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# Progesterone-Only Oral Contraceptive Pill, Breast Cancer, Heart Disease, and Stroke

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PROGESTERONE- ONLY ORAL CONTRACEPTIVE PILL, BREAST CANCER, HEART  
DISEASE, AND STROKE

by

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## ABSTRACT

There is evidence from earlier studies that oral contraceptive pills may be a risk factor for certain chronic diseases, including heart disease, stroke, and breast cancer. Previous studies mainly focus on the estrogen component of combined (estrogen+ progestin) oral contraceptives (COCs) due to their popularity. This focus limits our understanding of progestin-only contraceptives and its relationship to commonly occurring chronic diseases. To provide insight into alternative methods of oral contraception, this dissertation explores the relationship between progestin-only oral contraceptive (POC) pills and heart disease, stroke, and breast cancer. We hypothesize that women using POCs are less likely to have certain chronic diseases compared to women using COCs.

We conducted a retrospective cohort study using Medicaid data for 2000-2013 to (1) examine trends in OC medication use over time, (2) determine the association between the type of OC use and breast cancer mortality, and (3) compare estrogen+ progestin formulations with progestin-only regimens to understand the association of OC types and cardiovascular disease. We found an increasing trend of POC and POC+COC use in the Medicaid population from 2000 to 2013, which could reflect increased knowledge of POCs. However, COCs are still prescribed much more frequently than any other contraceptive method.

In further investigations, we found evidence that women using POCs had a significantly reduced risk of breast cancer mortality whereas women using COCs had an increased risk. Similarly, POCs decreased the risk of heart disease compared to COC use. Conversely, the relationship between POCs and stroke was more abstruse. All analyses were stratified by race to explore differences in oral contraceptive use among African American and European American

women in the South Carolina Medicaid registry. We aimed to study a population that is typically under-represented in the scientific literature.

The findings of this study suggest that there may be beneficial effects of using POCs in lieu of COCs to reduce estrogen-related complications of oral contraceptives. Additional studies are required to provide conclusive evidence.

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## CHAPTER I

### INTRODUCTION

#### 1.1 Study Objective

The objective of this dissertation is to examine the relationship between oral contraceptive use, progesterone-only or combined oral contraceptive pills, and the subsequent incidence of heart disease and stroke, as well as breast cancer mortality, in a cohort of South Carolinian women participating in Medicaid, a low-cost health care coverage program for individuals meeting income guidelines. This study will provide additional information about various types of oral contraceptives and further explain the benefits and drawbacks of progesterone-only contraceptive pills.

#### 1.2 Statement of the problem

In the United States (US), chronic diseases have a substantial effect on women's overall health and quality of life. Cardiovascular diseases (CVDs) and cancer are the leading causes of mortality in females living in South Carolina (SC) and the US (ISCD, 2015). The predominant causes of CVD deaths are coronary heart disease (CHD) and stroke (Go *et al.* 2013), and of cancer deaths: lung and breast cancer (Torre *et al.* 2015). A reduction in these fatalities is of great public health importance.

Public health researchers aim to control chronic diseases by early detection and prevention methods, and by addressing etiologic causes of the problem. CVDs are one of the most preventable diseases (Labarthe, 2011) that continue to plague our society. To improve the health of families, we must promote healthy lifestyles and reduce population exposures to adverse agents. The role

of oral contraceptives (OCs) as a possible risk factor for CHD, stroke, and breast cancer incidence and mortality has long been demonstrated in estrogen-dominant OCs (Marchbanks *et al.*, 2002; Bousser *et al.*, 2000; Wynn, 1991).

Current guidelines conclude that contraceptive's benefits outweigh the potential risks (FSRH, 2011; Bousser *et al.*, 2000); yet, these recommendations neglect to thoroughly consider demographic populations that are at a higher risk for CVD and cancer death. Furthermore, risk factors for chronic diseases, such as unhealthy diet, sedentary behavior, obesity, and raised blood glucose, are becoming more prevalent in our society and may cause women to suffer greater disease burden in the future (Shufelt *et al.*, 2009). Studies show that low-income women are more likely to experience a negative contraceptive counseling experience, be pressured by a healthcare clinician to use a contraceptive method, and to feel that the family planning service was not tailored to their needs and preferences (Becker *et al.*, 2003; Yee *et al.*, 2011). This perception may cause patients to share less information with their doctor and increase the chances of combined OC use in women who smoke, partake in less physical activity, and engage in other unhealthy behaviors. The prevention of unintended pregnancies through the use of estrogen-containing OCs may have adverse implications for the incidence and treatment of CVD and breast cancer. Thus, it is important to identify high-risk populations that may benefit from an alternative contraceptive method.

The effects of exogenous estrogen on the body's system have been studied in much greater detail than the effects of exogenous progesterone. The estrogen component of OCs is associated with nausea, vomiting, and several more severe adverse drug reactions (ADRs): an excess risk of venous thromboembolism (VTEs) (4.3- 16/ 100,000 woman-years) (FDA, 2015), cardiovascular death (1.5-4.8/ 100,000) (WHO 1996; Peck, 2012), and an increase risk breast cancers (Vesna *et al.*, 2010). Among smokers, the excess risk associated with combined OCs is 400/100,000 woman-

years (Peck, 2012). Total medical ADRs are estimated to cause approximately 1.5 million hospitalizations and 118 000 deaths in the US (IoM, 2006).

Calculating the intermediate and long-term events related to the use of OCs is challenging. Health care professionals and federal governing agencies have difficulty detecting, reporting, and/or analyzing ADRs related to drug use due to incomplete or inaccurate data, cost, and non-standardized source of data (Darzen, 2007; Thomas *et al.*, 2003) In addition, external factors, such as biological and environmental factors, may modify the relationship between OCs and the incidence, prevalence, and death rate of females (STAT, 2000).

The relationship between OC exposure and certain chronic disease outcomes have sparked research around combined estrogen + progestin OCs. The majority of studies support exogenous estrogen's potential to increase the risk of CVDs and breast cancer (Murphy, 2011; Pezzini *et al.*, 2007). To our knowledge, no studies shown a negative effect of exogenous progesterone on breast cancer and few studies have examined progesterone-only contraceptive pills (POCs) and these chronic disease outcomes.

A viable alternative to estrogen-containing pills for preventing unwanted pregnancies is critically important for women who already suffer from elevated risks. Healthy People (HP) 2020 aims to increase the proportion of sexually active women who receive reproductive health services to approximately 90% by 2020 (HP 2020, 2015), which, if successful, will further increase the number of women receiving OCs. With the risk of cardiovascular disease and breast cancer increasing, it is important to understand the impact that combined OC pills may pose on health for high-risk groups; estrogen-free pills may be a safer alternative.

In the US, vulnerable populations include women of certain age groups, race/ethnicity, geographic demarcations, urban-rural classifications, and low socioeconomic (SES) status. In terms of OC use, it is important to target women older than 35; minorities; the southeastern region of the

US; rural populations; and women who lack access to education, economic stability, safe neighborhoods, and to adequately built environments (Cole *et al.*, 2007).

SC is a “region of extreme disparities,”(Levin *et al.* 2001) located in the southeastern part of the US. Despite a recent 34% drop in CVD mortality rates, SC has a higher age-adjusted mortality rate than the US (Khosrow, 2010). In addition, SC has more than twice the percentage of African Americans (AAs) than the US overall (US Census Bureau, 2015). Studying SC can help us understand why AAs are 30% more likely to die from heart disease than the European American (EA) population (Khosrow, 2010). As a part of the “Stroke Belt,” SC has a higher percentage of stroke among adults compared to other states (3.1% vs. 2.4%, excluding people in long-term facilities) (Khosrow, 2010). Using the SC Medicaid cohort will improve our assessment of vulnerable populations and help us determine if the type of OC women use poses a great risk for breast cancer, stroke (Guidetti *et al.*, 2014) and CHD (US Census Bureau, 2015; Cunningham *et al.*, 2013; Boan *et al.*, 2014; Cooper *et al.*, 2000).

### 1.3 Significance

Approximately 70 million women in the US are in their childbearing years (15-44) (Dye, 2008) and more than 99% of women participating in sexual intercourse have used at least one contraception method; contraceptive pills and sterilization are the most common types of methods used (Rothman, *et al.*, 2008; Glaser *et al.*, 2009). With the high demand of OCs, researchers must continue to examine healthier alternatives to estrogen-containing OC pills for pregnancy prevention and family planning.

The associations between combined oral contraceptive pills (COCs) and breast cancer (Nguyen, *et al.*, 2007; Kumle *et al.*, 2002), venous thromboembolic events (Maxwell *et al.*, 2014; Spencer, *et al.*, 2009) , high blood pressure (FSRH, 2011), a temporary reduction in fecundity (FSRH, 2011), depression (FSRH, 2011), nausea (FSRH, 2011; Spencer, *et al.* 2009) headaches

(Spencer, *et al.*, 2009), heart attack (FSRH, 2011), myocardial infarction (MI) and stroke (Spencer *et al.*, 2009) have been established previously. To our knowledge, the relationship between POCs, breast cancer, and CVDs in vulnerable groups has not yet been established in the US. A recent systematic review of progestin and breast cancer risk published after the 1999 IARC review showed no overall association of progestin and breast cancer (Samson *et al.*, 2016).

The emphasis on primary prevention in CVD and cancer health is essential for both the improvement of population health and the advancement of the epidemiologic field. This dissertation will provide information to fill gaps regarding POC use and specific chronic diseases among underrepresented groups in SC. This research will consider the benefits and risks associated with the use of POC for the primary prevention of stroke, CHD and breast cancer for an at-risk population. Findings may guide us to formulate more appropriate reproduction and sexual health strategic plans for high-risk populations.

#### **1.4 Specific Aims**

SC Medicaid administrative enrollment and claims data (2000-13) from the Revenue and Fiscal Affairs Office will be used to investigate the association between POCs and breast cancer mortality, as well as stroke and CHD incidence, respectively. In 2010, the Medicaid Program provided comprehensive health care coverage to approximately 20% of SC residents (MLTSS, 2015); Medicaid is one of SC's largest insurance providers.

The dataset includes information on women between the ages of 18 and 65 during a 13-year period and their demographic, medical and pharmacy claims. Medicaid is a comprehensive and rich source of critical information that will allow us to study the following three specific aims:

- ✓ Aim I: Describe and compare secular trends between COCs and POCs among low-income populations by race/ ethnicity
  - ✓ Aim II: Evaluate the relationship between breast cancer mortality and POCs by race/ ethnicity
  - ✓ Aim III: Evaluate the relationship between heart disease and stroke incidence with POCs by race/ ethnicity
- 

### 1.5 Summary

There is an increasing number of Americans suffering from contraindications of combined OCs. These contraindications are more prevalent in underserved populations (i.e. hypertension, diabetes, tobacco use, cancer) (Adler *et al.*, 2002) and can be ignored when prescribing a contraceptive method due to miscommunication between health care providers and patients (Yee *et al.*, 2011; Isaacs *et al.*, 2003; Becker *et al.*, 2003). Although the general population may not suffer from current prescription practices, many will have an increased risk of ADRs. OCs may lead to severe arterial hypertension in approximately 5% of women using combined preparations (Olatunji and Soladoye, 2010) and will elevate blood pressure in the majority of women (Woods, 1988). This study may influence clinician prescription practices related to OC use for high-risk groups.

Identifying potential risk factors for the predominant causes of death for women will allow epidemiologists to initiate population-wide scale preventive interventions to reduce the burden of disease caused by certain background conditions. With the high burden of chronic diseases in the southeastern part of the US, SC is an ideal environment to study racial disparities associated with the type of contraceptive pill used, breast cancer, and CVD incidence and mortality. Focusing on preventive approaches to protect healthy individuals from developing CVD or cancer may be an effective means of reducing the burden and cost of implementing multiple methods of treatment.

The ultimate goal of this epidemiologic research is to provide an extensive and rich source of support for women's health that will positively impact societal health. This dissertation aims to inspire more research in POCs to determine which populations require this drug. More comprehensive oral contraception guidelines are necessary to offer a safe- and effective method of pregnancy prevention that does not contribute to chronic disease rates for high-risk groups. These findings may provide a pertinent piece of the puzzle to contraception health.



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## CHAPTER II.

### LITERATURE REVIEW

“An ounce of prevention is worth a pound of cure.” - Benjamin Franklin

#### 2.1 History of Oral Contraceptives

Oral contraceptives (OCs) equipped women with an effective means to prevent unwanted pregnancies and establish autonomy in their relationships. Many people acknowledge the political and social obstacles that preceded the recent and revolutionary advancements in women’s health. Prior to the 1920s, the female reproductive cycle was considered sporadic and uncontrollable (Viterbo, 2004) and many depended on unreliable means of pregnancy prevention. In addition to the general unawareness of women’s health, females were not allowed to make decisions or control their bodies. In fact, the United States (US) Comstock Act of 1873 criminalized contraceptives and the dissemination of birth control information (Cox, 2015). This act was a barrier to understanding many components of family planning and women’s health.

Margaret Sanger challenged these laws by opening America’s first birth control clinic in 1916 and educating women about pregnancy prevention (Cox, 2015). She is considered a pioneer in the American birth-control movement. Among the higher socioeconomic classes, the principal methods of contraception were the rhythm method, requiring abstinence from sexual intercourse during the “unsafe period,” or two weeks after menstruation (Viterbo, 2004) and the use of diaphragms, requiring internal fitting by doctors. Among lower classes, performing a self-administered abortion was not uncommon; it was a less costly alternative to prevent additional children (Cox, 2015).

Sanger advocated that a simpler and cheaper form of birth control would allow women to have greater access to birth control and therefore, more control of her own body. She believed: “No woman can call herself free until she can choose consciously whether she will or will not be a mother.” Mrs. Sanger allied herself with Drs. Gregory Pincus and John Rock, two scientists studying progestin, a synthetic progesterone, that could help reduce unwanted pregnancies. After discovering progesterone’s role in ovulation, these scientists developed an oral birth control agent that prevented ovulation in 90.0% of their cases (Viterbo, 2004; Dhont, 2010).

Despite opposition, the pill was an important step in reshaping women’s attitudes towards sex. It helped erase the foundation supporting gender and sexual inequalities and gave women more power to enjoy a healthier view of sex (Montagu, 1968) Feminist Sanger, with the assistance of Mrs. Katherine McCormick and scientists Pincus and Rock, made it possible for women of every socioeconomic class a more accessible form of birth control (Viterbo, 2004; Dhont, 2010).

### 2.1.1 Chemical compound

Since the body absorbs naturally occurring progesterone at very low levels, scientists searched for a chemical compound with potent progestogenic activity that would maximize its ovulatory prevention effects. Chemist Carl Djerassi discovered norethindrone, the first progestin that had the proper effect on the ovulatory system when given orally. Dr. Frank Colton developed norethynodrel, a close isomer of norethindrone and administered it to women in the first contraceptive trials. Scientists found it odd that a daily dose of 10 mg of norethynodrel resulted in no breakthrough bleeding but, when given norethindrone or a more purified version of norethynodrel, women typically experienced frequent bleeding (Dhont, 2010)

Later, scientists discovered that the original norethynodrel compound was contaminated with a synthetic estrogen, mestranol. This discovery encouraged the addition of 150  $\mu\text{g}$  of the synthetic estrogen, mestranol, to the 10 mg progestin compound, norethynodrel, which resulted in the first



contraceptive pill, Enovid® (Dhont, 2010). In 1960, the Food and Drug Administration (FDA) allowed the use of Enovid® for contraception purposes to married women in addition to menstrual disorders.

This previous finding also sparked interest in estrogen-only oral preparations because of estrogen's ability to suppress ovulation and control frequent bleeding (Viterbo, 2004; de Melo, 2010). Like progesterone, the naturally occurring estrogen was poorly absorbed by the body, and a synthetic version had to be used (Dhont, 2010). Adverse estrogen-related effects on cardiovascular health terminated future plans of estrogen-only pills for population-wide use (de Melo, 2010). In fact, researchers have modified the original pill by reducing estrogen dosages (Dhont, 2010) in an attempt to provide a safer alternative to women choosing to use OCs as their primary means of birth control.

Despite progesterone's critical role in the development of OCs, progesterone-only oral contraceptives (POCs) were ignored until the late 1960's, as a response to the growing concern of estrogen's side effects. It is important to examine the role of progesterone and estrogen in the female reproductive system in order for the reader to understand why these two hormones were targeted for pregnancy prevention therapies and the variations among current OCs.

## **2.2 Female Reproductive System**

### **2.2.1. The Menstrual Cycle**

The menstrual cycle is predominantly characterized by a sequence of follicular development, ovulation, and the luteal phase; altogether, the three phases typically last 28 days. The follicular phase may vary in length and is often responsible for the variability in the menstrual cycle. Ovulation is the midpoint of the cycle and separates the follicular and luteal phases; the latter is constant and occurs 14 days after ovulation. The luteal phase is responsible for the formation and

disintegration of the corpus luteum, which degenerates if a woman is not pregnant. This leads to a decline in progesterone levels, which stimulates menstruation (Bartke et al., 1998).

Estrogen and progesterone are responsible for the many changes in the cervix, endometrium, and vagina that occur during the menstrual cycle. These hormones are also responsible for feedback regulation of the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) secretion by the anterior pituitary gland. The follicular and luteal phases are characterized by negative feedback on the anterior pituitary by estradiol and progesterone, respectively, whereas the mid-cycle is characterized by positive feedback of estradiol on the anterior pituitary (Davis, 2015).

In each of the phases, the pulsatile activity of the hypothalamic-pituitary axis signals to the gonadotropin-releasing hormone (GnRH) to stimulate the anterior lobe of the pituitary and secrete gonadotropins: FSH and LH. Gonadotropins include several hormones that act on the gonads (ovaries or testes) to regulate normal growth, sexual development and reproductive function. In the mid-cycle, the secretion is mostly composed of LH to trigger ovulation and the corpus luteum (Davis, 2015; Wells *et al.*, 2008).

#### 2.2.1. a. Follicular Phase

In conjunction with FSH and LH, a dominant follicle develops and stimulates high amounts of estradiol. FSH regulates aromatase enzymes that induce conversions of androgens to estrogens in the follicle. Estradiol will stop the menstrual flow from the previous cycle, change the environment of the cervix, and thicken the endometrial lining of the uterus. This follicle will continue to grow and synthesize estradiol, progesterone, and androgen until it ruptures and releases the oocyte. This phase is dominated by negative feedback effects of estradiol on the GnRH, which inhibit FSH and LH secretion by the anterior pituitary (Davis, 2015).

### 2.2.1. b. Mid-cycle

As a result of follicular cell proliferation and estradiol synthesis that occurs during the follicular phase, estradiol levels rise sharply during the mid-cycle. When a critical level of estradiol is reached ( $\leq 200$  picograms per milliliter of plasma), an ovulatory surge of FSH and LH triggers ovulation of the mature oocyte. An ovulatory surge occurs due to estradiol's positive feedback effect on the anterior pituitary approximately 14 days prior to menses. During ovulation, cervical mucus increases in quantity and becomes watery and more penetrable by sperm. Conception is most successful when sexual intercourse takes place two days prior to ovulation until the day of ovulation (Wells *et al.*, 2008). Estradiol levels decrease soon after ovulation, but they will increase again during the luteal phase.

The progesterone component of oral contraceptives suppresses ovulation by changing the cervical mucus environment and making sperm hard to get through the cervix.

### 2.1.1. c. Luteal Phase

During the luteal phase, the corpus luteum develops and begins synthesizing both estradiol and progesterone. Progesterone is the major hormonal secretion of the ovaries, and its high levels will increase the vascularity and the secretory activity of the endometrium. Another action of this hormone is to inhibit the secretion of FSH and LH through negative feedback loops to the anterior pituitary. Compared to the follicular phase, where estradiol causes the endometrial lining to proliferate, progesterone, in the luteal phase, prepares the endometrium to receive a fertilized ovum.

Increased progesterone levels during the luteal phase may lead to noticeable changes in the body, such as increased hypothalamic temperature set-point (increase basal body temperature) and thicker and more abundant cervical mucus. During this phase, the sperm can no longer fertilize the ovum. If fertilization has not yet occurred by then, the corpus luteum regresses and blood levels of the hormones decrease abruptly (Davis, 2015).

#### 2.2.1. d. Ovaries and steroid sex hormones

Female gonads (ovaries) are involved in the production of steroid sex hormones, germ cells (ova), pregnancy, childbirth, and lactation. Steroid sex hormones are fundamental to normal development and function of the reproductive organs and differentiation of secondary sex characteristics. These hormones have both paracrine and endocrine functions: the ovarian steroid hormones paracrine function is to support the development of the ova within the ovaries and, its endocrine function, is to act on a variety of target tissues (uterus, breasts, and bones). Ovarian follicles synthesize female sex hormones through the functions of the theca (cholesterol desmolase) and granulosa cells (aromatase). In the biosynthetic pathway, these cells are stimulated by LH and FSH, respectively (Bartke *et al.*, 1998; Davis, 2015).

The three types of male and female sex hormones secreted are androgens, estrogens, and progestagens. Examples of each are testosterone, 17- $\beta$  estradiol, and progesterone, respectively. Ovaries only secrete the female sex steroid hormones: progesterone and estrogen (Bartke *et al.*, 1998). These sex steroid hormones are a vital part of hormonal contraceptive methods used in the US.

### 2.3 Contraception methods

Nowadays, there is a plethora of pharmacologic and non-pharmacologic contraception methods used to reduce the risk of unintended pregnancies, including diaphragms, condoms, spermicides, intrauterine devices, and hormonal contraceptions. These vary in effectiveness, popularity of use, and mechanism of prevention. Due to the widespread use of hormonal contraception's, such as oral contraception pills, transdermal contraceptives, contraceptive vaginal rings, long-acting injectable and implantable contraceptives (Wells *et al.*, 2008), there has been a lot of interest in the field of combined estrogen- and progestin- contraceptives. In recent years, this

interest has slightly dwindled despite the constant and relatively high rates of birth control use among women (OWH, 2014).

Healthy People (HP) was created to improve the health and quality of life of all Americans and provides 10-year national benchmark for a wide-variety of health issues. Reproductive and sexual health is one of the leading health indicators (LHI) of HP 2020 and includes unintended pregnancy prevention. As part of the LHI, HP 2020 aims to increase the proportion of females at risk of unintended pregnancies or their partners who use contraception at the most recent sexual intercourse. This requires targeting high-risk populations: females ages 15-44, non-white Hispanic women, and those whose family income are below the poverty threshold. The goal is to increase the amount of females from 83.3% to 91.6% (HP 2020, 2015). If this goal is reached, health care providers must consider unique considerations (e.g. family history, genetic predisposition, lifestyle factors) faced by women while prescribing the appropriate contraception method.

Young women typically consider OC pills as their preferred method of contraception (NCHS, 2014) and most women using OCs use combined oral contraceptive (COC) pills (Marchbanks *et al.*, 2002; Hall, *et al.*, 2012). Severe symptoms of COCs may be rare but include blurred vision, flashing lights, numbness and/or weakness (may be a sign of stroke), hypertension or vascular problems at many sites; breast mass (may be a symptom of breast cancer); and chest pain or shortness of breath (may be a sign of pulmonary embolism, heart disease or myocardial infarction (MI)) (Wells *et al.*, 2008). These risks are much lower in POC formulations.

There is a paucity of literature regarding POCs and thus will be the primary focus of my dissertation.

### 2.3.1 Progesterone-only contraception

Progestin-only contraceptives are available in many forms: injections, implants, oral preparations, hormone-releasing intrauterine devices and emergency contraceptives (IARC, 1999).

This dissertation will focus on oral preparations, or OC pills. It may be hard to distinguish between POC and preparations that contain estrogen and progestin, or combined oral contraceptives (COC) in the current literature because many respondents may not make the appropriate distinctions between the type of OC pill used when answering about their (any) use of the pill.

In the US, POCs, or the “mini pill,” are all composed of 0.35 mg norethindrone, a progesterone of the norethisterone family. Brands and generics of the pill include Camila, Errin, Micronor, Jolivette, Nora-be and Nor-QD (Marchbanks *et al.*, 2002). Compared to COC users, women using POCs have a much more limited variety of pills to choose from. The current POCs available tend to have low progestin activity, and range from none-to-low estrogen and androgen activity. Women using these compositions of pills experience a high percentage of spotting and breakthrough bleeding in the beginning of pill use; however, these effects attenuate over time (Marchbanks *et al.*, 2002).

Women who choose POCs must take into account certain considerations that may be less important for women with COCs. For example, doctors recommend that women using POCs adhere more strictly to current guidelines (table 2.1) regarding daily intake (within a three hour window) to maximize the pills effectiveness because the effect on the cervical mucus lessens 20-22 hours after administration (IARC, 1999). Table 2.1 shows the guidelines for OC use according to the US Medical Eligibility Criteria for Contraceptive Use (MEC) by OC type (COC or POC) (Curtis, 2010; CDC, 2013). The pregnancy rate among COC users and POC users is the same among perfect users, but in typical use (table 2.2), the rate is slightly higher among POC users (0.3-5 per 100 women per year of use) (IARC, 1999).

Progestin is useful in controlling uterine bleeding and menstrual disturbances, reducing pain related to dysmenorrhea or menorrhagia and premenstrual syndrome, treating endometriosis, and postponing menstruation. In some women, POCs suppression of gonadotropin secretion and

ovulation can cause them to no longer menstruate. Researchers and health care providers believe POCs are more suitable for women over the age of 35, heavy smokers, those with a history of thromboembolism or hypertension, or in women who estrogens are typically not advised (e.g. diabetic women) (Wells *et al.*, 2008). Scientists find that the small doses of progestin in POCs lead to minimal disruption of lipid or carbohydrate metabolism (Dhont, 2010; Wells *et al.*, 2008; Marchbanks *et al.*, 2002).

### 2.3.2 Pharmacoepidemiology

Pharmacoepidemiology is defined as the study of the utilization and effects of drugs in large numbers of people (Strom *et al.*, 2007). OC's are recommended for both preventing unintended pregnancies and for off-label uses; in the US, the use of approved drugs for non-approved indications is not prohibited (IARC, 1999). OC's can alleviate menstrual cramps and ovulatory pain; moderate blood flow and acne; reduce the risk of ovarian and endometrial cancer; and also reduce the risk of ovarian cysts, ectopic pregnancies, and pelvic inflammatory disease (Wells *et al.*, 2008) The pill has been used by approximately 200 million women (Gogos *et al.*, 2014) because of its ability to protect against pregnancy and to reduce menstrual cramps, acne, certain cancers and other female complications in a convenient way.

Due to the increased prevalence of medication use among women, it is becoming imperative to analyze the effects of drugs that are currently in the market. The passage of the Patient Protection and Affordable Care Act (ACA) may continue to play an increasingly vital role in the percentage of women using OC's in the future due to less health care barriers. Thus far, ACA has increased access to contraception methods by requiring health care among all American citizens, which includes women's preventive services without cost-sharing. Congress anticipates that more Americans will continue to sign up for the ACA to avoid penalty and thus use health care services more frequently. This highlights the time-sensitive nature of this study. Pharmacovigilance must

be practiced routinely to understand, detect, assess, and prevent adverse effects or other OC-related problems (Strom *et al.*, 2007).

Numerous studies have suggested that COCs may lead to certain adverse drug reactions (ADRs). Known ADRs of COCs are abdominal pain, nausea, vomiting, headaches, breast tenderness, dysmenorrhea, arterial thromboembolism, hypertension, venous thrombosis, pulmonary embolus, and cerebral thrombosis (Wells *et al.*, 2008; Micromedex, 2015; FSRH, 2011) Currently, the carcinogenicity of COC use is only confirmed in hepatocellular carcinoma with long-term use of COCs (Micromedex, 2015). Despite these risks, COCs are prescribed in the majority of women who use OCs. It is unclear how many women are counseled about the mini-pill when choosing the right OC for them. The POC may be another alternative, with similar efficacy, that has been overlooked due to bleeding disturbances in clinical trials in the past (Kovacs, 1996). POCs have thus far been associated with less ADRs and contraindications than COCs. It may be more suitable to consider POCs in more cases during contraceptive consultations.

We will now assess the complications related to non-bioidentical or synthetic versions of estrogen and progesterone, which play an important role in the make-up or composition of the different pills.

#### 2.3.2. a. Estrogen and Progesterone compounds

Naturally-occurring estrogen and progesterone chemical actions vary from their synthetic versions in physiology and clinical outcomes (Holtorf, 2009). Due to issues in absorption of bioidentical hormones (Dhont, 2010), birth control pills use the non-bioidentical versions, which are associated with increased risks of breast cancer and cardiovascular disease. We must assess effects of synthetic hormones on women's overall health if we want to continue prescribing these hormones to women in the future.



### 2.3.2. a. i. Synthetic Estrogen

In the US, ethinyl estradiol (EE) and mestranol are the two forms of synthetic estrogens typically used (Dhont, 2010; Wells *et al.*, 2008). Mestranol converts into EE in the liver (Wells *et al.*, 2008) and contains 67.0% of its estrogenic activity. Researchers found that estrogen and EE can stimulate the synthesis of several clotting factors and hepatic proteins and through observations of pregnant women, identified estrogen's link with thromboembolism (Dhont, 2010). A progressive reduction from 50 to 15  $\mu\text{g}$  of EE was associated with less side effects, such as breast tenderness, nausea, and bloating, but did not eliminate prothrombotic effects (Dhont, 2010).

In addition to the aforementioned complications, many estrogen-related side effects of COCs include, fluid retention, hypertension, leg pains, cramps, reduced sex drive, depression, migraine/headaches, visual disturbances, decreased tolerance to contact lenses, increased skin pigmentation and changes in glucose tolerance (diabetic patients) (Wells *et al.*, 2008). Uncommon, but estrogens increase in blood coagulation can sometimes lead to venous thromboembolism (VTE), cerebral hemorrhage, embolism, stroke, and MI. Women using COC's who are older than 35 and who smoke are at much higher risk for MI.

Due to the number of complications that can result from using this drug, official guideline recommendations that are based on good and consistent scientific evidence recommend COCs with 35 mcg or less of EE and less than 0.5 mg of norethindrone to women who are younger than 35 years until the ages of 50-55 if they are healthy, after weighing the risks and benefits (ACOG, 2006). Women with a history of benign breast disease or a positive family history of breast cancer should not be considered contraindicated for COC use. Women with a history of unexplained VTE, smoking, breastfeeding, hypertension, end-organ vascular disease, focal neurologic signs, and other certain predispositions should not use COCs. Furthermore, women are highly recommended to discontinue estrogen containing OCs prior to any significant surgery (Wells *et al.*, 2008). Whether

this recommendation, or other important considerations of the pill are articulated to women is undocumented and unknown. Many of these precautions do not exist for women who use POCs. In fact, based on consensus and expert opinion, POCs may be appropriate for women with CHD, heart failure, and cerebrovascular disease while COCs are contraindicated in these women (ACOG, 2006).

There are many more options of COCs to satisfy the user: monophasic, biphasic, triphasic, and extended-cycle pills. The first three types require women to take estrogen and progestin for 21 days followed by 7 days of placebo, while the extended-cycle pills increase the number of hormone-containing pills from 21 to 84 days, followed by a 7-day placebo phase. A monophasic combination tablet has a single synthetic estrogen and progesterone that mimics typical menstruation due to a decrease in progesterone levels. Many women might prefer this method because “breakthrough bleeding” can be psychologically reassuring of non-pregnancy. The biphasic and triphasic combinations have varying hormone levels of estrogen and progesterone as the cycle continues and tablets must be taken in a particular order throughout the month. The extended method reduces the yearly amount of menstrual cycles per year to only 4 (Wells *et al.*, 2008; FSRH, 2011).

All pills, despite phasic combination, should be taken at the same time daily and lose effectiveness if taken late (more than 12 hours) and in conjunction with other drugs that influence estrogen and progesterone metabolism or certain antibiotics that affect the flora (Wells *et al.* 2008; FSRH 2011).

#### 2.2.2. a. i.1. Progestin activity in combined pills

Despite norethindrone being the only progestin used in POC pills, desogestrel, norgestimate, levonorgestrel, dienogest, and other progestin compounds have been used in COCs, commonly referred to as “the pill.” The progestin component of COCs is essential for contraceptive efficacy; it suppresses LH secretion, thereby inhibiting gonadotropin secretion and preventing ovulation

(Barbieri *et al.*, 2009). The UK committee of safety of medicines found that COCs containing desogestrel or gestodene were associated with a two-fold increase in thromboembolism compared to COCs containing androgenic progesterone's, such as levonorgestrel or norethisterone (Wells *et al.*, 2008) The progestin activity in COCs is outside the scope of this work but can provide insight into the role of estrogens when combined with progestin.

#### 2.2.2. a. ii. Synthetic Progesterone or Progestin

Norethindrone is the primary form of synthetic progesterone and alone makes up the “mini-pill.” Progestins have many chemical structures: estranes, gonanes, and others. Gonanes, the norgestrel family of progestins, include: desogestrel, gestodene, norgestimate, and etonegestrel. The estrane family of progestin's, including norethindrone, norethynodrel, norethindrone acetate, and norgestimate among others, are converted to norethindrone when metabolized. Gonanes exhibit a higher progestational effect per unit weight than estranes (Marchbanks *et al.*, 2002; Barbieri *et al.*, 2009)

The synthetic form of progesterone closely resemble testosterone; may bind to progesterone receptors or activate other steroid receptors; and can metabolize as estrogenic substances (Dhont, 2010). Thus, progestin can demonstrate estrogenic, anti-estrogenic, and androgenic properties (Marchbanks *et al.*, 2002).

The current progestin dose used in POCs are lower than in COCs to minimize androgenic ADRs (de Melo, 2010). In the limited studies about POCs, low androgenic progesterone's reduced the increased risk of CVD seen in typical COCs and could reduce blood pressure (Wilson *et al.*, 1984; Staffa *et al.*, 1992). The major side effect of POCs are an increased occurrence of bleeding during the first cycle compared to COCs (excluding triphasic therapies) (Wells *et al.*, 2008; Barbieri *et al.*, 2009). There is also a weak risk of an ectopic pregnancy in patients who become pregnant while on the pill due to decreased tubal motility (Wells *et al.*, 2008). All other observed side-effects

of COCs are less prominent or nonexistent in POC users, such as headache, nausea, depression, acne, fluid retention, and breast discomfort. Furthermore, no significant increased risk of CVD and breast cancer has been demonstrated with POCs and researchers speculate that POCs may have fewer long-term consequences on health, including weight gain and increased appetite (FSRH, 2009).

More studies need to examine other contraindications for POCs and examine the types of progestin structures in OC formulations. Currently, POCs have fewer contraindications than COCs and are a much safer option for women choosing an OC therapy.

### 2.3.3 Choice of Oral Contraceptives

Studies assessing women's knowledge of OCs are outdated (Koch *et al.*, 1993; Smith *et al.*, 1995; Jones, 1999). With the new HP 2020 goals focusing on increasing contraception use to almost 100% (HP 2020, 2015), researchers should renew their focus on understanding the factors that promote and discourage women's choice of OCs. It is also important to examine the efficacy of healthcare provider's communication of contraceptive contraindications and alternative choices with patients.

Studies need to assess awareness of alternative OC types (mono-, bi-, tri-, or extended COCs or POCs) among past, current and future pill users and health care provider's ability to consider family history, genetic predisposition, and other important lifestyle factors with newly imposed time constraints when prescribing OCs.

Like many other medications, OC prescriptions requires special consideration of the individual. Contraindications of OCs consider age, behavior, family history, and coexisting conditions (Wells *et al.*, 2008; FSRH, 2009). A previous study showed that health care providers often do not provide the necessary provisions and advice about the best OC to use to women suffering from Type 1 or Type 2 Diabetes Mellitus (Shawe *et al.*, 2011). There is limited

information about other chronic diseases and OC counseling. Currently, we cannot compare the existence of a parallel relationship between diabetes and other chronic diseases and inadequate counseling of OCs. The growing prevalence of chronic diseases and their risk factors are putting high demands on clinicians to prescribe OCs with regards to patient-specific characteristics in order to increase OC safety among high-risk groups and decrease long-term ADRs.

## **2.4 South Carolina: Women's Health**

### 2.4.1 Demographic Characteristics

In 2012, more than half of the 4.72 million people living in SC were females. The racial/ethnic distribution of the female residents were primarily non-Hispanic white (64.3%) and black (29.1%) women. Combined, American Indian, Asian/Pacific Islander, and Hispanics made up less than 8% of the composition. Economically, approximately 20% of females in SC are below the poverty level. The highest rates of poverty disproportionately affect minority populations: Hispanics (33.5%), Blacks (31.4%), American Indian (26.3%), and Asian/ Pacific Islander (14.0%). White, non-Hispanic females (13.7%) have the lowest percentage of women below the poverty line.

Among those women 18 years of age and above, 20% were smokers, 40% were hypertensive, and 35% had high cholesterol. Of those who smoked, 23.6% were white, non-Hispanic, 14.1% black, non-Hispanic, and 13.4% Hispanic. Of those who were hypertensive, 31.4% were white and more than half were black. Of those with high cholesterol, 34.9% were white, and 34.7% were black (DHHS, 2015). SC is an important region to carefully consider contraindications during OC prescription. Due to heightened prevalence of chronic disease risk factors and OC contraindications in this population, women may be more at risk to suffer ADRs related to COCs.

Women in SC typically range between 15-44 years of age (6.2% 15-19 and 32.1% 20-44) (DHHS, 2015). About 40% of teenage girls living in SC are sexually active and the majority have or will consider using an OC pill (DHHS, 2015). Among women participating in sexual intercourse

in the US, more than 99% have used at least one contraception method (DHHS, 2010). From 2011-2013, approximately three-fifths of women 15-44 were using a type of contraception and COC pills were the most common form (CDC, 2013).

Despite higher use of contraceptives among women aged 24-34 (67.4%), almost half of women ages 15-24 (47.4%) and the majority of women 35-44 (70.0%) also used contraceptives. Pill use was higher among younger women (15-24 years of age), with almost 1 in 4 using the pill compared to older women (35-44 years) with about 1 in 12 women using the pill. Non-Hispanic white women (65.3%) were the most likely to use contraception's compared to Hispanic women and non-Hispanic black women (57.3 vs. 57.9 percent, respectively). The percentage of women aged 15-44 who used the pill is significantly higher than condom, and long-acting reversible contraceptives use (DHHS, 2015).

The National Survey of Family Growth (NSFG), a nationally representative survey conducted by the National Center for Health Statistics, collected information on use of contraception from 2006-2010. Among the 88% of women who reported having used a contraceptive (n=10,779), 73% reported having used an OC. The majority of OC users identified using a COC. Only 2.8% (n=57) of women who were currently using OCs (n=2032) identified a POC as their current method (Hall, *et al.*, 2012).

The proportion of women aged 15-44 in the US who used the pill were almost twice as high among non-Hispanic white women as compared to non-Hispanic black and Hispanic women. The percentage of women ages 15-44 using a contraceptive method in 2011 to 2013 is similar to 2006-2010 (62.0 vs. 62.2%) (NCHS, 2014) Additionally, the percentage of women who used the birth control pill the last time they had sex ranged from 12.3% in Oklahoma to 35.7% in Maine. In SC, black female students in grades 9-12 were significantly more likely to have sexual intercourse than their white student counterparts (52.8% vs. 40.2%). Insufficient data examines whether black

females used a condom, birth control pills, an IUD, or a shot (eg. Depo-Provera, patch, or birth control ring) before or during the last sexual intercourse among students who were sexually active but among whites, the majority of the students used a condom (51.8%) and/ or birth control pills (25.3%). Including male responses, both black and white students in SC high schools used birth control pills 17.0- 18.4% of times prior to the last time they had sexual intercourse. There was no significant difference between race and birth control pill use (CDC, 2013).

Due to the high use of OCs noted in women ages 15-44 and high prevalence of chronic disease risk factors and COC contraindications, the low percentage of women reporting POC use is of public health concern.

#### 2.4.2 Health disparities

The CDC defines health disparities as the ‘differences in health outcomes between groups that reflect social inequalities’(Frieden, 2011). Poorer health status can manifest as a result of marked differences in social economic status and access to care among racial/ ethnic groups. Other characteristics linked to poorer health outcomes include gender or gender identity, geographic location, religion, age, mental health, and disability.

Our SC Medicaid cohort of women primarily suffer discrimination by gender (female), race/ethnicity (black), and geographic location (Southeast US). To increase equality in health care among different groups, we must increase the information about excluded groups in science and adhere to quality measures that focus on action plans that aim to reduce disparities in health care. The Department of Health and Human Services (HHS) has created a few measures to transform health care and to achieve HP 2020’s goal of assessing health disparities for sub-populations to achieve health equity for all groups (DHHS, 2011).

#### 2.4.2. a. Medicaid

In accordance with the HHS Disparities Action Plan, I will use Medicaid data to assess racial and ethnic disparities in the state of SC. The HHS plan recommends increasing using administrative data as a surveillance system to monitor trends in health and quality of care measures (DHHS, 2011). Medicaid is an ideal source because it is representative of underrepresented populations and provides most medical expenses for low-income women and children.

Since 2014, a massive expansion of Medicaid eligibility for low-income Americans promised an increase in Medicaid recipients and, with respect to women, the ACA will increase coverage of preventive services for FDA-approved contraceptive services and supplies as prescribed. SC has opted out of Medicaid expansion programs; nevertheless, it will see a 16% increase in Medicaid enrollment and possibly in OC use after the full implementation of the ACA (Galewitz, 2015).

#### 2.4.2. b. Race, gender, and geographic location

SC is one of ten states located in the southeastern region of the US. It is uniquely positioned to study health disparities because it has a higher percentage (%) of black or African Americans (27.9), female persons (51.3) and persons below poverty level (18.1) than the rest of the US (13.2, 50.8, and 15.4, respectively) (US Census Bureau, 2015). Thus, an analysis of SC can provide valuable insight into gaps in health care outcomes between certain populations. In accordance with HP 2020, we hope that the studies undertaken in this dissertation will help achieve health equity, eliminate disparities, and improve the health of all underserved populations.

### 2.5 Chronic Diseases

In the US and SC, the burden of chronic diseases (stroke, heart disease, cancer, diabetes, arthritis) and their associated risk factors are the leading causes of morbidity and mortality for women (CDC, 2008). It is estimated that one in three women will die of heart disease, one in six of stroke, and one in twenty-five of breast carcinoma (Jordan, 2001). In 2010, the Centers for



Disease Control and Prevention (CDC) placed SC among the two highest quintiles for the following age-adjusted death rates: 1) all-cause (700.8-813.8), 2) heart disease (143.3-165.1), 3) all cancer (150.0-157.6), 4) stroke (43.9-80.6), and 5) diabetes-related illnesses (62.9-71.7) among females of all ages (per 100,000).

CVD was responsible for 30 percent of all deaths in 2008 and despite a noticeable decline in mortality rates since 1999, SC mortality rates remain higher than the national rate. In assessing relevant risk factors for chronic disease occurrence, SC high school students and adults are at a higher risk compared with the US in 90% of the risk factors (Khosrow, 2010) With the poor distribution of health status in the state, health care providers should prescribe more take this into account when considering the best OC formulation for women.

In SC, the distribution of major contraindications, including smoking status, age, hypertension, cholesterol diabetes, for COC prescriptions are relatively high. More than 20% of women in SC currently smoke, do not partake in leisure time physical activity (LTPA), are overweight, obese, hypertensive, have high cholesterol and arthritis. Despite a lower prevalence of diabetes (12.4%) in SC compared to other risk factors, there is a high prevalence of diabetes among blacks (19.4%) (DHHS, 2015). Therefore, there is a high prevalence of women in SC who should not be given COCs as a preferred contraceptive method.

HP 2020 aims to decrease overall morbidity and mortality related to breast cancer and CVDs, particularly CHD and stroke. Cardiovascular health can be improved drastically through prevention and treatment of risk factors (HP 2020, 2015). CHD and stroke are among the leading causes of death in females but also, one of the most preventable diseases. The leading modifiable risk factors for these CVDs are high blood pressure, high cholesterol, smoking, diabetes, physical inactivity, and weight. The national target for CHD and stroke rates are 100.8 and 33.8 per 100,000, respectively (OWH, 2014).

HP 2020 objectives include reducing the incidence of high blood pressure and obesity (age 20 and over) to 26.9 and 30.6 per 100,000 respectively; and increasing health insurance coverage for people 18-64 years old to 100.0%. The realization of these goals will reduce morbidity and mortality related to not only high blood pressure and obesity but to breast cancer and CVDs. To further control breast cancer, HP 2020 also wants to reduce the breast cancer mortality rate to 20.6 per 100,000. These goals are harder to reach among black populations because they tend to have higher mortality related to CVDs and breast cancer compared to whites. Non-Hispanic whites (21.2) have lower rates of death from breast cancer than non-Hispanic blacks (26.9). The same pattern is seen in stroke (41.7 vs 55.7) and CHD (77.6 vs. 98.5) mortality (per 100,000 rates age-adjusted) (OWH, 2014).

In SC, a large percentage of women have high blood pressure, are obese, smoke, eat less than five fruits and vegetables a day, and have sedentary lifestyles (OWH, 2014). In 2011-2012, SC ranked among the highest percentage of women 18+ with a diagnosis of high blood pressure (32.1-38%) and women aged 20+ who are obese.

We have the ability to analyze the SC Medicaid population, which is a high-risk group for chronic disease incidence. Studying this population may help us find a successful therapeutic intervention to decrease the risk of these disease. This study could have a large impact on women's health.

## 2.5.1 Breast Cancer

### 2.5.1. a. i. Hormone Role

Breast cancer occurs from uncontrolled cell growth in the breast tissue (Adami, *et al.*, 2008) It is the most common form of cancer in women and the second most common cause of cancer death in all women (Lopez-De *et al.*, 2010). A few of the strongest risk factors for breast cancer are gender, age, and race; studies have shown that there may be a strong link between race and breast

cancer severity (Boyle, 2012; Carey *et al.* 2006). Women with high-risk for breast cancer, should perform self-examinations and routinely undergo mammography screenings. Breast cancer can be characterized based on TNM staging—T refers to the size of the primary tumor, N refers to the lymph node involvement, and M stands for the presence or absence of metastasis. These breast cancers are divided into stage 0 *in situ*, stage I-II local, and stage IV distant (Adami *et al.*, 2008). The criteria used to determine stage and grade of breast cancer has been explained previously (AJCC Cancer Staging Manual, 2010). Due to the complicated nature of the disease, it is important to reduce a woman’s risk to breast cancer by reducing her exposure to possible carcinogens.

Studies of POC use and breast cancer ranging from 1968 to 1987 were inconclusive (IARC, 1999). Following studies of the relative risk of breast cancer among women with any versus no use of POCs showed no significant increased risk. “The Pill” is the “precursor of hormone regulators”(Montagu, 1968), and can interact with many hormone pathways that play a role in breast cancer. Hormone receptors play an important role in breast cancer prognosis.

Breast cancers with hormone receptor-positive (HR+) estrogen receptors (ERs) and progesterone receptors (PRs) often have a better prognosis. The expression of these receptors are often key to treatment and researchers suggest a potential significance of progestin’s in the treatment of breast cancer (Lin *et al.*, 2001). ER- and PR-negative breast cancers are hormone-independent breast cancers that account for almost half of all breast cancers and are associated with poorer diagnosis (Lin *et al.*, 2001). These are much more common among African American populations (Carey *et al.*, 2006). To improve disease prognosis, scientists have recommended possibly reactivating the PR gene expression in hormone-independent breast cancers to promote progesterone ability to inhibit tumor growth and metastasis (Lin *et al.*, 2001).

### 2.5.1. a. ii. Demographics/ Medicaid

Approximately 1 in 4 women ages 15-24 are using the pill. The National Institutes of Health (NIH) estimated the lifetime risk based on current rates: 1 in 8 women born today will be diagnosed with breast cancer (Lopez-De *et al.*, 2010). In 2010, 3,676 (0.39%) of SC Medicaid recipients paid claims associated with a primary diagnosis of breast cancer. The medical expenditures for this population (\$58,399,037) accounted for 1.13 percent of SC Medicaid expenditures (Lopez-De *et al.*, 2010). That year, the majority of the Medicaid population consisted mostly of women ages 19-64, living in urban areas. Among those with breast cancer, there were more women (n=3,675) than men (n=1); blacks (n=1,858) than white (n=1,474) and Hispanics (n=56) and urban (n=2,323) than rural (n=1,334). The age distribution ranged from 18 and under (n=6), 19-64 (n=2,367), to 65+ (n=1,303).

Currently, breast and cervical screening rates in SC are below the 50<sup>th</sup> National Medicaid Percentile Benchmark (DHEC, 2015). Compliance with screening guidelines is an important health care priority to reduce late-stage breast cancer, mortality, and associated health care expenditures.

### 2.5.2 Cardiovascular disease (Heart Disease and Stroke)

CVDs are diseases of the heart and blood vessels (Labarthe, 2011). CHD is the major component of cardiovascular morbidity and mortality and refers to atherosclerosis of the arteries supplying the muscles of the heart. The southeastern part of the US, is often referred to as the “Stroke Belt,” due to its high rates of hypertension-related CVD. In 2010, SC had the highest age-adjusted stroke mortality rate in the US. In addition to the geographic disparities, the prevalence of these diseases are much higher among Blacks (Cruz-Flores *et al.*, 2011; Cooper *et al.*, 2000)

CVD is currently the number one cause of death in men and women and it is estimated that more than 90 million Americans are living with some sort of CVD (Cruz-Flores *et al.*, 2011; Lopez-De *et al.*, 2010). Hypertension is currently the most expensive component of CVDs and is projected

to increase from 130 billion dollars to more than 200 billion dollars in 2030 (Lopez-De *et al.*, 2010) OCs have been found to increase the risk of hypertension among current users and the duration of pill use has increased this risk (Chasan-Taber *et al.*, 1996). CVDs have many opportunities for prevention and is thus a ripe area for public health interventions.

#### 2.5.2. a. i. Hormone

Estrogen has many cardiovascular effects, including modulating vascular function, metabolism, insulin sensitivity, cardiac myocyte, stem cell survival, hypertrophy development, and inflammatory responses (Murphy 2011). Estrogen has been shown to improve many of the cardiovascular functions and can reduce atherosclerosis. Many scientists have identified estrogen as “cardio protective” (Gouva *et al.*, 2004). Thus, it can be puzzling to hear that estrogen-related components of hormone replacement therapy or OCs are increasing negative health outcomes.

The Women’s Health Initiative (WHI) showed that estrogen may have detrimental effect on women’s health. In the study, women had an increased chance of blood clots and other health complications. Many OC pills have higher doses of estrogen than hormone replacement therapy (HRT) formulations, which caused scientists to question the safety of OCs. Women using COCs are at a higher risk for stroke than women of similar age groups who are not using estrogen-containing OCs because estrogen induces embolism. This risk may persist after OC is no longer being used but declines after a woman is no longer a current user. Furthermore, young women who consider themselves healthy may not know that they are predisposed to strokes and take COCs. After an injury, using COCs can lead to thrombosis or other complications among women with subclinical disease. Women who have a mutation in the prothrombin gene have a twenty-fold increased risk of stroke. Despite guidelines allowing women with lupus to use COCs, women with a lupus anticoagulant have a three-fold increased risk for arterial and venous thrombosis (Bier, 2011).

A possible explanation for the contradictory findings (“cardio protective vs. stroke-inducing) are the role of endogenous vs exogenous reproductive hormones. It is possible that endogenous estrogen may play an important role in reducing cardiovascular complications but exogenous estrogens bind to certain estrogen receptors that do not confer the same protective capabilities. It is not well understood how estrogen regulates cardiovascular function in pre- or post-menopausal women but scientists believe that the ER mediates the relationship between estrogen and cardiovascular health. Estrogen can increase, decrease, or have no effect on transcription depending on the receptor it binds to and thus far, estrogen has been shown to signal by at least three different receptors (Murphy, 2011; Trussell, *et al.*, 2009). Estrogen pathways are complex and still being studied in further detail (Davis, 2015).

#### 2.5.2. a. ii. Pro-inflammatory Indices

Estrogen containing oral contraceptives can have a negative effect on females due to their pro-inflammatory properties. The estrogen component can lead to significant increased on high-sensitive C-reactive proteins, which is an important marker of inflammation. C-reactive proteins can be an accurate method of identifying groups that are at high-risk for cardiovascular disease and cancer. Researchers found the effects of exogenous estrogen alarming: half of women who would otherwise be considered healthy women in the population exceeded recommend C-reactive protein levels (> 3 mg/l) after using oral contraceptives that included estrogen (Rietzschel *et al.* 2007; Kluff *et al.* 2002).

#### 2.5.2. a. iii. Medicaid Demographics

In 2010, 22,408 (2.37%) of SC Medicaid recipients paid claims associated with a primary diagnosis of CVD. The medical expenditures for this population (\$359,582,929) accounted for 7.0 percent of SC Medicaid expenditures (Lopez-De *et al.*, 2010). The 2010 SC Fiscal Year for the SC Medicaid population includes black (n=10,111), white (n=10,299), Hispanic (n=136), and other

(n=1,862) races/ ethnicities of men (n=8,125) and women (n=14,283). The majority of Medicaid recipients resided in urban (n=13,025) areas and were ages 19-64 (n=11,149) (Lopez-De *et al*, 2010).

#### 2.5.2. a. iv. Coronary Heart Disease

Ischemic heart disease occurs when an obstruction to the coronary artery results in a lack of oxygen to the myocardium, or the muscles supplying the heart (Labarthe, 2011) The classic symptoms (sweating, faintness, and pressing pain) of heart disease may not be present among women experiencing myocardial ischemia. This causes increased harm to women because it is more difficult to diagnose in this population.

Medicaid records use International Classification of Diseases (ICD) codes for CHD or ischemic heart disease. Ischemic heart disease or CHD includes angina pectoris, acute MI, subsequent MI, certain complications following acute MI, other acute ischemic heart disease and chronic ischemic heart disease (Labarthe, 2011). In 2011, 9,000,000 people lived with angina pectoris (chronic chest pain), 5,700,000 had heart failure and 16,300,000 had CHD nationwide (Lopez-De *et al.*, 2010). Thus, it is important to understand the disease and possible areas for prevention.

There are common features of coronary events (Figure 2.1). This figure depicts the clinical and biological progression of heart disease in four phases (Labarthe, 2011) —

##### 1) **Phase I: Background**

Atherogenesis leads to atherosclerotic lesions in the coronary arteries

- Formation of abnormal fatty deposit in the arteries (Merriam-Webster, 2015)

##### 2) **Phase II: Initial/ Potential Factors**

Presence of one or more potential factors may disrupt advanced atherosclerotic lesion or plaque at the surface or by fissuring deeper levels of the lesion

3) **Phase III: Acute Events**

An acute event, such as a thrombus (large occlusive clot) may form and produce acute symptoms, such as unstable angina; heart attack; MI; or sudden death.

4) **Phase IV: Medium to late development**

The last phase characterizes short-or long-term outcomes from the first three phases.

- Background conditions may lead to silent infarction/ asymptomatic disease
- Initial factors may lead to spontaneous resolution or plaque enlargement as well as silent infarction/ asymptomatic disease
- Acute events may lead to spontaneous recovery, short-term fatalities, late recurrence or late coronary death

From an epidemiologic perspective, it is important to understand these phases to reduce the role of extrinsic factors and intrinsic factors on disease occurrence/ progression. For example, a young woman who does not engage in physical activity and has a family history of MI might not be an ideal candidate for combined oral contraceptives. Overlooking her current and past behavior and family history due to age might be catastrophic after the incubation period necessary for background conditions to progress into more advanced phases.

2.5.2. a. v. Stroke

In the US, stroke death rate and prevalence are about 1/4<sup>th</sup> to 1/3<sup>rd</sup> as common as CHD. Stroke is a cerebrovascular accident (CVA) that occurs when there is an obstruction of flow in the cerebral circulation, which damages the brain (Labarthe, 2011). The classic symptoms of stroke include numbness or weakness of the face, arm, or leg, confusion, difficulty with pronunciation, or understanding, dizziness, reduced coordination, blurred vision, and a sudden headache. These symptoms last for a short period of time and are followed by a sudden loss of consciousness, motor and sensory function on one side of the body (Labarthe, 2011).



Environmental factors play a major role in stroke prevalence and those who have had a stroke often suffer permanent brain injury, disability, or death. Fortunately, stroke incidence has been decreasing in recent years but continues to disproportionately affect non-Hispanic whites in mortality rates (Labarthe, 2011). Risk factors for stroke include age, gender (male), race (Black, Asian, Hispanic), family history, low birth weight, hypertension and cardiac disease (Wells *et al.*, 2008), but the most prominent contributor and controllable factor of all types of stroke is high blood pressure (Labarthe, 2011). In 2011, 76,400,000 people were living with high blood pressure and 7,000,000 had strokes (Lopez-De *et al.*, 2010).

Similarly to coronary events, stroke has the following common features for clinical and biological progression (Figure 2): (Labarthe, 2011)—

### **Phase I: Background**

Atherogenesis leads to atherosclerotic lesions in the cerebral arteries or high blood pressure or both

#### **1) Phase II: Acute Events (<24 hours)**

Transient Ischemic Attack (TIA): an episode that ends within 24 hours

TIA may lead to a recurrent TIA

#### **2) Phase III: Acute Events (>24 hours)**

Completed stroke: an episode that ends after 24 hours

#### **3) Phase IV: Medium to late development**

Fatal stroke: a completed stroke that precedes death within 28 days from the episode

The last phase characterizes short-or long-term outcomes from the first three phases.

- Background conditions may lead to TIA or completed stroke
- Acute events (<24 hours) may lead to recurrent TIA or completed stroke

- Acute events (>24 hours) may lead to full recovery, residual disability, recurrent stroke, and/ or death

Stroke is a major public health concern because it is the third leading cause of death in females of all races in the US (CDC, 2011). Stroke has many potential manifestations and the most common form is the acute event (>24 hours).

Strokes diagnostic classification for stroke in population studies includes subcategories of stroke (subarachnoid hemorrhage, intracerebral hemorrhage, brain infarction due to occlusion of pre-cerebral arteries or due to cerebral thrombosis, and embolic brain function). Studies often define stroke disparately and thus the inclusion criteria is necessary to understand the inclusion criteria used (Lin *et al.*, 2001; Bier, 2011; Trussell *et al.*, 2009).

## 2.6 Definitions

Perfect use: refers to method failure; it “is a failure inherent to the proper use of the contraceptive alone.”

Typical use refers to user failure and takes into account “the user’s ability to follow the directions correctly and consistently.”

Understanding the distinction between “perfect-use” and “typical use” of the contraception method is essential to the contraception literature. Perfect use refers to method failure; it “is a failure inherent to the proper use of the contraceptive alone.” Typical use refers to user failure and takes into account “the user’s ability to follow the directions correctly and consistently” (Marchbanks *et al.*, 2002)

## 2.7 Tables and Figures

**Table 2.1 Guidelines for Oral Contraceptive Use Using the US Medical Eligibility Criteria for Contraceptive Use (MEC)**

Topic	Combined Oral Contraceptives	MEC <sup>±</sup>	Progestin-Only Oral Contraceptives	MEC <sup>±</sup>
<u>Age</u>				
< 40 years	If other lifestyle factors are reviewed, women from menarche through 40 years of age can use	1	No restrictions	1
≥ 40 years	Generally use COCs, slightly increased risk of adverse events	2	No restrictions	1
<u>Breastfeeding</u>				
<6weeks PP <sup>o</sup>	Should not use this method, especially women with risk factors for VTE	4	POCs can be started anytime, including immediately postpartum (MEC 2 is < 1 month)	2
≥6 weeks to <6 months PP	(Among women with VTEs, MEC 4)	3	MEC 1 ≥ 1 month postpartum	1
≥6 months PP	Generally safe to use if women do not have risk factors for VTE	2	Safe to use regardless of VTE risk factors	1
<u>Non-Breastfeeding women (PP)</u>				
< 21 days	(i) Without other risk factors for VTE	4	(i) Without other risk factors for VTE	1
	(ii) With other risk factors for VTE	3	(ii) With other risk factors for VTE	1
≥21 days to 42 days	(i) Without other risk factors for VTE	2	(i) Without other risk factors for VTE	1
	(ii) With other risk factors for VTE	3	(ii) With other risk factors for VTE	1
<u>Cardiovascular Disease</u>				
Risk Factors	Older age, smoking, diabetes, and hypertension	3/4		1
<u>Examinations and Tests</u> : blood pressure, baseline weight/ BMI, Clinical Breast Exam (CBE), and laboratory tests				
Blood pressure	Should be measured before initiating this OC method	3	No restrictions	1
	(i) Systolic 140-159 mm Hg or diastolic 90-99 mm Hg (ii) Systolic ≥ 160 mm Hg or diastolic ≥100 mm Hg	4		

Baseline Weight/ BMI	BMI = $\geq 30$ kg/m <sup>2</sup>	2	Obese women can use POCs	1
Hypertension	(i) Women who have more severe hypertension (systolic pressure of $\geq 160$ mm Hg or diastolic pressure of $\geq 100$ mm Hg) or vascular disease should not use combined OC (ii) Controlled hypertension or	4 3	No restrictions	1
Clinical Breast Exam	Undiagnosed mass Will not detect contraindications	2	Not necessary	1
<u>Lab Tests</u>				
Other	(i) Complicated diabetes (ii) Hyperlipidemias depending on the type and severity and presence of other CVDs (iii) Certain liver disease (iv) Thrombogenic mutations However, screening of diabetes, hyperlipidemia, liver disease, thrombogenic mutations is not necessary/ cost-effective	4 2/3 4/3 4	(i) Women with hypertension, diabetes, hyperlipidemia, anemia, thrombogenic mutations, cervical intraepithelial neoplasia, cervical cancer, STDs, or HIV infection can use POCs (MEC 1) or generally can use POCs (MEC 2) (ii) Certain liver disease	1 3
	Women with anemia, cervical intraepithelial neoplasia, cervical cancer, HIV infection, or other STDs can use (U.S. MEC 1 <sup>±</sup> ) or generally can use (U.S. MEC 2 <sup>±</sup> ) combined hormonal contraceptives			
<u>Other Contraindications</u>				
Contraindications	(i) Women with current breast cancer (ii) Severe hypertension or vascular disease (iii) Heart disease (iv) Migraine headaches with aura (v) Women ages $\geq 35$ years who smoke	4	(i) Women with current breast cancer (ii) Migraines with aura	4 1

<sup>±</sup> U.S. Medical Eligibility Criteria for Contraceptive Use (MEC) 1= A condition for which there is no restriction for the use of the contraceptive method; 2= A condition for which the advantages of using the method generally outweigh the theoretical or proven risks; 3= A condition for which the theoretical or

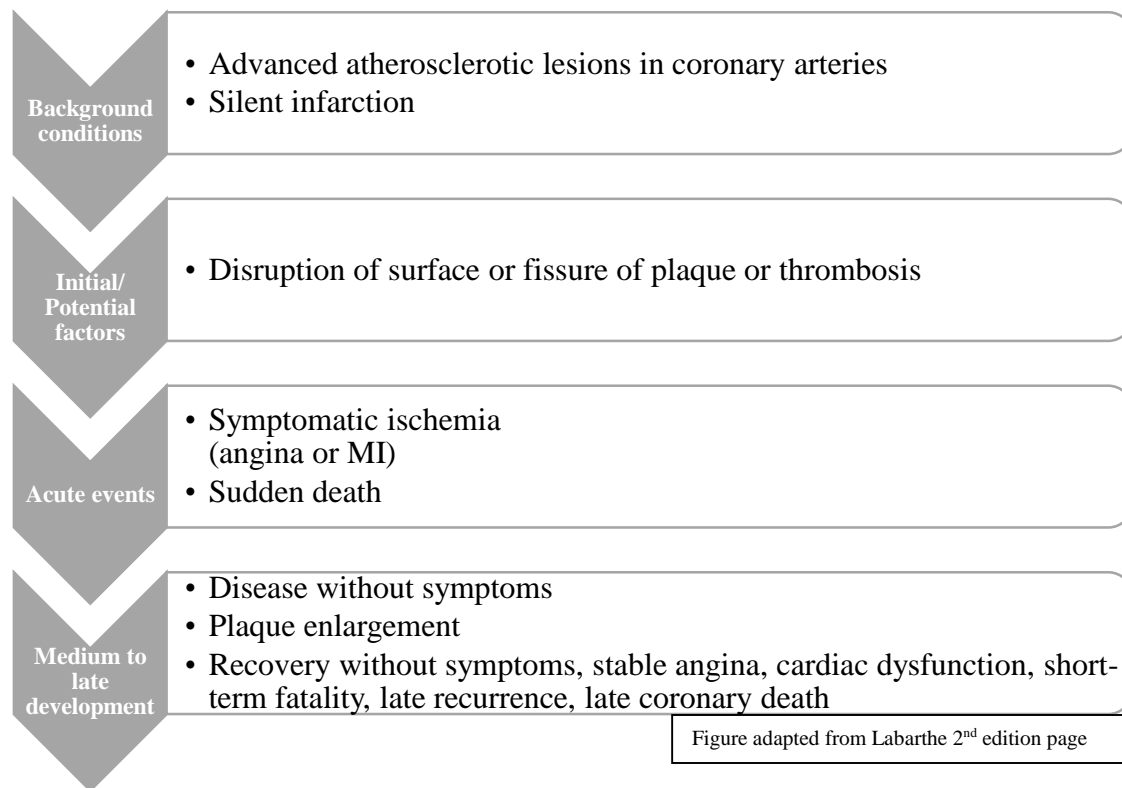
proven risks usually outweigh the advantages of using the method; 4= A condition that represents an unacceptable health risk if the contraceptive method is used

Abbreviations: BMI = body mass index; COC= Combined Oral Contraceptive; POC= Progestin-Only Contraceptive; HIV = human immunodeficiency virus; STD = sexually transmitted disease; VTE= venous thromboembolic event; PP<sup>o</sup>= Postpartum

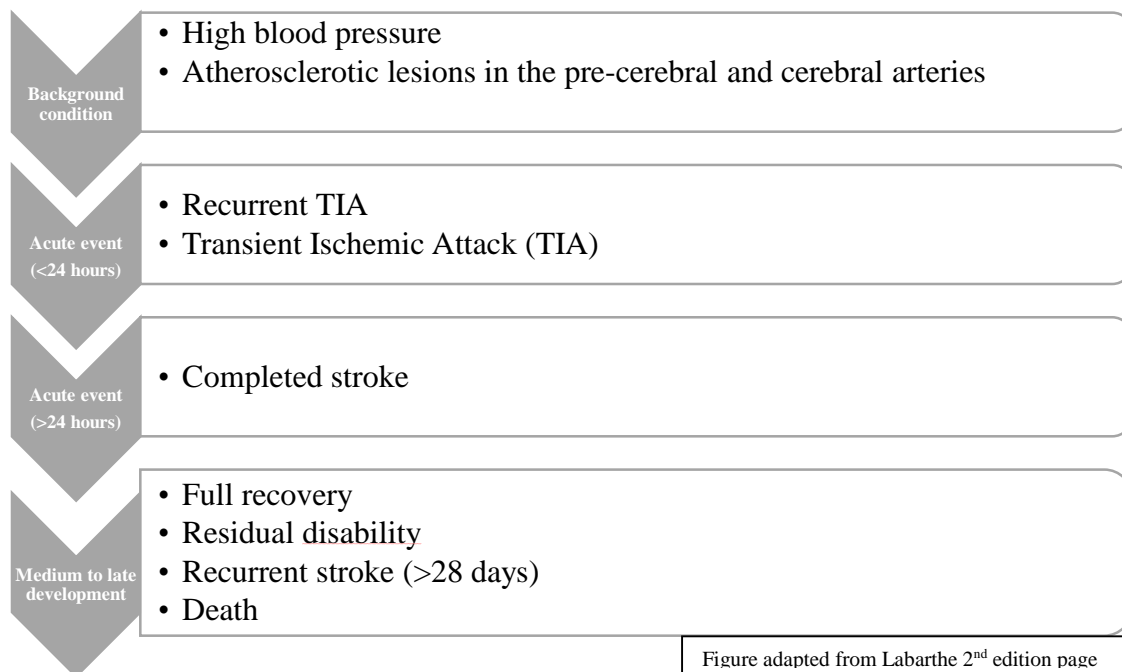
**Table 2.2 Comparison of Oral Contraceptives: Efficacy, Mechanism, Timing and Unintended Pregnancies**

	<b>Combined OC</b>	<b>Progestin-only OC</b>
<b>Efficacy</b>	9 out of 100 women become pregnant in the 1 <sup>st</sup> year of use	9 out of 100 women become pregnant in the 1 <sup>st</sup> year of use
<b>Mechanism</b>	COCs are reversible and do not protect against STDs. Consistent and correct use of condoms reduces the risk for STDs, including HIV	POCs are reversible and do not protect against STDs. Consistent and correct use of condoms reduces the risk for STDs, including HIV
<b>Timing</b>	Initiated at any time if woman is not pregnant; ideally started within the first 5 days since menstrual bleeding	Initiated at any time if woman is not pregnant; ideally started within the first 5 days since menstrual bleeding
<b>Unintended pregnancy</b> ¥		
Typical Use*	9.0%	9.0%
Perfect Use †	0.3%	0.3%

\*COC: Missed Pill (including vomiting or severe diarrhea) applies only to hormonally active pills (not placebo pills); ≥ 24 hours since the pill should have been taken and POCs Missed pill can occur any day of the month; no placebo pills; >3 hours since it should have been taken (Trussell, 2011); † Women who did not miss a pill; Women not using any method of contraception had 85% typical and perfect use; ¥Percentage of Women Who Experienced An Unintended Pregnancy During The First Year Of Oral Contraceptive Use: Typical Vs. Perfect Use (%)



**Figure 2.1 Common features of coronary events**



**Figure 2.2 Four phases of Clinical and biological progression of heart diseases**

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## CHAPTER III.

### MATERIALS AND METHODS

#### 3.1 Introduction

A population-based retrospective cohort study of the South Carolina (SC) Medicaid administrative enrollment and claims data were collected from January 1<sup>st</sup>, 2000 to December 31<sup>st</sup>, 2013. All of the information was gathered from the Revenue and Fiscal Affairs Office, located in Columbia, SC. The Medicaid program provides necessary health care services and other essential resources to low-income families who otherwise might not have access to care. SC Medicaid data is a unique source of information that represents low-income families and individuals who are underrepresented in health research.

The primary objective of this study is to compare oral contraceptive (OC) types [combined oral contraceptive (COC) or progesterone-only contraceptive (POC)] and evaluate chronic disease outcomes (breast cancer, coronary heart disease (CHD), and stroke). We are also interested in examining changes in OC use and disease outcome over time. Secondary data analyses were performed using the SC Medicaid data set. This original protocol was approved by the Institutional Review Board of the University of South Carolina (USC).

#### 3.2 South Carolina Medicaid

Medicaid is a federal and state government program that provides free or low-cost health coverage to millions of Americans. It is one of SC's largest insurance providers for low-income people, families and children, pregnant women, the elderly and people with disabilities (Medicaid, 2015). One fourth of SC residents receive health coverage from SC's Medicaid comprehensive

plan and 43% of SC Medicaid recipients are black (MLTSS, 2015). The distribution of the population will allow us to examine underserved populations by race.

### **3.3 Research Design, Methods, and Data Analysis**

Figure 3.1 shows the retrospective cohort design used in this study. The SC Medicaid population exposure status was determined through information on oral contraceptive exposures. The disease status was determined for exposed and unexposed groups (breast cancer mortality, heart disease incidence, and stroke incidence).

#### **3.3.1 SC Medicaid Population**

The enrollment period is necessary to capture a complete medical snapshot for each participant because women in the Medicaid cohort may alternate between periods of eligibility and ineligibility. Women were followed from 01/2000 to 12/2013 and included based on the inclusion/exclusion criteria:

##### **3.3.1. a Cohort Selection (Inclusion/ Exclusion criteria):**

###### *Inclusion*

- Permanent residents of SC during study period
- Among stroke and heart disease cohort: Women aged 18 to 55  
Among breast cancer cohort: Women aged 18 to 65
- Participants had at least twelve months of Medicaid enrollment during study period (01/01/2000- 12/31/2013)
- Race/ Ethnicity: Black/ African American or white/ European American

###### *Exclusion*

- Subjects who had a disease diagnosis (breast cancer, heart disease, stroke) prior to the study period (e.g. before 01/2000)

The inclusion/ exclusion criteria serves as the basis for the SC Medicaid population (Figure 1).

### 3.3.1. b Dataset

The Medicaid data set includes information about each participant's demographic information, as well as their medical and pharmacy claims.

Demographic information includes current and past educational achievement (less than high school, high school, some college, or more than a college degree), marital status (married or not married), race (Black/ African American (AA) or White/ European American (EA)), continuous eligibility ( $\geq 12$  months), age (18-65), OC use (yes/no) and type of OC used [progesterone-only oral contraceptive (POC), combined oral contraceptive (COC), and POC+COC]. Race was restricted to AA or EA because other races were less than 3% of the sample and oral contraceptive use could not be adequately stratified by OC type (i.e. low cell count).

The pharmacy claims provide information about the drug/ generic name, therapeutic class, age at claim, dispensed date (month/year), American Hospital Formulary Service (AHFS) drug codes, and type of OC pill used. Norethindrone is the only type of POC used and sold in the Medicaid population (Kaunitz 1997; McCann and Potter 1994; FSRH 2009).

The medical claims include the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, first and last dates of service, Healthcare Common Procedure Coding System (HCPCS) codes, primary diagnosis of disease, age at diagnosis (years), and disease outcome (breast cancer mortality; and CHD, and stroke incidence).

### 3.3.2. OC Exposure Status

We classified women as exposed or unexposed based on the following definition: (Figure 1)

- Exposed: Exposure to OC is determined by HCPCS code. Drug code/ name and therapeutic class listed in Appendix. Recipients are classified by exposure status (COC or POC).



- Unexposed: Women who did not have a COC or POC pharmaceutical claim during the study period were included in the ‘No OC’ group.

### 3.3.1. c Duration of exposure status

To accurately measure adherence and duration of medication use in COC and POC users, we calculated the proportion of days covered (PDC) using a macro (%PDC\_Change). The macro requires defining several parameters: input and output of dataset name, unique patient identifier, and prescription fill date, fill days of study period, and end date of study period. The Pharmacy Quality Alliance has supported PDC measure as the “preferred method” to calculate medication adherence and duration. This method corrects for overestimations noticed in previous methods and calculates the true rate of adherence and duration of use. We used % PDC\_Change to measure the number of days women were covered by a prescription, divided by the number of days in the measurement period. The PDC was calculated for each patient during their pregnancy prevention period using their drug therapy information. If a woman switched her medication during a measurement period, we adjusted accordingly using a modified version of the macro (Wang, *et al.*, 2013).

### 3.3.2 Disease Status

#### 3.3.2. a Medicaid ICD-9 codes

The following ICD-9 codes were used for each disease:

##### *3.3.2. a. i. Breast Cancer*

A medical claim with an ICD-9-CM diagnosis code of ‘174,’ ‘174.1,’ ‘174.2,’ ‘174.3,’ ‘174.4,’ ‘174.5,’ ‘174.6,’ ‘174.7,’ ‘174.8,’ ‘174.9,’ ‘233.0,’ ‘238.3,’ ‘239.3,’ These classifications represent portions of malignant neoplasm of breast, carcinoma *in situ*, neoplasms of uncertain behavior, neoplasms of unspecified nature and exclude the skin of the breast.

- **174** Malignant neoplasm of female breast
  - Includes: breast (female): connective tissue, soft parts; Paget's disease of breast and nipple
- **174.0** Malignant neoplasm of Nipple and areola of female breast
- **174.1** Malignant neoplasm of Central portion of female breast
- **174.2** Malignant neoplasm of Upper-inner quadrant of female breast
- **174.3** Malignant neoplasm of Lower-inner quadrant of female breast
- **174.4** Malignant neoplasm of Upper-outer quadrant of female breast
- **174.5** Malignant neoplasm of Lower-outer quadrant of female breast
- **174.6** Malignant neoplasm of Axillary tail of female breast
- **174.8** Malignant neoplasm of Other specified sites of female breast
- **174.9** Malignant neoplasm of Breast (female), unspecified
- **233.0** Breast
  - 233 Carcinoma in situ of breast and genitourinary system
- **238.3** breast (excludes skin of breast 238.2)
  - 238 Neoplasm of uncertain behavior of other and unspecified sites and tissues
- **239.3** breast (excludes skin of breast 239.2)
  - 239 Neoplasms of unspecified nature

The sample from Medicaid will be linked to the breast cancer data from the South Carolina Central Cancer Registry (SCCCR). Data is linked by last name, date of birth, social security number (SSN), and Medicaid number (if provided). The SCCCR is a North American Association of Central Cancer Registries (NAACCR) certified population-based registry that provides complete, timely, and quality information about cancers. Residents who are not

diagnosed or treated in South Carolina are still detected through case-sharing agreements with other state cancer registries.

### 3.3.2. a. ii. Stroke

There is a lack of consensus about the proper method to classify stroke patients (Goldstein, 1998; Roumie *et al.*, 2008). Based on the American Academy of Neurology, Stroke Practice Improvement Network (SPIN), American Stroke Association, Georgia Hospital Association, and the Joint Commission on Accreditation of Healthcare Organizations, stroke is defined using the codes below for ischemic and hemorrhagic strokes (The Joint Commission, 2015):

#### *Ischemic stroke*

- **433.01** occlusion and stenosis of basilar artery with cerebral infarction
- **433.11** occlusion and stenosis of carotid artery with cerebral infarction
- **433.21** occlusion and stenosis of vertebral artery with cerebral infarction
- **433.31** occlusion and stenosis of multiple and bilateral pre-cerebral arteries with cerebral infarction
- **433.81** occlusion and stenosis of other specified pre-cerebral artery with cerebral infarction
- **433.91** occlusion and stenosis of unspecified pre-cerebral artery with cerebral infarction
- **434.00** cerebral thrombosis without mention of cerebral infarction
- **434.01** cerebral thrombosis with cerebral infarction
- **434.11** cerebral embolism with cerebral infarction
- **434.91** cerebral artery occlusion unspecified with cerebral infarction
- **436** acute, but ill-defined, cerebrovascular disease

### *Hemorrhagic stroke*

- **430** subarachnoid hemorrhage
- **431** intracerebral hemorrhage
- **432** other and unspecified intracranial hemorrhage
- **432.0** nontraumatic extradural hemorrhage
- **432.1** subdural hemorrhage
- **432.9** unspecified intracranial hemorrhage

### *3.3.3. a. iii. Coronary Heart Disease*

A medical claim with an ICD-9-CM diagnosis code of '402,' '410,' '411,' '413,' '414,' and '429' was considered a claim for CHD. These classifications represent portions of chronic myocardial infarction, hypertensive heart disease, acute or subacute forms of ischemic heart disease, and other forms of CHD.

The ICD-9-CM code descriptions are as follows (CMS, 2005):

- **402** Hypertensive heart disease
  - Includes: hypertensive heart (disease) (failure), and any condition in 428, 429.0-429.3, 429.8, 429.9 due to hypertension
  - Benign and malignant hypertensive heart disease without and without heart failure
  - 402.90/91 Unspecified hypertensive heart disease with and without heart failure
- **410** Acute Myocardial Infarction
- **411** Other acute and subacute forms of ischemic heart disease

- Coronary: Microinfarction of heart failure, pre-infarction syndrome, insufficiency (acute), post- myocardial infarction or intermediate coronary syndrome, Dressler's syndrome
- **413** Angina Pectoris
- **414** Other forms of chronic ischemic coronary heart disease
  - Excludes: cardiovascular arteriosclerosis, degeneration, disease or sclerosis (429.2)
- **429.9** Unspecified
  - Includes: Heart disease (organic) NOS and Morbus Cordis NOS

### 3.3.3. b Terms (time-to-event, censorship)

- The event or outcome of interest is:
  - Binary variables:
    - Breast cancer mortality (yes/no)
    - CHD incidence (yes/ no)
    - Stroke incidence (yes/no)
- If the outcome of interest occurs ('yes'), the participant has the event or outcome of interest. If not ('no'), the participant did not have an event (Figure 1)
- Disease status was classified according to ICD-9 codes
- Time-to-event: the time from entry into the study until a subject has disease of interest (breast cancer)
  - The woman is no longer at risk when she experiences the event or is censored
- Exit date: defined as a date of outcome of interest for the study (breast cancer) or end of study period
- Right Censoring: subjects are censored if they are lost to follow up, or if the study ends before they have the outcome of interest

- Censoring is independent of disease outcome
- ‘Any OC’ refers to a woman using any OC (‘POC, COC, or POC+COC’ vs. ‘Never User’)

### 3.4 Specific Aims

#### 3.4.1 Specific Aim 1

- Describe the demographic characteristics of the SC Medicaid recipients
  - Compare and contrast demographic characteristics among Medicaid Participants by OC type used (Never use, POC, COC, and POC+COC)
  - Assess frequency distribution/ summary statistics for categorical/ continuous
- Determine the association between OC users and never users (‘Any OC’ –yes vs. no) using logistic regression analysis
  - Compared to the year 2000, we will assess ‘Any OC’ use between 2001 to 2013
  - Calculate the OR and 95% CI for ‘Any OC’ Use, crude and adjusted (age, year, race, marital status, education) models
  - Calculate the multinomial logistic regression models predicting the type of OC users in the SC Medicaid population among OC users
  - Evaluate trends of prescribing by race over time
    - The interaction of race and time and its association with the type of OC used
    - Calculate the annual percent change rate between 2000 and 2013 for Medicaid Users (Percent Growth Rate: [(Rate in 2013 minus rate in 2000) divided by (rate in 2000)] times 100)

*Hypothesis:* There is no difference between the type of OC used by race over the years

*Alternative Hypothesis:* There is a significant difference between the type of OC used by race over time

3.4.1. a *Guiding Framework*

For each disease, we will examine OC use by type. Below are 2x2 tables that depict our main areas of focus.

- a) Compare ‘Any OC’ Use: POC, COC, or POC+COC vs. Never User

	Disease	No Disease
Any OC	a	b
Never user	c	d

- b) Compare OC users only by type of OC (POC or POC+COC compared to COC)

	Disease	No Disease
COC	(ref)	(ref)
POC	a	b
POC+ COC	c	d

- c) Compare ‘Never User’ to the different types of OC’s (POC/ COC/ POC+COC)

	Disease	No Disease
Never use	(ref)	(ref)
OC type	a	b

- d) Repeat a-c by race

3.4.2 Specific Aim 2

- Compare time-to- mortality distributions of OC users by race (OC use→ death)

- Comparing Never User and ‘Any OC’
  - Null hypothesis: There is no difference between breast cancer mortality between Medicaid recipients with or without OC use ( $H_0: S(t)_{No\ OC} = S(t)_{COC\ or\ POC\ or\ POC+COC}$ )
  - Alternative hypothesis: There is a difference between breast cancer mortality and Medicaid recipients with or without OC use ( $H_1: S(t)_{OC} \neq S(t)_{COC\ or\ POC\ or\ POC+COC}$ )
- Comparing ‘OC Types’
  - Null hypothesis: There is no difference between breast cancer mortality between Medicaid recipients receiving different types of OCs ( $H_0: S(t)_{POC} = S(t)_{COC} = S(t)_{POC+COC}$ )
  - Alternative hypothesis: There is a difference between breast cancer mortality between Medicaid recipients depending on the type of OC used ( $H_1: S(t)_{POC} \neq S(t)_{COC} \neq S(t)_{POC+COC}$ )
- Comparing ‘Never Users OC’ to ‘OC Types’
  - Null hypothesis: There is no difference between breast cancer mortality among Medicaid recipients without prior OC use and OC use ( $H_0: S(t)_{No\ OC} = S(t)_{COC}$ ) and ( $H_0: S(t)_{No\ OC} = S(t)_{POC}$ ) and ( $H_0: S(t)_{No\ OC} = S(t)_{POC+COC}$ )
  - Alternative hypothesis: There is a difference between the breast cancer mortality among Medicaid recipients with or without prior OC use ( $H_1: S(t)_{No\ OC} \neq S(t)_{COC}$ ) and ( $H_1: S(t)_{No\ OC} \neq S(t)_{POC}$ ) and ( $H_1: S(t)_{No\ OC} \neq S(t)_{POC+COC}$ )

Where  $S(t)_{No\ OC}$  = Time-to-mortality function for women who have never used

OC



$S(t)_{COC}$  = Time-to-mortality function for women who have used  
combined OC

$S(t)_{POC}$  = Time-to- mortality function for women who have used  
progestin-only OC

$S(t)_{POC+COC}$  = Time-to- mortality function for women who have used  
both  
progestin-only OCs and combined OCs

- Compare each model by race (EA or AA)

To observe the relationship between OCs and breast cancer mortality, survival analysis, a non-parametric method was used to estimate the risk of disease while adjusting for potential confounders. Baseline demographic variables were calculated and categorical and continuous variables were assessed using chi-square test and two-tailed t-tests, respectively. POC, COC, and POC+COC users were compared; each group are mutually exclusive.

Kaplan-Meier survival curves and the log-rank test statistic were used to calculate the statistical differences between breast cancer mortality among different OC groups. The Kaplan-Meier method is a non-parametric maximum likelihood estimator that does not control for covariates but can test differences between groups. We calculated the crude differences between OC groups given the time-to- breast cancer mortality using the Kaplan-Meier method. Due to long latency periods in cancer, we used the log-rank test instead of the Wilcoxon test. The log-rank test is more powerful than the Wilcoxon test in detecting differences between groups that occur at greater intervals.

Total survival time was calculated for all subjects as the time from oral contraceptive exposures to the time of death or censoring. Using the Lunn McNeil approach to estimate cause-specific mortality (breast cancer and other cause mortality), we analyzed the relationship between type of

OC use and cause-specific mortality in a competing risk model adjusting for multiple covariates. Hazard ratios and 95% CIs were calculated. In the competing risk models, women survival time was calculated from type of oral contraceptive exposure to breast cancer mortality and in a separate model, from type of oral contraceptive exposure to non-breast cancer deaths, or other causes of deaths. Women were censored at either the date of death for their respective model or at the end of the study period, whichever occurred first. Separate competing risk models were performed by race (EA/ AA), adjusting for other baseline and demographic variables.

The univariate Cox proportional hazard (PH) analysis was also used 1) to assess each variables impact on the overall risk of developing the outcome and 2) to determine the adjusted time-to-all-cause mortality curves. The Cox PH regression model is a semiparametric approach that uses the Cox partial likelihood method to estimate regression models with censored data. To determine all-cause mortality, women were followed from OC exposure until any event occurred (breast cancer or other cause). The multivariate Cox PH model were also used to calculate the hazard ratios (HRs) and corresponding 95% confidence intervals for all-cause mortality given that women used POCs, COCs, POC+COCs or were never users of OC. We considered the following models:

- Model 1: The crude model-  $h(t, X) = h(t, X)\exp[\beta * OC\_use]$
- Model 2: adjusted for age
- Model 3: additionally adjusted for possible confounders (education, and marital status)

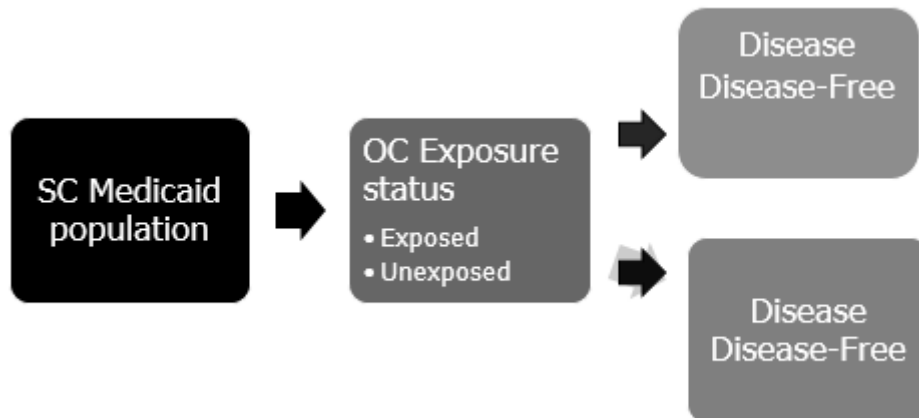
We evaluated PH assumption and the time-dependent relationship between OC exposure and all-cause mortality using Cox PH models. The Cox PH model assumes that there is independence between the hazard ratio and time. We assessed this assumption by adding time-dependent covariates to our model (i.e. interaction term with time in the model), and determined if it was significant ( $p < 0.05$ ). Model selection was based primarily on scientific knowledge (previous research and hypotheses) and backward selection procedures. All statistical analysis were

performed using the Statistical Analysis Systems software (SAS), version 9.4 (SAS Inc., Cary, NC) PHREG procedure (SAS, 2012). Statistical significance will be set at alpha level  $p < 0.05$  and hypotheses will be tested using a 2-sided tail test.

### 3.3.3 Specific Aim 3

Descriptive analysis were assessed using the Chi-square test for categorical variables and the t-test for continuous variables in each study. To observe the relationship between OCs and CVD incidence, we used conditional polytomous logistic regression. COC was the referent population because of its popularity (large sample size). Models were adjusted for variables related to our exposure and outcomes, age, race, education, and marital status. Results were presented as odds ratios and 95% confidence intervals. SAS (version 9.4) was used for all investigations, with an alpha level of 0.05.

### 3.5 Tables and Figures



**Figure 3.1 Retrospective cohort design where the outcome, or disease is the time between exposure status to disease (breast cancer, heart disease, or stroke) outcome**

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## CHAPTER IV.

### TRENDS

#### 4.1 Abstract

Background: Progestin-only oral contraceptives (POCs) remain unpopular among both clinicians and women because of unpredictable changes in future menstrual cycles. However, these contraceptive pills may be an alternative for women who are at an increased risk for complications related to the use of estrogen-containing oral contraceptives (OCs). Contraindications to estrogen+ progestin or combined OCs (COCs) are more prevalent in the Medicaid population than in the general population. Our study focuses on factors that influence (1) women's choice of any OC, (2) the type of OC used, and (3) trends in OC use.

Methods: This is a retrospective, observational study using de-identified information from women enrolled in Medicaid from 2000 to 2013 in South Carolina (n=204,762). Logistic regression analyses were conducted, adjusting for potential confounders.

Findings: POC use was more common among older women (OR: 1.05; 95% CI: 1.04, 1.06) and African-American women (OR: 1.09; 95% CI: 1.01, 1.16) compared to COC users. Married women were more likely to use POC (OR: 1.31; 95% CI: 1.20, 1.42) and POC+COC (OR: 1.45; 95% CI: 1.35, 1.55) formulations compared to COCs, but were not significantly more likely to use OCs overall ('any OC') compared to no OC use (OR: 1.02; 95% CI: 0.96, 1.09). There was an increasing trend in POC use over time, especially among European-American women.

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<sup>1</sup> Samson, M., Adams, SA., Zhang, J., Bennett, C., Hebert, JR. (2016) Trends in Oral Contraceptive Use by Race and Ethnicity in South Carolina among Medicaid-enrolled Women. *Under Revision*.

Conclusion: POCs have been associated with less detrimental health effects compared to COCs and may be a better alternative to reducing unintended pregnancies among women at high-risk of certain health complications. The public health community should focus on identifying the proper population to use progestin-only pills.

## 4.2 Introduction

The oral contraceptive (OC) pill remains the preferred method of contraception to prevent unintended pregnancies (Jones *et al.*, 2012). The probability of a contraceptive failure within the first year of typical use is lowest among injectable users (6.7%, 95% CI: 4.3-10.4) and pill users (8.7%, 95% CI: 7.2, 10.5) (Trussell, *et al.*, 2009). Due to their high effectiveness and marketing efforts, OCs have remained popular since the 1960s. However, most OC users are typically prescribed combined OCs (COCs), which contain both estrogen and progestin hormones. Despite reductions in estrogen dose in modern COCs, there is still controversy about the risks associated with COC use (ASRM, 2008; O'Brien 1999). Women using COCs with small doses of estrogen may still suffer clinically relevant side effects, such as abdominal or chest pain, headaches, eye problems, and/ or swelling of legs and thighs (Dawson, 1979), which may indicate a more serious problem, such as venous thromboembolism (VTE) (Hall *et al.*, 2012), liver disease, gallbladder disease, stroke, high blood pressure, or heart disease (Wolski, 2014; Dawson, 1979; Curtis, 2010). These risks are reduced among progestin-only oral contraceptive (POC) users (Mantha *et al.*, 2012). Furthermore, studies have shown that POCs have similar effectiveness as COCs (Contraceptive Technology, 1999; Trussell 2011).

Despite similar effectiveness, POCs remain unpopular among women (Grimes *et al.*, 2013). Physicians may be less likely to prescribe POCs to women because of POCs mechanism of action which may disrupt the normal menstrual patterns (Grimes *et al.*, 2013). To overcome a significant barrier to progress in women's health, we must understand factors that influence women's choice

of OC specifically by type (POC, COC, and POC+COC) of OC used. Given that approximately 70 million women in the United States are currently in their childbearing years (15-44 years of age) and of those participating in sexual intercourse, more than 99% have used at least one contraception method (barrier, hormonal, intrauterine, and/or sterilization), often in combination with one another (Dye, 2008; Jones *et al.*, 2012). It is imperative that research continues to identify healthier alternatives to COCs for pregnancy prevention and family planning.

Contraindications to COC use include tobacco smoking, obesity, and certain cardiovascular diseases (Curtis 2010). The presence of these contraindications are more common among low-income, or Medicaid recipients (Armour *et al.*, 2009; Lee *et al.*, 2010; Mateen *et al.*, 2014). Furthermore, minority women and women earning less than 150% of the federal poverty line (FPL) are least likely to be aware of OC use guidelines (Dehlendorf *et al.*, 2010). Among women who are at increased risk of complications due to estrogen, POCs are the preferred OC choice. However, factors influencing the use of OCs among these groups are understudied. South Carolina Medicaid administrative claims contain records of women's OC type used, age, calendar year of use, race, and marital status, from 2000 to 2013. Information on other contraceptive methods were excluded due to the popularity of OC use. We, used these data to (1) identify factors that influence any use of OC (yes or no) (2) identify factors that influence women's choices of contraception (POC, COC, POC+COC) in a diverse cohort of women typically under-represented in the literature, and (3) examined trends in OC medication use over time among SC Medicaid population from 2000 to 2013.

### **4.3 Materials and methods**

#### Study Design and Setting

We conducted a retrospective analysis of SC Medicaid claims data to determine factors that influence OC use and to examine the trends in OC use from 2000 to 2013. This study was



conducted after receiving approval from the Institutional Review Board of the University of South Carolina.

### Data Sources and Participants

The South Carolina Office of Research and Statistics (ORS) provided us demographic, medical, and pharmacy claims data for Medicaid patients between 2000 and 2013. Pharmacy claims, classified by the National Drug Code (NDC), supplied information on prescription drugs dispensed for contraception purposes (e.g. POC, COC). Study participants were located by searching Medicaid administrative database and identifying NDC codes related to the type of OC drug (therapeutic class: 681200). Criteria for inclusion in the analysis were as follows: (1)  $\geq 18$  years,  $\leq 65$  years, (2) African American (AA) or European American (EA), (2) sex (female only), and (3)  $\leq 12$  months of continuous Medicaid enrollment between January 1st, 2000 through December 31st, 2013. Our analysis included 204,762 women.

### Covariate Classification

Demographic data were obtained from Medicaid files. Age, in years, was determined as of January 1st, 2000 and assessed as a continuous variable. Calendar year of OC use was used as continuous or categorical variable where appropriate. Women were categorized by marital status (yes/ no), educational attainment (< high school/ some high school/ high school graduate/ > high school), race (EA/ AA), 'any OC' use (yes/no), and type of OC (progestin-only (POC)/ estrogen + progestin (COC)/ POC + COC). Type of OC use were mutually exclusive.

'Any OC' users were women who used either POC, COC, or POC+COC and were compared to women who never used OCs. However, never users were excluded from the study when comparing factors that influenced the type of OC use and assessing the trends of OC use from 2000 to 2013.

## Statistical Analysis

Standard univariate and other descriptive statistics were used for all study covariates. We fit various regression models to the data in order to understand the subjects' OC utilization: (1) logistic regression was used to examine the factors influencing a woman's decision to use 'any OC' (yes/ no) for the entire study sample; (2) a conditional polytomous logistic regression was used to discern variables influence on a woman's choice of OC (POC/ COC/ POC+COC); and (3) calculated rates of OC use during the period 2000-2013 by race.

For logistic regressions, backward stepwise selection procedures were used to predict the relevant variables. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated. The risk factors studied were age, race, marital status, calendar year, and education level. Conditional polytomous logistic regression was used to predict factors affecting the type of OC use; COC users were the referent population.

Never users of OC were excluded when comparing factors that influenced the type of OC use and assessing the trends of OC use from 2000 to 2013. Rates of OC use were calculated per 1,000 persons. Annual percentage change rates (PCRs), calculated as the (Rate in 2013 minus rate in 2000) divided by (rate in 2000) times 100, were considered to increase or decrease if the p-value was <0.05. All statistical analyses were conducted using SAS® version 9.4 software (NC, USA). For all calculations, statistical significance was defined by P-values < 0.05.

## **4.4 Results**

### Study Population

A total of 204,762 women were included in the study. For each year, the population was predominantly African American (>50%), OC users (>80%), and unmarried (>70%). Due to the high variability in Medicaid eligibility per year, we displayed the results per year (Table 1).

Among OC users, the majority of women used COCs (>60%/ year) and the mean duration of OC use was 16.2 (10.6) overall. From 18.4 (8.0) months in 2000 the use decreased to 14.3 (10.4) months in 2013. Since 2000, there also are fewer women reporting more than a high school degree, from 57.6% to 12.6%, and more women reporting less than a high school education, from 19.3% to 62.2%. The mean age of women in the sample decreased from 27.9 (6.3) years in 2000 to 24.3 (6.7) years in 2013 (Table 1).

### Any OC Use

There was a 2-4% increase in the odds of using any OC (POC/ COC/ POC+COC) per year, adjusting for other important variables. The odds of using any OC was similar in 2000 and 2013 (odds ratio (OR): 1.02; 95% CI: 0.88, 1.17). However, compared to the year 2000, there was a significant decrease in the odds of using any OC from 2001 to 2003. After reaching a nadir in 2003, the odds of using any OC began increasing in 2004, culminating in a return to 2000 levels in 2013, (all odds ratios adjusted for covariates) (Figure 1).

Similarly, after adjusting for age, race, marital status, education, and year, we observed an increased odds of using any OC among all women (OR: 1.07; 95% CI: 1.06, 1.07) with every unit increase in age. AA women had greater odds of using any OC than EA women in our sample (OR: 1.45; 95% CI: 1.38, 1.53). Furthermore, compared to having less than a high school education, high school graduates and those with more than a high school degree were significantly less likely to use an OC (OR: 0.75; 95% CI: 0.70, 0.81 and OR: 0.89; 95% CI: 0.83, 0.95, respectively). Being married did not significantly affect the odds of using any OCs (OR: 1.02; 95% CI: 0.96, 1.09) (Table 2).

## Type of OC

Trends. Figure 2 shows the types of OCs used by race excluding never users. Among women using OCs, the majority were COC users. Among COC users, AA women experienced a significant decrease in use from 2000 to 2013 time (Percent change rate (PCR): -1.28%), whereas EA women's rate of use remained relatively stable over time (p-value: 0.48) (Table 3). Over this period, the rate of POC and POC+COC use significantly increased for EA women (PCR: 10.78% and 6.32%, respectively) (Figure 2a). Use of POC+COC in AA women did not increase significantly from 2000 to 2013 (PCR: 3.80; p-value: 0.96) (Table 3) but from 2002 to 2013, there was a significant increase in POC+COC among AA women (PCR: 11.2%) (Figure 2b). There was a significant increase in POC use among AA women (PCR: 3.56%) from 2000 to 2013. Changes per year were also computed to show significant variations per year (Table 3b). The greatest variation were among never users, sometimes varying more than 20% on a yearly basis. Among OC users, the highest fluctuations were among POC users whereas AA women had greater yearly variations in the POC+COC group.

The multivariable-adjusted conditional logistic regression examining the factors that affect the type of OC use (POC/ POC+COC) compared to COC, are presented in Table 4. There was a significant increase in the odds of POC and POC+COC use from 2001 to 2013, compared to 2000, adjusting for other variables. Furthermore, AA women had higher odds of POC and POC+COC use compared to EA women (OR: 1.09; 95% CI: 1.01, 1.16 and OR: 1.09; 95% CI: 1.02, 1.15, respectively). Being married also increased the odds of POC and POC+COC use by approximately 30-45%. Compared with having less than a high school education, having at least some high school experience increased the chances of POC and POC+COC use (OR: 1.12; 95% CI: 1.02, 1.23 and OR: 1.26; 95% CI: 1.16, 1.37, respectively). However, having a high school education or more reduced the probability of using either POC or POC+COC. Age was associated

with a significantly increased odds of POC and POC+COC use. The point estimates and 95% CIs of POC and POC+COC use, adjusted for race, marital status, education, and age show a slightly higher increase in POC use compared to POC+COC use since 2000 (Figure 3).

#### 4.5 Discussion

Our study confirms that there is an increase in overall OC use over time despite a reduction in COC use, especially among AA (p-value: <0.01 vs 0.47 in EA women). The gradual reduction in COC use observed among AA women from 2000 to 2012 approaches typical rates of COC use among EA women (300-400/ 1,000) from 2000 to 2013. Unlike previous studies focusing on women's health in the general population (DHHS, 2010; Jones, 1999; Daniels, *et al.*, 2013), AA women on Medicaid were more likely to use OCs compared to their EA counterparts. The higher rates of OC use among AA were driven by the popularity of COC use (EA: 83.43% vs. 85.34%); EA women were more likely to use POCs (7.59% vs. 6.64%) and POC+COCs (8.98% vs. 8.01%) compared to AA women. Additionally, the increase in POC use over time was significantly higher among EAs compared to AAs (10.78% vs. 3.56%, respectively). From 2000 to 2012, there was a 14.90% increase rate of POC use among EA women; however, the use of POCs decreased slightly from 2012 to 2013.

The differences in OC use by race may be due to increased recommendation by physicians (Yee *et al.*, 2011), reduced sterilization rates among females (Daniels *et al.*, 2013) and our study's focus on low-income populations. Among Medicaid participants, EA women may be more likely to use female sterilization than AA women (K. White *et al.*, 2014), which may explain small differences in OC use. Potential reasons for the decline in COC use among AA women may include being/seeking to become pregnant, physician prescription changes due to estrogen contraindications, and use of alternative contraceptive methods. Oddly, more education was inversely related to OC use in our study. This inverse relationship may be due to various reasons:

1) lack of adequate information of education in our study population and/ or 2) women with higher educational status using different methods of contraception (e.g. depot medroxyprogesterone acetate (DMPA), intrauterine devices). More information about education status in this population may be necessary to interpret these findings thoroughly. When we excluded education from our analyses, our results (point estimates and confidence intervals) did not significantly change. Therefore, sensitivity analyses confirmed the stability of our results.

Contraceptive methods are continuing to remain a popular option for family planning and pregnancy prevention. It is important to understand the underlying reasons that may influence a user's choice of OC method. Analyzing type of OC is often restricted to COCs, which have a much more narrow medical eligibility criteria compared to POCs, based on the World Health Organization's (WHO) guidelines (Curtis 2010). There are many benefits to using COCs (Brynhildsen, 2014; Spencer *et al.*, 2009; AAFP, 2015); however, many contraindications to COC use are prevalent in the general population and particularly in the Medicaid population (Armour *et al.*, 2009; Mateen *et al.*, 2014; Lang *et al.*, 2015; Byrne *et al.*, 2014; Flattau *et al.*, 2011; Orsi *et al.*, 2010; R. H. White *et al.*, 2009). In addition, this study population is susceptible to societal barriers that can reduce proper communication with physician (Flattau *et al.*, 2011; McDoom *et al.*, 2012; Epstein *et al.*, 2007). Cardiovascular events among COC users who smoked could account for 80% of cardiovascular deaths among women aged 20-24 years (Farley *et al.*, 1998); however, incidence of fatal cardiovascular events remained low among women less than 35 years old.

Clinicians and researchers must pay particular attention to contraindications that are common in the population. In our population, more than 28.7% of COC users used tobacco products. Common contraindications to COC use include breastfeeding; smoking any cigarettes; risk factors for cardiovascular disease (older age, smoking, diabetes, hypertension); VTE; current

and/or history of ischemic heart disease or stroke; migraines with aura; inflammatory bowel disease; and gallbladder disease, among others (MMWR, 2010). POC formulations have significantly fewer contraindications (MMWR, 2010b). Counseling of OC options should be emphasized to reduce the possibility of side effects.

In the context of our findings, these contraindications highlight the importance of understanding the factors that influence women's decisions to use certain types of OCs. Communication with physicians and being informed about the health risks and benefits of each type of OC is a major contributor to OC choice (Merki-Feld *et al.*, 2012), in addition to age, race, and marital status. The high prevalence of certain illnesses in the Medicaid population highlights the importance for physicians and women to consider using POCs as an alternative to COCs. There are many women who do not consider the majority of these contraindications when choosing the proper contraceptive method, which make them more liable to suffer short- and long-term side-effects.

#### **4.6 Strengths and Limitations**

Our sample population is restricted to Medicaid enrollees, which provided us with a relatively homogeneous population. Though this may limit the generalizability of the study, it does provide us unique insight into an under-researched population. Furthermore, it may be that patterns seen in the general population may not be observed in the Medicaid population; thus, this study may help us adapt recommendations and policies specifically to these groups. Another strength of our study is the large sample size, which resulted in a high level of statistical power. We used information from administrative claim records, which reduced the potential of bias (e.g. self-report). The major limitation of this study is that we do not have information on physician prescription patterns, which could further influence OC patterns and use.

#### **4.7 Implications for Practice and/or Policy**

Given the prevalence of OC use by women in the United States every year, understanding the patterns of use, especially among underserved populations, is essential. Many women are unaware that POCs are an alternative to COCs, despite POCs having less contraindications (Mantha *et al.*, 2012). Several implications for practice and policy emerge from this study, such as 1) ensuring women of childbearing age who are considering OCs are given additional information on the various types of OCs and their benefits and risks; 2) encouraging patient-physician communication to provide more information related to reproductive healthcare; and 3) acknowledging racial/ethnic differences which may exist when counseling on reproductive options. Furthermore, women are demanding OCs be offered over-the-counter, which raises safety concerns among health care providers (Howard *et al.*, 2013). Over-the-counter availability of POCs may be a safer alternative to COCs, which may require women to self-screen for many diagnosed and undiagnosed contraindications. Similar studies may highlight additional need for practitioners to modify prescription patterns and recommendations depending on women's understanding of reproductive health information and perceived risk (e.g. geographic location, family history).

#### **4.8 Conclusion**

In conclusion, our data obtained from the Medicaid registry showed an increasing trend from 2000 to 2013 in OC use overall with a slight decrease of COC use among AA women and an increase in POC and POC+COC in both AA and EA women, albeit to varying extents by race. Information about oral birth control options need to be examined and discussions with health care providers need to highlight the benefits of POC, COC and possibly switching from COC to POC after a couple of years, depending on the presence of new risk factors (e.g. increased blood pressure, increased age, diabetes status). It is important for women to understand which OC is best for them and when to initiate a new contraceptive method. Future studies should evaluate the



presence of each contraindication in the Medicaid population and assess how many women are using a pill despite a present contraindication. Providing quality and patient-centered women's healthcare requires increased communication between health provider and patient about possible underlying conditions and alternative types of OCs.

#### 4.9 Tables and Figures

**Table 4.1 Characteristics of Medicaid Participants, 2000-2013**

Year	N(%)/ Mean (SD) N= 8859	OC Use		OC Type				Race		Education				Marital Status		Age	Duration
		No	Yes	Never Use	POC	COC	POC + COC	EA	AA	< HS	Some HS	HS Grad	> HS	No	Yes	(SD)	(SD)
<b>2000</b>		611	8248	611	299	7469	480	3997	4597	965	167	967	2895	6153	2540	27.9	18.4
	%	6.9	93.1	6.9	3.4	84.3	5.4	46.5	53.4	19.3	1.2	7.0	57.6	70.8	29.2	(6.3)	(8.0)
<b>2001</b>	N=9299	772	8527	772	423	7533	571	4220	4778	1370	210	886	2532	6383	2579	27.8	17.1
	%	8.3	91.7	8.3	4.6	81.0	6.14	46.9	53.1	27.4	4.2	17.7	50.7	71.2	28.8	(6.4)	(12.0)
<b>2002</b>	N=10604	1448	9156	1448	565	7910	681	4775	5465	1447	355	941	2297	7392	2799	27.5	17.1
	%	13.7	86.3	13.7	5.3	74.6	6.42	46.6	53.4	28.7	7	18.7	45.6	72.5	27.5	(6.4)	(28.3)
<b>2003</b>	N=11850	2072	9778	2072	653	8368	757	5479	5934	1471	472	940	1946	8468	2976	27.1	17.6
	%	17.5	82.5	17.4	5.51	70.6	6.39	48.0	52.0	30.5	9.8	19.5	40.3	74.0	26.0	(6.4)	(5.2)
<b>2004</b>	N=11681	2076	9605	2076	705	8050	850	5484	5761	1397	536	819	1564	8551	2858	27.0	18.0
	%	17.8	82.2	17.8	6.04	68.9	7.28	48.8	51.2	32.4	12	19	36.2	75	25	(6.5)	(5.0)
<b>2005</b>	N=11999	1983	10016	1983	748	8281	987	5533	5964	1544	709	817	1468	9034	2718	26.9 (6.6)	16.9
	%	16.5	83.4	16.5	6.23	69.0	8.23	48.1	51.9	34.0	15.6	18	32.3	76.9	23.1	(6.6)	(6.3)

<b>2006</b>	N=11632	1616	10016	1616	665	8395	956	5362	5792	1573	742	725	1207	8493	2494	26.4	15.3
	%	13.9	86.1	13.9	5.7	72.1	8.2	48.1	51.9	37.0	17.5	17.1	28.4	78.2	21.8	(6.5)	(7.9)
<b>2007</b>	N=11671	1422	10249	1422	697	8555	997	5415	5754	1649	856	641	1056	9154	2350	26.3	16.3
	%	12.2	87.8	12.2	6.0	73.3	8.5	48.5	51.5	39.2	20.4	15.3	25.1	79.6	20.4	(6.5)	(4.2)
<b>2008</b>	N=12854	1589	11265	1589	785	9429	1051	5924	6361	1826	1030	606	1046	10181	2530	26.0	15.3
	%	12.4	87.6	12.4	6.1	73.4	8.2	48.2	51.8	40.5	22.9	13.4	23.2	80.1	19.9	(6.5)	(37.5)
<b>2009</b>	N=15816	1930	13886	1930	1004	11516	1366	7191	7868	2565	1240	762	1091	12794	2876	25.4	16.3
	%	12.2	87.8	12.2	6.4	72.8	8.64	57.8	52.2	45.3	21.9	13.5	19.3	81.7	18.4	(6.2)	(1.5)
<b>2010</b>	N=17745	2116	15629	2116	1154	12955	1520	8311	8487	2983	1461	749	1110	14354	3218	25.1	15.0
	%	11.9	88.1	11.9	6.5	73.0	8.57	49.5	50.5	47.3	23.2	11.9	17.6	81.7	18.3	(6.2)	(5.6)
<b>2011</b>	N=21314	2302	19012	2302	1609	15869	1534	9986	10170	3730	1534	755	1197	17605	3442	24.8	14.7
	%	10.8	89.2	10.8	7.6	74.5	7.2	49.5	50.5	51.7	21.3	10.5	16.6	83.7	16.4	(6.3)	(7.3)
<b>2012</b>	N=22776	2005	20771	2005	1769	17312	1690	10854	10641	4308	1512	758	1121	19041	3382	24.7	14.6
	%	8.8	91.2	8.8	7.8	76.0	7.4	50.5	49.5	56.0	19.6	9.9	14.6	84.9	15.1	(6.5)	(9.1)
<b>2013</b>	N=26662	2039	24623	2039	1957	20781	1885	11967	13116	5875	1653	751	1189	22898	3279	24.3	14.3
	%	7.7	92.4	7.7	7.3	77.9	7.1	47.7	52.3	62.1	17.5	7.9	12.6	87.5	12.5	(6.7)	(10.4)

**Table 4.2 Logistic Regression Models Predicting ‘Any OC Use’ in South Carolina Medicaid population, 2000-2013**

Model and outcome covariates	Logistic regression predicting the use of any OCs*	
	OR <sup>a</sup>	95% CI <sup>b</sup>
<b>Age<sup>d</sup></b>	1.07 <sup>‡</sup>	1.06, 1.07
<b>Year</b>	1.03 <sup>‡</sup>	1.02, 1.04
<b>Race</b>		
EA	(ref)	(ref)
AA	1.45 <sup>‡</sup>	1.38, 1.53
<b>Marital status</b>		
No	(ref)	(ref)
Yes	1.02	0.96, 1.09
<b>Education</b>		
< High school	(ref)	(ref)
Some high school	0.98	0.92, 1.05
High school graduate	0.75 <sup>‡</sup>	0.70, 0.81
> High school	0.89 <sup>‡</sup>	0.83, 0.95

\* Models were adjusted for age, race, year, marital status, and education level;

<sup>a</sup>Odds Ratio; <sup>‡</sup> p-value < 0.05; <sup>b</sup> Confidence interval (95%)

**Table 4.3 Percent Change Rate (PCR) between 2000 and 2013, Medicaid Users in South Carolina**

OC Type	European American			African American		
	Percent Rate*	Change	P-value	Percent Rate*	Change	P-value
<b>None</b>	0.85*		<0.01	-2.36*		0.01
<b>POC</b>	10.78*		<0.01	3.56*		<0.01
<b>COC</b>	-0.21		0.48	-1.28*		<0.01
<b>POC+COC</b>	6.32*		0.02	3.80		0.96

\*Percent Change Rate: [(Rate in 2013 minus rate in 2000) divided by (rate in 2000)] times 100.

**Table 4.4 Percent Change Per Year Intervals Between 2000 and 2013, Medicaid users in South Carolina**

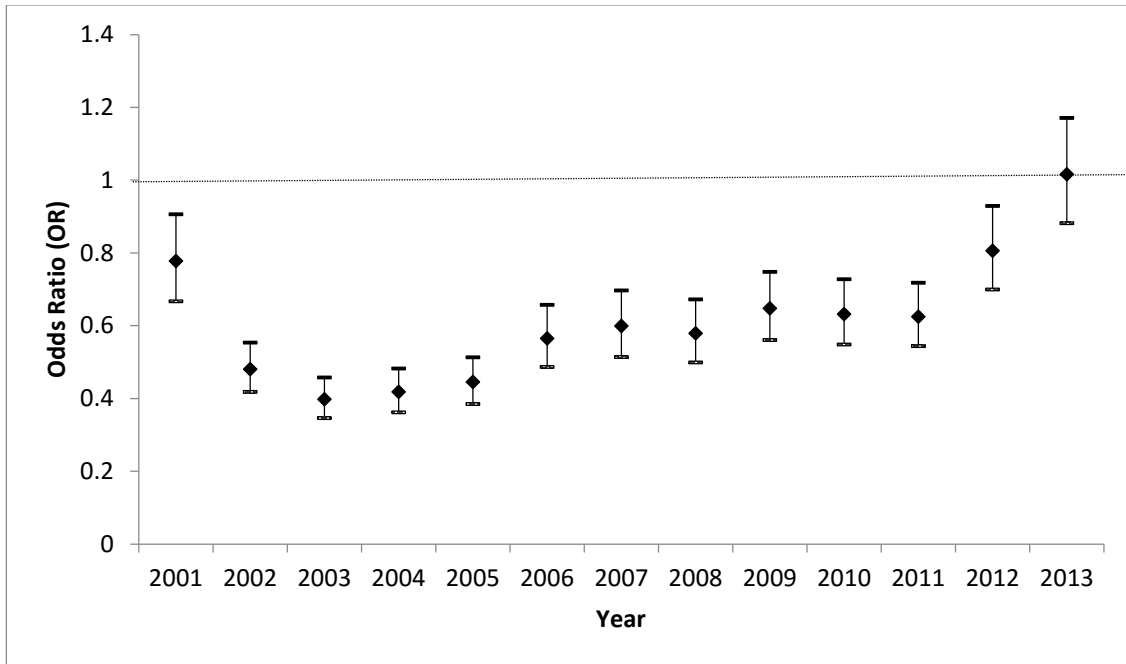
OC Type	European American				African American			
	None	POC	COC	POC+ COC	None	POC	COC	POC+ COC
<b>Year</b>								
2000-2001	24.30	36.05	-3.78	23.30	8.28	8.36	-4.76	15.88
2001-2002	84.52	8.09	1.19	10.40	47.84	6.49	-1.76	-83.87
2002-2003	16.26	7.48	1.65	9.04	8.75	0.74	-4.38	47.38
2003-2004	1.261	7.16	-0.93	9.30	-10.03	6.41	-3.98	29.11
2004-2005	-11.83	-1.66	3.66	8.95	-14.02	-10.13	0.02	11.71
2005-2006	-11.00	-14.39	3.86	0.31	-12.07	-11.33	0.61	20.04
2006-2007	-10.84	6.511	-2.22	13.77	-12.98	14.95	0.41	12.81
2007-2008	-1.62	-1.97	2.81	-1.69	-4.73	-4.17	-2.06	13.23
2008-2009	-0.62	6.86	-0.15	1.51	-6.54	3.81	-1.63	18.17
2009-2010	-4.54	16.83	0.87	1.80	-8.68	-3.12	-1.62	7.71
2010-2011	-20.03	32.33	-7.62	1.47	-7.87	31.44	-6.17	99.53
2011-2012	-20.69	19.78	0.35	-3.83	-16.39	4.39	-1.15	8.48
2012-2013	0.05	-14.83	-2.00	-5.77	3.78	0.03	7.57	-8.70

\*Percent Growth Rate: [(Rate in year (x) minus rate in previous) divided by (rate in previous)] times 100

**Table 4.5 Multinomial Logistic Regression Models Predicting ‘Type of OC Use’ in South Carolina Medicaid population Among OC users, 2000-2013**

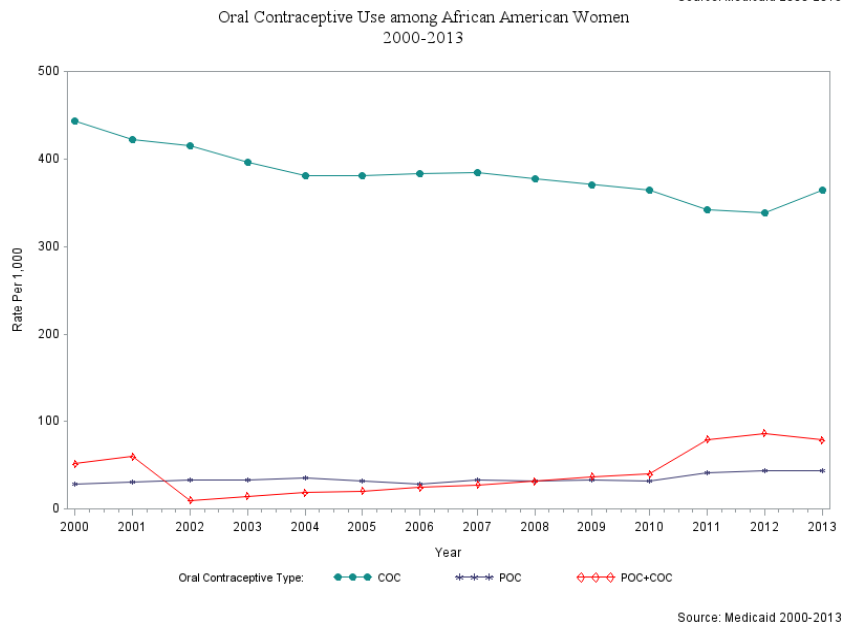
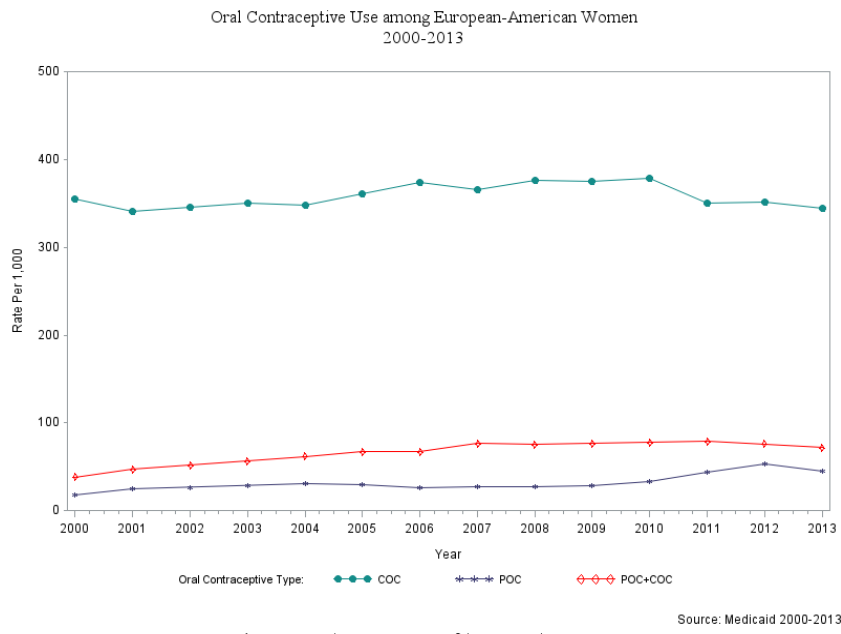
Covariates	Oral Contraceptives						
	COC §	POC‡			POC+ COC ±‡		
	N	N	OR <sup>a</sup>	95% CI <sup>b</sup>	N	OR <sup>a</sup>	95% CI <sup>b</sup>
<b>Year</b>			P-trend: <0.01			P-trend: <0.01	
2000	7469	299	1.00		480	1.00	
2001	7533	423	1.35	1.09,1.68	571	1.23	1.03,1.47
2002	7910	565	1.74	1.41,2.15	681	1.31	1.09,1.56
2003	8368	653	1.57	1.26,1.95	757	1.30	1.09,1.56
2004	8050	705	1.75	1.41,2.18	850	1.81	1.52,2.16
2005	8281	748	1.85	1.49,2.30	987	1.84	1.55,2.19
2006	8395	665	1.74	1.39,2.17	956	1.89	1.58,2.25
2007	8555	697	1.74	1.39,2.16	997	1.96	1.65,2.33
2008	9429	785	1.92	1.55,2.38	1051	1.80	1.51,2.15
2009	11516	1004	2.01	1.64,2.47	1366	1.97	1.66,2.32
2010	12955	1154	1.89	1.54,2.32	1520	2.02	1.71,2.37
2011	15869	1609	2.51	2.07,3.04	1534	1.77	1.50,2.09
2012	17312	1769	2.46	2.03,2.98	1690	1.82	1.55,2.15
2013	20781	1957	2.43	2.01,2.93	1885	1.81	1.55,2.12
<b>Race</b>							
EA	70664	6427	1.00		7603	1.00	
AA	74801	5824	1.09	1.01,1.16	7021	1.09	1.02,1.15
<b>Married</b>							
No	121,430	9375	1.00		10859	1.00	
Yes	27914	3517	1.31	1.20,1.42	4351	1.45	1.35,1.55
<b>Education</b>							
<High school	25229	1705	1.00		2156	1.00	
Some High School	9379	684	1.12	1.02,1.23	940	1.26	1.16,1.37
High School Graduate	8380	557	0.85	0.77,0.95	801	1.12	1.02, 1.23
>High school	16816	1107	0.79	0.72,0.86	1618	0.79	0.73,0.85
<b>Age (years)</b>	152,423	1303	1.05	1.04,1.06	15325	1.07	1.06,1.07

\* Adjusted for age, race, calendar year, marital status, and education level using conditional polytomous logistic model, ‡ p-value < 0.05; ± Mutually exclusive group (does not include either POC or COC users), <sup>a</sup> Odds Ratio; <sup>b</sup> Confidence interval (95%); § Referent group



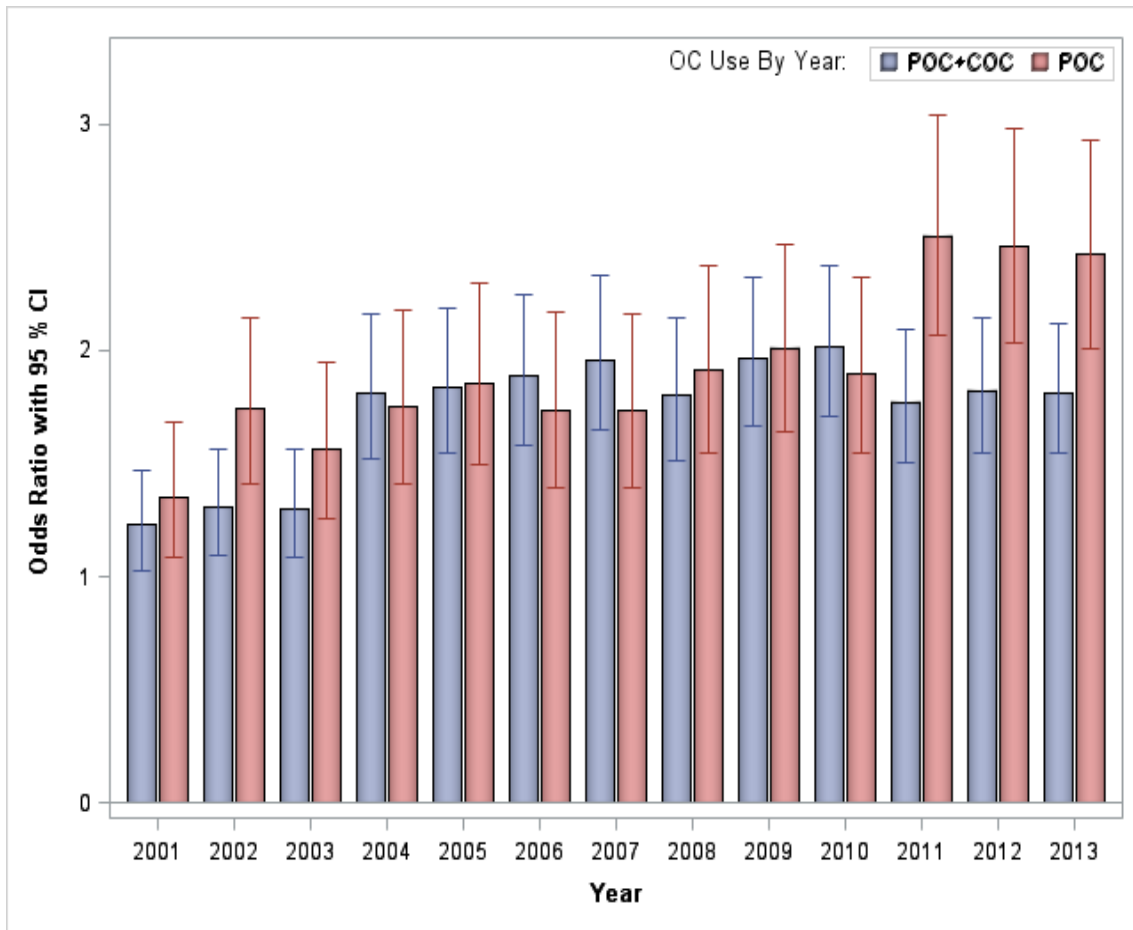
\*Odds Ratio of 'Any OC' use compared to no 'OC use' adjusted for age, race, marital status, education, and year; Referent year 2000 for any OC use compared to No OC use; p-value > 0.05 if OR > 1

**Figure 4.1 Association between year and 'Any OC' use (Odds Ratio and 95% Confidence Interval), South Carolina Medicaid Participants, 2000-2013**



**Figure 4.2 Trends in Oral Contraceptive use by Race and Type of Oral Contraceptive for European-American (top) and African American (bottom), South Carolina Medicaid Participants, 2000-2013**





**Figure 4.3 Association of Year and Type of OC Use (Odds Ratios and 95% CIs) South Carolina Medicaid Participants, 2000-2013.** Referent group: COC Users; Adjusted for calendar year, race, marital status, education, and age

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## CHAPTER V.

### ORAL CONTRACEPTIVES AND BREAST CANCER MORTALITY

#### 5.1 Abstract <sup>2</sup>

**Introduction:** Oral contraceptive pills have been implicated in the pathophysiology of breast cancer. Although many studies have examined the relationship between combined oral contraceptives (COCs) and breast cancer, there is a paucity of literature that discusses progestin-only oral contraceptives (POCs) and breast cancer. The purpose of this investigation is to examine the association of oral contraceptives by type and breast cancer mortality in the South Carolina Medicaid population among different racial/ethnic groups.

**Methods:** Subjects included 4,816 women diagnosed with breast cancer between 2000 and 2013. Kaplan-Meier curves were calculated to determine time-to-mortality rates among oral contraceptives users. Competing risks models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of breast cancer and other cause mortality.

**Results:** POCs were significantly associated with a decreased risk of breast cancer mortality (HR: 0.07; 95% CI: 0.01, 0.52) and a non-significant decreased risk of all-cause mortality (HR: 0.81; 95% CI: 0.41, 1.59). COCs increased the risk of breast cancer mortality (HR: 1.61; 95% CI: 1.14, 2.28) and all-cause mortality (HR: 2.19; 95% CI: 1.81, 3.86).

**Conclusion:** Use of POCs may be associated with a decreased risk of breast cancer mortality and should be considered as an alternative to COCs among high risk populations.

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<sup>2</sup> Samson, M., Adams, SA., Zhang, J., Bennett, C., Hebert, JR. (2016) The Association of Different Types of Oral Contraceptives and Breast Cancer Mortality: A Competing Risk Model. *Under Revision*.

## 5.2 Introduction

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among women (ACS, 2015). In 2015, approximately 30% of new female cancer cases were located in the breast. Reproductive factors, such as oral contraceptive (OC) use, late pregnancy, and nulliparity, as well as genetic factors, family history, and age, increase breast cancer risk (ACS, 2015; DHEC, 2015; Kumle *et al.*, 2002; Anders *et al.*, 2009; Carey *et al.*, 2006). There are currently approximately sixty-two million women in their childbearing years (15-44 years of age) and it is reported that more than 99% of those who are sexually active have used at least one contraception method during their lifetime (Dye, 2008). Contraceptive pills, specifically combined (estrogen+ progestin) oral contraceptives (COCs), and sterilization are the leading methods of choice (Daniels *et al.*, 2013). Since the introduction of the birth control pill in the 1960's, there has been a lot of debate about COCs potential health effects (Anders *et al.*, 2009; Hall *et al.*, 2012). With the increasing popularity of OCs, it is important to focus on the potential health risks they may have on society and to consider ways of reducing these risks.

In the National Survey of Family Growth (NFSG), three-fourths of American women who used a contraceptive method reported using OCs. Of those currently using an OC method, 98% used a COC method, and 2% reported using progestin-only contraceptive pills (POCs) (Hall *et al.*, 2012). Within one year of use, similar rates of unintended pregnancies are observed among COC and POC users with typical and perfect use (9 cases/ 100 women and 3 cases/ 1000 women, respectively) (Carey *et al.*, 2006; NCI, 2015). Typical use refers to pregnancy rates that include inconsistent or incorrect use and perfect use applies to pregnancy rates that reflect women following the directions (e.g. no missed pill) (Trussell, 2011). In fact, both COCs and POCs are more than 99% effective (Hussain, 2004; Kumle *et al.*, 2002; Trussell, 2015). However, COCs are associated with an increased risk of venous thromboembolic events (VTEs), high blood pressure, and breast cancer (Daniels *et al.*, 2013; Hussain, 2004; Kubba, 2003; FSRH, 2009). Compared to women who had



exclusively used POCs, exclusive users of COCs had a 30% increased risk of breast cancer (Kumle *et al.*, 2002). Despite similarities in efficacy and increased risks of adverse effects, COCs remain more popular than POCs. Plausible reasons for the existing disparities in OC use include physician prescription patterns, knowledge and attitudes of OC types, longer biological adjustment periods (Kovacs, 1996) and lack of communication between provider and patient.

Many studies have investigated whether COCs increase the risk of breast cancer (Hunter *et al.*, 2010; Longman *et al.*, 1987; Beaber *et al.*, 2014); however, there is a paucity of literature assessing different types of OCs (non-estrogen-containing formulations) and breast cancer risk. Due to significant health disparities in breast cancer mortality among African American (AA) and European American (EA) women, and potential differences in types of OCs used between races, we will focus on the differences in breast cancer mortality by race. South Carolina can provide insight into potential reasons for racial/ethnic disparities in cancer mortality, with EA women having a higher incidence of breast cancer yet higher survival than their AA counterpart. The purpose of this study is to determine the association between the type of OC use and breast cancer mortality in the South Carolina Medicaid population using a competing risk model (Kubba, 2003). Secondary goals include assessing type of OC use and all-cause mortality as well as mortality from other (or “non-breast cancer”) causes.

### **5.3 Methods**

#### Data Sources and Study Design

All data used for this analysis were collected through the Office of Research and Statistics (ORS)/ SC Revenue and Fiscal Affairs Office (RFA) Medicaid administrative enrollment and claims data and linked to the South Carolina Central Cancer Registry (SCCCR) using probabilistic matching techniques. The SCCCR maintains a gold-certified rating through the National Association of American Cancer Registries (NAACR), indicating data of exceptionally high quality, validity, and completeness. Data was linked by matching on name, social security

number (SSN), and other identifying variables. This study was granted an exemption from the institutional review board of the University of South Carolina.

We used a retrospective cohort to examine the relationship between OCs and breast cancer mortality among low-income populations by race/ ethnicity. Women exposed to POCs, COCs, or POC+COC are compared to individuals who have never been exposed to OCs. Our study is composed of an open cohort, where individuals can leave and enter the population at different time points, from 2000 to 2012.

### Study Population

Medicaid data consists of an open population limited to individuals with  $\geq 12$  months of eligibility. The study population included women diagnosed with a histopathologically confirmed, first primary breast cancer in South Carolina between 2000 and 2012. Women were excluded if they did not have a race designation of EA or AA. Medicaid pharmacy files, classified by the National Drug Code (NDC), included information regarding the pill type, date dispensed, quantity, and the number of refills. Women with NDC codes with therapeutic class 681200 were flagged and women with a prescription for a POC or a COC were included in our study. Women using both POC and COC were included in the POC+COC group.

### Covariates

To evaluate the association between OC use and breast cancer mortality risk, individual baseline and demographic variables were considered in the analysis: year of diagnosis (continuous), education (categorical), marital status (categorical), race (categorical), tobacco (categorical), duration of pill use (continuous), follow-up (continuous), stage of disease (categorical), age (continuous), duration (continuous) and time-to-mortality (continuous). Education was categorized as < high school/ some high school/ high school graduate/  $\geq$  high school; marital status: married/ not married; race: EA/ AA; tobacco: yes/ no; duration of pill use

(months); follow-up (months); stage of disease: stage 0- *in situ*/ stage I- local/ stage II- regional/ stage III- distant; age (years); duration (months); and time-to-mortality (days). Based on the directed acyclic graph (DAG, Figure 1), race and age are confounders, or covariates that create a biasing path (Textor *et al.*, 2011). Adjusting for age and race is a minimally sufficient set for estimating the direct effect of OC use on breast cancer (Samson *et al.*, 2015; Fleischer *et al.*, 2008).

### Main Outcome Measurement

Breast cancer occurrence was determined according to the International Classification of Diseases (ICD-9) codes from the ORS/RFA and SCCCR. Individuals with ICD-9 codes for malignant neoplasms of female breast: 174.X; carcinoma *in situ* of breast: 233.0; and neoplasms of uncertain or unspecified behavior (excluding skin of breast): 238.3 and 239.3. The SEER staging manual (2000) was used to classify breast cancer as *in situ* or noninvasive (stage 0), localized only (stage I), regional (stage II) or distant sites (stage III). Mortality was determined by the SCCCR. Cause of death was categorized as either breast cancer, other, or alive.

### Statistical Methods

Descriptive statistics, stratified by OC use, were calculated for all baseline demographic variables. All categorical and continuous variables were assessed using chi-square test and two-tailed t-tests, respectively. The continuous variables are presented by mean (standard deviation (SD)) and categorical variables by frequencies (percentages (%)). All *P* values were 2-tailed, and significance was assessed as a Type I error rate of alpha 0.05. Kaplan-Meier survival curves were calculated, and the log-rank test statistic was used to assess statistical differences between OC groups for breast cancer mortality. Competing risk models were performed and models fitted using the Lunn McNeil approach to estimate cause-specific mortality (breast cancer and other causes) (Lunn *et al.*, 1995). Associations among all-cause mortality rates, race, and other

important covariates were estimated using Cox proportional hazards (PH) model. In the competing risk model, events were classified as breast cancer or other cause mortality and in the Cox PH model, events were classified as all-cause mortality. Total survival time was calculated for all subjects as the time from oral contraceptive use to the time of death or censoring. In the Cox PH model, women were followed from OC use until any event occurred (breast cancer or other cause) to determine all-cause mortality. In the competing risk models, survival time was calculated from OC use to breast cancer mortality and in a separate model, from breast cancer diagnosis to non-breast cancer deaths, or other causes of deaths. Women were censored at either the date of death for their respective model or at the end of the study period, whichever occurred first.

Separate competing risk models were performed by race (EA/ AA), adjusting for other baseline and demographic variables. Cox PH models were used to assess the association between baseline and demographic variables with hazard risk from overall mortality by race. We evaluated PH assumption and the time-dependent relationship between OC exposure and all-cause mortality using Cox PH models. In our final competing risk model, we adjusted for OC use, marital status, year of diagnosis and age for EA women and OC use, stage, and age for AA women, when assessing breast cancer mortality. Duration was not a significant predictor in these models. Adjustments varied slightly when assessing other cause mortality by race (Table 2). Covariates were determined based on backward elimination with an entry level of 0.10. However, OC use, our main variable, was kept in all models based on the *a priori* research question. In the reduced model, the p-value < 0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (Cary, NC).

## 5.4 Results

### Participants

Baseline characteristics according to OC use are presented in Table 1. A total of 3,364 breast cancer patients diagnosed between 2000 and 2012 were included in the analysis. The OC distribution was POC (n= 135; 2.8%), COC (n= 3,958; 82.2%), and POC + COC (n= 265; 5.5%). Never users consisted of 9.5% of the study population. The highest mean age (41.5 years (SD: 8.2)) of use was seen among POC+COC users, a group which primarily consisted of married women (80.4%) and women who had more than a high school education. The shortest mean follow up was seen among POC users (99.3 months (SD: 43.7)). No women in our sample who used POC+COC or POC exclusively were diagnosed with stage III breast cancer.

Figure 2 presents the univariable hazard ratios for risk of breast cancer and all-cause mortality by race and OC type. The crude analysis suggests an increased risk of breast cancer mortality among COC users of all races (HR: 1.80; 95% CI: 1.29, 2.55) and among EA women (HR: 2.10; 95% CI: 1.44, 3.06), specifically. The decreased risk seen in AAs using COC is non-significant (p-value: 0.21). Similar findings were observed among COC users and all-cause mortality (all races- HR: 2.38; 95% CI: 1.71, 3.32, EA- HR: 2.85; 95% CI: 1.96, 4.14, AA- p-value: 0.26). POC was inversely associated with breast cancer-specific mortality among all races (HR: 0.04; 95% CI: 0.01, 0.33, p-value: < 0.01) but was not associated with all-cause mortality (HR: 0.60; 95% CI: 0.30, 1.20, p-value: 0.28). Competing risks regression analyses that controlled for marital status, follow up, year of diagnosis, age, and stage of breast cancer diagnosis were performed to assess whether the use of OC was associated with longer survival times compared to no OC use. Tobacco and duration were removed in the final model due to missing information and nonsignificant findings.

Kaplan-Meier survival curves of Medicaid cohort are stratified by their OC exposures (never users, POC, COC, or POC+COC) in Figure 3. There are significant differences in survival by OC

type. POC users performed worse than never users until approximately 6 years but performed better than COC and POC+COC users regardless of timing. As shown in the reduced models (Table 2), EA women had a significantly higher likelihood of breast cancer death when using either COC (HR: 1.91, p-value: <0.01) or POC+COC (HR: 3.02, p-value: <0.01) compared to never use. EA also had a reduction in risk of breast cancer mortality with each additional year of diagnosis and age. OC use was not significantly associated with an increased risk of other-cause mortality among EA and AA women and did not significantly decrease the risk of breast cancer mortality among AA women. Overall, POC was associated with a reduced risk of breast cancer mortality (HR: 0.07, p-value: <0.01) and both COC and POC+COC were associated with increased risks of breast cancer mortality (HR: 1.61 and 2.09, p-value: <0.01) (Table 3).

Table 4 shows the results of all-cause survival using the Cox PH model for AA, EA, and total (AA+EA) women. Overall, OC use was not significantly associated with all-cause mortality among AA women. However, without stratification, the total population had an increased mortality when using either COCs or POC+COC (HR: 2.19; 95% CI: 1.57, 3.07 and HR: 2.64, 95% CI: 1.59, 4.39, respectively). The increased all-cause mortality risk was also noted among EA women using COCs and POC+COC. EA women and the total population saw 2-3 fold increased risk of all-cause deaths among COC and POC+COC users.

## 5.5 Discussion

In this large study of 4,816 women (4,358 OC users) we found that COC and POC+COC use were positively associated with breast cancer mortality. After adjustment for relevant covariates, EA women using COCs and POC+COCs had 1.91 to 3.02 times the risk of breast cancer death and 2.65 to 3.25 times the risk of all-cause mortality compared with never users. The association between AAs OC use and breast cancer mortality was not significant. Mortality in the AA population was primarily determined by stage of breast cancer diagnosis.

Recently, a meta-analysis of contraceptive use and breast cancer risk showed POCs were not associated with increased breast cancer risk (Samson *et al.*, 2015). In this current study, we found a significantly reduced risk between POC use and breast cancer mortality in the total population (HR: 0.07; p-value: <0.01). Yet, POCs were associated with non-significantly increased likelihood of death from other causes (non-breast cancer mortality) and non-significantly reduced risk of all-cause mortality. Other studies have hypothesized that medical surveillance may bias the relationship between COCs and breast cancer (Shapiro, 2000; Kumle *et al.*, 2002) and similarly, access to health care may bias the relationship between COCs and breast cancer mortality. However, this biasing relationship is reduced in our study because POC and POC+COC users have undergone similar medical surveillance procedures and have similar access to health care.

This study suggests that OCs play a differential role in breast cancer, other cause and all-cause mortality by race. However, the lack of a clear association among AA women using OCs and our outcomes of interests requires more attention. Larger sample sizes of AA women may be necessary in the future to examine this relationship. There were only six AA women using POC+COCs, which reduces our power in interpreting POC+COC utilization in this population. Understanding the role of OC types on women's health could help minimize the burden of cancer and more epidemiologic studies need to be done to explore the effect of POCs. The only marketed POC in the United States is norethindrone .35 mg tablet, which includes Camila, Errin Nor-QD, Ovrette, Jolivette, OrthoMicronor and generic medications. Typically, POCs are recommended for women who have certain contraindications to estrogen-containing formulations. For example, in our population, smoking was more common among POC users (82.4%). Despite 28.7% of COC users being smokers, smoking is a known contraindication of COC use and may result in serious adverse events (e.g. VTE, stroke) (FSRH, 2009; FSRH, 2011; Curtis, 2010). Most of the available information about the risks of breast cancer focuses on COC

users and case-control studies. Comparing various types of contraceptive preparations may provide us with insight to safer alternatives to pregnancy prevention, especially among high-risk groups.

This study should be replicated in more generalizable populations but still provides with us with insight to a less risk adverse alternative to COCs. It is important to raise awareness of POCs in populations that have large numbers of smokers, family history of breast cancer, and cardiovascular disease, and who may be more susceptible to the estrogen component in the OC pill. The use of OCs can vary drastically by region. In the US, approximately 17% of women 15-45 use COCs, which is only half the number of women using OCs in Europe and twice the number of women in Africa (Brynhildsen, 2014). Future research should examine this relationship by region and using different cohorts.

#### Strengths and limitations

Strengths of our study include the large sample size and detailed information on medication use from enrollment and administrative claims data. Our study did not exclude POC formulations when considering types of OCs, which makes it unique. Furthermore, our sample population is restricted to Medicaid beneficiaries, which provides us with unique insight to underrepresented groups. However, this data registry did not provide information on potential confounders such as diet, physical activity, serum lipids, blood pressure, family history, and other reproductive factors (e.g. menstrual history). Limited information was provided on tobacco use. Studies have shown that there is a considerable amount of misinformation among health care providers and contraception health and that older providers, and primary care physicians tend to demonstrate a larger gap (Dehlendorf *et al.*, 2010).



## 5.6 Conclusion

Among premenopausal women using OCs, COCs were the strongest predictor of breast cancer mortality and POC+COCs were the strongest predictor of overall mortality. The type of OC used should be taken into account when assessing breast cancer mortality risk. POCs may be a safer alternative for women who may suffer short and long-term adverse events related to the estrogen component of COCs.

## 5.7 Tables and Figures

**Table 5.1 Baseline demographic characteristics of Medicaid Participants by OC use, 2000-2012**

Characteristics (N, %)	Never Use (n=458)	Oral Contraceptive Types			P Value
		POC (n=135)	COC (n=3958)	POC+ COC (n=265)	
<b>Breast Cancer</b>					0.24
Yes	342 (74.7)	96 (71.1)	2698 (68.2)	228 (86.0)	
No	116 (25.3)	39 (28.9)	1260 (31.8)	37 (14.0)	
<b>Race</b>					<0.01
White	427 (93.2)	118 (87.4)	3773 (95.3)	259 (97.7)	
Black	31 (6.8)	17 (12.6)	185 (4.7)	6 (2.3)	
<b>Education</b>					0.31
< High School	26 (12.2)	14 (53.9)	532 (28)	0 (0.0)	
Some high school	5 (2.3)	0 (0.0)	32 (1.7)	0 (0.0)	
High school graduate	12 (5.6)	2 (7.7)	121 (6.4)	0 (0.0)	
> High school	171 (79.9)	10 (38.5)	1215 (64.0)	111 (100.0)	
<b>Stage</b>					<0.01
Stage 0- In situ	17 (5.0)	3 (3.2)	343 (12.8)	22 (9.7)	
Stage I- Local	156 (45.8)	48 (51.1)	1175(44.0)	12(5.3)	
Stage II- Regional	166 (48.7)	43 (45.7)	978 (36.6)	194 (85.1)	
Stage III- Distant	2 (0.6)	0 (0.0)	178(6.7)	0 (0.0)	
<b>Tobacco</b>					0.31
Yes	17 (10.9)	28 (82.4)	352 (28.7)	0 (0.0)	
No	139 (89.1)	6 (17.7)	876 (71.3)	16 (100.0)	
<b>Married</b>					<0.01
Yes	128 (30.1)	45 (37.2)	992 (25.1)	213 (80.4)	
No	298 (70.0)	76 (62.8)	2954 (74.9)	52 (19.6)	
<b>Mean (SD)</b>					
Age	34.4 (5.3)	35.0 (6.7)	36.2 (7.3)	41.5 (8.2)	<0.01
Follow-up	121.9 (15.7)	99.3 (43.7)	139.4 (29.2)	135.7 (21.9)	<0.01
Year	2008.8 (2.4)	2008.1 (3.2)	2008.6 (2.8)	2010.0 (1.5)	<0.01
Duration of use	N/A	7.4 (4.4)	40.6 (34.4)	67.9 (43.6)	0.03

**Table 5.2 Competing Risk Regression Analysis for Death from Breast Cancer and Other Causes in Medicaid Patients by Race**

Variable	No. of Patients	No. of Events	Breast Cancer Mortality <sup>a</sup>			Other cause Mortality <sup>β</sup>		
			Estimate	HR	P-Value	Estimate	HR	P-Value
<b>European American</b>								
<b>Oral Contraceptive</b>								
Never use	427	320	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
POC	118	82	-12.88	<0.01	0.95	0.07	1.08	0.99
COC	3773	2575	0.65	1.91*	<0.01	0.08	1.08	0.99
POC+COC	259	225	1.11	3.02*	<0.01	0.08	1.09	0.99
<b>Married</b>								
No	3196	2391	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Yes	1327	795	0.13	1.13	0.21	-3.95	0.02*	<0.01
<b>Follow-up time</b>	4577	3202	£	£	£	0.01	1.01*	<0.01
<b>Year of Diagnosis</b>	4577	3202	-0.34	0.71*	<0.01	0.69	0.71*	<0.01
<b>Age</b>	4577	3202	-0.04	0.96*	<0.01	£	£	£
<b>African American</b>								
<b>Oral Contraceptive</b>								
Never use	31	22	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
POC	17	14	-1.49	0.23	0.17	-0.24	0.58	0.82
COC	185	123	-0.72	0.49	0.10	-0.55	0.50	0.71
POC+COC	06	03	-0.24	0.78	0.82	N/A <sup>±</sup>	N/A <sup>±</sup>	N/A <sup>±</sup>
<b>Stage</b>								
<i>In situ</i>	36	17	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
Local	94	62	1.47	4.34*	0.04	£	£	£
Regional	93	68	2.08	8.04*	<0.01	£	£	£
Distant	12	11	3.65	38.50*	<0.01	£	£	£
<b>Year of Diagnosis</b>	239	162	£	£	£	-0.51	0.60*	<0.01
<b>Age</b>	239	162	0.04	1.04*	0.05	£	£	£

<sup>a</sup> EA: adjusted for OC use, marital status, year of diagnosis, and age; AA: adjusted for OC use, stage, and age; <sup>β</sup> EA adjusted for OC use, marital status, follow-up, and year of diagnosis; AA: adjusted for OC use, and year of diagnosis; £ Not included in reduced model (Overall model >0.05); HR: Hazard Ratio; CI: Confidence Interval; <sup>±</sup> Sample size/ count < 5; \*Significant (p< 0.05)

**Table 5.3 Competing Risk for Breast Cancer Mortality Using the Total Population**

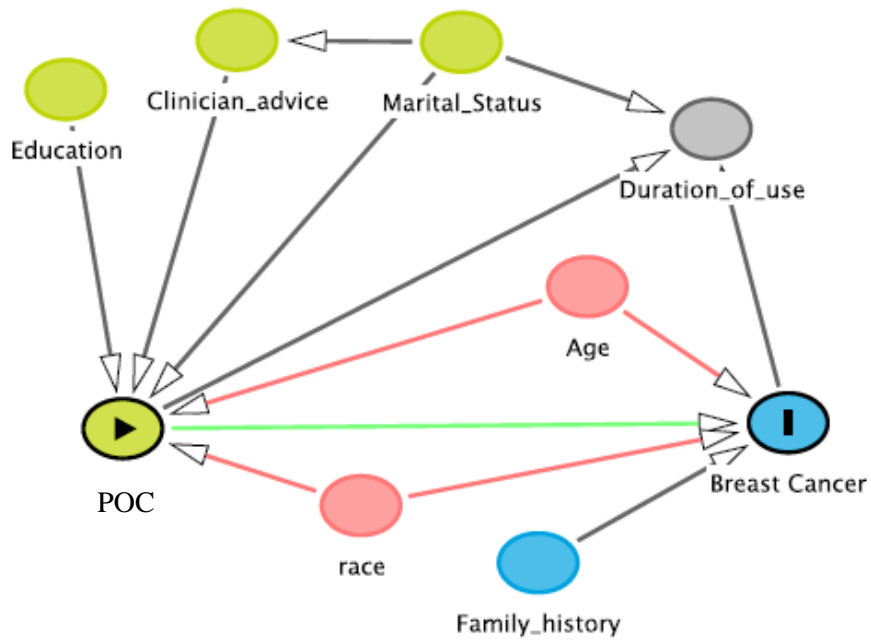
	No. of Patients	No. of Events	Estimate	HR	P-Value
Oral Contraceptive					
Never use	916	684	(ref)	(ref)	(ref)
POC	270	192	-2.65	0.07	<0.01
COC	7916	5396	0.48	1.61	<0.01
POC+COC	530	456	0.74	2.09	<0.01

\*Adjusted for OC use, marital status, stage, follow-up, year of diagnosis, and age; Adjusted for all races

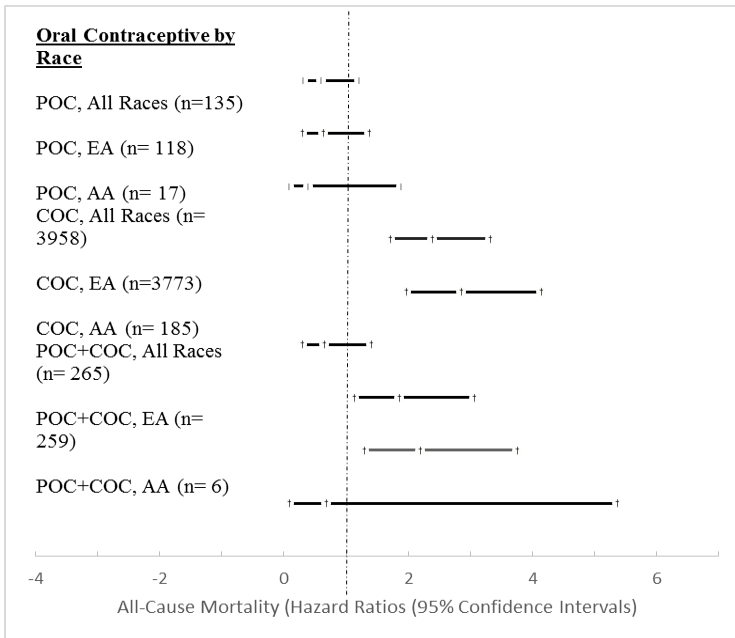
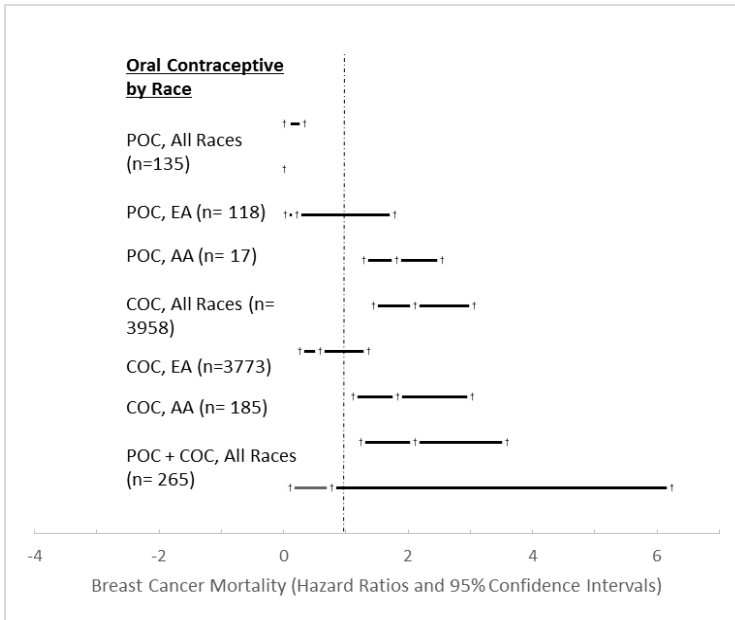
**Table 5.4 Cox regression analysis for overall survival deaths in the Medicaid cohort**

	Race	N	Overall Mortality <sup>β</sup>
Oral Contraceptives			
Never Use	EA £	427	1.00
	AA‡	31	1.00
	Total ¥	458	1.00
POC	EA	118	0.92 (0.43, 1.94)
	AA	17	0.24 (0.05, 1.19)
	Total	135	0.81 (0.41, 1.59)
COC	EA	3773	<b>2.65 (1.81, 3.86)*</b>
	AA	185	0.43 (0.19, 1.00)
	Total	3958	<b>2.19 (1.57, 3.07)*</b>
POC+ COC	EA	259	<b>3.25 (1.89, 5.58)*</b>
	AA	6	0.33 (0.39, 2.81)
	Total	265	<b>2.64 (1.59, 4.39)*</b>

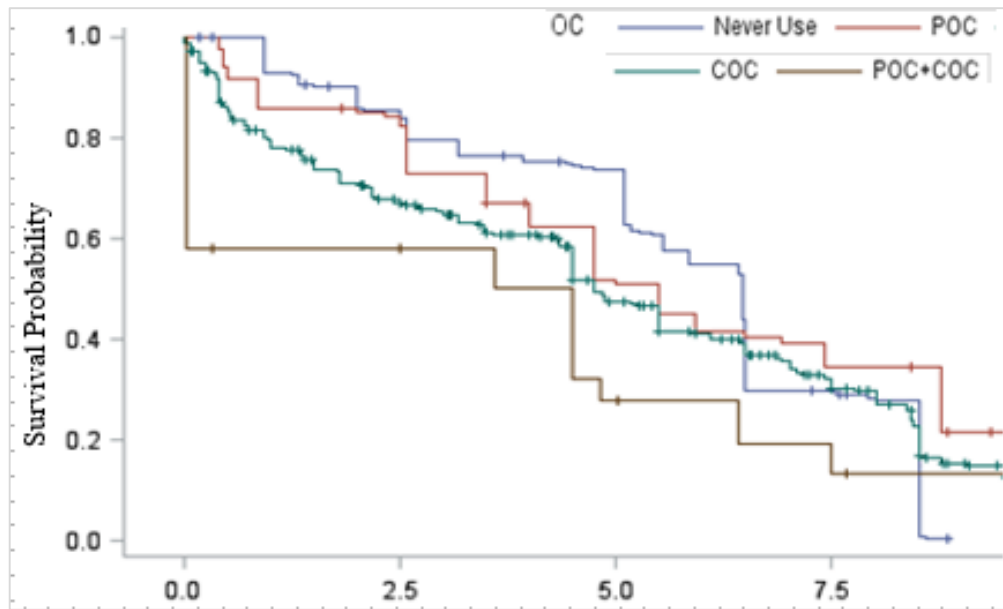
‡ AA satisfied PH assumption, no time-dependent covariates; £EA did not satisfy PH assumption, time-dependent model covariate (stage) used; ‡Model adjusted for OC use, stage, and year of diagnosis; £ Model adjusted for OC use, marital status, year of diagnosis, and (as a function of time) stage; ¥ Model adjusted for OC use, marital, follow-up time, year of diagnosis, and (as a function of time) stage



**Figure 5.1 Directed Acyclic Graph illustrating the association of POC use and breast cancer risk**



**Figure 5.2 Univariable hazard ratios for risk of breast cancer mortality (top) and all-cause mortality (bottom) by race and oral contraceptive type**



**Figure 5.3 Kaplan-Meier (KM) Survival Curves (“Time-to-mortality”) for different Oral Contraceptive Users (Never Users/ POC/COC/ POC+COC)**

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## CHAPTER VI.

### ORAL CONTRACEPTIVES AND CARDIOVASCULAR DISEASE

#### 6.1 Abstract

**Introduction:** Certain types of oral contraceptives (OCs) can produce favorable effects on lipid metabolism and vascular tone, while others have potentially detrimental effects. Endogenous and exogenous hormones exert different effects on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) depending on the type, combination, and dose of the hormone. The estrogenic and progestogenic effects of exogenous hormones on HDL and LDL are inconsistent. Studying surrogate end points (LDL, HDL levels) may provide a misleading picture of OCs.

**Methods:** Medicaid data (2000-13) were used to assess the relationship between the type of OCs and CVD incidence. Multivariable logistic regression was used to model relationships between cardiovascular disease and OC use adjusting for potential confounders.

**Results:** Compared to combined OCs (COC), progestin-only OCs (POC) decreased heart disease and stroke incidence after adjusting for important covariates (OR: 0.74 and 0.39, respectively; p-value: <0.05). However, POC+COC was associated with a significant increased risk of heart disease and stroke incidence (OR: 2.28 and 2.12, respectively; p-value: <0.05).

**Conclusion:** Careful consideration of women's CVD risk factors should influence choice of OC used. Baseline CVD risk should be a part of the discussion between women and their primary care providers when making choices regarding OCs.

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<sup>3</sup> Samson, M., Adams, SA., Zhang, J., Bennett, C., Hebert, JR. (2016) Cardiovascular Disease Incidence among Females in South Carolina by Type of Oral Contraceptives, 2000-2013: a retrospective cohort study. *Under Revision*.

## 6.2 Introduction

Cardiovascular diseases (CVDs), including hypertension, stroke, coronary heart disease (CHD), peripheral artery disease, and venous thromboembolism (VTE), are the leading causes of death among females in the United States (US) (Go *et al.* 2013; CDC, 2013a). Heart disease and its complications are the largest contributors to CVD incidence and mortality (Mosca *et al.*, 2011) and disproportionately affect women and African Americans (AA) (Albert *et al.* 2004). Over the past decades, there has been an increased use of oral contraceptives (OCs) (Shufelt *et al.*, 2009), as well as significant increase in heart disease and stroke morbidity and mortality rates (Go *et al.* 2013). OC use, body fat, and race can lead to lipid and lipoprotein abnormalities and are important contributors to CVD (Miller, 1994; Berenson *et al.*, 2009).

OCs modulate lipid metabolism differentially according to the hormone make-up (e.g. progestin-only, combined estrogen+ progestin), delivery route and the particular patterns of use (Crook *et al.*, 1988). High levels of low-density lipoprotein (LDL) cholesterol and triglyceride levels increase the risk of CVD in women while high-density-lipoprotein (HDL) may confer considerable protection against CVD incidence (Finks, 2015). Hormones may have both beneficial and harmful impacts on lipids, lipoproteins, and cardiovascular health. Ideally, women should use OCs that reduce their risk of CVDs and protect them from unwanted pregnancies.

Endogenous estrogen, or estrogen produced naturally within an individual, can decrease LDL and total cholesterol by 5-15% and increase HDL by 10% (Gouva *et al.*, 2004). However, exogenous estrogen, which is introduced to the body from an external source, has a diminished cardioprotective effect (Rosano *et al.* 2000). The relationship between hormones and CVD becomes more complex when accounting for specific types of estrogen and progestin formulations or progestin-only formulations, which vary by country and OC generation (Dumeaux, *et al.*, 2003). Exogenous progestins and estrogens have not been studied as extensively and may have no

influence on LDL and HDL levels (Chakhtoura *et al.*, 2009; Graff-Iversen, 2015). Thus, focusing on surrogate end points alone to predict clinical outcomes may be misleading (Herrington *et al.*, 2003). Although many pharmacologic agents (e.g., statins, PCSK9 inhibitors) that lower LDL significantly reduce cardiovascular events in many individuals, other interventions that increase HDL and reduce LDL have no beneficial effect on CVD health (AIM-High, 2011).

Additional studies are necessary to understand the role of OCs in the cardiovascular system, with a particular focus on progestin-only oral (POC) formulations. Due to the popularity of estrogen+ progestin, or combined oral contraceptives (COC), studies have focused mainly on these types of OCs and overlooked the action of progestin (or exogenous progesterone) on CHD and stroke incidence. We hypothesize that POC users have a reduced risk of CVD compared to current and past COC users. Studies have shown COC users are more likely to suffer from VTE, stroke, myocardial infarction, cancer, and other chronic diseases (Marchbanks *et al.*, 2002; ACOG, 2006; FSRH, 2009) compared to never users. The primary objective of the present retrospective cohort study was to compare the effect of COC formulations with progestin-only regimens to understand the association of OC types and CVD incidence. We also examined potential effect modification by race.

### **6.3 Methods**

#### **Setting**

South Carolina's (SC) Medicaid population is ideal for studying CVD incidence among racial/ethnic groups due to the high percentage of chronic disease, females and AAs in SC (Medicaid, 2015). SC is located in the southeastern part of the US, which is often referred to as both the "Stroke Belt" and the "Heart Failure Belt." This region of the US is known as such because of the excess incidence and mortality of strokes and heart failure compared to the rest of the nation (Montresor-López *et al.*, 2015; Mujib, Zhang, Feller, & Ahmed, 2011; Samson, Trivedi, & Heidari, 2015). Furthermore, Medicaid is one of SC's largest insurance providers, insuring 21% of SC

residents, of which, 43% are AA (Medicaid, 2015; MLTSS, 2015). There has been significant increase in POC use among European American (EA) and AA women in SC from 2000 to 2013 (Samson, Adams *et al.*, 2015), which will provide us with adequate sample sizes to study the role of progestin-only contraceptives on CVD incidence.

### Study Design and Participants

We constructed a retrospective cohort from the SC Revenue and Fiscal Affairs Office (RFA) Medicaid administrative enrollment and claims data to examine the relationship between OC type and CVD incidence among low-income populations by race/ethnicity. The SC RFA has information on OC prescriptions and the cardiovascular disease outcome (stroke and HD incidence). All women between the ages of 18 and 55 years (i.e., the usual age range for contraception use) with at least one type of OC prescription dispensed from 2000 to 2013 were included. All data were de-identified. Approval for the usage of this de-identified information was obtained by the University of South Carolina Institutional Review Board, as well as the Office of Research and Statistics/ SC Revenue and Fiscal Affairs Office.

### Definition of exposure

OC status was determined from pharmacy claims that included the drug/generic names, dispensed date (month/year), national drug codes (NDC), therapeutic class (681200), age at claim, and days supplied. Women with at least one type of OC prescription dispensed during our study period and between 18 and 55 years of age (i.e., the range for contraception use) were included as OC users in our study. Type of OCs to which women were exposed included progestin-only oral contraceptives (POC), estrogen+ progestin or combined contraceptives (COC), and POC+COC. POC formulations in our study population included norethindrone only. OC types (POC, COC, and POC+COC) are mutually exclusive. Never users, POC and POC+COC users were compared to

individuals who used COCs, the most popular OC type. Duration of OC use was calculated in months for each member using OCs.

#### Definition of outcome

The outcome was classified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes (50), collected from the each patients enrollment period. A primary diagnosis of HD was classified by the subcategory 414.XX. Major complications, such as myocardial infarction (410.XX), other acute or subacute forms of ischemic HD (411.XX), angina pectoris (413.XX), hypertensive HD, and diseases of pulmonary circulation related to HD, and other forms of HD resulted in a woman being flagged for HD. Similarly, primary diagnoses of ischemic or hemorrhagic stroke (ICD-9-CM code of '430,' '431,' '432.X,' '433.XX,' '434.XX,' and '436') (22) were flagged for stroke.

#### Other covariates

Information on demographics were included, such as race (African American/ European American), education (< high school/ some high school/ high school/ > high school), marital status (married/ not married), duration of OC use, follow-up time and age. SC Medicaid administrative claims data, included women between January 1st, 2000 to December 31st, 2013, who (1) were permanent residents of SC during the study period, (2) had  $\geq 12$  months of Medicaid eligibility (3) were between the ages of 18 and 55 years and (4) were either African American/ black or European American/ white. Other races accounted for less than 5 percent of our cohort.

#### Statistical Analysis

Univariate and descriptive statistics were calculated for all study covariates. Differences in continuous measures were assessed using 2-sample t-tests and categorical measures were assessed

using chi-square test. We evaluated the association between OCs and incident CVD using logistic regression analysis. Crude and adjusted odds ratios (ORs) were calculated with their corresponding 95% confidence intervals. There were four levels of exposure (never use, COC, POC, and POC+COC). Each group was compared to COC users, our referent group. Models controlled for important confounders, including year of diagnosis, age, race, duration of use, and education. Potential confounders that changed ORs by > 10% were retained in the final model. Analyses were stratified by race based on *a priori* hypotheses that there may be dissimilar effects by race. All p-values were two-tailed, and a value of less than or equal to 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

## 6.4 Results

### Study Participants

From 2000 to 2013, there were 1,396 incident CVD events (1,219 HD and 175 strokes). The mean age of women experiencing stroke (mean: 28.6 (7.5) years) was higher than those experiencing HD (mean: 30.1 (8.4)) (Table 1). The mean age of HD incidence for all women was higher among POC users (age: 31.4 SD: 8.8) than all other OC age groups (never user: 26.6 (SD: 7.0), COC: 28.7 (SD: 7.6), and POC+COC: 26.6 (SD: 7.0)). Similarly, the mean age of stroke incidence for all women was higher among POC (mean: 29.8 (SD: 10.4)) compared to all other women (Table 1).

Table 2 shows that after adjusting for important covariates, never users and POC users had a significantly reduced odds of HD compared to COC users (OR: 0.65; 95% CI: 0.52, 0.82 and OR: 0.74; 95% CI: 0.57, 0.97, respectively). POC+COC users had a significantly increased risk of HD (OR: 2.28; 95% CI: 1.92, 2.70) compared to COC users.

OC types conferred similar benefits and harms on both HD and stroke incidence, relative to COC users. The decreased risk seen among never users in predicting HD incidence compared to



COC users, was consistent among women who had strokes, albeit not significant (OR: 0.95; 95% CI: 0.57, 1.59). However, there were differential effects by race. AA women who never used OCs had a non-significantly higher incidence of stroke (OR: 1.28; 95% CI: 0.72, 2.27) compared to COC users, whereas EA women had a non-significantly decreased risk (OR: 0.46; 95% CI: 0.14, 1.46). Overall, POC users had significantly decreased risks of stroke (0.39; 95% CI: 0.16, 0.95) compared with COC users.

Unlike other OC methods, POC+COC users did not have a protective effect on heart disease or stroke risk. After adjusting for important covariates, women using POC+COC had twice the odds of heart disease (OR: 2.28; 95% CI: 1.92, 2.70) and stroke (OR: 2.12; 95% CI: 1.34, 3.35) compared to COC users.

## 6.5 Discussion

This retrospective analysis sought to examine the relationship between OC types among a population of low-income women and the incidence of heart disease and stroke. Our study findings show that POC users have a significantly reduced risk of heart disease and stroke compared to COC users. Never users also have a significantly reduced risk of heart disease; however, among stroke patients, the risk reduction is non-significant. Despite the non-significant association between never users, it is interesting to note that the point estimates for never users were in opposite directions for AA and EA women.

Among never users, AA women had a non-significantly higher risk of stroke compared to EA women (Bousser *et al.*, 2000; Roach *et al.*, 2015; Kemmeren *et al.*, 2002). Also, women had strokes at a younger age than expected. These results requires additional attention in future studies. The high prevalence of substance abuse in the Medicaid hospital care program (Fox *et al.*, 1995), as well as the association between young adults' abuse of amphetamines or cocaine and increased risk of stroke (Westover AN *et al.*, 2007) may have contributed to the unexpected results among women.

Other potential explanations for the differential stroke risk by race may be explained by environmental or genetic factors, as well as medical surveillance bias (Szklo *et al.*, 2012). AA women's higher risk of stroke incidence and mortality compared to EA women (Bhandari *et al.* 2005), may be associated with their higher BMI (Morales *et al.* 2014), differential lipid modulation, thrombophilia occurrence (Greenlund *et al.*, 1997) and the type of OC prescribed. Despite a decline in recent decades of CVD mortality in the US, the rate among younger women has plateaued (Chomistek *et al.*, 2015). Therefore, it remains critical for us to investigate risk factors for CVD and to identify sustainable methods to successfully prevent disease.

The current literature examining OCs and CVDs often consider surrogate end points, such as glucose tolerance and lipoproteins (Crook *et al.*, 1988; Miller, 1994; Graff-Iversen, 2015) to determine if an association exists. However, OC type and hormone interactions play an important role in modulating carbohydrate metabolism and lipoprotein risk factors. Due to the complex nature of this relationship, the role of exogenous progestin and estrogen on HD and stroke health is still not clearly understood (Miller, 1994). Additional studies need to focus on the cardiovascular health benefits of exogenous hormones contained in OCs.

Additional medical encounters may reduce stroke risk for high-risk COC users because physicians may be detecting subclinical cases or precursors of stroke (e.g. hypertension) (Chasan-Taber *et al.*, 1996) more frequently than for women who have less frequent clinical exposures. This may be more noticeable among AA women because of the known association between race and stroke (Longstreth, *et al.*, 2015). Increased physician-patient contact may also help explain why women in our sample had such a low mean age of disease incidence and why never users may have had more stroke events.

There are many barriers to women's health services (Gelberg *et al.*, 2004). The Patient Protection and Affordable Care Act (ACA) has many significant implications for women's health that may help reduce costs related to women's preventive care services, and that may improve

gynecological and reproductive health of low-income women. Future studies should consider the impact of ACA and Medicaid expansion on women's health (NWLC, 2015).

The widespread use of COCs may inadvertently ignore the guidelines for OC use. According to women who are older than 44 years of age should not use COCs (Longstreth *et al.*, 2015); however, in our sample, the majority of women older than 44 were using COCs. Furthermore, guidelines do not include women who have switched from COCs to POCs, or *vice versa*. The POC+COC group is a unique group that includes many women who have had to change from COC to POCs, potentially due to a CVD event, breastfeeding, or temporary loss of fecundity (FSRH, 2009); or women who switched from POCs to COCs due to irregular bleeding (CDC 2013b; FSRH 2009). We found that these women typically had a significantly higher risk of CVD incidence; however, additional research needs to focus on this understudied group.

### Strengths and Limitations

Our study has both strengths and limitations. A major strength is the large sample size, which allowed us to investigate racial disparities in CVD risk among OC users in South Carolina. Since SC has a high representation of AA residents (RFA, 2015), we were able to assess CVD incidence in a multi-ethnic cohort. Another strength of our study is we did not have to adjust for socioeconomic status because all women in the Medicaid population are low-income. This allowed us to study an underrepresented group. However, a limitation to our study is that we did not have information on important factors that may influence CVD incidence including lipoprotein levels, diet, BMI and tobacco smoking.

### **6.6 Conclusion**

Our research indicates POCs are associated with a significantly decreased risk of heart disease and stroke compared to COCs. High-risk groups should consider POCs as an alternative

contraceptive method that may reduce risk of certain cardiovascular diseases. If confirmed, these results suggest that careful considerations should be made when prescribing OCs. Determining which groups will benefit most from using POCs as their preferred contraceptive method may improve clinical CVD outcomes for women.

## 6.7 Tables and Figures

**Table 6.1 Characteristics of Medicaid Population with Heart Disease and Stroke, SC Medicaid Population, 2000-2013**

Exposure (Cases)	Heart Disease				Stroke				
	Never Use (n=84)	POC (n=64)	COC (n=898)	POC+COC (n=173)	Never Use (n=17)	POC (n=05)	COC (n=133)	POC+COC (n=22)	
Total Sample	7,604	3,500	51,901	4,729	8,233	3,792	56,578	5,225	
Year									
2000-2001	05 (6.0)	07 (10.9)	84 (9.4)	09 (5.2)	00 (0.0)	00 (0.0)	05 (3.8)	00 (0.0)	
2002-2003	13 (15.5)	07 (10.9)	97 (10.8)	13 (7.5)	01 (5.9)	01 (20.0)	13 (9.8)	01 (4.6)	
2004-2005	12 (14.3)	07 (10.9)	88 (9.8)	18 (10.4)	01 (5.9)	01 (20.0)	11 (8.3)	02 (9.1)	
2006-2007	7 (8.3)	06 (9.4)	140 (15.6)	32 (18.5)	02 (11.8)	00 (0.0)	14 (10.5)	01 (4.6)	
2008-2009	12 (14.3)	08 (12.5)	140 (15.6)	32 (18.5)	05 (29.4)	02 (40.0)	28 (21.1)	04 (18.2)	
2010-2011	16 (19.1)	14 (21.9)	177 (19.7)	40 (23.1)	04 (23.5)	00 (0.0)	29 (21.8)	06 (27.3)	
2012-2013	19 (22.6)	15 (23.4)	198 (22.1)	40 (23.1)	04 (23.5)	01 (20.0)	33 (24.8)	08 (36.4)	
Race									
EA	28 (33.3)	25 (39.1)	370 (41.2)	67 (38.7)	03 (17.7)	01 (20.0)	57 (42.9)	9 (40.9)	
AA	56 (66.7)	39 (5.4)	528 (58.8)	106 (61.3)	14 (82.4)	04 (80.0)	76 (57.1)	13 (59.1)	
Education									
<HS	26 (31.0)	21 (32.8)	319 (35.5)	56 (32.4)	07 (41.2)	02 (40.0)	47 (35.3)	12 (54.6)	
Some HS	11 (13.1)	06 (9.4)	94 (10.5)	31 (17.9)	00 (0.0)	02 (40.0)	13 (9.8)	02 (9.1)	
HS graduate	11 (13.1)	11 (17.2)	149 (16.6)	24 (13.9)	3 (17.7)	1 (20.0)	28 (21.1)	02 (9.1)	
>HS	36 (42.9)	26 (40.6)	336 (37.4)	62 (35.8)	07 (41.2)	00 (0.0)	45 (33.8)	06 (27.3)	
Marital Status									
Married	22 (26.8)	15 (23.8)	210 (23.8)	49 (28.7)	03 (17.7)	00 (0.0)	24 (18.3)	09 (40.9)	
Not Married	60 (73.2)	48 (76.2)	671 (76.2)	122 (71.4)	14 (82.4)	5 (100.0)	107 (81.7)	13 (59.1)	
Mean (Standard Error)									
Age (y)	26.6 (7.0)	31.4 (8.8)	28.7 (7.6)	26.6 (7.0)	26.1 (5.1)	29.8 (10.4)	27.5 (8.2)	28.9 (7.49)	
Duration (m)	N/A	12.2 (33.2)	12.1 (18.3)	37.8 (76.9)	N/A	49.2 (102.4)	11.9 (14.7)	14.7 (11.7)	

HS: High School; Rounding may cause columns not to equal 100 exactly

**Table 6.2 Unadjusted and adjusted Odds Ratios of Heart Disease and Stroke by OC status: Using Combined Oral Contraceptives (COCs) as the Referent Group**

	Heart Disease OR (95% CI)		Stroke OR (95% CI)	
	Unadjusted (n=1219 <sup>±</sup> )	Adjusted <sup>‡</sup> (n=1197 <sup>±</sup> )	Unadjusted (n=177 <sup>±</sup> )	Adjusted <sup>‡</sup> (n=175 <sup>±</sup> )
<b>COC</b>	1.00	.	1.00	.
<u>Never User</u>				
EA	0.62 (0.42, 0.91)*	0.64 (0.44, 0.96)*	0.44 (0.14, 1.40)	0.46 (0.14, 1.46)
AA	0.89 (0.81, 0.98)*	0.65 (0.49, 0.87)*	1.13 (0.64, 1.99)	1.28 (0.72, 2.27)
Total	0.63 (0.51, 0.79)*	0.65 (0.52, 0.82)*	0.88 (0.53, 1.46)	0.95 (0.57, 1.59)
<u>POC</u>				
EA	0.95 (0.63, 1.43)	0.74 (0.49, 1.12)	0.25 (0.04, 1.80)	0.19 (0.03, 1.38) <sup>¥</sup>
AA	1.13 (0.82, 1.58)	0.75 (0.53, 1.05) <sup>¥</sup>	0.81 (0.30, 2.22)	0.55 (0.20, 1.50)
Total	1.06 (0.82, 1.37)	0.74 (0.57, 0.97)*	0.56 (0.23, 1.37)	0.39 (0.16, 0.95)*
<u>POC+</u>				
<u>COC</u>				
EA	1.91 (1.46, 2.48)*	2.07 (1.58, 2.72)*	1.63 (0.81, 3.29)	1.98 (0.97, 4.05) <sup>¥</sup>
AA	2.36 (1.91, 2.91)*	2.42 (1.94, 3.01)*	1.93 (1.07, 3.48)*	2.21 (1.22, 4.01)*
Total	2.16 (1.83, 2.55)*	2.28 (1.92, 2.70)*	1.80 (1.14, 2.82)*	2.12 (1.34, 3.35)*

Referent group: COC (Combined oral contraceptive); POC (Progestin-only oral contraceptive); POC+COC (Combined progestin-only method and combined oral contraceptive method); Each oral contraceptive group is mutually exclusive; EA (European American); AA (African American); Total (All Races); <sup>‡</sup>Adjusted for age, years, duration of use, marital status, and education; <sup>±</sup> total; \*Significant (p < 0.05); <sup>¥</sup> Borderline significant (p < 0.10)

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## CHAPTER VII.

### SUMMARY

#### 7.1 Conclusion

The purpose of this dissertation is not to sway the reader into thinking that progesterone-only pills are the best solution for all women but to highlight the importance of considering a wider range of available oral hormonal contraceptive methods depending on the woman's individual lifestyle, family and medical history, attitudes, and perceptions. Over 100 million women worldwide are using oral contraception pills without understanding its mechanism of action, health risks, failure rates, costs, contraindications, and common adverse events. With the expansion of the Affordable Care Act, and growing support for providing over-the-counter oral contraceptive pills, the accessibility of the pill will continue to increase. Despite many changes in the composition of the pill, adverse drug events still occur. Albeit morbidity and mortality associated with the pill are considered to be low, their existence means that there is still room for improvement (Dhont, 2010).

Since POCs are considered similar in effectiveness for preventing unwanted pregnancies as COCs, we must make sure women are taking the safest preparations. Despite controversies about the proper estrogen dose, or the right progestin to use in conjunction with estrogen, there is some consensus in the literature that a reduction in estrogen is safer for women. Preparations that do not have estrogen reduce the thrombotic risk of women, myocardial infarction, heart disease, and breast cancer. Counselling women about their choice of contraception, in relation to family history, is good (Roach et al. 2015). Since only a small number of studies have looked at the risk of progestin-only contraceptives, it is important for us to remain current on this research.

Europeans have reintroduced certain forms of progestin-only oral contraceptives, notably desogestrel-only and levonorgestrel-only methods. The United States should consider expanding the types of progestin-only methods to see if these can perhaps reduce the irregular bleedings associated with progestin-only methods to make them more favorable among women, especially if other studies support the reduced risk associated with POCs.

Reduction in cardiovascular and cancer fatalities are of great public health importance. The benefits of oral contraceptives may outweigh the risks for a group of women in our society, but a large percentage of women are being overlooked. If the majority of women using the pill will have increased blood pressure and 5% will develop hypertension, we must determine alternatives that will reduce the adverse agent health exposures. Furthermore, low-income women are more likely to not have access to effective contraceptive counseling and use a method that is not tailored to their needs. This special population is also at higher risk for risk factors and co-morbidities that increase the risk of OC adverse events. We must make sure that our guidelines consider the needs of underrepresented groups as well as high-risk populations. To increase research related to these groups, increasing public access to underrepresented groups health data to promote disparities research is important. This will help policy-makers and health care providers understand what is needed for all groups to have access to the same, quality health outcomes.

Policymakers have considered making OCs accessible over-the-counter. Since the complications related to the estrogen-component of combined oral contraceptives may not be teased out, we should consider providing progestin-only contraceptives first. This method may be a safer alternative to combined oral contraceptives.

## **7.2 Interpretation of Findings**

COCs significantly decreased among AA women and approached rates of use among EA women. POC use increased slightly every year from 2000 to 2013. Furthermore, POCs

significantly decreased the risk of heart disease incidence and non-significantly decreased the risk of stroke incidence after adjusting for important covariates compared to COCs. In addition, compared to COCs, POC+COC did not have a significantly increased risk of stroke incidence. Perhaps prescription patterns are slowly changing because of the reduced risk or lack of association between POCs and certain chronic diseases. These findings suggest that women using POCs have less risk of OC-related adverse events.

### **7.3 Suggestions for Future Research**

Additional research is required to support these findings but POCs may have reduced risk of chronic disease incidence and mortality compared to COCs. Switching from POCs to COCs, and vice versa is not recommended for now. It is possible that our study was biased with women who had adverse health effects related to COCs and therefore had to switch to POCs, therefore biasing our results. The majority of POC+ COC users were women who switched from COCs to POCs. The reasons are not known but speculations have been made, including breastfeeding, or lots of complications related to the estrogen component of OCs. Researchers should study the effects of ACA expansion on OC use, and if women are being counseled appropriately to use POCs.

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