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1 **Safety of levonorgestrel 52 mg intrauterine system compared to copper intrauterine device: a**
2 **population-based cohort study**

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30 ABSTRACT

31 **Objective**

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

36 **Study design**

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

42 **Results:** We matched 9,318 LNG 52 mg IUS users (mean age 36.2 ± 6.8 years) to 10,185 copper-IUD
43 users (mean age 35.4 ± 7.1 years). After matching and age-adjustment, LNG 52 mg IUS users had a
44 slightly higher risk of anxiolytic drugs initiation (HR 1.08, 95%CI 1.01 to 1.15) and device removal (HR
45 1.05, 95%CI 1.01 to 1.10) compared to copper-IUD users, with no differences for other studied outcomes.

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

49

50 **Key words:** Intrauterine device; levonorgestrel 52 mg intrauterine system; safety; contraceptive

51

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

57

58 1. INTRODUCTION

59 Copper and levonorgestrel intrauterine devices are common and effective reversible methods of
60 contraception. In France, 22.8% of women aged between 15 and 49 years used an intrauterine device
61 (IUD) in 2013 [1]; this proportion increased to 25.6% in 2016 [2]. Although rather well tolerated, IUDs
62 can occasionally cause a variety of undesirable adverse events, which may lead to the device removal.
63 Women have reported rare but serious complications such as ectopic pregnancy, uterine perforation,
64 Pelvic Inflammatory Disease (PID) or infections [3–7], and also more common and benign adverse
65 events such as abnormal bleeding and cramping [8]. With levonorgestrel (LNG) intrauterine systems
66 (IUS), users have reported “hormonal” adverse events (ovarian cysts, acne, weight gain, depression and
67 decreased libido) [7]. Although most adverse events are mentioned in the device instructions, French
68 users denounced a lack of information on the possible occurrence of such events **at the time of** prescribing
69 or inserting the device [9]. Media issues in France through May 2017 led the French National Agency for
70 Medicines to require the conduct of a pharmacovigilance national-level study to review the safety profile
71 of LNG 52 mg IUS.

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

74

75 2. MATERIAL AND METHODS

76 2.1. Design, setting, and participants

77 We used a matched historical cohort study to compare women using LNG 52 mg IUS to women using
78 copper-IUD. We extracted data from the *Echantillon Généraliste de Bénéficiaires* (EGB), a representative
79 1/97th random sample of the national healthcare claims database (*Système National d'Informations Inter-*
80 *Régimes de l'Assurance Maladie*, SNIIRAM), which covers 98.8% of the French population [11]. The
81 EGB includes approximately 780 000 **individuals** and contains demographic information (gender, dates of
82 birth and death), data for out-patient reimbursed healthcare expenditures (drugs, medical devices, visits,

83 medical procedures, medical imageries or laboratory tests), hospital-discharge summaries including
84 medical diagnoses and procedures performed during the stay, and information on specific Long-Term
85 Diseases (LTDs), for which patients benefit from full coverage for all medical expenses related to the
86 disease. [12].

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

91

92 *2.2. Outcomes and follow-up*

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

105

106 *2.3. Covariates*

107 We included age at index date and baseline comorbidities and treatments during the 2 years prior to the
108 index date. We included information on medical comorbidities (identified using hospitalization, LTD

109 codes and specific drugs dispensing), gynecological history (*i.e.* pregnancy carried to term or miscarriage,
110 abortion, or ectopic pregnancy), gynecological services (cervical smear, pelvic ultrasonography, or
111 mammography), previous contraceptive methods, drugs used for neuro-psychiatric conditions such as
112 depressive disorder, psychotic disorder, anxiety or migraine, previous visits to a psychiatrist, and previous
113 visits to a gynecologist.

114

115 2.4. Statistical analysis

116 We used propensity score matching to balance all of the observed covariates between treatment groups.

117 We first estimated the regression model with treatment group (LNG 52 mg IUS /copper-IUD) as the

118 outcome; the coefficients of this model are the propensity to be in the treatment arm, given covariates. We

119 next used the **propensity score** to match LNG 52 mg IUS users with copper-IUD users applying the

120 nearest neighbor algorithm without replacement in a ratio of up to 1:10 (see additional information in the

121 supplementary material). We then compared covariate distributions in the full and matched samples to

122 assess whether the matching improved balance between the groups. We used absolute standardized

123 differences to examine covariate balance. In studies with large sample sizes, statistically significant

124 differences are often not meaningful; the absolute standardized difference is not influenced by sample

125 size. A standardized difference of 0.1 (10%) is commonly used to denote meaningful imbalance between

126 groups [14].

127 Next, we proceeded with the main analysis using the matched sample. We examined association of IUD

128 group and outcomes in an “*as treated*” survival analysis (women censored after IUD removal in case such

129 had been performed). We additionally carried out a sensitivity intent-to-treat analysis in which women

130 were considered as exposed from index date until end of follow-up, disregarding an IUD removal. For

131 both of these analyses, we used a Cox model stratified on the matching ratio and adjusted on covariates

132 that remained unbalanced after **propensity score** matching (standardized difference >10%). Association

133 estimates were expressed in terms of adjusted hazard ratios (HR) and associated 95% confidence intervals

134 (95%CI).

135

136 3. RESULTS

137 3.1. Patients' characteristics

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

141 Before matching, women who initiated LNG 52 mg IUS appeared older compared with women who
142 started copper-IUD (37.8±7.0 years for LNG 52 mg IUS vs. 35.4±7.1 years for copper-IUD). Over the
143 preceding two years, they had less history of pregnancy (31.4% vs. 39.0%), but more mammography
144 examinations (16.6% vs. 12.9%). A lower proportion of combined hormonal contraceptive use was also
145 found for LNG 52 mg IUS compared to copper-IUD initiators from this database, which only provides
146 information on reimbursed contraceptive pills. Compared to copper-IUDs users, women using LNG 52
147 mg IUS were more likely to have a history of neuro-psychiatric drug use (37.8% vs. 33.7%), that
148 especially concerned anxiolytic drugs and antidepressants (Table 2).

149 Overall 9,318 (78.4%) LNG 52 mg IUS users were matched to 10,185 (99.9%) copper IUD users with
150 similar characteristics. These characteristics were well balanced between both groups (absolute
151 standardized difference <10%; Table 1) except for age, which remained higher in LNG 52 mg IUS users
152 (36.2±6.8 years vs. 35.4±7.1 years). Unmatched patients' characteristics are described in Supplementary
153 Table 1.

154

155 3.2. Survival analysis results

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

158 Over a median follow-up of 3.3 years (InterQuartile Range, IQR: 2.3-4.6 years), in the overall population,
159 35 (0.2%) women died, 747 (3.3%) were admitted to hospital, 50 (0.2%) had an ectopic pregnancy, 13
160 (0.1%) had a pelvic inflammatory disease or infection due to IUD, and 42 (0.2%) had an uterine

161 perforation due to an IUD. Additionally, 10,379 (47.0%) removed their IUD, 5,540 (25.1%) initiated a
162 neuro-psychiatric drug, and 1,490 (6.7%) had a first visit with a psychiatrist.

163 In the “*as-treated*” analysis, we found no significant difference between LNG 52 mg IUS and copper-
164 IUD users for the risk of death (Hazard Ratio, HR: 1.02, 95%CI 0.52; 1.98), all-cause hospitalization
165 (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,
166 0.95-5.04), or new psychiatric visits (1.00, 0.90-1.11). Conversely, LNG 52 mg IUS users presented with
167 a higher risk of IUD removal (1.05, 1.01-1.10) and anxiolytic drugs initiation (1.10, 1.01-1.21). A
168 sensitivity analysis performed to identify IUD removal in women with at least two years of data after the
169 device insertion showed consistent results.

170 The results of the sensitivity intent-to-treat analysis were mostly similar (Table 3) except for the estimate
171 associated to the risk of uterine perforation in LNG 52 mg IUS compared to copper-IUD users (1.03,
172 0.56-1.89). We did not find significant association to the risk of anti-migraine drugs initiation (1.14, 1.00
173 to 1.30).

174

175

176 **4. DISCUSSION**

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

181 The age of our study population may appear old (25–35 years for copper-IUD and 27–35 years for LNG
182 IUS, [16]) compared to other populations, but it is consistent with results of an European prospective
183 cohort of new IUD users recruited in 6 countries (mean age 33.3 years for LNG IUS users and 37.4 for
184 copper IUD users [17;18]). Older age may be explained by French gynecologists' reluctance to insert IUD
185 in young and nulliparous women, although there is no contra indication. In France, IUD use concerns
186 4.7% of women aged 20-24 years increasing to 34.6 % in women aged 34-39 years [19]. Compared to
187 copper-IUD users, the LNG 52 mg IUS users were older users by an average of 2 years. This is consistent
188 with French guidelines, which specify that, unlike copper-IUDs, LNG 52 mg IUS is not recommended in
189 first intention for the contraception of nulliparous women [1,20].

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

200 responsivity of the progesterone contained in the LNG 52 mg IUS, responsible of an increasing cortisol
201 response [22,23].

202 Conversely, this study found no difference between LNG 52 mg IUS and copper-IUD users for the risk of
203 various serious adverse events known to be attributable to IUD such as ectopic pregnancy, uterine
204 perforation or PID. The low frequency we found for these events is consistent with previous published
205 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
206 year in LNG IUS users for ectopic pregnancy [17, 25], 1.1 to 1.5 per 1000 insertions in copper-IUD users
207 [18, 24] and 1.4 to 2.6 per 1000 insertions in LNG IUS users [18, 25] for uterine perforation). A
208 prospective European cohort study reported a significantly lower risk in LNG IUS users compared to
209 copper-IUD users for ectopic pregnancy (adjusted HR: 0.26, 95% CI 0.10;0.66 [17]) and a possible higher
210 risk of uterine perforation in LNG IUS users compared to copper-IUD users (adjusted Relative Risk: 1.6,
211 95%CI 1.0;2.7 [18]). Conflicting evidence persists for PID [6,19-21]. The present study also found that
212 LNG 52 mg IUS users had a slightly higher risk of IUD removal than copper-IUD users. This can be
213 considered as expected given that, in addition to having the same inconvenient adverse events as copper-
214 IUDs (*e.g.* pain, irregular bleeding), LNG 52 mg IUS also **may** present with adverse events relating to
215 local progestin release (bloating, weight gain, breast tenderness, or acne) [19]. These results are in line
216 with existing literature: 24% of LNG 52 mg IUS had been removed after 1 year and 33% after 2 years,
217 compared to 4-15% of copper-IUDs after 1 year and 22-33% after 2 years [6,19-21]. In these studies, the
218 most frequent reason for removal was irregular bleeding [19,20]. Also, the results are inconclusive
219 regarding the risk of migraine (as measured by anti-migraine drug initiation), being only almost
220 significant in the sensitivity analysis, and far from such in the main analysis.

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

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

233 The present study has also some limitations. This study was not a randomized clinical trial, so that the
234 results despite our best efforts might still suffer from unmeasured confounding. Although we included a
235 number of claim-based variables in the **propensity score** regression model, we were not able to include
236 variables not routinely captured in the database. For instance, some information such as results of medical
237 examination or pregnancy screening test are not available from the database, as well as some information
238 regarding the dispensing of non-reimbursed contraceptive pills, endometriosis. Parity is also an important
239 confounder, which cannot be identified with accuracy in our database. As it is very correlated with age,
240 the analyses ensure nevertheless a maximum control of this confounder by adjusting on age. As the EGB
241 is lacking information on the cause of in- or out-patient visits, the events that can be identified from the
242 database used are only those leading to drug prescription, medical procedure, or in-hospital diagnosis.
243 Thus it is possible we were not able to identify all events, especially mild or moderate adverse events.
244 However, this limitation in case identification is likely to be not differential between LNG 52 mg IUS and
245 copper-IUD. **While underascertainment of cases would decrease study power, we believe this would not**
246 **have biased** the effect estimates. IUD expulsion could also not be identified in the database, which could
247 have led us to erroneously classify women as still exposed. Once again however, this would only convey
248 a risk of bias if the risk of spontaneous expulsion was thought to differ between LNG 52 mg IUS and
249 copper-IUD users. Finally, we of course could not consider the size of the copper surface for copper-IUDs
250 in our analyses which, if less than 300 mm² can result in an increased risk of contraceptive failure [16].

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

257

258

259 .

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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)	1134760	GYNELLE 375	
24 (0.3)	1121125 ; 1171407	MONA LISA Cu 375	375 mm ²
34 (0.4)	1101938 ; 1152960	MULTI LOAD Cu 375	
118 (1.2)	1122283	7 MED 380 UT	
77 (0.8)	1103848	7 MED 380 TT	
215 (2.1)	1128370	7 MED 380 NT	
12 (0.2)	1106752	MONA LISA CuT 380	380 mm ²
74 (0.7)	1132519	MONA LISA NT Cu380A	
1 (0.0)	1132531	NOVAPLUS T380	
1 (0.0)	1187615	GYNE T 380	
1 (0.0)	1173062	GYNE T 200	200 mm ²
9571 (93.9)	1158536	Unspecified	-

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

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=9 318)	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-uterin device; SD: standard deviation

All data are presented as n (%), mean +/- standard deviation or median (1st Quartile; 3rd Quartile)

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=10185)			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)	16488	1.0	18 (0.2)	17632	1.0	1.02 (0.52; 1.98)
All-cause hospitalization	1968 (21.1)	13162	149.5	2085 (20.5)	14082	148.1	1.07 (1.00; 1.14)
Hospitalization for ectopic pregnancy	10 (0.2)	33095	0.3	15 (0.2)	33910	0.4	0.73 (0.33; 1.64)
Hospitalization for pelvic inflammatory disease or infection	3 (0.0)	33140	0.1	4 (0.0)	33996	0.1	0.80 (0.18; 3.62)
Hospitalization for uterine perforation	18 (0.2)	33087	0.5	8 (0.1)	33955	0.2	2.19 (0.95; 5.04)
IUD removal	5058 (54.3)	16488	306.8	5321 (52.2)	17632	301.8	1.05 (1.01; 1.10)
Neuro-psychiatric drugs initiation							
Antidepressant	504 (5.4)	29947	16.8	505 (5.0)	31100	16.2	1.04 (0.92; 1.18)
Neuroleptic	75 (0.8)	32745	2.3	69 (0.7)	33584	2.1	1.09 (0.78; 1.51)
Anxiolytic	970 (10.4)	27119	35.8	945 (9.3)	28422	33.3	1.10 (1.01; 1.21)
Anti-migraine	236 (2.5)	31573	7.5	240 (2.4)	32619	7.4	1.03 (0.86; 1.24)
New psychiatric visit(s)	719 (7.7)	30863	23.3	771 (7.6)	31507	24.5	1.00 (0.90; 1.11)
Intent-to-treat analysis							
All-cause death	17 (0.2)	33157	0.5	18 (0.2)	34019	0.5	0.99 (0.51; 1.93)
All-cause hospitalization	3821 (41.0)	24251	157.6	4026 (39.5)	25230	159.6	1.02 (0.97; 1.06)
Hospitalization for ectopic pregnancy	21 (0.2)	33116	0.6	35 (0.3)	33956	1.0	0.64 (0.37; 1.10)
Hospitalization for pelvic inflammatory disease or infection	5 (0.1)	33143	0.2	8 (0.1)	34000	0.2	0.74 (0.24; 2.3)
Hospitalization for uterine perforation	21 (0.2)	33090	0.6	21 (0.2)	33975	0.6	1.03 (0.56; 1.89)
IUD removal	5058 (54.3)	16535	305.9	5321 (52.2)	17685	300.9	1.05 (1.01; 1.10)
Neuro-psychiatric drugs initiation							
Antidepressant	1038 (11.1)	30948	33.5	1011 (10.0)	31980	31.6	1.06 (0.97; 1.16)
Neuroleptic	135 (1.4)	32875	4.1	140 (1.4)	33713	4.2	0.97 (0.77; 1.24)
Anxiolytic	1945 (20.9)	28802	67.5	1910 (18.8)	29970	63.7	1.08 (1.01; 1.15)
Anti-migraine	492 (5.3)	32011	15.4	454 (4.5)	32982	13.8	1.14 (1.0; 1.3)
New psychiatric visit(s)	719 (7.7)	31173	23.1	771 (7.6)	31982	24.1	1.0 (0.87; 1.13)

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