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Original article

Safety of levonorgestrel 52 mg intrauterine system compared to copper intrauterine device: a population-based cohort study☆,☆☆,★,★★

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ABSTRACT

Objective: To compare the risk of all-cause death, hospitalizations (any cause), ectopic pregnancy, pelvic inflammatory disease or infection, uterine perforation, device removal, neuro-psychiatric drugs initiation, or new psychiatric visit(s) between levonorgestrel (LNG) 52 mg intrauterine system (IUS) and copper intrauterine device (IUD) users in France.

Study design: We identified a historical cohort of women aged 20–55 years with a first dispensing of either LNG 52 mg IUS or copper-IUD between January 1, 2010, and December 31, 2014, in the French National Claims database, SNDS. We used propensity score matching to balance the two groups on baseline sociodemographic and clinical characteristics to minimize confounding. We estimated Cox proportional hazards models to compare health outcomes between LNG 52 mg IUS and copper-IUDs users.

Results: We matched 9318 LNG 52 mg IUS users (mean age 36.2±6.8 years) to 10,185 copper-IUD users (mean age 35.4±7.1 years). After matching and age-adjustment, LNG 52 mg IUS users had a slightly higher risk of anxiolytic drugs initiation (HR 1.08, 95%CI 1.01–1.15) and device removal (HR 1.05, 95%CI 1.01–1.10) compared to copper-IUD users, with no differences for other studied outcomes.

Conclusion: French IUS users report slightly more anxiolytic treatment initiation and IUD removal compared to copper-IUD users. These results are consistent with a potential pharmacovigilance signal of anxiety-related disorders in LNG 52 mg IUS users.

Implications statement: In French LNG 52 mg IUS users, there was slightly more anxiolytic treatment initiation and IUD removal compared to copper-IUD users. No risk difference was found for all-cause death, hospitalizations, ectopic pregnancy, pelvic disorders, and uterine perforation. We cannot exclude that the associations are related to differences in characteristics of women who chose each type of type of IUD.

1. Introduction

Copper and levonorgestrel intrauterine devices are common and effective reversible methods of contraception. In France, 22.8% of women aged between 15 and 49 years used an intrauterine device (IUD) in 2013 [1]; this proportion increased to 25.6% in 2016 [2]. Although rather well tolerated, IUDs can occasionally cause a variety of undesirable adverse events, which may lead to the device removal. Women have reported rare but serious complications such as ectopic pregnancy, uterine perforation, Pelvic Inflammatory Disease (PID) or infections [3–7], and also more common and benign adverse events such as abnormal bleeding and cramping [8]. With levonorgestrel (LNG) intrauterine systems (IUS), users have reported "hormonal" adverse events (ovarian cysts, acne, weight gain, depression and decreased libido) [7]. Although most adverse events are mentioned in the device instructions, French users denounced a lack of information on the possible occurrence of such events at the time of prescribing or

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inserting the device [9]. Media issues in France through May 2017 [10] led the French National Agency for Medicines to require the conduct of a pharmacovigilance national-level study to review the safety profile of LNG 52 mg IUS.

To further complement this pharmacovigilance study, we conducted a pharmacoepidemiology study to assess the risk in real-life of a range of health outcomes between LNG 52 mg IUS and copper-IUD users.

2. Material and methods

2.1. Design, setting, and participants

We used a matched historical cohort study to compare women using LNG 52 mg IUS to women using copper-IUD. We extracted data from the *Echantillon Généraliste de Bénéficiaires* (EGB), a representative 1/97th random sample of the national healthcare claims database (*Système National d'Informations Inter-Régimes de l'Assurance Maladie*, SNIIRAM), which covers 98.8% of the French population [11]. The EGB includes approximately 780,000 individuals and contains demographic information (gender, dates of birth and death), data for out-patient reimbursed healthcare expenditures (drugs, medical devices, visits, medical procedures, medical imageries or laboratory tests), hospital-discharge summaries including medical diagnoses and procedures performed during the stay, and information on specific long-term diseases (LTDs), for which patients benefit from full coverage for all medical expenses related to the disease. [12].

We included all women between 20 and 55 years who received a LNG 52 mg IUS or copper IUD between January 1, 2010 and December 31, 2014 with at least 2 years of database history, and no history of IUD use in the 2 years prior to insertion. The copper IUD types included 11 different products or an unspecified copper IUD (Table 1). The index date was the date of the first insertion.

2.2. Outcomes and follow-up

The study outcomes included a range of specific health outcomes: all-cause death, all-cause hospitalization, hospitalization for ectopic pregnancy (International Classification of Diseases-10th revision [ICD-10], code O00), hospitalization for PID (ICD-10 code T83.6), hospitalization for uterine perforation (ICD-10 code T83.3), IUD removal, and neuro-psychiatric drugs initiation or new psychiatric visit(s). We considered IUD removal when the IUD removal was not related to a subsequent hospitalization for pregnancy, childbirth or abortion identified over the following year. We defined neuro-psychiatric drugs initiation as new dispensing of antidepressant, neuroleptic, anxiolytic or anti-migraine medications among women without any dispensing of these treatments identified within the 2 years prior to index date. We identified new psychiatric visit(s) as the occurrence of new visits with a psychiatrist during the follow-up among women without any psychiatric visits identified within the 2 years prior to index date. The follow up continued from index date to the occurrence of the first identified outcome of interest or to the end of the study period (December 31, 2015), whichever came first.

Table 1
Description of the different types of copper intrauterine devices identified by their LLP code (*Liste des Produits et des Prestations*) among the users of copper intrauterine device in France (N=10,194)

n (%)	LLP Code	Commercial name	Copper surface
66 (0.7)	1,134,760	GYNELLE 375	375 mm2
24 (0.3)	1,121,125; 1,171,407	MONA LISA Cu 375	
34 (0.4)	1,101,938; 1,152,960	MULTI LOAD Cu 375	
118 (1.2)	1,122,283	7 MED 380 UT	380 mm2
77 (0.8)	1,103,848	7 MED 380 TT	
215 (2.1)	1,128,370	7 MED 380 NT	
12 (0.2)	1,106,752	MONA LISA CuT 380	
74 (0.7)	1,132,519	MONA LISA NT Cu380A	
1 (0.0)	1,132,531	NOVAPLUS T380	
1 (0.0)	1,187,615	GYNE T 380	
1 (0.0)	1,173,062	GYNE T 200	200 mm2
9571 (93.9)	1,158,536	Unspecified	-

LPP: *Liste des Produits et des Prestations* (List of Product and Benefits).

2.3. Covariates

We included age at index date and baseline comorbidities and treatments during the 2 years prior to the index date. We included information on medical comorbidities (identified using hospitalization, LTD codes and specific drugs dispensing), gynecological history (i.e., pregnancy carried to term or miscarriage, abortion, or ectopic pregnancy), gynecological services (cervical smear, pelvic ultrasonography, or mammography), previous contraceptive methods, drugs used for neuro-psychiatric conditions such as depressive disorder, psychotic disorder, anxiety or migraine, previous visits to a psychiatrist, and previous visits to a gynecologist.

2.4. Statistical analysis

We used propensity score matching to balance all of the observed covariates between treatment groups. We first estimated the regression model with treatment group (LNG 52 mg IUS /copper-IUD) as the outcome; the coefficients of this model are the propensity to be in the treatment arm, given covariates. We next used the propensity score to match LNG 52 mg IUS users with copper-IUD users applying the nearest neighbor algorithm without replacement in a ratio of up to 1:10 (see additional information in the supplementary material). We then compared covariate distributions in the full and matched samples to assess whether the matching improved balance between the groups. We used absolute standardized differences to examine covariate balance. In studies with large sample sizes, statistically significant differences are often not meaningful; the absolute standardized difference is not influenced by sample size. A standardized difference of 0.1 (10%) is commonly used to denote meaningful imbalance between groups [14].

Next, we proceeded with the main analysis using the matched sample. We examined association of IUD group and outcomes in an "*as treated*" survival analysis (women censored after IUD removal in case such had been performed). We additionally carried out a sensitivity intent-to-treat analysis in which women were considered as exposed from index date until end of follow-up, disregarding an IUD removal. For both of these analyses, we used a Cox model stratified on the matching ratio and adjusted on covariates that remained unbalanced after propensity score matching (standardized difference>10%). Association estimates were expressed in terms of adjusted hazard ratios (HR) and associated 95% confidence intervals (95%CI).

3. Results

3.1. Patients' characteristics

Overall, 22,085 women initiated LNG 52 mg IUS or copper-IUD use between January 1, 2010 and December 31, 2014, of whom 11,891 (53.8%) used LNG 52 mg IUS. Baseline characteristics of these women are described in Table 2.

Before matching, women who initiated LNG 52 mg IUS appeared older compared with women who started copper-IUD (37.8±7.0 years for LNG 52 mg IUS *vs.* 35.4±7.1 years for copper-IUD). Over the preceding 2 years, they had less history of pregnancy (31.4% *vs.* 39.0%), but more mammography examinations (16.6% *vs.* 12.9%). A lower proportion of combined hormonal contraceptive use was also found for LNG 52 mg IUS compared to copper-IUD initiators from this database, which only provides information on reimbursed contraceptive pills. Compared to copper-IUDs users, women using LNG 52 mg IUS were more likely to have a history of neuro-psychiatric drug use

Table 2
Description of patients 'characteristics at inclusion according to the type of the first reimbursed intrauterine device (levonorgestrel 52 mg or copper) over the inclusion period (2010–2014) in France, before and after matching on a propensity score (i.e., statistical analysis estimating the probability of being exposed to one or another intrauterine device conditionally on observed baseline characteristics in order to control to confounding); absolute standardized differences (in %) were used to examine covariates balance before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	LNG-IUS (n=11,891)	Copper-IUD (n=10,194)	Absolute standardized differences (%)	LNG-IUS (n=9318)	Copper-IUD (n=10,185)	Absolute standardized differences (%)
Age (years)	37.8±7.0	35.4±7.1	33.55	36.2±6.8	35.4±7.1	11.56
Comorbidities						
Ischemic heart disease	23 (0.2)	11 (0.1)	0.39	10 (0.1)	11 (0.1)	−0.01
Stroke	38 (0.3)	42 (0.4)	−0.42	30 (0.3)	41 (0.4)	−0.37
Heart failure	3 (0)	6 (0.1)	−0.15	3 (0.0)	6 (0.1)	−0.12
Peripheral arterial disease	5 (0)	10 (0.1)	−0.26	5 (0.1)	9 (0.1)	−0.16
Arrhythmias	29 (0.2)	15 (0.1)	0.44	10 (0.1)	15 (0.1)	−0.18
Valvulopathy	10 (0.1)	5 (0)	0.16	4 (0.0)	5 (0.0)	−0.03
Venous thrombosis or pulmonary embolism	16 (0.1)	29 (0.3)	−0.69	16 (0.2)	29 (0.3)	−0.52
Other cardiovascular diseases	135 (1.1)	117 (1.0)	−0.06	99 (1.1)	117 (1.1)	−0.40
Cancer	274 (2.3)	303 (3.0)	−3.07	255 (2.7)	302 (3.0)	−1.05
Diabetes	298 (2.5)	251 (2.5)	0.20	214 (2.3)	251 (2.5)	−0.77
Multiple sclerosis	47 (0.4)	35 (0.3)	0.24	36 (0.4)	35 (0.3)	0.20
Paraplegia	2 (0)	2 (0)	−0.01	2 (0.0)	2 (0.0)	0.01
Epilepsy	30 (0.3)	47 (0.5)	−0.95	29 (0.3)	46 (0.5)	−0.64
Psychiatric diseases	325 (2.7)	265 (2.6)	0.61	221 (2.4)	265 (2.6)	−1.06
Chronic respiratory insufficiency	2201 (18.5)	1822 (17.9)	1.65	1689 (18.1)	1822 (17.9)	0.62
Chronic inflammatory diseases	156 (1.3)	101 (1.0)	1.47	93 (1.0)	101 (1.0)	0.03
Chronic liver failure	42 (0.4)	43 (0.4)	−0.31	32 (0.3)	43 (0.4)	−0.36
Chronic renal failure	8 (0.1)	11 (0.1)	−0.19	6 (0.1)	11 (0.1)	−0.20
Human immunodeficiency virus	12 (0.1)	17 (0.2)	−0.30	11 (0.1)	17 (0.2)	−0.22
Chronic ethylism	52 (0.4)	50 (0.5)	−0.24	43 (0.5)	50 (0.5)	−0.14
Gynecological history						
Pregnancy (carried to term or terminated due to miscarriage)	3726 (31.3)	3973 (39.0)	−16.05	3495 (37.5)	3972 (39.0)	−3.07
Ectopic pregnancy	22 (0.2)	16 (0.2)	0.13	17 (0.2)	16 (0.2)	0.12
Abortion	538 (4.5)	588 (5.8)	−0.31	488 (5.2)	588 (5.8)	−2.35
Oestroprogestogenic contraception	3727 (31.3)	3999 (39.2)	−16.56	3428 (36.8)	3999 (39.3)	−5.10
Cervical smear,	1401 (11.8)	1273 (12.5)	−2.16	1090 (11.7)	1273 (12.5)	−2.46
Pelvic ultrasonography	1224 (10.3)	1031 (10.1)	0.59	930 (10.0)	1031 (10.1)	−0.47
Mammography	1969 (16.6)	1320 (12.9)	10.19	1256 (13.5)	1320 (13.0)	1.53
Number of gynecologist visits	2 (1;5)	2 (1;6)	−10.76	2 (0;4)	1 (0;4)	−2.10
At least one neuro-psychiatric drug	4496 (37.8)	3434 (33.7)	8.61	3178 (34.1)	3433 (33.7)	0.84
Antidepressant	1727 (14.5)	1278 (12.5)	5.81	1181 (12.7)	1278 (12.5)	0.38
Neuroleptic	196 (1.6)	190 (1.9)	−0.99	165 (1.8)	190 (1.9)	−0.43
Anxiolytic	3562 (30.0)	2748 (27.0)	6.65	2556 (27.4)	2747 (27.0)	1.03
Anti-migraine	1012 (8.5)	758 (7.4)	3.97	703 (7.5)	758 (7.4)	0.39
Number of psychiatric visits	0 (0;0)	0 (0;0)	−3.08	0 (0;0)	0 (0;0)	−2.32

LNG: levonorgestrel 52 mg intrauterine system; IUD: intra-uterine device; SD: standard deviation.
All data are presented as n (%), mean +/− standard deviation or median (1st Quartile; 3rd Quartile).

(37.8% *vs.* 33.7%), that especially concerned anxiolytic drugs and antidepressants (Table 2).

Overall 9318 (78.4%) LNG 52 mg IUS users were matched to 10,185 (99.9%) copper IUD users with similar characteristics. These characteristics were well balanced between both groups (absolute standardized difference <10%; Table 1) except for age, which remained higher in LNG 52 mg IUS users (36.2±6.8 years *vs.* 35.4±7.1 years). Unmatched patients' characteristics are described in Supplementary Table 1.

3.2. Survival analysis results

Results of the adjusted Cox regression analysis performed after propensity score matching are described in Table 3.

Over a median follow-up of 3.3 years (InterQuartile Range, IQR: 2.3–4.6 years), in the overall population, 35 (0.2%) women died, 747 (3.3%) were admitted to hospital, 50 (0.2%) had an ectopic pregnancy, 13 (0.1%) had a pelvic inflammatory disease or infection due to IUD, and 42 (0.2%) had a uterine perforation due to an IUD. Additionally, 10,379 (47.0%) removed their IUD, 5540 (25.1%) initiated a neuropsychiatric drug, and 1490 (6.7%) had a first visit with a psychiatrist.

In the *"as-treated"* analysis, we found no significant difference between LNG 52 mg IUS and copper-IUD users for the risk of death (Hazard Ratio, HR: 1.02, 95% CI 0.52–1.98), all-cause hospitalization (1.07, 1.00–1.14), ectopic pregnancy (0.73, 0.33–1.64), PID (0.80, 0.18–3.62), uterine perforation (2.19, 0.95–5.04), or new psychiatric visits (1.00, 0.90–1.11). Conversely, LNG 52 mg IUS users presented with a higher risk of IUD removal (1.05, 1.01–1.10) and anxiolytic drugs initiation (1.10, 1.01–1.21). A sensitivity analysis performed to identify IUD removal in women with at least two years of data after the device insertion showed consistent results.

The results of the sensitivity intent-to-treat analysis were mostly similar (Table 3) except for the estimate associated to the risk of uterine perforation in LNG 52 mg IUS compared to copper-IUD users (1.03, 0.56–1.89). We did not find significant association to the risk of antimigraine drugs initiation (1.14, 1.00–1.30).

4. Discussion

The present study conducted in a large cohort of French IUD users suggests that LNG 52 mg IUS present with a safety profile comparable to copper-IUDs but is associated with a significant but very low risk of anxiolytic drug use. This finding supports the safety signals identified from pharmacovigilance data in reports of adverse events from Germany or France [15].

The age of our study population may appear old (25–35 years for copper-IUD and 27–35 years for LNG IUS, [16]) compared to other populations, but it is consistent with results of an European prospective cohort of new IUD users recruited in 6 countries (mean age 33.3 years

for LNG IUS users and 37.4 for copper IUD users [17;18]). Older age may be explained by French gynecologists' reluctance to insert IUD in young and nulliparous women, although there is no contra indication. In France, IUD use concerns 4.7% of women aged 20–24 years increasing to 34.6% in women aged 34–39 years [19]. Compared to copper-IUD users, the LNG 52 mg IUS users were older users by an average of 2 years. This is consistent with French guidelines, which specify that, unlike copper-IUDs, LNG 52 mg IUS is not recommended in first intention for the contraception of nulliparous women [1,20].

As previously reported, we found a weak association of LNG exposure with anxiety. This finding is in line with results of an UK cohort study of new IUDs users (HR: 1.18, 95%CI 1.08–1.29, [21]). Our study used however a more robust statistical method. In observational studies in which treatment is not randomly assigned, PROPENSITY SCORE matching can help minimize selection bias by balancing treatment groups [13]. The use of an active comparator and of a reference group is also likely to have minimized the risk of confounding by indication or other residual confounding. In addition, as this estimate was obtained using data that pre-existed the airing of the safety signal relayed by the European Medicines Agency, it is unlikely that it has been affected by a greater scrutiny or screening in LNG 52 mg IUS compared to copper-IUD users. Although the observed association is weak, some explanations may be proposed: anxiety may be caused by the potentiation of hypothalamic–pituitary–adrenal axis responsivity of the progesterone contained in the LNG 52 mg IUS, responsible of an increasing cortisol response [22,23].

Conversely, this study found no difference between LNG 52 mg IUS and copper-IUD users for the risk of various serious adverse events known to be attributable to IUD such as ectopic pregnancy, uterine perforation or PID. The low frequency we found for these events is consistent with previous published data (0.08 to 0.20 per 1000 women-year in copper-IUD users [17,24] and 0.02 to 0.2 per 1000 women year in LNG IUS users for ectopic pregnancy [17,25], 1.1 to 1.5 per 1000 insertions in copper-IUD users [18,24] and 1.4 to 2.6 per 1000 insertions in LNG IUS users [18,25] for uterine perforation). A prospective European cohort study reported a significantly lower risk in LNG IUS users compared to copper-IUD users for ectopic pregnancy (adjusted HR: 0.26, 95% CI 0.10;0.66 [17]) and a possible higher risk of uterine perforation in LNG IUS users compared to copper-IUD users (adjusted Relative Risk: 1.6, 95%CI 1.0;2.7 [18]). Conflicting evidence persists for PID [6,19–21]. The present study also found that LNG 52 mg IUS users had a slightly higher risk of IUD removal than copper-IUD users. This can be considered as expected given that, in addition to having the same inconvenient adverse events as copper-IUDs (*e.g.* pain, irregular bleeding), LNG 52 mg IUS also may present with adverse events relating to local progestin release (bloating, weight gain, breast tenderness, or acne) [19]. These results are in line with existing literature: 24% of LNG 52 mg IUS had been removed after 1 year and 33% after 2 years, compared to 4–15% of copper-IUDs after 1 year and 22–33% after 2 years [6,19–21]. In these studies, the most frequent reason for removal was irregular bleeding [19,20]. Also, the results are inconclusive regarding the risk of migraine (as measured by anti-migraine drug initiation), being only almost significant in the sensitivity analysis, and far from such in the main analysis.

This study has several important strengths. First, it relies on a high-quality database, the EGB, which is widely used to conduct pharmacoepidemiology studies [11,26,27]. The analysis performed has strengths complementary to that relating to the nature and characteristics of the database used. We used propensity score matching to mitigate risk of confounding by both measured and unmeasured characteristics. As it was considered as a variable of primary importance, and even the matched cohort appeared mostly comparable regarding

Table 3
Description of the incidence rate and hazard ratios of various safety outcomes associated with levonorgestrel 52 mg intrauterine system (LNG 52 mg IUS) exposure in comparison with copper intrauterine device (copper-IUD) exposure estimated by a Cox regression model after propensity score matching, stratified on the matching ratio and adjusted on age, in as treated analysis (women censored after IUD removal in case such had been performed) or intent-to-treat analysis (women considered as exposed from index date until end of follow-up, disregarding an IUD removal) in France

	Patients with LNG 52 mg IUS (n=9318)			Patients with copper-IUD (n=10,185)			HR (95%CI)
	Events n (%)	Person years	Incidence/1000 person years	Events n (%)	Person years	Incidence/1000 person years	
As treated analysis							
All-cause death	17 (0.2)	16,488	1.0	18 (0.2)	17,632	1.0	1.02 (0.52; 1.98)
All-cause hospitalization	1968 (21.1)	13,162	149.5	2085 (20.5)	14,082	148.1	1.07 (1.00; 1.14)
Hospitalization for ectopic pregnancy	10 (0.2)	33,095	0.3	15 (0.2)	33,910	0.4	0.73 (0.33; 1.64)
Hospitalization for pelvic inflammatory disease or infection	3 (0.0)	33,140	0.1	4 (0.0)	33,996	0.1	0.80 (0.18; 3.62)
Hospitalization for uterine perforation	18 (0.2)	33,087	0.5	8 (0.1)	33,955	0.2	2.19 (0.95; 5.04)
IUD removal	5058 (54.3)	16,488	306.8	5321 (52.2)	17,632	301.8	1.05 (1.01; 1.10)
Neuro-psychiatric drugs initiation							
Antidepressant	504 (5.4)	29,947	16.8	505 (5.0)	31,100	16.2	1.04 (0.92; 1.18)
Neuroleptic	75 (0.8)	32,745	2.3	69 (0.7)	33,584	2.1	1.09 (0.78; 1.51)
Anxiolytic	970 (10.4)	27,119	35.8	945 (9.3)	28,422	33.3	1.10 (1.01; 1.21)
Anti-migraine	236 (2.5)	31,573	7.5	240 (2.4)	32,619	7.4	1.03 (0.86; 1.24)
New psychiatric visit(s)	719 (7.7)	30,863	23.3	771 (7.6)	31,507	24.5	1.00 (0.90; 1.11)
Intent-to-treat analysis							
All-cause death	17 (0.2)	33,157	0.5	18 (0.2)	34,019	0.5	0.99 (0.51; 1.93)
All-cause hospitalization	3821 (41.0)	24,251	157.6	4026 (39.5)	25,230	159.6	1.02 (0.97; 1.06)
Hospitalization for ectopic pregnancy	21 (0.2)	33,116	0.6	35 (0.3)	33,956	1.0	0.64 (0.37; 1.10)
Hospitalization for pelvic inflammatory disease or infection	5 (0.1)	33,143	0.2	8 (0.1)	34,000	0.2	0.74 (0.24; 2.3)
Hospitalization for uterine perforation	21 (0.2)	33,090	0.6	21 (0.2)	33,975	0.6	1.03 (0.56; 1.89)
IUD removal	5058 (54.3)	16,535	305.9	5321 (52.2)	17,685	300.9	1.05 (1.01; 1.10)
Neuro-psychiatric drugs initiation							
Antidepressant	1038 (11.1)	30,948	33.5	1011 (10.0)	31,980	31.6	1.06 (0.97; 1.16)
Neuroleptic	135 (1.4)	32,875	4.1	140 (1.4)	33,713	4.2	0.97 (0.77; 1.24)
Anxiolytic	1945 (20.9)	28,802	67.5	1910 (18.8)	29,970	63.7	1.08 (1.01; 1.15)
Anti-migraine	492 (5.3)	32,011	15.4	454 (4.5)	32,982	13.8	1.14 (1.0; 1.3)
New psychiatric visit(s)	719 (7.7)	31,173	23.1	771 (7.6)	31,982	24.1	1.0 (0.87; 1.13)

LNG 52 mg IUS: levonorgestrel 52 mg intrauterine system; IUD: intra-uterine device; HR: hazard ratio.

comorbidities and gynecological history, we also adjusted the analyses on age to strengthen the control of potential confounding. This was considered of utmost importance as the discrepancies observed for certain variables between the two patients groups after matching were likely to relate to this age difference (i.e., pregnancy history, gynecological monitoring by mammography, consumption of neuro-psychiatric drugs). Finally, the intent-to-treat sensitivity analysis performed provided similar results to those obtained using the main "*as treated*" analysis, which enhances the robustness of the results presented.

The present study has also some limitations. This study was not a randomized clinical trial, so that the results despite our best efforts might still suffer from unmeasured confounding. Although we included a number of claim-based variables in the propensity score regression model, we were not able to include variables not routinely captured in the database. For instance, some information such as results of medical examination or pregnancy screening test are not available from the database, as well as some information regarding the dispensing of non-reimbursed contraceptive pills, endometriosis. Parity is also an important confounder, which cannot be identified with accuracy in our database. As it is very correlated with age, the analyses ensure nevertheless a maximum control of this confounder by adjusting on age. As the EGB is lacking information on the cause of in- or out-patient visits, the events that can be identified from the database used are only those leading to drug prescription, medical procedure, or in-hospital diagnosis. Thus it is possible we were not able to identify all events, especially mild or moderate adverse events. However, this limitation in case identification is likely to be not differential between LNG 52 mg IUS and copper-IUD. While underascertainment of cases would decrease study power, we believe this would not have biased the effect estimates. IUD expulsion could also not be identified in the database, which could have led us to erroneously classify women as still exposed. Once again, however, this would only convey a risk of bias if the risk of spontaneous expulsion was thought to differ between LNG 52 mg IUS and copper-IUD users. Finally, we of course could not consider the size of the copper surface for copper-IUDs in our analyses which, if less than 300 mm^2 can result in an increased risk of contraceptive failure [16].

In conclusion, this study, which demonstrated a mostly similar safety profile between LNG 52 mg IUS and copper-IUD, highlighted a slight risk of anxiolytic use for LNG 52 mg IUS users. As this corroborates evidence from a recent publication and from pharmacovigilance data originating from different countries, it supports the signal of anxiety-related disorders for LNG 52 mg IUS users that was recently examined by the European authorities. However, the association we found was weak and may justify further investigation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.02.011.

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