ANALYSIS OF COMORBID CONDITIONS ASSOCIATED WITH INTRAUTERINE DEVICE REMOVAL WITHIN AN INPATIENT POPULATION

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BS in Biology, Grove City College, 2015

Submitted to the Graduate Faculty of

Epidemiology

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Public Health

University of Pittsburgh

2018

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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on

April 27, 2018

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ABSTRACT

Background: Intrauterine devices (IUD) are an increasingly popular form of contraception in the US due to their high level of effectiveness, reversibility, and lack of further maintenance after insertion, but they are not without their adverse events. Previous studies have found that local adverse events following IUD insertion can be problematic enough that women choose to remove them. While much research has been done on IUDs and their related adverse events, in outpatient settings, no research has been done regarding comorbid conditions associated with their removal in an inpatient setting. Comorbidities associated with IUD removal may point to systemic long-term effects of IUD use that can be further explored. The primary objective of this study is to describe and examine the association of patient factors and comorbid conditions with inpatient IUD placement and removal compared to the inpatient controls.

Methods: An analysis of data from the US National Inpatient Sample from 2010-2014 was performed looking for an association between various potential comorbidities (vascular, allergy/immune, and endometriosis) when the hospitalization includes an IUD insertion or no IUD procedure, compared to an IUD removal. The inpatient samples were matched using propensity score of having an IUD related ICD-9 code to create triplets of women with no IUD procedure, IUD insertion, and IUD removal.

Results: IUD removal is associated with a decreased likelihood of hypertension, cardiovascular disease and peripheral vascular disease, and an increased likelihood of endometriosis compared to women without an IUD procedure indicating they may be adverse events of using an IUD leading to an IUD removed. There were no significant statistical interactions found between race and IUD group, though some trends between races were seen.

Conclusion: As more women in the United States are choosing IUDs as their preferred contraceptive method, we have identified associated comorbid conditions among IUD users though we did not have strong evidence to support that these effects vary by race. This will have a public health impact by informing future research on the potential long-term systemic adverse events to allow women and their doctors to make their most informed decision about contraceptive use.

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1.0 INTRODUCTION

1.1 FAMILY PLANNING METHODS

In 2016, approximately 43 million of the 61 million women (70%) in the United States of child bearing age were at risk of an unplanned pregnancy. In order to prevent becoming pregnant while remaining sexually active, either the woman and/or her partner needs to engage in family planning methods. The typical American woman needs to use family planning methods for around 30 years[1].

There are many benefits to family planning. The ability to plan when a woman becomes pregnant allows her to better time and space births as well as meet her educational and workforce goals which have positive impacts on income, family stability, mental health and happiness, and children's well-being while also allowing for healthier pregnancies.

Though contraception use has many benefits, there are risks associated with it, particularly in contraceptive methods involving hormones. These risks include coronary heart disease, hypertension, stroke, venous thromboembolic disease, risk of breast cancer, change in cholesterol, liver disorders, and headache among others.

The contraception types available today fall into six general categories: natural family planning, barrier methods, oral contraceptives, emergency contraceptives, injectable progestin, long-acting reversible contraceptives (including intrauterine devices (IUD)), and sterilization[2].

Natural family planning involves tracking a woman's menstrual cycle through basal body temperature, cervical mucus, ovulation predictor kits, cycle beads, or the tracking of cycle days. The U.S. Department of Health and Human Services estimate that natural family planning is around 75% effective[2]. While this is not the most effective form of contraceptive, it does not require a physician's prescription.

Barrier methods include diaphragms, contraceptive sponges, cervical caps, female condoms, and spermicide for women and latex condoms for men which also help prevent the spread of sexually transmitted infections. These methods require personal skill for correct usage as well as continued use during each sexual intercourse encounter for effectiveness. In addition, diaphragm and cervical caps require a doctor's prescription to ensure the correct size, though other barrier methods can be used without the need for a physician. These methods have no major contraindications. The effectiveness varies by correct usage and method but ranges from approximately 75-90%[2]. Some couples use barrier methods along with the natural family planning method to increase the efficacy[2].

Oral contraceptives contain estrogen and progesterone or progesterone alone to prevent pregnancy[2]. Additionally, oral contraceptives are used to treat other clinical symptoms such as abnormal uterine bleeding, hyperandrogenism, dysmenorrhea, ovarian suppression, excess menstrual bleeding, menstrual pain, endometriosis, and acne[1-3]. Oral contraceptives have many contraindications and potential adverse events so they require a physician's prescription before initiating use to ensure an appropriate oral contraceptive is selected. Contraindications for use depend on the type of oral contraceptive and include cancer, cardiovascular diseases, migraines, hypertension, thromboembolic events, body mass index, smoking, and age, among others. Some

adverse events include breakthrough bleeding, amenorrhea, weight gain, and increased blood pressure. Oral contraceptives are approximately 91% effective[2].

Emergency contraception was developed to prevent fertilization after intercourse had already occurred and generally involves a high-dose administration of estrogen as soon as possible after intercourse, some without the need of a physician prescription. Emergency contraception has a higher risk for adverse events[2]. It is estimated that emergency contraception reduces the incidence of pregnancy by 90% when used after one unprotected sex event[1].

Depot formulations of progestin may be injected intramuscularly or subcutaneously by a physician every 13 weeks. It should not be used by women who may wish to become pregnant quickly after termination of use as fertility is not instantly regained upon discontinuation. Injectable progestin is 94% effective and can also be used for dysmenorrhea and amenorrhea[2].

Long-acting reversible contraception (LARC), including intrauterine devices and progesterone implants, provide contraception for a period of years after placement and are over 99% effective. Insertion in a physician's office is required to ensure proper placement. By definition, LARCs must be able to remain inserted for at least three years and are considered "forgettable" due to the lack of routine maintenance or further patient action after insertion. Due to their effectiveness, reversibility, and lack of further patient action, they are highly recommended by gynecologists[2].

Permanent sterilization includes tubal ligation for females and vasectomies for males. Effectiveness for permanent sterilization is similar to those of LARCs: 99.5% for tubal ligation and 99.85% for vasectomies. Vasectomy is an outpatient procedure while tubal ligation is often an inpatient procedure. Some hysteroscopic sterilization procedures, such as Essure, can be

performed in a doctor's office. Vasectomies are the safest and most cost effective sterilization procedure while tubal ligation can have adverse events including ectopic pregnancies[2].

1.2 INTRAUTERINE DEVICES (IUD)

1.2.1 What is an IUD?

An increasingly popular form of contraception is the intrauterine device (IUD) because it is long lasting as well as reversible; 3,884,000 American women used IUDs in 2011 [1,3-9]. An IUD is a small, t-shaped device that a healthcare provider inserts in the uterus and is held in place by the cervix[10]. The insertion and removal of an IUD usually occurs in an outpatient setting in the doctor's office. Once an IUD is inserted, it provides contraceptive benefits for up to ten years. There are two main types of IUDs in the US: copper and hormonal (Figures 1 and 2)[7,10,11]. Copper IUDs work by releasing copper ions that prevent sperm from reaching and therefore fertilizing the egg. These copper ions affect the mobility and viability of the sperm. In the rare case where the egg is fertilized, the inflammation caused by the copper IUD prevents the egg from implanting on the endometrium and, thereby, allows the copper IUD to be inserted up to five days after ovulation and still provide contraceptive benefit. As a result, copper IUDs are the most effective form of emergency contraception with nearly a 100% effectiveness rate [2,3,7,12,13]. Hormonal IUDs contain a progestin which causes cervical mucus to thicken and the uterine lining to thin which prevents the sperm from reaching the egg[10].

Figure 1. Picture of copper IUD.

Figure 2. Picture of hormonal IUD.

Both types of IUDs are approved with few contraindications. The common contraindications include known or suspected pregnancy, active pelvic infection (e.g. immediately after a septic abortion), and distortions of endometrial cavity (e.g. fibroids)[2]. IUDs are approved for immediate use after abortions and after giving birth (both vaginal and cesarean delivery), including while a woman is breast feeding.[3,7] They are also approved for use in adolescents and HIV-positive women, two groups that have difficulty accessing other forms of contraception such as oral pills[3]. In addition to contraceptive benefits, both hormonal and copper IUDs can be used to treat menorrhagia and endometrial hyperplasia.

IUDs are currently among the most effective form of birth control with less than 1 in 100 women getting pregnant while using an IUD (2 per 1000 in hormonal IUD and 8 per 1000 in copper IUDs) [2,3,10]. Because IUDs require no maintenance, it is the only form of contraception that has nearly perfect usage, allowing for the maximum contraceptive effect[1,3,4,9]. If a woman removes an IUD and uses a different form of contraception, she will always be switching to a less effective form of contraception (except for permanent sterilization or another LARC such as a progesterone

implant), so doctors discourage women from having their IUDs removed unless they have decided that they want to become pregnant.

1.2.2 Trends in use

According to a study that analyzed trends in IUD use in America using data from the National Surveys of Family Growth (NSFG), IUD use increased from 1.8% to 9.5% from 2002 and 2011-2013[14]. The increase in IUD use appears to largely have come from users of the oral contraceptive pill which have dropped from 26.4% to 22.0% from 2002 to 2012, while the rate of women not using contraception of any kind have remained the same (10.9% in 2002 and 10.2% in 2012). The increase in IUD use is concentrated in women aged 25-34 years. IUD usage increased in all ethnic groups with foreign-born Hispanic women having the highest rates of use (16.9%). According to the Reproductive Health Report, 2011, the increase in use from 2002-2012 was higher in women who wanted more children versus those that didn't (15.1% and 7.7% respectively)[14]. This implies that women use IUDs more frequently to help space out births compared to wanting to not have any more children or not having giving birth yet. IUDs have been found to have the highest rates of continuation and satisfaction compared to other forms of birth control (over 80%)[15,16].

While much literature supports the use of IUDs, there are widespread misconceptions about IUDs that present a barrier to women choosing to use IUDs. A review article on perceptions on IUD use found that only 20% of women in the primary care setting knew that IUDs are more effective than oral contraception with male knowledge of IUD effectiveness also being very poor[3]. In one study, almost half of the participants surveyed thought that IUDs were banned in the US[3]. The position in the body was also found to be a concern for many patients globally with a study in Scotland showing 24% of women fearing that the device could move in the body[3]. Global concerns

about IUD insertion or IUD removal showed that women were worried about pain and infringement on modesty. Two studies found that having an option for the patient to remove the IUD themselves would encourage them to choose an IUD[3].

IUD acceptability is not only a function of personal knowledge, but also of acceptability within a person's social group. A study by Gomez and Freihart found that interest in an IUD was influenced by experiences of people they know[17]. They found that even if women had heard positive things about IUDs, at least one person who had a peer with a negative experience caused them to no longer be interested in having an IUD inserted[17]. Women whose providers used IUDs themselves increased the likelihood of the woman choosing an IUD for herself, though qualitative studies in low-income settings found that reassurance from friends and families was a much more crucial factor to encourage IUD use with negative conversations having a more lasting impact than positive ones[3,18]. Women said that they don't necessarily discuss contraception when it works but rather only when there are concerns or problems. Women find these conversations to be memorable[18]. Patients were wary to use methods even if they were recommended by their doctor after hearing negative adverse events from people in their social circle[18]. Nearly 80% of users in the Anderson et al. study recommended the use of IUDs to their friends[18]. Positive perceptions received from social circles and patients include high effectiveness, long-lasting effect, and the potential for beneficially perceived adverse events such as amenorrhea[18]. Among women who are well informed about IUDs, high effectiveness, the quick return of fertility upon removal, the ability to use while breastfeeding, the potential for amenorrhea, and the lack of daily maintenance were cited as reasons for use of IUDs over other forms of contraception[3,18].

1.2.3 Factors influencing decision to remove IUD

IUDs are an excellent form of contraception, but when individuals discontinue their IUD, they often revert back to a contraception method of lesser efficacy. IUDs are usually well tolerated in patients with only 10-20% of women discontinuing use within the first year[19,20]. Two major factors that have been shown to impact a woman's decision to stop using an IUD are: 1) the symptoms and adverse events that they experience and 2) the perceptions of the patient which are largely influenced by their social circle.

1.2.3.1 IUD-related adverse events

While IUDs are considered by gynecologists to be a very effective and safe form of contraception, there are adverse events attributed to IUD use. The primary reason a woman requests an early IUD removal is due to these adverse events[19,20]. As an example, inflammation due to the insertion of a copper IUD leads to a 30% or more increase in menstrual flow which may or may not decrease with time and is the largest reason for discontinued use in copper IUDs[21,22].

Tables 1-3 present adverse events associated with IUD use and the studies that reported them. Table 1 presents the short term adverse event that can happen at the time of IUD insertion which consists of perforation of the uterus. This is a serious issue that requires surgery.

Table 1. Short term adverse events associated with IUD use as seen in the literature.

Short Term Adverse Event	Support
Perforation of the Uterine Wall	Howard et al[5], Bateson et al[21], Aoun et al[16]

Table 2 presents adverse events that can occur at any point while using an IUD with the most common being bleeding and pain. These adverse events include some of the most common issues that women report when they request to have an IUD removed.

Table 2. Short or long term adverse events with IUD use as seen in the literature.

Short or Long Term Adverse Event	Support
Menorrhagia	Nelson et al[4], Howard et al[5], Bateson et al[21], Bahamondes et al[8]
Menstrual Bleeding Irregularities	Nelson et al[4], Dickerson et al[9], Bahamondes et al[8], Amico et al (2016)[19], Amico et al (2017)[19]
Dysmenorrhea	Nelson et al[4], Howard et al[5], Bateson et al[21]
Pelvic Inflammatory Disease	Howard et al[5], Aoun et al[16]
Pelvic Pain	Howard et al[5], Bateson et al[21], Bahamondes et al[8]
Intermenstrual Bleeding	Bateson et al[21]
Dyspareunia	Bateson et al[21]
Malposition	Bateson et al[21]
Expulsion	Bateson et al[21]
Failures	Bateson et al[21]
Ectopic Pregnancy	Bateson et al[21], Aoun et al[16]
Increased Frequency of Menstrual Bleeding	Dickerson et al[9]
Lower Abdominal Pain	Bahamondes et al[8]
Prolonged Bleeding	Bahamondes et al[8]
Cramping	Amico et al (2016)[19], Amico et al (2017)[20]

Table 3 presents long term adverse events of IUD use which include local and systemic effects. Some of these systemic effects include increased blood pressure and dermatitis/eczema. It is well accepted that IUDs act locally so adverse events such as vaginal infections are expected. Women have also reported systemic adverse events such as weight gain which have mixed evidence in the literature and may be due to confounding[7]. This study attempts to look at both local and systemic adverse events that may be related to IUD use.

Table 3. Long term adverse events with IUD use as seen in the literature.

Long term adverse event	Support
Weight Gain	Nelson et al[4], Dickerson et al[9], Peipert et al[15]
Loss of Sexual Desire/Changes in Libido	Nelson et al[4]
Mood Changes	Nelson et al[4]
Amenorrhea	Nelson et al[4], Howard et al[5], Dickerson et al[9]
Breast Tenderness/Enlargement	Nelson et al[4]
Water Retention/Bloating	Nelson et al[4], Amico et al (2016)[19]
Headaches/Migraines	Nelson et al[4], Dickerson et al[9], Bahamondes et al[8]
Fatigue	Nelson et al[4]
Increase in Vaginal Discharge	Nelson et al[4], Bateson et al[21], Amico et al (2016)[19]
Concern About Not Being Able to Get Pregnant After Stopping	Nelson et al[4]
Nausea/Vomiting	Nelson et al[4]
Vaginal Dryness	Nelson et al[4]
Blood Clots/Risk of Stroke	Nelson et al[4]
Yeast Infection/Vaginal Iinfection	Nelson et al[4], Howard et al[5], Amico et al (2016)[19]
Dizziness	Nelson et al[4], Bahamondes et al[8]
Hair Loss	Nelson et al[4], Dickerson et al[9]
Increased Blood Pressure	Nelson et al[4]
Anemia	Howard et al[5]
Ovarian Cysts	Howard et al[5]
Acne	Bahamondes et al[8], Peipert et al[15]
Dermatitis/Eczema	Fage, Faurshou, & Thyssen[23]
Depression	Dickerson et al[9]

1.2.3.2 Perceptions of the patient and their social circle

Women's decisions regarding IUD removal are also influenced by the experiences and perceptions had by people in their social circles as introduced in section 1.2.2. Anderson et al. found that the major negative topic around IUDs women talk about are the adverse events such as perforation, migration, heavy bleeding, cramping, failure, problems with return of fertility, and death[18]. While some women admitted that they knew these stories may not be true, it was enough to scare them into having their IUD removed. The source of negative stories from family and friends most frequently came from television commercials as well as personal stories from family and friends[18].

Amico et al. (2016) found that potential or suspected adverse events were a contributing factor for the interest in removing the IUD such as concern for internal damage, that the IUD was not correctly placed, or that it was causing an infection[19]. Amico et al. also found that while patients

were warned about the potential for bleeding or cramping, the women who were considering the removal of IUDs had symptoms that were more severe or of longer duration than they expected or that they had additional adverse events such as vaginal discharge, bloating, yeast infections, and other urinary tract infections[19].

1.2.4 Removal of IUDs

When women request that their IUD be removed, doctors often advise they wait to determine if the adverse events resolve themselves[19]. This is especially true if the patient has had the IUD inserted for less than a year. This is frustrating to the patients because most of them have already waited what they consider a significant amount of time before consulting a doctor about getting their IUD removed[19].

Amico et al. (2016) found that many women who wanted to have their IUD removed felt that their doctor's expressed disinterest in removing the IUD discouraged them from having the IUD removed[19]. The required office visit along with perceived coercion into women not removing IUDs from their doctors can lead to perceived lack of autonomy in reproductive choice so some women choose to try to remove the IUD themselves[19,20,22]. While IUDs were designed to be removed by a healthcare professional, there is nothing dangerous about a woman removing an IUD herself. Foster et al. found that only 20% of these women were successful in removing their own IUD. The odds of success increased with each additional centimeter in length of the strings coming off the IUD and if the woman had previously felt the strings[22].

1.3 IUD USE IN THE INPATIENT SETTING

The insertion and removal of an IUD is usually performed within an outpatient setting in a doctor's office, not in the hospital. Insertion of an IUD in the hospital occurs as a concurrent procedure during another surgical procedure (e.g. placement of IUD after treating ovarian cysts or abnormal uterine bleeding) or is placed after recent pregnancy. Removal of an IUD is related to the treatment of another medical condition present during the inpatient hospitalization. Providers in the hospital would not generally address requests for the removal of an IUD when it is unrelated to the reason for hospitalization.

In most cases, a woman entering the hospital would not need to have her IUD removed. Women may have an IUD removed in the hospital if the symptoms are localized to the reproductive system such as pelvic pain or infection to rule out the IUD as related to the symptoms. For example, if a woman presented with persistent pelvic inflammatory disease even after antibiotic use, doctors may remove her IUD to see if that alleviates her symptoms and helps eliminate the infection. In general, an IUD should only be removed after careful discussion with her established women's health provider. When a woman's IUD is removed, she should use an alternate form of contraception and be informed that she is at an increased risk for pregnancy as other common types of contraception are less effective than an IUD. There is a gap in knowledge about why women have an IUD removed in a hospital, especially in regards to specific conditions that influenced her decision to have an IUD removed. In this study, we will focus on the association between comorbid medical conditions and IUD removal.

Little is known about IUD insertion and removal in a hospital setting. All previous research has been performed in outpatient settings. Yet, many serious conditions are treated in hospital settings, and so IUD insertion or removal in this setting are important to patients and providers.

This knowledge could help improve our knowledge of contraceptive services and risk for discontinuation of IUDs as well as potential IUD related complications and/or long-term systemic effects.

1.4 MAIN QUESTION/SETTING

We conducted explorative research on in-hospital comorbidities among IUD users in order to identify potential IUD-related adverse health outcomes that have not been fully recognized. Our study objectives included: 1) investigate if there is a correlation between putative adverse health outcomes and IUD use by comparing their frequencies among in-hospital women subpopulations with IUD removal and their counterparts with IUD insertion or no IUD procedure and 2) identify if there are racial differences in the prevalence of certain comorbidities among inpatient women with IUD removal vs. those with no IUD procedure. We used Data from the National Inpatient Sample from the Agency for Healthcare Research and Quality (NIS/AHRQ, 2010-2014) to meet our objectives. Our outcomes of interest were defined using International Classification of Diseases codes (ICD-9) corresponding to previously identified comorbidities to examine their association with patient factors (e.g., age and race) among the following inpatient women subpopulations: No IUD procedure, IUD removal, or IUD insertion. As a main result of this pharmacoepidemiologic research, we expected to elicit underlying conditions and demographic factors (e.g., race) that could precipitate the risk of adverse health outcomes in women using IUDs. Based on our previous analysis of the entire spectrum of comorbidities with substantially different frequencies among inpatient women subpopulations with IUD removal vs. IUD insertion, we

focused this analysis on comorbidities related to vascular disease, allergic conditions, and endometriosis.

Following the secondary study objective, we tried to identify if there are racial differences in the prevalence of certain comorbidities among inpatient women with IUD removal vs. those with IUD insertion. Potential evidence that factors associated with race may impact the risk for adverse events upon IUD use may help individualize the choice of best contraceptive methods for women. Future pharmacogenetic research, including *in silico* analysis of known biomarker databases, may help to identify putative biomarkers (e.g., Single Nucleotide Polymorphisms - SNPs) for certain IUD-associated conditions, thereby further promoting the individualized risk-benefit assessment and development of Precision Medicine applications pertaining to IUDs.

2.0 METHOD

2.1 STUDY POPULATION

2.1.1 Dataset

We performed an analysis on NIS data from 2010-2014 looking at IUD insertion and removal compared to women without an IUD procedure to examine potential comorbidities associated with IUD use. NIS data are sampled from the state inpatient databases as a 20% stratified sample of all discharges within United States hospitals (from participating states), excluding rehabilitation and long-term acute care hospitals. When the NIS started in 1988, only 8 states participated. With participation of 46 states plus Washington DC by 2014, recent NIS data cover 97% of the U.S. population and therefore are representative of national trends. The states not included are Alabama, New Hampshire, Delaware, and Idaho. The large sample sizes provided by the NIS allow for analysis of "rare conditions, uncommon treatments, and special patient populations"[24].

Addressing the need for filling the gap in the literature about the underlying conditions pertaining to IUD insertion and removal within the inpatient setting, the NIS dataset was used as a representative sample of hospitalizations within the US which contains information related to both the exposure (IUD use) and outcomes of interest (adverse health outcomes potentially attributable to IUDs). It is important to note, however, that this study is limited to the inpatient population and therefore is not representative of the vast majority of IUD insertions and removals that are conventionally performed in an outpatient setting.

2.1.2 Eligibility criteria

Inpatient entries from the NIS dataset for the years 2010-2014 were included if the person was female of reproductive age which we defined as 15-65 years. In order to be included in the propensity matching, the entry had to have complete information for all variables of interest (age, race, child delivery, year of inpatient visit, length of stay, quarter of year of discharge, and hospital classification). Any entries that had incomplete information were excluded from the matched sample.

2.1.3 Definition of variables

Cases were classified as having an IUD-related ICD-9 code within the 30 diagnosis codes allotted for each inpatient. Entries were classified as having an IUD insertion if their data contained the ICD-9 code V25.11, a billing code indicating the insertion of an IUD by a physician. Entries were classified as having an IUD removed if the entry contained the ICD-9 code V25.12, a billing code indicating the removal of an IUD by a physician. Entries were classified as having an IUD re-inserted if the entry contained the ICD-9 code V25.13, a billing code indicating the removal and re-insertion of an IUD by a physician in the same visit. Women with the re-insertion of an IUD were not included in the analysis due to the low frequency. Other entries meeting the eligibility criteria that did not have an IUD related billing code were classified as controls not having an IUD procedure.

Baseline characteristics of interest as potential confounders or predictors of IUD status were race, age, child delivery code, year of inpatient visit, length of stay, quarter of the year of discharge, and hospital classification. Race was classified in two different ways: 1) White, Black,

Hispanic, Asian, Native American, and other races and 2) White, Black, and other races. The main results are based on race as a three-category variable, but distribution of characteristics was analyzed using race in 6 categories. Age was considered both as a continuous variable and as a categorical variable with 5 categories: <21 years, 21-30 years, 31-40 years, 41-50 years, and >50 years. Child delivery code is a binomial variable indicating whether there were maternal codes in the inpatient entry. Year of inpatient visit include the years between 2010-2014 when the inpatient entry took place. Quarter of the year of discharge was classified as January-March, April-June, July-September, and October-December. Hospital classification is a 4-digit variable with each digit providing different information about the hospital. This information includes the hospital census geography, control (government or private, government nonfederal, private not-for-profit, private investor-owned, private neither not-for-profit or investor-owned), urban or rural, teaching (rural, urban teaching, urban non-teaching), and bed size (small, medium, large). NIS data prior to 2012 was classified by census region (Northeast, Midwest, South, West) but from 2012 on the data was classified as a more granular census division with two or three divisions corresponding to one region.

Outcomes of interest include potential comorbidities that are classified into vascular diseases, allergic/immune conditions, and endometriosis categories. Vascular diseases of interest include hypertension, cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. Allergic/immune disorders include autoimmune conditions, allergies, rheumatoid arthritis, lupus, and a combined variable of dermatitis/eczema/allergic urticaria. Endometriosis was classified as endometriosis overall, endometriosis of the uterus, and non-uterine endometriosis. The classification codes that were used for each disease are listed in Table 4.

Table 4. List of classification codes that defined the diseases of interest.

Disease	Code
Vascular Diseases	
Hypertension	CCS 98-99
Cardiovascular Disease	CCS 100-108
Cerebrovascular Disease	CCS 109-113
Peripheral Vascular Disease	CCS 114-121
Allergies and Immune Disorders	
Autoimmune Disorders	CCS 57, 80, 202, 210
Allergies	CCS 128, 198, 253
Rheumatoid Arthritis	CCS 202
Lupus	CCS 210
Dermatitis/Eczema/Allergic Urticaria	ICD-9 692.0-692.3, 693.4, 693.5, 692.6, 692.70, 692.74, 692.79, 692.81-692.84, 692.89, 692.9, 692.30, 692.31, 692.38, 693.9, 708.0
Endometriosis	
Endometriosis	CCS 169 (ICD 617.0-617.9)
Endometriosis of the Uterus (Adenomyosis)	ICD 617.0
Non-Uterine Endometriosis	ICD 617.1-617.9

2.2 STATISTICAL METHODS

2.2.1 Propensity matching

Due to the rare frequency of inpatient hospitalizations with IUD-related codes, propensity matching was performed to create more equally sized groups and make the cases and controls more comparable, giving better evidence that any differences found are due to IUD use. Due to the low number of women with IUD re-insertions (n=25), they were not included in the analysis. Since the IUD group was define as a three-category variable (IUD insertion, IUD removal, and no IUD procedure), a two-step propensity score matching process was performed to get matched triplets for the analysis. First, a logistic regression was run to determine the probability of having an IUD-related ICD-9 code based on race, age group, child delivery code, year of inpatient visit, length of

stay, quarter of the year of discharge, and the hospital stratum code. Then, women with IUD insertion were matched to women with IUD removal based on the propensity of having a diagnosis code related to an IUD. The matched women with the removal of an IUD were then matched to the control women with no IUD procedure codes. Using this sequence, we expected to create more equal groups between the IUD removal and the no IUD procedure group. While the insertions and removals were matched, they both were considered as having an IUD-related ICD-9 code and therefore, the propensity matching is expected to be less effective in creating comparable IUD insertion/IUD removal groups. As a result, we created a matched triplet of patients with an IUD insertion, IUD removal, and a no IUD procedure, giving two controls for each IUD removal case; matching was done using PROC PSMATCH in SAS using a greedy 1:1 match with a caliper of 0.25 standard deviations for each matching step[25].

2.2.2 Preliminary analysis

Association tests between IUD status group and the baseline characteristics of interest as well as between IUD status group and the comorbidities of interest were performed to get pair-wise comparison results by IUD status group (No IUD procedure vs. IUD insertion, No IUD procedure vs. IUD removal, and IUD insertion vs. IUD removal). In the full, pre-matched sample, categorical variables were analyzed using a chi-square test. In the matched sample, categorical variables were analyzed with Fisher's exact test where the expected value was less than 5 or otherwise a chi-square test for the matched analysis. Continuous variables were analyzed using GLM for both the pre-matched and matched samples. ANOVA could not be used because the groups has vastly different sample sizes.

2.2.3 Matched analysis

The matched triplets were analyzed using conditional logistic regression for the disease outcomes listed in Table 4 conditional on being in the given matched triplet.

The primary comparison of interest was the IUD removal group to the no IUD procedure group and of secondary interest is the IUD removal group compared to the IUD insertion group. Three models were used: 1) unadjusted, 2) adjusted for age, year, and child delivery code 3) adjusted for covariates from the second model and race. We expect that the added adjustment in the second and third models helped reduce the confounding in these variables due to the residual differences from the propensity matching of IUD removal and IUD insertion due to their being classified in the same propensity score group. The third model was aimed to identify if race may affect the relationship between IUD group and the outcome. To better answer this question, an analysis of odds ratios of comorbidity based on IUD group stratified by race was analyzed along with the interaction between race and IUD group in unadjusted models. If any race category for a given outcome was not estimable, the interaction was not tested. The race analysis was performed only between the IUD removal and no IUD procedure groups because the models became unstable with small sample size and low rates of events in the IUD insertion group. Associations with a p-value <0.01 were considered significant to account for multiple testing. All analysis was done using SAS 9.4.

3.0 RESULTS

3.1 PRE-MATCHING RESULTS

The total unmatched sample included 10,532,920 inpatient entries composing 1,822 IUD insertions, 613 IUD removals, and 10,530,485 controls with no IUD procedures. Figure 3 is a CONSORT chart showing how the sample population was formed. The distribution of the sample population for baseline characteristics is shown in Table 5. Overall, the removal group and no IUD procedure groups appeared to be more similar to each other than the IUD insertion group, though all pair-wise comparisons of the groups are statistically different except for length of stay and quarter of discharge for the comparisons between IUD removal vs. no IUD procedure and IUD removal vs. IUD insertion. Women who had an IUD inserted had the youngest mean age (27.9 years) and women without an IUD procedure had the oldest mean age (37.5 years). Women who had no IUD procedure or an IUD removed were more likely to be White (58.43% and 48.97% respectively) while women with an IUD inserted were more likely to be Hispanic (41.19%). Rates of insertion of an IUD increased each year from 6% in 2010 to 34% in 2014. Rates of no IUD procedure decreased slightly with subsequent years from 21% in 2010 to 19% in 2014. The average length of stay was highest among women without an IUD procedure (3.8 days) compared to women with an IUD removed or inserted (both 3.3 days), though only the difference between having an IUD inserted and having no IUD procedure reached statistical significance. Almost all (93%) of the women with an IUD inserted had a child delivery code, but this was much less frequent in women with an IUD removed or no IUD procedure (19% and 4% respectively). Rates

of IUD insertion and removal increased with quarter of the year (from around 20% to around 30%) while rates of no IUD procedure were largely the same by quarter (25%).

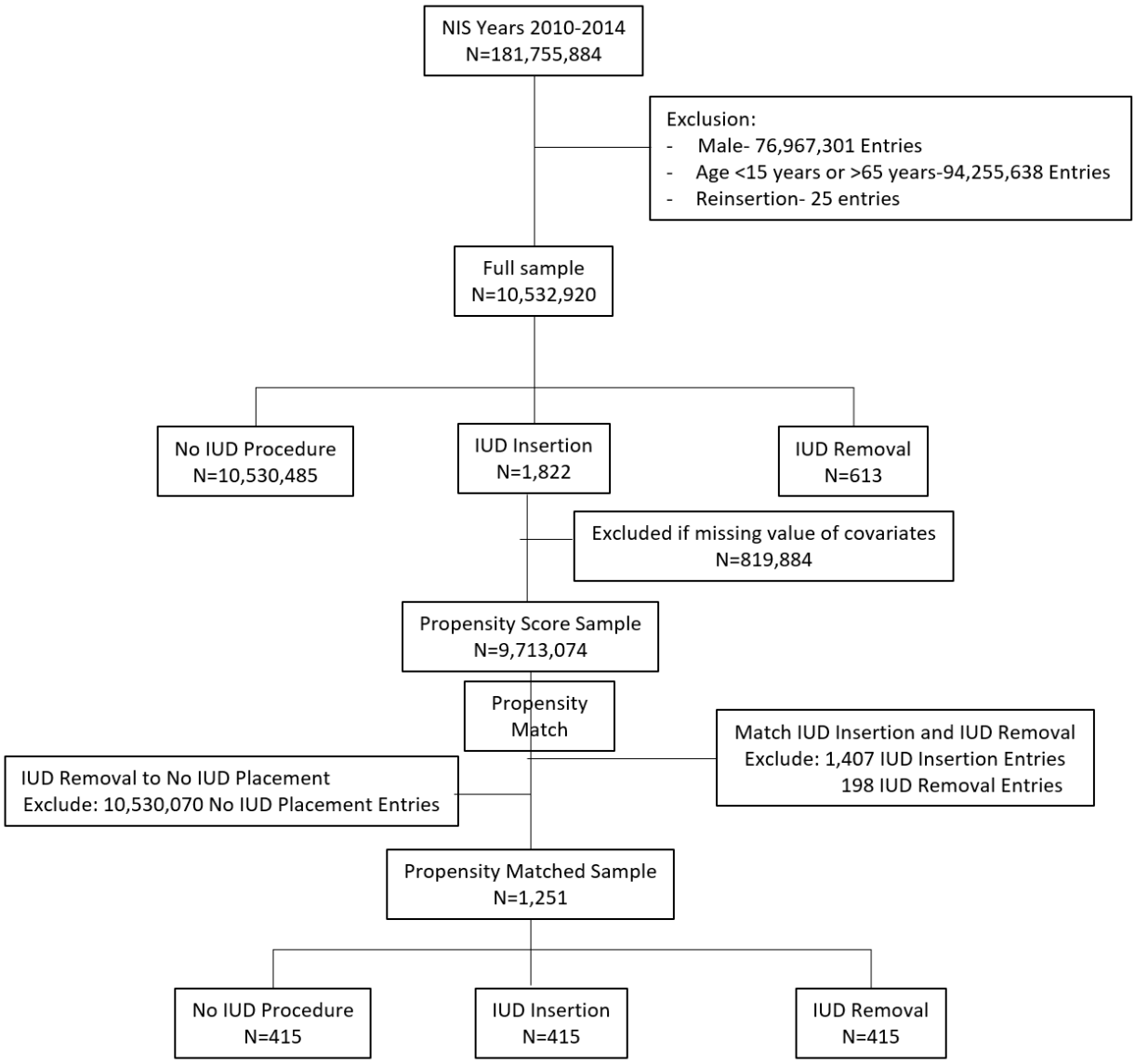


Figure 3. CONOSRT chart showing how both the full, pre-matched sample and matched samples were formed.

Table 5. Factors of interest potentially related to IUD status.

		No IUD Procedure n (%) (N=10,530,485)	**Insertion** n (%) (n=1,822)	**Removal** n (%) (n=613)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Age	*<21 Years*	825,753 (8)	242 (13)	30 (5)	<0.001**	<0.001**	<0.001**
	21-30 Years	3,012,709 (29)	938 (51)	180 (29)			
	31-40 Years	2,483,019 (24)	574 (32)	211 (34)			
	41-50 Years	1,823,764 (17)	59 (3)	153 (25)			
	>50 Years	2,385,240 (23)	9 (0.5)	29 (6)			
Age	*Mean (SD)*	37.5 (12.8)	27.9 (6.7)	35.6 (9.9)	<0.001**	<0.001**	<0.001**
Race	*White*	5,682,942 (58)	441 (25)	284 (49)	<0.001**	<0.001**	<0.001**
	Black	1,808,435 (19)	376 (21)	189 (17)			
	Hispanic	1,489,351 (15)	732 (41)	150 (26)			
	Asian	310,023 (3)	85 (5)	25 (4)			
	Native	7,7016 (1)	30 (2)	3 (1)			
	Other	358,691 (4)	113 (6)	22 (4)			
Year of Admission	*2010*	2,224,264 (21)	122 (6)	37 (6)	<0.001**	<0.001**	<0.001**
	2011	2,262,023 (21)	172 (9)	174 (28)			
	2012	2,062,754 (20)	414 (23)	130 (21)			
	2013	1,995,612 (19)	498 (27)	144 (23)			
	2014	1,985,832 (19)	626 (34)	128 (21)			
Length of Stay	*Mean (SD)*	3.8 (5.3)	3.3 (8.4)	3.3 (5.6)	0.05*	<0.001*	0.88
Child Delivery Codes	*Yes*	4,245,136 (40)	1694 (93)	116 (19)	<0.001**	<0.001**	<0.001**
Quarter of Discharge	*January-March*	2,582,110 (25)	375 (21)	146 (24)	0.05*	<0.001**	0.32
	April-June	2,625,705 (25)	413 (23)	139 (23)			
	July-September	2,700,559 (26)	440 (24)	147 (24)			
	October-December	2,606,490 (25)	592 (33)	181 (30)			

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

The prevalence of the comorbidities of interest by IUD status group are shown in Table 6. The percentage of patients with each comorbidity differed by IUD group with the exception of allergy and combined category of dermatitis/ eczema/ allergic urticaria. Comparison between women with no IUD procedure and those with removal of an IUD revealed significant differences in rates for hypertension, cardiovascular disease, peripheral vascular disease, and all endometriosis categories. Women with an IUD removed had a lower prevalence for vascular diseases (hypertension (12% vs. 23%, $p>0.001$), cardiovascular disease (6% vs. 14%, $p>0.001$), and peripheral vascular disease (5% vs. 10%, $p>0.001$)), but a higher prevalence for the endometriosis categories (7% vs. 1% for overall endometriosis, 5% vs. 0.4% for endometriosis of the uterus, and 2% vs. 1% for non-uterine endometriosis, $p>0.001$ for all three categories). There were also significant differences between women with no IUD procedure and those with the insertion of an IUD for most comorbidities of interest except allergy, dermatitis/eczema/allergic urticaria, endometriosis of the uterus, and non-uterine endometriosis with the insertion of an IUD showing a lower prevalence for each disease. The prevalence of hypertension was 3% among women with an IUD inserted compared to 23% in women with no IUD procedure ($p<0.001$). Women with an IUD inserted had a prevalence of 3% for cardiovascular disease compared to 14% in women without an IUD procedure ($p<0.001$). The prevalence of cerebrovascular disease was 0.3% in women with an IUD inserted compared to women with no IUD procedure (2%, $p<0.001$). The prevalence of peripheral vascular disease was 5% among women with an IUD inserted compared to 10% in women without an IUD procedure ($p<0.001$). Women with an IUD inserted had a prevalence of auto-immune disorders of 1% while women without an IUD procedure had a prevalence of 3% ($p<0.001$ respectively). The prevalence of endometriosis in women with an IUD inserted was 0.3% and 1% in women with no IUD procedure ($p=0.01$). The prevalence of both

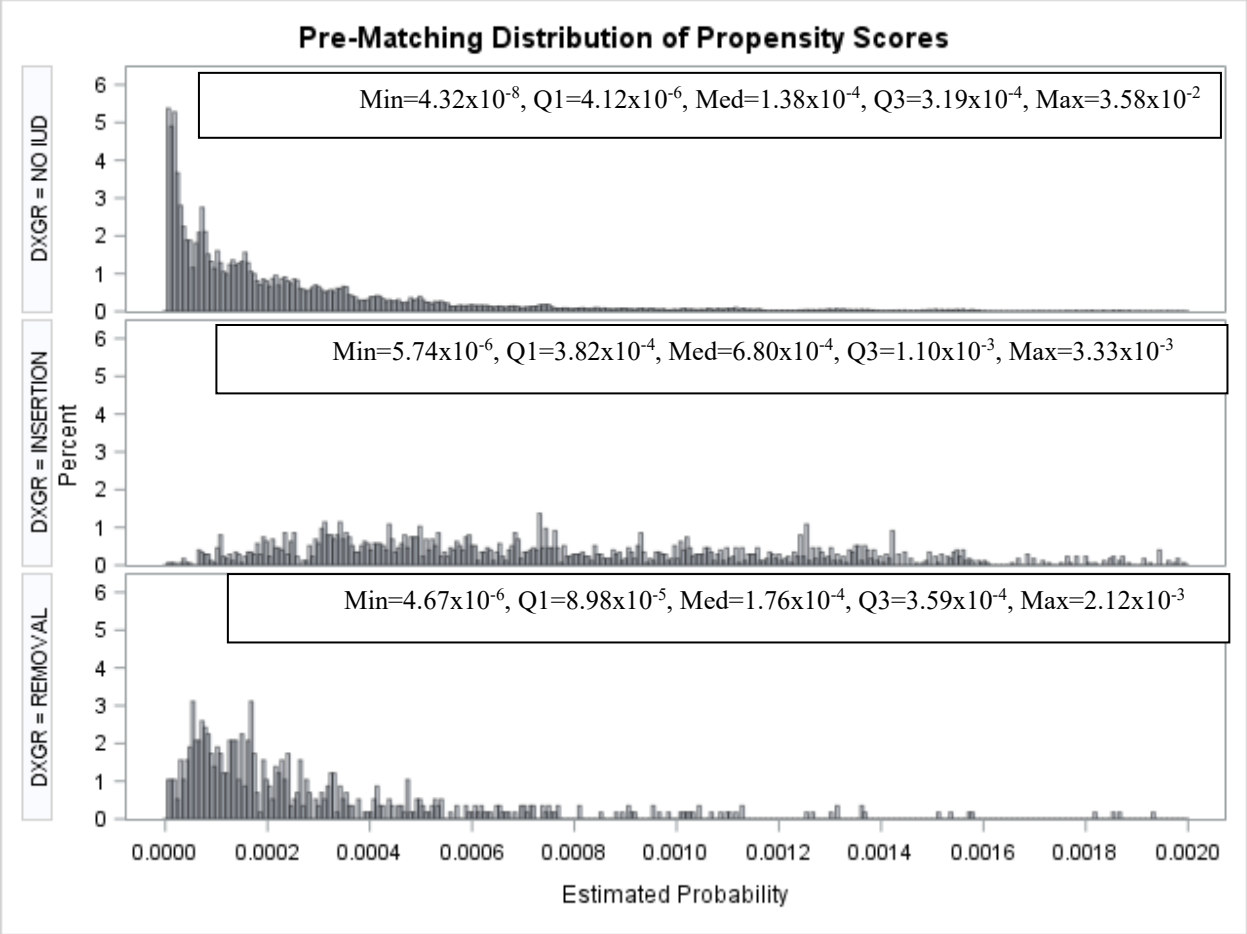
rheumatoid arthritis and lupus in women with an IUD inserted was 0.4% but 1% in women with an IUD removed (p=0.001). Prevalence of disease was similar between women with the insertion of an IUD and the removal of an IUD except for hypertension (12% vs. 3%, p>0.001), cerebrovascular (2% vs. 0.3%, p>0.001), and all the endometriosis categories (7% vs. 0.3% for overall endometriosis, 5% vs. 0.05% for endometriosis of the uterus, and 2% vs. 0.3% for non-uterine endometriosis, p>0.001 for all three categories). The prevalence of hypertension, cerebrovascular disease, and all endometriosis categories was lower in the insertion group compared to the removal group.

Table 6. Unmatched distribution of diseases of interest by IUD group.

	No IUD Procedure n (%) (N=10,530,485)	**Insertion** n (%) (N=1822)	**Removal** n (%) (N=613)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Vascular						
Hypertension	2,405,679 (23)	59 (3)	73 (12)	<0.001**	<0.001**	<0.001**
Cardiovascular	1,488,003 (14)	75 (4)	34 (6)	<0.001**	<0.001**	0.15
Cerebrovascular	223,097 (2)	6 (0.3)	10 (2)	0.40	<0.001	<0.001**
Peripheral Vascular	1,037,744 (10)	82 (5)	33 (5)	<0.001**	<0.001**	0.37
Auto-immune						
Auto-immune	335,323 (3)	16 (1)	11 (2)	0.05*	<0.001**	0.06
Allergy	1,715,429 (16)	271 (15)	100 (16)	0.99	0.10	0.39
Rheumatoid Arthritis	127,822 (1)	7 (0.4)	6 (1)	0.60	0.001**	0.08
Lupus	144,151 (1)	7 (0.4)	4 (1)	0.13	<0.001**	0.39
Dermatitis/Eczema /Allergic Urticaria	56,800 (1)	5 (0.3)	3 (0.5)	0.87	0.12	0.42
Endometriosis						
Endometriosis	90,752 (1)	9 (0.3)	44 (7)	<0.001**	0.01*	<0.001**
Endometriosis of the Uterus	41,083 (0.4)	1 (0.05)	32 (5)	<0.001**	0.23	<0.001**
Non-Uterine Endometriosis	56,317 (1)	6 (0.3)	15 (2)	<0.001**	0.02*	<0.001**

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

The distribution of propensity scores by IUD group before matching is shown in Figure 4. In order to improve the visualization of distribution which was initially affected by some outliers, the propensity scores were cut off at 0.002 which is the 99 percentile for insertion group which had the highest 99 percentile. Comparing the minimum, Q1, median, Q3, and maximum values across IUD status group, all but the median values were at least one order of magnitude different, indicating that the three groups are not comparable.



The distribution of the propensity scores was cut off at 0.002.

Figure 4. Pre-matching distribution of probability of an IUD-related ICD-9 code.

3.2 POST-MATCHING RESULTS

Because baseline characteristics were different between the groups, propensity matching was performed as an attempt to make the three groups (no IUD procedure, IUD removal, and IUD insertion) more comparable. After matching, 417 triplets were identified. The number of triplets was limited by the number of removals as it was the smallest group (n=613) before matching. The minimized sample size was expected to help prevent the study from being overpowered

(specifically, from the high number of controls, n=10,530,485) and ensure that significant results will be more likely to be clinically meaningful and reduce the impact of confounding. Some women with an IUD removed were not matched due to the inability to find a woman with an IUD inserted that had a similar propensity score.

As expected, the women without IUD procedures, insertion of an IUD and the removal of an IUD became more similar to each other after the propensity matching (Table 7). After matching, there was no difference in rates of any baseline factors between women with no IUD procedure and women with removal of an IUD. Statistically significant differences remained for all factors of interest between women without an IUD procedure and women with the insertion of an IUD, with the exception of length of stay and quarter of discharge. Women with the removal of an IUD and those with the insertion of an IUD are also different in all factors except for length of stay (though the results became more similar than they were initially). When comparing the three IUD groups, statistically significant differences were maintained for all factors except for length of stay and quarter of discharge (result not shown).

Compared to the unmatched data in Table 5, the matched subpopulations were younger for no IUD procedure (37.5 years vs. 33.3 years) and IUD removal (35.6 years vs. 33.3 years) but older for IUD insertion (35.6 years vs. 28.5 years). There were lower rates of Whites among women with no IUD procedure (58% vs. 38%) and an IUD removal (49% vs. 37%) and higher rates in women with an IUD insertion (25% vs 49%). There were higher rates of Hispanics in women with no IUD procedure (15% vs. 33%) and lower rates in women with an IUD removal (26% vs. 34%) or IUD insertion (26% vs. 19%). Within the matched sample, rates of not having an IUD procedure had a distinct increase with year of admission (from 4% to 24%), while rates of insertion were relatively constant from year to year (around 20%). Length of stay, child delivery

codes, and quarter of discharge after matching followed patterns similar to the pre-matching trends. When comparing the matched data to the unmatched data, the removal and no IUD procedure in the matched group were much more similar to each other, but the insertion group remained very different from both the removal and no IUD procedure groups, indicating the need for further adjustment in the analysis. The fact that the removal and no IUD procedure groups were very similar is an indication that the propensity score matching was successful.

Table 7. Baseline characteristics that may be related to IUD group after propensity matching.

		No IUD Procedure n (%) (N=417)	**Insertion** n (%) (n=417)	**Removal** n (%) (n=417)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Age	*<21 Years*	28 (7)	70 (17)	27 (6)	1.0	<0.001**	<0.001**
	21-30 Years	149 (36)	204 (49)	145 (35)			
	31-40 Years	150 (36)	101 (24)	153 (37)			
	41-50 Years	86 (21)	33 (8)	88 (21)			
	>51 Years	4 (1)	9 (2)	4 (1)			
Age	*Mean (SD)*	33.3 (8.9)	28.5 (8.3)	33.3 (8.6)	0.91	<0.001**	<0.001**
Race	*White*	157 (38)	203 (49)	154 (37)	0.87	<0.001**	<0.001**
	Black	82 (20)	86 (21)	80 (19)			
	Hispanic	139 (33)	81 (19)	142 (34)			
	Asian	15 (4)	17 (4)	19 (5)			
	Native	5 (1)	2 (0.5)	2 (0.5)			
	Other	19 (5)	28 (7)	20 (5)			
Year of Admission	*2010*	17 (4)	82 (20)	17 (4)	1.0	<0.001**	<0.001**
	2011	93 (22)	83 (20)	91 (22)			
	2012	92 (22)	81 (19)	93 (22)			
	2013	113 (27)	76 (18)	115 (28)			
	2014	102 (24)	95 (23)	101 (24)			
Length of Stay	*Mean (SD)*	3.0 (3.2)	3.0 (3.7)	3.4 (6.2)	0.25	0.88	0.31
Child Delivery Codes	*Yes*	113 (27)	328 (79)	110 (26)	0.81	<0.001**	<0.001**
Quarter of Discharge	*January-March*	92 (22)	69 (17)	94 (23)	0.96	0.03*	0.02*
	April-June	94 (23)	96 (23)	94 (23)			
	July-September	103 (25)	88 (21)	104 (25)			
	October-December	128 (31)	164 (39)	125 (30)			

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

The distribution of the propensity scores by IUD group after matching are shown in Figure 5. Compared to Figure 4, the distributions of propensity scores for all three IUD groups were much more similar to each other compared to the pre-matching distribution with the minimum, Q1, median, Q3, and maximum values all within one order of magnitude of each other when comparing across IUD status group. This is another indication that the matching was successful.

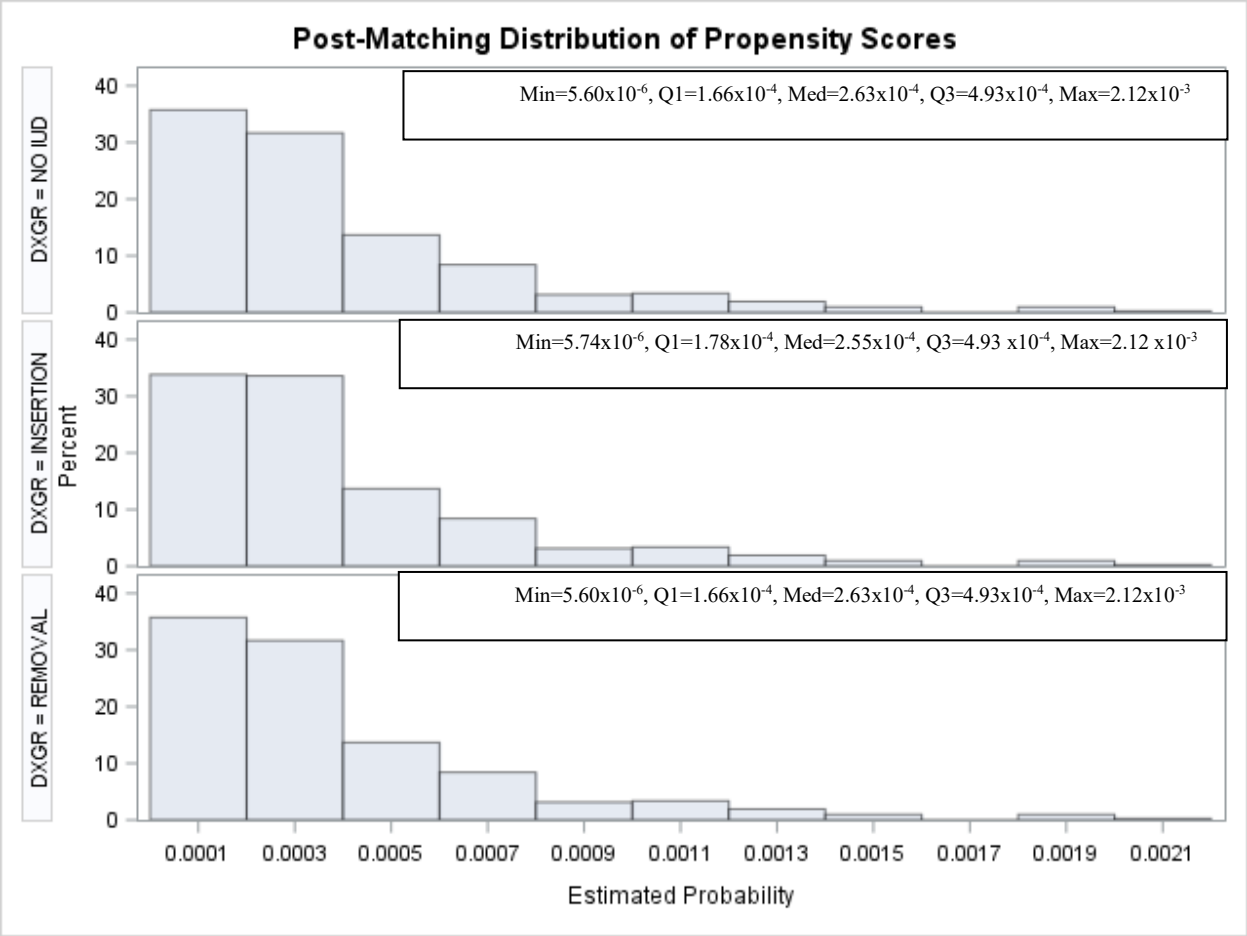


Figure 5. Post-matching distribution of propensity scores.

Post-matching results comparing the IUD status groups to the comorbidities of interest are shown in Table 8. Significant differences between the subpopulations with removal of an IUD and not having an IUD procedure remained for hypertension, cardiovascular disease, peripheral vascular disease, overall endometriosis, and endometriosis of the uterus. There was a lower prevalence of vascular diseases (9% vs. 17% in hypertension, $p<0.001$, 4% vs. 11% in cardiovascular disease, $p<0.001$, 4% vs. 9% in peripheral vascular disease, $p=0.002$), but an increased prevalence of all endometriosis categories in women with an IUD removed (7% vs. 2% in overall endometriosis, $p<0.001$, and 5% vs. 1% in endometriosis of the uterus, $p>0.001$). Statistically significant differences in the subpopulations with an IUD insertion compared to women without an IUD procedure showed a decreased prevalence of hypertension (6% vs 17%, $p>0.001$) and cardiovascular disease (1% vs. 2%, $p=0.002$).

Unlike in the comparison of baseline characteristics (Table 7), when looking at the comorbidities, IUD insertion group was fairly similar to the IUD removal and no IUD procedure groups, but the IUD removal and no IUD procedure groups were different from each other. The only comorbidities with different prevalences between IUD groups were overall endometriosis and endometriosis of the uterus with prevalences being highest when IUDs are removed (7% and 5% respectively) and lowest among women with IUDs inserted (1% and 0.2% respectively, $p<0.001$ for both. Disease prevalences within each IUD status group were relatively similar between the pre-matched and matched samples.

Table 8. Distribution of diseases of interest after propensity matching.

	No IUD Procedure n (%) (N=417)	**Insertion** n (%) (n=417)	**Removal** n (%) (n=417)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Vascular						
Hypertension	71 (17)	26 (6)	37 (9)	<0.001**	<0.001**	0.15
Cardiovascular	45 (11)	21 (5)	17 (4)	<0.001**	0.002**	0.51
Cerebrovascular	8 (2)	3 (1)	8 (2)	1.0	0.13	0.13
Peripheral Vascular	38 (9)	24 (6)	16 (4)	0.002**	0.06	0.19
Auto-immune						
Auto-immune	12 (3)	4 (1)	4 (1)	0.04*	0.04*	1.0
Allergy	62 (15)	73 (18)	62 (15)	1.0	0.30	0.3
Rheumatoid Arthritis	5 (1)	1 (0.2)	3 (1)	0.73	0.10	0.62
Lupus	4 (1)	2 (0.5)	1 (0.2)	0.37	0.69	1.0
Dermatitis/Eczema/ Allergic Urticaria	2 (0.5)	1 (0.2)	2 (0.5)	1.0	1.0	1.0
Endometriosis						
Endometriosis	8 (2)	3 (1)	30 (7)	<0.001**	0.13	<0.001**
Endometriosis of the Uterus	4 (1)	1 (0.2)	22 (5)	<0.001**	0.37	<0.001**
Non-Uterine Endometriosis	4 (1)	3 (0.7)	11 (3)	0.13	0.73	0.03*

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

The results of the conditional logistic regression models are shown in Tables 9-11. Model 1 is unadjusted, Model 2 adjusts for age, year, and child delivery code, and Model 3 adjusts for covariates from Model 2 along with race. Estimates for cerebrovascular disease, rheumatoid arthritis, dermatitis/eczema/allergic urticaria, and endometriosis of the uterus were not adjusted for child delivery code because it made the models unstable. Lupus was not included in the table because both adjusted models were unstable. The effect of IUD group on the comorbidities significantly varied across IUD status group for hypertension, cardiovascular disease, peripheral vascular disease, and endometriosis in all three models (Tables 9 and 11). Endometriosis of the uterus was significant in the unadjusted model and borderline significant in both adjusted models

(Table 11). In Table 10, after adjustment, the relationship between IUD group and autoimmune disorders and allergies was borderline significant (p=0.03 and 0.04 respectively). The estimates for model 2 and model 3 are nearly identical, indicating limited confounding by race.

The comparisons between women having an IUD removed and women without an IUD procedure are the main comparisons of interest and they followed similar significance patterns as the models looking at IUD status group overall. In Table 9, the results were similar between the three models with hypertension (Model 3 OR=2.3, p=0.004), cardiovascular disease (Model 3 OR=2.9, p=0.002), and peripheral vascular disease (Model 3 OR=2.9, p=0.002) showing a significant association with decreased likelihood among women with an IUD removed compared to not having an IUD procedure. The removal of an IUD had an increased association on overall endometriosis (Model 3 OR=0.13, p=0.004). Endometriosis of the uterus showed a borderline association between IUD removal compared to not having an IUD procedure (Model 3 OR=0.04, p=0.02). When compared to having an IUD inserted, there was a decreased relationship in cardiovascular disease (Model 3 OR=3.9, p=0.004) and peripheral vascular disease (Model 3 OR=4.8, p=0.001) and an increased relationship seen between overall endometriosis (Model 3 OR=0.10, p=0.006) and endometriosis of the uterus (Model 3 OR=0.06, p=0.03) in having an IUD removed.

Table 9. Results of conditional logistic regression models for vascular diseases.

		Model 1			Model 2			Model 3		
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Hypertension	IUD Group			<0.001 **			0.006 **			0.007 **
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	0.68	0.40, 1.1	0.15	2.5	1.2, 5.5	0.02 *	2.5	1.2, 5.6	0.02 *
	No IUD Procedure	2.2	1.4, 3.3	<0.001 **	2.4	1.3, 4.2	0.003 **	2.3	1.3, 4.1	0.004 **
Cardiovascular	IUD Group			<0.001 **			0.004 **			0.003 **
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	1.3	0.65, 2.4	0.50	3.6	1.5, 8.9	0.005 **	3.9	1.6, 9.9	0.004 **
	No IUD Procedure	2.9	1.6, 5.3	<0.001 **	2.9	1.5, 8.9	0.002 **	2.9	1.5, 5.7	0.002 **
Cerebrovascular***	IUD Group			0.28			0.36			0.36
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	0.36	0.09, 1.4	0.14	0.36	0.09, 1.5	0.15	0.36	009, 1.5	0.15
	No IUD Procedure	1.0	0.36, 2.8	1.0	0.71	0.21, 2.4	0.58	0.71	0.21, 2.4	0.58
Peripheral Vascular	IUD Group			<0.001 **			0.001 **			0.002 **
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	1.5	0.80, 2.9	0.20	5.0	2.0, 12.8	<0.001 **	4.8	1.9, 12.3	0.001 **
	No IUD Procedure	2.5	1.4, 4.6	0.003 **	2.9	1.5, 5.8	0.002 **	2.9	15, 5.7	0.002 **

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.
Model 1: Unadjusted
Model 2: Age, year, and child delivery code adjusted
Model 3: Model 2 plus race
*** Cerebrovascular disease not adjusted for child delivery code

Table 10. Results of conditional logistic regression models for allergic/immune conditions.

		Model 1			Model 2			Model 3		
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Autoimmune	IUD Group			0.06			0.08			0.03 *
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	1.0	0.25, 4.0	1.0	1.4	0.28, 7.5	0.67	1.1	0.21, 5.9	0.90
	No IUD Procedure	3.0	0.97, 9.3	0.06	3.9	1.1, 14.4	0.04	6.6	1.3, 34.8	0.03 *
Allergies	IUD Group			0.48			0.02 *			0.04 *
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	1.2	0.84, 1.8	0.30	1.8	1.2, 2.9	0.01 **	1.8	1.1, 2.8	0.02 *
	No IUD Procedure	1.0	0.8, 1.5	1.0	1.1	0.72, 1.6	0.77	1.1	0.71, 1.6	0.78
Rheumatoid Arthritis***	IUD Group			0.32			0.23	Not Estimable		
	Removal	1.0	Ref	Ref	1.0	Ref	Ref			
	Insertion	0.33	0.04, 3.2	0.34	0.46	0.03, 7.2	0.58			
	No IUD Procedure	1.7	0.40, 7.0	0.48	0.37	0.34, 40.9	0.28			
Dermatitis/Eczema/ Allergic Urticaria***	IUD Group			0.83			0.69	Not Estimable		
	Removal	1.0	Ref	Ref	1.0	Ref	Ref			
	Insertion	0.50	0.05, 5.5	0.57	0.69	0.04, 11.9	0.80			
	No IUD Procedure	1.0	0.14, 7.1	1.0	2.0	0.19, 20.3	0.57			

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.
Model 1: Unadjusted
Model 2: Age, year, and child delivery code adjusted
Model 3: Model 2 plus race
*** Rheumatoid arthritis and dermatitis/eczema/allergic urticaria not adjusted for child delivery code

Table 11. Results of conditional logistic regression models for endometriosis.

		Model 1			Model 2			Model 3		
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Endometriosis										
Endometriosis	IUD Group			<0.001 **			0.002 **			0.002 **
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	0.25	0.11, 0.56	<0.001 **	0.10	0.02, 0.52	0.006 **	0.10	0.02, 0.52	0.006 **
	No IUD Procedure	0.25	0.11, 0.56	<0.001 **	0.19	0.06, 0.57	0.003 **	0.13	0.03, 0.53	0.004 **
Endometriosis of the Uterus***	IUD Group			<0.001 **			0.02*			0.02*
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	0.04	0.01, 0.29	0.002 **	0.08	0.008, 0.74	0.03*	0.06	0.005, 0.7	0.03*
	No IUD Procedure	0.15	0.05, 0.48	0.001 **	0.08	0.009, 0.80	0.003*	0.04	0.002, 0.62	0.02*
Non-Uterine Endometriosis	IUD Group			0.08			0.11			0.18
	Removal	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref
	Insertion	0.25	0.07, 0.9	0.04 *	0.23	0.04, 1.4	0.11	0.04	0.001, 1.4	0.07
	No IUD Procedure	0.43	0.14, 1.3	0.13	0.36	0.09, 1.4	0.14	0.07	0.003, 1.5	0.09

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.
Model 1: Unadjusted
Model 2: Age, year, and child delivery code adjusted
Model 3: Model 2 plus race
*** Endometriosis of the uterus not adjusted for child delivery code

3.3 RACE ANALYSIS

Tables 12-14 show the distribution of the comorbid diseases by race. The distribution of races other than White and Black in the matched sample for no IUD procedure and removal was: 33% Hispanic, 4% Asian, 1% Native, and 5% other. It is important to note that due to too few cases of certain comorbidities, the race-stratified analysis was not performed for rheumatoid arthritis, lupus, and dermatitis/eczema/allergic urticaria. The significance patterns for disease by race generally reflect the patterns in the unstratified matched sample.

White women with no IUD procedure had a higher prevalence of hypertension (17%) compared to women with an IUD inserted (7%, $p=0.004$) or removed (3%, $p<0.001$) (Table 12). The only significant difference in prevalence of hypertension by IUD status group in Black women was a higher prevalence in women with no IUD procedure compared to women with an IUD inserted (23% vs. 9%, $p=0.01$) (Table 13). Women in the other race category who had no IUD procedure had a higher prevalence of hypertension (14%) compared to women with an IUD inserted (2%, $p<0.001$), and women with an IUD inserted also had a lower prevalence compared to women with an IUD removed (10%, $p=0.007$) (Table 14).

There were no significant differences in prevalence of cardiovascular disease in White women by IUD status group (Table 12). Among Blacks, the only significant difference in prevalence of cardiovascular disease was that women with an IUD removed had a lower prevalence (4%) compared to women without an IUD procedure (20%, $p=0.0020$) (Table 13). Among other races, women with an IUD removed had a lower prevalence of cardiovascular disease (3%) compared to women without an IUD (11%, $p=0.006$), and women without an IUD also had a higher

prevalence of cardiovascular disease compared to women with an IUD inserted (2%, p=0.005) (Table 14).

Women in the other race category who had an IUD removed had a higher prevalence of endometriosis of the uterus (5%) compared to women with an IUD inserted or women with no IUD procedure (0%, p=0.007 for both). This pattern is also seen among women with endometriosis, though only the difference between women with an IUD removed and no IUD procedure reached statistical significance (Table 14). This pattern is also seen in non-uterine endometriosis among women in the other race category as well as all three endometriosis categories for White women and Black women, though they fail to reach statistical significance (Tables 12 and 13).

The distribution of baseline characteristics by race are shown in Appendix A. The significance patterns for each race group among the baseline characteristics reflect those in Table 7: the removal and no IUD procedure groups being very similar and the insertion group being different from both, except for length of stay and quarter of discharge.

Table 12. Distribution of comorbid diseases of interest in Whites.

	No IUD Procedure n (%) (N=157)	**Insertion** n (%) (N=203)	**Removal** n (%) (N=154)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Vascular						
Hypertension	27(17)	15(7)	5(3)	<0.001**	0.004**	0.09
Cardiovascular	10(6)	11(5)	8(5)	0.66	0.70	0.93
Cerebrovascular	2(1)	2(1)	5(3)	0.28	1.0	0.15
Peripheral Vascular	14(9)	13(6)	6(4)	0.07	0.37	0.30
Allergy						
Auto-immune	5(3)	3(1)	1(1)	0.21	0.30	0.64
Allergy	20(13)	40(20)	22(14)	0.69	0.08	0.18
Rheumatoid Arthritis	2(1)	1(0.5)	1(1)	1.0	0.58	1.0
Lupus	0	1(0.5)	0	-	1.0	1.0
Dermatitis/Eczema/Allergic Urticaria	0	0	0	-	-	-
Endometriosis						
Endometriosis	5(3)	2(1)	17(11)	0.007**	0.25	<0.001**
Endometriosis of the Uterus	4(3)	1(0.5)	12(8)	0.04*	0.17	<0.001**
Non-Uterine Endometriosis	2(1)	2(1)	7(5)	0.10	1.0	0.04*

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

Table 13. Distribution of comorbid diseases of interest in Blacks.

	No IUD Procedure n (%) (N=82)	**Insertion** n (%) (N=86)	**Removal** n (%) (N=80)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Vascular						
Hypertension	19(23)	8(9)	13(16)	0.27	0.01*	0.18
Cardiovascular	16(20)	7(8)	3(4)	0.002**	0.03*	0.33
Cerebrovascular	1(1)	1(1)	0	1.0	1.0	1.0
Peripheral Vascular	9(11)	6(7)	5(6)	0.28	0.36	0.85
Allergy						
Auto-immune	4(5)	1(1)	2(3)	0.68	0.20	0.61
Allergy	21(26)	18(21)	19(24)	0.78	0.47	0.66
Rheumatoid Arthritis	2(2)	0	1(1)	1.0	0.24	0.48
Lupus	3(4)	1(1)	1(1)	0.62	0.36	1.0
Dermatitis/Eczema/ Allergic Urticaria	1(1)	0	1(1)	1.0	0.49	0.48
Endometriosis						
Endometriosis	1(1)	0	2(3)	0.62	0.49	0.23
Endometriosis of the Uterus	0	0	2(3)	0.24	-	0.23
Non-Uterine Endometriosis	1(1)	0	0	1.0	0.49	-

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

Table 14. Distribution of comorbid diseases of interest in other races.

	No IUD Procedure n (%) (N=179)	**Insertion** n (%) (N=128)	**Removal** n (%) (N=183)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Vascular						
Hypertension	25(14)	3(2)	19(10)	0.29	<0.001**	0.007**
Cardiovascular	19(11)	3(2)	6(3)	0.006**	0.005**	0.74
Cerebrovascular	5(3)	0	3(2)	0.50	0.08	0.27
Peripheral Vascular	15(8)	5(4)	5(3)	0.02*	0.11	0.75
Allergy						
Auto-immune	3(2)	0	1(1)	0.37	0.27	1.0
Allergy	21(12)	15(12)	21(11)	0.93	0.98	0.95
Rheumatoid Arthritis	1(1)	0	1(1)	1.0	1.0	1.0
Lupus	1(1)	0	0	0.49	1.0	-
Dermatitis/Eczema /Allergic Urticaria	1(1)	0	1(1)	1.0	1.0	1.0
Endometriosis						
Endometriosis	2(1)	1(1)	11(6)	0.01*	1.0	0.02*
Endometriosis of the Uterus	0	0	8(5)	0.007**	-	0.02*
Non-Uterine Endometriosis	2(1)	1(1)	4(2)	0.69	1.0	0.65

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

As shown in table 15, the overall effect of IUD status group on odds of comorbid disease by race was further analyzed based on the interaction between race and IUD status group. Analysis for cerebrovascular disease, rheumatoid arthritis, lupus, dermatitis/eczema/allergic urticaria, and endometriosis of the uterus were not reported in this table due to the small number of cases for each of these diseases. Unadjusted models were used for this analysis due to small samples and low event rates. In order to obtain estimable models, only the comparison between IUD removals to no IUD procedure were analyzed. We then tested for a statistical interaction between IUD status group (specifically IUD removal vs. no IUD procedure) and race. There were significant effects when comparing the IUD removal and no IUD procedure groups among Whites for hypertension (OR=0.007, 95% CI 0.01, 0.51) and endometriosis (OR=13.0, 95% CI 1.7, 99.4). There were no

significant associations among the Blacks or other race. None of the interactions tested were significant. Due to the low numbers of people in each category, results for many of the models and the interaction estimate were not able to be estimated. When testing the association between race and IUD status group in a chi-square test by comorbidity, the only significant relationship found was in women with hypertension ($p=0.0026$, results not shown). This gives some evidence for an interaction between race and IUD status on hypertension.

Table 15. Race and IUD group interaction on comorbid disease.

Outcome		White			Black			Other race			Inter
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	p-value
Vascular											
Hypertension	IUD Group										0.15
	No IUD Procedure	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref	
	Removal	0.07	0.01, 0.51	0.009 **	0.33	0.04, 3.2	0.34	0.91	0.39, 2.1	0.83	
Cardiovascular	IUD Group				Not Estimable						-
	No IUD Procedure	1.0	Ref	Ref				1.0	Ref	Ref	
	Removal	0.67	0.19, 2.4	0.53				0.13	0.02, 1.0	0.05	
Peripheral Vascular	IUD Group										0.98
	No IUD Procedure	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref	
	Removal	0.50	0.09, 2.7	0.42	0.50	0.05, 5.5	0.57	0.29	0.06, 1.4	0.12	
Allergy											
Autoimmune	IUD Group	Not Estimable			Not Estimable						-
	No IUD Procedure							1.0	Ref	Ref	
	Removal							1.0	0.06, 16.0	1.0	
Allergies	IUD Group										0.27
	No IUD Procedure	1.0	Ref	Ref	1.0	Ref	Ref	1.0	Ref	Ref	
	Removal	1.0	0.38, 2.7	1.0	0.20	0.02, 1.7	0.14	1.1	0.45, 2.7	0.82	
Endometriosis											
Endometriosis	IUD Group				Not Estimable						-
	No IUD Procedure	1.0	Ref	Ref				1.0	Ref	Ref	
	Removal	13.0	1.7, 99.4	0.01**				3.0	0.31, 28.8	0.34	
Non-Uterine Endometriosis	IUD Group	Not Estimable			Not Estimable						-
	No IUD Procedure							1.0	Ref	Ref	
	Removal							2.0	0.18, 22.1	0.57	

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

4.0 DISCUSSION

This study investigated if pre-specified comorbidities are associated with the removal of an IUD in an inpatient population. We also estimated if the effect of IUD status on the outcomes potentially differed by race. Within the triplet matched population, decreased likelihood of hypertension, cardiovascular disease, peripheral vascular disease, and higher likelihood of endometriosis were related to the removal of an IUD compared to women without an IUD procedure within both unadjusted and adjusted models. While the trends in significance levels varied in race-stratified analyses, there were no significant interactions between race and IUD status. This study helps build on to knowledge about IUD-related adverse events and will have an increasing public health impact as IUDs continue to gain popularity in the US.

While many demographic differences remained after propensity score matching between IUD removal and IUD insertion for baseline characteristics, the matching eliminated many of the measured differences between the IUD removal and no IUD procedure groups in baseline characteristics and between IUD removal and IUD insertion for comorbidities of interest.

4.1 DISCUSSION OF MAIN RESULTS

The conditional logistic regression models showed a decreased likelihood of hypertension, cardiovascular disease, and peripheral vascular disease in women with an IUD removed compared to women with no IUD procedure. These models also estimated an increased likelihood of overall endometriosis and endometriosis of the uterus in women with an IUD removed compared to

women with an IUD inserted or no IUD procedure within an inpatient population. While the race-stratified analysis varied in significance level trends, the results of the race-stratified analysis did show a statistical interaction between IUD status and any of the comorbidities of interest.

More of a difference in the outcomes is seen in the unadjusted and adjusted models (Tables 9-11) when comparing the IUD insertion to IUD removal groups than when comparing the IUD removal to the no IUD procedure group. This is expected because the no IUD procedure and IUD removal groups were very similar to each other after propensity score matching, so less adjustment needed to be done between the two groups. In the IUD insertion group there were statistically significant demographic characteristics compared to the IUD removal group after propensity score matching, so the adjustment in models for these characteristics had a larger impact and was more necessary for appropriate analysis. Unfortunately, we could not adjust for all differences in Table 7 for all comorbidities as the models became unstable.

4.1.1 Vascular disease results

Our study found a significant association between having an IUD removed and a decreased likelihood of having hypertension, cardiovascular disease, and peripheral vascular disease compared to women with no IUD procedure. This study didn't examine underlying reasons for this association, but there are several possibilities.

One possible reason could be that there is a causal relationship between women who have IUDs and a decreased risk for these vascular diseases. The mechanism for how this would happen is unclear. IUDs are known to affect local areas to the insertion site, but physicians are more skeptical in accepting that systemic events are causally related to the IUD as there is conflicting literature supporting systemic effects and IUD use.

Another reason for the association could be unmeasured confounders. For example, physician's may only want to insert IUDs in women who are healthier. Women who have an IUD may also be more integrated in the healthcare system as they need to have an IUD inserted in a physician's office. If so, women with an IUD may engage in more preventative care and therefore be healthier. Because IUDs are not the most popular form of contraception in the United States, women who choose to have an IUD inserted may actively make healthier choices than women who do not have an IUD. More research needs to be done to determine the reason for the association between having an IUD removed and a decreased likelihood for having vascular diseases.

4.1.2 Endometriosis results

Women who had an IUD removed were found to be at an increased risk for overall endometriosis in all models and for endometriosis of the uterus in the unadjusted model compared to both women with an IUD inserted and no IUD procedure. Women with endometriosis are more likely to be admitted to the hospital with pelvic pain and are at a higher risk for wanting their IUD removed than women without endometriosis. Women who are hospitalized for pelvic pain may request that they have their IUD removed as they feel it will relieve their symptoms, though the pelvic pain could be independent of the IUD. Women with endometriosis who desire to use IUDs should be counseled on their increased risk for pelvic pain and how this pain may not be due to the IUD, but due to their pre-existing endometriosis. The lack of significance between endometriosis of the uterus in the adjusted models is likely due to a lack of power as there were only 27 cases of endometriosis of the uterus in the matched sample. The odds of endometriosis of the uterus was 14 times higher in women with an IUD removed compared to women without an IUD procedure, indicating a clinical significance that was underpowered to reach statistical significance.

4.1.3 Race-stratified results

When trying to asses an interaction between IUD status and race, no significant statistical interactions were detected, though the fact that the odds ratio estimates for each comorbidity vary by race (Table 15) indicate that there may be clinically relevant differences in comorbidity use by race driven by IUD use. There is also evidence that both IUD use and comorbid diseases vary by race[26]. Therefore, any findings in this area have to be viewed critically to assess the relationship between race, IUD status, and comorbidity.

4.2 STRENGTHS AND LIMITATIONS

This study has several strengths including the propensity score matching and using a novel population. Some of the limitations associated with this study are being underpowered in some of the analyses, the fact that most IUD insertions and removals are not done in the inpatient setting, the difficulty in determining the best way to do propensity matching with multiple levels of exposure, the fact that the data source is from billing code data, and residual confounding.

The overall strength of this study was due to the use of propensity scores for selection of the appropriate controls. By using propensity scores instead of randomly choosing women who did not have an IUD, the controls are more similar to the cases (specifically for women with IUD removal vs no IUD procedure), creating more comparable groups at baseline. The fact that there were multiple IUD-related group categories made propensity score matching difficult. We used the probability of having any IUD-related code as our propensity score to allow for comparisons of women with both IUD removal and IUD insertion to women with no IUD procedure. In order

to get the most similar populations across the three groups, we implemented a 2-stage matching process (first matching IUD removals to IUD insertions and then taking the matched IUD removals and matching them to women without IUD procedures). This process worked very well for the IUD removal and no IUD procedure groups as after the matching they had similar baseline characteristics. However, this process did not work as well for the IUD insertions compared to the IUD removals or the no IUD procedure groups, which is likely due to the limited number of IUD insertions as well as inherent differences between women who get an IUD removed versus women who get an IUD inserted in the inpatient setting. This difference appears to be driven primarily through having a child delivery code as IUDs are common contraceptive choices in post-partem women. Another reason for this difference is due to matching within the same propensity group as both IUD insertion and IUD removal were classified in the IUD group when determining the propensity score. A way to remedy this would be to estimate the propensity scores using a polytomous logistic regression looking at no IUD procedure, IUD insertion, and IUD removal as separate categories (which, however, may not be feasible due to the uneven numbers in the IUD status groups). Another approach would be to rerun the propensity score analysis using the probability of an IUD removal. This approach may allow for the groups to be more similar to each other, compared to the propensity matching based on an IUD related ICD-9 code in general.

As a result of the performed matching procedure, almost 200 IUD removal cases and 1,400 IUD insertion cases were not matched for subsequent analysis which may have been underpowered for finding smaller effect sizes. However, use of propensity score matching was still a justifiable analytic strategy because it allowed for the study group to be more similar and therefore more comparable to each other. In the future, an analysis plan that can allow the population to be matched while allowing more of the IUD removals and IUD insertions to be included may give

more statistical power for identifying differences. This approach may be especially beneficial for outcomes such as allergic and autoimmune comorbidities (e.g., rheumatoid arthritis, lupus, and dermatitis/ eczema/ allergic urticaria) that did not have enough cases in the current propensity matched sample to estimate the adjusted models.

Another strength of this study is that it looks at IUD insertion and removal within an inpatient population which is not where the majority of IUD research is focused. In conjunction with other IUD research, this study allows for a more holistic view of IUD usage. Although the use of an inpatient study sample addresses the gap in the available published data, it also represents one of the limitations of this study. Since the majority of IUD insertions and removals occur in the outpatient setting, the obtained results may not be generalizable to the entire population of women with IUD-related procedures.

Another limitation is that the data are cross-sectional and uses billing code data. The goal is to try to predict reasons for IUD removal, which is not possible with cross-sectional data. The results of this study can help encourage further prospective studies that will incorporate the outpatient population of IUD users and will look at IUD use longitudinally. We are bound by the data that was collected at the time. Because of this, we are missing some information about the IUD that would have been useful such as if they are using a hormonal or copper IUD and how long the women had the IUD inserted. Knowledge about whether the IUD was hormonal or copper may allow for a better prediction of allergic conditions as previous studies have shown an association between copper IUD use and metal-related allergic reactions[23]. We are also bound by the way of recording in the dataset which is ICD-9 codes. This may not be the best way to collect data such as IUD status or pre-existing chronic diseases. This is especially true within the no IUD procedure group as some of the women may have an IUD but there is no code for a pre-inserted IUD upon

admittance. NIS/AHRQ based data also does not have information about severity, laboratory results such as blood tests, or satisfaction with the IUD and there may be residual confounding in our study.

4.3 FUTURE DIRECTIONS

A potential future study would be a cohort that could recruit women of reproductive age and track their contraceptive choices overtime along with the setting of any changes (i.e. removal or insertion of an IUD in a hospital versus in a doctor's office). This would help show the different adverse events of different forms of contraception, how the prevalence of different forms of contraception change over time, and patterns that form as women change from one form of contraception to another. However, a cohort has the problem of selection bias in who decides to join and remain in the cohort. This type of study would also be much more expensive and time intensive than this study.

An alternative future study could be a cross-sectional study that may be better suited to answering the research question than this study would be to partner with hospitals and doctor's offices so that any patient who has an IUD removed with one of the partners would be asked to answer some questions about their health. This study would allow us to collect the exact data that we want while also being able to compare inpatient to outpatient IUD removals.

Despite the limitations, the current study contributed to the IUD-related pharmacoepidemiologic and pharmacogenetic research conducted at the Food and Drug Agency. This initial research on comorbidities associated with IUD use within the inpatient population should be expanded for better understanding on how confounders impact IUD use, how IUD use

differs in the inpatient and outpatient settings, and, most importantly, what are the adverse outcomes exacerbated by use of an IUD and how to prevent them.

With many options for contraception, women want to choose the best option for them. The high effectiveness of IUDs and few known contraindications make them the ideal choice for many women. A thorough understanding of the adverse events women experience and the subpopulations most susceptible to them is crucial in educating women on the best contraceptive method for them. In educating women if they are at high risk for adverse events with IUDs, common misconceptions about IUDs can be displaced so that women can make the most informed choice about their contraception.

4.4 PUBLIC HEALTH SIGNIFICANCE

As healthcare providers continue to recommend IUDs to their patients, the prevalence of IUD use in the United States will continue to increase. With more women using IUDs, the prevalence of IUD related adverse events will also rise. In order to make these adverse events as preventable as possible, we need to gather comprehensive and actionable evidence on IUD use, which will help give a more holistic view of IUD benefits and potential adverse events in different women subpopulations. As more becomes known about IUDs, misconceptions about some exaggerated dangers of IUD use can be dispelled, aiding women and gynecologists in their individualized decisions about the best available contraception choices.

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APPENDIX: RACE-STRATIFIED DISTRIBUTION OF BASELINE CHARACTERISTICS

Tables 16-18 show the distribution of baseline characteristics by race. Overall, the trends are very similar to those of the matched sample.

Table 16. Distribution of baseline characteristics among Whites.

		No IUD Procedure n(%) (N=157)	**Insertion** n(%) (n=203)	**Removal** n(%) (n=154)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Age	*<21 Years*	11(7)	38(19)	11(7)	1.0	0.002**	<0.001**
	21-30Yyears	68(43)	95(47)	65(49)			
	31-40 Years	47(30)	49(24)	48(31)			
	41-50 Years	28(18)	18(9)	27(18)			
	>50 Years	3(2)	3(1)	3(2)			
Age	*Mean (SD)*	32.4(9.5)	28.0(8.1)	32.5(9.0)	0.92	<0.001**	<0.001**
Year of Admission	*2010*	6(4)	26(13)	6(4)	1.0	0.004**	0.003**
	2011	28(18)	46(23)	6(17)			
	2012	37(24)	41(20)	39(25)			
	2013	48(31)	37(18)	47(31)			
	2014	38(24)	53(26)	36(23)			
Length of stay	*Mean (SD)*	2.8(3.0)	3.2(4.5)	2.9(5.0)	0.89	0.38	0.55
Child Delivery Codes	*Yes*	39(25)	151(74)	38(25)	0.97	<0.001**	<0.001**
Quarter of Discharge	*January-March*	35(22)	35(17)	35(22)	1.0	0.10	0.10
	April-June	44(28)	48(24)	42(27)			
	July-September	37(24)	42(21)	37(24)			
	October-December	41(26)	78(38)	40(26)			

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

Table 17. Distribution of baseline characteristics among Blacks.

		No IUD Procedure n (%) (N=82)	**Insertion** n (%) (n=86)	**Removal** n (%) (n=80)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Age	*<21 Years*	7(9)	14(6)	6(8)	1.0	<0.001**	<0.001**
	21-30 Years	21(26)	49(57)	21(26)			
	31-40 Years	36(44)	14(16)	35(44)			
	41-50 Years	18(22)	8(9)	18(23)			
	>50 Years	0	1(1)	0			
Age	*Mean (SD)*	34.1(8.8)	28.2(8.0)	33.3(8.8)	0.58	<0.001**	<0.001**
Year of Admission	*2010*	4(5)	25(29)	4(5)	1.0	<0.001**	<0.001**
	2011	12(15)	16(19)	12(15)			
	2012	16(20)	18(2)	15(19)			
	2013	26(32)	14(16)	26(33)			
	2014	24(30)	13(15)	23(29)			
Length of Stay	*Mean (SD)*	3.2(3.0)	3.1(3.9)	3.0(2.6)	0.70	0.82	0.93
Child Delivery Codes	*Yes*	14(17)	70(21)	14(18)	0.94	<0.001**	<0.001**
Quarter of Discharge	*January-March*	1(21)	10(11)	17(21)	1.0	0.42	0.4
	April-June	18(22)	20(23)	18(23)			
	July-September	19(23)	20(23)	17(21)			
	October-December	28(34)	36(42)	28(35)			

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

Table 18. Distribution of baseline characteristics among other races.

		No IUD Procedure n (%) (N=178)	**Insertion** n (%) (N=128)	**Removal** n (%) (N=183)	Removal vs No IUD Proc p-value	Insertion vs No IUD Proc p-value	Removal vs Insertion p-value
Age	*<21 Years*	10(6)	18(14)	10(6)	1.0	<0.001**	<0.001**
	21-30 Years	60(34)	60(47)	59(32)			
	31-40 Years	67(38)	38(30)	70(38)			
	41-50 Years	40(22)	7(5)	43(24)			
	>50 Years	1(0.5)	5(4)	1(0.5)			
Age	*Mean (SD)*	33.5(8.5)	29.6(8.6)	33.9(8.2)	0.66	<0.001**	<0.001 **
Year of Admission	*2010*	7(4)	31(24)	7(4)	1.0	<0.001**	<0.001**
	2011	53(30)	21(16)	53(29)			
	2012	39(22)	22(17)	39(21)			
	2013	39(22)	25(20)	42(23)			
	2014	40(22)	29(23)	42(23)			
Length of Stay	*Mean (SD)*	3.0(3.6)	2.7(1.3)	3.9(8.0)	0.16	0.34	0.08
Child Delivery Codes	*Yes*	60(34)	107(84)	58(32)	0.68	<0.001**	<0.001**
Quarter of Discharge	*January-March*	40(22)	24(19)	42(23)	0.98	0.40	0.27
	April-June	32(18)	28(22)	34(19)			
	July-September	47(26)	26(20)	50(27)			
	October-December	59(33)	50(39)	57(31)			

*=significance at the nominal 0.05 level **= significance at the 0.01 level to account for multiple testing.

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