Hormonal Contraceptive Use Among Active Duty Army Servicewomen. Trends and Implications for Risk of Musculoskeletal Injury.

HORMONAL CONTRACEPTIVE USE AMONG ACTIVE DUTY ARMY SERVICEWOMEN.
TRENDS AND IMPLICATIONS FOR RISK OF MUSCULOSKELETAL INJURY.

A Dissertation Presented

by

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ABSTRACT

**HORMONAL CONTRACEPTIVE USE AMONG ACTIVE DUTY ARMY SERVICEWOMEN.
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Almost 40% of servicewomen use hormonal contraception every year, and 60% will use a contraceptive method in their military career. Rates of contraceptive use and musculoskeletal injury are higher among servicewomen as compared to civilians. Gender differences in rates of musculoskeletal injury have led investigators to question the role of sex hormones, including contraception. Recent studies suggest that hormonal contraceptives may decreased risk of anterior cruciate ligament (ACL) injury, potentially decreasing early onset osteoarthritis (OA). We utilized the Total Army Injury and Health Outcome Database, which prospectively captured demographics, clinical and pharmacy records on over 5.6 million Army soldiers since 1994. Hormonal contraceptive use was identified in the Pharmacy Data Transaction Service. The first project described changes in covariates and contraceptive use overtime. Over the ten years of follow-up, there were increases in age, education, and rank of servicewomen at entry. Among contraceptive users, rates of pill use decreased from 79.71% in 2002 to 51.67% in 2011 with increased use of the ring, implant and IUD. Contraceptive users were young, higher ranking and more likely to be nulliparous. Education varied widely by contraceptive method with injection and patch users having the lowest and ring users the highest level of education. The second and third projects examined the association of hormonal contraceptive and ACL injury or OA by

survival analysis using multivariate Cox proportional hazards models. In project two, a total of 2,253 incident ACL tears were identified from medical billing codes. In our final model, current users were 15% less likely to have incident ACL injury. Project 3 identified a total of 3,943 OA cases. In the final model, ever use of contraceptive was associated with a 19% reduced risk of OA compared to never users. Strengths of our study include the evaluation of all types of contraceptive use in a large, diverse, population-based cohort. Information gathered from this study informs future studies considering hormonal contraceptives a modifiable risk factor for ACL injury and OA, informing contraceptive decision making, clinical recommendations, and injury prevention strategies for servicewomen particularly around key career events including basic training and deployment.

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CHAPTER 1

HORMONAL CONTRACEPTIVE USE: TRENDS OVER TIME

Introduction

The numbers of servicewomen and the roles they play within the Unites States military are ever changing and expanding. As of 1994, women were allowed to serve in 64% of occupational career fields and basic training was remodeled to train men and women side by side (HQDA G-1, 2014). As of September 2012, women served in 95% of all Army occupational career fields. In May 2013, the ban on women entering combat and infantry occupations was lifted and women were allowed to attend training for these positions (HQDA G-1, 2014). As of 2010, women make up 20% of new recruits, 15% of active duty and 17% of reserve forces (Bean-Mayberry et al., 2010). Rates of field grade (O-4+, Major+) and senior enlisted (E7-E9, sergeant first class to first sergeant) female leaders have increased over the past decade emphasizing the growing leadership roles women hold (HQDA G-1, 2014). Given the growing numbers of women across the roles of the military, assessments of women's health issues are of increased importance as gender neutral standards are considered and women are integrated into combat positions.

Historical Contraceptive Use by Servicewomen

Historically, the use of hormonal contraception by servicewomen has been highly controversial. Military restrictions on intimate relationships while deployed, the geographical separation of servicewomen from their spouses during deployment, religious beliefs, and historically limited access to contraception have contributed to controversy. Three decades ago, epidemiological research within the military started to focus on gender differences in access to health care, reasons for clinical encounters and implications to a servicewoman's ability to complete her job without timely access to care (Cobb, 1987). In the survey they distributed at medical clinics, including 750 women, there was a limited focus on hormonal contraception,

though about 43% of the women surveyed were using oral contraceptives, 3% were surgically sterile and 2% were using an intrauterine device (IUD) (Cobb, 1987). Even with 50% using a contraceptive method, the need for evacuation of servicewomen from deployments due to pregnancy was considered to be the greatest threat to female troops during the Persian Gulf conflict. (Gallagher, Lall, & Johnson, 1997). Reports suggest that around 55% of pregnancies in servicewomen are unintended pregnancies (Duke & Ames, 2008; Chung-Park, 2007) similar to civilian counter parts. Although these three small studies (n=158, n=10 and n=52) focused on pregnancy, they identified correlation with knowledge and support with contraceptive use. They also identified barriers to use including association with promiscuity (Gallagher et al., 1997; Chung-Park, 2007; Duke et al., 2008). The goal of this research was to inspire educational interventions to decrease unintended pregnancies while on active duty, given the widespread implications for unit training, operations and readiness.

Contraceptive Type and Frequency of Use Changes Over Time

According to a summary report by Guttmacher Institute (2016), 62% of women 15 to 44 years old are currently using a reversible contraceptive method including barrier methods. Based on 2012 reported use in the last month, 44.6% were using hormonal contraception, 25.9% used the pill, 10.3% used the IUD, 4.5% used injection, 2.0% used the ring, 1.3% used the implant and 0.6% used the patch. The oral contraceptive pill was the most common method used among women, with 80% of sexually active women ever using the pill. The pill was used most commonly among white, young, single women with college education and no children. Women who were married were more likely to use any form of contraception compared to single women (77 vs 42%). IUD users were more likely to be 25-34 years old and parous. Between 2002 and 2010, they found a 10 fold increase of ever use of the patch (1 to 10%). There was also a steady increase in long activing reversible contraceptives (IUD and implant) with 2% use in 2002, 6% in 2007, 9% in 2009 and 12% in 2012. It is also notable that even among women who were sexually

active 52% were using contraceptives for non-contraceptive reasons including menstrual pain, menstrual regulation and acne. Similar research evaluating trends of contraceptive use, including all types, has not been published within the military though it is expected patterns would mirror that of their civilian counterparts (Guttmacher Institute, 2016).

Contraceptive Use Varies by Key Demographics

In the 1990s, Means-Markwell and colleagues noted the increasing use of other hormonal contraception types other than the pill, compared to a decade prior. In their survey including 628 women, they reported that 29% of servicewomen used oral contraceptive pills on Navy ships and 14% reported using depo injections (Means-Markwell et al., 1998). In 2010, Enewold and colleagues were the first to utilize the Pharmacy Data Transaction Service (PDTS), rather than using a survey, to quantify use of oral contraception by servicewomen and by military branch (Enewold et al., 2010). They considered a 12 month period of oral contraceptive use starting on October 1, 2004 including women on active duty (n=24,510) between the ages of 18-39. They found that OC use was significantly higher in the military than in the civilian population (34.4% versus 29.4%, p=0.05) for women greater than or equal to 20 years old, with an increasing difference with age. In addition, OC use was higher among married military women than married civilian women (34.0% versus 24.7%). There were racial differences noted as well with non-Hispanic white women having the highest use at with 32.2% servicewomen using contraception versus and 19.8% of the general population. However, among women that were 18 or 19 years old, the prevalence was lower in the military (33.2% versus 40.6%). The Army had the lowest OC use by any branch at 29.9%, 9% less than the Air Force and 5% less than both the Navy and Marines (Enewold et al., 2010).

Contraceptive Use Changes by Career Events

Differences in demographic composition as well as varying training intensity and demands may partially explain observed differences in contraceptive use among branches of the

military (Army, Marines, Air Force, Navy and Coast Guard). In addition, within a given branch, patterns of use may change around key career events including basic training and deployment (as compared to a home station in the U.S.). Prior studies suggest a decline in contraceptive use after entry into the military as well as during deployment (Holt, Grindlay, Taskier, & Grossman, 2011). Changes in training environment, location and duration may impact contraceptive choice for many reasons. Battista and colleagues reported use of contraceptives, as self-reported on a questionnaire, prior to and during basic training (BCT) among 564 soldiers, including 244 women, attending Army medical specialist training in Texas during January 1998. Compared to use before basic training, reported abstinence increased from 15.9 to 26.7% ($p<0.001$) and women not using any method increased from 5.6% to 12.3% ($p=0.005$). Oral contraceptive pill use dropped by half 30.5% vs 15.7% respectively ($p<0.001$) once women started basic training (Battista, Creedon, & Salyer, 1999; Holt et al., 2011). Of the 222 women surveyed, 62 (28%) requested a prescription for a contraceptive method. Of those, only 37% were able to obtain it, 32% were told a pelvic exam was required and no appointments were available, and 26% were advised they did not need contraception during basic training or to wait until their next duty station (Battista et al., 1999).

In 2013, Grindly conducted an online survey including current servicewomen and veterans (n=281) to assess contraceptive use during deployment. Almost 60% of servicewomen reported they did not speak with a provider about contraceptive options before deployment. Of those who required refills while deployed, one third said they could not access the method they wanted, and 41% found it difficult to obtain refills (Grindlay & Grossman, 2013). Nielsen and collages conducted a survey among deployed servicewomen in Iraq between August 2005 and March 2006. Of 397 surveyed, 44% reported using some type of hormonal contraceptive. However, 43% said they changed their method because of availability (Nielsen et al., 2009). In 2011, Holt and colleagues summarized reported use of contraceptives among eleven studies and

found that the overall prevalence of current use of contraceptive methods was 55-88% among soldiers stationed in the U.S. as compared to 39-77% among deployed soldiers (Holt et al., 2011). Two additional studies conducted during Operation Iraqi Freedom (OIF) using survey data, one collected from 251 women at a primary care clinic, the other from 397 women at an combat support hospital between 2005-2006, suggest that between 23-42% of women will change methods during deployment due to lack of availability (Nielsen et al., 2009; Thomson & Nielsen, 2006). In addition, in two surveys including 397 and 500 women, between 16-44% will forget to take or replace a contraceptive dose at the correct time and about 50% of women report patches falling off due deployment conditions (Nielsen et al., 2009; Thomson & Nielsen, 2006; N. Powell-Dunford, Cuda, Moore, Crago & Deuster, 2009). Recent literature reviews and research between 2002 and 2011 seeking to optimize readiness of servicewomen recommend that clinicians allow at least a 3 months and preferably a 6-12 month supply of hormonal contraception be dispensed to women expecting to be deployed (Bean-Mayberry et al., 2010). Goyal et al. noted that about 10% of women who are deployed will not use the prescription (Thomson et al., 2006). Concerns and tolerance for side effects (perceived and experienced) may also vary by career events. Common side effects that were noted as concerns included nausea, weight gain, headache, and irregular bleeding. The inconveniences of these side effects can be exacerbated during long shifts in harsh climates especially if they are unexpected (Goyal, Borrero, & Schwarz, 2012).

Physiological Implications of Use

Hormonal contraceptives are frequently used, regardless of whether a woman is sexually active, to treat menstrual symptoms and regulate or suppress menstrual cycles. Hormonal contraceptive use is impacted by the availability of clinical care and has been associated with both potentially beneficial and detrimental physiological impacts. Exogenous hormones from contraceptives impact follicle-stimulating hormone (FSH) and luteinizing hormone (LH) surges

mid-cycle as well as provide a predictable dose of estrogen and progesterone. The physiologic changes associated with contraceptive use vary between individuals and by contraceptive type and dose. Many contraceptives provide potential reduction in pre-menstrual syndromes, shorten menses, regulate or suppress a menstrual cycles. Hormonal contraceptives are also used for treatment of polycystic ovarian syndrome, as well as prevention of anemia and acne (Enewold et al., 2010). Contraceptives may also alleviate some of the symptoms that are reported to interfere with physical activity (including menstrual cramping) to enhance performance (Schneider, Fisher, Friedman, Bijur & Toffler, 1999) and an early study by Möller-Nielsen and Hammar in 1989 suggested contraceptives may reduce risk of traumatic lower extremity injury. In addition, contraceptives are suggested to play a role in prevention of the female athlete triad, a condition that occurs among young active females and includes bone loss, amenorrhea and low caloric intake. However, hormonal contraceptives are known to increase risk of cardiovascular disease, especially among smokers, as well as potentially increase risk for cervical and breast cancer (Enewold et al., 2010). It is important to consider the potential benefits, consequences and motivations for use by type of contraception among servicewomen who are generally young and active.

Changing Motivation for Use

The desire for contraceptive induced amenorrhea among service women has increased due to high frequency deployments in austere environments over the past decade. Continuous use of many contraceptive methods inhibits menstruation, and also can reduce headaches, dysmenorrhea, length of cycle and protect against anemia. In addition, the burden associated with sanitary product storage, hygiene and disposal, which may be avoided with induced amenorrhea, is reported as a substantial problem among servicewomen (N. C. Powell-Dunford, Deuster, Claybaugh, & Chapin, 2003). In 2001, Powell-Dunford and colleagues surveyed 154 U.S. Army active, Reserve and National Guard servicewomen. Over 80% of women surveyed desired

amenorrhea during deployment or training, but only 54% were aware that pills could suppress the menstrual cycle and only 7% actually used pills to suppress their cycle during a prior deployment (N. C. Powell-Dunford et al., 2003). A more recent study found that about 40% of women used contraceptives during deployment and about half of those used continuous methods (N. C. Powell-Dunford et al., 2011). Continuous use has potential advantages for servicewomen, especially during deployment, but requires women receiving contraceptive counseling and uninterrupted access to their continuous method of choice while deployed.

Summary

Servicewomen make up a young active population that has potentially greater access to contraception due to the full insurance coverage they receive from TRICARE while on active duty. They may be encouraged by medical providers to consider contraceptive use for menstrual suppression during deployments and training. The integration of women into previously male only combat roles may further increase consideration of use of contraceptives for menstrual suppression and pregnancy prevention.

Over the past thirty years many studies have utilized small convenience samples to assess contraceptive knowledge, use, changes and prevalence among servicewomen. These studies include women in all military branches, of all ages and stages of their career. However, diversity among studied populations, varying methods of data collection (including both self-report and pharmacy records) and inconsistency in the detail of contraceptive classification, has led to a lack of clear conclusions regarding changes of contraceptive use at a population level from the research to date. Changes in contraceptive use over time are important to consider in relation to other outcomes including pregnancy rates, musculoskeletal injury as well as establish baseline rates of use prior to participation of women in combat positions. In the only study to date to quantify contraceptive use at a population level within the Army (Enewold, 2010) using PDTS dataset among n=24,510 Army servicewomen, oral contraceptive use assessment was limited to a

dichotomous yes/no. Military rank, education and parity were not considered as potential predictors of use. In addition, 12 month yes/no capture of contraceptive use does not allow for consideration of changes in use and type over time.

Given the increasing participation of older, college educated women in the military as well as changes in the frequency of deployment and acceptability of long-acting reversible contraceptives, the prevalence reported by Enewold may not be accurate as a current assessment of contraceptive use in this population. Increased attention toward education programs in the Army surrounding contraceptive use along with changing demographic profile and increased social acceptability of long term contraceptive methods may have also led to altered use, and further supports the need for a contemporary assessment with more up-to-date data sources.

A large-scale descriptive study of hormonal contraception use by servicewomen could provide critical insight to how use may be related to key career events, as well as identify predictors of contraceptive use by type and regularity of use. Regardless of whether a woman is sexually active, hormonal contraceptives are commonly used among young reproductive aged women and have significant social, medical and physiological implications that may affect her ability to meet fitness and occupational standards. Therefore, it is important to establish a baseline of hormonal contraceptive use and correlates especially if sub-groups are identified to be at high risk for methods change or non-use. Contraceptive use is one key factor that cannot be ignored as women are integrated into previously male only occupational positions, for health care planning, and hypothesis generation for future analysis

Aims and Hypotheses

The overall objective of this study was to characterize the demographic profile of servicewomen and their use of contraceptives over time between 2002 and 2011 using the Total Army Injury and Health Outcomes Database (TAIHOD).

Specific Aim 1

To evaluate changes in contraceptive use among active duty servicewomen over time. Hypothesis 1: Compared to 2002, prevalence of alternative contraceptive methods (seasonal contraception, patch, ring, injection and implant) use will have increased as of 2011.

Specific Aim 2

To evaluate difference in key demographics among active duty servicewomen who use hormonal contraception. Hypothesis 2: Compared to soldiers who are enlisted and soldiers who do not have a college education, officers and college graduates will have higher prevalence of contraceptive use.

Specific Aim 3

To evaluate changes in contraceptive use surrounding key career events including basic training and deployment. Hypothesis 3: Compared to permanent station, women will experience lower prevalence of contraceptive use during basic training and deployment.

Methods

Study Design and Population

The study population consists of servicewomen between the ages of 17 and 45 who served at least two months on active duty between January 1st, 2002 and December 31st, 2011 using the TAIHOD. The TAIHOD was created in 1994 with the aim to study injuries among female soldiers, though the database captures servicemen and women. The database prospectively links administrative, clinical, pharmaceutical, occupational and health behavior data for all soldiers who have been on active duty. The TAIHOD currently contains data on over 5 million soldiers with active service and outpatient clinical records as far back as 1997. For the current study, the start date of January 1st, 2002 was selected as it marks the onset of electronic pharmacy record capture from the PDTS, which is integrated into the TAIHOD to determine hormonal contraceptive use. This timeframe captures Operation Enduring Freedom and Operation

Iraqi Freedom (OEF/OIF), which allows for evaluation of changes in contraceptive preference and use in austere environments as well as changes in number and frequency of deployments.

Exclusion

For the purpose of the current study, women with only one record in the DMDC were dropped due to the insufficient observation time to capture and quantify hormonal contraceptive use, changes in duty station and other undetermined cause for military discharge that make these women not generalizable to the active duty women who serve for longer periods of time. In order to restrict consideration to pre- and not peri-menopausal women, women were censored from the analysis at the age of 46. Thus, women who entered the cohort at age 46 did not contribute any observation time to the study; however, women who turned 46 during the study timeframe contributed person time up until censoring at age 46, with subsequent person time dropped. Participants who were missing age, education, marital status, race or ethnicity from the DMDC were excluded. From this population, we further excluded women who had medical record documentation of a hysterectomy, oophorectomy, clinically diagnosed menopause, or used hormone replacement therapy as these women likely have different comorbidities that may impact their use of hormonal contraceptives (Appendix A). In addition, women who experienced one of these events during the study cohort were dropped at the event date and person time following the event was also dropped. Women with greater than 120 pregnancy visits during the study cohort were also excluded. These women compromise a group of either implausible medical records or high risk pregnancies that are likely not generalizable. The number of women and person years excluded and dropped are shown in Table 1.

Contraception Use, Timing and Duration

Hormonal contraceptive use was assessed through pharmacy data recorded in the PDTS within the Medical Data Repository. The PDTS is a complete database capturing all prescription pick-ups at Military Treatment Facilities, TRICARE pharmacy networks, and mail orders

(Department of Defense, 2009; The Department of Defense Pharmacoeconomic Center, 2011). Pharmacy records contain information on: therapeutic class, product name, type of hormonal contraceptive, dosage, days' supply, quantity and date pick up. TRICARE covers hormonal contraceptives at no cost to soldiers (Enewold et al., 2010). Therapeutic class codes '681200, contraceptives' and '683200, progestins' were used to identify hormonal contraception. Prescriptions recorded with a dispense quantity equal to zero were considered as requested but not picked up. Prescriptions for HRT or treatment for amenorrhea and anovulation were not included in the analysis as hormonal exposure.

Statistical Methods

To evaluate the impact changing demographics may have on use of contraceptives, key variables were assessed and compared across ten year-long intervals during the study period using chi-square and ANOVA. Because of the large sample size, p-values were only reported if they were not statically significant ($p>0.05$) (Table 2). Demographics at entry into the study cohort were reported in a summary entry column. This column represents the first available demographics captured for each woman. For women who served prior to the study cohort, this represents their demographics as of January 2002. For women who joined the cohort as a new accession, this represents their demographics at the date of entry into the Army. The annual covariates represent the last record for each servicewoman in the given year.

Contraception Types

The PDTS dataset contains information on the date, quantity and contraceptive type dispensed. Product type other than: pill, patch, injectable, implant, vaginal ring were eliminated. Exposure was further categorized by type of contraceptive to evaluate differences in use of combined hormonal contraceptive versus progestin only. Combined hormonal contraceptives included monophasic, biphasic and triphasic oral contraceptives, Ortho-Evra (birth control patch), and Nuvaring. Progestin only contraceptives include progestin only pill, Depo-Provera

(injection), Mirena (intrauterine device) and implants (including: Noroplant, Implanon and Nexplaon). Timing and duration of use was determined from start and stop dates were calculated as follows: start date equals date of pick up plus one day and the end date is equal to the start date plus the quantity provided.

For consistency with prior literature, the initial analysis was performed using any hormonal contraceptive with dichotomization into ever versus never user. Additionally, we considered use as 'never', 'past' and 'current', contraceptive type, as well as cumulative exposure in months on any contraception within the study timeframe. A servicewoman's first ever and last contraceptive pick up during her career were presented in summary columns. Annual contraceptive use was determine by last contraceptive pick up in a given year among women who used any contraception during the year. Chi square and ANOVA were used and p-values were only reported if they were not statically significant ($p>0.05$) (Table 3).

It is important to note that women remain in the dataset multiple years and thus the same woman contributes her contraceptive status and demographics every year she is present in the database. It is also possible for a soldier to change her contraceptive type within a year. This information would not be captured in this table based on the hormonal contraceptive type definition used. A servicewoman may be on two types of contraception for a short duration of time (for example implant and pills) when transitioning between methods or when treating undesirable side effects of one method with another. In our study, it was assumed when a woman picked up a new contraceptive method that she stopped the previous method. Non-hormonal barrier methods including the diaphragm, condom and spermicide use were not be considered in this analysis. Paragard IUDs are non-hormonal methods and during use women were considered to be not exposed. Correlates of hormonal contraceptive use and demographics were evaluated based on ever versus never user and additionally stratified by first type of contraceptive method ever used (Table 4).

Contraceptive use was also compared at four key time points during a servicewoman's career: basic training, deployment, permanent overseas station and home station in the U.S. Basic training was identified as the first duty station of an enlisted servicewoman's career, typically the first 90 days. For enlisted women who entered the Army prior to 2002, their basic training was assumed to have been completed in the past. Deployment and overseas station dates were assessed from records including country name, start and end dates. Duration of time overseas was calculated based on start and end date. Frequency and duration of each event and associated contraceptive use was presented (Table 5). Change in contraceptive use relative to the BCT, deployment, overseas and home duty station were categorized into mutually exclusive categories: never user, started contraceptives, stopped contraceptives, changed contraceptive type, used one type of contraception the entire time (Table 6).

Combined Hormonal Contraception (CHC)

Oral contraceptives and emergency contraceptives were identified by a pill product type. Emergency contraceptives were identified by product name ("Ella" "Next Choice", "Plan B", and "Plan B One-Step") and were excluded. These products contain varying levels of progestin (0.75-30 mg) and two different types (ulipristal acetate and levonorgestrel). There are over 90 types of oral contraceptives dispensed between 2002 and 2011. Contraceptives were classified as: combined hormonal (including monophasic, biphasic and triphasic) and progestin only by product name and therapeutic class code.

Only one type of contraceptive patch is distributed to service members (OrthoEvra). This patch has a standard dose of 0.75 mg EE/week and 6 mg of norelgestromin/week making it a combined hormonal contraceptive method (RegenceRx, June 2012). For three consecutive weeks a single patch is worn for seven days then replaced with a new patch. The fourth week of this prescription is a no patch week which is when the woman experiences menstrual bleeding. Therefore, a quantity of three patches dispensed is equal to one month (28 day) supply.

NuvaRing is a contraceptive ring that has a standard dose of 15 mg EE/day and 0.12 mg of etonogestrel/day making it a combined hormonal contraceptive method (RegenceRx, June 2012). For three consecutive weeks one vaginal ring is used. The fourth week of this prescription is a no ring week which is when the woman experiences menstrual bleeding. Therefore, when one ring is dispensed it is equal to a one month (28 day) supply.

Progestin Only Methods

DepoProvera ("Depo") is the brand name for contraceptive injection. Depo is administered by one injection every 12-14 weeks with a dose of 104mg subcutaneously or 150mg intramuscularly of medroxyprogesterone acetate making this method progestin only (Cerner Multum, 2013). There is no break between injections for menstrual bleeding, therefore this method is used continuously. Medroxyprogesterone acetate is also used for treatment of endometriosis (same dose as subcutaneous), amenorrhea (with 5 to 10 mg oral tablets for 5 to 10 days), both of which were not included in contraceptive exposure classification.

Contraceptive implants were identified by the product type: implant. Possible brand names include Implanon and Nexplanon. The contraceptive implant is inserted during an outpatient office visit and can remain in place up to 3 years. Start dates of contraceptive implants were obtained by comparing pharmacy and clinical encounter dates, procedure code for insertion. End date of implant use was determined by clinical encounter procedure codes for implant removal. Contraceptive implants release 68 mg etonogestrel over 3 years making this method progestin only (RegenceRx, June 2012).

Intrauterine devices were identified by clinical encounter procedure codes for insertion and removal. An IUD is inserted during an outpatient office visit and can remain in place up to 5 years for Mirena. Mirena releases 20 mcg of levonorgestrel per day making method progestin only (RegenceRx, June 2012). The Healthcare Common Procedure Coding System (HCPCS) provides procedure codes that are intended to distinguish Mirena (J7302) from Paragard (J7300).

Validity of Exposure

Hormonal contraceptive pharmacy records have not been validated in the TAIHOD. However, in previous research pharmacy records are suggested to be a valid source of information regarding use, duration and timing of contraceptives when compared to self-report (which is the most frequently utilized method of exposure assessment), with correlation coefficients ranging from 0.84-0.93 (Norell, Boethius, & Persson, 1998). Discordance between pharmacy records and self-report may result from inaccurate self-reporting, or when prescriptions are filled but not used. Pharmacy records are suggested to be a more accurate source of information than self-report regarding type of oral contraceptives (high dose, low dose and progestin only pill) (Norell et al., 1998). Use of pharmacy records for assessment of duration of use requires assuming that any prescription dispensed was used for the entire days' supply as directed by the pharmacy. Inaccuracy in duration of use may result depending upon whether women use the week of inactive pills from a 28 day supply (in which case, the total number of pills equal duration) or if they discard the inactive pills and begin a new pack of pills to electively suppresses (or skip) her menstrual cycle (in which case, duration as determined from pharmacy records of supply overestimates actual duration of use by one week per 28 day supply).

Covariate Assessment

Demographic data including age, race, ethnicity, education, marital status, grade and length of service were extracted from the monthly DMDC data repository. When a service member joins the military without any previous military they are considered to be a new accession. For new accessions, length of service represents any time on active duty in the study cohort between 2002 and 2011. For women with active duty time prior to 2002, length of service a sum of all time on active duty prior to and including the cohort timeframe Ever attendance to BCT was identified from training records, however, dates of BCT were determined as discussed above. Deployment records and overseas station dates and location were merged in with DMDC

records. A single measurement of body mass index (BMI), as measured at accession, was also merged with the demographic data. Diagnostic and medical procedure billing codes from the time a woman entered active duty were available and utilized to identify lower extremity injury and delivery (Appendix A). Records for women who served on active duty prior to 2002 were included to capture the number of deliveries and lower body injuries prior to the cohort. Parity was determined by the number of dependents, marital status, age and delivery during the study cohort. Women with a known delivery during the study are automatically parous. Women without any documented deliveries, but were married with 2 or more dependents were also considered parous. Women who were, single with no dependents were considered nulliparous.

Results

Final Study Sample

Exclusions are detailed in Table 1. Of the 207,777 participants and 757,610 person years of total observation, the most common reason for exclusion was due to missing records (n=6,220). Over one third of those excluded (n=3,544) only had one month record in DMDC. An additional 2,676 women were missing age, education, marital status, race or ethnicity. An additional one percent of women were excluded from the study due to being age 46 or older at entry to the cohort or to the Army. Less than one percent of the study population were excluded due to a medical reason. Half of the women excluded at entry and 79% of the women dropped during the study time frame had service prior to 2002 (Table 1).

Demographics of Servicewomen

As shown in Table 2, an average of 82,000 women were on active duty in a given year (ranging from 80,504 to 84229) and on average 15% (12.57-17.18%) of these women are new accessions with about 9,000 women attending basic training every year. The average age at entry into the cohort was 23. More than 70% of women had less than high school level education (or equivalent) at entry to the Army, though the average age (26.46 to 27.86) and education level

(18.29 with college or graduate school to 22.77%) of servicewomen increased during the follow-up period. The proportion of women married as well as the average rank paralleled increasing age and education. Most women were enlisted members ranking E1-E9 (E1-Private through E-9 Sergeant Major) with 10% of women holding an officer position (Warrant Officer or Commissioned Officer) at entry to the cohort. The percentage of servicewomen identifying as African American declined 6% between 2002 and 2011. The average length of service was 3.5 years with the proportion of women serving 4 to 8 years doubling between 2002 and 2011. One quarter of the population was deployed in any given year with more than half ever deploying by the end of the follow-up. Equal portions of women were nulliparous/parous in a given year with 40% of women delivering while on active duty. At the start of the cohort, few women had a prior documented injury. However, by the end of the follow-up more than 50% of women had experienced a knee injury, 30% sustained a back injury and 15% sustained an ankle injury. Over 57% of women had a BMI in the normal range (18.5-25 kg/m2) at entry with less than 6% comprising extreme BMI categories underweight (<18.5 kg/m2) or obese (>30 kg/m2). More than 89% of women filled a prescription for NSAIDs during the study follow-up period (Table 2).

Contraceptive Use Over Time

As shown in Table 3, 60% of women on active duty between 2002 and 2011 used contraceptives by the end of follow-up. In a given year, use of hormonal contraception was over 40%, peaking 47.71% in 2006. Over the ten year period of observation, oral contraceptives remained the most frequently used method although the rates declined by 28% over follow-up. The contraceptive patch was popular in 2003-2006 with use over 10% that declined below 5% by the end of follow-up. Use of the vaginal ring was not common in 2002, however by the end of follow-up over 8% of contraceptive users selected this method. Rates of implant and IUD use increased overtime. Between the first type of hormonal contraceptive and last type, before a

servicewoman stopped using or was censored at the cohort end, there was a 6% decrease in pill use where women were more likely to use the ring, patch, IUD or implant (Table 3).

Correlates of Contraceptive Use

Compared to servicewomen reporting never having used contraceptives, women with ever use of contraceptives during the cohort were on average 1 year younger, had lower rates of college education, and were more likely to be single, nulliparous women with a shorter amount of time in the cohort. Ever users were less likely to have a known prior knee injury and more likely to have a back, hip, leg or ankle injury. IUD use was higher among older, married officers than women who chose the contraceptive implant. Over 75% of injection and implant users had only a high school education or equivalent compared to ring users having over 24% with completion of college or graduate school. The patch and injection were used more frequently by African American soldiers compared to other methods (Table 4).

Contraceptive Use by Career Event

Comparisons of contraception use and type by career events, including basic combat training, home station, first deployment, and first duty station overseas station, are shown in Table 5. Usage of contraceptives was highest for overseas station at 72%. While stationed in the U.S., 60% of servicewomen used some method of hormonal contraceptive, similar to 63% usage during deployment; whereas, only 9% use contraception at basic combat training. Among servicewomen, use of contraception, methods of use were largely similar across career events with a few notable differences. Among users of contraception at basic training, rates of depo injection use was 7% higher as compared to users of contraception at home station. During their first deployment, women were slightly more likely to use hormonal contraceptives, with a preference towards combined hormonal contraceptive pills and decreased use of the vaginal ring compared to use at the home station (Table 5).

Changes in Contraceptive Use By Career Event

Table 6 compares contraceptive use while stationed in the U.S. to any other career event. Servicewomen were more likely to start and change contraceptive types while stationed at home (33.45% and 21.73% respectively). During basic training, few women used contraceptives and of those who used contraceptives 71% started use during this timeframe. Women who were deployed or who were stationed overseas were more likely to stop their contraceptive type and also had higher rates of using one type the entire duration of the event as compared to women who were stationed in the United States. Over time, the number of women stationed in the U.S. who stopped a method and who used a single type of contraceptives increased. Rates of women who started a contraceptive type while stationed in the U.S. remained high. On a yearly basis, the rate of staying on one method increased during deployment and overseas station, while stopping a method was variable between years (Table 6).

Discussion

Summary of Findings

More than 60% of women had documented contraceptive use during the 10 year cohort. Oral contraceptives were the most popular, though over time an increased preference for alternative methods include the ring, implant and IUD were observed. Ever contraceptive users were more likely to be young, single nulliparous women at entry to the Army. IUDs were preferred among older married women whereas the injection and implant were preferred by younger women.

Hormonal contraception was rarely used during basic training and more frequently used while overseas as compared to home station. Women stationed overseas were more likely to stop and not restart a contraceptive method compared to women stationed in the U.S.

The annual cohort size of women in the Army remained relatively stable between 2002 and 2011. Over the cohort, the average age, education and rank increased. Few servicewomen had

a known prior knee injury at entry, over 50% had a knee injury during the study. In addition, it is important to note that by 2011 more than 89% of women ever received a prescription for NSAIDs during the cohort. Although it is not possible to identify the reason for NSAIDs use, it is possible that users, especially frequent users, may represent women who have a lower extremity injury, diagnosed or undiagnosed, or may represent more active women.

Implications of Main Findings

Overall, rates of hormonal contraceptive use were high in this young, active population. The ten year follow-up period captures a unique socioeconomic time where new contraceptive types were introduced to the market. In 2000, the FDA approved Mirena which replaced the Dalkon shield. Initially, Mirena was a popular method among parous women, however, the social acceptance for both patients to request and providers to insert the IUD in young nulliparous women has continued to increase over time. In late 2001, the FDA approved both Ortho Evra and Nuva Ring, giving women a chance to choose weekly or monthly methods rather than daily pill use. The five rod implant, Noroplant, was no longer distributed after 2002 though supplies remained and Implanaon was approved in 2006. The depo injection has been available for decades and may be preferred by patients who would like high efficacy method that minimizes daily, weekly or even monthly forgetfulness. Depo may be encouraged for younger women by providers because it does not rely on perfect use by the patient.

New accessions were more likely to use the ring and implant which may demonstrate temporal changes in availability with the introduction of these methods. Enlisted women were more likely to use the injection and implant as their first method which may represent social acceptance of the new contractive type but also potential encouragement from the provider to as discussed.

Findings in Comparison to Prior Studies

Enewold and colleague reported rates of oral contraceptive use in a given year to be around 30% in the Army (Enewold et al., 2010). Our database included an additional nine years of data and suggest that 60% of women have ever used hormonal contraception. Enewood's study was limited to oral contraceptive use only. When looking at last method of use, we found that 36.5% of women used oral contraceptives, higher than the 30% presented by Enewold. Our study adds to the literature by including the addition methods of use and changes in use over time. We observed that over time an increased preference for long acting reversible contraceptive methods occurs which mirrors the increase in acceptance of these methods among civilian counterparts.

Enewold and colleges also identified difference in contraceptive use by age, race and marital status. They found the highest rates of oral contraceptive use among married women and women between 25-29, 10% more than women less than 20 and or over 35 years old. They also noted that non-Hispanic white women had the higher rates overall use at 35%, 7% more than non-Hispanic black women. Our results, which considered demographics at entry into the cohort, suggest that contraceptive users were on average 1 year younger, on average 23 at entry to the Army. Use varied by marital status, and IUD rates were highest among older married service member and implant rates were more popular among younger single soldiers. This may be confounded by acceptance of IUD by women with prior pregnancy or by provider's preference of IUD use in parous women in monogamous relationships. In addition, we also noted a differences by rates of patch and injection use by race with 10% higher proportion of African Americans as compared to pill use.

A previous study, by Battista and colleague, suggested only 15% of women use the oral contraceptive pill during basic training (Battista, Creedon, & Salyer, 1999). We identified only 5% of women using oral contraceptive method during basic training which may indicate we are missing women who arrived at basic training with their own supply of their contraceptive

method. Prior studies also suggest a decrease in contraceptive use during deployment, with only 44% using a method and 43% changing methods (Nielsen et al., 2009). Our results suggest a much larger proportion of women are using some contraceptive method similar to estimates presented by Holt et al., in 2011 who reported 55-88% of women stationed at home use and 39-77% of deployed women use contraceptives (Holt et al., 2011) (Table 5).

Limitations

Misclassification of Exposure

Misclassification of the exposure is an important limitation to address in this study. This studies relies on pharmacy record pick-ups which assumes (1) all servicewomen use their health insurance to cover their prescriptions (2) all pharmacy perception pick-ups are used as directed (3) if two different types of birth control over lap the first is likely stopped at the time the second method is picked up. It is unlikely that rates of misclassification would vary by year with the exception of 2002. Contraceptive use prior to 2002 is not established in this study, therefore we acknowledge we are underestimating ever users as well as current users in 2002 until they picked up their next prescription. Prior studies suggest up to 10% of women forget or stop hormonal contraception while deployed and there may be variable rates of misclassification based on career event (Goyal, Borrero, & Schwarz, 2012). It is important to note that a large portion of many servicewomen's reproductive career is not captured in the study cohort. Our results present cohort prevalence not lifetime prevalence.

A survey by Esposito and collages estimated about 8% of military members had one unclaimed prescription in a the last year (Esposito, 2008). However, this is less likely with contraception as it is and elective prescription also we could be more confident that a woman is using at least most of her prescription if the next refill is picked up on a monthly basis, or at the appropriate time point based on previously dispensed quantity. It would be unlikely that a woman

women fills 3 packs of pills, does not use them and returns to pick up another 3 months more that she does not plan to take. In these circumstances, contraceptive use would be overestimated.

Though not a limitation to the study of hormonal contraception, it is also important to know that other contraceptive methods were used by soldiers and not captured in this analysis. These methods include barrier methods: condoms, diaphragm and spermicide. When considering contraception for pregnancy prevention, these methods are important to consider. However, these methods typically have no physiologic or clinical impact apart from adverse reactions (e.g. topical skin irritation and allergies) and unintended pregnancies.

In 1983, a study was published in Military Medicine to examine use, understanding and adherence to contraceptives. From a sample size of 81 women, only 57% could recall the name of their contraceptives, 27% indicated they did not take the pill at the same time each day and 70% had forgotten to take at least one pill at least in the past month (Casey, Fluitt, & Wiatt, 1983). Self-discontinuation of contraception was not measured during our cohort as there is no integrated data on self-reported contraceptive use and is a notable limitation of this research. Pharmacy records provide the type, brand, hormone dose and duration of a prescription but fail to account for missed pills, lost prescriptions and cessation of use.

Selection Bias

Selection, or participation, bias is often an important concern for studies hormonal contraceptive use. Women who use contraceptives may be disproportionally represented at clinical encounters due to the need for prescription refills or they may be more oversampled in health care surveys given need to pick up prescriptions. However, these potential issues are unlikely to substantially affect the current study for several reasons. TRICARE covers the cost contraception for servicewomen. Also, both the pharmacy database and personnel records for the Army have 100% capture of soldiers on Active duty, it is unlikely that any women would be

missed for this analysis. This study provides a population level capture of contraceptive use among all servicewomen on active duty between 2002 and 2011.

Incorrect Timing of Career Events

It is possible that both BCT and deployments may not be accurately captured and therefore changes in contraceptive use linked to these time points may be inaccurate. In prior TAIHOD studies, basic combat training has been defined as most likely occurring within the first 90 days of a soldier's career. In addition, service members may go on other training including Advanced Individual Training, Officer Basic Training, and other temporary duty. The dates of theses trainings are not be captured in the TAIHOD. These trainings may require a soldier relocate for periods of a few weeks to a few months, often involve both physically and mentally challenging standards and could impact contraceptive use. Our analysis was limited in ability to assess contraceptive changes for BCT only and should not be extrapolated to all courses servicewomen attend. Deployment dates captured in the electronic data system represent mobilization date. However, this date does not always match the date in country. Service members may be assigned to in or out processing time in country before their in country deployment. Therefore, changes in contraception may occur around these times rather than while deployed.

Strengths

There are many strengths to our study that contribute to the growing body of literature. Most notably was our sample size. Only a few population or registry based reports have been published to date, only one including service members. This research not only presents complete capture of all servicewomen between 2002-2011, but it also utilizes pharmacy, deployment and training records to assess temporal changes in rates and type of use by key career events. The TAIHOD provides a unique advantage to asses this relationship given the large diverse population. In addition, we have captured all types of hormonal contraception including progestin

only pills, patch, ring, injection, IUD and implant. Almost all previous studies have failed to consider these methods in their analysis. Finally, our population is comprised of a healthy, active, closely monitored group. This allows for consideration of many covariates and sub classification of contraceptive use and type.

Recommendations for Future Research

There are remaining areas of interest that deserve additional attention and were not addressed in this study. Temporality of contraceptive use cessation and resumption around pregnancy was not evaluated but could provide windows of time with unique endogenous and exogenous levels of hormonal exposure. In addition, use of hormone altering prescriptions including Tamoxifen, or treatment for medical conditions including polycystic ovarian syndrome were not considered in this analysis. The frequency of dual use of contraceptives for purposes of changing methods or suppressing undesirable side effects was not considered in this paper. Servicewomen complete annual health exams that collect self-reported prescription use. This data was not included with TAIHOD at the time of data extraction, therefore, self-reported contraceptive validation was not possible. In addition, only a small fraction of the HCPCS coded for IUD insertions differentiated the type of IUD, Mirena or Paragard, which could also be gathered from self-reported prescription use at annual periodic health exam.

It is important to consider the use of all contraceptive types and characteristics for a number of physiological, social economic and military readiness factors. From a physiologic standpoint, it is established that the total dose of exogenous hormones as well as the impact on endogenous hormones vary by contraceptive type. It is critical to include the additional 10-15% of women that are using a contraceptive type other than pills in a given year. Both the desirable (including decreased PMS and menstrual suppression) and undesirable (including weight gain) side effects vary by type of contraception and need to be considered in future research. Historically, there has been stigma (perceived promiscuity) surrounding the use and motivation of

hormonal contraception particularly in the active duty population where lost time due to menorrhagia, dysmenorrhea and unplanned pregnancies pose a threat to mission readiness.

Generalizability

The study results may not be generalizable beyond the active duty Army. It has been documented that rates of contraceptive use differ between military branch in addition contributing factors such as operational environment, length of training and deployment may impact rates and type of contraceptive use. Trends in contraceptive use may resemble national trends within civilian populations although the Army may have higher rates of use given the healthy population where by contraindications are otherwise screened out during entry processing. In addition, TRICARE provides complete coverage of hormonal contraceptive potentially increased access to contraceptives compared to their civilian counterparts during the same timeframe.

Conclusion

To date, research surrounding hormonal contractive use has been limited to select populations, small samples and incomplete capture of all available contraceptive options. Temporal changes in contraceptive availability, changes in demographics of servicewomen, and changes in frequency and location of deployments contribute to the increase use in alternative contraceptive methods. Preference for particular contraceptive methods varied by key demographics where by older, married women had higher rates of IUD use and young women had increased use of implant and injection. Rates of use during basic training were low, and although rates of use remained relatively stable between U.S. home station and deployment, women were more likely to start and change their method while stationed in the U.S. These results provide data for health care planning, and hypothesis generation for future analysis regarding contraceptive use within the Army especially if sub-groups are identified to be at high risk for methods change or non-use. The timing of this research is relevant to establish a baseline for future plans of gender neutral standards and gender integration in combat positions.

Human Subjects Protection

The TAIHOD database was created in 1994 in order to understand risk factors for injury within the active duty Army population. All active duty army soldiers are included in the database without database specific written consent. Study personnel are trained in privacy protocols and electronic study database will be stored with a nonmilitary study identification number on a secure server that is password protected. There are no known potential risks to participants, except for accidental breach of confidentiality which is unlikely to occur. Additionally there is no known benefit to participating in the study except for advancing science in research involving servicewomen. This study was approved by the Institutional Review Boards of the United States Army Research Institute of Environmental Medicine and the University of Massachusetts Amherst.

Permission to Access Data

Permission to access data was granted by the United States Army Research Institute for Environmental Medicine Military Performance Division Chief Edward J. Zambraski, Ph.D. and TAIHOD director MAJ Owen Hill Ph.D. MPAS, following IRB approval by USARIEM and the University of Massachusetts Amherst.

CHAPTER 2

HORMONAL CONTRACEPTIVE USE AND ACL INJURY

Introduction

Significance of Musculoskeletal Injuries in Active Duty Soldiers

Compared to their civilian counterparts, active duty soldiers are at particularly increased risk for injury due to high physical demands in occupational and fitness training (Sulsky, Mundt, Bigelow, & Amoroso, 2002). Service members are more physically active as compared to the general population, and may be required to work extended shifts in difficult environments, especially during basic training and deployment. Injuries are the leading cause of hospitalization, disability outpatient visits, and manpower loss in the military compared to all other causes of morbidity (Tiesman, Peek-Asa, Zwerling, Sprince, & Amoroso, 2007; Sulsky et al., 2002). For the past two decades, musculoskeletal injuries have contributed significantly to disability discharge from the Army (Sulsky et al., 2002). Between 1981 and 2005, rates of disability discharge due to musculoskeletal injury increased around 8 fold for men and 15 fold for women (N. S. Bell, Schwartz, Harford, Hollander, & Amoroso, 2008).

Women's participation in the military has increased over the past few decades and currently women comprise about 15% of the Army's active duty force (Department of Defense, 2009). Between 1997 and 2003, there were 4,480 female ACL injuries documented as a sprain or strain of the cruciate ligament (ICD-9 844.2) and 3,540 injuries documented as an old disruption of ACL (ICD-9 717.83) resulting in about 640 incident ACL injuries involving women in the military per year (Owens, Mountcastle, Dunn, DeBerardino, & Taylor, 2007). Despite conflicting evidence surrounding the etiology for gender differences of musculoskeletal injury in service members, disability discharge rates due to musculoskeletal injury in women are twice as high as those in men (N. S. Bell et al., 2008).

Knee Injuries and the Significance of ACL Injuries

Knee injuries represent one of the most common musculoskeletal injuries (Tiesman et al., 2007; Sulsky et al., 2002). Knee injuries often involve multi-structural damage and may compromise the four stabilizing and surrounding ligaments including the anterior cruciate ligament (ACL)(American Orthopaedic Society for Sports Medicine, 2007). Although ACL injuries are acute and traumatic in nature, the short and long-term implications for correction, recovery and subsequent injury warrant attention among highly active populations. Servicemen and women experience ACL injuries at rates ten times higher than the general population (Owens et al., 2007).

Risk Factors for ACL Injury

In the general population, risk for ACL injury is affected by non-physiological factors like skill level, shoe type, use of ankle brace/tape, and playing surfaces (Murphy, Connolly, & Beynnon, 2003); and physiological factors including body mass index (BMI), small femoral notch width and joint laxity (Uhorchak et al., 2003). To date, limited examination of ACL injury in the Army has identified risk factors including history of knee injury, junior enlisted rank, low fitness test scores, less than college education (Sulsky et al., 2002; N. S. Bell et al., 2008). Among female soldiers soft tissue knee injuries are inversely associated with age with the highest rates occurring among women under 20 years old (Hill et al., 2012).

High BMI, joint laxity, Q-angle, femoral notch width and low fitness test scores have been proposed to explain the differential injury rates between men and women. A study by Bell and colleagues found that the gender differences in injury rates were not significantly different after controlling for fitness level (N. S. Bell, Mangione, Hemenway, Amoroso, & Jones, 2000). However, given the increased rates of injury observed among female athletes following puberty, endogenous hormone levels that fluctuate during the menstrual cycle and exogenous hormonal

contraceptive use have been suggested as possible factors that may impact joint laxity and other properties of musculoskeletal tissue.

The Role of Endogenous and Exogenous Hormones

Evidence suggests that hormonal fluctuations during the menstrual cycle may impact risk for ACL injury directly or indirectly by altering physiological properties of the knee and lower extremity. Estrogen receptors have been identified on muscle and ligament tissue surrounding the knee and changes in muscle stiffness and joint laxity throughout the menstrual cycle have been noted (Hewett, Zazulak, & Myer, 2007). Studies have suggested that hormonal contraceptives may decrease risk for ACL injury by attenuating endogenous hormonal surges (D. R. Bell et al., 2012; Ruedl et al., 2009). Given the widespread use of contraception among servicewomen further evaluation is warranted to characterize contraceptive users and better understand the injury mechanisms.

Physiology of Hormonal Contraceptives and ACL Injury

Gender Differences in ACL Injury Rates

Over the past few decades, sex hormone profiles have been suggested as a contributor to the differential in lower extremity injury rates observed between men and women. Unlike anatomical sex differences (e.g. increased Q-angle among women due to a wider pelvis), hormonal contraceptive use is potentially modifiable. A link between endogenous hormones and ACL injury has been described, which holds physiologic relevance for non-contraceptive users and provides a foundation for understanding the implications of contraceptive use.

Impact of the Menstural Cycle on ACL Injury

The pathophysiology of the menstrual cycle in healthy ovulating women is well understood. Four key hormones regulate the menstrual cycle including two gonadotropic hormones (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) produced by the pituitary gland, and two sex steroids (estrogen and progesterone) (Shechter & Boivin, 2010).

Toward the end of the follicular phase both estrogen and LH spike 5 and 10 fold respectively (Shechter & Boivin, 2010). Following ovulation, hormonal secretion is regulated by the corpus luteum where progesterone rises 8 fold and a 2 fold increase in estrogen occurs (Shechter & Boivin, 2010). The presence of estrogen receptors on cells of the knee suggests a potential impact of estrogen on joint function. Estrogen receptors have been identified on the synoviocytes (cells that control fluid in joints) in the knee, fibroblasts in collagen of the ACL (Hewett, Myer, & Ford, 2006), and also on muscle tissue (D. R. Bell et al., 2009). Hormonal fluctuations may impact the ability of an individual to stabilize their knee by impacting the activation patterns (increased hamstring to quadriceps ratio) or reducing sagittal torques at the knee (Hewett, 2000). The reduced ability to control knee motion, with concurrent changes in laxity and reflexes result in a high risk situation particularly for the ACL. Joint laxity, in particular, has been widely studied and can increase risk for ACL injury by impacting hypermobility (hyperextension) and is more common among women (Griffin et al., 2000).

Epidemiologic studies suggest varying levels of risk for ACL injury across the menstrual cycle (Slauterbeck et al., 2002; Arendt, Bershadsky & Agel, 2002; Wojtys, Huston, Boynton, Spindler, & Lindenfeld, 2002; Lefevre, Bohu, Klouche, Lecocq & Herman, 2013; Hewett et al., 2006). One study found an increased risk for ACL injury during menses, three noted increased risk before ovulation and one noted increased risk at ovulation.

Impact Hormonal Contraception on ACL Injury

Hormonal contraception affects endogenous hormonal levels and changes through the menstrual cycle. Combined hormonal contraception (CHC) contains estrogen and progesterone and inhibits corpus luteum formation (Rivera, Yacobson, & Grimes, 1999). Some CHC lead to consistent hormone levels throughout the month, known as monophasic, whereas other CHC result in changes in the hormonal levels across weeks based on the type of pills (e.g. biphasic and triphasic). CHC inhibits pituitary production of follicle stimulating hormone (FSH) and

luteinizing hormone (LH) when they would normally surge mid-cycle preventing ovulation (Rivera et al., 1999). Endogenous FHS and LH levels decrease within a few days of initiation of CHC and will start to return to pre-CHC levels soon after cessation. Progestin only methods (pill, injection and implant) only partially suppress ovulation. The injection also prevents the mid-cycle surge of LH needed for ovulation (Rivera et al., 1999). Hormonal contraception impacts endogenous FSH and LH which would normally surge mid-cycle, interfere with ovulation influencing luteal hormonal exposure, as well as provide a predictable dose of hormones.

Prior research has evaluated serum hormone levels and joint functional movement by contraceptive status. Combined hormonal contraceptives appear to attenuate relaxin and progesterone profiles. A recent study found that crude levels of serum relaxin and progesterone levels in nulligravid athletes were significantly lower among hormonal contraceptives users compared to nonusers measured at the mid-luteal surge (Dragoo et al., 2011). Increased relaxin is associated with increased knee laxity, due to diminished collagen tension, and may increase risk of ACL rupture ((Dragoo et al., 2011; Wojtys, Huston, Lindenfeld, Hewett, & Greenfield, 1998)). Martineau and colleagues used laboratory based measurements to assess tibiofemoral anterior-posterior translation laxity between contraceptive users and nonusers finding significantly decreased laxity among contraceptive users (Martineau, Al-Jassir, Lenczner, & Burman, 2004). In contrast, a study by Hick-Little found no effect of hormonal contraceptives on laxity (Hicks-Little, Thatcher, Hauth, Goldfuss, & Cordova, 2007).

Differences in hormonal profiles between men and women may potentially play a role in differential risk of ACL injury. Estrogen receptors have been identified on the knee and it is plausible that changes in endogenous hormone may impact knee stability and injury risk. Hormonal contraception alters the natural level and fluctuation of endogenous hormones and therefore may also impact risk for ACL injury. Prior studies have shown hormone serum and biomechanical differences by contraceptive use. . Combined hormonal contraception more

completely suppresses ovulation and could potentially result in greater stability of cyclic variations, though, progestin only methods partially suppress surges and could offer some benefit. Hormonal contraceptive use could be a potentially important modifiable risk factor for ACL injury risk; however limited research to date warrants additional investigation.

Epidemiology of Hormonal Contraceptives and ACL Injury

Five epidemiological studies to date have evaluated the association between hormonal contraceptives and ACL injury, which have included a total of 68,150 participants and 17,464 ACL injuries (Agel, Bershadsky, & Arendt, 2006; Liederbach, Dilgen, & Rose, 2008; Ruedl et al., 2009; Rahr-Wagner, Thillemann, Mehnert, Pedersen & Lind, 2014; Gray, Gugala, & Baillargeon, 2016). Two of these studies were prospective in design, with self-report contraceptive exposure, capturing 55 ACL injuries among 3,333 athletes (Agel et al., 2006; Liederbach et al., 2008), and three were case-control. The first case-control study matched cases to controls (1:1) and collected self-report contraceptive use among186 skiers, while the latter two utilized medical billing codes to identify ACL surgical repair and contraceptive pick up among 47,315 controls and 17,316 cases in the general population (Ruedl et al., 2009; Rahr-Wagner et al., 2014; Gray et al., 2016). In addition, two systematic reviews published in 2017 both identified 7 studies that examined the association between hormonal contraceptive use and ACL injury, two of which were case series and not included in our review (Herzberg, Motu'apuaka, Lambert, Fu, Brady & Guise, 2017; Samuelson, Balk, Sevetson, Fleming, 2017).

In the largest prospective study of hormonal contraceptive use and ACL risk conducted to date, Agel et al. followed a cohort of 3,150 female basketball and soccer collegiate athletes over two seasons (Agel et al., 2006). Hormonal contraceptive status was collected by self-report of athletes to their athletic trainers at the beginning and end of the season and users were categorized as monophasic, triphasic or other (injectable, unidentified contraceptive or known change of contraceptives). Incident ACL injuries occurring by a noncontact mechanism were reported to the

research team by athletic trainers and confirmed with a clinical exam or diagnostic imaging. The rate of incident ACL injuries was analyzed by season (2000 and 2001) and by sport (basketball and soccer).

Compared to women who did not use hormonal contraceptives, women who used contraceptives had similar risk for ACL injury in unadjusted estimates for 2000 (OR 0.95, 95% CI 0.38-2.35) and for 2001 (OR 1.02, 95% CI 0.31-3.43)(Agel et al., 2006). Additionally, the authors found no statistically significant association between hormonal contraceptives and ACL injury in analyses stratified according to basketball players (OR 1.14, 95% CI 0.55-2.36) or soccer players (OR 1.17, 95% CI 0.36-3.85). Despite having a relatively large overall number of participants, the small number of ACL injuries observed (n=45) resulted in low statistical power, and complicated interpretation of the null findings. In addition, the authors did not evaluate other types of hormonal contraceptives (e.g., injectable, patch, ring) and failed to consider prior lower extremity injury and BMI. Withstanding these limitations, Agel and colleagues were the first to publish on the association between contraceptive use and ACL injury and provide a foundation for the studies that followed.

Liederbach et al. assessed ACL injury among 183 female ballet and modern dancers over a 5 year period, capturing a total of 10 ACL tears (Liederbach et al., 2008). Certified athletic trainers conducted annual screenings during the study period to assess contraceptive use. Standardized questionnaires were used to assess ACL injuries and were categorized as either partial or complete rupture of the ligament confirmed by diagnostic imaging. In an unadjusted comparison, women who used hormonal contraceptives had a 68% decrease in risk of ACL injury as compared to nonusers, though results were not statistically significant (calculated OR 0.32, 95% CI 0.09-1.16). This study, similar to Agel et al., was limited in power to adequately assess the association between hormonal contraceptives and ACL injury and was limited to oral contraceptive use. Although there was no significant association between hormonal contraceptive

use and ACL injury, the calculated OR has a magnitude of protection consistent with Möller-Nielsen and Hammar, encouraging larger future studies to continue to assess the association.

Ruedl et al. (2009), utilized a case-control study to assess oral contraceptive use and risk of ACL injury among 186 Austrian recreational skiers. Cases (n=93) included women treated for noncontact ACL injuries with MRI confirmed diagnosis at a local clinic. Controls (n=93) were skiers selected on five different days at the slopes and were age matched to cases. Oral contraceptive use was obtained on a questionnaire and dichotomized as use and nonuse. There was no difference in risk of ACL injury between those who used oral contraceptives and those who did not (unadjusted OR 0.95, 95% CI 0.52-1.74). The statistical power of this study was limited by the small sample size utilized, as well as by likely misclassification related to use of self-report for oral contraceptive status. Though limited in power, their results, utilizing a different study design, support the conclusion of the two prior studies. Ruedl and colleagues contributed to prior literature by readdressing the relationship between hormonal contraceptive use, menstrual cycle timing and ACL injury.

In the first study to consider ACL injury resulting in operative repair, Rahr-Wanger and colleagues (2014) identified women with cases of operatively treated ACL injury (n=4,497) in the Danish Knee Ligament Reconstruction Registry between 2005 and 2011 (Rahr-Wagner et al., 2014). Two population controls (n=8,858) per case were selected using risk-set sampling from the Danish Civil Registration system and were matched to cases on age. Contraception use was classified as ever/never and was determined from pharmacy records; use was defined as picking up at least 1 prescription for oral contraception during the study period. The authors additionally classified women as new users (i.e., first prescription in the last year), recent users (i.e., prescription >1 year before the index date), and long term users (i.e., prescription in the last 1 to 5 years before the index date). During the 5 year period, 45% of women ever used oral contraceptives. Ever contraceptive users had 18% decreased risk of ACL injury needing surgical

repair (RR 0.82, 95% 0.75-0.90) with similar findings among long term and recent users. There was no association between new use and ACL surgical repair. Additionally, they found deceased risk of ACL surgical repair among any duration of use up to four years with the greatest reduction in risk at 3 years (RR 0.75, 95% 0.64-0.90) as compared to never users. There was no significant protection among women who used contraceptives longer than 4 years. This study adds to prior literature by considering duration of contraceptive use as well as ensuring the temporality of hormonal use prior to ACL surgery. The most notable limitation of this study is the lack of complete capture of incident ACL injuries resulting from the case definition (i.e., those with operative repaired ACL injury). Because not everyone who sustains an ACL injury will proceed with surgical repair, it is possible that women who opt for surgical repair may be different than nonsurgical counterparts (Rahr-Wagner et al., 2014). Despite this limitation, Rahr-Wagner and colleagues add to existing literature by considering duration of use as recent use to assess time off contraceptives prior to operative repair.

In the largest published study to date, Gray and colleagues (2016) utilized the Clinformatics Data Mart, database of insurance claims in the United States to identify women who underwent ACL reconstruction (n=12,819) as cases of ACL injury over a 11 year timeframe. They matched controls to cases in a 3:1 ratio based on index date, age and region. The average age of women undergoing repairs was 24 which they noted was 3-4 years younger than a prior report from Maletis and colleagues suggested (Maletis, Granan, Inacio, Funahashi, Engebretsen, 2011). Hormonal contraception was measured as any oral contraceptive use in the 12 months prior to the index date. There was no difference in operative ACL among ever users of any hormonal contraception OR 0.98 (95% CI 0.94-1.04), though women with use less than 90 days were 11% less likely to need surgical repair (OR 0.89, 95% CI 0.81-0.99). The authors found that young women aged 15-19 using oral contraceptives were 18% less likely to have ACL surgery (OR 0.82, 95% CI 0.75-0.91) as compared to women aged 25-29 and 30-35 were 15% more

likely (OR 1.15, 95% CI 1.02-1.3 and OR, 1.16 95% CI 1.04-1.31 respectively). This study excluded all other types of hormonal contraception as well as women diagnosed with Turner Syndrome, follicular cyst, acquired atrophy of ovary or fallopian tube, benign or malignant neoplasm of ovary, which prior studies have not done. They also considered diabetes, asthma and any use of oral, injectable or inhaled steroids as covariates. A notable limitation is that this study did not consider women who sustained an ACL injury but did not have surgical repair. Gray and colleagues were the first to find a statistically significant association between hormonal contraception and operative repair of the ACL among recent users and among young (ages 15-19) ever users which suggest there could be underlying difference in both hormonal fluctuation, choice of exogenous hormone and injury risk by age. Although their study was the largest to date, the use of surgical repair as a proxy for incident injury leads to incomplete capture of ACL cases and future studies should aim to completely capture incident injury on a similarly large scale.

In 2017, two systematic analysis were published which summarized the studies to date including those discussed in detail above with the addition of Liederbach et al. (2008), which was not included in either review (Herzberg, Motu'apuaka, Lambert, Fu, Brady & Guise, 2017; Samuelson, Balk, Sevetson, Fleming, 2017). These literature reviews also included two case series (Lefevre, et. al, 2013; Wojtys, et. al, 2002).and one small cohort (n=83) (Arendt, et al., 2002) focused on the timing of ACL injury during the menstrual cycle, enrolling only women with ACL injuries. Without a comparison, uninjured, group we are unable to assess the direct impact of contraception on ACL injury in these studies; those studies with noninjured comparison groups were excluded from the review above. The systematic reviews suggest that, taken together, recent literature indicates a protective effect of hormonal contractive use with up to a 20% reduction in ACL injury. However, the authors of these reviews noted that although the literature has increased in number, the overall strength of the studies still remains poor due to

limited prospective capture, focus only on oral contraceptive pills, lack of consideration of appropriate confounders and sensitivity analysis.

Samuelson and colleagues (2017) at Brown also conducted a review of literature surrounding timing of menstrual cycle, including five studies published between 2002 and 2013. Although these results are inconclusive due to inconsistent classification of menstrual phase across studies, it is important to note there was no risk of ACL injury associated with the luteal phase (among contraceptive users or nonusers). Herzberg and colleagues (2017) at Oregon Health & Science University reported similar conclusions regarding menstrual phase timing. They additionally considered knee laxity across menstrual phase in six of twelve published studies, noting a greater laxity at ovulation compared to the follicular phase without a difference between follicular and luteal phases (Herzberg et al., 2017; Samuelson et al., 2017). In summary, previous studies of the relationship between hormonal contraceptive use and risk of ACL injury have been limited. The only three studies, two cohorts and one case-control, to consider incident ACL injury found no significant association (Agel et al., 2006; Liederbach et al., 2008; Ruedl et al., 2009).

The two most recent studies, both case-control in design, suggest there is a significant reduction in ACL surgical repair, as a proxy for ACL injury, among hormonal contraceptive users (Rahr-Wanger et al., 2014; Gray et al., 2016).The two most recent studies considered important covariates in their analysis including age, BMI, NSAID use, ethnicity, prior injury and pregnancy. Main limitations have included small sample size, incomplete ACL injury captures (e.g., inclusion of only those with surgical repair or only without surgical repair), assessment of OC use and issues related to establishing temporal ordering of OC use and ACL injury. Thus, while it has been suggested that contraceptive use may reduce risk of ACL injury by up to 20%, limitations in prior studies leave uncertainty regarding the association. Moreover, to our knowledge, no studies to date have assessed dose or contraceptive type other than the pill and only two have considered duration with regard to risk of ACL injury. These factors are likely to have varying impacts on

endogenous menstrual response, and the insufficient assessment of dose, duration and type of hormonal contraception on ACL injury risk is an important research gap. Because of the limited number of studies of the relationship between contraceptive use and risk of ACL injury, and the limitations of those previous epidemiologic studies, further research is warranted.

Knee injuries have contributed to a significant proportion of disability discharge from the Army over the past few decades (Sulsky et al., 2002; Hauret, Jones, Bullock, & Canham-Chervak, 2010). Women are a growing segment of the military population and have increasingly become involved in physically demanding jobs (Department of Defense, 2009). Between 1997 and 2003 there were over 4,000 ACL injuries among servicewomen alone (Owens et al., 2007). Women appear to be at increased risk for ACL as well as other knee injuries (N. S. Bell et al., 2008). Known modifiable risk factors for knee injury include fitness and BMI, however the gender inequality in injury risk is not well understood.

It has been suggested that hormonal contraceptive use may decrease risk of ACL injury by attenuating endogenous hormonal surges throughout the menstrual cycle which may impact neuromuscular strength, reaction and joint laxity (Hewett, 2000). Previous research has identified hormone receptors on muscles and ligaments which respond to endogenous hormone surges decreasing strength, and overall laxity (Renstrom et al., 2008). These characteristics of the knee are important predictors, and often components, of ACL injury.

Because of limitations of existing epidemiological studies evaluating the relationship between hormonal contraceptive use and risk of ACL injury, the relationship remains uncertain. Between 2006 and 2009, two prospective cohorts and one case-control study examined the association in dancers, basketball players, soccer players and skiers (Agel et al., 2006; Liederbach et al., 2008; Ruedl et al., 2009). These studies found no statistically significant association between hormonal contraceptive use and ACL injury, though they were limited in sample size and dichotomized self-report exposure assessment. Two case control studies were published in

the last 3 years using operative repair of the ACL as a proxy for injury found that contraceptives may decrease risk by 20% (Rahr-Wagner et al., 2014; Gray et al., 2016). No studies have included all contraceptive types or dose of contraceptive use and ACL injury in the military population. To address this research gap, we evaluated the relationship between type, dose, and duration of hormonal contraceptive use and risk of ACL injury in the active duty Army population over a ten year period between January 2002 and December 2011.

Aim and Hypotheses

Specific Aim: To evaluate the association between hormonal contraceptive use and risk of ACL injury among active duty Army servicewomen. Hypothesis 1: Compared to non-users, hormonal contraceptive users will have lower risk of ACL injury. Hypothesis 2: Compared to non-users, combined hormonal contraceptive users will have the lowest risk of ACL injury followed by progestin only users. Hypothesis 3: Compared to non-users, increasing duration of hormonal contraceptive use will have an inverse relationship with ACL injury.

Methods

Study Design and Population

The study population consists of servicewomen between the ages of 17 and 45 who served at least two months on active duty between January 1st, 2002 and December 31st, 2011 using the TAIHOD. The TAIHOD was created in 1994 with the aim to study injuries among female soldiers, though the database captures servicemen and women. The database prospectively links administrative, clinical, pharmaceutical, occupational and health behavior data for all soldiers who have been on active duty. The TAIHOD currently contains data on over 5 million soldiers with active service and outpatient clinical records as far back as 1997. For the current study, the start date of January 1st, 2002 was selected as it marks the onset of electronic pharmacy record capture from the PDTS, which is integrated into the TAIHOD to determine hormonal contraceptive use. This timeframe captures Operation Enduring Freedom and Operation

Iraqi Freedom (OEF/OIF), which allows for evaluation of changes in contraceptive preference and use in austere environments as well as changes in number and frequency of deployments.

Among active duty Army soldiers between 2002 and 2011, there were a total of 207,777 women. In any given year during this 10 year period, about 82,000 women were on active duty; servicewomen comprised between 13.6-15.8% of the active duty Army over the ten-year study period. Two thirds of the women on active duty between 2002 and 2011 were new accessions, entering the cohort in 2002 or later. The average age at entry into the cohort was 24. Most women had high school education or equivalent at entry. Less than one quarter of women had a rank of senior enlisted or officer at entry. At entry, 30% were overweight or obese. More than half were ever deployed at least once during the cohort and one quarter had a delivery during the cohort. Half had a documented knee injury during the cohort, 30% had a back injury and 15% an ankle. Most women ever used NSAIDs during the cohort.

Exclusion

For the purpose of the current study, women with only one record in the DMDC were dropped due to the insufficient observation time to capture and quantify hormonal contraceptive use, changes in duty station and other undetermined cause for military discharge that make these women not generalizable to the active duty women who serve for longer periods of time. In order to restrict consideration to pre- and not peri-menopausal women, women were censored from the analysis at the age of 46. Thus, women who entered the cohort at age 46 did not contribute any observation time to the study; however, women who turned 46 during the study timeframe contributed person time up until censoring at age 46, with subsequent person time dropped. Participants who were missing age, education, marital status, race or ethnicity from the DMDC were excluded. From this population, we further excluded women who had medical record documentation of a hysterectomy, oophorectomy, clinically diagnosed menopause, or used hormone replacement therapy as these women likely have different comorbidities that may

impact their use of hormonal contraceptives (Appendix A). In addition, women who experienced one of these events during the study cohort were dropped at the event date and person time following the event was also dropped. Women with greater than 120 pregnancy visits during the study cohort were also excluded. These women compromise a group of either implausible medical records or high risk pregnancies that are likely not generalizable. The number of women and person years excluded and dropped are shown in Table 7. Although rare, women with any lower extremity amputation were excluded or dropped as their risk for ACL injury is expected to be vastly different compared to other servicewomen. Women with known ACL injury prior to 2002, contralateral or recurrent injury, were dropped to identify incident ever ACL injuries. The number of women and person years excluded and dropped are shown in Table 7.

Exposure Assessment: Hormonal Contraception

Hormonal contraceptive use was assessed through pharmacy data recorded in the PDTS within the Medical Data Repository. The PDTS is a complete database capturing all prescription pick-ups at Military Treatment Facilities, TRICARE pharmacy networks, and mail orders (Department of Defense, 2009; The Department of Defense Pharmacoeconomic Center, 2011). Pharmacy records contain information on: therapeutic class, product name, type of hormonal contraceptive, dosage, days' supply, quantity and date pick up. TRICARE covers hormonal contraceptives at no cost to soldiers (Enewold et al., 2010). Therapeutic class codes '681200, contraceptives' and '683200, progestins' were used to identify hormonal contraception. Prescriptions recorded with a dispense quantity equal to zero were considered as requested but not picked up. Prescriptions for HRT or treatment for amenorrhea and anovulation were not included in the analysis as hormonal exposure.

The PDTS dataset contains information on the date, quantity and contraceptive type dispensed. Product type other than: pill, patch, injectable, implant, vaginal ring were eliminated. Exposure was further categorized by type of contraceptive to evaluate differences in use of

combined hormonal contraceptive versus progestin only. Combined hormonal contraceptives included monophasic, biphasic and triphasic oral contraceptives, Ortho-Evra (birth control patch), and Nuvaring. Progestin only contraceptives include progestin only pill, Depo-Provera (injection), Mirena (intrauterine device) and implants (including: Noroplant, Implanon and Nexplaon). Timing and duration of use was determined from start and stop dates were calculated as follows: start date equals date of pick up plus one day and the end date is equal to the start date plus the quantity provided.

For consistency with prior literature, we initially dichotomized hormonal contraceptive use as ever versus never user. Taking advantage of the extensive information included in the TAIHOD, we additionally considered use as 'never', 'past' and 'current', as well as contraceptive type (pills type, patch, ring, injection, IUD and implant). These methods were collapsed into combined hormonal contraceptive and progestin only. We also looked at duration of any contraceptive use as defined by short (<90 days), medium 90-365 and long 365+. Prior studies have identified 90 days as an appropriate cut point for short use as women are often encouraged to trial a new method and 97% of those that use for 3 months will continue using in month 4 (Rosenberg, M.J. & Waughm, M.S., 1988).

To examine the impact of never versus current use, the variable never', 'past' and 'current', was combined with both type and duration. Prior studies have not considered dose of contraceptives which is equivalent to the duration of use by type of use. To examine dose we created a 10 level mutually exclusive variable that incorporates both type of method and duration of use. Our final categorization of contraceptive use evaluated time since stopping use of any contraceptive method (Table 10).

Validity of Exposure

Hormonal contraceptive pharmacy records have not been validated in the TAIHOD. However, previous research have suggested that pharmacy records are a valid source of

information regarding use, duration and timing of contraceptives when compared to self-report (which is the most frequently utilized method of exposure assessment). Discordance between pharmacy records and self-report may result from inaccurate self-reporting, or when prescriptions are filled but not used. Pharmacy records have also been found to be a more accurate source of information than self-report for type of oral contraceptives (high dose, low dose and progestin only pill), with correlation coefficients between self-report and pharmacy records ranging from 0.84-0.93 (Norell et al., 1998). Use of pharmacy records for assessment of duration of use requires assuming that any prescription dispensed was used for the entire days' supply as directed by the pharmacy.

Outcome Assessment: ACL Injury

ACL injuries were the outcome of interest and were identified by ICD-9 code 844.2 in medical records. This code identifies 'sprain of cruciate ligament of the knee'. The first date of service for this ICD-9 code was selected to identify incident ACL cases (Table 8). Identification of ACL tears through medical records is considered to be the gold standard. It is important to note that this ICD 9 code also includes posterior cruciate ligament (PCL) tears. However, previous studies have continued to utilize this ICD-9 code for determination of ACL injury with confidence as PCL tears are rare. PCL tears occur from abrupt traumatic front end forces to the lower leg including a knee hitting a dashboard in a motor vehicle accident.

Records were also reviewed for CPT codes indicating diagnostic imagining (X-ray, magnetic resonance imaging-MRI). Procedure codes (81.43) triad of knee and (81.45) repair of cruciate ligament were abstracted to identify women who had surgical correction. Clinical encounter data for women who had been on active duty prior to 2002 was reviewed to exclude prior ACL injury. Because history of ACL injury is an important risk factor for recurrent injury, and has been most recently reported to increase risk 6 fold compared to primary injury

(Paterno.,M.V., Rauh, M.J., Schmitt, L.C., Ford, K.R., & Hewett, T.E., 2014), only first documented ACL injuries were considered in the TAIHOD.

Covariate Assessment

Demographic data including age, race, ethnicity, education, marital status, grade and length of service were extracted from the monthly DMDC data repository. When a service member joins the military without any previous military they are considered to be a new accession. For new accessions, length of service represents any time on active duty in the study cohort between 2002 and 2011. For women with active duty time prior to 2002, length of service a sum of all time on active duty prior to and including the cohort timeframe Ever attendance to BCT was identified from training records, however, dates of basic combat training (BCT) were determined as discussed above. Deployment records and overseas station dates and location were merged in with DMDC records. A single measurement of body mass index (BMI), as measured at accession, was also merged with the demographic data. Diagnostic and medical procedure billing codes from the time a woman entered active duty were available and utilized to identify lower extremity injury and delivery (Appendix A). Records for women who served on active duty prior to 2002 were included to capture the number of deliveries and lower body injuries prior to the cohort. Parity was determined by the number of dependents, marital status, age and delivery during the study cohort. Women with a known delivery during the study are automatically parous. Women without any documented deliveries, but were married with 2 or more dependents were also considered parous. Women who were, single with no dependents were considered nulliparous. Ever use of prescription NSAIDs and count were also determined from pharmacy records.

Univariate Analysis

We reported the number, percent and total active duty person years in TAIHOD and the number and percent of those who are excluded due to missing records, age over 45, previous

hysterectomy, oophorectomy, menopause, hormonal therapy, lower extremity amputation and previous ACL injury (Table 7). The percent distribution of ACL injuries as well as use of diagnostic technology and clinical interventions were presented (Table 8).

Bivariate Analysis

The association between entry covariates and ACL injury was assessed through chi-square tests and results of the cross tabulation were reported (Table 9). Percent and distribution of hormonal contraceptive exposure by ACL injury are presented in Table 10 across all contraceptive categorizations. Unadjusted relative risks and 95% confidence intervals were calculated to compare hormonal contraceptive users with non-users as the reference group, with regard to ACL injury (Table 10).

Multivariable Analysis

The relationship between hormonal contraceptive use and ACL injury was modeled using survival analysis to estimate hazard ratios and 95% confidence intervals (Table 10). Nine categorizations of contraceptive exposure were considered in this analysis. Potential confounders were identified as being significantly related to both contraceptive use and ACL injury. The only confounder consistently identified by prior literature included age which was automatically retained in the final model. Likelihood ratio tests comparing models with these covariates to the hormonal contraceptive ever/never model were conducted and models that remained significant ($p<0.05$) were retained for continued step-wise model building. The variables for the final model of hormonal contraceptive ever/never were then applied to the eight remaining categorizations of contraceptive exposure.

Three models were considered in the final analysis (Table 10) including: 1) unadjusted, 2) age adjusted and, 3) final adjusted model. A sensitivity analysis considered only new accessions during the study cohort to capture the full spectrum of career events servicewomen face to ensure inclusion of basic training, advanced individual training and deployment where

both contraceptive use and risk for ACL injury may differ from permanent duty station (Table 11).

Results

Final Study Sample

Exclusions are detailed in Table 7. Of the 207,777 participants and 757,610 person years of total observation, the most common reason for exclusion was due to missing records (n=6,347). Over one third of those excluded (n=3,544) only had one month record in DMDC. An additional 2,803 women were missing age, education, marital status, race or ethnicity. An additional one percent of women were excluded from the study due to being age 46 or older at entry to the cohort or to the Army. Less than one percent of the study population was excluded due to a medical reason. A total of 80 women were excluded from the study due to lower extremity amputation and an additional 1,501 women were excluded due to known prior ACL injury before 2002. Half of the women excluded at entry and the majority of women dropped during the study time frame had service prior to 2002 (Table 7).

ACL Injuries

We identified 195,815 eligible women in the TAIHOD between 2002 and 2011 resulting in 703,499 person years (Table 7). Of these women, 2,253 experienced an incident ACL injury representing a rate of 3.20 per 1,000 person years among the entire cohort and a rate of 3.28 per 1,000 person years among new accessions (Table 8). Less than 6% of incident ACL injury had a knee x-ray and less than 10% had an MRI around the time of injury. Only 15% of women would go on to have their ACL surgically repaired while in the Army.

Correlates of ACL Injury

Compared to women who did not have an ACL injury, women who did had 10% higher probability of service prior to 2002 (44.43% vs. 34.74%). These women were on average one year older, had slightly higher education, marital status and rank. Women with an ACL injury

were more likely to be African American, as well as with a prior knee, back, hip, ankle or leg injury. Women with incident ACL injury had 6% higher likelihood of being overweight or obese (36%) compared to women without ACL injury (30%) at entry to the Army (Table 9).

Hormonal Contraceptive Use and ACL Injury: Ever Use

Ever users of hormonal contraceptive had 14% decreased likelihood of ACL injury as compared to never users (HR 0.86, 95% CI 0.79-0.93) (Table 10). After adjusting for age, knee (never, past current injury), NSAID use (never, past or current), deployment (never, past or current), pregnancy (never, past current), race/ethnicity, back or hip injury (never, past current) and new accession, the overall protection of hormonal contraceptives was eliminated (HR 0.95, 95% CI 0.86-1.04). However, current users continued to have a 15% decrease in incident ACL injury (HR 0.85 95% CI 0.76-0.94).

Hormonal Contraceptive Use and ACL Injury: Type of Use

The seasonal contraceptive pill was associated with the lowest estimated hazard (HR 0.44, 95% CI 0.20-0.97) among evaluated methods. A nonsignificant increased risk was observed for the implant (HR 1.22, 95% CI 0.72-2.08) in the unadjusted model. In the analyses comparing methods grouped by type, progestin only users in their career had the lowest risk of ACL injury (HR 0.78, 95% CI 0.65-0.94) compared with 0.88 for users of a combined hormonal contraception (HR 0.88, 95%CI: 0.80-0.96) and 0.84 for users of both progestin only and combined contraceptive methods (HR 0.84, 95% CI 0.74-0.97) compared with non-users. A similar result was observed in analysis considering past use however, current users who had ever used either method had the most protection.

Hormonal Contraceptive Use and ACL Injury: Duration of Use

The longer women used any type of hormonal contraceptive the more protected they were against ACL injury (Table 10). As length of contraception use increased among combined only user, risk for ACL injury decreased. However, the opposite was true for progestin only users

who experienced the lowest risk in the short term use group. These results remained consistent after controlling for age and patterns remained similar while looking among only new accessions (Table 11). Among new accession, increasing time since last use appeared to have increasing trend of risk for ACL injury, though again none of these results were statistically significant.

In all models, with the exception of new accessions, women who recently stopped hormonal contraception in the past 90 days had an increased likelihood of ACL injury, compared to never users.

Discussion

Summary of Findings

Of the 195,815 women included in the cohort, 2,253 experienced an incident ACL injury resulting in a rate of 3.20 per 1,000 per years among the entire cohort and a rate of 3.28 per 1,000 among new accessions. Few had documented imaging or surgical repair. Women with ACL injury were on average one year older, had higher level of education and higher rank. Women with an ACL injury were more likely to have a prior knee, back, hip, ankle or leg injury and were 6% more likely to be overweight or obese at entry to the Army.

Ever users of hormonal contraceptive had 14% decreased likelihood of ACL injury as compared to never users in the unadjusted model, however in the final model the protection was attenuated. In the final model, current users saw a 15% decreased risk in ACL injury. These trends remained similar in the sensitivity analysis among new accessions, however, they were no long statistically significant.

Progestin only users had the lowest overall risk as a class with greater than 20% reduction in ACL injury the full unadjusted model and final model among new accessions only as compared to never users. Among all servicewomen, those who used the depo injection were significantly less likely to have an ACL injury with similar, nonsignificant, trends among IUD and Implant users. It is important to note pill and patch users had 13% and 45%, respectively,

reduced risk of ACL injury in the final model. When considering among new accessions only, IUD users had the lowest risk, with 40% reduction as compared to never users.

With regards to timing of contraceptive use, as duration of used increased, overall, the hazards decreased. Recent starters on any contraception saw no benefit or consequence from their short term use. However, among all models, with the exception of that limited to new accessions, women who recently stopped using contraceptives of any type in the last 90 days were more likely to have an ACL injury than never users.

Consistency with Prior Literature

Rates of ACL injury in women between 2002 and 2011 were slightly higher than reported by Owens and colleagues between 1997 and 2003 (3.2 versus 2.95 per 1,000 person years respectfully) (Owens et al., 2007). Consistent with our findings, previous studies also identified higher BMI and prior knee injury as risk factor for ACL injury. However, previous reports in the Army suggest service women who are younger, junior enlisted with lower rates of college education have the highest risk. Our results directly conflict with these prior reports likely due to the inclusion of women with service prior to 2002. These women contribute to more than half of ACL injuries and their characteristics at entry to the study cohort (January 2002) may not be representative of their true characteristics at entry to the Army.

The unadjusted hazard ratio in Table 10 suggests hormonal contraceptives may reduce ACL injuries by up to 14% although it does not hold true for ever users in the final adjusted model, current users continue to see a 15% lower hazard. These findings are consistent with the recent study by Gray et al. (2016) which found an 18% reduction among 15-19 year olds and the study by Rahr-Wagner et al. (2014) which found an 18% decrease among ever users. In contrast to our findings, Gray et al. found no protective effect over all among ever users, and a 15% increase among women 25-35 years old. Gray et al. were the first to consider the association by

age groups. Differences may be explained by the instituted exclusion criteria inherent to military selection and our inclusion of all contraceptive types which also vary by age.

With the exception of the contraceptive patch, we found progestin only use, as a class, as well as injection and IUD use had the lowest risk of ACL injury. Only one prior study has considered type of contraception. Gray et al. (2016) considered progestin only, monophasic and triphasic pills. They found a triphasic pills were 10% more likely to cause ACL surgical repair, although this result was not statically significant. Gray also found progestin only users were 10% less likely to have ACL surgical repair. We expected combined hormonal contraceptive users to have lower rates of ACL injury due to the direct receptors on the ACL as well as more complete inhibition of ovulation. However, our results compliment previous research on timing of ACL injury during menstrual phase suggesting increased risk of ACL injury during the follicular phase, when estrogen is high. There has been no associated risk with the luteal phase, when progesterone is relatively elevated.

We found that increasing protection against ACL injury with increasing duration in the unadjusted model. However, in the final model only short, <90 days, and long, >365 days duration of any use were both associated with 10% decrease in ACL injury. Gray et al. (2016) only considered use <90 or greater than and found similar results with 11% reduction in risk. Rahr-Wagner et al. (2014) considered duration of use in year intervals and found protection with all use under 4 years as compared to never users with the greatest reduction of 25% in ACL surgical repair in 3 years of contraceptive use. Differences in our findings again could be explained by difference in age, comorbidities and contraception type we considered, not reflected in previous research. Our results demonstrate the important of considering the use of all type of hormonal contraceptive as the risk for ACL injury varies widely by type.

Limitations

Non-differential Misclassification of Hormonal Contraceptive Use

Hormonal contraceptive use was determined using pharmacy records. Misclassification of hormonal contraceptive use based on pharmacy records will occur in a number of circumstances including: servicewomen who fill prescriptions for hormonal contraceptives but do not use them and are misclassified as users; servicewomen who have an IUD or Implant inserted before they joined the Army and are misclassified as non-users; servicewomen given multiple months of contraception coverage that was not documented in their medical records whose duration of use will be underestimated. Additionally, servicewomen who pay for hormonal contraceptives out of pocket from pharmacies not recorded in the database will be misclassified as non-users. We expect this misclassification to be minor due to insurance coverage for hormonal contraceptive by TRICARE which covers these prescriptions at no cost to active duty soldiers. Pharmacy records are maintained for all servicewomen by different database than where clinical records are maintained. Documentation of contraceptive prescription pick up would not be expected to differ by ACL injury and would bias results toward the null.

Non-differential Misclassification of Continuous Use

Due to the limitations of PDTS we are unable to identify continuous contraceptive users. Continuous use occurs when a woman intentionally discards the last week of inactive pills (the last seven pills in a normal 28 day oral contraceptive pack) and immediately starts a new cycle of active pills. This electively induces amenorrhea (skipping a menstrual cycle) and exposes the woman to additional 91 days (or 125%) exogenous hormones throughout the year compared to a traditional pill user. PTDS records do not indicate if a contraception method is being used continuously or as prescribed. It is unlikely that differential misclassification of hormonal contraception use occurred given the records were collected prospectively prior to ACL injury.

Non-differential Misclassification of ACL Injury

Soldiers with ACL injury were identified through medical records billing using ICD-9 codes, which have clear diagnostic criteria. It is unlikely that injured soldiers go undiagnosed due to the severity of symptoms associated with ACL injury. Because of the pain, swelling and inability to put weight on the injured leg related to ACL injury, and the high physical demands placed on soldiers, seeking medical treatment for the injury is likely. It is also unlikely that soldiers are incorrectly diagnosed as having an ACL injury. Both sources of misclassification of ACL injury (i.e., false negative and false positive for ACL injury) are not expected to differ according to hormonal contraceptive status, and would therefore tend to result in a bias toward the null. We expect this misclassification was minimal. It is unlikely that differential misclassification of ACL injury occurred given the traumatic natures of the injury and standardized clinical assessment.

Selection Bias

Given the cohort study design, and the real time capture of hormonal contraception use prior to the occurrence of ACL injury, selection bias is primarily a concern to the extent that women may have been differentially lost to follow-up based on hormonal contraceptive use and ACL injury. Soldiers are required to have regular medical exams, therefore the main way losses from the dataset may occur is due to separation from active duty. In addition, given the traumatic nature of ACL injuries and required medical documentation to receive disability benefits from occupational injuries, it is unlikely that a servicewoman would withhold medical evaluation until discharged from duty.

Confounding

We evaluated age, BMI and pregnancy as confounders that have been previously recognized in the literature. Education, rank (which may be a proxy for intensity of occupational requirements), were also considered as potential confounding factors, among others. We are

aware of at least three potential confounders that are not directly available through our dataset: BMI at time of injury, physical fitness and intensity of unit training. BMI at the time of injury is not available in the TAIHOD. Although BMI is a potential covariate of interest, the height/weight standards soldiers are required to maintain inherently controls for BMI as a confounder among this population. It is possible that women who are assigned to units that participate in above-average strenuous physical activity or high-intensity field training may be more likely to use contraceptives for menstrual regulation and may be at increased risk ACL injury given daily physical challenges. The expected result of this confounding would be to underestimate the protective relationship.

Prior literature has considered the role of menstrual phase as a risk factor for ACL injury in context of contraceptive use mitigating risk through a casual pathway alerting menstrual phase hormonal levels. To date, five studies have considered the timing of injury during the menstrual cycle and these studies suggest an increased risk around ovulation though due to inconsistent classification of menstrual phase, direct comparisons are difficult. No studies to date have identified the luteal phase, where progesterone is high, as increasing risk for ACL injury. It is unlikely that menstrual phase is a predictor of contraceptive use and should not be considered a confounder. Menstrual phase is not captured in the TAIHOD and the absence of menstrual phase as a possible risk factor should not be considered a major limitation. However, this information is critical to consider in context of the other findings. Our results suggest that progestin only methods as a class provide the greatest reduction in ACL injury. These findings warrant additional consideration of the role of progestin during the menstrual cycle, pregnancy (also a period of elevated progestin exposure) and exogenous contraceptive exposure.

Strengths

Our study adds to the literature in a number of ways. Prior literature had predominantly been limited to ever never use of oral contraception. We considered all hormonal types, the length

of use, time since last use and a combination of these factors. In addition, our study included a diverse population including women of all different ages and occupations whereas studies before 2014 had been limited to young athletes.

Generalizability

By its nature, this study focuses on a highly selected study sample – female members of the active duty Army. To the extent that the biological mechanism by which hormonal contraceptives impact risk of ACL injury does not vary by occupation or race or ethnic factors associated with armed service membership, the results of this study may be generalizable to all women.

Recommendations for Future Research

Future research should aim to include a number of covariates not considered in this analysis including BMI at time of injury, activity level, and participation in athletics. These factors may identify higher risk women both in occupational and recreational setting which we were unable to access. Women with knee injury are more likely to have subsequent injury though our study did not capture lower extremity injury prior to service and concurrent knee trauma (including triad injury) could be a proxy for severity of injury. Timing of pregnancy in relation to contraceptive use and ACL injury warrants additional investigation given the protection seen in progestin users. Ideally, future work will include detailed contraceptive use at time of ACL injury including validation of contraceptive use in pharmacy records by self-report to avoid misclassification among women who self-discontinue contraceptive use.

Conclusion

To date, few studies have evaluated the association between hormonal contraceptive use and risk of ACL injury. Given the serious repercussions an ACL injury may have on a service member's health, fitness, mission readiness and career, it is important to examine preventive measures. Due to the large number of contraceptive users, variety of contraceptive options,

increased participation of women in the military and the disproportionally high rate at which they are discharged to musculoskeletal injury, it is important that the association between hormonal contraceptives and ACL injury be fully understood. Reduction of occurrence, frequency or severity of ACL injury could also decrease subsequent early onset of osteoarthritis. Results of this study suggest contraceptive use may reduce ACL injury by 15%. Hormonal contraception is a potentially modifiable risk factor for ACL injury and inform warrant further investigation to integrate clinical recommendations and injury prevention strategies.

Human Subjects Protection

The TAIHOD database was created in 1994 in order to understand risk factors for injury within the active duty Army population. . All active duty army soldiers are included in the database without database specific written consent. Study personnel are trained in privacy protocols and electronic study database will be stored with a nonmilitary study identification number on a secure server that is password protected. There are no known potential risks to participants, expect for accidental breach of confidentiality which is unlikely to occur. Additionally there is no known benefit to participating in the study except for advancing science in research involving servicewomen. This study was approved by the Institutional Review Boards of the Unites States Army Research Institute of Environmental Medicine and the University of Massachusetts Amherst.

Permission to Access Data

Permission to access data was granted by the United States Army Research Institute for Environmental Medicine Military Performance Division Chief Edward J. Zambraski, Ph.D. and TAIHOD director MAJ Owen Hill Ph.D. MPAS, following IRB approval by USARIEM and the University of Massachusetts Amherst.

CHAPTER 3

HORMONAL CONTRACEPTIVE USE AND OSTEOARTHRITIS

Introduction

Osteoarthritis (OA) is a degenerative disease that occurs due to daily mechanical loading, overuse and aging (Nevitt & Felson, 1996). OA is a common chronic condition that is irreversible. Damage from OA can affect all joints or be site specific. OA is characterized by cartilage degradation, inflammation of synovial lining, bone spur formation and decreased muscle strength that ultimately can lead to joint failure (Roman-Blas, Castañeda, Largo, & Herrero-Beaumont, 2009). OA is diagnosed based on reported pain and diagnostic imagining identifying osteophytes (bone spurs), narrowing joint space (loss of cartilage), and changes to bone below the cartilage (Scher, Belmont, Mountcastle, & Owens, 2009). The onset of OA is difficult to determine as symptoms do not always correlate with radiographic severity. Severe OA based on imaging may be asymptomatic, or could be mild to severe friction, aching and pain particularly after long bouts of exercise or immobility (Scher et al., 2009). Incident OA may be untreated for years, therefore, first diagnosis is more likely a capture of prevalent cases that became severe enough to seek medical attention. OA is treated in an outpatient setting starting with over the counter Tylenol or nonsteroidal anti-inflammatories (NSAIDs). OA can be defined as primary or secondary. Primary OA is not caused by a preexisting condition, abnormality or disease whereas secondary OA follows a pre-existing condition (e.g. hip dysplasia, ACL injury) (Scher et al., 2009; Lohmander, Englund, Dahl & Roos, 2007).

Contributing Factors for Osteoarthritis

Osteoarthritis is a chronic condition that impacts cartilage, meniscus, ligaments and muscles around the joint (Heidari, 2010). There are many ways in which OA can manifest and many risk factors that contribute to the pathophysiology behind OA onset. Among the many risk

factors for OA, being overweight or obese, history of prior joint injuries and having occupations requiring knee bending and squatting repeatedly are primary contributors to the development and progression of OA (National Center for Chronic Disease Prevention and Health Promotion, 2014). In addition, older age, female gender, high bone density, muscle weakness, joint laxity, vitamin D deficiency and previous pregnancy all contribute to risk, with BMI as the most easily modifiable factor (Heidari, 2010). Genetic susceptibility also likely contributes to incidence of OA (Heidari, 2010).

Impact of Osteoarthritis on Public Health and the Military

OA significantly impacts occupational productivity and accounts for more than half of arthritis related hospitalizations, with annual costs for an individual estimated to be between $2,650 and $5,700 (Scher et al., 2009). It has been suggested that service members are at increased risk for OA given the high physical activity levels related to regular training, fitness and weight standards and occupational demands. At entry to the service, new recruits are evaluated for preexisting conditions and may be ineligible for service if recurrent, recent or unresolved injuries are noted (Scher et al., 2009). As a consequence of the high level of physical training, it is well documented that many of these service members will go on to experience a musculoskeletal injury during their career.

OA is typically thought of as a condition that affects sedentary, overweight, and/or elderly individuals; however, incidence rates of hip OA were noted at 35 cases per 100,000 person years (54 cases among women and 32 among men) among service members (Scher et al., 2009). It has been suggested that occupations requiring repetitive movements (e.g. running or loaded physical activity) may increase risk of OA though evidence is limited (Scher et al., 2009). Literature has established higher rates of OA among farmers and heavy manual laborers; similar trends may be expected among service members given occupational resemblance. More recently, literature suggests femoroacetabular impingement (FAI), boney abnormalities that cause friction

with motion which may contribute to OA. In a recent study by Scher and colleagues (2009), Army servicemen and women had the greatest odds of hip OA over other military branch with black service members, women and individuals over 40 years of age at the highest risk (Scher et al., 2009). After adjusting for age, rank, race and sex, rates of OA were higher in the Army (RR 1.9, 95% CI 1.75-2.07), Marines (RR 1.85, 95%CI 1.64-2.09) and Navy (RR 1.63, 95% CI 1.49-1.78) as compared to the Air Force (Scher et al., 2009). High rates were observed among junior enlisted soldiers, which represents a younger population that is more likely to face physical demands of combat positions, likely secondary to prior acute musculoskeletal injuries (Scher et al., 2009). OA is particularly important to consider among this population not only due to high health care costs, implications for medical readiness and lost duty days, but also due to the long term impact on quality of life and future medical costs.

Gender and Age Differences in Osteoarthritis

Although it is well known that rates of OA increase with age as a result of compounding exposures, literature to date has consistently suggested that women experience a spike in rates of OA following menopause greater than expected compared to their age matched male counterparts. Women between the ages of 45-64 are 3 times more likely than similar aged men to have OA confirmed by diagnostic imaging (Martín-Millán & Castañeda, 2013). Rates of OA in the general population spike among women following menopause. Compared to younger women, post-menopausal women have more severe self-report symptoms and experience rapid progression of the condition (Nevitt & Felson, 1996). Prevalence of symptomatic osteoarthritis among adults over 20 in the EPISER study was 10.2%, 14% among women compared to 5.8% among men (Martín-Millán & Castañeda, 2013). This was one of the few studies to consider rates of OA among younger adults which is more representative of the military population. In the first study of incident OA among service members, Scher and colleagues (2009) found that women had significantly increased rates of incident hip OA compared to men (adjusted incidence rate

ratio 1.87, 95% CI 1.73-2.01) (Scher et al., 2009). Contradicting the literature to date, when stratifying by age and gender, servicewomen less than age 20 had the greatest adjusted incidence rate ratio compared to servicemen (adjusting for age, service, rank and race) of 5.61 (95% CI 3.73-8.45) (Scher et al., 2009), with decreasing relative rates when comparing women to men as age increased. Given that differential rates of musculoskeletal injury and disability discharge due to musculoskeletal injury are observed between service men and women, it is important to consider implications of OA as a chronic disease which may have substantial impacts on medical cost, occupational productivity and quality of life.

Prior Knee Injury and Osteoarthritis

Many studies note prior local injury as of the strongest predictors for future OA. In one study 42% of women with history of ACL tear had symptomatic radiographic confirmed knee osteoarthritis within 12 years following an ACL injury, irrespective of surgical correction (Lohmander, Östenberg, Englund, & Roos, 2004). Women are at greater risk of ACL injury compared to men and previous ranges suggest 10-90% of women will have radiographic evidence of OA, with three times increased risk of OA in a knee with prior ACL tear as compared to the non-injured knee (Barenius, Ponzer, Shalabi, Bujak, Norlén & Eriksson, 2014). In a recent systematic review including 31 studies, OA occurred in 13% of individuals following an isolated ACL tear, whereas those who experienced an ACL tear with associated injuries along with a meniscus tear had roughly two-fold higher OA prevalence of 21-48% (Øiestad, Engebretsen, Storheim & Risberg, 2009).

Research in this area thus far has focused on predictors of OA among middle aged women in civilian populations, failing to adequately account for potential hormonal exposures outside of hormone replacement therapy (e.g. hormonal contraception). The unique occupational and physical demands that young service members face make this population particularly relevant to consider. To our knowledge, no research to date has examined predictors of knee OA among

service members. The purpose of this study was to identify predictors of knee and hip OA, with a focus on the impact of hormonal contraception among active duty army servicewomen. Results of this study add to the limited literature to date and aid in contraceptive decision making among women at high risk for osteoarthritis.

Physiology of Hormonal Contraceptives and Osteoarthritis

It is well understood that the rates of osteoarthritis increase disproportionately among women during and following menopause. Consistent documentation of increased rates of generalized OA among post-menopausal women has implicated sex hormones as a significant contributor in the development and severity of OA (Nevitt & Felson, 1996). This has led researchers to evaluate fluctuations in endogenous hormonal profiles during menopause as well as use of exogenous hormone replacement therapy and OA risk. However, literature to date provides conflicting evidence for the existence of a relationship studies considering the role of other sex hormones from contraceptive use have been limited.

Role of Estrogen on Joint Integrity

Estrogens act directly and indirectly on tissue impact normal cell growth and development which impact degenerative diseases (Martín-Millán & Castañeda, 2013). The role of estrogen on inflammation and immune disease is unclear, however the increased prevalence of autoimmune diseases among women and increased rates of OA are evidence that some relationship may exist (Martín-Millán & Castañeda, 2013). Two types of estrogen receptors (α and β) are found in the joint, on bone, growth plates, chondrocytes and synoviocytes (Martín-Millán & Castañeda, 2013). Data suggest that estrogen decreases cartilage damage, regulates bone growth, and retains bone mineralization preventing bone attrition, enhances muscle performance and structure in women. In mice, estrogen has been shown to reverse damage associated with autoimmune arthritis in the synovium. Conflicting findings have been reported on

effect of estrogen on ligaments with a trend toward high menstrual cyclic levels increasing risk for ACL rupture (Martín-Millán & Castañeda, 2013).

Role of Endogenous Hormones: Menopause

Given that menopause has been the most widely studied hormonal risk factor for OA it is relevant to understand the physiological mechanism proposed to drive this association. It is suggested that excess or unopposed oestrogens may influence risk of OA through receptors on articular chondrocytes or indirect pathways including cytokine levels and cartilage metabolism (Nevitt & Felson, 1996). However, no association between testosterone or oestradiol levels and knee OA have been found and case control studies show no relationship between time since menarche to menopause and parity with OA (Wluka, Cicuttini, & Spector, 2000). In the peri-menopausal period, progesterone levels rapidly decline and estrogen remains stable. After some time, significant variations occur with serum estrogen until eventually estrogen stabilizes at lower levels than before the onset of menopause. It has also been noted that this decrease of circulating hormones can alter joint structure. Animal studies suggest that extremes of hormonal exposure (both high and low) could adversely impact the integrity of the joint structure and function leading to increased risk for OA (Roman-Blas et al., 2009).

Many studies had been published to evaluate the use of HRT on hip and knee OA with conflicting results. A meta- analysis conducted in 1996 to synthesize available data from observational studies found a summary OR estimate of 0.76 (95% CI: 0.63-0.91), suggesting decreased risk of OA among hormone replacement therapy users compared to non-users (Nevitt & Felson, 1996). Menopause has been the primary time-frame of interest when considering OA. However, hormonal contraceptive use also alters endogenous hormone levels, and for potentially longer periods of time than menopause.

Hormonal Contraception and Osteoarthritis

Research is limited on the association between hormonal contraceptive use and OA, but previously discussed research of endogenous hormones and HRT and OA risk provide a potential physiological mechanism for the association. Both the acute effects of contraception on joint integrity during a menstrual cycle as well as long term effects on bone density and joint degradation may reduce or increase subsequent risk for OA development. Hormonal contraception is known to attenuate the hormonal spikes that women experience during a menstrual cycle. This acute impact on endogenous hormone levels has been suggested to stabilize joint laxity and strength within a cycle which may not only reduce risk for a traumatic musculoskeletal injury but also reduce micro-damage to joint tissue over time, reducing the long term risk of OA. However, given the availability of contraceptive options, it is important to differentiate between specific types (e.g. combined hormonal contraception and progestin only). Combined hormonal contraceptives containing estrogen and progesterone have relatively stable pre-set doses of both hormones that are administered on a daily (pill) weekly (patch) or monthly (ring) basis. The estrogen provided directly from these contraceptives may directly impact joint structural integrity and therefore impact mechanical loading and subsequent risk for OA. It is possible that short term use of combined hormonal contraception decreases risk for OA. However, long term use of estrogen containing contraception may increase risk for OA, particularly after prolonged use. Combined hormonal contraception is noted to stimulate osteoblasts which increases bone mineralization (preventing attrition) increasing bone density. Progestin only methods, including the pill, injection, implant and Mirena (IUD) should be considered separately from combined methods particularly when considering an association to OA. Not only do these methods lack estrogen, which changes the impact on endogenous monthly cyclic fluctuations and joint tissue, but all these methods (except the pill) are administered over prolonged periods of time where the level received may greatly vary from start to end of effective

use. In addition, prolonged use of depo Provera (the injection) is linked to loss in bone mineral density. Lower bone mineral density, increasing risk for osteoporosis, is inversely related to osteoarthritis given the reduced bone stress, stiffness and mechanical loading (Wluka et al., 2000).

Given the widespread use of hormonal contraceptives among servicewomen and the potential implications on chronic joint degradation it is important to better understand this relationship. The Total Army Injury Health Outcomes Database (TAIHOD) provides a large sample of young, highly active women to examine this association with up to 10 years of prospective data capture on pharmacy and clinical records.

Epidemiology of Hormonal Contraceptives and Osteoarthritis

Between 1993 and 2017, eleven epidemiological studies assessed the association between hormonal contraceptive use and OA (Vingård, Alfredsson, & Malchau, 1997; Dennison, Arden, Kellingray, Croft, Coggon & Cooper, 1998; Karlson, Mandl, Aweh, Sangha, Liang & Grodstein, 2003; Cooley, Stankovich & Jones, 2003; Liu, Balkwill, Cooper, Roddam, Brown, Beral, & Million Women Study Collaborators, 2009; Hellevik, Nordsletten, Johnsen, Fenstad, Furnes, Storheim, ... & Langhammer, 2017; Dawson, Juszczak, Thorogood, Marks, Dodd & Fitzpatrick, 2003; Sandmark, Hogstedt, Lewold & Vingard, 1999; Samanta, Jones, Regan, Wilson & Doherty, 1993; Wei, Venn, Ding, Martel-Pelletier, Pelletier, Abram, ... & Jones, 2011; Jung, Shin, Lee, Kim, Park, Choi, ... & Ha, 2015). Many of these studies considered other life course hormonal exposures including age at menstruation, parity, age at menopause, hormone replacement therapy use in addition to contraceptive use. Five of these studies were case-control in design (Vingård et al., 1997; Dennison et al., 1998; Dawson et al., 2003; Sandmark et al., 1999; Samanta, et al., 1993), three were cohorts (Karlson et al., 2003; Liu et al., 2009; Hellevik et al., 2017) and three were cross-sectional studies (Cooley et al., 2003; Wei et al., 2011; Jung et al.,, 2015). Most studies selected participants based on wait list status for joint replacement or recent surgery,

resulting in subjects being middle aged to elderly. Of the eleven studies, the most recent found a statistically significant association where oral contraceptive use increased the risk for total knee replacement (TKR) HR 1.37 (95% CI 1.03-1.84) (Hellevik et al., 2017). Of the remaining ten studies, four observed point estimates indicating reduced risk of OA with OC use (Cooley et al., 2003; Dawson et al., 2003; Sandmark et al., 1999; Samantha et al., 1993), three observed point estimates suggesting increased risk for OA with OC use (Vingard et al., 1997; Dennison et al., 1998), and four observed point estimates very close to null (Karlson et al., 2003; Liu et al., 2009; Wei et al., 2011; Jung et al., 2015). In these eleven studies, OA was evaluated in the knee only (Dawson et al., 2003; Sandmark et al., 1999; Samanta et al., 1993; Jung et al., 2015; Wei et al., 2011), knee and hip (Liu et al., 2009; Hellevik, et al., 2017), hip only (Vingård et al., 1997; Dennison et al., 1998; Karlson et al., 2003), and hand (Cooley et al., 2003). These eleven studies are described below and grouped by the joint in which OA was assessed.

Oral Contraceptive Use and Hip and Hand Osteoarthritis

Three studies to date have evaluated the relationship between oral contraceptives use and OA of the hip. Two of the three studies suggest that oral contraceptives increase risk of hip OA (Dennison et al., 1998; Karlson et al., 2003), with a borderline significant increase in risk observed in one study (Vingård et al., 1997). A case-control study (n=503) conducted by Vingård and colleagues (1997) assessed the relationship between hip arthrosis, hormone use, BMI and smoking among 230 cases and 273 controls and found that use of contraceptives for 1 year or more before the age of 50 conveyed an OR of 1.6 (95% CI 1.0-2.3) (Vingård et al., 1997). The authors also found an association between high BMI in early life and increased risk of subsequent hip arthrosis.

In 1998, Dennison and colleagues conducted a population based case-control study (n=816) to assess the relationship between OC use and other reproductive variables and symptomatic hip OA (Dennison et al., 1998). In an analysis comparing the 10% of women who

had used oral contraceptive pills with non-users that adjusted for BMI, Herberden's nodes, prior hip injury, leisure activity and all other reproductive variables, a non-statistically significant increase in risk of hip OA was observed for contraceptive users (OR 1.6, 95% CI 0.8-2.9) (Dennison et al., 1998). This study collected data on length of oral contraceptive use but did not report the results. Karlson et al. conducted the most recent study on oral contraceptive use and hip OA among 121,701women in the Nurses' Health Study (Karlson et al., 2003). Women in the highest BMI quintile at age 18 had a five-fold increase in risk of total hip replacement due to OA when compared to the lowest BMI quintile (<22 kg/m2 versus ≥35 kg/m2). Smoking, physical activity and hormone use were not associated with risk of a hip replacement.

Only one study to date has considered the relationship between hormonal factors and hand osteoarthritis. In 2003, Cooley and colleagues published a cross-sectional study of 348 Tasmanian women (Cooley et al., 2003). They recruited incident hand OA cases (index cases) as well as affected (non-index cases) and unaffected family members. They considered age at menarche, parity, breastfeeding, oral contraceptive use, age at menopause, years of menstruation, hysterectomy and HRT use as hormonal exposures of interest. Prevalence and severity of OA progression increased with parity, age at menopause, years between onset of menarche and menopause, as well as HRT use. Breastfeeding was found to be protective. Non-index cases (n=272), including both affected and unaffected family members were significantly more likely ($p<0.001$) to be ever oral contraceptive users (83%) as compared the proportion of ever users (24%) among cases (n=76). However, there were no statistically significant differences between oral contraceptive use (yes/no) for distal inter-phalangeal joint space narrowing (OR 0.8, 95% CI0.27-2.34), nor was there an association with duration of OC use (Cooley et al., 2003). Although mechanical loading experienced by the hand is not comparable to lower extremities it may still be of physiological relevance to consider other anatomical locations given the

potentially comparable mechanism by which circulating serum hormones impact chondrocyte metabolism.

The results of the three studies considering hip OA may be important to consider when evaluating contraceptive use and knee OA given the proximity of the joints and compensatory behaviors that may occur during weight bearing activity that impact proximal and distal segments. Because of differences in the structure and function of the hand and hip versus knee joint, the predictive factors for hip OA may not apply similarly for OA of the knee, but may provide insight to the physiological mechanism.

Oral Contraceptive Use and Knee Osteoarthritis

Seven studies to date have considered the association between oral contraceptives use and knee osteoarthritis, two which also consider hip OA. Three case control studies yielded non-significant results with point estimates suggesting protective effects of oral contraceptives use (Samanta et al., 1993; Sandmark et al., 1999; Dawson et al., 2003). Two cross sectional studies found null results (Wei et al., 2011; Jung et al., 2015). The one prospective cohort found null results (Liu et al., 2009) and the most recent cohort found a statically significant increased risk of OA with hormonal contraceptive use (Hellevik et al., 2017).

A case-control study (n=690) conducted in 1993 utilized mailed surveys to assess the relationship between sex hormones, smoking and OA among women (Samanta et al., 1993). The authors identified women with nodal generalized OA and (NGOA) as well as non-nodal pauciarticular large joint OA (LJOA) from an OA research clinic in Nottingham. The authors randomly selected three age-matched controls from medical records and mailed questionnaires to all 1096 cases and controls. A final sample size of 690 included: 95 NGOA cases (74% response rate) and 226 NGOA controls (58%), 113 LJOA cases (78%) and 256 LJOA controls (59%). NGOA most often develops around menopause and involves many small and large joints, whereas LJOA has no apparent correlation with menopause. The authors found that fewer LJOA

patients had ever smoked and prior successful pregnancy was protective against NGOA. Oral contraceptive use was not significantly associated with LJOA (OR 0.81, 95% CI 0.22-2.0) or NGOA (OR 2.0, 95% CI 0.63-6.37) (Samanta et al., 1993). Of note, this study included disproportionately low numbers of OC users, with less than 10% reporting any lifetime use, which would decrease statistical power, already limited by the modest overall sample size. Second, differing response rates by cases and controls (74 to 78% versus 58 and 59% respectively) raises the possibility of factors related to participation as a source of bias. Sandmark and colleagues considered knee OA in men and women (n=584) with a primary focus on weight, smoking and hormone therapy use (Sandmark et al., 1999). This case-control study included 300 female cases identified through a Swedish knee arthroplasty registry who were between 55 and 70 at the time of surgery, and 284 controls randomly selected from the population. Women in the highest quartile of BMI (≥24 kg/m2) at the age of 40 had almost ten times the risk for severe knee OA later in life compared to the lowest quartile (≤21 kg/m2) and, consistent with Samanta, smokers had lower risk than non-smokers. Women who used oral contraceptives pills for at least one year had similar risk of severe OA requiring knee surgery compared to non-users (RR 0.9, 95% CI 0.6-1.4) (Sandmark et al., 1999). Similar to Samanta, a small portion of the population was exposed to contraceptives and only 15% of cases and 17% of controls reported used OC.

In 2003, Dawson and colleagues examined risk factors for symptomatic knee osteoarthritis using a matched case-control design (n=101) (Dawson et al., 2003). The primary objective of their study was to consider the association between high heeled shoes and symptomatic knee OA. Cases were identified from a waiting list for total knee replacement and were restricted to those with moderate knee pain most days of the month. Controls were selected from general practice and matched by age to cases. The final sample size included 29 cases and 82 controls. Oral contraceptive use (ever/never) was not significantly associated with

symptomatic knee osteoarthritis (OR 0.87, 95% CI 0.35-2.15) (Dawson et al., 2003). This study was limited in power given the small sample size.

Liu and colleagues (2009), considered the relationship between contraceptive use and OA in the largest prospective cohort study to date (n=1.3 million). The authors examined the effect of reproductive history and use of hormones on risk of hip and knee joint replacement due to progressive OA (Liu et al., 2009). The authors included women in their 50s (average age = 56) and followed them for about 6 years. The study found an association with parity, with risk of joint replacement increasing by 2% (1 to 4%) per birth for hip OA and 8% (6 to 10%) for knee. Early menarche (<12) was also observed to be related to increased risk of hip and knee replacement. Menopausal status was not associated though current used of HRT increased risk of hip and knee replacement by 38% and 58% respectively. Women with hip and knee replacements were less likely to have used oral contraceptives; however, these associations with prior oral contraceptive use were not significant for either hip replacement (RR 1.02, 95% CI 0.98-1.06) or knee replacement (RR 1.0, 95% CI 0.96-1.04). This study also considered duration of contraceptive use in categories of <5 years, 5-9 years and 10+ years. There were significant linear trends for increasing risk of hip and knee replacements with increasing duration of use (p=0.03 and p=0.05 respectively), though none of the individual categories reached statistical significance. Though this study included a very large sample size, subjects were racially homogenous and limited consideration to OA that required hip or knee replacement.

Jung and colleagues (2015) used a cross-sectional approach (n=5,449) to consider the impact of pregnancy, parity (including abortions) and contraceptive use among Korean women at least 50 years old. The authors collected information on contraceptive use from the 5th Korean National Health and Nutrition Examination Survey and completed x-ray imaging of the knee to identify OA. They found no significant association between oral contraceptive use and OA (OR 1.00, 95% CI 0.83-1.2) after adjusting for age, income, education, BMI, smoking and mental

health. Although this study was large, the limitation of temporal bias associated with cross sectional designs cannot be overlooked (Jung et al., 2015).

Wei and colleagues (2011) conducted a population based cross-sectional study (n=489) with women 50-80 years of age. The authors considered hormonal exposures including parity, contraceptive use and HRT with knee OA. They used x-ray and MRI to assess volume of cartilage, joint space narrowing, and osteophytes. Although x-ray is the gold standard, MRI is able to quantify volume. Oral contraceptive use was not associated with cartilage volume, cartilage defect or radiographic change. Ever use of OC was not significantly associated with knee OA after adjustment for age, BMI, smoking, parity, pain score and use of HRT (OR 0.88, 95% CI 0.38-2.06). Parity was associated with a decreased volume and BMI was associated with increased OA risk. This study utilized detailed objective assessment for OA however, this does not measure functional impairment (Wei et al., 2011).

Most recently, Hellevick and colleagues (2017) conducted a cohort study (n=30,289) including women over the age of 30. The authors examined the relationship between self-reported contraceptive use and eventual total knee replacement (n=430) or total hip replacement (n=675). Ever users of hormonal contraceptive had an increased risk for total knee replacement (HR 1.37, 95% CI 1.03-1.84) and a non-statistically significant increased risk for OA leading to total hip replacement (HR 1.11 95% CI 0.87-1.42) after adjusting for age, BMI, smoking and physical activity compared to never users. Although this study considered both knee and hip OA, it failed to capture non-surgical cases of OA and the average age of cases was 64 with remote timing of contraceptive use limited to high dose pills.

In summary, evidence for the association between oral contraceptives use and knee and hip OA is limited; eleven epidemiological studies have considered this association, but small sample size and low prevalence of oral contraceptive use or cross-sectional study designs limited inferences. In addition, most of these studies were conducted with self -report dichotomized

exposure of contraceptive use yes/no, rather than more complete information including contraceptive type. In addition, despite some studies that have considered duration of OC use (Cooley et al., 2003; Liu et al., 2009; Wei et al., 2011), its relation with OA risk remains unclear. No study to date has considered contraceptive methods other than the oral contraceptives pill. The age range of these populations has been limited to women in their 50s to 70s. Moreover, these women represent prevalent, rather than incident, cases of OA. Additionally, changes in pharmaceutical composition of contraceptive and contraceptive type availability may be important to consider given the exposure window for contraceptives use represented by study populations to date.

Aim and Hypotheses

Specific Aim: To evaluate the association between hormonal contraceptive use and risk of knee and hip osteoarthritis among active duty servicewomen. Hypothesis 1: Compared to non-contraceptive users, rates of OA will be lower among hormonal contraceptive users. Hypothesis 2: Compared to combined hormonal contraceptive users, rates of OA will be lower among progestin only method users. Hypothesis 3: Rates of OA will be lower among those with longer duration of contraceptive use compared to those with shorter durations of use.

Methods

Study Design and Population

Using a retrospective cohort design, we assessed the relationship between hormonal contraceptive use and risk of osteoarthritis among active duty Army female soldiers age 17 to 45 who served on active duty for at least two months between January 1st, 2002 and December 31st, 2011 captured in the TAIHOD. The TAIHOD was created in 1994 to study injuries among female soldiers, though the database captures servicemen and women. The database prospectively links administrative, clinical, pharmaceutical, occupational and health behavior data for all soldiers who have been on active duty. The TAIHOD currently contains data on over 5 million soldiers

with active service and outpatient clinical records as far back as 1997. The start date of January 1st, 2002 was selected as it marks the onset of electronic pharmacy record capture from the Pharmacy Data Transaction Service (PDTS), which is integrated into the TAIHOD to determine hormonal contraceptive use. This timeframe captures Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF), which allows for evaluation of changes in contraceptive preference and use in austere environments as well as changes in number and frequency of deployments. It also provides a timeframe with potential periods of increased injury rates given the increased frequency of training and deployment.

Among active duty Army soldiers between 2002 and 2011, there were a total of 207,777 women. In any given year during this 10 year period, about 82,000 women were on active duty; servicewomen comprised between 13.6-15.8% of the active duty Army over the ten-year study period. Two thirds of the women on active duty between 2002 and 2011 were new accessions, entering the cohort in 2002 or later. The average age at entry into the cohort was 24. Most women had high school education or equivalent at entry. Less than one quarter of women had a rank of senior enlisted or officer at entry. At entry, 30% were overweight or obese. More than half were ever deployed at least once during the cohort and one quarter had a delivery during the cohort. Half had a documented knee injury during the cohort, 30% had a back injury and 15% an ankle. Most women ever used NSAIDs during the cohort.

Exclusion

For the purpose of the current study, women with only one record in the DMDC were dropped due to the insufficient observation time to capture and quantify hormonal contraceptive use, changes in duty station, and other undetermined cause for military discharge that make these women not representative of the active duty women who serve for longer periods of time. In order to restrict consideration to pre- and not peri-menopausal women, women were censored from the analysis at the age of 46. Thus, women who entered the cohort at age 46 did not

contribute any observation time to the study; however, women who turned 46 during the study timeframe contributed person time up until censoring at age 46, with subsequent person time dropped. Participants who were missing age, education, marital status, race or ethnicity from the DMDC were excluded. From this population, we further excluded women who had medical record documentation of a hysterectomy, oophorectomy, clinically diagnosed menopause, or used hormone replacement therapy as these women likely have different comorbidities that may impact their use of hormonal contraceptives. In addition, women who experienced one of these events during the study cohort were dropped at the event date and person time following the event was censored. Women with greater than 120 pregnancy visits during the study cohort were also excluded. These women compromise a group of either implausible medical records or high risk pregnancies that are likely not generalizable. Although rare, women with any lower extremity amputation were excluded or dropped as their risk for osteoarthritis is expected to be vastly different compared to other servicewomen. Women with known OA prior to 2002, contralateral or recurrent injury, were dropped to identify incident ever OA. The number of women and person years excluded and dropped are shown in Table 12.

Exposure Assessment: Hormonal Contraception

Hormonal contraceptive use was assessed through pharmacy data recorded in the PDTS within the Medical Data Repository. The PDTS is a complete database capturing all prescription pick-ups at Military Treatment Facilities, TRICARE pharmacy networks, and mail orders (Department of Defense, 2009; The Department of Defense Pharmacoeconomic Center, 2011). Pharmacy records contain information on: therapeutic class, product name, type of hormonal contraceptive, dosage, days' supply, quantity and date pick up. TRICARE covers hormonal contraceptives at no cost to soldiers (Enewold et al., 2010). Therapeutic class codes '681200, contraceptives' and '683200, progestins' were used to identify hormonal contraception. Prescriptions recorded with a dispense quantity equal to zero were considered as requested but

not picked up. Prescriptions for HRT or treatment for amenorrhea and anovulation were not included in the analysis as hormonal exposure.

The PDTS dataset contains information on the date, quantity and contraceptive type dispensed. Estrogen containing product type other than: pill, patch, injectable, implant, vaginal ring (e.g. estrogen gel) were categorized as non-contraceptive users. Exposure was further categorized by type of contraceptive to evaluate differences in use of combined hormonal contraceptive versus progestin only. Combined hormonal contraceptives included monophasic, biphasic and triphasic oral contraceptives, Ortho-Evra (birth control patch), and Nuvaring. Progestin only contraceptives include progestin only pill, Depo-Provera (injection), Mirena (intrauterine device) and implants (including: Noroplant, Implanon and Nexplaon). Timing and duration of use was determined from start and stop dates were calculated as follows: start date equals date of pick up plus one day and the end date is equal to the start date plus the quantity provided.

For consistency with prior literature, we initially dichotomized hormonal contraceptive use as ever versus never user. Taking advantage of the extensive information included in the TAIHOD, we additionally considered use as 'never', 'past' and 'current', as well as contraceptive type (pills type, patch, ring, injection, IUD and implant). These methods were collapsed into combined hormonal contraceptive and progestin only. We also looked at duration of any contraceptive use as defined by short (<90 days), medium (90-365 days) and long (365+ days). Prior studies have identified 90 days as an appropriate cut point for short use as women are often encouraged to trial a new method for at least 3 months and 97% of those using fgor 3 months will continue using in month 4 (Rosenberg & Waugh, 1998). To examine the impact of never versus current use, the variable 'never past current' was combined with both type and duration. Prior studies have not considered dose of contraceptives which is equivalent to the duration of use by type of use. To examine dose we created a 10 level mutually exclusive variable that incorporates

both type of method and duration of use. Our final categorization of contraceptive use evaluated time since stopping use of any contraceptive method (Table 15).

Validity of Exposure

Hormonal contraceptive pharmacy records have not been validated in the TAIHOD. However, previous research have suggested that pharmacy records are a valid source of information regarding use, duration and timing of contraceptives when compared to self-report (which is the most frequently utilized method of exposure assessment). Discordance between pharmacy records and self-report may result from inaccurate self-reporting, or when prescriptions are filled but not used. Pharmacy records have also been found to be a more accurate source of information than self-report for type of oral contraceptives (high dose, low dose and progestin only pill), with correlation coefficients between self-report and pharmacy records ranging from 0.84-0.93 (Norell, Boethius & Persson, 1998). Use of pharmacy records for assessment of duration of use requires assuming that any prescription dispensed was used for the entire days' supply as directed by the pharmacy.

Outcome Assessment: Osteoarthritis

OA was identified by international ICD-9 code 715 in medical records. OA cases were further classified with the fourth digit of the ICD-9 codes as 1 (localized, primary, idiopathic), 2 (localized, secondary), 3 (localized, unspecified), 9 (unspecified whether generalized or localized). The fifth digit of the ICD-9 code allowed for identification of the affected area of the body pelvic region and thigh cases (5) as well as lower leg cases, including the area below the thigh and above the ankle (6). The first date of service for this ICD-9 code was selected to identify the initial time of diagnosis (Table 13). Prior literature suggests identification of OA through medical records is superior to self-report. Clinical encounter billing codes for women who had been on active duty prior to 2002 were reviewed to exclude prior OA.

Covariate Assessment

Demographic data including age, race, ethnicity, education, marital status, grade and length of service were extracted from the monthly DMDC data repository. When a service member joins the military without any previous military they are considered to be a new accession. For new accessions, length of service represents the time in the study cohort between 2002 and 2011. For women with active duty time prior to 2002, length of service represents the sum of all time on active duty prior to and including the cohort timeframe Ever attendance to basic combat training was identified from training records, however, dates of BCT were determined as discussed above. Deployment records and overseas station dates and location were merged with DMDC records. A single measurement of body mass index (BMI), as measured at accession, was also merged with the demographic data. Diagnostic and medical procedure billing codes from the time a woman entered active duty were available and utilized to identify lower extremity injury and delivery (Appendix A). Records for women who served on active duty prior to 2002 were included to capture the number of deliveries and lower body injuries prior to the cohort. Parity was determined by the number of dependents, marital status, age and delivery during the study cohort. Specifically, women with a known delivery during the study are automatically parous. Women without any documented deliveries, but were married with 2 or more dependents were also considered parous. Women who were, single with no dependents were considered nulliparous. Ever use of prescription NSAIDs and count were also determined from pharmacy records.

Univariate Analysis

We reported the number, percent and total active duty person years in TAIHOD and the number and percent of those who are excluded due to missing records, age over 45, previous hysterectomy, oophorectomy, menopause, hormonal therapy, lower extremity amputation and

previous osteoarthritis (Table 12). The percent distribution of OA by primary location and type were presented (Table 13).

Bivariate Analysis

The association between entry covariates and osteoarthritis was assessed through chi-square tests and results of the cross tabulation were reported (Table 14). Percent and distribution of hormonal contraceptive exposure by osteoarthritis are presented across all contraceptive categorizations. Unadjusted relative risks and 95% confidence intervals were calculated to compare hormonal contraceptive users with non-users as the reference group, with regard to OA (Table 15).

Multivariable Analysis

The relationship between hormonal contraceptive use and OA was modeled using survival analysis to estimate hazard ratios and 95% confidence intervals (Table 15). Nine categorizations of contraceptive exposure were considered in this analysis. Potential confounders were identified as being significantly related to both contraceptive use and OA. The only confounder consistently identified by prior literature is age, which a priori was retained in the final model. Likelihood ratio tests comparing models with these covariates to the hormonal contraceptive ever/never model were conducted and models that remained significant ($p<0.05$) were retained for continued step-wise model building. The variables for the final model of hormonal contraceptive ever/never were then applied to the eight remaining categorizations of contraceptive exposure.

Three models were considered in the final set of analyses including: 1) unadjusted; 2) age adjusted; and 3) final adjusted model. A sensitivity analysis considered only new accessions during the study cohort to capture the full spectrum of career events servicewomen face to ensure inclusion of basic training, advanced individual training and deployment where both contraceptive use and risk for ACL injury may differ from permanent duty station (Table 16).

Results

Final Study Sample

Exclusions are detailed in Table 12. Of the 207,777 participants and 757,610 person years of total observation, the most common reason for exclusion was due to missing records (n=6,347). Over one third of those excluded (n=3,544) only had one month record in DMDC. An additional 2,803 women were missing age, education, marital status, race or ethnicity. An additional one percent of women were excluded from the study due to being age 46 or older at entry to the cohort or to the Army. Less than one percent of the study population was excluded due to a medical reason. A total of 80 women were excluded from the study due to lower extremity amputation and an additional 1,010 women were excluded due to known prior OA before 2002. Half of the women excluded at entry and the majority of women dropped during the study time frame had service prior to 2002 (Table 12).

Osteoarthritis

We identified 196,306 eligible women in the TAIHOD between 2002 and 2011 resulting in 706,978 person years of observation (Table 12). Of eligible women, 3,943 experienced incident OA, representing a rate of 558 per 100,000 per years among the entire cohort and a rate of 362 per 100,000 among new accessions (Table 13). Most incident cases of OA were identified in the lower leg (80.62%) without specified type (65.37%). Compared to the entire cohort, new accessions had a greater proportion of OA cases occurring in the pelvic and thigh region (19.38% vs. 26.70% respectively).

Correlates of Osteoarthritis

Compared to women without OA, women with OA had 30% higher probability of service prior to 2002 (64.95% vs. 34.38%). These women were on average almost six years older, had higher education, marital status and rank. Women with OA were more likely to be African American (50.87% vs 32.32%), 12% more likely to have prior back or hip injury as well as with a

prior knee, or leg injury. Women with incident OA had 17% higher likelihood of being overweight or obese at entry to the Army (47.73%) compared to women without OA (29.95%).Women with OA were twice as likely to be parous at entry (31.63% vs 15.31%) and twice as likely to ever be pregnant while on active duty (31.63% vs. 15.31%) (Table 14).

Hormonal Contraceptive Use and Osteoarthritis: Ever Use

Ever users of hormonal contraception had a 7% increased risk of OA compared to never users of hormonal contraceptive (HR 1.07, 95% CI 0.99- 1.14) though the results were not statistically significant in the unadjusted model (Table 15). After adjusting for age, knee (never, past, current injury), back or hip (never, past, current injury), leg or ankle (never, past, current injury), NSAID use, new accession, deployment, education, BMI, marital status, race, parity and rank, findings were opposite as seen in the unadjusted model, and a protective effect was seen. Specifically, ever users of contraception had a 19% decrease in OA (HR 0.81, 95% CI 0.76-0.87) which remained stable regardless if use was current or past (Table 15). Among new accessions (Table 16) a non-significant 12% decrease in risk was seen among ever users (HR 0.88, 95% CI 0.78-1.00). The key covariates responsible for the reversal of effect were: new accessions, prior knee injury, back or hip injury and NSAID use.

Hormonal Contraceptive Use and Osteoarthritis: Type of Use

In the unadjusted model, hazards were highest among women who ever used both combined contraception and progestin only (HR 1.11, 95% CI 1.01-1.22) and no specific type of contraception demonstrated any statistically significant association with OA. However, in the final adjusted model, women who ever used both types of contraception had the lowest risk of OA (HR 0.7, 95% CI 0.63-0.77). The patch and IUD were both significantly associated with OA (HR 0.73, 95% CI 0.57-0.94) and (HR 0.77, 95% CI 0.49-0.92) respectively in the final adjusted model. These trends remained similar in the sensitivity analysis, however, the magnitude of ever

using both contraceptives was attenuated (HR 0.79, 95%CI 0.66-0.94) and there was no single type of contraception associated with OA.

Hormonal Contraceptive Use and Osteoarthritis: Duration of Use

In the unadjusted full model, increasing length of use of any hormonal contraception was associated with increasing risk of OA whereby women who used contraception for at least a year had 28% increased likelihood of OA (HR 1.28, 95% CI 1.18-1.38) compared to never users. Similarly increased risks were observed regardless of past or current use and regardless of type of use (combined only, progestin only or both). However, in the final adjusted model, there was an increasingly protective effect of contraception as duration of use increased. Women using contraception longer than 1 year were observed to have a 21% lower risk of OA (HR 0.79, 95% CI 0.73-0.86). The greatest reduction in risk was among women who ever used both methods for over 1 year (HR 0.68, 95% CI 0.60-0.77). These trends remained stable in sensitivity analysis among new accessions only.

Discussion

Summary of Findings

In this large retrospective cohort study including nearly 200,000 US servicewomen, we observed an inverse relationship between OC use and risk of OA. Ever users of hormonal contraceptive had 19% decreased likelihood of OA as compared to never users in the final adjusted model, which was opposite of the unadjusted model due to key covariates including new accession, prior injury and NSAID use. With regards to type of contraceptive use, women who used both combined and progestin only during their career had the lowest hazard with a 30% decrease compared to never users. As duration of contraceptive use increased hazard of OA decreased, where by women with cumulative contraceptive use of at least 1 year were 21% less likely to be diagnosed with OA.

Consistency with Prior Literature

The unadjusted HR suggests there is a non-significant increased risk of OA among contraceptive users which is generally consistent with prior literature. However, in our final model, we find there is a 19% reduction in OA among ever users of contraception. Our unadjusted results were similar to the only study to find statically significant association between oral contraceptive use and total knee replacement which suggested a 37% increase in risk (Hellevik et al., 2017). In addition, Vingard et al. (1997), looked at oral contraceptive use and hip replacement has and found a borderline significant 60% increased risk.

Prior literature suggest that incidence rates of hip OA were noted in up to 88 cases per 100,000 person years among servicewomen members (Scher et al., 2009), whereas knee OA was observed in the general population at a rate of 20 per 100,000 person years (Oliveria, Felson, Reed, Cirillo, & Walker, 1995). Although we identified rates of hip OA at 108 per 100,000 similar to previously reported rates in the military, we found rates of knee OA to be more than 20 times previously documented in the general population (449 per 100,000). Similar to prior literature, we found that increasing age, pregnancy and BMI were associated with OA (Heidari, 2010) and a disproportionate rate of black service members diagnosed with OA (Scher et al., 2009). Our results do not agree with Scher and colleagues (2009) where we found higher rates among senior enlisted, though this is likely representative of increasing duration of military service and age.

There are a number of factors that could explain the difference in our results from previous studies. Our final model included adjustment for prior back, hip, knee, leg and ankle injuries which were not considered in the two studies demonstrating an increased risk for OA with contraceptive use. Both of those studies adjusted for BMI, age and smoking. It is worth noting that the magnitude of protection we found (19%), after adjusting for a number of factors, is similar as identified by Cooley et al. (2003), Dawson et al. (2003) and Samantha et al. (1993)

although those findings were not statistically significant. In addition to recently published literature suggesting an 18% reduction in ACL injuries among hormonal contraceptive users which is one of the major predisposing injuries to early onset OA and was controlled for in our final model.

In addition, the two studies which identified a potential increased risk among contraceptive user utilized joint replacement as their outcome of interest. It is possible that women with OA who go on to have a joint replacement differ significantly from women who do not have a replacement. In addition, it could be suggested these differences may also vary by contraceptive use including socio-economics and access to health care. However, both prior studies were conducted in Sweden and Norway where there was no cost to access care, similar to the health care for active duty military and lifetime ever use was similar among both populations.

Literature to dates has not considered all types of contraception including patch, ring, injection, IUD and implant. When considering only monthly oral contraceptive pills to be consistent with prior exposure assessment to date, our results are consistent with the majority of prior literature demonstrating no significant association with OA. It is also well established that there have been changes in the formulation of the oral contraceptive pill and the exposure experienced by Vingard and Hellevik's participants before 2000 contributes to differences in exposure whereby they may not be comparable. When considering the difference in hazards among types of contraceptive methods we found a significant reduction in OA among users of the patch and IUD (27% and 23% respectively). The protective effect may actually be due, at least in part, to confounding by indication. The FDA reports failure rates for the contraceptive patch to increase among women who weigh more than 198lbs. The patch is the only contraception method with a published weight recommendation and as a result the population who use the patch may have lower total body mass (or BMI) and lower BMI is associated with lower rates of OA as

compared to overweight or obese women. However, we adjusted for BMI at entry to the Army as well as weight standards.

Our study was only the second to report data on duration of contraceptive use. In our final model, we found increasing protection of risk as duration increased. Cooley et al., (2003) considered risk by yearly use of contraceptive risk, finding no significant difference with hand osteoarthritis at the distal interphalangeal joint 1.01 (95% CI 0.96-1.06). Four studies to date collected data on duration of contraceptive use. The others collected information on duration but did not report the results (Dennison et al., 1998; Liu et al., 2009; Wei et al., 2011).

Our findings differ from recent literature, indicating a protective relationship of hormonal contraception on OA. In the final model women who ever use contraception, particularly women who ever used both progestin only and combined types, as well as women who used any contraception for greater than a year had reduced risk of OA (19%, 30% and 21% respectively). This is the first known study to date to consider all types of hormonal contraception as well as duration by type.

Limitations

Non-differential Misclassification Hormonal Contraceptive Use

Hormonal contraceptive use was determined using pharmacy records. Misclassification of hormonal contraceptive use based on pharmacy records will occur in a number of circumstances including: servicewomen who fill prescriptions for hormonal contraceptives but do not use them and are misclassified as users; servicewomen who have an IUD or Implant inserted before they joined the Army and are misclassified as non-users; servicewomen given multiple months of contraception coverage that was not documented in their medical records whose duration of use will be underestimated. Additionally, servicewomen who pay for hormonal contraceptives out of pocket from pharmacies not recorded in the database will be misclassified as non-users. We expect this misclassification to be minor due to insurance coverage for

hormonal contraceptive by TRICARE which covers these prescriptions at no cost to active duty soldiers. Pharmacy records are maintained for all servicewomen by different database than where clinical records are maintained. Documentation of contraceptive prescription pick up would not be expected to differ by OA and would bias results toward the null.

Non-differential Misclassification of Continuous Use

Due to the limitations of PDTS we are unable to identify continuous contraceptive users. Continuous use occurs when a woman intentionally discards the last week of inactive pills (the last seven pills in a normal 28 day oral contraceptive pack) and immediately starts a new cycle of active pills. This electively induces amenorrhea (skipping a menstrual cycle) and exposes the woman to additional 91 days (or 125%) exogenous hormones throughout the year compared to a traditional pill user. PTDS records do not indicate if a contraception method is being used continuously or as prescribed. It is unlikely that differential misclassification of hormonal contraception use occurred given the records were collected prospectively prior to OA.

Non-differential Misclassification of Osteoarthritis

Soldiers with OA were identified through medical records abstraction using ICD-9 codes. Given the variation in severity and fluctuating nature of OA it is possible that OA may not be immediately diagnosed. Incident diagnosis may actually represent prevalent cases that reached a level of severity the led servicewomen to seek medical care, at which time a clinical diagnosis was made. There is also variability between the measurement and classification of OA, where the gold standard is through measured structural damage in radiographic imaging as well as presence of functional impairment (Richette, Corvol, & Bardin, 2003). Some cases, however, may be diagnosed exclusively based upon symptom reporting alone. Both situations would not differ according to hormonal contraceptive status given that the pain threshold which encourages a woman to seek care would not differ by HC status and there is no well-established link between HC and OA where clinicians would differentially examine and diagnose cases. Therefore, both

circumstances are expected to represent biases toward the null. Given women can go years with OA without diagnosis, and other women with chronic conditions, such as runner's knee, may be incorrectly diagnoses as OA, we expect this misclassification to be moderate.

Differential Misclassification of Osteoarthritis

Given the chronic nature of OA, it is possible that differential misclassification of the outcome occurred. Women who use hormonal contraception are required to visit their primary care provider at least annually for prescription renewals and may seek the care more often than non-contraceptive users for prescription changes and concerns. If contraceptive users have more frequent medical visits then they may be more likely to mention or be screened for chronic medical complaints, including musculoskeletal injuries such as OA. This misclassification represents a surveillance bias that would overestimate the effect of contraception use on OA. However, all service members are required to complete annual health exams, therefore it is less likely that OA would go undiagnosed for prolonged periods of time among non-contraception users. As a result, we expect this misclassification to be minimal.

Selection Bias

Given the cohort study design, and the fact that information on hormonal contraceptive use was collected prior to the occurrence of OA, selection bias is primarily a concern to the extent that women may have been differentially lost to follow-up based on hormonal contraceptive use and OA. Soldiers are required to have regular medical exams, therefore the main way losses from the dataset may occur is due to separation from active duty. Medical documentation is required to receive disability benefits from occupational injuries, therefore, it is less likely that a servicewoman would not have this documented before discharge from duty, although it is possible that women with severe OA may be more likely to leave earlier than no affected women.

Confounding

The large sample size and available data on covariates allowed to address a number of important potential confounders; however, uncontrolled confounding is likely still an issue to some extent. We evaluated age, BMI at baseline and pregnancy – all confounders that have been previously recognized in the literature. Education, rank (which may be a proxy for intensity of occupational requirements), were also considered as potential confounding factors, among others. We are aware of at least three potential confounders that are not directly available through our dataset: BMI throughout career, physical fitness and intensity of unit training and smoking.

Prior literature suggests that being overweight or obese increases risk for OA. BMI at the time of OA diagnosis is not available in the TAIHOD. Although BMI is a potential covariate of interest Army requires soldiers to meet height and weight standards, measured at least bi-annually, creating a more homogenous group of women with a BMI between 18.5-24.9 kg/m2. The height/weight standards soldiers are required to maintain provides a degree of control for confounding by BMI during their career through restriction. In addition, BMI at accession may be an important predictor for BMI prior to military career.

It is possible that women who are assigned to units that participate in above-average strenuous physical activity or high-intensity field training may be more likely to use contraceptives for menstrual regulation and may be at increased risk musculoskeletal injury, including early chronic degenerative changes given daily physical challenges. The expected result of this confounding by training intensity would be to underestimate the protective relationship.

In addition, smoking is not captured in the TAIHOD though prior studies suggest it may be protective against OA. Women who smoke may be less likely to use estrogen containing contraceptives due to increased risk of blood clots. Inability to control for smoking would underestimate the protective association of contraceptives and OA.

Strengths

Our study adds to the literature in a number of ways. Our study was the second largest sample size to date to consider the relationship between contraceptive use and OA. The Army is a closely followed population, and the TAIHOD allows for integration of prospectively captured contraceptive use by pharmacy records. Prior literature has been limited in its exposure assessment and operationalization, having considered only dichotomized ever vs. never use of oral contraception. We considered all hormonal types, the length of use, time since last use and a combination of type and length of use. In addition, our study included a diverse population including young women in many occupational roles whereas studies have been limited to middle age-older adults.

Generalizability

By its nature, this study focuses on a highly selected study sample – female members of the active duty Army. To the extent that the biological mechanism by which hormonal contraceptives impact risk of OA does not vary by occupation or race/ethnic factors associated with armed service membership, the results of this study may be generalizable to all women.

Recommendations for Future Research

Future research should aim to include a number of covariates not considered in this analysis including BMI at time of diagnosis, activity level, and participation in athletics, smoking and bone density. These factors may identify high risk women in occupational and recreational settings which we were unable to access. Women with knee injury are more likely to have subsequent OA though our study did not capture lower extremity injury prior to service. Timing of pregnancy in relation to contraceptive use and OA warrants additional investigation given the significance of results among nulliparous women. Ideally, future work will include detailed contraceptive use from menarche through menopause or diagnosis of OA (which ever one comes

earlier) including validation of contraceptive use in pharmacy records by self-report to avoid misclassification among women who self-discontinue contraceptive use.

Conclusion

To date, few studies have evaluated the association between hormonal contraceptive use and knee and hip OA. Given the long term consequences OA may have on a service members' fitness, mission readiness and career, it is important to examine possible risk factors. Due to the large number of contraceptives users, variety of contraceptive options, increased participation of women in the military and the disproportionally high rate at which they are discharged to musculoskeletal injury, it is important that the association between hormonal contraceptives and OA be fully understood. Results of this study suggest that hormonal contraceptive use may reduce OA by 19%. Hormonal contraception is a potentially modifiable risk factor and warrants further investigation to integrate in clinical recommendations and injury prevention strategies.

Human Subjects Protection

The TAIHOD database was created in 1994 in order to understand risk factors for injury within the active duty Army population. All active duty army soldiers are included in the database without database specific written consent. Study personnel are trained in privacy protocols and electronic study database will be stored with a nonmilitary study identification number on a secure server that is password protected. There are no known potential risks to participants, expect for accidental breach of confidentiality which is unlikely to occur. Additionally there is no known benefit to participating in the study except for advancing science in research involving servicewomen. This study was approved by the Institutional Review Boards of the Unites States Army Research Institute of Environmental Medicine and the University of Massachusetts Amherst.

Permission to Access Data

Permission to access data was granted by the United States Army Research Institute for Environmental Medicine Military Performance Division Chief Edward J. Zambraski, Ph.D. and TAIHOD director MAJ Owen Hill Ph.D. MPAS, following IRB approval by USARIEM and the University of Massachusetts Amherst.

CHAPTER 4

TABLES

Table 1. Exclusion Criteria: Trends Over Time

	Total		Excluded			Dropped		
	n	person years	n	%	person years	n	%	person years
All women on active duty	**207,777**	**757,610**						
1 month in DMDC[1]	3,544	295	3,544	1.71	295	.	.	.
Age ≥46	2,186	17,583	2,186	1.05	8,230	3,241	1.56	9,353
Missing covariates[2]	2,676	3,872	2,676	1.29	3,872	.	.	.
Hysterectomy	3,324	10,607	684	0.33	3,280	2,640	1.27	7,327
Oophorectomy	1,182	4,495	446	0.21	2,163	736	0.35	2,332
Menopause	1,986	7,392	573	0.28	2,975	1,413	0.68	4,417
Hormonal replacement therapy	331	1,430	133	0.06	637	198	0.10	792
Implausible Pregnancy	80	638	80	0.04	638	.	.	.
Final Cohort	**197,455**	**711,298**						
New accessions 2002-2011	**132,811**	**391,256**						
1 month in DMDC[1]	3,544	178	2,133	1.61	178	.	.	.
Age ≥46	605	2,560	605	0.46	1,568	444	0.33	993
Missing covariates[2]	2,290	3,289	2,290	1.72	3,289	.	.	.
Hysterectomy	556	1,143	17	0.01	63	539	0.41	1,080
Oophorectomy	241	576	6	0.00	34	235	0.18	542
Menopause	419	1,077	28	0.02	96	391	0.29	981
Hormonal replacement therapy	89	271	7	0.01	28	82	0.06	244
Implausible Pregnancy	17	119	17	0.01	119	.	.	.
Final Cohort	**127,708**	**382,043**						

[1] there is no reference to identify if these women had any service prior to 2002

[2]missing age, education, marital status or race/ethnicity completely

Table 2. Population Characteristics (1 of 6)

	Entry		2002		2003		2004		2005		2006	
	n	%	n	%	n	%	n	%	n	%	n	%
Women on Active Duty	197,455		82,500		84,093		84,229		80,897		80,504	
New Accession												
No	69,747	35.32	69,747	84.54	70,355	83.66	69,758	82.82	68,518	84.70	66,810	82.99
Yes	127,708	64.68	12,753	15.46	13,738	16.34	14,471	17.18	12,379	15.30	13,694	17.01
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Age (years)	23.44	5.98	26.46	6.68	26.59	6.65	26.71	6.66	26.95	6.69	27.03	6.71
Age (years)												
<20	63,097	31.96	9,470	11.48	8,643	10.28	8,116	9.64	6,942	8.58	7,091	8.81
20-24	73,384	37.16	31,215	37.84	32,246	38.35	32,146	38.17	30,184	37.31	29,245	36.33
25-29	29,939	15.16	17,851	21.64	18,642	22.17	19,204	22.80	19,222	23.76	19,599	24.35
30-34	16,357	8.28	11,696	14.18	11,965	14.23	11,873	14.10	11,480	14.19	11,024	13.69
35-39	9,787	4.96	7,756	9.40	7,836	9.32	7,866	9.34	7,939	9.81	8,342	10.36
40-45	4,891	2.48	4,512	5.47	4,761	5.66	5,024	5.96	5,130	6.34	5,203	6.46
Highest level of education attained												
≤High School Graduate	144,604	73.23	59,344	71.93	60,150	71.53	59,325	70.43	55,771	68.94	54,293	67.44
Some College/Certificate	22,184	11.23	8,063	9.77	8,139	9.68	8,407	9.98	8,559	10.58	9,542	11.85
College	24,275	12.29	10,988	13.32	11,527	13.71	11,959	14.20	11,866	14.67	11,900	14.78
Graduate Degree	6,392	3.24	4,105	4.98	4,277	5.09	4,538	5.39	4,701	5.81	4,769	5.92
Marital Status												
Single	128,891	65.28	39,845	48.30	40,912	48.65	40,169	47.69	36,434	45.04	35,264	43.80
Married	58,482	29.62	36,048	43.69	36,486	43.39	36,660	43.52	36,307	44.88	36,353	45.16
Divorced/Widowed/Separated	10,082	5.11	6,607	8.01	6,695	7.96	7,400	8.79	8,156	10.08	8,887	11.04
Race												
Caucasian	95,868	48.55	35,112	42.56	36,185	43.03	36,452	43.28	35,433	43.80	35,765	44.43
African American	64,633	32.73	33,249	40.30	32,606	38.77	31,472	37.36	29,088	35.96	28,021	34.81
Hispanic	22,349	11.32	8,203	9.94	9,034	10.74	9,663	11.47	9,643	11.92	9,754	12.12
American Indian	2,661	1.35	1,004	1.22	1,066	1.27	1,187	1.41	1,146	1.42	1,143	1.42
Asian	9,612	4.87	3,133	3.80	3,399	4.04	3,759	4.46	3,992	4.93	4,172	5.18
Other	2,332	1.18	1,799	2.18	1,803	2.14	1,696	2.01	1,595	1.97	1,649	2.05
Race												
African American	64,633	32.72	49,251	59.70	51,487	61.23	52,757	62.64	51,809	64.04	52,483	65.19
Other	132,822	67.28	33,249	40.30	32,606	38.77	31,472	37.36	29,088	35.96	28,021	34.81

p-value derived from chi-square , t-test and anova. p<0.01 unless otherwise noted

Table 2. Population Characteristics (2 of 6)

	2007		2008		2009		2010		2011	
	n	%	n	%	n	%	n	%	n	%
Women on Active Duty	80,638		81,873		81,631		82,040		81,059	
New Accession										
No	67,971	84.29	67,925	82.96	68,478	83.89	71,324	86.94	70,870	87.43
Yes	12,667	15.71	13,948	17.04	13,153	16.11	10,716	13.06	10,189	12.57
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Age (years)	27.19	6.71	27.28	6.76	27.57	6.73	27.75	6.72	27.86	6.72
Age (years)										
<20	6,755	8.38	6,874	8.40	5,726	7.01	4,800	5.85	4,772	5.89
20-24	28,605	35.47	28,323	34.59	27,560	33.76	27,264	33.23	26,188	32.31
25-29	20,244	25.10	21,012	25.66	21,704	26.59	22,421	27.33	22,339	27.56
30-34	11,112	13.78	11,293	13.79	11,960	14.65	12,647	15.42	12,974	16.01
35-39	8,648	10.72	8,800	10.75	8,779	10.75	8,624	10.51	8,303	10.24
40-45	5,274	6.54	5,571	6.80	5,902	7.23	6,284	7.66	6,483	8.00
Highest level of education attained										
≤High School Graduate	53,531	66.38	54,077	66.05	54,679	66.98	55,337	67.45	54,775	67.57
Some College/Certificate	10,317	12.79	10,745	13.12	9,567	11.72	8,706	10.61	7,829	9.66
College	11,944	14.81	11,969	14.62	12,013	14.72	12,399	15.11	12,620	15.57
Graduate Degree	4,846	6.01	5,082	6.21	5,372	6.58	5,598	6.82	5,835	7.20
Marital Status										
Single	33,984	42.14	33,707	41.17	32,459	39.76	32,187	39.23	31,768	39.19
Married	37,172	46.10	38,115	46.55	38,825	47.56	39,174	47.75	38,615	47.64
Divorced/Widowed/Separated	9,482	11.76	10,051	12.28	10,347	12.68	10,679	13.02	10,676	13.17
Race										
Caucasian	36,000	44.64	34,459	42.09	36,289	44.45	35,906	43.77	34,960	43.13
African American	27,378	33.95	27,592	33.70	27,832	34.09	28,351	34.56	28,333	34.95
Hispanic	9,912	12.29	10,117	12.36	10,096	12.37	10,268	12.52	10,226	12.62
American Indian	1,159	1.44	1,162	1.42	1,115	1.37	1,080	1.32	1,027	1.27
Asian	4,662	5.78	6,940	8.48	4,704	5.76	4,940	6.02	5,072	6.26
Other	1,527	1.89	1,603	1.96	1,595	1.95	1,495	1.82	1,441	1.78
Race										
African American	53,260	66.05	54,281	66.30	53,799	65.91	53,689	65.44	52,726	65.05
Other	27,378	33.95	27,592	33.70	27,832	34.09	28,351	34.56	28,333	34.95

p-value derived from chi-square , t-test and anova. $p<0.01$ unless otherwise noted

Table 2. Population Characteristics (3 of 6)

	Entry		2002		2003		2004		2005		2006	
	n	%	n	%	n	%	n	%	n	%	n	%
Rank												
E1-E4 (Private - Specialist)	153,943	77.96	46,917	56.87	47,468	56.45	46,181	54.83	41,936	51.84	41,681	51.78
E5-E9 (Sergeant-Sergeant Major)	23,141	11.72	24,389	29.56	24,880	29.59	25,868	30.71	26,493	32.75	26,055	32.36
Warrant/O1-O3 (Second Luteienant- Capta	17,696	8.96	8,444	10.24	9,001	10.70	9,358	11.11	9,577	11.84	9,731	12.09
O4+ (Major-General)	2,675	1.35	2,750	3.33	2,744	3.26	2,822	3.35	2,891	3.57	3,037	3.77
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Length of service, years	1.74	4.02	4.17	5.34	3.66	5.02	3.34	4.67	3.27	4.28	3.17	3.87
Time in Cohort (years)												
<2 years	152,660	77.31	37,705	45.70	46,065	54.78	43,337	51.45	36,671	45.33	34,165	42.44
2 to <4 years	14,132	7.16	14,132	17.13	11,261	13.39	17,850	21.19	24,559	30.36	23,213	28.83
4 to <6 years	8,606	4.36	8,606	10.43	7,293	8.67	5,915	7.02	4,794	5.93	10,281	12.77
6 to <8 years	4,834	2.45	4,834	5.86	4,136	4.92	3,571	4.24	3,099	3.83	2,715	3.37
8 + years	17,223	8.72	17,223	20.88	15,338	18.24	13,556	16.09	11,774	14.55	10,130	12.58
Basic Training												
Never	73,760	37.36	14,717	17.84	18,859	22.43	22,473	26.68	24,421	30.19	25,316	31.45
Past	59,881	30.33	59,882	72.58	55,891	66.46	51,626	61.29	47,908	59.22	44,263	54.98
Current	63,814	32.32	7,901	9.58	9,343	11.11	10,130	12.03	8,558	10.58	10,925	13.57
Deployment												
Never	196,518	99.53	79,562	96.44	64,323	76.49	57,153	67.85	49,138	60.74	46,341	57.56
Past	0	0.00	0	0.00	863	1.03	8,329	9.89	12,862	15.90	14,125	17.55
Current	937	0.73	2,938	3.56	18,907	22.48	18,747	22.26	18,897	23.36	20,038	24.89
Deployment Count												
Never	196,518	99.53	79,562	96.44	64,323	76.49	57,153	67.85	49,138	60.74	46,341	57.56
1	931	0.47	2,842	3.44	18,232	21.68	23,067	27.39	24,391	30.15	24,817	30.83
2	6	0.00	94	0.11	1,491	1.77	3,724	4.42	6,607	8.17	8,113	10.08
3	0	0.00	2	0.00	47	0.06	285	0.34	761	0.94	1,233	1.53
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Total Days Deployed	0.08	1.14	103.65	70.40	180.81	95.68	216.63	123.87	249.38	151.58	295.59	162.34
Permanent Stationed Overseas												
Never	197,380	99.96	82,336	99.80	83,809	99.66	83,656	99.32	80,088	99.00	79,411	98.64
Past	0	0.00	0	0.00	0	0.00	43	0.05	141	0.17	170	0.21
Current	75	0.04	164	0.20	284	0.34	530	0.63	668	0.83	923	1.15
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Total Days Stationed Overseas	0.01	0.31	218.41	119.59	368.18	221.72	370.67	236.63	458.78	246.99	501.22	261.19

p-value derived from chi-square , t-test and anova. p<0.01 unless otherwise noted

Table 2. Population Characteristics (4 of 6)

	2007		2008		2009		2010		2011	
	n	%	n	%	n	%	n	%	n	%
Rank										
E1-E4 (Private - Specialist)	41,893	51.95	42,458	51.86	42,694	52.30	43,272	52.75	43,086	53.15
E5-E9 (Sergeant-Sergeant Major)	25,709	31.88	26,010	31.77	24,986	30.61	24,601	29.99	23,896	29.48
Warrant/O1-O3 (Second Luteienant- Capta	9,984	12.38	10,375	12.67	10,771	13.19	10,848	13.22	10,660	13.15
O4+ (Major-General)	3,052	3.78	3,030	3.70	3,180	3.90	3,319	4.05	3,417	4.22
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Length of service, years	3.14	3.52	3.15	3.29	3.35	2.99	3.50	2.93	3.66	2.93
Time in Cohort (years)										
<2 years	32,704	40.56	31,274	38.20	29,844	36.56	17,792	21.69	24,460	30.18
2 to <4 years	21,679	26.88	21,813	26.64	21,416	26.24	30,985	37.77	21,858	26.97
4 to <6 years	15,079	18.70	15,169	18.53	14,269	17.48	14,951	18.22	14,975	18.47
6 to <8 years	2,458	3.05	5,984	7.31	9,627	11.79	10,118	12.33	9,801	12.09
8 + years	8,718	10.81	7,633	9.32	6,475	7.93	8,194	9.99	9,965	12.29
Basic Training										
Never	25,832	32.03	27,100	33.10	28,927	35.44	28,265	34.45	27,878	34.39
Past	44,917	55.70	44,616	54.49	44,105	54.03	44,681	54.46	45,026	55.55
Current	9,889	12.26	10,157	12.41	8,599	10.53	9,094	11.08	8,155	10.06
Deployment										
Never	43,203	53.58	42,336	51.71	39,480	48.36	37,371	45.55	36,077	44.51
Past	17,394	21.57	17,979	21.96	19,512	23.90	23,042	28.09	25,880	31.93
Current	20,041	24.85	21,558	26.33	22,639	27.73	21,627	26.36	19,102	23.57
Deployment Count										
Never	43,203	53.58	42,336	51.71	39,480	48.36	37,371	45.55	36,077	44.51
1	26,105	32.37	26,477	32.34	26,866	32.91	27,377	33.37	26,681	32.92
2	9,221	11.44	10,182	12.44	11,268	13.80	12,172	14.84	12,426	15.33
3	2,109	2.62	2,878	3.52	4,017	4.92	5,120	6.24	5,875	7.25
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Total Days Deployed	331.88	187.95	376.60	213.53	396.08	228.61	414.88	241.78	432.67	252.96
Permanent Stationed Overseas										
Never	79,444	98.52	80,698	98.56	80,428	98.53	80,928	98.64	80,038	98.74
Past	382	0.47	412	0.50	917	1.12	917	1.12	834	1.03
Current	812	1.01	763	0.93	657	0.80	195	0.24	187	0.23
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
Total Days Stationed Overseas	626.19	272.64	789.25	305.63	824.67	390.79	849.64	349.06	834.41	355.62

p-value derived from chi-square , t-test and anova. $p<0.01$ unless otherwise noted

Table 2. Population Characteristics (5 of 6)

	Entry		2002		2003		2004		2005		2006	
	n	%	n	%	n	%	n	%	n	%	n	%
Pregnancy count												
Number of deliveries	166,265	84.20	49,922	60.51	50,833	60.45	51,187	60.77	48,733	60.24	48,329	60.03
1	24,423	12.37	24,385	29.56	24,625	29.28	24,193	28.72	23,417	28.95	23,290	28.93
2	5,687	2.88	6,925	8.39	7,283	8.66	7,471	8.87	7,471	9.24	7,388	9.18
3+	1,080	0.55	1,268	1.54	1,352	1.61	1,378	1.64	1,378	1.70	1,497	1.86
Parity												
Nulliparous	117,941	59.73	34,770	42.15	35,371	42.06	33,670	39.97	32,268	39.89	31,840	39.55
Parous	31,190	15.80	32,578	39.49	33,260	39.55	33,042	39.23	32,164	39.76	32,175	39.97
Unknown	48,324	24.47	15,152	18.37	15,462	18.39	17,517	20.80	16,465	20.35	16,489	20.48
Knee Injury												
Never	190,597	96.53	66,498	80.60	59,251	70.46	53,425	63.43	47,764	59.04	45,204	56.15
Ever	6,858	3.47	16,002	19.40	24,842	29.54	30,804	36.57	33,133	40.96	35,300	43.85
Knee Injury Count												
None	190,597	96.53	66,498	80.60	59,251	70.46	53,425	63.43	47,764	59.04	45,204	56.15
1	6,200	3.14	11,513	13.96	16,622	19.77	19,664	23.35	20,402	25.22	21,506	26.71
2	601	0.30	3,283	3.98	5,642	6.71	7,456	8.85	8,402	10.39	9,151	11.37
3+	57	0.03	1,206	1.46	2,578	3.07	3,684	4.37	4,329	5.35	4,643	5.77
Back/Hip Injury												
Never	174,827	88.54	55,965	67.84	55,932	66.51	55,395	65.77	52,925	65.42	53,706	66.71
Ever	22,628	11.46	26,535	32.16	28,161	33.49	28,834	34.23	27,972	34.58	26,798	33.29
Back/Hip Injury Count												
None	174,827	88.54	55,965	67.84	55,932	66.51	55,395	65.77	52,925	65.42	53,706	66.71
1	20,436	10.35	23,543	28.54	24,513	29.15	24,801	29.44	23,565	29.13	21,990	27.32
2	1,949	0.99	2,644	3.20	3,181	3.78	3,452	4.10	3,740	4.62	4,086	5.08
3+	243	0.12	348	0.42	467	0.56	581	0.69	667	0.82	722	0.90
Leg/Ankle Injury												
Never	187,468	94.94	70,081	84.95	69,468	82.61	68,237	81.01	64,596	79.85	64,229	79.78
Ever	9,987	5.06	12,419	15.05	14,625	17.39	15,992	18.99	16,301	20.15	16,275	20.22
Leg/Ankle Injury Count												
None	187,468	94.94	70,081	84.95	69,468	82.61	68,237	81.01	64,596	79.85	64,229	79.78
1	9,162	4.64	11,086	13.44	12,742	15.15	13,644	16.20	13,776	17.03	13,624	16.92
2	782	0.40	1,255	1.52	1,733	2.06	2,084	2.47	2,245	2.78	2,345	2.91
3+	43	0.02	78	0.09	150	0.18	264	0.31	278	0.34	306	0.38
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
BMI at accession	23.81	3.11	24.32	3.33	24.16	3.25	23.98	3.16	23.92	3.11	23.92	3.09
BMI at accession, IOM categories												
Underweight BMI <18.5	5,145	2.61	1,403	1.70	1,577	1.88	1,794	2.13	1,773	2.19	1,841	2.29
Normal weight BMI 18.5-24.9	114,369	57.92	44,935	54.47	46,850	55.71	48,174	57.19	46,085	56.97	45,050	55.96
Overweight BMI 25.0-30	54,408	27.55	24,177	29.31	23,672	28.15	22,726	26.98	21,653	26.77	21,972	27.29
Obese BMI >30	5,590	2.83	4,112	4.98	3,595	4.28	2,945	3.50	2,469	3.05	2,314	2.87
Unknown	17,943	9.09	7,873	9.54	8,399	9.99	8,590	10.20	8,912	11.02	9,327	11.59
NSAID use												
Never	174,984	88.62	28,065	34.02	16,053	19.09	11,977	14.22	9,292	11.49	8,185	10.17
Ever	22,471	11.38	54,435	65.98	68,040	80.91	72,252	85.78	71,605	88.51	72,319	89.83
NSAID count												
0	174,984	88.62	28,081	34.04	16,074	19.11	11,991	14.24	9,309	11.51	8,203	10.19
1 to 5	22,471	11.38	52,879	64.10	58,146	69.14	52,800	62.69	45,857	56.69	42,475	52.76
6 to 10	0	0.00	1,531	1.86	9,161	10.89	16,308	19.36	19,626	24.26	20,922	25.99
11+	0	0.00	9	0.01	712	0.85	3,130	3.72	6,105	7.55	8,904	11.06
Duration NSAID Use	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
	0.54	1.99	40.2	30.76	60.98	51.60	78.23	71.12	92.48	87.93	103.55	101.56

p-value derived from chi-square , t-test and anova. p<0.01 unless otherwise noted

Table 2. Population Characteristics (6 of 6)

	2007		2008		2009		2010		2011	
	n	%	n	%	n	%	n	%	n	%
Pregnancy count										
Number of deliveries	48,137	59.70	49,274	60.18	49,274	60.36	48,600	59.24	49,217	60.72
1	23,265	28.85	23,034	28.13	23,034	28.22	22,708	27.68	21,459	26.47
2	7,632	9.46	7,816	9.55	7,816	9.57	8,704	10.61	8,427	10.40
3+	1,604	1.99	1,749	2.14	1,749	2.14	2,028	2.47	1,956	2.41
Parity										
Nulliparous	31,135	38.61	31,825	38.87	31,064	38.05	30,142	36.74	30,110	37.15
Parous	32,501	40.30	32,599	39.82	32,357	39.64	33,440	40.76	31,842	39.28
Unknown	17,002	21.08	17,449	21.31	18,210	22.31	18,458	22.50	19,107	23.57
Knee Injury										
Never	43,477	53.92	43,156	52.71	43,459	53.24	40,839	49.78	38,859	47.94
Ever	37,161	46.08	38,717	47.29	38,172	46.76	41,201	50.22	42,200	52.06
Knee Injury Count										
None	43,477	53.92	43,156	52.71	42,459	52.01	40,839	49.78	38,859	47.94
1	22,706	28.16	23,457	28.65	23,260	28.49	23,029	28.07	24,343	30.03
2	9,562	11.86	10,081	12.31	10,379	12.71	11,144	13.58	11,481	14.16
3+	4,893	6.07	5,179	6.33	5,533	6.78	6,028	7.35	6,376	7.87
Back/Hip Injury										
Never	53,193	65.97	53,225	65.01	51,631	63.25	49,720	60.60	47,310	58.36
Ever	27,445	34.03	28,648	34.99	30,000	36.75	32,320	39.40	33,749	41.64
Back/Hip Injury Count										
None	53,193	65.97	53,225	65.01	51,631	63.25	49,720	60.60	47,310	58.36
1	22,228	27.57	23,011	28.11	23,858	29.23	25,448	31.02	26,319	32.47
2	4,414	5.47	4,783	5.84	5,196	6.37	5,699	6.95	6,156	7.59
3+	803	1.00	854	1.04	946	1.16	1,173	1.43	1,274	1.57
Leg/Ankle Injury										
Never	64,227	79.65	65,421	79.91	65,183	79.85	65,071	79.32	64,020	78.98
Ever	16,411	20.35	16,452	20.09	16,448	20.15	16,969	20.68	17,039	21.02
Leg/Ankle Injury Count										
None	64,227	79.65	65,421	79.91	65,183	79.85	65,071	79.32	64,020	78.98
1	13,705	17.00	13,705	16.74	13,629	16.70	14,005	17.07	13,960	17.22
2	2,370	2.94	2,370	2.89	2,435	2.98	2,568	3.13	2,637	3.25
3+	336	0.42	336	0.41	384	0.47	396	0.48	442	0.55
	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
BMI at accession	23.89	3.07	23.83	3.05	23.79	3.02	23.71	2.95	23.61	2.87
BMI at accession, IOM categories										
Underweight BMI <18.5	1,942	2.41	2,089	2.55	2,116	2.59	2,134	2.60	2,131	2.63
Normal weight BMI 18.5-24.9	44,653	55.37	44,916	54.86	44,871	54.97	46,580	56.78	47,558	58.67
Overweight BMI 25.0-30	22,337	27.70	22,817	27.87	22,803	27.93	22,664	27.63	22,012	27.16
Obese BMI >30	2,091	2.59	1,890	2.31	22,803	27.93	1,501	1.83	1,221	1.51
Unknown	9,615	11.92	10,161	12.41	10,106	12.38	9,161	11.17	8,137	10.04
NSAID use										
Never	7,170	8.89	8,259	10.09	10,118	12.39	9,138	11.14	8,778	10.83
Ever	73,468	91.11	73,468	89.73	71,513	87.61	72,902	88.86	72,281	89.17
NSAID count										
0	7,190	8.92	8,273	10.10	10,131	12.41	9,142	11.14	8,787	10.84
1 to 5	40,626	50.38	38,691	47.26	35,752	43.80	35,685	43.50	33,885	41.80
6 to 10	21,346	26.47	21,163	25.85	20,424	25.02	20,114	24.52	19,897	24.55
11+	11,476	14.23	13,746	16.79	15,324	18.77	17,099	20.84	18,490	22.81
Duration NSAID Use	avg	SD	avg	SD	avg	SD	avg	SD	avg	SD
	112.95	114.87	121.54	128.51	129.9	139.87	135.5	150.05	142.01	158.46

p-value derived from chi-square , t-test and anova. $p<0.01$ unless otherwise noted

Table 3. Annual Distribution of Contraceptive Use (1 of 2)

	First Use		Last Use		2002		2003		2004	
	n	%	n	%	n	%	n	%	n	%
Population	197,455		197,445		82,500		84,093		84,229	
Non-user	190,045	96.25	79,669	40.35	49,779	60.34	41,243	49.04	36,302	43.10
User	7,410	3.75	117,786	59.66	32,701	39.64	42,850	50.96	47,927	56.90
Past	- - -	- - -	70,500	59.85	0	0.00	5,773	6.87	9,875	11.72
Current	7,410	100.00	47,286	40.15	32,701	39.64	37,077	44.09	38,052	45.18
Combined Hormonal Contraceptive (CHC)										
Combined Hormonal Pills	79,517	67.51	71,881	61.03	26,066	79.71	26,162	70.56	24,506	64.40
Seasonal/Extended Pills	372	0.32	385	0.33	3	0.01	8	0.02	119	0.31
Patch	8,828	7.49	9,785	8.31	857	2.62	4,160	11.22	5,900	15.51
Ring	3,787	3.22	6,844	5.81	45	0.14	167	0.45	401	1.05
Progestin Only										
Progestin Only Pills	4,599	3.90	3,998	3.39	1,083	3.31	1,131	3.05	1,206	3.17
Injection	15,760	13.38	13,303	11.29	4,032	12.33	4,557	12.29	4,788	12.58
IUD	4,000	3.40	9,224	7.83	580	1.77	846	2.28	1,068	2.81
Implant	923	0.78	2,366	2.01	35	0.11	46	0.12	64	0.17
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Cumulative Duration, any (months)	0.81	0.74	37.71	43.09	11.23	7.07	19.64	14.35	26	21.23
Cumulative Duration, CHC (months)	0.63	0.74	33.00	42.36	9.66	7.66	17.2	14.98	23.07	21.66
Cumulative Duration, PO (months)	0.17	0.47	12.63	29.02	1.84	4.81	3.54	8.90	5.11	12.59

$p<0.01$ unless otherwise noted

Table 3. Annual Distribution of Contraceptive Use (2 of 2)

2005		2006		2007		2008		2009		2010		2011	
n	%	n	%	n	%	n	%	n	%	n	%	n	%
80,897		80,504		80,638		81,873		81,631		82,040		81,059	
31,050	38.38	28,968	35.98	27,635	34.27	27,691	33.82	27,396	33.56	26,126	31.85	24,535	30.27
49,847	61.62	50,536	62.77	53,003	65.73	54,182	66.18	54,235	66.44	55,914	68.15	56,524	69.73
11,435	14.14	12,125	15.06	14,685	18.21	15,670	19.14	19,225	23.55	20,982	25.58	20,994	25.90
38,412	47.48	38,411	47.71	38,318	47.52	38,512	47.04	35,010	42.89	34,932	42.58	35,530	43.83
24,160	62.90	24,709	64.33	25,053	65.38	24,810	64.42	21,282	60.79	19,490	55.79	18,360	51.67
378	0.98	448	1.17	125	0.33	62	0.16	42	0.12	59	0.17	70	0.20
5,814	15.14	3,931	10.23	2,823	7.37	2,249	5.84	1,810	5.17	1,656	4.74	1,539	4.33
896	2.33	1,898	4.94	2,469	6.44	2,728	7.08	2,662	7.60	2,942	8.42	2,995	8.43
1,266	3.30	1,234	3.21	1,211	3.16	1,146	2.98	910	2.60	943	2.70	960	2.70
4,508	11.74	4,207	10.95	3,948	10.30	3,541	9.19	3,033	8.66	3,169	9.07	3,635	10.23
1,334	3.47	1,908	4.97	2,574	6.72	3,640	9.45	4,515	12.90	5,308	15.20	5,923	16.67
56	0.15	76	0.20	115	0.30	336	0.87	756	2.16	1,365	3.91	2,048	5.76
mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
31.74	27.56	36.49	33.50	40.8	38.86	44.31	43.66	48.49	48.67	51.13	52.79	54.39	55.65
28.33	27.87	32.77	33.63	36.59	38.90	39.82	43.66	43	48.64	44.68	52.61	46.92	55.49
6.81	16.27	8.49	19.89	10.61	23.88	12.7	27.44	15.99	32.23	19.3	36.62	22.98	40.64

$p<0.01$ unless otherwise noted

Table 4. Correlates of First Contraceptive Use with Baseline Covariates (1 of 6)

	Never User		Ever User		Pills		Patch	
	n	%	n	%	n	%	n	%
	79,669	40.35	117,786	59.65	84,488	71.73	8,828	7.49
New Accession								
No	24,434	30.67	45,313	38.47	35,029	41.46	2,655	30.07
Yes	55,235	69.33	72,473	61.53	49,459	58.54	6,173	69.93
	avg	SD	avg	SD	avg	SD	avg	SD
Age (years)	24.05	6.67	23.03	5.52	23.25	5.60	22.23	4.89
Age (years)								
<20	25,313	31.77	37,784	32.08	26,273	31.10	3,363	38.09
20-24	27,181	34.12	46,203	39.23	32,710	38.72	3,391	38.41
25-29	11,811	14.83	18,128	15.39	13,237	15.67	1,192	13.50
30-34	6,951	8.72	9,406	7.99	7,175	8.49	580	6.57
35-39	5,054	6.34	4,733	4.02	3,796	4.49	238	2.70
40-45	3,359	4.22	1,532	1.30	1,297	1.54	64	0.72
Highest level of education attained								
≤High School Graduate	57,056	71.62	87,548	74.33	61,715	73.05	6,974	79.00
Some College/Certificate	10,516	13.20	11,668	9.91	8,055	9.53	905	10.25
College	9,174	11.52	15,101	12.82	11,834	14.01	807	9.14
Graduate Degree	2,923	3.67	3,469	2.95	2,884	3.41	142	1.61
Marital Status								
Single	50,267	63.09	78,624	66.75	56,561	66.95	6,140	69.55
Married	24,887	31.24	33,595	28.52	23,820	28.19	2,314	26.21
Divorced/Widowed/Separated	4,515	5.67	5,567	4.73	4,107	4.86	374	4.24
Race								
Caucasian	40,252	50.52	55,616	47.22	41,621	49.26	3,286	37.22
African American	24,828	31.16	39,805	33.79	26,796	31.72	3,711	42.04
Hispanic	8,651	10.86	13,698	11.63	9,699	11.48	1,187	13.45
American Indian	1,133	1.42	1,528	1.30	1,071	1.27	113	1.28
Asian	3,982	5.00	5,630	4.78	4,142	4.90	437	4.95
Other	823	1.03	1,509	1.28	1,159	1.37	94	1.06
Race								
African American	54,841	68.84	77,981	66.21	57,692	68.28	5,117	57.96
Other	24,828	31.16	39,805	33.79	26,796	31.72	3,711	42.04

p-value derived from chi-square , t-test and anova. $p<0.05$ unless otherwise noted.

Table 4. Correlates of First Contraceptive Use with Baseline Covariates (2 of 6)

	Never User		Ever User		Pills		Patch	
	n	%	n	%	n	%	n	%
Rank								
E1-E4 (Private - Specialist)	63,703	79.96	90,240	76.61	62,778	74.30	7,378	83.57
E5-E9 (Sergeant-Sergeant Major)	8,124	10.20	15,017	12.75	11,660	13.80	844	9.56
Warrant/O1-O3 (Second Luteienant- Captain)	6,351	7.97	11,345	9.63	9,002	10.65	564	6.39
O4+ (Major-General)	1,491	1.87	1,184	1.01	1,048	1.24	42	0.48
	avg	SD	avg	SD	avg	SD	avg	SD
Length of service, years	1.76	4.33	1.73	3.79	1.93	4.01	1.22	3.15
Time in Cohort (years)								
<2 years	63,284	79.43	89,376	75.88	62,255	73.69	7,268	82.33
2 to <4 years	4,854	6.09	9,278	7.88	7,156	8.47	504	5.71
4 to <6 years	2,839	3.56	5,767	4.90	4,373	5.18	334	3.78
6 to <8 years	1,599	2.01	3,235	2.75	2,506	2.97	203	2.30
8 + years	7,093	8.90	10,130	8.60	8,198	9.70	519	5.88
Pregnancy count								
None	68,141	85.53	98,124	83.31	69,989	82.84	7,469	84.61
1	8,878	11.14	15,545	13.20	11,419	13.52	1,079	12.22
2	2,158	2.71	3,529	3.00	2,646	3.13	231	2.62
3+	492	0.62	588	0.50	434	0.51	49	0.56
Parity								
Nulliparous	45,286	56.84	72,655	61.68	53,095	62.84	5,379	60.93
Parous	11,528	14.47	19,662	16.69	14,499	17.16	1,359	15.39
Unknown	22,855	28.69	25,469	21.62	16,894	20.00	2,090	23.67

p-value derived from chi-square , t-test and anova. $p<0.05$ unless otherwise noted.

Table 4. Correlates of First Contraceptive Use with Baseline Covariates (3 of 6)

	Never User		Ever User		Pills		Patch	
	n	%	n	%	n	%	n	%
Knee Injury								
Never	76,228	95.68	114,369	97.10	82,195	97.29	8,524	96.56
Ever	3,441	4.32	3,417	2.90	2,293	2.71	304	3.44
Knee Injury Count								
None	76,228	95.68	114,369	97.10	82,195	97.29	8,524	96.56
1	3,057	3.84	3,143	2.67	2,106	2.49	279	3.16
2	347	0.44	254	0.22	187	0.22	25	0.28
3+	37	0.05	20	0.02	.	.	.	.
Back/Hip Injury								
Never	71,156	89.31	103,671	88.02	73,764	87.31	7,951	90.07
Ever	8,513	10.69	14,115	11.98	10,724	12.69	877	9.93
Back/Hip Injury Count								
None	71,156	89.31	103,671	88.02	73,764	87.31	7,951	90.07
1	7,603	9.54	12,833	10.90	9,712	11.50	818	9.27
2	799	1.00	1,150	0.98	1,012	1.20	59	0.67
3+	111	0.14	132	0.11	.	.	.	.
Leg/Ankle Injury								
Never	75,962	95.35	111,506	94.67	79,720	94.36	8,469	95.93
Ever	3,707	4.65	6,280	5.33	4,768	5.64	359	4.07
Leg/Ankle Injury Count								
None	75,962	95.35	111,506	94.67	79,720	94.36	8,469	95.93
1	3,386	4.25	5,776	4.90	4,768	5.64	359	4.07
2	302	0.38	480	0.41	.	.	.	.
3+	19	0.02	24	0.02	.	.	.	.
	avg	SD	avg	SD	avg	SD	avg	SD
BMI at accession	23.80	3.14	23.82	3.08	23.86	3.09	23.84	3.08
BMI at accession, IOM categories								
Underweight BMI <18.5	2,271	2.85	2,874	2.44	1,976	2.34	234	2.65
Normal weight BMI 18.5-24.9	46,020	57.76	68,349	58.03	48,466	57.36	5,138	58.20
Overweight BMI 25.0-30	22,328	28.03	32,080	27.24	22,967	27.18	2,509	28.42
Obese BMI >30	2,297	2.88	3,293	2.80	2,478	2.93	242	2.74
Unknown	6,753	8.48	11,190	9.50	8,601	10.18	705	7.99
NSAID use								
Never	69,965	87.82	105,019	89.16	75,813	89.73	7,705	87.28
Ever	9,704	12.18	12,767	10.84	8,775	10.39	1,123	12.72

p-value derived from chi-square , t-test and anova. $p<0.05$ unless otherwise noted.

Table 4. Correlates of First Contraceptive Use with Baseline Covariates (4 of 6)

	Ring		Injection		IUD		Implant	
	n	%	n	%	n	%	n	%
	3,787	3.22	15,760	13.38	4,000	3.40	923	0.78
New Accession								
No	250	6.60	6,225	39.50	1,084	27.10	70	7.58
Yes	3,527	93.13	9,535	60.50	2,916	72.90	853	92.42
	avg	SD	avg	SD	avg	SD	avg	SD
Age (years)	22.36	4.53	22.26	4.80	24.09	5.36	21.22	4.15
Age (years)								
<20	1,205	31.82	5,662	35.93	856	21.40	425	46.05
20-24	1,662	43.89	6,464	41.02	1,636	40.90	340	36.84
25-29	619	16.35	2,121	13.46	856	21.40	103	11.16
30-34	193	5.10	986	6.26	427	10.68	45	4.88
35-39	86	2.27	424	2.69	184	4.60	5	0.54
40-45	22	0.58	103	0.65	41	1.03	5	0.54
Highest level of education attained								
≤High School Graduate	2,449	64.67	12,830	81.41	2,872	71.80	708	76.71
Some College/Certificate	384	10.14	1,660	10.53	551	13.78	113	12.24
College	788	20.81	1,131	7.18	450	11.25	91	9.86
Graduate Degree	166	4.38	139	0.88	127	3.18	11	1.19
Marital Status								
Single	2,700	71.30	10,953	69.50	1,628	40.70	642	69.56
Married	954	25.19	4,151	26.34	2,117	52.93	239	25.89
Divorced/Widowed/Separated	133	3.51	656	4.16	255	6.38	42	4.55
Race								
Caucasian	2,094	55.29	6,273	39.80	1,868	46.70	474	51.35
African American	1,017	26.86	6,724	42.66	1,291	32.28	266	28.82
Hispanic	406	10.72	1,739	11.03	554	13.85	113	12.24
American Indian	39	1.03	234	1.48	64	1.60	7	0.76
Asian	196	5.18	620	3.93	177	4.43	58	6.28
Other	35	0.92	170	1.08	46	1.15	5	0.54
Race								
African American	2,770	73.14	9,036	57.34	2,709	67.73	657	71.18
Other	1,017	26.86	6,724	42.66	1,291	32.28	266	28.82

p-value derived from chi-square , t-test and anova. $p<0.05$ unless otherwise noted.

Table 4. Correlates of First Contraceptive Use with Baseline Covariates (5 of 6)

	Ring		Injection		IUD		Implant	
	n	%	n	%	n	%	n	%
Rank								
E1-E4 (Private - Specialist)	2,943	77.71	13,216	83.86	3,109	77.73	816	88.41
E5-E9 (Sergeant-Sergeant Major)	141	3.72	1,826	11.59	507	12.68	39	4.23
Warrant/O1-O3 (Second Luteienant- Captain	691	18.25	678	4.30	343	8.58	67	7.26
O4+ (Major-General)	12	0.32	40	0.25	41	1.03	1	0.11
	avg	SD	avg	SD	avg	SD	avg	SD
Length of service, years	0.32	1.71	1.43	3.21	1.54	3.60	0.44	1.94
Time in Cohort (years)								
<2 years	3,615	95.46	12,185	77.32	3,187	79.68	866	93.82
2 to <4 years	53	1.40	1,364	8.65	190	4.75	11	1.19
4 to <6 years	31	0.82	832	5.28	181	4.53	16	1.73
6 to <8 years	24	0.63	394	2.50	103	2.58	5	0.54
8 + years	64	1.69	985	6.25	339	8.48	25	2.71
Pregnancy count								
None	3,597	94.98	13,036	82.72	3,150	78.75	883	95.67
1	160	4.22	2,228	14.14	629	15.73	30	3.25
2	25	0.66	436	2.77	183	4.58	8	0.87
3+	5	0.13	60	0.38	38	0.95	2	0.22
Parity								
Nulliparous	2,642	69.76	9,513	60.36	1,399	34.98	627	67.93
Parous	190	5.02	2,724	17.28	850	21.25	40	4.33
Unknown	955	25.22	3,523	22.35	1,751	43.78	256	27.74

p-value derived from chi-square , t-test and anova. $p<0.05$ unless otherwise noted.

Table 4. Correlates of First Contraceptive Use with Baseline Covariates (6 of 6)

	Ring		Injection		IUD		Implant	
	n	%	n	%	n	%	n	%
Knee Injury								
Never	3,682	97.23	15,119	95.93	3,875	96.88	894	96.86
Ever	105	2.77	561	3.56	125	3.13	29	3.14
Knee Injury Count								
None	3,682	97.23	15,199	96.44	3,875	96.88	894	96.86
1	93	2.46	520	3.30	119	2.98	26	2.82
2	12	0.32	41	0.26	6	0.15	3	0.33
3+	.	.	.	.	.	.	.	.
Back/Hip Injury								
Never	3,668	96.86	13,806	87.60	3,598	89.95	884	95.77
Ever	119	3.14	1,954	12.40	402	10.05	39	4.23
Back/Hip Injury Count								
None	3,668	96.86	13,806	87.60	3,598	89.95	884	95.77
1	111	2.93	1,791	11.36	366	9.15	35	3.79
2	8	0.21	163	1.03	36	0.90	4	0.43
3+	.	.	.	.	.	.	.	.
Leg/Ankle Injury								
Never	3,721	98.26	14,858	94.28	3,831	95.78	907	98.27
Ever	66	1.74	902	5.72	169	4.23	16	1.73
Leg/Ankle Injury Count								
None	3,721	98.26	14,858	94.28	3,821	95.53	907	98.27
1	66	1.74	902	5.72	169	4.23	16	1.73
2	.	.	.	.	.	.	.	.
3+	.	.	.	.	.	.	.	.
	avg	SD	avg	SD	avg	SD	avg	SD
BMI at accession	23.87	2.80	23.50	3.09	24.19	2.96	23.50	2.87
BMI at accession, IOM categories								
Underweight BMI <18.5	68	1.80	525	3.33	50	1.25	21	2.28
Normal weight BMI 18.5-24.9	2,002	52.87	9,974	63.29	2,207	55.18	562	60.89
Overweight BMI 25.0-30	1,053	27.81	4,023	25.53	1,273	31.83	255	27.63
Obese BMI >30	58	1.53	391	2.48	111	2.78	13	1.41
Unknown	606	16.00	847	5.37	359	8.98	72	7.80
NSAID use								
Never	3,415	90.18	13,721	87.06	3,613	90.33	852	92.31
Ever	372	9.82	2,039	12.94	387	9.68	71	7.69

p-value derived from chi-square , t-test and anova. $p<0.05$ unless otherwise noted.

Table 5. Contraceptive Use by Career Event

	Home Station (in U.S.)		Basic Combat Training		1st Deployment		Stationed Overseas	
N	196,324		82,033		78,547		1,630	
Duration, Months (SD)	36.18 (30.80)		1.65 (1.01)		8.9 (4.10)		26.69 (11.37)	
	N	%	N	%	N	%	N	%
Never	77,845	39.65	75,439	91.96	29,025	36.95	454	27.85
Ever	117,479	59.84	7,340	8.95	49,522	63.05	1,176	72.15
Past	69,607	59.25	746	10.16	32,279	65.18	794	67.52
Current	47,872	40.75	6,594	89.84	17,243	34.82	382	32.48
Combined Hormonal Contraception	88,610	75.43	5,044	68.72	39,626	80.02	959	81.55
Combined Hormonal Pills	71,541	60.90	4,318	58.83	33,988	68.63	816	69.39
Seasonal/Extended Pills	375	0.32	19	0.26	218	0.44	4	0.34
Patch	9,776	8.32	456	6.21	3,911	7.90	90	7.65
Ring	6,918	5.89	251	3.42	1,509	3.05	49	4.17
Progestin Only	28,869	24.57	2,296	31.28	9,896	19.98	217	18.45
Progestin Only Pills	4,047	3.44	16	0.22	502	1.01	25	2.13
Injection	13,084	11.14	1,384	18.86	5,900	11.91	126	10.71
IUD	9,339	7.95	741	10.10	2,871	5.80	51	4.34
Implant	2,399	2.04	155	2.11	623	1.26	15	1.28
Cumulative Duration (months)	avg	SD	avg	SD	avg	SD	avg	SD
Total of all contraceptive methods	12.91	14.79	1.24	1.01	3.58	4.31	8.86	9.65

$p<0.01$ unless otherwise noted.

Table 6. Changes in Contraceptive Use by Career Event

	Entire Event		2002		2003		2004		2005	
	N	%	N	%	N	%	N	%	N	%
Home Station (in U.S.)	196,324		81,890		82,949		82,626		77,333	
Never user hormonal contraception	79,601	40.55	49,337	60.25	46,880	56.52	45,813	55.45	41,056	53.09
Started hormonal contraception	65,677	33.45	25,676	31.35	13,748	16.57	15,477	18.73	14,467	18.71
Stopped hormonal contraception	5,821	2.96	2,001	2.44	9,595	11.57	8,152	9,87	8,186	10.59
Changed hormonal contraception	42,659	21.73	2,584	3.16	3,643	4.39	4,299	5.20	4,449	5.75
Used one method of contraception entire time	2,566	1.31	2,292	2.80	9,083	10.95	8,885	10.75	9,175	11.86
Basic Training	83,997		7,901		9,343		10,130		8,558	
Never user hormonal contraception	76,250	90.78	7,436	94.11	8,631	92.38	9,421	93.00	7,781	90.92
Started hormonal contraception	5,012	5.97	284	3.59	416	4.45	321	3.17	438	5.12
Stopped hormonal contraception	456	0.54	29	0.37	51	0.55	57	0.56	39	0.46
Changed hormonal contraception	75	0.09	2	0.03	4	0.04	7	0.07	6	0.07
Used one method of contraception entire time	1,483	1.77	150	1.90	241	2.58	324	3.20	294	3.44
Deployed (first)	78,572		2,923		17,997		16,263		13,361	
Never user hormonal contraception	44,647	56.82	2,273	77.76	11,524	64.03	11,444	70.37	8,074	60.43
Started hormonal contraception	5,600	7.13	89	3.04	769	4.27	771	4.74	700	5.24
Stopped hormonal contraception	14,644	18.64	196	6.71	3,389	18.83	1,307	8.04	1,263	9.45
Changed hormonal contraception	1,577	2.01	2	0.07	203	1.13	115	0.71	101	0.76
Used one method of contraception entire time	12,104	15.40	363	12.42	2,112	11.74	2,626	16.15	3,223	24.12
Stationed Overseas (first)	1,641		164		284		529		667	
Never user hormonal contraception	651	39.67	105	64.02	178	62.68	306	57.84	359	53.82
Started hormonal contraception	337	20.54	27	16.46	39	13.73	63	11.91	66	9.90
Stopped hormonal contraception	364	22.18	17	10.37	37	13.03	51	9.64	84	12.59
Changed hormonal contraception	177	10.79	0	0.00	4	1.41	14	2.65	18	2.70
Used one method of contraception entire time	112	6.83	15	9.15	26	9.15	95	17.96	140	20.99

$p<0.01$ unless otherwise noted.

Table 6. Changes in Contraceptive Use by Career Event

	2006		2007		2008		2009		2010		2011	
	N	%	N	%	N	%	N	%	N	%	N	%
Home Station (in U.S.)	78,153		76,261		76,792		79,752		79,752		79,952	
Never user hormonal contraception	41,709	53.37	40,824	53.53	41,482	54.02	46,968	58.89	46,323	58.08	45,848	57.34
Started hormonal contraception	14,021	17.94	13,919	18.25	14,069	18.32	13,391	16.79	12,809	16.06	12,609	15.77
Stopped hormonal contraception	8,257	10.57	8,066	10.58	8,506	11.08	7,654	9.60	7,486	9.39	8,049	10.07
Changed hormonal contraception	4,057	5.19	3,799	4.98	3,482	4.53	2,995	3.76	2,977	3.73	2,642	3.30
Used one method of contraception entire time	10,109	12.93	9,653	12.66	9,253	12.05	8,877	11.13	10,248	12.85	10,804	13.51
Basic Training	10,925		9,889		10,157		8,599		9,094		8,155	
Never user hormonal contraception	9,832	90.00	9,019	91.20	9,254	91.11	7,665	89.14	8,145	89.56	7,232	88.68
Started hormonal contraception	677	6.20	480	4.85	482	4.75	506	5.88	556	6.11	556	6.82
Stopped hormonal contraception	53	0.49	40	0.40	60	0.59	60	0.70	42	0.46	37	0.45
Changed hormonal contraception	8	0.07	8	0.08	4	0.04	4	0.05	1	0.01	3	0.04
Used one method of contraception entire time	355	3.25	342	3.46	357	3.51	357	4.15	350	3.85	327	4.01
Deployed (first)	13,823		13,331		13,823		13,849		12,584		10,806	
Never user hormonal contraception	8,007	57.93	7,705	57.80	8,224	59.50	8,773	63.35	8,227	65.38	6,538	60.50
Started hormonal contraception	957	6.92	912	6.84	870	6.29	744	5.37	592	4.70	789	7.30
Stopped hormonal contraception	1,360	9.84	1,665	12.49	1,814	13.12	1,531	11.05	1,200	9.54	993	9.19
Changed hormonal contraception	143	1.03	130	0.98	130	0.94	109	0.79	73	0.58	72	0.67
Used one method of contraception entire time	3,356	24.28	2,919	21.90	2,785	20.15	2,692	19.44	2,492	19.80	2,414	22.34
Stationed Overseas (first)	920		809		759[a]		654		191[b]		185	
Never user hormonal contraception	515	55.98	409	50.56	367	48.35	422	64.53	115	60.21	115	62.16
Started hormonal contraception	103	11.20	133	16.44	141	18.58	46	7.03	20	10.47	15	8.11
Stopped hormonal contraception	97	10.54	121	14.96	111	14.62	68	10.40	25	13.09	13	7.03
Changed hormonal contraception	18	1.96	27	3.34	34	4.48	9	1.38	9	4.71	2	1.08
Used one method of contraception entire time	187	20.33	119	14.71	106	13.97	109	16.67	22	11.52	40	21.62

[a]p=0.716

[b]p=0.2862

Table 7. Exclusions and Dropout: Contraceptive Use and ACL Injury

	Excluded			Dropped		
	n	%	person years	n	%	person years
All women on active duty	**11,962**	**5.76**		**8,031**	**3.87**	
1 month in DMDC[1]	3,544	1.71	295	.	.	.
Age ≥46	2,186	1.05	8,230	3,124	1.50	8,718
Missing covariates[2]	2,803	1.35	4,601	.	.	.
Hysterectomy	684	0.33	3,280	2,547	1.23	6,848
Oophorectomy	446	0.21	2,163	717	0.35	2,226
Menopause	571	0.27	2,956	1,377	0.66	4,206
Hormonal replacement therapy	133	0.06	637	193	0.09	761
Amputation	14	0.01	77	73	0.04	228
Implausible Pregnancy	80	0.04	638	.	.	.
ACL Injury (before 2002)	1,501	0.72	8,247	.	.	.
Final Cohort	195,815		703,499			
New accessions 2002-2011	**5,248**	**3.95**		**1,723**	**1.30**	
1 month in DMDC[1]	2,133	1.61	178	.	.	.
Age ≥46	605	0.46	1,568	439	0.33	907
Missing covariates[2]	2,348	1.77	3,624	.	.	.
Hysterectomy	17	0.01	63	538	0.41	1,015
Oophorectomy	6	0.00	34	234	0.18	525
Menopause	28	0.02	96	391	0.29	946
Hormonal replacement therapy	7	0.01	28	81	0.06	240
Amputation	1	0.00	2	40	0.03	114
Implausible Pregnancy	17	0.01	119	.	.	.
ACL Injury (before 2002)	86	0.06	446	.	.	.
Final Cohort	127,563		382,104			

[1] there is no reference to identify if these women had any service prior to 2002

[2]missing age, education, marital status or race/ethnicity completely

Table 8. Distribution of ACL Injury

	n	%	n	%
	Study Cohort		New Accession	
ACL Injury	195,815		127,563	
No	193,562	98.85	126,311	99.02
Yes	2,253	1.15	1,252	0.98
Diagnosis and Intervention				
X-Ray				
No	2,243	99.56	1,211	96.73
Yes	134	5.95	74	5.91
MRI				
No	2,146	95.25	1,172	93.61
Yes	221	9.81	112	8.95
Surgical Correction				
No	2,040	90.55	1,105	88.26
Yes	332	14.74	178	14.22

*p-value derived from chi-square. $p<0.05$ unless otherwise noted.

Table 9. Correlates of ACL Injury (1 of 2)

	No ACL Injury		Incident ACL Injury	
	n	%	n	%
	193,562	98.85	2,253	1.15
New Accession				
No	67,251	34.74	1,001	44.43
Yes	126,311	65.26	1,252	55.57
	avg	SD	avg	SD
Age at entry(years)	23.37	5.94	24.62	6.17
Age at entry				
<20	62,491	32.28	562	24.94
20-24	72,199	37.30	755	33.51
25-29	29,116	15.04	451	20.02
30-34	15,725	8.12	284	12.61
35-39	9,361	4.84	140	6.21
40-45	4,670	2.41	61	2.71
Highest level of education attained				
≤High School Graduate	142,066	73.40	1,600	71.02
Some College/Certificate	21,782	11.25	231	10.25
College	23,572	12.18	319	14.16
Graduate Degree	6,142	3.17	103	4.57
Marital Status				
Single	126,823	65.52	1,417	62.89
Married	56,991	29.44	689	30.58
Divorced/Widowed/Separated	9,748	5.04	147	6.52
Race				
Caucasian	94,102	48.62	1,028	45.63
African American	63,207	32.65	817	36.26
Hispanic	22,028	11.38	209	9.28
American Indian	2,599	1.34	36	1.60
Asian	9,392	4.85	124	5.50
Other	2,234	1.15	39	1.73
Race				
African American	130,355	67.35	1,436	63.74
Other	63,207	32.65	817	36.26
Rank				
E1-E4 (Private - Specialist)	151,873	78.46	1,587	70.44
E5-E9 (Sergeant-Sergeant Major)	22,063	11.40	377	16.73
Warrant/O1-O3 (Second Luteienant- Captain)	17,134	8.85	234	10.39
O4+ (Major-General)	2,492	1.29	55	2.44
	avg	SD	avg	SD
Length of service, years	1.69	3.96	2.34	4.36
Time in Cohort (years)				
None	126,311	65.26	1,252	55.57
<2 years	24,660	12.74	332	14.74
2 to <4 years	13,550	7.00	158	7.01
4 to <6 years	8,179	4.23	131	5.81
6 to <8 years	4,606	2.38	79	3.51
8 + years	16,256	8.40	301	13.36

*p-value derived from chi-square , t-test. $p<0.05$ unless otherwise noted.

Table 9. Correlates of ACL Injury (2 of 2)

	No ACL Injury		Incident ACL Injury	
	n	%	n	%
Pregnancy count				
None	163,395	84.41	1,861	82.60
1	23,692	12.24	290	12.87
2	5,451	2.82	78	3.46
3+	1,024	0.53	24	1.07
Parity				
Nulliparous	115,967	59.91	1,318	58.50
Parous	30,167	15.59	392	17.40
Unknown	47,428	24.50	543	24.10
Knee Injury				
Never	186,954	96.59	2,103	93.34
Ever	6,608	3.41	150	6.66
Knee Injury Count				
None	186,954	96.59	2,103	93.34
1	5,985	3.09	122	5.42
2	571	0.29	27	1.20
3+	52	0.03	1	0.04
Back/Hip Injury				
Never	171,938	88.83	1,925	85.44
Ever	21,624	11.17	328	14.56
Back/Hip Injury Count				
None	171,938	88.83	1,925	85.44
1	19,572	10.11	293	13.00
2	1,833	0.95	28	1.24
3+	219	0.11	7	0.31
Leg/Ankle Injury				
Never	184,024	95.07	2,095	92.99
Ever	9,538	4.93	158	7.01
Leg/Ankle Injury Count				
None	184,024	95.07	2,095	92.99
1	8,765	4.53	140	6.21
2	732	0.38	18	0.80
3+	41	0.02	0	0.00
	avg	SD	avg	SD
BMI at accession	23.79	3.10	24.53	3.08
BMI at accession, IOM categories				
Underweight BMI <18.5	5,104	2.64	32	1.42
Normal weight BMI 18.5-24.9	112,492	58.12	1,147	50.91
Overweight BMI 25.0-30	53,181	27.47	724	32.13
Obese BMI >30	5,357	2.77	100	4.44
Unknown	17,428	9.00	250	11.10
NSAID use				
Never	171,522	88.61	1,961	87.04
Ever	22,040	11.39	292	12.96

*p-value derived from chi-square , t-test. $p<0.05$ unless otherwise noted.

Table 10. Hazard Ratio of ACL Injury by Contraceptive Use (1 of 2)

			Unadjusted HR		Age Adjusted HR		Final HR	
Person years	ACL Cases		696,992		696,992		696,992	
n	2,230		195,815		195,815		195,815	
Cases	n	%	2,230		2,230		2,230	
Use at Time of ACL Injury								
Nonuser	976	43.77	1	ref	1	ref	1	ref
User	1,254	56.23	0.86	0.79-0.93	0.86	0.79-0.94	0.95	0.86-1.04
Ever Use, Hormonal Contraceptives								
Never	976	43.77	1	ref	1	ref	1	ref
Past	708	31.75	0.9	0.81-0.99	0.9	0.82-0.99	1.07	0.96-1.19
Current	564	25.29	0.81	0.73-0.90	0.81	0.73-0.90	0.85	0.76-0.94
Homronal Contraceptive Method								
No use	1,684	75.52	1	ref	1	ref	1	ref
Pills, monthly	375	16.82	0.89	0.80-1.0	0.89	0.80-0.99	0.87	0.78-0.98
Pills, seasonal	6	0.27	0.44	0.20-0.97	0.44	0.20-0.97	0.54	0.24-1.21
Patch	28	1.26	0.62	0.42-0.90	0.62	0.42-0.90	0.56	0.39-0.82
Ring	20	0.90	0.82	0.53-1.27	0.82	0.53-1.27	0.73	0.47-1.13
Injection	50	2.24	0.88	0.66-1.16	0.87	0.66-1.16	0.75	0.57-0.99
IUD	53	2.38	0.77	0.59-1.02	0.77	0.59-1.02	0.78	0.51-1.03
Implant	14	0.63	1.22	0.72-2.08	1.22	0.72-2.07	1.22	0.72-2.08
Type, Hormonal Contraceptive Use								
Nonuser	976	43.77	1	ref	1	ref	1	ref
Combined Method	839	37.62	0.88	0.80-0.96	0.88	0.80-0.96	0.97	0.88-1.07
Progestin Only	129	5.78	0.78	0.65-0.94	0.78	0.65-0.94	0.85	0.70-1.02
Both	286	12.83	0.84	0.74-0.97	0.85	0.74-0.97	0.91	0.79-1.06
Never, Past or Current Use by Type								
Never	976	43.77	1	ref	1	ref	1	ref
Past use combined hormonal contraception	451	20.22	0.9	0.80-1.00	0.9	0.8-1.01	1.08	0.96-1.22
Past use progestin only	67	3.00	0.77	0.60-0.99	0.77	0.60-0.99	0.89	0,69-1.14
Past use both methods	190	8.52	0.96	0.82-1.13	0.96	0.82-1.13	1.1	0.93-1.30
Current use combined hormonal contraception	388	17.40	0.85	0.76-0.96	0.85	0.76-0.96	0.89	0.79-1.00
Current use progestin only	62	2.78	0.79	0.62-1.03	0.8	0.62-1.03	0.82	0.63-1.06
Current user both	96	4.30	0.68	0.55-0.84	0.68	0.55-0.84	0.71	0.57-0.88

Final model adjusted for: age, knee injury, NSAID use, deployment, pregnancy, race ethnicity, back/hip injury and new accession

Table 10. Hazard Ratio of ACL Injury by Contraceptive Use (2 of 2)

			Unadjusted HR		Age Adjusted HR		Final HR	
Person years	ACL Cases		696,992		696,992		696,992	
n	2,230		195,815		195,815		195,815	
Cases	n	%	2,230		2,230		2,230	
Duration								
Never	976	43.77	1	ref	1	ref	1	ref
Short (<90 days)	203	9.10	0.9	0.78-1.05	0.9	0.77-1.05	0.9	0.77-1.05
Medium (90-265 days)	557	24.98	0.87	0.78-0.97	0.87	0.78-0.97	0.99	0.89-1.11
Long (365+ days)	494	22.15	0.82	0.74-0.92	0.82	0.74-0.92	0.91	0.81-1.03
Never, Past or Current Use by Duration of Use								
Never user	976	43.77	1	ref	1	ref	1	ref
Past-short (<90 days)	124	5.56	0.96	0.79-1.16	0.96	0.79-1.15	1.13	0.93-1.36
Past-medium (90-365)	353	15.83	0.87	0.77-0.99	0.87	0.77-0.99	1.06	0.93-1.21
Past-long (365+)	231	10.36	0.91	0.78-1.05	0.91	0.79-1.06	1.07	0.91-1.26
Current-short (<90 days)	79	3.54	0.83	0.66-1.04	8.2	0.65-1.04	0.68	0.54-0.86
Current-medium (90-365)	204	9.15	0.87	0.75-1.02	0.87	0.75-1.01	0.93	0.80-1.08
Current-long (365+)	263	11.79	0.76	0.66-0.88	0.76	0.67-0.88	0.85	0.73-0.99
Type by Duration of Use								
Never user	976	43.77	1	ref	1	ref	1	ref
Combined Only-Short	147	6.59	0.99	0.83-1.18	0.99	0.83-1.17	0.96	0.81-1.14
Combined Only-Medium	380	17.04	0.88	0.78-0.99	0.88	0.78-0.99	1.01	0.90-1.15
Combined Only-Long	312	13.99	0.82	0.72-0.94	0.83	0.72-0.94	0.93	0.81-1.07
Progestin Only-Short	30	1.35	0.69	0.48-0.99	0.68	0.48-0.98	0.68	0.47-0.97
Progestin Only-Medium	63	2.83	0.85	0.66-1.09	0.84	0.65-1.09	0.95	0.73-1.22
Progestin Only-Long	36	1.61	0.77	0.55-1.08	0.77	0.55-1.08	0.86	0.61-1.21
Both-Short/Medium	140	6.28	0.85	0.71-1.02	0.85	0.71-1.02	0.94	0.78-1.13
Both-Long	146	6.55	0.83	0.70-0.99	0.83	0.70-0.99	0.88	0.73-1.07
Time Since Last Use (excluding current users n=564)								
Never	976	57.96	1	ref	1	ref	1	ref
Short (<90 days)	198	11.76	1.21	1.04-1.41	1.21	1.04-1.41	1.26	1.07-1.47
Medium (90-265 days)	241	14.31	0.83	0.72-0.95	0.83	0.72-0.95	1.02	0.88-1.18
Long (365+ days)	269	15.97	0.78	0.68-0.90	0.78	0.68-0.90	0.84	0.72-0.98

Final model adjusted for: age, knee injury, NSAID use, deployment, pregnancy, race ethnicity, back/hip injury and new accession

Table 11. Hazard Ratio of ACL Injury by Contraceptive Use Among New Accession (1 of 2)

	New Accession HR		New Accession HR (adjusted)	
Person years	378,559		378,559	
n	127,563		127,563	
Cases	1,243		1,243	
Use at Time of ACL Injury				
Nonuser	1	ref	1	ref
User	0.83	0.74-0.93	0.96	0.85-1.09
Ever Use, Hormonal Contraceptives				
Never	1	ref	1	ref
Past	0.86	0.75-0.98	1.07	0.92-1.24
Current	0.81	0.70-0.93	0.88	0.76-1.01
Homronal Contraceptive Method				
No use	1	ref	1	ref
Pills, monthly	0.94	0.81-1.10	0.95	0.82-1.11
Pills, seasonal	0.31	0.08-1.25	0.37	0.09-1.50
Patch	0.63	0.38-1.05	0.58	0.35-0.97
Ring	0.8	0.48-1.33	0.72	0.43-1.20
Injection	0.99	0.69-1.42	0.86	0.60-1.22
IUD	0.59	0.39-0.89	0.6	0.40-0.92
Implant	0.91	0.47-1.76	0.94	0.48-1.81
Type, Hormonal Contraceptive Use				
Nonuser	1	ref	1	ref
Combined Method	0.86	0.76-0.97	1	0.88-1.14
Progestin Only	0.7	0.54-0.90	0.76	0.58-0.99
Both	0.83	0.69-1.01	0.94	0.76-1.15
Never, Past or Current Use by Type				
Never	1	ref	1	ref
Past use combined hormonal contraception	0.87	0.74-1.01	1.1	0.93-1.30
Past use progestin only	0.62	0.43-0.91	0.73	0.50-1.07
Past use both methods	0.94	0.75-1.18	1.11	0.88-1.42
Current use combined hormonal contraception	0.85	0.73-0.99	0.92	0.79-1.09
Current use progestin only	0.77	0.55-1.08	0.79	0.56-1.10
Current user both	0.69	0.52-0.92	0.75	0.55-1.02

Final model adjusted for: age, knee injury, NSAID use, deployment, pregnancy, race ethnicity, back/hip injury and new accession

Table 11. Hazard Ratio of ACL Injury by Contraceptive Use Among New Accession (2 of 2)

	New Accession HR		New Accession HR (adjusted)	
Person years	378,559		378,559	
n	127,563		127,563	
Cases	1,243		1,243	
Duration				
Never	1	ref	1	ref
Short (<90 days)	0.86	0.70-1.04	0.87	0.72-1.06
Medium (90-265 days)	0.83	0.72-0.95	1	0.86-1.16
Long (365+ days)	0.83	0.71-0.97	0.97	0.82-1.16
Never, Past or Current by Duration of Use				
Never user	1	ref	1	ref
Past-short (<90 days)	0.85	0.66-1.10	1.05	0.81-1.36
Past-medium (90-365)	0.84	0.71-0.99	1.08	0.91-1.29
Past-long (365+)	0.89	0.71-1.12	1.1	0.86-1.39
Current-short (<90 days)	0.86	0.65-1.15	0.72	0.54-0.96
Current-medium (90-365)	0.81	0.66-0.98	0.92	0.75-1.12
Current-long (365+)	0.79	0.65-0.96	0.93	0.76-1.15
Type by Duration of Use				
Never user	1	ref	1	ref
Combined Only-Short	0.95	0.76-1.19	0.95	0.76-1.19
Combined Only-Medium	0.86	0.74-1.00	1.06	0.90-1.25
Combined Only-Long	0.8	0.66-0.97	0.96	0.78-1.17
Progestin Only-Short	0.71	0.44-1.13	0.68	0.43-1.09
Progestin Only-Medium	0.67	0.46-0.98	0.77	0.52-1.38
Progestin Only-Long	0.72	0.44-1.17	0.84	0.67-1.13
Both-Short/Medium	0.76	0.59-0.98	0.87	0.79-1.36
Both-Long	0.92	0.72-1.19	1.04	1.01-1.04
Time Since Last Use (excluding current users n=564)				
Never	1	ref	1	ref
Short (<90 days)	1.14	0.92-1.40	1.24	1.0-1.54
Medium (90-265 days)	0.76	0.63-0.92	1	0.81-1.22
Long (365+ days)	0.77	0.63-0.94	0.87	0.70-1.09

Final model adjusted for: age, knee injury, NSAID use, deployment, pregnancy, race ethnicity, back/hip injury and new accession

Table 12. Exclusion and Dropout: Contraceptive Use and Osteoarthritis

	Excluded				Dropped			
	n	%		person years	n	%		person years
All women on active duty	**11,471**	**5.52**			**8,085**	**3.89**		
1 month in DMDC[1]	3,544	1.71	3544	295	.	.		.
Age ≥46	2,186	1.05	98764	8,230	3,145	1.51	104947	8,746
Missing covariates[2]	2,803	1.35	55212	4,601	.	.		.
Hysterectomy	684	0.33	39355	3,280	2,582	1.24	82281	6,857
Oophorectomy	446	0.21	25952	2,163	719	0.35	26955	2,246
Menopause	571	0.27	35467	2,956	1,375	0.66	50315	4,193
Hormonal replacement therapy	133	0.06	7648	637	192	0.09	9207	767
Amputation	14	0.01	928	77	72	0.03	2739	228
Implausible Pregnancy	80	0.04	7656	638	.	.	.	.
OA (before 2002)	1,010	0.49	56611	4,718	.	.	.	.
Final Cohort	196,306			706,978				
New accessions 2002-2011	**5,177**	**3.90**			**1,728**	**1.30**		
1 month in DMDC[1]	2,133	1.61	2133	178	.	.		.
Age ≥46	605	0.46	18810	1,568	442	0.33	11023	919
Missing covariates[2]	2,348	1.77	43489	3,624	.	.		.
Hysterectomy	17	0.01	751	63	538	0.41	12196	1,016
Oophorectomy	6	0.00	403	34	235	0.18	6302	525
Menopause	28	0.02	1156	96	391	0.29	11357	946
Hormonal replacement therapy	7	0.01	333	28	82	0.06	2878	240
Amputation	1	0.00	18	2	40	0.03	1367	114
Implausible Pregnancy	17	0.01	1424	119	.	.	.	.
OA (before 2002)	15	0.01	833	69	.	.	.	.
Final Cohort	127,620			381,716				

[1]there is no reference to identify if these women had any service prior to 2002

[2]missing age, education, marital status or race/ethnicity completely

Table 13. Distribution of Osteoarthritis

	n	%	n	%
	Study Cohort		New Accession	
Osteoarthritis	196,306		127,620	
No	192,363	97.99	127,620	100.00
Yes	3,943	2.01	1,382	1.08
Lower Leg	3,179	80.62	1,013	73.30
Localized-Primary	514	16.17	160	15.79
Localized-Secondary	46	1.45	23	2.27
Localized-Unspecified	541	17.02	194	19.15
Unspecified	2,078	65.37	636	62.78
Pelvic Region and Thigh	764	19.38	369	26.70
Localized-Primary	150	19.63	67	18.16
Localized-Secondary	9	1.18	3	0.81
Localized-Unspecified	107	14.01	66	17.89
Unspecified	498	65.18	233	63.14

Table 14. Correlates of Osteoarthritis (1 of 2)

	No OA		Incident OA	
	n	%	n	%
	192,363	98.24	3,943	2.01
New Accession				
No	66,125	34.38	2,561	64.95
Yes	126,238	65.62	1,382	35.05
	avg	SD	avg	SD
Age at entry(years)	23.27	5.85	29.43	6.87
Age at entry				
<20	62,678	32.58	377	9.56
20-24	72,379	37.63	763	19.35
25-29	28,986	15.07	736	18.67
30-34	15,121	7.86	1,028	26.07
35-39	8,785	4.57	764	19.38
40-45	4,414	2.29	275	6.97
Highest level of education attained				
≤High School Graduate	141,372	73.49	2,542	64.47
Some College/Certificate	21,532	11.19	481	12.20
College	23,436	12.18	654	16.59
Graduate Degree	6,023	3.13	266	6.75
Marital Status				
Single	126,870	65.95	1,632	41.39
Married	56,059	29.14	1,823	46.23
Divorced/Widowed/Separated	9,434	4.90	488	12.38
Race				
Caucasian	94,011	48.87	1,377	34.92
African American	62,155	32.31	2,006	50.87
Hispanic	21,974	11.42	299	7.58
American Indian	2,604	1.35	46	1.17
Asian	9,406	4.89	141	3.58
Other	2,213	1.15	74	1.88
Race				
African American	130,208	67.69	1,937	49.13
Other	62,155	32.31	2,006	50.87
Rank				
E1-E4 (Private - Specialist)	151,714	78.87	1,839	46.64
E5-E9 (Sergeant-Sergeant Major)	21,114	10.98	1,492	37.84
Warrant/O1-O3 (Second Luteienant- Capta	17,125	8.90	439	11.13
O4+ (Major-General)	2,410	1.25	173	4.39
	avg	SD	avg	SD
Length of service, years	1.62	3.86	5.66	6.27
Time in Cohort (years)				
None	126,238	65.62	1,382	35.05
<2 years	24,680	12.83	391	9.92
2 to <4 years	13,499	7.02	267	6.77
4 to <6 years	8,185	4.25	231	5.86
6 to <8 years	4,539	2.36	194	4.92
8 + years	15,222	7.91	1,478	37.48

p-value derived from chi-square , t-test. $p<0.05$ unless otherwise noted

Table 14. Correlates of Osteoarthritis (2 of 2)

	No OA		Incident OA	
	n	%	n	%
Pregnancy count				
None	162,904	84.69	2,696	68.37
1	23,254	12.09	845	21.43
2	5,227	2.72	325	8.24
3+	978	0.51	77	1.95
Parity				
Nulliparous	116,050	60.33	1,534	38.90
Parous	29,459	15.31	1,247	31.63
Unknown	46,854	24.36	1,162	29.47
Knee Injury				
Never	185,769	96.57	3,737	94.78
Ever	6,594	3.43	206	5.22
Knee Injury Count				
None	185,769	96.57	3,737	94.78
1	5,967	3.10	183	4.64
2	573	0.30	21	0.53
3+	54	0.03	2	0.05
Back/Hip Injury				
Never	171,233	89.02	2,984	75.68
Ever	21,130	10.98	959	24.32
Back/Hip Injury Count				
None	171,233	89.02	2,984	75.68
1	19,153	9.96	839	21.28
2	1,765	0.92	102	2.59
3+	212	0.11	18	0.46
Leg/Ankle Injury				
Never	183,018	95.14	3,540	89.78
Ever	9,345	4.86	403	10.22
Leg/Ankle Injury Count				
None	183,018	95.14	3,540	89.78
1	8,582	4.46	369	9.36
2	724	0.38	32	0.81
3+	39	0.02	2	0.05
	avg	SD	avg	SD
BMI at accession	23.77	3.09	24.43	3.38
BMI at accession, IOM categories				
Underweight BMI <18.5	5,103	2.65	34	0.86
Normal weight BMI 18.5-24.9	112,256	58.36	1,613	40.91
Overweight BMI 25.0-30	52,431	27.26	1,572	39.87
Obese BMI >30	5,176	2.69	310	7.86
Unknown	17,397	9.04	414	10.50
NSAID use				
Never	170,503	88.64	3,455	87.62
Ever	21,860	11.36	488	12.38

p-value derived from chi-square , t-test. $p<0.05$ unless otherwise noted

Table 15. Hazard Ratio of Osteoarthritis by Contraceptive Use (1 of 2)

			Unadjusted HR		Age Adjusted HR		Final HR	
Person years	OA Cases		681,562		681,562		681,562	
n	3,924		196,306		196,306		196,306	
Cases	n	%	3,924		3,924		3,924	
Use at Time of OA Diagnosis								
Nonuser	1,454	37.05	1	ref	1	ref	1	ref
User	2,470	62.95	1.07	0.99-1.14	1.07	1.00-1.15	0.81	0.76-0.87
Ever Use, Hormonal Contraceptives								
Never	1,454	37.05	1	ref	1	ref	1	ref
Past	1,365	34.79	1.07	0.99-1.15	1.07	0.99-1.16	0.8	0.74-0.87
Current	1,105	28.16	1.06	0.98-1.15	1.08	0.99-1.16	0.82	0.76-0.89
Homronal Contraceptive Method								
No use	2,819	71.84	1	ref	1	ref	1	ref
Pills, monthly	730	18.60	1.08	0.99-1.17	1.09	1.00-1.18	1	0.92-1.08
Pills, seasonal	17	0.43	0.76	0.47-1.22	0.77	0.48-1.24	0.67	0.41-1.08
Pills, progestin only	6	0.15	2.06	0.93-4.60	2.1	0.94-4.68	1.82	0.82-4.06
Patch	64	1.63	0.87	0.68-1.11	0.89	0.69-1.14	0.73	0.57-0.94
Ring	46	1.17	0.99	0.74-1.33	1.01	0.76-1.35	0.87	0.65-1.16
Injection	99	2.52	1.05	0.86-1.29	1.07	0.88-1.31	0.95	0.78-1.16
IUD	126	3.21	0.97	0.81-1.16	0,97	0.81-1.16	0.77	0.64-0.92
Implant	17	0.43	0.69	0.43-1.12	0.71	0.44-1.14	0.78	0.49-1.26
Type, Hormonal Contraceptive Use								
Nonuser	1,454	37.05	1	ref	1	ref	1	ref
Combined Method	1,592	40.57	1.06	0.99-1.14	1.07	1.0-1.15	0.85	0.79-0.92
Progestin Only	256	6.52	0.99	0.87-1.13	1	0,88-1.15	0.83	0.73-0.95
Both	622	15.85	1.11	1.01-1.22	1.12	1.02-1.23	0.7	0.63-0.77
Never, Past or Current Use by Type								
Never	1,454	37.05	1	ref	1	ref	1	ref
Past use combined hormonal contraception	867	22.09	1.07	0.98-1.16	1.07	0.98-1.16	0.82	0.75-0.89
Past use progestin only	140	3.57	1.03	0.86-1.22	1.04	0.87-1.23	0.85	0.71-1.01
Past use both methods	358	9.12	1.1	0.97-1.23	1.11	0.98-1.24	0.7	0.62-0.79
Current use combined hormonal contraception	725	18.48	1.06	0.97-1.16	1.08	0.98-1.18	0.88	0.80-96
Current use progestin only	116	2.96	0.95	0.89-1.15	0.96	0.80-1.16	0.81	0.67-0.98
Current user both	264	6.73	1.12	0.98-1.28	1.14	0.99-1.30	0.68	0.59-0.78

Final model adjusted for: age, knee, back/hip, leg/ankle injury, nsaid use, new accession, deployment, education, BMI, marital status, race, parity and rank

Table 15. Hazard Ratio of Osteoarthritis by Contraceptive Use (2 of 2)

			Unadjusted HR		Age Adjusted HR		Final HR	
Person years	OA Cases		681,562		681,562		681,562	
n	3,924		196,306		196,306		196,306	
Cases	n	%	3,924		3,924		3,924	
Duration								
Never	1,454	37.05	1	ref	1	ref	1	ref
Short (<90 days)	295	7.52	0.89	0.78-1.01	0.91	0.80-1.03	0.85	0.75-0.97
Medium (90-265 days)	929	23.67	0.94	0.86-1.02	0.95	0.88-1.03	0.81	0.75-0.89
Long (365+ days)	1,246	31.75	1.28	1.18-1.38	1.27	1.02-1.03	0.79	0.73-0.86
Never, Past or Current Use by Duration of Use								
Never user	1,454	37.05	1	ref	1	ref	1	ref
Past-short (<90 days)	201	5.12	1.02	0.88-1.19	1.05	0.9-1.21	0.97	0.83-1.12
Past-medium (90-365)	615	15.67	0.96	0.87-1.06	0.97	0.88-1.07	0.79	0.71-0.87
Past-long (365+)	549	13.99	1.3	1.18-1.44	1.28	1.16-1.42	0.76	0.68-0.84
Current-short (<90 days)	94	2.40	0.69	0.56-0.86	0.71	0.58-0.88	0.69	0.56-0.85
Current-medium (90-365)	314	8.00	0.9	0.80-1.02	0.92	0.82-1.04	0.88	0.78-0.99
Current-long (365+)	697	17.76	1.27	1.16-1.4	1.27	1.16-1.40	0.82	0.74-0.90
Type by Duration of use								
Never user	1,454	37.05	1	ref	1	ref	1	ref
Combined Only-Short	190	4.84	0.87	0.74-1.01	0.89	0.76-1.03	0.82	0.71-0.96
Combined Only-Medium	636	16.21	0.96	0.87-1.05	0.97	0.88-1.06	0.87	0.79-0.95
Combined Only-Long	766	19.52	1.28	1.17-1.39	1.26	1.15-1.38	0.83	0.76-0.92
Progestin Only-Short	54	1.38	0.85	0.65-1.11	0.87	0.66-1.14	0.86	0.65-1.13
Progestin Only-Medium	103	2.62	0.89	0.73-1.08	0.9	0.74-1.10	0.8	0.65-0.97
Progestin Only-Long	99	2.52	1.29	1.05-1.58	1.27	1.04-1.56	0.86	0.70-1.05
Both-Short/Medium	241	6.14	0.93	0.81-1.07	0.95	0.83-1.09	0.71	0.62-0.82
Both-Long	381	9.71	1.29	1.15-1.145	1.29	1.14-1.44	0.68	0.60-0.77
Time Since Last Use (excluding current users n=973)								
Never	1,454	37.05	1	ref	1	ref	1	ref
Short (<90 days)	245	6.24	0.98	0.86-1.12	1	0.87-1.14	0.75	0.66-0.86
Medium (90-265 days)	414	10.55	0.91	0.81-1.01	0.92	0.82-1.03	0.8	0.71-0.89
Long (365+ days)	706	17.99	1.25	1.14-1.37	1.23	1.12-1.35	0.75	0.68-0.83

Final model adjusted for: age, knee, back/hip, leg/ankle injury, nsaid use, new accession, deployment, education, BMI, marital status, race, parity and rank

Table 16. Hazard Ratio of Osteoarthritis by Contraceptive Use Among New Accessions (1 of 2)

			New Accession HR		New Accession HR (adjusted)	
Person years	OA Cases		368,736		368,736	
n	1,378		127,620		127,620	
Cases	n	%	1,378		1,378	
Use at Time of OA Diagnosis						
Nonuser	552	40.06	1	ref	1	ref
User	826	59.94	1.04	0.93-1.16	0.88	0.78-1.00
Ever Use, Hormonal Contraceptives						
Never	552	40.06	1	ref	1	ref
Past	435	31.57	1.01	0.89-1.14	0.87	0.7601.00
Current	391	28.37	1.08	0.95-1.23	0.9	0.78-1.03
Homronal Contraceptive Method						
No use	987	71.63	1	ref	1	ref
Pills, monthly	237	17.20	1.1	0.95-1.26	1.04	0.90-1.20
Pills, seasonal	9	0.65	1.33	0.69-2.57	1.03	0.53-1.99
Pills, progestin only	1	0.07	0.94	0.13-6.68	0.83	0.17-5.89
Patch	25	1.81	1.15	0.77-1.71	0.94	0.63-1.40
Ring	23	1.67	1.02	0.67-1.54	0.8	0.53-1.22
Injection	35	2.54	1.09	0.78-1.53	0.95	0.68-1.34
IUD	49	3.56	0.99	0.75-1.33	0.77	0.58-1.04
Implant	12	0.87	0.84	0.47-1.49	0.82	0.46-1.45
Type, Hormonal Contraceptive Use						
Nonuser	552	40.06	1	ref	1	ref
Combined Method	528	38.32	1.02	0.90-1.15	0.91	0.80-1.03
Progestin Only	98	7.11	1.04	0.84-1.29	0.9	0.72-1.12
Both	200	14.51	1.1	0.93-1.29	0.79	0.66-0.94
Never, Past or Current Use by Type						
Never	552	40.06	1	ref	1	ref
Past use combined hormonal contraception	282	20.46	0.99	0.86-1.15	0.89	0.76-1.04
Past use progestin only	46	3.34	1.01	0.75-1.37	0.91	0.67-1.23
Past use both methods	107	7.76	1.05	0.85-1.29	0.78	0.62-0.97
Current use combined hormonal contraception	246	17.85	1.05	0.91-1.23	0.93	0.80-1.09
Current use progestin only	52	3.77	1.06	0.80-1.41	0.88	0.66-1.17
Current user both	93	6.75	1.15	0.93-1.44	0.79	0.62-1.00

Final model adjusted for: age, knee, back/hip, leg/ankle injury, nsaid use, new accession, deployment, education, BMI, marital status, race, parity and rank

Table 16. Hazard Ratio of Osteoarthritis by Contraceptive Use Among New Accessions (2 of 2)

			New Accession HR		New Accession HR (adjusted)	
Person years	OA Cases		368,736		368,736	
n	1,378		127,620		127,620	
Cases	n	%	1,378		1,378	
Duration						
Never	552	40.06	1	ref	1	ref
Short (<90 days)	120	8.71	1.02	0.84-1.23	0.93	0.77-1.13
Medium (90-265 days)	376	27.29	1	0.88-1.14	0.9	0.78-1.03
Long (365+ days)	320	23.22	1.1	0.95-1.26	0.83	0.71-0.97
Never, Past or Current Use by Duration of Use						
Never user	552	40.06	1	ref	1	ref
Past-short (<90 days)	79	5.73	1.05	0.83-1.33	1.03	0.81-1.31
Past-medium (90-365)	230	16.69	0.97	0.83-1.12	0.86	0.72-1.02
Past-long (365+)	126	9.14	1.06	0.87-1.29	0.78	0.63-0.96
Current-short (<90 days)	51	3.70	0.97	0.73-1.29	0.82	0.61-1.09
Current-medium (90-365)	146	10.60	1.06	0.88-1.27	0.96	0.80-1.16
Current-long (365+)	194	14.08	1.12	0.95-1.33	0.86	0.72-1.03
Type by Duration of use						
Never user	552	40.06	1	ref	1	ref
Combined Only-Short	84	6.10	0.97	0.77-1.22	0.89	0.70-1.12
Combined Only-Medium	260	18.87	1.02	0.88-1.18	0.96	0.83-1.12
Combined Only-Long	184	13.35	1.05	0.88-1.24	0.84	0.70-1.01
Progestin Only-Short	24	1.74	1.05	0.70-1.58	0.94	0.62-1.42
Progestin Only-Medium	42	3.05	0.95	0.69-1.30	0.85	0.62-1.17
Progestin Only-Long	32	2.32	1.18	0.82-1.69	0.91	0.62-1.31
Both-Short/Medium	96	6.97	1.02	0.82-1.27	0.8	0.64-1.00
Both-Long	104	7.55	1.18	0.95-1.46	0.77	0.61-0.97
Time Since Last Use (excluding current users n=973)						
Never	552	55.93	1	ref	1	ref
Short (<90 days)	97	9.83	1.04	0.89-1.37	0.91	0.72-1.14
Medium (90-265 days)	149	15.10	0.88	0.74-1.06	0.84	0.69-1.02
Long (365+ days)	189	19.15	1.05	0.89-1.25	0.8	0.66-0.97

Final model adjusted for: age, knee, back/hip, leg/ankle injury, nsaid use, new accession, deployment, education, BMI, marital status, race, parity and rank

APPENDIX

ICD-9, PROCEDURE AND CPT CODES (1 OF 4)

	Amputation
879.7 ICD-9	Bilateral [any level], complicated
895.0 ICD-9	Amputation of toe, without mention of complication
895.1 ICD-9	Complicated amputation of toe
896.0 ICD-9	Unilateral foot, without mention of complication
896.1 ICD-9	Unilateral, complicated
896.2 ICD-9	Bilateral, without mention of complication Excludes:one foot and other leg (897.6-897.7)
896.3 ICD-9	Bilateral, complicated
897.0 ICD-9	Unilateral, below knee, without mention of complication
897.1 ICD-9	Unilateral, below knee, complicated
897.2 ICD-9	Unilateral, at or above knee, without mention of complication
897.3 ICD-9	Unilateral, at or above knee, complicated
897.4 ICD-9	Unilateral, level not specified, without mention of complication
897.5 ICD-9	Unilateral, level not specified, complicated
897.6 ICD-9	Bilateral [any level], without mention of complication
V49.0 ICD-9	Unspecified level
V49.71 ICD-9	Great toe
V49.72 ICD-9	Other toe(s)
V49.73 ICD-9	Foot
V49.74 ICD-9	Ankle Disarticulation of ankle
V49.75 ICD-9	Below knee
V49.76 ICD-9	Above knee Disarticulation of knee
V49.77 ICD-9	Hip Disarticulation of hip
01404 CPT	Amputation at Knee
27290 CPT	Amputation on the Pelvis and Hip Joint
27295 CPT	Upper Amputation Procedure on the Pelvis and Hip Joint
27880 CPT	Disarticulation of Knee
27881 CPT	Under Amputation Procedures on the Leg (Tibia and Fibula) and Ankle Joint
27882 CPT	Under Amputation Procedures on the Leg (Tibia and Fibula) and Ankle Joint
27888 CPT	Under Amputation Procedures on the Leg (Tibia and Fibula) and Ankle Joint
27889 CPT	Under Amputation Procedures on the Leg (Tibia and Fibula) and Ankle Joint
28800 CPT	Under Amputation Procedures on the Foot and Toes
28805 CPT	Under Amputation Procedures on the Foot and Toes
28810 CPT	Under Amputation Procedures on the Foot and Toes
28820 CPT	Under Amputation Procedures on the Foot and Toes
28825 CPT	Under Amputation Procedures on the Foot and Toes
84.10 Procedure	Lower limb amputation not otherwise specified
84.11 Procedure	Amputation of toe
84.12 Procedure	Amputation through foot
84.13 Procedure	Disarticulation of the ankle
84.14 Procedure	Amputation through malleoli of tibia and fibula
84.15 Procedure	Amputation below the knee
84.16 Procedure	Disarticulation of the knee
84.17 Procedure	Amputation above the knee
84.18 Procedure	Disarticulation of hip
84.19 Procedure	Abdominopelvic amputation
	Hormone Replacement Therarpy
V07.4 ICD-9	Hormone replacement therapy (postmenopausal)
V07.5 ICD-9	Prophylactic use of agents affecting estrogen recrptors and estrogen levels

ICD-9, PROCEDURE AND CPT CODES (2 OF 4)

	Hysterectomy
58150 CPT	Under Hysterectomy Procedures
58152 CPT	Under Hysterectomy Procedures
58180 CPT	Under Hysterectomy Procedures
58200 CPT	Under Hysterectomy Procedures
58210 CPT	Under Hysterectomy Procedures
58260 CPT	Under Hysterectomy Procedures
58262 CPT	Under Hysterectomy Procedures
58263 CPT	Under Hysterectomy Procedures
58267 CPT	Under Hysterectomy Procedures
58270 CPT	Under Hysterectomy Procedures
58275 CPT	Under Hysterectomy Procedures
58280 CPT	Under Hysterectomy Procedures
58285 CPT	Under Hysterectomy Procedures
68.31 Procedure	Laparoscopic supracervical hysterectomy [LSH]
68.39 Procedure	Other and unspecified subtotal abdominal hysterectom
68.4 Procedure	Total abdominal hysterectomy
68.51 Procedure	Vaginal hysterectomy
68.59 Procedure	Other and unspecified vaginal hysterectomy
68.7 Procedure	Radical vaginal hysterectomy
68.8 Procedure	Pelvic evisceration
68.6 Procedure	Radical abdominal hysterectomy
68.9 Procedure	Other and unspecified hysterectomy
	Menopause
627.1 ICD-9	Postmenopausal bleeding
627.2 ICD-9	Symptomatic menopausal or female climacteric states
627.3 ICD-9	Postmenopausal atrophic vaginitis
627.4 ICD-9	Symptomatic states associated with artificial menopause
627.8 ICD-9	Other specified menopausal and postmenopausal disorders
627.9 ICD-9	Unspecified menopausal and postmenopausal disorder
V49.81 ICD-9	Asymptomatic postmenopausal status (age-related) (natural)
	Oopherectomy
58720 CPT	Salpingo-oopherectomy, complete or partial, unilateral or bilaterl (separate procedure)
65.09 Procedure	Other oophorectomy
65.31 Procedure	Other unilateral oophorectomy
65.39 Procedure	Other unilateral oophorectomy
65.41 Procedure	Laparoscopic unilateral salpingo-oophorectomy
65.49 Procedure	Other unilateral salpingo-oophorectomy
65.51 Procedure	Other removal of both ovaries at same operative episode
65.52 Procedure	Other removal of remaining ovary
65.53 Procedure	Laparoscopic removal of both ovaries at same operative episode
65.54 Procedure	Laparoscopic removal of remaining ovary
65.61 Procedure	Other removal of both ovaries and tubes at same operative episode Excludes:that by laparoscope (65.63)
65.62 Procedure	Other removal of remaining ovary and tube Removal of solitary ovary and tube Excludes: that by laparoscope (65.64)
65.63 Procedure	Laparoscopic removal of both ovaries and tubes at same operative episode
65.64 Procedure	Laparoscopic removal of remaining ovary and tube

ICD-9, PROCEDURE AND CPT CODES (3 OF 4)

	Pregnacy
V22.0 ICD-9	Normal first pregnancy
V22.1 ICD-9	Normal other pregnancy
V22.2 ICD-9	Pregnancy state incidental
	Delivery
648 ICD-9	Other current condition in pregnancy (.0-.9)
650 ICD-9	Normal delivery
V24.0 ICD-9	Postpartum care and exam- immediately after delivery
V27.0 ICD-9	Outcome of delivery
73 Procedure	Procedures inducing or assiting delivery non-ectopic (includes .01, .09, .1, .21,.22, .3, .4, .51,.59 .6, .8, .91,.93,.94,.99)
74 Procedure	Cesarean section (includes .0, .1,.2,.3,.4,.91, .99)
	Postpartum Care
V24.2 ICD 9	Postpartum care and exam -routine postpartum follow up
	Pregnancy Loss
633 ICD-9	Ectopic Pregnancy (inclide .00, .01, .10,.11,.20, .21, .80,.81, .90,.91)
634 ICD-9	Spotaneous abortion (includes .0-.9)
637 ICD-9	Unspecified abortion (includes .0-.9)
69 Procedure	Theraputic abortion, spontaenous abortion or ectopic (includes .01, .02, .51, .52, .59)
	Knee Injury
717.0 ICD-9	Old bucket handle
717.1 ICD-9	Derange ant. horn medial meniscus
717.2 ICD-9	Derange post. horn medial meniscus
717.3 ICD-9	Derange unspec meniscus
717.40 ICD-9	Derange lateral meniscus unspecified
717.41 ICD-9	Derange lateral meniscus-bucket handle tear
717.42 ICD-9	Derange lateral meniscus- anterior horn
717.43 ICD-9	Derange lateral meniscus-posterior horn
717.49 ICD-9	Derange lateral meniscus-other
717.5 ICD-9	Derangement of meniscus, not elsewhere classified
717.5 ICD-9	Derange of meniscus
717.6 ICD-9	Loose body in knee
717.7 ICD-9	Chondromalacia of patella
717.81 ICD-9	Other internal derange of knee-old disruption LCL
717.82 ICD-9	Other internal derange of knee-old disruption MCL
717.84 ICD-9	Other internal derange of knee-old disruption PCL
717.85 ICD-9	Other internal derange of knee-old disruption other
717.89 ICD-9	Other internal derange of knee
717.9 ICD-9	Unspec internal derange of knee
719.46 ICD-9	Patellar Femoral Pain Syndrome "runners knee"
726.60 ICD-9	Enthesopathy of knee, unspecified
726.61 ICD-9	Pes anserinus tendinitis or bursitis
726.62 ICD-9	Tibial collateral ligament bursitis
726.63 ICD-9	Fibular collateral ligament bursitis
726.64 ICD-9	Patellar tendinitis
726.64 ICD-9	Patellar tendititis/tendinosis ‘jumpers knee’
726.65 ICD-9	Prepatellar bursitis
726.69 ICD-9	Other enthesopathy of knee
727.51 ICD-9	Synovial cyst of popliteal space
727.83 ICD-9	Plica syndrome
728.89 ICD-9	Other disorders of muscle, ligament, and fascia
733.92 ICD-9	Chondromalacia of knee excluded patella (717.7)
822.1 ICD-9	Fracture of patella-open
836 ICD-9	Dislocation of Knee (0,.1,.2,.3, .4)
836.5 ICD-9	Other dislocation of knee, closed (.00, .01, .02, .03, .04, .09)
844.0 ICD-9	Sprains and strains of knee and leg- Lateral collateral ligament of knee
844.1 ICD-9	Sprains and strains of knee and leg-medial collateral ligament of the
844.3 ICD-9	Sprain of superior tibulofibular joint/ligament
844.8 ICD-9	Sprains and strains of knee and leg-Other specified sites of knee and leg
844.9 ICD-9	Sprains and strains of knee and leg- Unspecified site of knee and leg
882.0 ICD-9	Fracture of patella-closed

ICD-9, PROCEDURE AND CPT CODES (4 OF 4)

	Back/Hip Injury
718.85 ICD-9	Acetabular labral tear
722.10 ICD-9	Displacement of thoracic or lumbar intervertebral disc without myelopathy-lumbar intervertebral disc without myelopathy
722.11 ICD-9	Displacement of thoracic or lumbar intervertebral disc without myelopathy-Thoracic intervertebral disc without myelopathy
724.2 ICD-9	Lumbago' includes low back pain, low back syndrome, lumbalgia
724.6 ICD-9	Disorders of sacrum- ankylosis and instability of lumbosacral and sacroiliac
733.96 ICD-9	Stress fracture femoral neck
733.97 ICD-9	Stress fracture shaft of femur
733.98 ICD-9	Stress fracture pelvis includes pubic ramus
756.11 ICD-9	Spondyloysis-lumbosacral region
846.0 ICD-9	Sprain and strain of sacroiliac region Lumbosacral (joint) (ligament)
846.1 ICD-9	Sprain and strain of sacroiliac region Sacroiliac ligament
846.2 ICD-9	Sprain and strain of sacroiliac region Sacrospinatus (ligament)
846.3 ICD-9	Sprain and strain of sacroiliac region Sacrotuberous (ligament)
846.8 ICD-9	Sprain and strain of sacroiliac region Other specified sites of sacroiliac region
846.9 ICD-9	Sprain and strain of sacroiliac region Unspecified site of sacroiliac region
	Leg/Ankle Injury
715.17 ICD-9	OA ankle and foot
715.27 ICD-9	OA ankle and foot
715.37 ICD-9	OA ankle and foot
715.97 ICD-9	OA ankle and foot
726.71 ICD-9	Achilles tendinitis or tendinosis, also includes bursitis
726.72 ICD-9	Tibialis tendinitis/tendinosis
728.71 ICD-9	Plantar fascititis fibromatosis- includes contracture and traumatic (
729.72 ICD-9	Nontraumatic compartment syndrome of lower extremity
733.93 ICD-9	Stress fracture tibia/fibula
733.94 ICD-9	Stress fratcure metatarsals
V49.74 ICD-9	Disarticulation of the ankle
	ACL Injury
717.83 ICD-9	Old disruption of anterior cruciate ligament
844.2 ICD-9	Sprains and strains of knee and leg-cruiciate ligament, acl injury
	Osteoarthritis
715.15 ICD-9	Osteoarthrosis, localized, primary-pelvic region and thigh
715.16 ICD-9	Osteoarthrosis, localized, primary-lower leg (not ankle)
715.25 ICD-9	Osteoarthrosis, localized, secondary-pelvic region and thigh
715.26 ICD-9	Osteoarthrosis, localized, secondary-lower leg (not ankle)
715.35 ICD-9	Osteoarthrosis, localized, not specified whether primary or secondary-pelvic region and thigh
715.36 ICD-9	Osteoarthrosis, localized, not specified whether primary or secondary-lower leg (not ankle)
715.95 ICD-9	Osteoarthrosis, unspecified whether generalized or localized-pelvic region and thigh
715.96 ICD-9	Osteoarthrosis, unspecified whether generalized or localized-lower leg (not ankle)

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