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TABLE S1. Overview of registers, variables, and codes

Registers	Variables	Codes
Danish Civil Registration System (data since 1968)		
	Date of birth, immigration, emigration	
The Cause of Death Register (data since 1970)		
	Date of death	
Demographic Registers of Statistics Denmark		
	Educational degree	
Danish Medical Birth Register (complete data since 1973)		
	Date of childbirth	
Danish National Patient Register (complete data since 1977)		
	Polycystic ovary syndrome	ICD-8: 256.9 ICD-10: E282
	Endometriosis	ICD-8: 625.3 ICD-10: N80
	Dysmenorrhea	ICD-8: 626.3 ICD-10: N943-946
	Leiomyoma	ICD-8: 218 ICD-10: D25
	Menorrhagia	ICD-8: 626.2 ICD-10: N92
The Psychiatric Central Register (complete data since 1969 on hospital admission and 1995 on outpatient contacts)		
	Mental disorders	ICD-8: 290-315 (except 302.0 and 302.3) ICD-10: F00-99
	Depression	ICD-8: 296.09, 296.29, 298.09, 300.49, 301.19 ICD-10: F32-34, F38, F39
Danish Prescription Register (complete data since 1995)		
	LNG-IUS	ATC: G02BA03
	Other HC types	
	COC	ATC: G03AA* (except for G03AA13), G03AB*, and G03HB01
	Patch	ATC: G03AA13
	Vaginal ring	ATC: G02BB01
	POP	ATC: G03AC* (except for G03AC06 and G03AC08)
	Implant	ATC: G03AC08
	Depot injections	ATC: G03AC06
	Antidepressant medication	ATC: Codes starting with N06A
	Psychotropic drugs	ATC: Codes starting with N05 and N06

ATC, Anatomical Therapeutic Chemical Classification system; ICD-8, International Classification of Disease and Health Related Problems, 8th revision; COC, combined oral contraceptive; HC; hormonal contraception; ICD-10, 10th revision; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill

FIGURE S1. Flowchart of how study population was obtained from source population

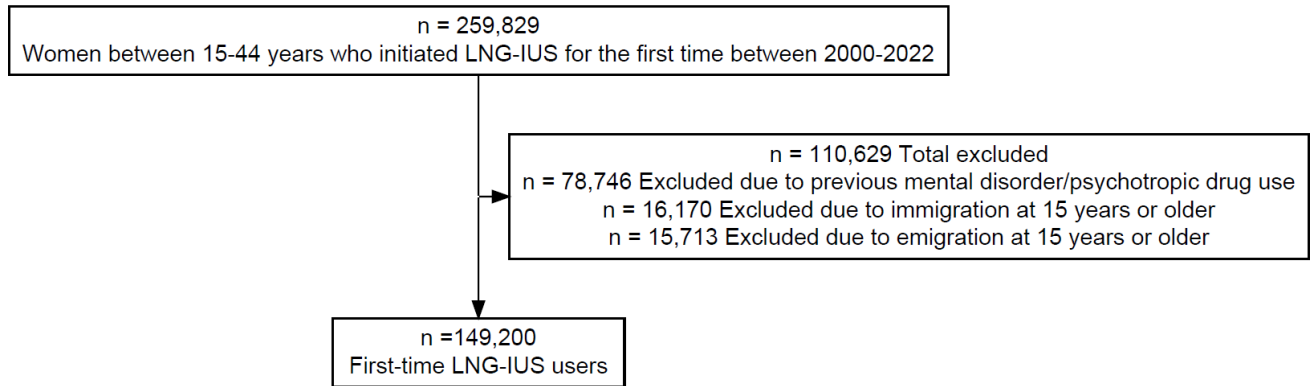


FIGURE S2. Forest plot with hazard ratios of developing depression for the complete output of the main analysis

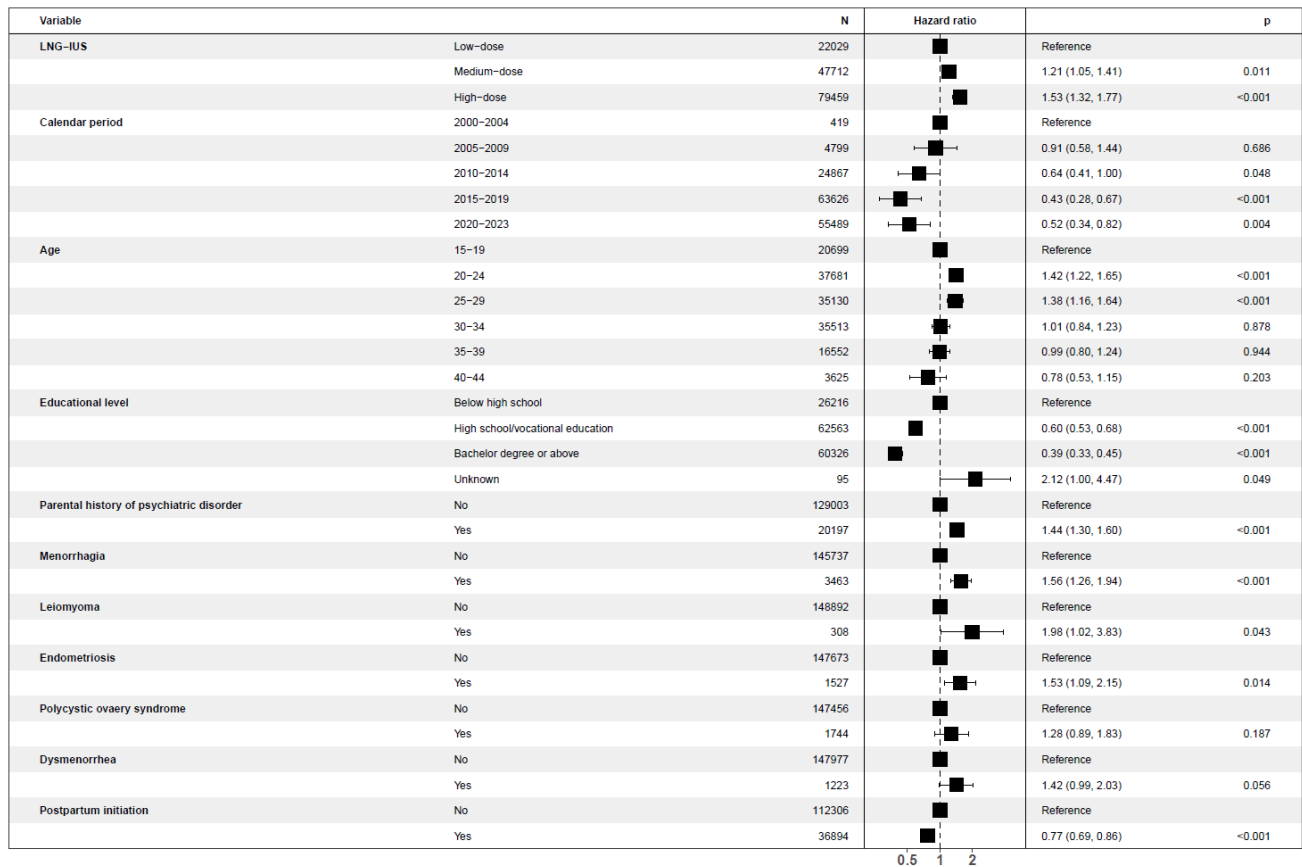


TABLE S2. Average absolute risks, risk differences, and risk ratios for depression diagnosis and antidepressant prescription

Antidepressant medication (n=2110)						
Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk ^a	1.06	0.92-1.21	1.33	1.20-1.45	1.77	1.65-1.88
Absolute risk ^b	1.08	0.94-1.22	1.35	1.23-1.48	1.73	1.62-1.85
Absolute risk difference ^b	Reference		0.27	0.09-0.46	0.65	0.46-0.85
RR ^b	Reference		1.25	1.05-1.45	1.61	1.36-1.86
Absolute risk difference ^b	-		Reference		0.38	0.19-0.58
RR ^b	-		Reference		1.28	1.11-1.45
Depression diagnosis^c (n=366)						
Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk ^a	0.20	0.15-0.25	0.25	0.21-0.30	0.32	0.26-0.37
Absolute risk ^b	0.21	0.16-0.26	0.26	0.21-0.31	0.30	0.24-0.35
Absolute risk difference ^b	Reference		0.05	-0.02-0.12	0.09	0.01-0.16
RR ^b	Reference		1.24	0.86-1.62	1.41	0.95-1.86
Absolute risk difference ^b	-		Reference		0.03	-0.05-0.12
RR ^b	-		Reference		1.13	0.80-1.47

LNG-IUS, levonorgestrel-releasing intrauterine system; RR, risk ratio.

^aStandardized over calendar period and age.

^bStandardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use. Data on education level were missing for 0.1%, 0.0%, 0.1% of low-, medium-, and high-dose LNG-IUS users, respectively. These were imputed to a separate group in the analyses.

^cSince no events were registered in the oldest age group and in women diagnosed with leiomyoma resulting in lack of convergence in the Cox regression, these categories were pooled with the second oldest age group and with menorrhagia, respectively.

TABLE S3. Average absolute risks, risk differences, and risk ratios of starting antidepressant not specifically prescribed for other indications

Depression as prescription indication (n=1198)						
Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk ^a	0.57	0.47-0.67	0.68	0.59-0.76	1.06	0.96-1.15
Absolute risk ^b	0.59	0.49-0.69	0.70	0.61-0.79	1.02	0.94-1.11
Absolute risk difference ^b	Reference		0.11	-0.03-0.24	0.43	0.29-0.58
RR ^b	Reference		1.18	0.93-1.43	1.73	1.38-2.08
Absolute risk difference ^b	-		Reference		0.33	0.18-0.47
RR ^b	-		Reference		1.47	1.21-1.73
Depression or missing prescription indication (n=1574)						
Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk ^a	0.74	0.62-0.85	0.93	0.82-1.04	1.33	1.23-1.43
Absolute risk ^b	0.75	0.63-0.87	0.95	0.83-1.06	1.31	1.21-1.41
Absolute risk difference ^b	Reference		0.19	0.03-0.36	0.56	0.40-0.71
RR ^b	Reference		1.26	1.02-1.50	1.74	1.43-2.05
Absolute risk difference ^b	-		Reference		0.36	0.19-0.53
RR ^b	-		Reference		1.38	1.16-1.60

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

^aStandardized over age and calendar year.

^bStandardized over age, calendar year, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use. Data on education level were missing for 0.1%, 0.0%, 0.1% of low-, medium-, and high-dose LNG-IUS users, respectively. These were imputed to a separate group in the analyses.

TABLE S4. Demographics and clinical profiles restricted to incident users between 2017-2022

Measure	LNG-IUS Exposure		
	Low Dose , no. (%)	Medium Dose , no. (%)	High Dose, no. (%)
Total	12,940 (13.3)	47,712 (48.9)	36,850 (37.8)
Age (years)			
15-19	3,768 (29.1)	10,498 (22.0)	1,467 (4.0)
20-24	5,560 (43.0)	17,175 (36.0)	4,119 (11.2)
25-29	2,541 (19.6)	9,282 (19.5)	8,633 (23.4)
30-34	837 (6.5)	6,429 (13.5)	11,348 (30.8)
35-39	207 (1.6)	3,348 (7.0)	8,665 (23.5)
40-44	27 (0.2)	980 (2.1)	2,618 (7.1)
Calendar year			
2017	3,186 (24.6)	1,855 (3.9)	7,749 (21.0)
2018	2,272 (17.6)	5,312 (11.1)	6,557 (17.8)
2019	1,758 (13.6)	7,436 (15.6)	5,888 (16.0)
2020	2,102 (16.2)	10,200 (21.4)	5,596 (15.2)
2021	2,053 (15.9)	12,221 (25.6)	5,950 (16.1)
2022	1,569 (12.1)	10,688 (22.4)	5,110 (13.9)
Education level ^a			
Below high school	3,620 (28.0)	10,484 (22.0)	3,209 (8.7)
High school/vocational education	6,016 (46.5)	21,506 (45.1)	13,818 (37.5)
Bachelor's degree or above	3,300 (25.5)	15,706 (32.9)	19,809 (53.8)
Postpartum initiation	858 (6.6)	7,135 (15.0)	12,353 (33.5)
Nulliparous	11,558 (89.3)	33,311 (69.8)	6,286 (17.1)
Parental history of mental disorder	1,846 (14.3)	6,930 (14.5)	5,115 (13.9)
Endometriosis	37 (0.3)	186 (0.4)	725 (2.0)
Polycystic ovarian syndrome	53 (0.4)	372 (0.8)	787 (2.1)
Dysmenorrhea	98 (0.8)	314 (0.7)	444 (1.2)
Leiomyoma	7 (0.1)	54 (0.1)	146 (0.4)
Menorrhagia	162 (1.3)	694 (1.5)	1,315 (3.6)
Menorrhagia as prescription indication ^b	555 (4.3)	2,926 (6.1)	4,774 (13.0)
Previous hormonal contraceptive use			
None	1,646 (12.7)	4,742 (9.9)	1,010 (2.7)
One type	9,111 (70.4)	32,871 (68.9)	23,711 (64.3)
Two types	2,010 (15.5)	9,232 (19.3)	10,748 (29.2)
Three or more types	173 (1.3)	867 (1.8)	1,381 (3.7)

LNG-IUS, levonorgestrel-releasing intrauterine system.

^a Data on education level were missing for 0.0%, 0.0%, 0.0% of low-, medium-, and high-dose LNG-IUS users, respectively.

^b Data on prescription indication were missing for 5.3%, 4.7%, and 5.1% of low-, medium-, and high-dose LNG-IUS users, respectively.

TABLE S5. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUSs restricted to incident users between 2017-2022

Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk^a	1.20	1.01-1.40	1.40	1.29-1.52	1.71	1.53-1.88
Absolute risk^b	1.21	1.02-1.41	1.42	1.30-1.53	1.66	1.49-1.83
Absolute risk difference^b	Reference		0.20	-0.03-0.43	0.45	0.18-0.71
RR^b	Reference		1.17	0.96-1.38	1.37	1.10-1.64
Absolute risk difference^b	-		Reference		0.24	0.02-0.46
RR^b	-		Reference		1.17	1.01-1.34

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

^aStandardized over age and calendar year.

^bStandardized over age, calendar year, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use. Data on education level were missing for 0.0%, 0.0%, 0.0% of low-, medium-, and high-dose LNG-IUS users, respectively. These were imputed to a separate group in the analyses.

TABLE S6. Demographics and clinical profiles restricted to nulliparous incident LNG-IUS users younger than 30 years of age

Measure	LNG-IUS Exposure		
	Low Dose, no. (%)	Medium Dose, no. (%)	High Dose, no. (%)
Total	19,042 (30.0)	31,949 (50.3)	12,576 (19.8)
Age (years)			
15-19	6,352 (33.4)	10,461 (32.7)	3,474 (27.6)
20-24	9,457 (49.7)	16,453 (51.5)	6,414 (51.0)
25-29	3,233 (17.0)	5,035 (15.8)	2,688 (21.4)
Calendar period			
2000-2004	0 (0.0)	0 (0.0)	147 (1.2)
2005-2009	0 (0.0)	0 (0.0)	921 (7.3)
2010-2014	1,666 (8.7)	0 (0.0)	4,145 (33.0)
2015-2019	12,388 (65.1)	9,020 (28.2)	4,661 (37.1)
2020-2022	4,988 (26.2)	22,929 (71.8)	2,702 (21.5)
Education level ^a			
Below high school	6,196 (32.5)	9,766 (30.6)	3,962 (31.5)
High school/vocational education	9,507 (49.9)	17,103 (53.5)	6,400 (50.9)
Bachelor's degree or above	3,329 (17.5)	5,070 (15.9)	2,201 (17.5)
Parental history of mental disorder	2,622 (13.8)	4,618 (14.5)	1,695 (13.5)
Endometriosis	46 (0.2)	50 (0.2)	122 (1.0)
Polycystic ovarian syndrome	67 (0.4)	86 (0.3)	57 (0.5)
Dysmenorrhea	144 (0.8)	196 (0.6)	165 (1.3)
Leiomyoma	5 (0.0)	6 (0.0)	11 (0.1)
Menorrhagia	270 (1.4)	355 (1.1)	342 (2.7)
Menorrhagia as prescription indication ^b	668 (3.5)	2,273 (7.1)	1,545 (12.3)
Previous hormonal contraceptive use			
None	2,525 (13.3)	4,432 (13.9)	1,176 (9.4)
One type	13,286 (69.8)	23,155 (72.5)	8,819 (70.1)
Two types	2,949 (15.5)	4,096 (12.8)	2,272 (18.1)
Three or more types	282 (1.5)	266 (0.8)	309 (2.5)

LNG-IUS, levonorgestrel-releasing intrauterine system.

^a Data on education level were missing for 0.1%, 0.0%, 0.1% of low-, medium-, and high-dose LNG-IUS users, respectively.

^b Data on prescription indication were missing for 11.4%, 4.6%, and 18.3% for low-, medium-, and high-dose LNG-IUS users, respectively.

TABLE S7. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUSs restricted to nulliparous incident LNG-IUS users younger than 30 years of age

Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk^a	1.45	1.26-1.64	1.71	1.54-1.88	2.14	1.85-2.44
Absolute risk^b	1.47	1.27-1.66	1.72	1.55-1.89	2.08	1.79-2.37
Absolute risk difference^b	Reference		0.26	-0.01-0.52	0.62	0.28-0.95
RR^b	Reference		1.17	0.97-1.38	1.42	1.16-1.68
Absolute risk difference^b	-		Reference		0.36	0.00-0.73
RR^b	-		Reference		1.21	0.98-1.44

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

^aStandardized over calendar period and age.

^bStandardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use. Data on education level were missing for 0.1%, 0.0%, 0.1% of low-, medium-, and high-dose LNG-IUS users, respectively. These were imputed to a separate group in the analyses.

TABLE S8. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUSs when adjusted for menorrhagia as prescription indication and previous hormonal contraceptive use

Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk	1.22	1.07-1.37	1.47	1.34-1.61	1.83	1.71-1.94
Absolute risk difference	Reference		0.25	0.06-0.45	0.60	0.40-0.81
RR	Reference		1.21	1.03-1.39	1.50	1.28-1.71
Absolute risk difference	-		Reference		0.35	0.15-0.56
RR	-		Reference		1.24	1.08-1.40

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

Estimates are standardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, postpartum incident LNG-IUS use, number of hormonal contraceptive types used previously, and menorrhagia as prescription indication of LNG-IUS.

Prescription information was missing for 11.5%, 4.7%, and 12.0% and education level for 0.1%, 0.0% and 0.1% of low-, medium-, and high-dose LNG-IUS users, respectively. This was handled by performing multiple imputations with the MICE package in R where prescription indication was imputed using logistic regression and educational level using polytomous logistic regression based on the listed covariates and outcome with 10 iterations and 5 imputations

TABLE S9. Standard means and standard mean differences of covariates between the groups before and after propensity score weighting

Covariates	Mean IUS-low	Mean IUS-med	Mean IUS-high	Pop.sd	Std.eff.sz high vs. low	Std.eff.sz high vs. med	Std.eff.sz med vs. low
Unweighted							
Age							
15-19	0.29	0.22	0.04	0.37	0.68	0.49	0.19
20-24	0.43	0.36	0.11	0.45	0.71	0.56	0.16
25-29	0.20	0.19	0.23	0.41	0.09	0.10	0.00
30-34	0.06	0.13	0.31	0.39	0.62	0.44	0.18
35-39	0.02	0.07	0.24	0.33	0.66	0.50	0.16
40-44	0.00	0.02	0.07	0.19	0.36	0.27	0.10
Calendar year							
2017	0.25	0.04	0.21	0.34	0.11	0.51	0.61
2018	0.18	0.11	0.18	0.35	0.01	0.19	0.18
2019	0.14	0.16	0.16	0.36	0.07	0.01	0.06
2020	0.16	0.21	0.15	0.39	0.03	0.16	0.13
2021	0.16	0.26	0.16	0.41	0.01	0.23	0.24
2022	0.12	0.22	0.14	0.38	0.05	0.22	0.27
Educational level ^a							
Below high school	0.28	0.22	0.09	0.38	0.50	0.35	0.16
High school/vocational education	0.46	0.45	0.37	0.49	0.18	0.15	0.03
Bachelor degree or above	0.26	0.33	0.54	0.49	0.58	0.43	0.15
Unknown	0.00	0.00	0.00	0.02	0.00	0.00	0.00
Postpartum initiation	0.07	0.15	0.34	0.41	0.66	0.46	0.20
Parental history of mental disorder	0.14	0.15	0.14	0.35	0.01	0.02	0.01
Endometriosis	0.00	0.00	0.02	0.10	0.17	0.16	0.01
Polycystic ovarian syndrome	0.00	0.01	0.02	0.11	0.16	0.12	0.03
Dysmenorrhea	0.01	0.01	0.01	0.09	0.05	0.06	0.01
Leiomyoma	0.00	0.00	0.00	0.05	0.07	0.06	0.01
Menorrhagia	0.01	0.01	0.04	0.15	0.16	0.14	0.01
Weighted							
Age							
15-19	0.16	0.16	0.16	0.37	0.01	0.00	0.01
20-24	0.28	0.28	0.28	0.45	0.01	0.00	0.01
25-29	0.21	0.21	0.21	0.41	0.01	0.00	0.00
30-34	0.19	0.19	0.19	0.39	0.00	0.00	0.00
35-39	0.12	0.12	0.13	0.33	0.01	0.00	0.00
40-44	0.03	0.04	0.04	0.19	0.03	0.00	0.03
Calendar year							
2017	0.14	0.13	0.13	0.34	0.01	0.01	0.02
2018	0.15	0.14	0.14	0.35	0.01	0.00	0.01
2019	0.16	0.16	0.16	0.36	0.00	0.00	0.00
2020	0.18	0.18	0.18	0.39	0.01	0.00	0.01
2021	0.20	0.21	0.21	0.41	0.01	0.00	0.02
2022	0.18	0.18	0.18	0.38	0.00	0.00	0.00
Educational level ^a							
Below high school	0.18	0.18	0.18	0.38	0.01	0.00	0.01
High school/vocational education	0.42	0.42	0.42	0.49	0.01	0.00	0.01
Bachelor degree or above	0.40	0.40	0.40	0.49	0.00	0.00	0.00
Unknown	0.00	0.00	0.00	0.02	0.01	0.00	0.00
Postpartum initiation	0.21	0.21	0.21	0.41	0.00	0.00	0.00
Parental history of mental disorder	0.15	0.14	0.14	0.35	0.01	0.00	0.01
Endometriosis	0.01	0.01	0.01	0.10	0.04	0.00	0.03
Polycystic ovarian syndrome	0.01	0.01	0.01	0.11	0.02	0.00	0.02
Dysmenorrhea	0.01	0.01	0.01	0.09	0.02	0.00	0.02
Leiomyoma	0.00	0.00	0.00	0.05	0.01	0.01	0.01
Menorrhagia	0.02	0.02	0.02	0.15	0.02	0.01	0.02

Standard mean and mean differences obtained before and after weighting on multinomial propensity scores obtained with gradient boosted logistic regression. The maximum number of iterations was set to 15000, and the measure of balance was summarized as the absolute standardized mean difference by setting the stop.method to "es.mean". After weighting, the effective sample sizes were; 4,779,442 for low-, 32,680.0 for medium-, and 19,066.4 for high-dose LNG-IUS users. The effective sample size is the number of observations which would give the same estimates when the sampling variation is similar to the variation obtained after the weighting. IUS-low, low-dose levonorgestrel-releasing intrauterine system; IUS-med, medium-dose levonorgestrel-releasing intrauterine system; IUS-high, high-dose levonorgestrel-releasing intrauterine system; Pop.sd, pooled sample standard deviation, Std.eff.sz, standardized effect size.

FIGURE S3. Multinomial propensity score distributions obtained with gradient boosted logistic regression

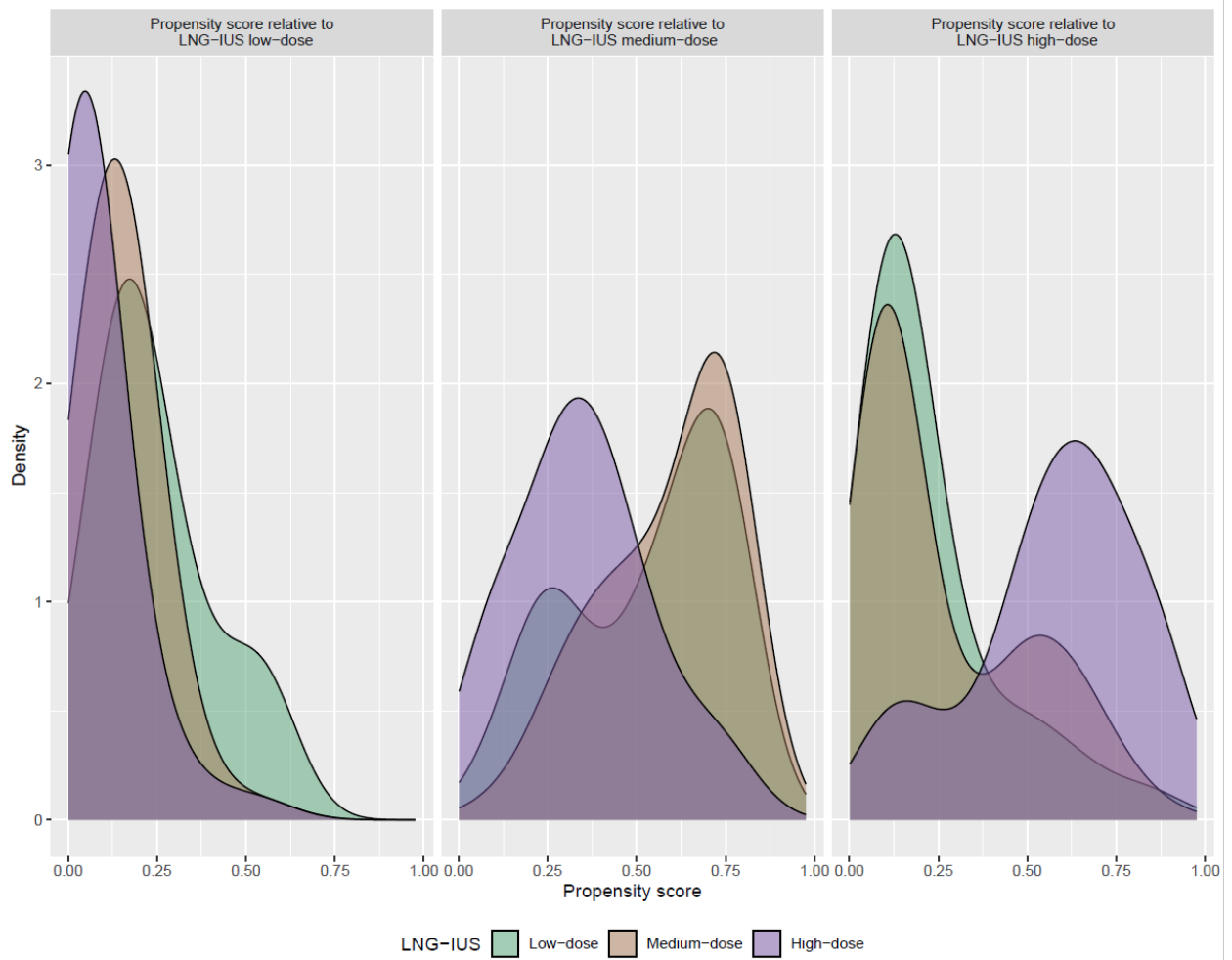


TABLE S10. Average absolute risks, risk differences, and relative risks of developing depression between different LNG-IUSs in women with history of mental disorder

Measure	LNG-IUS Exposure					
	Low Dose		Medium Dose		High Dose	
	%	95% CI	%	95% CI	%	95% CI
Absolute risk^a	4.77	4.20-5.34	5.12	4.69-5.55	5.96	5.65-6.27
Absolute risk^b	4.80	4.22-5.37	5.22	4.78-5.66	5.91	5.60-6.22
Absolute risk difference^b	Reference		0.42	-0.28-1.12	1.11	0.44-1.78
RR^b	Reference		1.09	0.93-1.24	1.23	1.07-1.40
Absolute risk difference^b	-		Reference		0.69	0.10-1.27
RR^b	-		Reference		1.13	1.01-1.25

LNG-IUS, levonorgestrel-releasing intrauterine system; AR, absolute risk; RR, risk ratio.

^aStandardized over calendar period and age.

^bStandardized over calendar period, age, education level, parental history of mental disorder, endometriosis, polycystic ovarian syndrome, dysmenorrhea, leiomyoma, menorrhagia, and postpartum incident LNG-IUS use. Data on education level were missing for 0.2%, 0.1%, 0.2% of low-, medium-, and high-dose LNG-IUS users, respectively. These were imputed to a separate group in the analyses.