84,989 (99.76)	118,013 (99.84)	118,791 (99.83)	104,619 (99.87)	120,831 (99.86)
Non-HRT users								
Concomitant conditions								
· Anxiety	325 (2.30)	1,637 (1.69)	3,158 (1.64)	5,607 (1.19)	5,716 (0.96)	5,003 (0.90)	2,556 (0.63)	1,432 (0.48)
· Cardiovascular disease	102 (0.72)	736 (0.76)	1,311 (0.68)	2,341 (0.5)	2,830 (0.47)	2,535 (0.46)	2,026 (0.50)	1,488 (0.50)
· Depression	463 (3.28)	2,984 (3.09)	4,900 (2.54)	9,875 (2.09)	9,476 (1.59)	6,568 (1.18)	2,371 (0.59)	1,120 (0.37)
· Diabetes mellitus	155 (1.10)	1,379 (1.43)	3,597 (1.86)	9,763 (2.07)	11,227 (1.88)	9,459 (1.70)	5,487 (1.36)	5,688 (1.90)
· Diabetes mellitus type 2	40 (0.28)	399 (0.41)	1,575 (0.82)	6,243 (1.32)	5,659 (0.95)	4,521 (0.81)	3,134 (0.78)	2,615 (0.87)
· Dyslipidaemia	180 (1.28)	1,121 (1.16)	2,583 (1.34)	7,781 (1.65)	5,551 (0.93)	2,878 (0.52)	1,102 (0.27)	917 (0.31)
· Hypertension	687 (4.87)	4,008 (4.15)	8,286 (4.29)	17,553 (3.72)	10,199 (1.71)	7,587 (1.36)	4,187 (1.04)	4,437 (1.48)
· Metabolic syndrome	0	0	0	45 (0.01)	11 (0)	16 (0)	<5	6 (0)

Variable	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
· Osteoporosis	178 (1.26)	579 (0.60)	1,291 (0.67)	2,868 (0.61)	3,396 (0.57)	3,156 (0.57)	1,481 (0.37)	1,532 (0.51)
· Sleep disorders	360 (2.55)	1,482 (1.53)	2,467 (1.28)	6,232 (1.32)	7,900 (1.32)	5,158 (0.93)	1,705 (0.42)	1,258 (0.42)
Uterus status:								
· Hysterectomised	77 (0.55)	358 (0.37)	504 (0.26)	1,067 (0.23)	1,141 (0.19)	867 (0.16)	466 (0.12)	336 (0.11)
· Intact uterus	14,036 (99.45)	96,276 (99.63)	192,616 (99.74)	470,394 (99.77)	596,445 (99.81)	555,537 (99.84)	403,639 (99.88)	299,089 (99.89)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; N = number of individuals; – = no data available.

Table S7. Comedication of postmenopausal women stratified by HRT use across selected calendar years by data source, at the pre-specified calendar date.

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR	HRT users							
1	-	-	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 5,504 (6.80%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 9,876 (6.70%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 11,353 (5.50%)	acetaminophen 500 MG Oral Tablet, 27,479 (10.30%)	acetaminophen 500 MG Oral Tablet, 35,571 (11.10%)	acetaminophen 500 MG Oral Tablet, 40,415 (11.20%)
2	-	-	acetaminophen 500 MG Oral Tablet, 1,974 (2.50%)	acetaminophen 500 MG Oral Tablet, 5,231 (3.60%)	simvastatin 40 MG Oral Tablet, 10,309 (5.00%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 25,319 (9.50%)	amlodipine 5 MG Oral Tablet, 25,479 (7.90%)	amlodipine 5 MG Oral Tablet, 33,513 (9.30%)
3	-	-	furosemide 40 MG Oral Tablet, 1,844 (2.30%)	aspirin 75 MG Oral Tablet, 3,784 (2.60%)	aspirin 75 MG Oral Tablet, 9,661 (4.70%)	aspirin 75 MG Oral Tablet, 23,969 (9.00%)	aspirin 75 MG Oral Tablet, 22,094 (6.90%)	losartan potassium 100 MG Oral Tablet, 33,372 (9.30%)
4	-	-	diazepam 5 MG Oral Tablet, 1,437 (1.80%)	furosemide 40 MG Oral Tablet, 2,849 (2.00%)	acetaminophen 500 MG Oral Tablet, 9,169 (4.40%)	simvastatin 40 MG Oral Tablet, 21,038 (7.90%)	losartan potassium 50 MG Oral Tablet, 21,692 (6.80%)	losartan potassium 50 MG Oral Tablet, 31,434 (8.70%)
5	-	-	amlodipine 5 MG Oral Tablet, 1,348 (1.70%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 2,614 (1.80%)	Amlodipine 5 MG Oral Tablet Box of 100, 4,542 (2.20%)	amlodipine 5 MG Oral Tablet, 17,278 (6.50%)	losartan potassium 100 MG Oral Tablet, 20,005 (6.20%)	atorvastatin 40 MG Oral Tablet, 27,617 (7.70%)
6	-	-	Potassium Chloride 750 MG Extended Release Oral Tablet, 1,314 (1.60%)	glucosamine sulfate 375 MG Oral Tablet, 2,384 (1.60%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 4,515 (2.20%)	alendronic acid 70 MG Oral Tablet, 14,928 (5.60%)	atorvastatin 40 MG Oral Tablet, 18,392 (5.70%)	aspirin 75 MG Oral Tablet, 23,780 (6.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
7	-	-	levothyroxine sodium 0.1 MG Oral Tablet, 1,300 (1.60%)	levothyroxine sodium 0.1 MG Oral Tablet, 2,314 (1.60%)	metformin hydrochloride 500 MG Oral Tablet, 4,447 (2.20%)	losartan potassium 50 MG Oral Tablet, 11,933 (4.50%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 16,906 (5.30%)	alendronic acid 70 MG Oral Tablet, 22,757 (6.30%)
8	-	-	aspirin 162 MG Oral Tablet, 1,121 (1.40%)	Glucosamine 400 MG Oral Capsule Box of 270, 2,241 (1.50%)	furosemide 40 MG Oral Tablet, 4,418 (2.10%)	pantoprazole 40 MG Delayed Release Oral Tablet, 10,605 (4.00%)	pantoprazole 40 MG Delayed Release Oral Tablet, 16,076 (5.00%)	pantoprazole 40 MG Delayed Release Oral Tablet, 22,540 (6.30%)
9	-	-	omeprazole 20 MG Delayed Release Oral Tablet, 1,028 (1.30%)	simvastatin 20 MG Oral Tablet, 2,147 (1.50%)	alendronic acid 70 MG Oral Tablet, 4,212 (2.00%)	furosemide 40 MG Oral Tablet, 10,079 (3.80%)	simvastatin 40 MG Oral Tablet, 15,404 (4.80%)	acetaminophen 665 MG Extended Release Oral Tablet, 21,769 (6.00%)
10	-	-	zopiclone 7.5 MG Oral Tablet, 972 (1.20%)	tramadol hydrochloride 50 MG Oral Capsule, 2,137 (1.50%)	glucosamine sulfate 375 MG Oral Tablet, 3,869 (1.90%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 8,588 (3.20%)	alendronic acid 70 MG Oral Tablet, 14,028 (4.40%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 20,208 (5.60%)
DK-DHR	**Non-HRT users**							
1	-	-	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 24,871 (6.40%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 25,951 (5.90%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 23,049 (4.70%)	acetaminophen 500 MG Oral Tablet, 41,332 (7.50%)	acetaminophen 500 MG Oral Tablet, 45,493 (7.80%)	acetaminophen 500 MG Oral Tablet, 47,837 (7.90%)
2	-	-	furosemide 40 MG Oral Tablet, 10,063 (2.60%)	acetaminophen 500 MG Oral Tablet, 11,801 (2.70%)	simvastatin 40 MG Oral Tablet, 20,839 (4.20%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 40,193 (7.30%)	amlodipine 5 MG Oral Tablet, 35,441 (6.00%)	losartan potassium 100 MG Oral Tablet, 42,664 (7.00%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
3	-	-	acetaminophen 500 MG Oral Tablet, 7,508 (1.90%)	aspirin 75 MG Oral Tablet, 9,351 (2.10%)	aspirin 75 MG Oral Tablet, 18,463 (3.70%)	simvastatin 40 MG Oral Tablet, 34,979 (6.40%)	losartan potassium 50 MG Oral Tablet, 28,687 (4.90%)	amlodipine 5 MG Oral Tablet, 42,520 (7.00%)
4	-	-	Potassium Chloride 750 MG Extended Release Oral Tablet, 6,433 (1.60%)	furosemide 40 MG Oral Tablet, 8,934 (2.00%)	acetaminophen 500 MG Oral Tablet, 15,640 (3.20%)	aspirin 75 MG Oral Tablet, 34,967 (6.40%)	losartan potassium 100 MG Oral Tablet, 27,144 (4.60%)	losartan potassium 50 MG Oral Tablet, 38,488 (6.40%)
5	-	-	amlodipine 5 MG Oral Tablet, 6,286 (1.60%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 7,454 (1.70%)	metformin hydrochloride 500 MG Oral Tablet, 10,575 (2.10%)	amlodipine 5 MG Oral Tablet, 28,476 (5.20%)	aspirin 75 MG Oral Tablet, 26,829 (4.60%)	atorvastatin 40 MG Oral Tablet, 37,025 (6.10%)
6	-	-	aspirin 162 MG Oral Tablet, 5,608 (1.40%)	metformin hydrochloride 500 MG Oral Tablet, 6,135 (1.40%)	furosemide 40 MG Oral Tablet, 9,950 (2.00%)	alendronic acid 70 MG Oral Tablet, 18,849 (3.40%)	atorvastatin 40 MG Oral Tablet, 26,213 (4.50%)	aspirin 75 MG Oral Tablet, 25,735 (4.30%)
7	-	-	diazepam 5 MG Oral Tablet, 5,486 (1.40%)	simvastatin 20 MG Oral Tablet, 5,598 (1.30%)	Amlodipine 5 MG Oral Tablet Box of 100, 9,460 (1.90%)	losartan potassium 50 MG Oral Tablet, 17,761 (3.20%)	simvastatin 40 MG Oral Tablet, 21,882 (3.70%)	atorvastatin 20 MG Oral Tablet, 23,526 (3.90%)
8	-	-	levothyroxine sodium 0.1 MG Oral Tablet, 5,212 (1.30%)	levothyroxine sodium 0.1 MG Oral Tablet, 5,429 (1.20%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 9,392 (1.90%)	furosemide 40 MG Oral Tablet, 17,157 (3.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 21,155 (3.60%)	pantoprazole 40 MG Delayed Release Oral Tablet, 23,495 (3.90%)
9	-	-	Amiloride 5 MG / Hydrochlorothiazide 50 MG Oral Tablet Box of 100, 4,279 (1.10%)	aspirin 162 MG Oral Tablet, 4,833 (1.10%)	levothyroxine sodium 0.1 MG Oral Tablet, 6,979 (1.40%)	amlodipine 10 MG Oral Tablet, 16,113 (2.90%)	bendroflumethiazide 2.5 MG / potassium chloride 630 MG Oral Tablet, 20,046 (3.40%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 23,460 (3.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	-	Budesonide 0.4 MG/ACTUAT Inhalation Powder, 4,208 (1.10%)	Terbutaline 0.5 MG/ACTUAT Inhalant Powder, 4,786 (1.10%)	metoprolol succinate 50 MG Extended Release Oral Tablet, 6,603 (1.30%)	metformin hydrochloride 500 MG Oral Tablet, 15,600 (2.80%)	furosemide 40 MG Oral Tablet, 18,311 (3.10%)	alendronic acid 70 MG Oral Tablet, 21,084 (3.50%)
IQVIA DA Germany	**HRT users**							
1	-	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 18 (1.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 53 (1.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 93 (1.20%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 138 (0.70%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 525 (1.30%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 978 (1.60%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 1,294 (2.00%)
2	-	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 11 (0.90%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 29 (0.80%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 50 (0.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 98 (0.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 168 (0.40%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 229 (0.40%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 284 (0.40%)
3	-	Calcium 500 MG / monofluorophosphate 38 MG Chewable Tablet [Tridin] Box of 100 by Meda, 10 (0.80%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 22 (0.60%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 38 (0.50%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 76 (0.40%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 150 (0.40%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 208 (0.30%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 258 (0.40%)
4	-	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 9 (0.70%)	Black Cohosh Extract / ST. JOHN'S WORT EXTRACT Oral Tablet [Remifemin], 19 (0.50%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 34 (0.40%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 57 (0.30%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 125 (0.30%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 191 (0.30%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 254 (0.40%)
5	-	Aspirin 100 MG Oral Tablet [Ass	Hydrochlorothiazide / Triamterene Oral	levothyroxine 0.05 MG Oral Tablet [L	levothyroxine 0.1 MG Oral Tablet [L	levothyroxine 0.15 MG Oral Tablet [L	Aspirin 100 MG Oral Tablet [Ass 1a	Cholecalciferol 20000 UNT Oral

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
		Ratiopharm] Box of 100 by Ratiopharm, 8 (0.70%)	Tablet [Dytide], 15 (0.40%)	Thyroxin Henning] Box of 100 by Sanofi, 32 (0.40%)	Thyrox Hexal] Box of 100 by Novartis, 57 (0.30%)	Thyroxin Henning] Box of 100 by Sanofi, 105 (0.30%)	Pharma] Box of 100 by 1 A, 177 (0.30%)	Capsule by Aristo, 241 (0.40%)
6	-	Calcium 3240 MG Oral Tablet [Calcium-Sandoz] Box of 100 by Novartis, 7 (0.60%)	Iodine 0.14 MG / levothyroxine 0.1 MG Oral Tablet [Jodthyrox] Box of 100 by Mylan, 15 (0.40%)	Metoprolol 100 MG Extended Release Oral Tablet [Beloc] Box of 100 by Astrazeneca, 29 (0.40%)	Iodine 0.2 MG / levothyroxine 0.05 MG Oral Tablet [Thyronajod] Box of 100 by Sanofi, 53 (0.20%)	Metoprolol 50 MG Oral Tablet [Metohexal] Box of 100 by Novartis, 100 (0.20%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 167 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 239 (0.40%)
7	-	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 7 (0.60%)	levothyroxine 0.075 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 14 (0.40%)	Alendronate 70 MG Oral Tablet [Fosamax] Box of 12 by Merck, 24 (0.30%)	Metoprolol 100 MG Extended Release Oral Tablet [Metohexal] Box of 100 by Novartis, 51 (0.20%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 100 (0.20%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 167 (0.30%)	candesartan 16 MG Oral Tablet [Candesartan 1a Pharma] Box of 98 by 1 A, 236 (0.40%)
8	-	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 7 (0.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 14 (0.40%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 24 (0.30%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 50 (0.20%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 96 (0.20%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 153 (0.20%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 235 (0.40%)
9	-	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 6 (0.50%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 13 (0.40%)	Iodine 0.14 MG / levothyroxine 0.1 MG Oral Tablet [Jodthyrox] Box of 100 by Mylan, 24 (0.30%)	levothyroxine 0.075 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 42 (0.20%)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A, 94 (0.20%)	Cholecalciferol 20000 UNT Oral Capsule by Aristo, 152 (0.20%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 214 (0.30%)
10	-	Aspirin 100 MG Oral Tablet Box of 100 by Bayer, 6 (0.50%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning]	nebivolol 5 MG Oral Tablet [Nebilet] Box of 100 by Berlin-Chemie, 24 (0.30%)	Aspirin 100 MG Oral Tablet [Ass Ratiopharm] Box of	pantoprazole 20 MG Oral Tablet [Pantoprazol - 1a	Amlodipine 5 MG Oral Tablet [Amlodipin Dexcel] Box of 100 by	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A, 209 (0.30%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
			Box of 100 by Sanofi, 13 (0.40%)		100 by Ratiopharm, 38 (0.20%)	Pharma] Box of 100 by 1 A, 89 (0.20%)	Dexcel-Pharma, 143 (0.20%)	
IQVIA DA Germany	**Non-HRT users**							
1	-	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 211 (0.60%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 316 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 869 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,811 (0.20%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 8,040 (0.60%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 19,800 (1.20%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 25,983 (2.10%)
2	-	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 136 (0.40%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 211 (0.20%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 492 (0.20%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,316 (0.20%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 3,409 (0.30%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 6,487 (0.40%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 9,685 (0.80%)
3	-	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 113 (0.30%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 158 (0.10%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 465 (0.20%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,224 (0.20%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 3,097 (0.20%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 6,343 (0.40%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 8,539 (0.70%)
4	-	Glyburide 3.5 MG Oral Tablet [Euglucon] Box of 120 by Sanofi, 103 (0.30%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 133 (0.10%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 408 (0.10%)	Metoprolol 100 MG Extended Release Oral Tablet [Metohexal] Box of 100 by Novartis, 979 (0.10%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 2,807 (0.20%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 6,096 (0.40%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 8,078 (0.70%)
5	-	Aspirin 100 MG Oral Tablet [Ass Ratiopharm] Box of	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning]	Metoprolol 100 MG Extended Release Oral Tablet [Beloc] Box of 100 by	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning]	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning]	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning]	candesartan 16 MG Oral Tablet [Candesartan 1a

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
		100 by Ratiopharm, 86 (0.30%)	Box of 100 by Sanofi, 125 (0.10%)	Astrazeneca, 375 (0.10%)	Box of 100 by Sanofi, 945 (0.10%)	Box of 100 by Sanofi, 2,539 (0.20%)	Box of 100 by Sanofi, 5,968 (0.40%)	Pharma] Box of 98 by 1 A, 7,823 (0.60%)
6	-	Hydrochlorothiazide / Triamterene Oral Tablet [Dytide], 58 (0.20%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 101 (0.10%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 357 (0.10%)	levothyroxine 0.1 MG Oral Tablet [L Thyrox Hexal] Box of 100 by Novartis, 831 (0.10%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 2,380 (0.20%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 5,156 (0.30%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 7,442 (0.60%)
7	-	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 55 (0.20%)	Iodine 0.14 MG / levothyroxine 0.1 MG Oral Tablet [Jodthyrox] Box of 100 by Mylan, 99 (0.10%)	Metoprolol 50 MG Oral Tablet [Beloc] Box of 100 by Astrazeneca, 345 (0.10%)	Metoprolol 50 MG Oral Tablet [Metohexal] Box of 100 by Novartis, 827 (0.10%)	Bisoprolol 5 MG Oral Tablet [Bisoprolol 1a Pharma] Box of 100 by 1 A, 2,339 (0.20%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 4,900 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 6,634 (0.50%)
8	-	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 54 (0.20%)	Metoprolol 50 MG Oral Tablet [Beloc] Box of 100 by Astrazeneca, 86 (0.10%)	nebivolol 5 MG Oral Tablet [Nebilet] Box of 100 by Berlin-Chemie, 267 (0.10%)	levothyroxine 0.075 MG Oral Tablet [L Thyrox Hexal] Box of 100 by Novartis, 759 (0.10%)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A, 2,207 (0.20%)	Bisoprolol 5 MG Oral Tablet [Bisoprolol 1a Pharma] Box of 100 by 1 A, 4,698 (0.30%)	Bisoprolol 5 MG Oral Tablet [Bisoprolol 1a Pharma] Box of 100 by 1 A, 6,554 (0.50%)
9	-	Bisoprolol 5 MG Oral Tablet [Concor] Box of 100 by Mylan, 50 (0.10%)	Amlodipine 5 MG Oral Tablet [Norvasc] Box of 100 by Pfizer, 80 (0.10%)	Iodine 0.2 MG / levothyroxine 0.075 MG Oral Tablet [Thyronajod] Box of 100 by Sanofi, 255 (0.10%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 753 (0.10%)	Metoprolol 50 MG Oral Tablet [Metohexal] Box of 100 by Novartis, 2,185 (0.20%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 4,447 (0.30%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 6,171 (0.50%)
10	-	Metoprolol 50 MG Oral Tablet [Beloc] Box of 100 by Astrazeneca, 50 (0.10%)	Acetyldigoxins 0.2 MG Oral Tablet [Novodigal] Box of 100 by Mibe, 77 (0.10%)	Phenprocoumon 3 MG Oral Tablet [Marcumar] Box of 100 by Roche, 254 (0.10%)	Iodine 0.2 MG / levothyroxine 0.075 MG Oral Tablet [Thyronajod] Box of 100 by Sanofi, 717 (0.10%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 2,180 (0.20%)	Metoprolol 50 MG Oral Tablet [Metohexal] Box of 100 by Novartis, 4,433 (0.30%)	atorvastatin 20 MG Oral Tablet [Atorvastatin 1a Pharma] Box of 100 by 1 A, 6,120 (0.50%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
BIFAP	HRT users							
1	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 169 (9.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 5,387 (16.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 10,367 (15.90%)	omeprazole 20 MG Delayed Release Oral Capsule, 15,541 (17.10%)	calcifediol, 40,284 (15.50%)
2	-	-	-	raloxifene hydrochloride 60 MG Oral Tablet, 115 (6.70%)	lorazepam 1 MG Oral Tablet, 2,337 (7.00%)	lorazepam 1 MG Oral Tablet, 5,586 (8.60%)	lorazepam 1 MG Oral Tablet, 9,555 (10.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 37,219 (14.30%)
3	-	-	-	lorazepam 1 MG Oral Tablet, 96 (5.60%)	acetaminophen, 1,516 (4.60%)	acetaminophen, 4,420 (6.80%)	calcifediol, 8,814 (9.70%)	acetaminophen, 28,520 (10.90%)
4	-	-	-	alendronic acid 70 MG Oral Tablet, 57 (3.30%)	aspirin, 1,385 (4.20%)	aspirin, 3,287 (5.00%)	acetaminophen, 8,627 (9.50%)	lorazepam 1 MG Oral Tablet, 21,278 (8.20%)
5	-	-	-	bromazepam, 48 (2.80%)	simvastatin 20 MG Oral Tablet, 1,281 (3.90%)	simvastatin 20 MG Oral Tablet, 3,166 (4.90%)	aspirin, 5,801 (6.40%)	cholecalciferol, 14,844 (5.70%)
6	-	-	-	paroxetine hydrochloride 20 MG Oral Tablet, 48 (2.80%)	chondroitin sulfates, 1,193 (3.60%)	bromazepam, 2,283 (3.50%)	simvastatin 20 MG Oral Tablet, 4,589 (5.00%)	aspirin, 13,551 (5.20%)
7	-	-	-	acetaminophen, 44 (2.50%)	ibuprofen 600 MG Oral Tablet, 1,168 (3.50%)	chondroitin sulfates, 2,231 (3.40%)	atorvastatin 20 MG Oral Tablet, 4,043 (4.40%)	atorvastatin 20 MG Oral Tablet, 11,893 (4.60%)
8	-	-	-	levothyroxine sodium 0.1 MG Oral Tablet, 38 (2.20%)	bromazepam, 1,106 (3.30%)	atorvastatin 20 MG Oral Tablet, 2,073 (3.20%)	levothyroxine sodium 0.075 MG Oral Tablet, 3,944 (4.30%)	simvastatin 20 MG Oral Tablet, 10,470 (4.00%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
9	-	-	-	glucosamine, 35 (2.00%)	metformin hydrochloride 850 MG Oral Tablet, 892 (2.70%)	ibuprofen 600 MG Oral Tablet, 2,042 (3.10%)	levothyroxine sodium 0.05 MG Oral Tablet, 3,651 (4.00%)	levothyroxine sodium 0.075 MG Oral Tablet, 10,345 (4.00%)
10	-	-	-	ibuprofen 600 MG Oral Tablet, 35 (2.00%)	diosmin, 887 (2.70%)	simvastatin 10 MG Oral Tablet, 1,924 (3.00%)	bromazepam, 3,516 (3.90%)	levothyroxine sodium 0.05 MG Oral Tablet, 9,610 (3.70%)
BIFAP	**Non-HRT users**							
1	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 9,220 (6.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 101,010 (10.60%)	omeprazole 20 MG Delayed Release Oral Capsule, 202,706 (12.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 374,252 (11.60%)	calcifediol, 444,078 (12.10%)
2	-	-	-	lorazepam 1 MG Oral Tablet, 4,904 (3.30%)	lorazepam 1 MG Oral Tablet, 36,730 (3.90%)	acetaminophen, 103,100 (6.20%)	calcifediol, 242,188 (7.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 401,690 (10.90%)
3	-	-	-	enalapril maleate 20 MG Oral Tablet, 3,585 (2.40%)	simvastatin 20 MG Oral Tablet, 35,201 (3.70%)	lorazepam 1 MG Oral Tablet, 92,622 (5.60%)	acetaminophen, 220,357 (6.80%)	acetaminophen, 300,848 (8.20%)
4	-	-	-	raloxifene hydrochloride 60 MG Oral Tablet, 3,493 (2.40%)	aspirin, 30,106 (3.10%)	simvastatin 20 MG Oral Tablet, 75,991 (4.60%)	lorazepam 1 MG Oral Tablet, 200,498 (6.20%)	lorazepam 1 MG Oral Tablet, 207,049 (5.60%)
5	-	-	-	paroxetine hydrochloride 20 MG Oral Tablet, 3,372 (2.30%)	metformin hydrochloride 850 MG Oral Tablet, 29,384 (3.10%)	aspirin, 60,724 (3.60%)	simvastatin 20 MG Oral Tablet, 130,807 (4.10%)	aspirin, 145,061 (4.00%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
6	-	-	-	bromazepam, 3,202 (2.10%)	acetaminophen, 25,991 (2.70%)	metformin hydrochloride 850 MG Oral Tablet, 53,996 (3.20%)	aspirin, 126,953 (4.00%)	cholecalciferol, 139,949 (3.80%)
7	-	-	-	aspirin, 2,698 (1.80%)	bromazepam, 23,463 (2.50%)	bromazepam, 47,858 (2.90%)	atorvastatin 20 MG Oral Tablet, 97,692 (3.00%)	atorvastatin 20 MG Oral Tablet, 131,455 (3.60%)
8	-	-	-	metformin hydrochloride 850 MG Oral Tablet, 2,695 (1.80%)	enalapril maleate 20 MG Oral Tablet, 22,006 (2.30%)	ibuprofen 600 MG Oral Tablet, 44,468 (2.70%)	levothyroxine sodium 0.075 MG Oral Tablet, 96,840 (3.00%)	simvastatin 20 MG Oral Tablet, 126,597 (3.50%)
9	-	-	-	levothyroxine sodium 0.1 MG Oral Tablet, 2,528 (1.70%)	ibuprofen 600 MG Oral Tablet, 19,673 (2.10%)	simvastatin 10 MG Oral Tablet, 44,300 (2.70%)	metformin hydrochloride 850 MG Oral Tablet, 94,139 (2.90%)	levothyroxine sodium 0.075 MG Oral Tablet, 106,771 (2.90%)
10	-	-	-	acetaminophen, 2,500 (1.70%)	simvastatin 10 MG Oral Tablet, 17,738 (1.90%)	atorvastatin 20 MG Oral Tablet, 39,753 (2.40%)	levothyroxine sodium 0.05 MG Oral Tablet, 89,878 (2.80%)	metformin hydrochloride 850 MG Oral Tablet, 101,166 (2.80%)
SIDIAP	**HRT users**							
1	-	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 2,283 (26.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 14,595 (29.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 17,528 (27.30%)	omeprazole 20 MG Delayed Release Oral Capsule, 26,469 (27.70%)
2	-	-	-	-	ibuprofen 600 MG Oral Tablet, 1,082 (12.40%)	acetaminophen 1000 MG Oral Tablet, 9,615 (19.60%)	acetaminophen 1000 MG Oral Tablet, 14,848 (23.20%)	acetaminophen 1000 MG Oral Tablet, 25,558 (26.80%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
3	-	-	-	-	simvastatin 20 MG Oral Tablet, 847 (9.70%)	lorazepam 1 MG Oral Tablet, 5,946 (12.20%)	lorazepam 1 MG Oral Tablet, 8,285 (12.90%)	calcifediol Oral Capsule, 13,158 (13.80%)
4	-	-	-	-	lorazepam 1 MG Oral Tablet, 820 (9.40%)	simvastatin 20 MG Oral Tablet, 5,779 (11.80%)	simvastatin 20 MG Oral Tablet, 6,014 (9.40%)	lorazepam 1 MG Oral Tablet, 12,555 (13.10%)
5	-	-	-	-	acetaminophen 1000 MG Oral Tablet, 708 (8.10%)	ibuprofen 600 MG Oral Tablet, 4,033 (8.20%)	calcifediol Oral Capsule, 5,024 (7.80%)	simvastatin 20 MG Oral Tablet, 9,345 (9.80%)
6	-	-	-	-	carboxymethylcellulose sodium 5 MG/ML Ophthalmic Solution, 602 (6.90%)	Calcifediol 0.15 MG/ML Oral Solution, 3,344 (6.80%)	dipyrone, 4,584 (7.20%)	dipyrone, 8,790 (9.20%)
7	-	-	-	-	hydrochlorothiazide 50 MG Oral Tablet, 518 (6.00%)	metformin hydrochloride 850 MG Oral Tablet, 2,983 (6.10%)	Calcifediol 0.15 MG/ML Oral Solution, 4,575 (7.10%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 6,751 (7.10%)
8	-	-	-	-	chondroitin sulfates 400 MG Oral Capsule, 447 (5.10%)	hydrochlorothiazide 50 MG Oral Tablet, 2,773 (5.70%)	metformin hydrochloride 850 MG Oral Tablet, 3,804 (5.90%)	aspirin 100 MG Delayed Release Oral Tablet, 6,566 (6.90%)
9	-	-	-	-	simvastatin 10 MG Oral Tablet, 441 (5.10%)	diazepam 5 MG Oral Tablet, 2,717 (5.60%)	diazepam 5 MG Oral Tablet, 3,797 (5.90%)	Calcifediol 0.15 MG/ML Oral Solution, 6,215 (6.50%)
10	-	-	-	-	alendronic acid 70 MG Oral Tablet, 438 (5.00%)	simvastatin 10 MG Oral Tablet, 2,564 (5.20%)	acetaminophen 325 MG / tramadol hydrochloride 37.5	acetaminophen 650 MG Oral Tablet, 5,637 (5.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
							MG Oral Tablet, 3,724 (5.80%)	
SIDIAP	**Non-HRT users**							
1	-	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 78,134 (16.00%)	omeprazole 20 MG Delayed Release Oral Capsule, 109,704 (17.60%)	omeprazole 20 MG Delayed Release Oral Capsule, 121,432 (15.10%)	omeprazole 20 MG Delayed Release Oral Capsule, 149,724 (16.10%)
2	-	-	-	-	ibuprofen 600 MG Oral Tablet, 35,643 (7.30%)	acetaminophen 1000 MG Oral Tablet, 67,964 (10.90%)	acetaminophen 1000 MG Oral Tablet, 100,028 (12.40%)	acetaminophen 1000 MG Oral Tablet, 144,515 (15.60%)
3	-	-	-	-	simvastatin 20 MG Oral Tablet, 34,469 (7.00%)	simvastatin 20 MG Oral Tablet, 51,244 (8.20%)	lorazepam 1 MG Oral Tablet, 60,942 (7.60%)	calcifediol Oral Capsule, 79,880 (8.60%)
4	-	-	-	-	lorazepam 1 MG Oral Tablet, 28,656 (5.90%)	lorazepam 1 MG Oral Tablet, 46,512 (7.40%)	simvastatin 20 MG Oral Tablet, 49,217 (6.10%)	lorazepam 1 MG Oral Tablet, 72,370 (7.80%)
5	-	-	-	-	acetaminophen 1000 MG Oral Tablet, 23,324 (4.80%)	metformin hydrochloride 850 MG Oral Tablet, 34,499 (5.50%)	metformin hydrochloride 850 MG Oral Tablet, 39,869 (5.00%)	simvastatin 20 MG Oral Tablet, 60,979 (6.60%)
6	-	-	-	-	hydrochlorothiazide 50 MG Oral Tablet, 22,947 (4.70%)	ibuprofen 600 MG Oral Tablet, 30,685 (4.90%)	calcifediol Oral Capsule, 38,015 (4.70%)	dipyrone, 51,697 (5.60%)
7	-	-	-	-	metformin hydrochloride 850 MG Oral Tablet, 16,979 (3.50%)	hydrochlorothiazide 50 MG Oral Tablet, 26,109 (4.20%)	dipyrone, 31,143 (3.90%)	metformin hydrochloride 850 MG Oral Tablet, 43,059 (4.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
8	-	-	-	-	paroxetine hydrochloride 20 MG Oral Tablet, 15,812 (3.20%)	Calcifediol 0.15 MG/ML Oral Solution, 22,592 (3.60%)	Calcifediol 0.15 MG/ML Oral Solution, 31,002 (3.90%)	aspirin 100 MG Delayed Release Oral Tablet, 40,501 (4.40%)
9	-	-	-	-	enalapril maleate 20 MG Oral Tablet, 15,194 (3.10%)	aspirin 100 MG Oral Tablet, 21,171 (3.40%)	diazepam 5 MG Oral Tablet, 29,147 (3.60%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 39,681 (4.30%)
10	-	-	-	-	simvastatin 10 MG Oral Tablet, 14,733 (3.00%)	diazepam 5 MG Oral Tablet, 20,653 (3.30%)	aspirin 100 MG Delayed Release Oral Tablet, 27,931 (3.50%)	acetaminophen 650 MG Oral Tablet, 33,500 (3.60%)
CPRD GOLD	**HRT users**							
1	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 15 (3.30%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 590 (3.10%)	bendroflumethiazide 2.5 MG Oral Tablet, 2,962 (6.30%)	bendroflumethiazide 2.5 MG Oral Tablet, 9,087 (10.70%)	bendroflumethiazide 2.5 MG Oral Tablet, 10,862 (9.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 12,549 (10.60%)	omeprazole 20 MG Delayed Release Oral Capsule, 12,423 (11.90%)	omeprazole 20 MG Delayed Release Oral Capsule, 15,379 (12.70%)
2	temazepam 10 MG Oral Capsule, 13 (2.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 484 (2.50%)	levothyroxine sodium 0.1 MG Oral Tablet, 1,588 (3.40%)	aspirin 75 MG Disintegrating Oral Tablet, 4,308 (5.10%)	simvastatin 40 MG Oral Tablet, 8,363 (7.10%)	levothyroxine sodium 0.1 MG Oral Tablet, 7,677 (6.40%)	levothyroxine sodium 0.1 MG Oral Tablet, 6,909 (6.60%)	atorvastatin 20 MG Oral Tablet, 9,480 (7.80%)
3	levothyroxine sodium 0.1 MG Oral Tablet, 11 (2.40%)	levothyroxine sodium 0.1 MG Oral Tablet, 426 (2.20%)	atenolol 50 MG Oral Tablet, 1,459 (3.10%)	levothyroxine sodium 0.1 MG Oral Tablet, 4,026 (4.70%)	omeprazole 20 MG Delayed Release Oral Capsule, 7,920 (6.70%)	bendroflumethiazide 2.5 MG Oral Tablet, 7,542 (6.30%)	amlodipine 5 MG Oral Tablet, 5,993 (5.70%)	amlodipine 5 MG Oral Tablet, 8,185 (6.80%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
4	lorazepam 1 MG Oral Tablet, 10 (2.20%)	levothyroxine sodium 0.05 MG Oral Tablet, 366 (1.90%)	levothyroxine sodium 0.05 MG Oral Tablet, 1,252 (2.70%)	atenolol 50 MG Oral Tablet, 3,592 (4.20%)	levothyroxine sodium 0.1 MG Oral Tablet, 6,943 (5.90%)	levothyroxine sodium 0.05 MG Oral Tablet, 6,674 (5.60%)	levothyroxine sodium 0.05 MG Oral Tablet, 5,487 (5.20%)	levothyroxine sodium 0.1 MG Oral Tablet, 7,866 (6.50%)
5	lactulose 670 MG/ML Oral Solution, 7 (1.50%)	atenolol 50 MG Oral Tablet, 339 (1.80%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 1,224 (2.60%)	levothyroxine sodium 0.05 MG Oral Tablet, 3,127 (3.70%)	aspirin 75 MG Disintegrating Oral Tablet, 6,891 (5.80%)	levothyroxine sodium 0.025 MG Oral Tablet, 6,614 (5.60%)	atorvastatin 20 MG Oral Tablet, 5,481 (5.20%)	levothyroxine sodium 0.05 MG Oral Tablet, 5,773 (4.80%)
6	nitrazepam 5 MG Oral Tablet, 7 (1.50%)	alginic acid Oral Solution [Gaviscon], 242 (1.20%)	aspirin 75 MG Disintegrating Oral Tablet, 1,070 (2.30%)	levothyroxine sodium 0.025 MG Oral Tablet, 2,719 (3.20%)	levothyroxine sodium 0.025 MG Oral Tablet, 5,493 (4.70%)	simvastatin 40 MG Oral Tablet, 6,610 (5.60%)	levothyroxine sodium 0.025 MG Oral Tablet, 5,321 (5.10%)	levothyroxine sodium 0.025 MG Oral Tablet, 5,633 (4.70%)
7	Clonidine 0.025 MG Oral Tablet [Dixarit] by Boehringer Ingelheim, 6 (1.30%)	omeprazole 20 MG Delayed Release Oral Capsule, 218 (1.10%)	levothyroxine sodium 0.025 MG Oral Tablet, 791 (1.70%)	atorvastatin 10 MG Oral Tablet, 2,091 (2.50%)	levothyroxine sodium 0.05 MG Oral Tablet, 5,487 (4.60%)	amlodipine 5 MG Oral Tablet, 6,127 (5.20%)	bendroflumethiazide 2.5 MG Oral Tablet, 4,283 (4.10%)	lansoprazole 30 MG Delayed Release Oral Capsule, 5,131 (4.20%)
8	atenolol 50 MG Oral Tablet, 6 (1.30%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 211 (1.10%)	amlodipine 5 MG Oral Tablet, 677 (1.40%)	acetaminophen 500 MG Oral Tablet, 2,034 (2.40%)	amlodipine 5 MG Oral Tablet, 4,510 (3.80%)	aspirin 75 MG Disintegrating Oral Tablet, 5,557 (4.70%)	lansoprazole 30 MG Delayed Release Oral Capsule, 4,112 (3.90%)	amitriptyline hydrochloride 10 MG Oral Tablet, 4,907 (4.10%)
9	bendroflumethiazide 2.5 MG Oral Tablet, 6 (1.30%)	bendroflumethiazide 5 MG Oral Tablet, 200 (1.00%)	omeprazole 20 MG Delayed Release Oral Capsule, 618 (1.30%)	simvastatin 20 MG Oral Tablet, 1,985 (2.30%)	acetaminophen 500 MG Oral Tablet, 4,206 (3.60%)	acetaminophen 500 MG Oral Tablet, 5,069 (4.30%)	acetaminophen 500 MG Oral Tablet, 4,041 (3.90%)	atorvastatin 40 MG Oral Tablet, 4,426 (3.70%)
10	Albuterol 0.1 MG [Ventolin], 5 (1.10%)	ranitidine 150 MG Oral Tablet, 200 (1.00%)	acetaminophen 500 MG Oral Tablet, 584 (1.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 1,814 (2.10%)	simvastatin 20 MG Oral Tablet, 4,065 (3.40%)	lansoprazole 30 MG Delayed Release Oral Capsule, 4,360 (3.70%)	simvastatin 40 MG Oral Tablet, 3,971 (3.80%)	lansoprazole 15 MG Delayed Release Oral Capsule, 4,352 (3.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CPRD GOLD	Non-HRT users							
1	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 272 (1.90%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 2,434 (2.50%)	bendroflumethiazide 2.5 MG Oral Tablet, 10,768 (5.60%)	bendroflumethiazide 2.5 MG Oral Tablet, 46,144 (9.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 52,514 (8.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 41,584 (7.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 34,795 (8.60%)	omeprazole 20 MG Delayed Release Oral Capsule, 30,160 (10.10%)
2	amiloride hydrochloride 5 MG / hydrochlorothiazide 50 MG Oral Tablet [Moduretic], 177 (1.20%)	bendroflumethiazide 2.5 MG Oral Tablet, 2,429 (2.50%)	atenolol 50 MG Oral Tablet, 5,642 (2.90%)	aspirin 75 MG Disintegrating Oral Tablet, 22,274 (4.70%)	simvastatin 40 MG Oral Tablet, 40,608 (6.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 33,918 (6.10%)	amlodipine 5 MG Oral Tablet, 21,545 (5.30%)	atorvastatin 20 MG Oral Tablet, 22,722 (7.60%)
3	Albuterol 0.1 MG [Ventolin], 160 (1.10%)	levothyroxine sodium 0.1 MG Oral Tablet, 1,687 (1.80%)	levothyroxine sodium 0.1 MG Oral Tablet, 4,884 (2.50%)	atenolol 50 MG Oral Tablet, 19,951 (4.20%)	aspirin 75 MG Disintegrating Oral Tablet, 32,584 (5.40%)	simvastatin 40 MG Oral Tablet, 29,612 (5.30%)	levothyroxine sodium 0.1 MG Oral Tablet, 21,099 (5.20%)	amlodipine 5 MG Oral Tablet, 21,284 (7.10%)
4	levothyroxine sodium 0.1 MG Oral Tablet, 157 (1.10%)	atenolol 50 MG Oral Tablet, 1,588 (1.60%)	aspirin 75 MG Disintegrating Oral Tablet, 4,604 (2.40%)	levothyroxine sodium 0.1 MG Oral Tablet, 18,274 (3.90%)	omeprazole 20 MG Delayed Release Oral Capsule, 28,435 (4.80%)	levothyroxine sodium 0.1 MG Oral Tablet, 28,317 (5.10%)	atorvastatin 20 MG Oral Tablet, 18,434 (4.60%)	levothyroxine sodium 0.1 MG Oral Tablet, 16,304 (5.40%)
5	levothyroxine sodium 0.05 MG Oral Tablet, 142 (1.00%)	levothyroxine sodium 0.05 MG Oral Tablet, 1,449 (1.50%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 4,182 (2.20%)	levothyroxine sodium 0.05 MG Oral Tablet, 14,016 (3.00%)	levothyroxine sodium 0.1 MG Oral Tablet, 27,906 (4.70%)	amlodipine 5 MG Oral Tablet, 26,108 (4.70%)	bendroflumethiazide 2.5 MG Oral Tablet, 16,521 (4.10%)	levothyroxine sodium 0.05 MG Oral Tablet, 11,842 (4.00%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
6	atenolol 50 MG Oral Tablet, 136 (1.00%)	atenolol 100 MG Oral Tablet, 1,224 (1.30%)	levothyroxine sodium 0.05 MG Oral Tablet, 3,991 (2.10%)	levothyroxine sodium 0.025 MG Oral Tablet, 12,374 (2.60%)	levothyroxine sodium 0.05 MG Oral Tablet, 22,136 (3.70%)	aspirin 75 MG Disintegrating Oral Tablet, 23,645 (4.20%)	levothyroxine sodium 0.05 MG Oral Tablet, 16,225 (4.00%)	levothyroxine sodium 0.025 MG Oral Tablet, 11,489 (3.80%)
7	bendroflumethiazide 5 MG Oral Tablet, 130 (0.90%)	bendroflumethiazide 5 MG Oral Tablet, 1,115 (1.10%)	furosemide 40 MG Oral Tablet, 2,782 (1.40%)	simvastatin 20 MG Oral Tablet, 10,457 (2.20%)	amlodipine 5 MG Oral Tablet, 22,073 (3.70%)	levothyroxine sodium 0.05 MG Oral Tablet, 23,623 (4.20%)	levothyroxine sodium 0.025 MG Oral Tablet, 15,775 (3.90%)	atorvastatin 40 MG Oral Tablet, 11,390 (3.80%)
8	temazepam 10 MG Oral Capsule, 130 (0.90%)	furosemide 40 MG Oral Tablet, 950 (1.00%)	atenolol 100 MG Oral Tablet, 2,760 (1.40%)	atorvastatin 10 MG Oral Tablet, 10,191 (2.20%)	levothyroxine sodium 0.025 MG Oral Tablet, 21,559 (3.60%)	levothyroxine sodium 0.025 MG Oral Tablet, 23,515 (4.20%)	simvastatin 40 MG Oral Tablet, 14,402 (3.60%)	aspirin 75 MG Disintegrating Oral Tablet, 11,013 (3.70%)
9	acetaminophen 500 MG Oral Tablet, 128 (0.90%)	Albuterol 0.1 MG/ACTUAT Metered Dose Inhaler, 933 (1.00%)	amlodipine 5 MG Oral Tablet, 2,468 (1.30%)	metformin hydrochloride 500 MG Oral Tablet, 8,973 (1.90%)	simvastatin 20 MG Oral Tablet, 18,953 (3.20%)	acetaminophen 500 MG Oral Tablet, 17,676 (3.20%)	aspirin 75 MG Disintegrating Oral Tablet, 13,860 (3.40%)	amlodipine 10 MG Oral Tablet, 10,114 (3.40%)
10	atenolol 100 MG Oral Tablet, 118 (0.80%)	tamoxifen 20 MG Oral Tablet, 926 (1.00%)	levothyroxine sodium 0.025 MG Oral Tablet, 2,448 (1.30%)	amlodipine 5 MG Oral Tablet, 8,896 (1.90%)	acetaminophen 500 MG Oral Tablet, 16,088 (2.70%)	simvastatin 20 MG Oral Tablet, 17,085 (3.10%)	acetaminophen 500 MG Oral Tablet, 12,449 (3.10%)	bendroflumethiazide 2.5 MG Oral Tablet, 9,868 (3.30%)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; ; N = number of individuals; – = no data available.

Table S8. Comedication of postmenopausal women recorded 1 year prior to the pre-specified calendar date stratified by HRT use across selected calendar years by data source.

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR	HRT users							
1	-	-	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 8,272 (10.30%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 22,067 (15.10%)	influenza B virus antigen Injectable Suspension [Afluria], 58,691 (28.50%)	acetaminophen 500 MG Oral Tablet, 91,295 (34.40%)	acetaminophen 500 MG Oral Tablet, 122,118 (38.00%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 OMICRON (XBB.1.5) 0.1 MG/ML [Comirnaty 2023-2024], 206,755 (57.50%)
2	-	-	penicillin V 750 MG Oral Tablet, 7,347 (9.10%)	acetaminophen 500 MG Oral Tablet, 16,397 (11.20%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 33,461 (16.20%)	influenza B virus antigen Injectable Suspension [Afluria], 79,067 (29.80%)	influenza B virus antigen Injectable Suspension [INFLUVAC], 60,898 (18.90%)	acetaminophen 500 MG Oral Tablet, 139,371 (38.70%)
3	-	-	sulfamethizole 500 MG Oral Tablet, 6,925 (8.60%)	penicillin V 654 MG Oral Tablet, 15,445 (10.50%)	acetaminophen 500 MG Oral Tablet, 29,087 (14.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 38,812 (14.60%)	Influenza A virus / Influenza B virus Injectable Suspension [VAXIGRIP], 54,510 (17.00%)	0.5 ML influenza A virus (H1N1) antigen 0.03 MG/ML Injectable Suspension [VAXIGRIP], 115,286 (32.00%)
4	-	-	acetaminophen 500 MG Oral Tablet, 6,569 (8.20%)	penicillin V 750 MG Oral Tablet, 15,340 (10.50%)	simvastatin 40 MG Oral Tablet, 27,671 (13.40%)	aspirin 75 MG Oral Tablet, 33,245 (12.50%)	0.5 ML pneumococcal capsular polysaccharide type 10A vaccine 0.025 MG/ML / pneumococcal capsular	Influenza A virus / Influenza B virus Injectable Suspension [INFLUVAC], 103,684 (28.80%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
							polysaccharide type 11A vaccine 0.025 MG/ML / pneumococcal capsular polysaccharide type 12F vaccine 0.025 MG/ML / ... Injection [Pneumovax 23], 42,714 (13.30%)	
5	-	-	penicillin V, 4,587 (5.70%)	sulfamethizole 500 MG Oral Tablet, 12,282 (8.40%)	aspirin 75 MG Oral Tablet, 25,928 (12.60%)	simvastatin 40 MG Oral Tablet, 32,633 (12.30%)	ibuprofen 400 MG Oral Tablet, 39,980 (12.40%)	acetaminophen 665 MG Extended Release Oral Tablet, 46,952 (13.10%)
6	-	-	Glycyrrhiza glabra extract, 4,301 (5.30%)	influenza B virus antigen Injectable Suspension [Afluria], 11,373 (7.80%)	penicillin V 750 MG Oral Tablet, 20,731 (10.10%)	ibuprofen 400 MG Oral Tablet, 30,807 (11.60%)	amlodipine 5 MG Oral Tablet, 35,629 (11.10%)	amlodipine 5 MG Oral Tablet, 46,185 (12.80%)
7	-	-	Opium 1 MG/ML Oral Solution, 4,301 (5.30%)	ibuprofen 600 MG Oral Tablet, 10,304 (7.00%)	penicillin V 654 MG Oral Tablet, 17,425 (8.50%)	penicillin V 750 MG Oral Tablet, 27,065 (10.20%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 33,519 (10.40%)	ibuprofen 400 MG Oral Tablet, 44,828 (12.50%)
8	-	-	camphor, 4,301 (5.30%)	glucosamine sulfate 375 MG Oral Tablet, 9,722 (6.60%)	tramadol hydrochloride 50 MG Oral Capsule, 17,289 (8.40%)	amlodipine 5 MG Oral Tablet, 24,805 (9.30%)	aspirin 75 MG Oral Tablet, 30,785 (9.60%)	losartan potassium 50 MG Oral Tablet, 42,845 (11.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
9	-	-	opium, 4,301 (5.30%)	tramadol hydrochloride 50 MG Oral Capsule, 9,256 (6.30%)	ibuprofen 400 MG Oral Tablet, 16,346 (7.90%)	tramadol hydrochloride 50 MG Oral Capsule, 21,827 (8.20%)	losartan potassium 50 MG Oral Tablet, 30,521 (9.50%)	pantoprazole 40 MG Delayed Release Oral Tablet, 41,082 (11.40%)
10	-	-	tramadol hydrochloride 50 MG Oral Capsule, 4,218 (5.20%)	aspirin 75 MG Oral Tablet, 9,115 (6.20%)	ibuprofen 600 MG Oral Tablet, 15,175 (7.40%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 21,216 (8.00%)	Amdinocillin Pivoxil 400 MG Oral Tablet, 30,064 (9.30%)	penicillin V 750 MG Oral Tablet, 38,586 (10.70%)
DK-DHR	**Non-HRT users**							
1	-	-	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 35,576 (9.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 56,870 (13.00%)	influenza B virus antigen Injectable Suspension [Afluria], 98,397 (19.90%)	acetaminophen 500 MG Oral Tablet, 144,406 (26.30%)	acetaminophen 500 MG Oral Tablet, 170,166 (29.00%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 OMICRON (XBB.1.5) 0.1 MG/ML [Comirnaty 2023-2024], 200,275 (33.10%)
2	-	-	penicillin V 750 MG Oral Tablet, 27,933 (7.20%)	penicillin V 654 MG Oral Tablet, 38,136 (8.70%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 66,073 (13.40%)	influenza B virus antigen Injectable Suspension [Afluria], 93,189 (17.00%)	ibuprofen 400 MG Oral Tablet, 64,961 (11.10%)	acetaminophen 500 MG Oral Tablet, 179,457 (29.70%)
3	-	-	acetaminophen 500 MG Oral Tablet, 25,603 (6.60%)	penicillin V 750 MG Oral Tablet, 37,354 (8.50%)	simvastatin 40 MG Oral Tablet, 54,599 (11.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 61,146 (11.20%)	influenza B virus antigen Injectable Suspension [INFLUVAC], 63,260 (10.80%)	0.5 ML influenza A virus (H1N1) antigen 0.03 MG/ML Injectable Suspension [VAXIGRIP], 127,965 (21.20%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
4	-	-	penicillin V, 18,390 (4.70%)	acetaminophen 500 MG Oral Tablet, 36,970 (8.40%)	acetaminophen 500 MG Oral Tablet, 50,255 (10.20%)	simvastatin 40 MG Oral Tablet, 53,927 (9.80%)	Influenza A virus / Influenza B virus Injectable Suspension [VAXIGRIP], 55,578 (9.50%)	Influenza A virus / Influenza B virus Injectable Suspension [INFLUVAC], 109,451 (18.10%)
5	-	-	sulfamethizole 500 MG Oral Tablet, 17,310 (4.40%)	influenza B virus antigen Injectable Suspension [Afluria], 30,384 (6.90%)	aspirin 75 MG Oral Tablet, 47,930 (9.70%)	ibuprofen 400 MG Oral Tablet, 53,824 (9.80%)	amlodipine 5 MG Oral Tablet, 49,115 (8.40%)	ibuprofen 400 MG Oral Tablet, 69,628 (11.50%)
6	-	-	Potassium Chloride 750 MG Extended Release Oral Tablet, 17,063 (4.40%)	ibuprofen 600 MG Oral Tablet, 25,708 (5.90%)	penicillin V 750 MG Oral Tablet, 41,584 (8.40%)	aspirin 75 MG Oral Tablet, 47,598 (8.70%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 42,680 (7.30%)	amlodipine 5 MG Oral Tablet, 58,247 (9.60%)
7	-	-	camphor, 15,039 (3.90%)	aspirin 75 MG Oral Tablet, 22,879 (5.20%)	penicillin V 654 MG Oral Tablet, 35,070 (7.10%)	penicillin V 750 MG Oral Tablet, 46,828 (8.50%)	0.5 ML pneumococcal capsular polysaccharide type 10A vaccine 0.025 MG/ML / pneumococcal capsular polysaccharide type 11A vaccine 0.025 MG/ML / pneumococcal capsular polysaccharide type 12F vaccine 0.025 MG/ML / ...	losartan potassium 50 MG Oral Tablet, 52,761 (8.70%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
							Injection [Pneumovax 23], 40,634 (6.90%)	
8	-	-	Glycyrrhiza glabra extract, 15,038 (3.90%)	ibuprofen 400 MG Oral Tablet, 21,573 (4.90%)	ibuprofen 600 MG Oral Tablet, 32,597 (6.60%)	amlodipine 5 MG Oral Tablet, 40,414 (7.40%)	losartan potassium 50 MG Oral Tablet, 40,323 (6.90%)	penicillin V 750 MG Oral Tablet, 51,765 (8.60%)
9	-	-	Opium 1 MG/ML Oral Solution, 15,038 (3.90%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 20,309 (4.60%)	ibuprofen 400 MG Oral Tablet, 31,331 (6.30%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 33,656 (6.10%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 38,699 (6.60%)	atorvastatin 40 MG Oral Tablet, 48,455 (8.00%)
10	-	-	opium, 15,038 (3.90%)	sulfamethizole 500 MG Oral Tablet, 19,872 (4.50%)	tramadol hydrochloride 50 MG Oral Capsule, 30,281 (6.10%)	tramadol hydrochloride 50 MG Oral Capsule, 32,258 (5.90%)	aspirin 75 MG Oral Tablet, 37,404 (6.40%)	acetaminophen 665 MG Extended Release Oral Tablet, 46,544 (7.70%)
IQVIA DA Germany	**HRT users**							
1	-	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 33 (2.70%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 94 (2.60%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 134 (1.70%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 186 (0.90%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 794 (2.00%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 1,526 (2.50%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 1,957 (3.10%)
2	-	1990 MG Acyclovir 0.025 MG/MG Topical Cream [Zovirax] Box of 1 by Johnson & Johnson, 32 (2.60%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 78 (2.20%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 127 (1.60%)	Clotrimazole Vaginal Suppository [Canifug], 141 (0.70%)	8000 MG Fosfomycin 0.704 MG/MG Oral Solution [Monuril] Box of 1 by Pierre Fabre, 515 (1.30%)	Chlorhexidine / Dexamethasone / Nystatin Topical Ointment [Nystalocal], 651 (1.00%)	Chlorhexidine / Dexamethasone / Nystatin Topical Ointment [Nystalocal], 926 (1.50%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
3	-	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 29 (2.40%)	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 53 (1.50%)	Clotrimazole 800 MG Vaginal Tablet [Kadefungin] Box of 1 by Dr. Kade, 87 (1.10%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 137 (0.70%)	Chlorhexidine / Dexamethasone / Nystatin Topical Ointment [Nystalocal], 292 (0.70%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 544 (0.90%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 796 (1.20%)
4	-	Magnesium 38 MG Oral Tablet [Magnesium Verla] Box of 100 by Verla, 26 (2.10%)	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 48 (1.30%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 20 by Novartis, 67 (0.80%)	Lactobacillus acidophilus 1000 MG Vaginal Tablet Box of 6 by Chiesi, 128 (0.60%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 257 (0.60%)	8000 MG Fosfomycin 0.704 MG/MG Oral Powder [Fosfomycin Aristo] Box of 1 by Aristo, 476 (0.80%)	Amdinocillin Pivoxil 400 MG Oral Tablet Box of 9, 687 (1.10%)
5	-	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 23 (1.90%)	Black Cohosh Extract / ST. JOHN'S WORT EXTRACT Oral Tablet [Remifemin], 43 (1.20%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 63 (0.80%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 50 by Novartis, 120 (0.60%)	Metronidazole 1000 MG Vaginal Tablet [Arilin] Box of 2 by Wolff Bielefeld, 256 (0.60%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 400 (0.60%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 509 (0.80%)
6	-	Calcium 3240 MG Oral Tablet [Calcium-Sandoz] Box of 100 by Novartis, 22 (1.80%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 43 (1.20%)	Black Cohosh Extract / ST. JOHN'S WORT EXTRACT Oral Tablet [Remifemin], 62 (0.80%)	Clotrimazole 1000 MG Vaginal Tablet [Kadefungin] Box of 1 by Dr. Kade, 119 (0.60%)	Dequalinium 10 MG Vaginal Tablet [Fluomycin] Box of 6 by Pierre Fabre, 213 (0.50%)	8000 MG Fosfomycin 0.704 MG/MG Oral Solution [Monuril] Box of 1 by Pierre Fabre, 386 (0.60%)	8000 MG Fosfomycin 0.704 MG/MG Oral Powder [Fosfomycin Aristo] Box of 1 by Aristo, 466 (0.70%)
7	-	20 ML Metoclopramide 1.18 MG/ML Oral Solution [Gastrosil] Box of 1 by	Clotrimazole 1000 MG Vaginal Tablet [Kadefungin] Box of 1 by Dr. Kade, 36 (1.00%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 59 (0.70%)	Clotrimazole 800 MG Vaginal Tablet [Kadefungin] Box of 1 by Dr. Kade, 118 (0.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 213 (0.50%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 360 (0.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 447 (0.70%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
		Heumann, 21 (1.70%)						
8	-	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 20 (1.60%)	Diclofenac 50 MG Disintegrating Oral Tablet [Voltaren] Box of 20 by Novartis, 36 (1.00%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 50 by Novartis, 54 (0.70%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 112 (0.50%)	Cholecalciferol 1000 UNT Oral Tablet [Vigantoletten] Box of 100 by Mylan, 198 (0.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 359 (0.60%)	FLUPREDNIDENE / Miconazole Topical Cream [Decoderm], 439 (0.70%)
9	-	Black Cohosh Extract 20 MG Oral Tablet [Remifemin] Box of 100 by Schaper & Bruemmer, 19 (1.50%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 34 (0.90%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 52 (0.70%)	Metronidazole 100 MG Vaginal Tablet [Arilin] Box of 6 by Wolff Bielefeld, 106 (0.50%)	Metronidazole 100 MG Vaginal Tablet [Arilin] Box of 6 by Wolff Bielefeld, 198 (0.50%)	FLUPREDNIDENE / Miconazole Topical Cream [Decoderm], 356 (0.60%)	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100 by 1 A, 427 (0.70%)
10	-	myrtol 300 MG Oral Capsule [Gelomyrtol] Box of 20 by G.Pohl-Boskamp Kg, 19 (1.50%)	Acetylcysteine 200 MG Oral Tablet [Fluimucil] Box of 20 by Zambon, 33 (0.90%)	Opipramol 50 MG Oral Tablet [Insidon] Box of 100 by Novartis, 51 (0.60%)	Metronidazole 1000 MG Vaginal Tablet [Arilin] Box of 2 by Wolff Bielefeld, 100 (0.50%)	FLUPREDNIDENE / Miconazole Topical Cream [Decoderm], 183 (0.40%)	Dequalinium 10 MG Vaginal Tablet [Fluomycin] Box of 6 by Pierre Fabre, 312 (0.50%)	Cholecalciferol 20000 UNT Oral Capsule by Aristo, 425 (0.70%)
IQVIA DA Germany	**Non-HRT users**							
1	-	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 349 (1.00%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 537 (0.50%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 1,416 (0.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 2,753 (0.40%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 12,289 (1.00%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 32,357 (1.90%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 40,262 (3.30%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
2	-	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 337 (1.00%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 473 (0.40%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,276 (0.40%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 2,066 (0.30%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 6,742 (0.50%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 14,825 (0.90%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 25,638 (2.10%)
3	-	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 241 (0.70%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 289 (0.30%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 726 (0.20%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,969 (0.30%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 5,236 (0.40%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 13,013 (0.80%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 17,842 (1.40%)
4	-	myrtol 300 MG Oral Capsule [Gelomyrtol] Box of 20 by G.Pohl-Boskamp Kg, 232 (0.70%)	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 276 (0.30%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 696 (0.20%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,839 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 5,172 (0.40%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 12,078 (0.70%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 14,589 (1.20%)
5	-	Acetaminophen 500 MG Oral Tablet [PARACETAMOL RATIOPHARM] Box of 30 by Ratiopharm, 207 (0.60%)	Diclofenac 50 MG Disintegrating Oral Tablet [Voltaren] Box of 20 by Novartis, 236 (0.20%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 605 (0.20%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 50 by Novartis, 1,636 (0.20%)	Ibuprofen 600 MG Extended Release Oral Tablet [Ibu 1a Pharma] Box of 20 by 1 A, 5,105 (0.40%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 10,016 (0.60%)	Beclomethasone / formoterol Dry Powder Inhaler [Foster], 13,112 (1.10%)
6	-	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 205 (0.60%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 233 (0.20%)	Metoprolol 100 MG Extended Release Oral Tablet [Beloc] Box of 100 by Astrazeneca, 574 (0.20%)	Budesonide / formoterol Dry Powder Inhaler [Symbicort], 1,597 (0.20%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 4,297 (0.30%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 9,822 (0.60%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 13,051 (1.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
7	-	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 195 (0.60%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 228 (0.20%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 537 (0.20%)	Ibuprofen 600 MG Extended Release Oral Tablet [Ibu 1a Pharma] Box of 20 by 1 A, 1,573 (0.20%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 4,068 (0.30%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 9,601 (0.60%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 12,738 (1.00%)
8	-	Acetylcysteine 200 MG Oral Tablet [Fluimucil] Box of 20 by Zambon, 184 (0.60%)	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 224 (0.20%)	Metoprolol 50 MG Oral Tablet [Beloc] Box of 100 by Astrazeneca, 507 (0.20%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,468 (0.20%)	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100 by 1 A, 4,044 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 9,521 (0.60%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 11,968 (1.00%)
9	-	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 184 (0.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 189 (0.20%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 20 by Novartis, 469 (0.20%)	Metoprolol 100 MG Extended Release Oral Tablet [Metohexal] Box of 100 by Novartis, 1,433 (0.20%)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A, 4,001 (0.30%)	Ibuprofen 600 MG Oral Tablet [Ibuflam] Box of 50 by Sanofi, 8,457 (0.50%)	candesartan 16 MG Oral Tablet [Candesartan 1a Pharma] Box of 98 by 1 A, 11,551 (0.90%)
10	-	Aspirin 100 MG Oral Tablet [Ass Ratiopharm] Box of 100 by Ratiopharm, 177 (0.50%)	Acetylcysteine 200 MG Oral Tablet [Fluimucil] Box of 20 by Zambon, 179 (0.20%)	Diclofenac 50 MG Disintegrating Oral Tablet [Voltaren] Box of 20 by Novartis, 446 (0.20%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 20 by Novartis, 1,417 (0.20%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 3,814 (0.30%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 8,392 (0.50%)	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100 by 1 A, 11,183 (0.90%)
BIFAP	**HRT users**							
1	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 514 (29.70%)	omeprazole 20 MG Delayed Release Oral Capsule, 14,303 (43.10%)	acetaminophen, 27,007 (41.50%)	acetaminophen, 41,153 (45.20%)	acetaminophen, 131,969 (50.60%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
2	-	-	-	acetaminophen, 495 (28.60%)	acetaminophen, 13,526 (40.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 25,711 (39.50%)	influenza virus vaccine, unspecified formulation, 34,902 (38.30%)	influenza virus vaccine, unspecified formulation, 109,027 (41.90%)
3	-	-	-	ibuprofen 600 MG Oral Tablet, 341 (19.70%)	ibuprofen 600 MG Oral Tablet, 10,184 (30.70%)	influenza virus vaccine, unspecified formulation, 19,783 (30.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 32,028 (35.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 82,344 (31.60%)
4	-	-	-	influenza virus vaccine, unspecified formulation, 339 (19.60%)	influenza virus vaccine, unspecified formulation, 9,943 (30.00%)	ibuprofen 600 MG Oral Tablet, 14,947 (23.00%)	dipyrone, 20,170 (22.20%)	calcifediol, 71,203 (27.30%)
5	-	-	-	acetaminophen 650 MG Oral Tablet, 298 (17.20%)	acetylcysteine, 6,783 (20.40%)	lorazepam 1 MG Oral Tablet, 12,664 (19.40%)	lorazepam 1 MG Oral Tablet, 18,092 (19.90%)	dipyrone, 66,848 (25.70%)
6	-	-	-	codeine, 269 (15.60%)	lorazepam 1 MG Oral Tablet, 6,216 (18.70%)	dipyrone, 10,951 (16.80%)	calcifediol, 15,795 (17.40%)	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein, 56,566 (21.70%)
7	-	-	-	acetylcysteine, 259 (15.00%)	codeine, 5,454 (16.40%)	azithromycin 500 MG Oral Tablet, 8,729 (13.40%)	ibuprofen 600 MG Oral Tablet, 14,011 (15.40%)	lorazepam 1 MG Oral Tablet, 43,317 (16.60%)
8	-	-	-	lorazepam 1 MG Oral Tablet, 250 (14.40%)	dipyrone, 4,950 (14.90%)	codeine, 8,415 (12.90%)	codeine, 11,500 (12.60%)	ibuprofen 600 MG Oral Tablet, 42,367 (16.30%)
9	-	-	-	amoxicillin, 166 (9.60%)	ibuprofen, 3,693 (11.10%)	acetaminophen 325 MG / tramadol hydrochloride 37.5	fosfomycin 3000 MG Granules for Oral Solution, 11,300 (12.40%)	fosfomycin 3000 MG Granules for Oral Solution, 41,543 (15.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
						MG Oral Tablet, 7,548 (11.60%)		
10	-	-	-	ibuprofen, 165 (9.50%)	ibuprofen 3 MG/ML Oral Suspension, 3,572 (10.80%)	dexketoprofen 25 MG Oral Tablet, 7,456 (11.40%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 11,211 (12.30%)	codeine, 41,242 (15.80%)
BIFAP	**Non-HRT users**							
1	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 30,411 (20.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 281,764 (29.50%)	acetaminophen, 533,097 (32.00%)	acetaminophen, 1,101,346 (34.30%)	acetaminophen, 1,428,966 (38.90%)
2	-	-	-	acetaminophen, 29,853 (20.10%)	acetaminophen, 252,510 (26.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 490,806 (29.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 812,036 (25.30%)	influenza virus vaccine, unspecified formulation, 1,124,432 (30.60%)
3	-	-	-	influenza virus vaccine, unspecified formulation, 25,355 (17.00%)	influenza virus vaccine, unspecified formulation, 237,867 (24.90%)	influenza virus vaccine, unspecified formulation, 365,487 (22.00%)	influenza virus vaccine, unspecified formulation, 706,897 (22.00%)	omeprazole 20 MG Delayed Release Oral Capsule, 880,957 (24.00%)
4	-	-	-	ibuprofen 600 MG Oral Tablet, 22,460 (15.10%)	ibuprofen 600 MG Oral Tablet, 210,633 (22.10%)	ibuprofen 600 MG Oral Tablet, 295,811 (17.80%)	dipyrone, 534,859 (16.60%)	calcifediol, 761,060 (20.70%)
5	-	-	-	acetaminophen 650 MG Oral Tablet, 18,979 (12.80%)	acetylcysteine, 109,206 (11.40%)	dipyrone, 218,628 (13.10%)	calcifediol, 418,990 (13.00%)	dipyrone, 713,624 (19.40%)
6	-	-	-	codeine, 16,667 (11.20%)	dipyrone, 91,071 (9.50%)	lorazepam 1 MG Oral Tablet, 189,608 (11.40%)	ibuprofen 600 MG Oral Tablet, 400,752 (12.50%)	SARS-CoV-2 (COVID-19) vaccine, mRNA

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
								spike protein, 604,974 (16.50%)
7	-	-	-	acetylcysteine, 14,304 (9.60%)	lorazepam 1 MG Oral Tablet, 91,037 (9.50%)	codeine, 144,176 (8.70%)	lorazepam 1 MG Oral Tablet, 373,094 (11.60%)	ibuprofen 600 MG Oral Tablet, 453,145 (12.30%)
8	-	-	-	lorazepam 1 MG Oral Tablet, 12,744 (8.60%)	codeine, 86,735 (9.10%)	azithromycin 500 MG Oral Tablet, 143,090 (8.60%)	dexketoprofen 25 MG Oral Tablet, 307,032 (9.60%)	codeine, 409,522 (11.20%)
9	-	-	-	amoxicillin, 10,515 (7.10%)	bromazepam, 70,341 (7.40%)	dexketoprofen 25 MG Oral Tablet, 141,170 (8.50%)	codeine, 276,889 (8.60%)	lorazepam 1 MG Oral Tablet, 406,894 (11.10%)
10	-	-	-	bromazepam, 10,237 (6.90%)	acetaminophen 650 MG Oral Tablet, 67,852 (7.10%)	amoxicillin, 131,882 (7.90%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 251,646 (7.80%)	dexketoprofen 25 MG Oral Tablet, 394,870 (10.80%)
SIDIAP	**HRT users**							
1	-	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 3,889 (44.70%)	omeprazole 20 MG Delayed Release Oral Capsule, 21,955 (44.90%)	acetaminophen 1000 MG Oral Tablet, 25,323 (39.50%)	acetaminophen 1000 MG Oral Tablet, 44,229 (46.30%)
2	-	-	-	-	ibuprofen 600 MG Oral Tablet, 3,439 (39.50%)	acetaminophen 1000 MG Oral Tablet, 18,475 (37.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 25,040 (39.00%)	Influenza, split virus, trivalent, injectable, contains preservative, 41,523 (43.50%)
3	-	-	-	-	Influenza, split virus, trivalent, injectable, contains	ibuprofen 600 MG Oral Tablet, 14,190 (29.00%)	Influenza, split virus, trivalent, injectable, contains	omeprazole 20 MG Delayed Release

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
					preservative, 2,457 (28.20%)		preservative, 21,558 (33.60%)	Oral Capsule, 38,835 (40.60%)
4	-	-	-	-	acetaminophen 1000 MG Oral Tablet, 1,961 (22.50%)	Influenza, split virus, trivalent, injectable, contains preservative, 14,117 (28.90%)	dipyrone, 13,454 (21.00%)	dipyrone, 26,054 (27.30%)
5	-	-	-	-	lorazepam 1 MG Oral Tablet, 1,270 (14.60%)	lorazepam 1 MG Oral Tablet, 7,953 (16.20%)	lorazepam 1 MG Oral Tablet, 10,331 (16.10%)	calcifediol Oral Capsule, 16,216 (17.00%)
6	-	-	-	-	diclofenac sodium 50 MG Delayed Release Oral Tablet, 1,258 (14.40%)	dipyrone, 7,638 (15.60%)	ibuprofen 600 MG Oral Tablet, 10,041 (15.70%)	ibuprofen 600 MG Oral Tablet, 15,881 (16.60%)
7	-	-	-	-	simvastatin 20 MG Oral Tablet, 1,095 (12.60%)	simvastatin 20 MG Oral Tablet, 7,345 (15.00%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 7,455 (11.60%)	lorazepam 1 MG Oral Tablet, 15,835 (16.60%)
8	-	-	-	-	acetaminophen 650 MG Oral Tablet, 1,033 (11.90%)	diazepam 5 MG Oral Tablet, 5,742 (11.70%)	fosfomycin 3000 MG Granules for Oral Solution, 7,366 (11.50%)	fosfomycin 3000 MG Granules for Oral Solution, 15,658 (16.40%)
9	-	-	-	-	diclofenac sodium 0.01 MG/MG Topical Gel, 979 (11.20%)	fosfomycin 3000 MG Granules for Oral Solution, 4,921 (10.10%)	diazepam 5 MG Oral Tablet, 7,209 (11.20%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 12,871 (13.50%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	-	-	-	carboxymethylcellulose sodium 5 MG/ML Ophthalmic Solution, 946 (10.90%)	naproxen sodium 550 MG Oral Tablet, 4,690 (9.60%)	simvastatin 20 MG Oral Tablet, 7,036 (11.00%)	acetaminophen 650 MG Oral Tablet, 12,595 (13.20%)
SIDIAP	**Non-HRT users**							
1	-	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 135,658 (27.70%)	omeprazole 20 MG Delayed Release Oral Capsule, 175,270 (28.00%)	acetaminophen 1000 MG Oral Tablet, 200,188 (24.90%)	acetaminophen 1000 MG Oral Tablet, 290,852 (31.30%)
2	-	-	-	-	ibuprofen 600 MG Oral Tablet, 120,734 (24.70%)	acetaminophen 1000 MG Oral Tablet, 147,279 (23.60%)	omeprazole 20 MG Delayed Release Oral Capsule, 189,779 (23.60%)	Influenza, split virus, trivalent, injectable, contains preservative, 242,127 (26.10%)
3	-	-	-	-	Influenza, split virus, trivalent, injectable, contains preservative, 92,376 (18.90%)	ibuprofen 600 MG Oral Tablet, 119,043 (19.00%)	Influenza, split virus, trivalent, injectable, contains preservative, 151,357 (18.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 236,502 (25.50%)
4	-	-	-	-	acetaminophen 1000 MG Oral Tablet, 71,857 (14.70%)	Influenza, split virus, trivalent, injectable, contains preservative, 108,311 (17.30%)	dipyrone, 105,085 (13.10%)	dipyrone, 165,854 (17.90%)
5	-	-	-	-	diclofenac sodium 50 MG Delayed Release Oral Tablet, 48,003 (9.80%)	simvastatin 20 MG Oral Tablet, 65,059 (10.40%)	ibuprofen 600 MG Oral Tablet, 93,844 (11.70%)	ibuprofen 600 MG Oral Tablet, 124,177 (13.40%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
6	-	-	-	-	simvastatin 20 MG Oral Tablet, 43,674 (8.90%)	lorazepam 1 MG Oral Tablet, 63,195 (10.10%)	lorazepam 1 MG Oral Tablet, 78,772 (9.80%)	calcifediol Oral Capsule, 101,956 (11.00%)
7	-	-	-	-	lorazepam 1 MG Oral Tablet, 42,893 (8.80%)	dipyrone, 59,510 (9.50%)	diazepam 5 MG Oral Tablet, 59,809 (7.40%)	lorazepam 1 MG Oral Tablet, 94,680 (10.20%)
8	-	-	-	-	acetaminophen 650 MG Oral Tablet, 36,402 (7.40%)	diazepam 5 MG Oral Tablet, 47,089 (7.50%)	simvastatin 20 MG Oral Tablet, 57,485 (7.20%)	acetaminophen 650 MG Oral Tablet, 88,586 (9.60%)
9	-	-	-	-	tetanus toxoid vaccine, inactivated, 34,154 (7.00%)	naproxen sodium 550 MG Oral Tablet, 39,638 (6.30%)	acetaminophen 650 MG Oral Tablet, 55,110 (6.90%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 78,663 (8.50%)
10	-	-	-	-	diphtheria toxoid vaccine, inactivated, 33,969 (7.00%)	metformin hydrochloride 850 MG Oral Tablet, 38,504 (6.20%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 54,369 (6.80%)	simvastatin 20 MG Oral Tablet, 72,502 (7.80%)
CPRD GOLD	**HRT users**							
1	tetanus toxoid vaccine, inactivated, 73 (15.90%)	amoxicillin 250 MG Oral Capsule, 2,653 (13.80%)	influenza virus vaccine, unspecified formulation, 9,097 (19.30%)	influenza virus vaccine, unspecified formulation, 29,349 (34.50%)	influenza virus vaccine, unspecified formulation, 46,655 (39.50%)	influenza virus vaccine, unspecified formulation, 51,645 (43.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 24,372 (23.30%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 36,406 (30.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
2	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 55 (12.00%)	influenza virus vaccine, unspecified formulation, 2,474 (12.80%)	amoxicillin 250 MG Oral Capsule, 5,586 (11.90%)	bendroflumethiazide 2.5 MG Oral Tablet, 12,004 (14.10%)	Novel influenza-H1N1-09, injectable, 18,810 (15.90%)	omeprazole 20 MG Delayed Release Oral Capsule, 25,830 (21.70%)	amoxicillin 500 MG Oral Capsule, 13,819 (13.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 29,648 (24.50%)
3	amoxicillin 250 MG Oral Capsule, 35 (7.60%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 2,240 (11.60%)	bendroflumethiazide 2.5 MG Oral Tablet, 4,311 (9.20%)	amoxicillin 250 MG Oral Capsule, 8,970 (10.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 17,269 (14.60%)	amoxicillin 500 MG Oral Capsule, 19,317 (16.20%)	acetaminophen 500 MG Oral Tablet, 10,134 (9.70%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension, 26,517 (21.90%)
4	trimethoprim 200 MG Oral Tablet, 33 (7.20%)	trimethoprim 200 MG Oral Tablet, 1,666 (8.60%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 4,268 (9.10%)	Influenza, split virus, trivalent, injectable, contains preservative, 8,329 (9.80%)	amoxicillin 500 MG Oral Capsule, 14,190 (12.00%)	acetaminophen 500 MG Oral Tablet, 15,177 (12.80%)	amitriptyline hydrochloride 10 MG Oral Tablet, 8,931 (8.50%)	amoxicillin 500 MG Oral Capsule, 18,798 (15.50%)
5	temazepam 10 MG Oral Capsule, 31 (6.80%)	ibuprofen 400 MG Oral Tablet, 1,622 (8.40%)	trimethoprim 200 MG Oral Tablet, 3,479 (7.40%)	trimethoprim 200 MG Oral Tablet, 7,180 (8.40%)	bendroflumethiazide 2.5 MG Oral Tablet, 14,036 (11.90%)	trimethoprim 200 MG Oral Tablet, 13,367 (11.20%)	Nitrofurantoin 100 MG Extended Release Oral Capsule, 8,822 (8.40%)	doxycycline hyclate 100 MG Oral Capsule, 13,870 (11.50%)
6	cefotetan, 29 (6.30%)	Influenza, split virus, trivalent, injectable, contains preservative, 1,264 (6.60%)	ibuprofen 400 MG Oral Tablet, 3,371 (7.20%)	acetaminophen 500 MG Oral Tablet, 6,910 (8.10%)	acetaminophen 500 MG Oral Tablet, 13,427 (11.40%)	bendroflumethiazide 2.5 MG Oral Tablet, 9,552 (8.00%)	trimethoprim 200 MG Oral Tablet, 8,729 (8.30%)	atorvastatin 20 MG Oral Tablet, 12,274 (10.10%)
7	influenza virus vaccine, split virus (incl. purified surface antigen)-	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG	Influenza, split virus, trivalent, injectable, contains preservative, 3,207 (6.80%)	diclofenac sodium 50 MG Delayed Release Oral Tablet, 6,521 (7.70%)	trimethoprim 200 MG Oral Tablet, 12,499 (10.60%)	amitriptyline hydrochloride 10 MG Oral Tablet, 9,433 (7.90%)	doxycycline hyclate 100 MG Oral Capsule, 8,671 (8.30%)	amlodipine 5 MG Oral Tablet, 11,411 (9.40%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
	retired CODE, 28 (6.10%)	Oral Tablet, 1,066 (5.50%)						
8	influenza virus vaccine, unspecified formulation, 27 (5.90%)	alginic acid Oral Solution [Gaviscon], 930 (4.80%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 2,523 (5.40%)	amoxicillin 500 MG Oral Capsule, 6,467 (7.60%)	simvastatin 40 MG Oral Tablet, 12,276 (10.40%)	simvastatin 40 MG Oral Tablet, 9,402 (7.90%)	levothyroxine sodium 0.1 MG Oral Tablet, 8,551 (8.20%)	amitriptyline hydrochloride 10 MG Oral Tablet, 11,132 (9.20%)
9	Amoxicillin 250 MG Oral Capsule [Amoxil] by Glaxosmithkline, 26 (5.70%)	tetanus toxoid vaccine, inactivated, 924 (4.80%)	acetaminophen 500 MG Oral Tablet, 2,379 (5.00%)	aspirin 75 MG Disintegrating Oral Tablet, 6,275 (7.40%)	aspirin 75 MG Disintegrating Oral Tablet, 10,537 (8.90%)	levothyroxine sodium 0.1 MG Oral Tablet, 9,224 (7.80%)	acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet, 8,451 (8.10%)	Nitrofurantoin 100 MG Extended Release Oral Capsule, 10,999 (9.10%)
10	Clonidine 0.025 MG Oral Tablet [Dixarit] by Boehringer Ingelheim, 26 (5.70%)	bendroflumethiazide 2.5 MG Oral Tablet, 901 (4.70%)	Albuterol 0.1 MG/ACTUAT Metered Dose Inhaler, 2,358 (5.00%)	atenolol 50 MG Oral Tablet, 4,966 (5.80%)	Influenza, split virus, trivalent, injectable, contains preservative, 9,615 (8.10%)	levothyroxine sodium 0.025 MG Oral Tablet, 9,034 (7.60%)	amlodipine 5 MG Oral Tablet, 8,268 (7.90%)	acetaminophen 500 MG Oral Tablet, 10,941 (9.00%)
CPRD GOLD	**Non-HRT users**							
1	tetanus toxoid vaccine, inactivated, 1,680 (11.90%)	influenza virus vaccine, unspecified formulation, 11,527 (11.90%)	influenza virus vaccine, unspecified formulation, 30,977 (16.00%)	influenza virus vaccine, unspecified formulation, 125,395 (26.60%)	influenza virus vaccine, unspecified formulation, 183,606 (30.70%)	influenza virus vaccine, unspecified formulation, 184,253 (33.10%)	omeprazole 20 MG Delayed Release Oral Capsule, 67,312 (16.70%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 82,837 (27.70%)
2	acetaminophen 325 MG / propoxyphene hydrochloride 32.5	amoxicillin 250 MG Oral Capsule, 9,962 (10.30%)	amoxicillin 250 MG Oral Capsule, 16,636 (8.60%)	bendroflumethiazide 2.5 MG Oral Tablet, 60,172 (12.80%)	Novel influenza-H1N1-09, injectable, 78,546 (13.10%)	omeprazole 20 MG Delayed Release Oral Capsule, 85,414 (15.30%)	amoxicillin 500 MG Oral Capsule, 40,393 (10.00%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
	MG Oral Tablet, 1,072 (7.60%)							Suspension, 65,190 (21.80%)
3	cefotetan, 953 (6.80%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 8,512 (8.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 15,375 (8.00%)	amoxicillin 250 MG Oral Capsule, 38,616 (8.20%)	bendroflumethiazide 2.5 MG Oral Tablet, 66,509 (11.10%)	amoxicillin 500 MG Oral Capsule, 71,914 (12.90%)	acetaminophen 500 MG Oral Tablet, 30,087 (7.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 55,477 (18.50%)
4	amoxicillin 250 MG Oral Capsule, 913 (6.50%)	ibuprofen 400 MG Oral Tablet, 6,110 (6.30%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 13,087 (6.80%)	aspirin 75 MG Disintegrating Oral Tablet, 31,505 (6.70%)	omeprazole 20 MG Delayed Release Oral Capsule, 61,649 (10.30%)	acetaminophen 500 MG Oral Tablet, 53,169 (9.60%)	amlodipine 5 MG Oral Tablet, 29,479 (7.30%)	amoxicillin 500 MG Oral Capsule, 36,758 (12.30%)
5	influenza virus vaccine, unspecified formulation, 747 (5.30%)	Influenza, split virus, trivalent, injectable, contains preservative, 6,070 (6.30%)	ibuprofen 400 MG Oral Tablet, 10,332 (5.30%)	amoxicillin 500 MG Oral Capsule, 30,518 (6.50%)	amoxicillin 500 MG Oral Capsule, 59,228 (9.90%)	bendroflumethiazide 2.5 MG Oral Tablet, 42,526 (7.60%)	acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet, 26,386 (6.50%)	atorvastatin 20 MG Oral Tablet, 28,732 (9.60%)
6	ibuprofen 400 MG Oral Tablet, 657 (4.70%)	trimethoprim 200 MG Oral Tablet, 4,548 (4.70%)	Influenza, split virus, trivalent, injectable, contains preservative, 9,687 (5.00%)	acetaminophen 500 MG Oral Tablet, 28,766 (6.10%)	simvastatin 40 MG Oral Tablet, 58,014 (9.70%)	simvastatin 40 MG Oral Tablet, 41,048 (7.40%)	levothyroxine sodium 0.1 MG Oral Tablet, 26,238 (6.50%)	amlodipine 5 MG Oral Tablet, 28,574 (9.50%)
7	Influenza, split virus, trivalent, injectable, contains preservative, 625 (4.40%)	tetanus toxoid vaccine, inactivated, 4,289 (4.40%)	acetaminophen 500 MG Oral Tablet, 8,514 (4.40%)	diclofenac sodium 50 MG Delayed Release Oral Tablet, 27,926 (5.90%)	acetaminophen 500 MG Oral Tablet, 50,604 (8.50%)	trimethoprim 200 MG Oral Tablet, 36,209 (6.50%)	doxycycline hyclate 100 MG Oral Capsule, 25,073 (6.20%)	doxycycline hyclate 100 MG Oral Capsule, 26,371 (8.80%)
8	influenza virus vaccine, split virus (incl. purified	bendroflumethiazide 2.5 MG Oral	trimethoprim 200 MG Oral Tablet, 8,351 (4.30%)	atenolol 50 MG Oral Tablet, 26,727 (5.70%)	aspirin 75 MG Disintegrating Oral	amlodipine 5 MG Oral Tablet, 36,066 (6.50%)	Albuterol 0.095 MG/ACTUAT Metered Dose	acetaminophen 500 MG Oral Tablet, 24,441 (8.20%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
	surface antigen)-retired CODE, 576 (4.10%)	Tablet, 3,947 (4.10%)			Tablet, 48,012 (8.00%)		Inhaler, 24,168 (6.00%)	
9	Amoxicillin 250 MG Oral Capsule [Amoxil] by Glaxosmithkline, 560 (4.00%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 3,804 (3.90%)	atenolol 50 MG Oral Tablet, 8,220 (4.30%)	Influenza, split virus, trivalent, injectable, contains preservative, 25,741 (5.50%)	trimethoprim 200 MG Oral Tablet, 37,122 (6.20%)	levothyroxine sodium 0.1 MG Oral Tablet, 34,252 (6.20%)	atorvastatin 20 MG Oral Tablet, 23,934 (5.90%)	acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet, 21,680 (7.20%)
10	trimethoprim 200 MG Oral Tablet, 524 (3.70%)	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE, 3,390 (3.50%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 7,721 (4.00%)	trimethoprim 200 MG Oral Tablet, 24,435 (5.20%)	Albuterol 0.095 MG/ACTUAT Metered Dose Inhaler, 34,702 (5.80%)	aspirin 75 MG Disintegrating Oral Tablet, 32,599 (5.90%)	prednisolone 5 MG Oral Tablet, 23,756 (5.90%)	prednisolone 5 MG Oral Tablet, 20,407 (6.80%)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; ; N = number of individuals; – = no data available.

Table S9. Comedication of postmenopausal women recorded 1 year post the pre-specified calendar date stratified by HRT use across selected calendar years by data source.

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR	HRT users							
1	-	-	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 8,967 (11.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 23,555 (16.10%)	influenza B virus antigen Injectable Suspension [Afluria], 54,563 (26.50%)	acetaminophen 500 MG Oral Tablet, 95,615 (36.00%)	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injection, 256,093 (79.70%)	Tozinameran 0.1 MG/ML [Comirnaty], 119,908 (33.30%)
2	-	-	penicillin V 750 MG Oral Tablet, 7,345 (9.10%)	acetaminophen 500 MG Oral Tablet, 17,666 (12.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 34,172 (16.60%)	influenza B virus antigen Injectable Suspension [Afluria], 80,090 (30.10%)	acetaminophen 500 MG Oral Tablet, 123,588 (38.40%)	influenza A virus (H1N1) antigen / influenza A virus (H3N2) antigen / influenza B virus antigen Prefilled Syringe, 91,173 (25.30%)
3	-	-	acetaminophen 500 MG Oral Tablet, 6,751 (8.40%)	penicillin V 750 MG Oral Tablet, 14,919 (10.20%)	acetaminophen 500 MG Oral Tablet, 30,970 (15.00%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 36,367 (13.70%)	0.5 ML pneumococcal capsular polysaccharide type 10A vaccine 0.025 MG/ML / pneumococcal capsular polysaccharide type 11A vaccine 0.025 MG/ML / pneumococcal capsular polysaccharide type 12F vaccine 0.025	acetaminophen 500 MG Oral Tablet, 82,783 (23.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
							MG/ML / ... Injection [Pneumovax 23], 112,878 (35.10%)	
4	-	-	sulfamethizole 500 MG Oral Tablet, 5,997 (7.40%)	influenza B virus antigen Injectable Suspension [Afluria], 14,650 (10.00%)	simvastatin 40 MG Oral Tablet, 29,933 (14.50%)	aspirin 75 MG Oral Tablet, 32,859 (12.40%)	Influenza A virus / Influenza B virus Injectable Suspension [VAXIGRIP], 92,470 (28.80%)	0.5 ML influenza A virus (H1N1) antigen 0.03 MG/ML Injectable Suspension [VAXIGRIP], 48,191 (13.40%)
5	-	-	penicillin V, 5,755 (7.20%)	penicillin V 654 MG Oral Tablet, 14,309 (9.80%)	aspirin 75 MG Oral Tablet, 27,973 (13.60%)	ibuprofen 400 MG Oral Tablet, 32,566 (12.30%)	influenza B virus antigen Injectable Suspension [INFLUVAC], 79,357 (24.70%)	amlodipine 5 MG Oral Tablet, 37,533 (10.40%)
6	-	-	Glycyrrhiza glabra extract, 4,370 (5.40%)	aspirin 75 MG Oral Tablet, 11,722 (8.00%)	penicillin V 750 MG Oral Tablet, 20,951 (10.20%)	simvastatin 40 MG Oral Tablet, 30,892 (11.60%)	amlodipine 5 MG Oral Tablet, 39,316 (12.20%)	losartan potassium 50 MG Oral Tablet, 36,181 (10.10%)
7	-	-	Opium 1 MG/ML Oral Solution, 4,370 (5.40%)	sulfamethizole 500 MG Oral Tablet, 11,680 (8.00%)	tramadol hydrochloride 50 MG Oral Capsule, 18,218 (8.80%)	penicillin V 750 MG Oral Tablet, 26,714 (10.10%)	ibuprofen 400 MG Oral Tablet, 38,997 (12.10%)	acetaminophen 665 MG Extended Release Oral Tablet, 35,697 (9.90%)
8	-	-	camphor, 4,370 (5.40%)	ibuprofen 600 MG Oral Tablet, 10,524 (7.20%)	ibuprofen 400 MG Oral Tablet, 17,520 (8.50%)	amlodipine 5 MG Oral Tablet, 26,711 (10.10%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 36,793 (11.40%)	losartan potassium 100 MG Oral Tablet, 35,152 (9.80%)
9	-	-	opium, 4,370 (5.40%)	tramadol hydrochloride 50	penicillin V 654 MG Oral Tablet, 17,430 (8.50%)	Potassium Chloride 750 MG Extended	pantoprazole 40 MG Delayed	atorvastatin 40 MG Oral Tablet, 32,116 (8.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
				MG Oral Capsule, 9,997 (6.80%)		Release Oral Tablet, 23,473 (8.80%)	Release Oral Tablet, 35,470 (11.00%)	
10	-	-	tramadol hydrochloride 50 MG Oral Capsule, 4,043 (5.00%)	ibuprofen 400 MG Oral Tablet, 9,597 (6.60%)	Amlodipine 5 MG Oral Tablet Box of 100, 16,234 (7.90%)	pantoprazole 40 MG Delayed Release Oral Tablet, 22,223 (8.40%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 34,150 (10.60%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension [Spikevax], 30,003 (8.30%)
DK-DHR	**Non-HRT users**							
1	-	-	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 38,960 (10.00%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 61,694 (14.10%)	influenza B virus antigen Injectable Suspension [Afluria], 87,651 (17.80%)	acetaminophen 500 MG Oral Tablet, 154,364 (28.10%)	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injection, 444,283 (75.70%)	Tozinameran 0.1 MG/ML [Comirnaty], 113,974 (18.90%)
2	-	-	penicillin V 750 MG Oral Tablet, 28,429 (7.30%)	acetaminophen 500 MG Oral Tablet, 41,457 (9.50%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 67,957 (13.80%)	influenza B virus antigen Injectable Suspension [Afluria], 93,402 (17.00%)	acetaminophen 500 MG Oral Tablet, 173,734 (29.60%)	acetaminophen 500 MG Oral Tablet, 102,925 (17.00%)
3	-	-	acetaminophen 500 MG Oral Tablet, 26,500 (6.80%)	influenza B virus antigen Injectable Suspension [Afluria], 38,115 (8.70%)	simvastatin 40 MG Oral Tablet, 60,195 (12.20%)	ibuprofen 400 MG Oral Tablet, 57,897 (10.60%)	0.5 ML pneumococcal capsular polysaccharide type 10A vaccine 0.025 MG/ML / pneumococcal capsular polysaccharide type 11A vaccine 0.025 MG/ML /	influenza A virus (H1N1) antigen / influenza A virus (H3N2) antigen / influenza B virus antigen Prefilled Syringe, 70,560 (11.70%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
							pneumococcal capsular polysaccharide type 12F vaccine 0.025 MG/ML / ... Injection [Pneumovax 23], 110,906 (18.90%)	
4	-	-	penicillin V, 23,109 (5.90%)	penicillin V 750 MG Oral Tablet, 36,502 (8.30%)	acetaminophen 500 MG Oral Tablet, 54,684 (11.10%)	bendroflumethiazide 2.5 MG / potassium chloride 500 MG Oral Tablet, 57,173 (10.40%)	Influenza A virus / Influenza B virus Injectable Suspension [VAXIGRIP], 108,628 (18.50%)	0.5 ML influenza A virus (H1N1) antigen 0.03 MG/ML Injectable Suspension [VAXIGRIP], 64,304 (10.60%)
5	-	-	Potassium Chloride 750 MG Extended Release Oral Tablet, 18,309 (4.70%)	penicillin V 654 MG Oral Tablet, 35,593 (8.10%)	aspirin 75 MG Oral Tablet, 52,255 (10.60%)	simvastatin 40 MG Oral Tablet, 51,869 (9.50%)	influenza B virus antigen Injectable Suspension [INFLUVAC], 92,330 (15.70%)	amlodipine 5 MG Oral Tablet, 47,763 (7.90%)
6	-	-	sulfamethizole 500 MG Oral Tablet, 18,237 (4.70%)	aspirin 75 MG Oral Tablet, 30,133 (6.90%)	penicillin V 750 MG Oral Tablet, 42,973 (8.70%)	aspirin 75 MG Oral Tablet, 47,586 (8.70%)	ibuprofen 400 MG Oral Tablet, 65,038 (11.10%)	losartan potassium 100 MG Oral Tablet, 45,225 (7.50%)
7	-	-	furosemide 40 MG Oral Tablet, 16,301 (4.20%)	ibuprofen 600 MG Oral Tablet, 26,661 (6.10%)	penicillin V 654 MG Oral Tablet, 35,808 (7.30%)	penicillin V 750 MG Oral Tablet, 47,110 (8.60%)	amlodipine 5 MG Oral Tablet, 54,527 (9.30%)	losartan potassium 50 MG Oral Tablet, 44,897 (7.40%)
8	-	-	Penicillin V 1000000 UNT Oral Tablet Box of 20, 15,986 (4.10%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 23,185 (5.30%)	ibuprofen 400 MG Oral Tablet, 34,071 (6.90%)	amlodipine 5 MG Oral Tablet, 43,966 (8.00%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML, 53,164 (9.10%)	atorvastatin 40 MG Oral Tablet, 43,602 (7.20%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
9	-	-	camphor, 15,721 (4.00%)	simvastatin 40 MG Oral Tablet, 23,162 (5.30%)	Amlodipine 5 MG Oral Tablet Box of 100, 33,758 (6.80%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 37,402 (6.80%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 49,486 (8.40%)	acetaminophen 665 MG Extended Release Oral Tablet, 34,425 (5.70%)
10	-	-	Glycyrrhiza glabra extract, 15,718 (4.00%)	ibuprofen 400 MG Oral Tablet, 22,631 (5.20%)	tramadol hydrochloride 50 MG Oral Capsule, 32,821 (6.70%)	pantoprazole 40 MG Delayed Release Oral Tablet, 30,176 (5.50%)	losartan potassium 50 MG Oral Tablet, 45,191 (7.70%)	Potassium Chloride 750 MG Extended Release Oral Tablet, 34,418 (5.70%)
IQVIA DA Germany	**HRT users**							
1	-	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 43 (3.50%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 85 (2.40%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 127 (1.60%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 187 (0.90%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 932 (2.30%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 2,733 (4.40%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 1,939 (3.10%)
2	-	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 29 (2.40%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 83 (2.30%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 121 (1.50%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 147 (0.70%)	8000 MG Fosfomycin 0.704 MG/MG Oral Solution [Monuril] Box of 1 by Pierre Fabre, 461 (1.10%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 1,590 (2.50%)	Chlorhexidine / Dexamethasone / Nystatin Topical Ointment [Nystalocal], 1,038 (1.60%)
3	-	Acetaminophen 500 MG Oral Tablet [PARACETAMOL RATIOPHARM] Box of 30 by Ratiopharm, 25 (2.00%)	Clotrimazole 1000 MG Vaginal Tablet [Kadefungin] Box of 1 by Dr. Kade, 58 (1.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 66 (0.80%)	Clotrimazole Vaginal Suppository [Canifug], 132 (0.60%)	Chlorhexidine / Dexamethasone / Nystatin Topical Ointment [Nystalocal], 334 (0.80%)	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free,	Amdinocillin Pivoxil 400 MG Oral Tablet Box of 9, 719 (1.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
							0.5 mL (non-US), 805 (1.30%)	
4	-	Acetylcysteine 200 MG Oral Tablet [Fluimucil] Box of 20 by Zambon, 22 (1.80%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 42 (1.20%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 50 by Novartis, 60 (0.80%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 50 by Novartis, 126 (0.60%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 244 (0.60%)	Chlorhexidine / Dexamethasone / Nystatin Topical Ointment [Nystalocal], 708 (1.10%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 691 (1.10%)
5	-	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 21 (1.70%)	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 40 (1.10%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 57 (0.70%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 114 (0.50%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 229 (0.60%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 617 (1.00%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 600 (0.90%)
6	-	Acetaminophen 500 MG / Codeine 30 MG Oral Tablet [Gelonida] Box of 20 by Pfizer, 20 (1.60%)	Black Cohosh Extract / ST. JOHN'S WORT EXTRACT Oral Tablet [Remifemin], 39 (1.10%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 55 (0.70%)	Cholecalciferol 500 UNT Oral Tablet [Vigantoletten] Box of 90 by Mylan, 112 (0.50%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 220 (0.60%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 426 (0.70%)	FLUPREDNIDENE / Miconazole Topical Cream [Decoderm], 448 (0.70%)
7	-	Calcium 500 MG / monofluorophosphate 38 MG Chewable Tablet [Tridin] Box of 100 by Meda, 19 (1.50%)	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 36 (1.00%)	Clotrimazole 800 MG Vaginal Tablet [Kadefungin] Box of 1 by Dr. Kade, 50 (0.60%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 103 (0.50%)	Metronidazole 1000 MG Vaginal Tablet [Arilin] Box of 2 by Wolff Bielefeld, 219 (0.50%)	influenza virus vaccine, unspecified formulation, 419 (0.70%)	8000 MG Fosfomycin 0.704 MG/MG Oral Powder [Fosfomycin Aristo] Box of 1 by Aristo, 445 (0.70%)
8	-	Camphor / CRATAEGUS LAEVIGATA FRUIT Oral Solution	Diclofenac 50 MG Disintegrating Oral Tablet [Voltaren]	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning]	Metronidazole 1000 MG Vaginal Tablet [Arilin] Box of 2 by	8000 MG Fosfomycin 0.704 MG/MG Oral Powder [Fosfomycin	8000 MG Fosfomycin 0.704 MG/MG Oral Powder [Fosfomycin	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning]

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
		[Korodin], 18 (1.50%)	Box of 20 by Novartis, 36 (1.00%)	Box of 100 by Sanofi, 50 (0.60%)	Wolff Bielefeld, 95 (0.40%)	Aristo] Box of 1 by Aristo, 193 (0.50%)	Aristo] Box of 1 by Aristo, 381 (0.60%)	Box of 100 by Sanofi, 436 (0.70%)
9	-	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 18 (1.50%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 35 (1.00%)	Metoprolol 100 MG Extended Release Oral Tablet [Beloc] Box of 100 by Astrazeneca, 48 (0.60%)	Lactobacillus acidophilus 1000 MG Vaginal Tablet Box of 6 by Chiesi, 91 (0.40%)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A, 190 (0.50%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 364 (0.60%)	Fosfomycin 3000 MG Oral Solution Box of 1, 431 (0.70%)
10	-	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 17 (1.40%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 32 (0.90%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 47 (0.60%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 91 (0.40%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 187 (0.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 336 (0.50%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 428 (0.70%)
IQVIA DA Germany	**Non-HRT users**							
1	-	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 442 (1.30%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 554 (0.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 1,486 (0.50%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 2,862 (0.40%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 16,167 (1.30%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 83,021 (5.00%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 41,210 (3.40%)
2	-	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 335 (1.00%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 490 (0.50%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 1,404 (0.50%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 2,068 (0.30%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 7,622 (0.60%)	Cholecalciferol 20 UNT Oral Capsule [Dekristol] Box of 50 by Mibe, 34,397 (2.00%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 22,306 (1.80%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
3	-	Acetaminophen 500 MG Oral Tablet [PARACETAMOL RATIOPHARM] Box of 30 by Ratiopharm, 259 (0.80%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 294 (0.30%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 871 (0.30%)	101000 MG Diclofenac 0.0116 MG/MG Topical Gel [Voltaren] Box of 1 by Glaxosmithkline, 2,037 (0.30%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 5,627 (0.40%)	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL (non-US), 22,967 (1.40%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 18,871 (1.50%)
4	-	myrtol 300 MG Oral Capsule [Gelomyrtol] Box of 20 by G.Pohl-Boskamp Kg, 257 (0.80%)	Aspirin 100 MG Oral Tablet Box of 100 by Ratiopharm, 254 (0.20%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 843 (0.30%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 2,031 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 5,454 (0.40%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 16,460 (1.00%)	Dipyrone 500 MG Oral Tablet Box of 50 by Sanofi, 15,853 (1.30%)
5	-	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin] Box of 1, 238 (0.70%)	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 245 (0.20%)	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 671 (0.20%)	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 50 by Novartis, 1,765 (0.20%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 5,435 (0.40%)	Dipyrone 500 MG Oral Tablet [Novaminsulfon 1a Pharma] Box of 50 by 1 A, 14,952 (0.90%)	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100 by 1 A, 14,649 (1.20%)
6	-	levothyroxine 0.1 MG Oral Tablet [Euthyrox] Box of 100 by Mylan, 213 (0.60%)	Diclofenac 50 MG Disintegrating Oral Tablet [Voltaren] Box of 20 by Novartis, 243 (0.20%)	levothyroxine 0.05 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 629 (0.20%)	Ibuprofen 600 MG Extended Release Oral Tablet [Ibu 1a Pharma] Box of 20 by 1 A, 1,732 (0.20%)	Ibuprofen 600 MG Extended Release Oral Tablet [Ibu 1a Pharma] Box of 20 by 1 A, 5,206 (0.40%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 13,053 (0.80%)	Amlodipine 5 MG Oral Tablet [Amlodipin 1a Pharma] Box of 100 by 1 A, 13,961 (1.10%)
7	-	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin]	15000 MG dihydrocodeine 0.01 MG/MG Oral Solution [Paracodin]	Diclofenac 75 MG Oral Capsule [Voltaren] Box of 20	Budesonide / formoterol Dry Powder Inhaler	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100	Ramipril 5 MG Oral Tablet [Ramipril 1a Pharma] Box of 100	Beclomethasone / formoterol Dry Powder Inhaler

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
		Box of 1 by Mylan, 190 (0.60%)	Box of 1, 238 (0.20%)	by Novartis, 625 (0.20%)	[Symbicort], 1,685 (0.20%)	by 1 A, 4,909 (0.40%)	by 1 A, 10,830 (0.70%)	[Foster], 12,984 (1.10%)
8	-	Aspirin 100 MG Oral Tablet [Ass Ratiopharm] Box of 100 by Ratiopharm, 189 (0.60%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 206 (0.20%)	Metoprolol 100 MG Extended Release Oral Tablet [Beloc] Box of 100 by Astrazeneca, 585 (0.20%)	myrtol 300 MG Oral Capsule [Gelomyrtol] Box of 20 by G.Pohl-Boskamp Kg, 1,578 (0.20%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 4,639 (0.40%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 10,810 (0.70%)	candesartan 16 MG Oral Tablet [Candesartan 1a Pharma] Box of 98 by 1 A, 12,227 (1.00%)
9	-	levothyroxine 0.15 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 182 (0.50%)	30 ML Metoclopramide 0.133 MG/ML Oral Solution [Paspertin] Box of 1 by Mylan, 202 (0.20%)	Phenprocoumon 3 MG Oral Tablet [Marcumar] Box of 100 by Roche, 552 (0.20%)	Ibuprofen 600 MG Oral Tablet [Ibu 1a Pharma] Box of 50 by 1 A, 1,564 (0.20%)	Aspirin 100 MG Oral Tablet [Ass 1a Pharma] Box of 100 by 1 A, 4,564 (0.40%)	levothyroxine 0.075 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 10,145 (0.60%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 11,834 (1.00%)
10	-	Glyburide 3.5 MG Oral Tablet [Euglucon] Box of 120 by Sanofi, 171 (0.50%)	myrtol 300 MG Oral Capsule [Gelomyrtol] Box of 20 by G.Pohl-Boskamp Kg, 169 (0.20%)	Metoprolol 50 MG Oral Tablet [Beloc] Box of 100 by Astrazeneca, 545 (0.20%)	Metoprolol 100 MG Extended Release Oral Tablet [Metohexal] Box of 100 by Novartis, 1,556 (0.20%)	Ramipril 5 MG Oral Tablet [Ramilich] Box of 100 by Sanofi, 4,292 (0.30%)	levothyroxine 0.1 MG Oral Tablet [L Thyroxin Henning] Box of 100 by Sanofi, 9,758 (0.60%)	pantoprazole 40 MG Oral Tablet [Pantoprazol - 1a Pharma] Box of 100 by 1 A, 11,441 (0.90%)
BIFAP	**HRT users**							
1	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 602 (34.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 14,529 (43.80%)	acetaminophen, 27,508 (42.20%)	influenza virus vaccine, unspecified formulation, 48,863 (53.70%)	influenza virus vaccine, unspecified formulation, 102,721 (39.40%)
2	-	-	-	acetaminophen, 535 (30.90%)	acetaminophen, 13,962 (42.10%)	omeprazole 20 MG Delayed Release Oral Capsule, 24,936 (38.30%)	SARS-COV-2 (COVID-19) vaccine, UNSPECIFIED, 45,779 (50.30%)	acetaminophen, 95,606 (36.70%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
3	-	-	-	influenza virus vaccine, unspecified formulation, 430 (24.90%)	ibuprofen 600 MG Oral Tablet, 10,098 (30.40%)	influenza virus vaccine, unspecified formulation, 21,116 (32.40%)	acetaminophen, 36,093 (39.60%)	omeprazole 20 MG Delayed Release Oral Capsule, 65,895 (25.30%)
4	-	-	-	ibuprofen 600 MG Oral Tablet, 366 (21.20%)	influenza virus vaccine, unspecified formulation, 9,264 (27.90%)	lorazepam 1 MG Oral Tablet, 12,822 (19.70%)	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein, 31,990 (35.10%)	calcifediol, 61,160 (23.50%)
5	-	-	-	acetaminophen 650 MG Oral Tablet, 305 (17.60%)	acetylcysteine, 6,998 (21.10%)	ibuprofen 600 MG Oral Tablet, 12,666 (19.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 31,620 (34.70%)	dipyrone, 42,984 (16.50%)
6	-	-	-	codeine, 264 (15.30%)	lorazepam 1 MG Oral Tablet, 6,543 (19.70%)	dipyrone, 11,753 (18.00%)	dipyrone, 20,324 (22.30%)	lorazepam 1 MG Oral Tablet, 36,232 (13.90%)
7	-	-	-	lorazepam 1 MG Oral Tablet, 254 (14.70%)	codeine, 5,947 (17.90%)	azithromycin 500 MG Oral Tablet, 9,367 (14.40%)	calcifediol, 19,303 (21.20%)	ibuprofen 600 MG Oral Tablet, 25,274 (9.70%)
8	-	-	-	acetylcysteine, 242 (14.00%)	dipyrone, 5,291 (15.90%)	codeine, 8,677 (13.30%)	lorazepam 1 MG Oral Tablet, 18,259 (20.10%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 23,913 (9.20%)
9	-	-	-	ibuprofen 3 MG/ML Oral Suspension, 189 (10.90%)	cloperastine, 3,882 (11.70%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 7,854 (12.10%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 11,202 (12.30%)	dexketoprofen 25 MG Oral Tablet, 22,376 (8.60%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	-	-	dipyrone, 181 (10.50%)	ibuprofen, 3,704 (11.20%)	dexketoprofen 25 MG Oral Tablet, 7,479 (11.50%)	fosfomycin 3000 MG Granules for Oral Solution, 10,946 (12.00%)	cholecalciferol, 22,295 (8.60%)
BIFAP	**Non-HRT users**							
1	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 35,844 (24.10%)	omeprazole 20 MG Delayed Release Oral Capsule, 305,358 (32.00%)	acetaminophen, 540,179 (32.40%)	SARS-COV-2 (COVID-19) vaccine, UNSPECIFIED, 1,446,177 (45.00%)	influenza virus vaccine, unspecified formulation, 1,060,059 (28.90%)
2	-	-	-	influenza virus vaccine, unspecified formulation, 33,499 (22.50%)	acetaminophen, 281,752 (29.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 486,984 (29.20%)	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein, 1,149,701 (35.80%)	acetaminophen, 1,023,168 (27.90%)
3	-	-	-	acetaminophen, 31,060 (20.90%)	influenza virus vaccine, unspecified formulation, 223,863 (23.40%)	influenza virus vaccine, unspecified formulation, 391,636 (23.50%)	influenza virus vaccine, unspecified formulation, 1,085,931 (33.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 709,827 (19.30%)
4	-	-	-	ibuprofen 600 MG Oral Tablet, 25,109 (16.90%)	ibuprofen 600 MG Oral Tablet, 217,522 (22.80%)	ibuprofen 600 MG Oral Tablet, 249,675 (15.00%)	acetaminophen, 982,175 (30.60%)	calcifediol, 660,737 (18.00%)
5	-	-	-	acetaminophen 650 MG Oral Tablet, 18,691 (12.60%)	acetylcysteine, 124,827 (13.10%)	dipyrone, 242,031 (14.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 823,672 (25.60%)	dipyrone, 466,998 (12.70%)
6	-	-	-	codeine, 15,127 (10.20%)	dipyrone, 105,240 (11.00%)	lorazepam 1 MG Oral Tablet, 197,950 (11.90%)	dipyrone, 551,909 (17.20%)	lorazepam 1 MG Oral Tablet, 343,258 (9.30%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
7	-	-	-	lorazepam 1 MG Oral Tablet, 14,324 (9.60%)	lorazepam 1 MG Oral Tablet, 100,645 (10.50%)	azithromycin 500 MG Oral Tablet, 152,835 (9.20%)	calcifediol, 514,065 (16.00%)	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein, 301,500 (8.20%)
8	-	-	-	acetylcysteine, 13,706 (9.20%)	codeine, 98,855 (10.30%)	codeine, 146,791 (8.80%)	lorazepam 1 MG Oral Tablet, 386,602 (12.00%)	ibuprofen 600 MG Oral Tablet, 271,882 (7.40%)
9	-	-	-	dipyrone, 12,193 (8.20%)	bromazepam, 76,224 (8.00%)	dexketoprofen 25 MG Oral Tablet, 137,439 (8.20%)	dexketoprofen 25 MG Oral Tablet, 299,826 (9.30%)	dexketoprofen 25 MG Oral Tablet, 237,214 (6.50%)
10	-	-	-	bromazepam, 10,678 (7.20%)	simvastatin 20 MG Oral Tablet, 72,401 (7.60%)	amoxicillin, 133,547 (8.00%)	ibuprofen 600 MG Oral Tablet, 298,764 (9.30%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 234,130 (6.40%)
SIDIAP	**HRT users**							
1	-	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 3,873 (44.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 21,451 (43.80%)	Influenza, split virus, trivalent, injectable, contains preservative, 33,251 (51.90%)	Influenza, split virus, trivalent, injectable, contains preservative, 39,218 (41.00%)
2	-	-	-	-	ibuprofen 600 MG Oral Tablet, 3,285 (37.70%)	acetaminophen 1000 MG Oral Tablet, 18,625 (38.10%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 28,600 (44.60%)	acetaminophen 1000 MG Oral Tablet, 33,938 (35.50%)
3	-	-	-	-	acetaminophen 1000 MG Oral	Influenza, split virus, trivalent, injectable, contains	acetaminophen 1000 MG Oral	omeprazole 20 MG Delayed Release

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
					Tablet, 2,351 (27.00%)	preservative, 14,690 (30.00%)	Tablet, 25,666 (40.00%)	Oral Capsule, 32,040 (33.50%)
4	-	-	-	-	Influenza, split virus, trivalent, injectable, contains preservative, 2,325 (26.70%)	ibuprofen 600 MG Oral Tablet, 12,162 (24.90%)	omeprazole 20 MG Delayed Release Oral Capsule, 25,636 (40.00%)	dipyrone, 16,783 (17.60%)
5	-	-	-	-	diclofenac sodium 50 MG Delayed Release Oral Tablet, 1,309 (15.00%)	dipyrone, 8,624 (17.60%)	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL (non-US), 23,337 (36.40%)	calcifediol Oral Capsule, 14,490 (15.20%)
6	-	-	-	-	lorazepam 1 MG Oral Tablet, 1,282 (14.70%)	lorazepam 1 MG Oral Tablet, 7,848 (16.00%)	dipyrone, 15,212 (23.70%)	lorazepam 1 MG Oral Tablet, 13,964 (14.60%)
7	-	-	-	-	simvastatin 20 MG Oral Tablet, 1,159 (13.30%)	simvastatin 20 MG Oral Tablet, 6,917 (14.10%)	lorazepam 1 MG Oral Tablet, 10,638 (16.60%)	acetaminophen 650 MG Oral Tablet, 10,582 (11.10%)
8	-	-	-	-	carboxymethylcellulose sodium 5 MG/ML Ophthalmic Solution, 1,007 (11.60%)	diazepam 5 MG Oral Tablet, 5,689 (11.60%)	ibuprofen 600 MG Oral Tablet, 8,003 (12.50%)	simvastatin 20 MG Oral Tablet, 10,211 (10.70%)
9	-	-	-	-	diclofenac sodium 0.01 MG/MG	Calcifediol 0.15 MG/ML Oral	fosfomycin 3000 MG Granules for	acetaminophen 325 MG / tramadol hydrochloride 37.5

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
					Topical Gel, 986 (11.30%)	Solution, 5,285 (10.80%)	Oral Solution, 7,906 (12.30%)	MG Oral Tablet, 10,011 (10.50%)
10	-	-	-	-	dipyrone, 926 (10.60%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 5,111 (10.40%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 7,850 (12.20%)	fosfomycin 3000 MG Granules for Oral Solution, 9,236 (9.70%)
SIDIAP	**Non-HRT users**							
1	-	-	-	-	omeprazole 20 MG Delayed Release Oral Capsule, 142,270 (29.10%)	omeprazole 20 MG Delayed Release Oral Capsule, 173,855 (27.80%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 370,698 (46.10%)	Influenza, split virus, trivalent, injectable, contains preservative, 230,998 (24.90%)
2	-	-	-	-	ibuprofen 600 MG Oral Tablet, 118,126 (24.10%)	acetaminophen 1000 MG Oral Tablet, 150,436 (24.10%)	Influenza, split virus, trivalent, injectable, contains preservative, 260,261 (32.40%)	acetaminophen 1000 MG Oral Tablet, 210,096 (22.60%)
3	-	-	-	-	Influenza, split virus, trivalent, injectable, contains preservative, 85,499 (17.50%)	Influenza, split virus, trivalent, injectable, contains preservative, 113,156 (18.10%)	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL (non-US), 211,528 (26.30%)	omeprazole 20 MG Delayed Release Oral Capsule, 190,858 (20.60%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
4	-	-	-	-	acetaminophen 1000 MG Oral Tablet, 85,280 (17.40%)	ibuprofen 600 MG Oral Tablet, 103,929 (16.60%)	acetaminophen 1000 MG Oral Tablet, 202,970 (25.30%)	dipyrone, 104,423 (11.20%)
5	-	-	-	-	simvastatin 20 MG Oral Tablet, 49,491 (10.10%)	dipyrone, 67,671 (10.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 196,358 (24.40%)	calcifediol Oral Capsule, 89,917 (9.70%)
6	-	-	-	-	diclofenac sodium 50 MG Delayed Release Oral Tablet, 48,261 (9.90%)	lorazepam 1 MG Oral Tablet, 64,258 (10.30%)	dipyrone, 117,122 (14.60%)	lorazepam 1 MG Oral Tablet, 82,529 (8.90%)
7	-	-	-	-	lorazepam 1 MG Oral Tablet, 45,171 (9.20%)	simvastatin 20 MG Oral Tablet, 62,685 (10.00%)	lorazepam 1 MG Oral Tablet, 82,782 (10.30%)	acetaminophen 650 MG Oral Tablet, 69,407 (7.50%)
8	-	-	-	-	acetaminophen 650 MG Oral Tablet, 32,592 (6.70%)	diazepam 5 MG Oral Tablet, 46,649 (7.50%)	ibuprofen 600 MG Oral Tablet, 75,044 (9.30%)	ibuprofen 600 MG Oral Tablet, 69,146 (7.40%)
9	-	-	-	-	dipyrone, 31,827 (6.50%)	naproxen sodium 550 MG Oral Tablet, 42,361 (6.80%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension, 67,652 (8.40%)	simvastatin 20 MG Oral Tablet, 67,504 (7.30%)
10	-	-	-	-	tetanus toxoid vaccine, inactivated, 30,155 (6.20%)	metformin hydrochloride 850 MG Oral Tablet, 40,102 (6.40%)	diazepam 5 MG Oral Tablet, 62,989 (7.80%)	acetaminophen 325 MG / tramadol hydrochloride 37.5 MG Oral Tablet, 60,293 (6.50%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CPRD GOLD	HRT users							
1	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 58 (12.60%)	influenza virus vaccine, unspecified formulation, 2,841 (14.70%)	influenza virus vaccine, unspecified formulation, 13,924 (29.60%)	influenza virus vaccine, unspecified formulation, 33,299 (39.10%)	influenza virus vaccine, unspecified formulation, 48,516 (41.00%)	influenza virus vaccine, unspecified formulation, 47,453 (39.90%)	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL (non-US), 58,409 (55.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 28,058 (23.20%)
2	Influenza, split virus, trivalent, injectable, contains preservative, 38 (8.30%)	amoxicillin 250 MG Oral Capsule, 2,832 (14.70%)	amoxicillin 250 MG Oral Capsule, 5,313 (11.30%)	bendroflumethiazide 2.5 MG Oral Tablet, 12,178 (14.30%)	omeprazole 20 MG Delayed Release Oral Capsule, 19,351 (16.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 25,342 (21.30%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 31,781 (30.30%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension, 27,316 (22.60%)
3	tetanus toxoid vaccine, inactivated, 37 (8.10%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 2,212 (11.50%)	bendroflumethiazide 2.5 MG Oral Tablet, 5,146 (10.90%)	pneumococcal vaccine, unspecified formulation, 9,434 (11.10%)	amoxicillin 500 MG Oral Capsule, 15,820 (13.40%)	amoxicillin 500 MG Oral Capsule, 16,364 (13.80%)	omeprazole 20 MG Delayed Release Oral Capsule, 24,332 (23.20%)	amoxicillin 500 MG Oral Capsule, 14,476 (12.00%)
4	amoxicillin 250 MG Oral Capsule, 36 (7.80%)	ibuprofen 400 MG Oral Tablet, 1,567 (8.10%)	Influenza, split virus, trivalent, injectable, contains preservative, 4,645 (9.90%)	Influenza, split virus, trivalent, injectable, contains preservative, 8,744 (10.30%)	acetaminophen 500 MG Oral Tablet, 14,650 (12.40%)	acetaminophen 500 MG Oral Tablet, 14,271 (12.00%)	acetaminophen 500 MG Oral Tablet, 9,917 (9.50%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 13,980 (11.60%)
5	ibuprofen 400 MG Oral Tablet, 35 (7.60%)	trimethoprim 200 MG Oral Tablet, 1,522 (7.90%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5	amoxicillin 250 MG Oral Capsule, 8,333 (9.80%)	bendroflumethiazide 2.5 MG Oral	trimethoprim 200 MG Oral Tablet, 11,560 (9.70%)	amitriptyline hydrochloride 10	atorvastatin 20 MG Oral Tablet, 13,244 (10.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
			MG Oral Tablet, 4,137 (8.80%)		Tablet, 14,104 (11.90%)		MG Oral Tablet, 8,953 (8.60%)	
6	influenza virus vaccine, unspecified formulation, 33 (7.20%)	Influenza, split virus, trivalent, injectable, contains preservative, 1,404 (7.30%)	trimethoprim 200 MG Oral Tablet, 3,233 (6.90%)	acetaminophen 500 MG Oral Tablet, 7,760 (9.10%)	simvastatin 40 MG Oral Tablet, 12,858 (10.90%)	levothyroxine sodium 0.1 MG Oral Tablet, 9,325 (7.80%)	amlodipine 5 MG Oral Tablet, 8,704 (8.30%)	amlodipine 5 MG Oral Tablet, 11,445 (9.50%)
7	temazepam 10 MG Oral Capsule, 33 (7.20%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 1,078 (5.60%)	ibuprofen 400 MG Oral Tablet, 3,191 (6.80%)	aspirin 75 MG Disintegrating Oral Tablet, 7,267 (8.50%)	trimethoprim 200 MG Oral Tablet, 11,981 (10.10%)	amitriptyline hydrochloride 10 MG Oral Tablet, 9,205 (7.70%)	levothyroxine sodium 0.1 MG Oral Tablet, 8,605 (8.20%)	doxycycline hyclate 100 MG Oral Capsule, 10,909 (9.00%)
8	Albuterol 0.1 MG [Ventolin], 22 (4.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 1,039 (5.40%)	acetaminophen 500 MG Oral Tablet, 2,702 (5.70%)	trimethoprim 200 MG Oral Tablet, 6,959 (8.20%)	aspirin 75 MG Disintegrating Oral Tablet, 10,170 (8.60%)	levothyroxine sodium 0.025 MG Oral Tablet, 9,126 (7.70%)	influenza virus vaccine, unspecified formulation, 8,407 (8.00%)	acetaminophen 500 MG Oral Tablet, 10,753 (8.90%)
9	alginic acid Oral Solution [Gaviscon], 22 (4.80%)	alginic acid Oral Solution [Gaviscon], 956 (5.00%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 2,566 (5.40%)	amoxicillin 500 MG Oral Capsule, 6,947 (8.20%)	Influenza, split virus, trivalent, injectable, contains preservative, 9,244 (7.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 9,080 (7.60%)	Nitrofurantoin 100 MG Extended Release Oral Capsule, 8,271 (7.90%)	amitriptyline hydrochloride 10 MG Oral Tablet, 10,259 (8.50%)
10	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE, 22 (4.80%)	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE, 873 (4.50%)	atenolol 50 MG Oral Tablet, 2,535 (5.40%)	omeprazole 20 MG Delayed Release Oral Capsule, 6,550 (7.70%)	levothyroxine sodium 0.1 MG Oral Tablet, 8,543 (7.20%)	amlodipine 5 MG Oral Tablet, 8,881 (7.50%)	acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet, 8,018 (7.70%)	levothyroxine sodium 0.1 MG Oral Tablet, 9,869 (8.20%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CPRD GOLD	Non-HRT users							
1	tetanus toxoid vaccine, inactivated, 1,293 (9.20%)	influenza virus vaccine, unspecified formulation, 12,943 (13.40%)	influenza virus vaccine, unspecified formulation, 51,747 (26.80%)	influenza virus vaccine, unspecified formulation, 147,838 (31.40%)	influenza virus vaccine, unspecified formulation, 190,719 (31.90%)	influenza virus vaccine, unspecified formulation, 174,116 (31.30%)	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL (non-US), 221,371 (54.80%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension, 67,333 (22.50%)
2	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 1,173 (8.30%)	amoxicillin 250 MG Oral Capsule, 10,296 (10.70%)	bendroflumethiazide 2.5 MG Oral Tablet, 18,407 (9.50%)	bendroflumethiazide 2.5 MG Oral Tablet, 62,166 (13.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 70,099 (11.70%)	omeprazole 20 MG Delayed Release Oral Capsule, 85,872 (15.40%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 104,684 (25.90%)	omeprazole 20 MG Delayed Release Oral Capsule, 53,404 (17.80%)
3	influenza virus vaccine, unspecified formulation, 1,083 (7.70%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5 MG Oral Tablet, 8,878 (9.20%)	amoxicillin 250 MG Oral Capsule, 16,364 (8.50%)	pneumococcal vaccine, unspecified formulation, 41,311 (8.80%)	amoxicillin 500 MG Oral Capsule, 67,412 (11.30%)	amoxicillin 500 MG Oral Capsule, 62,258 (11.20%)	omeprazole 20 MG Delayed Release Oral Capsule, 67,699 (16.80%)	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension, 31,609 (10.60%)
4	amoxicillin 250 MG Oral Capsule, 946 (6.70%)	Influenza, split virus, trivalent, injectable, contains preservative, 6,730 (7.00%)	Influenza, split virus, trivalent, injectable, contains preservative, 14,440 (7.50%)	aspirin 75 MG Disintegrating Oral Tablet, 36,564 (7.80%)	bendroflumethiazide 2.5 MG Oral Tablet, 67,213 (11.20%)	acetaminophen 500 MG Oral Tablet, 50,931 (9.20%)	amlodipine 5 MG Oral Tablet, 30,326 (7.50%)	atorvastatin 20 MG Oral Tablet, 31,287 (10.40%)
5	cefotetan, 825 (5.80%)	ibuprofen 400 MG Oral Tablet, 5,913 (6.10%)	acetaminophen 325 MG / propoxyphene hydrochloride 32.5	amoxicillin 250 MG Oral Capsule, 36,217 (7.70%)	simvastatin 40 MG Oral Tablet, 61,410 (10.30%)	bendroflumethiazide 2.5 MG Oral	acetaminophen 500 MG Oral Tablet, 29,528 (7.30%)	amlodipine 5 MG Oral Tablet, 28,990 (9.70%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
			MG Oral Tablet, 12,941 (6.70%)			Tablet, 40,363 (7.30%)		
6	Influenza, split virus, trivalent, injectable, contains preservative, 797 (5.70%)	bendroflumethiazide 2.5 MG Oral Tablet, 4,747 (4.90%)	ibuprofen 400 MG Oral Tablet, 9,994 (5.20%)	amoxicillin 500 MG Oral Capsule, 33,059 (7.00%)	acetaminophen 500 MG Oral Tablet, 56,213 (9.40%)	amlodipine 5 MG Oral Tablet, 37,897 (6.80%)	influenza virus vaccine, unspecified formulation, 26,654 (6.60%)	amoxicillin 500 MG Oral Capsule, 28,681 (9.60%)
7	ibuprofen 400 MG Oral Tablet, 714 (5.10%)	trimethoprim 200 MG Oral Tablet, 4,742 (4.90%)	acetaminophen 500 MG Oral Tablet, 9,624 (5.00%)	acetaminophen 500 MG Oral Tablet, 32,622 (6.90%)	aspirin 75 MG Disintegrating Oral Tablet, 46,832 (7.80%)	simvastatin 40 MG Oral Tablet, 37,885 (6.80%)	levothyroxine sodium 0.1 MG Oral Tablet, 26,543 (6.60%)	acetaminophen 500 MG Oral Tablet, 24,041 (8.00%)
8	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE, 705 (5.00%)	acetaminophen 500 MG / dihydrocodeine bitartrate 10 MG Oral Tablet, 3,930 (4.10%)	atenolol 50 MG Oral Tablet, 9,524 (4.90%)	diclofenac sodium 50 MG Delayed Release Oral Tablet, 28,661 (6.10%)	trimethoprim 200 MG Oral Tablet, 38,515 (6.40%)	levothyroxine sodium 0.1 MG Oral Tablet, 34,882 (6.30%)	atorvastatin 20 MG Oral Tablet, 25,847 (6.40%)	doxycycline hyclate 100 MG Oral Capsule, 21,435 (7.20%)
9	acetaminophen 500 MG Oral Tablet, 546 (3.90%)	tetanus toxoid vaccine, inactivated, 3,732 (3.90%)	aspirin 75 MG Disintegrating Oral Tablet, 8,646 (4.50%)	Influenza, split virus, trivalent, injectable, contains preservative, 28,126 (6.00%)	amlodipine 5 MG Oral Tablet, 34,719 (5.80%)	trimethoprim 200 MG Oral Tablet, 33,628 (6.00%)	acetaminophen 500 MG / codeine phosphate 30 MG Oral Tablet, 24,397 (6.00%)	folic acid 5 MG Oral Tablet, 20,509 (6.80%)
10	trimethoprim 200 MG Oral Tablet, 530 (3.80%)	influenza virus vaccine, split virus (incl. purified surface antigen)-retired CODE, 3,704 (3.80%)	trimethoprim 200 MG Oral Tablet, 8,625 (4.50%)	omeprazole 20 MG Delayed Release Oral Capsule, 26,371 (5.60%)	levothyroxine sodium 0.1 MG Oral Tablet, 34,532 (5.80%)	levothyroxine sodium 0.025 MG Oral Tablet, 32,878 (5.90%)	amitriptyline hydrochloride 10 MG Oral Tablet, 22,735 (5.60%)	levothyroxine sodium 0.1 MG Oral Tablet, 20,425 (6.80%)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; – = no data available.

Table S6. Comorbidities of postmenopausal women recorded one year prior to the pre-specified calendar date, stratified by HRT use across selected calendar years by data source.

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR	HRT users							
1	-	-	Essential hypertension, 1,064 (1.30%)	Pain, 36,029 (24.60%)	Pain, 59,187 (28.80%)	Pain, 107,969 (40.60%)	Pain, 146,281 (45.50%)	Pain, 176,677 (49.10%)
2	-	-	Primary malignant neoplasm of breast, 825 (1.00%)	Arthritis, 18,719 (12.80%)	Hypercholesterolemia, 48,630 (23.60%)	Hypercholesterolemia, 58,102 (21.90%)	Hypercholesterolemia, 79,229 (24.60%)	Hypercholesterolemia, 109,505 (30.40%)
3	-	-	Cystocele, 709 (0.90%)	Hypercholesterolemia, 14,761 (10.10%)	Esophageal reflux finding, 27,320 (13.30%)	Esophageal reflux finding, 36,173 (13.60%)	Hypertensive disorder, 58,363 (18.10%)	Hypertensive disorder, 82,781 (23.00%)
4	-	-	Urinary incontinence, 683 (0.80%)	Infectious disease, 14,737 (10.10%)	Cystitis, 24,625 (12.00%)	Hypertensive disorder, 28,693 (10.80%)	Esophageal reflux finding, 48,341 (15.00%)	Esophageal reflux finding, 55,182 (15.30%)
5	-	-	Angina pectoris, 628 (0.80%)	Depressive disorder, 12,541 (8.60%)	Infectious disease, 23,285 (11.30%)	Eczema, 28,640 (10.80%)	Cystitis, 39,519 (12.30%)	Osteoporosis, 44,857 (12.50%)
6	-	-	Type 2 diabetes mellitus without complication, 524 (0.70%)	Insomnia, 12,280 (8.40%)	Depressive disorder, 22,894 (11.10%)	Urinary tract infectious disease, 27,470 (10.30%)	Osteoporosis, 33,324 (10.40%)	Cystitis, 43,384 (12.10%)
7	-	-	Dislocations/sprains/strains, 520 (0.70%)	Cystitis, 11,860 (8.10%)	Arthritis, 21,881 (10.60%)	Severe pain, 27,145 (10.20%)	Severe pain, 32,954 (10.20%)	Severe pain, 36,344 (10.10%)
8	-	-	Varicose veins of lower limb without ulcer and without inflammation, 462 (0.60%)	Asthma, 11,127 (7.60%)	Eczema, 19,062 (9.30%)	Depressive disorder, 25,739 (9.70%)	Eczema, 31,545 (9.80%)	Depressive disorder, 35,406 (9.80%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
9	-	-	Uterine leiomyoma, 454 (0.60%)	Eczema, 11,022 (7.50%)	Insomnia, 18,269 (8.90%)	Cystitis, 24,718 (9.30%)	Depressive disorder, 31,165 (9.70%)	Eczema, 35,224 (9.80%)
10	-	-	Osteoarthritis of knee, 453 (0.60%)	Esophageal reflux finding, 9,206 (6.30%)	Hypertensive disorder, 17,942 (8.70%)	Osteoporosis, 24,043 (9.10%)	Hypothyroidism, 26,660 (8.30%)	Hypothyroidism, 32,414 (9.00%)
DK-DHR	**Non-HRT users**							
1	-	-	Primary malignant neoplasm of breast, 5,694 (1.50%)	Pain, 82,254 (18.80%)	Pain, 108,223 (21.90%)	Pain, 174,571 (31.80%)	Pain, 202,782 (34.50%)	Pain, 221,433 (36.60%)
2	-	-	Essential hypertension, 4,582 (1.20%)	Hypercholesterolemia, 37,590 (8.60%)	Hypercholesterolemia, 89,704 (18.20%)	Hypercholesterolemia, 86,673 (15.80%)	Hypercholesterolemia, 102,513 (17.50%)	Hypercholesterolemia, 131,795 (21.80%)
3	-	-	Type 2 diabetes mellitus without complication, 2,736 (0.70%)	Arthritis, 35,834 (8.20%)	Infectious disease, 41,951 (8.50%)	Hypertensive disorder, 47,429 (8.70%)	Hypertensive disorder, 82,092 (14.00%)	Hypertensive disorder, 106,829 (17.70%)
4	-	-	Angina pectoris, 2,458 (0.60%)	Infectious disease, 32,435 (7.40%)	Depressive disorder, 39,008 (7.90%)	Esophageal reflux finding, 42,706 (7.80%)	Esophageal reflux finding, 49,264 (8.40%)	Esophageal reflux finding, 52,545 (8.70%)
5	-	-	Chronic obstructive pulmonary disease, 2,246 (0.60%)	Asthma, 27,330 (6.20%)	Esophageal reflux finding, 36,918 (7.50%)	Eczema, 40,359 (7.40%)	Depressive disorder, 40,876 (7.00%)	Depressive disorder, 41,898 (6.90%)
6	-	-	Dislocations/sprains/strains, 2,153 (0.60%)	Depressive disorder, 25,055 (5.70%)	Hypertensive disorder, 36,770 (7.40%)	Depressive disorder, 38,503 (7.00%)	Severe pain, 40,013 (6.80%)	Hypothyroidism, 41,162 (6.80%)
7	-	-	Fracture of distal end of radius, 1,979 (0.50%)	Eczema, 24,192 (5.50%)	Arthritis, 33,037 (6.70%)	Severe pain, 38,155 (7.00%)	Eczema, 39,253 (6.70%)	Type 2 diabetes mellitus, 40,849 (6.80%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
8	-	-	Sprain of ankle, 1,918 (0.50%)	Insomnia, 22,947 (5.20%)	Asthma, 33,009 (6.70%)	Asthma, 32,604 (5.90%)	Hypothyroidism, 36,597 (6.20%)	Eczema, 39,911 (6.60%)
9	-	-	Seropositive rheumatoid arthritis, 1,728 (0.40%)	Hypertensive disorder, 22,108 (5.00%)	Eczema, 32,563 (6.60%)	Conjunctivitis, 29,966 (5.50%)	Asthma, 36,394 (6.20%)	Osteoporosis, 39,259 (6.50%)
10	-	-	Osteoarthritis of knee, 1,662 (0.40%)	Cystitis, 18,024 (4.10%)	Cystitis, 27,796 (5.60%)	Pneumonia, 29,654 (5.40%)	Osteoporosis, 32,940 (5.60%)	Asthma, 39,039 (6.50%)
IQVIA DA Germany	**HRT users**							
1	-	Perimenopausal disorder, 510 (41.40%)	Perimenopausal disorder, 1,035 (29.00%)	Perimenopausal disorder, 1,805 (22.70%)	Perimenopausal disorder, 2,822 (13.40%)	Perimenopausal disorder, 5,965 (14.80%)	Atrophic vaginitis, 7,658 (12.30%)	Atrophic vaginitis, 10,941 (17.20%)
2	-	Nerve root disorder, 193 (15.70%)	Essential hypertension, 483 (13.50%)	Essential hypertension, 1,242 (15.60%)	Atrophic vaginitis, 2,653 (12.60%)	Atrophic vaginitis, 5,760 (14.30%)	Perimenopausal disorder, 7,231 (11.60%)	Perimenopausal disorder, 10,496 (16.50%)
3	-	Essential hypertension, 170 (13.80%)	Menopausal syndrome, 470 (13.20%)	Noninflammatory disorder of the vagina, 929 (11.70%)	Essential hypertension, 2,192 (10.40%)	Noninflammatory disorder of the vagina, 3,367 (8.30%)	Essential hypertension, 3,926 (6.30%)	Noninflammatory disorder of the vagina, 7,602 (12.00%)
4	-	Bronchitis, 165 (13.40%)	Nerve root disorder, 335 (9.40%)	Menopausal syndrome, 925 (11.60%)	Menopausal syndrome, 1,689 (8.00%)	Essential hypertension, 3,205 (7.90%)	Noninflammatory disorder of the vagina, 3,807 (6.10%)	Essential hypertension, 5,336 (8.40%)
5	-	Menopausal syndrome, 164 (13.30%)	Noninflammatory disorder of the vagina, 302 (8.40%)	Atrophic vaginitis, 756 (9.50%)	Noninflammatory disorder of the vagina, 1,596 (7.60%)	Menopausal syndrome, 2,942 (7.30%)	Menopausal syndrome, 3,400 (5.40%)	Menopausal syndrome, 4,745 (7.50%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
6	-	Acute vaginitis, 95 (7.70%)	Bronchitis, 255 (7.10%)	Nerve root disorder, 606 (7.60%)	Acute vaginitis, 961 (4.60%)	Acute vaginitis, 1,821 (4.50%)	Illness, 2,274 (3.60%)	Illness, 2,932 (4.60%)
7	-	Osteoporosis, 95 (7.70%)	Osteoporosis, 199 (5.60%)	Acute vaginitis, 557 (7.00%)	Nerve root disorder, 802 (3.80%)	Urinary tract infectious disease, 1,259 (3.10%)	Acute vaginitis, 2,137 (3.40%)	Acute vaginitis, 2,644 (4.20%)
8	-	Noninflammatory disorder of the vagina, 84 (6.80%)	Bodily distress disorder, 167 (4.70%)	Illness, 439 (5.50%)	Urinary tract infectious disease, 756 (3.60%)	Lower abdominal pain, 1,245 (3.10%)	Urinary tract infectious disease, 1,908 (3.10%)	Urinary tract infectious disease, 2,605 (4.10%)
9	-	Varicose veins of lower limb without ulcer and without inflammation, 82 (6.70%)	Acute vaginitis, 164 (4.60%)	Bodily distress disorder, 419 (5.30%)	Illness, 722 (3.40%)	Urinary incontinence, 1,204 (3.00%)	Lower abdominal pain, 1,775 (2.90%)	Lower abdominal pain, 2,468 (3.90%)
10	-	Illness, 80 (6.50%)	Illness, 156 (4.40%)	Disorder of endocrine system, 341 (4.30%)	Lower abdominal pain, 617 (2.90%)	Nerve root disorder, 1,167 (2.90%)	Nerve root disorder, 1,474 (2.40%)	Urinary incontinence, 2,022 (3.20%)
IQVIA DA Germany	**Non-HRT users**							
1	-	Essential hypertension, 2,796 (8.40%)	Essential hypertension, 5,779 (5.60%)	Essential hypertension, 18,293 (6.40%)	Essential hypertension, 39,844 (5.50%)	Essential hypertension, 76,386 (6.00%)	Essential hypertension, 100,235 (6.00%)	Essential hypertension, 128,059 (10.40%)
2	-	Nerve root disorder, 2,177 (6.50%)	Nerve root disorder, 3,069 (3.00%)	Nerve root disorder, 8,156 (2.80%)	Nerve root disorder, 21,467 (3.00%)	Nerve root disorder, 40,851 (3.20%)	Illness, 68,159 (4.10%)	Illness, 109,756 (8.90%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
3	-	Bronchitis, 1,889 (5.70%)	Bronchitis, 1,938 (1.90%)	Simple goiter, 4,549 (1.60%)	Osteoarthritis of knee, 10,409 (1.40%)	Acute upper respiratory infection, 23,216 (1.80%)	Nerve root disorder, 62,405 (3.70%)	Acute upper respiratory infection, 75,914 (6.20%)
4	-	Perimenopausal disorder, 1,062 (3.20%)	Perimenopausal disorder, 1,775 (1.70%)	Pure hypercholesterolemia, 4,224 (1.50%)	Type 2 diabetes mellitus, 9,283 (1.30%)	Type 2 diabetes mellitus, 21,206 (1.70%)	Acute upper respiratory infection, 43,507 (2.60%)	Nerve root disorder, 73,077 (6.00%)
5	-	Varicose veins of lower limb without ulcer and without inflammation, 929 (2.80%)	Simple goiter, 1,615 (1.60%)	Hyperlipidemia, 3,958 (1.40%)	Neck pain, 9,264 (1.30%)	Osteoarthritis of knee, 20,366 (1.60%)	Disorder of musculoskeletal system, 30,514 (1.80%)	Type 2 diabetes mellitus, 38,892 (3.20%)
6	-	Hyperlipidemia, 818 (2.50%)	Illness, 1,503 (1.40%)	Osteoarthritis of knee, 3,874 (1.40%)	Disorder of musculoskeletal system, 9,172 (1.30%)	Disorder of musculoskeletal system, 20,358 (1.60%)	Type 2 diabetes mellitus, 28,631 (1.70%)	Pure hypercholesterolemia, 38,829 (3.20%)
7	-	Chronic ischemic heart disease, 786 (2.40%)	Hyperlipidemia, 1,316 (1.30%)	Type 2 diabetes mellitus, 3,639 (1.30%)	Pure hypercholesterolemia, 9,071 (1.30%)	Spondylosis, 18,573 (1.50%)	Osteoarthritis of knee, 28,305 (1.70%)	Osteoarthritis of knee, 36,291 (3.00%)
8	-	Simple goiter, 759 (2.30%)	Pure hypercholesterolemia, 1,167 (1.10%)	Neck pain, 3,465 (1.20%)	Spondylosis, 8,853 (1.20%)	Acute bronchitis, 18,183 (1.40%)	Spondylosis, 26,176 (1.60%)	Hypothyroidism, 32,000 (2.60%)
9	-	Illness, 744 (2.20%)	Chronic ischemic heart disease, 1,132 (1.10%)	Varicose veins of lower limb without ulcer and without inflammation, 3,436 (1.20%)	Simple goiter, 8,232 (1.10%)	Neck pain, 17,890 (1.40%)	Neck pain, 25,637 (1.50%)	Disorder of musculoskeletal system, 30,895 (2.50%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	Acute upper respiratory infection, 726 (2.20%)	Varicose veins of lower limb without ulcer and without inflammation, 1,098 (1.00%)	Spondylosis, 3,402 (1.20%)	Low back pain, 7,874 (1.10%)	Pure hypercholesterolemia, 16,864 (1.30%)	Hypothyroidism, 25,305 (1.50%)	Spondylosis, 30,720 (2.50%)
BIFAP	**HRT users**							
1	-	-	-	Common cold, 211 (12.20%)	Common cold, 3,629 (10.90%)	Common cold, 5,518 (8.50%)	Viral upper respiratory tract infection, 6,888 (7.60%)	Common cold, 20,321 (7.80%)
2	-	-	-	Atrophic vaginitis, 188 (10.90%)	Viral upper respiratory tract infection, 2,896 (8.70%)	Viral upper respiratory tract infection, 5,183 (8.00%)	Common cold, 4,650 (5.10%)	Viral upper respiratory tract infection, 19,194 (7.40%)
3	-	-	-	Viral upper respiratory tract infection, 163 (9.40%)	Pharyngitis, 2,627 (7.90%)	Urinary tract infectious disease, 4,771 (7.30%)	Urinary tract infectious disease, 4,512 (5.00%)	Urinary tract infectious disease, 17,657 (6.80%)
4	-	-	-	Pharyngitis, 156 (9.00%)	Urinary tract infectious disease, 2,399 (7.20%)	Pharyngitis, 4,106 (6.30%)	Low back pain, 4,137 (4.50%)	Low back pain, 15,528 (6.00%)
5	-	-	-	Urinary tract infectious disease, 138 (8.00%)	Low back pain, 2,037 (6.10%)	Low back pain, 3,522 (5.40%)	Pain of joint of knee, 3,227 (3.50%)	Atrophic vaginitis, 15,105 (5.80%)
6	-	-	-	Low back pain, 104 (6.00%)	Infectious gastroenteritis, 1,343 (4.00%)	Pain of joint of knee, 2,393 (3.70%)	Acute pharyngitis, 3,035 (3.30%)	Acute pharyngitis, 11,613 (4.50%)
7	-	-	-	Upper respiratory infection, 104 (6.00%)	Pain of joint of knee, 1,225 (3.70%)	Acute bronchitis, 2,072 (3.20%)	Essential hypertension, 2,585 (2.80%)	Essential hypertension, 10,690 (4.10%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
8	-	-	-	Neck pain, 66 (3.80%)	Upper respiratory infection, 1,038 (3.10%)	Acute respiratory infections, 1,788 (2.80%)	Impacted cerumen, 2,204 (2.40%)	Viral disease, 10,293 (4.00%)
9	-	-	-	Influenza, 63 (3.60%)	Atrophic vaginitis, 993 (3.00%)	Influenza, 1,665 (2.60%)	Acute bronchitis, 2,043 (2.20%)	Vitamin D deficiency, 9,679 (3.70%)
10	-	-	-	Pain of joint of knee, 60 (3.50%)	Toothache, 990 (3.00%)	Impacted cerumen, 1,638 (2.50%)	Vitamin D deficiency, 1,921 (2.10%)	Cough, 9,500 (3.60%)
BIFAP	**Non-HRT users**							
1	-	-	-	Common cold, 12,987 (8.70%)	Common cold, 69,770 (7.30%)	Viral upper respiratory tract infection, 83,422 (5.00%)	Common cold, 179,612 (5.60%)	Common cold, 220,820 (6.00%)
2	-	-	-	Viral upper respiratory tract infection, 10,619 (7.10%)	Viral upper respiratory tract infection, 58,770 (6.20%)	Common cold, 83,408 (5.00%)	Viral upper respiratory tract infection, 131,081 (4.10%)	Viral upper respiratory tract infection, 185,315 (5.00%)
3	-	-	-	Pharyngitis, 8,695 (5.80%)	Pharyngitis, 52,725 (5.50%)	Urinary tract infectious disease, 71,742 (4.30%)	Low back pain, 129,251 (4.00%)	Low back pain, 161,680 (4.40%)
4	-	-	-	Low back pain, 7,497 (5.00%)	Low back pain, 45,288 (4.70%)	Pharyngitis, 70,834 (4.20%)	Acute pharyngitis, 119,332 (3.70%)	Essential hypertension, 136,323 (3.70%)
5	-	-	-	Upper respiratory infection, 6,110 (4.10%)	Urinary tract infectious disease, 40,840 (4.30%)	Low back pain, 61,307 (3.70%)	Essential hypertension, 112,408 (3.50%)	Vitamin D deficiency, 132,683 (3.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
6	-	-	-	Urinary tract infectious disease, 5,999 (4.00%)	Infectious gastroenteritis, 33,370 (3.50%)	Acute respiratory infections, 57,813 (3.50%)	Urinary tract infectious disease, 84,120 (2.60%)	Urinary tract infectious disease, 121,964 (3.30%)
7	-	-	-	Influenza, 5,120 (3.40%)	Upper respiratory infection, 28,163 (3.00%)	Pain of joint of knee, 45,187 (2.70%)	Vitamin D deficiency, 71,135 (2.20%)	Acute pharyngitis, 121,893 (3.30%)
8	-	-	-	Pain of joint of knee, 4,008 (2.70%)	Pain of joint of knee, 26,762 (2.80%)	Acute bronchitis, 35,414 (2.10%)	Pain of joint of knee, 65,879 (2.00%)	Viral disease, 107,320 (2.90%)
9	-	-	-	Hypertensive disorder, 3,809 (2.60%)	Hypertensive disorder, 20,520 (2.10%)	Influenza, 33,027 (2.00%)	Neck pain, 60,895 (1.90%)	Acute bronchitis, 96,708 (2.60%)
10	-	-	-	Infectious gastroenteritis, 3,691 (2.50%)	Acute respiratory infections, 20,335 (2.10%)	Impacted cerumen, 32,924 (2.00%)	Acute bronchitis, 59,752 (1.90%)	Cough, 96,588 (2.60%)
SIDIAP	**HRT users**							
1	-	-	-	-	Common cold, 493 (5.70%)	Common cold, 5,534 (11.30%)	Urinary tract infectious disease, 6,612 (10.30%)	Urinary tract infectious disease, 13,395 (14.00%)
2	-	-	-	-	Low back pain, 325 (3.70%)	Urinary tract infectious disease, 3,872 (7.90%)	Common cold, 5,288 (8.20%)	Common cold, 12,109 (12.70%)
3	-	-	-	-	Atrophic vaginitis, 305 (3.50%)	Traumatic or non-traumatic injury, 2,670 (5.50%)	Low back pain, 3,383 (5.30%)	Acute cystitis, 6,624 (6.90%)
4	-	-	-	-	Menopausal syndrome, 276 (3.20%)	Low back pain, 2,563 (5.20%)	Traumatic or non-traumatic injury, 2,738 (4.30%)	Traumatic or non-traumatic injury, 6,572 (6.90%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
5	-	-	-	-	Multiple joint pain, 272 (3.10%)	Acute pharyngitis, 2,553 (5.20%)	Acute lower respiratory tract infection, 2,577 (4.00%)	Low back pain, 6,527 (6.80%)
6	-	-	-	-	Anxiety disorder, 267 (3.10%)	Cough, 2,203 (4.50%)	Cough, 2,552 (4.00%)	Acute lower respiratory tract infection, 5,957 (6.20%)
7	-	-	-	-	Urinary tract infectious disease, 261 (3.00%)	Acute lower respiratory tract infection, 2,102 (4.30%)	Abdominal pain, 2,453 (3.80%)	Inflammatory dermatosis, 5,858 (6.10%)
8	-	-	-	-	Acute pharyngitis, 257 (3.00%)	Multiple joint pain, 2,093 (4.30%)	Dizziness and giddiness, 2,369 (3.70%)	Cough, 5,586 (5.80%)
9	-	-	-	-	Neck pain, 232 (2.70%)	Abdominal pain, 1,864 (3.80%)	Acute pharyngitis, 2,167 (3.40%)	Vitamin D deficiency, 5,431 (5.70%)
10	-	-	-	-	Essential hypertension, 217 (2.50%)	Dizziness and giddiness, 1,730 (3.50%)	Coronavirus infection, 2,098 (3.30%)	Abdominal pain, 5,023 (5.30%)
SIDIAP	**Non-HRT users**							
1	-	-	-	-	Common cold, 18,775 (3.80%)	Common cold, 44,575 (7.10%)	Common cold, 45,264 (5.60%)	Common cold, 81,764 (8.80%)
2	-	-	-	-	Low back pain, 12,814 (2.60%)	Urinary tract infectious disease, 24,219 (3.90%)	Urinary tract infectious disease, 41,157 (5.10%)	Urinary tract infectious disease, 60,765 (6.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
3	-	-	-	-	Essential hypertension, 11,788 (2.40%)	Low back pain, 24,128 (3.90%)	Low back pain, 31,142 (3.90%)	Low back pain, 47,050 (5.10%)
4	-	-	-	-	Anxiety disorder, 10,950 (2.20%)	Traumatic or non-traumatic injury, 23,955 (3.80%)	Traumatic or non-traumatic injury, 26,197 (3.30%)	Traumatic or non-traumatic injury, 45,398 (4.90%)
5	-	-	-	-	Multiple joint pain, 10,345 (2.10%)	Multiple joint pain, 20,330 (3.20%)	Coronavirus infection, 22,431 (2.80%)	Vitamin D deficiency, 36,483 (3.90%)
6	-	-	-	-	Pure hypercholesterolemia, 9,046 (1.90%)	Acute pharyngitis, 18,250 (2.90%)	Anxiety disorder, 20,724 (2.60%)	Acute lower respiratory tract infection, 35,765 (3.90%)
7	-	-	-	-	Neck pain, 8,479 (1.70%)	Cough, 17,349 (2.80%)	Acute lower respiratory tract infection, 20,154 (2.50%)	Cough, 35,762 (3.90%)
8	-	-	-	-	Acute pharyngitis, 8,356 (1.70%)	Acute lower respiratory tract infection, 16,772 (2.70%)	Cough, 20,088 (2.50%)	Anxiety disorder, 31,831 (3.40%)
9	-	-	-	-	Disorder of lipid metabolism, 8,111 (1.70%)	Anxiety disorder, 16,669 (2.70%)	Dizziness and giddiness, 18,871 (2.40%)	Inflammatory dermatosis, 31,811 (3.40%)
10	-	-	-	-	Impacted cerumen, 7,599 (1.60%)	Acute bronchitis, 15,243 (2.40%)	Abdominal pain, 17,993 (2.20%)	Viral disease, 31,501 (3.40%)
CPRD GOLD	**HRT users**							

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
1	Atrophic vaginitis, 69 (15.00%)	Backache, 1,373 (7.10%)	Cough, 2,962 (6.30%)	Cough, 7,096 (8.30%)	Cough, 11,301 (9.60%)	Cough, 13,011 (10.90%)	Cough, 7,091 (6.80%)	Cough, 8,083 (6.70%)
2	Acute lower respiratory tract infection, 37 (8.10%)	Cough, 1,252 (6.50%)	Low back pain, 2,061 (4.40%)	Allergic reaction to drug, 4,251 (5.00%)	Allergic reaction to drug, 6,167 (5.20%)	Asthma not disturbing sleep, 6,391 (5.40%)	Asthma not limiting activities, 4,163 (4.00%)	Cervical smear - human papillomavirus negative, 7,409 (6.10%)
3	Urinary tract infectious disease, 31 (6.80%)	Upper respiratory infection, 1,207 (6.30%)	Upper respiratory infection, 1,998 (4.20%)	Low back pain, 3,635 (4.30%)	Pain of knee region, 5,772 (4.90%)	Asthma not limiting activities, 6,295 (5.30%)	Asthma not disturbing sleep, 4,091 (3.90%)	Clinical finding, 4,417 (3.60%)
4	Depressive disorder, 29 (6.30%)	Acute lower respiratory tract infection, 1,194 (6.20%)	Acute lower respiratory tract infection, 1,951 (4.10%)	Upper respiratory infection, 3,585 (4.20%)	Abdominal pain, 4,783 (4.00%)	Pain of knee region, 5,746 (4.80%)	Pain of knee region, 3,330 (3.20%)	Asthma not disturbing sleep, 4,340 (3.60%)
5	Upper respiratory infection, 29 (6.30%)	Urinary tract infectious disease, 1,064 (5.50%)	Urinary tract infectious disease, 1,930 (4.10%)	Pain of knee region, 3,536 (4.20%)	Eruption, 4,685 (4.00%)	Abdominal pain, 4,820 (4.00%)	Clinical finding, 3,293 (3.10%)	Asthma not limiting activities, 4,265 (3.50%)
6	Cough, 27 (5.90%)	Depressive disorder, 1,010 (5.20%)	Chest pain, 1,551 (3.30%)	Abdominal pain, 3,358 (3.90%)	Low back pain, 4,525 (3.80%)	Allergic reaction to drug, 4,772 (4.00%)	Abdominal pain, 2,956 (2.80%)	Pain of knee region, 3,769 (3.10%)
7	Abdominal pain, 25 (5.40%)	Atrophic vaginitis, 848 (4.40%)	Abdominal pain, 1,514 (3.20%)	Eruption, 3,094 (3.60%)	Backache, 4,366 (3.70%)	Eruption, 4,343 (3.70%)	Allergic reaction to drug, 2,882 (2.80%)	Asthma daytime symptoms, 3,171 (2.60%)
8	Allergic reaction to drug, 22 (4.80%)	Abdominal pain, 843 (4.40%)	Depressive disorder, 1,484 (3.10%)	Backache, 3,000 (3.50%)	Upper respiratory infection, 4,198 (3.60%)	Backache, 4,185 (3.50%)	Asthma daytime symptoms, 2,820 (2.70%)	Allergic reaction to drug, 3,138 (2.60%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
9	Disorder of back, 21 (4.60%)	Sinusitis, 772 (4.00%)	Backache, 1,435 (3.10%)	Lower respiratory tract infection, 2,905 (3.40%)	Lower respiratory tract infection, 3,972 (3.40%)	Low back pain, 3,910 (3.30%)	Eruption, 2,376 (2.30%)	Abdominal pain, 3,089 (2.60%)
10	Eruption, 20 (4.40%)	Indigestion, 693 (3.60%)	Indigestion, 1,347 (2.90%)	Chest pain, 2,827 (3.30%)	Shoulder pain, 3,870 (3.30%)	Clinical finding, 3,895 (3.30%)	Backache, 2,331 (2.20%)	Skin lesion, 2,805 (2.30%)
CPRD GOLD	**Non-HRT users**							
1	Acute lower respiratory tract infection, 787 (5.60%)	Cough, 4,727 (4.90%)	Cough, 8,599 (4.40%)	Cough, 26,285 (5.60%)	Cough, 42,318 (7.10%)	Cough, 45,052 (8.10%)	Cough, 20,850 (5.20%)	Cough, 15,403 (5.10%)
2	Cough, 687 (4.90%)	Acute lower respiratory tract infection, 4,725 (4.90%)	Acute lower respiratory tract infection, 5,860 (3.00%)	Allergic reaction to drug, 17,845 (3.80%)	Allergic reaction to drug, 20,862 (3.50%)	Asthma not disturbing sleep, 22,930 (4.10%)	Asthma not disturbing sleep, 11,727 (2.90%)	Cervical smear - human papillomavirus negative, 13,989 (4.70%)
3	Upper respiratory infection, 609 (4.30%)	Upper respiratory infection, 4,464 (4.60%)	Upper respiratory infection, 5,603 (2.90%)	All pulses present in right lower limb, 14,446 (3.10%)	Pain of knee region, 20,862 (3.50%)	Asthma not limiting activities, 22,586 (4.10%)	Asthma not limiting activities, 11,659 (2.90%)	Asthma not disturbing sleep, 8,215 (2.70%)
4	Urinary tract infectious disease, 438 (3.10%)	Backache, 4,054 (4.20%)	Low back pain, 5,043 (2.60%)	All pulses present in left lower limb, 14,434 (3.10%)	10g monofilament sensation L foot normal, 16,430 (2.80%)	Pain of knee region, 19,853 (3.60%)	Pain of knee region, 9,481 (2.40%)	Asthma not limiting activities, 8,030 (2.70%)
5	Allergic reaction to drug, 428 (3.00%)	Urinary tract infectious disease, 2,741 (2.80%)	Essential hypertension, 4,725 (2.50%)	Essential hypertension, 14,025 (3.00%)	10g monofilament sensation R foot normal, 16,302 (2.70%)	Allergic reaction to drug, 14,849 (2.70%)	Clinical finding, 8,669 (2.10%)	10g monofilament sensation R foot normal, 7,856 (2.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
6	Depressive disorder, 392 (2.80%)	Depressive disorder, 2,593 (2.70%)	Urinary tract infectious disease, 4,455 (2.30%)	Upper respiratory infection, 13,510 (2.90%)	Eruption, 16,205 (2.70%)	Eruption, 14,408 (2.60%)	Asthma daytime symptoms, 7,813 (1.90%)	10g monofilament sensation L foot normal, 7,854 (2.60%)
7	Hypertensive disorder, 381 (2.70%)	Hypertensive disorder, 2,500 (2.60%)	Chest pain, 4,105 (2.10%)	Pain of knee region, 11,988 (2.50%)	All pulses present in right lower limb, 15,698 (2.60%)	Backache, 13,955 (2.50%)	Allergic reaction to drug, 7,186 (1.80%)	Clinical finding, 7,314 (2.40%)
8	Bronchitis, 353 (2.50%)	Essential hypertension, 2,346 (2.40%)	Backache, 3,791 (2.00%)	Lower respiratory tract infection, 11,697 (2.50%)	All pulses present in left lower limb, 15,653 (2.60%)	Asthma daytime symptoms, 13,728 (2.50%)	10g monofilament sensation L foot normal, 7,103 (1.80%)	Pain of knee region, 7,110 (2.40%)
9	Indigestion, 352 (2.50%)	Eruption, 2,345 (2.40%)	Osteoarthritis, 3,786 (2.00%)	Increased blood pressure, 10,964 (2.30%)	Lower respiratory tract infection, 15,228 (2.60%)	Abdominal pain, 13,398 (2.40%)	10g monofilament sensation R foot normal, 7,083 (1.80%)	All pulses present in right foot, 6,401 (2.10%)
10	Sinusitis, 346 (2.50%)	Abdominal pain, 2,338 (2.40%)	Hypertensive disorder, 3,578 (1.90%)	Low back pain, 10,964 (2.30%)	Low back pain, 15,186 (2.50%)	Clinical finding, 13,243 (2.40%)	Abdominal pain, 6,776 (1.70%)	All pulses present in left foot, 6,362, (2.10%)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; ; N = number of individuals; – = no data available.

Table S11. Comorbidities of postmenopausal women recorded at the pre-specified calendar date, stratified by HRT use across selected calendar years by data source.

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR	HRT users							
1	-	-	Infiltrating duct carcinoma of breast, 10 (0.00%)	Pain, 565 (0.40%)	Pain, 1,016 (0.50%)	Pain, 1,647 (0.60%)	Pain, 2,178 (0.70%)	Pain, 2,723 (0.80%)
2	-	-	End-stage renal disease, 6 (0.00%)	Asthma, 276 (0.20%)	Hypercholesterolemia, 680 (0.30%)	Hypercholesterolemia, 796 (0.30%)	Hypercholesterolemia, 1,016 (0.30%)	Hypercholesterolemia, 1,965 (0.60%)
3	-	-	Basal cell carcinoma, NOS, of overlapping lesion of skin, 5 (0.00%)	Hypercholesterolemia, 236 (0.20%)	Depressive disorder, 432 (0.20%)	Severe pain, 532 (0.20%)	Hypertensive disorder, 883 (0.30%)	Hypertensive disorder, 1,487 (0.40%)
4	-	-	-	Depressive disorder, 233 (0.20%)	Esophageal reflux finding, 385 (0.20%)	Depressive disorder, 497 (0.20%)	Severe pain, 592 (0.20%)	Type 2 diabetes mellitus, 882 (0.20%)
5	-	-	-	Severe pain, 220 (0.10%)	Asthma, 379 (0.20%)	Esophageal reflux finding, 399 (0.10%)	Esophageal reflux finding, 572 (0.20%)	Depressive disorder, 742 (0.20%)
6	-	-	-	Arthritis, 204 (0.10%)	Severe pain, 375 (0.20%)	Hypertensive disorder, 393 (0.10%)	Depressive disorder, 514 (0.20%)	Esophageal reflux finding, 724 (0.20%)
7	-	-	-	Insomnia, 179 (0.10%)	Diabetes mellitus, 260 (0.10%)	Osteoporosis, 338 (0.10%)	Asthma, 474 (0.10%)	Osteoporosis, 670 (0.20%)
8	-	-	-	Diabetes mellitus, 145 (0.10%)	Insomnia, 233 (0.10%)	Asthma, 329 (0.10%)	Osteoporosis, 456 (0.10%)	Hypothyroidism, 604 (0.20%)
9	-	-	-	Seasonal allergic rhinitis, 139 (0.10%)	Arthritis, 224 (0.10%)	Diabetes mellitus, 298 (0.10%)	Hypothyroidism, 452 (0.10%)	Asthma, 563 (0.20%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	-	-	Hypertensive disorder, 130 (0.10%)	Hypertensive disorder, 213 (0.10%)	Hypothyroidism, 274 (0.10%)	Chronic obstructive pulmonary disease, 410 (0.10%)	Severe pain, 533 (0.10%)
DK-DHR	**Non-HRT users**							
1	-	-	Infiltrating duct carcinoma of breast, 50 (0.00%)	Pain, 1,284 (0.30%)	Pain, 1,661 (0.30%)	Pain, 2,558 (0.50%)	Pain, 2,829 (0.50%)	Pain, 3,043 (0.50%)
2	-	-	Basal cell carcinoma, NOS, of overlapping lesion of skin, 14 (0.00%)	Asthma, 734 (0.20%)	Hypercholesterolemia, 1,336 (0.30%)	Hypercholesterolemia, 1,181 (0.20%)	Hypercholesterolemia, 1,375 (0.20%)	Hypercholesterolemia, 2,146 (0.30%)
3	-	-	End-stage renal disease, 12 (0.00%)	Hypercholesterolemia, 574 (0.10%)	Asthma, 731 (0.10%)	Depressive disorder, 813 (0.10%)	Hypertensive disorder, 1,292 (0.20%)	Hypertensive disorder, 1,918 (0.30%)
4	-	-	Primary adenocarcinoma of lung, 10 (0.00%)	Diabetes mellitus, 464 (0.10%)	Depressive disorder, 718 (0.10%)	Severe pain, 723 (0.10%)	Type 2 diabetes mellitus, 785 (0.10%)	Type 2 diabetes mellitus, 1,378 (0.20%)
5	-	-	Renal failure syndrome, 10 (0.00%)	Depressive disorder, 461 (0.10%)	Diabetes mellitus, 701 (0.10%)	Hypertensive disorder, 650 (0.10%)	Depressive disorder, 732 (0.10%)	Obesity, 1,039 (0.20%)
6	-	-	Infiltrating lobular carcinoma of breast, 9 (0.00%)	Severe pain, 387 (0.10%)	Severe pain, 554 (0.10%)	Asthma, 631 (0.10%)	Asthma, 717 (0.10%)	Depressive disorder, 801 (0.10%)
7	-	-	Adenocarcinoma of rectum, 8 (0.00%)	Insomnia, 363 (0.10%)	Esophageal reflux finding, 524 (0.10%)	Esophageal reflux finding, 545 (0.10%)	Severe pain, 700 (0.10%)	Asthma, 779 (0.10%)
8	-	-	Endometrioid adenocarcinoma,	Arthritis, 356 (0.10%)	Hypertensive disorder, 518 (0.10%)	Diabetes mellitus, 540 (0.10%)	Esophageal reflux finding, 627 (0.10%)	Hypothyroidism, 761 (0.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
			NOS, of fundus uteri, 8 (0.00%)					
9	-	-	Adenocarcinoma, NOS, of sigmoid colon, 7 (0.00%)	Hypertensive disorder, 329 (0.10%)	Hypothyroidism, 426 (0.10%)	Hypothyroidism, 493 (0.10%)	Chronic obstructive pulmonary disease, 610 (0.10%)	Esophageal reflux finding, 730 (0.10%)
10	-	-	Primary malignant neoplasm of breast, 7 (0.00%)	Seasonal allergic rhinitis, 325 (0.10%)	Arthritis, 393 (0.10%)	Chronic obstructive pulmonary disease, 455 (0.10%)	Hypothyroidism, 605 (0.10%)	Osteoporosis, 593 (0.10%)
IQVIA DA Germany	**HRT users**							
1	-	-	-	Essential hypertension, 12 (0.10%)	Essential hypertension, 62 (0.30%)	Essential hypertension, 56 (0.10%)	Essential hypertension, 83 (0.10%)	Perimenopausal disorder, 288 (0.40%)
2	-	-	-	Perimenopausal disorder, 11 (0.10%)	Perimenopausal disorder, 25 (0.10%)	Perimenopausal disorder, 49 (0.10%)	Perimenopausal disorder, 71 (0.10%)	Essential hypertension, 221 (0.30%)
3	-	-	-	Menopausal syndrome, 8 (0.10%)	Menopausal syndrome, 18 (0.10%)	Atrophic vaginitis, 24 (0.10%)	Atrophic vaginitis, 45 (0.10%)	Acquired absence of genital organ, 131 (0.20%)
4	-	-	-	Nerve root disorder, 6 (0.10%)	Mixed hyperlipidemia, 17 (0.10%)	Menopausal syndrome, 24 (0.10%)	Type 2 diabetes mellitus, 24 (0.00%)	Atrophic vaginitis, 94 (0.10%)
5	-	-	-	Sleep disorder, 5 (0.10%)	Gastro-esophageal reflux disease with esophagitis, 13 (0.10%)	Acquired absence of genital organ, 19 (0.00%)	Chronic pain, 23 (0.00%)	Menopausal syndrome, 66 (0.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
6	-	-	-	-	Osteoarthritis of knee, 12 (0.10%)	Primary malignant neoplasm of breast, 12 (0.00%)	Pure hypercholesterolemia, 22 (0.00%)	Primary malignant neoplasm of breast, 62 (0.10%)
7	-	-	-	-	Osteoporosis, 12 (0.10%)	Type 2 diabetes mellitus, 12 (0.00%)	Menopausal syndrome, 21 (0.00%)	Illness, 56 (0.10%)
8	-	-	-	-	Bodily distress disorder, 11 (0.00%)	Pure hypercholesterolemia, 11 (0.00%)	Chronic ischemic heart disease, 18 (0.00%)	Type 2 diabetes mellitus, 56 (0.10%)
9	-	-	-	-	Varicose veins of lower limb without ulcer and without inflammation, 11 (0.00%)	Simple goiter, 11 (0.00%)	Simple goiter, 13 (0.00%)	Hypothyroidism, 52 (0.10%)
10	-	-	-	-	Chronic ischemic heart disease, 9 (0.00%)	Hypothyroidism, 10 (0.00%)	Osteoporosis, 12 (0.00%)	Obesity, 50 (0.10%)
IQVIA DA Germany	**Non-HRT users**							
1	-	Essential hypertension, 8 (0.00%)	Essential hypertension, 22 (0.00%)	Essential hypertension, 281 (0.10%)	Essential hypertension, 1,060 (0.10%)	Essential hypertension, 1,876 (0.10%)	Essential hypertension, 2,476 (0.10%)	Essential hypertension, 3,800 (0.30%)
2	-	Impacted cerumen, 6 (0.00%)	Pure hypercholesterolemia, 10 (0.00%)	Nerve root disorder, 72 (0.00%)	Type 2 diabetes mellitus, 231 (0.00%)	Nerve root disorder, 624 (0.00%)	Nerve root disorder, 1,035 (0.10%)	Illness, 2,457 (0.20%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
3	-	Otitis externa, 6 (0.00%)	Simple goiter, 9 (0.00%)	Simple goiter, 68 (0.00%)	Hyperlipidemia, 189 (0.00%)	Type 2 diabetes mellitus, 458 (0.00%)	Illness, 722 (0.00%)	Nerve root disorder, 1,353 (0.10%)
4	-	Spondylosis, 5 (0.00%)	Neck pain, 8 (0.00%)	Pure hypercholesterolemia, 57 (0.00%)	Nerve root disorder, 176 (0.00%)	Pure hypercholesterolemia, 441 (0.00%)	Chronic obstructive pulmonary disease, 642 (0.00%)	Type 2 diabetes mellitus, 1,138 (0.10%)
5	-	-	Obesity, 7 (0.00%)	Type 2 diabetes mellitus, 55 (0.00%)	Simple goiter, 170 (0.00%)	Chronic obstructive pulmonary disease, 436 (0.00%)	Pure hypercholesterolemia, 624 (0.00%)	Osteoarthritis of knee, 1,044 (0.10%)
6	-	-	Spondylosis, 6 (0.00%)	Hyperlipidemia, 48 (0.00%)	Osteoarthritis of knee, 158 (0.00%)	Neck pain, 396 (0.00%)	Osteoarthritis of knee, 584 (0.00%)	Pure hypercholesterolemia, 967 (0.10%)
7	-	-	Deviated nasal septum, 5 (0.00%)	Asthma, 42 (0.00%)	Pure hypercholesterolemia, 147 (0.00%)	Osteoarthritis of knee, 390 (0.00%)	Type 2 diabetes mellitus, 583 (0.00%)	Hypothyroidism, 962 (0.10%)
8	-	-	Disorder of ear, 5 (0.00%)	Gastro-esophageal reflux disease with esophagitis, 31 (0.00%)	Asthma, 140 (0.00%)	Simple goiter, 322 (0.00%)	Neck pain, 575 (0.00%)	Obesity, 678 (0.10%)
9	-	-	Osteoarthritis of knee, 5 (0.00%)	Osteoarthritis of knee, 31 (0.00%)	Osteoporosis, 111 (0.00%)	Spondylosis, 317 (0.00%)	Gastro-esophageal reflux disease with esophagitis, 536 (0.00%)	Neck pain, 662 (0.00%)
10	-	-	-	Osteoporosis, 31 (0.00%)	Chronic obstructive pulmonary disease, 108 (0.00%)	Osteoporosis, 311 (0.00%)	Chronic pain, 527 (0.00%)	Chronic pain, 646 (0.00%)
BIFAP	**HRT users**							

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
1	-	-	-	-	Common cold, 9 (0.00%)	Urinary tract infectious disease, 22 (0.00%)	Urinary tract infectious disease, 16 (0.00%)	Low back pain, 86 (0.00%)
2	-	-	-	-	Low back pain, 9 (0.00%)	Pharyngitis, 12 (0.00%)	Vitamin D deficiency, 13 (0.00%)	COVID-19, 83 (0.00%)
3	-	-	-	-	Urinary tract infectious disease, 9 (0.00%)	Inflammatory dermatosis, 11 (0.00%)	Acute urinary tract infection, 11 (0.00%)	Urinary tract infectious disease, 62 (0.00%)
4	-	-	-	-	Atrophic vaginitis, 8 (0.00%)	Common cold, 9 (0.00%)	Essential hypertension, 11 (0.00%)	Common cold, 57 (0.00%)
5	-	-	-	-	Pharyngitis, 8 (0.00%)	Low back pain, 9 (0.00%)	Pain of hip region, 11 (0.00%)	Essential hypertension, 54 (0.00%)
6	-	-	-	-	Pain of joint of knee, 7 (0.00%)	Pain of joint of knee, 9 (0.00%)	Pain of joint of knee, 10 (0.00%)	Atrophic vaginitis, 52 (0.00%)
7	-	-	-	-	Peripheral venous insufficiency, 6 (0.00%)	Insect sting, 8 (0.00%)	Low back pain, 9 (0.00%)	Viral disease, 48 (0.00%)
8	-	-	-	-	Viral upper respiratory tract infection, 6 (0.00%)	Insomnia, 8 (0.00%)	Toothache, 9 (0.00%)	Viral upper respiratory tract infection, 42 (0.00%)
9	-	-	-	-	Acute cystitis, 5 (0.00%)	Osteoporosis, 8 (0.00%)	Acute cystitis, 8 (0.00%)	Coronavirus infection, 40 (0.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	-	-	-	Hypertensive disorder, 5 (0.00%)	Toothache, 8 (0.00%)	Hyperlipidemia, 8 (0.00%)	Neck pain, 40 (0.00%)
BIFAP	**Non-HRT users**							
1	-	-	-	Low back pain, 35 (0.00%)	Urinary tract infectious disease, 160 (0.00%)	Urinary tract infectious disease, 282 (0.00%)	Essential hypertension, 652 (0.00%)	Low back pain, 869 (0.00%)
2	-	-	-	Urinary tract infectious disease, 31 (0.00%)	Low back pain, 157 (0.00%)	Low back pain, 203 (0.00%)	Low back pain, 522 (0.00%)	Essential hypertension, 863 (0.00%)
3	-	-	-	Common cold, 23 (0.00%)	Pharyngitis, 135 (0.00%)	Insect sting, 176 (0.00%)	Urinary tract infectious disease, 333 (0.00%)	COVID-19, 709 (0.00%)
4	-	-	-	Pain of joint of knee, 19 (0.00%)	Common cold, 128 (0.00%)	Pharyngitis, 176 (0.00%)	Vitamin D deficiency, 321 (0.00%)	Common cold, 597 (0.00%)
5	-	-	-	Pharyngitis, 19 (0.00%)	Pain of joint of knee, 103 (0.00%)	Pain of joint of knee, 168 (0.00%)	Pain of joint of knee, 300 (0.00%)	Vitamin D deficiency, 566 (0.00%)
6	-	-	-	Varicose veins of lower extremity, 19 (0.00%)	Viral upper respiratory tract infection, 98 (0.00%)	Common cold, 144 (0.00%)	Neck pain, 229 (0.00%)	Urinary tract infectious disease, 521 (0.00%)
7	-	-	-	Viral upper respiratory tract infection, 16 (0.00%)	Insect sting, 94 (0.00%)	Disorder of teeth AND/OR supporting structures, 133 (0.00%)	Impacted cerumen, 228 (0.00%)	Viral disease, 517 (0.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
8	-	-	-	Peripheral venous insufficiency, 14 (0.00%)	Peripheral venous insufficiency, 68 (0.00%)	Impacted cerumen, 128 (0.00%)	Abdominal pain, 224 (0.00%)	Pain of joint of knee, 497 (0.00%)
9	-	-	-	Neck pain, 13 (0.00%)	Varicose veins of lower extremity, 68 (0.00%)	Viral upper respiratory tract infection, 123 (0.00%)	Hyperlipidemia, 223 (0.00%)	Viral upper respiratory tract infection, 491 (0.00%)
10	-	-	-	Obesity, 12 (0.00%)	Dyslipidemia, 66 (0.00%)	Onychomycosis, 104 (0.00%)	Type 2 diabetes mellitus, 207 (0.00%)	Impacted cerumen, 456 (0.00%)
SIDIAP	**HRT users**							
1	-	-	-	-	-	Urinary tract infectious disease, 13 (0.00%)	Urinary tract infectious disease, 33 (0.00%)	Urinary tract infectious disease, 55 (0.10%)
2	-	-	-	-	-	Multiple joint pain, 12 (0.00%)	Low back pain, 13 (0.00%)	COVID-19, 43 (0.00%)
3	-	-	-	-	-	Traumatic or non-traumatic injury, 12 (0.00%)	Impacted cerumen, 12 (0.00%)	Common cold, 37 (0.00%)
4	-	-	-	-	-	Impacted cerumen, 7 (0.00%)	Traumatic or non-traumatic injury, 12 (0.00%)	Traumatic or non-traumatic injury, 28 (0.00%)
5	-	-	-	-	-	Low back pain, 7 (0.00%)	Abdominal pain, 9 (0.00%)	Inflammatory dermatosis, 27 (0.00%)
6	-	-	-	-	-	Primary insomnia, 7 (0.00%)	Dizziness and giddiness, 8 (0.00%)	Dizziness and giddiness, 24 (0.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
7	-	-	-	-	-	Abdominal pain, 6 (0.00%)	Inflammatory dermatosis, 8 (0.00%)	Viral disease, 24 (0.00%)
8	-	-	-	-	-	Acute conjunctivitis, 6 (0.00%)	Anxiety disorder, 7 (0.00%)	Acute cystitis, 23 (0.00%)
9	-	-	-	-	-	Common cold, 6 (0.00%)	Dyspnea, 7 (0.00%)	Low back pain, 22 (0.00%)
10	-	-	-	-	-	Obesity, 6 (0.00%)	Headache, 7 (0.00%)	Cough, 19 (0.00%)
SIDIAP	**Non-HRT users**							
1	-	-	-	-	Low back pain, 48 (0.00%)	Low back pain, 118 (0.00%)	Urinary tract infectious disease, 172 (0.00%)	COVID-19, 346 (0.00%)
2	-	-	-	-	Anxiety disorder, 46 (0.00%)	Traumatic or non-traumatic injury, 117 (0.00%)	Traumatic or non-traumatic injury, 101 (0.00%)	Common cold, 326 (0.00%)
3	-	-	-	-	Essential hypertension, 44 (0.00%)	Urinary tract infectious disease, 100 (0.00%)	Anxiety disorder, 93 (0.00%)	Urinary tract infectious disease, 270 (0.00%)
4	-	-	-	-	Impacted cerumen, 38 (0.00%)	Multiple joint pain, 84 (0.00%)	Low back pain, 91 (0.00%)	Traumatic or non-traumatic injury, 240 (0.00%)
5	-	-	-	-	Multiple joint pain, 38 (0.00%)	Impacted cerumen, 76 (0.00%)	Dizziness and giddiness, 83 (0.00%)	Low back pain, 209 (0.00%)
6	-	-	-	-	Nontraumatic rotator cuff tear, 36 (0.00%)	Obesity, 72 (0.00%)	Impacted cerumen, 77 (0.00%)	Viral disease, 149 (0.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
7	-	-	-	-	Pure hypercholesterolemia, 34 (0.00%)	Anxiety disorder, 64 (0.00%)	Abdominal pain, 73 (0.00%)	Anxiety disorder, 147 (0.00%)
8	-	-	-	-	Traumatic or non-traumatic injury, 34 (0.00%)	Dizziness and giddiness, 55 (0.00%)	Pain of knee region, 60 (0.00%)	Inflammatory dermatosis, 140 (0.00%)
9	-	-	-	-	Disorder of lipid metabolism, 31 (0.00%)	Abdominal pain, 54 (0.00%)	Multiple joint pain, 56 (0.00%)	Pain of knee region, 140 (0.00%)
10	-	-	-	-	Osteoporosis, 31 (0.00%)	Acute pharyngitis, 52 (0.00%)	Inflammatory dermatosis, 51 (0.00%)	Impacted cerumen, 120 (0.00%)
CPRD GOLD	**HRT users**							
1	-	-	Allergic reaction to drug, 6 (0.00%)	Pain of knee region, 25 (0.00%)	Pain of knee region, 40 (0.00%)	Cough, 42 (0.00%)	Evaluation finding, 15 (0.00%)	Cough, 54 (0.00%)
2	-	-	-	Eruption, 22 (0.00%)	Finding of pulse rate, 37 (0.00%)	Clinical finding, 29 (0.00%)	Asthma not disturbing sleep, 14 (0.00%)	Clinical finding, 39 (0.00%)
3	-	-	-	Cough, 21 (0.00%)	Skin lesion, 35 (0.00%)	Asthma not disturbing sleep, 25 (0.00%)	Pain of knee region, 12 (0.00%)	Cervical smear - human papillomavirus negative, 33 (0.00%)
4	-	-	-	Backache, 19 (0.00%)	Eruption, 28 (0.00%)	Low back pain, 23 (0.00%)	Asthma not limiting activities, 11 (0.00%)	Evaluation finding, 24 (0.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
5	-	-	-	Low back pain, 19 (0.00%)	Allergic reaction to drug, 27 (0.00%)	Allergic reaction to drug, 22 (0.00%)	Allergic reaction to drug, 9 (0.00%)	Abdominal pain, 21 (0.00%)
6	-	-	-	Abdominal pain, 18 (0.00%)	Cough, 27 (0.00%)	Asthma not limiting activities, 22 (0.00%)	Asthma daytime symptoms, 9 (0.00%)	Pain of knee region, 16 (0.00%)
7	-	-	-	Wax in ear canal, 18 (0.00%)	Low back pain, 24 (0.00%)	Backache, 20 (0.00%)	Asthma never causes daytime symptoms, 9 (0.00%)	Asthma not limiting activities, 15 (0.00%)
8	-	-	-	Allergic reaction to drug, 16 (0.00%)	Abdominal pain, 23 (0.00%)	Pain of knee region, 20 (0.00%)	Clinical finding, 9 (0.00%)	Shoulder pain, 15 (0.00%)
9	-	-	-	Headache, 16 (0.00%)	Backache, 22 (0.00%)	Eruption, 19 (0.00%)	Chest pain, 7 (0.00%)	Low back pain, 14 (0.00%)
10	-	-	-	Neck pain, 15 (0.00%)	Shoulder pain, 22 (0.00%)	Abdominal pain, 18 (0.00%)	Skin lesion, 7 (0.00%)	Skin lesion, 14 (0.00%)
CPRD GOLD	**Non-HRT users**							
1	-	Acute lower respiratory tract infection, 5 (0.00%)	Abdominal pain, 7 (0.00%)	Allergic reaction to drug, 102 (0.00%)	Cough, 122 (0.00%)	Cough, 138 (0.00%)	Asthma not disturbing sleep, 50 (0.00%)	Cough, 95 (0.00%)
2	-	Cough, 5 (0.00%)	Essential hypertension, 7 (0.00%)	Cough, 89 (0.00%)	Pain of knee region, 106 (0.00%)	Pain of knee region, 88 (0.00%)	Asthma not limiting activities, 46 (0.00%)	Clinical finding, 71 (0.00%)
3	-	-	Essential hypertension, 7 (0.00%)	Essential hypertension, 84 (0.00%)	Clinical finding, 98 (0.00%)	Clinical finding, 85 (0.00%)	Evaluation finding, 35 (0.00%)	Cervical smear - human papillomavirus negative, 53 (0.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
4	-	-	Type 2 diabetes mellitus, 7 (0.00%)	Clinical finding, 66 (0.00%)	Eruption, 98 (0.00%)	Asthma not limiting activities, 81 (0.00%)	Allergic reaction to drug, 32 (0.00%)	Pain of knee region, 46 (0.00%)
5	-	-	Cystitis, 6 (0.00%)	Eruption, 66 (0.00%)	Allergic reaction to drug, 90 (0.00%)	Asthma not disturbing sleep, 77 (0.00%)	Shoulder pain, 32 (0.00%)	Asthma not disturbing sleep, 43 (0.00%)
6	-	-	Ischemic heart disease, 6 (0.00%)	Pain of knee region, 58 (0.00%)	All pulses present in left lower limb, 79 (0.00%)	Allergic reaction to drug, 74 (0.00%)	Clinical finding, 30 (0.00%)	Asthma not limiting activities, 42 (0.00%)
7	-	-	Osteoarthritis, 6 (0.00%)	Increased blood pressure, 56 (0.00%)	All pulses present in right lower limb, 76 (0.00%)	Eruption, 70 (0.00%)	Asthma daytime symptoms, 29 (0.00%)	Evaluation finding, 37 (0.00%)
8	-	-	Pain of knee region, 6 (0.00%)	Chest pain, 48 (0.00%)	10g monofilament sensation L foot normal, 75 (0.00%)	Abdominal pain, 67 (0.00%)	Pain of knee region, 27 (0.00%)	Asthma daytime symptoms, 35 (0.00%)
9	-	-	Urinary tract infectious disease, 6 (0.00%)	Low back pain, 48 (0.00%)	10g monofilament sensation R foot normal, 75 (0.00%)	All pulses present in left lower limb, 67 (0.00%)	Asthma never causes daytime symptoms, 23 (0.00%)	10g monofilament sensation R foot normal, 32 (0.00%)
10	-	-	Cough, 5 (0.00%)	Abdominal pain, 46 (0.00%)	Backache, 75 (0.00%)	All pulses present in right lower limb, 67 (0.00%)	Skin lesion, 23 (0.00%)	10g monofilament sensation L foot normal, 31 (0.00%)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; – = no data available.

Table S12. Comorbidities of postmenopausal women recorded 1 year post the pre-specified calendar date, stratified by HRT use across selected calendar years by data source.

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
DK-DHR	HRT users							
1	-	-	Essential hypertension, 1,261 (1.60%)	Pain, 39,693 (27.10%)	Pain, 61,438 (29.80%)	Pain, 114,583 (43.10%)	Pain, 149,278 (46.40%)	Pain, 100,784 (28.00%)
2	-	-	Primary malignant neoplasm of breast, 970 (1.20%)	Hypercholesterolemia, 20,556 (14.00%)	Hypercholesterolemia, 52,264 (25.40%)	Hypercholesterolemia, 61,391 (23.10%)	Hypercholesterolemia, 83,084 (25.80%)	Hypercholesterolemia, 81,733 (22.70%)
3	-	-	Angina pectoris, 710 (0.90%)	Arthritis, 18,216 (12.40%)	Esophageal reflux finding, 30,509 (14.80%)	Esophageal reflux finding, 38,669 (14.60%)	Hypertensive disorder, 64,280 (20.00%)	Hypertensive disorder, 61,046 (17.00%)
4	-	-	Type 2 diabetes mellitus without complication, 604 (0.80%)	Infectious disease, 15,249 (10.40%)	Infectious disease, 25,720 (12.50%)	Hypertensive disorder, 35,785 (13.50%)	Esophageal reflux finding, 49,997 (15.60%)	Esophageal reflux finding, 33,477 (9.30%)
5	-	-	Urinary incontinence, 603 (0.80%)	Depressive disorder, 14,398 (9.80%)	Cystitis, 24,497 (11.90%)	Urinary tract infectious disease, 31,268 (11.80%)	Cystitis, 40,064 (12.50%)	Osteoporosis, 29,478 (8.20%)
6	-	-	Chronic obstructive pulmonary disease, 569 (0.70%)	Insomnia, 13,945 (9.50%)	Depressive disorder, 23,679 (11.50%)	Severe pain, 29,683 (11.20%)	Severe pain, 37,532 (11.70%)	Depressive disorder, 26,154 (7.30%)
7	-	-	Dislocations/sprains /strains, 545 (0.70%)	Cystitis, 12,846 (8.80%)	Arthritis, 21,439 (10.40%)	Eczema, 28,421 (10.70%)	Osteoporosis, 35,425 (11.00%)	Hypothyroidism, 24,761 (6.90%)
8	-	-	Osteoarthritis of knee, 540 (0.70%)	Asthma, 12,168 (8.30%)	Eczema, 19,361 (9.40%)	Depressive disorder, 26,563 (10.00%)	Depressive disorder, 31,355 (9.80%)	Type 2 diabetes mellitus, 22,145 (6.20%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
9	-	-	Cystocele, 499 (0.60%)	Esophageal reflux finding, 12,037 (8.20%)	Hypertensive disorder, 18,866 (9.20%)	Osteoporosis, 26,244 (9.90%)	Eczema, 31,169 (9.70%)	Asthma, 20,334 (5.70%)
10	-	-	Sprain of ankle, 472 (0.60%)	Eczema, 11,898 (8.10%)	Insomnia, 17,819 (8.70%)	Cystitis, 23,085 (8.70%)	Hypothyroidism, 27,302 (8.50%)	Severe pain, 18,269 (5.10%)
DK-DHR	**Non-HRT users**							
1	-	-	Primary malignant neoplasm of breast, 5,936 (1.50%)	Pain, 92,551 (21.10%)	Pain, 113,132 (22.90%)	Pain, 186,909 (34.10%)	Pain, 207,877 (35.40%)	Pain, 118,375 (19.60%)
2	-	-	Essential hypertension, 5,705 (1.50%)	Hypercholesterolemia, 52,080 (11.90%)	Hypercholesterolemia, 97,753 (19.80%)	Hypercholesterolemia, 93,319 (17.00%)	Hypercholesterolemia, 109,237 (18.60%)	Hypercholesterolemia, 98,612 (16.30%)
3	-	-	Type 2 diabetes mellitus without complication, 3,226 (0.80%)	Arthritis, 36,114 (8.20%)	Infectious disease, 48,463 (9.80%)	Hypertensive disorder, 59,714 (10.90%)	Hypertensive disorder, 91,248 (15.50%)	Hypertensive disorder, 79,526 (13.20%)
4	-	-	Chronic obstructive pulmonary disease, 2,945 (0.80%)	Infectious disease, 34,208 (7.80%)	Esophageal reflux finding, 42,541 (8.60%)	Esophageal reflux finding, 45,928 (8.40%)	Esophageal reflux finding, 52,018 (8.90%)	Type 2 diabetes mellitus, 34,710 (5.70%)
5	-	-	Angina pectoris, 2,696 (0.70%)	Asthma, 30,239 (6.90%)	Depressive disorder, 40,805 (8.30%)	Severe pain, 43,466 (7.90%)	Severe pain, 45,565 (7.80%)	Hypothyroidism, 31,509 (5.20%)
6	-	-	Dislocations/sprains/strains, 2,066 (0.50%)	Depressive disorder, 29,435 (6.70%)	Hypertensive disorder, 38,773 (7.90%)	Eczema, 41,042 (7.50%)	Depressive disorder, 40,685 (6.90%)	Depressive disorder, 30,495 (5.00%)
7	-	-	Fracture of distal end of radius, 2,010 (0.50%)	Hypertensive disorder, 29,200 (6.70%)	Asthma, 34,316 (7.00%)	Depressive disorder, 39,869 (7.30%)	Eczema, 39,777 (6.80%)	Esophageal reflux finding, 30,111 (5.00%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
8	-	-	Atrial arrhythmia, 1,995 (0.50%)	Eczema, 26,441 (6.00%)	Eczema, 33,682 (6.80%)	Urinary tract infectious disease, 34,158 (6.20%)	Hypothyroidism, 38,008 (6.50%)	Osteoporosis, 26,544 (4.40%)
9	-	-	Osteoarthritis of knee, 1,924 (0.50%)	Insomnia, 26,161 (6.00%)	Arthritis, 32,920 (6.70%)	Asthma, 33,072 (6.00%)	Asthma, 35,749 (6.10%)	Asthma, 25,339 (4.20%)
10	-	-	Pneumonia, 1,844 (0.50%)	Cystitis, 21,930 (5.00%)	Cystitis, 31,774 (6.40%)	Pneumonia, 32,518 (5.90%)	Osteoporosis, 35,559 (6.10%)	Obesity, 24,564 (4.10%)
IQVIA DA Germany	**HRT users**							
1	-	Perimenopausal disorder, 406 (33.00%)	Perimenopausal disorder, 782 (21.90%)	Perimenopausal disorder, 1,345 (16.90%)	Perimenopausal disorder, 2,384 (11.30%)	Perimenopausal disorder, 4,584 (11.40%)	Atrophic vaginitis, 6,788 (10.90%)	Atrophic vaginitis, 11,153 (17.60%)
2	-	Essential hypertension, 181 (14.70%)	Essential hypertension, 509 (14.20%)	Essential hypertension, 1,082 (13.60%)	Essential hypertension, 2,207 (10.50%)	Atrophic vaginitis, 4,484 (11.10%)	Perimenopausal disorder, 6,011 (9.70%)	Perimenopausal disorder, 9,215 (14.50%)
3	-	Nerve root disorder, 170 (13.80%)	Menopausal syndrome, 446 (12.50%)	Menopausal syndrome, 650 (8.20%)	Atrophic vaginitis, 1,979 (9.40%)	Essential hypertension, 3,186 (7.90%)	Essential hypertension, 4,242 (6.80%)	Noninflammatory disorder of the vagina, 7,780 (12.30%)
4	-	Menopausal syndrome, 152 (12.30%)	Nerve root disorder, 317 (8.90%)	Atrophic vaginitis, 562 (7.10%)	Menopausal syndrome, 1,350 (6.40%)	Noninflammatory disorder of the vagina, 2,708 (6.70%)	Noninflammatory disorder of the vagina, 3,633 (5.80%)	Essential hypertension, 4,968 (7.80%)
5	-	Bronchitis, 150 (12.20%)	Noninflammatory disorder of the vagina, 267 (7.50%)	Nerve root disorder, 543 (6.80%)	Noninflammatory disorder of the vagina, 1,229 (5.80%)	Menopausal syndrome, 2,153 (5.30%)	Menopausal syndrome, 2,796 (4.50%)	Menopausal syndrome, 3,967 (6.30%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
6	-	Acute upper respiratory infection, 88 (7.20%)	Bronchitis, 215 (6.00%)	Noninflammatory disorder of the vagina, 512 (6.40%)	Acute vaginitis, 791 (3.80%)	Acute vaginitis, 1,457 (3.60%)	Illness, 2,723 (4.40%)	Illness, 2,676 (4.20%)
7	-	Varicose veins of lower limb without ulcer and without inflammation, 88 (7.20%)	Acute vaginitis, 149 (4.20%)	Acute vaginitis, 457 (5.70%)	Nerve root disorder, 769 (3.60%)	Urinary tract infectious disease, 1,135 (2.80%)	Acute vaginitis, 1,835 (2.90%)	Acute vaginitis, 2,443 (3.90%)
8	-	Bodily distress disorder, 82 (6.70%)	Osteoporosis, 142 (4.00%)	Bodily distress disorder, 277 (3.50%)	Urinary tract infectious disease, 665 (3.10%)	Nerve root disorder, 1,112 (2.80%)	Urinary tract infectious disease, 1,687 (2.70%)	Lower abdominal pain, 2,416 (3.80%)
9	-	Illness, 81 (6.60%)	Congenital malformation, 141 (4.00%)	Illness, 273 (3.40%)	Illness, 627 (3.00%)	Lower abdominal pain, 1,075 (2.70%)	Lower abdominal pain, 1,610 (2.60%)	Urinary tract infectious disease, 2,356 (3.70%)
10	-	Acute vaginitis, 80 (6.50%)	Pure hypercholesterolemia, 135 (3.80%)	Urinary tract infectious disease, 264 (3.30%)	Urinary incontinence, 540 (2.60%)	Illness, 1,029 (2.50%)	Nerve root disorder, 1,492 (2.40%)	Urinary incontinence, 2,216 (3.50%)
IQVIA DA Germany	**Non-HRT users**							
1	-	Essential hypertension, 3,115 (9.30%)	Essential hypertension, 5,453 (5.20%)	Essential hypertension, 18,606 (6.50%)	Essential hypertension, 45,251 (6.30%)	Essential hypertension, 79,261 (6.20%)	Essential hypertension, 113,239 (6.80%)	Essential hypertension, 128,806 (10.50%)
2	-	Nerve root disorder, 2,042 (6.10%)	Nerve root disorder, 2,765 (2.60%)	Nerve root disorder, 8,497 (3.00%)	Nerve root disorder, 22,640 (3.10%)	Nerve root disorder, 42,801 (3.40%)	Illness, 107,094 (6.40%)	Illness, 113,574 (9.30%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
3	-	Bronchitis, 1,758 (5.30%)	Bronchitis, 1,802 (1.70%)	Simple goiter, 4,072 (1.40%)	Type 2 diabetes mellitus, 11,711 (1.60%)	Type 2 diabetes mellitus, 22,515 (1.80%)	Nerve root disorder, 67,038 (4.00%)	Nerve root disorder, 76,621 (6.30%)
4	-	Perimenopausal disorder, 1,183 (3.50%)	Perimenopausal disorder, 1,632 (1.60%)	Pure hypercholesterolemia, 4,062 (1.40%)	Osteoarthritis of knee, 11,636 (1.60%)	Osteoarthritis of knee, 22,012 (1.70%)	Disorder of musculoskeletal system, 33,053 (2.00%)	Acute upper respiratory infection, 71,610 (5.80%)
5	-	Varicose veins of lower limb without ulcer and without inflammation, 948 (2.80%)	Illness, 1,365 (1.30%)	Osteoarthritis of knee, 3,643 (1.30%)	Pure hypercholesterolemia, 9,945 (1.40%)	Disorder of musculoskeletal system, 20,843 (1.60%)	Type 2 diabetes mellitus, 31,711 (1.90%)	Osteoarthritis of knee, 41,521 (3.40%)
6	-	Simple goiter, 863 (2.60%)	Simple goiter, 1,313 (1.30%)	Spondylosis, 3,626 (1.30%)	Disorder of musculoskeletal system, 9,810 (1.40%)	Acute upper respiratory infection, 20,155 (1.60%)	Acute upper respiratory infection, 31,602 (1.90%)	Pure hypercholesterolemia, 39,896 (3.30%)
7	-	Acute upper respiratory infection, 857 (2.60%)	Hyperlipidemia, 1,308 (1.30%)	Neck pain, 3,620 (1.30%)	Neck pain, 9,766 (1.40%)	Spondylosis, 19,419 (1.50%)	Osteoarthritis of knee, 30,614 (1.80%)	Type 2 diabetes mellitus, 39,118 (3.20%)
8	-	Hyperlipidemia, 840 (2.50%)	Pure hypercholesterolemia, 1,209 (1.20%)	Hyperlipidemia, 3,527 (1.20%)	Spondylosis, 9,647 (1.30%)	Neck pain, 18,681 (1.50%)	Spondylosis, 28,521 (1.70%)	Disorder of musculoskeletal system, 35,344 (2.90%)
9	-	Chronic ischemic heart disease, 829 (2.50%)	Chronic ischemic heart disease, 1,078 (1.00%)	Type 2 diabetes mellitus, 3,465 (1.20%)	Simple goiter, 9,258 (1.30%)	Pure hypercholesterolemia, 17,314 (1.40%)	Hypothyroidism, 26,828 (1.60%)	Spondylosis, 34,539 (2.80%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	-	Illness, 777 (2.30%)	Osteoarthritis of knee, 1,006 (1.00%)	Perimenopausal disorder, 3,382 (1.20%)	Acute bronchitis, 8,314 (1.10%)	Hypothyroidism, 16,976 (1.30%)	Neck pain, 26,578 (1.60%)	Hypothyroidism, 32,044 (2.60%)
BIFAP	**HRT users**							
1	-	-	-	Viral upper respiratory tract infection, 175 (10.10%)	Common cold, 3,611 (10.90%)	Common cold, 5,403 (8.30%)	Urinary tract infectious disease, 4,530 (5.00%)	Common cold, 8,944 (3.40%)
2	-	-	-	Common cold, 164 (9.50%)	Viral upper respiratory tract infection, 3,028 (9.10%)	Viral upper respiratory tract infection, 5,207 (8.00%)	Low back pain, 3,827 (4.20%)	Urinary tract infectious disease, 8,267 (3.20%)
3	-	-	-	Pharyngitis, 136 (7.90%)	Pharyngitis, 2,576 (7.80%)	Urinary tract infectious disease, 4,855 (7.50%)	COVID-19, 3,369 (3.70%)	Viral upper respiratory tract infection, 7,867 (3.00%)
4	-	-	-	Urinary tract infectious disease, 113 (6.50%)	Urinary tract infectious disease, 2,483 (7.50%)	Pharyngitis, 4,090 (6.30%)	Pain of joint of knee, 3,145 (3.50%)	Low back pain, 6,837 (2.60%)
5	-	-	-	Low back pain, 99 (5.70%)	Low back pain, 2,084 (6.30%)	Low back pain, 3,515 (5.40%)	Coronavirus infection, 3,131 (3.40%)	Acute pharyngitis, 5,073 (2.00%)
6	-	-	-	Upper respiratory infection, 61 (3.50%)	Pain of joint of knee, 1,303 (3.90%)	Pain of joint of knee, 2,521 (3.90%)	Vitamin D deficiency, 2,892 (3.20%)	Essential hypertension, 4,992 (1.90%)
7	-	-	-	Infectious gastroenteritis, 56 (3.20%)	Upper respiratory infection, 1,167 (3.50%)	Acute bronchitis, 1,919 (3.00%)	Essential hypertension, 2,799 (3.10%)	Pain of joint of knee, 4,713 (1.80%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
8	-	-	-	Pain of joint of knee, 56 (3.20%)	Acute bronchitis, 1,068 (3.20%)	Impacted cerumen, 1,723 (2.60%)	Impacted cerumen, 2,191 (2.40%)	Impacted cerumen, 4,107 (1.60%)
9	-	-	-	Neck pain, 54 (3.10%)	Productive cough, 1,002 (3.00%)	Acute respiratory infections, 1,674 (2.60%)	Hyperlipidemia, 1,898 (2.10%)	Abdominal pain, 3,887 (1.50%)
10	-	-	-	Productive cough, 50 (2.90%)	Toothache, 985 (3.00%)	Abdominal pain, 1,527 (2.30%)	Abdominal pain, 1,888 (2.10%)	Viral disease, 3,819 (1.50%)
BIFAP	**Non-HRT users**							
1	-	-	-	Common cold, 11,561 (7.80%)	Common cold, 69,395 (7.30%)	Viral upper respiratory tract infection, 81,948 (4.90%)	COVID-19, 157,018 (4.90%)	Common cold, 95,581 (2.60%)
2	-	-	-	Viral upper respiratory tract infection, 9,996 (6.70%)	Viral upper respiratory tract infection, 59,990 (6.30%)	Common cold, 80,937 (4.90%)	Low back pain, 118,953 (3.70%)	Low back pain, 74,696 (2.00%)
3	-	-	-	Pharyngitis, 8,448 (5.70%)	Pharyngitis, 50,059 (5.20%)	Urinary tract infectious disease, 75,789 (4.60%)	Essential hypertension, 117,576 (3.70%)	Viral upper respiratory tract infection, 73,372 (2.00%)
4	-	-	-	Low back pain, 7,859 (5.30%)	Low back pain, 44,664 (4.70%)	Pharyngitis, 69,356 (4.20%)	Vitamin D deficiency, 108,501 (3.40%)	Essential hypertension, 70,940 (1.90%)
5	-	-	-	Urinary tract infectious disease, 6,132 (4.10%)	Urinary tract infectious disease, 43,478 (4.60%)	Low back pain, 63,636 (3.80%)	Urinary tract infectious disease, 92,754 (2.90%)	Urinary tract infectious disease, 65,688 (1.80%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
6	-	-	-	Upper respiratory infection, 4,396 (3.00%)	Pain of joint of knee, 27,911 (2.90%)	Acute respiratory infections, 56,024 (3.40%)	Pain of joint of knee, 66,672 (2.10%)	Vitamin D deficiency, 53,945 (1.50%)
7	-	-	-	Pain of joint of knee, 4,288 (2.90%)	Acute respiratory infections, 27,641 (2.90%)	Pain of joint of knee, 47,989 (2.90%)	Headache, 57,777 (1.80%)	Acute pharyngitis, 51,894 (1.40%)
8	-	-	-	Infectious gastroenteritis, 4,107 (2.80%)	Infectious gastroenteritis, 26,673 (2.80%)	Impacted cerumen, 34,819 (2.10%)	Abdominal pain, 57,297 (1.80%)	Pain of joint of knee, 48,081 (1.30%)
9	-	-	-	Productive cough, 3,215 (2.20%)	Upper respiratory infection, 25,154 (2.60%)	Acute bronchitis, 34,814 (2.10%)	Neck pain, 57,223 (1.80%)	Impacted cerumen, 44,157 (1.20%)
10	-	-	-	Hypertensive disorder, 3,176 (2.10%)	Acute bronchitis, 22,105 (2.30%)	Infectious gastroenteritis, 29,417 (1.80%)	Hyperlipidemia, 55,093 (1.70%)	Acute bronchitis, 41,094 (1.10%)
SIDIAP	**HRT users**							
1	-	-	-	-	Common cold, 460 (5.30%)	Common cold, 5,211 (10.70%)	Urinary tract infectious disease, 7,569 (11.80%)	Urinary tract infectious disease, 7,811 (8.20%)
2	-	-	-	-	Low back pain, 330 (3.80%)	Urinary tract infectious disease, 4,050 (8.30%)	COVID-19, 3,888 (6.10%)	Common cold, 6,038 (6.30%)
3	-	-	-	-	Urinary tract infectious disease, 255 (2.90%)	Traumatic or non-traumatic injury, 2,682 (5.50%)	Low back pain, 3,140 (4.90%)	Traumatic or non-traumatic injury, 3,779 (4.00%)
4	-	-	-	-	Traumatic or non-traumatic injury, 236 (2.70%)	Low back pain, 2,560 (5.20%)	Abdominal pain, 2,819 (4.40%)	Low back pain, 3,437 (3.60%)

Data source	1990	1995	2000	2005	2010	2015	2020	2024
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
5	-	-	-	-	Acute pharyngitis, 231 (2.60%)	Acute lower respiratory tract infection, 2,296 (4.70%)	Dizziness and giddiness, 2,617 (4.10%)	Acute cystitis, 3,384 (3.50%)
6	-	-	-	-	Anxiety disorder, 228 (2.60%)	Acute pharyngitis, 2,248 (4.60%)	Traumatic or non-traumatic injury, 2,383 (3.70%)	Inflammatory dermatosis, 2,891 (3.00%)
7	-	-	-	-	Multiple joint pain, 226 (2.60%)	Multiple joint pain, 2,151 (4.40%)	Impacted cerumen, 1,898 (3.00%)	Abdominal pain, 2,881 (3.00%)
8	-	-	-	-	Impacted cerumen, 210 (2.40%)	Abdominal pain, 2,045 (4.20%)	Pain of knee region, 1,890 (3.00%)	Acute lower respiratory tract infection, 2,540 (2.70%)
9	-	-	-	-	Essential hypertension, 201 (2.30%)	Cough, 2,040 (4.20%)	Neck pain, 1,805 (2.80%)	Pain of knee region, 2,328 (2.40%)
10	-	-	-	-	Neck pain, 189 (2.20%)	Dizziness and giddiness, 1,871 (3.80%)	Common cold, 1,665 (2.60%)	Impacted cerumen, 2,265 (2.40%)
SIDIAP	**Non-HRT users**							
1	-	-	-	-	Common cold, 18,845 (3.90%)	Common cold, 42,484 (6.80%)	COVID-19, 50,169 (6.20%)	Common cold, 40,581 (4.40%)
2	-	-	-	-	Low back pain, 12,898 (2.60%)	Urinary tract infectious disease, 25,908 (4.10%)	Urinary tract infectious disease, 49,545 (6.20%)	Urinary tract infectious disease, 36,266 (3.90%)
3	-	-	-	-	Essential hypertension, 10,976 (2.20%)	Traumatic or non-traumatic injury, 24,530 (3.90%)	Low back pain, 29,115 (3.60%)	Traumatic or non-traumatic injury, 26,042 (2.80%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
4	-	-	-	-	Anxiety disorder, 9,987 (2.00%)	Low back pain, 23,920 (3.80%)	Traumatic or non-traumatic injury, 22,143 (2.80%)	Low back pain, 25,270 (2.70%)
5	-	-	-	-	Traumatic or non-traumatic injury, 9,737 (2.00%)	Multiple joint pain, 20,655 (3.30%)	Abdominal pain, 20,392 (2.50%)	Inflammatory dermatosis, 16,273 (1.80%)
6	-	-	-	-	Multiple joint pain, 9,268 (1.90%)	Acute lower respiratory tract infection, 18,369 (2.90%)	Dizziness and giddiness, 20,215 (2.50%)	Abdominal pain, 16,132 (1.70%)
7	-	-	-	-	Impacted cerumen, 8,585 (1.80%)	Acute pharyngitis, 17,618 (2.80%)	Anxiety disorder, 17,817 (2.20%)	Pain of knee region, 16,027 (1.70%)
8	-	-	-	-	Pure hypercholesterolemia, 8,570 (1.80%)	Cough, 16,618 (2.70%)	Pain of knee region, 17,105 (2.10%)	Acute cystitis, 15,842 (1.70%)
9	-	-	-	-	Acute pharyngitis, 7,905 (1.60%)	Obesity, 16,074 (2.60%)	Neck pain, 15,502 (1.90%)	Acute lower respiratory tract infection, 15,718 (1.70%)
10	-	-	-	-	Neck pain, 7,833 (1.60%)	Impacted cerumen, 15,504 (2.50%)	Impacted cerumen, 15,347 (1.90%)	Impacted cerumen, 14,875 (1.60%)
CPRD GOLD	**HRT users**							
1	Acute lower respiratory tract infection, 42 (9.20%)	Backache, 1,266 (6.60%)	Cough, 3,066 (6.50%)	Cough, 7,219 (8.50%)	Cough, 12,316 (10.40%)	Cough, 10,359 (8.70%)	Asthma not disturbing sleep, 2,520 (2.40%)	Cough, 5,580 (4.60%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
2	Breast normal, 29 (6.30%)	Cough, 1,213 (6.30%)	Low back pain, 2,004 (4.30%)	Allergic reaction to drug, 4,055 (4.80%)	Pain of knee region, 5,752 (4.90%)	Asthma not disturbing sleep, 5,471 (4.60%)	Allergic reaction to drug, 2,481 (2.40%)	Cervical smear - human papillomavirus negative, 5,161 (4.30%)
3	Depressive disorder, 25 (5.40%)	Upper respiratory infection, 1,211 (6.30%)	Upper respiratory infection, 1,903 (4.00%)	Pain of knee region, 3,681 (4.30%)	Allergic reaction to drug, 5,712 (4.80%)	Asthma not limiting activities, 5,357 (4.50%)	Asthma not limiting activities, 2,390 (2.30%)	Clinical finding, 3,753 (3.10%)
4	Upper respiratory infection, 25 (5.40%)	Acute lower respiratory tract infection, 1,196 (6.20%)	Acute lower respiratory tract infection, 1,694 (3.60%)	Upper respiratory infection, 3,570 (4.20%)	Abdominal pain, 4,681 (4.00%)	Pain of knee region, 4,975 (4.20%)	Abdominal pain, 2,218 (2.10%)	Asthma not disturbing sleep, 3,522 (2.90%)
5	Abdominal pain, 24 (5.20%)	Urinary tract infectious disease, 973 (5.00%)	Abdominal pain, 1,562 (3.30%)	Low back pain, 3,485 (4.10%)	Eruption, 4,505 (3.80%)	Abdominal pain, 3,967 (3.30%)	Pain of knee region, 2,151 (2.00%)	Asthma not limiting activities, 3,490 (2.90%)
6	Backache, 23 (5.00%)	Depressive disorder, 912 (4.70%)	Urinary tract infectious disease, 1,553 (3.30%)	Abdominal pain, 3,266 (3.80%)	Upper respiratory infection, 4,429 (3.80%)	Allergic reaction to drug, 3,880 (3.30%)	Clinical finding, 2,032 (1.90%)	Pain of knee region, 2,912 (2.40%)
7	Cough, 21 (4.60%)	Abdominal pain, 749 (3.90%)	Chest pain, 1,532 (3.20%)	Backache, 3,165 (3.70%)	Lower respiratory tract infection, 4,368 (3.70%)	Clinical finding, 3,562 (3.00%)	Cough, 1,811 (1.70%)	Asthma daytime symptoms, 2,550 (2.10%)
8	Sinusitis, 21 (4.60%)	Sinusitis, 747 (3.90%)	Essential hypertension, 1,427 (3.00%)	Eruption, 3,113 (3.70%)	Low back pain, 4,266 (3.60%)	Eruption, 3,562 (3.00%)	Asthma daytime symptoms, 1,724 (1.70%)	Allergic reaction to drug, 2,522 (2.10%)
9	Asthma, 19	Chest pain, 709 (3.70%)	Indigestion, 1,395 (3.00%)	Chest pain, 2,967 (3.50%)	Backache, 4,144 (3.50%)	Backache, 3,547 (3.00%)	Shoulder pain, 1,722 (1.60%)	10g monofilament sensation L foot normal, 2,475 (2.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
10	Insomnia, 19	Indigestion, 635 (3.30%)	Backache, 1,360 (2.90%)	Lower respiratory tract infection, 2,887 (3.40%)	Shoulder pain, 3,856 (3.30%)	Skin lesion, 3,323 (2.80%)	Skin lesion, 1,718 (1.60%)	10g monofilament sensation R foot normal, 2,474 (2.00%)
CPRD GOLD	**Non-HRT users**							
1	Acute lower respiratory tract infection, 768 (5.40%)	Acute lower respiratory tract infection, 4,791 (5.00%)	Cough, 9,061 (4.70%)	Cough, 27,977 (5.90%)	Cough, 45,617 (7.60%)	Cough, 36,978 (6.70%)	Cervical smear - human papillomavirus negative, 7,441 (1.80%)	Cough, 10,718 (3.60%)
2	Upper respiratory infection, 703 (5.00%)	Cough, 4,604 (4.80%)	Upper respiratory infection, 5,335 (2.80%)	Allergic reaction to drug, 18,454 (3.90%)	Pain of knee region, 21,118 (3.50%)	Asthma not disturbing sleep, 20,402 (3.70%)	Asthma not disturbing sleep, 7,280 (1.80%)	Cervical smear - human papillomavirus negative, 9,087 (3.00%)
3	Cough, 689 (4.90%)	Upper respiratory infection, 4,327 (4.50%)	Essential hypertension, 5,321 (2.80%)	All pulses present in left lower limb, 15,448 (3.30%)	Allergic reaction to drug, 20,731 (3.50%)	Asthma not limiting activities, 19,873 (3.60%)	Asthma not limiting activities, 6,982 (1.70%)	10g monofilament sensation R foot normal, 6,877 (2.30%)
4	Breast normal, 490 (3.50%)	Backache, 3,916 (4.00%)	Low back pain, 5,238 (2.70%)	All pulses present in right lower limb, 15,439 (3.30%)	10g monofilament sensation L foot normal, 18,084 (3.00%)	Pain of knee region, 17,364 (3.10%)	Pain of knee region, 6,158 (1.50%)	10g monofilament sensation L foot normal, 6,870 (2.30%)
5	Hypertensive disorder, 470 (3.30%)	Urinary tract infectious disease, 2,898 (3.00%)	Acute lower respiratory tract infection, 5,081 (2.60%)	Upper respiratory infection, 13,058 (2.80%)	10g monofilament sensation R foot normal, 17,952 (3.00%)	Allergic reaction to drug, 12,685 (2.30%)	Allergic reaction to drug, 6,082 (1.50%)	Asthma not disturbing sleep, 6,435 (2.10%)

Data source	1990 N (%)	1995 N (%)	2000 N (%)	2005 N (%)	2010 N (%)	2015 N (%)	2020 N (%)	2024 N (%)
6	Urinary tract infectious disease, 452 (3.20%)	Depressive disorder, 2,542 (2.60%)	Chest pain, 4,256 (2.20%)	Pain of knee region, 12,779 (2.70%)	Lower respiratory tract infection, 16,971 (2.80%)	Asthma daytime symptoms, 12,398 (2.20%)	Cough, 5,374 (1.30%)	Asthma not limiting activities, 6,366 (2.10%)
7	Indigestion, 432 (3.10%)	Hypertensive disorder, 2,472 (2.60%)	Urinary tract infectious disease, 4,166 (2.20%)	Essential hypertension, 12,758 (2.70%)	All pulses present in right lower limb, 16,195 (2.70%)	Clinical finding, 12,155 (2.20%)	Clinical finding, 5,342 (1.30%)	Clinical finding, 6,208 (2.10%)
8	Backache, 383 (2.70%)	Abdominal pain, 2,332 (2.40%)	Allergic reaction to drug, 3,938 (2.00%)	Lower respiratory tract infection, 11,419 (2.40%)	All pulses present in left lower limb, 16,129 (2.70%)	Eruption, 12,113 (2.20%)	Abdominal pain, 5,108 (1.30%)	Pain of knee region, 5,637 (1.90%)
9	Chest pain, 370 (2.60%)	Chest pain, 2,269 (2.40%)	Osteoarthritis, 3,782 (2.00%)	Eruption, 11,410 (2.40%)	Upper respiratory infection, 16,081 (2.70%)	Backache, 11,892 (2.10%)	Asthma daytime symptoms, 5,039 (1.30%)	All pulses present in left foot, 5,612 (1.90%)
10	Depressive disorder, 366 (2.60%)	Essential hypertension, 2,219 (2.30%)	Backache, 3,733 (1.90%)	Clinical finding, 11,328 (2.40%)	Eruption, 15,749 (2.60%)	Abdominal pain, 11,586 (2.10%)	10g monofilament sensation R foot normal, 4,697 (1.20%)	All pulses present in right foot, 5,571 (1.90%)

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; ; N = number of individuals; – = no data available.

Table S13. Total duration of HRT treatment among postmenopausal women, overall, without application of the prespecified treatment gap.

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
Conjugated oestrogens plain	number records	N	206	1,947	270	65	17,144
	number subjects	N	206	1,947	270	65	17,144
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	3 (1 – 10)	4 (1 – 13)	2 (1 – 3)	3 (1 – 11)
	days exposed	Median (Q25 – Q75)	42 (42 – 168)	360 (84 – 1,446)	228 (57 – 677)	34 (31 – 156)	396 (84 – 1,564)
Ethinylestradiol plain	number records	N	1,148	125	7,501	–	222
	number subjects	N	1,148	125	7,501	–	222
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (2 – 6)	1 (1 – 1)	5 (1 – 16)	–	3 (1 – 9)
	days exposed	Median (Q25 – Q75)	188 (84 – 470)	11 (11 – 60)	253 (61 – 696)	–	302 (90 – 960)
Lynestrenol plain	number records	N	93	7	<5	<5	–
	number subjects	N	93	7	<5	<5	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	3 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	114 (30 – 850)	334 (60 – 465)	–	–	–
Medrogestone plain	number records	N	–	24	6	–	–
	number subjects	N	–	24	6	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 3)	2 (1 – 3)	–	–
	days exposed	Median (Q25 – Q75)	–	105 (41 – 346)	58 (38 – 89)	–	–
Medroxyprogesterone acetate plain	number records	N	2,713	136	437	84	531
	number subjects	N	2,713	136	437	84	531
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 5)	3 (1 – 11)	2 (1 – 3)	3 (1 – 7)
	days exposed	Median (Q25 – Q75)	243 (40 – 969)	57 (15 – 511)	152 (31 – 534)	43 (31 – 190)	183 (56 – 604)
Megesterol plain	number records	N	–	–	9	<5	10
	number subjects	N	–	–	9	<5	10
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	4 (1 – 10)	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	–	–	126 (31 – 354)	–	85 (28 – 309)
Nomegestrol plain	number records	N	–	9	185	–	–
	number subjects	N	–	9	185	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 3)	2 (1 – 5)	–	–
	days exposed	Median (Q25 – Q75)	–	168 (144 – 355)	146 (85 – 436)	–	–
Norethisterone plain	number records	N	2,427	342	4,064	42	751

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number subjects	N	2,427	342	4,064	42	751
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 3)	8 (2 – 18)	2 (1 – 2)	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	248 (84 – 816)	60 (12 – 548)	326 (84 – 640)	31 (31 – 90)	108 (28 – 504)
Oestradiol plain	number records	N	315,076	40,480	25,954	4,576	106,798
	number subjects	N	315,076	40,480	25,954	4,576	106,798
	number of prescription records/dispensings**	Median (Q25 – Q75)	8 (2 – 25)	2 (1 – 7)	4 (1 – 9)	2 (1 – 8)	3 (1 – 11)
	days exposed	Median (Q25 – Q75)	1,396 (154 – 3,769)	359 (30 – 1,276)	292 (61 – 558)	336 (85 – 623)	389 (84 – 1,322)
Oestriol plain	number records	N	28,269	69,919	84,556	21,369	77,439
	number subjects	N	28,269	69,919	84,556	21,369	77,439
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 3)	4 (1 – 10)	2 (1 – 4)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	133 (72 – 1,200)	90 (30 – 1,198)	310 (65 – 524)	321 (85 – 431)	105 (30 – 792)
Oestradiol norethisterone	number records	N	51,179	9,258	8,408	3,193	71,702
	number subjects	N	51,179	9,258	8,408	3,193	71,702
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 19)	2 (1 – 8)	12 (3 – 29)	7 (2 – 22)	4 (2 – 10)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	days exposed	Median (Q25 – Q75)	747 (109 – 1,897)	262 (84 – 1,260)	475 (111 – 1,057)	488 (183 – 1,076)	440 (90 – 1,134)
Progesterone plain	number records	N	459	13,080	3,045	831	8,847
	number subjects	N	459	13,080	3,045	831	8,847
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 9)	3 (1 – 8)	6 (2 – 15)	5 (2 – 13)	6 (2 – 11)
	days exposed	Median (Q25 – Q75)	398 (102 – 679)	302 (3 – 881)	355 (85 – 715)	389 (151 – 760)	430 (124 – 814)
Promestriene plain	number records	N	–	–	75,254	59,09	–
	number subjects	N	–	–	75,254	59,09	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 4)	2 (1 – 5)	–
	days exposed	Median (Q25 – Q75)	–	–	126 (31 – 667)	228 (38 – 792)	–
Tibolone plain	number records	N	2,204	827	23,807	7,217	9,942
	number subjects	N	2,204	827	23,807	7,217	9,942
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 15)	2 (1 – 7)	7 (2 – 22)	6 (2 – 19)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	416 (84 – 1,460)	285 (84 – 1,186)	348 (57 – 916)	394 (112 – 1,011)	274 (84 – 1,102)
Conjugated oestrogens and bazedoxifene	number records	N	<5	–	–	528	<5
	number subjects	N	<5	–	–	528	<5

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	5 (2 – 17)	–
	days exposed	Median (Q25 – Q75)	–	–	–	372 (102 – 817)	–
Conjugated oestrogens medroxyprogesterone	number records	N	–	481	–	–	10,887
	number subjects	N	–	481	–	–	10,887
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 8)	–	–	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	270 (84 – 1,083)	–	–	300 (84 – 1,026)
Dienestrol plain	number records	N	24,52	–	–	–	7,496
	number subjects	N	24,52	–	–	–	7,496
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	91 (7 – 730)	–	–	–	30 (28 – 307)
Diethylstilbestrol plain	number records	N	<5	–	–	–	23
	number subjects	N	<5	–	–	–	23
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	–	–	–	28 (10 – 43)
Dydrogesterone plain	number records	N	–	373	–	–	171

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	number subjects	N	–	373	–	–	171
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 4)	–	–	2 (1 – 7)
	days exposed	Median (Q25 – Q75)	–	84 (14 – 568)	–	–	140 (30 – 873)
Levonorgestrel IUD	number records	N	434	11	–	–	506
	number subjects	N	434	11	–	–	506
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	1 (1 – 1)	–	–	1 (1 – 1)
	days exposed	Median (Q25 – Q75)	1,826 (1,826 – 1,826)	1,826 (1,826 – 1,826)	–	–	1,826 (1,826 – 1,826)
Oestradiol drospirenone	number records	N	349	933	–	–	172
	number subjects	N	349	933	–	–	172
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (1 – 13)	2 (1 – 8)	–	–	2 (1 – 7)
	days exposed	Median (Q25 – Q75)	431 (84 – 1,393)	280 (84 – 1,272)	–	–	170 (84 – 749)
Oestradiol dydrogesterone	number records	N	–	5,081	–	–	8,41
	number subjects	N	–	5,081	–	–	8,41
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 9)	–	–	4 (1 – 9)
	days exposed	Median (Q25 – Q75)	–	240 (84 – 1,086)	–	–	358 (84 – 1,006)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
Oestradiol levonorgestrel	number records	N	5,623	4,902	–	–	5,338
	number subjects	N	5,623	4,902	–	–	5,338
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 12)	2 (1 – 5)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	491 (85 – 1,152)	84 (30 – 610)	–	–	168 (84 – 643)
Oestradiol medroxyprogesterone	number records	N	7,525	808	–	117	1,92
	number subjects	N	7,525	808	–	117	1,92
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 13)	3 (1 – 8)	–	3 (2 – 10)	3 (1 – 6)
	days exposed	Median (Q25 – Q75)	449 (91 – 1,260)	303 (84 – 1,088)	–	342 (71 – 719)	273 (91 – 784)
Chlorotrianisene plain	number records	N	–	<5	–	–	–
	number subjects	N	–	<5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Hydroxyprogesterone plain	number records	N	–	5	–	–	–
	number subjects	N	–	5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 1)	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
overall							
	days exposed	Median (Q25 – Q75)	–	25 (25 – 25)	–	–	–
Oestradiol prasterone	number records	N	–	527	–	–	–
	number subjects	N	–	527	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 9)	–	–	–
	days exposed	Median (Q25 – Q75)	–	261 (30 – 1,370)	–	–	–
Oestradiol progesterone	number records	N	–	561	–	–	–
	number subjects	N	–	561	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	–	109 (84 – 445)	–	–	–

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*Plain refers to products containing only the specified active substance (e.g. oestradiol plain = oestradiol-only product)
**Number of prescription records/dispensings = number of prescription records/dispensings contributing to treatment duration.

Table S14. Total duration of HRT treatment among postmenopausal women, stratified by age group, without application of the prespecified treatment gap.

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Age group <50 years							
Conjugated oestrogens plain	number records	N	<5	28	9	<5	2,765
	number subjects	N	<5	28	9	<5	2,765
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	7 (3 – 16)	–	8 (3 – 19)
	days exposed	Median (Q25 – Q75)	–	117.50 (84 – 430.25)	510 (277 – 805)	–	934 (233 – 2,437)
Ethinylestradiol plain	number records	N	10	10	1,336	–	43
	number subjects	N	10	10	1,336	–	43
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (1 – 4)	1 (1 – 2)	13 (4 – 33)	–	5 (2 – 10)
	days exposed	Median (Q25 – Q75)	256 (170 – 284)	63 (21 – 501.50)	638 (202 – 1,423)	–	447 (131 – 781)
Medroxyprogesterone acetate plain	number records	N	116	8	61	10	26
	number subjects	N	116	8	61	10	26
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (2 – 8)	1 (1 – 11.25)	8 (3 – 37)	2 (2 – 6)	3 (1 – 7)
	days exposed	Median (Q25 – Q75)	703 (304 – 1,453)	22.50 (11.50 – 830.75)	495 (136 – 1,170)	210 (88 – 485)	199 (90 – 503)
Megesterol plain	number records	N	–	–	<5	–	–
	number subjects	N	–	–	<5	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	17 (17 – 17)	–	–
	days exposed	Median (Q25 – Q75)	–	–	511 (511 – 511)	–	–
Nomegestrol plain	number records	N	–	<5	28	–	–
	number subjects	N	–	<5	28	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 6)	–	–
	days exposed	Median (Q25 – Q75)	–	–	234 (85 – 476)	–	–
Norethisterone plain	number records	N	63	17	537	<5	19
	number subjects	N	63	17	537	<5	19
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (1 – 6)	1 (1 – 2)	15 (4 – 33)	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	463 (84 – 1,028)	36 (12 – 259)	575 (197 – 1,144)	–	106 (42 – 280)
Oestradiol plain	number records	N	5,852	1,463	1,019	575	9,001
	number subjects	N	5,852	1,463	1,019	575	9,001
	number of prescription records/dispensings**	Median (Q25 – Q75)	21 (7 – 43)	2 (1 – 7)	8 (2 – 22)	7 (2 – 19)	13 (5 – 26)
	days exposed	Median (Q25 – Q75)	2,538 (841 – 4,946)	387 (29 – 1,452)	528 (155 – 1,210)	555 (263 – 1,370)	1,428 (470 – 2,915)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestriol plain	number records	N	110	879	187	124	285
	number subjects	N	110	879	187	124	285
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 2)	3 (1 – 8)	2 (1 – 3)	1 (1 – 3)
	days exposed	Median (Q25 – Q75)	141 (37 – 611)	30 (30 – 671)	252 (46 – 489)	360 (96 – 471)	105 (28 – 673)
Oestradiol norethisterone	number records	N	1,328	261	740	692	2,440
	number subjects	N	1,328	261	740	692	2,440
	number of prescription records/dispensings**	Median (Q25 – Q75)	11 (3 – 25)	2 (1 – 5)	17 (5 – 40)	6 (2 – 24)	6 (2 – 14)
	days exposed	Median (Q25 – Q75)	1,289 (318 – 2,673)	105 (84 – 930)	636 (230 – 1,449)	584 (285 – 1,165)	623 (155 – 1,779)
Progesterone plain	number records	N	28	582	335	160	141
	number subjects	N	28	582	335	160	141
	number of prescription records/dispensings**	Median (Q25 – Q75)	6 (2 – 11)	3 (1 – 8)	7 (2 – 18)	4 (2 – 15)	5 (2 – 11)
	days exposed	Median (Q25 – Q75)	316 (120 – 1,003)	321 (30 – 1,073.50)	489 (115 – 1,123)	392 (138 – 1,076)	336 (128 – 777)
Promestriene plain	number records	N	–	–	122	179	–
	number subjects	N	–	–	122	179	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	1 (1 – 3)	2 (1 – 3)	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	–	–	61 (31 – 526)	181 (40 – 622)	–
Tibolone plain	number records	N	64	8	664	341	815
	number subjects	N	64	8	664	341	815
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 16)	1 (1 – 2)	10 (3 – 32)	10 (2 – 29)	5 (2 – 15)
	days exposed	Median (Q25 – Q75)	578 (111 – 1,505)	84 (84 – 126)	462 (110 – 1,166)	613 (251 – 1,330)	436 (112 – 1,529)
Conjugated oestrogens medroxyprogesterone	number records	N	–	8	–	–	319
	number subjects	N	–	8	–	–	319
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (2 – 5)	–	–	3 (1 – 7)
	days exposed	Median (Q25 – Q75)	–	277 (162 – 843)	–	–	252 (84 – 992)
Dienestrol plain	number records	N	35	–	–	–	15
	number subjects	N	35	–	–	–	15
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	–	–	–	1 (1 – 4)
	days exposed	Median (Q25 – Q75)	15 (7 – 250)	–	–	–	28 (28 – 122)
Dydrogesterone plain	number records	N	–	27	–	–	8
	number subjects	N	–	27	–	–	8

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 3)	–	–	2 (2 – 3)
	days exposed	Median (Q25 – Q75)	–	84 (14 – 603)	–	–	178 (108 – 190)
Levonorgestrel IUD	number records	N	20	–	–	–	15
	number subjects	N	20	–	–	–	15
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	–	–	–	1 (1 – 1)
	days exposed	Median (Q25 – Q75)	1,826 (1,826 – 1,826)	–	–	–	1,826 (1,826 – 1,826)
Oestradiol drospirenone	number records	N	8	30	–	–	11
	number subjects	N	8	30	–	–	11
	number of prescription records/dispensings**	Median (Q25 – Q75)	6 (4 – 13)	2.50 (1 – 16)	–	–	10 (2 – 16)
	days exposed	Median (Q25 – Q75)	620 (318 – 1,191)	330 (84 – 2,376)	–	–	820 (84 – 1,450)
Oestradiol dydrogesterone	number records	N	–	348	–	–	387
	number subjects	N	–	348	–	–	387
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 9)	–	–	5 (2 – 12)
	days exposed	Median (Q25 – Q75)	–	184.50 (84 – 1,023)	–	–	658 (154 – 1,544)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestradiol levonorgestrel	number records	N	26	498	–	–	163
	number subjects	N	26	498	–	–	163
	number of prescription records/dispensings**	Median (Q25 – Q75)	6 (2 – 12)	2 (1 – 4)	–	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	504 (161 – 1,041)	94 (63 – 648.25)	–	–	168 (84 – 690)
Oestradiol medroxyprogesterone	number records	N	50	38	–	44	53
	number subjects	N	50	38	–	44	53
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (2 – 13)	3 (1 – 4)	–	3 (1 – 15)	3 (1 – 9)
	days exposed	Median (Q25 – Q75)	416 (164 – 1,417)	244.50 (78 – 490.75)	–	404 (119 – 1,025)	371 (136 – 931)
Lynestrenol plain	number records	N	<5	–	–	–	–
	number subjects	N	<5	–	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Oestradiol prasterone	number records	N	–	10	–	–	–
	number subjects	N	–	10	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 1)	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	–	30 (30 – 30)	–	–	–
Oestradiol progesterone	number records	N	–	13	–	–	–
	number subjects	N	–	13	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	–	252 (84 – 433)	–	–	–
Conjugated oestrogens and bazedoxifene	number records	N	–	–	–	74	–
	number subjects	N	–	–	–	74	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	5 (2 – 16)	–
	days exposed	Median (Q25 – Q75)	–	–	–	366 (125 – 798)	–
Age group 50–60 years							
Conjugated oestrogens plain	number records	N	127	1,110	221	57	11,027
	number subjects	N	127	1,110	221	57	11,027
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	2.50 (1 – 10)	4 (1 – 13)	2 (1 – 3)	3 (1 – 11)
	days exposed	Median (Q25 – Q75)	42 (42 – 213)	326 (84 – 1,435.25)	232 (57 – 777)	33 (31 – 146)	419 (84 – 1,556)
Ethinylestradiol plain	number records	N	1,112	113	5,974	–	154
	number subjects	N	1,112	113	5,974	–	154

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (2 – 6)	1 (1 – 1)	4 (1 – 13)	–	3 (1 – 9)
	days exposed	Median (Q25 – Q75)	190 (84 – 472)	11 (11 – 30)	197 (53 – 570)	–	254 (90 – 1,071)
Lynestrenol plain	number records	N	86	5	<5	<5	–
	number subjects	N	86	5	<5	<5	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 3)	–	–	–
	days exposed	Median (Q25 – Q75)	158 (30 – 847)	60 (60 – 334)	–	–	–
Medrogestone plain	number records	N	–	18	5	–	–
	number subjects	N	–	18	5	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 3)	1 (1 – 3)	–	–
	days exposed	Median (Q25 – Q75)	–	104.50 (49.50 – 285.50)	57 (31 – 99)	–	–
Medroxyprogesterone acetate plain	number records	N	2,487	109	360	67	458
	number subjects	N	2,487	109	360	67	458
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 4)	3 (1 – 9)	2 (1 – 2)	2 (1 – 7)
	days exposed	Median (Q25 – Q75)	233 (40 – 948)	63 (15 – 504)	106 (29 – 426)	31 (31 – 108)	181 (56 – 602)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Megesterol plain	number records	N	–	–	5	<5	7
	number subjects	N	–	–	5	<5	7
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	4 (1 – 5)	–	2 (2 – 5)
	days exposed	Median (Q25 – Q75)	–	–	126 (31 – 156)	–	86 (28 – 246)
Nomegestrol plain	number records	N	–	7	156	–	–
	number subjects	N	–	7	156	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 2)	2 (1 – 5)	–	–
	days exposed	Median (Q25 – Q75)	–	168 (114 – 261.50)	126 (59 – 416)	–	–
Norethisterone plain	number records	N	2,286	285	3,467	40	665
	number subjects	N	2,286	285	3,467	40	665
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 6)	1 (1 – 3)	7 (2 – 17)	2 (1 – 2)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	246 (84 – 808)	50 (11 – 572)	296 (76 – 572)	32 (31 – 107)	100 (28 – 498)
Oestradiol plain	number records	N	194,602	31,998	17,826	3,021	71,129
	number subjects	N	194,602	31,998	17,826	3,021	71,129
	number of prescription records/dispensings**	Median (Q25 – Q75)	9 (2 – 27)	2 (1 – 7)	4 (1 – 9)	2 (1 – 7)	4 (1 – 11)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	1,701 (229 – 4,241)	360 (10 – 1,245.50)	296 (63 – 568)	320 (82 – 608)	440 (84 – 1,291)
Oestriol plain	number records	N	16,738	39,850	43,995	10,060	40,880
	number subjects	N	16,738	39,850	43,995	10,060	40,880
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	2 (1 – 3)	4 (1 – 9)	2 (1 – 4)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	144 (67 – 1,315)	116 (30 – 1,334)	293 (61 – 518)	321 (85 – 419)	105 (30 – 909)
Oestradiol norethisterone	number records	N	47,185	7,094	7,340	2,394	66,460
	number subjects	N	47,185	7,094	7,340	2,394	66,460
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 19)	2 (1 – 8)	12 (3 – 28)	7 (2 – 22)	4 (2 – 10)
	days exposed	Median (Q25 – Q75)	758 (114 – 1,904)	246 (84 – 1,194)	467 (106 – 1,028)	474 (181 – 1,053)	444 (92 – 1,127)
Progesterone plain	number records	N	424	11,727	2,568	646	8,360
	number subjects	N	424	11,727	2,568	646	8,360
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 9)	3 (1 – 8)	6 (2 – 15)	5 (2 – 13)	6 (2 – 11)
	days exposed	Median (Q25 – Q75)	401 (112 – 679)	321 (10 – 895)	351 (85 – 687)	392 (162 – 713)	435 (125 – 818)
Promestriene plain	number records	N	–	–	40,208	32,604	–
	number subjects	N	–	–	40,208	32,604	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 4)	2 (1 – 5)	–
	days exposed	Median (Q25 – Q75)	–	–	110 (31 – 722)	215 (38 – 810)	–
Tibolone plain	number records	N	1,926	589	21,403	6,313	7,767
	number subjects	N	1,926	589	21,403	6,313	7,767
	number exposures	Median (Q25 – Q75)	5 (1 – 16)	2 (1 – 7)	7 (2 – 22)	6 (2 – 20)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	424 (84 – 1,459)	232 (84 – 1,021)	352 (57 – 916)	397 (115 – 1,017)	260 (84 – 1,066)
Conjugated oestrogens and bazedoxifene	number records	N	<5	–	–	422	<5
	number subjects	N	<5	–	–	422	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	5 (2 – 17)	–
	days exposed	Median (Q25 – Q75)	–	–	–	374 (100 – 817)	–
Conjugated oestrogens medroxyprogesterone	number records	N	–	347	–	–	9,590
	number subjects	N	–	347	–	–	9,590
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 8)	–	–	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	315 (84 – 1,105)	–	–	303 (84 – 1,022)
Dienestrol plain	number records	N	15,866	–	–	–	3,807

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number subjects	N	15,866	–	–	–	3,807
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	92 (7 – 753)	–	–	–	30 (28 – 336)
Diethylstilbestrol plain	number records	N	–	–	–	–	11
	number subjects	N	–	–	–	–	11
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	–	–	–	28 (10 – 57)
Dydrogesterone plain	number records	N	–	330	–	–	146
	number subjects	N	–	330	–	–	146
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 4)	–	–	2 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	84 (14 – 546.75)	–	–	141 (30 – 974)
Levonorgestrel IUD	number records	N	414	11	–	–	489
	number subjects	N	414	11	–	–	489
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	1 (1 – 1)	–	–	1 (1 – 1)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	1,826 (1,826 – 1,826)	1,826 (1,826 – 1,826)	–	–	1,826 (1,826 – 1,826)
Oestradiol drospirenone	number records	N	331	751	–	–	152
	number subjects	N	331	751	–	–	152
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 13)	2 (1 – 8)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	474 (84 – 1,414)	292 (84 – 1,286.50)	–	–	164 (84 – 620)
Oestradiol dydrogesterone	number records	N	–	4,110	–	–	7,827
	number subjects	N	–	4,110	–	–	7,827
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 9)	–	–	4 (1 – 9)
	days exposed	Median (Q25 – Q75)	–	232.50 (84 – 1,043)	–	–	356 (84 – 996)
Oestradiol levonorgestrel	number records	N	5,540	3,967	–	–	5,011
	number subjects	N	5,540	3,967	–	–	5,011
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (2 – 12)	1 (1 – 5)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	496 (95 – 1,161)	84 (30 – 586.50)	–	–	168 (84 – 644)
Oestradiol medroxyprogesterone	number records	N	7,243	633	–	71	1,810
	number subjects	N	7,243	633	–	71	1,810

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	5 (1 – 13)	3 (1 – 8)	–	4 (2 – 10)	3 (1 – 6)
	days exposed	Median (Q25 – Q75)	450 (91 – 1,260)	281 (84 – 1,030)	–	299 (65 – 504)	272 (91 – 777)
Hydroxyprogesterone plain	number records	N	–	5	–	–	–
	number subjects	N	–	5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 1)	–	–	–
	days exposed	Median (Q25 – Q75)	–	25 (25 – 25)	–	–	–
Oestradiol prasterone	number records	N	–	337	–	–	–
	number subjects	N	–	337	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 7)	–	–	–
	days exposed	Median (Q25 – Q75)	–	216 (30 – 1,252)	–	–	–
Oestradiol progesterone	number records	N	–	518	–	–	–
	number subjects	N	–	518	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 5)	–	–	–
	days exposed	Median (Q25 – Q75)	–	127 (84 – 448)	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Age group >60 years							
Conjugated oestrogens plain	number records	N	78	809	40	5	3,352
	number subjects	N	78	809	40	5	3,352
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	3 (1 – 10)	3 (1 – 10)	1 (1 – 2)	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	42 (42 – 84)	417 (84 – 1,483)	150 (29 – 472)	213 (65 – 300)	90 (30 – 774)
Ethinylestradiol plain	number records	N	26	<5	191	–	25
	number subjects	N	26	<5	191	–	25
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	1 (1 – 4)	–	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	114 (84 – 410)	–	61 (29 – 262)	–	185 (30 – 874)
Medrogestone plain	number records	N	–	6	<5	–	–
	number subjects	N	–	6	<5	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1.50 (1 – 2)	–	–	–
	days exposed	Median (Q25 – Q75)	–	181.50 (33 – 521.25)	–	–	–
Medroxyprogesterone acetate plain	number records	N	110	19	16	7	47
	number subjects	N	110	19	16	7	47

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 4)	1 (1 – 6)	4 (1 – 10)	3 (2 – 4)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	50 (30 – 484)	50 (30 – 599)	259 (43 – 703)	213 (156 – 963)	294 (72 – 669)
Megesterol plain	number records	N	–	–	<5	–	<5
	number subjects	N	–	–	<5	–	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Nomegestrol plain	number records	N	–	–	<5	–	–
	number subjects	N	–	–	<5	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Norethisterone plain	number records	N	78	40	60	–	67
	number subjects	N	78	40	60	–	67
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 8)	2 (1 – 4)	3 (1 – 6)	–	2 (1 – 10)
	days exposed	Median (Q25 – Q75)	116 (20 – 1,282)	214 (36 – 559.25)	94 (29 – 330)	–	168 (67 – 766)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestradiol plain	number records	N	114,622	7,019	7,109	980	26,668
	number subjects	N	114,622	7,019	7,109	980	26,668
	number of prescription records/dispensings**	Median (Q25 – Q75)	7 (2 – 20)	2 (1 – 6)	3 (1 – 7)	2 (1 – 5)	2 (1 – 5)
	days exposed	Median (Q25 – Q75)	940 (84 – 2,897)	302 (30 – 1,397)	257 (55 – 490)	210 (51 – 405)	127 (84 – 811)
Oestriol plain	number records	N	11,421	29,190	40,374	11,185	36,274
	number subjects	N	11,421	29,190	40,374	11,185	36,274
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	1 (1 – 3)	4 (1 – 10)	2 (1 – 4)	2 (1 – 4)
	days exposed	Median (Q25 – Q75)	118 (75 – 1,062)	60 (30 – 1,056)	328 (74 – 529)	321 (90 – 440)	105 (34 – 682)
Oestradiol norethisterone	number records	N	2,666	1,903	328	107	2,802
	number subjects	N	2,666	1,903	328	107	2,802
	number of prescription records/dispensings**	Median (Q25 – Q75)	3 (1 – 12)	3 (1 – 10)	7 (2 – 23)	3 (1 – 14)	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	256 (84 – 1,304)	399 (84 – 1,512.50)	342 (57 – 871)	351 (58 – 812)	262 (84 – 882)
Progesterone plain	number records	N	7	771	142	25	346
	number subjects	N	7	771	142	25	346
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 2)	1 (1 – 5)	4 (1 – 15)	2 (2 – 10)	5 (2 – 10)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	15 (8 – 30)	90 (2 – 589)	229 (44 – 583)	366 (112 – 552)	338 (92 – 684)
Promestriene plain	number records	N	–	–	34,924	26,307	–
	number subjects	N	–	–	34,924	26,307	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	2 (1 – 4)	2 (1 – 5)	–
	days exposed	Median (Q25 – Q75)	–	–	154 (31 – 607)	241 (38 – 769)	–
Tibolone plain	number records	N	214	230	1,740	563	1,360
	number subjects	N	214	230	1,740	563	1,360
	number prescription records/dispensings**	Median (Q25 – Q75)	3 (1 – 14)	3.50 (1 – 10)	4 (1 – 18)	4 (2 – 14)	3 (1 – 10)
	days exposed	Median (Q25 – Q75)	242 (84 – 1,424)	597.50 (84 – 1,530.75)	238 (48 – 828)	254 (61 – 695)	278 (84 – 1,088)
Conjugated oestrogens medroxyprogesterone	number records	N	–	126	–	–	978
	number subjects	N	–	126	–	–	978
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2 (1 – 6)	–	–	3 (1 – 8)
	days exposed	Median (Q25 – Q75)	–	200.50 (84 – 915.50)	–	–	288 (84 – 1,070)
Dienestrol plain	number records	N	8,619	–	–	–	3,674
	number subjects	N	8,619	–	–	–	3,674

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	–	–	–	1 (1 – 3)
	days exposed	Median (Q25 – Q75)	89 (7 – 688)	–	–	–	30 (28 – 285)
Diethylstilbestrol plain	number records	N	<5	–	–	–	12
	number subjects	N	<5	–	–	–	12
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	–	–	–	28 (13 – 38)
Dydrogesterone plain	number records	N	–	16	–	–	17
	number subjects	N	–	16	–	–	17
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	2.50 (1 – 7.25)	–	–	1 (1 – 2)
	days exposed	Median (Q25 – Q75)	–	207.50 (84 – 734)	–	–	30 (28 – 290)
Levonorgestrel IUD	number records	N	–	–	–	–	<5
	number subjects	N	–	–	–	–	<5
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
Oestradiol drospirenone	number records	N	10	152	–	–	9
	number subjects	N	10	152	–	–	9
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	2 (1 – 6)	–	–	6 (3 – 10)
	days exposed	Median (Q25 – Q75)	57 (30 – 147)	213 (84 – 990)	–	–	700 (441 – 959)
Oestradiol dydrogesterone	number records	N	–	623	–	–	196
	number subjects	N	–	623	–	–	196
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 10)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	–	314 (84 – 1,319)	–	–	173 (84 – 697)
Oestradiol levonorgestrel	number records	N	57	437	–	–	164
	number subjects	N	57	437	–	–	164
	number of prescription records/dispensings**	Median (Q25 – Q75)	2 (1 – 5)	2 (1 – 7)	–	–	2 (1 – 6)
	days exposed	Median (Q25 – Q75)	168 (84 – 627)	157 (30 – 924)	–	–	165 (84 – 594)
Oestradiol medroxyprogesterone	number records	N	232	137	–	<5	57
	number subjects	N	232	137	–	<5	57
	number of prescription records/dispensings**	Median (Q25 – Q75)	4 (1 – 12)	4 (1 – 9)	–	–	2 (1 – 7)

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	days exposed	Median (Q25 – Q75)	394 (91 – 1,170)	497 (84 – 1,190)	–	–	336 (91 – 728)
Lynestrenol plain	number records	N	6	<5	–	–	–
	number subjects	N	6	<5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	1 (1 – 1)	–	–	–	–
	days exposed	Median (Q25 – Q75)	30 (30 – 70)	–	–	–	–
Chlorotrianisene plain	number records	N	–	<5	–	–	–
	number subjects	N	–	<5	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	–	–
	days exposed	Median (Q25 – Q75)	–	–	–	–	–
Oestradiol prasterone	number records	N	–	180	–	–	–
	number subjects	N	–	180	–	–	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	3 (1 – 10)	–	–	–
	days exposed	Median (Q25 – Q75)	–	615.50 (30 – 1,832.25)	–	–	–
Oestradiol progesterone	number records	N	–	30	–	–	–
	number subjects	N	–	30	–	–	–

Group level*	Variable name	Estimate name	Data source				
			DK–DHR	IQVIA DA Germany	BIFAP	SIDIAP	CPRD GOLD
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	1 (1 – 3)	–	–	–
	days exposed	Median (Q25 – Q75)	–	84 (84 – 259.75)	–	–	–
Conjugated oestrogens and bazedoxifene	number records	N	–	–	–	32	–
	number subjects	N	–	–	–	32	–
	number of prescription records/dispensings**	Median (Q25 – Q75)	–	–	–	2 (2 – 21)	–
	days exposed	Median (Q25 – Q75)	–	–	–	348 (84 – 832)	–

DK-DHR = Danish Data Health Registries; IQVIA DA Germany = IQVIA Disease Analyzer Germany; BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público; SIDIAP = The Information System for Research in Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD; days exposed = time in days a person has been exposed to the drug of interest; N = number of individuals; Q25 = 25th percentile; Q75 = 75th percentile; – = no data available.
*Number of prescription records/dispensings = number of prescription records/dispensings contributing to treatment duration.

ANNEX VII. Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g. side effects).

Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g. its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.