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THE EFFECTS OF ORAL CONTRACEPTIVE USE ON LIGAMENTOUS INJURY INCIDENCE IN FEMALES: A POTENTIAL FOR PREVENTION

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THE EFFECTS OF ORAL CONTRACEPTIVE USE ON LIGAMENTOUS INJURY INCIDENCE IN FEMALES: A POTENTIAL FOR PREVENTION

by

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Dedication

This work is dedicated to my wife, Melanie, for all the support she has shown since beginning graduate school and the continued support I will need to complete my medical training. It is also dedicated to my parents Mike and Cindy Gray for never stifling my curious mind and allowing me to freely pursue all my passions and whims. Without freedom and encouragement I may have never found my calling in medicine and science.

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Female athletes have higher incidence of anterior cruciate ligament (ACL) injury compared to males among sports requiring lower limb agility such as soccer and basketball. Often blamed on sex differences in biomechanics and neuromuscular control, current literature has failed to demonstrate specific mechanisms capable of explaining sex-related differences injury rates. Consequentially, techniques intended to prevent ACL injury in female athletes, primarily strength and conditioning programs, have yielded mixed results. Alternatively, sex hormone differences between the sexes, specifically serum estrogen levels, appears to be an underlying cause for differences in ACL injury rates. In relation to the menstrual cycle, female athletes sustain more ACL injuries than expected during the first 14 days of the cycle (follicular and ovulatory phases) and less injuries than expected during the last 14 days (luteal phase). Increased serum estrogen levels increase ACL laxity and potentially are to blame for an increased injury risk. Estrogen receptors located within human ACL fibroblasts, when activated, decrease collagen production, which leads to decreased ligament strength and increased laxity. Estrogen levels and knee joint laxity are greatest during the phases of the menstrual cycle in which ACL injury is over-represented. In theory, a reduction in serum estrogen levels should increase and stabilize ACL strength in females, potentially reducing injury risk. Hormonal contraceptives, through their negative feedback function, reduce estrogen levels. We hypothesize that females using oral contraceptives (OCs) will have lower rates of ACL injury compared to nonusers. To assess this relationship we performed a case-control study using national commercial insurance claims data. Cases were defined as females undergoing ACL reconstruction and OC use was determined from a 12 month history of OC prescription fulfillment previous to reconstruction or matched index date. We found that in females aged 15-19 years, the ages with the highest ACL injury incidence, OC users were 18% less likely to undergo ACL reconstruction than OC nonusers. This is the first evidence suggesting protection from injury among OC users and it creates a foundation for future prospective efforts. We conclude that OC use may help prevent ACL injury in specific female populations.

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List of Abbreviations

ACL	Anterior Cruciate Ligament
OC	Oral Contraceptive
NCAA	National Collegiate Athletic Association
NBA	National Basketball Association
NEISS	National Electronic Injury Surveillance System
CI	Confidence Interval
FSH	Follicle Stimulating Hormone
LH	Luteinizing Hormone
GnRH	Gonadotropin-Releasing Hormone
PCL	Posterior Cruciate Ligament
OR	Odds Ratio
SD	Standard Deviation
AP	Anterior-Posterior
IE	Inversion-Eversion

Chapter 1: Introduction

Female athletes experience higher rates of anterior cruciate ligament (ACL) injury than their male counterparts in pivoting sports with rates 1.75 to 2.4 times that of males in soccer.[1,2] Potentially accounting for this sex difference, females experience a disproportionality higher number of these injuries during the first 14 days of the menstrual cycle (follicular and ovulatory phases).[3] Estrogen receptors exist in ACL fibroblasts and their activation results in decreased fibroblast activity and increased joint laxity, which possibly pre-disposes the ligament to injury.[4-6] Estrogen levels are elevated throughout the menstrual cycle phases associated with an increased ACL injury risk. It has been hypothesized that the cyclic fluctuations of estrogen levels prevent female athletes from every fully adapting neuromuscular coordination to a stable ligament laxity, causing them to progress in and out of an injury-prone state as the menstrual cycle progresses.[3] Oral contraceptives (OCs) act on the menstrual cycle in such a way as to decrease and stabilize estrogen levels throughout the menstrual cycle. In theory, this should prevent an injury-prone state from occurring and decrease ACL injury risk in females. Currently, limited research exists in regards to the assessment of OC use and ACL injury risk.

ATHLETIC INJURY: A PERVASIVE PROBLEM AND ELUSIVE SOLUTION

In 2012, approximately 1.35 million children and adolescents ages 6-19 years in the United States presented to an emergency department with an athletic injury.[7] In relative terms, approximately 1 in every 34 youth athletes experienced an injury severe enough to warrant emergency intervention. That same year approximately 27.4 million individuals aged 6-17 years (54% of the entire age-matched United States population) participated in some form of sports, including casual participation.[8] Data gathered on athletic participation in high school confirms these numbers; during the 2010-2011 academic year approximately

55.5% of high school students in the United States participated in some form of organized athletic activity.[9]

Athletic participation has risen over the past three decades and is currently at an all-time high. Involvement in high school athletics has risen each year from 5.26 million in 1988-1989 to 7.71 million in 2012-2013, an increase of about 47%.[10] Females have comprised an increasing proportion of this number from 35% in 1988-1989 to 42% in 2012-2013. This rise in participation is not restricted to high school athletics, but can be seen among college programs as well. Participation in all divisions of championship sports within the National Collegiate Athletic Association (NCAA) has risen annually for all but two years from 275,309 during the 1990-1991 academic year to 463,202 during 2012-2013, an increase of approximately 68%.[11] The percentage of collegiate female athletes compared to all collegiate athletes has, similarly to that of high school athletes, increased from about 34% in 1990-91 to 43% in 2012-13. Assuming that the incidence of athletic injuries remains unchanged as participation numbers increase, more athletes are getting injured and the population at risk for athletic injury is now larger than it has ever been before.

The consequences of athletic injury commonly include rest from training, abstinence from competition, and focused rehabilitation. The magnitude of each of these, however, varies greatly with the severity of the injury. In fact, many studies set a threshold by defining a reportable injury as one that has resulted in missed games or practices. One such study of National Basketball Association (NBA) players revealed that, on average, 4.7 games were missed per injury.[12] Missing a few days of practice and competition due to a minor injury can affect peak performance and planning, however, severe injuries can lead to abstinence lasting weeks or months, drastically affecting an athlete's performance. Severe injury has been defined in one report as resulting in 10 or more days of activity time lost. In NCAA women's soccer, 22% of all in-game and 17% of all in-practice injuries resulted in 10 or more days of activity loss.[13] The most common injuries in that study were

internal derangement of the knee, ankle sprains, concussions, and upper-leg muscle strain. If severe enough, these injuries can end an athlete's season or career.

Injury to the ACL is among those severe injuries that can change the course of an athlete's career. In a study of Norwegian soccer players ages 15-38, 50.6% of those with an ACL injury did not return to play at any level.[1] Of those who did return, only about 62% were able to return to play at the same or higher level of competition previous to injury. The poorest return to play rates were seen in women under the age of 19 at 34% and men over the age of 34 at 22.9%. Hence, second chances are not guaranteed for athletes sustaining ACL injuries; therefore the only valid solution to this problem may be to prevent these injuries from happening.

KNEE AND CRUCIATE LIGAMENT INJURIES

Sports injuries to the knee are not only among the most serious in terms of missed days and return to sport, but they are also among the most common. Depending on the sport, knee injury accounts for 15% to 50% of all injuries.[14] A study of all injuries in NCAA championship leagues revealed that more than 50% of all sports injuries involved the lower extremity; the ankle and knee were the two most commonly injured structures.[15] Internal derangement of the knee was the leading cause of 10 or more days missed from training for 13 NCAA sports including both men and women's soccer and basketball.[13,16-28] In the NBA, 31.7% of all games missed over a 17-year period involved injury to the knee.[12] Among high schools, a study of seven popular sports revealed that injury to the knee was responsible for 49.4% of all sports injuries requiring surgery.[29] The most common of these injuries were ligament sprains to the knee accounting for 29% of all injuries requiring surgery. Athletic knee injury is such a problem that of 6.6 million knee injuries presenting to United State emergency departments for any cause over a 10 year period, 49.3% were the result of sports and recreation.[30] Protecting the knee and preventing even a fraction of

these injuries would have a great impact on athlete well-being, and substantially reduce total injury incidence across many sports.

The ACL attaches proximally to posterior distal femur and distally to the anterior intercondylar eminence of the proximal tibia. Its main purpose is to provide stability to the knee by limiting anterior translation and rotation of the tibia on the femur. Both contact and non-contact athletic injuries causing knee hyperextension or internal rotation can tear or rupture the ACL. Injury resulting from a direct blow to the knee due to player-to-player physical interactions are known as contact injuries.[31-33] Injuries resulting from poor biomechanics and movement are referred to as non-contact injuries.[34] Injuries resulting from player-to-player contact without a direct force to the knee are more appropriately labeled as non-contact with perturbation.[34] In collegiate soccer and basketball about 50% to 75% off all ACL injuries were non-contact in nature, whereas the rest were due to contact or had an unknown cause.[35] Non-contact injury mechanisms are much more common than contact injuries in most sports. The reverse can also be true as observed in American football where 53% of ACL injuries are the result of contact, with 40% occurring through non-contact means.[36] Contact injury is much more difficult to prevent as rule changes, rule enforcement, or a reduction in the intensity of play are necessary to make an impact.

It has been hypothesized that non-contact ACL injuries are readily preventable since movements resulting in injury can be modified, conditioned, eliminated, or reduced through training programs or individual self-regulation. Non-contact movements that are known to strain and potentially injure the ACL include hyperextension, deceleration with or without tibial medial rotation or femoral lateral rotation on a fixed tibia, and hyperflexion.[37] In lay terms, movements causing these outcomes include planting and cutting, straight-knee landing, one-step-stop landing with knee hyper-extended, pivoting, pivoting while decelerating, and pure deceleration.[38,39] Popular sports relying on these motions for effective play include soccer, basketball, American football, rugby, and volleyball.

Although sports-related knee injuries are quite common, ACL injury is actually quite rare. Among 15 NCAA sports ACL injury accounted for 2.6% off all injuries over a 15-year period.[15] This study cited percentages ranging from 0.7% (men's baseball and women's ice hockey) to 4.9% (women's basketball and gymnastics). Men's football had the highest total number of ACL injuries, but they comprised only 3% of all injuries. Sports with the highest incidence included men's spring football (0.33/1,000 athletic exposures), women's gymnastics (0.33/1000 000 athletic exposures), women's soccer (0.28/1000 000 athletic exposures), and women's basketball (0.23/1000 000 athletic exposures). Longitudinally, ACL injury rates remained wholly unchanged, ranging from 0.11 to 0.17 injuries per 1,000 AEs annually.

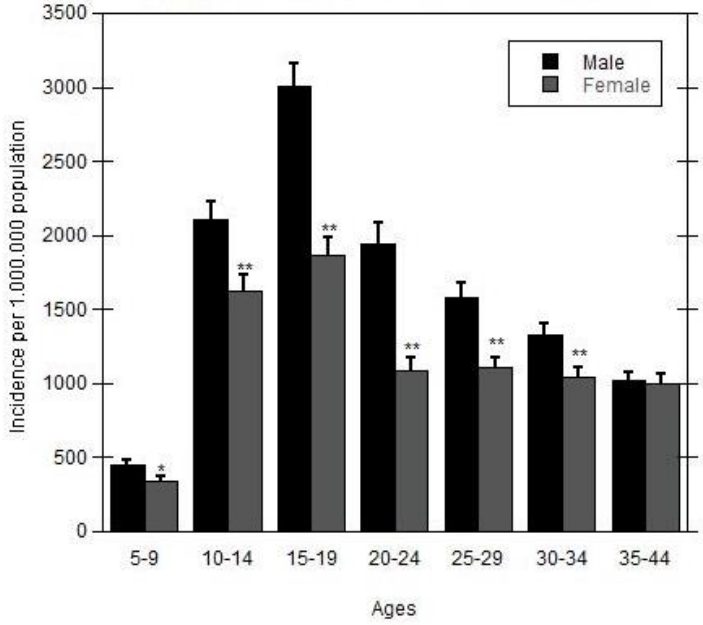
ACL injury can have far reaching impacts on an athlete's career. Return-to-play rates after ACL injury have been estimated to be as low as 49.4% in a study of soccer players.[1] An article on athletes receiving patellar tendon autograft ACL repair had return rates of 74% for school-aged and collegiate athletes and 69% for adult recreational athletes.[40] Re-injury rates over the next five years for that study ranged between 2% and 5%. In an earlier study, re-injury rates to the same knee were 4.3% within the first 5 years after reconstruction, and 5.3% in the contralateral knee.[41] The highest rates of 5-year re-injury were seen in athletes 18 years and younger, with a rate of 17.4%. Further, athletes undergoing reconstruction have been observed to have deficits in sensorimotor control, coordination, and posture in the effected limb.[42-44] These deficits appear to result in higher knee abductor and internal rotator moments and, thus, greater forces on the knee during high-speed maneuvers, increasing the risk for re-injury.[45] Even after an athlete is cleared to return to play after ACL reconstruction he or she faces the risk of re-injury and most likely will experience a decrease in athletic skill that may significantly impact the ability to compete at the same level as prior to reconstruction. Due to the severity of ACL injury outcomes it has become a primary focus for injury prevention research.

SEX DISCREPANCIES IN ANTERIOR CRUCIATE LIGAMENT INJURY

Typically, males have higher overall ACL injury rates, however, they are surpassed by their female counterparts in specific sports. According to a broad 8-year study of cruciate ligament injury in Sweden, males accounted for 60% of all injuries and the average age at injury was 27 years.[46] Studies of both New Zealand and Finish populations found similar results.[47,48] In the general sense, males tend to injure the ACL more often than females, however, in specific sports, that is those involving pivoting and stop motions such as soccer, basketball, volleyball, and gymnastics, females have much higher injury rates.[35,49-52] Soccer exemplifies this discrepancy by having some of the largest sex differences in injury rates.[2,15,35,53] Females are 1.75-2.4 times more likely to sustain an ACL injury in soccer than males with an event rate between 0.06 and 3.7 per 1000 hours of activity.[1,2] Most of these injuries are non-contact in nature, suggesting that a property inherent to the female sex predisposes to such higher injury incidence.[2,38]

In our own research, we have found that this sex-related injury discrepancy extends to knee strain and sprain. Using the National Electronic Injury Surveillance System (NEISS), information regarding all knee strain/sprain injuries from 2002-2012 presenting to United States emergency departments was extracted for ages 10-44 years.[54] These data were used to calculate national estimates of knee strain/sprain injuries. The 10-year injury estimates were then divided by the sum of 10 years of population estimates from the United States Census Bureau to obtain average national injury rates over the 10-year period.[55] **Figure 1.1** displays these injury rates by age and sex for all causes of knee strain/sprain injury (including non-athletic related injuries). The distribution, with an injury peak at ages 15-19, is similar to what has been reported for all cause ACL injury rates.[46] Consistent with the literature, males have higher absolute rates of knee strain/sprain injury for all age groups when cause is not considered.

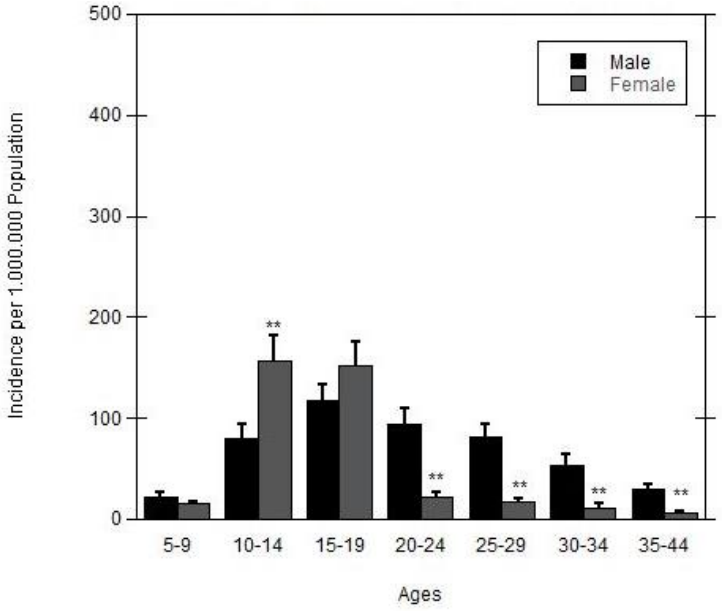
Figure 1.1: All Cause Knee Strains & Sprains Presenting to United States Emergency Departments Cumulative 2002-2012



Significant difference between sexes, *p<0.05, ** p<0.01

Sport specific knee strain/sprain data were also extracted and analyzed for 14 activities. Of those activities, females had higher rates of knee strain/sprain for at least one age group in soccer, gymnastics, and volleyball. Like previous studies concerned with ACL injury incidence, soccer demonstrated the most striking difference, which can be seen in **Figure 1.2**. Interestingly, females only had higher injury rates for the ages 15-24 years. It is difficult to determine why the sex difference disappears in ages below 14 and above 25, but it may be a consequence of participation numbers and athletic opportunities. Uniquely, this data yields national injury rates across many age groups using the same population, something not previously demonstrated in the literature.

Figure 1.2: Soccer Associated Knee Strains & Sprains Presenting to United States Emergency Departments Cumulative 2002-2012



Significant difference between sexes, *p<0.05, ** p<0.01

The difference in athletic ACL injury rates between sexes has been the focus of numerous studies. [2,15,35,49-53] Epidemiology reports have served to determine how far and wide this sex gap extends. Biomechanical investigations have sought to determine kinematic and kinetic differences in movement between the sexes in hopes of discovering an explanation. Prevention guidelines and interventions based whole or in-part on these reports have attempted to curb high injury rates in females. The common aim of these publications has been to determine a universal cause and provide a solution for elevated ACL injury rates in female athletes. Unfortunately, most fall very short of that goal.

BIOMECHANICAL CAUSATION AND INJURY PREVENTION SHORTCOMINGS

Researchers have sought to determine if sex differences exist in agility, player experience, neuromuscular control, and raw anatomy that predispose or protect one sex from non-contact ACL injury. Great focus has been placed on the common maneuvers, planting, cutting, pivoting, and deceleration, which are known ACL injury risks. Reports

investigating cutting maneuvers found equivocal differences between sexes in lower limb kinematics (e.g. knee angle, hip angle, etc.). Significant differences in neuromuscular activation, timing, and intensity were identified, namely increased quadriceps activity in females.[56-60] In another report, females had slightly lower knee flexor moments and greater knee abductor moments than males while cutting.[61] During the stop phase of cutting, thought to be the moment of highest risk for ACL injury, knee valgus angles and quadriceps activation peak in females, however, the reporting study lacked a male control.[62] Other reports also lacking a male comparison reported higher knee moments in fatigued athletes, even after 40 minutes of recovery, and in more highly skilled athletes.[63,64] Further analysis has determined that novice athletes had greater concentric co-contraction about the knee when performing novel maneuvers, which served to better protect the knee joint. This response had been lost in skilled athletes. Each of these investigations represents an advance in knowledge about the mechanisms involved in non-contact ACL injury regardless of sex, but the subtle differences found between sexes offer little explanation as to why females might be more at risk.

Biomechanics investigations, at present, have failed to demonstrate sex-specific injury causation. Contradictions are rife across studies, but most are in agreement that females have greater activation of the quadriceps and rectus femoris during injury-prone maneuvers. Over-activation of the quadriceps muscle does increase anterior motion and internal rotation of the tibia and both are motions that load the ACL potentially leading to injury.[65] It has also been demonstrated that maximal isometric contraction force of the quadriceps in females can exceed the tolerable range of the ACL.[60] Compounding these forces, females have a shorter moment arm over the patella compared to males.[66] This means that for proportional quadriceps forces between the sexes, females place more load on the ACL. This makes for a compelling argument that neuromuscular differences place females at a greater risk for non-contact ACL injury, but it has yet to be shown whether quadriceps contraction is sufficient to generate the forces required to rupture an ACL

during practical, real-world athletic maneuvers. In the absence of such evidence we can only speculate that increased quadriceps activation may contribute to an athlete's ACL injury risk, but to what extent remains unknown.

In regards to anatomy, females may have inherent predispositions to athletic ACL injury compared to their male counterparts. Among the most obvious differences, females have wider pelvises and larger Q-angles (quadriceps angle) than males.[67] It has been hypothesized that the observed increases in rectus femoris activation (quadriceps) is a result of the larger Q-angles in females and operates primarily to stabilize the hip during athletic maneuvers and secondarily may cause anterior tibial translation that strains the ACL.[58] This hypothesis was indirectly tested by looking at the prediction power of lateral trunk displacement or knee abduction angles on ACL injury in females.[68-70] Increased trunk motion or knee abduction angles should cause proprioceptive feedback requesting more stabilization of the hips, which may happen through quadriceps activation. Males sustaining ACL injury did not show as much lateral trunk motion or knee abduction as females, suggesting that this may be a sex-related mechanism of injury. Since lateral trunk placement highly predicts ACL injury in females, but not males, it may be that biomechanical testing before injury happens may be a solution to identifying those female athletes who are at greater risk for injury.[69] Identifying the subset of athletes at risk for injury may be an effective first step in developing successful prevention strategies.

Biomechanical studies laid the foundation for the development of injury prevention programs. Most of these programs are focused on neuromuscular training and conscious efforts to modify maneuver techniques. In a meta-analysis of 6 studies testing the effectiveness of neuromuscular training interventions at reducing ACL injury rates the incidence rate ratio was not significantly different than 1, meaning that prevention programs did not significantly reduce the rate of ACL injury in female athletes.[71] In another study, the same investigators calculated that 108-120 athletes would need to be enrolled in currently tested prevention programs to prevent a single ACL injury.[72] The authors admit

that this is a very large number needed to treat and that future research efforts should rather focus on identifying at-risk athletes. If prevention programs were only recommended for at-risk athletes, as opposed to all athletes, the number needed to treat could potentially be greatly reduced, and thereby, become more efficacious

However, contradicting meta-analyses also exist and they conclude that conditioning prevention programs effectively reduce ACL injury incidence among athletes. One such report indicates that prevention programs can reduce ACL injury by 62% (a pooled risk ratio of 0.38).[73] The number needed to treat to prevent a single ACL injury ranged from 5-187 for the individual studies included. Stratified by sex, the pooled risk ratio for females was 0.48 with a 95% confidence interval (CI) of 0.26-0.89 and for males was 0.15 with a 95% CI of 0.08-0.28. This suggests that conditioning as a prevention reduces injury in males at a much greater rate than in female athletes, appearing to have no specificity for the latter. Preventive conditioning may be a solution to decreasing non sex specific ACL injury event rates, but it seems that these programs cannot prevent ACL injuries attributed to the female sex. In another meta-analysis, investigators reported a reduction in ACL injury rates due to prevention programs with an overall odds ratio (OR) of 0.61.[74] However, not one of the included studies for the meta-analysis found significant risk reduction compared to no prevention intervention. The major shortcoming to these types of meta-analyses is the comparison and pooling of dissimilar approaches to injury prevention. Many differences in duration, components, and emphasis exist between each individual study. Even with positive results in a meta-analysis, we are left no closer in determining which protocols effectively reduce injury or whether simply being conscious about injury prevention is the real cause for injury reduction.

Prevention programs are not quite ready for prime time; their efficacy is not definitive, implementation and compliance strategies are difficult to construct, and gaining universal acceptance among all leagues could take years. This is not to say that training-based prevention programs are not valuable, but rather their value is currently vague at

best. Notably, blanket prevention programs relying on conditioning have been reported to be the most cost-effective solution when compared to no intervention and intervention for only athletes deemed as "high risk."[75] The difficulty in implementing these programs (i.e. local logistical support) and compliance was not included in these calculations and may well be the greatest barrier.[76] To increase the chance of success, any injury prevention strategy must be distilled down to its essential components required for proven effectiveness. The simpler and less time consuming a strategy is, the greater chance it has of being adopted as a universal guideline, policy, or common practice. It is these ideas that guide the search for more effective, female-specific prevention strategies.

THE MENSTRUAL CYCLE AND ANTERIOR CRUCIATE LIGAMENT INJURY

Among the basic differences between male and female physiology is the existence of a hormonal cycle in females known as the menstrual cycle. The menstrual cycle serves to prepare the uterus for the implantation of a fertilized egg resulting in pregnancy or, in the absence of fertilization, dispose of the egg and uterine lining so that preparation for another egg release and potential fertilization can subsequently occur. This process is controlled via interactions of sex hormones, mainly progesterone and estrogen, communicating through the endocrine system between the hypothalamus and ovaries. Changing levels of these hormones drive the cycle through all of its typical 28 day duration.

The 28 day menstrual cycle can be split into three phases. Days 1-9, known as the follicular phase, are marked by rising estrogen levels and very low progesterone levels. A spike in estrogen levels toward the end of this phase stimulates a large release of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Days 10-14 are when ovulation occurs. Days 15-28 are known as the luteal phase and are marked by high progesterone levels and reduced estrogen levels. If implantation doesn't occur by about 28 days,

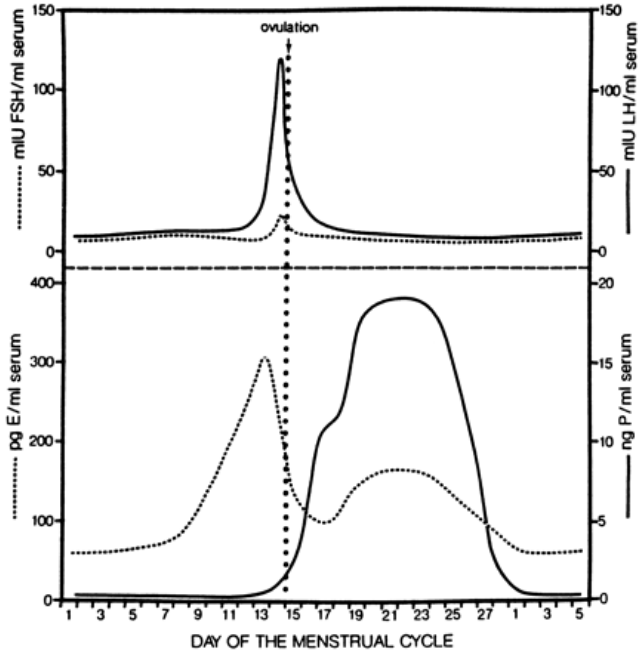
menstruation, or sloughing and disposal of the uterine wall, begins to start the cycle over again.[77] A depiction of hormone levels throughout the cycle can be seen in **Figure 1.3.**

The levels of these hormones are responsible for many physiological change in the body as well. Commonly recognized effects include changes in body temperature, skin hydration, and water retention.[78] In relation to neuromuscular coordination, it has been indirectly demonstrated that muscles have increased fatigability and a sluggish relaxation phase during ovulation.[79] Of particular interest, these hormones may also affect collagen synthesis and structure. Estrogen decreases collagen content in soft tissues.[6,80] Specifically, estrogen receptors have been localized to human ACLs and their activation negatively effects the tensile strength of these ligaments.[4,81,82] Relaxin, another steroid hormone produced during the follicular phase of the menstrual cycle, has been implicated to reduce collagen content in the pubic symphysis of animals.[82,83] Because the ACL is a soft-tissue structure comprised primarily of collagen, it is plausible that estrogen and the menstrual cycle could place females at risk for injury.

The first report exploring a link between menstrual cycle day or phase and ACL injury came from Wojtys et al. in 1998.[84] Over a 3 month period, 40 women presenting to a select group of hospitals having sustained an ACL injury were asked to complete a short questionnaire detailing the relationship of her ACL injury date and menstrual cycle history. From this information it was estimated on what day of the menstrual cycle the ACL injury occurred. These women were not necessarily athletes and, in fact, 11% had sustained injury due to non-athletic means. Split into three segments, follicular, ovulation, and luteal phases, a chi-square test was used to determine if the actual incidence of ACL injury for each phase was different from the expected amount. The results showed that significantly less ACL injuries, about half of what was expected by random chance, occurred during the follicular phase, more than expected, nearly double, occurred in the 5-day ovulation phase, and as many as predicted occurred during the luteal phase. It appeared that the menstrual cycle did indeed influence ACL injury patterns. This was enough evidence to spur researchers

into studying the phenomenon exclusively in athletic cohorts and utilize more sophisticated means to determine cycle day.

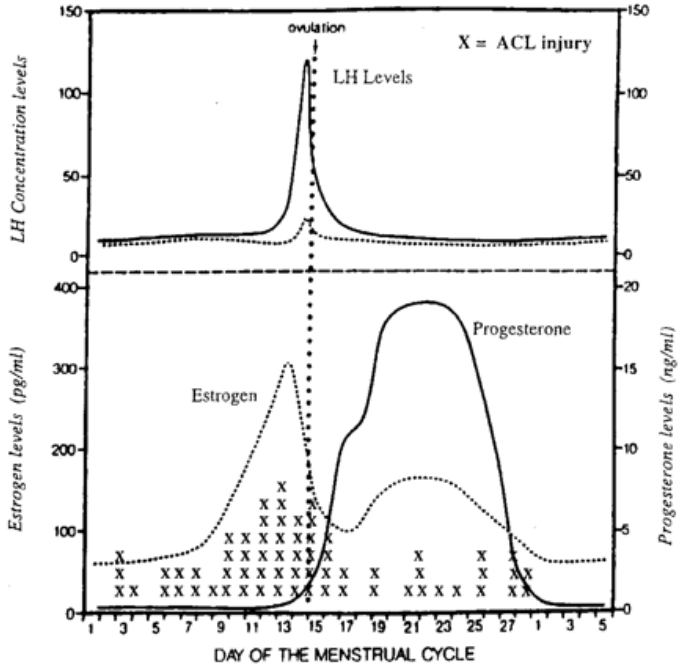
Figure 1.3: Hormone Levels throughout the Menstrual Cycle



Top: Levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Bottom: Levels of estrogen (E) and progesterone (P). Used with permission.[85]

As more sophisticated research was conducted, it came to light that the window for increased injury risk may be larger than just the simplified 5-day ovulation phase window. In 2002, Wojtys et al. repeated the experiment in a prospective setting using a cohort of recreational skiers and urine samples to more accurately determine cycle day.[86] The results, graphically depicted in **Figure 1.4,** demonstrated the significant increase in ACL injuries during ovulation (days 10-14) and even a possible increase injury rates for a few days before and after.

Figure 1.4: ACL Injury Incidence by Menstrual Cycle Day



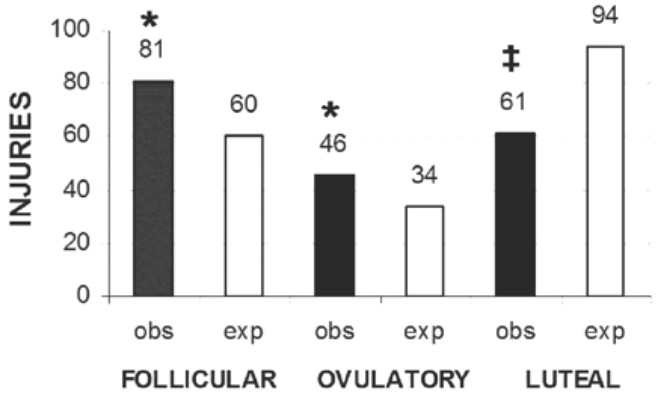
Each "X" along the bottom axis represents a single ACL injury. Used with permission.[86]

Over a 10-year period, 6 different studies were performed to define how ACL injury incidence changes throughout the menstrual cycle in females not taking oral contraceptives. This information was compiled in a systematic review in 2007.[3] Combining the data from the studies solidified the menstrual cycle and ACL injury link and provided very powerful evidence that most ACL injuries in females were occurring during the follicular and ovulatory phases of the cycle, at rates 35% greater than expected for both phases. The combined numbers from all 6 studies can be seen in **Figure 1.5.**

While the timing of increased injury incidence and menstrual cycle day was being elucidated, other researchers focused their efforts on determining how ACL tissue physiologically responds to hormonal changes, specifically in estrogen, throughout the cycle. An animal model was able to demonstrate that the absolute strength of the ACL can be affected by the presence of estrogen.[6] In the experiment, rabbits were ovariectomized and split into control and estrogen supplementation groups for 30 days. ACL rupture in

estrogen the supplementation group occurred at lesser loads than in the controls. In humans, knee joint laxity was assessed in females versus males daily throughout a complete menstrual cycle using a knee arthrometer.[87] Results concluded that anterior knee laxity coincided significantly with elevations in estrogen. Specifically, females had greater knee laxity than males toward the end of menses, near ovulation, and during the early luteal phase. In a related study, hormone levels were determined by blood draw to strengthen this correlation. A graphic depiction from that study of serum hormone levels and knee laxity (KD-134, knee deflection with the knee flexed at a 134° angle) in a single volunteer can be seen in **Figure 1.6**.[5] This study concluded that 63% of the variation in knee laxity throughout the cycle can be attributed to fluctuating hormone levels. Estrogen, specifically, causes joint laxity effects approximately 3 days after a rise in hormone levels, explaining why ACL injury risk increases during ovulation, about 3 days after estrogen levels have risen in females.

Figure 1.5: Expected and Observed Numbers of ACL Injury by Menstrual Cycle Phase

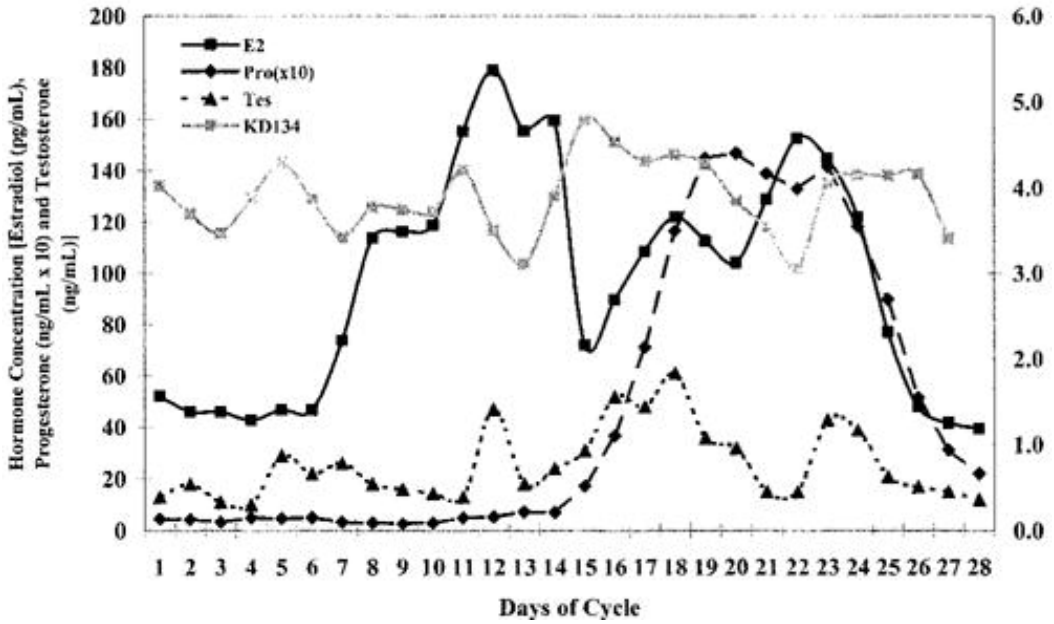


*Significant increase from expected number of ACL injuries. ‡Significant decrease from expected number of ACL injuries. Used with permission.[3]

Many more studies observed this phenomenon of knee joint laxity variance coincident with the menstrual cycle and in 2006 Zazulak et al. brought them together in a systematic review.[88] The conclusion was that knee joint laxity was the greatest during

ovulation (days 10-14), followed by the luteal phase (days 15-28), and laxity was least during the follicular phase (days 1-9). This coincides fairly well with the research concerning ACL risk that also found the greatest increase over the expected number of injuries during the ovulation phase. Hewett et al. has depicted both peak ACL injury incidence and knee joint laxity on a single graphic of the menstrual cycle in **Figure 1.7**.[3] The continuums of ACL injury and peak knee joint laxity created by these studies overlaps exactly at the ovulation phase of the cycle. ACL injury in females is not random, but rather heavily influenced by biology. Rising estrogen levels throughout the follicular phase eventually cause increased knee laxity throughout the ovulation phase and an increased risk for ACL injury.

Figure 1.6: Hormone Levels and Knee Laxity through the Menstrual Cycle in a Single Volunteer

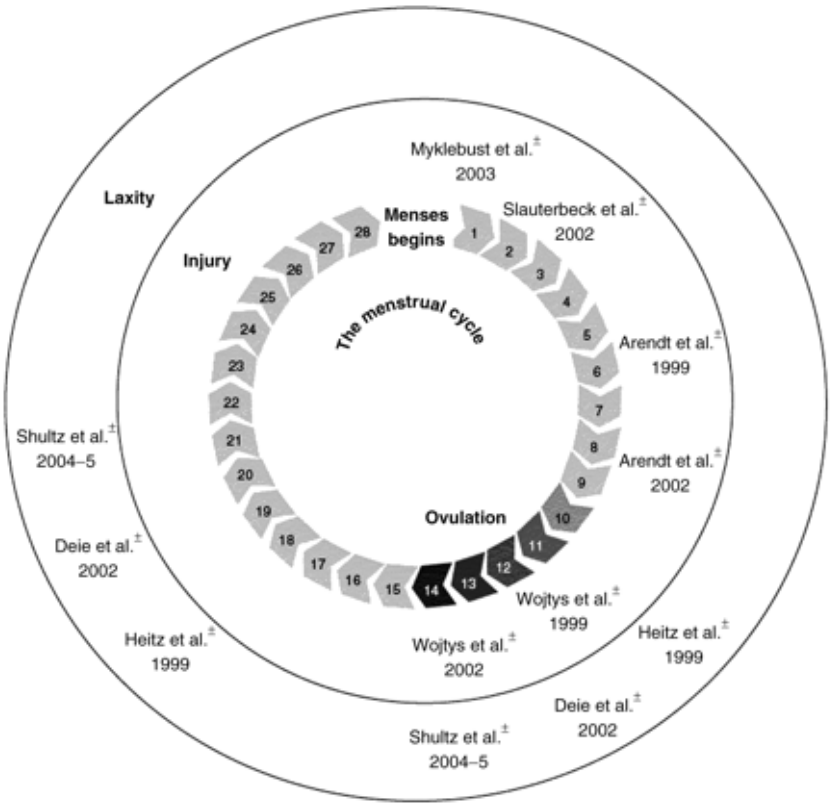


E2 – estrogen, Pro – Progesterone, Tes – Testosterone, KD134 – knee deflection at 134°. Used with permission.[5]

The evidence is very incriminating that high estrogen levels are to blame for an increased propensity to ACL injury in women. It follow that an effective means of reducing estrogen levels in females may also reduce a fraction of the ACL injuries they sustain.

Hormonal contraception is effective in reducing estrogen levels throughout the menstrual cycle, but it's effectiveness in reducing ACL injury incidence had yet to be properly scrutinized.

Figure 1.7: Temporal Relationship between the Menstrual Cycle, ACL Injury, and Knee Laxity



Inner Ring: The Menstrual cycle. Days 1-9 – follicular phase, days 10-14 – ovulation, days 16-28 – luteal phase. Middle Ring: Peak ACL injury incidence as reported by individual studies. Outer Ring: Peak knee laxity as reported by individual studies. Used with permission.[3]

ORAL CONTRACEPTIVES: A PILL WITH THE POTENTIAL FOR INJURY PREVENTION

The menstrual cycle is controlled by a complex interweave of hormones, signaling, and feedback culminating in ovulation and the preparation of the uterus to receive a newly fertilized egg. Hormonal contraception mechanistically disrupts this signaling cascade to prevent ovulation from occurring, resulting in contraception. In a normal cycle (**Figure**

1.3) increased levels of FSH promote follicular development (days 1-10). As the follicle matures it produces estrogen, which below a signaling threshold suppresses the release of LH from the anterior pituitary (days 1-10). Near follicle maturity, estrogen levels rise dramatically and surpass that threshold causing a surge of LH to be released (days 8-13). This LH surge causes the follicle to rupture, releasing the ovum into the fallopian tube for fertilization (days 10-14). After rupture, the follicle transforms into the corpus luteum and begins producing progesterone (days 14-28). Progesterone inhibits the release of FSH and LH and mildly stimulates estrogen production in the adrenal glands. If fertilization does not occur after about 14 days from ovulation, the corpus luteum atrophies, progesterone levels drop, and menstruation begins, starting a new cycle on day 1.

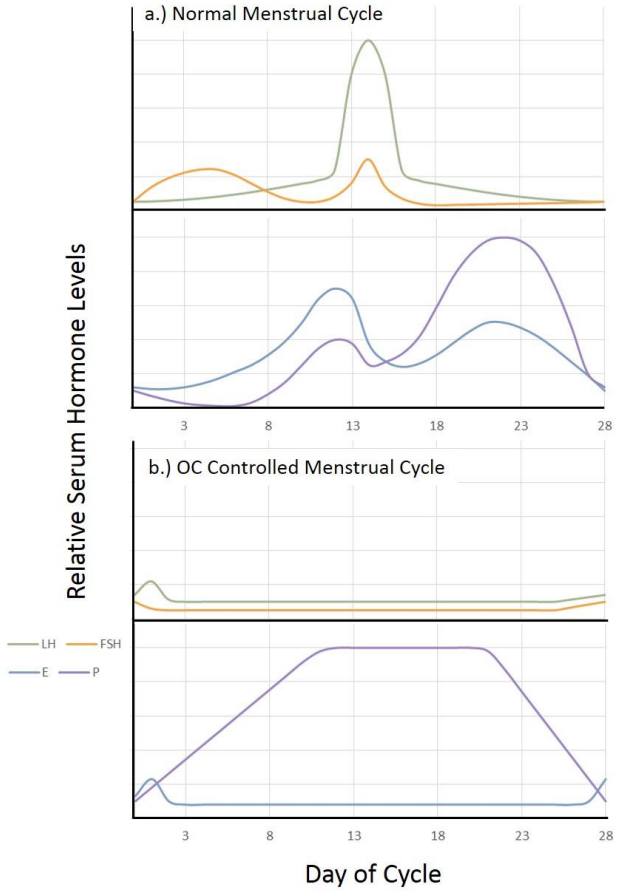
Hormonal contraception takes advantage of this complex hormonal interplay to prevent follicle development, rupture, and ovulation. Hormonal contraceptives all contain a progesterone analog. This exogenous progesterone molecule decreases the pulse of gonadotropin-releasing hormone (GnRH) through negative feedback. A decreased GnRH pulse decreases FSH release. Decreased FSH release fails to stimulate a follicle. Without follicular development, estrogen levels remain depressed and fail to rise and signal the release of LH and the subsequent spike that induces ovulation. Without ovulation, pregnancy cannot occur. A depiction of hormone levels in a normal cycle (A) and in a cycle controlled by a progesterone only hormonal contraceptive (B) can be seen it **Figure 1.8**. The net effect of hormonal contraception on hormones throughout the menstrual cycle is an elevated and sustained serum progesterone level and a decreased, stable serum estrogen level.

Combination hormonal contraceptives, containing both progesterone and estrogen, are also available. The addition of estrogen is intended to better control the cycle and reduce the side effects of progesterone only contraception. The added estrogen keeps serum levels at a much lower level than physiologic levels seen in a normal cycle. Combination pills come in two main varieties, monophasic and triphasic. Monophasic pills have the same

level of hormones throughout 21 days of the cycle and 7 days of placebo to induce menstruation. Triphasic pills have a stepwise increase in progesterone or both progesterone and estrogen each 7 days for 21 days followed by 7 days of placebo to induce menstruation. Though it was believed that triphasic preparations may lead to better cycle control, there is currently no evidence supporting this proclamation.[89]

In theory, if estrogen increases ACL laxity and the risk of AVL injury and hormonal contraception reduces overall estrogen levels throughout the menstrual cycle, then the use of hormonal contraceptives may reduce the risk of ACL rupture in females. As early as 1991, researchers observed supposed benefits of OC use in female athletes. A review at the time claimed that female soccer players using OCs had fewer traumatic sports injuries than nonusers and OCs eliminated a premenstrual fall in physical fitness observed during the normal menstrual cycle.[90] Soccer players were also shown to be prone to athletic injury during the premenstrual and menstrual phases and that females exhibiting no pre-menstrual syndromes, implying they had lower levels of circulating hormones, didn't experience this proneness.[90] Further, athletes on OCs anecdotally reported that they felt more "stable" while participating in athletics.[91] Complimentary to these benefits, many studies have demonstrated that OCs do not negatively affect athletic performance.[92-95] More recent studies have found that most of the benefits of OCs in athletes are thought to be more personal in nature, such as predictable cycles, reduced pre-menstrual symptoms, and lighter or reduced number of periods.[96,97] In regards to injury reduction, OCs may improve bone density leading to fewer stress fractures.[97] In the prevention of soft tissue injury, the issue is a bit more unclear.

Figure 1.8: Hormone Levels throughout a Normal Menstrual Cycle (a) and One Being Controlled by Hormonal Contraceptives (b)



Relative levels of follicle stimulating hormone (FSH) luteinizing hormone (LH), estrogen (E), and progesterone (P) in a normal cycle (a) and a cycle under the control of hormonal contraceptives (b). Adapted from figure published by Scientopia.org.[98]

To date there are only two articles assessing the ACL injury reduction potential of OCs. Agel et al. retrospectively studied female NCAA soccer and basketball players to assess for a link between oral contraceptive use and ACL injury and ankle sprains.[99] The study found no difference in any injury rates between those using and not using OCs at the time of injury. However, the study did suffer from a few weaknesses. First, the study used retrospective injury data paired with later, prospectively collected OC use data. This recall data did not produce the same results on injury periodicity with the menstrual cycle that the original data demonstrated. Second, the study was grossly underpowered to detect any meaningful effect size. Even with the inclusion of ankle injuries as an outcome (to increase

the size of the dataset), "the final power for [the] sample combining both ACL and ankle injuries is 0.06. This data allows for a detection of five times or greater difference in injury rates between the "on hormonal therapy" and "off hormonal therapy" groups."[99] Female soccer and basketball players are only about twice as likely to have an ACL injury as males. At the most, OCs can reasonably be expected to reduce injury by half, not five-fold. Inadequate recall and power prevent this study from providing a definitive answer as to whether OCs can reduce ACL injury rates in female athletes.

In 2009, Reudl et al. recruited 93 female recreational skiers sustaining non-contact ACL injuries.[100] These volunteers were then age matched to 93 uninjured controls solicited at a local ski resort. All were questioned on cycle regularity and OC use. Results showed that there was no difference in OC use between the two groups, implying that OCs had no protective effect against ACL injury. There are, however, a few shortcomings of the study and they include a cohort of advanced age and one-to-one matching based on voluntary response. The average age of those injured in this study was 38 and hormone levels may begin dropping in women at this age. Menopause typically begins between ages 45 and 55, but can occur as early as the late 30s and early 40s. As a result, OCs may not have as much of an effect in this older population compared to a population of young adults. Further, ACL injury rates are highest in younger populations, typically under the age of 25. With an average age of 38, this study does not focus on the most commonly injured demographic and is therefore difficult to interpret when trying to apply the results to common injury mechanisms and patterns. Lastly, the study matching protocol was not robust. Each case of ACL injury was matched to a single control, rather than a set of controls which would better estimate the population OC use rate. The controls were also solicited at a ski resort to participate and were then matched on age to cases. Although the controls were randomly selected to participate in the study, they had the option to not participate, introducing an unknown magnitude of selection bias.

There is significant biological plausibility that OC use should positively affect ACL strength and decrease injury risk in female athletes, but no study has been robust enough to confirm or disprove such a mitigating effect. A gold standard study design to answer such a question would involve prospectively following an athletic cohort over multiple seasons and recording OC use to accrue enough injuries to detect a clinically meaningful difference. The logistics of such a study are difficult and the required time and effort for possibly attaining negative results may not exceed the pros of discovering a protective effect. A large retrospective study using administrative claims data offers a relatively time-efficient and inexpensive way to examine this research question. If such a study were to find a protective effect of OC use it would provide strong justification for pursuing a prospective investigation.

CLOSING REMARKS

In the present era of athletic research, injury prevention holds promise to reduce the risk for sports injury, thereby preserving an athlete's quality of life and reducing the public health costs consumed by these injuries. Only through controlled research can we determine whether effective prevention will come from athletic regulations, focused conditioning, or a widely available pharmacotherapy.

In this study of one of the nation's largest commercial insurance databases we aim to determine whether OC use reduces the risk of ACL injury. We believe this investigation will make an important contribution to the ongoing discussion regarding optimal forms of injury prevention among female athletes.

Chapter 2: Purpose

STUDY AIMS AND HYPOTHESES

The primary objective of this study is to evaluate the relationship between OC use and subsequent ACL injury, defined by ACL reconstruction, in a female population. Secondary to this, risk status, OC type, exposure time, other medication exposure, and comorbidities will be evaluated for their effects on ACL reconstruction. Subsequently, similar relationships will be tested for with the outcomes of ligamentous ankle injury and superficial shoulder injury. These objectives can be summarized in three specific aims.

Specific Aim 1: To evaluate OC use as a protective measure against ACL injury in females ages 15 to 39 years.

This aim will be evaluated through use of a case-control study defining the outcome as receiving an ACL repair surgery and the exposure as use or non-use of OCs. The outcome of ACL reconstruction was used, as opposed to ACL injury diagnosis, because diagnoses may be unconfirmed and have the potential to be coded vaguely in the medical record. In order to guarantee that our cases in this study have sustained a cruciate ligament injury we only looked at those women that have received a repair surgery. Another advantage to this outcome definition is the focus on severe ACL injury and cases that intend to be mobile after the injury insult. The relationship between these repairs and OC use will be evaluated through the use of logistic regression to obtain unadjusted and multivariate adjusted odds ratios.

Hypothesis: Females undergoing repair surgery for an ACL injury are less likely to have used OCs than females not undergoing ACL reconstruction in the 12 months previous to repair or index date.

Specific Aim 2: To assess how risk status, OC type, exposure time, other medication exposure, and comorbidity differ between cases (ACL reconstruction) and controls (no ACL reconstruction). It will be further determined, through multivariate logistic regression, whether these variables influence the relationship between OC use and ACL repair.

Risk Status

This variable will act as a surrogate for athletic participation/exposure. High risk cases will be defined as those individuals who have sustained another sport-related injury in the previous 12 months from ACL repair. Low-risk cases are those without such past injury.

Hypothesis: Cases have a greater odds of being labeled as high risk than controls.

OC Type

OCs are available in many formulations. The two major categories of OCs include progesterone only pills and pills combining progesterone and estrogen. Combination pills also come in two varieties, monophasic and multiphasic (triphasic) types. Monophasic OCs contain the same amount of hormones throughout each course (usually 28 days), whereas multiphasic contain increasing amounts of progesterone, and sometimes estrogen, throughout each pill course. OC formulation and dosage affects the serum level of hormones in the body throughout the cycle.

Hypothesis: The risk for ACL reconstruction will be comparable across OC formulation.

Therapeutic Exposure Time

Serum hormone levels may spike and fall during the initiation of supplements intended to regulate the hormonal cycle. Adaptation to OC use eventually occurs and serum hormone levels become predictable. This adaptation period varies and may affect serum estrogen levels differently than a long term OC user.

Hypothesis: ACL reconstruction rates vary based on the duration of OC use with long-term use associated with lower CL injury rates and short-term use associated with higher rates.

Relevant Comorbidities

There is evidence that certain diseases may affect the menstrual cycle. Of our interest are diabetes and asthma. Patients with type 1 diabetes mellitus are more likely to experience long cycles, long menstruation, and heavy menstruation.[101] This suggest a change in serum progesterone and or estrogen levels may occur in women with type 1 diabetes mellitus compared to those without. Asthma sufferers are more likely to have irregular periods than non-sufferers.[102] The extent to how asthma affects serum hormone levels is unknown. Our logistic model was adjusted specifically for the presence of these disease states. Additionally, the Elixhauser Comorbidity Index score was also utilized in model adjustment.

Medication Use

Certain medications have been shown to affect general ligament strength. These medications include injectable corticosteroids and quinolone antibiotics. Corticosteroids have been shown to weaken tendons, making them prone to rupture.[103-105] Quinolone

antibiotics have also been shown to increase the risk of ligament rupture.[106,107] Use of these medications in the 12 months prior to reconstruction/index date was included as a covariate in our logistic model. We also included model adjustment for the use of inhaled or oral corticosteroids. Though there is no evidence that the use of these forms of steroids causes a decrease in ligament strength, it is biologically possible that they do. Oral corticosteroids may also be prescribed to reduce pain and inflammation in cases of ligamentous or tendinous injury. This pain reduction may allow an active individual to return to athletics and further injure the weakened structure.

Hypothesis: The use of either of these medications does not significantly affect the influence of OC use on ACL repair surgery.

Specific Aim 3: To determine if the relationship between ACL reconstruction and OC use extends to other ligamentous injuries, specifically ankle sprains. Further, to provide evidence that this relationship is exclusive to ligamentous injury by testing for an association between OC use and superficial injury of the shoulder.

Estrogen receptors are assumed to exist in all ligament fibroblasts throughout the body. In such a case, the presence of estrogen may also affect the strength of these ligaments. If OCs are associated with fewer ankle sprains, it may be that all ligamentous injury is affected by the menstrual cycle and can be prevented by the use of OCs. In order to show that any ACL reconstruction and OC use relationship does not extend to all injuries, OC use will be used to predict the outcome of a superficial shoulder injury.

Hypothesis: Relationships for ligamentous ankle injury and OC use are similar to that of ACL reconstruction and OC use. Further, there is no significant relationship between OC use and superficial injury of the upper extremity.

STUDY SIGNIFICANCE

We hypothesize that OC use can help prevent ligamentous knee injury. Past studies aimed at assessing OC use and non-use as an injury mediator were not able to capture large enough numbers of those injured to draw clinically meaningful conclusions. These studies were under-powered for the detection of a reasonable effect size in ACL injury reduction. ACL injury as an outcome is rather rare, and a focused approach using specific athletic cohorts cannot provide the numbers necessary in any practical terms without a lengthy study. The present case-control study utilizes insurance claims data from Clinformatics Data Mart and has a high degree of statistical power to ensure that even very small effect sizes are captured. This advantage makes the present study unique in being able to identify the plausible relationship between OC use and ACL injury. Using this large dataset, we hypothesize that females undergoing ACL repair surgery will have a lower rate of OC use than control matched females who have not experience ACL repair. We further hypothesize that ligamentous ankle injury will also be associated with lower OC use rates.

The implications of proving such a hypothesis are quite broad. Primarily, such results would validate the results of numerous studies that have found a correlation between ACL injury rates and the hormonal periodicity of the menstrual cycle. If increased serum estrogen levels really are to blame for a subset of ACL injuries in female athletes, then the inverse should also be proven true. This involves observing a decrease in ACL injuries when estrogen levels are dropped. Fortunately, OCs elicit this response to varying degrees and provide the impetus for further investigation. Moreover, this research has the potential to validate anecdotal accounts of decreased traumatic injury rates and increased neuromuscular coordination and stability in female athletes taking OCs. Current literature has not adequately proven or disproven an injury preventive effect of OC use. The goal of this study is to comprehensively produce evidence on the matter that, if in line with our

hypothesis, may reignite interest and discussion on the topic leading to the development of prospective, controlled studies with a greater level of evidence.

A significant public health impact of the findings in the present study is the recommendation of the use of OCs as a potential injury prevention for female athletes. In addition to contraception, OCs are currently used as a primary treatments for acne, menstrual cycle irregularity, menorrhagia, anovulatory cycles, endometriosis, dysmenorrhea, premenstrual syndrome, and menstrual migraines. OC use is also associated with a decreased cancer risk.[108] Per this study, ligamentous injury prevention may become part of the conversation about the initiation of OC use in female athletes. Complimentary to this, more at risk athletes, and those not taking OCs, may benefit from focused strength and conditioning programs aimed at preventing ligamentous injury, specifically knee injuries. Knowing an athlete's risk status for ligamentous injury is the first step in developing proper prevention protocol and provides the scale by which to measure success. Additionally, increased ACL strength due to OC use may potentiate neuromuscular control and conditioning programs to enhance injury prevention. Training with controlled knee laxity could assist in the development of a consistent, protective neuromuscular coordination.

Traditional injury prevention incorporates conditioning (release to play by physical assessment), safety equipment, and governing rules that work in unison to create a safe atmosphere and develop healthy athletes. To our knowledge, pharmacologic intervention has never been considered as an injury prevention method. So long as the use of a drug does not cause harm to athlete, pharmacotherapy could be an important alternative or complementary approach to injury prevention.

Chapter 3: Methods

Our primary research aim was to determine if OC use in females confers a protective effect from ACL injuries. To accomplish this we have conducted a case-control study using commercial insurance claims data from Clinformatics Data Mart. Cases were defined as females aged 15-39 years that have undergone any ACL repair surgery. Controls were matched to cases at a 3:1 ratio by age, region, and date of repair surgery (index date). Logistic regression was used to obtain both adjusted and unadjusted odds ratios, as well as their 95% confidence intervals, for the use of oral contraceptives in the 12 months previous to surgery or index date. This procedure was also used with two additional case definitions, ligamentous ankle injury and superficial injury of the upper extremity.

DATA SOURCE

All data for this study were obtained from Clinformatics Data Mart database, one of the largest commercial insurance databases in the United States. This de-identified longitudinal data source contains 11 years of data from over 50 million unique members across all regions of the U.S. It includes medical claims, pharmacy claims, lab analytic results, and administrative data. These data have been the primary data source for numerous National Institutes of Health-funded studies and over 75 peer-reviewed journal articles. We will use data from the following Clinformatics Data Mart Files: 1) Administrative, 2) Medical, and 3) Prescription Drug. **Table 3.1** includes a brief description of the Clinformatics Data Mart files.

Table 3.1: Summary of Data Elements Available in Clinformatics Data Mart

File	Data Description
Administrative	member identifier, month and year of birth, enrollment start date, enrollment end date, state of residence, insurance plan type
Medical (inpatient and outpatient)	member identifier, hospital admission date, hospital discharge date, physician, facility, dates of service, diagnostic codes (ICD-9-CM code, DRG code), procedure codes (CPT, HCPCS, ICD-9-CM code), date and place of service
Prescription Drug	member identifier, drug name, national drug code (NDC), drug dose, drug class, drug formulation (e.g., oral, transdermal, injectable), prescription date, prescription duration (days of supply), pharmacy code, drug cost
Laboratory	member identifier, test description, test code, test name, test date, laboratory test value, test unit of measure

STUDY DESIGN

We conducted a case-control study utilizing 11 years (2002-2012) of insurance claims data from Clinformatics Data Mart. To be included in the study, enrollees had to have an ICD-9-CM or HCPCS diagnosis or procedure code as described for each particular study in **Table 3.2** during this 11 year period and have 12 months of continuous enrollment previous to the recorded procedure date. All enrollees were female and between the ages of 15 and 39.

Cases and controls were defined as OC users if any prescription for OCs had been filled in the 12 months prior to the index/diagnosis date. Since it is common for females to start and stop OC use when trying the therapy, as well as change brand, the total number of days prescription issued in the 12 month period was recorded. This number was used to perform sensitivity analysis to determine if duration of use confounded the relationship between case definition and OC use. In other words, we are interested if the exposure-disease relationship varies across the duration of use. Though we can define how many days of prescription were filled in the 12 month period, we cannot calculate the number of continuous months use before index date due to the nature of how OC prescriptions can be filled and prescribed. That is, some brands of OCs operate on an 84 day cycle for a single

prescription, while others operate on a 28 day cycle for a single fill. Even the shorter course therapies may be filled multiple months at a time. This makes determining continuous use from a particular index date complicated and difficult with the numbers gathered in this study. This study was reviewed and exempted from the need for approval by the internal review board of the University of Texas Medical Branch in Galveston, TX.

Table 3.2: Case Definitions

Injury Class / Purpose	Specific Injury	ICD-9-CM Code	CPT / HCPCS Code
Cruciate Ligament Injury	Triad Knee Repair [a]	81.43	
	Other Repair of Cruciate Ligaments	81.45	
	Scoped ACL Repair		29888
	Scoped PCL Repair		29889
Ligamentous Ankle Injury	Ankle Sprain	845.00, 845.01, 845.02, 845.03, 845.09	
	Ankle Dislocation	837.0, 837.1	
Injury Not Suspected of OC Association	Superficial injury of Shoulder and Upper Arm	912.0, 912.1, 912.2, 912.3, 912.4, 912.5, 912.6, 912.7, 912.8, 912.9	

[a]Includes ACL repair, medial meniscus repair, and medial collateral ligament repair

CASES

Cases were defined as enrollees who underwent repair surgery for the posterior cruciate ligament (PCL) or ACL at any time between 2002-2012 based on the following ICD-9-CM codes (81.43, 81.45) and CPT codes (29888, 29889). Cases sustaining ligamentous ankle injury were defined by ICD-9-M codes for ankle sprain (845.xx) and ankle dislocation (837.xx). To demonstrate the uniqueness of any association between OC use and ligamentous injury, we performed analysis assessing OC use rates, compared to controls, in cases of injury not suspected to be influenced by OC use. These cases were

defined by superficial injury of the shoulder and upper extremity or ICD-9-M codes (912.xx). All codes used for case definitions can be found in **Table 3.2**. The date of procedure or diagnosis defining cases were used as the index date for controls

No ICD-9-CM code exists for ACL repair, but rather two codes include such a procedure, one for repair of the cruciate ligaments (81.43) and the other for triad repair surgery of the knee (81.45). It is true that PCL repair surgery is rather rare and one report found that 99.3% of 81.45 codes involved a repair of the ACL in the outpatient setting.[109] At the beginning of that particular study, about 18% of inpatient codes involved a PCL repair, but by 2006 this number had dropped to less than 5% of inpatient codes. From here forward we will refer to our case outcome as repair of the anterior cruciate ligament for simplicity sake and to allow for meaningful comparison with the current literature.

CONTROLS

Controls were assigned an index month corresponding to the surgery date of the matched cases. Cases were matched with controls at a 1:3 ratio based on index date, sex, age at procedure (+/- 6 months), and region. Controls had a 12 month look back period of Clinformatics Data Mart coverage from the index date, and met all of the inclusion and exclusion criteria. We matched 100% of cases for all three data sets, ACL repair, ligamentous ankle injury, and superficial injury to the upper extremity.

INCLUSION AND EXCLUSION CRITERIA

To be included in this study cases and controls were required to meet the following criteria: be female, between the ages of 15-39 at the age of procedure or index date, and have 12 months of continuous enrollment prior to the procedure or index date. We excluded enrollees with any documented history, by ICD-9-CM codes, of the hormonally disruptive conditions listed in **Table 3.3**. Enrollees with documented use of non-oral, hormonal based

contraceptives, including emergency contraception, were excluded based on national drug codes (NDCs), ICD-9-CM codes, CPT codes, J codes, or brand name listed in **Appendix A**.

Table 3.3: Conditions Associated with Hormonal Imbalance

Condition / Procedure / State	ICD-9-CM Code
Polycystic Ovarian Syndrome	256.4
Hysterectomy	68.9
Turner Syndrome (Gonadal Dysgenesis)	758.6
Pregnant State (Last 12 Months)	v22.2
Twin Pregnancy (Last 12 Months)	651
Ectopic Pregnancy (Last 12 Months)	633
Follicular Cyst of Ovary	620
Unspecified Ovarian Cyst	620.2
Acquired Atrophy of Ovary or Fallopian Tube	620.3
Benign Neoplasm of the Ovary	220
Malignant Neoplasm of the Ovary	183
Oophorectomy	65.3, 65.4, 65.6

EXPOSURE

OC use status was determined using a 12 month look back from the date of procedure or index date. OCs were identified by brand name and NDCs in the pharmacy data. All brand names, along with formulation and NDCs (when available) are listed in **Appendix A**. Each filled prescription of OCs is listed in the patient pharmacy data along with the number of days each prescription fill covers. OC exposure was analyzed as both a binary variable, any use in the previous 12 months vs no use in the previous 12 months (labeled as "OC use"), and as a class variable, greater than 90 days of filled prescriptions, 90 days or less of filled prescriptions, or no prescriptions in the previous 12 months (labeled as "OC Use Time"). The selection of a 90-day cut-off was due to a study that found 15% of women discontinue OC use within the first two months, whereas 97% of women who

took OCs for 3 months continued use into month 4.[110] Due to the nature of the data, some enrollees will have had multiple prescriptions filled at or near the same time, due to switching OC type or filling multiple prescriptions at once, leading to inflated number for their days of OC supply. We recognize that the group with less than 90 days OC use is specific, but not sensitive to that duration of time. That is, if an enrollee has less than 90 days of filled prescription for OCs in the previous 12 months we can be sure the she has used OCs for 90 days or less. The caveat to this is that enrollees with multiple prescriptions in a short period of time could have over 90 days of prescriptions for OCs filled appearing in the medical record, whereas they may have been using OCs for 90 days or less. These women will be grouped with the greater than 90 days users as, by number of days prescription filled, they have more than 90 days of OCs. Therefore, the reliability of the outcome of testing for an interaction with less than 90 days of prescription filled is greater than that for the group with greater than 90 days of prescription filled. Due to the nature of OC prescription fills (i.e. multiple fills at one time, duration of course, multiple prescription fills, etc), we were unable to calculate months or days continuous use previous to index date with any level of accuracy.

In addition to use and exposure time, OCs were also analyzed and grouped based on formulation as two different class variables. The first variable splits OC users into those using progesterone only therapy or progesterone and estrogen combination therapy pills (labeled as "OC Formulation"). The second splits OC users into monophasic pill users, OCs that contain the same does of hormones for each pill throughout the course, and triphasic pill users, OCs that contain incrementally increasing amounts of progesterone and/or estrogen throughout the course of pills (labeled as "OC Dosage"). Pharmacy claims data from Clinformatics Data Mart included all OC prescriptions filled in the previous 12 months. Often, this file contained multiple brands and even types of OCs for a single patient. Using a custom MatLab (MathWorks Inc., Natick, Massachusetts) code (**Appendix B**), all unique brand names of OC use were summed by the number of days

prescription filled for each patient. The brand name of OC with the most days prescription filled was retained and manually coded to the patient as a class variable to determine formulation effects. In the event that two or more OCs had the same amount of days prescription filled in the previous 12 months, favor was given to the brand most recently filled in relation to index date. Definitions of these variables and coding can be found in **Table 3.4**.

COVARIATES

Covariates suspected of influencing ACL or ligamentous ankle injury were identified for statistical model adjustment and model stratification. These variables include age, risk status, previous medication use, and relevant comorbidities present in the patient record in the 12 months previous to procedure or index date. A list of all variables considered in statistical analysis can be found in **Table 3.4**.

Risk status was defined as a dummy variable. If a case or control sustained any of the injuries identified by ICD-9-CM codes listed in **Table 3.5** in the previous 12 months to index or procedure date, she was coded as high risk. The absence of any of these injuries was considered low risk. These injuries are somewhat specific to athletic activity and will assist in identifying those cases and controls most prone to lower extremity injury.

Dummy variables for any steroid injection, antibiotic, or oral/inhaled corticosteroid use were considered in statistical model adjustment as each has been, in some capacity, related to ligament health and predisposition to injury. In addition, asthma and type 1 diabetes mellitus have both been associated with hormonal dysregulation in females and the presence of either was recorded as a dummy variable for consideration.

Elixhauser Comorbidity Index was also calculated for analysis and adjustment as a class variable. The Elixhauser Comorbidity Index was developed to create an index score to represent total patient disease burden and is a good indicator of overall health.[111] Since

our cohort is very young, ages 15-39, the Elixhauser Comorbidity Index was coded as a class variable with classes of 0 comorbidities, 1, 2, and 3 or more.

Table 3.4: Study Variable List, Definition, and Coding

Variable Name	Definition	Coding
OC Use	Use of any OC within the 12 month look back. (Dummy variable)	1 = use, 0 = non-use
OC Use Time	Number of days OC prescription filled in 12 month look back. (Class Variable)	2 = >90 days, 1 = <=90 days, 0 = Non-use
Age	Age in years. (Discrete Variable)	# in years
Risk Status	High risk or Low risk status. (Dummy Variable)	1 = High Risk, 0 = Low Risk
OC Type	Progesterone only versus progesterone AND estrogen OC use. (Categorical Variable)	0 = Non-Use, 1 = Progesterone Only, 2 = Combined Monophasic Therapy, 3 = Combined Triphasic Therapy
Comorbidity - Asthma	Presence of asthma diagnosis. (Dummy Variable)	1= Presence, 0=absence
Comorbidity – Diabetes	Presence of type I diabetes diagnosis. (Dummy Variable)	1= Presence, 0=absence
Meds - Injectable Corticosteroids	Use of Injectable corticosteroids in 12 month look back. (Dummy Variable)	1=use, 0=non=use
Meds - Inhaled or Oral Corticosteroid Use	Use of inhaled or oral corticosteroids in 12 month look back. (Dummy Variable)	1=use, 0=non=use
Meds - Antibiotics	Use of antibiotics in 12 month look back. (Dummy Variable)	1=use, 0=non=use
Elixhauser Comorbidity Index	Total number of present comorbidities from a list of 30 in 12 month look back. (Class Variable)	3 = 3+, 2 = 2, 1 = 1, 0 = 0

Table 3.5: Injuries Defining High Risk Status

Lower Extremity Related Injury	ICD9-M Code
Achilles bursitis or tendinitis	726.71
Tibialis tendinitis	726.72
Dislocation of the knee	836
Dislocation of the ankle	837
Sprains or strains of the knee and leg	844
Sprains or strains of the ankle and foot	845
Rupture of muscle nontraumatic	728.83
Nontraumatic compartment syndrome of the lower extremity	729.72
Stress fracture of the tibia or fibula	733.93
Stress fracture of the metatarsals	733.94

STATISTICAL ANALYSIS

Univariate statistics, including means and frequencies, were calculated for each of the three sets of case-control data. Differences between groups was tested with the use of analysis of variance tests for differences of proportions.

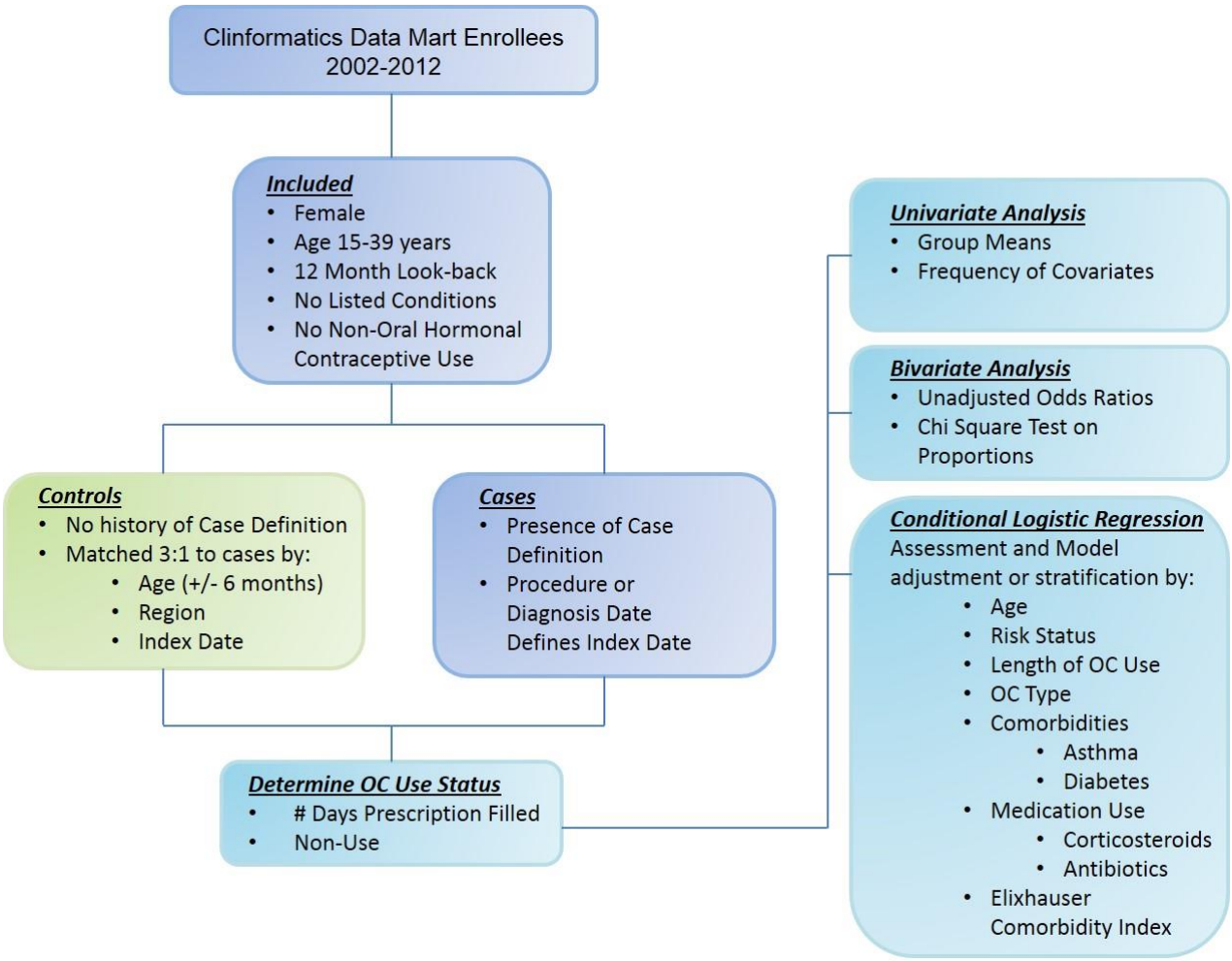
Conditional logistic regression was used to obtain both adjusted odds ratios (ORs) and unadjusted ORs, assessing the association of each covariate with the binary outcome presence (1) or absence (0) of a procedure or diagnosis. Since controls were age matched, unadjusted ORs and adjusted ORs for exposure outcomes were also obtained for all 5-year age group strata to assess whether the exposure-disease association varied by age group. A formal test for interaction between age and OC use in association with each outcome was also performed. Differences in adjusted ORs between classes of a single variable were assessed for significance by direct contrast. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

SUMMARY

Figure 3.1 is a visual illustration of how the data will be extracted from Clinformatics Data Mart and analyzed. The definition of case patients will change for each

of our three defined outcome variables, CL repair surgery, ligamentous ankle injury diagnosis, and superficial injury of the upper extremity diagnosis.

Figure 3.1: Summary Flowchart of Methods

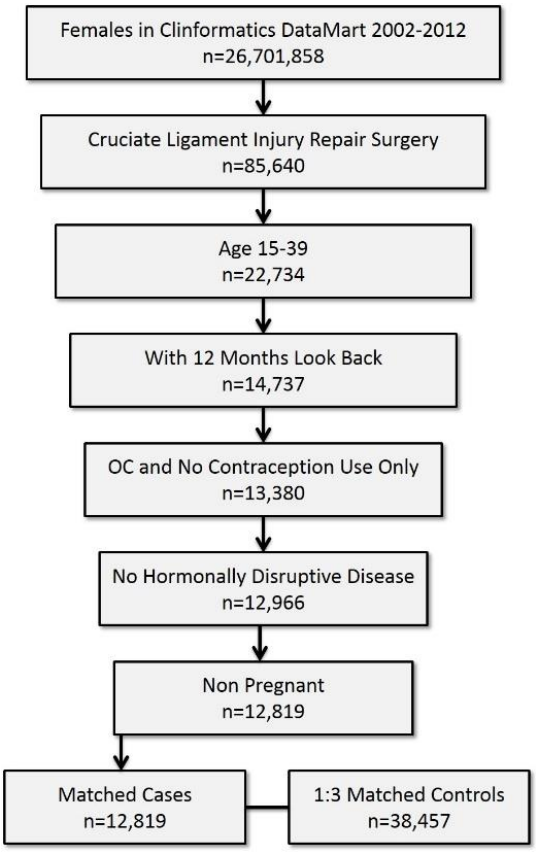


Chapter 4: Results

CRUCIATE LIGAMENT REPAIR

There were 26.7 million female enrollees in Clinformatics Data Mart from 2002 to 2012. Of these, 12,819 underwent an ACL or PCL surgery and met the inclusion and exclusion criteria for this study. A summary chart of exclusion numbers can be seen in **Figure 4.1**. 100% of identified cases were matched 1:3 to controls also meeting our inclusion/exclusion criteria.

Figure 4.1: Flow Chart of ACL Reconstruction Cohort Selection



A summary of case and control cohort study variables is presented in **Table 4.1**. The mean age for both cases and controls was 24.11 years with a standard deviation (SD) of 8.12. Cases had a higher raw percentage of OC users than controls. Though significantly different, cases and controls had similar distributions of OC users by formulation (progesterone only vs. combination therapy) and dosage (monophasic vs. triphasic). Cases had significantly higher percentages of enrollees labeled high risk, receiving steroid injection, prescribed inhaled or oral steroids, prescribed antibiotics, and diagnosed with asthma. Type 1 diabetes mellitus was more common among controls.

Unadjusted ORs obtained by conditional logistic regression for all exposure variables as well as covariates are presented it **Table 4.2**. The adjusted OR from the multivariate model defined in **Table 4.2** showed that cases did not differ from controls in OC use (adjusted OR: 0.99, 95% CI: 0.94-1.04). Of note, cases were nearly three times more likely to be considered high risk (adjusted OR: 2.76, 95% CI: 2.52-3.03) and approximately two times (adjusted OR: 2.08, 95% CI: 1.84-2.34) more likely to have received a steroid injection compare to controls.

Stratification by 5-year age groups revealed that cases in age groups 15-19 years were significantly less likely to use OCs than controls (adjusted ORs: 0.82, 95% CI: 0.75-0.91). Formal testing determined there was a significant interaction between age and OC use (p=<.0001). **Table 4.3** contains all unadjusted ORs and adjusted ORs for OC use for all 5-year age groups. Cases in age groups 25-29 years and 30-34 years were significantly more likely to have used OCs than controls. Sensitivity analysis revealed that the duration of OC use may modify the effect of OC use on CL injury risk. Specifically, enrollees using OCs for less than or equal to 90 days had a lower adjusted OR than those using OCs for greater than 90 days in the logistic model concerning all ages (p=0.0185, **Table 4.4**). Differences in duration of use for individual age groups, however, was not always significant.

Multivariate analysis of OC formulation (progesterone only vs. combined therapy), in total and by 5-year age groups, revealed no remarkable findings or trends. Analysis by dosage, monophasic (includes progesterone only OCs) and triphasic, revealed that monophasic formulations had a lower adjusted OR than triphasic formulations (p=0.0248, **Table 4.5**). This differences in adjusted ORs between formulations within each age group were not significant.

Table 4.1: Summary of Study Variables for Cases of ACL Reconstruction

Variables	Cases n(%) n=12819	Controls n(%) n=38457	p-value[a]
Age, mean(SD[b])	24.11 (8.12)	24.11 (8.12)	
Age Group			
15-19	5857 (45.69)	17571 (45.69)	
20-24	1632 (12.73)	4869 (12.73)	
25-29	1368 (10.67)	4104 (10.67)	
30-34	1745 (13.61)	5235 (13.61)	
35-39	2217 (17.29)	6651 (17.29)	
Any OC Use	2999 (23.39)	8775 (22.82)	0.008
OC Use (among users)			
≤90 Days	593 (19.79)	1911 (21.78)	<.0001
>90 days	2406 (80.21)	6864 (78.22)	
OC Formulation (among users)			
Progesterone Only	83 (2.78)	276 (3.16)	0.0003
Estrogen + Progesterone	2916 (97.22)	8499 (96.84)	
OC Dosage (among users)			
Monophasic	1966 (65.58)	5945 (67.75)	<.0001
Triphasic	1033 (34.42)	2830 (32.25)	
High Risk[c]	964 (7.52)	1033 (2.69)	<.0001
Steroid Injection[d]	511 (3.99)	680 (1.77)	<.0001
Inhaled or Oral Steroid[d]	1563 (12.19)	3578 (9.77)	<.0001
Antibiotics[d]	6370 (49.69)	16477 (42.85)	<.0001
Asthma[d]	825 (6.44)	1806 (4.70)	<.0001
Diabetes[d]	104 (0.81)	461 (1.20)	<.0001
Elixhauser Comorbidity Index			
0	10961 (85.51)	33418 (86.90)	<.0001
1	1489 (11.62)	3869 (10.06)	
2	274 (2.14)	861 (2.24)	
3+	95 (0.74)	309 (0.80)	

[a]Only significant (<0.05) p-values are reported. [b]SD, standard deviation. [c]High risk status defined by conditions in Table 3.7. [d]Diagnosis or prescription within the previous 12 months from index date.

Table 4.2: Conditional Logistic Regression Predicting ACL Reconstruction

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate OR[a]	95% CI[b]	p-value
OC Use						
Non-Use	1.00	REF	0.1589	1.00	REF	0.6164
Any Use	1.04	(0.99-1.09)		0.99	(0.94-1.04)	
OC Formulation						
Non-Use	1	REF	0.6963	1	REF	0.6023
Progesterone Only	0.90	(0.70-1.15)		0.885	(0.69-1.14)	
Estrogen + Progesterone	0.99	(0.94-1.05)		0.99	(0.94-1.04)	
OC Dosing						
Non-Use	1	REF	**0.0300**	1	REF	0.0717
Monophasic	1.00	(0.95-1.06)		0.95	(0.90-1.01)	
Triphasic	1.11	(1.03-1.20)		1.06	(0.98-1.14)	
Risk Status[c,d]						
Low	1	REF	**<.0001**	1	REF	**<.0001**
High	2.93	(2.67-3.20)		2.76	(2.52-3.03)	
Elixhauser Comorbidity Index						
0	1	REF	**<.0001**	1	REF	0.0648
1	1.18	(1.10-1.25)		1.02	(0.95-1.10)	
2	0.97	(0.85-1.11)		0.86	(0.74-0.99)	
3+	0.94	(0.75-1.18)		0.83	(0.65-1.06)	
Steroid Injection[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	2.33	(2.08-2.63)		2.08	(1.84-2.34)	
Inhaled or Oral Steroid[d]						
No	1	REF	**<.0001**	1	REF	**0.0361**
Yes	1.28	(1.21-1.37)		1.08	(1.01-1.15)	
Antibiotics[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.32	(1.27-1.38)		1.25	(1.20-1.31)	
Asthma[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.399	(1.29-1.52)		1.25	(1.13-1.38)	
Diabetes[d]						
No	1	REF	**0.0003**	1	REF	**0.0007**
Yes	0.67	(0.54-0.83)		0.68	(0.54-0.85)	

[a]OR, odds ratio, [b]CI, confidence interval, [c]High risk status defined by conditions in Table 3.7. [d]Diagnosis or prescription within the previous 12 months from index date. adjusted ORs for OC use, formulation, and dosing determined by mutually exclusive models. All covariate adjusted ORs determined by the OC Use model.

Table 4.3: Odds of OC Use in ACL Reconstruction Cases by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate[c] OR[a]	95% CI[b]	p-value
Test for Interaction by Age Groups			**<.0001**			**<.0001**
Age 15-19						
Non-Use	1.00	REF	**0.007**	1.00	REF	**<.0001**
Any Use	0.88	(0.80-0.97)		0.82	(0.75-0.91)	
Age 20-24						
Non-Use	1.00	REF	0.4549	1.00	REF	0.0719
Any Use	0.96	(0.85-1.08)		0.89	(0.79-1.01)	
Age 25-29						
Non-Use	1.00	REF	**0.0115**	1.00	REF	**0.0269**
Any Use	1.17	(1.04-1.32)		1.15	(1.02-1.30)	
Age 30-34						
Non-Use	1.00	REF	**0.0029**	1.00	REF	**0.011**
Any Use	1.19	(1.06-1.34)		1.16	(1.04-1.31)	
Age 35-39						
Non-Use	1.00	REF	**0.0366**	1.00	REF	0.1297
Any Use	1.13	(1.01-1.27)		1.10	(0.97-1.23)	

[a]OR odds ratio. [b]CI, confidence interval . [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. Formal test for an age interaction in both the adjusted and unadjusted model including all cases is presented at the top.

Table 4.4: Sensitivity Analysis of the effect of OC use Duration on ACL Reconstruction by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate[c] OR[a]	95% CI[b]	p-value
All Ages						
Non-Use	1	REF	**0.0225**	1	REF	0.0557
≤90 Days	0.94	(0.86-1.03)		0.89	(0.81-0.99)	**0.0185**
>90 Days	1.07	(1.01-1.12)		1.02	(096-1.07)	
Age 15-19						
Non-Use	1.00	REF	**0.0197**	1.00	REF	**0.0004**
≤90 Days	0.83	(0.70-0.98)		0.79	(0.67-0.94)	0.5657
>90 Days	0.90	(0.81-1.00)		0.84	(0.75-0.94)	
Age 20-24						
Non-Use	1.00	REF	0.6088	1.00	REF	0.1729
≤90 Days	0.90	(0.72-1.12)		0.85	(0.68-1.07)	0.5953
>90 Days	0.97	(0.86-1.10)		0.91	(0.80-1.03)	
Age 25-29						
Non-Use	1.00	REF	**0.0024**	1.00	REF	**0.0034**
≤90 Days	0.90	(0.69-1.16)		0.86	(0.66-1.12)	**0.0125**
>90 Days	1.23	(1.08-1.40)		1.21	(1.07-1.38	
Age 30-34						
Non-Use	1.00	REF	**0.0015**	1.00	REF	**0.004**
≤90 Days	0.98	(0.78-1.23)		0.94	(0.75-1.19)	**0.0359**
>90 Days	1.25	(1.10-1.41)		1.22	(1.08-1.39	
Age 35-39						
Non-Use	1.00	REF	**0.0319**	1.00	REF	0.1153
≤90 Days	1.33	(1.05-1.68)		1.27	(1.00-1.61)	0.1604
>90 Days	1.09	(0.96-1.23)		1.06	(0.93-1.20)	

[a]OR, odds ratio. [b]CI, confidence interval . [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. For each group, 2 p-values are listed for the adjusted ORs. The top tests for significance of the duration class variable in the model, the bottom tests for a difference in adjusted ORs between ≤90 Days use and >90 days use.

Table 4.5: Effect of OC Dosage on ACL Reconstruction by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-vlalue	Multivariate[c] OR[a]	95% CI[b]	p-value
All Ages						
Non-Use	1	REF	**0.0030**	1	REF	0.0717
Monophasic	1.00	(0.95-1.06)		0.95	(0.90-1.01)	**0.0248**
Triphasic	1.11	(1.03-1.20)		1.06	(0.98-1.14)	
Age 15-19						
Non-Use	1.00	REF	**0.0066**	1.00	REF	**0.0001**
Monophasic	0.83	(0.74-0.93)		0.78	(0.70-0.88)	0.1062
Triphasic	0.97	(0.84-1.14)		0.91	(0.78-1.06)	
Age 20-24						
Non-Use	1.00	REF	0.214	1.00	REF	0.0779
Monophasic	0.90	(0.78-1.03)		0.85	(0.74-0.98)	0.1651
Triphasic	1.05	(0.89-1.25)		0.98	(0.82-1.16)	
Age 25-29						
Non-Use	1.00	REF	**0.0172**	1.00	REF	**0.0300**
Monophasic	1.11	(0.97-1.28)		1.09	(0.95-1.26)	0.1526
Triphasic	1.27	(1.06-1.49)		1.26	(1.06-1.50)	
Age 30-34						
Non-Use	1.00	REF	**0.0094**	1.00	REF	**0.0323**
Monophasic	1.16	(1.02-1.33)		1.14	(1.00-1.30)	0.5343
Triphasic	1.25	(1.04-1.49)		1.22	(1.01-1.46)	
Age 35-39						
Non-Use	1.00	REF	0.111	1.00	REF	0.3173
Monophasic	1.14	(1.00-1.30)		1.10	(0.96-1.25)	0.9857
Triphasic	1.11	(0.91-1.37)		1.09	(0.89-1.35)	

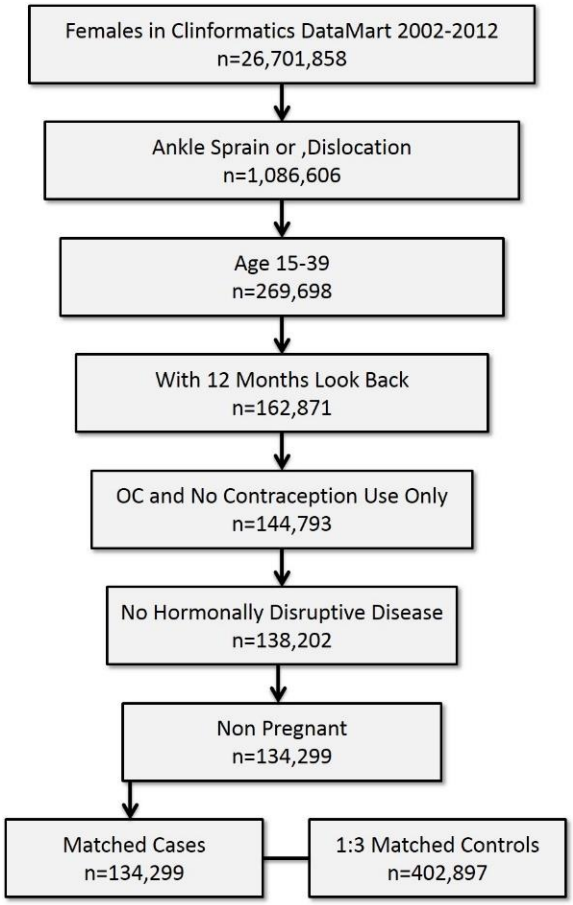
[a]OR, odds ratio. [b]CI, confidence interval . [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. For each group, 2 p-values are listed for the adjusted ORs. The top tests for significance of the formulation class variable in the model, the bottom tests for a difference in adjusted ORs between monophasic and triphasic therapies.

LIGAMENTOUS ANKLE INJURY

Of the 26.7 million female enrollees in Clinformatics Data Mart 2002-2012, 134,299 were diagnosed with an ankle sprain, dislocation, or both and met our inclusion and exclusion criteria. **Figure 4.2** depicts a flow chart detailing why cases were excluded

and how many were excluded at each step. All identified cases (100%) were matched 1:3 to controls also meeting inclusion exclusion criteria.

Figure 4.2: Flow Chart of Ligamentous Ankle Injury Cohort Selection



A summary of study variables for cases and controls can be found in **Table 4.6**. The mean age for both cohorts was 25.55 with a SD of 8.25. Cases had a slightly higher percentage of OC users (25%) compared to controls (24%). The percentage of OC users with greater than 90 days prescription was nearly identical between the two groups at about 79%. Both OC formulation and dosage were nearly identical between groups as well, differing by about 1% for each measure. Cases had significantly higher percentages of high risk patients, injectable steroid use, inhaled or oral steroid use, antibiotic use, and asthma

diagnosis. A diagnoses of diabetes was also slightly more prevalent among cases. Cases also had greater percentages of individuals with 1, 2, and 3 or more comorbidities included in the Elixhauser Comorbidity Index.

Table 4.7 contains all ORs for all variables calculated using conditional logistic regression. The multivariate model determined that OC use was not significantly predictive of ligamentous ankle injury (adjusted OR: 1.01, 95% CI: 0.99-1.02). In the multivariate model, however, cases were four times more likely to be labeled high risk (adjusted OR: 4.08, 95% CI: 3.96-4.20). Also, as the total value of the Elixhauser Comorbidity Index increased, patients were increasingly more likely to be cases than controls.

Unlike ACL reconstructions, though there was a significant age interaction with OC use ($p<.0001$), stratification by 5-year age groups showed the magnitude of adjusted ORs to be rather small (range: 0.96-1.06, **Table 4.8)**. Sensitivity analysis by duration of use, using a 90 day cut-off, did not demonstrate a significant effect ($p=0.6174$)

Multivariate analysis of OC formulation, in total and by 5-year age groups, revealed no remarkable findings or trends. Analysis by dosage is depicted in **Table 4.9**. Though a significant adjusted OR was discovered for monophasic and triphasic therapies in the model including all ages ($p=0.0334$), the dosage class variable was not significant in the model ($p=0.0778$). Further, there was no discernable trend as a function of age between these regimens.

Table 4.6: Summary of Study Variables for Cases of Ligamentous Ankle Injury

Variables	Cases n(%) n=134299	Controls n(%) n=402897	p-value[a]
Age, mean(SD[b])	25.55 (8.25)	25.55 (8.25)	
Age Group			
15-19	48552 (36.15)	145656 (36.15)	
20-24	16556 (12.33)	49668 (12.33)	
25-29	18069 (13.45)	54207 (13.45)	
30-34	23656 (17.61)	70968 (17.61)	
35-39	27466 (20.45)	82398 (20.45)	
Any OC Use	33584 (25.01)	95220 (23.63)	<.0001
OC Use (Among Users)			
≤90 Days	7056 (21.01)	19897 (20.89)	
>90 days	26528 (78.99)	75323 (79.11)	
OC Formulation (Among Users)			
Progesterone Only	974 (2.90)	3583 (3.76)	<.0001
Estrogen + Progesterone	32608 (97.10)	91632 (96.24)	
OC Dosage (Among Users)			
Monophasic	22664 (67.49)	63261 (66.44)	<.0001
Triphasic	10918 (32.51)	31954 (33.56)	
High Risk[c]	12120 (9.02)	8822 (2.19)	<.0001
Steroid Injection[d]	4732 (3.52)	7791 (1.93)	<.0001
Inhaled or Oral Steroid[d]	19676 (14.65)	39482 (9.8)	<.0001
Antibiotics[d]	72787 (54.20)	171882 (42.66)	<.0001
Asthma[d]	10323 (7.69)	17572 (4.36)	<.0001
Diabetes[d]	2579 (1.92)	5316 (1.32)	<.0001
Elixhauser Comorbidity Index			
0	106087 (78.99)	346426 (85.98)	<.0001
1	20168 (15.02)	42811 (10.63)	
2	5412 (4.03)	9924 (2.46)	
3+	2632 (1.96)	3736 (0.93)	

[a]Only significant (<0.05) p-values are reported. [b]SD, standard deviation. [c]High risk status defined by conditions in Table 3.7. [d]Diagnosis or prescription within the previous 12 months from index date.

Table 4.7: Conditional Logistic Regression Predicting Ligamentous Ankle Injury

Exposure	*Unadjusted OR[a]*	*95% CI[b]*	*p-value*	*Multivariate OR[a]*	*95% CI[b]*	*p-value*
OC Use						
Non-Use	1	REF	**<.0001**	1	REF	0.4487
Any Use	1.09	(1.07-1.10)		1.01	(0.99-1.02)	
OC Formulation						
Non-Use	1	REF	**<.0001**	1	REF	**<.0001**
Progesterone Only	0.84	(0.78-0.90)		0.81	(0.75-0.87)	
Estrogen + Progesterone	1.10	(1.08-1.11)		1.01	(1.00-1.03)	
OC Dosing						
Non-Use	1	REF	**<.0001**	1	REF	0.0778
Monophasic	1.10	(1.08-1.12)		1.02	(1.00-1.03)	
Triphasic	1.05	(1.03-1.08)		0.99	(0.96-1.01)	
Risk Status[c,d]						
Low	1	REF	**<.0001**	1	REF	**<.0001**
High	4.44	(4.32-4.57)		4.08	(3.96-4.20)	
Elixhauser Comorbidity Index						
0	1	REF	**<.0001**	1	REF	**<.0001**
1	1.55	(1.53-1.58)		1.31	(1.29-1.34)	
2	1.81	(1.75-1.87)		1.47	(1.42-1.53)	
3+	2.35	(2.23-2.47)		1.76	(1.67-1.86)	
Steroid Injection[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.87	(1.80-1.94)		1.41	(1.35-1.46)	
Inhaled or Oral Steroid[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.58	(1.55-1.61)		1.21	(1.19-1.24)	
Antibiotics[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.60	(1.58-1.62)		1.44	(1.42-1.46)	
Asthma[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.83	(1.78-1.87)		1.21	(1.17-1.25)	
Diabetes[d]						
No	1	REF	**<.0001**	1	REF	0.3766
Yes	1.47	(1.40-1.54)		1.02	(1.19-1.24)	

[a]OR, odds ratio, [b]CI, confidence interval, [c]High risk status defined by conditions in Table 3.7. [d]Diagnosis or prescription within the previous 12 months from index date. adjusted ORs for OC use, formulation, and dosing determined by mutually exclusive models. All covariate adjusted ORs determined by the OC use model.

Table 4.8: Odds of OC Use in Ligamentous Ankle Injury Cases by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate[c] OR[a]	95% CI[b]	p-value
Test for Interaction by Age Groups			**<.0001**			**<.0001**
Age 15-19						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**0.0005**
Any Use	1.20	(1.16-1.24)		1.06	(1.03-1.10)	
Age 20-24						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**<.0001**
Any Use	1.22	(1.18-1.26)		1.09	(1.05-1.13)	
Age 25-29						
Non-Use	1.00	REF	**0.0451**	1.00	REF	0.2254
Any Use	1.04	(1.00-1.07)		0.98	(0.94-1.01)	
Age 30-34						
Non-Use	1.00	REF	0.4890	1.00	REF	0.0878
Any Use	1.01	(0.98-1.04)		0.97	(0.94-1.00)	
Age 35-39						
Non-Use	1.00	REF	0.7305	1.00	REF	**0.0196**
Any Use	1.00	(0.97-1.03)		0.96	(0.93-0.99)	

[a]OR, odds ratio. [b]CI, confidence interval . [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. Formal test for an age interaction in both the adjusted and unadjusted model including all cases is presented at the top.

Table 4.9: Effect of OC Dosage on Ligamentous Ankle Injury by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-vlalue	Multivariate[c] OR[a]	95% CI[b]	p-value
All Ages						
Non-Use	1	REF	**<.0001**	1	REF	0.0788
Monophasic	1.10	(1.08-1.12)		1.02	(1.00-1.03)	**0.0334**
Triphasic	1.05	(1.03-1.08)		0.99	(0.96-1.01)	
Age 15-19						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**0.0005**
Monophasic	1.23	(1.18-1.27)		1.08	(1.04-1.13)	0.0798
Triphasic	1.15	(1.09-1.21)		1.02	(0.97-1.08)	
Age 20-24						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**<.0001**
Monophasic	1.24	(1.19-1.29)		1.10	(1.05-1.15)	0.3797
Triphasic	1.18	(1.12-1.25)		1.07	(1.01-1.13)	
Age 25-29						
Non-Use	1.00	REF	0.1310	1.00	REF	0.4061
Monophasic	1.04	(1.00-1.08)		0.97	(0.93-1.01)	0.5628
Triphasic	1.03	(0.98-1.09)		0.99	(0.94-1.04)	
Age 30-34						
Non-Use	1.00	REF	**0.0218**	1.00	REF	**0.043**
Monophasic	1.04	(1.00-1.08)		0.99	(0.95-1.03)	0.0648
Triphasic	0.96	(0.91-1.01)		0.94	(0.89-0.99)	
Age 35-39						
Non-Use	1.00	REF	**0.0337**	1.00	REF	**0.0169**
Monophasic	1.03	(0.99-1.07)		0.98	(0.94-1.01)	0.0969
Triphasic	0.94	(0.88-1.00)		0.92	(0.86-0.98)	

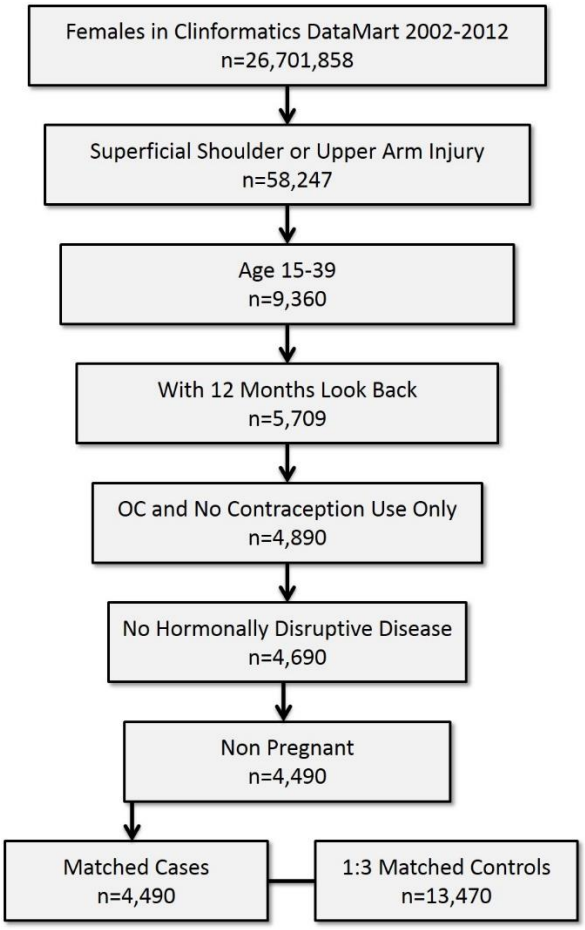
[a]OR, odds ratio. [b]CI, confidence interval . [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. For each group, 2 p-values are listed for the adjusted ORs. The top tests for significance of the formulation class variable in the model, the bottom tests for a difference in adjusted ORs between monophasic and triphasic therapies.

SUPERFICIAL INJURY OF THE UPPER EXTREMITY

From 2002-2012, 4,490 females meeting our inclusion and exclusion criteria enrolled in Clinformatics Data Mart were diagnosed with a superficial injury of the upper extremity (i.e. cut, puncture abrasion, etc.). All cases were matched 100% to controls in a

1:3 ratio. **Figure 4.3** provides a detailed overview of the selection of cases included in this study.

Figure 4.1: Flow Chart of Superficial Shoulder Injury Cohort Selection



A comparison of cohort study variables for case and controls is presented in **Table 4.10**. The mean age for both cohorts was 25.8 with a SD of 7.8. Cases had significantly higher uses rates of OCs (30%) when compared to controls (26%). Breakdown of OC users by the duration of use (>90 days vs. <90 days), formulation, and dosage were similar between cases and controls. Controls had moderately lower rates of high risk individuals, those diagnosed with asthma, and those having received a steroid injection, inhaled or oral corticosteroids, or antibiotics in the previous year to index date. The control cohort had a

higher rate of individuals with an Elixhauser comorbidity score of 0. For all scores greater than 0, cases had higher rates.

Table 4.10: Summary of Study Variables for Cases of Superficial Shoulder Injury

Variables	Cases n(%) n=12819	Controls n(%) n=38457	p-value[a]
Age, mean(SD[b])	25.80 (7.80)	25.80 (7.80)	
Age Group			
15-19	1405 (31.29)	425 (31.29)	
20-24	739 (16.46)	2217 (16.46)	
25-29	726 (16.17)	2178 (16.17)	
30-34	748 (16.66)	2244 (16.66)	
35-39	872 (19.42)	2616 (19.42)	
Any OC Use	1336 (29.76)	3519 (26.12)	**<.0001**
OC Use (among users)			
≤90 Days	272 (20.36)	702 (19.95)	
>90 days	1064 (79.64)	2817 (80.05)	
OC Formulation (among users)			
Progesterone Only	31 (2.32)	120 (3.41)	**0.0282**
Estrogen + Progesterone	1305 (97.68)	3399 (96.59)	
OC Dosage (among users)			
Monophasic	916 (68.56)	2356 (66.95)	
Triphasic	420 (31.44)	1163 (33.05)	
High Risk[c]	267 (5.95)	457 (3.39)	**<.0001**
Steroid Injection[d]	164 (3.65)	241 (1.79)	**<.0001**
Inhaled or Oral Steroid[d]	657 (14.63)	13.45 (9.99)	**<.0001**
Antibiotics[d]	2397 (53.39)	5903 (43.82)	**<.0001**
Asthma[d]	308 (6.86)	596 (4.42)	**<.0001**
Diabetes[d]	61 (1.36)	192 (1.43)	
Elixhauser Comorbidity Index			
0	3504 (78.04)	11532 (85.61)	**<.0001**
1	660 (14.70)	1441 (10.70)	
2	218 (4.86)	361 (2.68)	
3+	108 (2.41)	136 (1.01)	

[a]Only significant (<0.05) p-values are reported. [b]SD, standard deviation. [c]High risk status defined by conditions in Table 3.7. [d]Diagnosis or prescription within the previous 12 months from index date.

Conditional logistic regression predicting case status can be seen in **Table 4.11**. The adjusted model predicting superficial shoulder injury utilized all listed covariates. The multivariate model determined that cases were, overall, slightly more likely to use OCs than controls (adjusted OR: 1.15, p<.001). Case were also more likely to be labeled as high risk (adjusted OR: 1.61, 95% CI: 1.37-1.89), have had a steroid injection (adjusted OR: 1.67, 95% CI: 1.36-2.06), and have used antibiotics (adjusted OR: 1.31 95% CI: 1.22-1.41). Adjusted ORs also increased as the Elixhauser comorbidity scores increased, meaning that individuals with higher comorbidity scores were more likely to be cases than controls

Though a significant interaction between age and OC use is reported (p=0.0027), stratification by 5-year age groups did not yield any trends in OC use as it relates to case status (**Table 4.12)**. Only for the age group 15-19 years did OCs significantly predict case status. For that age group, OC users were more likely to be cases with an adjusted OR of 1.45 (95% CI: 1.22-1.71). Sensitivity analysis revealed that duration of use had no major effect on these odds ratios for the model including all cases (p=0.7405).

Multivariate analysis of OC formulation, in total and by 5-year age groups, revealed no remarkable findings or trends. Analysis by dosage is depicted in **Table 4.13**. Odds ratios were reported as both greater and lesser than 1 for triphasic regimens compared to monophasic therapies depending on the age group referenced. However, for all groups tested there was no difference in adjusted ORs between monophasic and triphasic therapies (**Table 4.13**).

Table 4.11: Conditional Logistic Regression Predicting Superficial Shoulder Injury

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate OR[a]	95% CI[b]	p-value
All Ages						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**0.0008**
Any Use	1.21	(1.12-1.31)		1.15	(1.06-1.24)	
OC Formulation						
Non-Use	1	REF	**<.0001**	1.00	REF	**0.0009**
Progesterone Only	0.83	(0.55-1.23)		0.83	(0.56-1.25)	
Estrogen + Progesterone	1.23	(1.14-1.33)		1.16	(1.07-1.25)	
OC Dosing						
Non-Use	1	REF	**<.0001**	1.00	REF	**0.0023**
Monophasic	1.24	(1.14-1.36)		1.17	(1.07-1.28)	
Triphasic	1.15	(1.02-1.30)		1.10	(0.97-1.24)	
Risk Status[c,d]						
Low	1	REF	**<.0001**	1	REF	**<.0001**
High	1.80	(1.54-2.10)		1.61	(1.37-1.89)	
Elixhauser Comorbidity Index						
0	1	REF	**<.0001**	1	REF	**<.0001**
1	1.52	(1.38-1.69)		1.40	(1.25-1.56)	
2	2.00	(1.68-2.37)		1.86	(1.55-2.23)	
3+	2.66	(2.06-3.43)		2.62	(1.99-3.44)	
Steroid Injection[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	2.09	(1.71-2.56)		1.67	(1.36-2.06)	
Inhaled or Oral Steroid[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.55	(1.40-1.72)		1.28	(1.14-1.42)	
Antibiotics[d]						
No	1	REF	**<.0001**	1	REF	**<.0001**
Yes	1.48	(1.38-1.58)		1.31	(1.22-1.41)	
Asthma[d]						
No	1	REF	**<.0001**	1	REF	0.8672
Yes	1.60	(1.39-1.85)		0.99	(0.84-1.16)	
Diabetes[d]						
No	1	REF	0.7423	1	REF	**0.0002**
Yes	0.95	(0.71-1.27)		0.56	(0.41-0.76)	

[a]OR, odds ratio, [b]CI, confidence interval, [c]High risk status defined by conditions in Table 3.7. [d]Diagnosis or prescription within the previous 12 months from index date. adjusted ORs for OC use, formulation, and dosing determined by mutually exclusive models. All covariate adjusted ORs determined by the OC use model.

Table 4.12: Odds of OC Use in Supeficial Shoulder Injury Cases by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate[c] OR[a]	95% CI[b]	p-value
Test for Interaction by Age Groups			**<.0001**			**0.0027**
Age 15-19						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**<.0001**
Any Use	1.62	(1.38-1.91)		1.45	(1.22-1.71)	
Age 20-24						
Non-Use	1.00	REF	**0.0065**	1.00	REF	0.1148
Any Use	1.27	(1.07-1.51)		1.15	(0.97-1.38)	
Age 25-29						
Non-Use	1.00	REF	0.0658	1.00	REF	0.1545
Any Use	1.17	(0.99-1.39)		1.14	(0.95-1.35)	
Age 30-34						
Non-Use	1.00	REF	0.1097	1.00	REF	0.1949
Any Use	1.16	(0.97-1.39)		1.13	(0.94-1.36)	
Age 35-39						
Non-Use	1.00	REF	0.1602	1.00	REF	0.0958
Any Use	0.87	(0.72-1.06)		0.85	(0.70-1.03)	

[a]OR, odds ratio. [b]CI, confidence interval . [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. Formal test for an age interaction in both the adjusted and unadjusted model including all cases is presented at the top.

Table 4.13: Effect of OC Dosage on Superficial Shoulder Injury by 5-year Age Groups

Exposure	Unadjusted OR[a]	95% CI[b]	p-value	Multivariate[c] OR[a]	95% CI[b]	p-value
All Ages						
Non-Use	1	REF	**<.0001**	1.00	REF	**0.0023**
Monophasic	1.24	(1.14-1.36)		1.17	(1.07-1.28)	0.3747
Triphasic	1.15	(1.02-1.30)		1.10	(0.97-1.24)	
Age 15-19						
Non-Use	1.00	REF	**<.0001**	1.00	REF	**<.0001**
Monophasic	1.65	(1.37-2.00)		1.46	(1.20-1.78)	0.8185
Triphasic	1.56	(1.21-2.01)		1.41	(1.09-1.83)	
Age 20-24						
Non-Use	1.00	REF	**0.0242**	1.00	REF	0.2836
Monophasic	1.28	(1.05-1.56)		1.16	(0.95-1.42)	0.8562
Triphasic	1.25	(0.97-1.60)		1.13	(0.88-1.46)	
Age 25-29						
Non-Use	1.00	REF	**0.0161**	1.00	REF	0.0654
Monophasic	1.30	(1.07-1.57)		1.24	(1.02-1.51)	0.0686
Triphasic	0.95	(0.74-1.23)		0.95	(0.73-1.23)	
Age 30-34						
Non-Use	1.00	REF	0.1070	1.00	REF	0.2228
Monophasic	1.08	(0.87-1.33)		1.06	(0.86-1.31)	0.2578
Triphasic	1.34	(1.02-1.75)		1.28	(0.97-1.68)	
Age 35-39						
Non-Use	1.00	REF	0.1239	1.00	REF	0.1062
Monophasic	0.95	(0.76-1.17)		0.91	(0.73-1.13)	0.1739
Triphasic	0.69	(0.48-0.99)		0.69	(0.47-0.99)	

[a]OR, odds ratio. [b]CI, confidence interval. [c]Multivarate model includes adjustment for all study variables. Significant p-values (<0.05) are bolded. For each group, 2 p-values are listed for the adjusted ORs. The top tests for significance of the formulation class variable in the model, the bottom tests for a difference in adjusted ORs between monophasic and triphasic therapies.

Chapter 5: Discussion

This study represents the first population-based study of OC use and ACL injury receiving reconstruction. It is the first study to report that females aged 15-19 years who use OCs receive 18% fewer ACL reconstructions than age-matched nonusers. This age group also received the greatest number of ACL reconstructions. Our findings showed specificity towards ACL injury as similar associations were not established for ligamentous ankle injury or superficial injury of the upper extremity. These results strengthen previously reported associations between ACL injury and menstrual cycle hormone fluctuations, and further imply that pharmacologic intervention might be a viable method for preventing these injuries. Prospective efforts are not only warranted but necessary to establish a causative relationship between the two.

CRUCIATE LIGAMENT REPAIR

Many reports delineate ACL injury rates in athletes.[2,15,35,49-53] The present study includes both athletes and non-athletes with no means of distinguishing the two. Currently, there is no published literature on the rate of ACL injuries in the general population in the United States. In lieu of such data, four countries, New Zealand, Sweden, Norway, and Denmark, have national ACL injury databases established to track incidence, management, and prognosis. In Sweden, the average incidence of cruciate ligament injury was 78 per 100,000 people.[46] Sex-specific injury rates were not reported, but 36% of females and 37% of males sustaining an ACL injury underwent reconstruction, which averages to 32 ACL reconstructions per 100,000 people.[112] The average percentage of ACL injuries undergoing reconstruction in the U.S. is only 22.6%.[113] The most at risk age range for both sexes for each national cohort had much higher incidence of ACL reconstructions with Norway (16-39 years) at 82, Denmark (15-39 years) at 92, and Sweden (20-39 years) at 71

reconstructions per 100,000 people.[112] Females had slightly lower rates of reconstruction that ranged from 39 to 88 per 100,000 persons for those reported age groups among the three countries.[112] Incidence rates from the New Zealand study were presented in person years making it difficult to compare to our study.[47]

It is estimated that 80,000 to 100,000 ACL reconstructions take place annually in the U.S.[114] This would mean that on average 25.5 to 32 reconstructions take place per 100,000 people in the U.S. (based on the U.S population of 313.9 million in 2012), which is comparable to all the average rates of reconstruction for the general population in the Scandinavian studies. This study estimates that, for females in Clinformatics Data Mart, there were 320 ACL reconstructions per 100,000 people. This is much greater than reported rates from the Norway joint database, reporting about 77 reconstructions for females per 100,000.[112]

Due to the nature of Clinformatics Data Mart we expected our incidence to be higher than other reports. We speculated that this very large incidence rate is due to a bias inherent to private insurance data. All enrollees in Clinformatics Data Mart hold a private national insurance. Collins et al. reported that patients with ACL injury and private insurance were nearly 2 times more likely to receive an ACL reconstruction than those with Medicare/Medicaid or self-pay.[113] Another report on pediatric ACL reconstructions revealed that privately insured patients with ACL injury were 57 times more likely to be offered an appointment for assessment and management of the injury.[115]

Among the Scandinavian joint registries the mean age of those undergoing ACL reconstruction was 27 years old.[116] From the same article, a similar database at Kaiser Permanente in the U.S. reported an average age of 27.8 years for those undergoing reconstruction. Our cases had an average age of 24.11 years. The slightly lower average is most likely due to the exclusion of females 40 years and older in our study. We also excluded females under the age of 15 years, but this cohort accounts for very few ACL injuries and reconstructions. ACL injury in children 12 years and younger is rare and one

report found that only 3% of injuries presenting to a sports medicine clinic were in children 14 years and younger.[117,118] Though very young females do not have a high injury risk, girls ages 15-20 years have the highest number of ACL injuries by a wide margin.[119] The distribution of ACL injuries by 5 year age groups can be seen in **Figure 5.1**. Observationally, females aged 15 to 19 years had approximately 2.5 times more injuries than the next 4 age categories (up to 39 years). Comparably, females ages 11 to 20 years, had the highest percentage of injuries that eventually underwent reconstruction at 55%.[46] Reconstruction rates decreased over the next two decades of age groups and reconstruction percentages were reported to be about 48% for ages 21-30 years and 32% for ages 31-40 years. In agreement, Collins et al. reported that although a greater total number of injuries occur in older populations, younger populations were 1.5 to 2 times more likely to undergo reconstruction.[113] Nearly half of all cases in our cohort, 46%, were ages 15-19 years, consistent with the published literature. Each of the remaining 4 age groups made up anywhere from 10% to 17% of our cohort. We did not gather data to determine the distribution of injury diagnosis for this particular database, but the reconstruction rates, depicted in **Figure 5.2**, are the greatest in the same age group that injury rates have also been reported to be the greatest (**Figure 5.1**).

Figure 5.1: All ACL injuries by age and sex in the Norwegian Registry

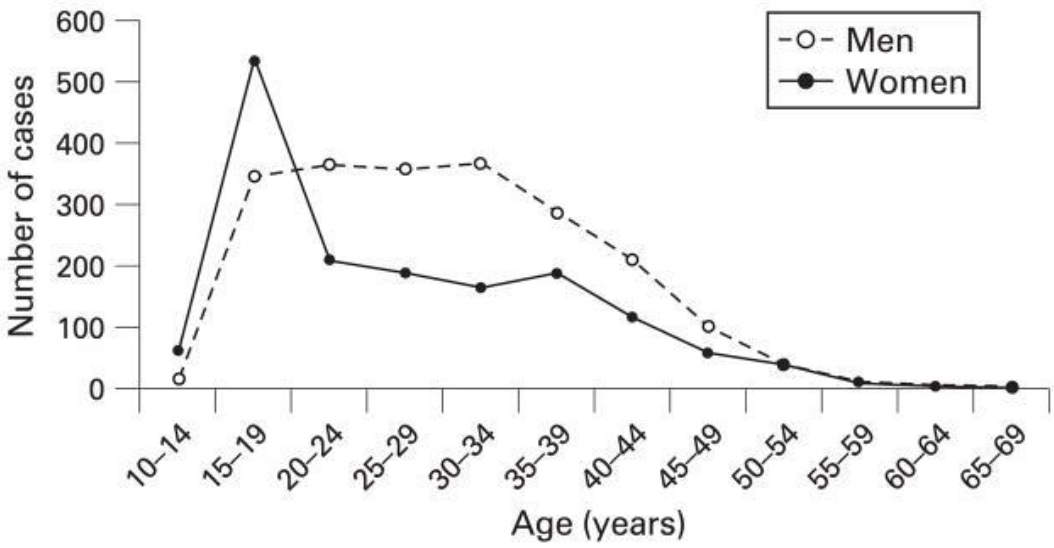
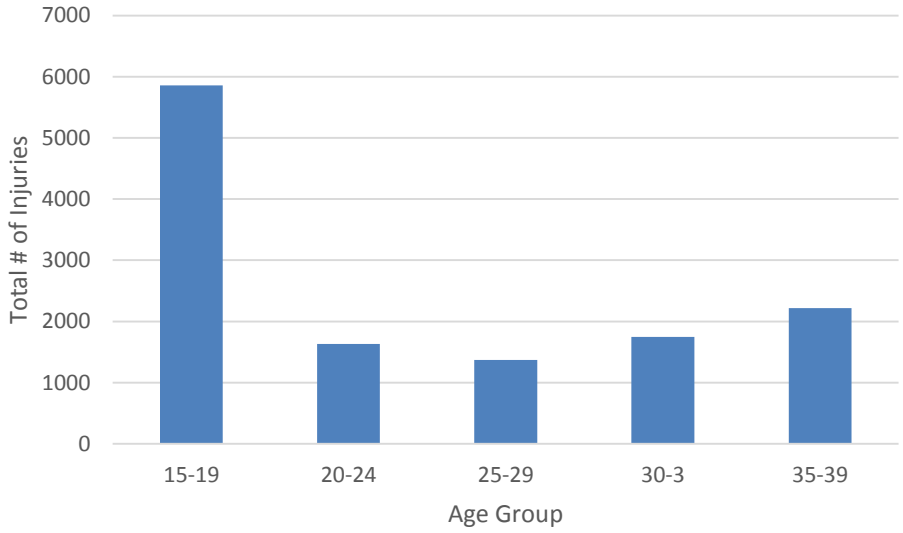


Figure used with permission.[119]

Figure 5.2: Female ACL Tears Requiring Reconstruction by Age Group



Females aged 15-19 years who underwent ACL repair surgery were 1.22 times more likely to not use OCs than controls in the 12 months prior to injury ($p<0.0001$). For the age groups 25-39 years cases were more likely to use OCs than controls in rates ranging from 1.1 to 1.16 higher. When the ORs are presented as a forest plot a clear trend emerges,

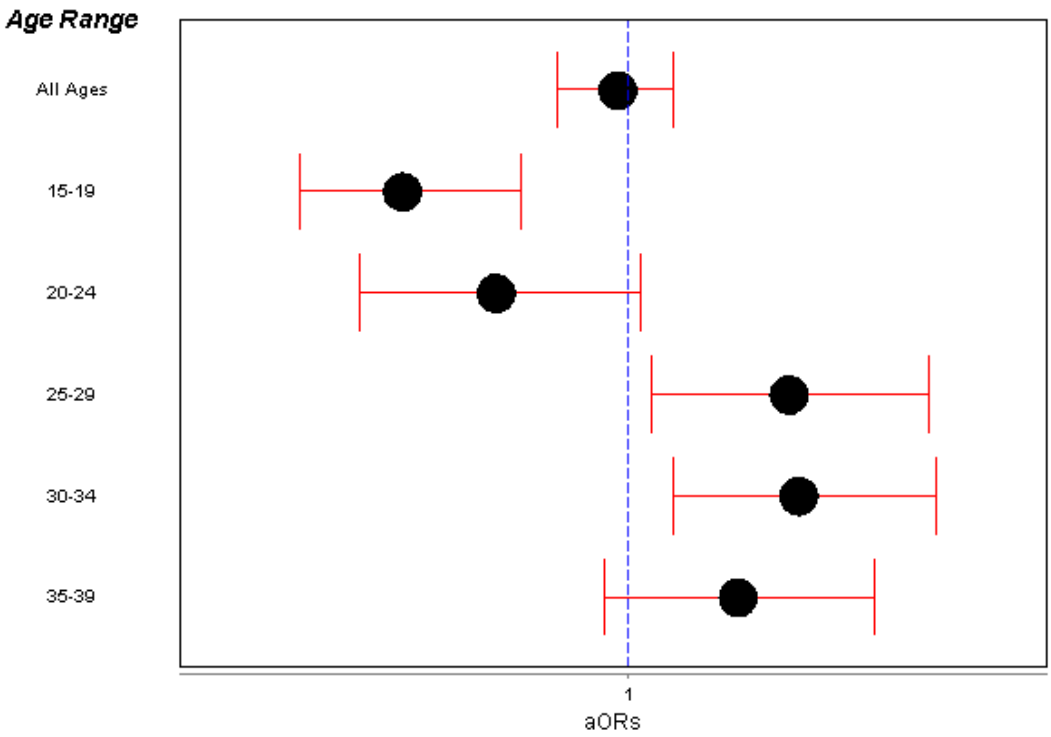
that is the ORs increase as age increase until the age group 35-39 years (**Figure 5.3**). Recall that in a meta-analysis women in their follicular and ovulatory phases sustained injury at approximately 1.35 times more than expected.[3] Women in their luteal phase sustained 35% fewer ACL injuries than expected. This means that if ACL injuries in the follicular and ovulatory phase could be reduced by 35%, the total number of ACL injuries expected during each phase would also be reduced and all observed values would match expected values for ACL injury during each phase of the cycle. In other words, about 35% of ACL injuries in women athletes can be attributed to cycle phase and hormonal changes. At most we would expected to see a 35% reduction in ACL injuries among OC users and anything more should raise a red flag. Our results show that OCs users had 18% fewer ACL injuries than OC nonusers in those aged 15-19 years. This modest decrease accounts for about half of the maximum expected effect suggesting that hormones appear to play a role, but are not the complete solution to ACL injury reduction occurring as a result of menstrual cycle hormonal changes.

We believe this trend in ORs is an artifact of association biases inherent in the large data set. Clinformatics Data Mart offers no means to determine athletic status or body habitus. In short, we believe athletes are more likely to injure the ACL than non-athletes, OC use in athletes is greater than the general population, and as age increases the percentage of athletes among controls in an age group decreases whereas it remains constant among cases. If this is the case, this change in control group composition relative to case group composition acts to artificially inflate the odds ratio, leading to the pattern we see in the data, increasing adjusted ORs with age.

Of 40 consecutive ACL injury presentations by females in a study of menstrual cycle association, 89% of injuries were due to participation in sport.[84] More comparable to our outcome variables, activity level is the only significant predictor of deciding to undergo reconstruction after surgery.[120] Patients with the highest activity levels were the most likely to choose reconstruction over non-treatment and those with moderate to low activity levels

were less likely to undergo reconstruction. In a cohort of soccer players, 54% of athletes sustaining ACL injury underwent reconstruction.[1] To compare, when athletics was not the cause of injury only 17% had reconstruction performed.[121] The evidence suggests that athletes are not only more likely to sustain an ACL injury, but they are more likely to choose reconstruction over non-treatment compared to non-athletes. That means that enrollees in our cohort of cases are much more likely to be athletes than those in the control selection introducing bias. By what magnitude is unknown.

Figure 5.3: Adjusted Odds ratios and their 95% CIs of ACL reconstruction in OC Users Compared with Nonusers by Age

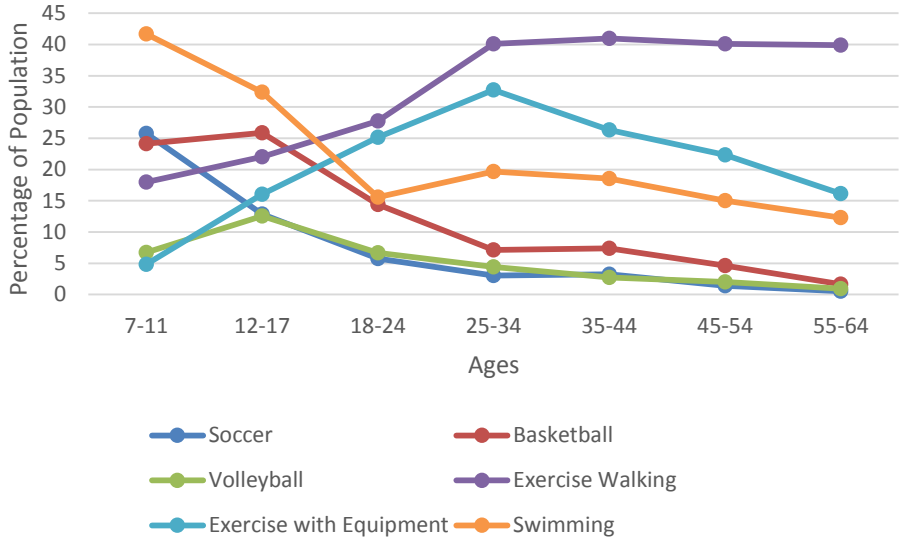


aORs, adjusted odds ratios

All cases, regardless of age, are more likely to be athletes than controls. Additionally, as age increases, controls are even less likely to be athletes in sports that have a high risk of ACL injury. The Physical Activity Council reports that the percentage of the

U.S. population that is inactive remains wholly unchanged from age 18 years to 44 years, ranging from 24.7% to 26.4%.[122] Ages over 44 years have higher percentages of inactivity and ages below 18 have slightly lower percentages of inactivity. In terms of total physical activity, the U.S. Census Bureau reported similar trends.[123] These trends are plotted in **Figure 5.4** for selected sports. Participation in the three high risk sports presented, basketball, soccer, and volleyball, drops drastically after the age of 17 years and then again, though not as great, after the age of 24 years. Low ACL injury risk activity, including walking, swimming, and exercise with equipment, participation rates do not drop as drastically and, in some cases, increase with age. In light of this and previously presented evidence it is conservative to say that our case group is comprised of a larger proportion of athletes than controls. As age increases, the proportion of athletes participating in high risk sports among our controls most likely decreases. This bias is inherent to the data and cannot be reasonably accounted for in multivariate analysis.

Figure 5.4: Percentage of U.S. Population Participating in Selected Sports and Activities by Age



Constructed with data provided by the U.S. Census Bureau.[123]

This bias is important in interpreting our results regarding OC use influencing ACL reconstruction because athletes are more likely to use OCs than non-athletes. The Centers for Disease Control report that 68% of women 15 to 44 years use some form of contraception and that of these, 28% use birth control pills.[124] Overall, this calculates to use rate of 17.4% among the general population of females in the U.S. ages 15 to 44 years. Another takeaway is that contraception use increases along with age. That is in the age group 15 to 19 years, only 32% reported using some type of contraception, whereas for the 40 to 44 years age group, 75% reported using contraception. Birth control pills are more popular in younger women and female/male sterilization is more popular in the older groups. In contrast, a cohort of soccer players had an oral contraceptive use rate of 39%, OC users had an average age of 20.6 years and nonusers had an average age of 19 years.[91] Another observational study reported an OC use rate of 32.9% among a group of collegiate soccer and basketball players.[99] Roughly, athletes are approximately twice as likely to use oral contraceptives as their non-athletic peers. In our study the average use rate for oral contraceptives across ages 15 to 39 years was 23.4% for cases and 22.8% for controls, elevated a bit above the national average for women 15 to 44 years. This may be due to the fact that women 40 to 44 years of age are less likely to use OCs than younger cohorts. If our cases are more likely to be athletes, it follows that they should have higher rates of OC use. However, in our study we are attempting to demonstrate that the use of OCs may protect against ACL injury. A lower use rate among cases, with a high expectation to be athletes, in the age group 15-19 years as opposed to an expected higher use rate in athletes supported by the current literature, as was found in our study is actually a strong indicator that we are really seeing lower ACL reconstruction rates among OC users.

In summary, cases in this study are more likely to be athletes than controls because athletes are much more likely to injure the ACL than non-athletes. As age increase, the magnitude of this difference increases such that controls become less and less likely to participate in sports that risk ACL injury as they age. Due to the specificity of ACL

reconstruction, we still assume that cases of ACL reconstruction across all ages are equally likely to be athletes. Finally, athletes are more likely to use OCs than non-athletes. None of these can be adjusted for as we do not know the athletic status of enrollees. All of these biases work in opposition to the direction of association we hypothesized between ACL reconstruction and OC use, that OC users would be less likely to undergo ACL reconstruction. This means that if anything our estimates are conservative and that the true ORs describing the relationship between ACL reconstruction and OC use are much lower than what we report here.

According to our data, females ages 15 to 19 are most at risk for undergoing ACL reconstruction (45.69% of cases) and OC use in this age group has the greatest influence on that outcome such that OC users are less likely to be cases than nonusers. Pubertal changes in this age group may explain the high number of cases and protection granted by OC use. In chapter 1 it is explained how estrogen decreases collagen synthesis in ACL fibroblasts leading to increased knee joint laxity and, ultimately, an increased risk for ACL injury. Puberty, starting around ages 10 to 11 years and ending around 15 to 17 years in females, incurs a rather steep rise in estrogen levels increasing the magnitude of knee joint laxity compared to older populations and compared to Tanner stage matched males.[125-128] Additionally, pubertal changes that may contribute to an increased risk of ACL injury include rapid limb growth with muscle inadequacy and incoordination as the neuromuscular system lags in development behind limb growth.[127] In fact, sex differences in ACL injury rates do not exist before puberty and are only observed beginning around ages 10 to 11 years in females, the same as the onset of puberty.[50,129,130] The evidence suggests that estrogen reducing drugs, such as OCs, would exhibit the greatest reduction in ACL injuries among this age group and that is what our data shows. Girls using OCs in this age range may experience a greater magnitude of protection from ACL injury as never before experienced increases in estrogen are subdued and knee joint stability remains intact as limb growth and neuromuscular coordination develops in the pubertal female. In the

years following puberty and beyond, unprecedented rises in estrogen levels are rare. Additionally, the neuromuscular system has adapted to the now adult body. The presence of fewer risk factors to ACL injury in the post-pubescent female may explain both the decreased incidence of ACL injury as well as the decreased effectiveness of OC use in preventing injury, that is to say that acquired coordination is preventing the same injuries that would have been prevented by OC use in a younger individual.

Additionally, estrogen effects the central nervous system and possibly effects coordination and fine motor skills, a property that would affect all women of child bearing age. In general, estrogens and testosterone exhibit a stimulatory effect on neuronal communication, while progesterone exhibits an inhibitory effect.[131] The magnitude of this effect is dependent on both serum levels of these hormones as well as local synthesis. Gross manifestations of increased serum estrogen levels possibly include decreases in dominant limb coordination asymmetries and enhancement of fine motor skills with a concomitant decreases in spatial ability.[132,133] Though these changes can be demonstrated in a lab setting, fine motor coordination, postural stability, knee strength, and knee joint kinematics and kinetics have been shown to not significantly vary as a function of menstrual cycle serum hormone concentrations in healthy, active young females.[134] This suggests that although estrogen does have neurostimulatory effects on the central nervous system those effects most likely are not severe enough to predispose to ACL injury. Rather, the estrogenic effects on pure ligament strength and laxity which have been shown to cyclically align with menstrual cycle estrogen concentrations are a more likely culprit in female predisposition to ACL injury.

As mentioned in Chapter 1, there have been two previous studies attempting to identify an association between OC use and a decreased incidence in ACL injury. The major drawback to these projects were the limited sample sizes resulting in a low degree of power. Agel et al. reported that their study would detect a fivefold difference in ACL rates between OC users and nonusers at a minimum.[99] Reudl et al., without reporting power

analysis analyzed 93 cases of ACL injury in skiers matched 1:1 to controls by age alone and the authors admit this is too low of a number to arrive at a firm conclusion.[100] Our reported adjusted ORs are smaller than the magnitudes detectable by the previous studies. Compared to a 500% reduction, we found approximately an 18% reduction in injury among our youngest age group possibly due to OC use. The range of ages in our study is also a great advance over previous work. Agel et al. reviewed only injuries in collegiate athletes and Ruedl et al. utilized a cohort whose average age was 38 years. Both of these works do not attempt to demonstrate trends in ACL injury in OC use as they might vary with age. In both detecting differences in ACL injury rates between OC users and nonusers as well as reporting age specific outcomes out study is unique, the first of its kind, and one of only three known studies on the topic.

Our results also demonstrated that for logistic regression including all ages, monophasic prescriptions had a significantly lower adjusted OR than triphasic prescriptions in predicting our outcome of ACL reconstructions. By age groups, there were not statistical differences between these therapies suggesting a weak association at best as we still had very large degree of power among the younger age groups. The difference between these two therapies is the dosing of hormones throughout a single menstrual cycle. Monophasic pills contain the same amount of hormone throughout the entire menstrual cycle. Triphasic pills have increasing amounts of progesterone and sometimes estrogen that change on a weekly basis throughout the menstrual cycle. It has been hypothesized that laxity caused by estrogen alone is only part of the equation resulting in an increased risk for ACL injury. Rather, the changes in laxity throughout the menstrual cycle prevents the neuromuscular system from adapting to instability creating a prone phase within each cycle. Regardless of absolute values, if laxity is held constant the neuromuscular system should be able to adapt in such a way to protect the knee joint and ACL. For this reason, monophasic treatments may have added benefit over triphasic therapies. Whereas both medications should decrease estrogen levels and decrease knee joint laxity, only

monophasic pills, in theory, should keep the knee joint laxity constant throughout the menstrual cycle whereas triphasic pills may be associated with small cyclic changes in laxity. We do not believe there to be a difference in therapy type as it relates to ACL reconstruction and injury, but suggest that formulation and dosage be analyzed as potential confounders in any future prospective endeavors.

In addition to reporting on the influence of OC use on ACL reconstruction, we found significant associations with ACL reconstruction among our covariates. Our largest adjusted OR was associated with athlete risk status. Those athletes who had a lower limb injury commonly resulting from athletic participation in the 12 months previous to index or procedure date were labeled as high risk and were 2.77 (95% CI: 2.53-3.04) times more likely to undergo an ACL reconstruction than those without a history of injury. Though previous ACL injury or reconstruction has been associated with an increased risk for re-rupture or ACL injury, no reports have found a link between previous lower limb injury and ACL injury risk. It may be that specific lower limb injuries lead to muscle imbalance, incoordination, or functional limitations that predispose an athlete to ACL risk. There is also the possibility that the insult that caused the ACL injury in our cases also caused the injury labeling one as high risk. Our data cannot quantify or comment on how exactly this relationship is mediated and further investigation is needed.

Expectedly, we also report that cases with a steroid joint injection as well as antibiotic use in the 12 months previous to index date were at greater risk to undergo ACL reconstruction than those who had not received either of the two. In regards to joint injections, there is evidence that corticosteroids weaken soft tissues such as articular cartilage and tendons by decreasing collagen synthesis and, in the case of tendons, forming fatty nodules that increase the potential to rupture.[103,135] Either joint steroid injections are directly weakening ligamentous structures or previous knee injury requiring a joint injection for pain management, along with the increased capacity for exercise with the reduction in pain, is responsible for the increased risk for ACL reconstruction. Regardless,

it is the recommendation of these authors that athletes receiving joint steroid injections abstain from activities and maneuvers that are known high risk for ACL injury. In regards to antibiotic use, there are many reports of tendon rupture, and a few of ligament rupture, associated with the previous use of fluoroquinolone antibitiotics.[107,136,137] In our study we included any antibiotic use and found a modest increased risk for ACL reconstruction over non antibiotic users (adjusted OR: 1.26). We were not able to determine the proximity of antibiotic use to actual ligament rupture. Even so, antibiotic use may play a minor role in the risk of ACL rupture and caution should be taken when using antibiotics, particularly fluoroquinolones, and participating in athletics. It was also noted that increase Elixhauser Comorbidity Indices were associated with less risk for ACL reconstruction. This is most likely because those with comorbidities should be less likely to participate in athletics, decreasing the risk for rupture of the ACL. A similar association was observed in patients diagnosed with type 1 diabetes mellitus and we assume that these patients are also less likely to participate in athletic activity, leading to lower adjusted ORs. Lastly, inhaled and oral corticosteroid users had greater odds of undergoing ACL reconstruction than nonusers. Though the current literature does not support the idea that inhaled or oral steroid use can lead to weakened ligamentous structures as injected steroids do, it does remain a possibility. More likely, users of oral corticosteroids are likely to have ligamentous or tendinous injury for which they were originally described. Pain and inflammation reduction through the use of the oral corticosteroids could lead to over-confidence or a premature return to intense athletics, predisposing to serious injury such as ACL rupture.

LIGAMENTOUS ANKLE INJURY

As mentioned in the methods, our definition of ligamentous ankle injury includes ICD-9-M codes for the diagnoses of ankle sprains and ankle dislocations. An ankle sprain is considered any injury involving ligaments about the ankle, including rupture, tear, or

stretching. Ankle dislocations, a more severe and rare injury, will often involve damage to a ligament structure, if not a complete rupture.[138] Ankle dislocations have also been associated with a fair amount of ankle fractures.[139] Even in athletics, ankle dislocation is rather rare. In a cohort of three soccer leagues over a single season, 56 total ankle injuries were sustained by players of which 43 were sprains and only 1 was a dislocation.[140] Diagnosis of dislocation was included in this study to ensure a complete picture ligamentous ankle injury and, for the sake of this discussion, ligamentous ankle injury will be referred to as ankle sprain.

In a study of the NEISS database, 3.1 million total ankle sprains were recorded over the course of 5 years in the United States.[141] Incidence for this at-risk population presenting to the emergency department was 2.15 per 1000 person hours. Athletic activity was the number one cause of ankle sprains at 49.3%, stairs accounted for the second most at 26.6%. Most ankle sprains occurred at home (47.9%) as opposed to a place of recreation (28.5%) or at school (14.5%). No major differences in rates between males and females were reported. In another report detailing ankle sprain incidence among high school athletes, the overall incidence rate was 3.65 per 10,000 AEs.[142] Overall, boys had lightly higher rates of ankle sprain than girls. However, for the sports of soccer, softball/baseball, and track and field, girls had significantly higher rates of ankle sprain than boys. According to this study, unlike ACL injury, ankle sprains occur primarily as a result of person-to-person contact (42.4%), playing surface contact (26.7%), and, lastly, non-contact mechanisms (25.5%).

It is apparent that ankle sprains are much more common than ACL injuries or, in the case of this report, ACL reconstructions. With our data, we calculated an incidence rate for ligamentous ankle injury of 40.7 per 1000 enrollees. Whether this number is high, low, or reasonable is unknown as we cannot compute person years from our data set. Most of these injuries, 75%, occur outside the age range of 15-39 years. We also do not know how many of these injuries are recurrent or misdiagnosed. Even with these limitations, we can internally report that ankle sprains were 13 times more common than ACL reconstructions.

Assuming the reconstruction rate in our cohort is similar to that of the U.S. national average of 23%, our study reports ankle sprains to be about 2.9 times more common than ACL injury.[113] Agel et al. reported ankle sprains to be about 2.6-3.1 times more common than ACL injuries in a cohort of collegiate basketball and soccer players.[99] Internally, our numbers are consistent with the current literature and we have no reason to believe that they are artificially inflated or deflated.

Athletes most commonly suffer from lateral ankle injuries due to inversion.[143] In fact, 25% of all injuries to the musculoskeletal system, and 50% of athletic injuries, involve inversion about the ankle.[144] Forces generated during inversion determine the extent of ligament sprain. The anterior talofibular ligament is the most commonly injured structure, followed by the calcaneofibular ligament.[145] Medial sided ankle sprains are much less common as eversion injury is also less common. Further, the medial sided deltoid ligament, comprised of 4 structures, is the strongest ligament about the ankle.[146] Ankle sprains are the most common musculoskeletal injury due to the vulnerability of the ankle joint while walking and maneuvering during everyday activities. These common motions include "stepping up or down on an uneven surface, particularly when wearing shoes with platform soles or high heels; stepping wrong off a curb or into a hole; or stepping on an object left in the wrong place."[146] Unlike motions that predispose to ACL injury, the average person is very likely to encounter obstacles requiring motions that will risk an ankle sprain on a daily basis.

We hypothesized that ligamentous ankle injury would be more common among OC nonusers compared with users. Results show that this is not the case and we obtained adjusted ORs very close to 1 for all age groups in regards to OC use status. Ankle sprain incidence also did not vary significantly as a function of OC formulation or dosage. There are a multitude of reasons explaining why a clear association between ACL reconstruction and OC use was observed, but was not observed between ligamentous ankle injury and OC use. These include the comparison of a diagnosis outcome to a procedure outcome,

different thresholds to injury, and possible biological differences in ligament structure. These arguments are discussed in depth in the next section.

As with ACL reconstruction, ligamentous ankle injury was significantly associated with a few covariates. Enrollees labeled as high risk were 4 times more likely to sustain an ankle injury than those labeled as low risk. This could mean that those sustaining an ankle injury also sustained another athletic type injury at the same time, that a previous athletic type injury caused a functional deficit increasing the risk for ankle injury, or that the patient participates often in risky activities, leading to multiple unrelated athletic type injuries. The bottom line is that individuals with an athletic type lower extremity injury should be cautious as the risk for a ligamentous ankle injury may be increased. Also of note, the odds of sustaining an ankle injury increased as the Elixhauser Comorbidity Index increased, opposite of what was seen with ACL reconstructions. Whereas ACL reconstructions are occurring primarily in athletes and comorbidity may prevent a person from participating in athletics, thus reducing the odds of injury as the Elixhauser Comorbidity Index rises, ankle sprains are very common among non-athletes as well as athletes. We speculate that comorbidity among non-athletes is the reason for this trend. Many of the comorbidities included in the calculation of the Elixhauser Comorbidity Index affect mobility and include paralysis, neurodegenerative disorders, rheumatoid arthritis, collagen vascular disease, and obesity.[111] As the Elixhauser Comorbidity Index increase, the odds that mobility has been affected should also increase and if mobility and coordination is negatively affected, the risk for an ankle sprain increases. We also reported modestly increased odds of previous injectable steroid use, antibiotic use, and asthma diagnosis among those with ankle injury.

There is no evidence to support a protective relationship between OC use and ligamentous ankle injury. Factors influencing ankle injury may be too complex to be affected by a potential minor increase in ankle joint stability theoretically offered by OC use.

OC USE IN ACL TEARS REQUIRING RECONSTRUCTION VERSUS ANKLE SPRAINS

We initially hypothesized that OC users would have lower rates of both ACL reconstruction and ankle sprain. Our results determined that this is the case for females ages 24 and younger in regards to ACL reconstruction, but no such association exists in regards to ankle sprain. Further, results from the ACL reconstruction outcome exhibit a trend of increasing rates that is potentially explained by a data source bias. No such trend exists in the ankle sprain data. In fact, the adjusted ORs for ankle sprain in OC users for all age groups were within 10% of the reference group of nonusers. This means that ACL injuries and their subsequent reconstructions respond differently to OC use than do ankle sprains as a result of biology, mechanism of injury, or a procedural bias has introduced noise into the system, specifically the data regarding ankle sprains, obscuring any association that might be present. In practical terms the different results could be a result of differences in ACL and ankle ligament strength, concentration of estrogen receptors, mechanism and commonality of injury, or coding and injury diagnosis.

The ACL and the major ankle ligaments act in biomechanically different ways to stabilize their respective joint. The primary function of the ACL is to prevent excessive anterior tibial translation at all degrees of knee flexion.[147] The ACL also functions to prevent excessive hyperextension and tibial rotation and acts as a secondary stabilizer during knee valgus and varus loading.[148] In testing, the human ACL will rupture at around 1725 Newtons.[149] As total knee joint forces during intense maneuvers can exceed this amount, the functional stability of the knee may be of greater importance than simple ligament strength.[150] How much load is transferred through the ACL during high intensity maneuvers is a function of complex neuromuscular control dictated by both muscle and ligament mechanorecpetors.[151] Ideally, load is balanced and transferred through tense muscles/tendons as well other ligamentous structures of the knee. Failure of the neuromuscular system to respond properly or rapidly enough during these high loads to

produce muscular tension can result in excessively high loads being placed on the ACL, even for a very brief time, which can result in a tear or total rupture. Some speculate that neuromuscular incoordination during puberty operates in this manor mechanistically and is to blame for such high ACL injury rates in young female athletes.[127] Traumatic rupture of the ACL, though much less common than non-contact means, is thought not to contribute to sex differences in injury rates and therefore is not examined here.

In regards to ankle sprain, there are many ligamentous structures at risk of being injured under a variety of circumstances. Here we will focus on the most commonly injured ligaments of the ankle. 85% of all ankles sprains occur as the result of an inversion incident and risk injury to the following three ligaments listed in order from weakest to strongest: anterior talofibular ligament, calcaneofibular ligament, and posterior talofibular ligament.[152] Intact anterior talofibular ligaments rupture under loads of around 154 Newtons.[153] While the underlying cause of most ankle sprains is poor proprioception, insufficient ankle dorsiflexion strength, and poor flexibility, the primary mechanism resulting in an ankle sprain, and injury to the anterior talofibular ligament, occurs due to improper foot positioning during ground contact resulting in a medially deviated force and rapid inversion of the foot on the order of 50 ms.[152,154] This force need not be the result of athletic participation, but can commonly occur when going down stairs/steps or traversing uneven terrain. For this reason, ankle sprains should be tied less to age than ACL rupture/reconstruction is and, indeed, in our data only 36% of ankle sprains occurred in females aged 15-19 years, whereas that same age group incurred 45% of all studied ACL reconstructions.

The tolerable forces and failure loads of each of these ligaments tells us little as to why ankle sprains are more common than ACL ruptures or why one may respond to changes in hormone levels artificially induced by OC use. However, epidemiology demonstrates that ankle sprains are much more common than ACL injuries in all cohorts. The anterior talofibular ligament is a relatively weak ligament compared to those of the

knee and the ankle is a much less stable joint than the knee. Whereas the knee moves within one plane, the ankle can move in all planes, requiring more coordination to provide stability. As a result, the ankle can be sprained during common, everyday activities whereas the ACL requires very specific circumstances that rarely occur outside of athletics. Opportunities for ankle sprains are ever present and even if ankle ligament laxity is decreased with OC use it may be that injury is inevitable in an at-risk population with poor proprioception, weak dorsiflexors, or weak flexibility. Increased ligament strength could prevent a few adverse incidents along the road to injury, but by sheer number of risky activities, an ankle sprain could be destined to occur regardless of increased ligament strength. In contrast, risky maneuvers predisposing to ACL injury are less common and only a handful may even reach the threshold for injury. The hypothetical increased strength of the ACL may only be tested a handful of times, giving it less chance to rupture and providing a possible explanation as to why ACL rupture risk appears to respond to OC use.

The previous speculation assumes that OCs affect both the ACL and the ligaments about the ankle in the same manor, but the literature does not necessarily support this hypothesis. In regards to the ACL, estrogen and progesterone receptors have been localized to stromal fibroblasts.[4] In a receptor binding study, estrogen receptors were present in 4-10% of all ACL cells.[155] The presence of estrogen has been demonstrated to reduce ACL strength in rabbits by about 11% , most likely due to decreased collagen synthesis by embedded fibroblasts.[6] No similar studies have been performed in regards to the ligaments of the ankle. Agel et al. speculates that ankle ligaments ought to have the same biology as the ACL, but no published researched has reported the presence of estrogen receptors or decreased ligament strength in the presence of estrogen. It is altogether possible that ankle ligaments do not respond to estrogen in the same manner in which ACLs do.[99] Ericksen et al. assessed ankle anterior-posterior (AP) and inversion-eversion (IE) laxity in males in females to determine if the hormonal milieu 5 days pre and 5 days post ovulation had any measurable effect.[156] Though females were found to have greater IE laxity than males, there

was no time course difference in AP or IE laxity within females. Menstrual cycle hormones had no effect on ankle ligament laxity. In another study, investigators found no differences in ankle or knee laxity in relationship to the changing levels of estrogen throughout the menstrual cycle.[157] Their findings regarding knee laxity, however, are not supported by a multitude of research that did find differences in knee laxity throughout the menstrual cycle.[88] If ankle ligament laxity does not vary as does ACL laxity, OC use should not have the same effect on ankle sprains that we have demonstrated it has on ACL reconstructions.

Though it is likely that mechanism of injury and biological influences are responsible for the difference in responses to OC use between ACL reconstruction and ankle sprains exhibited, ICD-9-CM coding could also be biasing our results. We selected ACL reconstruction, rather than a diagnosis of ACL sprain, as our determinant of ACL injury because the procedure code is less ambiguous and may have more integrity than the diagnosis code. It has been observed that diagnosis codes have the potential to be non-specific, or even incorrect in the translation from a doctor's note to medical billing and data entry.[158] There is also the possibility that a recorded diagnosis can be wrong from the initial encounter. For example, injury to the ACL could be coded as ACL sprain, internal derangement of the knee, or sprain of the knee (non-specific). These diagnoses also do not convey injury severity. The procedure codes of triad repair of the knee and repair of the cruciate ligaments assume injury sever enough to warrant surgery and, as explained earlier, are quite specific to ACL repair. Our decision to use diagnosis codes to identify ankle sprains was based on the common treatment protocol for them. ACL injuries are commonly treated surgically in athletes, but ankle sprain are not.[159] All but the most severe sprains, or those with chronic instability, can be treated reasonably well with rest and bracing. Unfortunately this forces us to compare diagnosis outcomes with procedural outcomes. Though we are confident that patients undergoing ACL reconstruction incurred a severe ACL injury, we cannot be certain of the severity or specificity of ankle sprains among those sustaining them. This means that even mild sprains with no ligamentous rupture may be

included in our cohort. These are the most common sprains and may occur regardless of any OC use. Additionally, by limiting our cohort to ACL reconstructions we introduce a bias that enrollees are more likely to be athletes. This bias does not carry over to our definition of ankle sprain as both athletic and non-athletic injuries ought to be diagnosed the same. This is important because most athletic ACL injuries are non-contact. Many ankle sprains occur under non-contact circumstances as well, but there is no selection bias for this cohort. Our hypothesis supposes that OC use would only affect non-contact injury, not traumatic injury. A large amount of traumatic ankle sprain injury could dilute the percentage of diagnosed non-contact ankle sprains. Traumatic injuries would not respond to OC use and could therefore pull our adjusted ORs toward 1. This selection bias could explain why OC use influenced ACL reconstruction incidence, but did not affect the incidence of ankle sprain diagnosis.

We cannot be certain as to why ACL tears requiring reconstructions are tied to OC use status in our results but ankles sprains are not. Mechanical joint properties offer few comparable differences other than differences in raw ligament strength. Injury mechanism commonality supports the idea that ankle sprains will happen regardless of a decrease in ligament laxity that may or may not occur with the use of OCs. Even supposing these theories are wrong, selection bias in ICD-9-CM coding is consistent with our reported results. This study supports the wealth of knowledge professing a link between knee laxity and menstrual cycle phase and provides an integral step in confirming that low estrogen levels strengthen the ACL and may prevent subsequent injury. Literature regarding ankle sprains, menstrual cycle phase, and joint laxity are sparse and report no connection. Consistent with these findings our study reports no connection in the reduction of estrogen through oral contraception use and a decreased risk for ankle sprain.

SUPERFICIAL INJURY OF THE UPPER EXTREMITY

Superficial injury of the upper extremity was selected as an outcome variable to act as a control that would demonstrate the uniqueness of any association between OC use and ACL reconstruction uncovered by this study. To verify our hypotheses, we have demonstrated that there is good evidence that OC use does influence the incidence of ACL reconstruction and, most likely, ACL injury as well. We hypothesized that OC use would not be associated with a diagnosis of superficial injury of the upper extremity as there is no known biological plausibility for such association. Logistic regression for this outcome variable was also intended to yield valuable information about our selected covariates and how they are affected in terms of an injury that is less associated with athletics than ACL rupture or ankle sprain.

Superficial injuries of the upper extremity are defined by the ICD-9-CM codes beginning with 912 (912.0-912.9). This list includes all diagnoses of abrasions, burns, blisters, insect bites, superficial foreign body, splinter, and unspecified superficial injury affecting the upper arm or shoulder with or without infection noted. This covers a broad range of injuries that are often treated conservatively. In Clinformatics Data Mart there were 58,247 females with a diagnosis of superficial shoulder injury. Most of these were either in an older or younger population than our inclusion ages of 15-39 years as only 9,360 cases met this criterion. Superficial shoulder injury incidence was much lower than both ankle sprain and ACL reconstruction incidence at 218 per 100,000. Common sense tells us that these injuries should be much more common than both ACL reconstructions and ankle sprains since they are relatively minor and anecdotally common. Indeed, most of these injuries should be sub-clinical and will be treated without consulting a physician meaning that they will not appear in the medical record. This implies that there is the possibility that these diagnoses were not the primary concern, but rather presented in

conjunction with a more serious injury. This possible selection bias may be important in understanding the influence of our covariates on superficial shoulder injury.

We hypothesized that OC use status would not significantly predict the outcome of superficial shoulder injury. In our multivariate conditional logistic regression model, this was not the case. OC users were slightly more likely to incur a superficial injury than nonusers with an adjusted OR of 1.15 (95% CI 1.06-1.25). Stratification by 5-year age group, however, revealed that OC use for all age groups besides females aged 15-19 years did not predict superficial shoulder injury. In the age group 15-19 years, girls with superficial injury were 1.45 time more likely to use OCs than those without such a diagnosis. There isn't any literature capable of explaining this particular association. This association is most likely the result of a selection bias. To speculate, we have already provided evidence that athletes are more likely to use OCs than non-athletes. It could be possible that this extends to all active females. In that case, superficial shoulder injury may be more common in an active population that is also more likely to use OCs. This association may only appear in this age group as it makes up the greatest percentage of our selected cohort. Even though one age group of those with superficial shoulder injury appears to be significantly associated with OC use, there is no extended trend passing through all age groups that offers explanation. In contrast, our cohort of females with ACL reconstruction demonstrate a distinct trend in OC use suggesting a direct association. The most likely explanation concerning superficial shoulder injury is that OC use does not affect injury rates.

Specific covariates revealed more information about who was being diagnosed with superficial shoulder injury. Patients labeled as high risk were slightly more likely to have a superficial injury with an adjusted OR of 1.61. This is much lower than adjusted ORs reported for ACL reconstruction and ankle injury. Our definition of high risk only included injuries of the lower extremity. Logically, having one of these injuries may predispose one to another lower extremity injury, such as our outcome variables, or a second injury could

have occurred at the same time. We would not expect shoulder injury to be associated strongly with our high risk category. This minor association that we do report may be a consequence of a superficial shoulder injury occurring at the same time as one of the labeled high risk injuries. Antibiotic use was also much more prevalent among this cohort compared to the ACL or ankle cohort. We speculate that this is mainly due to the fact that ICD-9-CM 912 codes include infection as a diagnosis. Antibiotics for these infections could have been prescribed before an official diagnosis was ever made in the chart. Steroid injections were significantly higher in the case group of superficial injuries. Steroid injections are often given to active individuals for the purpose of pain reduction so that one can return to normal activities. These patients are often more active, which should increase their risk for a superficial shoulder injury. Lastly, as the Elixhauser comorbidity scores increased, patients were more likely to have had a superficial injury. We cannot decisively say, however, why this is the case. Either functional deficits included as comorbidity could increase the risk of a superficial injury, or disease diagnoses included as comorbidity could increase the chance of a superficial infection or blister. In any case, this pattern is consistent with the Elixhauser comorbidity association seen with ankle sprains, but opposite of that seen with ACL reconstruction.

The purpose of our superficial injury cohort was to act as a control and an indicator of the significance of our findings in regards to ACL reconstruction and ankle sprain. In this respect, the cohort acted quite well. OC use rates among our age groups in this cohort provided little predictive power in regards to injury. In the one age group it did, 15-19 years, OC use was associated with the outcome of injury, the opposite of what we found with ACL reconstruction. Analysis of the covariates also demonstrated that our high risk variable has a higher specificity to other lower extremity injuries. The Elixhauser Comorbidity Index score also follows the expected patter of an increased score associated with an increased incidence of injury. Only in our ACL cohort did this pattern break down. We believe that comorbidity is prohibitive for the activity that causes ACL injury, but not

of activity that causes ankle sprains or superficial shoulder injury. This adds to the evidence that our ACL reconstruction cohort is comprised of mostly athletes, strengthening the argument that our adjusted OR estimates for that cohort are conservative and that the true adjusted ORs should be much lower. By showing the absence of an association between OC use and an injury with no known biological relationship to female hormones we are able to demonstrate that the relationship we did find in regards to ACL tears requiring reconstruction does not exist simply by chance.

SUMMARY AND CONCLUSIONS

Surgical reconstruction is currently the best treatment option for typical ACL injuries in athletes wishing to return to their sport as soon as possible. As stated earlier, ACL reconstruction offers no guarantee for future function, and athletes often cannot return to the same level of play prior to the ACL tear. Occasionally they do not return to play at all.[1] Among those that do return, re-rupture becomes a significant concern, and athletes status post-ACL reconstruction may be up to 15 times more likely to have another ACL injury in the next 12 months compared to uninjured colleagues.[160] In addition to these risks and limitations, ACL reconstructions generally costs $17,000 to $25,000 per procedure.[117] Due to the limitations in surgical outcomes in patients with ACL injury, only injury prevention offers an effective approach to keep athletes healthy and able to participate at a high level throughout their career. Current evidence regarding ACL injury prevention through training and conditioning has yielded inconclusive results. Diverse and novel prevention techniques need to be explored and implemented if ACL injury among female athletes is to be effectively reduced.

The literature suggests that up to 35% of ACL injuries in female athletes may be a direct results of cyclic estrogen levels inherent to the menstrual cycle. Although this does not explain the entire gap in injury rates between males and females, it indeed can explain

a significant portion of the female ACL injury incidence. We originally hypothesized that OC use in females would be associated with fewer ACL reconstructions. In other terms, females undergoing ACL reconstruction should have a greater odds of not using OCs compared to non-injured controls. Our hypothesis proved true for the two age groups 15-19 and 20-24 years, which also had the highest incidence of both ACL injury and ACL reconstruction. Additionally, monophasic treatments were associated with slightly lower adjusted ORs than triphasic therapies suggesting they may be more effective in preventing ACL injury. We also hypothesized that this association would extend to ankle sprains, another very common athletic ligamentous injury. However, we did not find such an association. We believe that ankle sprains are much more frequent than ACL injuries, and also they differ significantly in the injury mechanisms that involve loads of high magnitude. Simply, there are more instances for ankle sprains to occur and OC use may just delay the inevitable sprain. However, the extent of movement and loads resulting in ACL injury are distinctly lower, and OC use may provide just enough boost in ligament strength to prevent injury. Additionally, current research has failed to demonstrate ligament laxity changes in the ankle as a result of fluctuating estrogen levels—such an association does indeed exist with the ACL. It is biologically plausible that OCs and the concomitant reduction in estrogen levels could prevent ACL injuries through a decreased ACL laxity.

Results of this study suggest that OC use in females aged 15-19 years exhibit the highest reduction of the incidence of ACL tear requiring surgical reconstruction. By proxy, OC uses in this cohort should reduce the incidence of ACL injury. This statement is further substantiated by previous epidemiology studies demonstrating an association between estrogen and ACL strength. It has already been reported that athletes are more likely to use OCs than non-athletes. This occurs presumably due to reports of OC users having the benefit of predictable and shorter menses and therefore more consistent performance along with a greater feeling of stability during competition and training.[90,91] The prevention of ACL injury is just one more reason as to why OC use may be justified for young athletes.

However, this recommendation may not be without controversy. The use of OCs as an injury prevention device could include labeling of the drug as a performance enhancing drug. A performance enhancing drug is a substance used by an athlete to enhance performance and can be considered unethical or even illegal depending on the substance being used. Although it has already been recognized that OCs may enhance athletic performance through the reduction of menstrual symptoms and iron deficiency anemia, their wide availability, generally recognized safety, broad medical indication for use, and pivotal role in women's empowerment mean they are very unlikely to end up on a list of banned substances for competitive athletes.

Past research concerning OC use and ACL injuries was both retrospective and limited in scope. Our report expands the scope of observation by utilizing a national database. The large numbers we obtained allowed us to have increased power over previous studies, which proved inconsequential in finding the subtle difference in OC use status between ACL reconstruction patients and controls. However, our study also suffers from the common limitations of a case-control study. We cannot establish a causal relationship and speculation as to the practical outcome of OC use on ACL injury escapes our data. The next step in establishing a preventive relationship between OC use and ACL injury is the development of a broad prospective study. Ideally, a national cohort of female athletes will be followed over multiple seasons, tracking ACL injuries, OC use, and a list of pertinent covariates. This may be a question best answered by slight modifications to a systems already in place such as the NCAA Datalys injury surveillance program. The purpose of this particular study was to act as a bridge to spur higher level of evidence studies, demonstrating that OC use may prevent ACL injury. In that respect, it was a success.

Appendix A: Oral Contraceptive Exposure Definitions

A list of all oral contraceptives considered as exposure are found in **Table 6.1** and **6.2**. A list of oral contraceptives constituting grounds for exclusion in this study are presented in **Table 6.3**.

Table 6.1: Oral Contraceptives: Progesterone Only

Drug (generic)	Brand Name	NDC Code
Norethindrone	Camila	0555-0715; 54868-4814
	Errin	0555-0344
	Heather	68462-303
	Jolivette	52544-892
	Nor QD	52544-235
	Nora-BE	52544-629
	Norethisterone	68462-304; 65162-475; 0555-0211; 68462-305; 68180-876
	Aygestin	51285-424
	Micronor	54868-4369
	Ortho Micronor	0062-1411; 54868-4369; 50458-194

Table 6.2: Oral Contraceptives: Progesterone and Estrogen Containing Pills

Drug (generic)	Brand Name	NDC Code
Levonorgestrel Oral / Ethinylestradiol	altavera	0781-5583
	amethia	52544-268
	amethia Lo	52544-228
	amethyst	52544-295
	aviane	0555-9045; 21695-995; 54868-5356
	camrese	0093-3134
	camrese Lo	0093-6148
	Chateal	50102-130
	Enpresse	0555-9047; 21695-855; 54868-4860
	Falmina	16714-359
	Introvale	0781-5584
	Kurvelo	68180-844
	Lessina 21	0555-9013
	Lessina 28	0555-9014
	Levonest	16714-340; 34908-620
	Levora	42254-260; 52544-279; 54868-4607
	LoSeasonique	54868-6275; 51285-092
	Lybrel	0008-1117
	Marlissa	68462-388
	Microgynon	
	Nordette	51285-091
	Orsythia	0603-7634
	Ovranette	
	Portia 21	0555-9020; 0555-9019
	Portia 28	
	Quasense	52544-966
	Sronyx	52544-967
	Trivora 28	54868-4239; 52544-291
	Seasonale	51285-058
	Seasonique	54868-6276; 51285-087
	Lutera	54868-6210; 52544-949
	Jolessa	0555-9123; 54868-6044
	Myzilra	0603-7625
Norgestimate / ethinylestradiol	Mononessa	52544-247
	Ortho Cyclen-28	50458-197
	Ortho Tri-Cyclen	50458-191; 54868-4093
	Ortho Tri Cyclen Lo	54868-4730; 50458-251
	Mono-Linyah	16714-360
	Tri Linyah	16714-363
	Previfem	0603-7642; 0603-7663
	Sprintec 28	0555-9016; 21695-769

Table 6.2…Continued

Drug (generic)	Brand Name	NDC Code
Norgestimate / ethinylestradiol	TriCyclen	
	Tri-Lo Sprintec	0093-2140; 21695-770
	Trinessa	52544-248; 54868-5826; 21695-407
	TriNessa Lo	
	Triprevifem	0603-7663
	Tri Sprintec	0555-9018; 66116-436; 54868-5028
Etynodiol / Ethinylestradiol	Kelnor	0555-9064; 54868-5942
	Zovia	52544-383; 54868-4240; 54868-4778; 52544-384
Desogestrel / ethinylestradiol	Ortho-Cept	50458-196
	Desogen	0052-0261
	Apri	54868-4754; 0555-9043
	Caziant	52544-959
	Cyclessa	0052-0283
	Emoquette	0603-7540
	Kariva	54868-4742; 0555-9050
	Mircette	51285-114
	Reclipsen	52544-954
	Solia	66993-611
	Velivet	54868-5031; 0555-9051
	Viorele	68462-318
Drospirenone / ethinylestradiol	Yasmin	50419-402; 54868-4590
	Yaz	54868-5828; 50419-405
	Gianvi	66116-470; 54868-6162; 0093-5423
	Beyaz	50419-407
	Loryna	0781-5656
	Ocella	0555-9131; 54868-5922
	Syeda	0781-5658
	Vestura	52544-982
	Safyral	50419-403
	Zarah	52544-981
Norethindrone acetate / ethinylestradiol	femhrt	54868-4679; 0430-0145
	Jinteli	54868-6251; 0093-3122
	loestrin 1.5/30	51285-082
	Loestrin 1/20	51285-079
	microgestin 1.5/30	52544-950; 52544-951; 54868-6213
	microgestin 1/20	
	Junel 1.5/30	0555-9027; 54868-6272
	Junel 1/20	0555-9025
	Gildess 1.5/30	0603-7606
	Gildess 1/20	0603-7607
Norethindrone Acetate / Ethinylestradiol / ferrous fumarate	Loestrin 24 Fe	0430-0530; 54868-6100
	Lestrin Fe 1.5/30	51285-083; 51285-084
	Lestrin Fe 1/20	51285-080; 51285-081
	Lo Loestrin Fe	0430-0420
	Estrostep Fe	0430-0570
	Gildess Fe 1.5/30	0603-7608
	Gildess Fe 1/20	0603-7609
	Junel Fe 1.5/30	0555-9028; 42254-242; 54868-5935
	Junel Fe 1/20	54868-5326; 0555-9026
	Microgestin Fe 1.5/30	54868-4744; 52544-630; 52544-631
	Microgestin Fe 1/20	
	Tilia Fe	52544-143; 52544-175; 21695-685; 54868-6274
	TriLegest Fe	0555-9032
Norethindrone / ethinylestradiol	Aranelle	0555-9066
	Balziva 28	0555-9034
	Alyacen 1/35	68462-394
	Alyacen 7/7/7	68462-556
	Briellyn	68462-316
	Brevicon	52544-254
	Cyclafem 7/7/7	0603-7525
	Cyclafem 1/35	0603-7521
	Dasetta 1/35	16714-348
	Dasetta 7/7/7	16714-346
	Gildagia	0603-3590
	Leena	52544-219
	Necon 0.5/35	42254-287; 52544-550
	Necon 1/35	52544-552; 54868-4045
	Necon 10/11	52544-554
	Necon 7/7/7	68258-5005; 52544-936
	Necon	52544-245; 21695-857
	Norethin 1/35E	68180-897; 54868-4677; 51991-623; 51991-474
	Norinyl 1+35	52544-274
	Nortrel 0.5/35	0555-9008
	Nortrel 1/35	0555-9009; 0555-9010
	Nortrel 7/7/7	54868-5286; 0555-9012;
	Ortho Novum 7/7/7	50458-178; 54569-0689
	Ortho Novum 1/35-28	50458-176
	Ovcon 35	0430-0580
	Ovcon 50	

Table 6.2…Continued

Drug (generic)	Brand Name	NDC Code
Norethindrone / ethinylestradiol	Philith Modicon 28 TriNorinyl Wera Zenchent	16714-347 50458-171 52544-274 16714-370 52544-953; 52544-210; 54868-6273
Norethindrone / ethinylestradiol / ferrous fumarate	Femcon Fe Generess Fe Zenchent Fe Zeosa	0430-0482; 54868-6161 52544-204 52544-292 0093-2090
Drug (generic)	**Brand Name**	**NDC Code**
Norgestrel / Ethinylestradiol	Cryselle Lo/Ovral-28 LoFemanal Low-Ogestrel Elinest Ogestrel	0555-9049; 54868-4851 0008-2514; 54569-0679; 24090-801 52544-847; 54868-4850 16714-365 52544-848
Mestranol / Norethindrone	Necon 1/50 Norinyl 1+50	 52544-265
Estradiol Valerage / Dienogest	Natazia	50419-409; 54868-6183

Table 6.3: Non-Oral Hormonal Contraceptive Devices

Drug	Type	NDC	ICD-9-CM	CPT Code	J-Code
Implanon	Implantable	0052-0272	V25.50, V25.43	11981, 11982,	J7307
Nexplanon	Implantable	0052-0272	V25.50, V25.43	11983	J7307
DepoProvera	Injection	54868-3613; 54868-3348;	v25.49	90772, 96372	J1051, J1055,
Depo-SubQ Provera 104	Injection	54868-4100; 0009-7376;	v25.49	90772, 96372	J1056, J1050,
MPA	Injection	0009-0746; 0009-0626	v25.49	90772, 96372	
Mirena	IUD[a]	50419-421	V25.1, 69.7	58300	J7300, J7302
Skyla	IUD[a]	50419-422	V25.1, 69.7	58300	J7300, J7302
Ortho Evra	IUD[a]	50458-192			
Nuva Ring	IUD[a]	54868-4832; 0052-0273			
Ella	EC[b]	52544-0238			
Next Choice	EC[b]	52544-287-54			
Ovrette	EC[b]				
Plan B	EC[b]	51285-0769			
Plan B One-Step	EC[b]	51285-963-19			
Preven	EC[b]	63955-0020			

[a]IUD, intrauterine device, [b]EC, emergency contraception

Appendix B: MatLab Code for Pharmacy Claims Data Compression

The following is custom the custom MatLab code used to compress pharmacy claims today in order to determine the most commonly and most recent brand of oral contraceptive prescription filled by each enrollee defined as an oral contraceptive user.

```
function zz=occompress(input,output)
[num,txt,raw]=xlsread(input);
raw(1,:)=[];
raw=sortrows(raw,1);
num=sortrows(num,1);
length=size(raw,1);
patid=num(:,1);
cases=num(:,2);
days_sup=num(:,5);
ndc=raw(:,6);
brnd_name=raw(:,7);
fill_date=raw(:,4);
fill_day=zeros(length,1);
fill_mnth=zeros(length,1);
fill_year=zeros(length,1);
for y=1:length
    date=char(fill_date(y,1));
    if date(1,2)==char('/')
        if date(1,4)==char('/')
            mnth=str2double(date(1,1));
            day=str2double(date(1,3));
            year=str2double(date(1,5:8));
        else
            mnth=str2double(date(1,1));
            day=str2double(date(1,3:4));
            year=str2double(date(1,6:9));
        end
    else
        if date(1,5)==char('/')
            mnth=str2double(date(1,1:2));
            day=str2double(date(1,4));
            year=str2double(date(1,6:9));
        else
            mnth=str2double(date(1,1:2));
            day=str2double(date(1,4:5));
            year=str2double(date(1,7:10));
        end
    end
    fill_mnth(y,1)=mnth;
    fill_day(y,1)=day;
    fill_year(y,1)=year;
end
index_id=patid(1,1);
pat_store=[patid(1,1), cases(1,1), days_sup(1,1), brnd_name(1,1),...
```

```
    fill_year(1,1), fill_mnth(1,1), fill_day(1,1)];
master_out=[];
for x=2:length
    id=patid(x,1);
    if index_id==id
        lengthpat=size(pat_store,1);
        for m=1:lengthpat
            if size(char(pat_store(m,4)),2) ...
                ==size(char(brnd_name(x,1)),2)
                if char(pat_store(m,4))==char(brnd_name(x,1))
                    pat_store(m,3)={cell2mat(pat_store(m,3))...
                       + days_sup(x,1)};
                    if fill_year(x,1)>=cell2mat(pat_store(m,5))
                       pat_store(m,5)={fill_year(x,1)};
                       if fill_mnth(x,1)>=cell2mat(pat_store(m,6))
                           pat_store(m,6)={fill_mnth(x,1)};
                           if fill_day(x,1)>=cell2mat(pat_store(m,7))
                               pat_store(m,7)={fill_day(x,1)};
                           end
                       end
                    end
                elseif char(pat_store(m,4))~=char(brnd_name(x,1))
                    pat_store=[pat_store; patid(x,1), cases(x,1),...
                        days_sup(x,1),brnd_name(x,1),fill_year(x,1),...
                        fill_mnth(x,1), fill_day(x,1)];
                end
            else
               pat_store=[pat_store; patid(x,1), cases(x,1),...
                   days_sup(x,1),brnd_name(x,1), fill_year(x,1),...
                   fill_mnth(x,1), fill_day(x,1)];
            end
        end
        if x==length
            pat_store=sortrows(pat_store,[-3,-5,-6,-7]);
            mnth=cell2mat(pat_store(1,6));
            day=cell2mat(pat_store(1,7));
            year=cell2mat(pat_store(1,5));
            date={[num2str(mnth) '/' num2str(day) '/' num2str(year)]};
            master_out=[master_out; pat_store(1,1:4), date];
            end
    elseif index_id~=id
        if x~=length
            pat_store=sortrows(pat_store,[-3,-5,-6,-7]);
            mnth=cell2mat(pat_store(1,6));
            day=cell2mat(pat_store(1,7));
            year=cell2mat(pat_store(1,5));
            date={[num2str(mnth) '/' num2str(day) '/' num2str(year)]};
            master_out=[master_out; pat_store(1,1:4), date];
            index_id=patid(x,1);
            pat_store=[patid(x,1), cases(x,1), days_sup(x,1),...
                brnd_name(x,1),fill_year(x,1), fill_mnth(x,1...
            fill_day(x,1)];
        elseif x==length
            pat_store=sortrows(pat_store,[-3,-5,-6,-7]);
            mnth=cell2mat(pat_store(1,6));
            day=cell2mat(pat_store(1,7));
            year=cell2mat(pat_store(1,5));
```

```
            date={[num2str(mnth) '/' num2str(day) '/' num2str(year)]};
            master_out=[master_out; pat_store(1,1:4), date];
        end
    end
end
masterlength=size(master_out,1);
for x=1:masterlength-1
    if cell2mat(master_out(masterlength-x+1,3))==0
        master_out(masterlength-x+1,:)=[];
    end
end
header={'patid', 'case', 'days_sup', 'brndname', 'lastfill'};
final_output=[header; master_out];
xlswrite(output,final_output);
header2={'In Files', 'Out Files'};
zz=[header2; {length, size(master_out,1)}];
end
```

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Vita

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Education

Institution and Location	Degree	Begin	End	Field of Study	GPA
Norman North High School, Norman, OK		08/02	05/06		4.0
Texas A&M University, College Station, TX	B.A.	08/06	12/09	Biology, Mathematics	3.887
University of Texas Medical Branch, Galveston, TX	Ph.D.	06/10	08/14 (Anticipated)	Rehab Science	
University of Texas Medical Branch, Galveston, TX	M.D.	06/10	08/16 (Anticipated)	Medicine	

Work Experience

Activity/Occupation	Begin	End	Field	Institution/Company	Employer/Supervisor
Undergraduate Research	01/07	12/09	Biology	Texas A&M University	Dr. Gil Rosenthal
Physician Shadowing	07/08	07/08	Orthopedics		Dr. Alexander L'Heureux
Research Internship, Germany	05/09	08/09	Chemistry	DAAD & ACS	Dr. Martin von Berger
Substitute Teaching	01/10	05/10		CSISD & BISD	
MD-PHD Student	8/10		Medicine	UTMB	Dr. Zbigniew Gugala

Academic and Professional Honors

Honor / Award	Granting Institute	Year(s)
McFadden Scholarship	Texas A&M University	2006-2009
Keys to Aggieland Scholarship	Texas A&M University	2006
University Scholar	Texas A&M University	2007-2009
Emerging Scholar Award	Phi Kappa Phi	2007
ACS IREU Scholar	American Chemical Society	2009
DAAD RISE Scholar	German Academic Exchange(DAAD)	2009
Phi Beta Kappa Honor Society	Phi Beta Kappa	2009
Foundation Honors Graduate	Texas A&M University Honors Program	2009
Graduation Magna Cum Laude	Texas A&M University	2009
Boyd Scholarship	University of Texas Medical Branch	2012
James A. Hoakanson, PhD, Scholarship	University of Texas Medical Branch	2013

Publications

Accepted & Published

Gray, AM, Ellison, KT, Buford, WL. Effects of the Use of Knee Savers on Lower Extremity Kinematics in Male Collegiate Baseball Catchers during Squatting. Texas Orthopaedics [Accepted]

Butkowski, T, Yan, W, **Gray, AM,** Cui, R, Verzijden, MN, Rosenthal, GG. Automated interactive video playback for studies of animal communication. *J Vis Exp.* 2011; 48:2374

Abstracts and Presentations

Gray, AM, Buford, WL. Incidence of Sports-related Knee Strain and Sprain Presented to Hospital Emergency Departments, 2002-2011. Abstract presented in poster form. American College of Sport's Medicine 61st Annual Meeting, Orlando, FL, May 2014

Gray, AM, Buford, WL. Incidence of Sports-related Knee Strain and Sprain Presented to Hospital Emergency Departments, 2002-2011. Abstract presented in poster form. Award: Overall Poster and Presentation. Preventive Medicine and Community Health Public Health Symposium, Galveston, TX, April 2014

Gray, AM. Cruciate Ligament Injury and Oral contraceptives: Is Prevention just a Pill Away? Abstract presented in lecture format. 32nd Annual GWN Eggers Lectureship, Galveston, TX, April 2014

Gray, AM, Mörbt, N, Tomm, JM, von Bergen, M. Characterization of lung epithelial cell in response to long term exposure to volatile organic compounds. Abstracted presented in poster form. The 238th ACS National Meeting, Washington, DC, August 2009

Membership in Professional Societies

Society	Begin	End
American Chemical Society	2009	2010
UTMB Sport's Medicine Initiative	2013	Current
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