COMBINED ORAL CONTRACEPTIVE UTILIZATION AND UTERINE FIBROID INCIDENCE AND PREVALENCE IN THE STUDY OF ENVIRONMENT, LIFESTYLE, AND FIBROIDS (SELF)

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2019

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ABSTRACT

Sarah Ruth Hoffman: Combined oral contraceptive utilization and uterine fibroid incidence and prevalence in the Study of Environment, Lifestyle, and Fibroids (SELF)
(Under the direction of Jennifer S. Smith)

Estrogen and progesterone play complex, interrelated roles in fibroid tumor development. Hormonal contraceptives are composed of progestin (synthetic progesterone) and may also include estrogen. The most common form of hormonal contraception used in the United States is combined oral contraception. To date, existing published literature regarding the association between combined oral contraceptives (COC) use and uterine fibroid development have yielded mixed findings, limited by lack of baseline ultrasounds that could establish temporality, and often restricted to outcome ascertainment among symptomatic, mostly white, women seeking treatment.

The Study of Environment, Lifestyle, and Fibroids (SELF) was the first prospective, ultrasound-based study of risk factors for uterine fibroids. SELF consists of 1,696 young (23-34 years), black women living in the Detroit, Michigan area in 2010-2017. We examined associations between different levels of COC use and the 40-month cumulative risk of uterine fibroids, and baseline fibroid prevalence. Specifically, we examined ever use of COCs, and age at first use, duration of use, and time since last use among ever COC users. Inverse probability weights were constructed for all exposures, and censoring. Standardized mortality ratio weights were constructed for ever COC use. At ~40-months' follow-up, we observed a possible protective association between ever use of COCs and cumulative fibroid incidence among women who were without fibroids at study enrollment (wRR: 0.78; 95% CI: 0.60, 1.00). When restricting the "Never" comparator group to ever hormonal contraceptive (HC) users, the observed association between COC use and fibroid incidence was attenuated (wRR: 0.92; 95% CI: 0.60, 1.40). The protective association re-emerged when restricting the "Never" group to women with no history of HC use (wRR: 0.72; 95% CI: 0.51, 1.01). No associations were found between fibroid prevalence or incidence and the remaining exposures. It remains unclear how differing levels of COC use among ever COC users might confer differing levels of protection or harm, if any.

For Marlene Forbes Pensinger (1933-2009) and Ruth Marcus Williams (1929-1984).

ACKNOWLEDGEMENTS

The author wishes to thank the nearly 1,700 women who participated in the Study of Environment, Lifestyle, and Fibroids (SELF), and Dr. Donna D. Baird for her enduring efforts to elucidate the biology of uterine fibroids.

The author would also like to thank committee members, Dr. Smith, Dr. Baird, Dr. Harmon, Dr. Poole, Dr. Jonsson Funk, Dr. Nicholson, and Dr. Hudgens for their insight and guidance, and express sincere appreciation to her advisor, Dr. Smith, for her dedicated time and assistance through the years.

Appreciation is also extended to Mitch Conover, Alex Breskin, Michael Webster-Clark, Ashley Naimi, Paul Zivich, Maya Wright and others for their technical assistance and expertise during the design and analysis process, and to the staff of the School of Public Health and Carolina Square where most of the present manuscript was planned and written.

Finally, the author would like to thank her parents for their enduring support from start to finish, and the many friends, colleagues, and institutions that made this work possible.

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LIST OF ABBREVIATIONS

ASD	absolute standardized difference
COC	combined oral contraceptive(s); combined oral contraception
DAG	directed acyclic graph(s)
HC	hormonal contraceptive(s); hormonal contraception
H-IUD	hormonal intrauterine device(s)
IP	inverse probability
IUD	intrauterine device
IPW	inverse probability weight(s)
MP	medroxyprogesterone acetate
OC	oral contraceptive(s); oral contraception
OR	odds ratio
PR	prevalence ratio
PS	propensity score(s)
RR	risk ratio
SELF	study of environment, lifestyle, and fibroids
SMR	standardized morbidity ratio; standardized mortality ratio
UF	uterine fibroids
wPR	weighted prevalence ratio
wRR	weighted risk ratio

CHAPTER ONE: STATEMENT OF SPECIFIC AIMS

More than 1 billion U.S. dollars are spent each year to treat uterine fibroids.[1] In the U.S., black women experience greater risk of, and a 10-year earlier onset of, fibroids than white women, and their fibroids are more severe.[2] **At least 80% of black women will develop uterine fibroids in their lifetime.**[3] Fibroid symptoms include pelvic pressure, pain, and heavy menstrual bleeding leading to iron deficiency anemia.[4] Fibroids can cause infertility and obstetric complications, and may be associated with preterm delivery.[4,5] Unfortunately, there is currently no known approach to prevent or permanently cure uterine fibroids while leaving the uterus and fertility intact.

Estrogen and progesterone have complex, interrelated roles in fibroid tumor development.[6,7] Progesterone appears to cause fibroid growth, and estrogen increases availability of progesterone receptors.[7] Oral contraceptives (OCs) are generally composed of both estrogen and progestin (synthetic progestogen).[8] Exposure to OCs is widespread in the U.S.[9–11] Among sexually experienced black women aged 15-44, 80% have used OCs in their lifetime.[9]

The data on oral contraceptives and fibroid risk have been mixed, with some studies showing a detrimental association if taken early in life,[12,13] and others demonstrating a protective association[14–16] or no associaion at all.[17–20] Studies of OC use and fibroid development to date have lacked baseline fibroid assessments and are unable to establish temporality of OC use and fibroid occurrence. Furthermore, studies of OC use and fibroid development are limited to fibroid assessment by clinical recognition; i.e., only women who sought treatment for fibroid symptoms and who had access to care were screened. Thus, the resulting associations may have been biased by factors related to clinical or surgical detection, including perception of symptoms and access to medical treatment.[2]

This study addressed these concerns by leveraging existing prospective data from the **Study of Environment, Lifestyle & Fibroids (SELF)**. SELF consists of 1,696 young (23-34 years), black women living in the Detroit, Michigan area in 2010-2017. SELF was designed specifically for the study of the effect of vitamin D on the risk of uterine fibroids.[2,21,22] SELF performs baseline and follow-up

ultrasounds in all study participants, not just those with symptoms. Study retention rate was high at >85% for the 40-month follow-up.

Specifically, we aimed to:

Aim 1: Describe the patterns of and reasons for hormonal contraceptive use prior to and at enrollment among women enrolled in SELF, including the duration of and time since last use of OCs. Switching contraceptive methods is common.[9,23,24] However, no data are published on lifetime patterns of hormonal contraceptive use among U.S. black women [24] Contraceptive biographies[24] were constructed for each participant. We described the distribution of HC utilization by HC type for HCs ever used and currently in use at enrollment. We also report number of HC types ever used, first HC type used, age of first HC use and total duration of HC use in years. For each HC type (e.g., COC, patch, ring, shot, H-IUD, mini-pill, and implant) we report age at first use, years since menarche of first use, total months used, and reasons for using (e.g., birth control, menstrual problems). Annual initiation rates were plotted, and compared to regulatory approval timelines. We constructed Sankey diagrams to depict HC sequences of use, and plotted cumulative incidence curves for menarche and HC initiation. Knowledge of these patterns provided meaningful context to the findings from the following aim.

Aim 2: Examine the associations between different levels of combined oral contraceptive (COC) use and the 40-month cumulative risk of uterine fibroids, and baseline fibroid prevalence. Women were counted as having uterine fibroids if they had one or more lesions of 0.5 cm maximum diameter or larger that could be visualized in all three planes.[25] Ten percent of SELF participants without fibroids at baseline had fibroids detected at the 20-month follow-up.[2] Ever use and age at first use of COCs were analyzed as dichotomous variables. Age at first use was dichotomized as less than 17 years and 17 years or older, based on findings from prior literature.[12,13,26] Cumulative lifetime exposure (duration of use) and time since last use were analyzed as ordinal variables, to allow for comparison to findings of previous studies. Pregnancy and hormonal contraceptive use during follow-up were taken into account in sensitivity analyses. Risk and prevalence ratios were calculated comparing each level of COC to the lowest level of use.

This research addressed the longstanding question of whether COC use is associated with fibroid development using a novel cohort created specifically for prospective studies of fibroid incidence and

growth. Temporality was established and common sources of bias in the study of COCs and fibroid risk were addressed.[2,27]

Results of this study estimated the association between estrogen-containing oral contraception and fibroid incidence and prevalence. The findings from these analyses contribute to the evidence base for oral contraceptive safety and effectiveness, allowing providers and patients to make better, evidence-based decisions regarding oral contraception in young women.

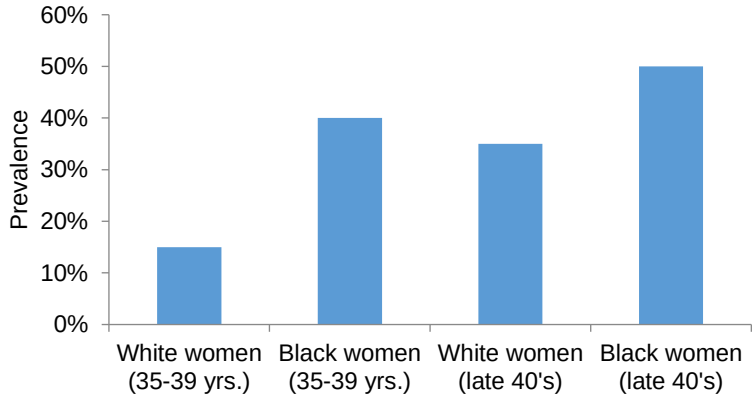
CHAPTER TWO: INTRODUCTION

Uterine Fibroids

Uterine fibroids are prevalent, costly, and affect black women disproportionately. Uterine fibroids are found in 70 to 80% of reproductive-age women in the U.S.[3] Clinically relevant leiomyomas (i.e., fibroids requiring treatment) are found in 10-50% of women, depending on race and age (Figure 2.1).[3] Incidence of symptomatic fibroids generally increases with age and declines after menopause.[6]

Black women are three times as likely as white women to develop fibroids over a 4 year time-period, even after adjustment for many other factors.[28] Fibroids in black women tend to occur earlier in life than in white women, and are often more severe.[29,30] As a result, black women are 6.8 times as likely as white women to undergo uterine fibroid removal surgery (myomectomy).[31]

Figure 2.1. Race and age specific prevalence of symptomatic uterine fibroids among randomly selected members of an urban health plan (Baird, 2003).[3]



Fibroid symptoms include pelvic pressure, pain, and heavy menstrual bleeding leading to iron deficiency anemia.[4]

Fibroids can cause infertility and obstetric complications, and are strongly associated with preterm delivery.[4,5] Between 10% and 30% of women with uterine fibroids will experience complications during pregnancy.[5]

Fibroids can grow to be so large that they mimic the uterine volume and pressure of pregnancy. Clinicians often refer to fibroid size as if they were discussing a gravid uterus (i.e., “18-week myomatous

uterus"). A 20-week size uterus is not uncommon among non-pregnant women with fibroids.[32] The pelvic pressure associated with these fibroids can cause bladder and bowel dysfunction.[4]

Fibroid symptoms cause substantial impairment in health-related quality of life and create fear, anxiety, and depression for women with the disease.[33,34] Patients also report that their symptoms are a source of financial burden.[33] Women with fibroids incur higher healthcare costs than patients without fibroids.[35]

More than $1 billion U.S. dollars are spent each year to treat uterine fibroids.[1] Fibroid treatment can be quite costly. In the 2003-2010 MarketScan Commercial Claims and Encounters database, the average cost for a myomectomy was $15,459, while mean cost for magnetic resonance guided focused ultrasound (MRgFUS) was $15,249, and the mean cost for uterine artery embolization (UAE) was $18,653.[36] Fibroid treatments that reverse infertility must often be repeated, for the fibroids often return, adding to the financial burden of this disease.[37,38] These costs do not incorporate loss of income during procedure and recovery time.

The financial burden of uterine fibroids (which are more common among black women) is a source of unjust financial burden on black families. Among women with symptomatic fibroids, black women disproportionately report having inadequate health insurance coverage or no coverage at all to treat their fibroids.[39] Even with health insurance that offers to cover 80% of the cost of care, fibroid removal procedures can be out of reach financially; 20% of the aforementioned cost for a myomectomy amounts to just over $3,000. Thus the coinsurance for a single treatment amounts to more than 8% of the annual median household income of a black family living in the U.S.[36,40]

Unfortunately, there is currently no known way to prevent or permanently cure uterine fibroids while leaving the uterus and fertility intact. If oral contraceptives decrease the risk of uterine fibroids or shrink existing fibroids, it could help address the unjust emotional, physical, and financial burdens of this disease.

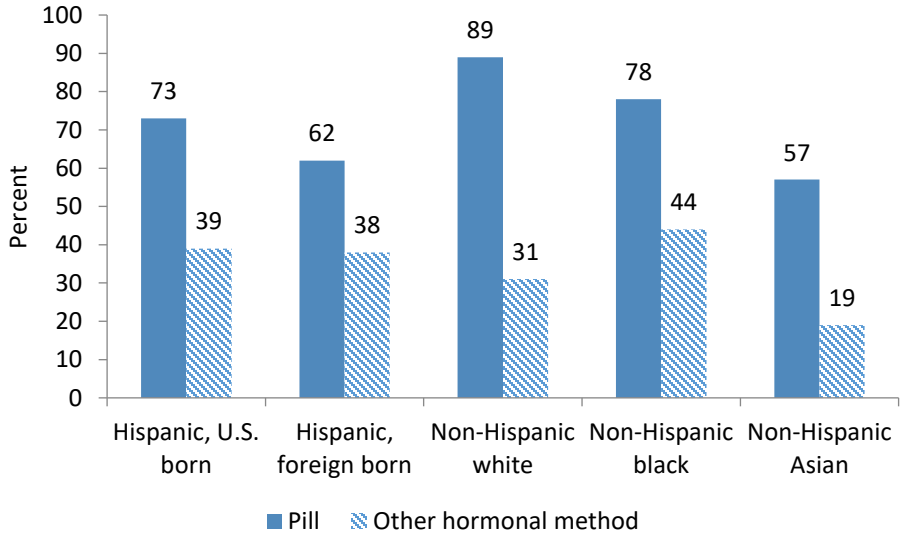
Oral Contraceptives

Oral contraceptives are the most widely used reversible contraception in the United States. The use of hormonal contraceptive methods in the U.S. has increased since the 1990s and

continues to rise.[10,41] According to the 2006-2010 National Survey of Family Growth (NSFG), 62% of reproductive age women are using contraception, and hormonal contraception is the most common type used.[41] Of women using a contraceptive method in the 2011-2013 NSFG, 45% were using a hormonal method as compared to up to 39% in 2002.[10]

Oral contraception is the most common type of contraceptive used, along with female sterilization.[10] Most women are exposed to oral contraceptives at some point in their lives.[9] Repeated surveys reveal that 82% of sexually active women have ever used oral contraception, a figure that remained stable from 1995 through 2010. This is despite the introduction of other effective contraceptives over the same time period.[9] Among black women specifically, 78% of sexually experienced women have used oral contraception (Figure 2.2).[9] According to the 2006-2010 NSFG, 50% of women under age 25 are currently using oral contraception.[9]

Figure 2.2. Percentage of sexually experienced women aged 15–44 who have ever used oral contraceptive pills versus other hormonal methods, by race/ethnicity, in the United States, 2006–2010. Data are from the National Survey of Family Growth (NSFG). Figure adapted from Daniels, 2013.[9]



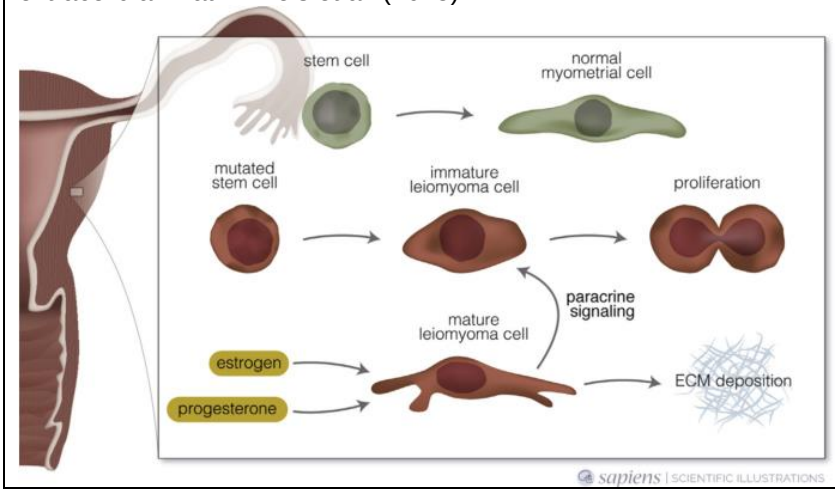
A variety of hormonal contraceptive routes of administration are available in the U.S.: oral contraceptives, intrauterine devices (IUDs), transdermal patches, vaginal rings, implants, and injectables. The patch and the ring contain both estrogen and progestin.[42] Hormonal implants, IUDs, and injectables contain only progestin.[43] Oral contraceptives almost always contain both hormones, but are also available in progestin-only form.[42,44]

Switching contraceptive routes is common.[9,23] According to the 2006-2010 NSFG, 78% of women aged 15-44 who have ever had sex have tried 3 or more different contraceptive methods, and 29% have

tried 5 or more methods. Black women had the highest proportion of those who had ever used a hormonal method other than oral contraception (44%; Figure 2.2).[9]

Many women use oral contraceptives for reasons other than pregnancy prevention. It is estimated that more than 1.5 million women (14% of pill users) use oral contraceptives for noncontraceptive purposes only. In fact, nearly 1 in 10 women who have never had sex use oral contraception, most commonly for menstrual pain and regulation.[11] Of all current pill users in the 2006-2008 NSFG, 58% of oral contraceptive users used oral contraceptives for at least one reason other than pregnancy prevention. Cramps and menstrual pain, menstrual regulation, and acne were the most common noncontraceptive reasons for which women used oral contraception. About 50% of women who were currently using oral contraception used it for more than one reason.[11] Menstrual pain and irregularity are common symptoms of uterine fibroids. It is possible that oral contraceptives are used by many women to alleviate symptoms of undiagnosed uterine fibroids.

Figure 2.3. "Diagrammatic representation of the roles of estrogen and progesterone in the pathogenesis of uterine fibroids." ECM: extracellular matrix. Reis et al. (2015)[7]



There is evidence that oral contraceptive exposure reduces fibroid tumor development. Uterine fibroids are influenced by steroid hormones, primarily estrogen and progesterone.[6,7] Estrogen and progesterone have complex, interrelated roles in fibroid tumor development. Progesterone is necessary for the development of fibroid cells, and estrogen increases the availability of progesterone receptors.[7] There is no documented case of uterine fibroid(s) before puberty, and incidence declines (along with estrogen and progesterone) after menopause.[7] Despite the elevation of estrogen and progesterone during pregnancy, parity is associated with a reduced risk of uterine fibroids.[7,45] There is no firmly established reason for this paradox. A similar paradox has also been observed for hormonal contraceptives, and has yet to be confirmed or explained.[7]

Overall, the exact mechanisms of uterine fibroid development remain unclear, and have been described as “enigmatic”.[46] It is still unknown whether the cells from which fibroids arise are stem cells or differentiated myometrial cells.[7] Estrogen and progesterone could influence the transformation of stem cells into fibroid cells, exert some effect on already differentiated myometrial cells, or both (Fig. 3).

Interestingly, current use of an estrogen-containing contraceptive is associated with an increase in serum vitamin D levels.[21] Vitamin D is significantly lower in women with fibroids than in healthy controls.[47] There is a strong dose-response relationship between low serum vitamin D and uterine fibroid severity.[47] Thus it is possible that some of the effect of OCs on fibroids might be related to their effect on vitamin D levels.

Oral contraceptives, with few exceptions, are composed of both estrogen and progestin (synthetic progestogen that binds to progesterone receptors).[8] Compared to women who have never used oral contraception, women who have ever taken oral contraception appear to be less likely to develop uterine fibroids, even after advanced modeling to control for confounding by other factors.[13,14,16,48] Additional evidence suggests that longer duration of oral contraceptive use may also be protective against fibroids.[13–16,49] These studies enrolled exclusively[15] or mostly[13,16,19,20,26,48] non-black participants and examined only clinically diagnosed leiomyomas.

A recent cross-sectional analysis of SELF data found a strong, protective association between ever use of injectable progestin (widely known as Depo-Provera) and the presence of uterine fibroids at study baseline.[50] This protective association was seen even among women who had not used injectable progestin for several years. Furthermore, the higher a woman’s cumulative lifetime exposure to injectable progestin, the lower her chance of having a fibroid.[50] The finding that injectable progestin is protective against uterine fibroids is supported by previous findings.[12,48] One study[48] found a protective association for injectable progestin lasting for more than 10 years after the final dose.

Innovation

This study was able to capture a higher proportion of fibroid cases than previous studies could. With the exception of one study[49] which screened women for reproductive outcomes after a dioxin releasing chemical plant explosion in 1976, previous studies of oral contraceptive use and fibroid

development were limited to clinical or surgical recognition of fibroids. In other words, results may have been biased by factors related to clinical or surgical detection, including perception of symptoms and access to medical treatment.[2] For instance, oral contraceptives might mask fibroid symptoms, preventing women from seeking diagnosis. This would make oral contraceptives appear protective when they are not. SELF addresses this potential bias by performing ultrasounds in all women, not just women with symptoms.

The 1997-2001 Black Women's Health Study (BWHS)[12] assessed the association between self-reported hormonal contraceptive use and self-reported clinical or surgical diagnosis of uterine fibroids. About 10% of participants reported a diagnosis of fibroids during approximately 40-months of follow-up. In our cohort (SELF), the same incidence (10%) was found in 20-months of follow-up. Both cohorts are composed entirely of black women. The BWHS included an older cohort than SELF (median age of 34 years with an IQR of 29-40), as SELF only enrolled participants aged 23-34 years at recruitment. Given that fibroids tend to be diagnosed in older women, we would expect the BWHS cohort to have a higher rate of fibroid incidence, not lower.[6,28] This finding could be due to the fact that **SELF does not require women to seek medical treatment in order to be screened for fibroids**. SELF performs fibroid screening for all participants at regular intervals regardless of the presence or absence of symptoms. Because of this, SELF data captures a higher proportion of fibroid cases than previous studies.

This study was able to verify that oral contraceptive exposure occurred prior to the appearance of fibroids. The temporal relationship between oral contraceptive use and fibroid development in existing literature is unclear. Oral contraceptives can mask fibroid symptoms by reducing heavy menstrual bleeding, pain, or irregularity. Women whose fibroids are small or asymptomatic at the time of oral contraceptive initiation may go undiagnosed. Previous studies were unable to assess fibroid status prior to oral contraceptive exposure. Thus, it is unknown how many women already had fibroids before they began taking oral contraceptives. This study used baseline ultrasound to identify women with preexisting fibroids. The incidence of fibroid development among women without fibroids at the start of the study was measured. This study was able to verify that oral contraceptive exposure occurred prior to the appearance of fibroids. Because it can establish **temporality** in this way, this study was able to more

clearly delineate the relationship between oral contraceptive use and fibroid development than prior studies could.

Contraceptive biographies[24] for each study participant were constructed. Switching contraceptive methods is common.[9,23,24] Despite this fact, there have been no published reports of lifetime patterns of hormonal contraceptive use among black women living in the U.S.[24] Aim 1 described the patterns of and reasons for hormonal contraceptive use in the SELF cohort. Knowledge of these patterns in our cohort was necessary for the completion of Aim 2, and offered meaningful context to those findings. Furthermore, the completion of this aim serves as an example for future studies of contraceptive sequences of use across the lifespan.

CHAPTER 3: CRITICAL REVIEW OF THE LITERATURE

Pathogenesis of Uterine Fibroids and the Potential Role of Hormonal Contraception

Fibroids consist of multiple, clonal (*cells that share a common ancestry*) cell types: smooth muscle cells, vascular smooth muscle cells, fibroblasts, and fibroid-associated fibroblasts.[51] Fibroblasts are known to be important in wound healing, and are responsible for the wealth of extracellular matrix (ECM) found in fibroid tumors. Fibroblasts are most critical to the pathophysiology of fibroid disease. All four of these clonal cell types originate from *fibroid progenitor cells*.[51]

Hormonal contraceptives may influence fibroid development in at least three different places: (1) the transformation of myometrial stem cells into fibroid progenitor cells, (2) the differentiation of fibroid progenitor cells into preclinical fibroids, (3) the proliferation of fibroid cells into clinically relevant disease.[51]

Myometrial stem cells → Fibroid progenitor cells → Preclinical fibroids → Clinically relevant disease

First arrow: It is not well understood how or why myometrial stem cells transform into fibroid progenitor cells, but sex steroid hormones appear to play an important part.[51] Myometrial stem cells require sex steroid hormones for their growth, and yet lack the receptors for these hormones.[51] The mechanism for their growth and subsequent transformation is thought to involve paracrine (*cell-to-cell*) signaling mediated by the Wnt/β-catenin pathway, estrogen, and progesterone.[51] If the steroid hormones from hormonal contraceptives reach the uterus via circulation, they may contribute to the paracrine signaling mechanism by which fibroid progenitor cells develop. If these cells persist, it may explain why exposure to oral contraceptives at an early age has been associated with later fibroid development.[12,13]

Second arrow: Fibroid progenitor cells differentiate into the four cell types comprising fibroid tumors: smooth muscle cells, vascular smooth muscle cells, fibroblasts, and fibroid-associated fibroblasts.[51] The different fibroid cell types exhibit differential expression of various genes, including

progesterone receptor genes.[51] The heterogeneity of fibroid biology and clinical presentation are at least partially explained by these differences in gene profiles. The expression of these genes is influenced by the hormones involved in the menstrual cycle, mainly estrogen and progesterone.[51] Thus, it is plausible that circulating sex steroid hormones from oral contraceptives could influence gene expression in a way that influences fibroid cell differentiation.

Third arrow: Fibroid cells contain both estrogen and progesterone receptors.[7] Progesterone is thought to be the primary regulator* of fibroid growth, with estrogen supporting this function by increasing progesterone receptor expression in fibroid cells.[7] Oral contraceptive use has been associated with potentially long-lasting or irreversible changes in estrogen receptor expression in macrophages (increased estrogen receptor α and decreased estrogen receptor β);[52] hence, it is plausible that oral contraceptives induce similarly lasting changes in progesterone and/or estrogen receptor expression in the cells of the uterus, including preclinical fibroid cells.

*Concerning progesterone, while laboratory studies demonstrate that progesterone *promotes* fibroid growth, epidemiological studies of the effects of pregnancy and synthetic progesterone use suggest something entirely different.[51] The role of progesterone is likely complex and interdependent with other pathways.[51]

Pharmacology of Oral Contraceptives

Oral contraceptive pills contain synthetic progesterone (progestin), and are available with and without estrogen. Estrogen-containing oral contraceptives are commonly referred to as “combined oral contraceptives” (COCs). Most oral contraceptives on the market are COCs. COCs may be monophasic, biphasic, or triphasic. Monophasic pills deliver a stable dose of progesterone and estrogen throughout the menstrual cycle. Biphasic or triphasic pills alter the dose of estrogen and/or progestin at specific time points in the menstrual cycle.

The most common form of estrogen in COCs is ethinyl estradiol . Estradiol valerate and mestranol are also available (Table 3.1). In contrast, there are over eight types of synthetic progesterone (progestin) on the oral contraceptive market (Table 3.1). Progestins are grouped into generational classes and vary in androgenic, estrogenic,[53]and progestogenic effects (i.e., varying affinities for binding to

androgen, estrogen, and progesterone receptors). These varying affinities coupled with differences in dosage may produce varying effects on uterine fibroid development (see Aim 2 literature review).

Slightly estrogenic progestins include norethindrone, norenthindrone acetate, and ethynodiol diacetate.[54] Androgenic progestins include medroxyprogesterone acetate (MPA), norethindrone, norenthindrone acetate, and ethynodiol diacetate.[54] These four drugs also possess antiestrogenic properties.[54] Norethindrone and norethindrone acetate are first-generation progestins with low progestational and estrogenic qualities.[55] These progestins are less androgenic than second-generation progestins and more androgenic than later generation progestins.[55] In contrast, norgestrel (also first generation) has strong antiestrogen and androgenic effects.[55] At present day, the most widely prescribed progestin is levonorgestrel, a second-generation progestin with high progestational and androgenic activity.[55] A complete summary of all currently available progestins in terms of their affinities for androgen, estrogen, and progesterone receptors was not available after extensive searching.

Table 3.1. Compounds used in commercially available hormonal contraceptives in the U.S.

Compound	Oral	Injectable	Implant	Patch	Ring	IUD	Brand Names	Progestin Generation
Estrogens								
estradiol valerate	x						Natazia	
ethinylestradiol	x			x	x		Yasmin, Seasonale, Ortho Tri-Cyclen	
mestranol	x						Norinyl	
Progestins								
MPA	x	x					Depo-Provera	First
norethindrone	x						Femcon Fe, Dasetta, Norinyl, Camila	First
etynodiol diacetate	x						Demulen, Zovia	First
norgestrel	x						Cryselle, Ovrette	First
norethindrone acetate	x						Aygestin	First
levonorgestrel	x		x			x	Seasonale, Mirena, Plan B, Norplant	Second
norgestimate	x						Ortho Tri-Cyclen	Third
desogestrel	x						Desogen, Ortho-Cept	Third
etonogestrel			x		x		NuvaRing, Implanon	Third
norelgestromin				x			Ortho Evra	Third
drospirenone	x						Beyaz, Yasmin	Fourth

Abbreviations: MPA, Medroxyprogesterone acetate.

Aim 1: Women's Reasons for and Patterns of Hormonal Contraceptive Use

Aim 1: Describe the patterns of and reasons for hormonal contraceptive use [prior to and at enrollment] among women enrolled in SELF, including the duration of and time since last use of OCs.

While there are many published works regarding women's reasons for discontinuing hormonal contraceptives, studies of reasons for *initiating* use appear relatively scarce. A broad literature search revealed a single report, out of the Guttmacher Institute, using nationally representative data from the 2006-2008 National Survey of Family Growth (NSFG). The NSFG contains contraceptive history with dates of use for the four years prior to the interview date, and ever/never use for each type of contraception.[24] Data were not stratified by race or fibroid status, but do provide a national-level look into why women use hormonal contraceptives.

Birth control was the most commonly cited reason for using oral contraceptives in NSFG.[11] Of women using oral contraception for non-contraceptive reasons (alone or in addition to birth control as a reason), menstrual pain and menstrual regulation were the leading causes for use, followed by acne. When data were stratified by age group, non-contraceptive reasons were the leading indication for oral contraceptive use in 15-19 year olds, with menstrual pain as the most common reason for use. While ~49% of U.S. women used oral contraception for more than one reason, fourteen percent of users (more than 1.5 million women) used the pill for noncontraceptive purposes only.

No published data were found regarding lifetime patterns of hormonal contraceptive use.

Aim 2: Oral Contraceptives and Fibroid Incidence

Aim 2: Examine the associations between different levels of combined oral contraceptive (COC) use and the 40-month cumulative risk of uterine fibroids, and baseline fibroid prevalence.

For Aim 2, a systematic search of the literature was performed during the summer of 2016 and updated in January 2018. PubMed was searched with the following algorithm: *(uterine fibroid[title] OR uterine fibroids[title] OR leiomyoma[title] OR leiomyomata[title]) AND (("contraception"[MeSH Terms] OR "contraception"[All Fields]) OR ("contraceptive agents"[Pharmacological Action] OR "contraceptive devices"[MeSH Terms] OR ("contraceptive"[All Fields] AND "devices"[All Fields]) OR "contraceptive devices"[All Fields] OR "contraceptive"[All Fields] OR "contraceptive agents"[MeSH Terms] OR*

("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields]) OR ("contraceptive agents"[Pharmacological Action] OR "contraceptive agents"[MeSH Terms] OR ("contraceptive"[All Fields] AND "agents"[All Fields]) OR "contraceptive agents"[All Fields] OR "contraceptives"[All Fields])).

Studies were considered eligible if they were non-experimental (i.e., observational) studies of the association between oral contraceptive use and fibroid risk. Twelve eligible studies[12–20,26,48,49] were identified from 184 abstracts and are described in Table 3.2.

Overall, the literature on oral contraceptive use and fibroid status suffers from great heterogeneity in populations, methods, and comparisons, as well as several limitations described in Table 3.3.[56] The most prevalent limitations were lack of baseline fibroid screening, and lack of outcome screening for all participants.[12] Five studies[12,13,19,20,26] relied on self-report for fibroid status. Sensitivity of fibroid self-report is low, and is highest (41%) in black women aged 35-45 years.[57] Most studies (n=8)[13,16,18–20,26,48,49]did not describe which types of oral contraceptives were used by participants (e.g., combined or progesterone-only). All studies took place after progestin-only oral contraceptives were introduced (as early as 1973).[58] Given that more recent literature suggests a protective association for progestin-only methods in African American women,[12,50] perhaps conflicting results are due, in part, to differences in the proportion of women using estrogen-containing pills in each study, or differences in the distribution of formulations taken between studies.

Table 3.4 describes the distribution of available comparisons in the literature. The most common assessment was for oral contraceptive exposure by duration of use (n=9), followed by time since last use (n=7), and ever versus never use of oral contraceptives (n=4).

Table 3.2. Characteristics of twelve observational studies of oral contraceptive use and fibroid risk

Study (Country, period)	Exposure	Outcome	Comparator	Design	Analysis	Effect Measure	Key Findings
1: Histologic detection of uterine leiomyoma							
Chiaffarino, 1999 (Italy, 1986-97)	COC	Fibroids, Histologic	Never users	Case-control	Logistic regression	OR	Current use protective (OR 0.3, 95% CI: 0.2, 0.6)
Lumbiganon, 1995 (Thailand, 1991-3)	COC †	Fibroids, Histologic	Never users	Case-control	Logistic regression	OR	Ever use protective (OR 0.76, 95% CI: 0.66, 0.92)
Parazzini, 1992 (Italy, 1986-90)	COC	Fibroids, Histologic	Never users	Case-control	Logistic regression	RR	No association
Parazzini, 1988 (Italy, 1986-7)	COC	Fibroids, Histologic	Never users	Case-control	Logistic regression	OR	No association
Ross, 1986 (UK, 1968-74)	COC	Fibroids, Histologic	Diaphragm or IUD users	Case-control	Logistic regression	OR -> RR	OCs protective. OR -> RR = 0.54 to 0.90 (varies by time since last use and duration of use)
2: Ultrasound detection of uterine leiomyoma							
Marino, 2004 (Italy, 1996-8)	COC † >= 1 yr.	Fibroids, Ultrasound	COC † < 1 yr.	Cross-sectional	Fisher's exact test	None	Shorter duration of use associated with UF (p < 0.01)
Faerstein, 2001 (USA, 1990-93)	COC †	Fibroids, Ultrasound **or histologic**	Never use	Case-control	Logistic regression	OR	Current use protective (OR = 0.2, 95% CI: 0.1, 0.6)
3: Self-reported uterine leiomyoma							
Martin, 2011 (USA, 2003-04)	COC †	Fibroids, Self-reported	Non-users	Cross-sectional	Unadjusted	OR	Current users vs. non-users: 0.36 (0.12-1.04)
Wise, 2004 (USA, 1997-2001)	COC	Fibroids, Self-reported	Never users	Prospective*	Age- and time- stratified Cox regression	IRR	Early age of first OC use increased risk (IRR = 1.2)
Chen, 2001 (USA, 1978-87)	COC †	Fibroids, Self-reported or visualized during tubal sterilization	No contraceptive use	Case-control	Logistic regression	OR	No association (OR not reported)
Marshall, 1998 (USA, 1989-93)	COC †	Fibroids, Self-reported	Never users	Prospective*	Logistic regression	RR	OCs harmful when first used at ages 13-16 years: RR= 1.39 (95% CI: 1.17–1.66)
Samadi, 1996 (USA, 1980-82)	COC † >= 3 mo.	Fibroids, Self-reported	COC † < 3 mo.	Case-control	Logistic regression	OR	No association. OR = 1.0 (0.7-1.6) (overall) to 5.0 (infrequent pap smears group, significant)

*While the parent study was prospective, the contraception/fibroid relationship examined was usually cross-sectional or retrospective in nature. No baseline screening was performed.

†Oral contraceptives not otherwise specified, i.e., the study exposure was oral contraceptives but the authors did not describe what types were used (e.g., progestin-only or combined). Since combined formulations are more commonly used, we assume that the exposure under study was combined oral contraceptives.

Abbreviations: BWHS=Black Women's Health Study; CI=Confidence Interval; COC=combined oral contraceptive; HC=hormonal contraceptive; DMPA= depot medroxyprogesterone acetate ; IRR=Incidence Rate Ratio; IUD=intrauterine device; mo.=month(s); NHS=Nurse's Health Study; OC=oral contraceptive; OR=Odds Ratio; PRR=Prevalence Risk Ratio; RR=Risk Ratio; SELF= Study of Environment, Lifestyle and Fibroids; SWHS=Seveso Women's Health Study; UF=uterine fibroids; yr.=year(s).

Table 3.3. Key limitations of twelve observational studies of oral contraceptive use and fibroid risk

Author	No baseline screening	Not Everyone Assessed for Outcome	OC NOS	Surgical Cases Only	Other Major Limitation	Percent Black Women
Chen (2001)	x		x		x[c]	22%
Chiaffarino (1999)	x	x		x		Not reported
Faerstein (2001)	x	x	x			10% to 40%[b]
Lumbiganon (1995)	x	x	**x**	x		< 1%
Marino (2004)	x		x		x[a]	Not reported
Marshall (1998)	x	x	x			Not reported
Martin (2011)	x	x	x			22%
Parazzini (1988)	x	x	x[d]	x		Not reported
Parazzini (1992)	x	x		x		Not reported
Ross (1986)	x	x		x	x[e]	0%
Samadi (1996)	x	x	x			9%
Wise (2004)	x	x				100%

Abbreviations: OC NOS=oral contraceptives not otherwise specified, i.e., the study exposure was oral contraceptives but the authors did not describe what types were used (e.g., progestin-only or combined).

[a]All women resided near Seveso, Italy in 1976 at the time of a chemical plant explosion which released high levels of dioxin. The study is intended to examine the reproductive health outcomes of these women. Current users were excluded, study includes former users only.

[b]10% of controls, 40% of cases

[c]Conditioned on tubal sterilization. Mostly white, married, educated.

[d]Parazinni (1988) uses the same population as Parazinni (1992) which states that combined oral contraceptives were the type studied and that combined oral contraceptives represent most of the oral contraceptive use in Italy.

[e]Conditioned on positive marital status, and > 5 months of continuous use of oral contraceptives, diaphragm, or intrauterine device (IUD). All participants were Caucasian.

Table 3.4. Comparisons reported in twelve observational studies of oral contraceptive use and fibroid risk

Comparison	Studies (n)	References
Duration of use	9	Chiaffarino; Faerstein; Marino; Marshall; Parazzini; Parazzini; Ross; Samadi; Wise
Time since last use	7	Faerstein; Marino; Marshall; Parazzini; Parazzini; Ross; Wise
Ever vs. Never	4	Chiaffarino; Lumbiganon; Parazzini; Parazzini
Current vs. Never	4	Chiaffarino; Faerstein; Marshall; Wise
Past vs. Never	4	Chiaffarino; Faerstein; Marshall; Wise
Age at first use	4	Faerstein; Marshall; Martin; Wise
Formulation	3	Chiaffarino; Ross; Wise
Current vs. Non-user	2	Chen; Martin
Time since first use	2	Chiaffarino; Parazzini

Duration of use: Duration of use was never categorized the same way between any two studies. Three studies reported a protective association for longer duration of use: Chiaffarino et al. (1999) divided duration of use into 4 categories: 1 or fewer years, 2-3 years, 4-6 years, 7 or more years. Fibroid risk decreased with increasing duration of use (p-trend = 0.03) with ORs ranging from 1.4 (1 or fewer years) to 0.5 (7 or more years). Ross et al. (1986) observed a linear trend for duration of use; fibroid risk was reduced by 17% for every 5 years of oral contraceptive use. Marino et al. (2004) reported that shorter duration of oral contraceptive use (< 1 year versus $\geq$ 1 year) was associated with uterine fibroid prevalence ($p < 0.01$). The remaining six studies did not find any association between duration of use and fibroid status.

Time since last use: Seven studies reported associations for time since last oral contraceptive use and fibroid status. No two studies used the same categorization scheme for time since last use. Marino et al. (2004) reported that longer time since last oral contraceptive use (> 5 year versus < 5 years) was associated with uterine fibroid prevalence ($p < 0.01$). The remaining six studies observed no association.

Ever vs. Never use: Four studies reported odds ratios comparing ever to never oral contraceptive users. Lumbiganon et al. (1995) reported a protective association of OR = 0.76 (95% CI: 0.66-0.92). Three studies reported null findings: Chiaffarino et al. (1999) OR = 1.1 (95% CI: 0.8-1.3); Parazzini et al. (1988) OR = 1.4 (95% CI: 0.9-2.1); Parazzini et al. (1992) OR = 1.1 (95% CI: 0.8-1.5).

Current vs. Never use: Two studies reported a protective association between current use of oral contraceptives and fibroid status, when comparing current to never users: Chiaffarino et al. (1999) [OR =

0.3, 95% CI: 0.2-0.6], and Faerstein et al. (2001) [OR = 0.2, 95% CI: 0.1-0.6]. The remaining two studies reported no association.

Past use vs. Never use: Marshall et al. (1998) found a potentially harmful association (RR = 1.31, 95% CI: 1.03-1.66) between past oral contraceptive use and fibroid incidence when comparing former to never users. The remaining three studies found no association.

Age at first use: Two studies reported a potentially harmful effect of early onset oral contraceptive use. Marshall et al. (1998) divided age at first use into four categories: 13-16 years, 17-20, 21-24, 25 years or older. Women who started oral contraception between ages 13 and 16 years were 1.26 times as likely to develop uterine fibroids when compared to never users (RR = 1.26, 95% CI: 1.05-1.51). The RR was higher when counting only hysterectomy confirmed cases (RR = 1.90, 95% CI: 1.29-2.79). Overall, earlier age at first use was associated with positive fibroid status (p-trend 0.003) when only hysterectomy confirmed cases were counted. Wise et al. (2004) divided age at first use into four categories: < 17 years, 17-20 years, 21-24 years, 25 years or older. Initiating oral contraceptive use prior to age 20 was associated with fibroid incidence when compared to never-use: IRR = 1.2 for both the < 17 and 17-20 years groups, 95% CIs: 1.0-1.4 and 1.0-1.3, respectively. Earlier onset of oral contraceptive use was associated with fibroid status (p-trend 0.005). The remaining two studies reported no association: Martin et al. (2011) found no association when comparing oral contraceptive initiation before and after age 17. Faerstein et al. (2001) found no association between age at first oral contraceptive use and fibroid status (OR and age categories not reported).

Formulation: To account for differences in oral contraceptive formulation over time, Chiaffarino et al. (1999) stratified their results by time period (high and lower estrogen eras). For oral contraceptive use prior to 1991, a null but potentially protective association was found between current versus never use of oral contraceptives and fibroid status (OR = 0.4, 95% CI: 0.1-1.8). For oral contraceptive use 1992 and later, a protective association was found (OR = 0.3, 95% CI: 0.2-0.7). Ross et al. (1986) reported that higher doses of progesterone in combined oral contraceptive pills yielded greater protection against fibroids. However, formulations containing ethynodiol diacetate (a form of progesterone) were not protective. Interestingly, Wise et al. (2004) later found that hormonal contraceptives containing ethynodiol diacetate may yield a harmful effect on fibroid risk (IRR = 1.6, 95% CI: 1.1-2.5, never use of any oral

contraceptive as comparator). Wise et al. (2004) found no relationship between fibroid risk and estrogenic potency, progestational potency, progestin classification, monophasic, biphasic or triphasic estrogen formulations.

Current vs. non-user: Martin et al. (2011) compared current users to non-users and found a protective association (OR = 0.36, 95% CI: 0.12, 1.04). Chen et al. (2001) found no association.

Time since first use: Two studies reported a null association between time since first oral contraceptive use and fibroid status. Chiaffarino et al. (1999) divided time since first use into four categories: 5 or fewer years, 6-10 years, 11-15 years, 15 or more years, comparing each category to Never use. The OR for the "5 or fewer years" group was 0.6 (95% CI: 0.4-1.1). The remaining ORs were also null (1, 1.1, and 1). Parazzini et al. (1992) also reported no association between time since first oral contraceptive use and fibroid status, comparing time since first use less than 15 years, and time since first use 15 years or longer to never-use.

Black Women's Health Study (BWHS): The most similar study to the one proposed was published in 2004. Lauren Wise et al. (2004)[12] assessed the association between self-reported hormonal contraceptive use and self-reported uterine fibroids identified by ultrasound or hysterectomy (of which a subsample were validated) in 22,895 premenopausal black women with no prior diagnosis of fibroids who participated in the Black Women's Health Study (BWHS) in 1997-2001. Associations were explored using age- and time-stratified Cox regression models. The average follow-up time was 40 months (76,711 person-years/22,895 women = 3.35 x 12 = 40.2) and 10% of participants reported fibroids by the end of the study period (2,279 new cases in 22,895 women). In contrast, the SELF cohort (also 100% black women) reported the same incidence in half the follow-up time. SELF does not require women to seek medical treatment in order to be screened for fibroids, as fibroid screening is performed for all women. Furthermore, the BWHS included an older cohort than SELF (BWHS median age = 34 years [IQR 29-40], SELF median age = 29 years [range 23-35]). Given that fibroids tend to occur in older women, we would expect an older cohort to have more fibroids, not fewer.[6,28] Our prospective design with baseline and follow-up screening in all participants represents a substantial step forward.

CHAPTER 4: RESEARCH PLAN AND METHODS

Study Design

This cross-sectional (Aims 1-2) and prospective (Aims 2) cohort study investigated whether oral contraceptive use (including age at first use, duration of and time since last use) is associated with incidence and prevalence of uterine fibroids. To do this, we leveraged existing prospective data from the **Study of Environment, Lifestyle & Fibroids (SELF)**, based on the follow-up of 1,696 young (23-34 years), black women living in the Detroit, Michigan area in 2010-2016.

Using SELF as a parent study for these aims allowed us to capitalize on a rich, existing database created specifically to examine fibroid development. SELF data are uniquely poised to discover factors operating early in the development of fibroid tumors.[27] This is because SELF conducts routine ultrasounds on black women in the relevant age-range for initial fibroid disease, and is therefore able to capture new fibroids soon after they form (and prior to the onset of symptoms). The SELF cohort was also created specifically to monitor growth of existing fibroids.[2,25] There is no comparable existing database, to our knowledge, and no more efficient way to study the risk factors for this disease.

Study Population

SELF focuses on black women since this ethnic group experiences greater risk and earlier onset of fibroids.[2] SELF enrolled 1,696 African American women aged 23-34, meeting the study inclusion/exclusion criteria described below. Our study did not impose any additional eligibility criteria.

Inclusion/Exclusion Criteria:

- Ages 23-34 years
- Self-identify as Black, African American, or part-African American
- No prior clinical diagnosis of uterine fibroids
- Intact uterus (no prior hysterectomy)
- Not currently pregnant (may enter study 3 months after pregnancy)

- Residence in the United States
- Able to attend clinic visits in Detroit, MI
- Committed to remain in study for five years
- No prior diagnosis of cancer that required radiation or chemotherapy
- No prior diagnosis of lupus, Grave's disease, Sjogren's scleroderma, or multiple sclerosis that required medication

Women were recruited from the entire Detroit area via local radio and television commercials, advertisements in newspapers and magazines, brochures at healthcare clinics, and information booths at community events. In addition, African American women aged 23-34 seen at the Henry Ford Health System (HFHS) were sent letters describing SELF and inviting them to participate.[2]

Participants received $150-200 for enrollment activities, $100-120 for follow-up activities every 15 months (4 follow-ups), and $100 bonus for completing all study activities. Enrollment required a telephone eligibility screening, a 30-60 minute orientation done in-person or over the phone, a self-administered pre-enrollment questionnaire, informed consent, a clinic visit, and three questionnaires before or during the clinic visit.

Retention rate was high at 87% for the 20-month follow-up.[2] The 20-month follow-up produced useable ultrasounds for 1,421 participants. To ensure high retention at 40-months' follow-up, three mailings per year were sent to study participants: two newsletters and a holiday card. Data collection for the 40-month follow-up is currently ongoing.

Similar to the Black Women's Health Study, SELF participants are more educated than U.S. black women overall (78% versus 60% with more than a high school education at 25-34 years of age)[2] We believe this to be a result of enrolling only women who could committ to participating for the full 5-year study period.[2]

In recognition of the potential for recruitment bias, women were asked about their three main reasons for enrolling in the study. Options included: family history, a friend or relative told me I should participate, I worry that I might have fibroids, desire to contribute to knowledge about African-American women's health issues, to get general health information, and other (please specify).

Preliminary Data

Previous studies confirm the suitability of SELF data for the study of fibroid growth and related risk factors. The SELF data have been used in multiple, published studies of uterine fibroid development.[25,50,59,60] Most relevant is a cross-sectional study of the association between depot medroxyprogesterone acetate (DMPA; a progestin-only, injectable hormonal contraceptive) duration of and time since last use and uterine fibroid prevalence. A strong protective association was found between ever use of DMPA and the presence of uterine fibroids. Longer duration of DMPA use (i.e., greater cumulative lifetime exposure) was associated with a lower prevalence of uterine fibroids. This protective association was seen even among women who had not used DMPA for several years.[50] This published study confirms the suitability of the SELF data for the investigation of duration and time since last use of a specific contraceptive type in relation to uterine fibroids. Our study combined this exposure data with prospective data on incident fibroids and prevalent fibroids, with a focus on oral contraceptives. An analogous, prospective study of DMPA use and fibroid incidence is currently being carried out by members of our team at NIEHS, specifically, Quaker Harmon, PhD and Donna Baird, PhD.

Exposure Assessment and Quality Assurance

HC Utilization

History of hormonal contraceptive use for SELF was collected via telephone interview as part of the enrollment questionnaire. Participants were asked if they had ever used each of the following types of contraception: birth control pills, a hormonal implant, a hormonal patch, a hormonal vaginal ring, a hormonal shot, an intrauterine device (IUD), and emergency contraception. Brief descriptions and examples of common brand names were provided for hormonal implants, shots, and emergency contraception.

For each type of contraceptive, excluding emergency contraception, women were asked about their (i) age at first use, (ii) whether or not they were currently still using, (iii) how old they were when they stopped using, and (iv) their reasons for using. In addition, women who had used oral contraceptives were asked whether or not they had ever stopped using for a month or longer, and if so, their reasons for stopping, and the proportion of time that they spent on oral contraception.

Ever use of combined oral contraceptives (COCs)

COC users were identified based on their responses to items in the Contraceptive History questionnaire, as read by a telephone interviewer. Women were first asked, ***"Have you ever used birth control pills,"*** and were later asked, ***"Have you ever used a progesterone-only birth control pill, or "mini-pill", such as Micronor, Nora-BE, or Ovrette?"*** If women answered affirmatively to both questions, we used further data to determine whether or not they had used COCs, the mini-pill, or both. In order to do this, we assessed age at first use data (i.e., ***"How old were you when you started using birth control pills, whether or not it was to prevent pregnancy?"*** and ***"How old were you when you started taking a progesterone (pro-JES-ter-own)-only pill or "mini-pill" (such as Micronor (MY-cro-nor), Nora-BE (NOR-ah-BEE), or Ovrette (oh-VRETT))?"***), and data regarding timing of discontinuation. For the non-specific "pill" questions, women were asked whether or not they were still currently using the pill and if not, how old they were when they stopped. For the mini-pill women were not asked how old they were when the stopped using, but were instead asked how many years and months in total that they used the mini-pill. If age at first mini-pill use was equal to age at first pill use, and age at last pill use minus age at first pill use was the same as the years of mini-pill use, then women were considered to have used the mini-pill only. If age at first mini-pill use was equal to age at first pill use, and age at last pill use minus age at first pill use *plus one additional year* was the same as the years of mini-pill use, then these women too were considered to have used only the mini-pill and not combined oral contraceptives. Additionally, for current pill users, if start age for pill and mini-pill were the same, and current age minus pill start age was the same as years of mini-pill use, then these women too were considered to have used only the mini-pill. Data were quality checked by examination of individual records as well as re-coding in SAS using different logic to achieve the same results for verification. Additional code was written to take months of mini-pill use into consideration, as a quality assurance investigation.

Women who were not found to have used the mini-pill only based on these rules were considered to have used combined oral contraceptives in addition to or instead of the mini-pill. Women who answered "Unsure" to ***"Have you ever used a progesterone-only birth control pill, or "mini-pill", such as Micronor, Nora-BE, or Ovrette?"*** were considered to have used combined oral contraceptives only (n=48). Records for these 48 women were hand checked for signs of incorrect classification.

HC Sequences of Use

For HC sequencing for our Aim 1 analyses, each participant's list of HC types was sorted by age at first use. When two or more HCs of different types were initiated at the same age, additional steps were taken to determine which HC was used first. Note that while the data provided for each hormonal intrauterine device (H-IUD) to be listed separately, the age at first use for any H-IUD was used, and repeat use of the same HC type was not included in our final sequencing. Furthermore, due to data sparsity and interpretability of the resulting figures, use of emergency contraceptives was ultimately not included in our HC sequence analyses.

There were n=148 women with one or more age at first use ties. Of these, n=13 were determined to have used progestin-only pills only, and thus their data for COCs and mini-pill were merged and re-labeled "mini-pill." An additional n=39 women were found to have the same start and stop age for one HC type and not the other (e.g., used patch at ages 17-17 years and mini-pill at ages 17-19 years). For these cases, the HC type with the same start and stop age was considered to have come first. Data for n=9 users was resolved using additional available data regarding HC use and pregnancy timing. The HC type reportedly used within 12-14 months of a pregnancy that occurred one year prior to the tied age was considered to have come first. For n=7 women, mini-pill stop age was less than the stop age reported for "the pill." Since age at first use of "the pill" was not specific to combined or progestin-only types, when age at first use of "the pill" was the same as age at first use of the mini-pill, and mini-pill stop age was less than "pill" stop age, we considered mini-pill use to have come first. One additional tie was resolved after examining the data and discovering a subject with duplicate intrauterine device data (i.e., the same device was reported twice). By these same rules, n=29 individuals were found to have data that was already in the proper order for sequence of use. Thus, of 148 women with age at first use ties, data were corrected for 68, while 29 were already in the correct order, and 50 remained unresolved. The 50 unresolved records were not included in analyses regarding sequences of use. Of these unresolved ties, 43 involved the first two HC types used, and 7 involved order of use of later types.

Duration of Use of COCs

Cumulative lifetime exposure to (duration of use of) combined oral contraceptives (COCs) was calculated by subtracting age at first OC use from age at last OC use (or current age, if the woman is a current user). For women who stopped using OCs for a month or longer, we multiplied the resulting difference in years by the proportion of time they spent using OCs. For women who reported a history of mini-pill use, we subtracted the total amount of time that they were using the mini-pill from the total amount of time that they had spent using OCs. For quality assurance, we tested two different orders of operation, one in which weighting preceded subtraction of mini-pill duration, and another in which subtraction of mini-pill duration preceded weighting. We then examined the resulting distributions for plausibility (e.g., negative durations of use), and compared individual durations of use to length of time using OCs for heavy menstrual bleeding among the subset of women who used OCs for relief from perceived menorrhagia. We found that the weighted last approach (i.e., subtracting mini-pill duration of use from OC duration of use prior to applying weights for proportion of time spent using OCs) yielded more plausible and reliable estimates. Women who reported the same stop and start age for OCs and had not used the mini-pill were assigned a value of 6 months for duration of COC use.

Duration of use could not be calculated using the above methods for n=2 women due to missing data. For our Aim 2 analyses, we hard-coded age at first pill use for one woman with missing data for that variable, based on determinations made during a careful record review of her individual data. This determination was made using additional HC data that was available for the time period surrounding a particular pregnancy. Duration of use was hard-coded for an additional woman for whom information on pill discontinuation was missing. Adjudication for this case was also based upon pregnancy history.

Time since Last Use of COCs

Time since last combined oral contraceptive use was calculated by subtracting the age at last pill use from current age at baseline. Current pill users who were not mini-pill users were assigned a time since last use value of zero. Of n=64 women who had used both COCs and the mini-pill, time since last COC use could not be determined for n=33. Case-by-case adjudication and subsequent application of logic (i.e., SAS code) allowed for determination of the remaining n=31. It was determined that if times

since last use as calculated for OCs and mini-pill worked out to be at least 3 years apart, we could be relatively sure that the time since last "pill" use was referring to COCs and not the mini-pill (n=31).

Reliability of Self-Reported COC Data

Self-reported history of oral contraceptive use, as collected by telephone interview, has been found to be reliable compared to automated pharmacy dispensing data.[61] A study of women aged 45-59 years found almost perfect (95%) agreement for use in the last 5 years, and substantial agreement (85%) for use in the last 15 to 20 years.[61] SELF participants were much younger (23-34 years of age at enrollment) and should have comparable, if not better, recall of their oral contraceptive history.

Outcome Assessment and Quality Assurance

Fibroid identification was performed with the iU22 ultrasound system (Philips Healthcare, Bothell, WA) or a LOGIQ9 system (GE Healthcare, Milwaukee, WI) of a similar age.[2,25] A standardized data collection form was used by all sonographers, with a diagram of the uterus so that fibroids could be mapped for future reference. Fibroids were carefully mapped, measured, and numbered.[2] Sonsographer, machine, and probe IDs were recorded for most exams.

SELF sonographers are registered diagnostic sonographers with at least 3 years of experience in gynecologic sonography. All sonographers were given additional, study specific training, and training to distinguish fibroids from other uterine pathologies.[2]

Quality control procedures were carried out. The head sonographer reviewed 8% of each sonographer's examinations each month. It is estimated that 98.5% of women considered fibroid free at baseline were truly fibroid free, and 99.6% of women with fibroids at baseline truly had fibroids.[2]

At each SELF study visit (i.e., baseline and follow-up visits), each individual fibroid was measured 3 times in 3 perpendicular planes, resulting in 9 diameter measurements for each fibroid.[25] Fibroid diameters were measured in centimeters (cm). When transvaginal ultrasound (TVUS) was infeasible (e.g., patient discomfort), transabdominal ultrasound was used instead. This was quite rare (~2%), however.[25]

To examine the associations between oral contraceptive use and risk or prevelance of uterine fibroids (Aim 2), women were counted as having uterine fibroids if they had one or more lesions of 0.5 cm maximum diameter or larger that could be visualized in all three planes.[25]

Transvaginal ultrasound (TVUS) is the current standard of care for uterine fibroid assessment.[62] TVUS has 99% sensitivity and 91% specificity for detecting uterine fibroids.[63] Furthermore, TVUS has high and equal accuracy to magnetic resonance imaging (MRI) at measuring fibroid diameter.[63]

Covariates

Covariate Assessment

The following covariate data were collected by telephone interview near the time of enrollment: current age, age at menarche, family history of uterine fibroids, smoking status (never, past, current), alcohol intake, parity, breastfeeding history, reason(s) for hormonal contraceptive use (including oral contraceptive use), history of using other types of hormonal contraceptives, and history of sexually transmitted diseases (gonorrhea, chlamydia, trichomonas, syphilis, bacterial vaginosis, mycoplasma genitalium, genital warts, human papillomavirus, and herpes). Body mass index (BMI) was calculated from height and weight as measured at the baseline clinic visit. Each of these covariates could be related to uterine fibroid development, as previously documented in the literature.[6]

Covariate Selection

For Aim 2 analyses, two sets of covariates were utilized: one for inverse probability of treatment and standardized mortality ratio weighting and the other for inverse probability of censoring weighting. Covariates were selected after a several-months' long process of discussion with committee members, including senior fibroid epidemiologists (DB, QH), a practicing OB/GYN clinician-researcher (WKN), pharmacoepidemiologists (MJF), general epidemiologic methodologists (CP), a biostatistician (MH), and the dissertation chair (JSS). Discussion of covariate selection drew from a combination of directed acyclic graphs (DAGs), existing literature, clinical knowledge, and knowledge from decades of combined prior experience studying fibroids or hormonal contraceptive use. These discussions along with the available data informed covariate selection as well as the cut points chosen for those covariates.

Covariate Sets for Weight Calculations

The covariate set for calculating inverse probability of treatment and standardized mortality ratio weights included age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (>24 months), time since last birth (<5 years, 5-9.99 years, >10 years and no birth), parity (nulliparous, 1-2 births, >3 births), BMI (>30, remaining values according to tertile), and education (Bachelor's degree or higher).

The covariate set for calculating inverse probability of censoring weights included the exposure relevant to the present model, the covariate set for the inverse probability of treatment weights as described above, as well as annual household income (<$20,000, $20,000-49,999, and $\geq$$50,000), baseline employment status (not employed, employed <30 hours per week, employed $\geq$30 hours per week), smoking history (never smoked, former smoker, current smoker of <10 years, current smoker of $\geq$10 years) and history of heavy "gushing" type menstrual bleeding (yes/no).

Because parity and Depo-Provera use have been shown to be highly protective against uterine fibroids[45,48,50] and would likely be associated with COC use and levels of COC use, sensitivity analyses were carried out that took into account parity and Depo-Provera use during follow-up. For these analyses, parity during follow-up was dichotomized (yes/no), and Depo-Provera use during follow-up was dichotomized as 9 months or less and greater than 9 months of use during follow-up.

Body Mass Index (BMI) Tertiles for Aim 2 Analyses

It was agreed upon by the main author (SRH) and committee members with expertise in fibroid epidemiology (QH, DB) that body mass index (BMI) would be divided into four categories: BMI $\geq$30 (obese) with the remaining values divided into thirds. Since our ever/never COC comparisons were among the entire cohort while the within COC users comparisons were among COC users only, tertiles for BMI <30 differed for these two analytic cohorts. BMI tertile cut points for the ever/never (full) cohort were 23.5468 and 26.7127. BMI tertile cut points for the COC users for the remaining analyses were 23.7395 and 26.8021.

Data Analysis Plan

Aim 1. Describe the patterns of and reasons for hormonal contraceptive use prior to and at enrollment among women enrolled in SELF, including the duration of and time since last use of oral contraceptives.

For Aim 1, we constructed hormonal contraceptive biographies[24] for each study participant. A woman's contraceptive biography consisted of a timeline of her hormonal contraceptive use, including the types of hormones and routes of administration used, in order of initiation. We also examined participants' primary reasons for using each type of hormonal contraceptive (e.g., to prevent pregnancy, control menstrual bleeding, treat acne).

We described the distribution of HC utilization by HC type for HCs ever used and currently in use at enrollment. We also report number of HC types ever used, first HC type used, age of first HC use and total duration of HC use in years. For each HC type (e.g., COC, patch, ring, shot, H-IUD, mini-pill, and implant) we report age at first use, years since menarche of first use, total months used, and reasons for using (e.g., birth control, menstrual problems). Annual initiation rates were plotted, and compared to regulatory approval timelines. We constructed Sankey diagrams to depict HC sequences of use, and plotted cumulative incidence curves for menarche and HC initiation. Knowledge of these patterns provided meaningful context to the findings from the following aim.

These descriptive findings characterized hormonal contraceptive use sequences and characteristics among a cohort of black women living in the Detroit, Michigan area in 2010-2016. Knowledge of these patterns gave meaningful context to findings for the subsequent study aim.

Aim 2. Examine the associations between different levels of combined oral contraceptive (COC) use and the 40-month cumulative risk of uterine fibroids, and baseline fibroid prevalence.

To examine the association between combined oral contraceptive (COC) use and 40-month cumulative risk of uterine fibroids, as well as fibroid prevalence at baseline, women were counted as having uterine fibroids if they had one or more lesions of 0.5 cm maximum diameter or larger that could be visualized in all three planes.[25] Cumulative lifetime exposure (duration of use) and time since last use of COCs were treated as ordinal variables, i.e., <1 year, 1-1.99 years, 2-4.99 years, and $\geq$5 years for duration of use, and 0 [current], 1-2 years, 3-4 years, and $\geq$5 years for time since last use. Joint duration

of and time since last COC use was also examined. For this variable, duration of use was characterized as short (< 2 years) or long (> 2 years), and time since last use was characterized as recent (< 5 years) or past (> 5 years). Selection of all cut points was informed by a variety of factors including prior literature, clinical utility, and ability to achieve covariate balance in the propensity score analyses (i.e., strata sample size).

Ever use and age at first use of COCs were analyzed as dichotomous variables in the entire cohort. The following comparisons were restricted to ever COC users. Age at first use was dichotomized as less than 17 years and 17 years or older, based on findings from prior literature.[12,13,26] The lowest age at first use category (i.e., <17 years) served as the referent. Cumulative lifetime exposure (duration of use) and time since last use were analyzed as ordinal variables, to allow for comparison to findings of previous studies. The lowest amount of cumulative lifetime exposure and the shortest time since last use (i.e., current users) served as referents.

First, we examined the association between ever COC use and prevalent fibroids at baseline. This cross-sectional analysis included all women enrolled in SELF. Subsequently, we examined the associations between prevalent fibroids and each of four exposures: age at first COC use, duration of COC use, time since last COC use, and joint duration of and time since last COC use. These analyses were restricted to COC users, comparing each category of use to the lowest level. Second, we carried out incidence analyses analogous to the prevalence analyses just described. This allowed us to examine the associations between incident fibroids and different levels of COC use. To establish temporality, women were included in our incidence analyses if their baseline ultrasound showed no fibroids. Further details regarding follow-up and censoring are presented in Chapter 6.

All analyses for Aim 2 were performed in SAS 9.3 or higher. We report our propensity score (PS) based methods in greater detail in Chapter 6. In brief, inverse probability (IP) weights were constructed for all exposures, and censoring. Standardized mortality ratio (SMR) weights were constructed for ever COC use. For incidence analyses, the IP and SMR weights were multiplied by the inverse probability of censoring weights. Weighted risk and prevalence ratios were calculated comparing each level of COC to the lowest level of use, and comparing ever to never COC use. Pregnancy and hormonal contraceptive

use during follow-up were taken into account in sensitivity analyses (see Chapter 6 for further description of sensitivity analyses).

Study Power

With data from the SELF cohort, we were well powered to rule out strong protective or harmful associations. A priori power analyses were carried out using PROC POWER in SAS 9.4 to determine which magnitude associations could be "ruled out" by our data.

Initially we had planned to perform survival analysis and to calculate risk differences. For Aim 2, comparing ever oral contraceptive users to never users, we determined that we had >80% power to detect a protective risk difference of -0.068 percentage-points and lower. Furthermore, we had >80% power to detect a harmful risk difference of 0.080 and higher. For the Cox proportional hazards model, treating competing risks as censored events, and comparing ever to never oral contraceptive users, we determined that we would have >80% power to detect a protective hazard ratio of 0.645 and lower. Thus we determined that we had excellent power to detect associations of clinical and public health relevance.

Our a priori calculations assumed that 20% of women in the never-users group would develop fibroids by 40-months' follow-up. This was a reasonable assumption given the 10% incidence observed for the 20-month follow-up, and based on the fact that SELF consists of a race and age groups known for elevated fibroid incidence. These calculations were restricted to women without fibroids at baseline for whom 20-month follow-up ultrasounds were available (n=1,119).

Using the exposure and outcome distributions of the final analytic cohort, further power analyses were conducted. In actuality, 17% of women who were fibroid-free at baseline (n=1,308) developed uterine fibroids by 40-months' follow-up. We went further to calculate power for COC levels of use comparisons and for risk ratios rather than hazard ratios as originally planned for.

For our **Aim 2 prevalence analysis**, comparing ever combined oral contraceptive users to never users, we had >80% power to detect a protective risk ratio of 0.739 and lower. Furthermore, we had >80% power to detect a harmful risk ratio of 1.295 and higher. For our smallest number comparisons (time since last use 1-2 years ago versus current users), we had >80% power to detect a protective risk ratio of 0.538 and lower and a harmful risk ratio of 1.545 and higher.

For our **Aim 2 incidence analysis**, comparing ever combined oral contraceptive users to never users (among those not censored), we had >80% power to detect a protective risk ratio of 0.689 and lower. Furthermore, we had >80% power to detect a harmful risk ratio of 1.356 and higher. For our smallest number comparisons among those not censored (time since last use 3-4 years ago versus current users), we had >80% power to detect a protective risk ratio of 0.345 and lower and a harmful risk ratio of 1.835 and higher.

Thus we had excellent power to detect associations of high clinical and public health relevance. **We were extremely well powered to rule out two-fold harmful associations, with power ranging from 0.913 to >0.999 for risk ratios of 2.00 in our main analyses**. We could universally rule out associations of 0.345 magnitude and lower in all of our analyses, and 0.50 and lower in most of our analyses. Thus, our study is of tremendous value to both patients and prescribers.

CHAPTER 5: PATTERNS OF AND REASONS FOR HORMONAL CONTRACEPTIVE USE IN THE SELF COHORT (PAPER 1)

Introduction

The use of hormonal contraceptives (HCs) in the U.S. has increased since the 1990s and continues to rise.[10,41] At least 80% of American women are ever users of HCs, [9,64] and approximately 20% of U.S. reproductive-age women are current HC users.[10]

In the 1990s and early 2000s, the U.S. saw a dramatic increase in the number of available HCs, from the initial approvals of implantable and injectable contraceptives (referred to as long-acting reversible contraceptives, or LARC) to the introduction of the patch and the ring.[9,65] Prior to these advances, options for HC use were largely limited to oral contraceptive pills. Newer, longer acting HC options promised greater convenience for users, theoretically translating to improved uptake and correct and consistent use, thereby preventing more unwanted pregnancies – an issue of tremendous public health importance.[66–68]

In this new context, contraceptive selection is related to convenience, cost, side effects, peer utilization, and awareness of method,[69–72] and many women try more than one HC route in their lifetime.[9,23] Yet, there are no published reports on women's lifetime trajectories or sequence of HC use, cumulative lifetime exposure to HCs, or biological timing of use (i.e., initiation relative to menarche). Studies of reasons for HC use are relatively limited, and mainly concern reasons for choosing one HC type over another,[69–72] as opposed to clinical indication(s) for use.

We collected HC history in a cohort of women who came of age during the 20-year period in which the variety of available HCs increased dramatically in the U.S.[9,65] Our objective was to describe their patterns of and reasons for HC use, as well as cumulative HC exposure, age at first use, initiation relative to menarche, and uptake relative to regulatory approval.

Methods

Study Population

The Study of Environment, Lifestyle & Fibroids (SELF) is a prospective cohort study of 1,693 young (23-35 years), African American women living in the Detroit, Michigan area. SELF was designed to investigate risk factors for uterine fibroid incidence and growth.[2,21,22] Recruitment and baseline data collection were completed in 2010-2013.[50] Participants were recruited from the Detroit area via local radio and television commercials, advertisements in newspapers and magazines, brochures at healthcare clinics, information booths at community events, and via the Henry Ford Health System (HFHS).[2] The primary eligibility requirements were age, self-identified African American/black, and having no prior clinical diagnosis of uterine fibroids. SELF was approved by the institutional review boards of the National Institute of Environmental Health Sciences and the Henry Ford Health System.

Data Collection on HC Use

As part of participation in SELF, the lifetime history of HC use to date was collected via telephone interview as part of an enrollment questionnaire. Women were asked if they had ever used each of the following types of HC: “birth control pills” (oral contraceptives; OCs), “mini-pill” (progestin-only OCs), hormonal implant, hormonal patch, vaginal ring, “hormone shots like Depo-Provera,” and hormonal intrauterine devices (H-IUD). Brief descriptions and examples of common brand names were provided for hormonal implants and shots.

For each HC type (and separately for each H-IUD), women were asked about their age at first use, whether or not they were currently using, how old they were when they stopped using, and their reason(s) for using. Women who had used OCs were asked whether or not they had ever stopped using for a month or longer, and if so, the proportion of time between start and stop that they spent on OCs (“very little of that time,” “less than half of that time,” “about half,” “more than half,” “most of that time,” “the entire time”). Women who used the “mini-pill,” implant, patch, ring, or shot were asked to state the total number of months and years that they had used each method prior to study enrollment. This study focuses primarily on the ever users of HC types described above. Emergency contraception (EC) is not

included as an HC method, but age of first use of EC was collected and is examined in some aspects of the analysis.

Chronological Sequence of HC Use by Type

Chronological sequences of HC use for each woman was constructed by sorting each woman's HC types by age at first use. When a woman started more than one HC at the same age, records were adjudicated for correct order of use. Ties were resolved by examining discontinuation ages and pregnancy information. The relatively few records that could not be resolved were excluded from relevant analyses. EC was not included in the sequence analysis.

Duration of Use for COCs and H-IUDs

Duration of use estimates for combined oral contraceptives (COCs) were calculated in three steps: (1) Subtract age at first OC use from age at last OC use, or age at enrollment for current users, (2) Subtract months and years on the mini-pill, (3) Multiply by the proportion of time spent using OCs. Weights were applied as follows: 10% for "very little of that time," 25% for "less than half of that time," 50% for "about half," 75% for "more than half," 90% for "most of that time," and 100% for "the entire time." When age at first use and age at last use were identical, a duration of six months was assigned. Duration of use for H-IUDs was calculated by subtracting age at first use from age at last use, or age at enrollment for current users, for each H-IUD.

Reasons for HC Use

Women were asked about each of the following reasons for using each HC type: "to prevent pregnancy;" "irregular menstrual cycles, or to regulate how often you had periods;" "heavy bleeding;" "menstrual pain;" or "any other reason." Women who reported "any other reason" were asked to report the other reason(s).

Data Management and Analysis

All data management and analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA). Sankey diagrams for sequences of HC use were created using a free online tool called SankeyMATIC

(http://sankeymatic.com/). Annual initiation rates for seven HC types were plotted using age at first use for each type (methods are further described in Figure 5.1 and Appendices 1.2 and 1.3). Cumulative incidence of menarche was plotted alongside cumulative incidence of HC initiation, using age at menarche and earliest age of use for any HC type (methods are further described in Appendix 1.1).

Results

Characteristics of SELF Cohort

Age at enrollment ranged from 23 to 35 years, with a median age of 29 (IQR = 26, 32; Table 5.1). The majority (82%) of participants reported a gross annual household income of less than $50,000. Most (62%) were employed (data not shown). Many women who enrolled in SELF had completed a bachelor's degree or higher (28%). A majority (80%) were overweight or obese. Twenty-six percent were current or former smokers (Table 5.1).

Menarche was most frequently (64%) reported to have occurred during ages 11-13 years (Median [IQR] = 12 [11, 13]; Table 5.1). Mean and median time between menarche and enrollment were 16.7 and 17.0 years respectively (range: 5-26 years; IQR 14-20 years).Thirty-seven percent reported a history of heavy menstrual bleeding, with a median age of onset of 19 years. Sexual debut was most often (61%) reported to occur during ages 14-17 years. Majority (61%) had given birth at least once. Median age for first pregnancy and birth were 19 and 20, respectively (data not shown).

HC Utilization

Ever use of HCs was common in this cohort (n=1,455; 86%). HC initiation took place in 1988-2012. Self-reported HC initiation dates were well aligned with regulatory approval dates (Figure 5.1).

Ever use of estrogen-containing HCs was reported by 87% of ever-HC users (Table 5.2). COCs were the most frequently reported HC type ever used (81%). Ever use of progestin-only HCs was reported by 59% of ever-HC users. Depo-Provera shot was the most commonly reported progestin-only HC type used, with ever-use reported by 49% of ever-HC users. More than half of ever-HC users (58%) had used both estrogen-containing and progestin-only HCs (Table 5.2). One in four (25%) reported use of EC (Table 5.1).

Twenty-eight percent of participants were using HCs at the time of study enrollment (Table 5.2). Of those women using HCs at the time of enrollment, half were using an estrogen-containing type, and half were using a progestin-only type (Table 5.2). The most frequently reported “current” HC types used were COCs (43%), H-IUDs (26%), and Depo-Provera (21%).

HC Sequences of Use

Among women who ever used HC, most (57%) reported using two or more HC types (Table 5.2). Many (22%) reported using three or more HC types (Table 5.2). Median number of HC types used was 2 (Range: 1-6). Chronologic sequences of HC use are displayed in Figure 5.2. The most common type of HC used first was COCs (70%) (Table 5.2). Among these women, 42% never used another type of HC. Among those who used an additional HC type, the second type of HC used was commonly Depo-Provera (30%) or patch/ring (21%). Depo-Provera was the first HC for 20% of ever HC users (Table 5.2). Among these women 55% never used another type of HC. For women who used another HC type after starting with Depo-Provera, the most common second type was COCs (31%) or patch/ring (8%).

Individual Timing and Duration of HC Use

Median age at first HC use was 18 years (Table 5.2). Some (22%) experienced pregnancy prior to their first HC exposure, and 13% experienced their first birth prior to initiating HCs (data not shown).

Median age at first use was lowest for COCs and Depo-Provera (Table 5.3), consistent with the finding that these HC types were the most common initial HCs in this cohort (Table 5.2). H-IUDs and the ring demonstrated a later median age of initiation (Table 5.3).

Figure 5.3 displays HC/EC initiation relative to menarche in the SELF cohort. The curves are similar, with HC initiation following menarche. Median time from menarche to HC or EC initiation was 6 years (range: -2 to 23 years). Median time from menarche to initiation was shortest for COCs and Depo-Provera (Table 5.3). H-IUDs and the ring demonstrated a longer median time from menarche to initiation (Table 5.3). Alternative versions of Figure 5.3 are presented in Appendices 1.2 and 1.3.

Median duration of HC use (sum of durations across types) was 50 months (Mean = 62 months; SD = 49 months; range: 1 to 237 months; Table 5.2). Duration of use was longest for COCs, Depo-Provera, H-IUDs, and the implant (Table 5.3).

Reasons for HC Use

Nearly half of ever HC users reported using HCs for non-contraceptive purposes (49%), including irregular menstrual cycles (40%) and heavy menstrual bleeding (22%; Table 5.4). About half (48%) of COC users reported non-contraceptive reasons for use, along with ~25% of patch, ring, shot, and H-IUD users, and 10% of implant users. Menstrual problems were reported as a reason for use by 45% of COC users, ~25% of ring, shot, and H-IUD users, 21% of patch users, and 7% of implant users. Seven percent of all HC users used HCs exclusively for non-contraceptive purposes: 11% of COC users, and 4-5% of users for each of the other HC types. Most (90%) implant users reported birth control as their only reason for use (Table 5.4).

Sensitivity Analyses

Since characteristics and patterns of HC use may be a function of age at enrollment and calendar time, we stratified our findings by time between menarche and enrollment (in three, 10-year periods: <10, 10-19, and 20+ years) and decade of menarche (Appendices 1.4 and 1.5). Oral contraceptives remained the first HC type used for majority of participants, followed by Depo-Provera, regardless of menarche decade. Number of HC types used and total duration of HC use increased with increasing time between menarche and enrollment. Women whose menarche occurred closer to study enrollment were more likely to select “irregular periods” as a reason for use (Appendix 1.4).

Discussion

In this large cohort of young, black women, COCs were the most commonly used HC, despite the introduction of longer acting methods during that same time period.[9,65] Non-contraceptive reasons for HC use were common, and reasons for use varied by HC type. Menstrual problems were the most frequently cited non-contraceptive reason for HC use. Approximately 10% of COC users used COCs for relief from menstrual problems exclusively.

Our findings that COCs were the most common HC type used and were frequently used for non-contraceptive purposes are consistent with earlier, nationally representative findings.[10,11,73] It is estimated

that more than 1.5 million U.S. women use OCs for non-contraceptive purposes alone, most commonly to relieve menstrual pain and irregularity.[11]

Our study had several strengths. First, we were able to assess HC use in a cohort of young, black women who came of age as five new HC options came to market: the implant, Depo-Provera, H-IUDs, the ring, and the patch. Second, we examined uptake of these new methods relative to contextual and individual factors: regulatory approval and menarche, respectively. Third, to our knowledge, we are the first to examine temporal sequencing of HC use, and to find that COCs are the most common first HC among women who use multiple HC types, even among those initiating HC use well after other types became available. Fourth, our examination of reasons for use was specific to each HC type, and participants could report multiple reasons for use for each type. Finally, we compared our findings to unpublished NSFG analyses, and considered the potential for selection bias. Given the similarity of our findings to national estimates, our findings are likely generalizable to the broader population of U.S. black women of similar age (Appendix 1.6).

Our findings have the following limitations. First, HC data were self-reported as recalled during a telephone interview. Self-reported history of OC use, as collected by telephone interview, has been found to be reliable when compared to automated pharmacy dispensing data.[61] Second, we did not have exact duration of use estimates for COCs or H-IUDs and had to use limited available information to estimate duration of use for these HC types. Third, reasons for use were self-reported and women's definitions of heavy bleeding or irregular periods may vary. Finally, the data in this analysis are cross-sectional. All analyses, including Figures 5.1-5.3, relied on retrospectively recalled data.

To our knowledge, this is the first study to examine timing of HC initiation relative to menarche (Table 5.3 and Figure 5.3). Timing of HC initiation relative to menarche could be a meaningful marker for the developmental timing of HC exposure. Future research could consider the effect of this timing on gynecological health endpoints, including fibroids.

The emphasis of most public health research and interventions regarding HCs to date has been on pregnancy prevention. Our finding that a sizeable proportion of women used HCs for non-contraceptive purposes are reinforced by prior, nationally representative findings[11] and point to HCs as

important for management of conditions that affect quality of life. Further research could explore clinical factors and patient preferences underlying HC selection, particularly for non-contraceptive purposes.

Table 5.1. Characteristics of 1,693 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

	Overall	Never used HCs	Ever used HCs*
	N=1,693	N=238	N=1,455
	n (%)	n (%)	n (%)
Age at enrollment (years)			
23 – 26	519 (31)	98 (41)	421 (29)
27 – 30	581 (34)	83 (35)	498 (34)
31 – 35	593 (35)	57 (24)	536 (37)
Annual household income†			
< $20,000	766 (45)	123 (52)	643 (44)
$20,000 to $50,000	628 (37)	73 (31)	555 (38)
≥ $50,000	287 (17)	39 (17)	248 (17)
Education‡			
HS/GED or less	369 (22)	69 (29)	300 (21)
Some college/associates/technical	848 (50)	107 (45)	741 (51)
Bachelors/masters/PhD	475 (28)	62 (26)	413 (28)
Body mass index (kg/m^2)			
< 25	335 (20)	50 (21)	285 (20)
25-29	350 (21)	32 (13)	318 (22)
30-34	328 (19)	45 (19)	283 (19)
≥ 35	680 (40)	111 (47)	569 (39)
Smoking history			
Never smoked	1,245 (74)	168 (71)	1,077 (74)
Former smoker	125 (7)	16 (7)	109 (7)
Current smoker (< 10 years)	238 (14)	41 (17)	197 (14)
Current smoker (≥ 10 years)	85 (5)	13 (5)	72 (5)
Age at menarche			
< 10 years	310 (18)	39 (16)	271 (19)
11	334 (20)	48 (20)	286 (20)
12	458 (27)	68 (29)	390 (27)
13	286 (17)	42 (18)	244 (17)
> 14 years	305 (18)	41 (17)	264 (18)
Heavy menstrual bleeding (HMB)			
History of heavy (gushing) menstrual bleeding§	625 (37)	80 (34)	545 (37)
Talked to doctor about HMB	338 (20)	34 (14)	304 (21)
Age at first sex‖			
Never had sex	35 (2)	26 (11)	9 (1)
< 14 years	239 (14)	17 (7)	222 (15)
14-17	1,036 (61)	120 (50)	916 (63)
18-21	332 (20)	58 (24)	274 (19)
> 21 years	49 (3)	17 (7)	32 (2)
Reproductive history			
Never pregnant	451 (27)	124 (52)	327 (22)
Parous	1,031 (61)	81 (34)	950 (65)
1 birth	432 (26)	39 (16)	393 (27)
2 births	313 (18)	18 (8)	295 (20)
3+ births	286 (17)	24 (10)	262 (18)
Emergency contraception (EC)			
Ever used EC	402 (24)	39 (16)	363 (25)

*HC use prior to (and during) enrollment in SELF. Includes combined oral contraceptives (COCs), the patch, the ring, Depo-Provera, hormonal intrauterine devices (H-IUDs), the implant, and the mini-pill (progestin-only pill). Non-hormonal IUDs and emergency contraceptives are not included.

[†]Annual household income was missing for n=12 participants.

[‡]Education was missing for n=1 participants.

[§]"The next questions are about heavy, gushing (GUH-shing) type menstrual bleeding that was too much for your pads or tampons to absorb, even when changed frequently. Have you ever had heavy, gushing type bleeding?"

[‖]Age at first sex was missing for n=2 participants**.**

Abbreviations: EC, emergency contraception; HCs, hormonal contraceptives; HS, high school graduate; GED, general education development; HMB, heavy menstrual bleeding; PhD, doctor of philosophy; SELF, Study of Environment, Lifestyle, and Fibroids.

Table 5.2. Characteristics of hormonal contraceptive (HC)* use in 1,455 ever HC users who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

	n (%)
Ever use of HCs by type	**1,455 (100)**
Estrogen-containing	
Any route	1,272 (87)
Combined oral contraceptives (COCs)	1,185 (81)
Patch	303 (21)
Ring	227 (16)
Progestin-only contraceptives	
Any route	864 (59)
Depo-Provera	720 (49)
Hormonal intrauterine device (H-IUD)	177 (12)
Implant	42 (3)
Mini-pill	77 (5)
Mini-pill and COC's	64 (4)
Mini-pill only	13 (1)
Hormonal contraceptives currently in use at enrollment‡	**469 (100)**
Estrogen-containing	
Any route	237 (51)
Combined oral contraceptives (COCs)	200 (43)
Patch	6 (1)
Ring	31 (7)
Progestin-only contraceptives	
Any route	234 (50)
Depo-Provera	100 (21)
Hormonal intrauterine device (H-IUD)	120 (26)
Implant	13 (3)
Mini-pill	1 (0)
Number of HC types* ever used	**1,455 (100)**
1	617 (42)
2	510 (35)
3	238 (16)
≥ 4	90 (6)
First hormonal contraceptive type used§	**1,412 (100)**
Estrogen-containing	
Any route	1,077 (76)
Combined oral contraceptives (COCs)	993 (70)
Patch	66 (5)
Ring	18 (1)
Progestin-only contraceptives	
Any route	335 (24)
Depo-Provera	278 (20)
Hormonal intrauterine device (H-IUD)	15 (1)
Implant	12 (1)
Mini-pill	30 (2)
Age at first HC* use (years)‖	**1,454 (100)**
< 17	520 (36)
17 – 20	643 (44)
≥ 21	291 (20)
Total duration of HC use (complete years)*¶	**1,452 (100)**
≤ 2	541 (37)

3-4	253 (17)
5-6	219 (15)
7-8	163 (11)
> 8	276 (19)

*Includes combined oral contraceptives (COCs), the patch, the ring, Depo-Provera, hormonal intrauterine devices (H-IUDs), the implant, and the mini-pill (progestin-only pill). Non-hormonal IUDs and emergency contraceptives are not included.

†Women who used progestin-only methods and never used an estrogen containing method.

‡Some women (n=2) used two HC methods simultaneously at enrollment.

§Excludes n=43 women for whom order of use for first and second HC types could not be determined. For women who used EC before other HC types (n=43), EC was discarded and the next HC type was counted as the first HC type when generating this list.

‖Age at first HC use was missing for n=1 individual.

¶Duration of use was missing for n=1 patch user and n=2 pill users.

Abbreviations: COCs, combined oral contraceptives; HC, hormonal contraceptives; H-IUD, hormonal intrauterine device; IUD, intrauterine device; SELF, Study of Environment, Lifestyle, and Fibroids.

Table 5.3. Age at first HC use, time from menarche to initiation, and duration of use by hormonal contraceptive type in 1,455 ever HC users* who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

	Age at first use[†] Median (IQR)	Years since menarche[‡] Median (IQR)	Total months used[§] Median (IQR)
Estrogen-containing Types			
COC (n=1,185)	18 (16, 20)	6 (4, 8)	24 (10, 61)
Patch (n=303)	21 (19, 23)	9 (7, 11)	12 (3, 24)
Ring (n=227)	24 (21, 26)	12 (10, 14)	8 (3, 18)
Progestin-only Types			
Shot (n=720)	19 (17, 22)	7 (5, 10)	24 (7.5, 48)
H-IUD (n=177)	25 (23, 28)	14 (11, 17)	24 (12, 36)
Mini-Pill (n=77)	21 (17, 25)	9 (5, 13)	12 (4, 24)
Implant (n=42)	22 (19, 26)	10 (5, 15)	23 (12, 48)
EC (n=402)[‖]	23 (20, 26)	11 (8, 14)	1 (1, 2)

*Includes combined oral contraceptives (COCs), the patch, the ring, Depo-Provera, hormonal intrauterine devices (H-IUDs), the implant, and the mini-pill (progestin-only pill).

[†]Age at first use was missing for n=1 COC users, n=1 patch users, and n=1 shot users. Up to 2% (n=24) of age at first COC use reported in this table could represent age at first mini-pill use.

[‡]Calculated by subtracting age at menarche from age at first use.

[§]Duration of use was missing for n=1 patch user and n=2 pill users. For ECs, number of times took ECs is reported instead.

[‖]Includes n=39 women who used EC only, plus n=363 women who used ECs in addition to COC, the patch, the ring, Depo-Provera, H-IUD, implant, or mini-pill.

Abbreviations: COC, combined oral contraceptive; EC, emergency contraception; HC, hormonal contraceptive; H-IUD, hormonal intrauterine device; IQR, interquartile range; NA, not applicable; SELF, Study of Environment, Lifestyle, and Fibroids.

Table 5.4. Reasons for use, by HC type, in 1,455 ever HC users who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

Reason for Use*	Total (n=1,455)	Estrogen-containing			Progestin-only		
		COCs† (n=1,185)	Patch‡ (n=302)	Ring (n=227)	Shot (n=720)	H-IUD (n=177)	Implant (n=42)
Contraceptive Reasons							
Birth control	1,357 (93)	1,051 (89)	286 (95)	219 (96)	685 (95)	170 (96)	42 (100)
Birth control only	745 (51)	619 (52)	229 (76)	165 (73)	520 (72)	130 (73)	38 (90)
Non-contraceptive Reasons							
Non-contraceptive reasons only§	98 (7)	134 (11)	16 (5)	8 (4)	34 (5)	7 (4)	0 (0)
Menstrual problems‖	671 (46)	529 (45)	63 (21)	57 (25)	186 (26)	47 (27)	3 (7)
Menstrual problems only§	79 (5)	107 (9)	9 (3)	8 (4)	26 (4)	5 (3)	0 (0)
Irregular cycles	587 (40)	465 (39)	52 (17)	50 (22)	159 (22)	37 (21)	2 (5)
Heavy bleeding	323 (22)	267 (23)	21 (7)	13 (6)	77 (11)	28 (16)	2 (5)
Menstrual pain	255 (18)	202 (17)	23 (8)	16 (7)	70 (10)	16 (9)	1 (2)
Other¶	100 (7)	76 (6)	8 (3)	8 (4)	15 (2)	3 (2)	1 (2)

*Women could report multiple reasons for use.

†Reason(s) for use for oral contraceptives could not be stratified by mini-pill versus combined oral contraceptives for women who had used both types (n=64, 5% of pill users); few used only the mini-pill, n=13, so no data are shown for mini-pill.

‡Reasons for use data were missing for n=1 patch user.

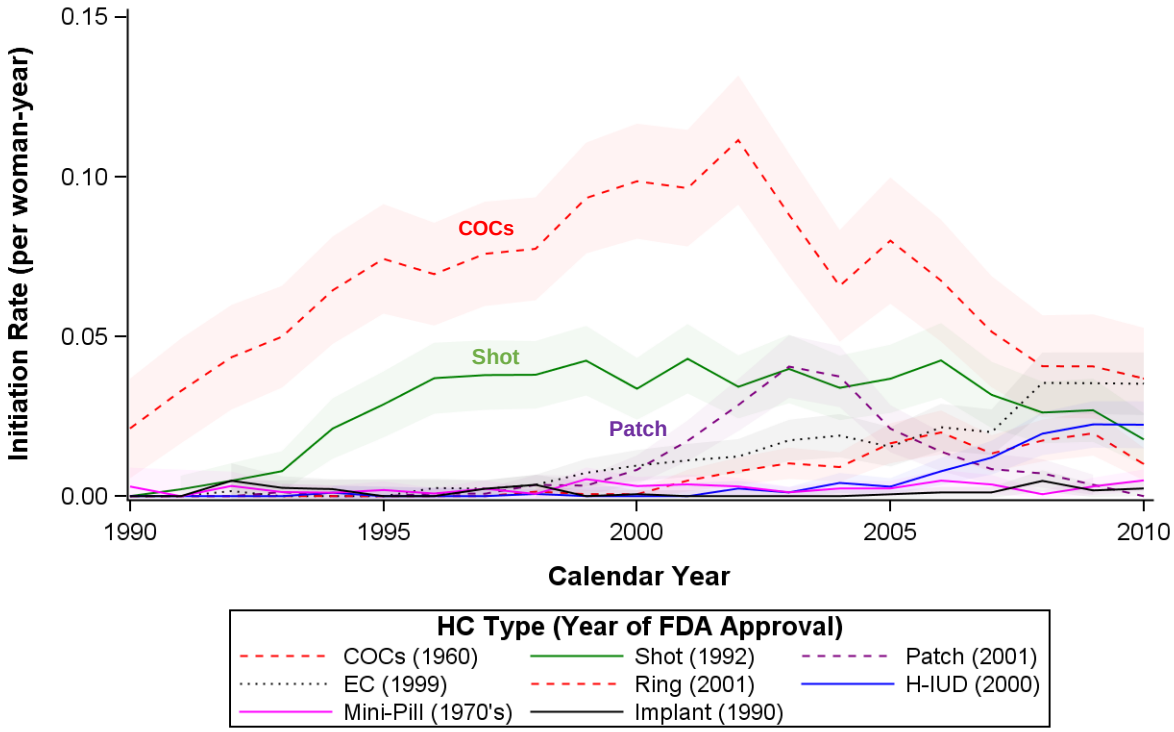
§To the exclusion of all other reasons for use, by HC type. For the "Total" column and "Non-contraceptive reasons only" row, the participant could not have used any type of HC for contraceptive purposes, ever. For the "Total" column and "Menstrual problems only" row, participants could not have ever used any type of HC for reasons other than irregular cycles, heavy bleeding, or menstrual pain.

‖Includes irregular cycles, heavy bleeding, or menstrual pain.

¶Other non-contraceptive reasons included acne, endometriosis, menstrual migraines/headaches, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), polycystic ovary syndrome (PCOS), and ovarian cysts.

Abbreviations: COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device.

Figure 5.1. Annual initiation rates (with 95% CIs) for seven HC types and emergency contraception in 1,693 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)*†‡ § ‖



*For each year and hormonal contraceptive type, Rate = number of women who recalled initiating the given HC type in that year, divided by the number of women who had reached menarche by that year and had not yet initiated that HC type.

†Excluded from this figure are 6 women who used a hormonal contraceptive prior to menarche (n=5) or were missing age-at-first-use data (n=1).

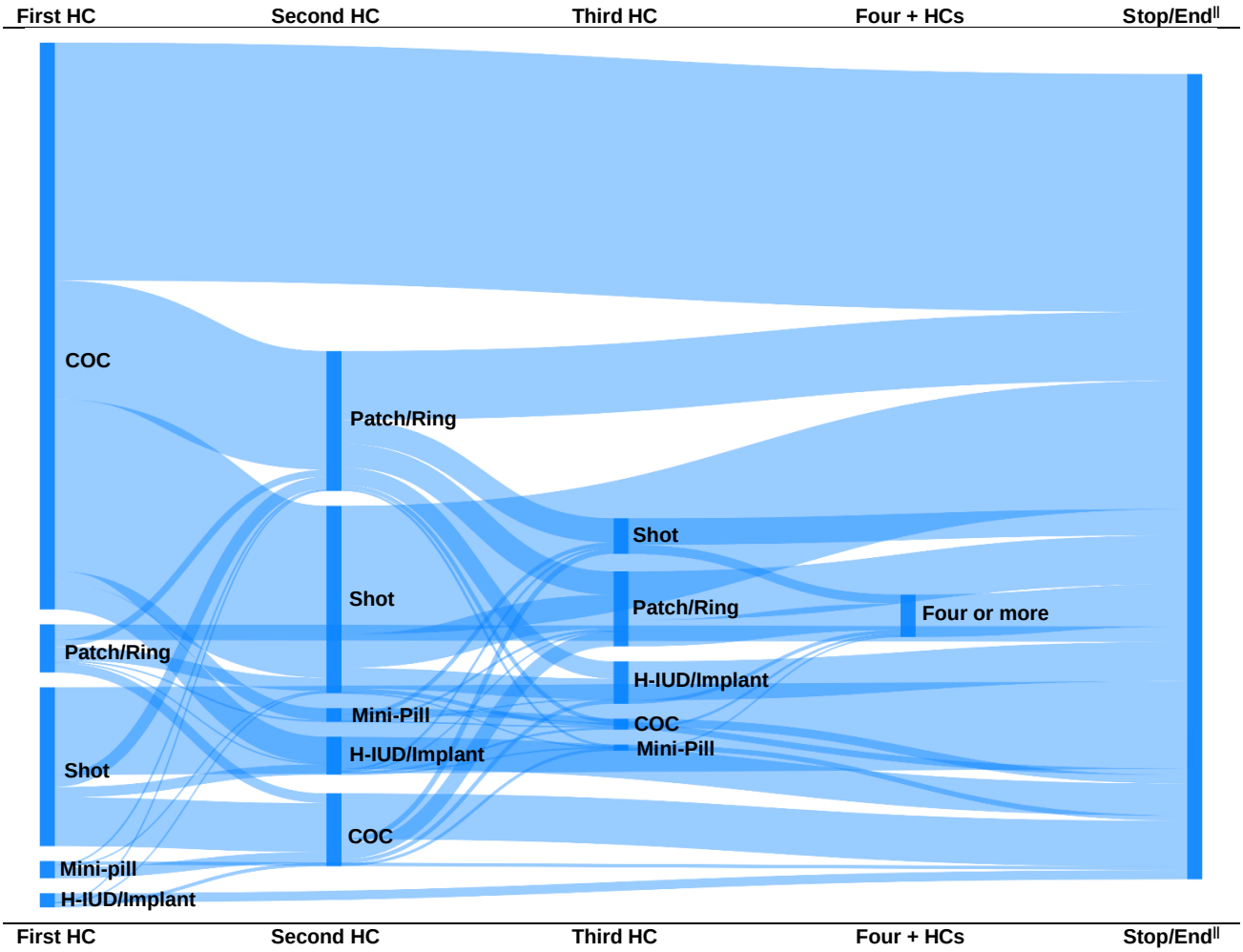
‡Data not shown before 1990 or after 2010 due to sparsity.

§Dashed lines represent estrogen-containing HCs (COC, patch, ring). Dotted line represents EC.

‖Up to 2% (n=24) of COC initiation depicted in this figure could represent mini-pill initiation.

Abbreviations: CIs, confidence intervals; COCs, combined oral contraceptives; EC, emergency contraception; HC, hormonal contraceptive; H-IUD, hormonal intrauterine device; SELF, Study of Environment, Lifestyle, and Fibroids.

Figure 5.2. Sankey* diagram depicting self-reported HC sequences of use in 1,405 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA) (represents utilization occurring in 1988-2012)[†‡§]



*A Sankey diagram is a flow diagram, in which the width of the bands are proportional to the quantity (in this case, people) in that band. For example, far more women in the SELF cohort used COC followed by the Patch/Ring than had used H-IUD/Implant followed by COC. The depicted changes in HC could have occurred immediately or could have been separated by long periods of time without HC, and may have included intervening pregnancies.

[†]Excludes n=50 women for whom order of use could not be determined: n=43 women for whom order of use for the first two HC types could not be determined, and n=7 women for whom order of use of later types could not be determined.

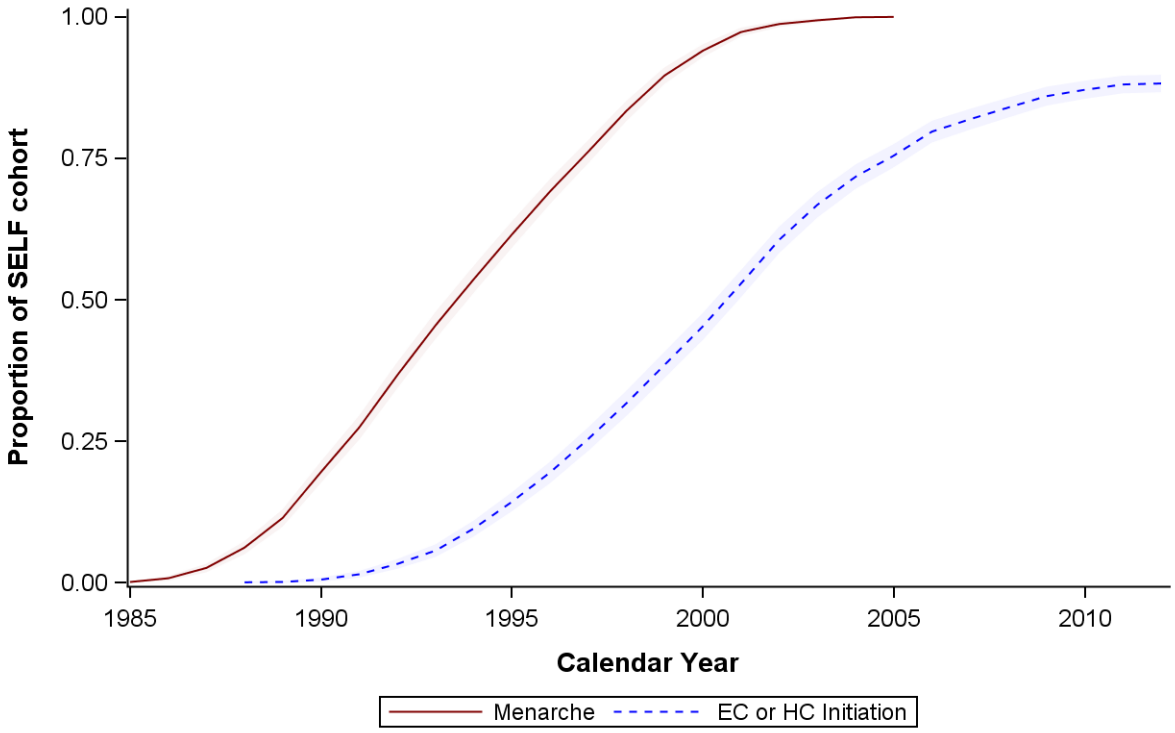
[‡]"Mini-pill" refers to progestin-only oral contraceptives.

[§]Repeat use of the same method is not depicted. For instance, Patch/Ring to Patch/Ring represents a change between the patch and the ring. Similarly, H-IUD/Implant to H-IUD/Implant represents a change from H-IUD to implant, or from implant to H-IUD.

[‖]"Stop/End" refers to the end of the recorded history and includes current users. For example, a woman who is currently using the patch will appear in one of the lines that goes straight from "Patch/Ring" to "Stop/End."

Abbreviations: COC, combined oral contraceptive; HC, hormonal contraceptive; H-IUD, hormonal intrauterine device; SELF, Study of Environment, Lifestyle, and Fibroids.

Figure 5.3. Cumulative incidence curves (with 95% CIs) for menarche and HC/EC initiation, by year, in 1,693 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)



Abbreviations: CIs, confidence intervals; EC, emergency contraception; HC, hormonal contraceptive; SELF, Study of Environment, Lifestyle, and Fibroids.

CHAPTER 6: COMBINED ORAL CONTRACEPTIVE UTLIZATION AND UTERINE FIBROID PREVALENCE AND INCIDENCE IN THE SELF COHORT (PAPER 2)

Introduction

More than 1 billion U.S. dollars are spent each year to treat uterine fibroids (benign tumors of the uterus).[1] Fibroid symptoms include pelvic pressure, pain, and heavy menstrual bleeding leading to iron deficiency anemia.[4] Fibroids can cause infertility and obstetric complications, and may be associated with preterm delivery.[4,5] In the U.S., black women experience greater risk of, and a 10-year earlier onset of, fibroids than white women, and their fibroids are more severe.[2] At least 80% of black women will develop uterine fibroids in their lifetime.[3]

While a great deal is already known about how to identify and treat symptomatic uterine fibroids, considerably less is known about fibroid prevention. This is surprising given the high prevalence and public health burden of the disease.

It is currently thought that estrogen and progesterone have complex, interrelated roles in fibroid tumor development.[6,7] Progesterone appears to cause fibroid growth, and estrogen increases availability of progesterone receptors.[7] Yet, injectable progesterone may offer lasting protection against uterine fibroids,[50] and oral doses of these hormones are commonly used as a first-line treatment for fibroid symptoms.[23]

Oral contraceptives (OCs) are generally composed of both estrogen and progestin (synthetic progestogen).[8] Exposure to OCs is widespread in the U.S.[9–11] Among sexually experienced black women aged 15-44, 80% have used OCs in their lifetime.[9] Despite the availability of longer acting methods in the U.S., OCs remain the most commonly used form of hormonal contraception.[41]

The data on oral contraceptives and fibroid risk have been mixed, with some studies suggesting a detrimental effect if taken early in life,[12,13] and others suggesting a protective effect[14–16] or no effect at all.[17–20] Studies of OC use and fibroid development to date have lacked baseline fibroid assessments and were unable to establish temporality of OC use and fibroid occurrence. Furthermore, fibroid assessment

was most often by clinical recognition; i.e., only women who sought treatment for fibroid symptoms and who had access to care were screened. Thus, the resulting associations may have been biased by factors related to clinical or surgical detection, including perception of symptoms and access to medical treatment.[2] Majority of studies to date examined OC use and fibroids in all white or mostly white women, despite the fact that black women are much more likely to be affected by the condition. Finally, existing studies of OC use and fibroid incidence have yet to employ propensity score based methods and counterfactual thinking.

We addressed the longstanding question of how oral contraceptive use influences uterine fibroid development using data from the Study of Environment, Lifestyle & Fibroids (SELF) – the first prospective, ultrasound-based study specifically designed to capture uterine fibroid incidence in young, black women. Specifically, we examined the associations between different levels of COC use and (a) prevalent fibroids at baseline and (b) incident fibroids at ~40 months of follow-up.

Methods

Study population

The Study of Environment, Lifestyle & Fibroids (SELF) is a prospective cohort study of 1,693 young (23-35 years), African American women living in the Detroit, Michigan area. SELF was designed to investigate risk factors for uterine fibroid incidence and growth.[2,21,22] Recruitment and baseline data collection were completed in 2010-2013.[50] Participants were recruited from the Detroit area via local radio and television commercials, advertisements in newspapers and magazines, brochures at healthcare clinics, information booths at community events, and via the Henry Ford Health System (HFHS).[2] The primary eligibility requirements were age, self-identified African American/black, and having no prior clinical diagnosis of uterine fibroids. The retention rate for SELF was high at >85% for the 40-month follow-up.

SELF was approved by the institutional review boards of the National Institute of Environmental Health Sciences and the Henry Ford Health System.

Data collection

Fibroid identification was performed using transvaginal ultrasonography (TVUS). All exposure and covariate data were self-reported, with the exception of BMI, which was calculated using height and weight as measured at the baseline clinic visit.

Hormonal contraceptive use

As part of participation in SELF, history of hormonal contraceptive (HC) use was collected via telephone interview as part of an enrollment questionnaire. Women were asked if they had ever used each of the following types of HC: "birth control pills" (OCs), "mini-pill" (progestin-only OCs), hormonal implant, hormonal patch, vaginal ring, "hormone shots like Depo-Provera," and hormonal intrauterine devices (H-IUD). Brief descriptions and examples of common brand names were provided for hormonal implants and shots.

For each HC type (and separately for each H-IUD), women were asked about their age at first use, whether or not they were currently using, how old they were when they stopped using, and their reason(s) for using. For age at first use, women were asked, *"How old were you when you started using birth control pills, whether or not it was to prevent pregnancy?"* Women who had used OCs were asked whether or not they had ever stopped using for a month or longer, and if so, the proportion of time between start and stop that they spent on OCs ("very little of that time," "less than half of that time," "about half," "more than half," "most of that time," "the entire time"). Women who used the "mini-pill," implant, patch, ring, or shot were asked to state the total number of months and years that they had used each method prior to study enrollment.

Uterine fibroids

Fibroid identification was performed as previously described[25] using transvaginal ultrasonography (TVUS) – the current standard of care for uterine fibroid assessment.[62] TVUS has 99% sensitivity and 91% specificity (relative to histology) for detecting uterine fibroids.[63] SELF sonographers were specially trained, registered diagnostic sonographers with at least 3 years of experience in gynecologic

sonography.[2] All sonographers were given additional, study specific training.[2] Fibroids were carefully mapped, measured, and numbered on a standardized form.[2] Each fibroid was measured 3 times in 3 perpendicular planes, resulting in 9 diameter measurements for each fibroid at each visit.[25] Quality control procedures were carried out.[2] The head sonographer reviewed still and video images for 8% of each sonographer's examinations each month. It is estimated that 98.5% of women considered fibroid free at baseline were truly fibroid free, and 99.6% of women with fibroids at baseline truly had fibroids.[2]

Exposure and outcome classification

Ever use and age at first use of COCs

Women who reported using "the pill" were considered to have used combined oral contraceptives (COCs) if they answered "No" or "I don't know" to *"Have you ever used a progesterone-only birth control pill, or "mini-pill", such as Micronor, Nora-BE, or Ovrette?"* Age at first COC use was dichotomized into <17 and ≥17 based on findings in previous literature suggesting that COC initiation prior to age 17 years may be associated with fibroid development later in life.[12,13]

Duration of use for COCs

For the purposes of this study, "duration of use" refers to cumulative lifetime exposure from birth until study enrollment. We used women's self-reported ages of first and last COC use to approximate duration of use. Many women reported stopping use of COCs for one month or more, and were asked to answer a question regarding the proportion of time between start and stop age that they had been using COCs. Using these data, duration of use estimates for combined oral contraceptives (COCs) were calculated in three steps, as follows: (1) Subtract age at first OC use from age at last OC use, or age at enrollment for current users, (2) Subtract months and years on the mini-pill, (3) Multiply by the proportion of time spent using OCs. Weights were applied as follows: 10% for "very little of that time," 25% for "less than half of that time," 50% for "about half," 75% for "more than half," 90% for "most of that time," and 100% for "the entire time." When age at first use and age at last use were identical, a duration of 6 months was assigned.

Time since last use of COCs

For past COC users, time since last COC use was calculated by subtracting self-reported age at last pill use from age at enrollment. Current users were assigned a time since last use value of 0. For n=64 women who used both combined and progestin-only OCs, time since last COC use specifically could be determined for 31 subjects. Time since last use of COCs could not be determined for the remaining 33 women due to the structure of the enrollment questionnaire, which did not initially distinguish between COCs and progestin-only pills. These were women who provided the same discontinuation age for both OCs and progestin-only OCs, but who had used both COCs and progestin-only OCs.

Joint duration of and time since last use

Duration of use was characterized as short (< 2 years) or long (≥ 2 years). Time since last use was characterized as recent (< 5 years) or past (≥ 5 years).

Uterine Fibroids

Women were considered positive for uterine fibroids if they had one or more lesions of at least 0.5 cm maximum diameter that could be visualized in all three planes, as previously described.[25]

Prevalence study design

First, we examined the association between ever COC use and prevalent fibroids at baseline. This cross-sectional analysis included all women enrolled in SELF. Subsequently, we examined the associations between prevalent fibroids and each of four exposures: age at first use, duration of COC use, time since last COC use, and joint duration of and time since last COC use. These analyses were restricted to COC users, comparing each category of use to the lowest level.

Incidence study design

Second, we carried out incidence analyses analogous to the prevalence analyses just described. This allowed us to examine the associations between incident fibroids and different levels of COC use. To

establish temporality, women were included in our incidence analyses if their baseline ultrasound showed no fibroids.

SELF included baseline ultrasounds and three follow-up ultrasounds for all participants. Follow-up ultrasounds took place at ~20 months, ~40 months, and ~60 months. Ultrasound data were available for the first two follow-up visits at the time of this analysis. We examined cumulative incidence at ~40 months of follow-up. Women were considered outcome positive if their ~20-month or ~40-month ultrasounds revealed uterine fibroids.

Flow diagrams depicting inclusion and exclusion criteria for our incidence analyses appear in Appendix 2.1. Women were considered to have missing outcomes if ultrasound data were not available for both follow-up study visits. Additionally, women were also considered to have missing outcomes if their ~20-month ultrasound was negative for fibroids and no ~40-month ultrasound data were available. This was done since their cumulative fibroid status at 40 months was unknown. Reasons for missing follow-up ultrasounds are quantified in Appendix 2.1 and included hysterectomy, uterine surgery, and inability to adequately visualize the uterus. Individuals with missing outcomes were included in our propensity score calculations, and inverse probability of censoring (i.e., missing outcomes) weights were applied in order to upweight similar individuals in the calculations of our risk ratio estimates (see Appendix 2.2).

Statistical analyses

All data management and analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA). We report our propensity score (PS) based methods in accordance with the recommendations provided by Ali et al. (2014)[74] in the *Journal of Clinical Epidemiology* in Appendix 2.2. In brief, inverse probability (IP) weights were constructed for all exposures, and censoring. Standardized mortality ratio (SMR) type weights were constructed for ever COC use, i.e., the weights for the ever-never use analyses were based upon the covariate distribution of the “treated,” in this case, the “ever users.” For incidence analyses, the IP and SMR weights were multiplied by the inverse probability of censoring weights. Weighted log-binomial regression models were used to estimate prevalence ratios and risk ratios for uterine fibroids. No

additional covariates were included in the weighted models. Confidence intervals for weighted models were generated using robust variance (“sandwich”) estimator by use of the SAS REPEAT statement.

The covariate set for all weight calculations were measured at baseline (and thus not time-varying in this analysis) and included: age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (>24 months), time since last birth (<5 years, 5-9.99 years, >10 years and no birth), parity (nulliparous, 1-2 births, >3 births), BMI (>30, remaining values according to tertile), and education (Bachelor’s degree or higher). In addition to these covariates, censoring weights also included the exposure of interest, annual household income (<$20,000, $20,000-49,999, and ≥$50,000), baseline employment status (not employed, employed <30 hours per week, employed ≥30 hours per week), smoking history (never smoked, former smoker, current smoker of <10 years, current smoker of ≥10 years) and history of heavy “gushing” type menstrual bleeding (yes/no).

Results

Study population

Median age at enrollment for the entire cohort was 29 years [IQR: 26, 32]. Age did not differ appreciably between COC users and never-users, but was slightly higher among women with prevalent fibroids (Table 6.1). The majority (83%) of women participating in SELF had an annual household income of less than $50,000 per year. Income distribution appeared lower among never COC users as compared to ever users, and higher among women with prevalent fibroids as compared to women without. Most (62%) of the women were employed, and employment appeared more common among ever COC users and those with prevalent fibroids. Approximately 28% of SELF participants had earned at least a Bachelor’s degree. Bachelor’s or higher educational attainment was more common among the ever COC users and women with prevalent fibroids.

Overweight (21%) and obesity (60%) were common in this cohort, and did not appreciably vary by COC use or uterine fibroid status. Approximately 26% of the women were ever-smokers, and current smoking was more frequent among women who had never used COCs.

Median age at menarche was 12 years, with only 18% reporting onset of menses prior to age 11. Earlier menarche was more common among women with prevalent fibroids. Nearly 37% of the cohort experienced heavy “gushing” type menstrual bleeding. Heavy “gushing” type bleeding was more frequent among ever COC users and those with prevalent fibroids at baseline. Approximately 60% of the cohort had given birth. Birth was more common among ever COC users and women without prevalent fibroids. Approximately one-third (32%) of the cohort had given birth within the last 5 years. Birth was more recent for those without prevalent fibroids (Table 6.1).

About 42% of the cohort had used Depo-Provera. Depo-Provera use was less common among women with prevalent fibroids (Table 6.1). Only 7% of SELF participants had used the patch or a hormonal intrauterine device (H-IUD) for 24 months or longer in total. Patch and H-IUD use did not differ appreciably by COC use or baseline fibroid status, though appeared less common among women with prevalent fibroids (Table 6.1).

Exposure and outcome prevalence

Nearly 70% of SELF participants reported a history of COC use (Table 6.2). Of those who did not report a history of COC use, 53% had used another HC, principally Depo-Provera (41%). Of the 1,185 women who reported COC use, 35% reported initiating COCs prior to age 17 (Table 6.2). Most (73%) used COCs for less than 5 years in total. Relatively few (23%) were currently using COCs at study enrollment. Nearly half (48%) had used COCs 5 or more years ago (Table 6.2). Uterine fibroids were detected in 23% (n=385) of baseline ultrasounds. Among women who were fibroid-free at baseline (n=1,308), 17% (n=221) developed fibroids by ~40 months of follow-up.

Prevalence Findings

Main findings

We observed no association between ever use of COCs and fibroid prevalence (Table 6.2, Figure 6.1). Similarly, we observed no association between COC initiation prior to age 17 and fibroid prevalence, among COC users. Comparing each level of duration of COC use to < 1 year of use, weighted prevalence ratios varied from 0.88 to 1.15. Weighted prevalence ratios (wPR) comparing each level of time since last use to current use ranged from 1.13 to 1.45, declining with increasing time since last use. All estimated

associations were null, with the possible exception of COC use 1-2 years ago (wPR: 1.45; 95% confidence interval: 1.00, 2.10). Multivariable log-binomial regression results are presented alongside weighted estimates in Table 6.2 and were found to be similar.

Sensitivity analyses

We re-ran our ever COC use weighted analysis to determine what influence, if any, the composition of the "Never" comparator group had on our findings. When the "Never" group was restricted to women who had never used any form of hormonal contraception (HC), a possible protective association emerged (wPR: 0.83; 95% confidence interval: 0.65, 1.06). When the "Never" group was restricted to ever HC users, our findings were null (wPR: 0.93; 95% confidence interval: 0.68, 1.27).

Incidence Findings

Main findings

At ~40-months' follow-up, we observed a possible protective association between ever use of COCs and fibroid cumulative incidence among women who were without fibroids at study enrollment (Table 6.3, Figure 6.2). The weighted risk ratio comparing ever to never COC use was 0.78 (95% confidence interval: 0.60, 1.00). However, all estimated associations among COC users did not suggest a discernable pattern of harm or protection. Our age at first use estimates showed no strong association between COC initiation prior to age 17 and fibroid incidence among COC users. Comparing each level of duration of COC use to < 1 year of use, weighted risk ratios varied from 1.10 to 1.49, with overlapping confidence intervals ranging from 0.69 to 2.38. Weighted risk ratios (wRR) comparing each level of time since last use to current use ranged from 0.87 to 1.23, declining with increased time since last use, with overlapping confidence intervals ranging from 0.50 to 2.10. Multivariable log-binomial regression results were similar to weighted estimates (Table 6.3).

Sensitivity analyses

When restricting the "Never" comparator group to ever HC users, the observed association between COC use and fibroid incidence disappeared (wRR: 0.92, 95% CI: 0.60, 1.40). The association re-emerged when restricting the "Never" comparator group to women with no history of HC use (wRR:

0.72; 95% CI: 0.51, 1.01). We also examined 20-month incidence of fibroids and noted a possible protective association for ever-COC use, and time since last use 5 or more years ago (Appendix 2.7.3). When multi-level outcome models were implemented with parity and uterine fibroid incidence as a single joint outcome, all associations were null. Potentially protective associations were observed for ever COC use and the incident fibroids, regardless of childbirth during follow-up (Appendix 2.7). The direction of the association between fibroid incidence and later age of COC initiation was reversed when birth was considered, such that a protective association was observed for the joint outcome of incident fibroids and childbirth during follow-up, while a harmful association was apparent for incident fibroids and no childbirth during follow-up. For instance, women who initiated COC use at age 17 or older experienced 0.47 times the odds of developing a fibroid and giving birth during follow-up as women who initiated COC use prior to age 17 (95% CI: 0.11, 2.00; Appendix 2.7.2). When pregnancy and Depo-Provera use during follow-up were added to the IP and censoring weighted incidence models, results did not noticeably differ from those in our main analysis (Appendix 2.7.1).

Discussion

In this study of 1,693 young, black women living in Detroit, we found that ever use of COCs might be protective against uterine fibroids when compared to use of no hormonal contraceptives (HCs) at all. This protective association disappeared when comparing COC users to ever-users of any other HC type, suggesting that HC and not necessarily COC use may be protective against uterine fibroids. Four prior studies reported odds ratios (OR) comparing ever to never oral contraceptive users.[14,17,18,48] Lumbiganon et al. (1995)[48] reported a protective association of OR = 0.76 (95% CI: 0.66-0.92). This is similar to our incidence wRR of 0.78 (95% CI: 0.60, 1.00). Three other studies reported null findings.[14,17,18] It is unclear whether women in the “Never” comparison groups for these four studies had used other HCs. All four studies were case-control studies in which cases were defined as surgically treated leiomyomas and controls were other hospitalized patients. None of the four studies reported on race, with the exception of Lumbiganon et al. (1995)[48] in which <1% of study participants were neither Thai nor Chinese. All four studies were conducted at least 20 years ago in Italy[14,17,18] or Thailand,[48] where oral contraceptive formulations were likely different from the ones used by women in SELF. It is difficult to make direct

comparisons between our work and others' due to these differences in time period, population, and study design.

While two prior studies reported a harmful association between COC initiation before age 17 years,[12,13] we did not observe this association in our data. While these studies compared each age at first use category to never users, our age at first use comparisons were restricted to ever COC users. One study[26] found no association between age at OC initiation and uterine fibroids when comparing OC initiation before and after age 17 among ever OC users, similar to our study. However the reported association (OR: 1.12: 95% CI: 0.57, 2.18) was unadjusted.[26]

Though our study design and population differed considerably, our null findings for duration of use and time since last use of COCs are in concurrence with most prior literature,[12,13,15–18,20] including the Black Women's Health Study (BWHS).[12] However, three studies did report a protective association for longer duration of use of OCs,[14,15,49] and one study reported that longer time since last OC use (> 5 year versus $\leq$ 5 years) was associated with uterine fibroid prevalence (unadjusted $p < 0.01$).[49] Never users served as the referent for two of these three studies,[14,15] and the third study did not report adjusted associations.[49] Black women were not represented in these studies which took place in Italy during the 1990s[14,49] or among contracepting, married white women in England or Scotland in 1968-1985.[15]

Strengths and limitations

Ours was the first prospective, ultrasound-based study to examine the association between COC use and uterine fibroids in young, black women. SELF performed ultrasounds in all study participants, including at baseline and follow-up, regardless of symptoms or health care access. Incidence analyses were restricted to women without fibroids at baseline, strengthening the temporality[75] basis of our observed associations. Use or propensity score (PS) based methods allowed for greater transparency and interpretability of our findings. We are the first study to examine COC use and uterine fibroid outcomes using PS-based methods. Prior studies used multivariable regression models and most often compared different levels of COC user to never users, which may not be the most relevant comparison as women are unlikely to choose between a specific level of COC use (e.g., duration of use 3-4 years) and never using COCs at all. Analogous to the counterfactual conundrum of smoking, we are unlikely to ever

live in a world in which no women ever use COCs. Therefore, our within-COC users comparisons are likely to be more relevant to prescribers, patients, and policymakers.

Our findings should be considered in light of our study's limitations. First, we did not have adequate statistical power to rule out small associations.[76] The estimates reported are measures of association from a single cohort study and should be considered in context of a broader literature base. Second, all exposure and covariate data with the exception of BMI were self-reported. Self-reported history of OC use, as collected by telephone interview, has been found to be reliable when compared to automated pharmacy dispensing data [61]. Third, we did not have exact duration of use estimates for COCs or H-IUDs and had to use limited available information to estimate duration of use for these HC types. Finally, women with prior clinical diagnosis were excluded from participating in SELF. While exclusion of women with clinical diagnosis of fibroids may have resulted in selection bias, only 5.87% (95% CI: 4.32, 7.42) of U.S. black women aged 23-35 in 2011-2013 had ever been diagnosed with uterine fibroids, and the possible selection bias is expected to be small (unpublished analysis).[77–79]

Conclusion

Ever use of COCs may be protective against uterine fibroid development, though no more protective than other HC types. It is unclear how differing levels of COC use among COC users might confer differing levels of protection or harm, if any. Further studies may be warranted in larger cohorts that would lead to estimates that are more precise and that build upon the methodological improvements represented by this study. The findings from these analyses contribute to the evidence base for oral contraceptive safety and effectiveness, allowing providers and patients to make better, evidence-based decisions regarding oral contraception in women with or without fibroids.

Table 6.1. Characteristics of 1,693 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

	COC use		Uterine fibroids at baseline	
	Never	Ever	No	Yes
	N=508	N=1,185	N=1,308	N=385
	n (%)	n (%)	n (%)	n (%)
Age at enrollment (years)				
Median [IQR]	28 [25, 31]	29 [26, 32]	28 [25, 31]	30 [28, 33]
Annual household income*				
< $20,000	288 (57)	478 (41)	607 (47)	159 (41)
$20,000 to $50,000	146 (29)	482 (41)	489 (38)	139 (36)
≥ $50,000	70 (14)	217 (18)	201 (15)	86 (22)
Baseline employment status*				
Not employed	231 (45)	409 (35)	518 (40)	122 (32)
Employed, but less than 30 hrs/wk	68 (13)	142 (12)	172 (13)	38 (10)
Employed, 30 or more hrs/wk	209 (41)	630 (53)	615 (47)	224 (58)
Education*				
Bachelors/master's/PhD	110 (22)	365 (31)	336 (26)	139 (36)
Body mass index (kg/m^2)				
< 25	107 (21)	228 (19)	260 (20)	75 (19)
25-29	101 (20)	249 (21)	279 (21)	71 (18)
≥ 30	300 (59)	708 (60)	769 (59)	239 (62)
Smoking history				
Never smoked	345 (68)	900 (76)	959 (73)	286 (74)
Former smoker	30 (6)	95 (8)	97 (7)	28 (7)
Current smoker (< 10 years)	95 (19)	143 (12)	193 (15)	45 (12)
Current smoker (≥ 10 years)	38 (7)	47 (4)	59 (5)	26 (7)
Age at menarche				
≤ 10 years	91 (18)	219 (18)	226 (17)	84 (22)
Heavy menstrual bleeding				
Ever had heavy gushing type bleeding	169 (33)	456 (38)	466 (36)	159 (41)
Reproductive history				
Nulliparous or never pregnant	222 (44)	440 (37)	477 (36)	185 (48)
1 birth	120 (24)	312 (26)	344 (26)	88 (23)
2 births	74 (15)	239 (20)	246 (19)	67 (17)
≥ 3 births	92 (18)	194 (16)	241 (18)	45 (12)
Time since last birth				
0-4 years	167 (33)	379 (32)	467 (36)	79 (21)
5-9 years	81 (16)	255 (22)	265 (20)	71 (18)
Nulliparous or ≥ 10 years ago	260 (51)	551 (47)	576 (44)	235 (61)
Depo-Provera history*				
Never used Depo-Provera	301 (59)	672 (57)	715 (55)	258 (67)
Short/Past (≤ 24 months, > 8 years ago)	25 (5)	128 (11)	113 (9)	40 (10)
Long/Past (> 24 months, > 8 years ago)	16 (3)	43 (4)	47 (4)	12 (3)
Short/Recent(≤ 24 months, within 8 years)	74 (15)	184 (16)	214 (16)	44 (11)
Long/Recent (> 24 months, within 8 years)	92 (18)	157 (13)	219 (17)	30 (8)
Implant and H-IUD history				
Used ≥ 24 months	28 (6)	85 (7)	93 (7)	20 (5)

*Annual household income was missing for n=12 participants. Employment was missing for n=4 participants. Education was missing for n=1 participants. Time since Depo-Provera use was missing for n=1 participant.

Abbreviations: SELF, Study of Environment, Lifestyle, and Fibroids; COC, combined oral contraceptives; IQR, interquartile range; hrs, hours; wk, week; PhD, doctor of philosophy; kg/m^2, kilograms per square meter; H-IUD, hormonal intrauterine device.

Table 6.2. Combined oral contraceptive utilization and baseline fibroid prevalence in 1,693 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

COC use	Prevalent Fibroids n (%)	Prevalence Ratios (95% CI)		
		Age-Adjusted	Fully Adjusted*	
		MVR	IPW/SMR	MVR
Ever use				
Never (N=508)	113 (22)	Ref.	Ref.	Ref.
Ever (N=1,185)	272 (23)	0.91 (0.76, 1.11)	0.90 (0.74, 1.10)†	0.90 (0.75, 1.08)
Age at first use (years)				
< 17 (N=410)	90 (22)	Ref.	Ref.	Ref.
≥ 17 (N=775)	182 (23)	1.05 (0.84, 1.31)	1.00 (0.80, 1.26)	0.98 (0.79, 1.22)
Duration of use (years)				
< 1 (N=345)	67 (19)	Ref.	Ref.	Ref.
1-1.99 (N=208)	44 (21)	1.06 (0.76, 1.48)	0.91 (0.64, 1.28)	0.93 (0.67, 1.28)
2-4.99 (N=310)	81 (26)	1.28 (0.97, 1.70)	1.15 (0.86, 1.54)	1.18 (0.90, 1.55)
≥ 5 (N=322)	80 (25)	1.16 (0.87, 1.54)	0.88 (0.65, 1.21)	0.91 (0.68, 1.21)
Time since last use (years)‡				
Current user (N=277)	61 (22)	Ref.	Ref.	Ref.
1-2 (N=178)	44 (25)	1.16 (0.83, 1.61)	1.45 (1.00, 2.10)	1.26 (0.92, 1.75)
3-4 (N=125)	30 (24)	1.10 (0.76, 1.60)	1.14 (0.73, 1.79)	1.10 (0.76, 1.59)
≥ 5 (N=572)	131 (23)	0.89 (0.68, 1.16)	1.13 (0.83, 1.53)	1.06 (0.81, 1.39)
Characteristics of use‡§				
Short/past (N=327)	71 (22)	Ref.	Ref.	Ref.
Short/recent (N=209)	37 (18)	1.02 (0.71, 1.46)	0.96 (0.65, 1.42)	0.89 (0.62, 1.27)
Long/past (N=245)	60 (24)	1.06 (0.78, 1.42)	0.93 (0.67, 1.30)	0.97 (0.73, 1.30)
Long/recent (N=371)	98 (26)	1.32 (1.02, 1.72)	0.99 (0.73, 1.33)	1.07 (0.82, 1.39)

*Weighted (IPW/SMR) or Adjusted (MVR) for age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (≥24 months), time since last birth (<5 years, 5-9.99 years, ≥10 years and no birth), parity (nulliparous, 1-2 births, ≥3 births), BMI (≥30, remaining values according to tertile), education (Bachelor's degree or higher). Excludes n=1 participants for whom time since Depo-Provera use was missing.

†The weighted estimate for Ever-use was weighted according to the covariate distribution of COC users; i.e., standardized mortality ratio [SMR] weighting was employed for this exposure.

‡Excludes n=33 participants who used both pill and mini-pill, for whom time since last COC use could not be distinguished.

§Duration of use was characterized as short (< 2 years) or long (≥ 2 years). Time since last use was characterized as recent (< 5 years) or past (≥ 5 years).

Abbreviations: SELF, Study of Environment, Lifestyle, and Fibroids; CI, confidence interval; MVR, multivariable logistic regression; IPW, inverse probability weighting; SMR, standardized mortality ratio; H-IUD, hormonal intrauterine device; BMI, body mass index.

Table 6.3. Combined oral contraceptive utilization and fibroid incidence in 1,308 fibroid-free women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)

COC use	Incident Fibroids	Risk Ratios (95% CI)		
	n (%)	Age-Adjusted	Fully Adjusted*	
		MVR	IPW/SMR	MVR
Ever use				
Never (N=395)	77 (23)	Ref.	Ref.	Ref.
Ever (N=913)	144 (19)	0.77 (0.60, 0.99)	0.78 (0.60, 1.00)†	0.76 (0.60, 0.98)
Age at first use (years)				
< 17 (N=320)	42 (16)	Ref.	Ref.	Ref.
≥ 17 (N=593)	102 (20)	1.25 (0.90, 1.74)	1.25 (0.89, 1.76)	1.20 (0.86, 1.67)
Duration of use (years)				
< 1 (N=278)	34 (14)	Ref.	Ref.	Ref.
1-1.99 (N=164)	29 (22)	1.49 (0.95, 2.33)	1.49 (0.94, 2.38)	1.43 (0.92, 2.22)
2-4.99 (N=229)	34 (17)	1.18 (0.76, 1.82)	1.10 (0.69, 1.74)	1.11 (0.72, 1.70)
≥ 5 (N=242)	47 (22)	1.48 (0.99, 2.21)	1.30 (0.83, 2.04)	1.23 (0.81, 1.86)
Time since last use (years)‡				
Current user (N=216)	36 (20)	Ref.	Ref.	Ref.
1-2 (N=134)	25 (23)	1.18 (0.75, 1.85)	1.23 (0.72, 2.10)	1.23 (0.79, 1.92)
3-4 (N=95)	16 (19)	1.01 (0.60, 1.70)	0.96 (0.50, 1.85)	1.09 (0.64, 1.84)
≥ 5 (N=441)	64 (17)	0.77 (0.53, 1.12)	0.87 (0.55, 1.37)	0.91 (0.62, 1.33)
Characteristics of use‡§				
Short/past (N=256)	37 (17)	Ref.	Ref.	Ref.
Short/recent (N=172)	25 (18)	1.25 (0.78, 2.00)	0.97 (0.58, 1.62)	1.09 (0.68, 1.74)
Long/past (N=185)	27 (17)	0.96 (0.61, 1.51)	0.92 (0.55, 1.54)	0.86 (0.55, 1.35)
Long/recent (N=273)	52 (22)	1.39 (0.95, 2.04)	1.19 (0.77, 1.83)	1.13 (0.76, 1.68)

*Weighted (IPW/SMR) or Adjusted (MVR) for age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (≥24 months), time since last birth (<5 years, 5-9.99 years, ≥10 years and no birth), parity (nulliparous, 1-2 births, ≥3 births), BMI (≥30, remaining values according to tertile), education (Bachelor's degree or higher).

A total of n=198 women in SELF were censored, including n=136 COC users. Inverse probability of censoring weights were applied to upweight individuals most likely to have been censored who remained in the study. The model for probability of censoring included the exposure of interest (e.g., duration of use), all covariates used in the IPW/SMR models, with the addition of annual household income, baseline employment status, smoking history, and history of heavy gushing type bleeding.

Annual household income was missing for n=12 participants. Education was missing for n=1 participants. Time since Depo-Provera use was missing for n=1 participant.

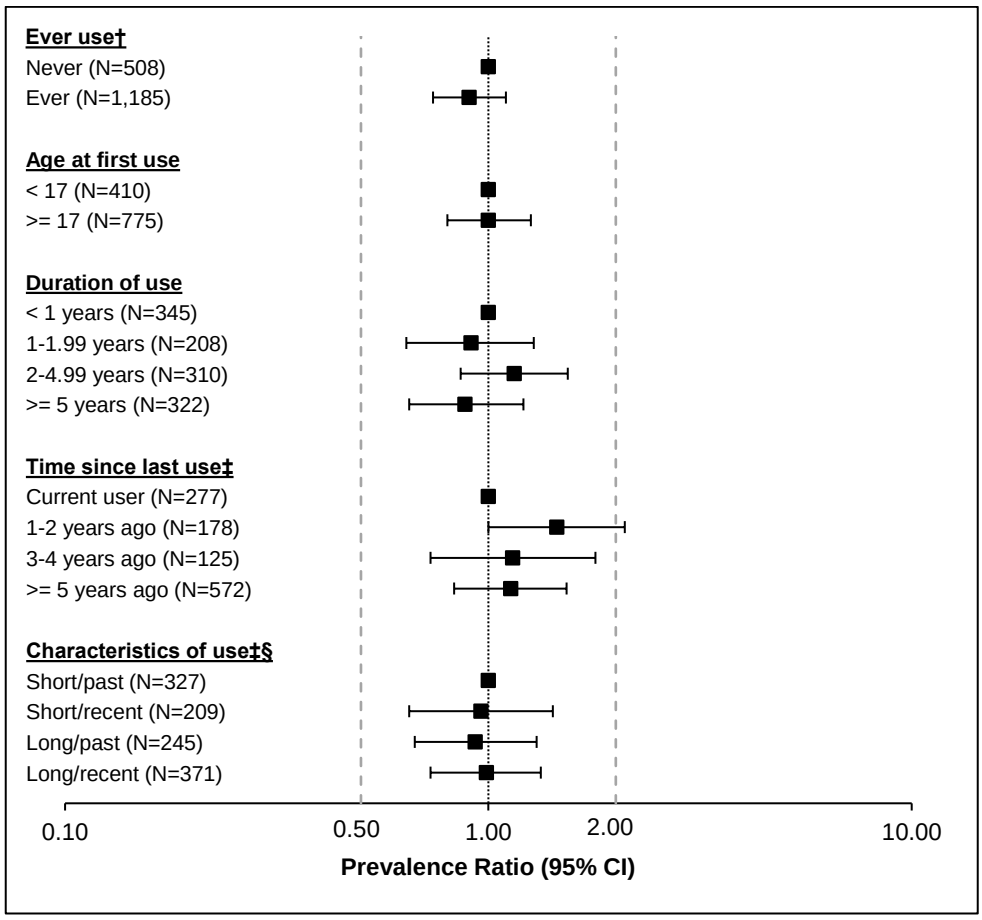
†The weighted estimate for Ever-use was weighted according to the covariate distribution of COC users; i.e., standardized mortality ratio [SMR] weighting was employed for this exposure.

‡Excludes n=33 participants who used both pill and mini-pill, for whom time since last COC use could not be distinguished.

§Duration of use was characterized as short (< 2 years) or long (≥ 2 years). Time since last use was characterized as recent (< 5 years) or past (≥ 5 years).

Abbreviations: SELF, Study of Environment, Lifestyle, and Fibroids; CI, confidence interval; MVR, multivariable logistic regression; IPW, inverse probability weighting; SMR, standardized mortality ratio; H-IUD, hormonal intrauterine device; BMI, body mass index.

Figure 6.1. IPW/SMR* associations between levels of combined oral contraceptive utilization and baseline fibroid prevalence among 1,683 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)



*Weighted (IPW/SMR) or Adjusted (MVR) for age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (≥24 months), time since last birth (<5 years, 5-9.99 years, ≥10 years and no birth), parity (nulliparous, 1-2 births, ≥3 births), BMI (≥30, remaining values according to tertile), education (Bachelor's degree or higher). Excludes n=1 participants for whom time since Depo-Provera use was missing.

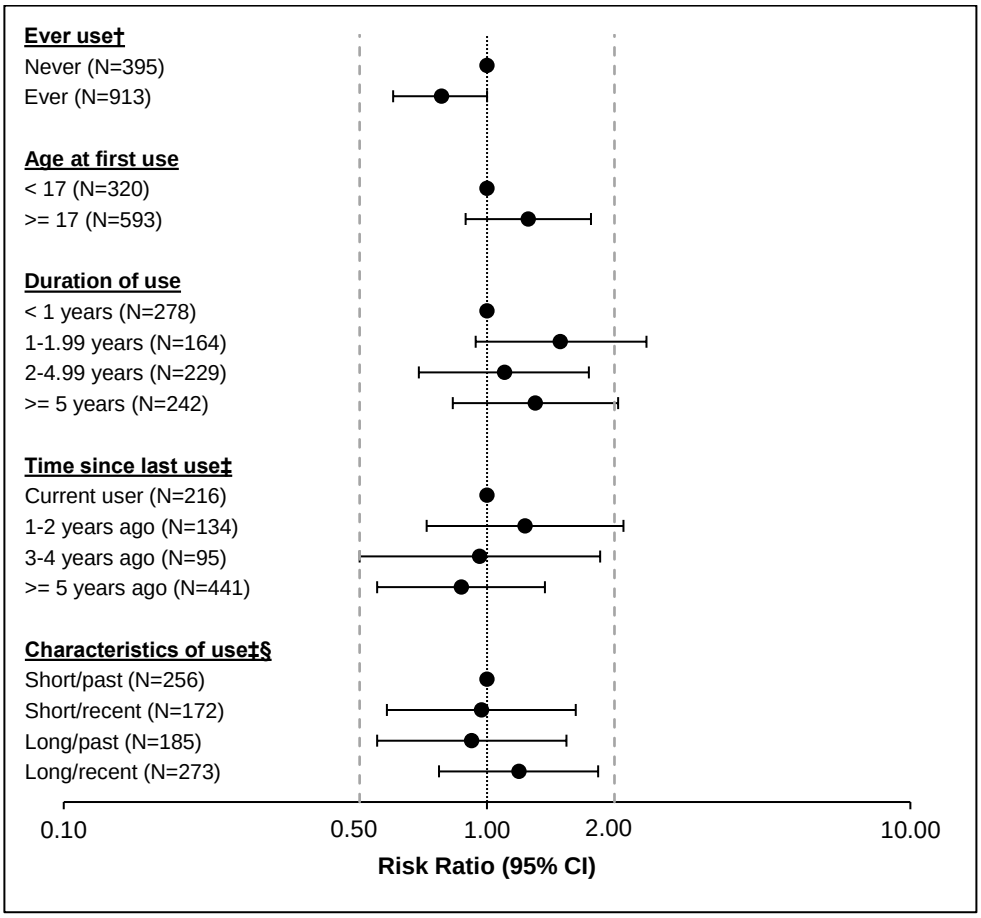
†The weighted estimate for Ever-use was weighted according to the covariate distribution of COC users; i.e., standardized mortality ratio [SMR] weighting was employed for this exposure.

‡Excludes n=33 participants who used both pill and mini-pill, for whom time since last COC use could not be distinguished.

§Duration of use was characterized as short (< 2 years) or long (≥ 2 years). Time since last use was characterized as recent (< 5 years) or past (≥ 5 years).

Abbreviations: IPW, inverse probability weighting; SMR, standardized mortality ratio; SELF, Study of Environment, Lifestyle, and Fibroids; CI, confidence interval; MVR, multivariable logistic regression; H-IUD, hormonal intrauterine device; BMI, body mass index.

Figure 6.2. IPW/SMR* associations between levels of combined oral contraceptive utilization and fibroid incidence among 1,308 fibroid-free women who enrolled in SELF in 2010-2012 (Detroit, MI, USA)



*Weighted (IPW/SMR) or Adjusted (MVR) for age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (≥24 months), time since last birth (<5 years, 5-9.99 years, ≥10 years and no birth), parity (nulliparous, 1-2 births, ≥3 births), BMI (≥30, remaining values according to tertile), education (Bachelor's degree or higher).

A total of n=198 women in SELF were censored, including n=136 COC users. Inverse probability of censoring weights were applied to upweight individuals most likely to have been censored who remained in the study. The model for probability of censoring included the exposure of interest (e.g., duration of use), all covariates used in the IPW/SMR models, with the addition of annual household income, baseline employment status, smoking history, and history of heavy gushing type bleeding.

Annual household income was missing for n=12 participants. Education was missing for n=1 participants. Time since Depo-Provera use was missing for n=1 participant.

†The weighted estimate for Ever-use was weighted according to the covariate distribution of COC users; i.e., standardized mortality ratio [SMR] weighting was employed for this exposure.

‡Excludes n=33 participants who used both pill and mini-pill, for whom time since last COC use could not be distinguished.

[§]Duration of use was characterized as short (< 2 years) or long (≥ 2 years). Time since last use was characterized as recent (< 5 years) or past (≥ 5 years).

Abbreviations: IPW, inverse probability weighting; SMR, standardized mortality ratio; SELF, Study of Environment, Lifestyle, and Fibroids; CI, confidence interval; MVR, multivariable logistic regression; H-IUD, hormonal intrauterine device; BMI, body mass index.

CHAPTER 7: DISCUSSION

This study was the first to investigate the association between fibroids and COC use in a prospective ultrasound-based study specifically designed to discover risk factors for uterine fibroids. This was also the first study to apply propensity-scored based methods to the problem of COC use and fibroids. Further, through the Study of Environment, Lifestyle, and Fibroids (SELF), we had access to high quality outcome data, detailed self-reported exposure data, and rich covariate data.

Our Aim 1 results revealed widespread HC utilization in this cohort, namely Depo-Provera utilization and extensive COC use. COCs were the most common HC type used, and were the most common first HC type used, even among women who began using HCs after all other types became available. Many women reported using COCs exclusively for relief from menstrual problems, including irregular bleeding and painful periods.

Our Aim 2 findings revealed that COC use or HC use in general might be protective against uterine fibroids. We report this finding cautiously, as when comparing never to ever users of any substance, there is always the potential for unmeasured confounding and limited public health utility of such estimates. However, our ever-never comparisons utilized standardized mortality ratio (SMR) weighting, which estimates the effect of treatment in the treated population, which may be more useful than findings from conditional estimates (i.e., our study explicitly seeks the answer to *"what if the COC users had used something different or nothing at all?"*). We were unable to endorse a protective or harmful association for age at first use, duration of use, or time since last use, among COC users. Associations found in previous literature may have been driven by the "Never" comparator group that was used for all levels of COC use. Our findings for these exposures may have been null in part because we chose to restrict our comparisons to women who had ever used COCs – comparing each level of COC use to the lowest level of use among users. We felt that this approach would be less biased and more meaningful than comparing each level of use to "Never" use, as is common practice in the existing literature.

Limitations

Our findings should be considered in light of our study's limitations. First, we did not have adequate statistical power to rule out small associations.[76] The estimates reported are measures of association from a single cohort study and should be considered in context of a broader literature base. Second, all exposure and covariate data with the exception of BMI were self-reported. Self-reported history of OC use, as collected by telephone interview, has been found to be reliable when compared to automated pharmacy dispensing data.[61] Third, we did not have exact duration of use estimates for COCs or H-IUDs and had to use limited available information to estimate duration of use for these HC types. Finally, women with prior clinical diagnosis were excluded from participating in SELF. While exclusion of women with clinical diagnosis of fibroids may have resulted in selection bias, only 5.87% (95% CI: 4.32, 7.42) of U.S. black women aged 23-35 in 2011-2013 had ever been diagnosed with uterine fibroids, and the possible selection bias is expected to be small (unpublished analysis).[77–79]

Our Aim 1 findings have the following, additional limitations. Reasons for HC use were self-reported, and women's definitions of heavy bleeding or irregular periods may vary. The data in our Aim 1 analyses were exclusively cross-sectional. All Aim 1 analyses relied on retrospectively recalled data, including the incidence figures for HC initiation and menarche.

Strengths

This study has several strengths. Ours was the first prospective, ultrasound-based study to examine the association between COC use and uterine fibroids in young, black women. SELF performed ultrasounds in all study participants, including at baseline and follow-up, regardless of symptoms or health care access. Incidence analyses were restricted to women without fibroids at baseline, strengthening the temporality[75] basis of our observed associations.

Use or propensity score (PS) based methods allowed for greater transparency and interpretability of our findings. We are the first study to examine COC use and uterine fibroid outcomes using PS-based methods. Prior studies used multivariable regression models and most often compared different levels of COC user to never users, which may not be the most relevant comparison, as women are unlikely to choose between a specific level of COC use (e.g., duration of use 3-4 years) and never using COCs at

all. Analogous to the counterfactual conundrum of smoking, we are unlikely to ever live in a world in which no women ever use COCs. Therefore, our within-COC users comparisons are likely to be more relevant to prescribers, patients, and policymakers.

Our Aim 1 analyses also had several strengths. First, we were able to assess HC use in a cohort of young, black women who came of age as five new HC options came to market: the implant, Depo-Provera, H-IUDs, the ring, and the patch. Second, we examined uptake of these new methods relative to contextual and individual factors: regulatory approval and menarche, respectively. Third, to our knowledge, we were the first to examine temporal sequencing of HC use, and to find that COCs are the most common first HC among women who use multiple HC types, even among those initiating HC use well after other types became available. Fourth, our examination of reasons for use was specific to each HC type, and participants could report multiple reasons for use for each type. Finally, we compared our findings to unpublished NSFG analyses, and considered the potential for selection bias. Given the similarity of our findings to national estimates, our findings are likely generalizable to the broader population of U.S. black women of similar age.

Public Health Implications

In this study of 1,693 young, black women living in Detroit, we found that ever use of COCs might be protective against uterine fibroids when compared to use of no hormonal contraceptives (HCs) at all. This protective association disappeared when comparing COC users to ever-users of any other HC type, suggesting that HCs, and not necessarily COCs, may be protective against uterine fibroids. The findings from Aim 2 contribute to the evidence base for oral contraceptive safety and effectiveness, allowing providers and patients to make better, evidence-based decisions regarding oral contraception in women with or without fibroids.

The emphasis of most public health research and interventions regarding HCs to date has been on pregnancy prevention. Our Aim 1 finding that a sizeable proportion of women used HCs for non-contraceptive purposes are reinforced by prior, nationally representative findings [11] and point to HCs as important for management of conditions that affect quality of life.

Future Research

Further research could explore clinical factors and patient preferences and values underlying HC selection, particularly for non-contraceptive purposes. If any HC use, and not necessarily COC use is protective against fibroids, then an additional non-contraceptive reason for HC use may become emergent. It is unclear how specific HC types compare to each other in terms of fibroid prevention, or how differing levels of COC use among COC users might confer differing levels of protection or harm, if any. Further studies are warranted in larger cohorts that would lead to estimates that are more precise and that build upon the methodological improvements represented by this study.

APPENDIX 1: CHAPTER 5 SUPPLEMENTAL TABLES

Appendix 1.1. Additional Methods

Appendix 1.2. Alternative Figure 3 (Age Time Scale)

Appendix 1.3. Alternative Figure 3 (Non-Cumulative)

Appendix 1.4. Results Stratified by Time between Menarche and SELF Enrollment

Appendix 1.5. Sankey Diagrams Stratified by Menarche Decade

Appendix 1.6. NSFG Data Analyses, Supplement to Discussion

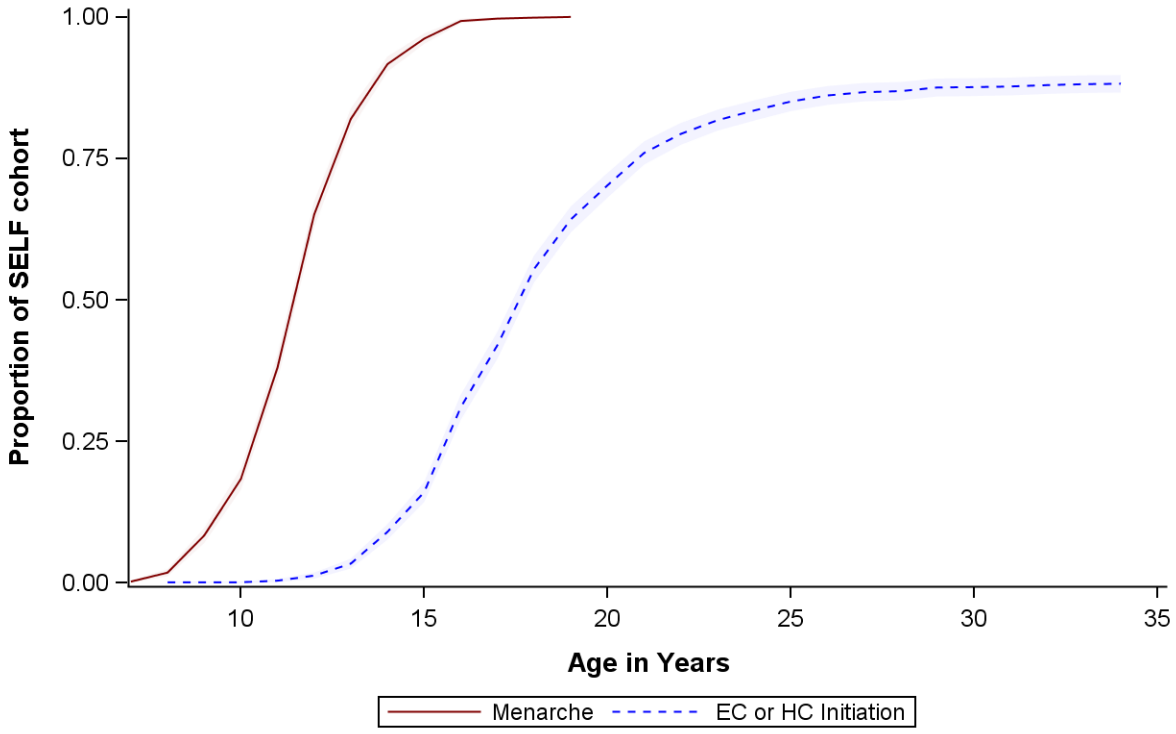
Appendix 1.1. Additional Methods

Figure 5.1. We used the following formula for the standard errors to construct confidence bands: SE = sqrt(p*(1-p)/n). Where n is number in denominator for the proportion (i.e., number of women who had reached menarche by that year and had not yet initiated that HC type).

Figure 5.3. We used the following formula for the standard errors to construct confidence bands: SE = sqrt(p*(1-p)/n). Where n is number in denominator for the proportion (in this case 1,693 women).

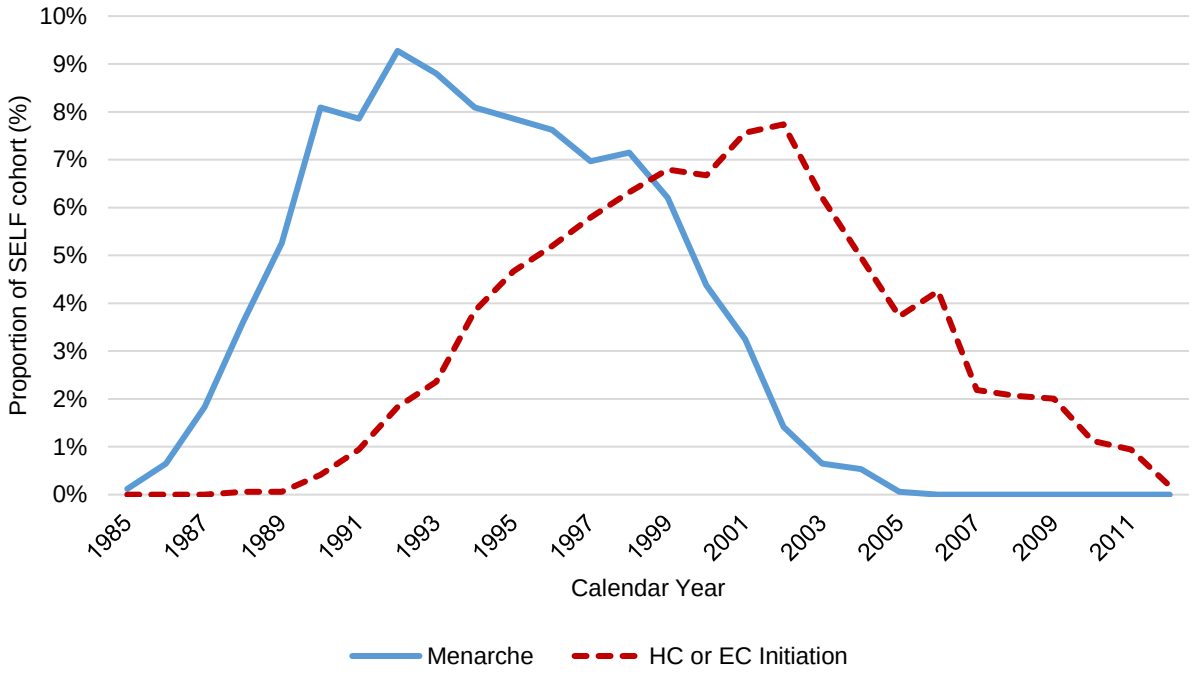
Appendix 1.2. Figure 5.3 (Age Time Scale)

Figure 1.2. Cumulative incidence curves (with 95% CIs) for menarche and HC/EC initiation, by year, in 1,693 women who enrolled in SELF in 2010-2012 (Detroit, MI, USA) in age time scale



Appendix 1.3. Figure 5.3 (Non-Cumulative)

Figure 1.3. Number of women reaching menarche and initiating first HC or EC use, by year, in 1,693 women who enrolled in SELF in 2010-2013 (Detroit, MI, USA)*†



*HC initiation counts in this figure include emergency contraception (n=82, 5.5% of depicted initiations).

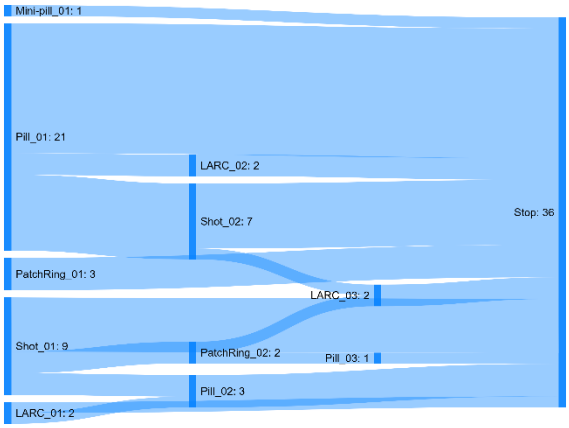
†Excludes n=5 women who reported HC initiation prior to menarche and n=1 individual for whom age at first HC use was missing.

Abbreviations: EC, emergency contraception; HC, hormonal contraceptive; SELF, Study of Environment, Lifestyle, and Fibroids.

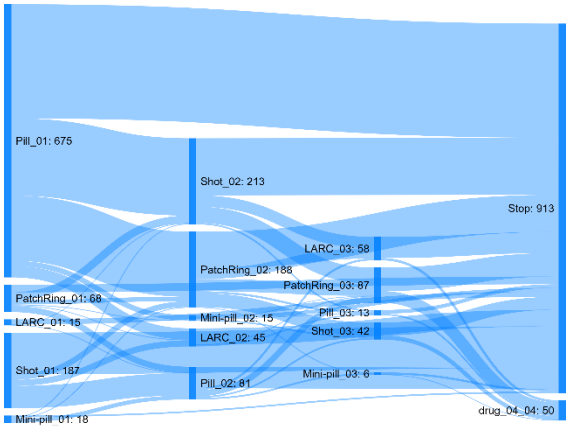
Appendix 1.4. Results Stratified by Time between Menarche and SELF Enrollment

Figures 1.4.(1-3). Sankey Diagram Stratified by Length of Observation Period (Time between Menarche and Cohort Entry)

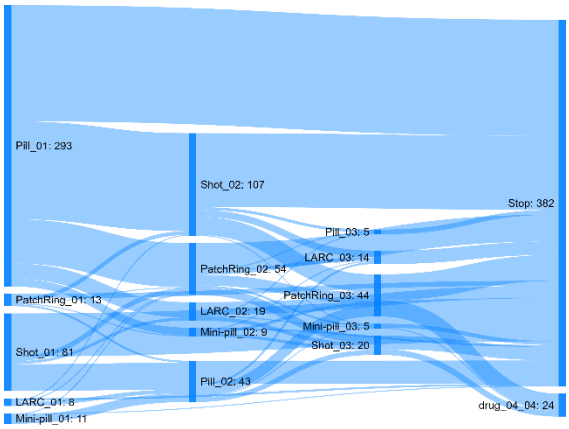
1. Window 1 (1-9 years)



2. Window 2 (10-19 years)



3. Window 3 (20+ years)



Tables 1.4.(1-5). Select Variables Stratified by Length of Observation Period (Time between Menarche and Cohort Entry)

1. Number of HCs used (Continuous)

Years between menarche and enrollment	*N*	*Minimum*	*Lower Quartile*	*Mean*	*Median*	*Upper Quartile*	*Maximum*
0-9 years	36	1.0	1.0	1.5	1.0	2.0	3.0
10-19 years	997	1.0	1.0	1.9	2.0	2.0	6.0
20+ years	422	1.0	1.0	1.9	2.0	2.0	6.0

2. Number of HCs used (Categorical)

n (%)	*1 HC Type*	*2 HC Types*	*3+ HC Types*
0-9 years menarche to baseline (n=36)	21 (58)	12 (33)	3 (8)
10-19 years menarche to baseline (n=997)	417 (42)	345 (35)	235 (24)
20+ years menarche to baseline (n=422)	172 (41)	150 (36)	100 (24)

3. Duration of HC use in years (Continuous)

Years between menarche and enrollment	*N*	*Minimum*	*Lower Quartile*	*Mean*	*Median*	*Upper Quartile*	*Maximum*
0-9 years	36	0	1.0	2.9	2.0	4.0	10.0
10-19 years	997	0	1.0	4.4	4.0	7.0	19.0
20+ years	422	0	2.0	5.9	5.0	9.0	19.0

4. Duration of HC use in years (Categorical)

n (%)	*< 3 y*	*3-4 y*	*5-6 y*	*7-8 y*	*> 8 y*
0-9 years menarche to baseline (n=36)	20 (56)	10 (28)	2 (6)	2 (6)	2 (6)
10-19 years menarche to baseline (n=996)	393 (39)	182 (18)	157 (16)	109 (11)	155 (16)
20+ years menarche to baseline (n=420)	128 (30)	61 (15)	60 (14)	52 (12)	119 (28)

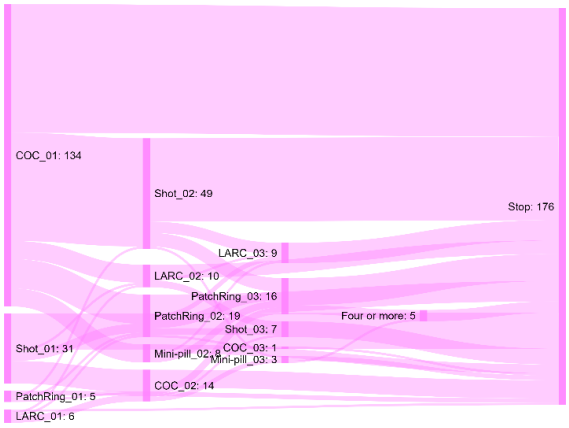
5. Reasons for HC use (Total)

n (%)	*Birth Control*	*Irregular Cycles*	*Heavy Bleeding*	*Menstrual Pain*
0-9 years menarche to baseline (n=36)	29 (81)	19 (53)	8 (22)	6 (17)
10-19 years menarche to baseline (n=997)	929 (93)	408 (41)	218 (22)	168 (17)
20+ years menarche to baseline (n=422)	399 (95)	160 (38)	97 (23)	81 (19)

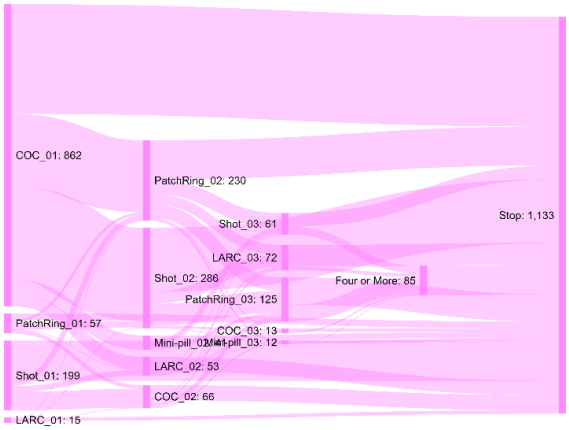
Appendix 1.5. Sankey Diagrams Stratified by Menarche Decade

Figures 1.5.(1-3). Sankey Diagrams Stratified by Menarche Decade

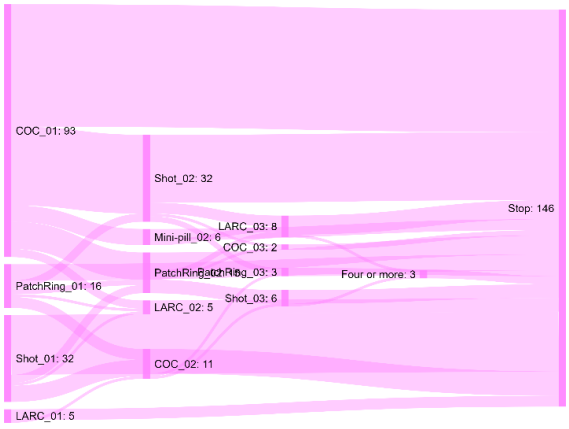
1. Menarche Before 1990



2. Menarche 1990-1999



3. Menarche after 1999



Appendix 1.6. NSFG Data Analyses, Supplement to Discussion

Data

Using publicly available data from the 2011-2013 National Survey for Family Growth (NSFG), in which women were asked whether they had ever been diagnosed with uterine fibroids, we produced national estimates for ever fibroid diagnosis among black women in the same age range as our cohort. We found that 5.87% (95% CI: 4.32, 7.42) of U.S. black women aged 23-35 in 2011-2013 had ever been diagnosed with uterine fibroids. With these same data, we also produced national estimates of current HC use by type in black women in this age range.

Using both existing, published NSFG estimates and our age- and race- specific NSFG estimates, we compared NSFG findings for ever- and current HC use in SELF and U.S. black women in the same age range. In SELF, 86% of participants had ever used HCs and 70% had used COCs. In the 2006-2010 NSFG, 86% of black women aged 15-44 had ever used HCs and 78% had used OCs [3]. Prevalences of current use at baseline for each HC type in SELF were similar to current use among black women of the same age (23-35 years) in the 2011-2013 NSFG (unpublished analyses), with Depo-Provera use slightly higher in the SELF cohort than in the NSFG (6% vs. 3%).

Comment

The generalizability of our findings should be considered in the context of the selection criteria of SELF, principally the age range, geographic location and the exclusion of women with clinically diagnosed fibroids.

While exclusion of women with clinical diagnosis of fibroids may have resulted in selection bias, only 5.87% (95% CI: 4.32, 7.42) of U.S. black women aged 23-35 in 2011-2013 had ever been diagnosed with uterine fibroids, and the possible selection bias is expected to be small. Inclusion of these women would most likely have strengthened our findings, namely that COCs were the most common HC type used, most often the first HC type used, and that menstrual problems were a common reason for HC use – as COCs are a common first-line treatment for symptomatic uterine fibroids [23].

With respect to the generalizability given the age range and geographic location of the SELF participants, we found that overall prevalences of HC and COC use in our cohort were similar to national estimates for reproductive aged black women. Given the similarity of the overall prevalences of HC use to

national estimates, our main findings are likely generalizable to the broader population of U.S. black women of similar age.

APPENDIX 2: CHAPTER 6 SUPPLEMENTAL TABLES

Appendix 2.1. Inclusion and exclusion flow diagrams for incidence analyses

Appendix 2.2. Detailed description of propensity score based methods

Appendix 2.3. Sample sizes and mean weights for prevalence models

Appendix 2.4. Sample sizes and mean weights for incidence models

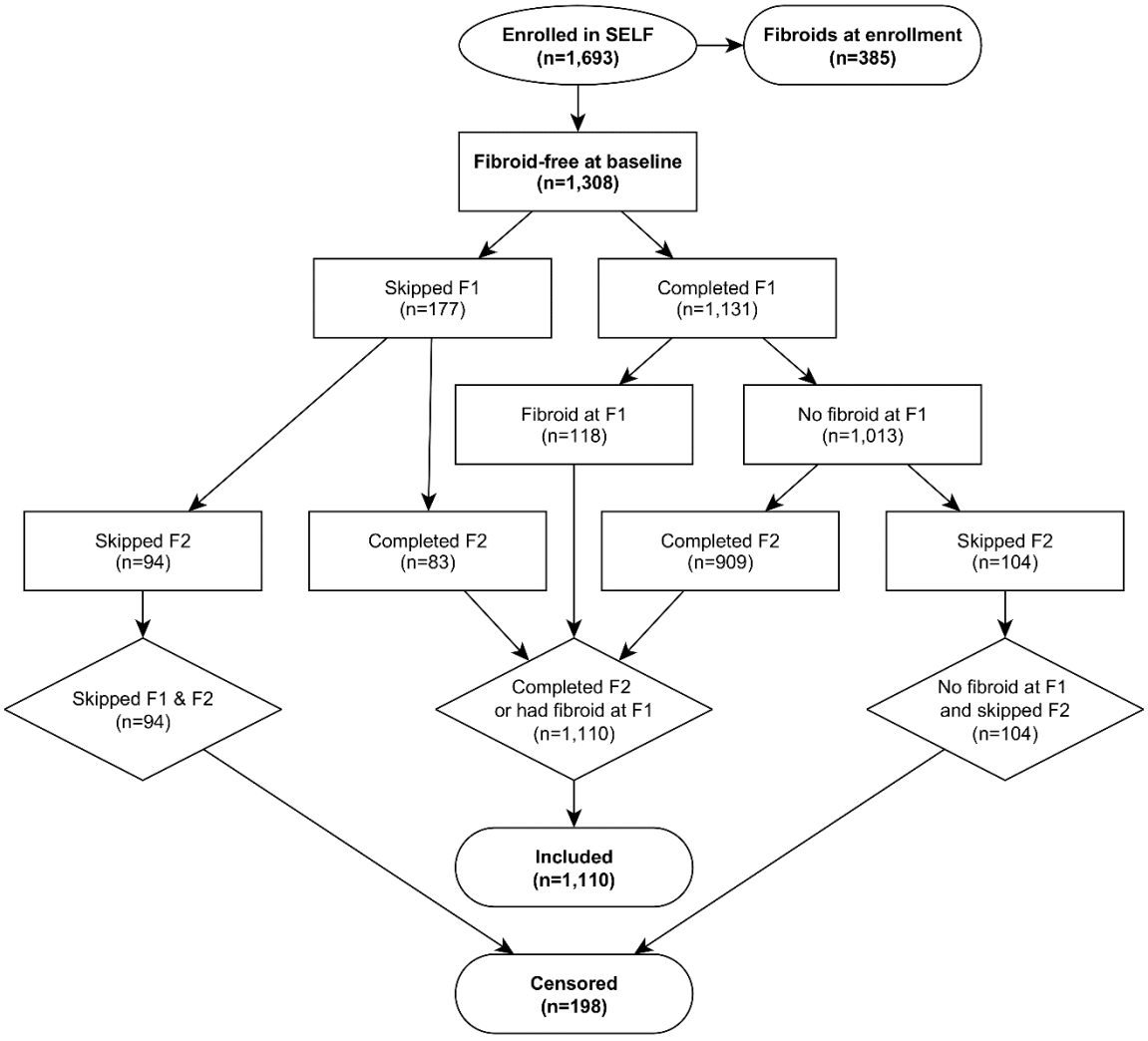
Appendix 2.5. Covariate balance & propensity score curves for prevalence models

Appendix 2.6. Covariate balance & propensity score curves for incidence models

Appendix 2.7. Sensitivity analyses

Appendix 2.1. Inclusion and exclusion flow diagrams for incidence analyses

Figure 2.1.1. Flow diagram for the analysis of the association between ever COC use and incident fibroids in the Study of Environment, Lifestyle, and Fibroids (SELF).



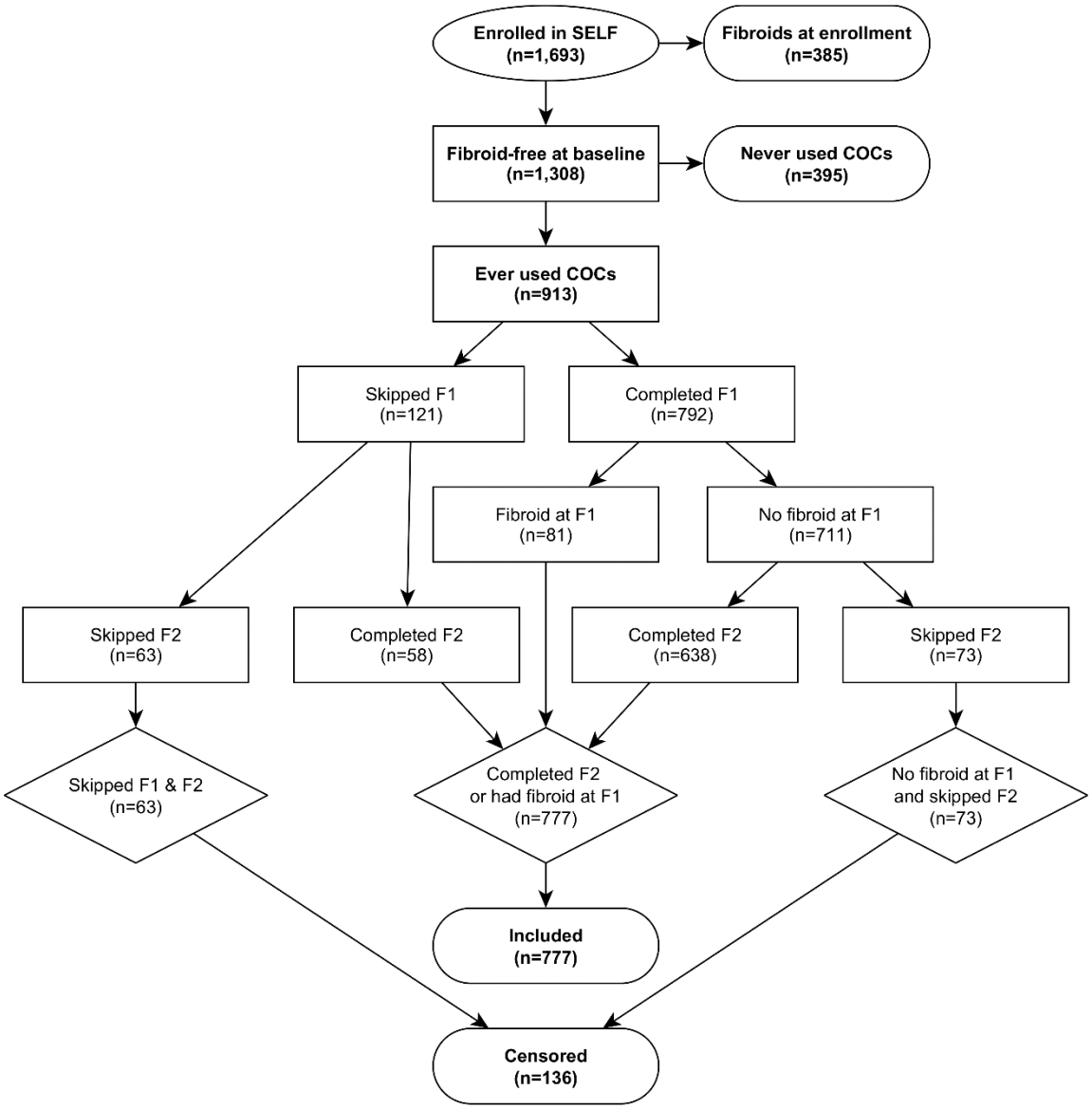
"Skipped" F1/F2 ultrasounds may indicate uterine surgery (n=0 visits), censoring due to hysterectomy (n=11 visits), or missing ultrasound data due to pregnancy or other reasons (n=24 visits).

Key: Oval, start; Pill, terminator (denotes final decision to include or exclude); Rectangle, process; Diamond, decision point.

Abbreviations: SELF, Study of Environment, Lifestyle, and Fibroids; F1, first follow-up ultrasound (~20 months); F2, second follow-up ultrasound (~40 months).

Appendix 2.1. Inclusion and exclusion flow diagrams for incidence analyses (cont'd)

Figure 2.1.2. Flow diagram for the analysis of the association of levels of COC use and incident fibroids among ever COC users in the Study of Environment, Lifestyle, and Fibroids (SELF).



"Skipped" F1/F2 ultrasounds may indicate uterine surgery (n=0 visits), censoring due to hysterectomy (n=8 visits), or missing ultrasound data due to pregnancy or other difficulties visualizing the uterus (n=18 visits).

Key: Oval, start; Pill, terminator (denotes final decision to include or exclude); Rectangle, process; Diamond, decision point.

Abbreviations: SELF, Study of Environment, Lifestyle, and Fibroids; F1, first follow-up ultrasound (~20 months); F2, second follow-up ultrasound (~40 months).

Appendix 2.2. Detailed Description of Propensity Score Based Methods

Variable selection for PS model

Substantive knowledge and directed acyclic graphs (DAGs) were used to determine which covariates to place into the propensity score and censoring models. Two experienced fibroid epidemiologists (DBB & QH) and one practicing OB/GYN (WKN) were consulted.

Propensity score estimation

Propensity scores were estimated by logistic regression and multinomial logistic regression for binary and non-binary exposures, respectively.[80,81] The following variables were included in all propensity score models: age in years (continuous), age at menarche (<11 years), Depo-Provera duration of and time since last use (never use, short/past, long/past, short/recent, long/recent), total implant and H-IUD duration of use (>24 months), time since last birth (<5 years, 5-9.99 years, >10 years and no birth), parity (nulliparous, 1-2 births, >3 births), BMI (>30, and remaining values were divided into tertiles specific to each analysis, as described in Chapter 4), and education (Bachelor's degree or higher).

Censoring weights estimation

The probability of remaining in the study conditional on covariates was estimated by logistic regression. For each model, we included the exposure of interest, all covariates used to estimate the PS for the exposure of interest, and annual household income (<$20,000, $20,000-49,999, and $\geq$$50,000), baseline employment status (not employed, employed <30 hours per week, employed $\geq$30 hours per week), smoking history (never smoked, former smoker, current smoker of <10 years, current smoker of $\geq$10 years) and history of heavy "gushing" type menstrual bleeding (yes/no).

Applying the PS method: PS weighting

Inverse probability (IP) weights were constructed for all exposures, and censoring. Standardized mortality ratio (SMR) type (see Chapter 4) weights were constructed for COC use. Use of weighting methods provided for clearer interpretation of findings, and the ability to intentionally define the hypothetical comparisons being made (i.e., average effect in the treated [ATT] versus average treatment effect [ATE]). These weights were easily combined with weights for missing outcomes.

For incidence analyses, the IP and SMR weights were multiplied by the inverse probability of censoring weights. The range (mean, max, min) of unstabilized and stabilized weights are available in

Appendix 2.3 for prevalence models and 2.4 for incidence models. Weights were not truncated. Covariate balance tables appear in Appendix 2.5 for prevalence models and 2.6 for incidence models.

Balance assessment

Absolute standardized differences (ASD) were used to assess covariate balance with an a priori threshold of 0.1. Propensity score distributions were examined before and after weighting to assess for positivity and covariate balance, respectively. Stabilized weights did not confer any benefit in terms of covariate balance, as ASDs were lower for the non-stabilized weights. Since stabilized and unstabilized weights inherently produce the same point estimates and confidence intervals when the final, weighted model is saturated (see Hernán & Robins, 2016, section 12.3, page 16), we report the covariate balance and findings for the unstabilized weights.[82]

Treatment effect estimation

Weighted log-binomial regression models were used to estimate prevalence ratios and risk ratios for uterine fibroids. No additional covariates were included in the weighted models. Confidence intervals for weighted models were generated using robust variance ("sandwich") estimator by use of the SAS REPEAT statement. Multivariable log-binomial regression models with the same covariates as used in the propensity score models were run for comparison. Sensitivity analyses were carried out to examine the potential influence of pregnancy and Depo-Provera use during follow-up on our findings. Multi-level outcome models were implemented with pregnancy and uterine fibroid incidence as a single joint outcome. To achieve this, we ran multinomial generalized logit models with robust variance estimation in PROC GEE. In a separate analysis, we added parity and Depo-Provera use during follow-up (as separate binary variables) to the IP and censoring weighted incidence models. Additionally, we examined fibroid incidence at 20-months in a multivariable logistic regression model. Finally, we re-defined the "Never" COC users group (in the prevalent and incident analyses for "Ever" COC use) to include only ever-HC users or only never-HC users to better understand how the composition of the "Never" group influenced our findings.

Interpretation of effect estimates

The prevalence and risk ratios computed for age at first COC use, duration of use, time since last use, and joint duration of and time since last use represent contrasts analogous to the average treatment

effect (ATE), i.e., the weights balance the covariate distribution to reflect the distribution among all COC users across all levels of COC use. For each comparison made, the corresponding counterfactual comparison to our weighted analysis was, *"if the entire sample of COC users had used at this level versus the referent level."* The prevalence and risk ratios computed for ever-use of COCs represent contrasts analogous to the average effect in the treated (ATT), i.e., the weights balance the covariate distribution to reflect the distribution among COC users (i.e., the "treated" group). The relevant counterfactual comparison to our weighted analysis was, *"if all COC users had not used COCs."*

Appendix 2.3. Sample Sizes and Mean Weights for Prevalence Models

Table 2.3. Sample Sizes and Mean Weights for Prevalence Models

Model	Age-adjusted MVR	Fully adjusted IPW/SMR	Fully adjusted MVR	IPW	S_IPW/SMRW
	N	N	N	Mean [Range]	Mean [Range]
Ever use	1,693	1,691*	1,691	NA	1.40 [1.00, 7.00]*
Age at first use	1,185	1,184	1,184	2.00 [1.19, 6.23]	1.00 [0.64, 2.15]
Duration of use	1,185	1,184	1,184	4.01 [1.67, 21.25]	1.00 [0.45, 5.77]
Time since last use	1,152	1,151	1,151	4.04 [1.11, 45.31]	1.00 [0.31, 9.86]
Characteristics of use	1,152	1,151	1,151	4.01 [1.58, 22.58]	1.00 [0.39, 6.50]

*SMR weights

Abbreviations: MVR, multivariable regression; IPW, unstabilized inverse probability weighted; S_IPW, stabilized inverse probability weighted; SMR(W), standardized mortality ratio (weighted).

Appendix 2.4. Sample Sizes and Mean Weights for Incidence Models

Table 2.4. Sample Sizes and Mean Weights for Incidence Models

Model	Age-adjusted MVR	Fully adjusted IPW/SMR**	MVR	IPW	S_IPW/SMRW	Censoring weight	Final weight**
	N	N	N	Mean [Range]	Mean [Range]	Mean [Range]	Mean [Range]
Ever use	1,110	1,098*	1,109	NA	1.39 [0.91, 6.37]*	1.00 [0.89, 1.33]	1.39 [0.87, 6.81]*
Age at first use	777	769	777	1.99 [1.18, 6.49]	1.00 [0.66, 2.27]	1.00 [0.87, 1.49]	1.98 [1.11, 6.58]
Duration of use	777	769	777	4.00 [1.65, 21.04]	1.00 [0.44, 5.58]	1.00 [0.88, 1.42]	3.99 [1.51, 22.89]
Time since last use	754	747	754	4.06 [1.09, 45.72]	1.01 [0.27, 8.79]	1.00 [0.89, 1.39]	4.04 [1.03, 43.83]
Characteristics of use	754	747	754	3.95 [1.49, 21.34]	0.99 [0.40, 5.75]	1.00 [0.88, 1.40]	3.93 [1.43, 21.23]

*SMR weights

**Includes censoring weights. For Ever use, final weights consisted of SMR multiplied by the censoring weight. For all other exposures, final weight consisted of IPW multiplied by censoring weight.

Abbreviations: MVR, multivariable regression; IPW, unstabilized inverse probability weighted; SMR(W), standardized mortality ratio (weighted); S_IPW, stabilized inverse probability weighted.

Appendix 2.5. Covariate Balance & Propensity Score Curves for Prevalence Models

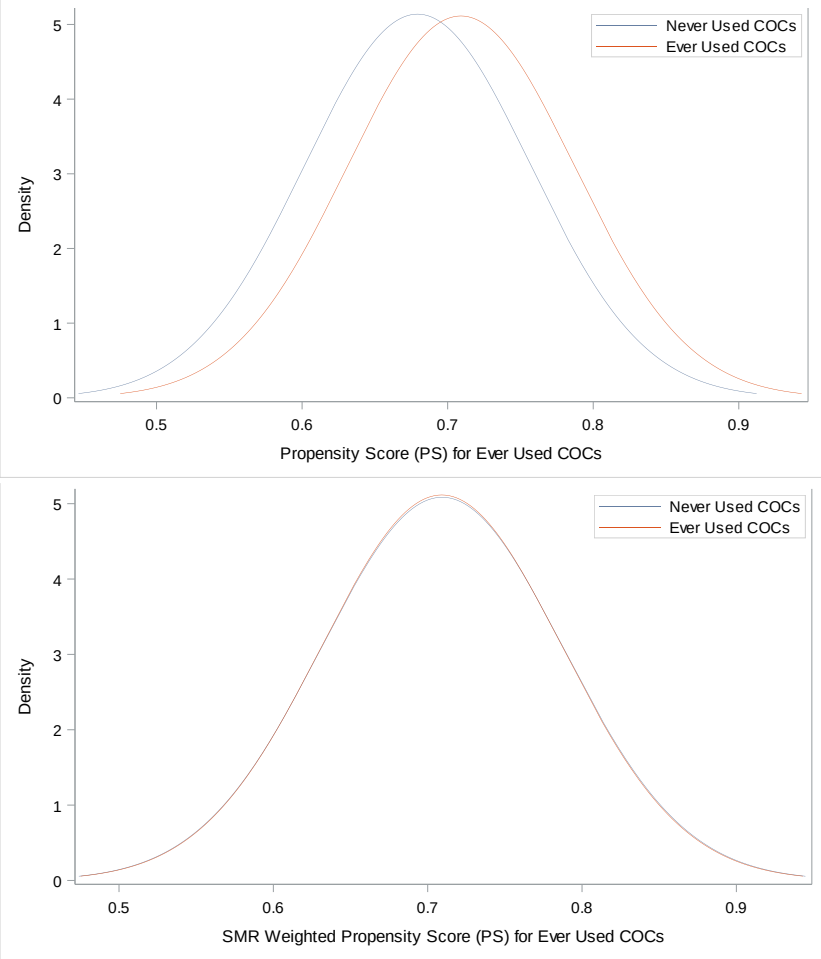
Exposure 1: Ever used COCs

Table 2.5.1. Covariate balance before and after SMR weighting for Ever/Never COC use among 1,696 SELF participants*†

	Unweighted			SMR Weighted		
Variable Name	**Never COCs**	**Ever COCs**	**ASD**	**Never COCs**	**Ever COCs**	**ASD**
Age at enrollment	27.99	29.06	0.31	29.06	29.06	0.00
BMI category	2.16	2.21	0.04	2.22	2.21	0.01
Depo-Provera use	1.27	1.18	0.06	1.18	1.18	0.00
H-IUD/Implant use	0.06	0.07	0.07	0.08	0.07	0.01
Bachelor's degree	0.22	0.31	0.21	0.31	0.31	0.01
Menarche age < 11 yrs.	0.18	0.18	0.02	0.18	0.19	0.01
Parity category	1.07	1.16	0.08	1.17	1.16	0.01
Time since last birth	1.18	1.15	0.04	1.12	1.15	0.02

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device; SELF, study of environment lifestyle and fibroids; SMR, standardized mortality ratio.

Figure 2.5.1. Unweighted & weighted PS distributions for Ever/Never Prevalence SMR weighted model.



Appendix 2.5. Covariate Balance & Propensity Score Curves for Prevalence Models (Cont'd)

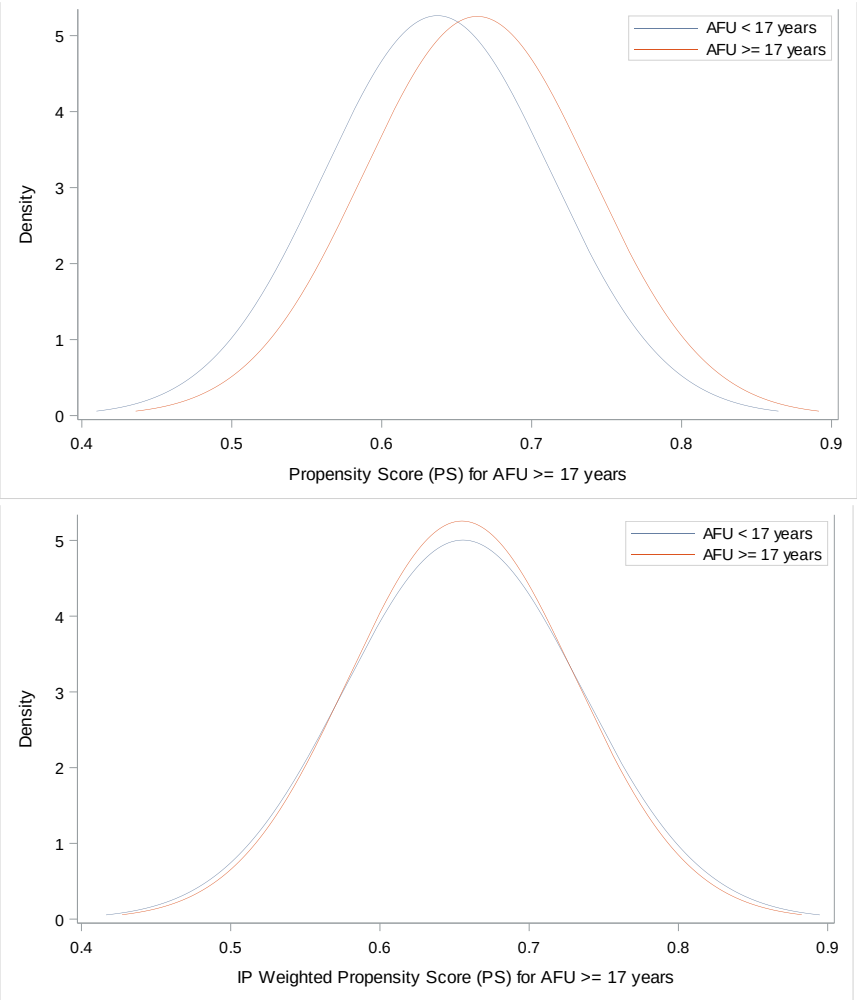
Exposure 2: Age at first COC use

Table 2.5.2. Covariate balance before and after IP weighting for Age at first COC use among 1,696 SELF participants*†

Variable Name	Unweighted			IP Weighted		
	AFU < 17 years	AFU ≥ 17 years	ASD	AFU < 17 years	AFU ≥ 17 years	ASD
Age at enrollment	29.03	29.08	0.01	29.08	29.05	0.00
BMI category	2.30	2.14	0.14	2.19	2.19	0.00
Depo-Provera use	1.34	1.09	0.17	1.19	1.18	0.00
H-IUD/Implant use	0.07	0.07	0.04	0.08	0.07	0.01
Bachelor's degree	0.23	0.35	0.27	0.31	0.31	0.00
Menarche age < 11 yrs.	0.20	0.18	0.06	0.18	0.18	0.00
Parity category	1.27	1.10	0.15	1.15	1.15	0.00
Time since last birth	1.13	1.15	0.03	1.13	1.14	0.01

Abbreviations: AFU, age at first use; ASD, absolute standardized difference; BMI, body mass index; COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device; SELF, study of environment lifestyle and fibroids; IP, inverse probability.

Figure 2.5.2. Unweighted & weighted PS distributions for Age at first COC use Prevalence IPW model.



Appendix 2.5. Covariate Balance & Propensity Score Curves for Prevalence Models (Cont'd)

Exposure 3: Duration of COC use

Table 2.5.3.a. Unweighted covariate balance table for Duration of COC use among 1,184 COC users in SELF*†

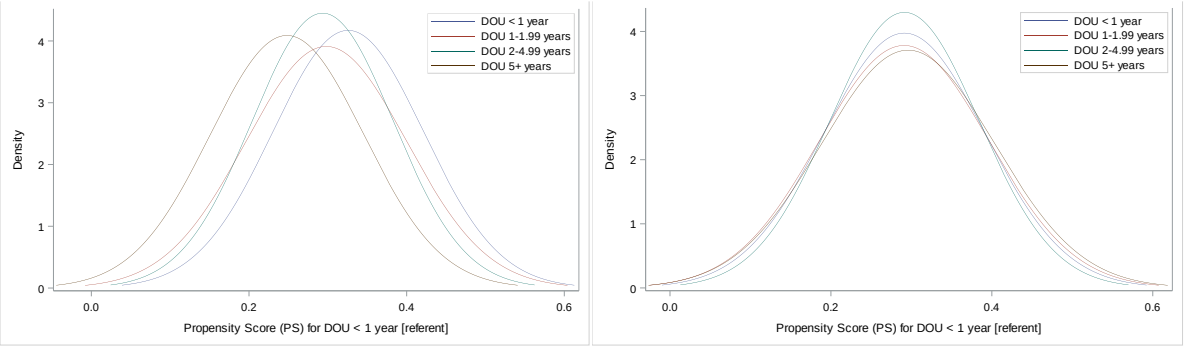
Variable Name	< 1 year (0)	1 - 1.99 years (1)	2 - 4.99 years (2)	5 + years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	28.54	29.12	28.87	29.75	0.17	0.10	0.36
BMIcategory	2.21	2.10	2.19	2.24	0.10	0.02	0.03
Depo-Provera use	1.45	1.26	1.25	0.75	0.11	0.12	0.47
H-IUD/Implant use	0.10	0.08	0.05	0.06	0.05	0.15	0.15
Bachelor's degree	0.19	0.27	0.31	0.45	0.18	0.27	0.58
Menarche age < 11 yrs.	0.20	0.17	0.18	0.19	0.08	0.06	0.03
Parity category	1.34	1.19	1.16	0.93	0.13	0.16	0.38
Time since last birth	1.01	1.16	1.18	1.25	0.18	0.20	0.28

Table 2.5.3.b. IP weighted covariate balance table for Duration of COC use among 1,184 COC users in SELF*†

Variable Name	< 1 year (0)	1 - 1.99 years (1)	2 - 4.99 years (2)	5 + years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	29.04	29.12	29.06	29.00	0.01	0.00	0.01
BMI category	2.21	2.19	2.20	2.19	0.01	0.00	0.01
Depo-Provera use	1.18	1.19	1.17	1.22	0.00	0.00	0.02
H-IUD/Implant use	0.08	0.07	0.07	0.09	0.01	0.01	0.02
Bachelor's degree	0.31	0.31	0.30	0.30	0.00	0.01	0.01
Menarche age < 11 yrs.	0.19	0.19	0.18	0.19	0.01	0.01	0.00
Parity category	1.13	1.15	1.16	1.15	0.01	0.01	0.01
Time since last birth	1.17	1.15	1.13	1.14	0.01	0.02	0.02

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device; IPW, inverse probability weighting; SELF, study of environment lifestyle and fibroids.

Figure 2.5.3. Unweighted & weighted PS distributions for duration of COC use prevalence IP weighted model.



Appendix 2.5. Covariate Balance & Propensity Score Curves for Prevalence Models (Cont'd)

Exposure 4: Time since last COC use

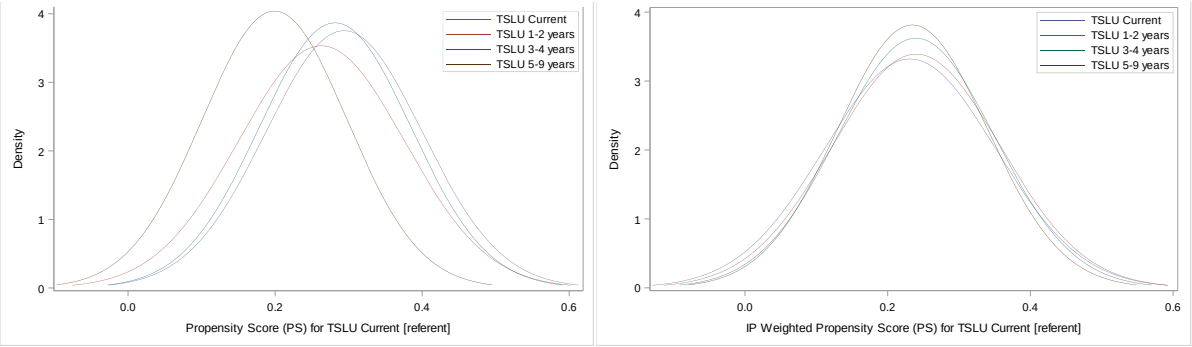
Table 2.5.4.a. Unweighted covariate balance table for time since last COC use among 1,184 COC users in SELF

Variable Name	Current users (0)	1-2 years (1)	3-4 years (2)	5+ years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	28.26	28.06	28.03	29.99	0.06	0.06	0.53
BMI category	2.12	2.19	2.21	2.23	0.06	0.08	0.10
Depo-Provera use	0.77	1.33	0.91	1.38	0.38	0.10	0.41
H-IUD/Implant use	0.05	0.04	0.10	0.09	0.04	0.22	0.16
Bachelor's degree	0.42	0.34	0.38	0.22	0.16	0.09	0.44
Menarche age < 11 y	0.16	0.19	0.19	0.19	0.06	0.08	0.08
Parity category	0.82	0.96	0.81	1.45	0.15	0.01	0.61
Time since last birth	1.23	1.19	1.22	1.09	0.05	0.02	0.17

Table 2.5.4.b. IP Weighted covariate balance table for time since last COC use among 1,184 COC users in SELF

Variable Name	Current users (0)	1-2 years (1)	3-4 years (2)	5+ years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	29.30	29.13	29.31	29.20	0.02	0.00	0.02
BMI category	2.27	2.16	2.22	2.21	0.04	0.01	0.03
Depo-Provera use	1.40	1.23	1.06	1.22	0.05	0.09	0.06
H-IUD/Implant use	0.07	0.07	0.07	0.08	0.00	0.00	0.01
Bachelor's degree	0.29	0.30	0.33	0.29	0.01	0.03	0.01
Menarche age < 11 y	0.17	0.18	0.20	0.19	0.00	0.03	0.02
Parity category	1.21	1.13	1.15	1.16	0.03	0.02	0.02
Time since last birth	1.17	1.18	1.17	1.15	0.00	0.00	0.01

Figure 2.5.4. Unweighted & weighted PS distributions for time since last COC use prevalence IP weighted model.



Appendix 2.5. Covariate Balance & Propensity Score Curves for Prevalence Models (Cont'd)

Exposure 5: Joint duration of and time since last COC use

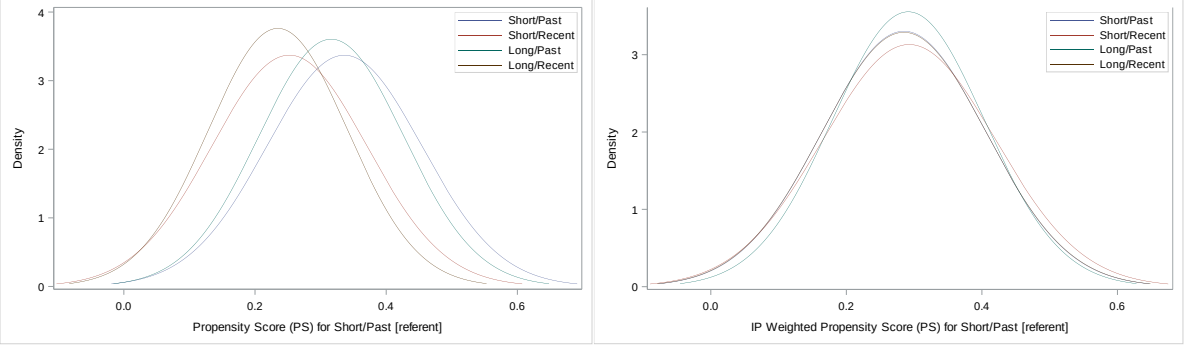
Table 2.5.5.a. Unweighted covariate balance table for joint duration of and time since last COC use among 1,184 COC users in SELF

Variable Name	Short/Past (0)	Short/Recent (1)	Long/Past (2)	Long/Recent (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	29.68	27.31	30.40	28.62	0.72	0.23	0.32
BMI category	2.20	2.11	2.27	2.18	0.08	0.06	0.02
Depo-Provera use	1.47	1.23	1.26	0.82	0.15	0.13	0.43
H-IUD/Implant use	0.10	0.08	0.07	0.05	0.09	0.13	0.21
Bachelor's degree	0.17	0.30	0.28	0.44	0.29	0.25	0.59
Menarche age < 11 y	0.20	0.17	0.18	0.18	0.09	0.05	0.05
Parity category	1.50	0.93	1.39	0.82	0.52	0.10	0.64
Time since last birth	1.03	1.12	1.16	1.27	0.10	0.14	0.27

Table 2.5.5.b. IP Weighted covariate balance table for joint duration of and time since last COC use among 1,184 COC users in SELF

Variable Name	Short/Past (0)	Short/Recent (1)	Long/Past (2)	Long/Recent (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	29.19	29.31	29.23	29.19	0.02	0.01	0.00
BMI category	2.22	2.14	2.24	2.21	0.03	0.01	0.01
Depo-Provera use	1.19	1.29	1.28	1.25	0.03	0.03	0.02
H-IUD/Implant use	0.08	0.07	0.07	0.07	0.01	0.00	0.01
Bachelor's degree	0.31	0.28	0.28	0.31	0.02	0.03	0.00
Menarche age < 11 y	0.19	0.18	0.20	0.19	0.01	0.01	0.00
Parity category	1.12	1.16	1.18	1.13	0.02	0.03	0.01
Time since last birth	1.19	1.15	1.11	1.19	0.02	0.04	0.00

Figure 2.5.5. Unweighted & weighted PS distributions for JOINT duration of and time since last COC use prevalence IP weighted model.



Appendix 2.6. Covariate Balance & Propensity Score Curves for Incidence Models

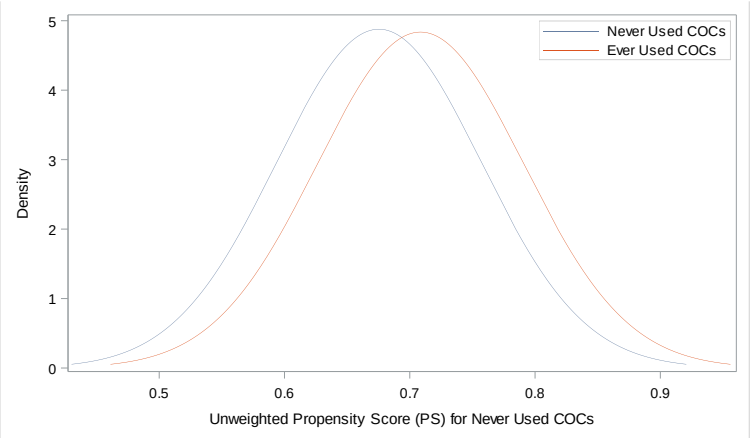
Exposure 1: Ever used COCs

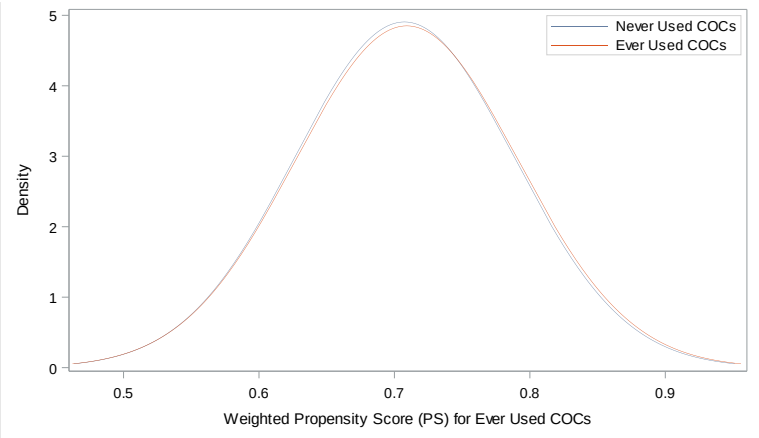
Table 2.6.1. Covariate balance before and after SMR weighting for Ever/Never COC use among 1,308 SELF participants*†

	Unweighted			SMR & Censoring Weighted		
Variable Name	**Never COCs**	**Ever COCs**	**ASD**	**Never COCs**	**Ever COCs**	**ASD**
Age at enrollment	27.57	28.73	0.34	28.65	28.75	0.02
BMI category	2.11	2.21	0.09	2.20	2.21	0.01
Depo-Provera use	1.41	1.28	0.08	1.30	1.26	0.02
H-IUD/Implant use	0.06	0.07	0.04	0.08	0.07	0.01
Bachelor's degree	0.20	0.28	0.18	0.27	0.28	0.03
Menarche age < 11 yrs.	0.16	0.18	0.03	0.17	0.17	0.00
Parity category	1.13	1.22	0.08	1.25	1.21	0.03
Time since last birth	1.12	1.07	0.06	1.01	1.08	0.06

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device; SELF, study of environment lifestyle and fibroids; SMR, standardized mortality ratio.

Figure 2.6.1. Unweighted & weighted PS distributions for Ever/Never Incidence Censor/SMR weighted model.





Appendix 2.6. Covariate Balance & Propensity Score Curves for Incidence Models (Cont'd)

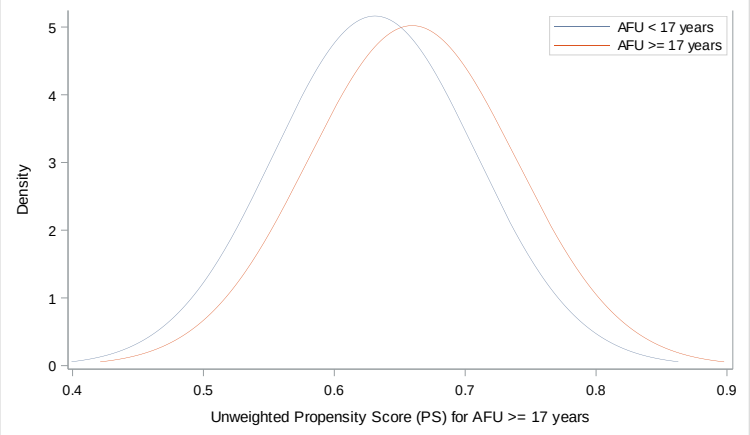
Exposure 2: Age at first COC use

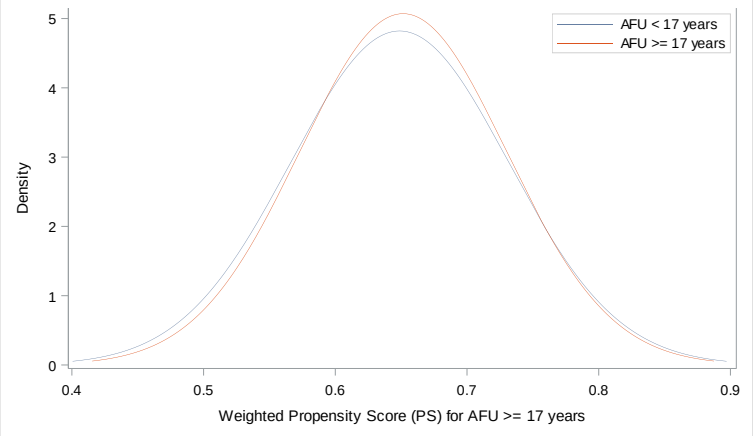
Table 2.6.2. Covariate balance before and after IP weighting for Age at first COC use among 1,308 SELF participants*†

Variable Name	Unweighted			IP & Censoring Weighted		
	AFU < 17 years	AFU ≥ 17 years	ASD	AFU < 17 years	AFU ≥ 17 years	ASD
Age at enrollment	28.64	28.78	0.04	28.79	28.66	0.03
BMI category	2.35	2.12	0.21	2.21	2.19	0.01
Depo-Provera use	1.40	1.22	0.11	1.30	1.26	0.01
H-IUD/Implant use	0.07	0.08	0.05	0.08	0.08	0.00
Bachelor's degree	0.21	0.32	0.26	0.28	0.28	0.01
Menarche age < 11 yrs.	0.18	0.17	0.02	0.17	0.17	-
Parity category	1.32	1.17	0.13	1.23	1.19	0.02
Time since last birth	1.05	1.08	0.04	1.06	1.07	0.01

Abbreviations: AFU, age at first use; ASD, absolute standardized difference; BMI, body mass index; COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device; SELF, study of environment lifestyle and fibroids; IPW, inverse probability.

Figure 2.6.2. Unweighted & weighted PS distributions for age at first COC use incidence Censoring/IP weighted model.





Appendix 2.6. Covariate Balance & Propensity Score Curves for Incidence Models (Cont'd)

Exposure 3: Duration of COC use

Table 2.6.3.a. Unweighted covariate balance table for Duration of COC use among 913 COC users in SELF*†

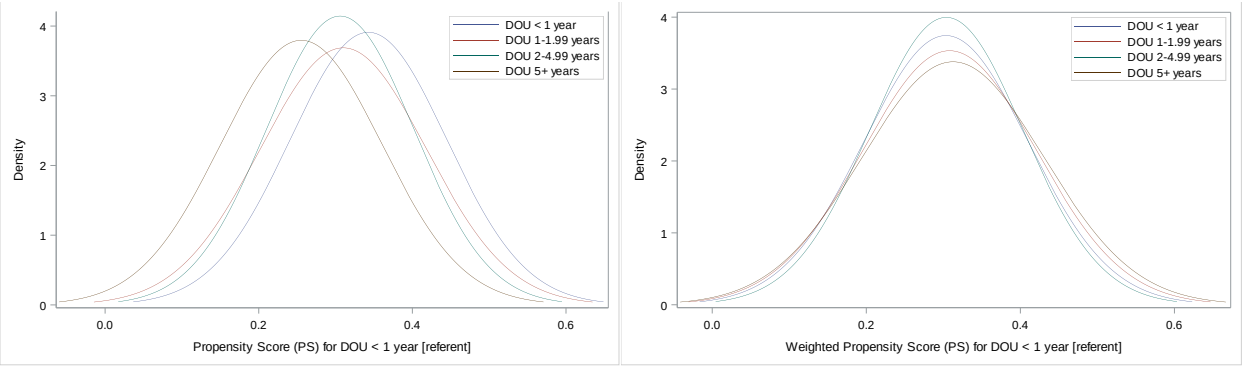
Variable Name	< 1 year (0)	1 - 1.99 years (1)	2 - 4.99 years (2)	5 + years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	28.27	28.63	28.67	29.38	0.10	0.12	0.33
BMIcategory	2.19	2.14	2.23	2.24	0.04	0.04	0.05
Depo-Provera use	1.56	1.37	1.36	0.83	0.12	0.12	0.48
H-IUD/Implant use	0.09	0.09	0.05	0.06	0.01	0.16	0.12
Bachelor's degree	0.17	0.26	0.28	0.43	0.24	0.28	0.59
Menarche age < 11 yrs.	0.19	0.18	0.16	0.17	0.04	0.09	0.06
Parity category	1.43	1.20	1.25	0.96	0.20	0.16	0.44
Time since last birth	0.92	1.10	1.11	1.17	0.21	0.23	0.29

Table 2.6.3.b. IP and censoring weighted covariate balance table for Duration of COC use among 1,184 COC users in SELF*†

Variable Name	< 1 year (0)	1 - 1.99 years (1)	2 - 4.99 years (2)	5 + years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	28.67	28.67	28.67	28.76	0.00	0.00	0.01
BMI category	2.22	2.19	2.21	2.21	0.02	0.01	0.01
Depo-Provera use	1.25	1.31	1.31	1.37	0.02	0.02	0.04
H-IUD/Implant use	0.08	0.08	0.07	0.10	0.00	0.03	0.04
Bachelor's degree	0.27	0.28	0.28	0.26	0.01	0.01	0.01
Menarche age < 11 yrs.	0.17	0.18	0.18	0.19	0.01	0.01	0.03
Parity category	1.17	1.26	1.20	1.27	0.04	0.01	0.05
Time since last birth	1.12	1.05	1.06	1.02	0.04	0.04	0.06

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; COCs, combined oral contraceptives; H-IUD, hormonal intrauterine device; IPW, inverse probability weighting; SELF, study of environment lifestyle and fibroids.

Figure 2.6.3. Unweighted & weighted PS distributions for duration of COC use incidence Censoring/IP weighted model.



Appendix 2.6. Covariate Balance & Propensity Score Curves for Incidence Models (Cont'd)

Exposure 4: Time since last COC use

Table 2.6.4.a. Unweighted covariate balance for time since last COC use among 913 COC users who were fibroid-free at enrollment in SELF

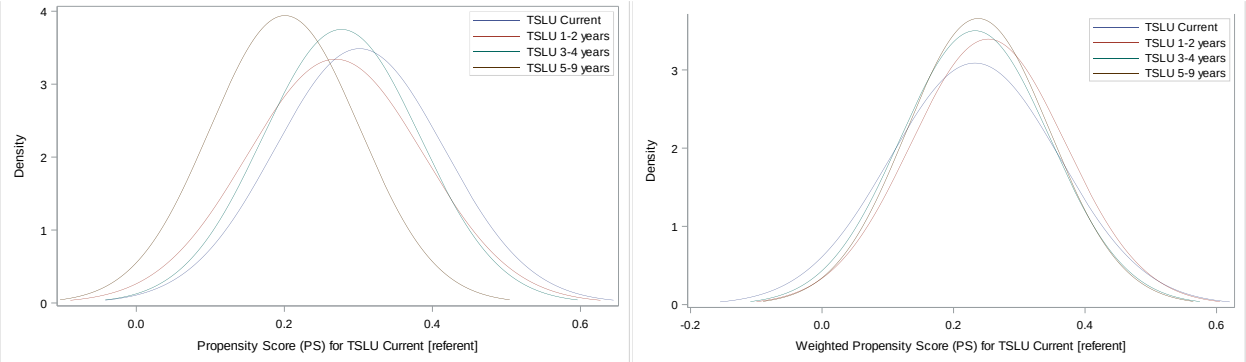
Variable Name	Current users (0)	1-2 years (1)	3-4 years (2)	5+ years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	27.88	27.56	27.64	29.77	0.10	0.07	0.56
BMI category	2.12	2.20	2.24	2.24	0.07	0.11	0.11
Depo-Provera use	0.81	1.50	0.99	1.50	0.46	0.13	0.45
H-IUD/Implant use	0.05	0.04	0.13	0.09	0.04	0.29	0.18
Bachelor's degree	0.38	0.32	0.29	0.20	0.11	0.17	0.38
Menarche age < 11 y	0.14	0.16	0.19	0.19	0.06	0.12	0.13
Parity category	0.88	0.99	0.84	1.53	0.11	0.04	0.62
Time since last birth	1.17	1.12	1.16	0.99	0.06	0.01	0.20

Table 2.6.4.b. Censoring Weighted and IPW Weighted covariate balance for time since last COC use among 913 COC users who were fibroid-free at enrollment in SELF

Variable Name	Current users (0)	1-2 years (1)	3-4 years (2)	5+ years (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	29.09	28.51	29.23	28.89	0.07	0.01	0.03
BMI category	2.32	2.20	2.20	2.23	0.05	0.04	0.04
Depo-Provera use	1.49	1.33	1.25	1.29	0.04	0.06	0.07
H-IUD/Implant use	0.08	0.10	0.07	0.08	0.02	0.03	0.01
Bachelor's degree	0.26	0.27	0.30	0.26	0.01	0.04	0.00
Menarche age < 11 y	0.16	0.15	0.20	0.18	0.01	0.03	0.02
Parity category	1.27	1.03	1.30	1.24	0.10*	0.01	0.01
Time since last birth	1.14	1.16	1.02	1.07	0.01	0.05	0.05

*0.09992

Figure 2.6.4. Unweighted & weighted PS distributions for time since last COC use incidence Censoring/IP weighted model.



Appendix 2.6. Covariate Balance & Propensity Score Curves for Incidence Models (Cont'd)

Exposure 5: Joint duration of and time since last COC use

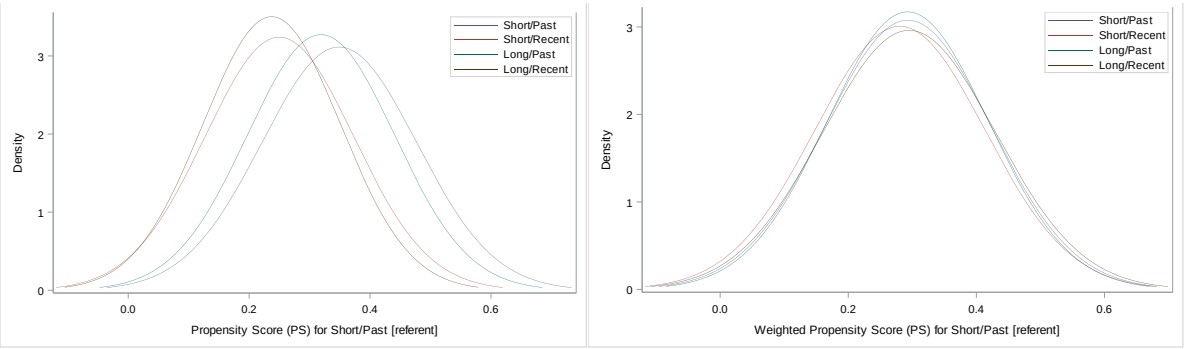
Table 2.6.5.a. Unweighted covariate balance for joint duration of and time since last COC use among 913 COC users who were fibroid-free at enrollment in SELF

Variable Name	Short/Past (0)	Short/Recent (1)	Long/Past (2)	Long/Recent (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	29.45	26.88	30.21	28.27	0.78	0.24	0.35
BMI category	2.20	2.14	2.30	2.19	0.05	0.10	0.00
Depo-Provera use	1.61	1.28	1.34	0.91	0.20	0.17	0.45
H-IUD/Implant use	0.11	0.08	0.07	0.05	0.08	0.12	0.22
Bachelor's degree	0.15	0.27	0.28	0.39	0.28	0.30	0.55
Menarche age < 11 y	0.20	0.17	0.18	0.15	0.05	0.03	0.12
Parity category	1.60	0.96	1.43	0.87	0.59	0.15	0.68
Time since last birth	0.93	1.07	1.08	1.21	0.16	0.18	0.32

Table 2.6.5.b Censoring Weighted and IPW Weighted covariate balance for joint duration of and time since last COC use among 913 COC users who were fibroid-free at enrollment in SELF

Variable Name	Short/Past (0)	Short/Recent (1)	Long/Past (2)	Long/Recent (3)	ASD 1 vs. 0	ASD 2 vs. 0	ASD 3 vs. 0
Age at enrollment	28.90	28.58	28.83	29.03	0.04	0.01	0.02
BMI category	2.21	2.20	2.29	2.23	0.01	0.04	0.01
Depo-Provera use	1.25	1.32	1.39	1.38	0.02	0.04	0.04
H-IUD/Implant use	0.08	0.09	0.07	0.08	0.01	0.02	0.01
Bachelor's degree	0.26	0.30	0.26	0.27	0.04	0.01	0.01
Menarche age < 11 y	0.18	0.16	0.18	0.19	0.03	0.00	0.01
Parity category	1.21	1.11	1.24	1.19	0.04	0.02	0.01
Time since last birth	1.11	1.15	1.01	1.13	0.03	0.05	0.01

Figure 2.6.5. Unweighted & weighted PS distributions for JOINT duration of and time since last COC use incidence Censoring/IP weighted model.



Appendix 2.7. Sensitivity Analyses

Appendix 2.7.1. Incidence Models Taking Into Consideration Depo-Provera Use and Pregnancy During Follow-Up

In these models, Depo-Provera use (>9 months duration) and parity (yes/no) during follow-up were added to the IPW and censoring weighted models, as well as the traditional log binomial regression models.

Table 2.7.1. Incidence Models Taking Into Consideration Depo-Provera Use and Pregnancy during Follow-Up

	MVR	IP/SMR Weighted
Ever use	**N=1,096**	**N=1,085**
Never (N=395)	Ref.	Ref.
Ever (N=913)	0.76 (0.59, 0.99)	0.79 (0.60, 1.03)
Age at first use (years)	**N=769**	**N=761**
< 17 (N=320)	Ref.	Ref.
≥ 17 (N=593)	1.22 (0.87, 1.72)	1.29 (0.91, 1.84)
Duration of use (years)	**N=769**	**N=761**
< 1 (N=278)	Ref.	Ref.
1-1.99 (N=164)	1.39 (0.89, 2.18)	1.43 (0.88, 2.31)
2-4.99 (N=229)	1.06 (0.68, 1.65)	1.04 (0.64, 1.67)
≥ 5 (N=242)	1.16 (0.76, 1.78)	1.21 (0.76, 1.93)
Time since last use (years)	**N=746**	**N=739**
Current user (N=216)	Ref.	Ref.
1-2 (N=134)	1.15 (0.72, 1.84)	1.10 (0.63, 1.91)
3-4 (N=95)	1.07 (0.62, 1.83)	0.95 (0.49, 1.84)
≥ 5 (N=441)	0.84 (0.57, 1.25)	0.77 (0.47, 1.28)
Characteristics of use	**N=746**	**N=739**
Short/past (N=256)	Ref.	Ref.
Short/recent (N=172)	1.13 (0.69, 1.85)	0.92 (0.53, 1.59)
Long/past (N=185)	0.82 (0.51, 1.30)	0.83 (0.49, 1.41)
Long/recent (N=273)	1.15 (0.77, 1.71)	1.17 (0.74, 1.86)

Appendix 2.7. Sensitivity Analyses (Cont'd)

Appendix 2.7.2. Mutli-Level Outcome Models for Parity during Follow-Up

In this sensitivity analysis, multinomial generalized logit models with robust variance estimation were run in PROC GEE. These findings represent the main IPW/Censoring weighted models, with a multi-level outcome that takes into account parity during follow-up.

Table 2.7.2. Mutli-Level Outcome Models for Parity during Follow-Up

Outcome	IPW/SMR Odds Ratio	95% CI Lower	95% CI Upper
Ever use versus never use (referent)			
No fibroid, Births	0.89	0.52	1.50
Fibroid, No births	0.74	0.48	1.15
Fibroid & Births	0.66	0.25	1.74
Age at first use <17 years versus ≤17 years (referent)			
No fibroid, Births	1.03	0.53	2.02
Fibroid, No births	1.71	0.90	3.25
Fibroid & Births	0.47	0.11	2.00
Duration of use 1-1.99 years versus <1 year (referent)			
No fibroid, Births	0.98	0.28	3.44
Fibroid, No births	1.39	0.39	4.97
Fibroid & Births	3.98	0.20	80.95
Duration of use 2-4.99 years versus <1 year (referent)			
No fibroid, Births	0.72	0.21	2.49
Fibroid, No births	0.98	0.30	3.20
Fibroid & Births	1.44	0.06	33.00
Duration of use ≥5 years versus <1 year (referent)			
No fibroid, Births	0.81	0.16	4.16
Fibroid, No births	1.13	0.34	3.78
Fibroid & Births	1.99	0.08	46.46
Time since last use 1-2 years versus <1 year (referent)			
No fibroid, Births	0.69	0.08	5.71
Fibroid, No births	1.14	0.22	5.75
Fibroid & Births	0.42	0.01	17.31
Time since last use 3-4 years versus <1 year (referent)			
No fibroid, Births	1.34	0.14	12.62
Fibroid, No births	1.09	0.20	5.99
Fibroid & Births	0.19	0.00	32.53
Time since last use ≥5 years versus <1 year (referent)			
No fibroid, Births	0.57	0.08	4.04
Fibroid, No births	0.67	0.21	2.12
Fibroid & Births	0.66	0.02	20.76
Long/Past versus Short/Past (referent)			
No fibroid, Births	0.85	0.11	6.42
Fibroid, No births	0.73	0.19	2.85
Fibroid & Births	0.97	0.05	18.79
Long/Recent versus Short/Past (referent)			
No fibroid, Births	1.16	0.21	6.48
Fibroid, No births	1.29	0.35	4.68
Fibroid & Births	1.06	0.09	12.91
Short/Recent versus Short/Past (referent)			
No fibroid, Births	2.62	0.64	10.68
Fibroid, No births	1.15	0.29	4.64
Fibroid & Births	1.05	0.04	25.59

Appendix 2.7. Sensitivity Analyses (Cont'd)

Appendix 2.7.3. Incidence Models for Fibroids at First Follow-Up (~20 months)

Traditional log binomial regression models for fibroid status at first follow-up time point, using the same adjustment set as the main analyses. Censored individuals (n=198 SELF participants; n=136 COC users) were excluded from this sensitivity analysis.

Table 2.7.3. Incidence Models for Fibroids at First Follow-Up (~20 months)

	MVR Risk Ratio (95% CI)
Ever use	**N=1,130**
Never	Ref.
Ever	0.85 (0.58, 1.23)
Age at first use	**N=792**
< 17 years	Ref.
≥ 17 years	1.14 (0.72, 1.80)
Duration of use	**N=792**
< 1 years	Ref.
1-1.99 years	1.44 (0.74, 2.77)
2-4.99 years	1.46 (0.80, 2.64)
≥ 5 years	1.33 (0.73, 2.42)
Time since last use	**N=767**
Current user	Ref.
1-2 years	0.87 (0.46, 1.67)
3-4 years	0.93 (0.47, 1.85)
≥ 5 years	0.62 (0.37, 1.02)
Characteristics of use	**N=767**
Short/past	Ref.
Short/recent	1.08 (0.54, 2.17)
Long/past	0.78 (0.41, 1.50)
Long/recent	1.52 (0.89, 2.59)

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