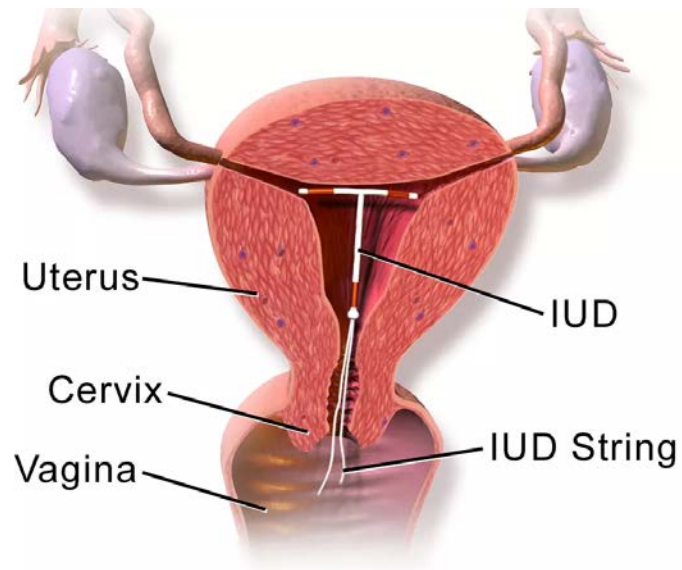


Relative risk of cervical neoplasms among copper and levonorgestrel intrauterine device users

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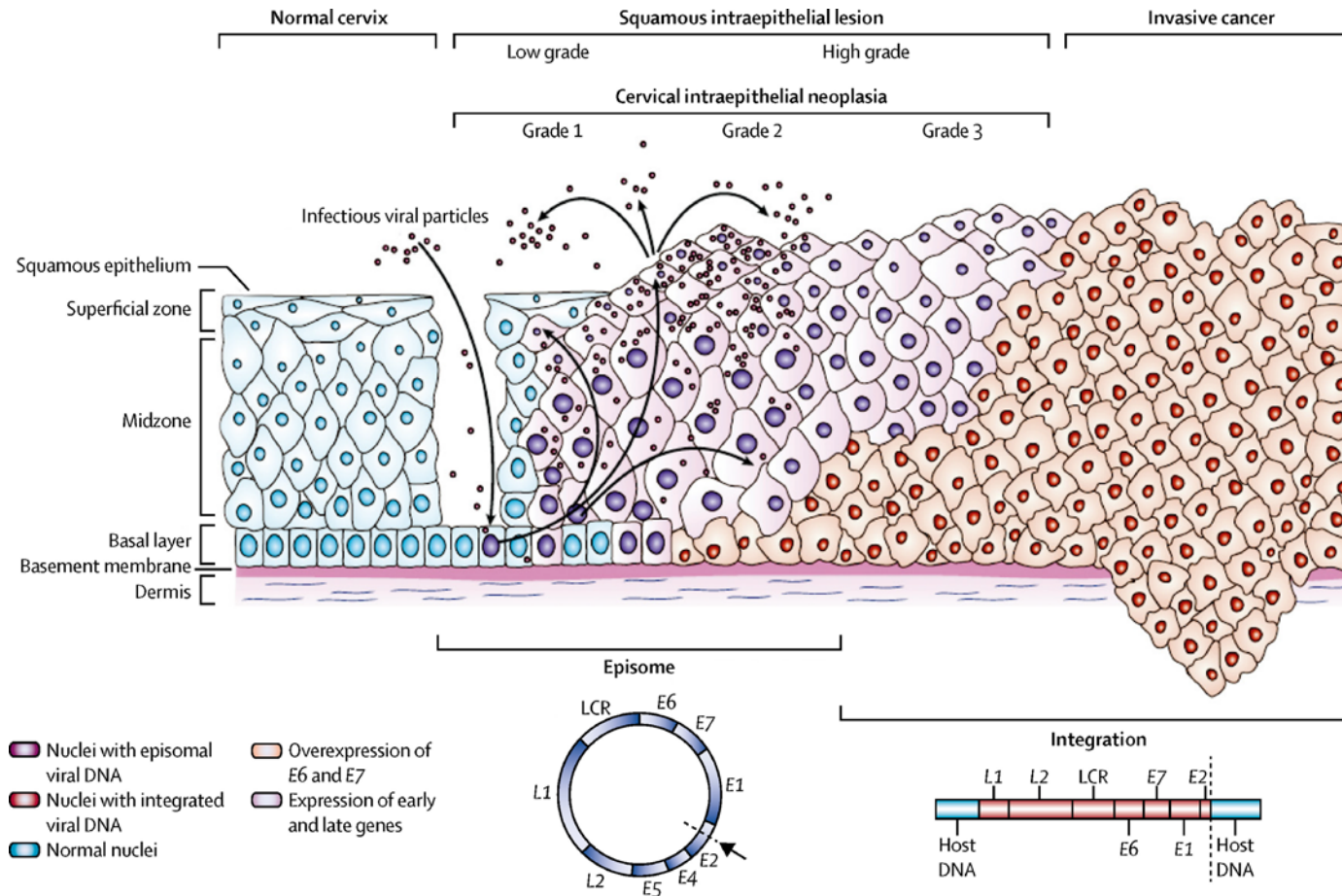
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Intrauterine Devices (IUDs)



Variable	Cu-IUD ("Copper")	LNG-IUS ("Hormonal")
Available in US	1988 (Paragard)	2000 (Mirena)
Number of Users	~80 Million	~20 Million
Prevents Pregnancy	>99%	>99%
Inhibits Sperm	Yes	Yes
Thins Uterine Lining	No	Yes
Thickens Mucous	No	Yes
Decreases Bleeding	No	Yes
Decreases Pain	No	Yes
Approximate Cost	\$700	\$800

Cervical Cancer Pathophysiology



IUDs and Cervical Cancer: Systematic Review

1st Author	Location	Data Collection	Control Source	Case Participants	Control Participants
Celentano ³⁵	United States	1982–1984	Mixed	153	153
Brinton ³²	Multisite ^s	1986–1987	Mixed	568	1,071
Lassise ³⁶	United States	1982–1984	Population	479	789
Parazzini ³⁷	Italy	1990	Clinic or hospital	720	820
Williams ³³	Kenya	1981–1988	Clinical or hospital	112	749
Li ³⁸	China	1989–1991	Population	272	893
Shields ³⁴	United States	1982–1984	Population	235	486
Hammouda ¹⁶	Algeria	1997–1999	Clinic or hospital	198	202
Castellsagué ¹⁰	Morocco	1991–1993	Clinic or hospital	202	214
Castellsagué ¹⁰	Philippines	1991–1993	Clinic or hospital	383	387
Castellsagué ¹⁰	Thailand	1990–1993	Clinic or hospital	348	385
Castellsagué ¹⁰	Peru	1996–1998	Clinic or hospital	137	140
Castellsagué ¹⁰	India	1998–1999	Clinic or hospital	76	60
Castellsagué ¹⁰	Spain	1985–1987	Population	480	472
Castellsagué ¹⁰	Colombia	1985–1988	Population	448	452
Roura ¹⁵	Multisite ^{ll}	1992–2006	Cohort	134	264

Methods: Cohorts

- Retrospective observational cohort study
- Cohorts and estimation analysis were designed in ATLAS
- Cu-IUD Cohort (T): CPT Code for first IUD placement, no subsequent LNG-IUS exposure
- LNG-IUS Cohort (C): CPT Code for first IUD placement, at least 1 subsequent LNG-IUS exposure
- Cervical Neoplasm Cohort (O): Condition code of a high grade cervical neoplasm (i.e. SNOMED "Primary Malignant Neoplasm of Uterine Cervix")
- All study patients had 365 days prior observation, no history of endometrial or cervical cancer, and were 45 years or younger

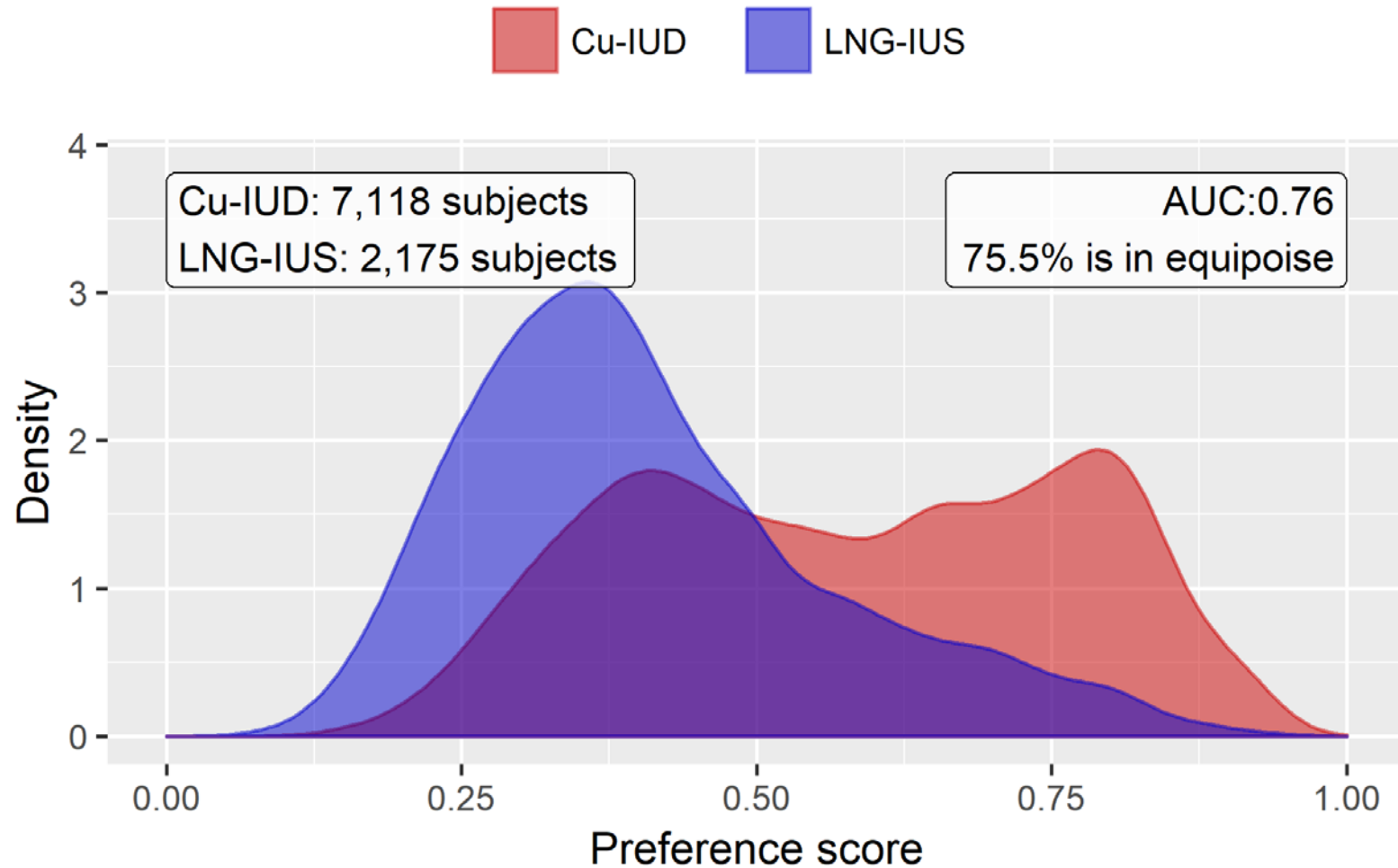
Methods: Analysis

- Study Window: 1/1/2003 – 12/15/2018
- Study Period: 30 days to 15 years post placement
- Subgroup Analysis: 1 to 15 years post placement
- Propensity score stratification, propensity score matching, and propensity score matching for the subgroup were performed
- Adjusted over more than 10,000 covariates in each analysis and balance was achieved

Cervical Neoplasm Phenotype Validation

- Under CUIMC IRB approval (IRB #AAAO7805), we identified 115 cervical neoplasm patients with our phenotype
- 90% of cervical neoplasm cases had concordant biopsy diagnosis
- 100% of LNG-IUS exposures were identified properly
- 10% of Cu-IUD exposures were actually LNG-IUS exposures

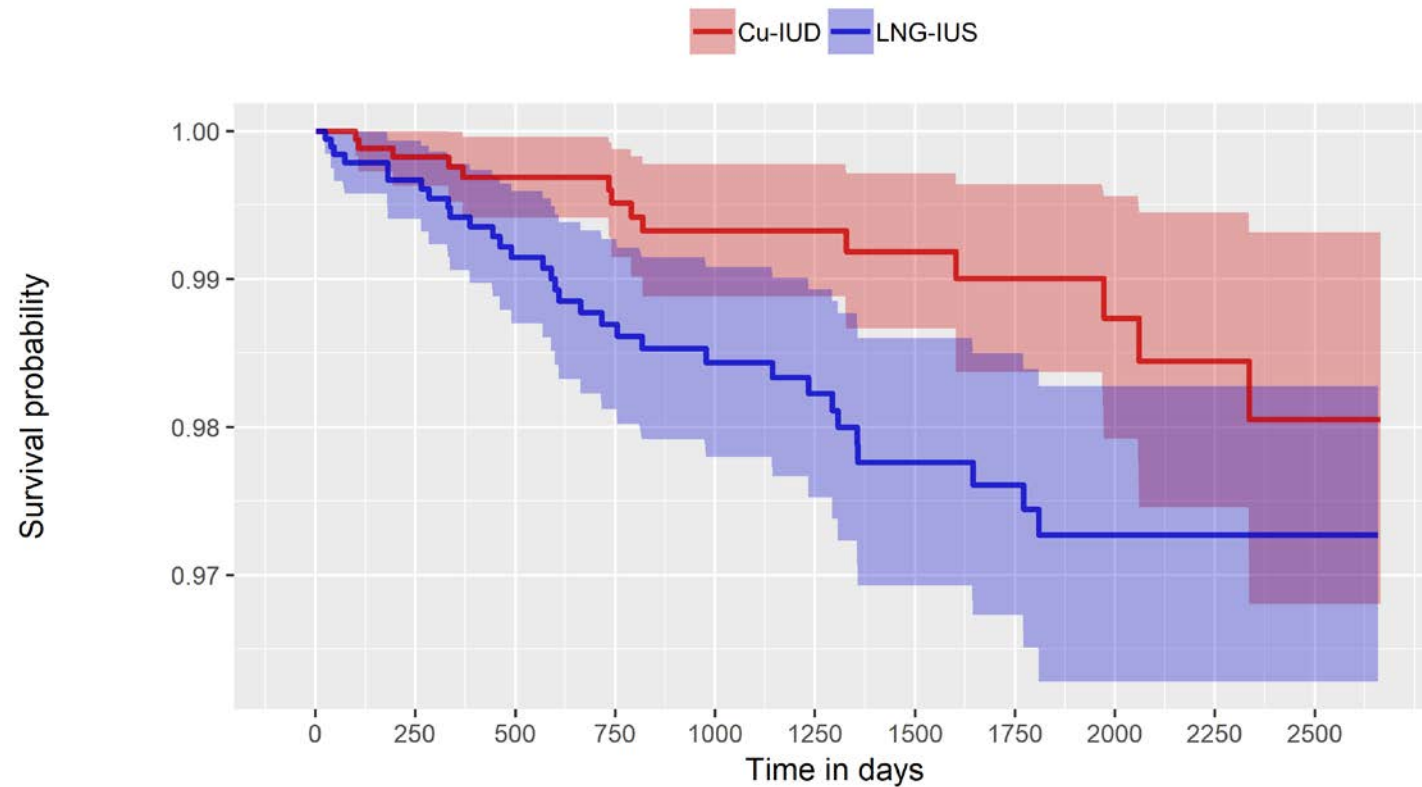
Propensity Score Distribution



Matched Cervical Cancer Risk Factors

Variable (n, %)	Copper Before Matching (n=8274)	Hormonal Before Matching (n=2400)	Before PS Matching Std. Diff
Tobacco Smoking Behavior	3261 (39.4%)	1290 (53.8%)	0.49*
HPV Vaccine	43 (0.5%)	27 (1.1%)	-0.07
HPV Test Positive	210 (2.5%)	59 (2.5%)	0.03

Kaplan-Meier Plot: PS Matching



Number at risk											
Cu-IUD	2,039	1,579	1,327	1,115	937	759	601	464	359	277	203
LNG-IUS	2,039	1,639	1,413	1,213	1,057	895	730	599	457	373	299

Possible Explanations for Effect

- Differences in risk factors or screening uptake
- Harmful effect of synthetic hormones
- Protective effect from copper

Screening Uptake Characterization

Variable (n, %)	Copper (n=8274)	Hormonal (n=2400)
Median Follow-Up Years	2.8 [0.5-6.5]	2.6 [0.6-5.0]
Subsequent Cervical Cancer Screening	2560 (30.9%)	835 (34.8%)
Subsequent Preventive Health Visits	1893 (22.9%)	695 (29.0%)

Premarket Randomized Control Trial (RCT): Mirena FDA Application, 2000

- “In the study report based on annual PAP smear data from 2758 women, investigators reported no difference in the rate of dysplasia or cancer between women using Mirena (1821) and those using a copper IUD (937). There were 46 subjects who developed abnormal cervical cytology (Class III, IV, V), 13 in the copper IUD group and 33 in the Mirena group. There was one invasive cervical cancer in the Mirena group (described in section 3.10.1). These differences were not statistically significant.”
- No reporting of cervical neoplasms in peer reviewed publications

Proportional Copper vs. Hormonal Results

Cohort	RCT	CUIMC PS Strat	CUIMC PS Match	CUIMC Crude
Cu-IUD	1.4%	1.1%	0.7%	0.9%
LNG-IUS	1.8%	1.7%	1.8%	1.5%

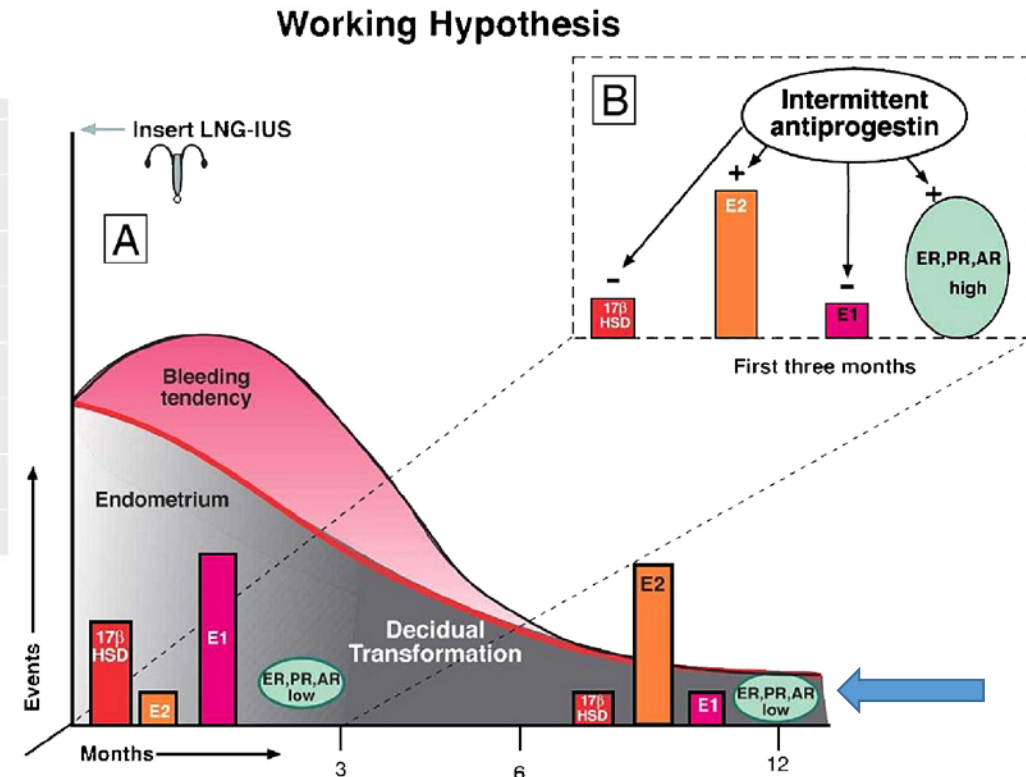
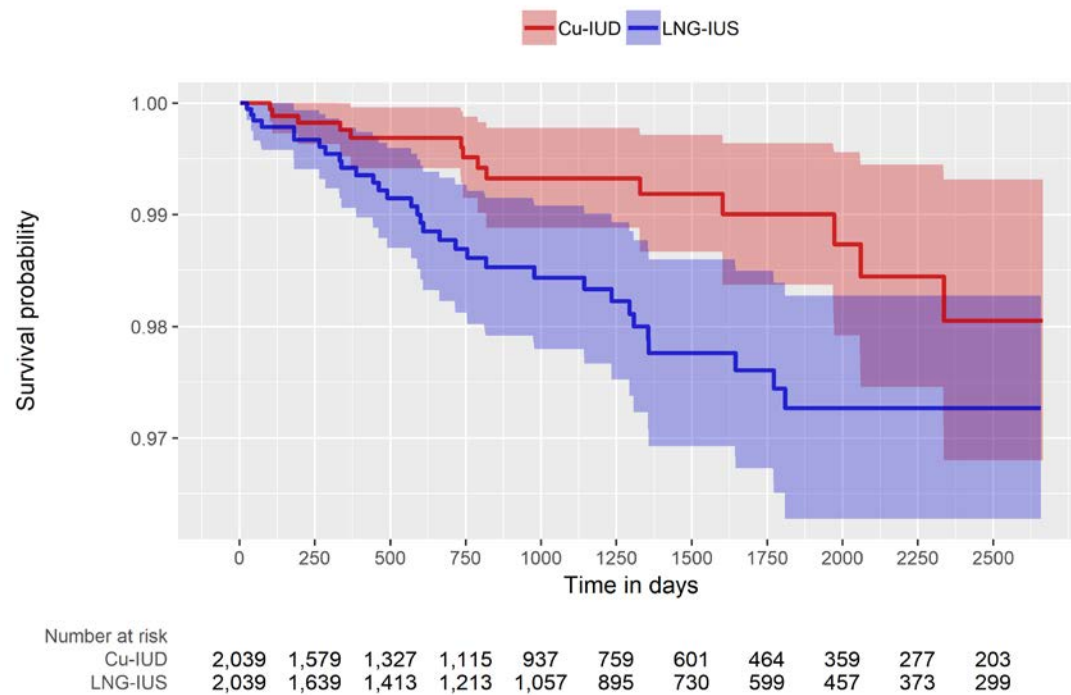
Analysis Summary

Analysis	RR [95% CI]
Propensity Score Stratification	0.49 [0.32-0.76]
Propensity Score Matching	0.38 [0.16-0.78]
Propensity Score Matching Subgroup	0.64 [0.27-1.47]
Premarket RCT (n=2758)	0.76 [0.40-1.40]

Hormonal Device Toxicity

- “The local endometrial concentrations of levonorgestrel, however, are over 100 times higher in Mirena users than in users of oral contraceptive containing 0.25 mg levonorgestrel.”
- Continuous intrauterine exposure for years

Endometrial Effects of Progesterone Exposure



- Increased Angiogenesis
- Increased MMP Activity

Absolute vs. relative effects

- Although a direct comparison between IUD users and non-IUD users would be informative, it is difficult to do so in practice
- Confounding by intermittent vs. continuous contraception use, and number of pregnancies during the study interval
- Therefore, we focus on relative effects of Cu-IUD vs. LNG-IUS

Conclusion

- The relative risk of cervical neoplasms for Cu-IUD users was less than that of LNG-IUS users
- Our findings were internally consistent and consistent with a premarket RCT
- High external validity with healthcare implications for approximately 1 million women
- OHDSI is uniquely situated to study the relative risk for other device related adverse events

Future Studies

- IUD Cervical Neoplasms Network Study
- IUD Cervical Neoplasms Prediction Studies
- IUD Ovarian Cancer Network Study

Thanks!

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