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Population characteristics of intrauterine device users in real-world clinical practice across Europe – insights from the EURAS-LCS12 study

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Abstract

Background The European Active Surveillance Study of LCS12 (EURAS-LCS12) investigates effectiveness and safety of intrauterine devices (IUDs) in routine clinical practice. Here, we aim to characterise the general population of IUD users across Europe recorded in a real-world setting.

Methods EURAS-LCS12 is a prospective, non-interventional cohort study in ten European countries, that started in 2014. All types of approved IUDs were enrolled: levonorgestrel (LNG)-IUS 8 (LNG release rate ~ 8 µg/day); LNG-IUS 12 (LNG release rate ~ 12 µg/day; LNG-IUS 20 (LNG release rate ~ 20 µg/day;); copper IUDs and other hormonal IUDs (OHIUD). A great variety of baseline characteristics and endpoints are assessed in patient-reported questionnaires. The follow-up duration aligns with the intended maximum duration of use of 3 to 5 years, depending on the respective IUD.

Results Currently, 97,187 users are enrolled in the study, of whom the vast majority uses IUDs for contraceptive purposes (96.3%), and roughly two thirds are first-time IUD users (64.1%). Heavy menstrual bleeding (HMB) was reported as the second most common reason for IUD use but with apparent variations between devices and countries. Mean age of LNG-IUD 8 users was about 9 years lower compared with LNG-IUD 20 (26.2 vs. 34.6 years). Greatest differences in the proportion of gravid and parous women were observed between LNG-IUS 8 and OHIUD users (gravid: 38.6% vs. 89.8%; para: 30.6% vs. 88.0%).

Conclusions With more than 97,000 IUD users, EURAS-LCS12 is one of the largest contemporary studies focusing on IUD usage and provides a substantial source of real-world data. IUD prescription patterns appear in line with assumptions that high-dose LNG-IUDs with longer approved durations of use are predominantly prescribed among older, gravid women, who may have completed their family planning, as opposed to younger nulligravidae. Overall,

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the study is a great source to depict which IUD type fits women with certain characteristics and needs at a certain time of life.

Trial registration NCT02146950.

Keywords Prospective cohort study, Active surveillance, Intrauterine device, Levonorgestrel, Prescription determinants, Baseline characteristics

Background

Worldwide, intrauterine devices (IUDs) are the most widely used reversible method of contraception today; over 160 million reproductive-aged women currently rely on them for protection from pregnancy [1, 2]. Intrauterine contraception is available as either a copper intrauterine device (Cu-IUD) or the levonorgestrel intrauterine system (LNG-IUD). As of 2023, there are several approved LNG-IUDs available in Europe [2]. Most widely distributed available versions include: LNG-IUD 20 (20 µg/day LNG release rate; Mirena; Bayer AG; approved for contraception [licensed use duration up to 8 years], heavy menstrual bleeding (HMB), endometrial protection during hormone therapy; [3]; LNG-IUD 18.6 (18.6 µg/day LNG release rate; Levosert/Liletta; Allergan PLC, Irvine, CA, USA; approved for contraception and HMB; licensed use duration up to 6 years); LNG-IUD 12 (12 µg/day average LNG release rate during first year of use; Kyleena; Bayer AG; approved for contraception; licensed use duration up to 5 years) [4]; LNG-IUD 8 (8 µg daily release rate; Jaydess/Luadei/Skyla/Fleree; Bayer Healthcare, Whippany, NJ, USA; approved for contraception; licensed use duration up to 3 years) [5]. LNG-IUD 12 and LNG-IUD 8 have the smallest frame and insertion tube diameter, and the lowest levonorgestrel (LNG) content compared to other approved IUDs.

In a randomised phase II study, LNG-IUD 8 and LNG-IUD 12 demonstrated good contraceptive efficacy and safety (i.e., no apparent dose-response, generally well tolerated, easier and less painful to place) over 3 years compared with LNG-IUD 20 [6]. LNG-IUD 8 and LNG-IUD 12 subsequently underwent further evaluation in a phase III study where the overall results of the previous study have been confirmed [7].

Based on the results of these two studies, LNG-IUD 8 was approved by the US Food and Drug Administration (FDA; as Skyla) for up to 3 years of contraceptive use. In addition, LNG-IUD 8 was subsequently approved by the decentralised procedure in the EU (as Jaydess) in most European countries, Canada and some countries in Latin America [5, 8]. LNG-IUD 8 has proven its efficiency and safety in clinical trials. However, compared to premarketing phase I–III trials, phase IV studies generate evidence in a real-world setting, which helps to further refine the safety profile of approved drugs and potentially discover long-term rare adverse events.

The European Active Surveillance Study on LCS12 (EURAS-LCS12) is an ongoing prospective, non-interventional, long-term active surveillance cohort study of women with a newly inserted IUD, requested by the European Medical Agency as a mandatory post-authorisation safety study (PASS; ct.gov NCT02146950) to assess the effectiveness and safety of LNG-IUD 8. The study expands on previous findings from the European Active Surveillance Study on Intrauterine Devices (EURAS-IUD) that focused on the occurrence of uterine perforations and unintended pregnancies in LNG-IUD 20 and Cu-IUD users [9, 10].

The here presented data aim to describe characteristics of IUD users and prescription determinants. Also, country-specific differences in routine clinical practice will be assessed to describe general trends in IUD use across Europe.

Methods

Study design

EURAS-LCS12 was approved by the Pharmacovigilance Risk Assessment Committee (PRAC), and the protocol and redacted abstract are available on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (www.ENCePP.com, EU PAS registry number EUPAS6476). Enrolment started in June 2014. The study is ongoing and planned to end by mid-2026. The study is conducted in multiple sites in ten European countries (Austria, Czech Republic, Finland, France, Germany, Italy, Poland, Spain, Sweden, United Kingdom [UK]). After enrolment, study participants are followed-up via direct contact for 3 to 5 years, depending on the inserted IUD type, or until the discontinuation of the treatment. The primary endpoint is unintended pregnancy. Secondary endpoints include ectopic pregnancy, pelvic inflammatory disease, uterine perforation, IUD dislocations and partial expulsions. Here, we present a secondary analysis from EURAS-LCS12, which evaluated the characteristics of IUD users and reasons for IUD use.

Study setting and study population

The study population of the EURAS-LCS12 study consists of women with a newly inserted IUD. Users of all IUDs marketed in the participating countries are eligible for enrolment. Study participation is independent from IUD prescription and therefore does not interfere with

the prescription choice of the participant or the health care professional (HCP). Initially, two hormonal IUDs (LNG-IUD 8, LNG-IUD 20) and many different types of Cu-IUDs were available on the market. However, after study start in 2017, LNG-IUD 12 was introduced to the European market and also qualified users for study participation. The study now consists of five different user cohorts: LNG-IUD 8, LNG-IUD 12, LNG-IUD 20, Cu-IUDs and any other hormonal IUDs (OHIUD).

Study enrolment was carried out by medical specialists (gynaecologists), midwifes, specialised nurses, and general practitioners. Due to the observational nature of the study, participating HCPs prescribed and provided the method as they normally would. They were instructed to make treatment decisions independent of the study and then determine whether women where eligible for the study based on defined inclusion criteria. All women with a newly prescribed IUD could participate if they signed an informed consent form. Exclusion criteria were 'aged higher than 39 years' (introduced later in the study, October 2016), 'contraindications for IUD use according to the Summary of Product Characteristics' (responsibility lies with prescribing HCP), 'participation in an interventional trial on IUDs', and 'lack of written informed consent'. At study entry, the recruiting HCP and the study participant complete a baseline questionnaire capturing general characteristics, medical, sexual, and reproductive history, current co-medications, lifestyle as well as insertion-related information from the HCP for each woman (i.e., type of IUD, procedures prior/after insertion, issues after insertions, reason for IUD insertion).

The here presented data includes all women enrolled in the study until February 29, 2024 (including women > 40 years of age recruited before October 2016). The cost of IUDs or their placement was not covered or reimbursed by the study sponsor.

Statistics

Baseline characteristics of IUD user cohorts and prescription determinants were described by summary measures (arithmetic mean and standard deviation, absolute and relative frequencies) using the Statistical Analysis System (SAS; version 9.4, SAS Institute Inc. Cary, North Carolina, USA). Descriptive statistics were not hypothesis driven and did not comprise formal statistical testing.

Results

Study population and IUD usage by country

At the time of analysis (database lock February 29, 2024), 97,187 women (thereof 88,399 women < 40 years of age) were enrolled at 1,633 sites. The distribution of women across countries was as follows: Germany $N = 25{,}934$ (26.7%); UK $N = 15{,}798$ (16.3%); Spain $N = 17{,}705$ (18.2%); Sweden $N = 10{,}972$ (11.3%); France $N = 7{,}974$ (8.2%); Czech Republic $N = 7{,}155$ (7.4%); Austria $N = 4{,}502$ (4.6%); Poland $N = 3{,}243$ (3.3%); Finland $N = 2{,}646$ (2.7%); Italy $N = 1{,}258$ (1.3%). Figure 1 shows the distribution of IUD types by participating countries, whereas **Fig. 2** gives an overview of the recruitment distribution of IUDs over time in EURAS-LCS12. At study start in 2014, the distribution among available IUDs was as follows: LNG-IUD 8: 7.4%; LNG-IUD 20: 63.0%; Cu-IUD: 29.6%; OHIUD: 0.04%. The proportion of LNG-IUD 8 changed only slightly over the study period of 8 years, with the highest peak in the year 2017 of around 11.5%. In mid-2022, the proportion has dropped to 9.2%. The proportion of LNG-IUD 20 users has constantly decreased from 63.0% (year 2014) to 37.2% (year 2024), whereas the greatest decrease can be observed after 2017. LNG-IUD 12 was introduced to the European market in 2017 and showed a rapid increase of prescriptions by HCPs. Demand for Cu-IUD has risen throughout the study period by roughly 0.4% per quarter, reaching a maximum of 36.9% in the second quarter of 2022.

Participant characteristics

Baseline characteristics of the study population are summarised in Table 1. Of the 97,187 enrolled women until February 29, 2024, the mean age was 30.9 ± 7.5 years. The mean age of LNG-IUD 8 users was about 9 years lower compared with LNG-IUD 20 users and about 3 years lower in comparison with Cu-IUD users, however, the difference was smallest between LNG-IUD 8 and LNG-IUD 12 users (about 1.7 years). The body mass index (BMI) was comparable across all IUD cohorts, although LNG-IUD 20 users had a slightly higher mean BMI with the highest proportion of obese women (BMI ≥ 30 kg/m^2; 17.7%). Smokers accounted for 20.9% of the total study population, and the distribution of current smokers was comparable between the cohorts.

A higher proportion of women using LNG-IUD 8 was living single (35.6%) as compared to LNG-IUD 20 (18.7%), LNG-IUD 12 (31.7%) and Cu-IUD users (27.5%). The cohorts showed differences with respect to education and income. The proportion of study participants with a university degree was highest among Cu-IUD users (36.6%). The proportion of women without a university entrance level education was highest among the LNG-IUD 20 and LNG-IUD 12 cohorts. More LNG-IUD 8, LNG-IUD 12 and Cu-IUD users were categorised in the two lower income categories (57.2%, 56.2% and 58.9%, respectively), whereas LNG-IUD 20 users were more often classified in the two higher income categories (51.0%).

The study questionnaire at baseline also asked about the sexual history and behaviour of participants: most participants (61.3%) reported up to five sexual partners in their lifetime, about a third (30.2%) reported more than

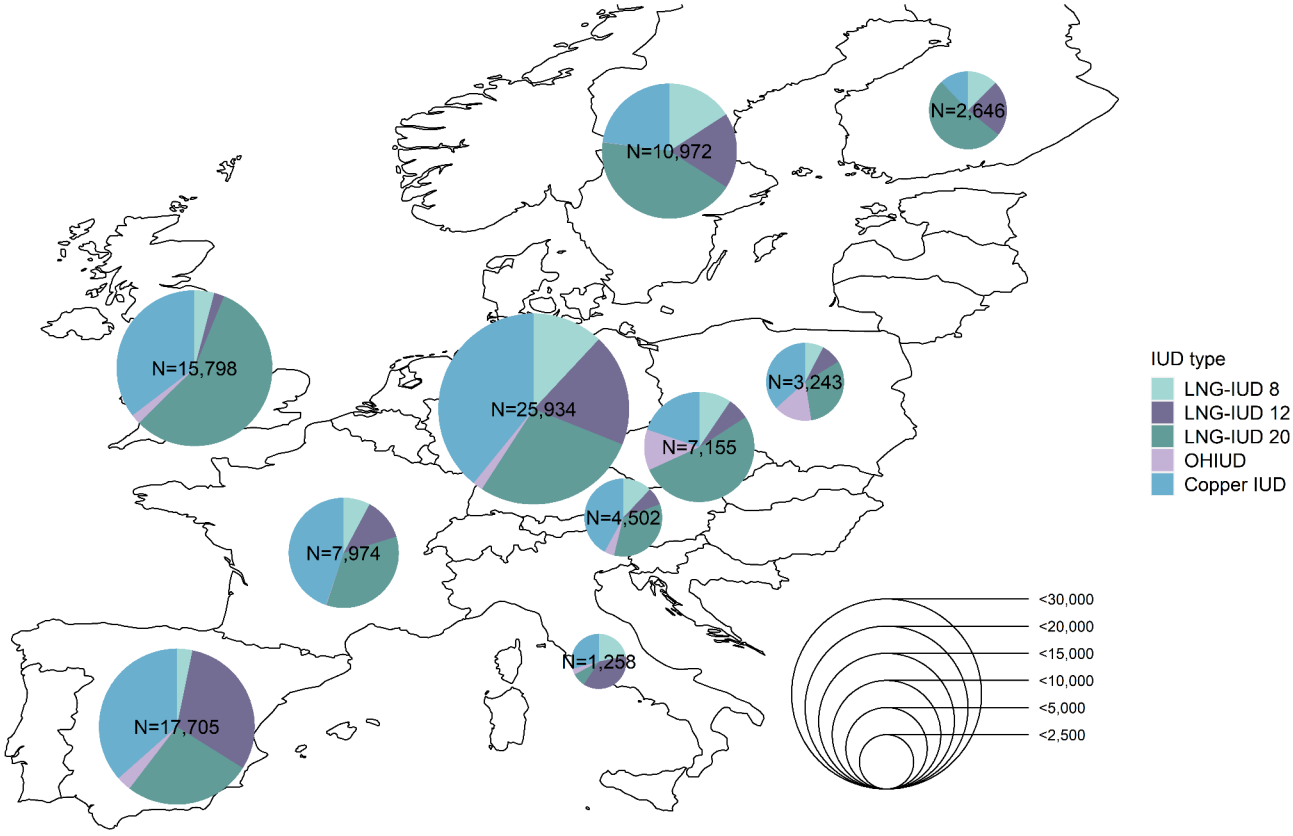

Fig. 1 Distribution of different IUD type users by country

five and up to 20 sexual partners, 5.4% had more than 20 sexual partners in their lifetime, and no values were reported by 3.1% of participants. Proportions within each category were comparable among cohorts. Similarly, the number of sexual partners during the past 12 months was also comparable between cohorts: most participants (81.7%) reported one sexual partner, followed by two to five sexual partners which were reported by 11.9% of all participants.

80% of participants had previously used any form of hormonal contraception before study start and 35.6% reported to have previously used an IUD.

Gynaecological and medical history of IUD users

The gynaecological and medical history of participants is summarised in Table 2. IUD cohorts differed by IUD user status: 76.4% of LNG-IUD 8 users and 77.0% of LNG-IUD 12 users were first time IUD users, compared to 51.9% of LNG-IUD 20 users and 67.3% of Cu-IUD users. Of all 8,746 LNG-IUD 8 users, 932 (10.7%) were consecutive users (i.e., the previous IUD was removed immediately before insertion of the new IUD). Approximately 27% of all LNG-IUD 20 users were consecutive users.

Notable differences were seen with regards to gravidity and parity: 38.6% of LNG-IUD 8 and 52.2% of LNG-IUD 12 users had ever been pregnant compared to 87.0% of LNG-IUD 20 and 64.4% of Cu-IUD users. Among gravid women of all IUDs, 40.8% of women had experienced a miscarriage or stillbirth, or had a termination of the pregnancy. There, the highest proportion was found in LNG-IUD 8 users with 46.5%, whereas the lowest proportion was documented for users of OHIUD with 31.2%. The proportion of parous women (i.e., having had at least one live birth) among those who had been pregnant was lowest in the LNG-IUD 8 cohort (79.4%) and highest in users of OHIUD (98.0%). The mean number of pregnancies was comparable between cohorts, ranging from an average of 1.9 pregnancies among LNG-IUD 8 users to 2.5 pregnancies in the LNG-IUD 20 cohort.

The medical history (e.g., occurrence of pulmonary embolism, deep-vein thrombosis, sexually transmitted disease, other serious disease or any surgery) of women was comparable between cohorts except for history of endometriosis and benign tumor of the uterus which were slightly more pronounced in the LNG-IUD 20 users.

Reasons for IUD use

HCP-reported reasons for choosing an IUD are shown in Table 3. The most frequent reason was birth control for all five cohorts (93.0–99.0%). The second most frequently reported reason for use of hormonal IUDs was HMB (LNG-IUD 8: 9.0%, LNG-IUD 12: 13.4%, and LNG-IUD

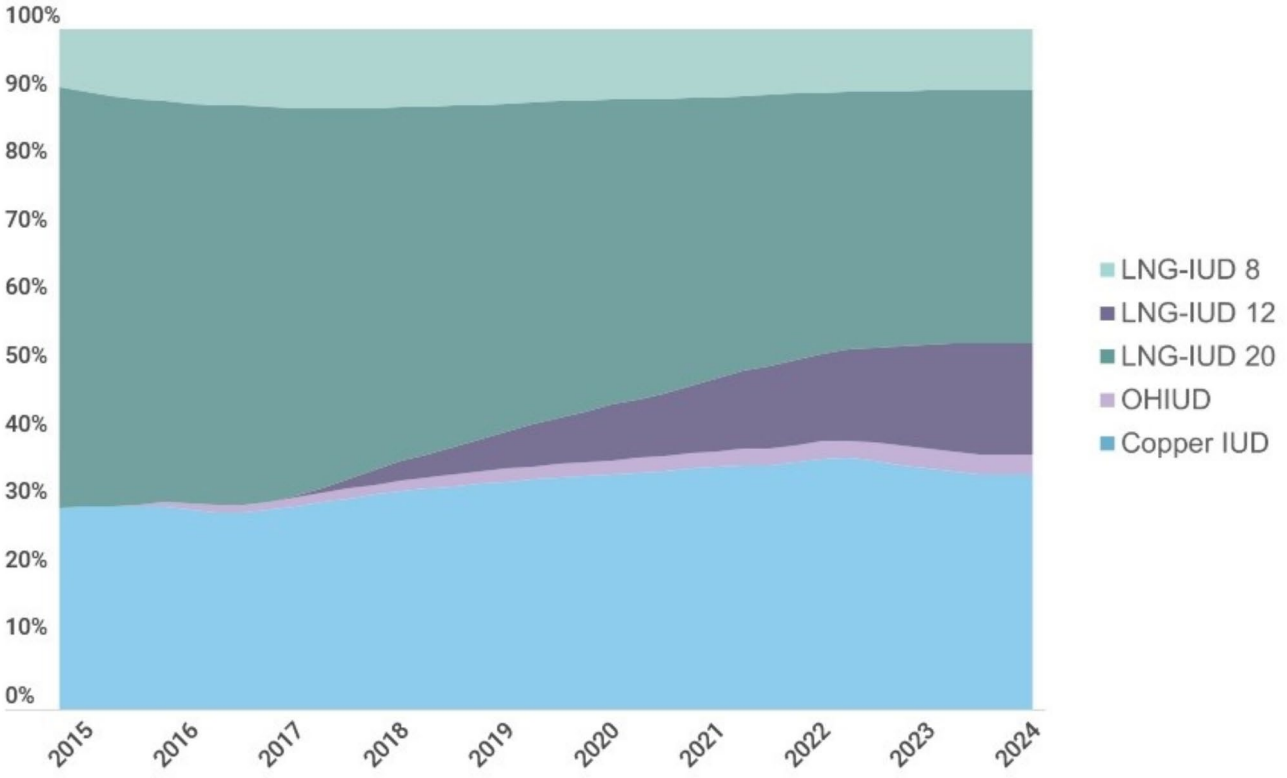

Fig. 2 Time-dependent cohort distribution

20: 25.8%; multiple reasons allowed). For Cu-IUDs, emergency contraception was the second most common reported reason in 1.9% of the women. Other reasons which were reported by HCPs included endometriosis, dysmenorrhea or cycle control. Among women prescribed with hormonal IUDs, 0.7% of LNG-IUD 8, 1.2% of LNG-IUD 12 and 5.4% of LNG-IUD 20 users chose the device solely for the treatment of HMB.

Regional differences regarding reasons for IUD use are displayed in **Fig. 3**. The main reason for using LNG-IUD 8 was contraception across all countries (between 93.2% and 99.6%), followed by HMB (between 2.8% and 35.5%). Across all IUDs, the lowest proportion of women naming contraception as main reason for IUD use was recorded in Spanish LNG-IUD 20 users with 84.6%. Among hormonal IUD users, the highest proportion of women with an indication for emergency contraception was found in Italian LNG-IUD 20 users (1.0%).

A similar picture was found for LNG-IUD 12: In addition to contraception, between 4.8% (Sweden) and 34.8% (Italy) of participating women were using LNG IUD 12 for HMB. The proportion of women naming HMB as reason for IUD use was highest in LNG-IUD 20 users (between 9.9% in Germany and 68.0% in Italy).

Across all devices and countries, 0.7% of all IUD insertions were due to emergency contraception, which were mainly driven by Cu-IUD users in the UK (6.7%) and Germany (1.9%). Though, like hormonal IUDs, Cu-IUDs were primarily used for contraception (98.2–100% across all countries).

Discussion

Findings and interpretation

Our description of a very large population of IUD users provides valuable insights in IUD use across Europe: besides a comprehensive characterisation of IUD users, prescription and usage patterns can be observed regarding the participating countries, as well as the IUDs included in the study. As expected, most of the investigated aspects varied only slightly across cohorts and countries, yet some trends and differences were still noteworthy.

While women using the lower dose LNG-IUDs (i.e., LNG-IUD 8 and LNG-IUD 12) showed a similar demographic and clinical profile to participants using Cu-IUD, users of the highest dose LNG-IUD (i.e., LNG-IUD 20) differed in age, parity and indications. This disparity might even have been mitigated by an age restriction of a maximum of 40 years introduced shortly after study start. There were notable differences in prescription of IUDs across age groups, with users of low-dose LNG-IUDs being younger and more often nulliparous. Since prescribing HCPs could actively influence the women's choice of IUD, one might think that low prescription

Table 1 Population characteristics of study participants with IUD

	LNG-IUD 8	LNG-IUD 12	LNG-IUD 20	Copper IUD	OHIUD	Total
Total number of women	8,746 (100%)	15,857 (100%)	36,185 (100%)	33,468 (100%)	2,931 (100%)	97,187 (100%)
Population characteristics						
Age [Mean ± SD]	26.2 ± 6.6	27.9 ± 6.6	34.6 ± 7.3	29.5 ± 6.6	32.9 ± 5.8	30.9 ± 7.5
Age category:						
< 20 years	1,570 (18.0%)	2,074 (13.1%)	968 (2.7%)	2,367 (7.1%)	62 (2.1%)	7,041 (7.2%)
20 to < 30 years	4,898 (56.0%)	7,391 (46.6%)	8,150 (22.5%)	15,616 (46.7%)	794 (27.1%)	36,849 (37.9%)
30 to < 40 years	2,034 (23.3%)	6,392 (40.3%)	20,040 (55.4%)	14,099 (42.1%)	1,944 (66.3%)	44,509 (45.8%)
≥ 40 years*	244 (2.8%)	0 (0.00%)	7,027 (19.4%)	1,386 (4.1%)	131 (4.5%)	8,788 (9.0%)
BMI [Mean ± SD]	23.8 ± 4.6	24.3 ± 4.9	25.6 ± 5.4	24.5 ± 4.9	25.5 ± 5.3	24.9 ± 5.1
BMI category:						
< 20	1,352 (15.5%)	2,179 (13.7%)	3,304 (9.1%)	4,463 (13.3%)	244 (8.3%)	11,542 (11.9%)
≥ 20 and < 25	4,909 (56.1%)	8,229 (51.9%)	16,616 (45.9%)	16,873 (50.4%)	1,363 (46.5%)	47,990 (49.4%)
≥ 25 and < 30	1,600 (18.3%)	3,482 (22.0%)	9,473 (26.2%)	7,498 (22.4%)	812 (27.7%)	22,865 (23.5%)
≥ 30 and < 35	581 (6.6%)	1,208 (7.6%)	4,134 (11.4%)	2,916 (8.7%)	337 (11.5%)	9,176 (9.4%)
≥ 35	252 (2.9%)	581 (3.7%)	2,296 (6.3%)	1,370 (4.1%)	148 (5.0%)	4,647 (4.8%)
Missing	52 (0.6%)	178 (1.1%)	362 (1.0%)	348 (1.0%)	27 (0.9%)	967 (1.0%)
Educational level						
Less than university entrance level	2,182 (24.9%)	4,902 (30.9%)	11,411 (31.5%)	9,394 (28.1%)	836 (28.5%)	28,725 (29.6%)
University entrance level	3,571 (40.8%)	5,189 (32.7%)	11,415 (31.5%)	11,069 (33.1%)	895 (30.5%)	32,139 (33.1%)
More than university entrance level	2,802 (32.0%)	5,241 (33.1%)	12,676 (35.0%)	12,235 (36.6%)	1,069 (36.5%)	34,023 (35.0%)
Missing	191 (2.2%)	525 (3.3%)	683 (1.9%)	770 (2.3%)	131 (4.5%)	2,300 (2.4%)
Smoking status						
Ex-smoker	1,262 (14.4%)	2,296 (14.5%)	7,347 (20.3%)	5,510 (16.5%)	556 (19.0%)	16,971 (17.5%)
Never smoker	5,567 (63.7%)	10,019 (63.2%)	21,319 (58.9%)	20,496 (61.2%)	1,691 (57.7%)	59,092 (60.8%)
Current smoker	1,861 (21.3%)	3,390 (21.4%)	7,302 (20.2%)	7,164 (21.4%)	638 (21.8%)	20,355 (20.9%)
Missing	56 (0.6%)	152 (1.0%)	217 (0.6%)	298 (0.9%)	46 (1.6%)	769 (0.8%)
Alcohol consumption						
Once/week or less	7,597 (86.9%)	13,651 (86.1%)	30,486 (84.3%)	28,766 (86.0%)	2,518 (85.9%)	83,018 (85.4%)
More than once/week	952 (10.9%)	1,717 (10.8%)	4,883 (13.5%)	3,793 (11.3%)	286 (9.8%)	11,631 (12.0%)
Missing	197 (2.3%)	489 (3.1%)	816 (2.3%)	909 (2.7%)	127 (4.3%)	2,538 (2.6%)
Marital status						
Living single	3,116 (35.6%)	50,23 (31.7%)	6,757 (18.7%)	9,211 (27.5%)	427 (14.6%)	24,534 (25.2%)
Living together with a partner	5,304 (60.6%)	9,972 (62.9%)	28,628 (79.1%)	23,313 (69.7%)	2,368 (80.8%)	69,585 (71.6%)
Missing	326 (3.7%)	862 (5.4%)	800 (2.2%)	944 (2.8%)	136 (4.6%)	3,068 (3.2%)
Monthly household income						
Two lowest categories	4,999 (57.1%)	8,915 (56.2%)	14,768 (40.8%)	19,698 (58.8%)	1,141 (38.9%)	49,521 (50.9%)
Two highest categories	2,883 (33.0%)	5,388 (33.9%)	18,461 (51.1%)	11,382 (34.0%)	1,544 (52.7%)	39,658 (40.8%)
Missing	864 (9.9%)	1,554 (9.8%)	2,956 (8.2%)	2,388 (7.1%)	246 (8.4%)	8,008 (8.2%)
Sexual history						
Number of sexual partners in lifetime						
1–5	5,150 (58.9%)	10,011 (63.1%)	21,966 (60.7%)	20,545 (61.4%)	1,923 (65.6%)	59,595 (61.3%)
6–20	2839 (32.5%)	4482 (28.3%)	11,116 (30.7%)	10,161 (30.4%)	777 (26.5%)	29,375 (30.2%)
More than 20	542 (6.2%)	833 (5.3%)	1,912 (5.3%)	1,863 (5.6%)	88 (3.0%)	5,238 (5.4%)
Missing	215 (2.5%)	531 (3.3%)	1,191 (3.3%)	899 (2.7%)	143 (4.9%)	2,979 (3.1%)
Number of sexual partners in last 12 months						
0	243 (2.8%)	447 (2.8%)	944 (2.6%)	693 (2.1%)	167 (5.7%)	2,494 (2.6%)
1	6,394 (73.1%)	12,301 (77.6%)	31,423 (86.8%)	26,788 (80.0%)	2,463 (84.0%)	79,369 (81.7%)
2–5	1,721 (19.7%)	2,370 (14.9%)	2,534 (7.0%)	4,740 (14.2%)	158 (5.4%)	11,523 (11.9%)
More than 5	180 (2.1%)	244 (1.5%)	300 (0.8%)	443 (1.3%)	9 (0.3%)	1,176 (1.2%)
Missing	208 (2.4%)	495 (3.1%)	984 (2.7%)	804 (2.4%)	134 (4.6%)	2,625 (2.7%)
Vaccinated against HPV						
Yes	2,872 (32.8%)	6,098 (38.5%)	4,691 (13.0%)	8,100 (24.2%)	477 (16.3%)	22,238 (22.9%)
No	5,243 (59.9%)	8,595 (54.2%)	29,639 (81.9%)	23,340 (69.7%)	2,298 (78.4%)	69,115 (71.1%)

Table 1 (continued)

	LNG-IUD 8	LNG-IUD 12	LNG-IUD 20	Copper IUD	OHIUD	Total
Missing	631 (7.2%)	1,164 (7.3%)	1,855 (5.1%)	2,028 (6.1%)	156 (5.3%)	5,834 (6.0%)
Previous use of any hormonal contraception						
Yes	7,245 (82.8%)	12,401 (78.2%)	29,395 (81.2%)	26,010 (77.7%)	2,253 (76.9%)	77,304 (79.5%)
No	1,386 (15.8%)	3,198 (20.2%)	6,066 (16.8%)	6,990 (20.9%)	644 (22.0%)	18,284 (18.8%)
Missing	115 (1.3%)	258 (1.6%)	724 (2.0%)	468 (1.4%)	34 (1.2%)	1,599 (1.6%)
Previous IUD use						
Yes	2,049 (23.4%)	3,574 (22.5%)	17,308 (47.8%)	10,856 (32.4%)	856 (29.2%)	34,643 (35.6%)
No	6,682 (76.4%)	12,209 (77.0%)	18,784 (51.9%)	22,525 (67.3%)	2,072 (70.7%)	62,272 (64.1%)
Missing	15 (0.2%)	74 (0.5%)	93 (0.3%)	87 (0.3%)	3 (0.1%)	272 (0.3%)

BMI: body mass index; HPV: human papillomavirus; IUD: intrauterine device; LNG: levonorgestrel; OHIUD: other hormonal IUD; SD: standard deviation

Note: Data are presented for all women enrolled (including women > 39 years of age). *Exclusion criterion 'aged higher than 39 years' was introduced to the study in October 2016

Table 2 Medical characteristics of study participants

	LNG-IUD 8	LNG-IUD 12	LNG-IUD 20	Copper IUD	OHIUD	Total
Total number of women	8,746 (100%)	15,857 (100%)	36,185 (100%)	33,468 (100%)	2,931 (100%)	97,187 (100%)
Gynaecological history						
IUD user status						
First-time user	6,682 (76.4%)	12,209 (77.0%)	18,784 (51.9%)	22,525 (67.3%)	2,072 (70.7%)	62,272 (64.1%)
Repeated user	1,117 (12.8%)	2,028 (12.8%)	7,602 (21.0%)	6,773 (20.2%)	469 (16.0%)	17,989 (18.5%)
Consecutive user	932 (10.7%)	1546 (9.7%)	9,706 (26.8%)	4,083 (12.2%)	387 (13.2%)	16,654 (17.1%)
Ever been pregnant (Gravidity)	3,374 (38.6%)	8,279 (52.2%)	31,467 (87.0%)	21,543 (64.4%)	2,632 (89.8%)	67,295 (69.2%)
Thereof						
Ever had a termination/miscarriage/ stillbirth[a]	1,570 (46.5%)	3,446 (41.6%)	11,794 (37.5%)	9,821 (45.6%)	822 (31.2%)	27,453 (40.8%)
At least one live birth[a]	2,678 (79.4%)	7,379 (89.1%)	30,566 (97.1%)	19,381 (90.0%)	2,580 (98.0%)	62,584 (93.0%)
Ever had an ectopic pregnancy[a]	59 (1.7%)	185 (2.2%)	664 (2.1%)	404 (1.9%)	62 (2.4%)	1,374 (2.0%)
Number of pregnancies [Mean ± SD][a]	1.9 ± 1.2	2.1 ± 1.2	2.5 ± 1.3	2.4 ± 1.4	2.3 ± 1.2	2.4 ± 1.3
Breastfeeding at time of IUD insertion[b]	761 (28.4%)	1,853 (25.1%)	4,710 (15.4%)	4,400 (22.7%)	585 (22.7%)	12,309 (19.7%)
Medical history[c]						
PE or DVT	80 (0.9%)	116 (0.7%)	403 (1.1%)	357 (1.1%)	25 (0.9%)	981 (1.0%)
Endometriosis	86 (1.0%)	194 (1.2%)	1,111 (3.1%)	170 (0.5%)	73 (2.5%)	1,634 (1.7%)
Benign tumor of the uterus	68 (0.8%)	167 (1.1%)	906 (2.5%)	273 (0.8%)	109 (3.7%)	1,523 (1.6%)
Sexually transmitted diseases	654 (7.5%)	972 (6.1%)	2,211 (6.1%)	1,985 (5.9%)	72 (2.5%)	5,894 (6.1%)
Cancer	37 (0.4%)	101 (0.6%)	295 (0.8%)	260 (0.8%)	22 (0.8%)	715 (0.7%)
Other serious diseases	359 (4.1%)	740 (4.7%)	1,757 (4.9%)	1,318 (3.9%)	142 (4.8%)	4,316 (4.4%)
Any surgery	2,405 (27.5%)	4,629 (29.2%)	12,366 (34.2%)	9,514 (28.4%)	961 (32.8%)	29,875 (30.7%)

DVT: deep vein thrombosis; IUD: intrauterine device; LNG: levonorgestrel; OHIUD: other hormonal IUD; PE: pulmonary embolism; SD: standard deviation

[a]Number of women ever been pregnant is taken as the denominator; [b]Number of women with at least one live birth is taken as the denominator; [c]Women may appear in more than one category

Note: Data are presented for all women enrolled (including women > 40 years of age). Frequencies might not always add up to 100% since the number of missing values is not reported in the table

Table 3 Prescription determinants of intrauterine devices

	LNG-IUD 8	LNG-IUD 12	LNG-IUD 20	Copper IUD	OHIUD	Total
Total number of women	8,746 (100%)	15,857 (100%)	36,185 (100%)	33,468 (100%)	2,931 (100%)	97,187 (100%)
Contraception	8,596 (98.3%)	15,490 (97.7%)	33,566 (92.8%)	33,134 (99.0%)	2,774 (94.6%)	93,560 (96.3%)
Emergency contraception	6 (0.07%)	14 (0.09%)	33 (0.09%)	648 (1.9%)	1 (0.03%)	702 (0.7%)
Heavy menstrual bleeding	789 (9.0%)	2,123 (13.4%)	9,350 (25.8%)	68 (0.2%)	645 (22.0%)	12,975 (13.4%)
Heavy menstrual bleeding only	60 (0.7%)	196 (1.2%)	1,958 (5.4%)	6 (0.02%)	102 (3.5%)	2,322 (2.4%)
Hormonal replacement therapy	26 (0.3%)	29 (0.2%)	288 (0.8%)	0 (0.00%)	14 (0.5%)	357 (0.4%)
Others	265 (3.0%)	660 (4.2%)	1,413 (3.9%)	31 (0.09%)	165 (5.6%)	2,534 (2.6%)

IUD: intrauterine device; LNG: levonorgestrel; OHIUD: other hormonal IUD

Note: Women may appear in more than one category

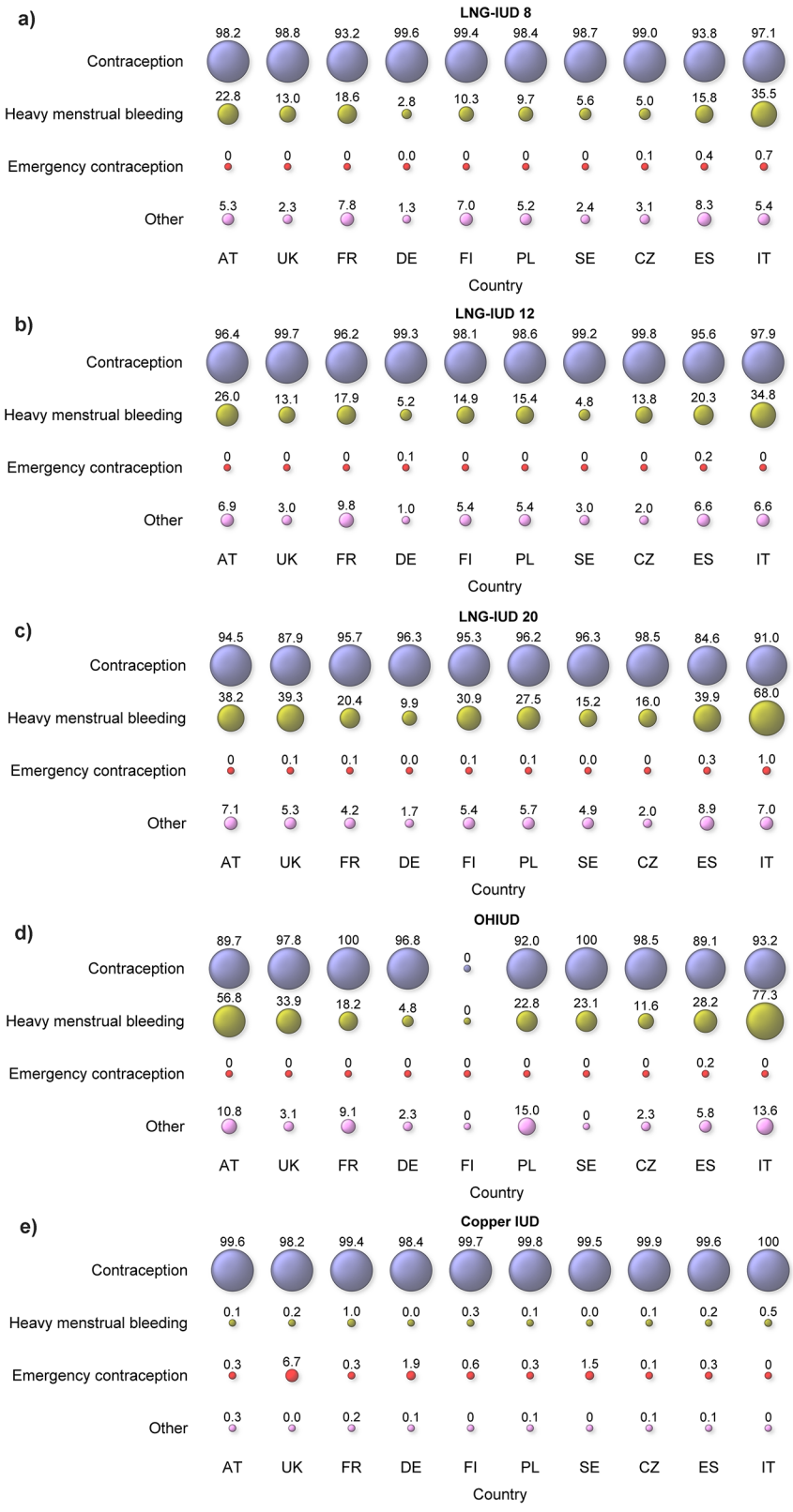

Fig. 3 Determinants for prescribing IUDs per country

rates of higher-dose LNG-IUDs in younger cohorts may result from the assumption that smaller forms of LNG-IUDs may be easier to insert in younger and/or nulliparous women [11] and are associated with less pain [12]. Since older women are more likely to have had children and have completed their family planning, they might rather use an IUD which is approved for a longer time of usage. Despite a lack of recommendations regarding which IUD model to insert [13, 14], it has been shown that parous women use more frequently larger IUDs and IUDs with a longer labelled duration of use compared to nulliparous women [15]. In line with this, a woman's parity appeared to be the most important influencing factor for the largely varying Cu-IUD types prescribed by HCPs in the LCS12 study [15]. In countries, where contraception methods were not reimbursed (i.e., Germany) costs of the IUD might also have impacted the women's choice.

Among devices, LNG-IUD 20 users had the highest mean BMI (25.6 kg/m²). The mechanism of action of IUDs is based on local effects and does not depend on plasma levels. Therefore, body weight was not expected to affect contraceptive effectiveness. However, it seemed that HCPs tended to prescribe higher-dose LNG IUDs to women with higher BMI nevertheless. Also, with a mean BMI of 26.3 kg/m² across all IUDs, IUD users in the UK tended to be heavier than the overall study population (mean BMI: 24.9 kg/m²; across all IUDs and countries). This also mirrored trends in the general population [16], and could suggest that the study population is a fair representation of the general population.

Since LNG-IUD 20 was also approved for the treatment of HMB and endometrium protection during post menopause hormone therapy [3, 17, 18], the prescribing behaviour of HCPs showed that it is frequently used for its non-contraceptive benefits. Its use was frequent in women suffering from HMB and appeared to be the preferred therapy for these symptoms [19]. Other uterine diseases (e.g., adenomyosis and the presence of fibroids) were found to be independent factors associated with the prescription of high-dose LNG-IUDs [18]. Findings of EURAS-LCS12 were consistent with research showing that during unbiased counselling, many older women (≥ 35 years) preferred LNG-IUDs over Cu-IUDs because of their benefits in management of menstrual irregularities or HMB [20, 21]. Frequencies of HMB as a reason for LNG-IUD 20 use varied by countries, with Italy and Spain showing the highest proportions. The National Health System in Spain offered this device free of charge only to women with HMB. Although menstrual bleeding could be measured in straightforward clinical categories [22, 23], these clinical definitions might not be in line with the women's or HCPs' perception of normal or HMB which also significantly varies by country [24]. Contrary to our findings, it has been shown that women's preference for less frequent menstrual bleeding or amenorrhea, which are characteristics induced by LNG-IUDs use, was between 4% and 22% in Mediterranean countries [25], whereas in other European countries it varied between 19% and 53% [25, 26]. Women from predominantly Roman Catholic countries (e.g., Spain, Italy, Poland, Hungary) seemed to have similar preferences on the frequency of menstrual bleeding [25, 27]. Alternatively, observed differences could also be based on different marketing orientations throughout Europe. Furthermore, access to surgical procedures (i.e., endometrial ablation/resection; hysterectomy) or dissimilar advice on treatment given by the HCP (LNG-IUD vs. hysterectomy) might have been related to these differences.

Our results also demonstrated a frequent usage of LNG-IUD 8 and LNG-IUD 12 for HMB in addition to contraception. However, the only approved indication for LNG-IUDs containing less than 52 mg LNG (e.g., LNG-IUD 8 and LNG-IUD 12) is contraception [4, 5]. Since high-dose LNG-IUD therapy significantly and effectively reduces menstrual bleeding in participants with HMB, it might seem reasonable to the prescribing HCPs that this was also true for low-dose IUDs. To the best of our knowledge, studies on the frequency and effectiveness of low-dose LNG-IUD in women suffering from HMB are not available. Insertions of low-dose LNG-IUDs also resulted in uniform suppression of endometrial proliferation, thin epithelium and decidualisation of the stroma which decreased menstrual blood loss [28]. However, it remains to be evaluated whether also low-dose LNG-IUDs are effective in treating abnormal uterine bleeding without structural etiology. Generally, IUDs were used almost exclusively for contraceptive reasons, so that off-label use was negligible. However, favourable concomitant effects such as reduction of bleeding intensity and emergency contraception may have impacted the choice between hormonal and copper IUDs.

Strengths and limitations

With a current study population of close to 100,000 IUD users from ten European countries, findings of the EURAS-LCS12 rest on a robust dataset that may be considered representative for the general population of European IUD users. Designed as an observational real-world study, prescription and use of IUDs are unaffected by study participation, and thus allows for a credible representation of routine practice. With a follow-up duration of 3 to 5 years (depending on the IUD), not only snapshots can be derived from the study, but rather comprehensive overviews of IUD usage throughout the approved duration of the respective devices.

Yet, observational studies may be prone to selection and recall bias. While the strength of an observational design is its ability to closely observe individuals in a

real-world setting and to better reflect clinical practice, the resulting populations of study participants and treating HCPs may be determined by individual preferences, practice patterns, or policy decisions. In addition, there are disparities in access to care, and absence of reimbursement of contraceptives in some of the study countries. Still, the chosen study design minimises the impact of bias and loss-to-follow-up. Additionally, since the enrolled cohort was mainly limited to women below the age of 40 years, frequencies of reasons for IUD use beyond contraception, especially with respect to HMB might differ in women of higher age.

Conclusion

We described a large European population of IUD users within the framework of the observational EURAS-LCS12 study. It is a thoroughly designed post-market surveillance study providing insight on the use of IUDs. Users of low-dose LNG-IUDs and Cu-IUDs showed a similar demographic and clinical profile, while the higher-dose LNG-IUDs appeared to be used increasingly among older and parous women. LNG-IUD 20 was frequently used for its additional approved indication of HMB. LNG-IUD 8 and LNG-IUD 12 were occasionally used for HMB in addition to contraception, especially in Italy, Spain, and Austria. It remains to be evaluated whether also low-dose LNG-IUDs are effective in treating abnormal uterine bleeding.

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Author contributions

Conception and study design: K.H., A.B., L.E., C.H. Substantial contribution to acquisition, analysis, or interpretation of data: all authors. Data management and statistical analysis: A.B., M.R., T.B., J.L., M.V., Drafting the manuscript: L.E., M.K., T.B., S.v.S., K.H. Revising manuscript critically for important intellectual content: all authors.All authors have read and approved the manuscript in its current form.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

EURAS-LCS12 was approved by the relevant Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and was conducted in compliance with the IEC/IRB, informed consent regulations, the declaration of Helsinki [29], and the Good Epidemiological Practice (GEP)/ Good pharmacovigilance practices (GVP)/ Good Pharmacoepidemiology Practice (GPP) guidelines [30]. Written informed consent for use of a participant's sensitive data was obtained from the participant, or their legally acceptable representative, before entry into the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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