

The Epidemiology of Androgen Toxicity: A Six-Year Retrospective Cohort Study of the Risk of
Primary Health Outcomes Among Inpatients with Androgen Toxicity in the United States

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Abstract

Background: Androgen prescriptions have increased substantially from 2000 to 2010. In response to the rise in prescriptions and a questionably credible cardiovascular risk study in 2013, the FDA issued mandates on testosterone labeling requirements to include consumer risk warnings. Despite the FDA mandates and well-established side effects, the reported risk estimates of health outcomes associated with androgen therapies remain equivocal across study populations with little evidence to characterize risk in an inpatient population. The epidemiological research detailed herein addressed this knowledge gap by identifying androgen toxicity types and classifying androgen-induced disease states from the literature into testable primary outcomes. As of 2019, no large-scale nationally representative studies have examined the risk of primary health outcomes with androgen toxicity among inpatients.

Objective: The objective of this study was to characterize the epidemiology of androgen toxicity by examining the risk of primary health outcomes, incidence of inpatient variables, and mean healthcare costs in a nationally representative population of inpatients with and without androgen toxicity exposure.

Design: A quantitative population-based retrospective cohort design was employed using National Inpatient Sample data spanning a period of six years (2010-2015) to identify an index cohort of 488 androgen toxicity exposures and a reference cohort of nearly 34 million non-exposures for the analysis.

Results: In log-binomial GLM regression analysis adjusting for demographic characteristics, androgen toxicity exposure was associated with an increased risk of polycythemia ($RR = 152.49$, 95% CI [120.97, 192.22], $p < .001$), hypercoagulability ($RR = 6.28$, 95% CI [3.59, 10.98], $p <$

.001), drug-induced liver injury ($RR = 47.27$, 95% CI [27.65, 80.81], $p < .001$), and venous thromboembolism ($RR = 6.42$, 95% CI [4.77, 8.63], $p < .001$), but not mortality ($RR = 0.50$, 95% CI [0.20, 1.19], $p = .119$). In negative binomial GLM regression analysis adjusting for demographic characteristics, exposure was associated with an increased incidence of chronic conditions ($IRR = 1.20$, 95% CI [1.14, 1.27], $p < .001$), diagnoses ($IRR = 1.18$, 95% CI [1.12, 1.23], $p < .001$), external causes of injury ($IRR = 4.88$, 95% CI [4.08, 5.83], $p < .001$), but not length of stay ($IRR = 1.03$, 95% CI [0.96, 1.12], $p = .324$). Exposure was also associated with a decreased incidence of procedures ($IRR = 0.86$, 95% CI [0.77, 0.96], $p = .009$). In log-gamma GLM regression analysis adjusting for demographic characteristics, exposure increased mean healthcare costs ($\Delta = 4,178.53$, $p = .206$), although the effect was not statistically significant. An odds weighted, inverse probability of treatment weighted, and propensity score weighted analysis replicated that exposure increased the risk of polycythemia, hypercoagulability, drug-induced liver injury, and venous thromboembolism, but not mortality. The weighted analysis also replicated that exposure increased the incidence of chronic conditions, diagnoses, and external causes of injury, but not length of stay. The decreased incidence of procedures found in the main adjusted negative binomial GLM analysis failed replication in the weighted analysis. Graphical trend analysis showed consistent year-to-year trends in relative risk estimates of mortality, hypercoagulability, drug-induced liver injury, and venous thromboembolism but not polycythemia. The incidence rate ratio estimates of length of stay, diagnoses, chronic conditions, external causes of injury, and procedures trended consistently from year-to-year. Mean healthcare costs dropped 14.24% from 2010 to 2011, trended upwards 52.55% from 2011 to 2014, and dropped 24.01% from 2014 to 2015.

Conclusion: Androgen toxicity increased the risk of several primary health outcomes including polycythemia, hypercoagulability, drug-induced liver injury, and venous thromboembolism in this epidemiologic study. Given the importance of reducing inpatient risk factors and adverse health outcomes in U.S. hospital admissions, further exploration of androgen toxicity has extensive clinical and public health relevance.

Keywords: androgen, adverse, epidemiology, inpatient, health, mortality, outcome, steroid, toxicity.

Biographical Sketch

As the research director of Tier 1 Health and Wellness, Dr. Scott Howell integrates current research into evidence-based practice in the field of endocrinology. Dr. Howell has the responsibility for developing and executing meaningful research to assess the physiological impact of endocrine disrupting chemicals and sex hormones on men's and women's health drawing on his expertise in androgen metabolism and illicit anabolic steroid use. Dr. Howell works as part of a multidisciplinary team to plan, develop, and utilize evidence-based practice in hormone replacement therapy. He provides extensive health, nutrition, and physical training consultations to men of all ages and advocates the importance of taking responsibility for personal health.

Dr. Howell became a Certified Strength and Conditioning Specialist and Certified Personal Trainer by the National Strength and Conditioning Association in 2013. He received his Master of Science in Sport and Health Science from American Military University in August 2015; Bachelor of Science in Sport and Health Science from American Military University in August 2013; and Associate of Science in Mechanical Engineering from Forsyth Technical College in May 2011.

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My journey to this point in my life began in one the darkest years of my life in 2004. It was then, that I made the decision to earn a doctoral education and committed myself to earning a Ph.D. I am deeply indebted to Brandon Washam for helping me in my greatest hour of need. I will not forget your kindness and unconditional friendship.

I want to extend my warmest thanks to Dr. Mickey Shachar for challenging me throughout my time at Trident, showing me that learning is a never-ending endeavor, and most importantly allowing me to teach students. You were instrumental in helping me stand back up when things went South. Your help and encouragement was essential throughout the Ph.D. program. You showed me the true value of quality education and embody what educational leaders should strive to be.

I never knew the value of a mentor until Dr. Ryan Dwight became my Dissertation Chair. You saw potential in me and understood my thinking patterns. You were instrumental to my success and put me in the right places at the right times. You allowed me to work at my ridiculously fast pace and showed me the importance of using the literature to defend each research decision. My first class with you set the seed in my mind that to be a competent researcher I had to immerse myself in research methodology and statistics and find my own answers from the literature. That is, I had to develop knowledge and competency in each area I was deficient, become the expert, allow the data ‘speak,’ and update my beliefs when faced with compelling evidence. You helped and encouraged me to get back in the saddle again from an unplanned break in school. You responded to my emails, assessed my prospectus on your own time, held me accountable for my research, and suggested I teach other students. I appreciate

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Chapter I: Introduction

Background

Androgens are sex hormones or steroids that possess several distinct properties critical to normal physiologic function and health, yet, the therapeutic use of synthetic androgens has been implicated in the development of pathological toxicity leading to several induced disease states. Steroids, often associated with anabolic-androgenic steroids, are a family of naturally occurring hormones synthesized by cholesterol and categorized as mineralocorticoids, glucocorticoids, estrogens, and androgens (Gardner & Shoback, 2011). Androgens provide vital pleiotropic and biologic functions in both sexes within the human body and naturally exist in predominantly higher levels in males, but are also found in females at lower amounts (Gardner & Shoback, 2011).

Exogenous androgens or congeners are considered anabolic-androgenic steroids, however, this term is a misnomer since the dissociation of anabolic effects from androgenic effects has been proven to be impossible (A. Goldman & Basaria, 2017). Each androgen has a degree of both qualities; hence, the term “androgen” is preferred and considered more accurate. In this study, the term “androgen” refers to exogenous testosterone or any derivatives of testosterone used in clinical practice to treat disease.

All exogenous androgens have fundamental pharmacologic properties with which they exert their effects:

1. Exogenous androgens are a chemically modified form of a four-carbon ring structure derived from cholesterol;
2. Exogenous androgens have fundamental genomic (pleiotropic) effects on target tissues;

3. Target tissues are any tissues that contain androgen receptors;
4. Alkylation at the 17th position of the four-carbon ring results in predictable and consistent liver enzyme activities and liver-specific disease-states;
5. Exogenous androgens follow three parental endogenous forms: (a) testosterone, (b) 19-nor nandrolone, and (c) dihydrotestosterone (DHT);
6. The exogenous parental forms are further categorized in their ability to undergo enzymatic reduction by aromatase (into estrogens) or 5-alpha-reductase (into DHT);
7. Each type of reduction or lack thereof corresponds to specific effects in target tissues;
8. Exogenous androgens have non-genomic actions that lie beyond classical transcriptional and translational processes and simple ligand-receptor actions;
9. These qualities have been implicitly explained in the literature and apply directly to the fundamental principles of toxicology and pharmacology, referred to as drug type, dose, duration, and mode of administration, and absorption, distribution, metabolism, and excretion, respectively; and
10. These implied qualities constitute the theoretical framework that may be used to identify and classify, organ-specific, androgen-induced disease states reported in the literature and statistically test the risk of identified disease states associated with androgen toxicity in specific populations, such as an inpatient population (A. Goldman & Basaria, 2017).

The adverse effects of synthetic androgens used in clinical practice have been well documented in the literature for over 70 years with an additional 50 years of accumulated scientific reports detailing the adverse effects of illicit androgen use by athletes and bodybuilders (Kanayama, Hudson, & Pope, 2010; Abraham Morgentaler & Traish, 2018; E. Nieschlag, 2005;

Eberhard Nieschlag & Nieschlag, 2014). Despite well-established adverse effects, the global utilization of androgens has substantially increased over recent decades in Western countries rooted in allopathic medicine (Anaissie, DeLay, Wang, Hatzichristodoulou, & Hellstrom, 2017). In the United Kingdom, annual testosterone utilization increased by ~ 90% over the period from 2000 to 2010 (Gan, Pattman, H. S. Pearce, & Quinton, 2013). In the United States, the trends of testosterone sales during the periods, spanning the years 2000 to 2010 and the years 2001 to 2011, showed percentage increases in androgen utilization by 374% and 359%, respectively (Gabrielsen, Najari, Alukal, & Eisenberg, 2016). Other researchers have noted an approximate two- to four-fold increase in U.S. androgen prescriptions over the past two decades (Bandari, Ayyash, Emery, Wessel, & Davies, 2018). On January 31, 2014, the U.S. Food and Drug Administration (FDA) and the Department of Health in Canada issued mandates for labeling testosterone products to include risk warnings for stroke, heart attack, and death (FDA, 2014; Health Canada, 2014). Then, on October 25, 2016, the FDA added additional warnings to include the risks of abuse and dependence associated with prescription androgens (FDA, 2016).

The literature detailing the adverse effects of androgen therapeutics is extensive with no uniform scientific consensus on the risk of health outcomes. Since the FDA-issued mandate, thousands of lawsuits have been filed against drug manufacturers by individuals experiencing certain adverse health outcomes associated with prescribed androgens (Connolly, 2017). Scientific discourse on this issue has resulted in claims of medical hysteria, “hormonophobia,” and unethical reporting of research findings (Abraham Morgentaler, 2014, 2018). In one instance, a group of world experts called for the retraction of a key study by Vigen et al. (2013b) and correction of the researchers’ mistakes that were used as the primary scientific evidence by

the FDA to determine that a mandate for testosterone labeling was warranted to inform consumers of the associated risks (Abraham Morgentaler & Lunenfeld, 2014). Currently, the adverse effects of androgens are now situated in a vigorous, contentious, and demarcated academic debate with nearly all studies reporting either increased risks or no risks and protective effects resulting from androgen therapy. One body of research has demonstrated an increased risk of numerous adverse health outcomes related to androgen therapies (Baggish et al., 2017; S. Basaria et al., 2010; Budoff et al., 2017; Choi et al., 2005; Finkle et al., 2014; C. J. Glueck et al., 2011; C. J. Glueck et al., 2016; Martinez et al., 2016; Tse, Zuraw, Chen, & Christiansen, 2017; Vigen et al., 2013b; Westerman et al., 2016; Xu, Freeman, Cowling, & Schooling, 2013). In contrast, another body of research has shown no increased risk of adverse health outcomes, and in most instances, protective health effects have been reported (Baillargeon et al., 2016; Baillargeon et al., 2014; Baillargeon et al., 2015; Bhasin et al., 1996; Chao et al., 2017; Dolan, Collins, Lee, & Grinspoon, 2009; Gagliano-Juca & Basaria, 2017; Gagliano-Juca et al., 2017; Haider, Gooren, Padungtod, & Saad, 2010; Hartgens, Cheriex, & Kuipers, 2003; Ng Tang Fui et al., 2016; Shufelt & Braunstein, 2009; Sinclair, Grossmann, Hoermann, Angus, & Gow, 2016; P. J. Snyder et al., 2016; van Staa & Sprafka, 2009).

Androgens are arguably one of the most studied drug classes in history, however, the literature is deficient in linking the mechanisms of toxicity derived from *in vitro* and *in vivo* studies to causal inference of health outcomes risk in different human populations. Although much of the mechanisms by which androgens induce adverse effects are well-established, the ***manifestation of deleterious health outcomes in different populations is not well understood*** (Aparicio et al., 2017; Binayi et al., 2016; Bissoli et al., 2009; Ghorbani, Joukar, Fathpour, &

Kordestani, 2015; Phillis, Abeywardena, Adams, Kennedy, & Irvine, 2007; Phillis, Irvine, & Kennedy, 2000). Most studies have focused on androgen therapies using populations of elderly, young, or transgender in controlled or observational settings (Baillargeon et al., 2016; Baillargeon et al., 2014; Baillargeon et al., 2015; Budoff et al., 2017; Finkle et al., 2014; P. J. Snyder et al., 2016; Snyder et al., 2014; Van Caenegem et al., 2015; Vigen et al., 2013b; Xu et al., 2013).

Problem Statement

A major obstacle to the field is that findings of equivocal health risks across study populations have impeded reasonable interpretation of risk in different settings. The *problem addressed by this study* was a lack of knowledge and meaningful data in an inpatient population regarding the effect of androgen toxicity exposure on the risk of primary health outcomes and the economic burden of disease. Currently, *only two studies* have focused on inpatient populations. The first study indirectly assessed rehospitalization without considering the duration of inpatient stay (Baillargeon et al., 2016). The latter study focused on androgen-related outcomes in an *inpatient population* but for only one androgen-related health outcome (Martinez et al., 2016). The implication for this epidemiologic study is that inpatient general characteristics and specific risk factors may predispose greater health outcomes risk and economic burden of disease with androgen toxicity exposure than other previously studied populations. Therefore, omitting this study carried potentially negative implications to the health of a key portion of the U.S. population, whereas, conducting this research provided meaningful data to inform clinicians on the risk-to-benefit of prescribed androgens and lower potential harm to inpatients.

Purpose of the Study

The *primary purpose* of this study was to characterize the epidemiology of androgen toxicity by determining the relationship between androgen toxicity exposure and the risk of inpatient health outcomes in nationally representative cohorts of inpatients. The *secondary study purpose* was to further detail the epidemiology of androgen toxicity by determining the relationship between androgen toxicity exposure, incidence of inpatient variables, and the economic burden of disease among inpatient cohorts. A population-based quantitative retrospective cohort design using secondary data was used in this investigation to assess the risk of health outcomes, incidence of inpatient variables, and total healthcare costs associated with androgen toxicity.

The research addressed previous attempts to integrate toxicity mechanisms from the literature and equivocal research findings using a systematic method to find and classify, tissue- and organ-level toxicity into distinct disease states based on the fundamental implicit qualities of androgens. Therefore, a novel androgen toxicity framework was developed based on pharmacologic qualities and toxicological principles to classify androgen-related disease states reported in the literature. The most frequently reported disease states were used as variables in a comprehensive long-term study of inpatients. National Inpatient Sample and the Nationwide Inpatient Sample (NIS) data were used as the study sampling frame (HCUP NIS, 2012). Samples taken from the NIS data included male and female inpatients of all ages, races, and socioeconomic status to include special inpatients such as transgender and other inpatients with special clinical characteristics.

Hospitalized patients undergoing androgen treatment and diagnosed with androgen toxicity were compared to those without androgen toxicity or androgen treatment to determine the relationship between androgen toxicity exposure, health outcomes, inpatient variables, and total health care costs. Specifically, two comparable inpatient cohorts (androgen therapy + toxicity vs. no androgen therapy + no androgen toxicity) were constructed to estimate the risk of health outcome variables and the incidence of inpatient variables and characterize the economic burden of disease, in terms of total healthcare costs, associated with inpatient androgen toxicity exposure.

Research Questions

Aim 1 [RQ 1]. What is the relationship between androgen toxicity and risk of health outcomes?

Health outcome variables. Literature-reported disease states, mortality, mortality likelihood, disease severity, non-elective admission, major operating room procedure, and procedure class.

Aim 1 [RQ 2]. What is the relationship between androgen toxicity and incidence of inpatient variables?

Inpatient variables. The incidence of chronic conditions, diagnoses, external causes of injury, length of stay, and procedures.

Aim 2 [RQ 3]. What is the relationship between androgen toxicity and healthcare costs?

Geographic covariates. Patient residence, hospital division, hospital location, and hospital region.

Aim 3 [RQ 4]. What is the relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and total healthcare costs over the study period?

Aim 4 [RQ 5]. What is the relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied?

Nature of the Study

Two cohorts for each year were constructed according to androgen toxicity exposure. Assignment to an index (exposure) cohort was based on the independent variable, diagnosed androgen toxicity (IV; external cause of injury code E932.1), using the procedures outlined by Woodward (2014) and K. J. Rothman, Greenland, and Lash (2010). All inpatients without a diagnosis for androgen toxicity were assigned to a reference (non-exposure) cohort. For the main analysis, a total of 12 cohorts, two cohorts for each year, were included in this study. A separate analysis merged all yearly cohorts to assess yearly trends in all health outcome variables, inpatient variables, and total healthcare costs.

Aim one compared the index and reference cohorts to assess the relationship between androgen toxicity exposure (IV) and the risk of health outcome variables (DVs). Cohort comparisons also assessed the relationship between androgen toxicity exposure and the incidence of inpatient variables (DVs) to identify disparities and patterns among the cohorts. Reported disease states, identified in the literature and matched to specific International Classification of Disease (ICD-9-CM) diagnosis codes (nominal; yes or no), were the first set of health outcome variables (DVs). Additional nominal health outcome variables (DVs) coded as (yes or no) included mortality, non-elective admission, and major operating room procedure. Ordinal health outcome variables (DVs) consisted of mortality likelihood (coded at five levels), disease severity

(coded at five levels), and procedure class (coded at four levels). Ratio (discrete) inpatient variables (DVs) included the number (incidence rates) of chronic conditions, diagnoses, external causes of injury, length of stay, and procedures.

Aim two assessed the relationship between the economic burden of disease and androgen toxicity exposure. The (IV) was androgen toxicity exposure (E932.1; yes or no) as previously defined using the same exposure and non-exposure cohorts. The ratio (DV) was total healthcare costs and nominal geographic covariates (GCoVs) represented distinct hospital and inpatient locations in the U.S. Comparisons of the cohorts were used to determine the relationship between androgen toxicity (IV) and total healthcare costs (DV) across geographic locations (GCoVs).

Aim three evaluated the annual trends in effect measures for all health outcome variables (DVs), inpatient variables (DVs), and total healthcare costs (DV) over a six-year period across androgen toxicity exposure (IV). Aim four implemented propensity score methods such as inverse probability of treatment weighting (IPT) as replication and sensitivity analyses. Specifically, odds weighting, IPT, and propensity score weighting were applied in the analysis of the index and reference cohorts to balance demographic characteristics, replicate all main analyses, assess different strata, and estimate treatment effects to protect against confirmation bias and selection bias.

Significance of the Study

The therapeutic use of androgens in the overall inpatient population among U.S. hospitals is associated with health and economic consequences. Therefore, the feasibility of the androgen toxicity framework was supported by implicit literature-established mechanisms resulting in the

development of organ system toxicity and organ-specific disease states that correspond to distinct health outcomes at specific levels of use. Thus, comparisons of cohorts were hypothesized to correspond with a greater risk of health outcomes and a higher economic burden of disease associated with androgen toxicity exposure. Further cohort comparisons were hypothesized to coincide with a higher incidence of chronic conditions, medical diagnoses, procedures, length of stay, and external causes of injury among inpatients with exposure. Using a novel androgen toxicity framework, the effects of diagnosed androgen toxicity in an inpatient population were mapped for the first time to provide needed clinical information to inform the risk-to-benefit of androgen treatments, prevent androgen-related disease states, identify disparities, quantify the economic burden of disease, and determine cost-effectiveness of treatments to focus future research and influence public health policy.

Previous population-based studies focused on insurance records, health records, and government-linked databases (Baillargeon et al., 2014; Baillargeon et al., 2015; C. J. Glueck et al., 2016; Martinez et al., 2016). One study assessed rehospitalization after inpatient discharge but failed to address the duration of inpatient stay (Baillargeon et al., 2016). Another study used a large UK database linked with general primary care practices, hospital discharges, and in-hospital procedures to partially assess an inpatient population but focused only on the single health outcome of venous thromboembolism and a small number of comorbidities (Martinez et al., 2016). To date, no large-scale nationally representative study has examined the effect of androgen toxicity on all clinical health outcomes, such as mortality and morbidity, in an inpatient setting. The present retrospective cohort study filled this evidence gap by investigating androgen-related health outcomes through the application of a novel androgen toxicity

framework focused entirely on a representative inpatient population. The comparisons made in this study provided the first meaningful risk data on an inpatient population to guide future efforts in the standardization of androgen risk screening for blood-borne disorders.

A quantitative population-based retrospective cohort study of inpatient health outcomes utilizing an androgen toxicity framework was important for several reasons. First, the framework provided the basis for predicting and testing hypotheses involving the relationships between reported disease states, health outcomes, and androgen toxicity. There are numerous case reports and studies reporting specific diseases as consequences of androgen therapy and illicit use (Colburn et al., 2017; Ge, Liu, & Singh, 2017; Joseph, Yaseen Naqvi, & Sturm, 2017; Sabzi & Faraji, 2017). Therefore, testing the specific literature-reported disease states based on International Classification of Diseases (ICD) diagnosis codes, added to the literature by confirming case reports and previous study findings (WHO, 2017). The cohort study approach allowed the assessment of incidence rates, risks, disparities, and patterns, characterizing how adverse health outcomes manifest in an inpatient population. Second, the use of secondary data allowed a larger sample of an inpatient population, unfeasible in prospective cohorts or randomized controlled trials, which was more likely to capture the true nature of androgen toxicity. Third, physicians, physician assistants, and nurse practitioners must make the fundamental decision of which therapy is best to treat patients without causing harm. The study provided a comprehensive understanding of these relationships to improve practice by informing androgen prescription guidelines, providing direction for treatment screening protocols, and identifying high-risk groups. The salient value of this study was the development of informative data to lower the occurrence of preventable adverse events given the marked increases in

androgen prescriptions. Finally, the economic burden of androgen toxicity, in relation to measured risks of health outcomes and incidence of inpatient variables, may be used to better inform clinicians on the decision to retain current therapies or opt to choose safer and more cost-effective alternatives given the estimated risks found in this study.

Answering the research questions was novel, realistic, feasible, and added useful and practical information to the knowledge base in the literature through this epidemiologic investigation. In this study, the relevant data related to the research questions was important, since the data addressed a previously unstudied representative inpatient population and characterized how androgen toxicity manifests in this setting. The target population of all inpatient hospitalizations was unique because androgen therapy utilization was varied, and the NIS sampling frame was large. The inherent characteristics of the NIS data increased the likelihood of capturing true androgen-related disease states observed in hospitalizations across the entire United States allowing inferences of risk to the target population to be more accurate and reliable. The research questions addressed the core of this study because they answered whether diagnosed androgen toxicity exposure was associated with an increased risk of health outcomes, a higher incidence of inpatient variables, and greater total health care costs, coinciding with frequent utilization of androgens as treatments. The study also provided additional insight into whether those with diagnosed androgen toxicity, as a consequence of androgen therapy, had preventable disease states that could be identified using androgen treatment screening tests. These data may be used to develop standard androgen screening tests that establish the predisposition for androgen toxicity before androgen treatment and thereby reduce the risk of developing androgen-related disease states in clinical settings.

Chapter II: Literature Review

Historical Perspective

The first androgen, androsterone, was first isolated from an extraordinary quantity of policeman urine by Adolf Butenandt in 1931, thus, increasing scientific interest in this area (Freeman, Bloom, & McGuire, 2001; J. M. Hoberman & Yesalis, 1995). Ultimately, interest further increased in 1935 when three pharmaceutical-sponsored (Organon, Schering, and Ciba) and independent research teams led by Karoly David, Adolf Butenandt, and Leopold Ružicka attempted to isolate a more powerful unknown testicular hormone (Morales, 2013). The team led by David, Dingemans, Freud, and Laqueur (1935) were the first to identify the unknown hormone in 1935 and used the term “testosterone” to describe it based on the origin (testicles), class (sterols), and its notable chemical characteristic (ketone). The research team led by Butenandt and Hanisch (1935) rudimentarily synthesized testosterone three months later the identification, whereas only one week after the synthesis, the team led by Ruzicka and Wettstein (1935) published a patent for a commercially viable methylated testosterone synthesis from cholesterol. For the extensive pharmaceutical-sponsored work of these highly competitive researchers, in 1939 Ružicka and Butenandt, were awarded two half-Nobel prizes in chemistry for their unique contributions to chemistry while devising viable sex hormone synthesis methods and discovering the molecular structure of testosterone (Freeman et al., 2001; Morales, 2013).

After the “birth” of synthetic testosterone, several pharmaceutical companies began developing an array of testosterone derivatives that continues to this day (A. Goldman & Basaria, 2017). In the late 1930s preceding the second World War, oral methyltestosterone and injectable forms of testosterone were created and widely used to treat a primitive syndrome called the

“male climacteric” (Morales, 2013). The first use of testosterone for increasing aggression was rumored to occur in Nazi soldiers during World War II (Wade, 1972). After World War II, other synthetic androgens were developed and used alongside testosterone to treat muscle wasting in prisoners of war, warfare-related trauma, peripheral vascular disease, angina associated with cardiovascular disease, involuted psychoses, melancholia, and depression (J. M. Hoberman & Yesalis, 1995; Abraham Morgentaler & Traish, 2018). By the late 1940s, synthetic androgen use first began in athletics and bodybuilding to enhance physical performance (J. Hoberman, 2017).

As indications for use were developed, commercial interests in androgens continued to climb despite warnings of adverse effects. Warnings of adverse outcomes such as prostate cancer were reported in the literature as early as 1941 and, in the same period, several medical journals noted widespread misuse and dangers of unnecessary testosterone prescriptions (Morales, 2013; Abraham Morgentaler & Traish, 2018). Over 70 years later, a prodigious accumulation of literature has amassed, almost equally divided. One body of research demonstrated an increased risk for several adverse health outcomes linked to androgen therapies (Baggish et al., 2017; S. Basaria et al., 2010; Budoff et al., 2017; Choi et al., 2005; Finkle et al., 2014; C. J. Glueck et al., 2011; C. J. Glueck et al., 2016; Martinez et al., 2016; Tse et al., 2017; Vigen et al., 2013b; Westerman et al., 2016; Xu et al., 2013). In contrast, an opposing body of research established favorable protective effects and decreased risk associated with therapeutic androgens using similar research designs and analyses on identical health outcomes (Baillargeon et al., 2016; Baillargeon et al., 2014; Baillargeon et al., 2015; Bhasin et al., 1996; Chao et al., 2017; Dolan et al., 2009; Gagliano-Juca & Basaria, 2017; Gagliano-Juca et al., 2017; Haider et al., 2010; Hartgens et al., 2003; Ng Tang Fui et al., 2016; Shufelt & Braunstein, 2009; Sinclair et

al., 2016; P. J. Snyder et al., 2016; van Staa & Sprafka, 2009). In spite of equivocal bodies of evidence, the adverse effects and health risks of some androgens are well-established in the literature and differentiated in large by either illicit or therapeutic androgen use (A. Goldman & Basaria, 2017).

The Epidemiology of Androgen Use

Illicit use. In the United States, the use of illicit androgens rose sporadically in the late 1970s, steadily increasing through the early 1980s, however, a sharp increase occurred in early 1990s dramatically increasing to the present day (H. G. Pope et al., 2014). In males, most illicit androgen use is initiated after 20 years of age. In 2014, conservative estimates showed that between three and four million American males aged 13 to 50 years have used illicit androgens at some point in their lives for recreational purposes outside of athletics (H. G. Pope et al., 2014). The phenomenon of increasing illicit androgen use is not confined to the United States. A meta-analysis and meta-regression by Dominic Sagoe, Torsheim, Molde, Andreassen, and Pallesen (2014) showed the increasing prevalence of illicit use observed in the U.S. was reflected in most Western countries, increasing in Middle Eastern countries, and lowest in Eastern countries with collectivist societies. It is now estimated that almost 3.5% of the global population have used illicit androgens at some point in life (D. Sagoe, Molde, Andreassen, Torsheim, & Pallesen, 2014). The global lifetime prevalence of illicit use for males (6.4%) is over three times greater than the global lifetime prevalence for females (1.6%) (D. Sagoe et al., 2014).

Therapeutic use. The global utilization of androgen therapies has substantially increased over recent decades in Western countries rooted in allopathic medicine (Anaissie et al., 2017). In the United Kingdom, annual testosterone utilization increased by ~ 90% over the

period from 2000 to 2010 (Gan et al., 2013). In the United States, the trends of testosterone sales during the periods, spanning the years 2000 to 2010 and the years 2001 to 2011, showed percentage increases in androgen utilization by 374% and 359%, respectively (Gabrielsen et al., 2016). In 2013, men received 97% of all testosterone prescriptions compared to 3% in women (Gabrielsen et al., 2016). Older men aged 40 to 60 years accounted for 70% of male prescriptions, whereas 13% of male prescriptions were received by men less than 40 years of age (Gabrielsen et al., 2016). Public health concern has focused attention to the sharp rise in androgen utilization among younger men. An insurance claims study by Rao et al. (2017) noted the rate of androgen utilization among men aged 18 to 45 years quadrupled from 2003 to 2013, whereas the rate for men aged 56 to 64 years only tripled during the same period. The majority of androgen prescribers in the U.S. are primary care physicians, although androgen prescribing falls formally under the specialties of endocrinologists and urologists (Gabrielsen et al., 2016).

The dramatic increase in androgen utilization has been considered from several perspectives. One explanation attributes the increase in androgen prescriptions to population-level declines of endogenous testosterone in adult men from 1990 to 2010 leading some researchers to assert the widespread need for androgen replacement (Travison, Araujo, O'Donnell, Kupelian, & McKinlay, 2007). Another view justifies increased prescriptions by noting decreases in endogenous testosterone bioavailability and heritable effects altering sex hormone synthesis resulting from lifelong exposure to endocrine disrupting chemicals (EDCs) common in plastics, cooking utensils, and many household items (Schug, 2017; Zhang et al., 2019). Still others warn of a looming public health problem and explain increased androgen utilization is driven by overprescribing in off-label use exacerbated by pharmaceutical direct-to-

consumer advertising evidenced by noting that most testosterone prescriptions are received without proper diagnosis or bloodwork contrary to consensus statements (Bandari et al., 2018; Gabrielsen et al., 2016; Morden, Woloshin, Brooks, & Schwartz, 2018). Such opposing views build a case for further exploration; however, none of these viewpoints presented considered the wide-ranging and growing indications for synthetic androgen (SA) use.

Indications. Androgens are utilized in diverse clinical applications and indicated to treat a variety of medical conditions. The most common application is the use of testosterone as hormone replacement therapy to treat primary and secondary hypogonadism in men, albeit testosterone is also used as a component of hormone replacement, as a novel treatment for poor ovarian response in women, and many other applications (Islam, Bell, Green, & Davis, 2019; Noventa et al., 2019; Yeap & Wu, 2019). The anabolic tissue growth-promoting effects of androgens are used to effectively treat age-related sarcopenia in elderly patients and disease-related cachexia (Bélanger et al., 2003; Bross et al., 2015; Choi et al., 2005; Gullett, Hebbar, & Ziegler, 2010). Given the marked capacity of certain 17 alpha-alkylated (17AA) androgens like oxandrolone to increase muscle mass and influence tissue regeneration, they are often selected as first-level therapeutics or adjuvants to treat severe burns in children and adults after initial stabilization (Chao et al., 2017; Demling & Desanti, 2003; H. Li, Guo, Yang, Roy, & Guo, 2016). With conditions such as Turner's syndrome and Klinefelter's syndrome SAs are the only viable treatments for these rare genetic diseases (Ross et al., 2017; Shankar & Backeljauw, 2018).

The same mechanisms involving organ and organ system level androgen toxicity are paradoxically and therapeutically beneficial in some clinical applications (Hardy, 2003). One

example is the use of supraphysiologic bipolar androgen therapy in men to treat castration resistant prostate cancer (M. T. Schweizer et al., 2015; Michael Thomas Schweizer et al., 2014). Another example is the ability of non-aromatizable androgens to offset estrogen levels to reduce cancer tumor size in breast cancer treatment (Dillon et al., 2012). Furthermore, since some methylated androgens exert an unusual effect on the blood acting to stabilize complement protein levels involved with blood clotting, they are a first line therapeutic to treat hereditary angioedema although recent evidence suggests increased comorbidity in long-term 17AA exposure (Kóhalmi et al., 2016; Sloane, Lee, & Sheffer, 2007; Tse et al., 2017). The strong ability of SAs to stimulate hematopoiesis in red marrow make them highly effective treatments for blood disorders such as anemia, sickle cell anemia, aplastic anemia, refractory anemias, myelosclerosis, myeloid metaplasia, myelofibrosis, and secondary anemias induced by cancer treatments (Llewellyn, 2011; Shahani, Braga-Basaria, Maggio, & Basaria, 2009; Shimoda et al., 2007). Unsurprisingly, the versatility of SAs to act on many tissues has been leveraged to facilitate treatment and recovery from prostatectomy, spinal cord injury, pressure ulcers, neonatal congenital heart surgery, osteoporotic hip fracture, chronic obstructive pulmonary disease (COPD), and cystic fibrosis among many other diseases (Burch et al., 2016; El-Khatib, Huynh, Towe, Yafi, & Ahlering, 2019; Gorgey et al., 2019; Green, Barry, & Jones, 2015; Naing & Whittaker, 2017; Pan, Wang, Xie, Du, & Guo, 2014).

Genomic Mechanisms of Action

Structure. In normal human physiology, endogenous testosterone is derived cholesterol through four intermediate biochemical steps to yield a four-carbon ring molecule that is also the basic structure of all SAs (Figure 1) (Eberhard Nieschlag, Nieschlag, & Behre, 2012; Rogozkin,

2000). The molecular structure of the steran nucleus is chemically modified to produce various types of SAs that follow three parental endogenous forms: testosterone, 19-nor nandrolone, and dihydrotestosterone (DHT). The SA parental forms are further categorized in their ability to be reduced by aromatase (into estrogens) or 5- α -reductase (into DHT). Each type of reduction or lack thereof corresponds to specific effects in target tissues (Melmed, Polonsky, Larsen, & Kronenberg, 2016). Thus, the pleiotropic effects of SAs in human physiology proceed by either direct genomic action, indirect genomic action through the reduced metabolites (DHT) and estradiol (17 β E₂), or non-genomic actions.

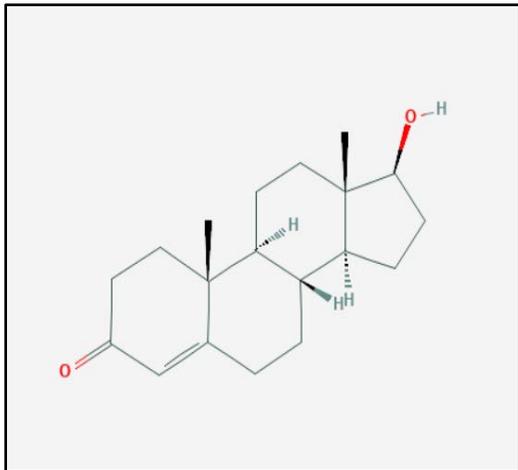


Figure 1. Molecular structure of testosterone C₁₉H₂₈O₂ (PubChem, 2019).

Pathway to action. The nuclear actions of synthetic androgens are characteristically slow and process in a stepwise fashion. After absorption into the bloodstream, the SA pathway to action is constrained by molecular structure, androgen receptors, binding proteins, ligand-receptor binding, nuclear transcription, and cytoplasmic translation (Melmed et al., 2016). In the bloodstream, SAs circulate to first pass metabolism in the liver and target tissues freely unbound (1-4%) and bound to steroid hormone binding globulin (SHBG) (30-45% in males; 70% in

females), albumin (50-68% in males; ~25% in females), orosomucoid, and cortisol binding globulin (A. L. Goldman et al., 2017). The process, described as the free hormone hypothesis (FHH), indicates that only free unbound androgens are physiologically active to passively diffuse unencumbered through cellular lipid-bilayers to bind to intracellular receptor sites in the cytosol to form ligand-receptor complexes (Hammond, 2016; Laurent, Hammond, et al., 2016). Given the FHH, only the free unbound fraction of androgens can exercise biologically active effects (Bhasin & Jasuja, 2019). Another view considers androgens that are unbound to SHBG to be bioavailable, i.e., free- and albumin-bound androgen account for the dissociation of albumin-bound androgens in capillary beds in the brain and liver and passive diffusion of free unbound androgens (A. L. Goldman et al., 2017; Laurent, Helsen, et al., 2016). Czub et al. (2019) characterized the difficulty of reconciling these mechanisms and determining the bioavailability of androgens in biological systems by demonstrating that various drugs and fatty acids compete for binding at two sites on serum albumin.

Although the FHH and other theories are useful to understand the complex nature of androgen actions, the discovery of the steroid hormone binding globulin (SHBG) and androgen binding protein (ABP) receptor, megalin, demonstrated the ability of SHBG to intracellularly transport androgens and access target tissues via megalin-modulated endocytosis (Hammes et al., 2005). Current evidence suggests that SHBG and other binding proteins adjust the physiologic effects of androgens through controlling movement, removal, and, subsequently, bioavailability (Bhasin & Jasuja, 2019; A. Goldman & Basaria, 2017). Regardless of the path to the interior of target tissue, once the ligand-receptor complex is formed in the cytosol, it translocates into the nucleus by binding to importins and, once inside, binds to the hormone response element of the

deoxyribonucleic acid (DNA) interacting with coactivator proteins to initiate gene transcription and produce messenger ribonucleic acid (mRNA) (Gardner & Shoback, 2011; Katzung, 2018). Once mRNA is synthesized through the genomic transcriptional process, the mRNA translocates back into the cytoplasm where it docks with ribosomal ribonucleic acid (rRNA) on rough endoplasmic reticulum (RER) to allow transfer ribonucleic acid (tRNA) to produce specific proteins through the process of translation (Gardner & Shoback, 2011; Katzung, 2018; Scott & Pierce, 2018).

Androgen receptors and target tissues. The genomic effects of androgens rely on the androgen receptor (AR), coded on the AR gene, which belongs to a super-family of nuclear hormone receptors (Herbst & Bhasin, 2004; J. Li & Al-Azzawi, 2009; NIH, 2019; Palvimo, 2012; Ruizeveld de Winter et al., 1991; Sengelaub & Forger, 2008). In adults, ARs are found in several organs, target tissues, and cell types including the integument, accessory sex organs, breast, liver, kidney, myocardium, brain tissue (neocortex, subcortex, hypothalamus, substantia nigra), nerve cells, bone, adipose tissue, skeletal muscle, and notably in mesenchymal pluripotent stem cells inside of muscle tissue and myeloid tissues (Almeida et al., 2017; Bhasin & Jasuja, 2019; Ceruti, Leirós, & Balañá, 2018; De Gendt & Verhoeven, 2012; Haendler & Cleve, 2012; Herbst & Bhasin, 2004; Karlsson, Studer, Kettunen, & Westberg, 2016; J. Li & Al-Azzawi, 2009; Sengelaub & Forger, 2008). These tissues are considered target tissues, however, the effects of ligand-AR binding in these tissues vary in targeted genes and, subsequently, proteins resulting from genomic transcriptional and translational processes that also differ. For genomic effects to occur, androgens must effectively bind and activate the AR in target tissues with the aid of over 200 proteins (coregulators), termed coactivators and corepressors (van de Wijngaart,

Dubbink, van Royen, Trapman, & Jenster, 2012). The binding of AR, specifically the ligand-binding domain and shape of the AR coactivator binding pocket, is distinctively different from other steroid receptors due to preferential binding motifs, thus, this distinction is pivotal to the enlistment of specific coregulators and control particular sets of target genes in target tissues (van de Wijngaart et al., 2012). The number of AR in target tissues is directly controlled by transcription of the AR gene and proteins comprising the AR in the post-translational period, whereas androgens autoregulate the AR gene up or down via coregulators given different tissue types and different cell types in the same target tissue depending on androgen load at any given time (Hunter, Hay, Esswein, Watt, & McEwan, 2018). Taken together, each of these aspects show that target tissues possess the ability to locally predominate androgen actions by up-regulation with increasing androgen load or down-regulation with decreasing androgen load.

Direct genomic effects. Testosterone stimulates many pleiotropic effects throughout the body. Synthetic androgens derived from the parental form of testosterone exert direct nuclear effects on erythropoiesis, bone, muscle, and the metabolism of lipids (Melmed et al., 2016). Exogenous testosterone and most SAs have been repeatedly shown to increase lean body mass and reduce global body fat and regional fat mass in androgen-deficient men, eugonadal men, and women (Bhasin & Herbst, 2003; Bhasin, Woodhouse, & Storer, 2001; Bhasin, Woodhouse, & Storer, 2003; Huang & Basaria, 2017; Huang et al., 2014). The effect of androgen action is dose-responsive increasing lean body mass, voluntary muscle strength, and decreasing body fat as dose increases, and opposite effects as dose decreases. Furthermore, SAs induce hypertrophy through increased protein synthesis and protein recycling, type I and type II myofiber volume,

satellite cell number, myonuclear number, myogenesis of pluripotent stem cells, and AR number in pluripotent stem cells.

Indirect effects. Many favorable effects of SAs on adipose tissue, serum cholesterol, libido, atherosclerosis, and bone resorption are mediated indirectly by the aromatase enzyme gene CYP19A1 (Cytochrome p450, Family 19, Subfamily A, Member 1) that converts aromatizable androgens into $17\beta_2$ estradiol (Katzung, 2018; Laurent et al., 2019; Laurent et al., 2014). In contrast, androgens reduced to DHT through 5α -reductase enzyme activity modulate known side effects including acne, prostate growth, integument, and hair follicle life cycle (Lazar & Birnbaum, 2016; Melmed et al., 2016). Indirect enzyme-converted metabolites of SAs are responsible for downstream metabolism beyond direct ligand-receptor mediated effects with both the potential for favorable protective effects and harmful effects.

Non-genomic effects. In the classical steroid receptor signaling model, androgens diffuse through plasma membranes to the cytoplasm binding to AR forming androgen-AR complexes and then translocate to the nucleus activating distinct androgen response elements in the process of mRNA transcription while returning mRNA to cytoplasmic ribosomes initiating translational processes, finally producing functional proteins for the cell. Recent evidence suggests that androgens mediate very rapid non-nuclear effects unexplainable by the classical genomic model (Levin & Hammes, 2016; Michels & Hoppe, 2008). The key distinctive feature of non-genomic action is ligand signaling without transcription of mRNA. In non-classical signaling, AR become localized near the plasma membrane allowing androgen-AR complex formation to regulate membrane responses acting to inhibit guanine nucleotide-binding protein (G-protein) signaling, thus, decreasing intracellular cyclic adenosine monophosphate (cAMP) to

activate extracellular-signal-regulated kinase (ERK) signaling without the transcription of mRNA (Dent, Fletcher, & McGuigan, 2012; Foradori, Weiser, & Handa, 2008; Michels & Hoppe, 2008). Fast-acting, non-genomic effects accomplished by secondary messengers include direct regulation of ligand- and voltage-gated ion channels, stimulation of protein kinases, and activation of G-protein combined membrane ARs (Foradori et al., 2008). Depending on the tissue, non-genomic signaling may result in differential downstream tissue-specific effects. For instance in skeletal muscle, non-genomic signaling stimulates the Ras/MAPK/ERK pathway resulting in direct, immediate effects to increase inositol triphosphate mass and sarcoplasmic release of calcium ions (Dent et al., 2012). Seemingly discrepant SA-induced toxic effects in different tissues and organ systems may be mediated by fast non-genomic signaling wherein experimental research shows future promise.

Toxicologic and Pharmacologic Properties of Androgens

Synthetic androgens have fundamental pharmacologic properties with which they exert direct genomic effects on target tissues containing androgen receptors and indirect non-genomic fast-acting effects without mRNA transcription or cytoplasmic and nuclear androgen-receptor interaction. Furthermore, fundamental toxicologic principles of absorption, distribution, metabolism, and excretion are intimately intertwined with androgen exposure through the unique pharmacologic characteristics of different androgen classes. Briefly the review explores the pharmacologic qualities of drug type, dose, duration, frequency, and mode of administration along with the toxicologic principles of absorption, distribution, metabolism, and excretion, influence pathologic androgen toxicity in different tissues and organ systems.

Androgen types and administration modes. Structural modifications to the parental forms, testosterone, 19-nortestosterone, and DHT directly influence the mode of androgen administration and in what manner SAs are metabolized and distributed in the body (A. Goldman & Basaria, 2017; Kicman, 2008). Modifications of parental forms also impact target tissue effects from androgen-receptor binding, enzymatic reduction, and the affinity of SAs to bind to ARs (Llewellyn, 2011). Given the fact that oral parental forms have short circulating half-lives, low bioavailability, and are not absorbed effectively through normal digestion, SAs (except methyltestosterone) were developed to bypass this process and increase bioavailability resulting in different androgen types:

1. Alkylated orals;
2. Non-alkylated orals; and
3. Esterized injectables (Handelsman, 2016; Kicman, 2008; Llewellyn, 2011).

Alkylation at the 17th position of the four-carbon ring prevents first pass metabolism in the liver and allows distribution throughout the body since the added functional group cannot be separated (P. Bond, W. Llewellyn, & P. Van Mol, 2016). Alkylated oral SAs prevent hepatic metabolism, but in doing so produce consistently elevated liver enzyme activities and oxidative stress sometimes resulting in liver adenoma and hepatocellular carcinoma (P. Bond et al., 2016). Non-alkylated oral forms are dissolved in oil solutions to facilitate intestinal lymphatic absorption to circumvent first pass metabolism by the liver and prevent liver-specific effects (Llewellyn, 2011). Most esterized injectable SAs are formed by attaching carboxylic acid esters at the 17- β -hydroxyl group to the four-carbon ring and dissolved in oil to increase hormone half-life and bioavailability (Kicman, 2008). Esterized injectables, non-alkylated orals, and

transdermal preparations are considered safer than alkylated orals for liver-specific effects, however, all modes of administration exert organ-specific effects outside of the liver to any target tissue (Llewellyn, 2011). Nevertheless, toxicity resulting from the metabolism of SAs is a separate from adverse target tissue effects making up the majority of androgen toxicity forms.

Androgen typology can also be roughly divided into two classifications: aromatizable and non-aromatizable (A. Goldman & Basaria, 2017). Aromatizable refers to the ability of SAs to be reduced by aromatase, whereas non-aromatizable refers to SA reduction ability through the enzyme 5- α -reductase. The aromatase enzyme reduces aromatizable SAs into the metabolites, estradiol (E₂), 19-nor-nandrolone related estrogens, or alkylated estradiol forms, which are responsible for favorable downstream effects on the cardiovascular system and skeletal system (Ghosh, Egbuta, & Lo, 2018; Kuhl & Wiegratz, 2007). The effects of aromatization depends on aromatase enzyme levels in neural, vascular, sex organ, adipose, skeletal muscle, cardiac, bone, and liver tissues (Blakemore & Naftolin, 2016; Patel, 2017). Remarkably, the majority of circulating E₂ and other reduced estrogen forms results from peripheral aromatization of SAs in adipose tissue (Lakshman et al., 2010).

Similar to aromatase, 5- α -reductase reduces non-aromatizable SAs (except DHT-derivatives) into the DHT metabolite by removing the 4-5 carbon double-bond from testosterone (or testosterone derivatives) and adding two hydrogen atoms to the four-carbon ring structure (Llewellyn, 2011). The effects of this reduction depend on 5- α -reductase levels in the central nervous system, liver, integument, prostate, scalp, and skeletal muscle tissues (Llewellyn, 2011; Yarrow, McCoy, & Borst, 2012). Dihydrotestosterone and derivatives have the greatest AR binding affinity leading to an almost four-fold greater potency than testosterone. The increased

binding affinity is thought to mediate many androgenic effects such as alopecia, acne, muscle mass, and benign prostate hypertrophy in men and masculinization in women (Llewellyn, 2011). Synthetic androgens that are amenable to 5- α -reduction lead to higher DHT levels in the blood when administered by transdermal patch or cream application (Handelsman, 2016).

Dose, frequency, and duration. Total dose, frequency of dosing, and duration of administration directly affect the absorption, distribution, metabolism, and excretion of SAs. Normal therapeutic doses for testosterone replacement therapy are 100-200 mg split into bi-weekly injections, 6 mg/day scrotal transdermal patch, and 100-200 mg gel applied daily (Hohl, 2017). Given the different therapeutic uses, doses of SAs rarely exceed 200 mg with any mode of administration, frequency, and duration. For injectable SAs, pharmacokinetics depends on the volume of the oil depot, ester chain link, duration of injection, access of the oil depot, and esterified androgen in the extracellular fluid compartment (Handelsman, 2016). In general, the half-life of injectable SAs range from one to two days, up to several weeks or months, whereas orals and transdermal forms are metabolized within a 24-hour window (Handelsman, 2016). Metabolites of non-alkylated SAs at therapeutic doses and durations are normally metabolized by a system of enzymes in the liver and excreted uneventfully in the urine except in conditions of severe disease (Handelsman, 2016; Katzung, 2018). In contrast, frequent exposure to high dose alkylated and non-alkylated SAs for long durations exerts greater allostatic organ load on the kidneys and liver often leading to tissue damage (Llewellyn, 2011). Long duration with frequent dosing plays a large role in the summation of adverse tissue- and organ-specific effects eventually leading to androgen toxicity and disease.

Androgen Toxicity

Toxicity is defined as “any toxic (adverse) effect that a chemical or physical agent might produce in a living organism” (Roberts, James, & Williams, 2015, p. 1). Although androgens are hormones, they can be considered physical agents acting in exposure through various modes of administration. Much of what is known about androgen toxicity was developed from *in vitro* research using supraphysiologic doses of different androgens applied directly to numerous specific cell types (Melchert, Herron, & Welder, 1992; Vicencio et al., 2006; Welder, Robertson, Fugate, & Melchert, 1995). The first explicitly reported form of androgen toxicity was referred to as cardiotoxicity. The term “cardiotoxicity” became apparent in the literature in the early 1990s when Melchert et al. (1992) directly exposed primary rat myocardial cell cultures to three androgen types reporting mild to severe dose-responsive changes in cell morphology. In general, the dominant toxicologic aspects of androgen toxicity are predictable and adverse dose-responsive health effects at supraphysiologic or extreme doses and deleterious health effects increasing in severity at common therapeutic doses with longer durations of exposure. Hepatotoxicity and cardiotoxicity are the most widely recognized forms of androgen toxicity in the literature, however, there are several levels of evidence to suggest neurotoxicity, vasculotoxicity, hematotoxicity, and nephrotoxicity (Aparicio et al., 2017; Baggish et al., 2017; Kaufman, Kanayama, Hudson, & Pope, 2019; R. D. Rothman et al., 2011; Solimini et al., 2017).

Animal models. In addition to *in vitro* studies, *in vivo* research of animal models have provided insight into the mechanisms leading to androgen toxicity, however, the early animal literature dominantly emphasized cardiotoxicity to the expense of other areas. Recent animal

research has now expanded to include evidence of neurotoxicity, vasculotoxicity, hematotoxicity, hepatotoxicity, and nephrotoxicity.

Early literature. Early animal research assessed morphological changes of cardiac tissue such as global myocardial hypertrophy and ventricular hypertrophy, and vascular changes involving increased platelet aggregation and a tendency for thrombotic events. Initial findings of pathologic heart remodeling and the increased tendency for platelet aggregation continue to be a keen interest of researchers and source of contentious debate.

Cardiac morphology. Woodwiss, Trifunovic, Phillippides, and Norton (2000) used an experimental design to expose male Sprague-Dawley rats to supraphysiologic doses of nandrolone decanoate (ND) and exercise or no exercise. The researchers found that ND administration 10 mg/kg/week (900 mg/week equivalent dose for a 200 lb. man) resulted in nonsignificant differential effects on left ventricular remodeling and minor collagen infiltration leading to altered cardiac function and reduced heart weight in exposed rats compared to unexposed rats. In contrast, Do Carmo et al. (2011) also applied the same ND dose to trained male Wistar rats using additional experimental groups. No exercise and ND exposure resulted in a 10% increase in cardiac hypertrophy, whereas training and ND exposure showed a 17% increase in cardiac hypertrophy ($p < .05$)(Do Carmo et al., 2011). Collagen volumetric fraction and cardiac collagen type III expression increased in both groups ($p < .05$) (Do Carmo et al., 2011). El-Mas, Afify, Omar, and Sharabi (2002) exposed male Wistar rats to extremely high-dose testosterone undecanoate 500 mg/kg/month (45,454.5 mg/kg/month equivalent dose for a 200 lb. man) for three months to determine the effects of chronic androgen exposure on left ventricular remodeling post myocardial infarction. Chronic exposure to supraphysiologic

androgen resulted in cardiac hypertrophy without upregulation of atrial natriuretic peptide mRNA, increased α -MHC leading to a significantly higher α -MHC/ β -MHC ratio, and significantly greater IGF-1 mRNA expression in exposed rats compared to unexposed rats. Following coronary artery ligation, there was no difference in mortality or infarct size between each of the groups. Exposed rats showed lower wall stress and left ventricular end-diastolic pressure with no changes in cardiac output and mean arterial pressure. The findings suggest that high-dose androgen exposure improves long-term post-infarction outcomes by reducing wall stress and end-diastolic pressure with no deleterious effects in the post-infarction period.

Reflexes and cardiovascular control. Initial morphology studies showed possible alteration of cardiac function; thus, the research focus shifted to neural cardiovascular control and reflexes. The study by El-Mas, Afify, Mohy El-Din, Omar, and Sharabi (2001) exposed male Wistar rats to (1 mg) androgen as a replacement dose to determine the capacity of testosterone to facilitate baroreflex responsiveness through vagal and sympathetic autonomic mechanisms. The investigators found that castrated and replacement levels of testosterone had no effect on baroreceptor control of reflex tachycardia, however, testosterone modulated reflex bradycardia by stimulation of cardiac vagal pathways. Beutel, Bergamaschi, and Campos (2005) used an experimental design to expose male Wistar rats to stanozolol at two supraphysiologic dose levels, low (5 mg/kg/week; 200 lb. human equivalent 454.5 mg/kg/week) and high (10 mg/kg/week; 200 lb. human equivalent 1,818 mg/kg/week), to determine whether high-dose androgen induced cardiovascular effects and baroreceptor reflex sensitivity. The researchers found no difference in heart weights between exposed rats and control rats, however, androgen administration significantly increased mean arterial pressure in low-dose (122 ± 1

mmHg) and high-dose (124 ± 2 mmHg) in comparison to controls (99 ± 2 mmHg, $p < .05$) (Beutel et al., 2005). Cardiac output increased only in the low-dose rats, whereas vascular peripheral resistance increased only in high-dose rats. Similarly, low-dose, but not high-dose exposed rats demonstrated small changes in heart rate.

Vascular changes. Matsuda, Ruff, Morinelli, Mathur, and Halushka (1994) exposed male Long-Evans rats to testosterone cypionate 20 mg/kg/week for two weeks to determine the effects of SA administration on platelet aggregation responses, expression of platelet and vascular thromboxane A_2 /PGH₂ receptors, and aortic contractile responses to thromboxane A_2 (Tx A_2). Exposed and uncastrated rats experienced significant increases in thromboxane A_2 receptor density in aortic membranes and platelets. A similar study by Gonzales, Ghaffari, Duckles, and Krause (2005) exposed male Fischer rats to testosterone propionate pellets for four weeks demonstrating greater amounts of thromboxane A_2 synthase in middle cerebral arteries in smooth muscle and endothelial layers in exposed compared to unexposed rates. The researchers also found testosterone to increase endothelial thromboxane A_2 synthesis with no effect on vasoconstriction mediated by thromboxane A_2 -endoperoxide receptors, thus, concluding chronic androgen administration might increase vasospasm and thrombosis risk associated with stroke. In contrast, a study by ShiJun, XiaoYing, Jian, Xinli, and Yan (2007) exposed male Wistar rats to DHT 0.25 mg/rat daily for two weeks to determine the effects of physiologic androgen dose on regulating platelet aggregation to offset oxidative injury. Analysis of DHT-exposed rats showed significant inhibition of platelet aggregation with oxidative injury induced by hydrogen peroxide, whereas unexposed and castrated rats had higher platelet aggregation with induced oxidative injury.

Recent literature. Current androgen research on animals has given more attention to neurotoxicity, vasculotoxicity, hematotoxicity, hepatotoxicity, and nephrotoxicity although most studies have focused on various aspects of cardiotoxicity.

Cardiotoxicity. The study by Vasilaki et al. (2016) of young rabbits exposed to ND, at 4 mg/kg and 10 mg/kg bi-weekly for six months, reported inflammatory collagen infiltration and focal fibrosis in histologic specimens, significantly increased thiobarbituric acid-reactive species and myocardium thickness, and decreased catalase function leading to oxidative stress and impaired diastolic function in exposed rabbits. Another high-dose study by Karbasi, Zaeemi, Mohri, Rashidlamir, and Moosavi (2017) exposing male Wistar rats to testosterone enanthate, 40 mg/kg/week for two months, reported significant differences in biomarkers of muscle damage and slight myocardial hypertrophy in resistance-trained rats and androgen-exposed resistance trained rats, but not in untrained androgen-exposed rats. A swimming study by Tofighi, Shirpoor, Ansari, Shirpoor, and Zerehpooosh (2017) exposing male Wistar rats to ND, 30 mg/kg/week over six weeks, showed lipid peroxidation, proliferation of coronary artery smooth muscle cells and myocardium tissue, significant increases in homocysteine, nicotinamide adenine dinucleotide phosphate oxidase, 8-hydroxy-2'-deoxyguanosine, cholesterol, low-density lipoprotein and apolipoprotein B, along with substantial cardiac tissue and coronary artery fibrosis, in ND-exposed rats plus forced swimming compared to control rats. An endurance training study by Żebrowska, Sadowska-Krępa, Jagsz, Kłapcińska, and Langfort (2017) exposing male Wistar rats to testosterone propionate, 20 mg/250 g body weight/week, demonstrated significant increases in heart weight of trained and testosterone-exposed rats (0.99 g, $p = .02$), whereas changes in heart weight of non-trained and testosterone-exposed rats (0.90 g) were not

significant.

Other cardiac studies focused on mechanisms involved in pathologic cardiovascular remodeling given equivocal heart weight findings across different animal species, the tendency of current animal researchers not to ethically disclose wet heart weights, and inconsistencies in the reporting of heart weight to body weight ratios in the assessment of rat studies. The multi-exercise study by Bai et al. (2018) exposed male inbred strain laboratory (C57B1) mice to ND, 20 mg/kg/week for eight weeks, to investigate morphologic changes to heart mass coinciding with differential metalloproteinase-2 expression and fibrotic remodeling between heart ventricles. The investigators reported no differences in heart weight of all exposed and unexposed mice, increased right ventricle fibrosis (2.59%) compared to left ventricle fibrosis (2.21%) in trained and ND-exposed mice, and significantly higher matrix metalloproteinase-2 expression in the right ventricles, compared to the left ventricles of trained and ND-exposed mice (Bai et al., 2018). The research of Melo Junior et al. (2018) focused on the effects of ND on left ventricular contractility, calcium-handling proteins involved with pathologic remodeling, and activation of the renin-angiotensin system in male spontaneously hypertensive rats exposed to ND, 20 mg/kg/week, over four weeks. Compared to non-exposed rats, ND-exposed rats experienced an increase in hypertension and left ventricular mass without any changes in heart rate, reduced number of myocytes, increased myonuclei area, perimeter, and length, greater fibrotic collagen infiltration, and higher left ventricular systolic blood pressure. Exposed rats also demonstrated activation of the renin-angiotensin system and pathological remodeling through increased levels of TNF- α , AT₁R, ACE, and β 1-AR proteins and increased calcium ion flow by higher expression of SERCA2a and PLB.

Hematotoxicity. The most frequently reported and debated adverse effect of all androgen therapies is secondary erythrocytosis which results in increased hematocrit by direct stimulation of hematopoietic stem cells to increase red blood cells without stimulation of erythropoietin. The high-dose study by Karbasi et al. (2017) exposing male Wistar rats to testosterone enanthate, 40 mg/kg/week for two months, reported no differences in red blood cells, hemoglobin, and hematocrit between exposed and unexposed groups. In contrast, the research of Zarei, Zaeemi, and Rashidlamir (2017) exposing male Wistar rats to testosterone, (LD 25 mg/kg/week) and (HD 50 mg/kg/week) for two months, reported high-dose testosterone significantly increased red blood cells (HD 9.228 ± 0.16), packed cell volume (HD 48.80 ± 0.61), and hemoglobin (HD 16.56 ± 0.10) compared to unexposed rats (7.912 ± 0.38 ; 48.05 ± 0.49 ; 14.32 ± 0.44 , $p < .05$). High-dose testosterone also significantly increased neutrophils compared to controls, whereas high-dose and resistance training significantly decreased eosinophils compared to low-dose and controls. The research of W. Guo et al. (2013) conducted a comprehensive investigation of erythropoiesis by exposing male and female mice to subcutaneous testosterone, short-term 1 mg/day and long-term 2 mg/week for up to two weeks. In female and male mice compared to placebo, testosterone exposure increased transferrin, transferrin saturation, serum iron, reticulocytes, reticulocyte concentration, hematocrit, and hemoglobin. The researchers observed increased circulating erythropoietin, upregulation of ferroportin expression, lowered splenic iron retention, and an upregulation of renal erythropoietin mRNA expression coupled with a downregulation of hepatic hepcidin mRNA expression at all doses and durations of testosterone exposure. Suppression of hepcidin by testosterone occurred without the action of hypoxia sensing mechanisms or erythropoietin, whereas the association of iron to red blood cells

significantly increased. Testosterone increased red blood cells by mediating BMP/Smad signaling to impede hepcidin mRNA transcription without affecting mRNA stability.

Hepatotoxicity. The toxic effects of oral 17AA androgens were observed in early clinical practice and later confirmed in decades of animal research. A toxicology study by El-Halwagy et al. (2016) exposing male albino rats to oral methandienone (17β -OH- 17α -CH₃-1), (low 0.9 mg/kg; therapeutic 5 mg/kg; high 18 mg/kg) for three months, reported increases in total proteins and albumin, and in the liver biomarkers, aspartateaminotransferase and alaninaminotransferase, in all exposures groups after one month of exposure. Superoxide dismutase, catalase, and lipid peroxidation activity increased, whereas glutathione levels decreased in methandienone-exposed rats. Morphological changes to liver tissue architecture occurred in all dose-exposure groups, however, congestion and dilation of the sinusoids and central vein, loss of nuclei, hepatocyte degeneration and vacuolation, necrosis with hyalinization, and edema increased with dose-response but mostly reverting to normal upon cessation of exposure for one month.

Although 17AA androgens have well documented toxic effects, non-17AA androgens are have also been scrutinized for their possible roles in liver pathology. Sadowska-Krepa et al. (2017) exposed male adolescent and sedentary Wistar rats to testosterone enanthate, (low 8 mg/kg/week; high 80 mg/kg/week) for six weeks, reporting significant dose-exposure dependent increases in liver thiobarbituric acid-reactive chemicals in both exposure groups compared to controls. Rats exposed to the high dose observed significant liver enzymes elevations and heat shock protein content with significant decreases in the rate of body mass gain resulting in a lower liver weight to body weight ratio. No differences were found in the antioxidant enzymes, catalase, glutathione reductase, and glutathione peroxidase, at both exposures, although,

superoxide dismutase relatively increased at high-dose exposure. The findings reaffirm a lack of liver toxicity with injectable forms of testosterone, however, SAs composed of 19-nor nandrolone or derivatives have demonstrated moderate liver toxicity. The study by Shalaby and Bahey (2018) exposing male Wistar rats to nandrolone decanoate, 10 mg/kg/week for four weeks, reported significant increases in aspartate transaminase, serum alanine, and body weight gain. Histological analysis revealed loss of hepatocyte mitochondrial cristae, blood vessel congestion and dilatation, apoptotic hyperchromatic nuclei, inflammatory cellular infiltration characteristic of fibrosis, substantial vacuolar cytoplasmic deterioration, and increased area of cells positive for glial fibrillary acid proteins and apoptotic index with four weeks of ND exposure. The effects fully reversed upon exposure cessation.

Nephrotoxicity. Renal toxicity attributed to SAs has been hypothesized to be the indirect result of direct toxicity to other organ systems such as the liver and tissue-level SA metabolism, thereby increasing allostatic load on the renal system. Since both the kidneys and liver are key organs involved with distribution, metabolism, and excretion, any direct adverse effects on one organ have the potential to induce toxicity in the other organ. Regardless of this view, current evidence suggest renal toxicity results from direct effects and toxicity to other organs, thus, increasing the magnitude of renal toxicity. The research of Riezzo et al. (2014) assessed direct nephrotoxicity by exposing male CD1 mice to nandrolone decanoate, (low 7.5 mg/kg/week; high 10 mg/kg/week) for six weeks, reporting dose-dependent oxidative kidney damage evidenced by reductions in glutathione reductase and glutathione peroxidase antioxidant enzymes and elevations in malondialdehyde concentrations. Histological analysis showed focal segmental glomerulosclerosis by increased protein expression and positive immunostaining, increased

activity of proinflammatory cytokine expression, and apoptotic injury due to TNF- α . The study by Brasil et al. (2015) investigated renal remodeling by exposing female Wistar rats to ND, 20 mg/kg/week for four weeks, demonstrating decreased kidney expression of type-A and type-C natriuretic peptide receptors, and renal hypertrophy with collagen deposition. Another study by Aparicio et al. (2017) exposing male Wistar rats to stanozolol, 10 mg/kg/week for three months, reported greater urinary acidity, 15% greater kidney weight ($p < .001$), 12% larger glomerular area ($p = .001$) in exposed rats compared to controls. Exposed rats also experienced a non-significant $\sim 20\%$ increase in glomerular mesangiums, tufts, and interstitial connective tissue. Exploring deeper into nephrotoxic mechanisms, Asghar Tofighi et al. (2017) exposed male Wistar rats to ND, 30 mg/kg/week for six weeks reporting significant increases in kidney 8-OHdG, serum cystatin C, and podocin and nephrin gene expression, as well as lowered creatinine clearance in ND-exposed rats compared to controls. Using the same exposure comparisons, the researchers observed nephritic cellular proliferation and fibrosis on histology specimens. Kahal and Allem (2018) also used ND, 30 mg/kg/week for exposure, but extended the exposure duration to two- and three-month periods using male (*Mus musculus*) mice instead of male Wistar rats, to determine reversibility of toxic effects. After three months, rupture of tubular walls, atrophy and fragmentation of glomerular structures, enlargement of convoluted tubule basal lamina, between-tubule hemorrhage, proximal convoluted tubule epithelial lining vacuolar deterioration, increased hyaline content, necrosis, tubes without other cell layers, and chronicity and vascular congestion in eosinophil cytoplasm, were noted. Following six weeks cessation of androgen exposure, hemorrhage, convoluted tubule epithelial lining vacuolar deterioration, vast areas of necrosis and hyaline content, glomerular rarefaction, and greater

glomerular atrophy and rupture of tubular walls, were observed suggesting non-reversible kidney structure and loss of functional capacity.

Neurotoxicity. The study by Bueno, Carvalho, Gutierrez, Lhamas, and Andrade (2017) assessed the influence of exposure to boldenone and stanozolol at (5 mg/kg/week; 2.5 mg/kg/week; 1.25 mg/kg/week) for (4 weeks; 8 weeks; 12 weeks) on oxidative stress in two brain structures and cholinergic regulation in male Wistar rats. Exposure to both androgens, 5 mg/kg/week over four weeks and 1.25 mg/kg/week over 12 weeks, led to significant increases in oxidative stress in the cerebral cortex and hippocampus, whereas only exposure to boldenone, 1.25 mg/kg/week over 12 weeks, resulted in increased ACh. A similar study by Joukar, Vahidi, Farsinejad, Asadi-shekaari, and Shahouzehi (2017) investigated oxidative and apoptotic systems involved with ND-induced neurodegeneration of the hippocampus in male Wistar rats exposed to 5 mg/kg/week over an eight weeks. The total antioxidant capacity of hippocampal cells, TAC/MDA ratio, and Bcl-2 were significantly decreased with ND exposure, whereas ND exposure raised the brain tissue Bax/Bcl-2 ratio. The findings suggest cell homeostasis and oxidative regulation are impaired with sub-acute ND exposure. Although the studies by Joukar et al. (2017) and Bueno et al. (2017) showed evidence of neuronal toxicity with androgen exposure, the studies by Yan et al. (2019) and Carteri et al. (2019) demonstrated protective neuronal effects with therapeutic and supraphysiologic androgen doses.

Vasculotoxicity. The study by Guzzoni et al. (2018) assessed the effects of ND exposure (5 mg/kg/week over six weeks) and training, on vascular nitric oxide bioavailability and endothelium-dependent vasodilation of the thoracic aorta in male Wistar rats. In ND-exposed and trained rats, the aortic endothelial ACh-regulated relaxation response diminished, whereas

aortic production and bioavailability of nitric oxide decreased in ND-exposed rats, compared to trained and ND-exposed rats. Oxidative damage and aortic vessel morphology, evidenced by increased reactive oxygen species and tunica media thickness, only occurred in trained and ND-exposed rats. Assessing the same vascular structure, Andrade et al. (2018) investigated the effects of stanozolol exposure, 20 mg/kg/week for eight weeks, on inflammatory cytokine dysregulation and oxidative status involved with aortic lipid deposition in male, low density lipid receptor-deficient, knockout mice. After the exposure period, stanozolol-exposed mice exhibited increased non-HDL cholesterol and triglycerides with vascular lipid deposition. Stanozolol exposure lowered interleukin-10 and raised TNF- α resulting in an increased TNF- α to interleukin-10 ratio. Global oxidative stress by stanozolol exposure was demonstrated in liver protein oxidation and lipid peroxidation along with increased plasma oxidized LDL.

Forensic studies. The toxic effects demonstrated by animal studies does not always correspond to similar effects in humans due to inherent species-specific differences in metabolism, therefore, forensic studies add another level of evidence moving away from animals to real world human conditions. A morphology and toxicology post-mortem study of four illicit androgen users, showed concentric cardiac hypertrophy with focalized fibrosis, cardiomyopathy with sparse myocyte death, and eosinophilic myocarditis (Montisci et al., 2012). The most common pathological finding among each autopsy case was left ventricular hypertrophy with myocytolysis and fibrosis. The histopathologic autopsy study by Frati, Busardò, Cipolloni, Dominicis, and Fineschi (2015) assessing 19 fatal cases of illicit androgen use, also found that left ventricular hypertrophy with myocytolysis and fibrosis were the most frequent androgen-induced changes, thus, adding greater confirmation to the cardiovascular mechanisms (direct

myocardial injury, vasospastic, atherogenic, and thrombotic) hypothesized by Melchert and Welder (1995). Similarly, an autopsy and immunohistochemical study of androgen-induced heart ventricle remodeling found that under conditions of illicit use and intensive physical training, apoptotic degeneration occurred in endothelial cells and myocytes of the heart ventricles (Cecchi et al., 2017).

Adding to these findings, another autopsy and immunohistochemical study of androgen-induced heart remodeling reported that all cases demonstrated perivascular, interstitial, and perineural fibrosis with fibroadipose metaplasia in the left ventricle myocardium (M. Lusetti, Licata, Silingardi, Reggiani Bonetti, & Palmiere, 2015). The autopsy research of M. Lusetti et al. (2015) offered additional confirmation of previously reported histological changes to cardiac tissue, normal or mild intima enlargement of subepicardial coronary artery areas, infrequent and disarrayed fatty streaks with media and intima enlargement of coronary arteries, and interstitial myocardial fibrosis. Again, the researchers confirmed the most frequent autopsy findings of illicit androgen users was left ventricular hypertrophy, left ventricular and right ventricular hypertrophy, and infrequent left ventricular myocyte necrosis.

Toxicity findings. The mechanisms reported in the *in vitro*, *in vivo* animal, and forensic studies of this chapter constitute the theoretical basis for *direct* androgen toxicity. On the other hand, *indirect* toxicity is explained through the genomic and non-genomic actions of androgens, general risk factors, and genetic risk factors. Total toxicity is the sum of direct and indirect toxicity at the cellular, tissue, organ, and organ system levels represented as distinct disease states. The body of evidence reported in benchwork, animal research and forensic studies, suggested cardiotoxicity, neurotoxicity, vasculotoxicity, hematotoxicity, hepatotoxicity, and

nephrotoxicity as the six primary forms of androgen toxicity. Therefore, each toxicity category was incorporated into an androgen toxicity framework using pharmacologic and toxicologic principles to systematically identify and classify androgen-induced disease states reported in the reviewed animal and forensic studies. The androgen toxicity framework was applied to each study throughout the remainder of the chapter and integrated in the conceptual framework of this study.

Evidence of Increased Risk

Several studies have reported evidence of an increased risk for many health outcomes resulting from androgen exposure in the literature. The following chapter section reviews each case report, observational study, clinical trial, and meta-analysis to identify specific health outcomes, disease states, toxicity classifications, and characteristics of health outcomes risk associated with androgen exposure across a broad range of settings

Case reports. The literature contains hundreds of case reports involving toxic effects of androgen exposure. Toxicity to the cardiovascular system is distinct but closely related to vasculotoxicity through interdependent mechanisms under conditions of androgen abuse. Hence, the coincidental relationship between these toxicity forms often masks and complicates the identification of disease etiology and disease progression. Hematotoxicity is the most frequently reported androgen toxicity and involves the stimulation of the hematopoietic system into many blood cell types hematopoietic stem cells → myeloid progenitor cells → erythrocytes and megakaryocytes; megakaryocytes → thrombocytes. Although toxic effects to the liver and kidneys are regularly reported together in the literature, hepatotoxicity involves direct hepatocellular damage from one class of SAs, whereas nephrotoxicity involves direct nephron

damage from many SA classes. As metabolic stress on the liver increases through 17AA exposure, stress on the excretion capacity of the kidneys also increases. Several studies have reported neurotoxicity mostly occurring secondary to hematotoxicity, hepatotoxicity, nephrotoxicity, and vasculotoxicity.

Cardiotoxicity. Several case reports detail varying severity of cardiovascular outcomes resulting from androgen exposure. In each case, androgens induced vascular and cardiac changes resulting in cardiomyopathy or acute myocardial infarction. White, Brennan, Mi Ren, Shi, and Thakrar (2018) reported a case of fulminant heart failure in a 39-year-old male weightlifter who admitted using testosterone and boldenone three months prior to emergency department presentation. On a six-month follow-up, the echocardiogram showed a 39% LV ejection fraction demonstrating partial recovery suggestive of permanent damage. In contrast, a case of reversible cardiomyopathy involved a 53-year-old male fitness trainer who reported using multiple androgens over a 20-year period prior to requesting emergency services (Gangadharamurthy, Pandian, Malhotra, Tahir, & Mukherjee, 2018). At the time of presentation, the patient experienced a stroke and heart failure requiring therapeutic phlebotomy to decrease high hematocrit due to secondary erythrocytosis and pharmacologic intervention. The patient improved with at each echocardiogram assessment at four, eight, and twelve months following admission and achieved almost complete reversal of cardiomyopathy with an ejection fraction of 30-35%. Garner, Iardino, Ramirez, and Yakoby (2018) reported another case of cardiomyopathy and elevated hematocrit in a 60-year-old Caucasian male using high-dose testosterone to prepare for a weightlifting competition. The patient's condition was treated by surgery and therapeutics with full recovery of left ventricular function at a six-month follow-up.

Many cases of acute myocardial infarction are associated with androgen use in the literature. Christou, Christou, Nikas, and Goudevenos (2016) reported a case of a 30-year-old male presenting for emergency services with diaphoresis and severe substernal chest pain that was currently using five different androgens. After a diagnosis of acute myocardial infarction, the patient was assessed by coronary angiography and treated with therapeutics, declining further medical treatment and follow-up. Some cases of androgen-induced heart attack are severe ultimately affecting many organ systems. The case study by Flo, Kanu, Teleb, Chen, and Siddiqui (2018) reported a 41-year-old male with 20 years of androgen abuse that experienced acute myocardial infarction and multiorgan failure. Echocardiography showed concentric left ventricle hypertrophy and lowered left ventricular ejection fraction. Assessment by angiography revealed a complete right coronary artery occlusion necessitating a percutaneous coronary intervention. The patient's clinical condition worsened until acute liver and kidney failure occurred by the second day, post-procedure, however, by the seventh day the condition improved sufficiently for discharge on the following day.

Hematotoxicity. Toxicity to the hematologic system is evident in almost every case report reviewed in this chapter, evidenced by increased red blood cell concentration and hematocrit. The case by Ammatuna and Nijziel (2014) reported polycythemia in a 40-year-old male weight lifter with a history of consuming an oral 17AA androgen, oxymetholone, commonly used to treat anemia. On examination, blood measures showed hemoglobin at 17.9 g/dL and a hematocrit of 0.52. Further assessments revealed a kidney infarction thought to be facilitated by elevated hemoglobin and hematocrit. The ability of androgens to stimulate erythropoiesis and directly influence the hematologic system has also been implicated in surgical

complications. Fox, Varadharajan, Patel, and Beegun (2014) reported a case of recurrent hemorrhage after tonsillectomy in a 31-year-old bodybuilder with a history of illicit androgen and insulin use. After release from medical services post-operation, the patient returned due to excessive bleeding necessitating bipolar cauterization to several surgical sites and comprehensive coagulation analysis. No coagulation disorders were found but hemorrhaging occurred again three hours after the second surgery requiring additional surgery, intubation, excision of inferior poles, throat packs, and intensive care admission. Afterwards, hemostasis was complicated with fluctuating hypertension and bleeding requiring observation in intensive care for two weeks until hemostasis and bleeding were resolved.

The effects of hematologic toxicity on the entire vascular system have the capacity to affect most tissues in the body. As such, several reports of intestinal effects involving hemorrhage and coagulation are noted in the literature. Randhawa, Denunzio, and El-Tahir (2013) reported spontaneous intramural bowel hematoma in a 24-year-old male illicit androgen user. Imaging showed active mural hemorrhage and colonic mural hematoma, necessitating emergency endovascular arterial embolization of bleeding foci and surgery to resect a length of the bowel. Immediately post-surgery, the clinical condition deteriorated with massive blood loss until hemostasis was achieved and ileostomy was set, although a developing deep venous thrombosis required an inferior vena cava filter placement. The clinicians attributed these complications to androgen induction of fluid accumulation in the bowel and intramural hematoma secondary to intramural vessel shearing. Another case by Cavanagh, Shah, Thomas, and Gupta (2015) reported intestinal intussusceptions and polycythemia in a 34-year-old male with history of hypertension, irritable bowel syndrome, hypercholesteremia, anxiety, and illicit use of

high-dose injectable testosterone and nandrolone. Examination and imaging showed elevated hematocrit and two areas of small bowel intussusceptions without obstruction. Colonoscopy indicated erythema and edema in the colon and lower ileum along with ischemic colitis of the rectum and chronic colitis in the descending colon towards the rectum. The patient's polycythemia was the presumed etiologic factor for the intussusceptions and colonic ischemia.

Hepatotoxicity. The hepatotoxic effects of methylated androgens are universally accepted by scientists and have been repeatedly demonstrated throughout the literature in both therapeutic and illicit use. The case of Kato et al. (2018) reported liver tumor of hepatocellular adenoma in a 32-year-old Japanese woman with history of smoking, epilepsy, renal infarction, and hypertension treated with testosterone enanthate injections, 125 mg bi-weekly for 12 years, to non-surgically gender transition from female to male. Laboratory analysis showed dyslipidemia, liver dysfunction connected with non-alcoholic fatty liver disease, and high testosterone levels well beyond the normative range for males. Resected tissues revealed six well-differentiated tumors positively identified as hepatocellular adenoma. Liver adenomas are the most frequent benign liver tumor associated with androgen exposure, although other tumor types are noted in the literature. Romano et al. (2017) reported a case of a larger focal nodular hyperplasia, the second most frequent benign liver tumor, in a 30-year-old male with a two-year history of illicit androgen use requiring left hepatectomy. Surgery was performed to resect the mass from three of the liver segments and histological analysis showed abnormal vascularization and ductal reaction. A unique case series of nine patients aged 20 to 58 years old detail an array of benign liver tumor characteristics associated with illicit androgen exposure (Gupta et al., 2016). In all case histology samples, mitotic activity and fatty infiltration were not present,

whereas congestion and cholestasis were the next most frequent tissue change, followed by focal disruption of reticulin, and patchy architectural atypia.

Androgen-induced liver tumors were initially linked to treatment of a distinct anemia through the observation that Fanconi's anemic patients treated with androgens had a greater tendency to develop hepatocellular carcinoma (Takahashi et al., 2017; Velazquez & Alter, 2004). Three 17AA androgens (danazol, oxymetholone, and methyltestosterone) are *causally* associated with hepatocellular carcinoma. Hardt et al. (2012) reported hepatocellular carcinoma in a 37-year-old male professional bodybuilder abusing numerous androgens over five years necessitating a laparoscopic segmentectomy of the right hepatic lobe and full recovery after 27 months. Kesler, Sandhu, and Krishnamoorthy (2014) also noted hepatocellular carcinoma in a 24-year-old male competitive bodybuilder abusing androgens for seven years, first presenting with liver adenoma. The patient was advised to withdraw androgen use but continued abusing androgens for nine years going on to develop coronary artery disease, chronic kidney disease, and hepatocellular carcinoma requiring hemodialysis, multiple coronary artery stents, and placement onto an organ transplant list. Similarly, Solbach et al. (2015) reported hepatocellular carcinoma associated with long-term illicit androgen abuse in a 29-year-old male professional bodybuilder that required liver transplantation. Remarkably, Leone, G. Santos, Finan, E. Alsina, and S. Franco (2016) noted β -catenin-activated adenomas that underwent malignant transformation into hepatocellular carcinoma in a 39-year-old former athlete with previous androgen abuse also requiring liver transplantation.

Nephrotoxicity. Androgens exert toxic effects on the renal system directly by tissue damage with altered function and indirectly by toxicity to other organ systems. The case by

Winnett, Cranfield, and Almond (2011) reported the development of renal disease with increased creatinine levels in a 37-year-old male using boldenone. Repeated analysis showed increasingly extreme fluctuations in creatine and increased liver enzyme ALT levels leading the physicians to suspect a degree of focal segmental glomerular sclerosis. Similarly, the case series of four patients using testosterone propionate or nandrolone decanoate by Almukhtar, Abbas, Muhealdeen, and Hughson (2015) reported serum creatinine levels ranging from 2.6-3.8 mg/dL and estimated glomerular filtration rates between 22-34 mL/min indicating lowered kidney function and advancing renal disease. Patient biopsies showed blebbing and desquamation of epithelial cells, loss of epithelial nuclei, areas of compressed tubular epithelium, hematoxylin positive stains of formless deposits, and compact densifications in injured tubules and interstitium. Further analysis revealed tubular atrophy and interstitial fibrosis in two patients and lymphocytic inflammation and degenerated glomeruli in one patient. Although the findings demonstrate cellular changes in morphology, the effects are often reversible and overall organ tissue damage is not distinct. The case of Colburn et al. (2017) reported distinct kidney tissue damage, primary renal infarction and recurring renal infarction, in a 43-year-old male with a pattern of injectable testosterone and trenbolone acetate abuse. Imaging showed areas of damage in the left kidney necessitating anticoagulants to counteract an androgen-induced thrombophilic state to prevent additional infarcts.

Specific types of renal dysfunction occur when androgens induce hepatotoxicity. The case report by Milla Castellanos, Gutiérrez Martínez, Sevillano Prieto, Rodríguez Ramos, and Praga Terente (2018) reported acute kidney injury secondary to androgen-induced hepatotoxicity resulting in extreme hyperbilirubinemia in a 40-year-old male with a history of consuming a

methylated oral derivative of dihydrotestosterone. Renal evaluation showed bile cast nephropathy with characteristic urine bilirubin casts evidencing possible direct damage to kidney tubules with bilirubin accumulation in glomerular fenestrations. Similarly, Fisler et al. (2018) reported bile case nephropathy secondary to androgen-induced hepatotoxicity with an identical pattern of extreme hyperbilirubinemia in a 56-year-old man with a history of androgen use. Biopsy revealed a distinct arrangement of tubular damage and obstruction of renal tubules by intratubular bile casts necessitating the need for four weeks of dialysis treatment to restore kidney function. A common indirect form of nephrotoxicity occurs as a consequence of androgen-induced hematologic toxicity. Merino García, Borrego Utiel, Martínez Arcos, Borrego Hinojosa, and Pérez del Barrio (2018) reported a case of acute kidney failure secondary to hematologic toxicity resulting in chronic untreated malignant hypertension in a 37-year-old male with history of illicit androgen use and high-protein consumption. Upon presentation to emergency services, the patient's blood pressure was 250/180 mmHg and an assessment revealed extreme acute kidney failure. Dialysis was initiated and imaging showed a calcified and thrombosed portion of the left renal artery along with an aneurysm. Biopsy revealed long-term interstitial kidney disease and hypertensive damage to small vessels demonstrating nephrotoxicity secondary to chronic androgen-induced hematotoxicity.

Neurotoxicity. Most neurotoxic effects of androgens are indirect resulting from toxicity to the liver, kidneys, or hematologic system although some evidence suggests direct neurotoxicity to the central and peripheral nervous systems is possible. One example of direct neurotoxicity was presented by Maini, Maxwell-Scott, and Marks (2014) reporting severe metabolic alkalosis and extreme hypokalemia in a 30-year-old male that consumed 50,000 mg of

stanozolol for a week before presenting to emergency services. The unusually high dose of oral androgen in such a short period resulted in severe mineralocorticoid excess, electrolyte imbalance, altered consciousness, and borderline coma. When indirect toxicity is sufficient to cause harm in the nervous system, the conditions are usually severe or life-threatening. Cooper, Reeve, and Doherty (2011) reported atherosclerotic stroke in a 46-year-old recreational bodybuilder abusing nandrolone and testosterone over 20 years. In this case, the stroke represents indirect neurotoxicity secondary to hematotoxicity, nephrotoxicity, and vasculotoxicity given the presence of thromboembolic events and chronic renal failure. Harston et al. (2014) reported lacunar infarction in a 40-year-old bodybuilder admitting frequent abuse of many androgens with no risk factors for ischemic stroke. The ischemic injury of this case exemplifies indirect neurotoxicity secondary to hematotoxicity by increasing erythrocytosis and vasculotoxicity by the release of clotting factors and an increase in thromboxane A₂-receptor density. The two secondary toxicities ultimately result in hyperviscosity and hypercoagulability of the blood leading to ischemic injury. Another case of indirect neurotoxicity by Omar, Abdul, Panday, and Teelucksingh (2017) reported a cortical based acute infarct in the right parietal lobe and increased erythrocytosis resulting acute superior sagittal sinus thrombosis in a 30-year-old male bodybuilder with chronic illicit androgen exposure presenting with dyscognitive changes, frequent focal motor seizures, dysarthria, left-sided hemiparesis, and elevated hematocrit. Tikka, Mistry, and Janjua (2016) also detailed a case involving vertebrobasilar infarct and polycythemia resulting in sudden unilateral sensorineural hearing loss in a 32-year-old male with history of frequent androgen abuse and no risk factors for ischemic stroke.

Indirect neurotoxicity has been implicated in the development of encephalopathy in cases with no history of neurological disease or traditional risk factors. For instance, Edvardsson (2015) reported hypertensive encephalopathy in a 20-year-old male with a three-month history of methandrostenolone and methenolone enanthate abuse leading to confusion, nausea, vomiting, and visual disturbances. The hypertensive state in this case report also represents indirect toxicity secondary to nephrotoxicity, hematotoxicity, and vasculotoxicity by altering the blood pressure control hormones of the kidneys and shifting the fluid compartment of the blood increasing blood pressure and resulting in altered consciousness. A recent pathology report by Bolster (2017) that detailed the death of 18-year-old Luke O'Brien-May referenced the case report of Edvardsson (2015) as evidence to determine cause of death at autopsy. The report noted severe brain swelling, extensive brain stem injury, and presumed encephalitis post-mortem after presentation to emergency services with agitation, behavioral disturbances, and roving disconjugate eye movements following short-term ingestion of stanozolol. Ruling out viral encephalitis and vasculitis, Bolster (2017) attributed the death of the deceased to the ingestion of stanozolol through indirect toxicity.

Vasculotoxicity. Reports of vasculotoxicity span several decades often coinciding with cardiotoxicity and related outcomes. Dickerman, McConathy, Schaller, and Zachariah (1996) reported sudden death in a 26-year-old bodybuilder with history of androgen abuse. The manner of death was bilateral pulmonary embolism after deep venous thrombosis of the lower legs resulting in right heart failure. Pathology showed increased heart mass (440 g) and left ventricular hypertrophy with no signs of atherosclerosis (Dickerman et al., 1996). The evidence

in this case points to increased platelet density and aggregation leading to deep venous thrombosis to eventually result in pulmonary embolism.

The study by McCarthy, Tang, Dalrymple-Hay, and Haw (2000) reported two cases of thrombosis and embolism leading to cardiomyopathies. The first case, a 35-year-old male bodybuilder with a long history of cyclic nandrolone decanoate and testosterone abuse, showed left ventricular dysfunction, dilated cardiomyopathy, thrombus in the left ventricle, and acute embolic blockage of the tibial arteries. Similarly, the second case, a 31-year-old male bodybuilder with long-term history of cyclic testosterone and dianabol abuse, demonstrated complete embolic occlusion in the right superficial femoral artery, partial occlusion in the left popliteal artery, and thrombus in the left ventricle. In both cases, left ventricular thrombus formation resulted in downstream emboli and artery occlusions.

Androgen-induced toxicity of the vasculature is expressed in effects on the endothelium, coagulation factors, fibrinolysis, platelets, and inflammation resulting in hypercoagulable states and an increased tendency for thrombotic and embolic events. The increased propensity for pro-thrombotic and pro-embolic events due to androgen exposure is exacerbated in many health conditions. For instance, Amjad, Khatoon, Tarasaria, and Sharifova (2018) reported expansive portal vein thrombosis in a 35-year-old male with Klinefelter syndrome after two months of testosterone therapy with negative findings for thrombophilia.

In some instances, vasculotoxicity is so closely linked to hematotoxicity, they cannot be clearly differentiated. Rimmer, Seftel, Israels, and Houston (2012) reported familial hemophilia B Leiden causing reduced levels of factor IX in a 29-year-old male admitted to emergency services due to an infection resulting from a quadriceps injection of water-base stanozolol. The

physicians observed stanozolol-induced increases in factor IX that were mapped over the course of 25 days after plasma-derived factor IX was initially applied intravenously to treat the deficiency. Given the half-life of the applied plasma-derived factor IX is almost 17 hours, the increased factor IX levels after the first day until the 25th day demonstrated the ability of the androgen to increase clotting factors. Although the case by Rimmer et al. (2012) is closely related to hematotoxicity by altering blood composition, favorable effects in hemophilia patients mediated by androgen-induced changes to blood clotting factors might also lead to vasculotoxicity resulting in thrombus formation and embolic occlusions in cases of androgen abuse or non-hemophilia patients therapeutically treated with androgens.

Observational studies. Several of the observational studies critically reviewed in this section were used by the FDA as evidence to issue risk labeling mandates for testosterone.

Vigen et al. (2013b). The study by Vigen et al. (2013b) was conducted to assess specific health outcomes related to androgen therapy and used to compare the results to the adverse outcome findings of S. Basaria et al. (2010). Vigen et al. (2013b) measured the differences in all-cause mortality, myocardial infarction, and ischemic stroke across androgen treatment status using a retrospective design of a cohort of 8,709 male veterans with clinically measured hypogonadism that received coronary angiography.

A total of 1,710 adverse events occurred out of the cohort of 8,709 veterans (Vigen et al., 2013b). Those not treated with androgens had 1,587 events in the form of 486 ischemic strokes, 420 myocardial infarctions, and 681 deaths. Individuals receiving androgen treatment had 123 adverse events of 33 ischemic strokes, 23 myocardial infarctions, and 67 deaths. Three-year post-angiography survival analysis showed an absolute risk difference of 5.8%, 95% CI [-1.4%,

13.1%] in favor of increased risk in the androgen group (Vigen et al., 2013b). After adjustment for coronary artery disease, androgen therapy was associated with an increased risk of adverse outcomes, $HR = 1.29$, 95% CI [1.04, 1.58] (Vigen et al., 2013b).

The findings were consistent with previous findings of increased cardiovascular events but raised the question whether this retrospective study was amenable to post hoc survival analysis because the treatment condition was not randomly allocated. For instance, the proportion of androgen recipients that died was 0.052, whereas the proportion of deaths in the non-androgen group was 0.083. Remarkably, the odds ratio and risk ratio of death in the androgen group were $OR = 0.60$, 95% CI [.45, .78], $p = .0001$ and $RR = 0.64$, 95% CI [.50, 0.81], $p = .0001$ using the reported number of reported deaths and manual calculation. The odds of death in the nontreated groups were almost 1.7 times greater than in the treated group. Further, the study findings were questionable at best since there was a call for retraction since it was found that women were included in the analysis sample.

Disease state-toxicity-risk. Stroke, heart attack, and mortality; neurotoxicity and cardiotoxicity; increased risk.

Finkle et al. (2014). Another closely related study by Finkle et al. (2014) used a retrospective cohort methodology with data from a commercial insurance database to assess the risk of myocardial infarction associated with androgen therapy. The researchers developed one cohort based on testosterone prescriptions ($n = 55,593$, mean age = 54.4 years) and a comparison cohort based on phosphodiesterase type 5 inhibitor (PDE5I) prescriptions ($n = 167,279$, mean age = 56 years) (Finkle et al., 2014). For all subjects, in each age group strata, the rate ratio

referring to pre- and post-testosterone prescriptions was $RR = 1.36$, 95% CI [1.03, 1.81], whereas in those aged 65 years or greater it was $RR = 2.19$, 95% CI [1.27, 3.77] (Finkle et al., 2014).

There were several limitations of this study. The cohort selections to determine risk of myocardial infarction were indirect and based on several assumptions, one of which was that testosterone prescriptions and PDE5I prescriptions were comparable. None of the rate ratio measures were statistically significant and even though trends were established there were several confounders such as behaviors, diagnoses leading to testosterone prescription, and differing forms of heart disease in the sample. Like the study by Vigen et al. (2013b), this study was also highly criticized for methodological issues suggesting limited applicability of the findings.

Disease state-toxicity-risk. Myocardial infarction; cardiotoxicity; increased risk.

Glueck et al. (2011). A seminal case-series study by (C. J. Glueck et al., 2011) investigated six men with no previous history of thrombotic events and undiagnosed familial thrombophilia that underwent androgen treatment. Androgen dose in the study was 50 mg/day administered as a patch or gel or 400 mg/month administered as intramuscular injections (C. J. Glueck et al., 2011). Two men experienced bilateral hip osteonecrosis at five and six months after initiation of androgen therapy (C. J. Glueck et al., 2011). Three men experience pulmonary embolism at approximately the 3rd, 7th, and 17th month of androgen therapy (C. J. Glueck et al., 2011). The last subject experienced amaurosis fugax after 18 months of androgen gel therapy (50 mg/day) (C. J. Glueck et al., 2011). A key finding of the study was that 83% (five out of six) subjects had undetected factor V Leiden heterozygosity (C. J. Glueck et al., 2011). One subject was MTHR C677T homozygous, whereas two others were MTHR C677T-A1298C compound

heterozygous (C. J. Glueck et al., 2011). Another subject had extremely high levels of factor VIII, factor XI, and homocysteine reported at 195%, 179%, and 29.3 $\mu\text{mol/L}$, respectively (C. J. Glueck et al., 2011).

The salient information in this study was that all cases developed distinct androgen-induced disease states including osteonecrosis, pulmonary embolism, and amaurosis fugax (C. J. Glueck et al., 2011). The findings are extremely important because each disease state was the result of an interaction between a specific genetic risk factor and/or an acquired risk factor and androgen therapy. Each disease state was specific regardless of androgen type, dose, duration, or mode of administration. In addition, the onset of disease states was predictable when considering the initiation of androgen therapy. Finally, the reported disease states were austere. For example, amaurosis fugax is a severe disease that is considered a type of cerebral infarct or stroke leading to a monocular loss of vision affecting the ophthalmic artery, whereas osteonecrosis is an infarct leading to localized death of osteocytes in bone tissue that eventually worsens to severe disability (Merck, 2018). Pulmonary embolism occurs when one or more pulmonary arteries are occluded by thrombi that originate in the extremities due to hypercoagulable states or endothelial dysfunction, often resulting in death (Merck, 2018). Each disease state identified in this study was severe and potentially life-threatening, but more importantly the disease states were preventable through standardized screening procedures before the initiation of androgen therapy.

Disease state-toxicity-risk. Osteonecrosis, pulmonary embolism, and amaurosis fugax; hematotoxicity and vasculotoxicity; increased risk.

Baggish et al. (2017). A case-cohort study conducted by a team of Harvard researchers sought to determine the cardiovascular effects associated with illicit supraphysiologic androgen use in a sample of recreational weightlifting men (Baggish et al., 2017). Personal correspondence with one of the primary researchers detailed that this type of design was used because of the inability to obtain institutional review board approval for a long-term prospective cohort of illicit androgen users (H. Pope, 2017). The sample comprised 140 male recreational weightlifters divided into one group of 86 anabolic steroid users (both on-drug and off-drug) and a control group of 54 non-using men (Baggish et al., 2017). The three primary outcomes measured were (a) left ventricular systolic function, (b) left ventricular diastolic function, and (c) coronary atherosclerotic volume.

Androgen users showed lower left ventricular ejection fraction than non-users (mean \pm *SD*, [52 \pm 11%] vs. [63 \pm 8%], $p < .001$) (Baggish et al., 2017). Diastolic function was also reduced compared with non-users (relaxation velocity \pm cm/second, [9.3 \pm 2.4] vs. [11.1 \pm 2.0], $p < .001$) (Baggish et al., 2017). Individuals on-drug during evaluation, compared to those off-drug, demonstrated reduced left ventricular ejection fraction [49 \pm 10%] vs. [58 \pm 10%], $p < .001$ (Baggish et al., 2017). The same comparison groups demonstrated early relaxation velocity [8.9 \pm 2.4] vs. [10.1 \pm 2.4], $p = .035$). Anabolic steroid users, on-drug or off-drug, showed greater coronary artery plaque volume compared with nonusers (median mL³; interquartile range (IQR) = 3 mL³, IQR [0, 174] vs. 0 mL³, IQR [0, 69], $p = .012$) (Baggish et al., 2017). Cumulative lifetime anabolic steroid dose corresponded with ranked advances in coronary atherosclerotic plaque volume (rise *SD*; 95% CI *SD*) for every 10-year advance in duration of use, *SD* increased = 0.60, 95% CI [0.16, 1.03], $p = .008$ (Baggish et al., 2017).

The study suggested that cumulative exposure was more critical to long-term cardiovascular effects than dose response. Both temporary and more permanent cardiovascular dysfunction were similar regardless of total cumulative exposure. Stable dysfunction was attributed to architectural changes in heart structure evidenced by higher left ventricular mass in the off-drug group compared to non-users. In addition, the confidence intervals for standard deviation increases in atherosclerotic volume per 10-year cumulative dose were large, suggesting a genetic or some other confounding factor.

The use of a case-cohort design was the main limitation of this study. The Harvard team went to exceptional lengths to maintain internal validity and reduce bias (H. Pope, 2017). A sensitivity analysis helped to validate adjustments for confounders; however, recall errors in self-reported doses could not be eliminated. Hence, the results detailed a broad picture of illicit androgen use that could not be reduced to normal dose response patterns observed in clinical practice.

Disease state-toxicity-risk. Coronary artery disease; cardiotoxicity and vasculotoxicity; cumulative androgen exposure as an increased risk factor.

van Velzen et al. (2019). The large prospective transgender cohort study by van Velzen et al. (2019) sought to assess the influence of transdermal or intramuscular testosterone in 188 transmen and estrogen with cyproterone in 242 transwomen to alter blood pressure and circulating lipids. Transwomen received estradiol valerate (2 mg twice daily) and cyproterone acetate (50 mg/day), whereas transmen received either testosterone undecanoate (1,000 mg once per three months), testosterone gel (50 mg/day), or combined short- and medium-acting testosterone esters (250 mg bi-weekly). Blood samples were collected at baseline, at a 12-month

follow-up, and during scheduled clinical visits. Blood pressure and anthropometric assessments were also collected during clinical visits. The research problem was oriented towards using a large study population to clarify conflicting lipid and blood pressure effects in the transgender literature in low powered studies.

The researchers found a minor decrease in blood pressure (systolic BP: -2.6%; diastolic BP: -2.2%) among transwomen and an increase in diastolic blood pressure (2.5%) among transmen (van Velzen et al., 2019). In transwomen, treatment decreased triglycerides (-10.2%), total cholesterol (-9.7%), HDL-C (-9.3%), and LDL-C (-6.0%), whereas, in transmen, treatment increased triglycerides (36.9%), total cholesterol (4.1%) and LDL-C (13.0%) while decreasing HDL-C (-10.8%) (van Velzen et al., 2019).

The study findings suggest no effect of hormone treatment on blood pressure in transwomen or transmen. In addition, there were beneficial effects of estradiol valerate combined with cyproterone acetate on lipid profiles in transwomen. The findings also indicate harmful effects of testosterone occur in all modes of administration on the lipid profiles of transmen. The latter was evidenced by increased total cholesterol, LDL-cholesterol, and triglycerides with simultaneous decreased HDL-cholesterol. Hence, the long-term alteration of the lipid profile in this manner could increase to risk of developing atherosclerosis and cardiovascular disease.

Disease state-toxicity-risk. Dyslipidemia; possible cardiotoxicity and vasculotoxicity; long-term androgen exposure suggests an increased risk of atherosclerosis and cardiovascular disease.

Loo et al. (2019). A large retrospective study by Loo et al. (2019) investigated the risk of myocardial infarction, transient ischemic attack, and ischemic stroke in men (age ≥ 45 years) with signs of hypogonadism or diagnosed hypogonadism under testosterone therapy. A cohort methodology was used to identify eligible men from medical records in the UK Clinical Practice Research Datalink spanning from 1995 to 2017 resulting in a cohort of 15,401 men with 71,541 person-years of follow-up. Testosterone exposure was confirmed through prescription records and categorized as current use, past use in the previous 60 days, and nonuse. The researchers employed Poisson regression to estimate crude incidence rates and time-dependent Cox proportional hazards models to estimate hazard ratios.

Among cohort members, the incidence rate, per 100 person-years, of composite myocardial infarction, transient ischemic attack, and ischemic stroke was $IR = 1.19$, 95% CI [1.11, 1.27] (Loo et al., 2019). Current androgen use compared to nonuse was related to an increased risk of the composite outcome, $HR = 1.21$, 95% CI [1.00, 1.46] (Loo et al., 2019). Subgroup analysis showed that the greatest risks of the composite outcome occurred in men aged 45-59 years old, $HR = 1.44$, 95% CI [1.07, 1.92] and within the first two years of continuous androgen therapy, $HR = 1.35$, 95% CI [1.01, 1.79] with risk decreasing thereafter (Loo et al., 2019). Compared to nonuse, current androgen use was associated with a significantly lower risk of all-cause mortality, $HR = 0.64$, 95% CI [0.52, 0.78] and past androgen use was associated with a higher risk of all-cause mortality, $HR = 1.72$, 95% CI [1.21, 2.45] (Loo et al., 2019).

The study findings suggest the initial period of consistent androgen therapy carries the highest risk of experiencing a composite myocardial infarction, transient ischemic attack, and ischemic stroke. Overall the findings add to the current knowledge gap relating to equivocal risk

findings in observational studies. The questions arising from the study relate to the validity of using composite outcomes when unadjusted analyses on each single outcome showed hazard ratios far below 1.00. Statistically, grouping all outcomes increases the probability of an outcome to occur so it is unclear whether composite outcomes such as the one used in this study provide valid estimates of risk for any individual outcome.

Disease state-toxicity-risk. Myocardial infarction, transient ischemic attack, and ischemic stroke; cardiotoxicity, vasculotoxicity, and neurotoxicity; increased risk of the composite outcome without increased risk of single outcomes.

Trials. Many trials have been conducted using different androgens and populations showing an increased risk of certain health outcomes.

Ajayi et al. (1995). The *Testosterone increased human platelet thromboxane A₂ receptor density and aggregation responses* study sought to determine whether testosterone regulates human platelet thromboxane A₂ receptor expression (Ajayi, Mathur, & Halushka, 1995). The research problem was framed as an increased risk for thrombotic events resulting in cardiovascular disease, acute myocardial infarction, and stroke due to androgen abuse in young men. As such, a double-blind, placebo-controlled, randomized, parallel-group design was used to assess the effects of testosterone cypionate exposure, 400 mg bi-weekly for eight weeks, on thromboxane A₂ receptor density and platelet aggregation responses.

Androgen exposure significantly increased thromboxane A₂ receptor density from (0.95 ± 0.13 pmol/mg) up to (2.10 ± 0.4 pmol/mg) cresting at four weeks and returning to baseline values at eight weeks ($p < .001$) (Ajayi et al., 1995). At four weeks, androgen exposure significantly increased the platelet aggregation response before returning to baseline in week

eight ($p < .001$) (Ajayi et al., 1995). Baseline androgen levels before treatment were positively correlated ($r = .56, p < .001, n = 32$) with thromboxane A₂ receptor density (Ajayi et al., 1995).

The findings confirm that the androgen regulation of thromboxane A₂ receptors found in animals also occurs in humans. The results suggest that androgen abuse and some conditions of therapeutic use predispose an increased risk for thrombotic and embolic events through platelet aggregation and increased thromboxane A₂ receptor expression.

Disease state-toxicity-risk. Thrombosis secondary to increased platelet aggregation and thromboxane receptor density; vasculotoxicity; increased hypercoagulability and indirect thrombosis risk.

Choi et al. (2005). The *Effects of testosterone replacement in human immunodeficiency virus-infected women with weight loss* study was conducted to assess whether six months of androgen replacement therapy would facilitate muscle mass and strength to offset HIV-related cachexia in female patients (Choi et al., 2005). The research problem was described as cachexia, the main complication of HIV leading to “mortality, disability, and opportunistic infections” (Choi et al., 2005, p. 1531). Accordingly, the research question asked whether physiologic androgen replacement would offset HIV-related cachexia. The methodology was a randomized double-blinded, placebo-controlled trial with allocation to either physiologic androgen replacement or placebo.

Interestingly, no changes in fat free mass, fat mass, bodyweight, strength measures, or quality of life were found between the groups (Choi et al., 2005). Significant decreases in serum high-density lipoprotein (HDL) levels occurred in the androgen group was the only major adverse finding of the study. No major androgen adverse events were reported. There were

seven minor adverse events in the androgen groups, mostly expressed as acne. Importantly, there was no evidence of hirsutism, decreases in immune cell counts, and increases in hemoglobin.

This study suggests that androgen therapy to treat HIV-related cachexia is ineffective and indirectly increases the risk of atherosclerosis. The main knowledge gap (represented by the findings) was the disparity between androgen replacement in men expressing differently in women. The questions raised by this study were related to the explanation for the absence of adverse events and favorable body composition in women, compared to nearly opposite effects in men.

Disease state-toxicity-risk. Dyslipidemia; vasculotoxicity; indirect increased atherosclerosis risk.

Coviello et al. (2008). The trial by A. D. Coviello et al. (2008) sought to determine the dose-response effects of intramuscular injectable testosterone enanthate doses (25 mg/week; 50 mg/week; 125 mg/week; 300 mg/week; 600 mg/week) over a period of 20 weeks on hematologic measures. The researchers used a randomized double-blind design to randomly allocate 61 young men and 50 older men to each of the five dose groups orienting the research problem as determining the dose-response changes to hemoglobin and hematocrit by age and further, elucidating the mechanisms of age-related differences in the hematologic system with alterations in soluble transferrin receptor concentrations and erythropoietin.

As expected, there was a significant dose-response increase in hemoglobin and hematocrit in both age categories ($p < .0001$) (A. D. Coviello et al., 2008). In younger men, the greatest increase in hemoglobin and hematocrit up to day 56 occurred in the 50 mg/week dose,

whereas beyond day 56 to day 84, the 600 mg/week dose observed the greatest increase leveling out at day 112 dropping slightly until study conclusion. In older men, the greatest increase in hemoglobin and hematocrit occurred in the 300 mg/week dose up to day 112, whereas beyond day 112 to day 140, hemoglobin and hematocrit peaked sharply and then dropped towards the study conclusion at the 600 mg/week dose. Older men compared to younger men had greater free and total testosterone levels at 125 mg, 300 mg, and 600 mg doses. After adjustment for testosterone levels, older men had significantly higher hematocrit and hemoglobin compared to younger men ($p \leq .0001$) (A. D. Coviello et al., 2008). No dose-response effects of testosterone to change soluble transferrin receptors or erythropoietin concentrations were found.

The study findings suggest that older men exposed to graded doses of androgens experience greater secondary erythrocytosis induced by direct stimulation of hematopoietic stem cells than do younger men. The study findings also demonstrated that dose-response androgen exposure increased hematocrit and hemoglobin to maximum safety and data monitoring thresholds in some men resulting in hematotoxicity in the 600 mg dose group by week 12. The safety board allowed the subjects who experienced hematotoxicity to be allocated to lower exposure groups, although discontinuations were reported. The knowledge gap of this study represents the mechanisms behind age-related differential dose-response effects. The questions arising from the results relate to whether increases in hematocrit are causally linked to adverse vascular and cardiovascular outcomes and which mechanisms are involved in age-related hematocrit levels.

Disease state-toxicity-risk. Secondary erythrocytosis; hematotoxicity; increased hematocrit is thought to predispose risk for thrombotic events.

S. Basaria et al. (2010). The *Testosterone in Older Men with Mobility Limitations (TOM)* trial conducted by S. Basaria et al. (2010) assessed the safety and efficacy of testosterone therapy in 209 community-dwelling men ages 65 years or greater. Each subject was stratified according to age and randomly allocated to either 100 mg of testosterone gel or placebo with the dose was titrated up or down depending on the serum levels of testosterone to remain near the upper normal physiologic range. Each subject had numerous comorbidities at baseline associated with cardiovascular disease. The study was halted by a safety monitoring board due to a greater incidence of cardiovascular adverse events (23 in treatment vs. 5 in placebo) (S. Basaria et al., 2010). The study was well designed although it was not powered to assess adverse events. The salient feature and limited implication for this study was that all subjects had severe comorbidity as would be expected in this age group and a community-dwelling setting.

Disease state-toxicity-risk. Acute coronary syndrome, myocardial infarction, hypertension, atrial fibrillation, heart failure, stroke, and mortality; cardiotoxicity, vasculotoxicity, hematotoxicity.

Supasyndh et al. (2013). The trial by Supasyndh et al. (2013) sought to determine the effectiveness of a 17AA androgen (oxymetholone) to increase lean body mass and grip strength in hemodialysis patients. The researchers used a randomized, double-blinded, placebo-controlled design to allocate 43 dialysis patients to 100 mg/day oxymetholone or placebo for six months.

Increases in lean body mass and grip strength were found with simultaneous decreases in adipose tissue. Almost all measured variables increased as would be expected with this androgen. One key finding was significant increases in liver enzyme levels with 17AA exposure

compared to placebo, however, the researchers noted that the frequency of enzyme values greater than three times upper threshold values were not significantly different between androgen and placebo groups. Two patients were withdrawn from the study, with one patient developing cholestatic jaundice and the other refusing to participate due to unwanted weight gain. Oxymetholone decreased serum HDL cholesterol in 14.3% of subjects, whereas urea nitrogen and creatinine levels increased while hemoglobin remained unchanged (Supasyndh et al., 2013). Androgen exposure significantly ($p < .01$) increased liver AST ($31.7 \text{ U/L} \pm 32.5 \text{ U/L}$), liver ALT ($55.5 \text{ U/L} \pm 50.6 \text{ U/L}$), total bilirubin ($0.5 \text{ mg/dl} \pm 0.7 \text{ mg/dl}$), and direct bilirubin ($0.42 \text{ mg/dl} \pm 0.54 \text{ mg/dl}$) compared to placebo (Supasyndh et al., 2013).

The researchers claimed their findings demonstrated that the long-term use of methylated oxymetholone is safe and effective to treat hemodialysis-related cachexia in men and women. Although oxymetholone was shown to be effective to increase lean body mass and reduce adipose tissue, six months of exposure to a 17AA also showed increased liver load and laboratory measures that do not coincide with safe exposure in a diseased population. The knowledge gap arising from this study involves whether non-methylated androgens are effective in treating hemodialysis-related cachexia. The question also arising from this study relates is how safety thresholds can be constructed in such a manner that three times an upper limit in a diseased population is acceptable. Given the literature evidence, any long-term elevated liver enzyme levels well above normal, indicates the initiation and progression of liver damage.

Disease state-toxicity-risk. Dyslipidemia and liver injury; hepatotoxicity; the findings suggest an increased risk of liver disorders despite the researchers' claims.

Budoff et al. (2017). A double-blinded placebo-controlled trial conducted by Budoff et al. (2017) assessed whether androgen treatment in older men with low endogenous testosterone levels influenced noncalcified coronary artery plaque volume in a sample of 170 men aged 65 years or older with at least two serum measures of testosterone less than 275 ng/dL over a 12-month period. The men were assigned to either placebo ($n = 82$) or treatment ($n = 88$). Treatment was 1% testosterone gel adjusted to the therapeutic range of 280-873 ng/dL.

Baseline coronary artery calcification scores of 70 men (50.7%) were greater than 300 Agatston units, indicating extreme atherosclerosis (Budoff et al., 2017). The treatment group compared to placebo showed significantly higher expansion of noncalcified plaque volume from baseline to 12 months with median values (204 mm³ to 232 mm³) vs. (317 mm³ to 325 mm³); mean difference = 41 mm³, 95% CI [14 mm³, 67 mm³], $p = .003$ (Budoff et al., 2017). The total plaque volume increase from baseline to 12 months in the treatment group compared to placebo was (272 mm³ to 318 mm³) vs. (499 mm³ to 541 mm³); mean difference = 47 mm³, 95% CI [13 mm³, 80 mm³], $p = .006$ (Budoff et al., 2017). The coronary artery calcification scores comparing treatment to placebo in median Agatston units were (255 to 494) at baseline and (244 to 503) at 12 months; median difference = -27, 95% CI [-80, 26] (Budoff et al., 2017). Remarkably, the coronary calcium score changes from baseline comparing treatment to non-treatment were (25 to 82) in the treated and (73 to 164) in the non-treated. Although no major adverse cardiovascular events were reported the study suggested that one year of therapeutic titer-adjusted testosterone treatment was related to an increase in noncalcified coronary artery plaque volume and total plaque volume, while coronary artery calcium scores remained constant. The overall results suggest greater risk through undetected increases in noncalcified plaque since

this plaque type requires advanced computed tomographic angiography, which is usually restricted to research centers and not readily available to clinicians.

Although the study was designed specifically to detect calcified and noncalcified coronary artery plaque progression, there were several limitations. The primary limitation was extreme baseline atherosclerosis in more than 50% of the sample and 43.8% of androgen treated men had a coronary artery calcium score ≥ 300 , whereas 60.3% of the non-treated men had scores ≥ 300 . Of the treated men, 46.6% had scores (0 to < 300), compared to 34.9% of non-treated men with scores (0 to < 300). Additional limitations included a lack of attention directed towards fibrous plaque and stability of reported plaques, although, the researchers asserted that the total plaque burden was likely more important than any individual plaque characteristics.

Disease state-toxicity-risk. Atherosclerosis; cardiotoxicity and vasculotoxicity; increased risk.

Meta-analyses. Several meta-analyses have provided aggregated estimates of randomized controlled trials that suggest an increased risk for some health outcomes.

Calof et al. (2005). The meta-analysis of Calof et al. (2005) assessed 19 randomized, placebo-controlled trials to determine the risk of adverse events related to testosterone replacement therapy in aging men. The inclusion criteria required that the studies were randomized, placebo-controlled trials including medically stable men aged 45 years or older with low or low-normal testosterone levels and hormone replacement for no less than 90 days. The researchers used a random effects model with weighting of assumed heterogeneity to pool the odds ratios of all the studies.

Among the 19 studies included in the analysis, 433 men received placebo and 651 men were treated with testosterone (Calof et al., 2005). There were no significant differences in the occurrence of death, cardiovascular events, or sleep apnea between the treatment and placebo groups. When all prostate events were combined, the rate of the composite was significantly higher in the testosterone group compared to placebo $OR = 1.78$, 95% CI [1.07, 2.95] (Calof et al., 2005). The likelihood of experiencing hematocrit levels $> 50\%$ was higher in men treated with testosterone compared to placebo, $OR = 3.69$, 95%CI [1.82, 7.51] (Calof et al., 2005). The findings demonstrated the hematotoxicity of androgens to increase hematocrit levels, which reiterated the predictability of this process. The findings also suggest an increased frequency of prostate events when composite outcomes were used, but no increased occurrence or risk of cardiovascular outcomes.

Disease state-toxicity-risk. Secondary erythrocytosis and prostate conditions; hematotoxicity; evidence of predictable increases in hematocrit but no evidence of cardiovascular risk.

Xu et al. (2013). A meta-analysis and systematic review by Xu et al. (2013) pooled the estimates of randomized placebo-controlled trials with durations lasting at least 12 weeks that reported cardiovascular events. The researchers used both random and fixed effects models in addition to inverse variance weighting to complete the analysis. Twenty-seven trials consisting of 2,994 subjects reported 180 cardiovascular events (Xu et al., 2013). The odds ratio, interpreted as the risk of cardiovascular events under androgen therapy, was $OR = 1.54$, 95% CI [1.09, 2.18] (Xu et al., 2013). The researchers noted that the events reported in the analyzed trials varied by funding source. The trials without pharmaceutical industry funding were $OR =$

2.06, 95%CI [1.34, 3.17], whereas those with pharmaceutical funding were $OR = 0.89$, 95%CI [0.50, 1.60] (Xu et al., 2013). Although the main analysis was statistically significant, neither of the funding analyses were statistically significant.

Disease state-toxicity-risk. Serious cardiovascular events and mortality; cardiotoxicity; increased risk.

Andrews et al. (2018). The systematic review and meta-analysis by Andrews, Magee, Combest, Allard, and Douglas (2018) sought to determine the effect magnitude for muscular performance and adverse effects in androgen use for performance enhancement. Inclusion criteria required the studies were randomized placebo-controlled trials assessing power, endurance, muscular strength, and body composition. Cochrane review methods were used to determine study quality, whereas DerSimonian and Laird methods were used to pool data into a random effects model and estimate standardized mean differences.

In alignment with the literature, substantial differences were found in strength and lean body mass in those with androgen exposure compared to placebo, however, there was insufficient to estimate mean differences in adverse effects, adipose tissue, endurance, and power. In three studies, significant decreases in HDL with androgen use were noted and one study reported significant increases in LDL with androgen use. Greater irritability in androgen exposed groups was reported in two studies, whereas four studies reported significant increases in aspartate aminotransferase in androgen exposure groups. Notably, a common reported adverse effect in several studies was increased hematocrit levels. The findings of this meta-analysis offered no knowledge gaps, as most reported adverse effects are well-known. The

finding of increased hematocrit and lowered HDL levels reconfirmed most findings in the literature.

Disease state-toxicity-risk. Secondary erythrocytosis; hematotoxicity; none.

Houghton et al. (2018). The systematic review and meta-analysis of Houghton et al. (2018) was conducted to investigate the relationship between venous thromboembolism and testosterone therapy in men. Inclusion criteria required that observational studies were either cohort or case control studies that assessed testosterone therapy using comparisons of study participants in an appropriate manner aligning to study design. Each randomized controlled trial reporting VTE outcomes was allowed. The study findings were pooled to estimate odds ratios using a random effects model and heterogeneity was assessed with the I^2 statistic estimated from Cochran's Q. Five observational studies ($n = 1,249,640$) and six randomized controlled trials ($n = 2,236$) met the inclusion criteria and were included in the analysis.

After pooling the data in a random effects model, a non-significant association between testosterone and VTE risk was found, $OR = 1.41$, 95%CI [0.96, 2.07] likely due to substantial heterogeneity, $I^2 = 84.4\%$ (Houghton et al., 2018). Upon stratification by study design, the association between testosterone and VTE in randomized controlled trials, $OR = 2.05$, 95%CI [0.78, 5.39], cohorts, $OR = 1.06$, 95%CI [0.85, 1.33], and case-controls, $OR = 1.34$, 95%CI [0.78, 2.28], was not significant (Houghton et al., 2018).

In general, the findings suggest no associational risk of VTE with testosterone therapy in combined studies or subgroup analysis by each study design. The researchers claimed that the evidence did not support a relationship between androgens and VTE risk. The claim related to the study findings adds to the knowledge gap by reporting conflicting findings that do not align

with previous studies. Statisticians, researchers, and epidemiologists have recently acknowledged the limited value of p -value thresholds to determine clinical significance, advising instead to use expert knowledge, effect magnitude, precision, and model uncertainty to fully characterize and interpret findings like those reported in this meta-analysis (A. A. Anderson, 2019). As such, considering the body of evidence, the non-significant relationships found may be interpreted based on magnitude and consistency alone. Hence, the findings support two previously reported study findings and significant risks with similar magnitudes in different settings (C. J. Glueck et al., 2016; Martinez et al., 2016).

Disease state-toxicity-risk. Venous thromboembolism; hematotoxicity and vasculotoxicity; non-significant increased risk of VTE.

Evidence of Decreased Risk

Several studies in the literature report evidence of a decreased risk of health outcomes or disease states and protective effects resulting from androgen exposure. The following chapter section reviewed observational studies, clinical trials, and meta-analyses to identify specific instances and characteristics of decreased risk or protective effects associated with androgen exposure across different settings.

Observational studies.

Hartgens et al. (2003). A quasi-experimental study conducted Maastricht University researchers assessed the effects of different levels of supraphysiologic doses of androgens and durations of use on heart function and morphology (Hartgens et al., 2003). The sample consisted of 32 strength athletes divided into two groups of androgen users ($n = 17$, mean age = 31 ± 7 years) and nonusers ($n = 15$, mean age = 33 ± 7 years) (Hartgens et al., 2003). Heart function

and morphology were investigated with pre- and post-echocardiographic assessments over a period of eight weeks. Over 10 different drugs were self-reported covering the full range of aromatizable, nonaromatizable, and 17 alpha-alkylated androgens. The total self-reported dose range was 1,560 to 10,636 mg/week, partially confirmed with hematologic measures (Hartgens et al., 2003). No changes in blood pressure, cardiac size, or cardiac function were found.

Previous androgen use duration did not influence any measured parameters. No adverse events associated with any organ systems were reported.

This study suggested that short-term, multi-androgen administration of substantial and varied supraphysiologic doses and prior history of androgen use exerted no adverse effects to any organ systems. The study also highlighted conflicting evidence between human and animal studies. Animal studies using similar doses and durations have reported severe androgen-induced cardiac diseases, which could be the artifact of constitutional differences in androgen metabolism between animals and humans (Chicco & Brown, 2014; Franquni et al., 2013; Pereira-Junior et al., 2006; Sretenovic, Zivkovic, Srejoic, & Milosavljevic, 2016; Tostes, Carneiro, Carvalho, & Reckelhoff, 2016; Vasilaki et al., 2016).

Several limitations were inherent to this study. First, the duration was short, lasting only eight weeks. Second, although biomarkers were used to confirm usage, these did not assess actual administered dose. Third, drug type, dose, duration of use, and mode of administration were self-reported, which detailed an inaccurate measure of total exposure. Lastly, selection bias could not be eliminated due to subject self-selection.

Characteristics-protective effects. Subchronic extreme supraphysiologic androgen exposure exerts no toxic effects on organs or organ systems.

van Staa and Sprafka (2009). Study of adverse outcomes in women using testosterone therapy was conducted to ascertain the safety of androgen or androgen-estrogen therapy in women (van Staa & Sprafka, 2009). The sample included 8,412 women, 2,103 testosterone users, and 6,309 controls. The researchers used a retrospective cohort design matching age and practice to controls (one subject [age and practice]; three subjects [controls]) (van Staa & Sprafka, 2009).

Cox proportional hazard analyses showed no significant differences between cohorts in rates of acute hepatitis, deep venous thrombosis, pulmonary embolism, breast cancer, diabetes mellitus, ischemic heart disease, and cerebrovascular disease. The testosterone cohort revealed increased numbers of androgen events relating to acne, voice hoarseness, alopecia, hirsutism, and clitorimegaly (relative rate = 1.55, 95% CI [1.21, 1.97]) (van Staa & Sprafka, 2009).

The study suggested no differences in major disease states, such as ischemic heart disease and breast cancer, in women treated with androgens or androgens coupled with estrogens. In addition, similar differences across subgroups suggested no underlying disparities. The mode of androgen administration (injections, oral, or implants) did not influence any outcomes. Finally, although no increased risk of major outcomes was identified, commonly known androgen-specific effects were observed, consistent with gender-based response to exogenous androgens.

The study was limited by insufficient power, but no power analysis was provided to detail this conclusion. Lack of randomization was also a limiting factor. Retrospective cohorts cannot be randomized unless advanced statistical methods, such as bootstrapping, or propensity matching were used prior to cohort creation, but even so the assumption of identical and

independently distributed variables remains problematic. One salient limitation was the possibility that treated patient characteristics differed from nontreated patient characteristics.

Characteristics-protective effects. No evidence of cardiotoxicity or vasculotoxicity and no differential effect on cancer; side effects of acne, voice hoarseness, alopecia, hirsutism, and clitorimegaly.

Shufelt and Braunstein (2009). The *Safety of testosterone use in women* study was conducted to detail the beneficial and adverse effects of endogenous and exogenous androgens in women (Shufelt & Braunstein, 2009). The research problem was described as a lack of knowledge regarding the adverse effects of androgen therapy in women. The exploratory research aim was to discern a rough safety profile of androgen therapy using a systematic review methodology.

Hirsutism (4-6%) and acne (3-8%) were the most frequent reported androgenic effects, but differed in dose response between oral and transdermal administration (Shufelt & Braunstein, 2009). Virilization was relatively rare, but dose and androgen type were implicated as mediating factors. Breast cancer risk did not increase via androgen therapy evidenced by therapeutic-based findings from a non-human primate study and human prospective biopsy study, and one supraphysiologic female-to-male transitioning study. Endometrial cancer risk was non-existent through bench studies that established an inhibitory effect and a non-proliferation effect on endometrial tissue. Several cardiovascular effects were reported. Atherosclerosis was improved in non-human primate studies, whereas trials of oral androgens showed reductions in HDL. The authors reported that this decrease was not observed in transdermal androgen administration studies. The researchers also asserted there was no evidence of hypertension, blood viscosity, or

hypercoagulable states, but noted favorable vascular reactivity and polycythemia. Liver toxicity was only found in 17AA oral androgens.

The study suggested that the occurrence of androgen adverse events depends on the mode of administration and type, with no negative effect on breast or endometrial cancer in women. The main gap arising from this study involves the reporting of HDL decreases due to 17AA oral androgens. The finding directly conflicts with the results of two trials that used transdermal testosterone instead of 17AA androgens (Choi et al., 2005; Dolan et al., 2009). The gap further expands by the claim of non-existent blood viscosity without concurrent secondary erythrocytosis. Any increase in blood cellular components arising from secondary erythrocytosis increases hematocrit and in theory, blood viscosity although the findings of pharmacokinetic studies of animals suggest hemodynamic changes are favorable rather than harmful. The question raised by this study was related to whether toxicity characteristics of dose, type, and duration may explain these different findings given HDL and secondary erythrocytosis have been well established in men.

Characteristics-protective effects. No evidence of risk for breast or endometrial cancer, liver toxicity, and hematotoxicity; adverse effects in females are mediated by androgen type, dose, and mode of administration.

Haider et al. (2010). Haider et al. (2010) conducted a prospective cohort study of 117 men (age range in years [34, 69]) and (mean age \pm SD; 59.5 \pm 6.0) with titer testosterone levels in the physiologic range [5.9 nmol/L, 12.1 nmol/L] that assessed a treatment for urological issues and erectile dysfunction. The cohort of patients was treated with parenteral testosterone undecanoate, at baseline, and six weeks to titrate their serum testosterone levels within the

normal range (Haider et al., 2010). Afterwards, the patients were maintained on the treatment and followed up every 12 weeks for one year to measure values of testosterone, cholesterol, C-reactive protein (CRP), liver function, body weight, and body mass index (BMI), with an additional metabolic syndrome assessment using a standardized definition guideline (Haider et al., 2010).

As expected, the treatment increased circulating testosterone levels at three months ($M = 9.3 \pm 1.7$ nmol/L) vs. ($M = 14.0 \pm 1.7$ nmol/L), $p < .01$ to ($M = 17.0 \pm 2.2$ nmol/L, $p < .05$) at six months (Haider et al., 2010). Past six months, the androgen titers stabilized to ($M = 18.7 \pm 2.1$ nmol/L) vs. ($M = 19.4 \pm 2.2$ nmol/L) at nine and 12 months, respectively (Haider et al., 2010). Levels of HDL remained stable for six months, followed by a significant increase thereafter to 12 months. Plasma levels of LDL followed an opposite pattern of decreases during the first six months and stabilization up to 12 months. Liver enzyme values of AST and ALT decreased for nine months until stabilization, whereas CRP increased over the initial three months, followed by a significant decrease over six months until stabilization at 12 months. Seventy-four out of 117 men in the cohort were clinically classed with metabolic syndrome, however, after one year of androgen therapy, only 42 men met the classification criteria for metabolic syndrome (Haider et al., 2010).

The study findings suggest that long-term androgen treatment confers protective beneficial effects on cardiovascular markers, lipid metabolism, liver function, and metabolic syndrome. One caveat was that even with androgen treatment, the plasma titers remained in the low-normal range. In addition, the study was a single prospective of older men with similar

characteristics and morbidities; thus, there was no attempt to randomize or utilize a comparison cohort.

Characteristics-protective effects. No evidence of hepatotoxicity and cardiotoxicity in long-term androgen therapy; protective effects on cardiovascular biomarkers, lipid metabolism, liver function, and metabolic syndrome in older males.

Gagliano-Juca et al. (2017). A secondary data analysis by Gagliano-Juca et al. (2017) analyzed electrocardiogram (ECG) data from two clinical trials to investigate the effects of androgen therapy on QT (Q wave to T wave) intervals. The researchers were interested in determining how previously reported cardiovascular events like ventricular arrhythmias occurred in previous clinical trials. Specifically, the researchers sought to determine arrhythmia risk using heart rate corrected QT intervals. As such, the analysis included patient ECG, laboratory, and demographic data from two clinical trials that reported cardiac arrhythmias.

Titer androgen levels increased in the treated groups as per expectations (Gagliano-Juca et al., 2017). In the first trial, there was a reduction in average corrected QT duration in treatment versus placebo, but this finding was not statistically significant. There was also a negative association between the average corrected QT interval and differences in serum androgen titers ($p = .036$) (Gagliano-Juca et al., 2017). In the second trial, the normal age-associated increase in average corrected QT interval duration was ameliorated in the androgen-treated group compared to the placebo group (effect size [ES] = - 6.30 ms, $p < .001$) (Gagliano-Juca et al., 2017).

The study findings suggest no increased risk of arrhythmias, but rather a protective effect due to androgen therapy. The questions raised by this study relate to reasons for the

discrepancies in findings between the two trials. For example, the researchers pondered whether the attenuation of the QT interval might hold across androgen administration, dose, and duration.

Characteristics-protective effects. Therapeutic androgen exposure exerts protective effects on cardiac function while lowering the tendency for major cardiac events involving arrhythmias.

Gagliano-Juca and Basaria (2017). A study by two Harvard Medical School researchers was conducted to discern reported clinical trials limitations and assessments of cardiovascular risk associated with androgen therapy (Gagliano-Juca & Basaria, 2017). The researchers used secondary post hoc power analysis to assess recent clinical trials reporting cardiovascular events and atherosclerosis progression. Potential mechanisms involved with increased cardiovascular risk in seven recent clinical trials were examined.

The first trial reported a 17% higher mortality rate (than placebo) and one myocardial infarction in an intervention to treat alcoholic cirrhosis. The second trial, involving androgen replacement in men aged 65 and older, showed a higher number of cardiovascular events (9 vs. 5 in placebo) with three of the events being arrhythmias without alterations in lipoprotein measures. The third trial reported a higher number of cardiovascular events (7 vs. 3 in placebo) in an intervention to reduce the requirement for erythropoietin in dialysis patients. The fourth trial, involving an intervention to treat mobility limitation in comorbid men aged 65 and older, was stopped prematurely because of a higher incidence of cardiovascular-related events (23 vs. 5 in placebo). The fifth trial reported only a single cardiovascular event in both treatment and placebo groups in an intervention to treat frailty. The sixth trial, involving an intervention to evaluate the effect of androgen therapy on subclinical atherosclerosis, reported small numbers of

cardiovascular events between treatment and placebo and no significant difference in coronary calcium scores between both groups. The seventh and largest multi-center trial reported no difference in cardiovascular events between treatment and placebo in 790 men aged 65 years or older.

The study suggests that the number of cardiovascular events associated with androgen therapy in older men was lower than the expected age-standardized rates and comorbidities of the subjects. Meta-analytic pooling of trials further suggest only minor differences in the odds of cardiovascular events for patients with a lower morbidity but higher odds for those with a greater morbidity. In trials reporting disproportionate events between groups, time-to-event analysis results suggested an acute mechanism behind initial cardiovascular events in more morbid patients.

The authors offered several plausible mechanisms to explain the differences in androgen-related adverse events between the trials analyzed in the study. The mechanisms included increased platelet aggregability through increases in thromboxane A2 receptor density, thrombosis as the result of platelet aggregation by higher circulating free testosterone and estradiol, plaque destabilization and rupture due to increased erythrocytosis, and fluid retention through increased renal sodium reabsorption expanding extracellular volume.

Characteristics-protective effects. Risk predisposition for platelet disorders, imbalance of free testosterone and estradiol, secondary erythrocytosis, plaque destabilization, and kidney disease account for the findings of increased risk in clinical trials.

Trials. Numerous clinical trials have reported safety of certain androgens therapeutically used to treat disease. Early trials by Harvard researchers are some of the few trials that were able to gain ethical approval to use supraphysiologic androgen doses in humans.

Bhasin et al. (1996). The first seminal clinical trial using supraphysiologic doses of testosterone in healthy males was conducted by Harvard researchers to assess the influence of high-dose androgens primarily on muscle growth and strength (Bhasin et al., 1996). The sample included 43 healthy men aged 19 to 40 years (Bhasin et al., 1996). The study design was a randomized, placebo-controlled trial lasting 10 weeks. Testosterone (600 mg) was administered weekly by intramuscular injection, resulting in a total androgen load of 6,000 mg per subject (Bhasin et al., 1996).

The only adverse effects reported were acne ($n = 3$) and breast tenderness ($n = 2$) (Bhasin et al., 1996). In addition, there were no changes in hematocrit, hemoglobin, red blood cell counts, liver enzyme levels, or cholesterol concentrations. Results of a multidimensional anger inventory showed no differences in anger between groups or significant changes in mood or behavior.

The work of Bhasin et al. (1996) is considered a pivotal seminal study, the results of which suggest there is no systemic organ toxicity with a supraphysiologic androgen dose of 600 mg per week over a 10-week period. Given the dose-response aspect of androgen-induced toxicity theory, the results also suggest that other mechanisms outside of dose-response may be involved with the development of adverse effects from androgen therapies. The only organ-system specific effects observed were musculoskeletal effects (lean muscle mass increases) and minor integumentary effects (acne) (Bhasin et al., 1996).

One limitation of the study was its short duration. The pharmacokinetic curve of the administered testosterone ester lasts for up to four weeks with primary half-life at 7-9 days (Gardner & Shoback, 2011). Although the metabolism of the ester and subsequent release of bioavailable testosterone tends to remain stable, the full effect assessment period spans beginning seven days after first administration and up to four weeks after the last administration. As such, the complete window of bioactive hormone was only assessed for approximately nine weeks and adverse effects might be manifested after this period. Finally, androgens were administered to healthy men to assess beneficial effects, not as a treatment for disease.

Characteristics-protective effects. Subchronic supraphysiologic androgen exposure in healthy men exerts no organ system toxicity.

Zitzmann et al. (2002). The randomized, placebo-controlled trial by Zitzmann, Junker, Kamischke, and Nieschlag (2002) assessed the effects of long-term testosterone undecanoate (1,000 mg every six weeks for 24 weeks) and gestagens on cardiovascular risk. The research problem was presented as a cardiovascular risk predisposed by hemostatic system activation due to androgen or gestagen exposure. Gestagens shifted hemostatic balance by increasing fibrinogen and other coagulation factors, however, androgen exposure significantly decreased hemostatic turnover rate and down-regulated fibrinolysis (Zitzmann et al., 2002). The findings suggest that androgen exposure down-regulates hemostatic activation and produces a favorable antithrombotic influence.

Characteristics-protective effects. Chronic therapeutic androgen exposure for male contraception reduced thrombosis risk by the down-regulation of the hemostatic system.

Dolan Looby et al. (2009). A randomized, placebo-controlled trial by Dolan et al. (2009) was conducted to assess long-term androgen effects on body composition, adverse events, and quality of life in female HIV patients. The research problem was presented as HIV-related cachexia, specifically related to changes in fat-free mass and bone mineral density. As such, the research questions were aimed at whether higher androgen dose (twice the physiologic level in previous studies) and duration (one year longer than previous studies) would exert favorable effects on cachexia related variables. The trial lasted 18 months with simple allocation to androgen or placebo.

There were no changes in fat mass, however, significant changes in (fat-free mass [1.8 ± 0.5 kg] vs. [0.8 ± 0.9 kg], $p = .04$) and (body mass index [1.6 ± 0.4 kg/m²] vs. [0.8 ± 0.6 kg/m²], $p = .03$) were found in the androgen group compared to placebo (Dolan et al., 2009). Favorable and significant effects on bone mineral density were found, but the effect size was not clinically meaningful. Improvements in depression and sexual function measures were significant and substantial. There were no changes in liver enzymes, lipids, or fasting glucose between groups. No major adverse events occurred, nor frequency of adverse effects such as hirsutism, acne, or menstrual alterations.

The study results suggest that higher dose androgen therapy is effective in treating HIV-related cachexia without altering lipid levels in women. The study also addressed one knowledge gap regarding long-term and high-dose androgen administration, demonstrating favorable body composition effects, but highlighted another gap by reporting no alteration in lipid levels, conflicting with previous findings of significant decreases in high-density lipoprotein values (Choi et al., 2005).

The main question raised by this study pertains to why lipid alterations were not reported as a trend, given the fact the androgen group experienced a higher decrease in HDL values at all measures after baseline. Another question relates to whether toxicity (expressed as drug type, dose, duration, and mode of administration), gender, unidentified factors, or a combination of all these factors serves as the main mediator of androgen-induced adverse events.

Characteristics-protective effects. No evidence of androgen toxicity at higher dose androgen in females treated for HIV-related cachexia or unfavorable effects on lipid metabolism.

Snyder et al. (2016). The *Effects of testosterone treatment in older men* study was part of a multi-component trial conducted to determine the efficacy of androgen therapy on sexual function, physical function, and vitality (P. J. Snyder et al., 2016). The sample included 790 men aged 65 years or older with serum testosterone concentrations below 275 ng/dL. The study design was double-blinded and placebo-controlled, lasting one year. The men were assigned to either placebo or 1% testosterone gel treatment using a probability balancing method.

Compared to placebo, those assigned to treatment had prostate-specific antigen increases of 1.0 ng/mL or more during the study (23 vs. 8) and a single case of diagnosed prostate cancer. In the year following study completion, one man from the placebo group and two men from the treatment group developed prostate cancer. Hemoglobin increases of 17.5 g/dL occurred with seven treated men with no increases in placebo. During the treatment period, seven men in each group experienced major cardiovascular events, including myocardial infarction, stroke, or death. In the year following treatment, two subjects from the treatment group and nine subjects from the placebo group experienced major cardiovascular events. The differences in adverse events

between groups were similar. Interestingly, the rate of death was twice as high in the placebo group, with approximately 13% greater hospitalizations.

The study suggests androgen therapy exerts no major cardiovascular toxic effects leading to defined cardiovascular-related events such as myocardial infarction, stroke, or death and serious adverse events such as death or hospitalization. The main limitation of this study was the degree of baseline comorbidity of all patients. The study was designed only to assess efficacy and report adverse events per ethical requirements; hence, measures of risk were not calculated.

Characteristics-protective effects. No evidence of cardiotoxicity, serious adverse events, mortality, or rehospitalization; evidence of hematotoxicity and prostate-specific antigen increases.

Sinclair et al. (2016). The study entitled *Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial* was conducted to clarify previous research regarding the effects of androgen therapy in patients diagnosed with cirrhosis suffering from sarcopenia (Sinclair et al., 2016). The research problem was situated by the lack of quality evidence regarding the efficacy of androgen therapy to attenuate muscle wasting associated with cirrhosis. One research question was related to whether androgens would improve body composition and bone mass. Another question focused on adverse events and mortality. Both questions were assessed methodologically using a double-blinded, placebo-controlled trial lasting one year with three outcome measures taken at baseline, six months, and 12 months.

The main outcome of lean appendicular mass was substantially higher in treatment versus placebo, (mean adjusted difference = +1.69 kg, 95% CI [+0.40, +2.97], $p = .021$) (Sinclair et al.,

2016). Secondary outcomes of total lean mass, reduction in fat mass, and bone mass were significantly influenced in the treatment group, (mean adjusted difference = +4.74 kg, 95% CI [+1.75, +7.74], $p = .008$), (mean adjusted difference = - 4.34 kg, 95% CI [-6.65, -2.04], $p < .001$), and (mean adjusted difference = +0.08 kg, 95% CI [+0.01, +0.15], $p = .009$), respectively (Sinclair et al., 2016). Hemoglobin increased, whereas glycosylated hemoglobin decreased in treatment compared to controls. No adverse events were reported, and although mortality was not statistically significant between groups, the treatment allocation observed 9.5% lower mortality than placebo.

The study suggests that androgen therapy administered to cirrhosis patients is effective in managing sarcopenia in this population with no increase in adverse events. More importantly, the study indicates a reduction in mortality in the androgen treatment group. A general question derived from this study relates to whether inference from this population can be applied to a broader population without diagnosed cirrhosis.

Characteristics-protective effects. No evidence of hepatotoxicity, reductions in mortality, and lowered (protective effect) glycosylated hemoglobin (A1c); evidence of hematotoxicity.

Ng Tang Fui et al. (2016). The study by Ng Tang Fui et al. (2016) was conducted to assess the effects of androgen therapy on body composition with caloric dietary restrictions. The research problem was based on the obesity management goal of retaining lean muscle mass and decreasing fat mass. The research question was directed towards whether androgen therapy would preserve lean body mass and prevent fat mass accretion. The research question was investigated using a randomized, double-blinded, placebo-controlled trial of 100 subjects assigned to treatment ($n = 49$) or placebo ($n = 51$).

The main outcome findings were favorable in relation to body composition, given the known properties of androgens and body composition. Both total and serious adverse events were similar between the treatment and control groups (total events, 20% vs. 16%; serious adverse events, 4% vs. 2%) (Ng Tang Fui et al., 2016). There was a statistically significant increase in prostate-specific antigen in five cases ($p = .02$) (Ng Tang Fui et al., 2016).

Interestingly, hemoglobin increased above the predefined safety threshold (values greater than 180 g/L) in only one case towards the end of the study period. The finding was predictable given that androgens directly suppress hepcidin and stimulate hematopoietic stem cell production with or without altering erythropoietin levels (Bachman et al., 2010; Bachman et al., 2014; A. D. Coviello et al., 2008; Kim et al., 2005). Given that the mature red blood cells (RBCs) life cycle proceeds for nearly 120 days in healthy humans, any increase of RBCs by direct or indirect hematopoietic mechanisms cannot be offset by the RBC life cycle and RBCs would tend to accumulate over the study.

The study suggests that androgen therapy is safe and effective in treating obesity in men without an increased risk of adverse events. A question derived from this study relates to whether a longer study period would yield more cases of hemoglobin levels above the safety threshold.

Characteristics-protective effects. Protective and favorable effects on obesity; hematotoxicity.

Chao et al. (2017). The study by Chao et al. (2017) was conducted to determine the combined effects of exercise training with an androgen and beta blocker in severely burned children. The research problem was related to determining the optimal intervention given the

efficacy of a single beta blocker (propranolol) and a single androgen (oxandrolone) given previous efficacy of these drugs demonstrated, separately, as burn injury interventions coupled with rehabilitative exercise. The research question referred to whether the proposed combination of exercise, androgen, and beta blocker would increase protein turnover, muscle mass, and function greater than exercise alone. The methodology was a randomized, placebo-controlled trial using a sample of 42 severely burned children (age range, [7, 17] years) (Chao et al., 2017).

The results were substantially favorable on all measures of fat-free mass, strength, power, aerobic capacity, and resting energy expenditure (Chao et al., 2017). No adverse effects or events were reported in either combined treatment or control. One interesting effect of this combination was a decrease in resting energy expenditure coupled with a higher fractional protein synthesis and decreased protein breakdown. The latter two aspects of the findings may be attributed solely to the administered androgen, whereas with the first, the beta blocker slowed energy expenditure indirectly by reducing the heart rate.

The study suggested that oxandrolone (a 17-alpha-alkylated androgen) was effective and safe to treat severely burned children when administered in a combined therapy. The study filled a knowledge gap by synthesizing primary research findings, using proven individually efficacy of two separate drugs and combining them into a more effective treatment. The questions raised by this study involve how no toxicity occurred with an oral 17AA androgen given androgen toxicity theory. Reasonably, the dose of 0.2 mg/kg/day, equating to 18.18 mg/day for a 90-kg adult, was low enough to avoid liver toxicity, but the duration of treatment was six weeks beginning 96 hours after admission to a burn center and children may be more resilient to subacute liver injury (Chao et al., 2017).

Characteristics-protective effects. No hepatotoxicity with 17AA androgens or side effects in severely burned children.

Meta-analyses.

Fernandez-Balsells et al. (2010). The systematic review and meta-analysis by Fernandez-Balsells et al. (2010) sought to assess adverse effects associated with androgen treatment in several testosterone trials. The inclusion criteria required study group comparisons, with or without randomization, reporting specific outcomes (death, cardiovascular events, risk factors, prostate conditions, and erythrocytosis). Study quality was assessed with the GRADE methodology. The researchers assessed heterogeneity with the I^2 statistic after combining the reported studies' estimates to calculate pooled relative risks for nominal binary outcomes and weighted mean differences in the DerSimonian and Laird random-effects model. Fifty-one trials were deemed eligible and included in the analysis.

Upon pooling the data in a random effects model, there were no significant differences in diabetes mellitus incidence between androgen therapy and placebo or nonintervention comparison groups. No significant differences from baseline in systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, total cholesterol, and LDL-C (cardiometabolic risk factors) were observed. Androgen-treated men showed significantly lower HDL-C concentrations than non-treated men, weighted mean difference (WMD) = -0.49 mg/dl, 95% CI [-0.85, 0.13], $I^2 = 69%$ (Fernandez-Balsells et al., 2010). There were no significant differences in the incidence of prostate cancer or the risk of PSA, lower urinary tract symptoms, or composite prostate outcomes, between androgen-treated men and non-treated men. Androgen-treated men experienced significant increases in hematocrit, $WMD = 3.18$ g/dl, 95% CI [1.35, 5.01], $I^2 = 91%$

and hemoglobin, $WMD = 0.80$ g/dl, 95% CI [0.45, 1.14], $I^2 = 95\%$, compared to non-treated men (Fernandez-Balsells et al., 2010). Similarly, those treated with androgens had a greater risk of secondary erythrocytosis compared to placebo or nonintervention group, $RR = 3.15$, 95% CI [1.56, 6.35], $I^2 = 0\%$ (Fernandez-Balsells et al., 2010). No significant differences in the incidence rates of cardiac arrhythmias, deaths, revascularization procedures, and myocardial infarction were found between androgen treatment and placebo or nonintervention comparison groups.

The study findings suggest testosterone treatment does not increase the incidence of major adverse health outcomes such as death or heart attack. In addition, the findings mitigate the knowledge gap by confirming hematotoxicity evidenced by predictable increases in hemoglobin and hematocrit.

Characteristics-protective effects. Evidence of no increased risk of major health outcomes or composite outcomes and reconfirming evidence of increased risk of secondary erythropoiesis and modifications of the lipid profile; none.

Corona et al. (2014). Corona et al. (2014) used a systematic review and meta-analysis methodology to investigate the risk of cardiovascular outcomes associated with testosterone therapy to resolve conflicting findings in the literature. Study inclusion required randomized placebo-controlled trials, androgen-treatment and placebo groups, and cardiovascular events without restriction resulting in the assessment of 74 trials composed of 3,016 androgen-treated patients and 2,448 placebo patients. Since 47 trials did not report adverse events, 26 trials that reported composite cardiovascular outcomes were used in the main analysis. The main outcome of the analysis was the incidence of major cardiovascular events (MACE) defined as the

composite of acute coronary syndrome, new heart failure, cardiovascular-related death, stroke, and non-fatal acute myocardial infarction. Any reported cardiovascular-related events, disorders, complaints, vascular disorders, or cardiovascular-related events meeting ICD diagnosis criteria were considered secondary outcomes. Study quality was assessed with the Cochrane review methodology. The researchers assessed heterogeneity on a composite cardiovascular outcome with the I^2 statistic and used the Mantel-Haenszel method to estimate the odds ratios for all adverse events. Meta-regression was conducted to test the effect of several parameters on MACE.

In the main analysis, there was no statistically significant difference in MACE incidence between androgen-treatment and placebo, $OR = 1.01$, 95% CI [0.57, 1.77], $p = .98$, $I^2 = 0\%$ (Corona et al., 2014). Meta-regression analysis revealed no significant difference in MACE incidence adjusting for the effects of androgen dose, $S = -0.14$, [-1.17, 0.89], $p = .79$, baseline age, $S = 0.03$, [-0.04, 0.10], $p = .40$, or body mass index, $S = -0.07$, [-0.29, 0.14], $p = .51$ (Corona et al., 2014). Separate analyses for acute coronary syndrome, new heart failure, cardiovascular-related death, stroke, and non-fatal acute myocardial infarction showed no significant associations of risk between each outcome and androgen therapy.

The findings of this comprehensive study suggest no risk of cardiovascular outcomes and androgen treatment in general or effect modification of risk by dose, baseline age, or body mass index, in contrast to the findings of Xu et al. (2013). The study adds to the knowledge base further widening the gap in the literature.

Characteristics-protective effects. Evidence of no risk for cardiovascular outcomes; pooled odds ratios suggest global cardiovascular protective effects.

Li et al. (2016). H. Li et al. (2016) conducted a systematic review and meta-analysis to assess the safety and efficacy of the 17AA androgen, oxandrolone, in severely burned patients. The researchers included 15 randomized controlled trials with 806 subjects and select clinical measures.

After pooling the studies, there was no significant association between oxandrolone and infection, $RR = 0.87$, 95% CI [0.69, 1.11], $p < .26$ or mortality risk, $RR = 0.85$, 95% CI [0.38, 1.89], $p < .69$ (H. Li et al., 2016). Similarly, no occurrence of hepatic insufficiency was reported in all 15 trials and no significant difference in liver dysfunction was found between treated or non-treated burn patients, $RR = 1.15$, 95% CI [0.83, 1.59], $p < .41$ (H. Li et al., 2016). The efficacy of oxandrolone to facilitate healing of burns was demonstrated long term (12 months) and in both the catabolic and rehabilitative phases of treatment.

The study findings suggest that oxandrolone is highly effective in treating severe burns and exerts no appreciable side effects at therapeutic doses. The findings add to the knowledge gap by reporting the favorable effects of a methylated androgen. The question arising from this study relates to differential effects on the hepatic system by different types of 17AA androgens.

Characteristics-protective effects. No evidence of increased risk for death, infection, or hepatotoxicity; favorable effects on body composition and severe burn healing.

Alexander et al. (2017). The systematic review and meta-analysis by Alexander, Iyer, Lucas, Lin, and Singh (2017) was conducted to investigate the association between exogenous testosterone and the risk of major cardiovascular events. Randomized controlled trials and observational studies with men aged ≥ 18 years under testosterone therapy for no less than three days. All-cause mortality, stroke, and myocardial infarction were considered primary outcomes,

whereas cardiac procedures, heart failure, and arrhythmias were used as secondary outcomes. Data from 30 randomized controlled trials were pooled using the Peto odds ratio method with bias assessment following Newcastle and Cochrane review guidelines.

The investigators found androgen exposure, compared to placebo, was not significantly associated with an increased risk of stroke, $OR = 2.17$, 95% CI [0.63, 7.54], mortality, $OR = 0.88$, 95% CI [0.55, 1.41], or myocardial infarction, $OR = 0.87$, 95% CI [0.39, 1.93] (Alexander et al., 2017). The study findings suggest exogenous testosterone treatment exerts no harmful effects on the risk of death, heart attack, or ischemic cerebrovascular events and confirms the meta-analysis by Elliott et al. (2017) that found no significant association between testosterone treatment and risk of adverse events. The study adds to the knowledge gap by providing equivocal evidence of androgen-related risk and confirming the findings of some studies. The questions arising from this study involve the process of selecting subgroup analysis methods and the rationale for favoring single outcomes over composite outcomes contrary to other meta-analyses.

Characteristics-protective effects. Evidence of no increased risk for death, heart attack, or ischemic cerebrovascular events; favorable effects with death and heart attack but not stroke.

Zhao et al. (2018). The meta-analysis conducted by Zhou et al. (2018) sought to assess the adverse effects and effectiveness of androgen therapy in the treatment of HIV-related cachexia. Inclusion criteria required each study to be a randomized, placebo-controlled trial evaluating androgen therapy and body composition in HIV patients with sufficient data to pool for analysis. Primary outcomes were considered body composition effects, adverse events, and

sex hormone concentrations. The analysis included 14 trials with 349 randomized HIV patients to placebo or androgen treatment.

The researchers found significant effects of androgen exposure on body composition measures in both men and women comparing androgen treatment to placebo. Although no significant differences were reported between androgen treatment and placebo, adverse androgen effects such as erythrocytosis, liver dysfunction, dyslipidemia, or cardiovascular events were not tabulated or presented in this study. The study findings add to the knowledge gap by reporting equivocal findings.

Characteristics-protective effects. Evidence of low risk; protective effects against HIV-related cachexia on body composition in a disease population.

Closely Aligned Studies

The brief literature review moves forward with the five fundamental studies, chosen to orient this study, that have tested the association between androgens and risk of specific health outcomes. Each study has utilized an observational methodology, a retrospective cohort design using secondary data or case-control design using secondary data that closely aligns to the proposed research. Two studies assessed inpatient populations, either indirectly or incompletely, focusing on specific health outcomes. One study assessed comorbidities and the burden of disease associated with a specific androgen class implicated in liver pathology. Each study is explored with a thorough but practical critique of the design, sampling procedures, statistical analyses, measured effects, results, strength, limitations, claims, knowledge gaps, and funding sources.

Anderson et al. (2016). A retrospective cohort using secondary data by J. L. Anderson et al. (2016) entitled *Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated healthcare system* sought to investigate the association between androgen replacement therapy and cardiovascular outcomes in men with documented low testosterone over a 15-year period. Using several *a priori* hypotheses, the researchers sampled a cohort of men from an integrated healthcare system aged 50 years or older with documented low testosterone levels, evidenced by an initial blood test measure (< 212 ng/dl) and a second blood test measure with at least three years of follow-up. Men with a baseline diagnosis of cancer, except for basal cell and squamous cell carcinoma, were excluded leaving a cohort of 4,736 patients. Androgen exposure was verified as the receipt or no receipt of a testosterone prescription and defined with each patient's blood test results to quantify the internal testosterone levels achieved by treatment, dividing the results into three exposure categories of low (< 212 ng/mL), normal (212-742 ng/mL), and high (> 742 ng/mL) (J. L. Anderson et al., 2016).

The three levels of achieved testosterone levels were used as the nominal independent variable. The primary health endpoint in this study was a composite major cardiac event MACE, with secondary health endpoints defined as each individual component of MACE along with cardiovascular-, coronary-, or cancer-related death. Other key variables included the Charlson comorbidity index, and covariates composed of age, hypertension, hyperlipidemia, smoking, diabetes, renal failure, previous coronary artery disease, previous myocardial infarction, previous stroke, atrial fibrillation, heart failure, peripheral vascular disease, previous pulmonary embolism, chronic obstructive pulmonary disease, baseline testosterone levels, angiotensin-

converting enzyme inhibitors, angiotensin renin blockers, calcium channel blockers, diuretics, and statins.

The overall 3-year rates of MACE and mortality were 6.6% and 4.3%, respectively (J. L. Anderson et al., 2016). Superiority testing revealed favorable outcomes for 3-year MACE, $HR = 0.74$, 95% CI [0.56, 0.98], $p = .04$, which was influenced heavily by superiority for all-cause death, $HR = 0.65$, 95% CI [0.47, 0.90], $p = .009$ (J. L. Anderson et al., 2016). For the highest achieved testosterone levels, the adjusted hazard ratio for 3-year MACE was shown to be non-inferior but not superior to the lowest achieved levels of testosterone, $HR_{adj} = 0.77$, 95% CI [0.57, 1.04], $p = .09$ (J. L. Anderson et al., 2016). The risk over the 3-year period for myocardial infarction and stroke were low, however, there was a trend towards greater stroke rates in the high achieved testosterone category compared to the lowest achieved level, $HR = 1.69$, 95% CI [0.82, 3.50], $p = .16$, with no favorable effect on the rate of myocardial infarction (J. L. Anderson et al., 2016).

The results of this well-designed and meticulous study suggest that normal and high achieved androgen levels were associated with lower risks of death and major cardiac events, whereas low achieved androgen levels were associated with an increased risk of major cardiac events. These data also indicate that, in general, testosterone replacement therapy is safe and conducive to male health. The major strengths of this study include a well-planned analysis with explicitly stated *a priori* hypotheses and the assessment of multiple health outcomes. In addition, much effort was taken to adjust as many confounders as could be identified given the data limitations, adjust on many stratifications, and account for differences in baseline risk. Limitations of this research include possible selection bias and inaccuracies in electronic medical

record data used as the sampling frame. Furthermore, the researchers used the receipt of a testosterone prescription and achieved blood levels of androgens to stratify dose-response without using a diagnosis of hypogonadism. As such, the researchers had to assume that patients followed their treatment plans as indicated, which left considerable room for under- or overestimation of androgen exposure.

Characteristics-knowledge gap-funding. Evidence of safety and protective effects for health outcomes in men; the findings of this study contradicted the findings of Vigen et al. (2013b), confirmed some of the protective effects found by Cheetham et al. (2017), noted differential risk among several restricted analyses, and added new gaps to the literature; no funding or conflict disclosure.

Tse et al. (2017). The retrospective cohort study by Tse et al. (2017) entitled *Anabolic androgen use in the management of hereditary angioedema: Not so cheap after all* sought to assess the risk of comorbidity associated with 17AA androgen therapies commonly used to treat hereditary angioedema. In doing so, the intent of this study was to characterize the economic burden of disease linked to androgen-induced comorbidity. The research problem was framed from an economic perspective focusing on a single research question regarding increases in the number of comorbidities related to androgen therapies and the resultant increase in healthcare costs associated with increases in comorbidity. A Kaiser Permanente health insurance database was used as the sampling frame to identify a cohort of patients with HAE. The HAE cohort was stratified by androgen exposure into two groups (androgen exposure and non-exposure). Each patient with HAE was matched to five controls without HAE or androgen exposure on the

demographic variables of sex, ethnicity, age, date of enrollment, median income, and percentage achievement of a high school diploma.

Out of the 50 patients identified with HAE, 14 had no exposure to 17AA androgens, whereas 36 were exposed to at least one 17AA androgen prescription (Tse et al., 2017). Those with HAE and treated with 17AA androgens showed a 28% ($p = .04$) increase in comorbidities compared to those not treated with androgens (Tse et al., 2017). With each gram increase in 17AA androgen dose per month, the number of comorbid diseases increased by 12% ($p < 0.01$) (Tse et al., 2017). The incidence of comorbidities in exposed patients, according to one-month dose, was significant, $IRR = 1.12$, 95% CI [1.06-1.18] (Tse et al., 2017). Similarly, the incidence of comorbidities in exposed patients, according to total androgen dose, was also significant, but the effect was not clinically meaningful, $IRR = 1.0005$, 95% CI [1.0003-1.0007] (Tse et al., 2017). The highest rates of comorbid disease associated with HAE and 17AA androgen treatment were anxiety and depression (14), dyslipidemia (11), hypertension (11), obesity (8), muscle cramps (6), insomnia (5), menstrual dysfunction (5), and cancer (5) (Tse et al., 2017).

The study effectively assessed the incidence rate increase of diagnosed comorbid diseases associated with dosage unit increases in ingested 17AA androgens. These findings suggest that the healthcare costs associated of treating HAE with 17AA androgens was comparable to other modalities in the short-term, however, the long-term use of 17AA would likely inflate total healthcare costs through increased medical expenses directed towards treating comorbid diseases resulting from 17AA use. One concern arising from this study relates to the widespread use of low-cost androgen therapies, at the expense of greater comorbidity and increased total healthcare

costs, when other efficacious, non-androgen, therapies could be used in place of 17AA androgens.

The strengths of this study include (a) a targeted analysis of literature identified comorbid diseases, (b) use of a large secondary database as a representative sampling frame, and (c) use of appropriate Poisson regression models incorporating advanced generalized estimation equations. The limitations of this study were (a) an age discrepancy across exposure status, (b) differential intensity of medical care, (c) use of a private pharmaceutical company healthcare sampling frame, (d) potential confirmation bias, and (e) a possible common and undetected factor in the exposure group leading to information bias.

Characteristics-knowledge gap-funding. Evidence of 17AA toxicity in HAE treatment increases the incidence of comorbidity (by androgen type and dose-response) and total healthcare costs thereby skewing the risk-to-benefit of androgen utilization in this population; direct and indirect costs of androgen utilization are relatively unknown in most clinical settings; no funding disclosure.

Martinez et al. (2016). Martinez et al. (2016) conducted a population-based case-control study entitled *Testosterone treatment and risk of venous thromboembolism: Population based case-control study* to investigate the risk of VTE associated with testosterone treatment in men (Martinez et al., 2016). A timing of risk perspective focused the research problem given previously reported delays in VTE onset, such as the six-month time-to-event reported by C. J. Glueck et al. (2016), between the initiation of androgen therapy and the onset of thrombotic events. The sampling frame used to sample cases was the UK CPRD (Martinez et al., 2016). The CPRD included data from 370 clinical practices that linked hospital discharge diagnoses, in-

hospital procedures, and information on all-cause mortality over the study assessment period (January 1st, 2001 to May 31st, 2013) (Martinez et al., 2016). The researchers identified ($n = 19,215$) VTE cases and randomly matched ($n = 909,530$) controls ($1: \leq 50$) with no known history of VTE on case index date, age, all known or suspected VTE risk factors, history of cancer, and history of hypogonadism (Martinez et al., 2016). Androgen exposure was divided into three groups including current treatment, recent treatment, and no treatment within the preceding two years.

The overall risk of VTE, comparing current androgen treatment to no androgen treatment, was $RR_{adj} = 1.25$, 95% CI [0.94, 1.66], while the overall risk of VTE during the initial six months of androgen treatment was considerably higher, $RR_{adj} = 1.63$, 95% CI [1.12, 2.37] (Martinez et al., 2016). The findings aligned to additional VTE events at a rate of 10.0 per 10,000 person-years (range [1.9, 21.6] over the base rate of 15.8 per 10,000 person-years (Martinez et al., 2016). Beyond six months of androgen treatment the risk of VTE reduced substantially, $RR_{adj} = 1.00$, 95% CI [0.68, 1.47] and after androgen treatment the risk was fully attenuated, $RR_{adj} = 0.68$, 95% CI [0.43, 1.07] (Martinez et al., 2016). The risk of VTE reappeared, upon stratification within the initial six months of androgen treatment of cases with pathological hypogonadism, $RR_{adj} = 1.52$, 95% CI [0.94, 2.46], cases without pathological hypogonadism, $RR_{adj} = 1.88$, 95% CI [1.02, 3.45], cases with a known risk factor for VTE, $RR_{adj} = 1.41$, 95% CI [0.82, 2.41], and cases without a known VTE risk factor, $RR_{adj} = 1.91$, 95% CI [1.13, 3.23] (Martinez et al., 2016).

The strengths of this study included (a) use of a validated VTE algorithm, (b) use of a non-VTE cohort matched on confounders associated with the presumed indications for androgen

prescriptions or presumed cause of VTE, (c) use of full prescription data, (d) adjustment for known confounders associated with future risk of VTE, (e) matching on hypogonadal history to reduce confounding, and (f) using sensitivity analyses to verify the findings. The findings of increased VTE risk during the first six months of treatment reconfirmed the six-month window reported by C. J. Glueck et al. (2016) but directly opposed the findings reported by Baillargeon et al. (2015).

The study limitations comprised (a) possible reduction of VTE susceptible patients by limitations of health records, (b) effect modification through differential baseline VTE risks in those with and without hypogonadism, (c) undetected residual confounding or bias, (d) lack of statistical significance in several reported analyses, (e) misclassification of exposure, and (f) a considerably limited number of cases, with only 69 cases out of 19,215 that were classified to the “current” androgen exposure category. It was unclear why the researchers chose a case-control methodology over a retrospective cohort design after acknowledging that exposure to testosterone was rare, instead justifying the rare exposure for the inflated matching of VTE case to controls. Rare exposures are best studied by the cohort design and involve the use of incidence rates to estimate rate ratios (K. J. Rothman et al., 2010; Woodward, 2014). As such, case-control analyses cannot be used to calculate risk ratios because this requires incident cases (K. J. Rothman et al., 2010; Woodward, 2014). Subsequently, the estimation of rate ratios, although theoretically unfit in a case-control study, likely approximate any odds ratios that would be estimated using the correct analysis.

Characteristics-knowledge gap-funding. Evidence of hematotoxicity and increased risk of VTE peaking at six months and reducing in VTE risk sharply, thereafter; the findings of this

study, showing increased VTE risk during the first six months of androgen treatment, confirm the six-month risk window reported by C. J. Glueck et al. (2016) but directly oppose the findings reported by Baillargeon et al. (2015). The researchers received personal fees, grants, and non-financial support from numerous pharmaceutical companies, and one researchers affiliated institution received direct funding.

Baillargeon et al. (2016). The study entitled *Androgen therapy and rehospitalization in older men with testosterone deficiency* was conducted to determine whether androgen therapy would reduce the rate of rehospitalization in older men with diagnosed testosterone deficiency (Baillargeon et al., 2016). The subjects included 6,372 men aged 66 years or greater with nonsurgical hospitalizations that were enrolled over a six-year period sampled from a five percent national sample of Medicare beneficiaries (Baillargeon et al., 2016). The researchers used a retrospective cohort design including only those with a diagnosis of hypogonadism, any nonsurgical diagnosis, and continuous insurance enrollment in the 12 months preceding hospital admission. Androgen exposure was established by the fulfillment of an androgen prescription or administered intramuscular androgen injection that spanned no less than the patient's hospitalization index date. Androgen exposure duration was considered equivalent as a one-month supply of prescribed androgens. Androgen mode of administration and dose were determined by National Drug Code numbers and Healthcare Common Procedural Coding System codes (Baillargeon et al., 2016). The covariates included age at index hospitalization, sociodemographic factors, race, median income, the proportion of those with at least a high school education, and the Elixhauser comorbidity index (Baillargeon et al., 2016). The primary outcome was all acute care hospital readmissions within 30 days after discharge (patient index

hospitalization). The secondary outcome was unplanned readmissions coded as “emergency” or “urgent” (Baillargeon et al., 2016, p. 588).

Older patients that received androgen therapy (9.8%), compared to those without androgen therapy (13.0%), were found to have a reduced risk of rehospitalization in the 30-day period after hospital discharge, $OR = 0.73$, 95% CI [0.58, 0.92] (Baillargeon et al., 2016). Adjustment for covariates yielded comparable results, $OR = 0.75$, 95% CI [0.59, 0.95] (Baillargeon et al., 2016). The rate of unplanned 30-day readmissions was (6.2%) for androgen therapy and (10.0%) for nonusers with reduced risk in the androgen therapy group, $OR = 0.60$, 95% CI [0.45, 0.78] (Baillargeon et al., 2016). Upon adjustment for covariates, a reduction in risk of unplanned 30-day hospital readmissions persisted, $OR = 0.62$, 95% CI [0.47, 0.83] (Baillargeon et al., 2016). These findings endured across three propensity score analyses: adjustment, stratification, and inverse probability of treatment weighting. A sensitivity analysis implemented by the iterative removal of elevated diagnoses in the androgen therapy group did not reveal any significant findings or biased results.

The findings suggest that androgen therapy reduces the risk of rehospitalization and unplanned readmissions in older men with diagnosed hypogonadism. The authors concluded that androgen therapy extols extensive public health benefit and should be further investigated as an intervention in this population to reduce readmission rates. The salient strengths of this study included (a) a nationally representative sample, (b) elaborate adjustment for a comprehensive compilation of covariates, and (c) replication of findings across multiple propensity scores, and (d) sensitivity analyses. The main limitations of this study were (a) diagnostic coding errors, (b) possible unintentional or undiscovered selection bias, (c) lack of data on behavioral and

environmental factors, (d) lack of information on androgens purchased outside the Medicare plan, and (e) the assumption that all patients followed their prescribed treatments.

Characteristics-knowledge gap-funding. Reduced risk of rehospitalizations and unplanned readmissions in older men with hypogonadism; second of only two studies in the literature that assessed androgen therapy using partial inpatient data, however, it only focused on the initial hospitalization and risk of rehospitalization and unplanned readmissions, not the actual duration of inpatient stay; research was supported by two grants from the National Institutes of Health and one grant from the Agency for Healthcare Research and Quality.

Cheetham et al. (2017). A retrospective cohort study using secondary data by Cheetham et al. (2017) entitled *Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency* was conducted to assess the association between androgen replacement therapy and cardiovascular outcomes. Using a Kaiser Permanente database as the sampling frame, the researchers established a cohort of men ($n = 44,335$) by including those with a coded diagnosis for hypogonadism and/or records of serum testosterone levels < 300 ng/dL over an 11-year period spanning from 1999 to 2010 (Cheetham et al., 2017). The date of the initial diagnosis or blood test result was defined as the index date with the cohort divided into exposure ($n = 8,808$) and non-exposure ($n = 35,527$) groups based on receipt of a testosterone prescription following the index date (Cheetham et al., 2017). Exclusion criteria included restriction to incident exposure excluding those with prescriptions prior to the index date, to less than 12 months of continuous enrollment in the insurance plan with drug benefit prior to cohort entry, to men less than 40 years old at the index date, and to those diagnosed with testicular or

prostate cancer, pituitary gland disorders, androgen insensitivity syndrome, or Klinefelter syndrome (Cheetham et al., 2017).

The study follow-up was defined as the period until patients reached a study endpoint, dis-enrolled from the insurance plan, death, or termination of the study. Androgen exposure was defined through dispensed androgen prescriptions or electronic medical records evidence of androgen administration by medical personnel. Study outcomes, defined as the principal diagnosis in inpatient hospitalization records, included AMI or PCI, unstable angina, combined stroke (ischemic or [TIA]), SCD, and all-cause mortality.

The average age of the exposure group was 58.4 years with 1.4% experiencing prior cardiovascular events, whereas the average age in the non-exposure group was 59.8 years with 2.0% experiencing prior cardiovascular events (Cheetham et al., 2017). Median follow-up was 3.2 years (*IQR*, 1.7 to 6.6 years) in the exposure group vs. 4.2 (*IQR*, 2.1 to 7.8 years) in the non-exposure group (Cheetham et al., 2017). Composite cardiovascular end-point rates were 23.9 vs. 16.9 per 1000 person-years in the non-exposure and exposure groups, respectively (Cheetham et al., 2017). The hazard ratio for the composite cardiovascular end-point in the exposure group compared to the non-exposure group was $HR_{adj} = 0.67$, 95% CI [0.62, 0.73] (Cheetham et al., 2017). Similar results were reported upon outcome restriction to combined stroke events (stroke and TIA), $HR = 0.72$, 95% CI [0.62, 0.84] and combined cardiac events (AMI, SCD, unstable angina, revascularization procedures), $HR = 0.66$, 95% CI [0.60, 0.72] (Cheetham et al., 2017).

The research had several strengths including (a) large representative sample, (b) use of blood test results and diagnosis codes to establish hypogonadal patients, (c) long assessment period spanning 11 years, (d) targeted endpoints and composite endpoints, (e) reasonable

inclusion and exclusion criteria, (f) adjusting for baseline characteristics and comorbidity via propensity score methods, and (g) sensitivity analyses. The limitations of this study included (a) non-adherence to Endocrine Society guidelines (≥ 2 morning testosterone tests as diagnostic criteria) for identification of androgen-deficient males (possible misclassification of cases), (b) unmeasured confounding inherent to the study design (clinicians might selectively use testosterone in healthier patients), (c) some risk factors for cardiovascular disease, such as nutrition and physical activity, were not accessible in the secondary data, (d) competing risk analysis was not conducted, (e) ascertainment bias could not be ruled out if androgen patients were followed more closely than those without androgens, (f) drug characteristics of dose and duration were not designed into the analysis, and (g) possible misclassification of some unexposed patients due to the use of physicians and pharmacies outside the insurance plan, due to the stigma associated with androgen replacement therapy, could not be ruled out.

Characteristics-knowledge gap-funding. Evidence of cardioprotective effects and decreased risk of cardiovascular outcomes in men prescribed testosterone for androgen deficiency; the study provided new data clarifying equivocal health outcomes risk found in the literature that directly opposes the reported results of Vigen et al. (2013b); Grant (1 RO1 AG042921-01) from the National Institutes of Health, National Institute on Aging.

Theoretical Framework

The pharmacologic qualities of SAs, considered in the scope of toxicology principles, and mechanisms demonstrated in animal and forensic studies constitute the theoretical basis for direct androgen toxicity and were used as the theoretical framework of this study. Indirect toxicity is explained through enzyme-reduced androgen metabolites and non-genomic actions of

SAs, general risk factors, and genetic risk factors. Taken together, total toxicity is the sum of direct and indirect toxicity at the cellular, tissue, organ, and organ system levels, resulting in distinct disease states.

The androgen toxicity framework of this study linked organ systems and reported disease states to a) androgen type, b) dose, c) duration, and d) mode of administration. The framework assumed that the pharmacologic principles of absorption, distribution, metabolism, and excretion (ADME) hold constant given that individual-to-individual variation in the inner physiologic environment remains stable i.e. ADME processes are relatively fixed in each inpatient. Figure 2 shows the relationships between the pharmacologic properties of androgens and risk levels for developing androgen toxicity resulting in disease states. Most reported adverse events in the literature are organ-specific disease states that directly correspond to ICD-9 diagnoses.

Three emergent lines of thought are deduced from the androgen toxicity framework: a) illicit androgen use above physiologic levels causes organ-specific effects leading to an increased risk of developing specific disease states relative to androgen type, dose, duration, and mode of administration, b) therapeutic androgen use also confers an increased risk of advancing organ-specific diseases states, relative to specific androgen type, dose, duration, and mode of administration, and c) therapeutic androgen use, compared to illicit androgen use, results in less potential risk of organ-specific disease induction because of lower total organ system toxicity. These distinctive lines offer heuristic predictions regardless of setting, population, or specific androgen characteristics.

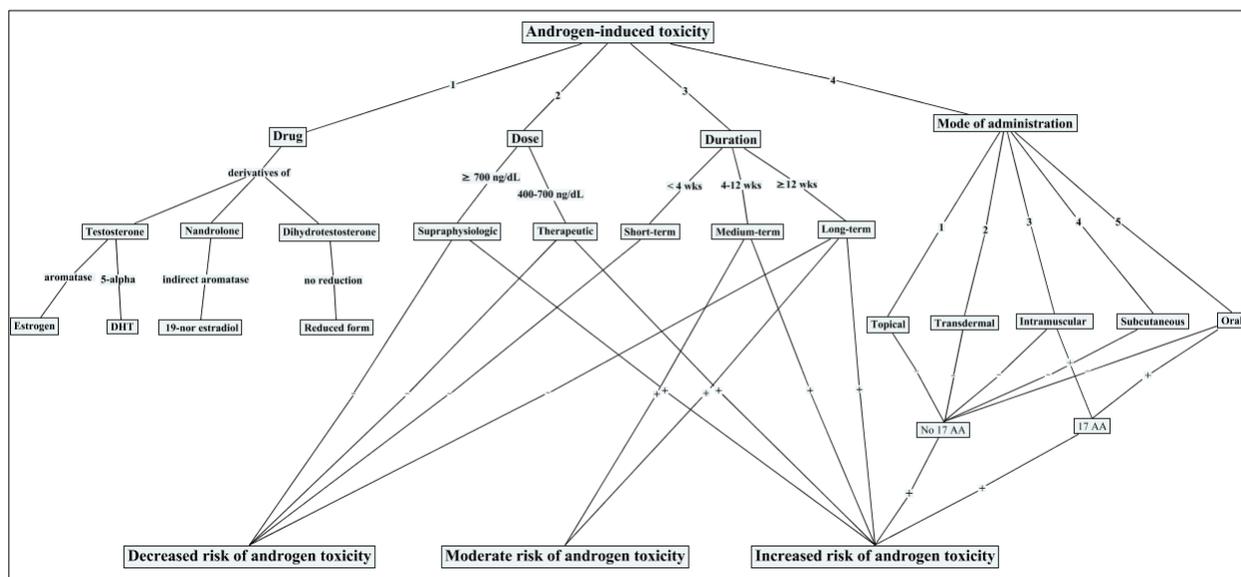


Figure 2. Pharmacological aspects of androgen toxicity.

Animal and forensic studies were used to classify androgen toxicity, according to the affected organ or organ system and pharmacologic characteristics, into six distinct categories of cardiotoxicity, neurotoxicity, vasculotoxicity, hematotoxicity, hepatotoxicity, and nephrotoxicity (Table 1-Table 6).

Table 1

Cardiotoxicity in Animal Studies

Author (year)	Disease	Type	Characteristics
Woodwiss (2000)	LVH	A/5- α /N17AA	10 mg/kg/week
Beutel (2005)	Hypertension/tachycardia	A/5- α /17AA	5-10 mg/kg/week
Do Carmo (2011)	Cardiac hyper.	A/5- α /N17AA	10 mg/kg/week
Vasilaki (2016)	Cardiac hyp./hypertension	A/5- α /N17AA	8-10 mg/kg/week
Karbasi (2017)	Cardiac hyp.	A/5- α /N17AA	40 mg/kg/week
Tofighi (2017)	Cardiac hyper./CAD	A/5- α /N17AA	30 mg/kg/week

Żebrowska (2017)	Cardiac hyp.	A/5- α /N17AA	20 mg/0.25 kg/week
Bai (2018)	R. ventricular remodeling	A/5- α /N17AA	20 mg/kg/week
Melo Junior (2018)	Hypertension/LVH	A/5- α /N17AA	20 mg/kg/week

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, LVH = left ventricular hypertrophy, hyp. = hypertrophy, CAD = coronary artery disease, R = right.

Table 2

Hematotoxicity in Animal Studies

Author (year)	Disease	Type	Characteristics
Zarei (2017)	Erythrocytosis	A/5- α / N17AA	50 mg/kg/week
Guo (2013)	Erythrocytosis/hepcidin suppression	A/5- α / N17AA	1-2 mg/kg/week

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible.

Table 3

Hepatotoxicity in Animal Studies

Author (year)	Disease	Type	Characteristics
El-Halwagy (2016)	Hepatocyte degeneration/ROS	A/5- α /17AA	5 mg/kg/week
Sadowska-Krepa (2017)	Liver enzyme elevations	A/5- α /N17AA	80 mg/kg/week
Shalaby (2018)	Liver enzyme elevations/apoptosis	A/5- α /N17AA	10 mg/kg/week

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, ROS = reactive oxygen species.

Table 4

Nephrotoxicity in Animal Studies

Author (year)	Disease	Type	Characteristics
Riezzo (2014)	ROS/FSGS	A/5- α /N17AA	10 mg/kg/week
Brasil (2015)	Renal tissue remodeling	A/5- α /N17AA	20 mg/kg/week
Aparicio (2017)	Renal hypertrophy/infiltration	A/5- α /17AA	10 mg/kg/week

Tofighi (2017)	Renal fibrosis/cellular proliferation	A/5- α /N17AA	30 mg/kg/week
Kahal (2018)	Irreversible kidney damage	A/5- α /N17AA	30 mg/kg/week

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible.

Table 5

Neurotoxicity in Animal Studies

Author (year)	Disease	Type	Characteristics
Bueno (2017)	Oxidative stress	A/5- α /17AA	5 mg/kg/week
Joukar (2017)	Neurodegeneration/ROS	A/5- α /N17AA	5 mg/kg/week

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, ROS = reactive oxygen species.

Table 6

Vasculotoxicity in Animal Studies

Author (year)	Disease	Type	Characteristics
Matsuda (1994)	↑ TxA ₂ R/hypercoagulability	A/5- α /N17AA	20 mg/kg/week
Gonzales (2005)	↑ TxA ₂ synthase cerebral arteries	A/5- α /N17AA	Pellets/4 weeks
Li (2007)	↓ Platelet aggregation/ROS	NA/N5- α /N17AA	0.25 mg/day/2 weeks
Guzzoni (2018)	ROS/endothelial vasodilation	A/5- α /N17AA	5 mg/kg/week
Andrade (2018)	Cytokine dysregulation/ROS	A/5- α /17AA	20 mg/kg/week

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, TxA₂ = thromboxane, TxA₂R = thromboxane receptor, ROS = reactive oxygen species.

Using pharmacologic qualities, toxicology principles, and androgen theory, androgen toxicity was reduced to assess the studies of the literature review according to each androgen toxicity classification. The reduced framework included each study, disease state, androgen toxicity type (17AA or non-17AA; 5- α reducible or non-5- α reducible; aromatizable or non-

aromatizable; or poly-drug combinations of all types), and key pharmacologic characteristics (Table 7-Table 15).

Table 7

Cardiotoxicity in Forensic and Case Reports

Author (year)	Disease state	Type	Characteristics
<i>Forensic reports</i>			
Lusetti (2015)	Cardiac remodeling/LVH	Poly-drug	Abuse; long-term
Cecchi (2017)	LVH/Endothelial apoptosis	Poly-drug	Abuse; long-term
Fрати (2017)	LVH	Poly-drug	Abuse; long-term
<i>Case reports</i>			
Gangadhara. (2011)	Cardiomyopathy	Omitted	Abuse; 20 ⁺ years
Kesler (2014)	CAD	Poly-drug	Abuse; long-term
Cavanagh (2015)	Chronic hypertension	A/5- α /N17AA	Abuse; 3 months
Edvardsson (2015)	Hypertension	A/5- α /17AA	Abuse; 3 months
Christou (2016)	AMI	A/5- α /17AA	Abuse; 2 months
Flo (2018)	AMI/LVH/arrhythmia	Poly-drug	Abuse; 20 years
Garner (2018)	Cardiomyopathy	A/5- α /N17AA	Abuse; long-term
Kato (2018)	Dyslipidemia	A/5- α /N17AA	Therapeutic; 12 years
García (2018)	Malignant hypertension/LVH	A/5- α /17AA	Abuse; 10 years
White (2018)	Fulminant heart failure/LVH	A/5- α /N17AA	Abuse; 3 months

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, LVH = left ventricular hypertrophy, hyp. = hypertrophy, CAD = coronary artery disease, R = right, AMI = acute myocardial infarction.

Table 8

Cardiotoxicity in Observational Studies, Trials, and Meta-Analyses

Author (year)	Disease	Androgen	Characteristics
<i>Observational</i>			
Vigen (2013)	Mortality/MI	A/5- α /N17AA	Therapeutic
Finkle (2014)	MI	A/5- α /N17AA	Therapeutic
Baggish (2017)	CAD	Poly-drug	Abuse; long-term
van Velzen (2019)	Dyslipidemia/atherosclerosis	A/5- α /N17AA	Therapeutic
Loo (2019)	MI	A/5- α /N17AA	Therapeutic
<i>Trials</i>			
Choi (2005)	Dyslipidemia/atherosclerosis	A/5- α /N17AA	Therapeutic
Basaria (2010)	Mortality/MI/hypertension/HF	A/5- α /N17AA	Therapeutic
Supasyndh (2013)	Dyslipidemia	A/5- α /17AA	Therapeutic
<i>Meta-analyses</i>			
Xu (2013)	Mortality/MI	A/5- α /N17AA	Therapeutic
Budoff (2017)	Atherosclerosis	A/5- α /N17AA	Therapeutic

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible
MI = myocardial infarction, CAD = coronary artery disease, HF = heart failure.

Table 9

Hematotoxicity in Case Reports

Author (year)	Disease	Type	Characteristics
Gangadhara (2011)	Erythrocytosis	Omitted	Abuse; 20+ years
Garner (2018)	Erythrocytosis	A/5- α / N17AA	Abuse; long-term
Harston (2014)	Polycythemia/hyperviscosity	Poly-drug	Abuse; long-term
Omar (2017)	Erythrocytosis	A/5- α /N5- α /N17AA	Abuse; 2 years
Tikka (2016)	Erythrocytosis/hypercoagulability	Poly-drug	Abuse; 3 years

Ammatuna (2014)	Polycythemia	A/5- α /17AA	Abuse; 3 months
Fox (2014)	Recurrent hemorrhage/erythrocytosis	A/5- α /N17AA	Abuse; 2 months
Randhawa (2013)	Intramural bowel hematoma/bleeding	A/5- α /N17AA	Undisclosed
Cavanagh (2015)	Intest. intussceptions/polycythemia	A/5- α /N17AA	Abuse; 3 months
Colburn (2017)	Thrombophilic state	A/5- α /N5- α /N17AA	Abuse; 5 ⁺ years
García (2018)	Hemo. anemia/thrombocytopenia	A/5- α /17AA	Abuse; 10 years
Edvardsson (2015)	Hyper-viscosity/coagulability	A/5- α /17AA	Abuse; 3 months

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, Intest. = intestinal, hemo = hemolytic.

Table 10

Hematotoxicity in Observational Studies, Trials, and Meta-Analyses

Author (year)	Disease	Type	Characteristics
<i>Observational</i>			
Glueck (2011)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
Martinez (2016)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
<i>Trials</i>			
Ajayi (1995)	<p>↑ A₂ receptor density</p> <p>↑ Platelet aggregation</p> <p>Hypercoagulability</p>	A/5- α /N17AA	Therapeutic; 8 weeks
Coviello (2008)	Secondary erythrocytosis	A/5- α /N17AA	Supraphysiologic
Snyder (2016)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
Sinclair (2016)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
Ng Tang Fui (2016)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
<i>Meta-analyses</i>			

Calof (2005)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
Fernandez-Balsells (2010)	Secondary erythrocytosis	A/5- α /N17AA	Therapeutic
Andrews (2018)	Secondary erythrocytosis	Poly-drug	Abuse

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible A₂ = thromboxane.

Table 11

Hepatotoxicity in Case Reports and One Randomized Trial

Author (year)	Disease	Type	Characteristics
<i>Case reports</i>			
Flo (2018)	Acute liver failure	A/5- α /N17AA	Abuse; 3 months
Kato (2018)	Adenoma/NAFLD	A/5- α /N17AA	Therapeutic; 12 years
Romano (2017)	Focal nodular hyperplasia	Omitted	Abuse; 2 years
Gupta (2016)	Many benign liver tumors	Omitted	Abuse; long-term
Hardt (2012)	HCC	Poly-drug	Abuse; 5 ⁺ years
Kesler (2014)	HCC	Poly-drug	Abuse; long-term
Solbach (2014)	HCC/adenomas	Poly-drug	Abuse; long-term
Leone (2016)	HCC/adenomas	Poly-drug	Abuse; long-term
Castellanos (2018)	Cholestasis/hepatitis/DILI	A/5- α /17AA	Use; 1 month
Fisler (2018)	Cholestasis/hepatitis/DILI	A/5- α /17AA	Abuse; long-term
<i>Trial</i>			
Supasyndh (2013)	Liver injury	A/5- α /17AA	Therapeutic

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, NAFLD = non-alcoholic fatty liver disease, HCC = hepatocellular carcinoma, DILI drug-induced liver injury.

Table 12

Nephrotoxicity in Case Reports

Author (year)	Disease	Type	Characteristics
Cooper (2011)	Chronic renal failure	A/5- α /N17AA	Abuse; 3 months
Winnett (2011)	Renal disease/FSGS	A/5- α /N17AA	Abuse; long-term
Almukhtar (2014)	AKI/FSGS	A/5- α /N17AA	Abuse; long-term
Ammatuna (2014)	Renal infarction	A/5- α /17AA	Abuse; 3 months
Kesler (2014)	CKD/dialysis	Poly-drug	Abuse; long-term
Edvardsson (2015)	Reduced kidney BP control	A/5- α /N17AA	Abuse; 3 months
Colburn (2017)	Recurrent renal infarction	A/5- α /N17AA	Abuse; 5 ⁺ years
Castellanos (2018)	AKI/bile cast nephropathy	A/5- α /17AA	Use; 1 month
Fisler (2018)	AKI/bile cast nephropathy	A/5- α /17AA	Abuse; long-term
García (2018)	Acute kidney failure	A/5- α /N17AA	Abuse; 10 years

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, BP = blood pressure, CKD = chronic kidney disease, FSGS = focal segmental glomerulosclerosis, AKI = acute kidney injury.

Table 13

Neurotoxicity in Case Reports

Author (year)	Disease	Androgen	Characteristics
Maini (2014)	Alkalosis/hypokalemia	A/5- α /17AA	Abuse; prior week
Cooper (2011)	Atherosclerotic stroke	A/5- α /N17AA	Abuse; 20 ⁺ years
Harston (2014)	Lacunar ischemic stroke	Poly-drug	Abuse; long-term
Omar (2017)	Ischemic stroke/hemiparesis	A/5- α /N17AA	Abuse; 2 years
Tikka (2016)	Ischemic stroke/hearing loss	Poly-drug	Abuse; 3 years
Edvardsson (2015)	Hypertensive encephalopathy	Poly-drug	Abuse; 3 months
Bolster (2017)	Death/encephalopathy	A/5- α /17AA	Abuse; short-term

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible.

Table 14

Neurotoxicity in Observational Studies and One Randomized Trial

Author (year)	Disease	Androgen	Characteristics
<i>Observational</i>			
Vigen (2013)	Mortality/MI	A/5- α	Therapeutic
Loo (2019)	TIA/ischemic stroke	A/5- α	Therapeutic
<i>Trial</i>			
Basaria (2010)	Stroke	A/5- α	Therapeutic

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, 5- α reducible, MI = myocardial infarction, TIA = transient ischemic attack.

Table 15

Vasculotoxicity in Case Reports, Observational Studies, and One Meta-Analysis

Author (year)	Disease state	Type	Characteristics
<i>Case reports</i>			
Dickerman (1996)	DVT/pulmonary embolism	Poly-drug	Abuse; long-term
McCarthy (2000)	Thrombus/embolism	A/5- α /N17AA	Abuse; long-term
Cooper (2011)	Thromboembolism	A/5- α /N17AA	Abuse; 20+ years
Omar (2017)	Sagittal thrombosis	A/5- α /N5- α /N17AA	Abuse; 2 years
Amjad (2018)	Portal vein thrombosis	Poly-drug	Abuse; long-term
<i>Observational</i>			
Glueck (2011)	Pulmonary embolism	A/5- α /N17AA	Therapeutic
Martinez (2016)	Ven. thromboembolism	A/5- α /N17AA	Therapeutic
<i>Meta-analysis</i>			
Houghton (2018)	Ven. thromboembolism	A/5- α /N17AA	Therapeutic

Note. 17AA = 17- α alkylated, N17AA = non-17- α alkylated, A = aromatizable, NA = non-aromatizable, 5- α = 5- α reducible, N5- α = non-5- α reducible, poly-drug = combinations of 17- α alkylated, aromatizable, and 5- α reducible, Ven. = venous, DVT = deep venous thromboembolism.

The most common disease states that were found included secondary erythrocytosis (polycythemia), drug-induced liver injury, hypercoagulability, venous thromboembolism, acute myocardial infarction, left ventricular hypertrophy, stroke, hepatocellular carcinoma, and acute kidney injury. Table 16 details the disease states and corresponding ICD-9 codes identified from case reports, observational studies, human trials, and meta-analyses that were selected as variables and integrated into the conceptual framework to guide this study.

Table 16

Disease States for Statistical Testing in an Inpatient Population

Disease	ICD-9-CM description	ICD-9-CM range
Polycythemia	Secondary polycythemia	289.0-289.6
Erythrocytosis		
Hypercoagulability	Primary hypercoagulable state	289.81-289.89
	Secondary hypercoagulable state	
Drug-induced liver injury	Drug or toxin induced hepatitis	573.3
Venous thromboembolism	Other venous embolism and thrombosis	453.0-453.9

Conceptual Framework

Figure 3 shows the conceptual framework used to integrate implicit androgen toxicity theory into an inpatient setting. Specifically, androgen toxicity predicts that the inpatients undergoing androgen therapy with a confirmed external cause of injury due to androgen toxicity (E932.1) will have greater risks of literature-reported disease states, mortality, non-elective admission, major operating room procedure, and procedure class than inpatients unexposed to androgen toxicity. The framework also suggests an increased likelihood of mortality and disease

severity among those exposed to androgen toxicity compared to those that are not exposed. In addition, the incidence of chronic conditions, diagnoses, external causes of injury, procedures, and length of stay, along with total healthcare costs, are expected to be higher in exposed patients versus nonexposed patients. The effects are expected to result in foreseeable trends in all primary and secondary outcomes, across all cohorts for each year, and from year-to-year.

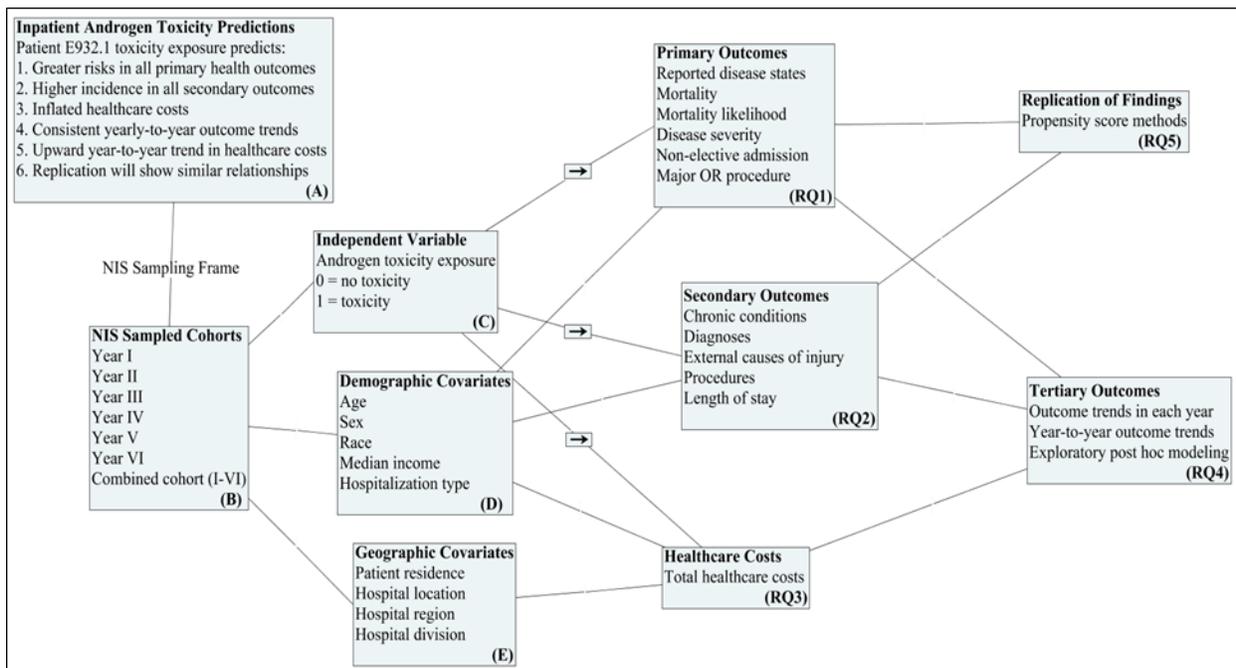


Figure 3. Conceptual framework of inpatient androgen toxicity.

Hypotheses

Figures 4-8 show the relationships between the variables in this proposed study followed by research and statistical hypotheses.

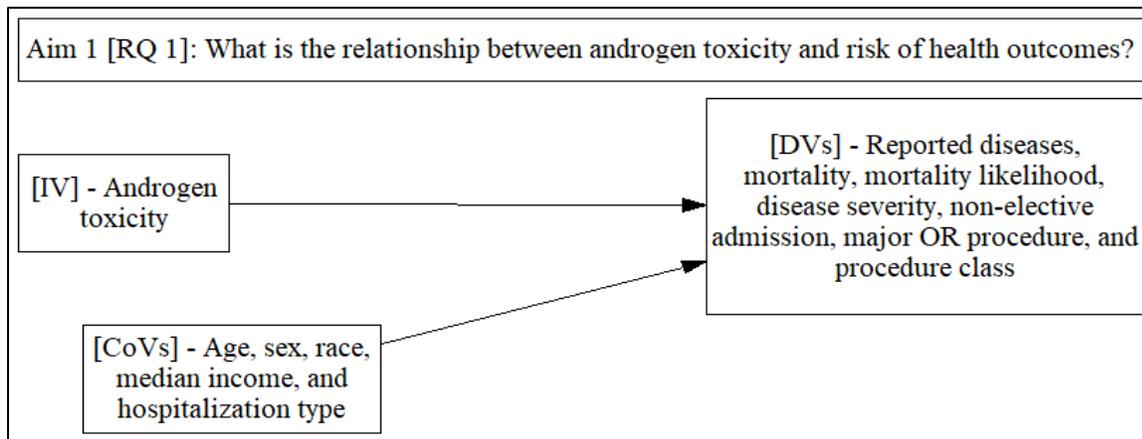


Figure 4. Research question one.

Aim 1 **[RQ 1]**. What is the relationship between androgen toxicity and risk of health outcomes?

Research hypothesis. There will be substantially greater risks of health outcomes in index cohorts compared to reference cohorts. There will also be a greater incidence of literature-identified disease states in all index cohorts compared to reference cohorts.

Null hypothesis **[H₀₁]**. There is no relationship between androgen toxicity and risk of health outcomes.

Alternative hypothesis **[H_{a1}]**. There is a relationship between androgen toxicity and risk of health outcomes.

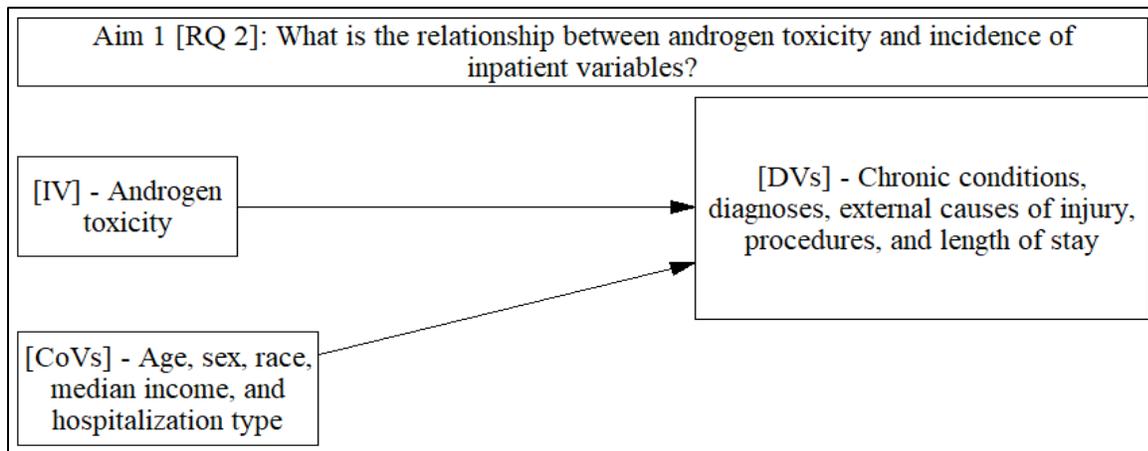


Figure 5. Research question two.

Aim 1 [RQ 2]. What is the relationship between androgen toxicity and incidence of inpatient variables?

Research hypothesis. The incidence of chronic conditions, diagnoses, external causes of injury, medical procedures, and length of stay will be higher in index cohorts compared to reference cohorts.

Null hypothesis [H₀₂]. There is no relationship between androgen toxicity and incidence of inpatient variables.

Alternative hypothesis [H_{a2}]. There is a relationship between androgen toxicity and incidence of inpatient variables.

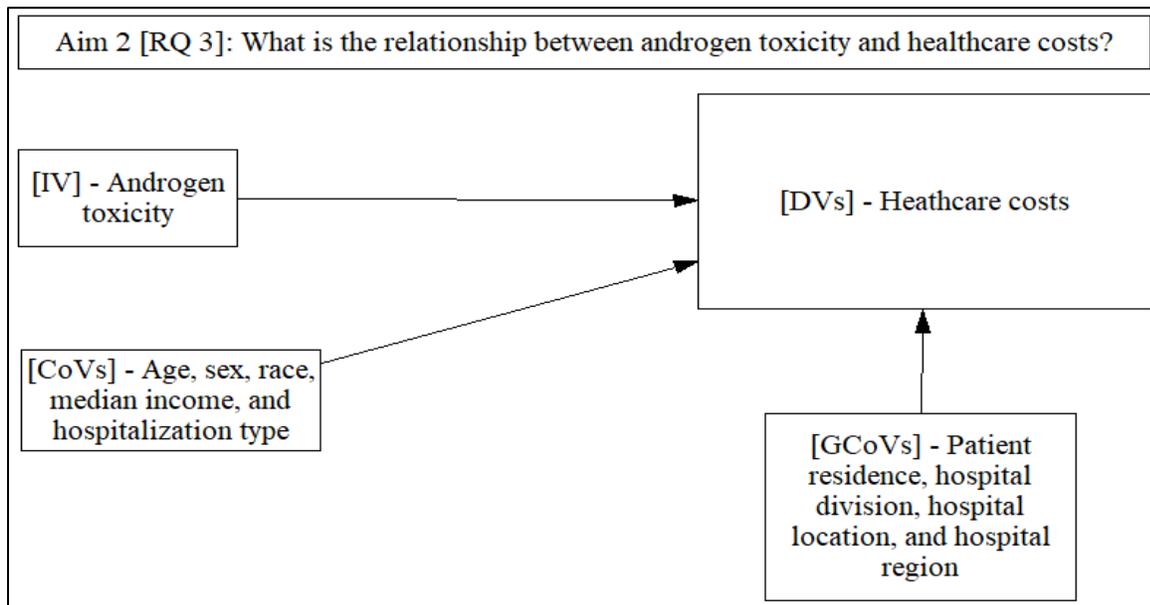


Figure 6. Research question three.

Aim 2 [RQ 3]. What is the relationship between androgen toxicity and healthcare costs?

Research hypothesis. The burden of disease will be greater in the index cohort compared to the reference cohort.

Null hypothesis [H₀₃]. There is no relationship between androgen toxicity and healthcare costs.

Alternative hypothesis [H_{a3}]. There is a relationship between androgen toxicity and healthcare costs.

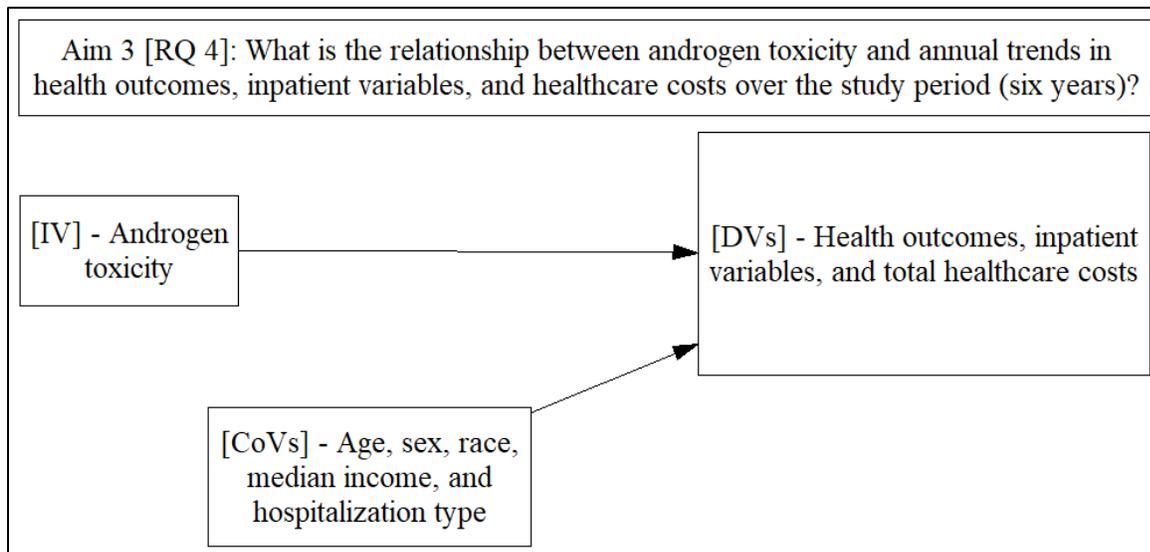


Figure 7. Research question four.

Aim 3 **[RQ 4]**. What is the relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and healthcare costs over the study period (six years)?

Research hypothesis. Greater risk and incidence will trend consistently from year-to-year for health outcomes and inpatient variables, whereas higher healthcare costs will trend upwards, consistently, from year-to-year, reflecting increases in androgen prescriptions during the study period.

Null hypothesis **[H₀₄]**. There is no relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and healthcare costs over the study period.

Alternative hypothesis **[H_{a4}]**. There is a relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and healthcare costs over the study period.

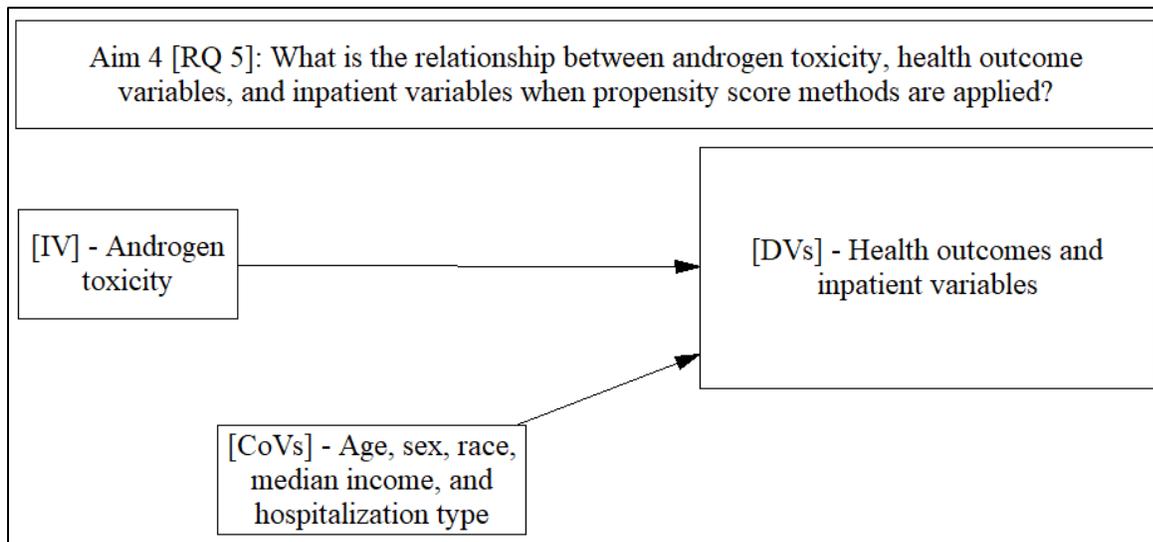


Figure 8. Research question five.

Aim 4 **[RQ 5]**. What is the relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied?

Research hypothesis. The relationships resulting from all main analyses will persist and be reflected when inverse probability of treatment weighting is used to balance demographic variables. On stratification, the associations will be stronger with increasing age and decreasing median income.

Null hypothesis [H₀₅]. There is no relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied.

Alternative hypothesis [H_{a5}]. There is a relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied.

Summary

The initial synthesis of testosterone occurred through a methylated synthesis devised by Ruzika in 1935. Since this time, the indications for synthetic androgens in clinical practice have

grown substantially to the current day. Two forms of androgen use are broadly accepted as illicit use by athletes and bodybuilders and therapeutic use in clinical practice. The pleiotropic effects of androgens are mediated by genomic mechanisms that are essential to normal physiological function in both sexes. Androgens also act through non-genomic actions or fast signaling pathways that fall outside classical transcription and translation of proteins. Synthetic androgens have pharmacologic properties with which they exert favorable treatment effects but have also been implicated in the development of pathological toxicity to many organ systems.

Cardiotoxicity was the first explicitly reported form of androgen toxicity that became apparent in the literature from benchwork studies that applied androgens directly to myocardial cell cultures. Six forms of androgen toxicity were derived from animal model and forensic study evidence including cardiotoxicity, neurotoxicity, vasculotoxicity, hematotoxicity, hepatotoxicity, and nephrotoxicity. The literature composed of case reports, observational studies, controlled trials, and meta-analyses is roughly divided into a dichotomous body of evidence including many populations. One body provides evidence of increased risk from androgen exposure and the other body provides evidence of decreased risk and protective effects.

The studies closely aligned to this dissertation research addressed several knowledge gaps while revealing many others. One clear knowledge deficiency, and the focus of this study, was the insufficient assessment of an inpatient population with a limited number of health outcomes. The theory of androgen toxicity carries specific implications for an inpatient population and was identified for this investigation to characterize adverse health outcomes among the inpatient population in the United States. As such, the androgen toxicity framework was theoretical underpinning of this study and was used to identify and classify disease states

into six categories of androgen toxicity according to principles of pharmacology and toxicology. Androgen toxicity theory was integrated into a conceptual framework using identified disease states as primary health outcomes that formed the basis for the study hypotheses. The conceptual framework was used to guide the study, allow the statistical testing of specific primary health outcomes, and answer five research questions.

Chapter III: Methodology

Research Design

A quantitative population-based retrospective cohort design using secondary data was selected as the ideal epidemiologic approach to test the association between a rare exposure to androgen toxicity and the risk of health outcomes, incidence of inpatient variables, and total healthcare costs, thereby answering the research questions. The overall intent of a cohort study is to assess and differentiate disease incidence among cohorts following the fundamental design principle of defining two or more groups (cohorts of inpatients) that vary, as specified by the magnitude of exposure, as the probable cause of disease (K. J. Rothman et al., 2010). Hence, two comparable cohorts for each year were constructed according to androgen toxicity exposure. Inpatient assignment to an index (exposure) cohort was based on diagnosed androgen toxicity exposure (IV; E932.1) using the procedures outlined by Woodward (2014) and K. J. Rothman et al. (2010). Each inpatient without a diagnosis for androgen toxicity also meeting the inclusion and exclusion criteria was assigned to the reference (non-exposure) cohort.

The retrospective cohort design allows the assessment of incidence rates attributed to each health outcome and the valid estimation of relative risk by drawing comparisons of exposure and non-exposure groups (K. J. Rothman et al., 2010). After all the main analyses for each pair of yearly cohorts, demographic variables were balanced using odds weighting, inverse probability or treatment weighting, and propensity score weighting to replicate the main analyses and estimate causal treatment effects, thus guarding against confirmation and selection bias. For the main analyses, a total of 12 cohorts, two cohorts for each year (one index and one reference

cohort), were included in this study. A separate analysis merged all yearly cohorts into a combined cohort to assess the year-to-year trends in all effect measures in research question four.

Study design justification and rationale. The retrospective cohort design was selected and justified based on exposure and outcome criteria noted by several leading epidemiologists (K. J. Rothman et al., 2010; Woodward, 2014). Some health outcomes assessed in this study may be considered rare (low incidence), in which a case-control methodology would have been the ideal approach. However, even with low mortality or morbidity rates in the NIS, it was reasonable to expect at least some deaths and comorbidity diagnoses in each year among patients with and without diagnosed androgen toxicity. Woodward (2014, p. 212) indicated that the case-control “can investigate only one disease outcome because sampling is carried out separately within study groups (case and control), which are defined according to the disease outcome. Other diseases would produce different study groups.” In this study, there were numerous health outcomes of interest. Here, the selection of research design rested upon using the best approach to assess a rare or uncommon exposure to androgen toxicity and not investigate a rare outcome associated with androgen toxicity. K. J. Rothman et al. (2010, p. 91) characterized this issue as the cohort’s ability to assess the effects of a solitary exposure on a wide assortment of possible health outcomes. Woodward (2014, p. 166) also indicated that cohort studies are only unsuitable for rare diseases when the incidence of the outcome is so low it would require an extraordinary sample size or unacceptably long observation period. In this study, the sample was larger than that of any conceivable or practical randomized control trial to investigate common diseases (as opposed to rare diseases) associated with a rare exposure to androgen toxicity. Several recent studies successfully implemented the retrospective cohort approach using secondary NIS data or

other secondary HCUP data to study a wide a range of inpatient health outcomes and inpatient variables (Buchanan et al., 2019; Hofler, Swong, Martin, Wemhoff, & Jones, 2018; Piyush et al., 2015; Quist-Nelson, Hua Parker, Berghella, & Biba Nijjar, 2017; Sharma, Ferries, Yucel, Johnson, & Aparasu, 2015; Stein, Matta, & Goldman, 2011).

The three primary advantages and, consequently, justifications for using the retrospective cohort design in this epidemiologic study included: 1) an ideal suitability for rare exposures, 2) the ability to concurrently assess many health outcomes related to a single exposure, and 3) the existence of temporality, i.e. an essential condition for causal inference (K. J. Rothman et al., 2010; Woodward, 2014). The disadvantages of using a cohort design were: 1) long-term observation periods, 2) exorbitant costs, and 3) unsuitability for rare diseases, diseases with long latency periods, and exposures that tend to vary over long periods (K. J. Rothman et al., 2010; Woodward, 2014). Given the merits and detriments of using the cohort methodology, there were no known theoretical or statistical reasons precluding the use of this approach to investigate the association of androgen toxicity and risk of health outcomes using secondary NIS data. The only practical drawbacks were the utilization of personal resources to purchase the data and investment of time to conduct the research.

The secondary NIS data used in this retrospective cohort study was considered ideal since diagnosed androgen toxicity (E932.1) was not previously studied in the NIS sampling frame or any other secondary data likely due to a lack of awareness about this external cause of injury code. Several other reasons may exist for the discrepancy, such as lack of interest or institutional funding. Since androgen toxicity, as defined in this study, represents an adverse effect resulting from therapeutic androgen use, there was no linkage to the actual androgen treatment leading to

the diagnosis of E932.1 other than toxicity as the result of androgen therapy. Another reason for a lack of previous androgen toxicity studies using NIS data may be the omission of information on prescribed androgens such as specific drug type and characteristics. Previous androgen studies utilizing secondary data included sampling frames with specific androgen treatment characteristics like androgen type, dose, duration, and mode of administration. The main differences between this retrospective cohort study and previous androgen studies involves the consideration of androgen therapies resulting in certain health outcomes not classified as androgen toxicity and the consideration of androgen toxicity as a defined clinical entity which directly influences health outcomes.

Study Population

The target population of this study was all inpatient admissions in the United States. The sample population was any inpatient hospitalization for any reason over the defined study period. A nationally representative inpatient sampling frame, aligning to the target and sample populations, was obtained from the HCUP and Agency for Healthcare Research and Quality consisting of NIS inpatient discharge data spanning six years (2010-2015) (HCUP NIS, 2012). The study sample included male and female inpatients of all ages, races, and socioeconomic status to include special inpatients such as transgender and other inpatients with special clinical characteristics.

Inclusion and exclusion criteria. Inpatients less than 18 years of age were excluded from the study. All de-identified inpatients 18 years or older were sampled by (1) identification of androgen toxicity exposure and assignment to either an index or reference cohort and (2) odds

weighting, inverse probability of treatment weighting, and propensity score weighting to balance demographic variables by exposure. Figure 9 details the sampling strategy used in the study.

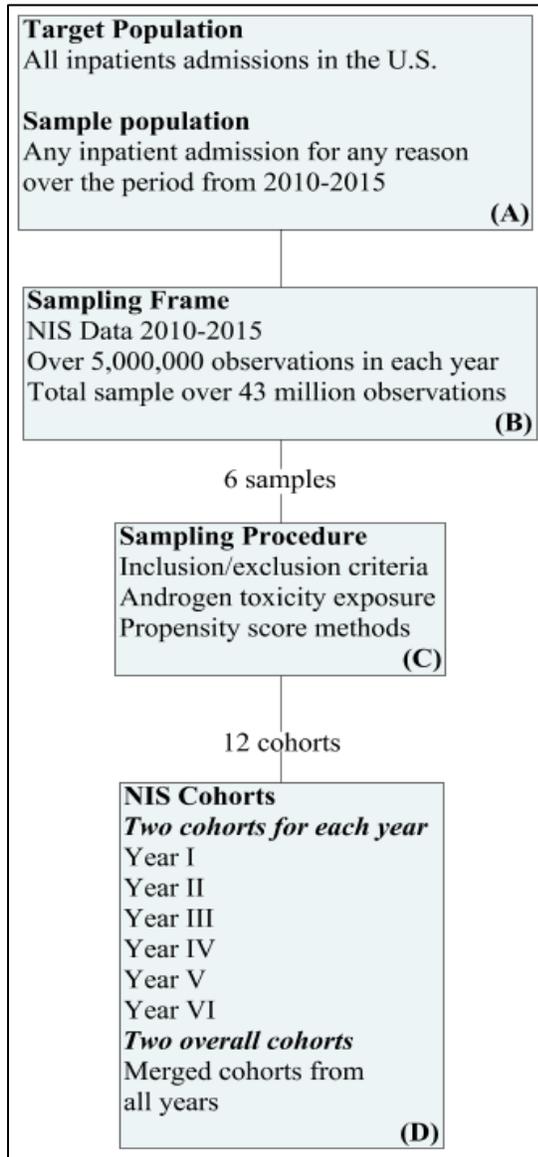


Figure 9. Sampling flowchart.

Sample Size and Power Analysis

The sample sizes of each year from 2010, 2011, 2012, 2013, 2014, and 2015 were 7,800,441, 8,023,590, 5,901,607, 7,119,563, 7,071,762, and 7,153,989, respectively. The total

sample combining all years was 43,070,952. Hence, power analyses for any of the proposed statistical analyses to compute the needed sample sizes was not warranted. However, PS Power software was used to assess the required sample size of a retrospective study of independent exposure subjects and non-exposure subjects, 10 non-exposure subjects per each exposure subject, using a relative risk estimate of (1.25) reported by Martinez et al. (2016) and an odds ratio estimate of (0.73) reported by Baillargeon et al. (2016) with the failure rate among non-exposure subjects estimated at 0.75 (Dupont & Plummer Jr., 1990). For the first estimate by Martinez et al. (2016), if the true relative risk of failure for exposure subjects relative to non-exposure subjects was 1.25, study 41 exposure subjects and 410 non-exposure subjects were needed to be able to reject the null hypothesis that this relative risk equaled one with probability (power) 0.8 and the type I error probability associated with this test of this null hypothesis set at 0.05. For the second estimate by Baillargeon et al. (2016), if the true relative risk of failure for exposure subjects relative to non-exposure subjects was 0.73, 49 exposure subjects and 490 non-exposure subjects were needed to be able to reject the null hypothesis that this relative risk equaled one with probability (power) 0.8 and the type I error probability associated with this test of this null hypothesis set at 0.05.

Data Collection Tools

The initial cleaning and coding of the NIS data to ICD-9-CM codes was performed using Stata statistical software recommended by HCUP (HCUP NIS, 2012; StataCorp, 2017). The Stata software was used to read the original NIS files into memory and then save them as data format files. Proprietary code-based algorithms were written and developed to identify ICD-9-CM diagnosis, external cause of injury, and medical procedure codes that were used as direct

NIS data element variables and to construct study-specific variables. The NIS data elements were coded into variables using the exact levels of measurement shown in the documentation. The NIS data element variables included all the demographic variables, inpatient variables, geographic variables, and most of the health outcome variables. A set of study-specific variables included indicator variables constructed by assigning ICD-9-CM codes to each disease state identified in the literature review of Chapter II. The cleaning and coding of the data and all proprietary written code was developed in accordance with the principle of reproducibility (Munafò et al., 2017).

Variables

The nominal independent variable (IV) was androgen toxicity exposure (yes or no) as defined by the ICD-9-CM external cause of injury code E932.1 (HCUP NIS, 2012). The E932.1 code was used to establish androgen toxicity exposure i.e. that a patient was under androgen treatment at the time of hospitalization and suffered an external cause of injury due to androgen toxicity from an applied treatment without information regarding properties such as androgen type, dose, duration, and mode of administration. The androgen toxicity exposure variable served as a dichotomous indicator to code the assignment of each patient to either index or reference cohorts (Table 17). The exposure variable was the basis for sampling, comparing, and analyzing the study cohorts.

Reported disease states, identified in the literature and matched to specific ICD-9 diagnosis codes (yes or no), were the first set of nominal dependent variables (Table 18). Additional nominal (DVs), coded as (yes or no), were mortality, non-elective admission, and major operating room procedures (Table 18). Ordinal (DVs) included mortality likelihood

(coded at five levels), disease severity (coded at five levels), and procedure class (coded at four levels) (Table 18). Ratio (discrete; DVs) comprised the number of chronic conditions, diagnoses, external causes of injury, length of stay, and procedures (Table 18). Demographic variables included the covariates of sex (nominal; male or female), race (nominal; coded at six levels), median income (ordinal; coded at four levels), hospitalization type (nominal; five levels), and age (interval) (Table 17). Geographic covariates (GCoVs) consisted of patient residence (nominal; six NCHS urban-rural codes), hospital division (nominal; nine census-defined levels), hospital region (nominal; four levels), and hospital location (nominal; urban or rural) (Table 17).

Table 17

Summary of the Independent Variable, Covariates, and Geographic Covariates

Variable	Type	LoM	Levels	Use	Values
Androgen toxicity	IV	Nominal	2	Exposure	[0, 1]
Age	CoV1	Interval	Discrete	Demographic	18-124 years
Sex	CoV2	Nominal	2	Demographic	[0, 1]
Race	CoV3	Nominal	6	Demographic	[0, 6]
Median income	CoV4	Ordinal	4	Demographic	[1, 4]
Hospitalization type	CoV5	Nominal	5	Demographic	[1, 5]
Patient residence	GCoV1	Nominal	2	Geographic	[1, 6]
Hospital location	GCoV2	Nominal	2	Geographic	[1, 2]
Hospital division	GCoV3	Nominal	9	Geographic	[1, 9]
Hospital region	GCoV4	Nominal	4	Geographic	[1, 4]

Table 18

Summary of Dependent Variables

Variable	Type	LoM	Levels	Use	Values
Reported diseases	DV1	Nominal	2	Outcome	[0, 1]
Mortality	DV2	Nominal	2	Outcome	[0, 1]
Non-elective admission	DV3	Nominal	2	Outcome	[1, 2]
Major OR procedure	DV4	Nominal	2	Outcome	[0, 1]
Procedure class	DV5	Ordinal	4	Outcome	[1, 4]
Mortality likelihood	DV6	Ordinal	5	Outcome	[0, 5]
Disease severity	DV7	Ordinal	5	Outcome	[0, 5]
Chronic conditions	DV8	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Diagnoses	DV9	Ratio	Discrete	Inpatient	0, 1, 2, ...n
External causes of injury	DV10	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Procedures	DV11	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Length of stay	DV12	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Healthcare costs	DV13	Ratio	Discrete	Cost	0, 1, 2, ...n

Statistical Analysis

Statistical analysis for each study aim and research question are presented in list format with key variables followed by the analysis and effect measure. Univariate descriptive analyses were not presented in tables but were included with appropriate measures of mean, variance,

frequency, and percentage tabulated by each level of the independent variable, covariates, health outcome variables, inpatient variables, and total healthcare costs.

Aim 1 [RQ 1]. Statistical analysis and effect measure.

1. Bivariate binomial regression, bivariate ordinal logistic regression.
2. Multivariate binomial regression, multivariate ordinal logistic regression.
3. Risk ratios, odds ratios.

Variables. [IV] Androgen toxicity exposure (nominal); [DVs] *health outcome variables* (nominal; ordinal); [CoVs] age (interval), race (nominal; six levels), sex (nominal), median income (ordinal; four levels), and hospitalization type (nominal; five levels).

Health outcome variables. Literature-reported disease states (nominal), mortality (nominal), mortality likelihood (ordinal; five levels), disease severity (ordinal; five levels), non-elective admission (nominal), major operating room procedure (nominal), and procedure class (ordinal; four levels).

Aim 1 [RQ 2]. Statistical analysis and effect measure.

1. Bivariate Poisson regression or negative binomial regression depending on dispersion of the data.
2. Multivariate Poisson regression or negative binomial regression depending on dispersion of the data.
3. Incidence rates and incidence rate ratios.

Variables. [IV] Androgen toxicity exposure (nominal); [DVs] *inpatient variables* (ratio; discrete); [CoVs] age (interval), race (nominal; six levels), sex (nominal), median income (ordinal; four levels), and hospitalization type (nominal; five levels).

Inpatient variables. Incidence of chronic conditions (ratio; discrete), diagnoses (ratio; discrete), external causes of injury (ratio; discrete), procedures (ratio; discrete), and length of stay (ratio; discrete).

Aim 2 [RQ 3]. Statistical analysis and effect measure.

1. Independent samples t-test; Multivariate mixed effects variance-components modeling with geographic covariates.
2. Mean, mean difference, predicted probabilities.

Variables. [IV] Androgen toxicity exposure (nominal); [DV] total healthcare costs (ratio); [GCoVs] *geographic covariates*; [CoVs] age (interval), race (nominal; six levels), sex (nominal), median income (ordinal; four levels), and hospitalization type (nominal; five levels).

Geographic covariates. Patient residence (nominal; six NCHS urban-rural codes), hospital location (nominal; urban or rural), hospital division (nominal; nine census-defined levels), and hospital region (nominal; four levels).

Aim 3 [RQ 4]. Statistical analysis and effect measure I.

1. Multivariate binomial regression, multivariate ordinal logistic regression.
2. Risk ratios, odds ratios.

Aim 3 [RQ 4]. Statistical analysis and effect measure II.

1. Multivariate Poisson regression or negative binomial regression depending on dispersion of the data.
2. Incidence rates and incidence rate ratios.

Aim 3 [RQ 4]. Statistical analysis and effect measure III.

1. Multivariate mixed effects variance-components modeling.

2. Mean, mean difference, predicted probabilities.

Variables. [IV] Androgen toxicity exposure (nominal); [DVs] health outcome variables (nominal; ordinal) and inpatient variables (ratio; discrete); [GCoVs] geographic covariates (nominal; 2-9 levels); [CoVs] age (interval), race (nominal; six levels), sex (nominal), median income (ordinal; four levels), and hospitalization type (nominal; five levels).

Aim 4 [RQ 5]. Statistical methods, analysis, and effect measure.

1. Stratification and inverse probability of treatment weighting.
2. Multivariate treatment effects modeling for binary, ordinal, and discrete outcomes.
3. Coefficients.

Variables. [IV] Androgen toxicity exposure (nominal); [DVs] *health outcome variables* (nominal; ordinal) and *inpatient variables* (ratio; discrete); [CoVs] age (interval), race (nominal; six levels), sex (nominal), median income (ordinal; four levels), and hospitalization type (nominal; five levels).

Table 19 details the bivariate analysis for research questions one, two, and three. Each dependent variable was regressed, one at a time, on the independent variable, androgen toxicity.

Table 19

Summary of Bivariate Analysis

RQ #	IV	DVs	Analysis
RQ 1	Androgen toxicity	Outcomes [DV1-DV4]	Binomial regression
		Outcomes [DV5-DV7]	Ordinal logistic regression
RQ 2	Androgen toxicity	Inpatient [DV8-DV12]	Poisson regression

RQ 3	Androgen toxicity	Healthcare costs [DV13]	Independent samples t-test
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Table 20 shows the multivariate analyses of all the research questions. Each dependent variable was regressed, one at a time, on the independent variable, androgen toxicity, and all demographic covariates or geographic covariates depending on the research question.

Table 20

Summary of Multivariate Analysis

RQ #	IV/CoVs/GCoVs	DVs	Analysis
RQ 1	Androgen toxicity [IV]	Outcomes [DV1-DV4]	Binomial regression
	Demographic [CoV1-CoV5]	Outcomes [DV5-DV7]	Ordinal logistic regression
RQ 2	Androgen toxicity [IV]	Inpatient [DV8-DV12]	Poisson regression
	Demographic [CoV1-CoV5]		
RQ 3	Androgen toxicity [IV]	Healthcare costs [DV13]	Mixed-effect VC modeling
	Demographic [CoV1-CoV5]		
	Geographic [GCoV1-GCoV4]		
RQ 4	Androgen toxicity [IV]	Outcomes [DV1-DV4]	RR trend analysis
	Demographic [CoV1-CoV5]	Outcomes [DV5-DV7]	OR trend analysis
		Inpatient [DV8-DV12]	IRR trend analysis
		Healthcare costs [DV13]	Mean trend analysis
RQ 5	Androgen toxicity [IV]	Outcomes [DV1-DV4]	Propensity score methods
	Demographic [CoV1-CoV5]	Outcomes [DV5-DV7]	Propensity score methods
		Inpatient [DV8-DV12]	Propensity score methods

Limitations

The primary goal of the research was to determine the relationship between androgen toxicity, risk of inpatient health outcomes, incidence of inpatient variables, and economic burden of disease in nationally representative cohorts of inpatients; however, there were several limitations to the achievement of this goal inherent with the use of a retrospective cohort design and secondary data in this epidemiologic investigation. First, assigning androgen toxicity exposure using the external cause of injury code E.932.1 only demonstrated a patient experienced androgen toxicity from some unknown androgen therapy, which may or may not be the reason for hospitalization. The assignment confirmed inpatients were treated with androgens and suffered a consequence of the therapy but did not provide any information on pharmacologic properties such as androgen type, dose, duration, or mode of administration. To mitigate this limitation, the primary diagnosis of each exposed inpatient was explored to offer clues to possible reasons why androgens were prescribed but could not confirm the disease that the androgen therapy was intended to treat.

A second limitation was possible data inaccuracies included in the NIS sampling frame relating to misclassification bias of health outcome variables. The creation of study variables that used diagnosis codes for specific disease states potentially introduced another level of information bias into the study if the original data was misclassified. A third limitation was the low incidence of androgen toxicity exposure in each NIS sample. According to the HCUP public analysis page for the NIS in 2012, there were only 65 patients exposed to androgen toxicity aged 19 to 88 years old out of 5,901,607 patients (HCUP NIS, 2012). A fourth limitation was the possibility that androgen-treated patients existed in the data without resultant androgen toxicity

(E932.1). Hence, information bias and residual confounding of this effect could not be ruled out. Another limitation was that the inclusive nature of the sampling frame and limited variables did not allow the adjustment of confounding factors occurring outside the data but did offer to remove potential researcher bias because the variables and levels of measurement were fixed *a priori*. Finally, the major limitation of the study was that the retrospective analysis only demonstrated a measure of association to quantify the relationship between exposure and disease among the index and reference cohorts (K. J. Rothman et al., 2010). In this study, causal inference methods were employed and offered insight into whether the measured associations were more or less likely to be genuine causal effects or mere coincidental relationships (Hernán & Robins, 2019).

Delimitations

The primary delimitation of the study was the singular focus on an inpatient population. The population was selected because of a lack of androgen-related information on inpatients during the entire duration of hospitalization instead of reliance on the indirect inpatient data on the occurrence of hospitalizations, rehospitalizations, and limited outcomes, as reported in previous studies (J. L. Anderson et al., 2016; Baillargeon et al., 2016; Cheetham et al., 2017; Martinez et al., 2016; Tse et al., 2017). Another delimitation was the assessment of yearly index and reference cohorts for health outcomes, inpatient variables, and healthcare cost analysis while also merging all cohorts for a combined analysis. Given the sample sizes for each cohort, the overall outcomes and analyses retained comparability and validity of inference to the target population for each cohort analysis. Comorbidity measures were excluded because of the sheer number of comorbidity measures included in the NIS data elements and the study focus on

primary health outcomes. The omission of comorbidities reduced a broader picture of each patient's health status, however, the assessment of diagnoses and chronic conditions served as a surrogate measure of comorbidity via incidence rate ratios.

Expected Findings and Anticipated Contribution

The research was expected to confirm whether literature-reported disease states and previously reported risk estimates correspond to hospitalized patients. Ascertaining this knowledge in a previously unstudied and nationally representative inpatient population over the entire length of stay was expected to provide accurate and valid estimates of the risk regarding primary health outcomes such as comorbidity and mortality. The use of secondary data along with replication analysis countered unintended but possible researcher bias, information bias, and confirmation bias. Given the previous equivocal results reported in other populations and partial inpatient populations, the study findings added to the field and knowledge base by clarifying health outcome risk, characterizing the economic burden of disease, and mapping disparities associated with androgen toxicity for the first time in an inpatient setting.

Expected Influences in Future Research and Clinical Practice

The study findings were expected to provide useful, practical, and meaningful information that would impact clinical practice in several ways. The salient value of the study was the discovery, development, and organization of informative data to lower the occurrence of preventable adverse events given the marked increases in androgen prescriptions. The findings may be used by clinicians to provide direction for the establishment of standardized patient screening protocols for blood disorders to be implemented before androgen therapies are administered in order to prevent adverse events and the development of comorbidity. The

findings may be used to improve clinical practice by providing a comprehensive and thorough understanding of androgen toxicity in an inpatient setting by the identification of high-risk groups to better inform current androgen prescription guidelines in hospitals. Policy regarding the utilization of androgen therapies may be influenced by the study findings through the demonstration of the relationship between the economic burden of disease and health outcomes associated with androgen toxicity. Clinicians may use the study data to better inform the decision of whether to retain current androgen therapies or opt to choose safer and more cost-effective therapies. As such, filling the current evidence gap was expected to reveal patterns, disparities, and annual trends associated with androgen toxicity exposure that may serve to guide the focus of future research.

Additional Information

The IRB requirements for this study included a HIPAA waiver request, the completion of an online training course to protect human research subjects, IRB application, approval of the study methodology, and documentation of research funding or financial support (Sato, 2018). Previous clinical trial training courses and certificates obtained through trial interventionist training at Wake Forest University were approved by the Trident University IRB. The study did not require informed consent, participant assent forms, recruitment documents, and study site approvals (Sato, 2018). Permission to access restricted NIS data was granted after completion of an HCUP training course requiring data use agreements detailing the guidelines for analyzing and reporting NIS information (HCUP NIS, 2012). The data use agreements detailed the confidentiality and privacy restrictions that must be taken with all users of NIS data. Given the restricted nature of the sampling frame, use of existing secondary data, and Institutional Review

Board expectations in this study, all inpatients 18 years or older were sampled and analyzed with no personal- or hospital-level identifiers that could reveal protected patient information in the reporting of findings, in compliance with HIPAA guidelines (Sato, 2018). Each IRB requirement was completed before the study was conducted.

Chapter IV: Data Analysis and Results

The purpose of this epidemiologic study was to determine the relationship between androgen toxicity exposure and the risk of inpatient health outcomes, incidence of inpatient variables, and economic burden of disease in nationally representative inpatient cohorts over a six-year period. Chapter IV presents the data analysis and results starting with data screening, followed by descriptive statistics. Bivariate analyses and multivariate analyses are presented and organized around each research question.

Data Screening

Agent character storage (ACS) files of the National Inpatient Sample provided by HCUP for the years 2010 to 2015 were imported into Stata to create four separate datasets in long data format corresponding to a core, diagnosis group, hospital, and severity dataset for each year. The four files for each year were merged to create a single analysis dataset for each cohort (1-6). Each of the cohort datasets was then merged into an overall cohort for the analysis. Due to inconsistencies in the NIS data from year-to-year and high numbers of missing values, the variables hospitalization type, hospital location, hospital division, hospital region, and procedure class were omitted. Each missing value was dropped in each dataset except those for the variables race, median income, and total healthcare costs. For the nominal variables race and median income, missing values were assigned to another level of the coding to increase the level of measurement by one category termed “missing.” Missing values for total healthcare costs were recoded to the average of the median estimate between the two levels (exposure and non-exposure) of the nominal dichotomous variable, androgen toxicity since dropping missing values for healthcare costs would also drop observations of the independent variable. The averaged

median was used instead of multiple imputation, given that any effect on the estimate would bias towards the null and not away from the null. The averaged median values were 21,965, 25,062, 31,850, and 28,334 corresponding to the years 2011, 2013, 2014, and 2015, respectively. In the 2015 cohort, only three quarters of the year were used since the HCUP switched from ICD-9 to ICD-10 codes. A flowchart of the data management used in this study is presented in Figure 10.

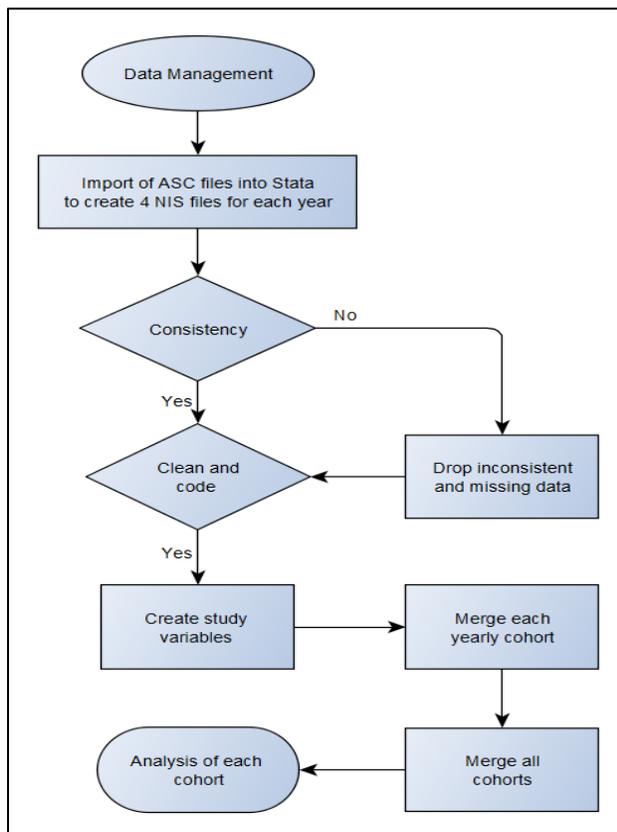


Figure 10. Data management.

After the initial cleaning and dropping of missing values, the NIS data element covariates and dependent variables included in the analysis were coded to the levels of measurement shown in the NIS documentation except for the addition of a “missing” category for the variables race, and median income. Five study-specific variables (one independent variable and four dependent

variables) were created by running a written Stata code algorithm to search for diagnosis and external cause of injury codes to generate nominal dichotomous indicator variables. The final 16 variables that were used in the analysis are presented in Table 21. The final sample characteristics are shown in Table 22.

Table 21

Analysis Variables after Data Cleaning and Coding

Variable	Type	LoM	Levels	Use	Values
Androgen toxicity	IV	Nominal	2	Exposure	[0, 1]
Age	CoV1	Interval	Discrete	Demographic	18-124 years
Sex	CoV2	Nominal	2	Demographic	[0, 1]
Race	CoV3	Nominal	7	Demographic	[0, 6]
Median income	CoV4	Ordinal	5	Demographic	[1, 4]
Mortality	DV1	Nominal	2	Outcome	[0, 1]
Polycythemia	DV2	Nominal	2	Outcome	[0, 1]
Hypercoagulable state	DV3	Nominal	2	Outcome	[0, 1]
Drug-induce liver injury	DV4	Nominal	2	Outcome	[0, 1]
Venous thromboembolism	DV5	Nominal	2	Outcome	[0, 1]
Chronic conditions	DV6	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Diagnoses	DV7	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Ecodes	DV8	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Procedures	DV9	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Length of stay	DV10	Ratio	Discrete	Inpatient	0, 1, 2, ...n
Healthcare costs	DV11	Ratio	Discrete	Cost	0, 1, 2, ...n

Table 22

Sample and Cohort Characteristics

Cohort	Year	Sample <i>N</i>	Androgen toxicity <i>n</i> (%)	
			No	Yes
Cohort I	2010	6,291,750	6,291,703 (99.9)	47 (< 0.01)
Cohort II	2011	6,568,366	6,568,282 (99.9)	84 (< 0.01)
Cohort III	2012	4,963,014	4,962,949 (99.9)	65 (< 0.01)
Cohort IV	2013	5,878,588	5,878,488 (99.9)	100 (< 0.01)
Cohort V	2014	5,835,146	5,835,034 (99.9)	112 (< 0.01)
Cohort VI	2015	4,459,492	4,459,412 (99.9)	80 (< 0.01)
Total	2010-2015	33,996,356	33,995,868 (99.9)	488 (< 0.01)

Descriptive Statistics

Table 23 shows the inpatient characteristics of the combined cohort broken into non-exposures for the reference cohort and exposures for the index cohort. The distribution of age was homogenous over the non-exposures with an average age slightly above 57 years old (Table 4.3). The age distribution of the non-exposures is shown in Figure 11. The proportion of sex, 59.05% female and 40.95% male, was also homogenous for the combined reference cohort and across the yearly reference cohorts (Table 23). Inpatient racial composition was heterogenous, 63.79% White, 14.26% Black, 9.34% Hispanic, 2.01% Asian and Pacific Islander, and 0.56% Native American (Table 23). The percentage of inpatients across each of the four categories median income categories were 29.73% (\$1-\$38,999), 25.34% (\$39,000-\$47,999), 23.24% (\$48,000-\$62,999), and 19.40% (\$63,000 or more) (Table 23).

Table 23

Inpatient Characteristics

Variable	Combined cohort		Total
	Non-exposures	Exposures	
Age in years <i>M (SD)</i>	57.16 (20.43)	56.33 (16.96)	57.16 (20.43)
Sex <i>n (%)</i>			
Male	13,922,786 (40.95)	404 (82.79)	13,923,190 (40.95)
Female	20,073,082 (59.05)	84 (17.21)	20,073,166 (59.05)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.00)
Race <i>n (%)</i>			
White	21,685,975 (63.79)	369 (75.61)	21,686,344 (63.79)
Black	4,846,224 (14.26)	36 (7.38)	4,846,260 (14.26)
Hispanic	3,174,574 (9.34)	37 (7.58)	3,174,611 (9.34)
Asian/Pacific Islander	682,568 (2.01)	3 (0.61)	682,571 (2.01)
Native American	190,642 (0.56)	2 (0.41)	190,644 (0.56)
Other	944,038 (2.78)	18 (3.69)	944,056 (2.78)
Missing	2,471,847 (7.27)	23 (4.71)	2,471,870 (7.27)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.00)
Median Income <i>n (%)</i>			
\$1 - \$38,999	10,107,583 (29.73)	108 (22.13)	10,107,691 (29.73)
\$39,000 - \$47,999	8,615,392 (25.34)	110 (22.54)	8,615,502 (25.34)
\$48,000 - \$62,999	7,901,203 (23.24)	126 (25.82)	7,901,329 (23.24)
\$63,000 or more	6,594,680 (19.40)	133 (27.25)	6,594,813 (19.40)
Missing	777,010 (2.29)	11 (2.25)	777,021 (2.29)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.00)

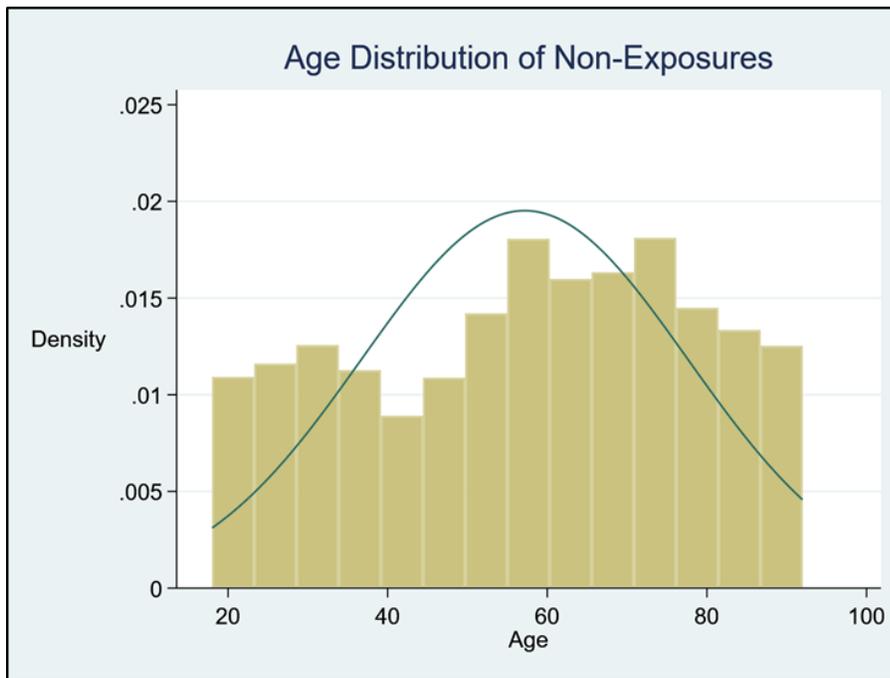


Figure 11. Age distribution of the non-exposure (reference cohort).

Inpatients with androgen toxicity exposure were 17.21% female and 82.79% male with a lower average age, 56.33 (16.96) years, than inpatients without exposure, 57.16 (20.43) (Table 23). The age distribution of exposed inpatients is shown in Figure 12. The racial composition of exposed inpatients was 75.61% White, 7.38% Black, 7.58% Hispanic, 0.61% Asian and Pacific Islander, and 0.41% Native American (Table 23). Median income levels of exposed inpatients were roughly comparable across each of the four classifications, 22.13% (\$1-\$38,999), 22.54% (\$39,000-\$47,999), 25.82% (\$48,000-\$62,999) and 27.25% (\$63,000 or more) (Table 23). An ideal type of inpatient with androgen toxicity exposure was a White male approximately 56 years old in the highest median income class.

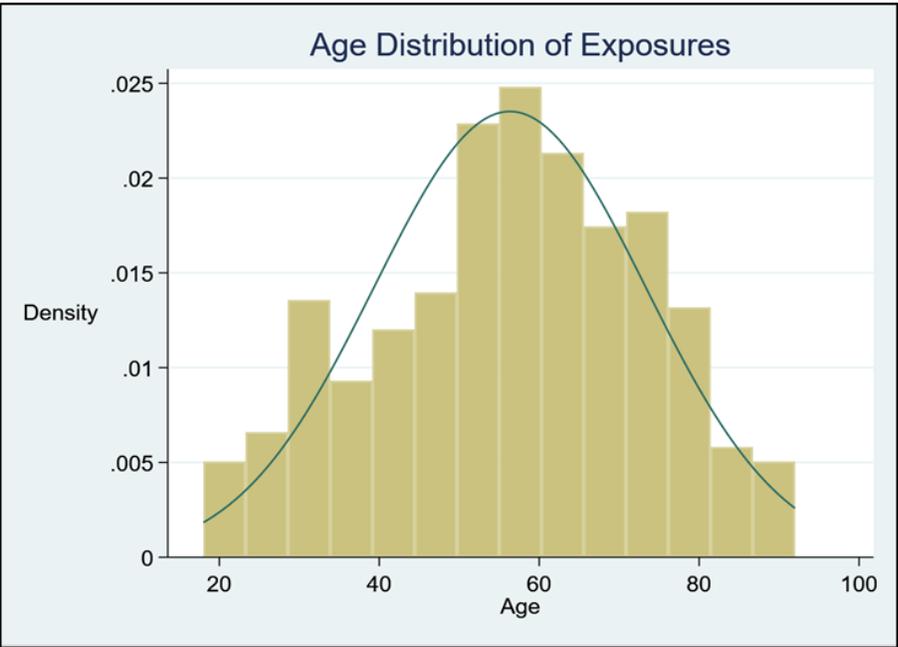


Figure 12. Age distribution among the 488 exposures (index cohort).

Characteristics of the health outcomes are presented in Tables 24. Nearly 1% of exposed inpatients died during hospitalization compared to 2.14% of the non-exposures. Less than 0.10% of non-exposures developed polycythemia compared to 12.5% of the exposures. Less than one half of one percent of non-exposures developed hypercoagulability compared to almost 2.5% of the exposures. Over 2.5% of exposures developed drug-induced liver injury compared to 0.05% of the non-exposures. Over 8% of exposures developed venous thromboembolism compared to 1.21% of non-exposures.

Table 24

Descriptive Statistics for Health Outcomes

Health outcome <i>n</i> (%)	Androgen toxicity		Total
	No	Yes	
Mortality			
No	33,266,368 (97.86)	483 (98.98)	33,266,851 (97.86)

Yes	726,671 (2.14)	5 (1.02)	726,676 (2.14)
Total	33,993,039 (100.00)	488 (100.00)	33,993,527 (100.00)
<hr/>			
Polycythemia			
No	33,975,173 (99.94)	427 (87.50)	33,975,600 (99.94)
Yes	20,695 (0.06)	61 (12.50)	20,756 (0.06)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.0)
<hr/>			
Hypercoagulability			
No	33,863,128 (99.61)	476 (97.54)	33,863,604 (99.61)
Yes	132,740 (0.39)	12 (2.46)	132,752 (0.39)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.0)
<hr/>			
Drug-induced liver injury			
No	33,978,646 (99.95)	475 (97.34)	33,979,121 (99.95)
Yes	17,222 (0.05)	13 (2.66)	17,235 (0.05)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.0)
<hr/>			
Venous thromboembolism			
No	33,585,749 (98.79)	448 (91.80)	33,586,197 (98.79)
Yes	410,119 (1.21)	40 (8.20)	410,159 (1.21)
Total	33,995,868 (100.00)	488 (100.00)	33,996,356 (100.0)

Characteristics of inpatient variables are shown in Table 25. On average, the length of stay for non-exposures was lower than exposures, 4.73 days, compared to 5.01 days in the exposures. The average number of chronic conditions for non-exposures was 4.9 compared to 5.87 for exposures. On average, the number of diagnoses for non-exposures, 10.09, was lower than exposures, 11.89. The average number of external causes of injury for non-exposures was 0.29 compared to 1.56 for exposures. On average, the number of procedures for non-exposures, 1.72, was higher than exposures, 1.56.

Table 25

Descriptive Statistics for Inpatient Variables

Inpatient Variable	Androgen toxicity		Total
	No	Yes	
<i>N</i>	34,000,000	488	34,000,488

Length of stay	<i>Min</i>	0	0	0
	<i>Max</i>	365	129	365
	<i>M (SD)</i>	4.73 (6.27)	5.01 (8.39)	4.73 (6.27)
Chronic conditions	<i>N</i>	34,000,000	488	34,000,488
	<i>Min</i>	0	0	0
	<i>Max</i>	31	16	31
	<i>M (SD)</i>	4.90 (3.46)	5.87 (3.31)	4.90 (3.46)
	<i>N</i>	34,000,000	488	34,000,488
	<i>Min</i>	0	1	0
Diagnoses	<i>Max</i>	74	28	74
	<i>M (SD)</i>	10.09 (5.90)	11.89 (5.66)	10.09 (5.90)
	<i>N</i>	34,000,000	488	34,000,488
Ecodes	<i>Min</i>	0	1	0
	<i>Max</i>	14	4	14
	<i>M (SD)</i>	0.29 (0.72)	1.56 (0.76)	0.29 (0.72)
Procedures	<i>N</i>	34,000,000	488	34,000,488
	<i>Min</i>	0	0	0
	<i>Max</i>	47	15	47
	<i>M (SD)</i>	1.72 (2.18)	1.56 (2.36)	1.72 (2.18)

Note. Ecodes = external causes of injury, *N* = count, *Min* = minimum, and *Max* = maximum, *M* = mean, *SD* = standard deviation.

Table 26 includes the means, standard deviations, medians, minimums, and maximums of healthcare costs by exposure level. The average healthcare costs for exposures was 48,327.53, an increase of 7,533.32 over the average for non-exposures. The median healthcare costs for exposures was 24,386.50, an increase of 1,107.50 over the median costs for non-exposures. The graph in Figure 13 shows the healthcare cost distribution in the non-exposures (overall sample). There was a gamma-2 density distribution with an extremely high peak and extended tail due to an outlier of 4,991,688.00, the maximum cost for one observation in the reference cohort. The graph in Figure 14 shows the healthcare cost distribution of exposures. Like the reference cohort

of non-exposures, there was a gamma-2 density distribution with a high peak and extended tail due to an outlier of 2,367,358.00, the maximum cost for one observation in the exposures.

Table 26

Descriptive Statistics for Total Healthcare Costs in Dollars

Androgen toxicity	<i>M (SD)</i>	<i>Median</i>	<i>Min</i>	<i>Max</i>
No	40,794.21 (66,048.55)	23,279.00	100.00	4,991,688.00
Yes	48,327.53 (124,802.70)	24,386.50	4,594.00	2,367,358.00
Total	40,794.32 (66,049.77)	23,279.00	100.00	4,991,688.00

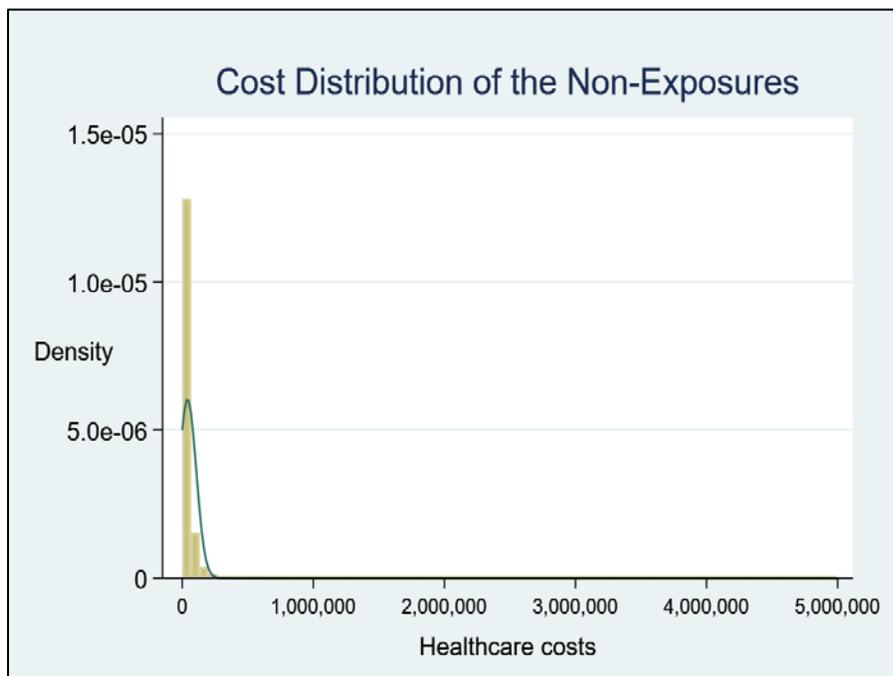


Figure 13. Healthcare cost distribution of non-exposures.

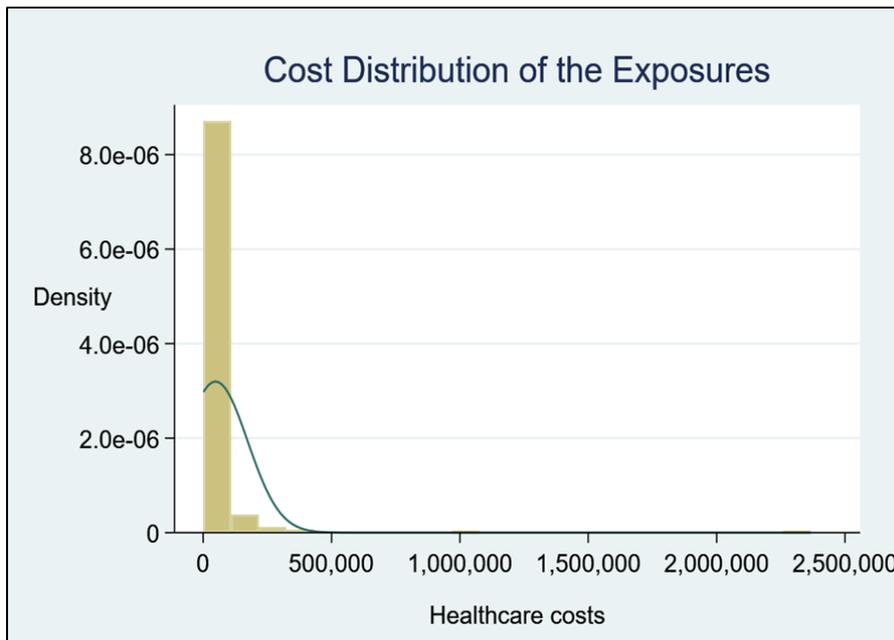


Figure 14. Healthcare cost distribution of exposures.

Bivariate Analysis

Aim 1 [RQ 1]. What is the relationship between androgen toxicity and risk of health outcomes?

H₀₁. There is no relationship between androgen toxicity and risk of health outcomes.

H_{a1}. There is a relationship between androgen toxicity and risk of health outcomes.

Noncanonical generalized linear log-linked binomial regression was conducted to examine the bivariate risk relationship between androgen toxicity and the risk of nominal dichotomous health outcomes. The study design assumptions for GLM binomial regression models (BRM) were (a) one dependent variable measured on the nominal dichotomous scale, (b) one or more independent variables measured on an interval, ratio, or nominal scale, (c) independence of observations, (d) mutual exclusiveness and full exhaustiveness of each category of the dependent variable and the nominal independent variable, and (e) no linear relationship

among the variables (Hardin & Hilbe, 2012). The data assumptions for GLM binomial regression include (a) no substantive outliers or influential observations among ratio or interval independent variables and (b) lack of data collinearity (Hardin & Hilbe, 2012). Prior to the analysis, the assumptions of no substantive outliers or influential observations and lack of collinearity were assessed.

Outliers and influential observations. The independent variable and each dependent variable were measured on a nominal dichotomous scale. Therefore, the outliers and influential observations assumption did not apply to the bivariate analysis and were not tested.

Collinearity. A collinearity diagnostic was conducted to determine the variance inflation factors among the independent variable and the dependent variables. The results of the collinearity diagnostics showed variance inflation factors of less than a value of four, suggesting that the collinearity assumption was met for each of the variables. The mean variance inflation factors among the study variables were 1.01, 1.01, 1.01, 1.01, 1.01, and 1.01 for cohorts one, two, three, four, five, and six, respectively. The mean variance inflation factor for the combined cohort was 1.01.

Mortality results. A binomial regression was conducted to examine the relationship between androgen toxicity and mortality in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.00, p = .981$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of death, $RR = 1.02, 95\% \text{ CI } [0.14, 7.10], z = 0.02, p = .982$ (Table 27).

A binomial regression was conducted to examine the relationship between androgen toxicity and mortality in cohort two. The log likelihood ratio chi-square test statistic for the one-

predictor model, $LR \chi^2(1) = 0.39, p = .530$, indicated that the model fit was not significant.

Androgen toxicity exposure did not have a significant effect on the risk of death, $RR = 0.56$, 95% CI [0.08, 3.99], $z = -0.57, p = .571$ (Table 27).

A binomial regression was conducted to examine the relationship between androgen toxicity and mortality in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.12, p = .729$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of death, $RR = 0.72$, 95% CI [0.10, 5.06], $z = -0.33, p = .744$ (Table 27).

A binomial regression was conducted to examine the relationship between androgen toxicity and mortality in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.81, p = .368$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of death, $RR = 0.45$, 95% CI [0.06, 3.23], $z = -0.78, p = .435$ (Table 27).

A binomial regression was conducted to examine the relationship between androgen toxicity and mortality in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 1.13, p = .287$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of death, $RR = 0.40$, 95% CI [0.05, 2.86], $z = -0.90, p = .367$ (Table 27).

A binomial regression was not conducted to examine the relationship between androgen toxicity and mortality in cohort six due to perfect prediction. No inpatients with androgen toxicity exposure died in cohort six for the 2015 year.

Table 27

Bivariate BRM of Mortality in Each Yearly Cohort

Mortality	RR	SE	z	p	95% CI
Androgen toxicity ^a	1.02	1.01	0.02	.982	[0.14, 7.10]
Constant ^a	0.02	< 0.01	-1415.87	< .001	[0.02, 0.02]
Androgen toxicity ^b	0.56	0.56	-0.57	.571	[0.08, 3.99]
Constant ^b	0.02	< 0.01	-1448.45	< .001	[0.02, 0.02]
Androgen toxicity ^c	0.72	0.71	-0.33	.744	[0.10, 5.06]
Constant ^c	0.02	< 0.01	-1664.40	< .001	[0.02, 0.02]
Androgen toxicity ^d	0.45	0.45	-0.78	.435	[0.06, 3.23]
Constant ^d	0.02	< 0.01	-1383.80	< .001	[0.02, 0.02]
Androgen toxicity ^e	0.40	0.40	-0.90	0.367	[0.05, 2.86]
Constant ^e	0.02	< 0.01	-1381.20	< .001	[0.02, 0.02]
Androgen toxicity ^f	*	*	*	*	*
Constant ^f	0.21	< 0.01	-1206.39	< .001	[0.02, 0.02]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, * = cannot be estimated (no observations).

Polycythemia results. A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 22.17, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 105.01, 95\% \text{ CI } [35.12, 313.97], z = 8.33, p < .001$, hence, the null hypothesis was rejected (Table 28).

A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 120.19, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 254.44$, 95% CI [154.21, 419.81], $z = 21.68, p < .001$, hence, the null hypothesis was rejected (Table 28).

A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 59.55, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 180.19$, 95% CI [89.42, 363.13], $z = 14.53, p < .001$, hence, the null hypothesis was rejected (Table 28).

A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 82.44, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 158.50$, 95% CI [87.96, 285.60], $z = 16.86, p < .001$, hence, the null hypothesis was rejected (Table 28).

A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 122.70, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 203.22$, 95% CI [124.36, 332.08], $z = 21.21, p < .001$, hence, the null hypothesis was rejected (Table 28).

A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in cohort six. The log likelihood ratio chi-square test statistic for the

one-predictor model, $LR \chi^2(1) = 134.21, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 298.88$, 95% CI [185.44, 481.73], $z = 23.41, p < .001$, hence, the null hypothesis was rejected (Table 28).

Table 28

Bivariate BRM of Polycythemia in Each Yearly Cohort

Polycythemia	RR	SE	z	p	95% CI
Androgen toxicity ^a	105.01	58.68	8.33	< .001	[35.12, 313.97]
Constant ^a	0.0006	9.83e-6	-458.14	< .001	[0.0005, 0.0006]
Androgen toxicity ^b	254.44	65.00	21.68	< .001	[154.21, 419.81]
Constant ^b	0.0006	9.62e-06	-468.18	< .001	[0.0005, 0.0006]
Androgen toxicity ^c	180.19	64.42	14.53	< .001	[89.42, 363.13]
Constant ^c	0.0005	0.00001	-404.36	< .001	[0.0005, 0.0006]
Androgen toxicity ^d	158.50	47.62	16.86	< .001	[87.96, 285.60]
Constant ^d	0.0006	0.00001	-448.88	< .001	[0.00061, 0.00065]
Androgen toxicity ^e	203.22	50.91	21.21	< .001	[124.36, 332.08]
Constant ^e	0.0006	0.00001	-443.08	< .001	[0.0005, 0.0006]
Androgen toxicity ^f	298.88	72.79	23.41	< .001	[185.44, 481.73]
Constant ^f	0.0005	0.00001	-380.44	< .001	[0.0005, 0.0006]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval.

Hypercoagulability results. A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 1.99, p = .1588$, indicated

that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of hypercoagulable states, $RR = 6.20$, 95% CI [0.89, 43.07], $z = 1.85$, $p = .065$ (Table 29).

A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 4.09$, $p = .043$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of hypercoagulable states, $RR = 6.41$, 95% CI [1.63, 25.24], $z = 2.66$, $p = .008$, hence, the null hypothesis was rejected (Table 29).

A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 9.65$, $p = .001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of hypercoagulable states, $RR = 12.27$, 95% CI [4.06, 37.07], $z = 4.45$, $p < .001$, hence, the null hypothesis was rejected (Table 29).

A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 7.05$, $p = .007$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of hypercoagulable states, $RR = 7.63$, 95% CI [2.50, 23.25], $z = 3.58$, $p < .001$, hence, the null hypothesis was rejected (Table 29).

A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 2.79, p = .095$, indicated that the model fit was not significant. Androgen toxicity exposure had a significant effect on the risk of hypercoagulable states, $RR = 4.30, 95\% \text{ CI } [1.08, 16.98], z = 2.08, p = .037$, hence, the null hypothesis was rejected (Table 29).

A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.73, p = .3945$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of hypercoagulable states, $RR = 2.68, 95\% \text{ CI } [0.38, 18.82], z = 0.99, p = .320$ (Table 29).

Table 29

Bivariate BRM of Hypercoagulability in Each Yearly Cohort

Hypercoagulability	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	6.20	6.13	1.85	.065	[0.89, 43.07]
Constant ^a	0.003	< 0.001	-835.47	< .001	[0.003, 0.003]
Androgen toxicity ^b	6.41	4.48	2.66	.008	[1.63, 25.24]
Constant ^b	0.003	< 0.001	-875.24	< .001	[0.003, 0.003]
Androgen toxicity ^c	12.27	6.92	4.45	< .001	[4.06, 37.07]
Constant ^c	0.003	< 0.001	-764.14	< .001	[0.003, 0.003]
Androgen toxicity ^d	7.63	4.33	3.58	< .001	[2.50, 23.25]
Constant ^d	0.003	< 0.001	-843.75	< .001	[0.003, 0.003]

Androgen toxicity ^e	4.30	3.01	2.08	.037	[1.08, 16.98]
Constant ^e	0.004	< 0.001	-855.43	< .001	[0.004, 0.004]
Androgen toxicity ^f	2.68	2.66	0.99	.320	[0.38, 18.82]
Constant ^f	0.004	< 0.001	-775.51	< .001	[0.004, 0.004]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval.

Drug-induced liver injury results. A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 13.25, p = .0003$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver injury, $RR = 72.11, 95\% \text{ CI } [18.57, 279.90], z = 6.18, p < .001$, hence, the null hypothesis was rejected (Table 30).

A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 19.47, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver injury, $RR = 67.54, 95\% \text{ CI } [22.22, 205.30], z = 7.43, p < .001$, hence, the null hypothesis was rejected (Table 30).

A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 4.97, p = .025$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver injury, $RR =$

31.43, 95% CI [4.49, 219.88], $z = 3.47$, $p = .001$, hence, the null hypothesis was rejected (Table 30).

A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 18.80$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver injury, $RR = 60.45$, 95% CI [19.82, 184.38], $z = 7.21$, $p < .001$, hence, the null hypothesis was rejected (Table 30).

A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 10.76$, $p = .001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver injury, $RR = 38.67$, 95% CI [9.78, 152.77], $z = 5.21$, $p < .001$, hence, the null hypothesis was rejected (Table 30).

A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 12.21$, $p = .0005$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver injury, $RR = 55.91$, 95% CI [14.22, 219.84], $z = 5.76$, $p < .001$, hence, the null hypothesis was rejected (Table 30).

Table 30

Bivariate BRM of Drug-Induced Liver Injury in Each Yearly Cohort

DILI	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	72.11	49.89	6.18	< .001	[18.57, 279.90]
Constant ^a	0.001	< 0.001	-453.23	< .001	[0.0005, 0.0006]
Androgen toxicity ^b	67.54	7.43	7.43	< .001	[22.22, 205.30]
Constant ^b	0.0005	8.97e-06	-444.76	< .001	[0.00051, 0.00054]
Androgen toxicity ^c	31.43	31.19	3.47	.001	[4.49, 219.88]
Constant ^c	0.001	< 0.001	-375.75	< .001	[0.0004, 0.0005]
Androgen toxicity ^d	60.45	34.39	7.21	< .001	[19.82, 184.38]
Constant ^d	0.001	< 0.001	-411.03	< .001	[0.0004, 0.0005]
Androgen toxicity ^e	38.67	27.10	5.21	< .001	[9.78, 152.77]
Constant ^e	0.001	< 0.001	-398.80	< .001	[0.0004, 0.0004]
Androgen toxicity ^f	55.91	39.05	5.76	< .001	[14.22, 219.84]
Constant ^f	0.001	< 0.001	-344.48	< .001	[0.0004, 0.0004]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval.

Venous thromboembolism results. A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 2.08, p = .1492$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of venous thromboembolism, $RR = 3.35, 95\% CI [0.86, 13.03], z = 1.75, p = .080$ (Table 31).

A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in cohort two. The log likelihood ratio chi-square test

statistic for the one-predictor model, $LR \chi^2(1) = 11.30, p = .0008$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of venous thromboembolism, $RR = 5.70, 95\% \text{ CI } [2.63, 12.32], z = 4.43, p < .001$, hence, the null hypothesis was rejected (Table 31).

A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.04, p = .8399$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of venous thromboembolism, $RR = 1.23, 95\% \text{ CI } [0.17, 8.60], z = 0.21, p = .834$ (Table 31).

A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 21.73, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of venous thromboembolism, $RR = 7.70, 95\% \text{ CI } [4.13, 14.37], z = 6.42, p < .001$, hence, the null hypothesis was rejected (Table 31).

A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 38.11, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of venous thromboembolism, $RR = 10.15, 95\% \text{ CI } [6.09, 16.92], z = 8.89, p < .001$, hence, the null hypothesis was rejected (Table 31).

A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 25.91, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of venous thromboembolism, $RR = 9.88, 95\% \text{ CI } [5.34, 18.29], z = 7.29, p < .001$, hence, the null hypothesis was rejected (Table 31).

Table 31

Bivariate BRM of Venous Thromboembolism in Each Yearly Cohort

VTE	RR	SE	z	p	95% CI
Androgen toxicity ^a	3.35	2.32	1.75	.080	[0.86, 13.03]
Constant ^a	0.01	< 0.001	-1241.21	< .001	[0.01, 0.01]
Androgen toxicity ^b	5.70	2.24	4.43	< .001	[2.63, 12.32]
Constant ^b	0.01	< 0.001	-1264.29	< .001	[0.01, 0.01]
Androgen toxicity ^c	1.23	1.22	0.21	.834	[0.17, 8.60]
Constant ^c	0.01	< 0.001	-1098.34	< .001	[0.01, 0.01]
Androgen toxicity ^d	7.70	2.45	6.42	< .001	[4.13, 14.37]
Constant ^d	0.01	< 0.001	-1172.81	< .001	[0.01, 0.01]
Androgen toxicity ^e	10.15	2.64	8.89	< .001	[6.09, 16.92]
Constant ^e	0.01	< 0.001	-1161.45	< .001	[0.01, 0.01]
Androgen toxicity ^f	9.88	3.10	7.29	< .001	[5.34, 18.29]
Constant ^f	0.01	< 0.001	-1014.15	< .001	[0.01, 0.01]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval.

Combined cohort analysis. A binomial regression was conducted to examine the relationship between androgen toxicity and mortality in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 3.57, p = .0588$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the risk of death, $RR = 0.47, 95\% \text{ CI } [0.20, 1.14], z = -1.65, p = .098$ (Table 32).

A binomial regression was conducted to examine the relationship between androgen toxicity and polycythemia in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 535.91, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of polycythemia, $RR = 205.34, 95\% \text{ CI } [162.32, 259.77], z = 44.39, p < .001$, hence, the null hypothesis was rejected (Table 32).

A binomial regression was conducted to examine the relationship between androgen toxicity and hypercoagulability in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 24.19, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of hypercoagulable states, $RR = 6.29, 95\% \text{ CI } [3.60, 11.01], z = 6.45, p < .001$, hence, the null hypothesis was rejected (Table 32).

A binomial regression was conducted to examine the relationship between androgen toxicity and drug-induced liver injury in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 77.84, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of liver

injury, $RR = 52.58$, 95% CI [30.75, 89.92], $z = 14.48$, $p < .001$, hence, the null hypothesis was rejected (Table 32).

A binomial regression was conducted to examine the relationship between androgen toxicity and venous thromboembolism in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 87.53$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the risk of venous thromboembolism, $RR = 6.79$, 95% CI [5.04, 9.14], $z = 12.65$, $p < .001$, hence, the null hypothesis was rejected (Table 32).

The combined cohort analysis of health outcomes is shown in Table 32. Health outcome point estimates for the bivariate analysis of the combined cohort are presented in Figure 15.

Table 32

Bivariate BRM of Health Outcomes in the Combined Cohort

Variable	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Mortality					
Androgen toxicity	0.47	0.213	-1.65	.098	[0.20, 1.14]
Constant	0.02	2.48e-05	-3313.65	< .001	[0.023, 0.024]
Polycythemia					
Androgen toxicity	205.34	24.634	44.39	< .001	[162.32, 259.77]
Constant	0.0006	4.23e-06	-1065.46	< .001	[0.00060, 0.00061]
Hypercoagulability					
Androgen toxicity	6.29	1.795	6.45	< .001	[3.60, 11.01]
Constant	0.003	1.07e-05	-2024.41	< .001	[0.0038, 0.0039]

DILI

Androgen toxicity	52.58	14.394	14.48	< .001	[30.75, 89.92]
Constant	0.0005	3.86e-06	-996.02	< .001	[0.0004, 0.0005]

VTE

Androgen toxicity	6.79	1.029	12.65	< .001	[5.04, 9.14]
Constant	0.01	1.87e-05	-2846.24	< .001	[0.0120, 0.0121]

Note. RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, DILI = drug-induced liver injury, VTE = venous thromboembolism.

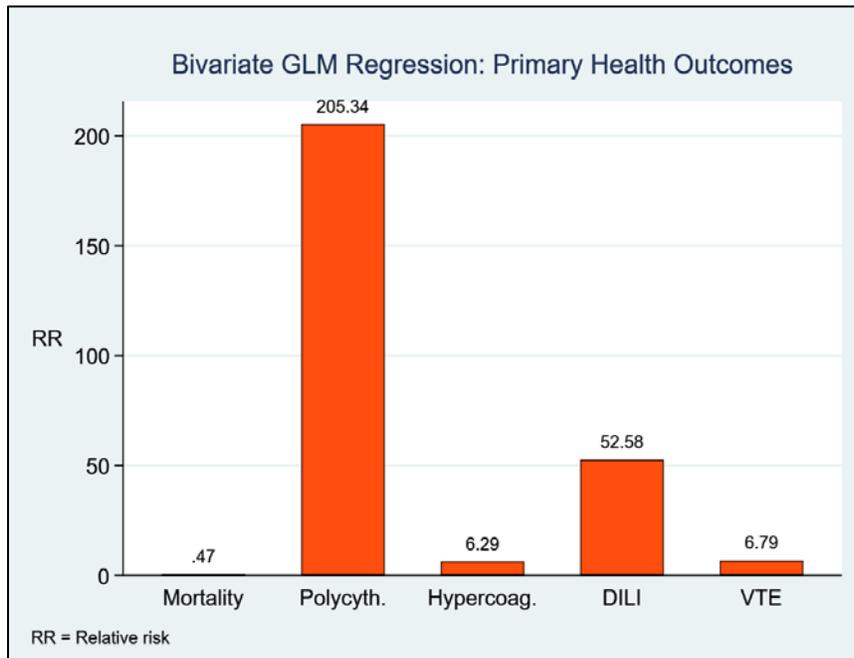


Figure 15. Health outcome point estimates of the combined cohort.

Aim 1 [RQ 2]. What is the relationship between androgen toxicity and incidence of inpatient variables?

H02. There is no relationship between androgen toxicity and incidence of inpatient variables.

H_{a2}. There is a relationship between androgen toxicity and incidence of inpatient variables.

Generalized linear negative binomial regression (NBRM) was conducted to examine the bivariate incidence relationship between androgen toxicity and inpatient variables while providing better data fit in conditions of data overdispersion. The study design assumptions of the NBRM were (a) ratio discrete count values for dependent variables and (b) independent variables measured on ratio, interval, ordinal, or nominal scales (Hardin & Hilbe, 2012; Long & Freese, 2014). The data assumptions of the NBRM were (a) dependent variable values that follow a Poisson distribution, (b) lack of collinearity, and (c) overdispersion of data values (Hardin & Hilbe, 2012). Prior to the analysis, the assumptions of a Poisson distribution and a lack of collinearity were assessed. The overdispersion assumption was tested and reported with each analysis.

Poisson distribution. Long format tabulation with detailed summary statistics was conducted to determine the data distribution of each ratio discrete inpatient variable. The results of visual inspection of the tabulation showed characteristic Poisson distributions for each inpatient variable for each yearly cohort. The results of the detailed summary of means and standard deviations of the combined cohort were 4.73 (6.27), 4.90 (3.46), 10.09 (5.90), 0.29 (0.72), and 1.72 (2.18) for the variables length of stay, chronic conditions, diagnoses, ecodes, and procedures, respectively. The summary results showed substantially higher variance than the mean for each inpatient variable, suggesting considerable overdispersion of the data.

Collinearity. A collinearity diagnostic was conducted to determine the variance inflation factors among the independent variable and the dependent variables. The results of the

collinearity diagnostics showed variance inflation factors of less than a value of four, suggesting that the collinearity assumption was met for each of the variables. The mean variance inflation factors among the study variables were 1.87, 1.92, 1.92, 1.93, 1.95, and 1.97 for cohorts one, two, three, four, five, and six, respectively. The mean variance inflation factor for the combined cohort was 1.65.

Length of stay results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.4e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.00$, $p = .9806$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of length of stay, $IRR = 0.99$, 95% CI [0.77, 1.28], $z = -0.02$, $p = .981$ (Table 33).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.4e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 1.62$, $p = .2032$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of length of stay, $IRR = 0.88$, 95% CI [0.72, 1.06], $z = -1.28$, $p = .199$ (Table 33).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 9.0e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay

in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 1.16, p = .2816$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of length of stay, $IRR = 0.88, 95\% \text{ CI } [0.71, 1.09], z = -1.08, p = .278$ (Table 33).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.1e+07, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 4.47, p = .0344$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of length of stay, $IRR = 1.19, 95\% \text{ CI } [1.01, 1.40], z = 2.09, p = .037$, hence, the null hypothesis was rejected (Table 33).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.1e+07, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 16.32, p = .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of length of stay, $IRR = 1.36, 95\% \text{ CI } [1.16, 1.58], z = 3.93, p < .001$, hence, the null hypothesis was rejected (Table 33).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 8.8e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2$

(1) = 3.59, $p = .0582$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of length of stay, $IRR = 0.82$, 95% CI [0.67, 1.00], $z = -1.92$, $p = .055$ (Table 33).

Table 33

Bivariate NBRM of Length of Stay in Each Yearly Cohort

Length of stay	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	0.99	0.129	-0.01	.981	[0.77, 1.28]
Constant ^a	4.78	0.001	4407.76	< .001	[4.77, 4.78]
Androgen toxicity ^b	0.88	0.086	-1.28	.199	[0.72, 1.06]
Constant ^b	4.74	0.001	4509.53	< .001	[4.73, 4.74]
Androgen toxicity ^c	0.88	0.096	-1.08	.278	[0.71, 1.09]
Constant ^c	4.69	0.001	4005.78	< .001	[4.68, 4.69]
Androgen toxicity ^d	1.19	0.100	2.09	.037	[1.01, 1.40]
Constant ^d	4.68	0.001	4321.37	< .001	[4.682, 4.688]
Androgen toxicity ^e	1.36	0.107	3.93	< .001	[1.16, 1.58]
Constant ^e	4.75	0.001	4347.78	< .001	[4.74, 4.75]
Androgen toxicity ^f	0.82	0.082	-1.92	.055	[0.67, 1.00]
Constant ^f	4.76	0.001	3810.08	< .001	[4.761, 4.769]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Constant = baseline incidence rate.

Chronic condition results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between

androgen toxicity and chronic conditions in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 8.22, p = .0041$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of chronic conditions, $IRR = 1.35, 95\% \text{ CI } [1.09, 1.67], z = 2.81, p = .005$, hence, the null hypothesis was rejected (Table 34).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.8e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and chronic conditions in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 8.41, p = .0037$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of chronic conditions, $IRR = 1.26, 95\% \text{ CI } [1.07, 1.48], z = 2.86, p = .004$, hence, the null hypothesis was rejected (Table 34).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.8e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and chronic conditions in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.24, p = .6229$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of chronic conditions, $IRR = 1.04, 95\% \text{ CI } [0.87, 1.25], z = 0.49, p = .624$ (Table 34).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.7e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and chronic

conditions in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 9.32, p = .0023$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of chronic conditions, $IRR = 1.25$, 95% CI [1.08, 1.44], $z = 3.01, p = .003$, hence, the null hypothesis was rejected (Table 34).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 4.0e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and chronic conditions in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 5.55, p = .0185$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of chronic conditions, $IRR = 1.17$, 95% CI [1.02, 1.35], $z = 2.33, p = .020$, hence, the null hypothesis was rejected (Table 34).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.1e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and chronic conditions in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.24, p = .622$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of chronic conditions, $IRR = 1.04$, 95% CI [0.88, 1.23], $z = 0.49, p = .623$ (Table 34).

Table 34

Bivariate NBRM of Chronic Conditions in Each Yearly Cohort

Chronic conditions	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	1.35	.146	2.81	.005	[1.09, 1.67]

Constant ^a	4.42	0.001	4789.55	< .001	[4.42, 4.43]
Androgen toxicity ^b	1.26	0.102	2.86	.004	[1.07, 1.48]
Constant ^b	4.73	0.001	5141.42	< .001	[4.732, 4.738]
Androgen toxicity ^c	1.04	0.097	0.49	.624	[0.87, 1.25]
Constant ^c	4.92	0.001	4694.60	< .001	[4.920, 4.927]
Androgen toxicity ^d	1.25	0.093	3.01	.003	[1.08, 1.44]
Constant ^d	4.99	0.001	5057.54	< .001	[4.992, 4.999]
Androgen toxicity ^e	1.17	0.083	2.33	.020	[1.02, 1.35]
Constant ^e	5.15	0.001	5145.27	< .001	[5.151, 5.157]
Androgen toxicity ^f	1.04	0.088	0.49	.623	[0.88, 1.23]
Constant ^f	5.32	0.001	4632.87	< .001	[5.31, 5.32]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval, Constant = baseline incidence rate.

Diagnosis results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 5.5e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 7.50$, $p = .0062$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of diagnoses, $IRR = 1.24$, 95% *CI* [1.06, 1.46], $z = 2.70$, $p = .007$, hence, the null hypothesis was rejected (Table 35).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 7.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in

cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 7.41, p = .0065$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of diagnoses, $IRR = 1.18, 95\% \text{ CI } [1.04, 1.34], z = 2.69, p = .007$, hence, the null hypothesis was rejected (Table 35).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 5.4e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.23, p = .6303$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of diagnoses, $IRR = 1.03, 95\% \text{ CI } [0.89, 1.19], z = 0.48, p = .631$ (Table 35).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.7e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 13.47, p = .0002$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of diagnoses, $IRR = 1.22, 95\% \text{ CI } [1.09, 1.37], z = 3.61, p < .001$, hence, the null hypothesis was rejected (Table 35).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 7.7e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2$

(1) = 10.57, $p = .0012$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of diagnoses, $IRR = 1.19$, 95% CI [1.06, 1.32], $z = 3.20$, $p = .001$, hence, the null hypothesis was rejected (Table 35).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.28$, $p = .5938$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of diagnoses, $IRR = 1.03$, 95% CI [0.91, 1.17], $z = 0.53$, $p = .595$ (Table 35).

Table 35

Bivariate NBRM of Diagnoses in Each Yearly Cohort

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	1.24	0.102	2.70	.007	[1.06, 1.46]
Constant ^a	8.91	0.002	9432.15	< .001	[8.91, 8.92]
Androgen toxicity ^b	1.18	0.074	2.69	.007	[1.04, 1.34]
Constant ^b	9.62	0.002	9774.97	< .001	[9.61, 9.62]
Androgen toxicity ^c	1.03	0.074	0.48	.631	[0.89, 1.19]
Constant ^c	9.98	0.002	8798.81	< .001	[9.98, 9.99]
Androgen toxicity ^d	1.22	0.069	3.61	< .001	[1.09, 1.37]
Constant ^d	10.32	0.002	9703.62	< .001	[10.31, 13.32]
Androgen toxicity ^e	1.19	0.064	3.20	.001	[1.06, 1.32]

Constant ^e	10.86	0.002	9795.39	< .001	[10.86, 10.87]
Androgen toxicity ^f	1.03	0.067	0.53	.595	[0.91, 1.17]
Constant ^f	11.28	0.003	8714.79	< .001	[11.28, 11.29]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Constant = baseline incidence rate.

External cause of injury results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.0e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and external causes of injury in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 46.31$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure has a significant effect on the incidence of external causes of injury, $IRR = 5.65$, 95% CI [3.11, 10.25], $z = 5.70$, $p < .001$, hence, the null hypothesis was rejected (Table 36).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.1e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and external causes of injury in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 77.33$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure has a significant effect on the incidence of external causes of injury, $IRR = 5.39$, 95% CI [3.44, 8.43], $z = 7.38$, $p < .001$, hence, the null hypothesis was rejected (Table 36).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.9e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis.

NBRM was conducted to examine the relationship between androgen toxicity and external causes of injury in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 68.02, p < .0001$, indicated that the model fit was significant.

Androgen toxicity exposure had a significant effect on the incidence of external causes of injury, $IRR = 5.75, 95\% \text{ CI } [3.51, 9.43], z = 6.96, p < .001$, hence, the null hypothesis was rejected (Table 36).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 9.2e+05, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis.

NBRM was conducted to examine the relationship between androgen toxicity and external causes of injury in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 88.81, p < .0001$, indicated that the model fit was significant.

Androgen toxicity exposure had a significant effect on the incidence of external causes of injury, $IRR = 5.21, 95\% \text{ CI } [3.47, 7.81], z = 8.00, p < .001$, hence, the null hypothesis was rejected (Table 36).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 9.1e+05, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis.

NBRM was conducted to examine the relationship between androgen toxicity and external causes of injury in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 97.75, p < .0001$, indicated that the model fit was significant.

Androgen toxicity exposure had a significant effect on the incidence of external causes of injury, $IRR = 5.05, 95\% \text{ CI } [3.46, 7.35], z = 8.45, p < .001$, hence, the null hypothesis was rejected (Table 36).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.9e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and external causes of injury in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 68.53$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of external causes of injury, $IRR = 4.93$, 95% CI [3.17, 7.65], $z = 7.11$, $p < .001$, hence, the null hypothesis was rejected (Table 36).

Table 36

Bivariate NBRM of External Causes of Injury in Each Yearly Cohort

Ecodes	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	5.65	1.718	5.70	< .001	[3.11, 10.25]
Constant ^a	0.28	< 0.001	-1178.42	< .001	[0.281, 0.282]
Androgen toxicity ^b	5.39	1.23	7.38	< .001	[3.44, 8.43]
Constant ^b	0.29	< 0.001	-1163.69	< .001	[0.297, 0.298]
Androgen toxicity ^c	5.75	1.44	6.96	< .001	[3.51, 9.43]
Constant ^c	0.27	< 0.001	-1077.60	< .001	[0.274, 0.275]
Androgen toxicity ^d	5.21	1.07	8.00	< .001	[3.47, 7.81]
Constant ^d	0.29	< 0.001	-1117.92	< .001	[0.294, 0.295]
Androgen toxicity ^e	5.05	0.96	8.45	< .001	[3.46, 7.35]
Constant ^e	0.30	< 0.001	-1102.27	< .001	[0.305, 0.306]
Androgen toxicity ^f	4.93	1.10	7.11	< .001	[3.17, 7.65]

Constant ^f	0.30	< 0.001	-964.68	< .001	[0.308, 0.309]
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Note. a-f = cohort 1 (2010) – cohort 6 (2015), *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Constant = baseline incidence rate.

Procedure results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.5e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.01$, $p = .9328$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of medical procedures, $IRR = 0.98$, 95% CI [0.69, 1.39], $z = -0.08$, $p = .933$ (Table 37).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.7e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 1.34$, $p = .2476$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of medical procedures, $IRR = 0.85$, 95% CI [0.64, 1.11], $z = -1.16$, $p = .245$ (Table 37).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.8e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 6.51$, $p = .0107$, indicated that the model fit was significant. Androgen toxicity exposure

had a significant effect on the incidence of medical procedures, $IRR = 0.64$, 95% CI [0.46, 0.90], $z = -2.57$, $p = .010$, hence, the null hypothesis was rejected (Table 37).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.01$, $p = .9226$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of medical procedures, $IRR = 0.98$, 95% CI [0.77, 1.25], $z = -0.10$, $p = .923$ (Table 37).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.3e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.25$, $p = .6166$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of medical procedures, $IRR = 0.94$, 95% CI [0.74, 1.18], $z = -0.50$, $p = .616$ (Table 37).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.6e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.00$, $p = .9979$, indicated that the model fit was not significant. Androgen toxicity exposure

did not have a significant effect on the incidence of medical procedures, $IRR = 0.99$, 95% CI [0.75, 1.31], $z = -0.00$, $p = .998$ (Table 37).

Table 37

Bivariate NBRM of Procedures in Each Yearly Cohort

Procedures	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a	0.98	0.176	-0.08	.933	[0.69, 1.39]
Constant ^a	1.74	< 0.001	1147.32	< .001	[1.74, 1.75]
Androgen toxicity ^b	0.85	0.118	-1.16	.245	[0.64, 1.11]
Constant ^b	1.73	< 0.001	1145.76	< .001	[1.732, 1.736]
Androgen toxicity ^c	0.64	0.110	-2.57	.010	[0.46, 0.90]
Constant ^c	1.69	< 0.001	935.83	< .001	[1.693, 1.697]
Androgen toxicity ^d	0.98	0.122	-0.10	.923	[0.77, 1.25]
Constant ^d	1.73	< 0.001	1079.30	< .001	[1.72, 1.73]
Androgen toxicity ^e	0.94	0.111	-0.50	.616	[0.74, 1.18]
Constant ^e	1.73	< 0.001	1073.60	< .001	[1.732, 1.735]
Androgen toxicity ^f	0.99	0.140	-0.00	.998	[0.75, 1.31]
Constant ^f	1.70	0.001	892.97	< .001	[1.69, 1.70]

Note. a-f = cohort 1 (2010) – cohort 6 (2015), *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Constant = baseline incidence rate.

Combined cohort analysis. In the combined cohort, overdispersion test results showed significant evidence of dispersion, $G^2 = 6.5e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and length of stay in the combined cohort. The log

likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 2.07, p = .1498$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of length of stay, $IRR = 1.05, 95\% \text{ CI } [0.97, 1.14], z = 1.43, p = .152$ (Table 38).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 7.5e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and chronic conditions in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 29.45, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of chronic conditions, $IRR = 1.19, 95\% \text{ CI } [1.12, 1.28], z = 5.36, p < .001$, hence, the null hypothesis was rejected (Table 38).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.4e+07, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and diagnoses in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 40.04, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of diagnoses, $IRR = 1.17, 95\% \text{ CI } [1.11, 1.23], z = 6.24, p < .001$, hence, the null hypothesis was rejected (Table 38).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 5.0e+06, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and ecodes in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model,

$LR \chi^2(1) = 448.50, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect on the incidence of external causes of injury, $IRR = 5.31$, 95% CI [4.42, 6.37], $z = 17.94, p < .001$, hence, the null hypothesis was rejected (Table 38).

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.9e+07, p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. NBRM was conducted to examine the relationship between androgen toxicity and procedures in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 2.76, p = .0966$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on the incidence of medical procedures, $IRR = 0.90$, 95% CI [0.81, 1.01], $z = -1.67, p = .095$ (Table 38).

The combined cohort analysis of inpatient variables is shown in Table 38. Inpatient variable point estimates for the bivariate analysis of the combined cohort are presented in Figure 16.

Table 38

Bivariate NBRM of Inpatient Variables in the Combined Cohort

Variable	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Length of stay					
Androgen toxicity	1.05	0.041	1.43	.152	[0.97, 1.14]
Constant	4.73	0.0007	1.0e+04	< .001	[4.734, 4.737]
Chronic conditions					
Androgen toxicity	1.19	0.040	5.36	< .001	[1.12, 1.28]
Constant	4.90	0.0006	1.2e+04	< .001	[4.89, 4.90]

Diagnoses					
Androgen toxicity	1.17	0.030	6.24	< .001	[1.11, 1.23]
Constant	10.09	0.001	2.3e+04	< .001	[10.09, 10.10]
Ecodes					
Androgen toxicity	5.31	0.494	17.94	< .001	[4.42, 6.37]
Constant	0.29	0.0001	-2700.00	< .001	[0.293, 0.294]
Procedures					
Androgen toxicity	0.90	0.051	-1.67	.095	[0.81, 1.01]
Constant	1.72	0.0003	2571.42	< .001	[1.725, 1.727]

Note. IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Constant = baseline incidence rate.

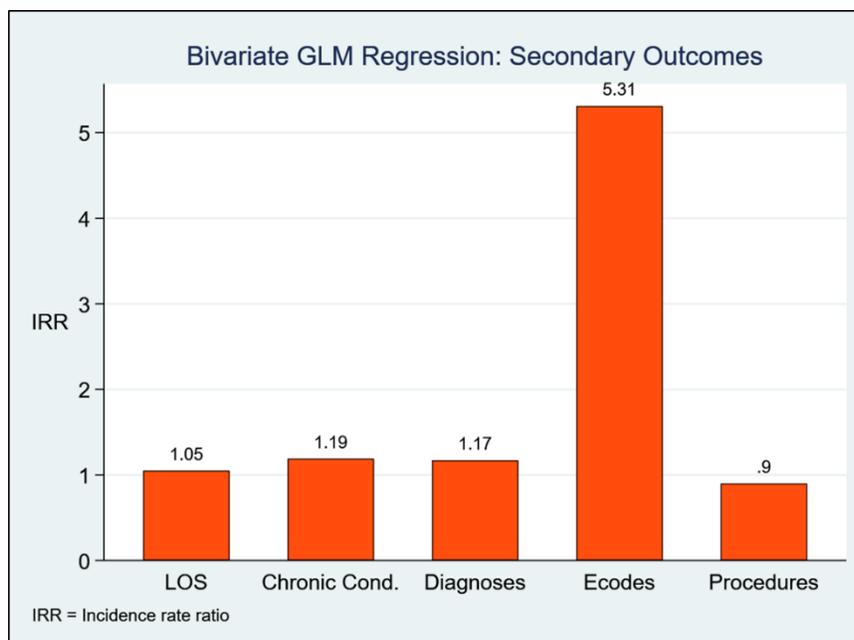


Figure 16. Combined cohort inpatient variable point estimates.

Aim 2 [RQ 3]. What is the relationship between androgen toxicity and healthcare costs?

H₀₃. There is no relationship between androgen toxicity and healthcare costs.

H_{a3}. There is a relationship between androgen toxicity and healthcare costs.

Log-gamma generalized linear model analysis was conducted to determine the relationship between androgen toxicity and healthcare costs. The study design assumptions of the log-gamma GLM were (a) a dependent variable measured on the ratio or interval scale, (b) statistical independence of observations, (c) correct specification of variance function $v(\mu)$, and (d) correct specification of the link function (Hardin & Hilbe, 2012). The data assumptions of the log-gamma GLM were (a) non-negative dependent variable values, (b) positively skewed dependent variable values, and (c) variance held nearly constant on the log-scale (Hardin & Hilbe, 2012). Prior to the analysis, the assumptions of non-negative values, positive skew, and nearly constant variance on the log-scale were assessed.

Non-negative and positively skewed values. Long format tabulation and detailed summary statistics were conducted to determine the data characteristics of the healthcare cost variable. The results of visual inspection of the tabulation showed non-negative values and positive skew for each cohort. The minimum values for healthcare costs were (≥ 100) for each yearly cohort and the combined cohort. The skewness and kurtosis statistics were ($Sk = 7.43$; $Ku = 100.83$) cohort one, ($Sk = 12.47$; $Ku = 388.79$) cohort two, ($Sk = 12.01$; $Ku = 387.59$) cohort three, ($Sk = 12.55$; $Ku = 384.79$) cohort four, ($Sk = 11.42$; $Ku = 311.58$) cohort five, ($Sk = 11.52$; $Ku = 316.88$) cohort six, and ($Sk = 11.64$; $Ku = 341.54$) combined cohort. The summary results suggested that the log-gamma model was superior to the specification of Gaussian regression with a log-transformed response. Therefore, the log-gamma GLM was considered preferable and suitable for the analysis.

Near constant variance. Anscombe residuals were generated using the method by Hardin and Hilbe (2012) to determine whether the variance was held near constant on the log-scale by the estimated scale parameter ensuring log-transformed normality. The plotted results confirmed that the Anscombe residuals were within the range of constant variance and showed a good approximation of log normality. The Anscombe residual plots of the cohorts (I-VI) are presented in Figure 17. The Anscombe residual plots for the combined cohort are shown in Figure 18.

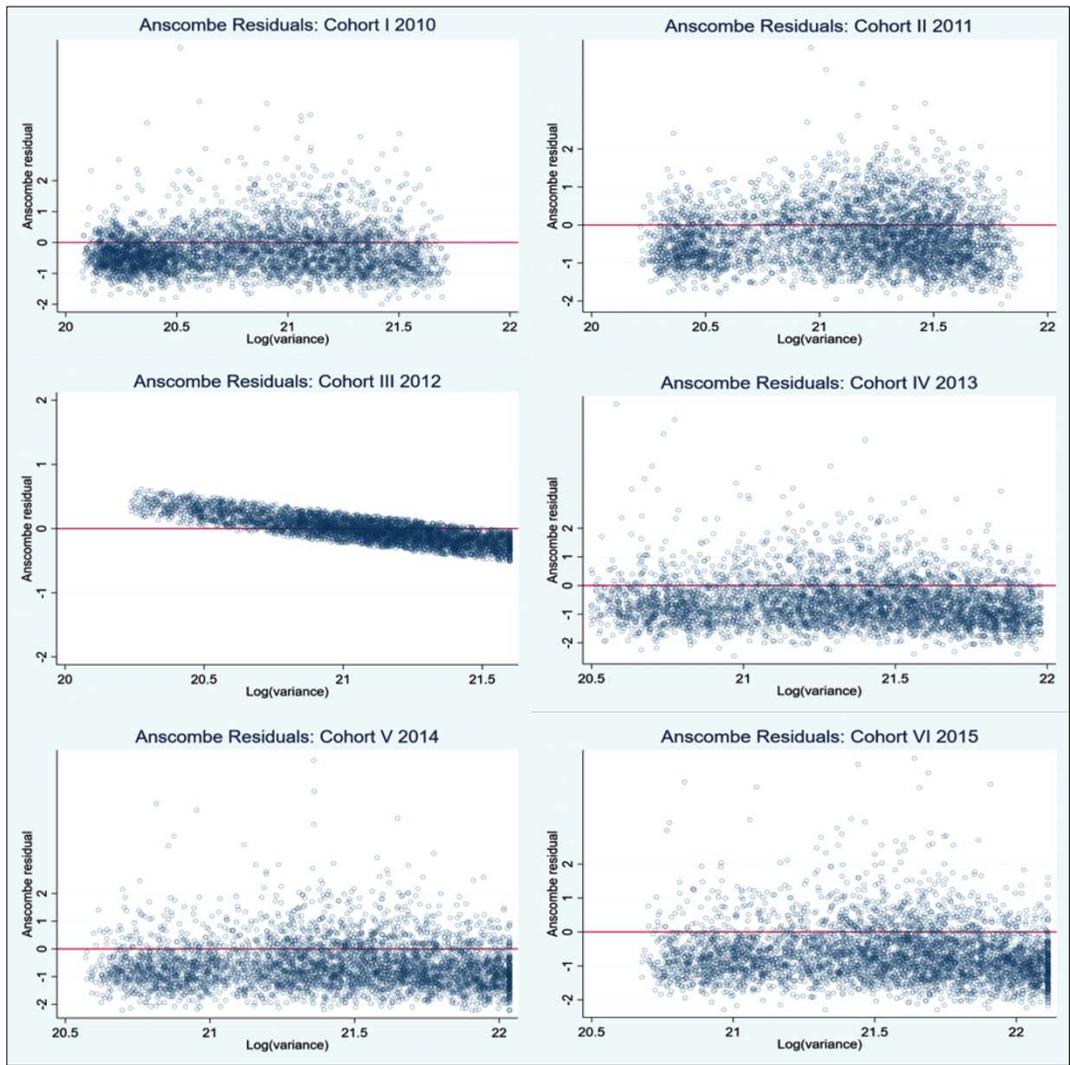


Figure 17. Anscombe residuals of each yearly cohort.

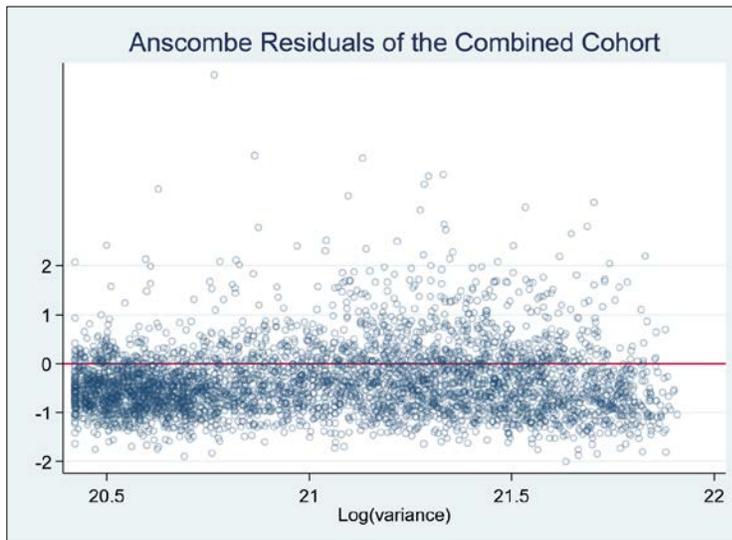


Figure 18. Anscombe residuals of the combined cohort.

Healthcare cost results. A log-gamma GLM regression was conducted to examine the bivariate relationship between androgen toxicity and healthcare cost in cohort one. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.43, p = .5113$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.09, 95\% \text{ CI } [-0.54, 0.34], z = -0.43, p = .667$ (Table 39). The predicted margins of healthcare costs by androgen toxicity exposure (no = 36,004.26, $p < .001$) and (yes = 32,664.36, $p < .001$) indicated a significant marginal difference ($MD = 3,339.90$) in healthcare cost difference between the two levels of exposure.

A log-gamma GLM regression was conducted to examine the relationship between androgen toxicity and healthcare cost in cohort two. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 1.45, p = .2284$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.13, 95\% \text{ CI } [-0.48, 0.21], z = -0.75, p = .454$ (Table 39). The predicted margins of

healthcare costs by androgen toxicity exposure (no = 38,670.50, $p < .001$) and (yes = 33,808.31, $p < .001$) indicated a significant marginal difference ($MD = 4,862.19$) in healthcare cost difference between the two levels of exposure.

A log-gamma GLM regression was conducted to examine the relationship between androgen toxicity and healthcare cost in cohort three. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.93, p = .3341$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.12, 95\% \text{ CI } [-0.50, 0.25], z = -0.63, p = .531$ (Table 39). The predicted margins of healthcare costs by androgen toxicity exposure (no = 36,867.30, $p < .001$) and (yes = 32,625.35, $p < .001$) indicated a significant marginal difference ($MD = 4,241.95$) in healthcare cost difference between the two levels of exposure.

A log-gamma GLM regression was conducted to examine the relationship between androgen toxicity and healthcare cost in cohort four. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 2.95, p = .0859$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = 0.16, 95\% \text{ CI } [-0.15, 0.48], z = 1.02, p = .308$ (Table 39). The predicted margins of healthcare costs by androgen toxicity exposure (no = 42,680.02, $p < .001$) and (yes = 50,435.02, $p < .001$) indicated a significant marginal difference ($MD = -7,755.00$) in healthcare cost difference between the two levels of exposure.

A log-gamma GLM regression was conducted to examine the relationship between androgen toxicity and healthcare cost in cohort five. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 25.88, p < .0001$, indicated that the model fit

was significant. Androgen toxicity exposure had a significant effect on healthcare cost, $\beta = 0.44$, 95% CI [0.14, 0.74], $z = 2.92$, $p = .003$, hence, the null hypothesis was rejected (Table 39). The predicted margins of healthcare costs by androgen toxicity exposure (no = 44,993.60, $p < .001$) and (yes = 70,219.07, $p < .001$) indicated a significant marginal difference ($MD = -25,225.47$) in healthcare cost difference between the two levels of exposure.

A log-gamma GLM regression was conducted to examine the relationship between androgen toxicity and healthcare cost in cohort six. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 0.90$, $p = .3420$, indicated that the model fit was not significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = 0.10$, 95% CI [-0.24, 0.45], $z = 0.58$, $p = .562$ (Table 39). The predicted margins of healthcare costs by androgen toxicity exposure (no = 47,069.90, $p < .001$) and (yes = 52,249.37, $p < .001$) indicated a significant marginal difference ($MD = -5,179.47$) in healthcare cost difference between the two levels of exposure.

Table 39

Bivariate GLM Regression of Total Healthcare Costs in Each Yearly Cohort

Healthcare costs	β	SE	z	p	95% CI
Androgen toxicity ^a	-0.09	0.225	-0.43	.667	[-0.54, 0.34]
Constant ^a	10.49	< 0.001	1.7e+4	< .001	[10.490, 10.492]
Androgen toxicity ^b	-0.13	0.179	-0.75	.454	[-0.48, 0.21]
Constant ^b	10.56	< 0.001	1.6e+4	< .001	[10.561, 10.564]
Androgen toxicity ^c	0.12	0.194	-0.63	.531	[-0.50, 0.25]
Constant ^c	10.51	< 0.001	1.5e+4	< .001	[10.513, 10.516]

Androgen toxicity ^d	0.16	0.163	1.02	.308	[-0.15, 0.48]
Constant ^d	10.66	< 0.001	1.6e+4	< .001	[10.660, 10.662]
Androgen toxicity ^e	0.44	0.152	2.92	.003	[0.14, 0.74]
Constant ^e	10.71	< 0.001	1.6e+4	< .001	[10.712, 10.715]
Androgen toxicity ^f	0.10	0.180	0.58	.562	[-0.12, 0.45]
Constant ^f	10.75	< 0.001	1.4e+4	< .001	[10.75, 10.76]

Note. a-f = 2010-2015, β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Constant = baseline cost.

Combined cohort analysis. A log-gamma GLM regression was conducted to examine the relationship between androgen toxicity and healthcare cost in the combined cohort. The log likelihood ratio chi-square test statistic for the one-predictor model, $LR \chi^2(1) = 14.84, p = .0001$, indicated the model fit was significant. Androgen toxicity exposure had a significant effect on healthcare cost, $\beta = 0.16$, 95% CI [0.02, 0.31], $z = 2.31, p = .021$, hence, the null hypothesis was rejected (Table 40). The predicted margins of healthcare costs by androgen toxicity exposure (no = 40,794.21, $p < .001$) and (yes = 48,327.52, $p < .001$) indicated a significant marginal difference ($MD = -7,533.31$) in healthcare cost difference between the two levels of exposure.

Table 40

Bivariate GLM Regression of Total Healthcare Costs in the Combined Cohort

Healthcare costs	β	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity	0.16	0.073	2.31	.021	[0.02, 0.31]
Constant	10.61	2.777e-04	3.8e+04	< .001	[10.615, 10.616]

Note. β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval.

Marginal estimates of total healthcare costs for the bivariate analysis of the combined cohort are shown in Figure 19.

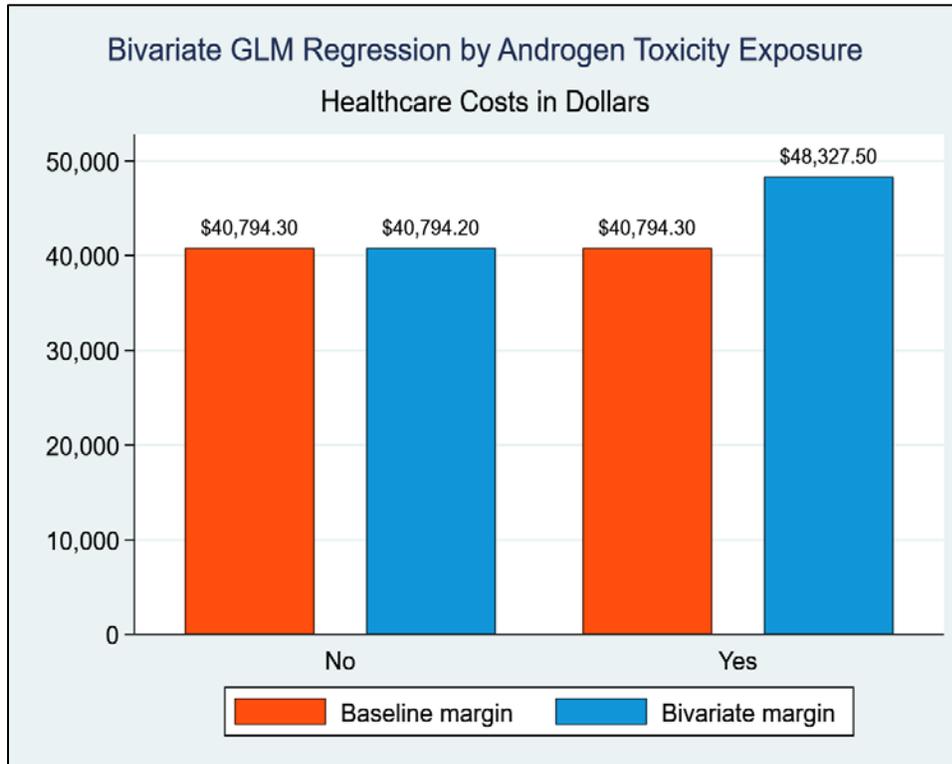


Figure 19. Bivariate margins of the combined cohort.

Multivariate Analysis

Aim 1 [RQ 1]. What is the relationship between androgen toxicity and risk of health outcomes?

H₀₁. There is no relationship between androgen toxicity and risk of health outcomes.

H_{a1}. There is a relationship between androgen toxicity and risk of health outcomes.

Noncanonical generalized linear log-linked binomial regression was conducted to examine the multivariate risk relationship between androgen toxicity and the risk of nominal dichotomous health outcomes. The study design assumptions for GLM binomial regression

models (BRM) were (a) one dependent variable measured on the nominal dichotomous scale, (b) one or more independent variables measured on an interval, ratio, or nominal scale, (c) independence of observations, (d) mutual exclusiveness and full exhaustiveness of each category of the dependent variable and the nominal independent variable, and (e) no linear relationship among the variables (Hardin & Hilbe, 2012). The data assumptions for GLM binomial regression included (a) no substantive outliers or influential observations among ratio or interval independent variables and (b) lack of data collinearity (Hardin & Hilbe, 2012). Prior to the analysis, the assumptions of no substantive outliers or influential observations and lack of collinearity were assessed.

Outliers and influential observations. A Grubbs test was conducted to identify outliers and influential observations for the sole interval measured covariate of age (Couderc, 2007). The results of the Grubbs test of age for each cohort were negative for outliers. An extreme value test using the method of Cox (2003) was also conducted to determine extreme values for age. The results showed high values within three standard deviations of the mean: Cohort one (44,703 with age = 18; 38,928 with age = 91), cohort two (39,974 with age = 18; 35,672 with age = 92), cohort three (28,597 with age = 18; 193,414 with age = 90), cohort four (33,373 with age = 18; 230,219 with age = 90), cohort five (31,527 with age = 18; 228,229 with age = 90), and cohort six (22,622 with age = 18; 181,043 with age = 90). Since the variable 'age' was specified as a covariate and exclusion criteria restricted the sampled cohorts to observations of 18 years or older, the extreme values were an expected consequence of the sampling and deemed appropriate for the intended analysis.

Collinearity. A collinearity diagnostic was conducted to determine the variance inflation factors among the independent variable and the dependent variables. The results of the collinearity diagnostics showed variance inflation factors of less than a value of four, suggesting the collinearity assumption was met for each of the variables. The mean variance inflation factors among the study variables were 1.01, 1.01, 1.01, 1.01, 1.01, and 1.01 for cohorts one, two, three, four, five, and six, respectively. The mean variance inflation factor for the combined cohort was 1.01.

Mortality results. An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, mortality, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 79,270, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of death, $RR = 1.09, 95\% CI [0.15, 7.49], z = 0.09, p = .929$ (Table 41).

Table 41

Multivariate BRM of Mortality in Cohort I (2010)

Mortality	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.09	1.07	0.09	.925	[0.15, 7.53]
Age	1.04	< 0.001	241.02	< .001	[1.04, 1.04]
Sex ^b					
Male	1.41	0.007	63.89	< .001	[1.40, 1.43]
Race ^c					

White	1.12	0.010	12.48	< .001	[1.10, 1.14]
Black	1.27	0.014	21.08	< .001	[1.24, 1.30]
Hispanic	1.15	0.015	10.30	< .001	[1.12, 1.18]
Asian\Pac. Islander	1.45	0.029	18.80	< .001	[1.40, 1.51]
Native American	1.11	0.040	2.89	.004	[1.03, 1.19]
Other	0.23	0.024	10.55	< .001	[1.18, 1.28]
Median income ^d					
\$1 - \$38,999	0.92	0.015	-4.59	< .001	[0.89, 0.95]
\$39,000 - \$47,999	0.82	0.013	-11.29	< .001	[0.79, 0.85]
\$48,000 - \$62,999	0.80	0.013	-12.41	< .001	[0.78, 0.83]
\$63,000 or more	0.78	0.013	-13.71	< .001	[0.76, 0.81]
Constant	0.001	< 0.0001	-306.78	< .001	[0.001, 0.001]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, mortality, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 80,565, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of death, $RR = 0.56, 95\% CI [0.08, 3.90], z = -0.58, p = .559$ (Table 42).

Table 42

Multivariate BRM of Mortality in Cohort II (2011)

Mortality	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.56	0.555	-0.58	.559	[0.08, 3.90]
Age	1.04	.0001	244.13	< .001	[1.04, 1.04]
Sex ^b					
Male	1.39	0.007	62.78	< .001	[1.38, 1.41]
Race ^c					
White	1.04	0.010	4.76	< .001	[1.02, 1.06]
Black	1.19	0.014	15.21	< .001	[1.16, 1.22]
Hispanic	1.05	0.014	3.82	< .001	[1.02, 1.08]
Asian\Pac. Islander	1.37	0.029	14.77	< .001	[1.31, 1.42]
Native American	1.27	0.050	6.31	.004	[1.18, 1.38]
Other	1.23	0.023	11.26	< .001	[1.19, 1.28]
Median income ^d					
\$1 - \$38,999	0.89	0.016	-6.21	< .001	[0.86, 0.92]
\$39,000 - \$47,999	0.83	0.015	-10.01	< .001	[0.80, 0.86]
\$48,000 - \$62,999	0.78	0.014	-12.88	< .001	[0.76, 0.81]
\$63,000 or more	0.78	0.014	-12.78	< .001	[0.76, 0.81]
Constant	0.001	< 0.0001	-287.14	< .001	[0.001, 0.001]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, mortality, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 62,804.38, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of death, $RR = 0.89, 95\% \text{ CI } [0.12, 6.19], z = -0.11, p = .909$ (Table 43).

Table 43
Multivariate BRM of Mortality in Cohort III (2012)

Mortality	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.89	0.882	-0.11	.909	[0.12, 6.19]
Age	1.04	0.0002	215.65	< .001	[1.04, 1.04]
Sex ^b					
Male	1.37	0.008	52.37	< .001	[1.35, 1.39]
Race ^c					
White	0.95	0.012	-3.77	< .001	[0.92, 0.97]
Black	1.04	0.015	3.00	.003	[1.01, 1.07]
Hispanic	0.91	0.016	-4.95	< .001	[0.88, 0.94]
Asian\Pac. Islander	1.11	0.035	3.32	< .001	[1.04, 1.18]
Native American	1.00	0.049	0.01	.004	[0.90, 1.10]
Other	1.06	0.023	2.93	< .001	[1.02, 1.11]
Median income ^d					

\$1 - \$38,999	0.87	0.017	-6.41	< .001	[0.84, 0.91]
\$39,000 - \$47,999	0.81	0.016	-10.00	< .001	[0.78, 0.84]
\$48,000 - \$62,999	0.78	0.016	-11.51	< .001	[0.75, 0.82]
\$63,000 or more	0.75	0.015	-13.60	< .001	[0.72, 0.78]
Constant	0.001	< 0.0001	-241.27	< .001	[0.001, 0.001]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, mortality, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 76,337.97, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of death, $RR = 0.43, 95\% \text{ CI } [0.06, 3.06], z = -0.83, p = .405$ (Table 44).

Table 44

Multivariate BRM of Mortality in Cohort IV (2013)

Mortality	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.43	0.434	-0.83	.405	[0.06, 3.06]
Age	1.04	0.0001	237.70	< .001	[1.042, 1.043]
Sex ^b					
Male	1.37	0.007	57.26	< .001	[1.35, 1.38]
Race ^c					

White	0.91	0.011	-6.98	< .001	[0.89, 0.94]
Black	1.01	0.014	0.86	.389	[0.98, 0.94]
Hispanic	0.92	0.014	-5.16	< .001	[0.89, 0.95]
Asian\Pac. Islander	1.20	0.024	9.07	< .001	[1.15, 1.25]
Native American	1.15	0.045	3.77	< .001	[1.07, 1.25]
Other	1.05	0.021	2.56	.010	[1.01, 1.09]
Median income ^d					
\$1 - \$38,999	0.95	0.017	-2.33	.020	[0.92, 0.99]
\$39,000 - \$47,999	0.89	0.016	-5.74	< .001	[0.86, 0.93]
\$48,000 - \$62,999	0.86	0.016	-7.95	< .001	[0.83, 0.89]
\$63,000 or more	0.85	0.016	-8.10	< .001	[0.82, 0.89]
Constant	0.001	< 0.0001	-267.68	< .001	[0.0013, 0.0014]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, mortality, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 74,293.11, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of death, $RR = 0.43, 95\% CI [0.06, 3.04], z = -0.84, p = .401$ (Table 45).

Table 45

Multivariate BRM of Mortality in Cohort V (2014)

Mortality	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.43	0.431	-0.84	.401	[0.06, 3.04]
Age	1.04	0.0001	234.30	< .001	[1.041, 1.042]
Sex ^b					
Male	1.37	0.007	58.39	< .001	[1.36, 1.39]
Race ^c					
White	0.90	0.011	-8.15	< .001	[0.88, 0.92]
Black	0.97	0.014	-1.88	< .001	[0.94, 1.00]
Hispanic	0.87	0.013	-8.53	< .001	[0.84, 0.90]
Asian\Pac. Islander	1.14	0.024	6.52	< .001	[1.10, 1.19]
Native American	1.21	0.045	5.14	.004	[1.12, 1.30]
Other	1.03	0.021	1.82	< .001	[0.99, 1.08]
Median income ^d					
\$1 - \$38,999	0.93	0.017	-3.53	< .001	[0.90, 0.97]
\$39,000 - \$47,999	0.88	0.016	-6.61	< .001	[0.85, 0.91]
\$48,000 - \$62,999	0.84	0.015	-9.05	< .001	[0.81, 0.87]
\$63,000 or more	0.81	0.015	-10.47	< .001	[0.78, 0.85]
Constant	0.001	< 0.0001	-260.19	< .001	[0.0014, 0.0016]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was not conducted to examine the relationship between androgen toxicity, mortality, and covariates in cohort six due to perfect prediction. No inpatients with androgen toxicity exposure died in cohort six for the 2015 year.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, mortality, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 428,942.01, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of death, $RR = 0.50, 95\% CI [0.20, 1.19], z = -1.56, p = .119$ (Table 46).

Table 46

Multivariate BRM of Mortality in the Combined Cohort

Mortality	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.50	0.222	-1.56	.119	[0.20, 1.19]
Age	1.04	7.8e-05	563.24	< .001	[1.042, 1.043]
Sex ^b					
Male	1.38	0.003	141.46	< .001	[1.37, 1.39]
Race ^c					
White	1.00	0.004	0.21	.830	[0.99,1.01]
Black	1.11	0.006	19.51	< .001	[1.10, 1.12]
Hispanic	0.99	0.006	-1.17	.242	[0.98, 1.00]
Asian\Pac. Islander	1.27	0.011	27.19	< .001	[1.25, 1.29]

Native American	1.18	0.019	10.22	< .001	[1.14, 1.22]
Other	1.14	0.009	16.18	< .001	[1.12, 1.16]
Median income ^d					
\$1 - \$38,999	0.92	0.007	-10.03	< .001	[0.91, 0.93]
\$39,000 - \$47,999	0.86	0.006	-19.18	< .001	[0.84, 0.87]
\$48,000 - \$62,999	0.82	0.006	-24.07	< .001	[0.81, 0.84]
\$63,000 or more	0.81	0.006	-26.41	< .001	[0.79, 0.82]
Constant	0.001	1.35e-05	-655.28	< .001	[0.00131, 0.00136]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

Polycythemia results. An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 943.90, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of polycythemia, $RR = 74.39, 95\% CI [25.05, 220.90], z = 7.76, p < .001$, hence, the null hypothesis was rejected (Table 47).

Table 47

Multivariate BRM of Polycythemia in Cohort I (2010)

Polycythemia	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	74.39	41.310	7.76	< .001	[25.05, 220.90]
Age	0.97	0.0008	-26.87	< .001	[0.975, 0.979]

Sex ^b					
Male	1.78	0.059	17.55	< .001	[1.67, 1.90]
Race ^c					
White	1.07	0.056	1.36	.175	[0.96, 1.19]
Black	0.80	0.053	-3.28	< .001	[0.70, 0.91]
Hispanic	0.98	0.68	-0.16	.873	[0.86, 1.13]
Asian\Pac. Islander	1.15	0.134	1.24	.215	[0.91, 1.45]
Native American	0.63	0.156	-1.86	.063	[0.38, 1.02]
Other	0.70	0.090	-2.74	.006	[0.54, 0.90]
Median income ^d					
\$1 - \$38,999	1.05	0.107	0.49	.621	[0.86, 1.28]
\$39,000 - \$47,999	1.06	0.109	0.59	.557	[0.86, 1.30]
\$48,000 - \$62,999	1.02	0.106	0.26	.793	[0.83, 1.25]
\$63,000 or more	1.03	0.108	0.35	.724	[0.84, 1.27]
Constant	0.001	0.0001	-56.16	< .001	[0.0011, 0.0018]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 932.99, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a

significant effect on the risk of polycythemia, $RR = 197.26$, 95% CI [120.81, 322.08], $z = 21.13$, $p < .001$, hence, the null hypothesis was rejected (Table 48).

Table 48

Multivariate BRM of Polycythemia on Cohort II (2011)

Polycythemia	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	197.26	49.344	21.13	< .001	[120.81, 322.08]
Age	0.97	0.0008	-25.39	< .001	[0.97, 0.98]
Sex ^b					
Male	1.86	0.060	19.25	< .001	[1.74, 1.98]
Race ^c					
White	1.05	0.058	1.02	.307	[0.94, 1.17]
Black	0.77	0.053	-3.76	< .001	[0.67, 0.88]
Hispanic	0.82	0.060	-2.66	.008	[0.70, 0.94]
Asian\Pac. Islander	0.93	0.121	-0.48	.629	[0.72, 1.21]
Native American	0.67	0.171	-1.55	.121	[0.40, 1.11]
Other	1.20	0.115	1.90	.057	[0.99, 1.45]
Median income ^d					
\$1 - \$38,999	0.84	0.086	-1.69	.092	[0.68, 1.02]
\$39,000 - \$47,999	0.80	0.083	-2.12	.034	[0.65, 0.98]
\$48,000 - \$62,999	0.90	0.093	-1.00	.318	[0.73, 1.10]
\$63,000 or more	0.85	0.090	-1.46	.144	[0.69, 1.05]

Constant	0.001	0.0001	-54.53	< .001	[0.001, 0.002]
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Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 615.94, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of polycythemia, $RR = 125.26, 95\% CI [62.65, 250.42], z = 21.13, p < .001$, hence, the null hypothesis was rejected (Table 49).

Table 49

Multivariate BRM of Polycythemia in Cohort III (2012)

Polycythemia	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	125.26	44.275	13.67	< .001	[62.65, 250.42]
Age	0.98	0.0009	-21.17	< .001	[0.97, 0.98]
Sex ^b					
Male	1.77	0.066	15.32	< .001	[1.64, 1.90]
Race ^c					
White	1.09	0.088	1.15	.252	[0.93, 1.28]
Black	0.83	0.077	-1.93	.053	[0.69, 1.28]
Hispanic	0.91	0.094	-0.82	.413	[0.75, 1.12]
Asian\Pac. Islander	0.92	0.171	-0.40	.690	[0.64, 1.33]

Native American	0.70	0.230	-1.06	.287	[0.37, 1.33]
Other	0.96	0.122	-0.27	.785	[0.75, 1.23]
Median income ^d					
\$1 - \$38,999	1.05	0.134	0.43	.664	[0.82, 1.35]
\$39,000 - \$47,999	1.05	0.135	0.42	.674	[0.82, 1.35]
\$48,000 - \$62,999	0.97	0.126	-0.23	.819	[0.75, 1.25]
\$63,000 or more	1.00	0.131	0.05	.959	[0.77, 1.30]
Constant	0.001	0.0001	-43.85	< .001	[0.0009, 0.0017]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 842.91, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of polycythemia, $RR = 127.42, 95\% CI [71.30, 227.71], z = 16.37, p < .001$, hence, the null hypothesis was rejected (Table 50).

Table 50

Multivariate BRM of Polycythemia in Cohort IV (2013)

Polycythemia	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	127.42	37.744	16.37	< .001	[71.30, 227.71]
Age	0.97	0.0008	-24.42	< .001	[0.97, 0.98]

Sex ^b					
Male	1.84	0.062	18.23	< .001	[1.72, 1.97]
Race ^c					
White	1.26	0.095	3.08	.002	[1.08, 1.46]
Black	0.89	0.078	-1.23	.219	[0.75, 1.06]
Hispanic	1.07	0.095	0.79	.429	[0.90, 1.27]
Asian\Pac. Islander	1.03	0.141	0.22	.828	[0.78, 1.34]
Native American	1.21	0.264	0.90	.366	[0.79, 1.86]
Other	0.91	0.118	-0.68	.499	[0.71, 1.17]
Median income ^d					
\$1 - \$38,999	1.05	0.119	0.49	.621	[0.84, 1.31]
\$39,000 - \$47,999	1.10	0.125	0.92	.360	[0.88, 1.38]
\$48,000 - \$62,999	1.13	0.129	1.15	.251	[0.91, 1.42]
\$63,000 or more	1.03	0.119	0.27	.789	[0.82, 1.29]
Constant	0.001	0.0001	-49.62	< .001	[0.0008, 0.0014]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 826.75, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a

significant effect on the risk of polycythemia, $RR = 143.27$, 95% CI [88.29, 232.50], $z = 20.10$, $p < .001$, hence, the null hypothesis was rejected (Table 51).

Table 51

Multivariate BRM of Polycythemia in Cohort V (2014)

Polycythemia	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	143.27	35.390	20.10	< .001	[88.29, 232.50]
Age	0.98	0.0008	-23.14	< .001	[0.97, 0.98]
Sex ^b					
Male	1.98	0.068	20.00	< .001	[1.85, 2.12]
Race ^c					
White	1.09	0.083	1.23	.219	[0.94, 1.27]
Black	0.85	0.074	-1.85	.064	[0.71, 1.00]
Hispanic	0.95	0.085	-0.53	.833	[0.80, 1.13]
Asian\Pac. Islander	0.81	0.115	-1.45	.148	[0.61, 1.07]
Native American	1.04	0.231	0.21	.833	[0.67, 1.61]
Other	0.81	0.104	-1.60	.110	[0.63, 1.04]
Median income ^d					
\$1 - \$38,999	0.99	0.112	-0.04	.969	[0.79, 1.24]
\$39,000 - \$47,999	1.02	0.116	0.25	.802	[0.82, 1.28]
\$48,000 - \$62,999	1.05	0.120	0.45	.653	[0.84, 1.31]
\$63,000 or more	1.09	0.125	0.78	.438	[0.87, 1.37]

Constant	0.001	0.0001	-48.95	< .001	[0.0009, 0.0015]
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Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 558.49, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of polycythemia, $RR = 222.86, 95\% CI [139.39, 356.33], z = 22.58, p < .001$, hence, the null hypothesis was rejected (Table 52).

Table 52

Multivariate BRM of Polycythemia in Cohort VI (2015)

Polycythemia	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	222.86	53.362	22.58	< .001	[139.39, 356.33]
Age	0.98	0.0009	-19.17	< .001	[0.97, 0.98]
Sex ^b					
Male	1.18	0.075	15.77	< .001	[1.73, 2.03]
Race ^c					
White	1.28	0.120	2.70	.007	[1.07, 1.54]
Black	0.99	0.105	-0.09	.928	[0.80, 1.21]
Hispanic	0.98	0.108	-0.16	.876	[0.79, 1.22]
Asian\Pac. Islander	1.01	0.164	0.10	.918	[0.74, 1.39]

Native American	0.75	0.238	-0.88	.378	[0.40, 1.40]
Other	1.07	0.162	0.51	.611	[0.80, 1.45]
Median income ^d					
\$1 - \$38,999	0.88	0.119	-0.89	.373	[0.68, 1.15]
\$39,000 - \$47,999	1.04	0.140	0.31	.757	[0.80, 1.35]
\$48,000 - \$62,999	0.91	0.124	-0.64	.525	[0.70, 1.19]
\$63,000 or more	0.94	0.129	-0.39	.695	[0.72, 1.23]
Constant	0.001	0.0001	-41.40	< .001	[0.0008, 0.0015]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, polycythemia, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 4,620.18, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of polycythemia, $RR = 152.49, 95\% \text{ CI } [120.97, 192.22], z = 42.56, p < .001$, hence, the null hypothesis was rejected (Table 53).

Table 53

Multivariate BRM of Polycythemia in the Combined Cohort

Polycythemia	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	152.49	18.014	42.56	< .001	[120.97, 192.22]
Age	0.97	3.52e-04	-57.48	< .001	[0.97, 0.98]

Sex ^b					
Male	1.85	0.026	43.44	< .001	[1.80, 1.90]
Race ^c					
White	1.12	0.030	4.17	< .001	[1.06, 1.18]
Black	0.83	0.027	-5.45	< .001	[0.78, 0.89]
Hispanic	0.94	0.032	-1.74	.082	[0.88, 1.00]
Asian\Pac. Islander	0.96	0.054	-0.63	.528	[0.86, 1.07]
Native American	0.82	0.084	-1.88	.060	[0.67, 1.00]
Other	0.93	0.046	-1.32	.186	[0.85, 1.03]
Median income ^d					
\$1 - \$38,999	0.98	0.045	-0.37	.711	[0.89, 1.07]
\$39,000 - \$47,999	1.01	0.047	0.22	.827	[0.92, 1.10]
\$48,000 - \$62,999	1.00	0.047	0.18	.861	[0.91, 1.10]
\$63,000 or more	0.99	0.047	-0.09	.931	[0.90, 1.09]
Constant	0.001	7.19e-05	-122.01	< .001	[0.0011, 0.0014]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

Hypercoagulability results. An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,137.22, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure,

upon an adjustment of covariates, did not have a significant effect on the risk of hypercoagulable states, $RR = 6.08$, 95% CI [0.87, 42.27], $z = 1.83$, $p = .068$ (Table 54).

Table 54

Multivariate BRM of Hypercoagulability in Cohort I (2010)

Hypercoagulability	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	6.08	6.020	1.83	.068	[0.87, 42.27]
Age	0.98	0.0003	-30.40	< .001	[0.98, 0.99]
Sex ^b					
Male	0.88	0.012	-8.45	< .001	[0.86, 0.91]
Race ^c					
White	0.93	0.019	-3.11	.002	[0.90, 0.97]
Black	0.75	0.020	-10.58	< .001	[0.71, 0.79]
Hispanic	0.48	0.016	-21.42	< .001	[0.45, 0.51]
Asian\Pac. Islander	0.34	0.025	-14.34	< .001	[0.29, 0.40]
Native American	0.58	0.059	-5.28	< .001	[0.47, 0.71]
Other	0.53	0.030	-11.04	< .001	[0.47, 0.59]
Median income ^d					
\$1 - \$38,999	0.99	0.047	-0.11	.915	[0.90, 1.09]
\$39,000 - \$47,999	1.16	0.055	3.28	.001	[1.06, 1.28]
\$48,000 - \$62,999	1.20	0.057	3.96	< .001	[1.09, 1.32]
\$63,000 or more	1.34	0.064	6.20	< .001	[1.22, 1.47]

Constant	0.006	0.0003	-96.98	< .001	[0.005, 0.007]
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Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,305.42, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of hypercoagulable states, $RR = 6.45, 95\% CI [1.64, 25.35], z = 2.67, p = .008$, hence, the null hypothesis was rejected (Table 55).

Table 55

Multivariate BRM of Hypercoagulability in Cohort II (2011)

Hypercoagulability	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	6.45	4.506	2.67	.008	[1.64, 25.35]
Age	0.98	0.0003	-33.91	< .001	[0.988, 0.989]
Sex ^b					
Male	0.88	0.011	-9.39	< .001	[0.85, 0.90]
Race ^c					
White	0.94	0.019	-2.47	.013	[0.91, 0.98]
Black	0.75	0.020	-10.27	< .001	[0.71, 0.79]
Hispanic	0.51	0.016	-20.11	< .001	[0.48, 0.55]
Asian\Pac. Islander	0.36	0.026	-13.95	< .001	[0.31, 0.42]

Native American	0.40	0.053	-6.88	< .001	[0.31, 0.52]
Other	0.71	0.032	-7.30	< .001	[0.65, 0.78]
Median income ^d					
\$1 - \$38,999	0.94	0.046	-1.18	.237	[0.85, 1.03]
\$39,000 - \$47,999	1.06	0.052	1.29	.198	[0.96, 1.17]
\$48,000 - \$62,999	1.14	0.056	2.85	.004	[1.04, 1.26]
\$63,000 or more	1.26	0.062	4.82	< .001	[1.15, 1.39]
Constant	0.007	0.0003	-91.97	< .001	[0.006, 0.008]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,047.54, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of hypercoagulable states, $RR = 11.65, 95\% CI [3.86, 35.12], z = 4.36, p < .001$, hence, the null hypothesis was rejected (Table 56).

Table 56

Multivariate BRM of Hypercoagulability in Cohort III (2012)

Hypercoagulability	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	11.65	6.559	4.36	< .001	[3.86, 35.12]
Age	0.98	0.0003	-32.83	< .001	[0.987, 0.988]

Sex ^b					
Male	0.85	0.013	-10.25	< .001	[0.82, 0.87]
Race ^c					
White	0.98	0.030	-0.42	.671	[0.93, 1.04]
Black	0.77	0.027	-7.30	< .001	[0.71, 0.82]
Hispanic	0.57	0.025	-12.63	< .001	[0.52, 0.62]
Asian\Pac. Islander	0.33	0.034	-10.66	< .001	[0.27, 0.41]
Native American	0.65	0.086	-3.20	.001	[0.50, 0.85]
Other	0.71	0.037	-6.53	< .001	[0.64, 0.78]
Median income ^d					
\$1 - \$38,999	0.96	0.054	-0.61	.545	[0.86, 1.07]
\$39,000 - \$47,999	1.08	0.061	1.41	.158	[0.96, 1.20]
\$48,000 - \$62,999	1.21	0.068	3.42	.001	[1.08, 1.35]
\$63,000 or more	1.42	0.080	6.23	< .001	[1.27, 1.58]
Constant	0.007	0.0004	-76.67	< .001	[0.006, 0.008]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,249.14, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of hypercoagulable states, $RR = 7.74, 95\% \text{ CI } [2.54, 23.58], z = 3.60, p < .001$, hence, the null hypothesis was rejected (Table 57).

Table 57

Multivariate BRM of Hypercoagulability in Cohort IV (2013)

Hypercoagulability	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	7.74	4.401	3.60	< .001	[2.54, 23.58]
Age	0.99	0.0003	-29.56	< .001	[0.98, 0.99]
Sex ^b					
Male	0.87	0.012	-9.61	< .001	[0.85, 0.89]
Race ^c					
White	0.88	0.022	-4.94	< .001	[0.83, 0.92]
Black	0.66	0.020	-12.89	< .001	[0.62, 0.71]
Hispanic	0.46	0.016	-21.16	< .001	[0.43, 0.50]
Asian\Pac. Islander	0.32	0.022	-16.14	< .001	[0.28, 0.37]
Native American	0.46	0.054	-6.53	< .001	[0.36, 0.58]
Other	0.57	0.029	-10.78	< .001	[0.52, 0.63]
Median income ^d					
\$1 - \$38,999	1.08	0.054	1.55	.121	[0.97, 1.19]
\$39,000 - \$47,999	1.20	0.061	3.75	< .001	[1.09, 1.33]
\$48,000 - \$62,999	1.31	0.066	5.38	< .001	[1.18, 1.45]
\$63,000 or more	1.45	0.074	7.38	< .001	[1.31, 1.61]
Constant	0.007	0.0004	-86.81	< .001	[0.006, 0.008]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,031.97$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of hypercoagulable states, $RR = 4.37$, 95% CI [1.10, 17.24], $z = 2.11$, $p = .035$, hence, the null hypothesis was rejected (Table 58).

Table 58

Multivariate BRM of Hypercoagulability in Cohort V (2014)

Hypercoagulability	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	4.37	3.061	2.11	.035	[1.10, 17.24]
Age	0.99	0.0003	-26.71	< .001	[0.990, 0.992]
Sex ^b					
Male	0.85	0.011	-11.58	< .001	[0.83, 0.87]
Race ^c					
White	1.02	0.028	0.81	.417	[0.96, 1.07]
Black	0.77	0.025	-7.66	< .001	[0.73, 0.83]
Hispanic	0.57	0.021	-15.01	< .001	[0.53, 0.62]
Asian\Pac. Islander	0.37	0.025	-14.40	< .001	[0.33, 0.43]
Native American	0.61	0.065	-4.50	< .001	[0.50, 0.76]
Other	0.71	0.035	-6.93	< .001	[0.64, 0.78]
Median income ^d					

\$1 - \$38,999	0.97	0.046	-0.45	.651	[0.89, 1.07]
\$39,000 - \$47,999	1.09	0.052	1.96	.050	[0.99, 1.20]
\$48,000 - \$62,999	1.16	0.056	3.14	.002	[1.05, 1.27]
\$63,000 or more	1.32	0.064	5.91	< .001	[1.20, 1.46]
Constant	0.006	0.0003	-89.65	< .001	[0.006, 0.007]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,474.71, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of hypercoagulable states, $RR = 2.61, 95\% CI [0.37, 18.45], z = 0.97, p = .330$ (Table 59).

Table 59

Multivariate BRM of Hypercoagulability in Cohort VI (2015)

Hypercoagulability	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	2.63	2.615	0.97	.330	[0.37, 18.45]
Age	0.99	0.0003	-18.47	< .001	[0.993, 0.994]
Sex ^b					
Male	0.85	0.012	-11.15	< .001	[0.82, 0.87]
Race ^c					

White	1.04	0.031	1.52	.129	[0.98, 1.10]
Black	0.80	0.028	-5.99	< .001	[0.75, 0.86]
Hispanic	0.63	0.024	-11.66	< .001	[0.58, 0.68]
Asian\Pac. Islander	0.39	0.028	-13.05	< .001	[0.33, 0.45]
Native American	0.43	0.059	-6.03	< .001	[0.33, 0.57]
Other	1.02	0.050	0.52	.605	[0.93, 1.12]
Median income ^d					
\$1 - \$38,999	1.04	0.058	0.80	.422	[0.93, 1.16]
\$39,000 - \$47,999	1.18	0.066	3.07	.002	[1.06, 1.32]
\$48,000 - \$62,999	1.26	0.070	4.18	< .001	[1.13, 1.41]
\$63,000 or more	1.43	0.080	6.39	< .001	[1.28, 1.59]
Constant	0.006	0.0003	-79.74	< .001	[0.005, 0.007]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, hypercoagulability, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 11,697.99, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of hypercoagulable states, $RR = 6.28, 95\% \text{ CI } [3.59, 10.98], z = 6.45, p < .001$, hence, the null hypothesis was rejected (Table 60).

Table 60

Multivariate BRM of Hypercoagulability in the Combined Cohort

Hypercoagulability	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	6.28	1.789	6.45	< .001	[3.59, 10.98]
Age	0.99	1.34e-04	-69.68	< .001	[0.9903, 0.9908]
Sex ^b					
Male	0.86	0.004	-24.53	< .001	[0.85, 0.87]
Race ^c					
White	0.98	0.009	-1.37	.171	[0.96, 1.00]
Black	0.76	0.009	-21.31	< .001	[0.74, 0.78]
Hispanic	0.54	0.008	-40.95	< .001	[0.53, 0.56]
Asian\Pac. Islander	0.36	0.011	-33.21	< .001	[0.34, 0.39]
Native American	0.53	0.025	-13.03	< .001	[0.48, 0.58]
Other	0.71	0.014	-16.40	< .001	[0.69, 0.74]
Median income ^d					
\$1 - \$38,999	1.00	0.020	0.38	.704	[0.96, 1.04]
\$39,000 - \$47,999	1.14	0.023	6.44	< .001	[1.09, 1.19]
\$48,000 - \$62,999	1.22	0.025	9.70	< .001	[1.17, 1.27]
\$63,000 or more	1.37	0.028	15.35	< .001	[1.32, 1.43]
Constant	0.006	1.0e-4	-216.22	< .001	[0.006, 0.007]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

Drug-induced liver injury results. An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 343.67, p < .001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 60.75, 95\% CI [15.67, 235.43], z = 5.94, p < .001$, hence, the null hypothesis was rejected (Table 61).

Table 61

Multivariate BRM of Drug-Induced Liver Injury in Cohort I (2010)

DILI	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	60.75	41.989	5.94	< .001	[15.67, 235.43]
Age	0.98	0.0008	-17.05	< .001	[0.984, 0.987]
Sex ^b					
Male	1.29	0.043	7.61	< .001	[1.20, 1.37]
Race ^c					
White	1.13	0.062	2.23	.026	[1.01, 1.26]
Black	0.96	0.066	-0.47	.637	[0.84, 1.10]
Hispanic	1.04	0.076	0.62	.536	[0.90, 1.20]
Asian\Pac. Islander	1.52	0.166	3.85	< .001	[1.22, 1.88]
Native American	0.85	0.196	-0.67	.503	[0.54, 1.34]
Other	1.03	0.123	0.51	.608	[0.84, 1.33]

Median income ^d					
\$1 - \$38,999	1.05	0.112	0.54	.591	[0.85, 1.30]
\$39,000 - \$47,999	1.08	0.116	0.77	.440	[0.88, 1.34]
\$48,000 - \$62,999	1.08	0.116	0.74	.458	[0.87, 1.33]
\$63,000 or more	1.15	0.125	1.36	.175	[0.93, 1.43]
Constant	0.0009	0.001	-57.27	< .001	[0.0007, 0.0012]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 299.47, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 63.31, 95\% \text{ CI } [20.85, 192.26], z = 7.32, p < .001$, hence, the null hypothesis was rejected (Table 62).

Table 62

Multivariate BRM of Drug-Induced Liver Injury in Cohort II (2011)

DILI	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	63.31	35.881	7.32	< .001	[20.85, 192.26]
Age	0.98	0.0008	-15.72	< .001	[0.984, 0.988]
Sex ^b					
Male	1.23	0.042	6.00	< .001	[1.15, 1.31]

Race ^c					
White	0.94	0.054	-1.04	.299	[0.84, 1.05]
Black	0.74	0.054	-4.09	< .001	[0.64, 0.85]
Hispanic	0.98	0.073	-0.23	.821	[0.84, 1.13]
Asian\Pac. Islander	1.15	0.142	1.18	.239	[0.90, 1.47]
Native American	1.22	0.249	1.00	.315	[0.82, 1.82]
Other	0.94	0.105	-0.49	.622	[0.76, 1.17]
Median income ^d					
\$1 - \$38,999	1.04	0.128	0.39	.696	[0.82, 1.33]
\$39,000 - \$47,999	1.03	0.126	0.24	.807	[0.80, 1.31]
\$48,000 - \$62,999	0.97	0.120	-0.19	.853	[0.76, 1.24]
\$63,000 or more	1.09	0.135	0.71	.481	[0.85, 1.39]
Constant	0.001	0.0001	-50.39	< .001	[0.0008, 0.0013]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 290.30, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 26.29, 95\% CI [3.76, 183.71]$, $z = 3.30, p = .001$, hence, the null hypothesis was rejected (Table 63).

Table 63

Multivariate BRM of Drug-Induced Liver Injury in Cohort III (2012)

DILI	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	26.29	26.078	3.30	.001	[3.76, 183.71]
Age	0.98	0.001	-15.99	< .001	[0.981, 0.985]
Sex ^b					
Male	1.24	0.051	5.26	< .001	[1.14, 1.35]
Race ^c					
White	1.05	0.094	0.55	.579	[0.88, 1.25]
Black	0.85	0.087	-1.50	.134	[0.70, 1.04]
Hispanic	1.07	0.118	0.63	.527	[0.86, 1.33]
Asian\Pac. Islander	1.23	0.220	1.16	.244	[0.86, 1.74]
Native American	1.40	0.371	1.28	.199	[0.83, 2.36]
Other	1.13	0.151	0.94	.346	[0.87, 1.47]
Median income ^d					
\$1 - \$38,999	1.01	0.142	0.13	.895	[0.77, 1.33]
\$39,000 - \$47,999	0.94	0.133	-0.41	.682	[0.71, 1.24]
\$48,000 - \$62,999	0.96	0.137	-0.25	.799	[0.72, 1.27]
\$63,000 or more	1.08	0.155	0.59	.556	[0.82, 1.43]
Constant	0.001	0.0001	-40.99	< .001	[0.0007, 0.0014]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 241.57, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 58.09, 95\% \text{ CI } [19.06, 177.02], z = 7.15, p < .001$, hence, the null hypothesis was rejected (Table 64).

Table 64

Multivariate BRM of Drug-Induced Liver Injury in Cohort VI (2013)

DILI	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	58.09	33.025	7.15	< .001	[19.06, 177.02]
Age	0.98	0.0009	-14.34	< .001	[0.984, 0.988]
Sex ^b					
Male	1.19	0.045	4.72	< .001	[1.11, 1.28]
Race ^c					
White	1.16	0.098	1.76	.079	[0.98, 1.37]
Black	0.90	0.088	-1.06	.290	[0.74, 1.09]
Hispanic	1.10	0.109	0.97	.334	[0.90, 1.33]
Asian\Pac. Islander	1.36	0.186	2.28	.022	[1.04, 1.78]
Native American	0.74	0.224	-0.97	.333	[0.41, 1.34]
Other	1.16	0.154	1.14	.253	[0.89, 1.51]
Median income ^d					

\$1 - \$38,999	0.88	0.102	-1.08	.282	[0.70, 1.10]
\$39,000 - \$47,999	0.81	0.094	-1.77	.077	[0.64, 1.02]
\$48,000 - \$62,999	0.79	0.093	-1.98	.047	[0.62, 0.99]
\$63,000 or more	0.90	0.106	-0.89	.374	[0.71, 1.13]
Constant	0.001	0.0001	-47.78	< .001	[0.0007, 0.0013]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 250.59, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 33.80, 95\% CI [8.55, 133.49], z = 5.02, p < .001$, hence, the null hypothesis was rejected (Table 65).

Table 65

Multivariate BRM of Drug-Induced Liver Injury in Cohort V (2014)

DILI	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	33.80	23.688	5.02	< .001	[8.55, 133.49]
Age	0.98	0.0009	-14.04	< .001	[0.984, 0.988]
Sex ^b					
Male	1.28	0.050	6.45	< .001	[1.19, 1.39]
Race ^c					

White	1.15	0.106	1.55	.120	[0.96, 1.38]
Black	0.88	0.093	-1.14	.254	[0.72, 1.09]
Hispanic	1.16	0.123	1.45	.147	[0.94, 1.43]
Asian\Pac. Islander	1.40	0.201	2.38	.017	[1.06, 1.86]
Native American	1.16	0.292	0.59	.554	[0.70, 1.90]
Other	1.03	0.149	0.26	.798	[0.78, 1.37]
Median income ^d					
\$1 - \$38,999	0.84	0.097	-1.49	.136	[0.66, 1.05]
\$39,000 - \$47,999	0.76	0.090	-2.25	.024	[0.60, 0.96]
\$48,000 - \$62,999	0.75	0.089	-2.35	.019	[0.59, 0.95]
\$63,000 or more	0.73	0.088	-2.54	.011	[0.58, 0.93]
Constant	0.001	0.0001	-46.02	< .001	[0.0007, 0.0013]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 231.04, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 49.66, 95\% \text{ CI } [12.64, 195.14], z = 5.59, p < .001$, hence, the null hypothesis was rejected (Table 66).

Table 66

Multivariate BRM of Drug-Induced Liver Injury in Cohort VI (2015)

DILI	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	49.66	34.676	5.59	< .001	[12.64, 195.14]
Age	0.98	0.001	-13.68	< .001	[0.982, 0.986]
Sex ^b					
Male	1.35	0.061	6.57	< .001	[1.23, 1.47]
Race ^c					
White	1.00	0.101	0.08	.939	[0.82, 1.22]
Black	0.86	0.099	-1.27	.203	[0.68, 1.08]
Hispanic	1.08	0.125	0.68	.497	[0.86, 1.35]
Asian\Pac. Islander	0.89	0.159	-0.65	.517	[0.62, 1.26]
Native American	0.83	0.264	-0.57	.568	[0.44, 1.55]
Other	1.11	0.176	0.66	.511	[0.81, 1.51]
Median income ^d					
\$1 - \$38,999	1.15	0.188	0.90	.367	[0.84, 1.59]
\$39,000 - \$47,999	1.06	0.174	0.36	.721	[0.76, 1.46]
\$48,000 - \$62,999	1.05	0.174	0.31	.754	[0.76, 1.45]
\$63,000 or more	0.99	0.165	-0.05	.958	[0.71, 1.37]
Constant	0.0008	0.0001	-36.61	< .001	[0.0005, 0.0012]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, drug-induced liver injury, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,592.67, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of liver injury, $RR = 47.27, 95\% CI [27.65, 80.81], z = 14.10, p < .001$, hence, the null hypothesis was rejected (Table 67).

Table 67

Multivariate BRM of Drug-Induced Liver Injury in the Combined Cohort

DILI	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	47.27	12.932	14.10	< .001	[27.65, 80.81]
Age	0.98	3.81e-04	-37.30	< .001	[0.984, 0.986]
Sex ^b					
Male	1.26	0.019	14.95	< .001	[1.22, 1.30]
Race ^c					
White	1.03	0.031	1.23	.218	[0.97, 1.10]
Black	0.84	0.029	-4.85	< .001	[0.78, 0.90]
Hispanic	1.03	0.038	0.92	.357	[0.96, 1.11]
Asian\Pac. Islander	1.22	0.068	3.70	< .001	[1.10, 1.37]
Native American	0.99	0.102	-0.05	.957	[0.81, 1.21]
Other	1.03	0.053	0.58	.561	[0.93, 1.14]

Median income^d

\$1 - \$38,999	0.98	0.049	-0.40	.689	[0.88, 1.08]
\$39,000 - \$47,999	0.93	0.047	-1.36	.175	[0.84, 1.03]
\$48,000 - \$62,999	0.92	0.047	-1.60	.109	[0.83, 1.01]
\$63,000 or more	0.98	0.050	-0.31	.759	[0.88, 1.08]
Constant	0.001	6.16e-05	-116.22	< .001	[0.0009, 0.0011]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval, *DILI* =
drug-induced liver injury, *Pac.* = pacific, *Constant* = baseline risk.

Venous thromboembolism results. An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 11,333.45, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of venous thromboembolism, $RR = 3.23, 95\% CI [0.83, 12.50], z = 1.70, p = .089$ (Table 68).

Table 68

Multivariate BRM of Venous Thromboembolism in Cohort I (2010)

VTE	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% <i>CI</i>
Androgen toxicity ^a					
Yes	3.23	2.231	1.70	.089	[0.83, 12.50]
Age	1.01	0.0001	85.81	< .001	[1.0161, 1.0169]
Sex ^b					
Male	1.24	0.008	30.62	< .001	[1.22, 1.25]
Race ^c					

White	1.03	0.011	2.68	.007	[1.00, 1.05]
Black	1.33	0.018	20.95	< .001	[1.30, 1.37]
Hispanic	0.81	0.014	-11.59	< .001	[0.78, 0.84]
Asian\Pac. Islander	0.51	0.019	-17.60	< .001	[0.47, 0.55]
Native American	0.90	0.044	-1.94	.052	[0.82, 1.00]
Other	0.85	0.024	-5.71	< .001	[0.80, 0.89]
Median income ^d					
\$1 - \$38,999	1.05	0.024	2.11	.035	[1.00, 1.09]
\$39,000 - \$47,999	1.06	0.025	2.59	.010	[1.01, 1.11]
\$48,000 - \$62,999	1.08	0.025	3.51	< .001	[1.03, 1.13]
\$63,000 or more	1.10	0.026	4.22	< .001	[1.05, 1.15]
Constant	0.003	0.0001	-201.97	< .001	[0.003, 0.004]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 11,534.88, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of venous thromboembolism, $RR = 5.29, 95\% CI [2.45, 11.42], z = 4.25, p < .001$, hence, the null hypothesis was rejected (Table 69).

Table 69

Multivariate BRM of Venous Thromboembolism in Cohort II (2011)

VTE	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	5.29	2.078	4.25	< .001	[2.45, 11.42]
Age	1.01	0.0001	86.77	< .001	[1.0161, 1.0168]
Sex ^b					
Male	1.25	0.008	33.15	< .001	[1.24, 1.27]
Race ^c					
White	0.96	0.011	-3.32	.001	[0.93, 0.98]
Black	1.21	0.017	13.85	< .001	[1.18, 1.25]
Hispanic	0.79	0.014	-13.04	< .001	[0.76, 0.82]
Asian\Pac. Islander	0.45	0.018	-19.20	< .001	[0.41, 0.49]
Native American	0.66	0.042	-6.50	< .001	[0.58, 0.74]
Other	0.84	0.021	-6.58	< .001	[0.80, 0.88]
Median income ^d					
\$1 - \$38,999	0.98	0.024	-0.48	.628	[0.94, 1.03]
\$39,000 - \$47,999	0.97	0.024	-0.85	.397	[0.93, 1.02]
\$48,000 - \$62,999	1.02	0.026	1.10	.269	[0.97, 1.08]
\$63,000 or more	1.05	0.026	1.95	.052	[0.99, 1.10]
Constant	0.004	0.0001	-186.69	< .001	[0.0040, 0.0045]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 8,446.96, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the risk of venous thromboembolism, $RR = 1.24$, 95% CI [0.17, 8.70], $z = 0.22, p = .824$ (Table 70).

Table 70

Multivariate BRM of Venous Thromboembolism in Cohort III (2012)

VTE	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	1.24	1.236	0.22	.824	[0.17, 8.70]
Age	1.01	0.0002	75.95	< .001	[1.0160, 1.0168]
Sex ^b					
Male	1.25	0.010	28.20	< .001	[1.23, 1.27]
Race ^c					
White	1.01	0.018	0.91	.363	[0.98, 1.05]
Black	1.35	0.027	15.32	< .001	[1.30, 1.41]
Hispanic	0.90	0.022	-4.17	< .001	[0.86, 0.94]
Asian\Pac. Islander	0.56	0.030	-10.62	< .001	[0.50, 0.62]
Native American	0.76	0.057	-3.54	< .001	[0.66, 0.88]
Other	0.97	0.028	-0.78	.438	[0.92, 1.03]

Median income^d

\$1 - \$38,999	1.00	0.029	0.09	.928	[0.94, 1.06]
\$39,000 - \$47,999	1.01	0.029	0.53	.595	[0.95, 1.07]
\$48,000 - \$62,999	1.07	0.031	2.56	.010	[1.01, 1.14]
\$63,000 or more	1.17	0.034	5.52	< .001	[1.11, 1.24]
Constant	0.003	0.0001	-156.65	< .001	[0.003, 0.004]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval, *Pac.* =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 9,322.98, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of venous thromboembolism, $RR = 6.96, 95\% CI [3.74, 12.95], z = 6.12, p < .0001$, hence, the null hypothesis was rejected (Table 71).

Table 71

Multivariate BRM of Venous Thromboembolism in Cohort IV (2013)

VTE	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% <i>CI</i>
Androgen toxicity ^a					
Yes	6.96	2.205	6.12	< .001	[3.74, 12.95]
Age	1.01	0.0002	74.68	< .001	[1.014, 1.015]
Sex ^b					
Male	1.28	0.009	33.22	< .001	[1.26, 1.30]
Race ^c					

White	1.00	0.016	0.01	.993	[0.96, 1.03]
Black	1.35	0.025	16.19	< .001	[1.30, 1.40]
Hispanic	0.81	0.017	-9.53	< .001	[0.77, 0.84]
Asian\Pac. Islander	0.53	0.021	-15.91	< .001	[0.49, 0.57]
Native American	0.77	0.049	-3.91	< .001	[0.68, 0.88]
Other	0.91	0.027	-2.95	.003	[0.86, 0.97]
Median income ^d					
\$1 - \$38,999	1.07	0.028	2.50	.012	[1.01, 1.12]
\$39,000 - \$47,999	1.05	0.028	2.13	.033	[1.00, 1.11]
\$48,000 - \$62,999	1.08	0.029	3.13	.002	[1.03, 1.14]
\$63,000 or more	1.15	0.031	5.32	< .001	[1.09, 1.22]
Constant	0.003	0.0001	-168.81	< .001	[0.003, 0.004]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 9,197.33, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of venous thromboembolism, $RR = 9.57, 95\% CI [5.76, 15.91], z = 8.72, p < .0001$, hence, the null hypothesis was rejected (Table 72).

Table 72

Multivariate BRM of Venous Thromboembolism in Cohort V (2014)

VTE	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	9.57	2.481	8.72		[5.76, 15.91]
Age	1.01	0.0002	73.62		[1.014, 1.015]
Sex ^b					
Male	1.28	0.009	32.11		[1.26, 1.30]
Race ^c					
White	1.07	0.019	3.70		[1.03, 1.10]
Black	1.44	0.029	17.93		[1.38, 1.49]
Hispanic	0.86	0.020	-6.31		[0.82, 0.90]
Asian\Pac. Islander	0.52	0.021	-15.53		[0.48, 0.57]
Native American	0.87	0.054	-2.10		[0.77, 0.99]
Other	0.94	0.029	-1.80		[0.89, 1.00]
Median income ^d					
\$1 - \$38,999	1.00	0.027	0.19		[0.95, 1.05]
\$39,000 - \$47,999	0.99	0.027	-0.18		[0.94, 1.04]
\$48,000 - \$62,999	1.03	0.028	1.30		[0.98, 1.09]
\$63,000 or more	1.09	0.030	3.18		[1.03, 1.15]
Constant	0.003	0.0001	-164.86		[0.0034, 0.0039]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *RR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 6,520.45, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of venous thromboembolism, $RR = 9.37, 95\% CI [5.07, 17.30], z = 7.16, p < .001$, hence, the null hypothesis was rejected (Table 73).

Table 73

Multivariate BRM of Venous Thromboembolism in Cohort VI (2015)

VTE	RR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	9.37	2.930	7.16	< .001	[5.07, 17.30]
Age	1.01	0.0002	61.53	< .001	[1.014, 1.015]
Sex ^b					
Male	1.28	0.011	28.56	< .001	[1.26, 1.31]
Race ^c					
White	1.09	0.023	4.39	< .001	[1.05, 1.14]
Black	1.54	0.036	18.49	< .001	[1.47, 1.61]
Hispanic	0.98	0.025	-0.50	.614	[0.93, 1.03]
Asian\Pac. Islander	0.57	0.026	-12.15	< .001	[0.52, 0.63]
Native American	0.86	0.063	-1.99	.046	[0.74, 0.99]
Other	1.04	0.037	1.28	.200	[0.97, 1.12]

Median income^d

\$1 - \$38,999	0.98	0.031	-0.61	.544	[0.92, 1.04]
\$39,000 - \$47,999	0.98	0.031	-0.52	.604	[0.92, 1.04]
\$48,000 - \$62,999	1.03	0.033	1.12	.263	[0.97, 1.10]
\$63,000 or more	1.10	0.036	3.05	.002	[1.03, 1.17]
Constant	0.003	0.0001	-140.41	< .001	[0.0033, 0.039]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline risk.

An adjusted binomial regression was conducted to examine the relationship between androgen toxicity, venous thromboembolism, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 55,876.02$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the risk of venous thromboembolism, $RR = 6.42$, 95% CI [4.77, 8.63], $z = 12.32$, $p < .001$, hence, the null hypothesis was rejected (Table 74).

Table 74

Multivariate BRM of Venous Thromboembolism in the Combined Cohort

VTE	<i>RR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	6.42	0.969	12.32	< .001	[4.77, 8.63]
Age	1.01	8.51e-05	187.88	< .001	[1.015, 1.016]
Sex ^b					
Male	1.26	0.003	75.76	< .001	[1.25, 1.27]

Race ^c					
White	0.99	0.006	-0.50	.619	[0.98, 1.00]
Black	1.32	0.009	-40.18	< .001	[1.30, 1.34]
Hispanic	0.82	0.006	-22.55	< .001	[0.81, 0.84]
Asian\Pac. Islander	0.50	0.008	-40.21	< .001	[0.48, 0.52]
Native American	0.79	0.020	-9.07	< .001	[0.75, 0.83]
Other	0.89	0.010	-9.14	< .001	[0.87, 0.91]
Median income ^d					
\$1 - \$38,999	1.01	0.011	1.58	.114	[0.99, 1.03]
\$39,000 - \$47,999	1.01	0.011	1.43	.154	[0.99, 1.03]
\$48,000 - \$62,999	1.05	0.011	5.24	< .001	[1.03, 1.08]
\$63,000 or more	1.11	0.012	9.47	< .001	[1.08, 1.13]
Constant	0.003	5.2e-05	-421.28	< .001	[0.003, 0.004]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
RR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, *CI* = confidence interval, *VTE* =
venous thromboembolism, *Pac.* = pacific, *Constant* = baseline risk.

Bivariate and multivariate point estimates of each health outcome in the combined cohort are compared in Figure 20.

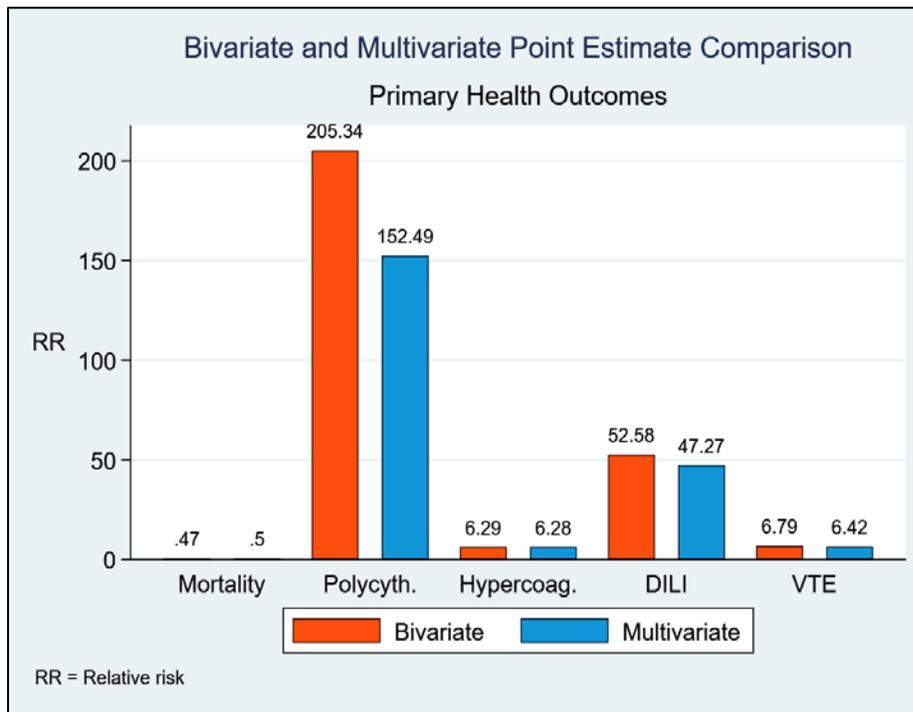


Figure 20. Bivariate and multivariate health outcomes point estimates.

Aim 1 [RQ 2]. What is the relationship between androgen toxicity and incidence of inpatient variables?

H₀₂. There is no relationship between androgen toxicity and incidence of inpatient variables.

H_{a2}. There is a relationship between androgen toxicity and incidence of inpatient variables.

Generalized linear negative binomial regression was conducted to examine the multivariate incidence relationship between androgen toxicity, inpatient variables, and covariates while providing better data fit in conditions of data overdispersion. The study design assumptions of the NBRM were (a) ratio discrete count values for dependent variables and (b) independent variables measured on ratio, interval, ordinal, or nominal scales (Hardin & Hilbe,

2012). The data assumptions of the NBRM were (a) dependent variable values that follow a Poisson distribution, (b) lack of collinearity, and (c) overdispersion of data values (Hardin & Hilbe, 2012). Prior to the analysis, the assumptions of a Poisson distribution and a lack of collinearity were assessed. The overdispersion assumption was tested and reported with each NBRM analysis.

Poisson distribution. Long format tabulation with detailed summary statistics was conducted to determine the data distribution of each ratio discrete inpatient variable. The results of visual inspection of the tabulation showed characteristic Poisson distributions for each inpatient variable for each yearly cohort. The results of the detailed summary of means and standard deviations of the combined cohort were 4.73 (6.27), 4.90 (3.46), 10.09 (5.90), 0.29 (0.72), and 1.72 (2.18) for the variables length of stay, chronic conditions, diagnoses, ecodes, and procedures, respectively. The summary results showed substantially higher variance than the mean for each inpatient variable, suggesting considerable overdispersion of the data.

Collinearity. A collinearity diagnostic was conducted to determine the variance inflation factors among the independent variable and the dependent variables. The results of the collinearity diagnostics showed variance inflation factors of less than a value of four, suggesting that the collinearity assumption was met for each of the variables. The mean variance inflation factors among the study variables were 1.87, 1.92, 1.92, 1.93, 1.95, and 1.97 for cohorts one, two, three, four, five, and six, respectively. The mean variance inflation factor for the combined cohort was 1.65.

Length of stay results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.3e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was

deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 292,313.87, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of length of stay, $IRR = 0.96, 95\% \text{ CI } [0.75, 1.24], z = -0.24, p = .807$ (Table 75).

Table 75

Multivariate NBRM of Length of Stay in Cohort I (2010)

Length of stay	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.96	0.123	-0.24	.807	[0.75, 1.24]
Age	1.00	< 0.001	457.93	< .001	[1.0082, 1.0083]
Sex ^b					
Male	1.14	< 0.001	192.08	< .001	[1.144, 1.147]
Race ^c					
White	1.04	0.001	35.83	< .001	[1.03, 1.04]
Black	1.22	0.001	146.92	< .001	[1.22, 1.23]
Hispanic	1.06	0.001	38.50	< .001	[1.05, 1.06]
Asian\Pac. Islander	1.12	0.003	43.05	< .001	[1.11, 1.12]
Native American	1.04	0.004	8.95	< .001	[1.03, 1.04]
Other	1.15	0.002	59.12	< .001	[1.15, 1.16]

Median income^d

\$1 - \$38,999	0.83	0.001	-81.41	< .001	[0.83, 0.84]
\$39,000 - \$47,999	0.80	0.001	-100.86	< .001	[0.79, 0.80]
\$48,000 - \$62,999	0.80	0.001	-98.51	< .001	[0.801, 0.808]
\$63,000 or more	0.79	0.001	-102.11	< .001	[0.79, 0.80]
Constant	3.20	0.008	461.05	< .001	[3.18, 3.21]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.3e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 267,963.62$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of length of stay, $IRR = 0.86$, 95% CI [0.71, 1.04], $z = -1.51$, $p = .132$ (Table 76).

Table 76

Multivariate NBRM of Length of Stay in Cohort II (2011)

Length of stay	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.86	0.083	-1.51	.132	[0.71, 1.04]
Age	1.00	< 0.001	442.40	< .001	[1.0077, 1.0078]
Sex ^b					

Male	1.13	< 0.001	184.65	< .001	[1.134, 1.137]
Race ^c					
White	1.05	0.001	43.64	< .001	[1.051, 1.056]
Black	1.22	0.001	137.15	< .001	[1.21, 1.22]
Hispanic	1.05	0.001	35.86	< .001	[1.05, 1.06]
Asian\Pac. Islander	1.09	0.003	32.04	< .001	[1.08, 1.10]
Native American	1.06	0.005	13.24	< .001	[1.05, 1.07]
Other	1.17	0.002	68.44	< .001	[1.16, 1.17]
Median income ^d					
\$1 - \$38,999	0.92	0.002	-32.23	< .001	[0.920, 0.929]
\$39,000 - \$47,999	0.88	0.002	-49.75	< .001	[0.88, 0.89]
\$48,000 - \$62,999	0.87	0.002	-57.12	< .001	[0.86, 0.87]
\$63,000 or more	0.87	0.002	-55.79	< .001	[0.86, 0.87]
Constant	2.96	0.008	394.32	< .001	[2.94, 2.98]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 8.6e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 188,218.53$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a

significant effect on the incidence of length of stay, $IRR = 0.92$, 95% CI [0.74, 1.14], $z = -0.24$, $p = .465$ (Table 77).

Table 77

Multivariate NBRM of Length of Stay in Cohort III (2012)

Length of stay	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.92	0.098	-0.73	.465	[0.74, 1.14]
Age	1.00	< 0.001	375.86	< .001	[1.0072, 1.0073]
Sex ^b					
Male	1.12	< 0.001	155.32	< .001	[1.126, 1.129]
Race ^c					
White	1.01	0.001	7.98	< .001	[1.010, 1.016]
Black	1.16	0.002	82.82	< .001	[1.16, 1.17]
Hispanic	1.02	0.002	10.42	< .001	[1.01, 1.02]
Asian\Pac. Islander	1.05	0.003	12.90	< .001	[1.04, 1.05]
Native American	0.99	0.005	-1.61	.108	[0.97, 1.00]
Other	1.12	0.002	42.93	< .001	[1.11, 1.12]
Median income ^d					
\$1 - \$38,999	0.86	0.002	-55.02	< .001	[0.86, 0.87]
\$39,000 - \$47,999	0.83	0.002	-66.04	< .001	[0.83, 0.84]
\$48,000 - \$62,999	0.83	0.002	-66.53	< .001	[0.83, 0.84]
\$63,000 or more	0.83	0.002	-66.52	< .001	[0.83, 0.84]

Constant	3.27	0.010	372.56	< .001	[3.25, 3.29]
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Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.1e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 230,395.33$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of length of stay, $IRR = 1.14$, 95% CI [0.97, 1.34], $z = 1.60$, $p = .109$ (Table 78).

Table 78

Multivariate NBRM of Length of Stay in Cohort IV (2013)

Length of stay	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	1.14	0.095	1.60	.109	[0.97, 1.34]
Age	1.00	< 0.001	404.28	< .001	[1.0072, 1.0073]
Sex ^b					
Male	1.14	< 0.001	190.44	< .001	[1.144, 1.147]
Race ^c					
White	1.00	0.001	5.41	< .001	[1.00, 1.01]
Black	1.17	0.002	88.89	< .001	[1.16, 1.17]

Hispanic	1.01	0.001	7.48	< .001	[1.010, 1.017]
Asian\Pac. Islander	1.06	0.002	23.04	< .001	[1.06, 1.07]
Native American	1.03	0.005	7.74	< .001	[1.02, 1.04]
Other	1.10	0.002	37.10	< .001	[1.09, 1.10]
Median income ^d					
\$1 - \$38,999	0.89	0.002	-48.97	< .001	[0.88, 0.89]
\$39,000 - \$47,999	0.86	0.002	-61.53	< .001	[0.860, 0.868]
\$48,000 - \$62,999	0.85	0.002	-64.42	< .001	[0.85, 0.86]
\$63,000 or more	0.86	0.002	-62.55	< .001	[0.85, 0.86]
Constant	3.18	0.009	402.56	< .001	[3.17, 3.20]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.1e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 229,103.06$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of length of stay, $IRR = 1.33$, 95% CI [1.14, 1.54], $z = 3.69$, $p < .001$, hence, the null hypothesis was rejected (Table 79).

Table 79

Multivariate NBRM of Length of Stay in Cohort V (2014)

Length of stay	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.33	0.102	3.69	< .001	[1.14, 1.54]
Age	1.00	< 0.001	388.94	< .001	[1.0070, 1.0071]
Sex ^b					
Male	1.15	< 0.001	204.03	< .001	[1.156, 1.159]
Race ^c					
White	1.00	0.001	4.14	< .001	[1.003, 1.009]
Black	1.18	0.002	90.04	< .001	[1.17, 1.18]
Hispanic	1.00	0.001	3.92	< .001	[1.00, 1.01]
Asian\Pac. Islander	1.05	0.002	17.94	< .001	[1.04, 1.05]
Native American	1.04	0.005	8.73	< .001	[1.03, 1.05]
Other	1.09	0.002	34.48	< .001	[1.08, 1.09]
Median income ^d					
\$1 - \$38,999	0.88	0.002	-49.71	< .001	[0.88, 0.89]
\$39,000 - \$47,999	0.85	0.002	-64.42	< .001	[0.85, 0.86]
\$48,000 - \$62,999	0.85	0.002	-65.82	< .001	[0.84, 0.85]
\$63,000 or more	0.85	0.002	-66.41	< .001	[0.84, 0.85]
Constant	3.28	0.009	403.00	< .001	[3.26, 3.30]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 8.4e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 173,696.21$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of length of stay, $IRR = 0.81$, 95% CI [0.67, 0.98], $z = -2.08$, $p = .037$, hence, the null hypothesis was rejected (Table 80).

Table 80

Multivariate NBRM of Length of Stay in Cohort VI (2015)

Length of stay	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.81	0.080	-2.08	.037	[0.67, 0.98]
Age	1.00	< 0.001	342.34	< .001	[1.0070, 1.0071]
Sex ^b					
Male	1.15	< 0.001	179.82	< .001	[1.15, 1.16]
Race ^c					
White	1.00	0.001	3.34	.001	[1.002, 1.009]
Black	1.16	0.002	72.17	< .001	[1.15, 1.16]
Hispanic	1.00	0.002	4.14	< .001	[1.00, 1.01]
Asian\Pac. Islander	1.06	0.003	20.23	< .001	[1.05, 1.07]
Native American	1.06	0.005	12.01	< .001	[1.05, 1.08]

Other	1.09	0.003	30.01	< .001	[1.08, 1.10]
Median income ^d					
\$1 - \$38,999	0.90	0.002	-34.67	< .001	[0.90, 0.91]
\$39,000 - \$47,999	0.87	0.002	-46.52	< .001	[0.86, 0.87]
\$48,000 - \$62,999	0.86	0.002	-49.21	< .001	[0.86, 0.87]
\$63,000 or more	0.86	0.002	-49.82	< .001	[0.85, 0.86]
Constant	3.22	0.011	336.78	< .001	[3.20, 3.24]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.5e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, length of stay, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 137,4023.84$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of length of stay, $IRR = 1.03$, 95% CI [0.96, 1.12], $z = 0.99$, $p = .324$ (Table 81).

Table 81

Multivariate NBRM of Length of Stay in the Combined Cohort

Length of stay	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	1.03	0.040	0.99	.324	[0.96, 1.12]

Age	1.00	7.63e-06	987.66	< .001	[1.0074, 1.0075]
Sex ^b					
Male	1.14	0.0003	452.19	< .001	[1.144, 1.146]
Race ^c					
White	1.02	0.0005	44.62	< .001	[1.025, 1.027]
Black	1.19	0.0008	262.40	< .001	[1.193, 1.196]
Hispanic	1.03	0.0007	45.41	< .001	[1.032, 1.035]
Asian\Pac. Islander	1.08	0.001	67.01	< .001	[1.080, 1.085]
Native American	1.04	0.002	22.57	< .001	[1.04, 1.05]
Other	1.12	0.001	116.74	< .001	[1.12, 1.13]
Median income ^d					
\$1 - \$38,999	0.88	0.0008	-126.97	< .001	[0.87, 0.88]
\$39,000 - \$47,999	0.84	0.0008	-162.66	< .001	[0.84, 0.85]
\$48,000 - \$62,999	0.84	0.0008	-168.04	< .001	[0.842, 0.845]
\$63,000 or more	0.84	0.0008	-168.27	< .001	[0.840, 0.844]
Constant	3.18	0.003	981.04	< .001	[3.17, 3.19]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Chronic condition results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.0e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,390,798.88$, $p < .0001$,

indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of chronic conditions, $IRR = 1.37$, 95% CI [1.15, 1.62], $z = 3.66$, $p < .0001$, hence, the null hypothesis was rejected (Table 82).

Table 82

Multivariate NBRM of Chronic Conditions in Cohort I (2010)

Chronic conditions	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.37	0.118	3.66	< .001	[1.15, 1.62]
Age	1.02	< 0.001	1526.71	< .001	[1.0218, 1.0219]
Sex ^b					
Male	1.19	< 0.001	340.62	< .001	[1.191, 1.194]
Race ^c					
White	0.97	< 0.001	-29.58	< .001	[0.974, 0.977]
Black	1.07	0.001	65.98	< .001	[1.06, 1.07]
Hispanic	0.82	< 0.001	-159.25	< .001	[0.823, 0.827]
Asian\Pac. Islander	0.78	0.001	-116.50	< .001	[0.77, 0.78]
Native American	0.95	0.003	-14.73	< .001	[0.94, 0.95]
Other	0.88	0.001	-61.53	< .001	[0.88, 0.89]
Median income ^d					
\$1 - \$38,999	1.01	0.001	6.91	< .001	[1.00, 1.01]
\$39,000 - \$47,999	0.99	0.001	-0.87	.386	[0.99, 1.00]
\$48,000 - \$62,999	0.97	0.001	-15.22	< .001	[0.971, 0.978]

\$63,000 or more	0.92	0.001	-45.86	< .001	[0.922, 0.928]
Constant	1.16	0.002	76.49	< .001	[1.15, 1.16]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.3e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,468,801.47$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of chronic conditions, $IRR = 1.23$, 95% CI [1.08, 1.40], $z = 3.25$, $p = .001$, hence, the null hypothesis was rejected (Table 83).

Table 83

Multivariate NBRM of Chronic Conditions in Cohort II (2011)

Chronic conditions	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	1.23	0.080	3.25	.001	[1.08, 1.40]
Age	1.02	< 0.001	1553.27	< .001	[1.0216, 1.0217]
Sex ^b					
Male	1.19	< 0.001	356.85	< .001	[1.196, 1.198]
Race ^c					
White	0.97	< 0.001	-31.20	< .001	[0.971, 0.974]

Black	1.07	0.001	69.18	< .001	[1.074, 1.078]
Hispanic	0.83	0.001	-147.30	< .001	[0.833, 0.837]
Asian\Pac. Islander	0.74	0.001	-132.85	< .001	[0.73, 0.74]
Native American	1.00	0.003	1.25	.212	[0.99, 1.01]
Other	0.87	0.001	-74.70	< .001	[0.871, 0.877]
Median income ^d					
\$1 - \$38,999	1.02	0.001	11.49	< .001	[1.01, 1.02]
\$39,000 - \$47,999	0.98	0.001	-10.72	< .001	[0.97, 0.98]
\$48,000 - \$62,999	0.95	0.001	-23.68	< .001	[0.95, 0.96]
\$63,000 or more	0.90	0.001	-54.61	< .001	[0.901, 0.907]
Constant	1.24	0.002	105.60	< .001	[1.24, 1.25]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 9.9e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,826,722.07$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of chronic conditions, $IRR = 1.14$, 95% CI [0.98, 1.32], $z = 1.73$, $p = .083$ (Table 84).

Table 84

Multivariate NBRM of Chronic Conditions in Cohort III (2012)

Chronic conditions	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.44	0.087	1.73	.083	[0.98, 1.32]
Age	1.02	< 0.001	1340.17	< .001	[1.0208, 1.0209]
Sex ^b					
Male	1.19	< 0.001	309.24	< .001	[1.191, 1.193]
Race ^c					
White	1.02	0.001	23.27	< .001	[1.02, 1.03]
Black	1.12	0.001	85.69	< .001	[1.12, 1.13]
Hispanic	0.87	0.001	-79.45	< .001	[0.874, 0.879]
Asian\Pac. Islander	0.72	0.002	-99.99	< .001	[0.72, 0.73]
Native American	1.04	0.004	9.67	< .001	[1.03, 1.05]
Other	0.92	0.001	-37.29	< .001	[0.92, 0.93]
Median income ^d					
\$1 - \$38,999	1.01	0.002	8.62	< .001	[1.01, 1.02]
\$39,000 - \$47,999	0.98	0.001	-7.24	< .001	[0.981, 0.989]
\$48,000 - \$62,999	0.96	0.001	-17.05	< .001	[0.962, 0.969]
\$63,000 or more	0.90	0.001	-46.43	< .001	[0.90, 0.91]
Constant	1.27	0.003	99.09	< .001	[1.26, 1.28]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.3e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,236,404.47$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of chronic conditions, $IRR = 1.17$, 95% CI [1.04, 1.31], $z = 2.68$, $p = .007$, hence, the null hypothesis was rejected (Table 85).

Table 85

Multivariate NBRM of Chronic Conditions in Cohort IV (2013)

Chronic conditions	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.17	0.069	2.68	.007	[1.04, 1.31]
Age	1.02	< 0.001	1475.77	< .001	[1.0213, 1.0214]
Sex ^b					
Male	1.20	< 0.001	354.41	< .001	[1.204, 1.207]
Race ^c					
White	1.03	0.001	29.51	< .001	[1.032, 1.037]
Black	1.13	0.001	97.55	< .001	[1.13, 1.14]
Hispanic	0.88	0.001	-81.96	< .001	[0.88, 0.89]
Asian\Pac. Islander	0.81	0.001	-94.87	< .001	[0.80, 0.81]
Native American	1.09	0.004	23.50	< .001	[1.08, 1.09]

Other	0.90	0.001	-48.58	< .001	[0.90, 0.91]
Median income ^d					
\$1 - \$38,999	1.03	0.001	16.88	< .001	[1.02, 1.03]
\$39,000 - \$47,999	0.98	0.001	-6.90	< .001	[0.98, 0.99]
\$48,000 - \$62,999	0.96	0.001	-22.03	< .001	[0.95, 0.96]
\$63,000 or more	0.90	0.001	-56.45	< .001	[0.89, 0.90]
Constant	1.25	0.002	101.03	< .001	[1.24, 1.25]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.4e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 2,210,288.65$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of chronic conditions, $IRR = 1.21$, 95% CI [1.08, 1.36], $z = 3.42$, $p = .001$, hence, the null hypothesis was rejected (Table 86).

Table 86

Multivariate NBRM of Chronic Conditions in Cohort V (2014)

Chronic conditions	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.21	0.069	3.42	.001	[1.08, 1.36]

Age	1.02	< 0.001	1465.77	< .001	[1.0213, 1.0214]
Sex ^b					
Male	1.20	< 0.001	352.64	< .001	[1.204, 1.207]
Race ^c					
White	1.03	0.001	31.14	< .001	[1.03, 1.04]
Black	1.14	0.001	97.8	< .001	[1.142, 1.148]
Hispanic	0.88	0.001	-79.92	< .001	[0.88, 0.89]
Asian\Pac. Islander	0.80	0.001	-97.46	< .001	[0.801, 0.808]
Native American	1.10	0.004	27.30	< .001	[1.09, 1.11]
Other	0.92	0.001	-41.19	< .001	[0.91, 0.92]
Median income ^d					
\$1 - \$38,999	1.04	0.001	25.00	< .001	[1.04, 1.05]
\$39,000 - \$47,999	1.00	0.001	3.11	.002	[1.002, 1.009]
\$48,000 - \$62,999	0.97	0.001	-11.57	< .001	[0.97, 0.98]
\$63,000 or more	0.92	0.001	-42.94	< .001	[0.91, 0.92]
Constant	1.26	0.002	104.13	< .001	[1.26, 1.27]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis.

An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,654,118.95$, $p < .0001$, indicated that the model fit

was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of chronic conditions, $IRR = 1.05$, 95% CI [0.92, 1.20], $z = 0.79$, $p = .430$ (Table 87).

Table 87

Multivariate NBRM of Chronic Conditions in Cohort VI (2015)

Chronic conditions	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.05	0.073	0.79	.430	[0.92, 1.20]
Age	1.02	< 0.001	1270.32	< .001	[1.0210, 1.0211]
Sex ^b					
Male	1.20	< 0.001	306.98	< 0.001	[1.201, 1.204]
Race ^c					
White	1.20	0.001	20.84	< .001	[1.02, 1.03]
Black	1.13	0.001	80.74	< .001	[1.130, 1.137]
Hispanic	0.88	0.001	-73.06	< .001	[0.881, 0.887]
Asian\Pac. Islander	0.82	0.002	-79.64	< .001	[0.819, 0.827]
Native American	1.10	0.004	23.94	< .001	[1.09, 1.11]
Other	0.90	0.002	-40.49	< .001	[0.90, 0.91]
Median income ^d					
\$1 - \$38,999	1.03	0.002	16.36	< .001	[1.03, 1.04]
\$39,000 - \$47,999	1.00	0.002	0.22	.824	[0.99, 1.00]
\$48,000 - \$62,999	0.97	0.002	-10.14	< .001	[0.97, 0.98]

\$63,000 or more	0.92	0.002	-35.50	< .001	[0.920, 0.928]
Constant	1.34	0.003	111.42	< .001	[1.33, 1.35]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 7.5e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, chronic conditions, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1.27e+07$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of chronic conditions, $IRR = 1.20$, 95% CI [1.14, 1.27], $z = 6.77$, $p < .001$, hence, the null hypothesis was rejected (Table 88).

Table 88

Multivariate NBRM of Chronic Conditions in the Combined Cohort

Chronic conditions	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	1.20	0.033	6.77	< .001	[1.14, 1.27]
Age	1.02	6.16e-06	3528.57	< .001	[1.0214, 1.0215]
Sex ^b					
Male	1.20	0.0002	826.48	< .001	[1.200, 1.201]
Race ^c					
White	1.02	0.0004	48.68	< .001	[1.020, 1.022]

Black	1.12	0.0005	228.81	< .001	[1.121, 1.124]
Hispanic	0.87	0.0004	-237.13	< .001	[0.873, 0.874]
Asian\Pac. Islander	0.79	0.0007	-240.11	< .001	[0.796, 0.798]
Native American	1.05	0.001	33.73	< .001	[1.050, 1.056]
Other	0.91	0.0007	-114.28	< .001	[0.910, 0.913]
Median income ^d					
\$1 - \$38,999	1.03	0.0007	40.31	< .001	[1.02, 1.03]
\$39,000 - \$47,999	0.99	0.0007	-4.13	< .001	[0.995, 0.998]
\$48,000 - \$62,999	0.97	0.0007	-37.64	< .001	[0.970, 0.972]
\$63,000 or more	0.91	0.0007	-113.26	< .001	[0.914, 0.917]
Constant	1.23	0.001	229.94	< .001	[1.230, 1.235]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Diagnosis results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,556,646.48$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of diagnoses, $IRR = 1.26$, 95% CI [1.10, 1.46], $z = 3.29$, $p = .001$, hence, the null hypothesis was rejected (Table 89).

Table 89

Multivariate NBRM of Diagnoses in Cohort I (2010)

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.26	0.91	3.29	.001	[1.10, 1.46]
Age	1.01	< 0.001	1237.20	< .001	[1.0134, 1.0135]
Sex ^b					
Male	1.06	< 0.001	155.82	< .001	[1.067, 1.068]
Race ^c					
White	1.00	< 0.001	8.75	< .001	[1.004, 1.007]
Black	1.04	< 0.001	56.91	< .001	[1.04, 1.05]
Hispanic	0.91	< 0.001	-94.77	< .001	[0.912, 0.916]
Asian\Pac. Islander	0.91	0.001	-51.59	< .001	[0.91, 0.92]
Native American	0.96	0.002	-14.91	< .001	[0.95, 0.96]
Other	0.96	0.001	-26.09	< .001	[0.95, 0.96]
Median income ^d					
\$1 - \$38,999	1.02	0.001	20.00	< .001	[1.024, 1.029]
\$39,000 - \$47,999	1.02	0.001	19.12	< .001	[1.023, 1.028]
\$48,000 - \$62,999	1.02	0.001	15.92	< .001	[1.01, 1.02]
\$63,000 or more	1.00	0.001	0.28	.776	[0.99, 1.00]
Constant	3.85	0.005	875.67	< .001	[3.84, 3.86]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 4.3e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,609,663.62$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of diagnoses, $IRR = 1.17$, 95% CI [1.05, 1.31], $z = 2.89$, $p = .004$, hence, the null hypothesis was rejected (Table 90).

Table 90

Multivariate NBRM of Diagnoses in Cohort II (2011)

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.17	0.065	2.89	.004	[1.05, 1.31]
Age	1.01	< 0.001	1261.65	< .001	[1.01375, 1.01379]
Sex ^b					
Male	1.07	< 0.001	175.31	< .001	[1.075, 1.077]
Race ^c					
White	0.99	< 0.001	-4.06	< .001	[0.995, 0.998]
Black	1.04	< 0.001	49.66	< .001	[1.043, 1.046]
Hispanic	0.93	< 0.001	-73.42	< .001	[0.92, 0.93]
Asian\Pac. Islander	0.87	0.001	-74.69	< .001	[0.87, 0.88]
Native American	1.04	0.003	14.84	< .001	[1.03, 1.05]

Other	0.92	0.001	-57.17	< .001	[0.91, 0.92]
Median income ^d					
\$1 - \$38,999	1.02	0.001	18.67	< .001	[1.02, 1.03]
\$39,000 - \$47,999	1.00	0.001	0.94	.348	[0.99, 1.00]
\$48,000 - \$62,999	0.99	0.001	-1.68	.092	[0.99, 1.00]
\$63,000 or more	0.96	0.001	-23.49	< .001	[0.962, 0.967]
Constant	4.13	0.007	833.34	< .001	[4.12, 4.14]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,234,236.41$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of diagnoses, $IRR = 1.10$, 95% CI [0.97, 1.24], $z = 1.52$, $p = .128$ (Table 91).

Table 91

Multivariate NBRM of Diagnoses in Cohort III (2012)

Diagnoses	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	1.10	0.070	1.52	.128	[0.97, 1.24]

Age	1.01	< 0.001	1106.72	< .001	[1.0134, 1.0135]
Sex ^b					
Male	1.07	< 0.001	152.35	< .001	[1.073, 1.075]
Race ^c					
White	1.02	0.001	27.25	< .001	[1.02, 1.03]
Black	1.08	0.001	69.96	< .001	[1.082, 1.087]
Hispanic	0.92	0.001	-57.61	< .001	[0.923, 0.928]
Asian\Pac. Islander	0.87	0.002	-56.71	< .001	[0.86, 0.87]
Native American	1.02	0.003	8.01	< .001	[1.02, 1.03]
Other	0.97	0.001	-15.03	< .001	[0.972, 0.978]
Median income ^d					
\$1 - \$38,999	1.03	0.001	20.44	< .001	[1.030, 1.037]
\$39,000 - \$47,999	1.01	0.001	8.37	< .001	[1.010, 1.017]
\$48,000 - \$62,999	1.00	0.001	4.87	< .001	[1.00, 1.01]
\$63,000 or more	0.97	0.001	-17.28	< .001	[0.96, 0.97]
Constant	4.16	0.008	715.62	< .001	[4.15, 4.18]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.9e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the

five-predictor model, $LR \chi^2(12) = 1,523,983.83, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon adjustment of covariates, had a significant effect on the incidence of diagnoses, $IRR = 1.18, 95\% \text{ CI } [1.07, 1.30], z = 3.35, p = .001$, hence, the null hypothesis was rejected (Table 92).

Table 92

Multivariate NBRM of Diagnoses in Cohort IV (2013)

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.18	0.058	3.35	.001	[1.07, 1.30]
Age	1.01	< 0.001	1223.77	< .001	[1.01362, 1.01367]
Sex ^b					
Male	1.08	< 0.001	179.82	< .001	[1.080, 1.081]
Race ^c					
White	1.02	< 0.001	31.27	< .001	[1.02, 1.03]
Black	1.08	0.001	72.36	< .001	[1.07, 1.08]
Hispanic	0.94	0.001	-50.86	< .001	[0.941, 0.945]
Asian\Pac. Islander	0.92	0.001	-47.97	< .001	[0.91, 0.92]
Native American	1.10	0.003	32.45	< .001	[1.09, 1.10]
Other	0.94	0.001	-38.49	< .001	[0.93, 0.94]
Median income ^d					
\$1 - \$38,999	1.03	0.001	24.02	< .001	[1.032, 1.038]
\$39,000 - \$47,999	1.00	0.001	5.05	< .001	[1.00, 1.01]

\$48,000 - \$62,999	0.99	0.001	-4.13	< .001	[0.991, 0.996]
\$63,000 or more	0.95	0.001	-29.94	< .001	[0.953, 0.959]
Constant	4.31	0.007	824.52	< .001	[4.30, 4.33]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 4.6e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,490,831.47$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of diagnoses, $IRR = 1.20$, 95% CI [1.10, 1.32], $z = 3.98$, $p < .001$, hence, the null hypothesis was rejected (Table 93).

Table 93

Multivariate NBRM of Diagnoses in Cohort V (2014)

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.20	0.57	3.98	< .001	[1.10, 1.32]
Age	1.01	< 0.001	1204.54	< .001	[1.0136, 1.0137]
Sex ^b					
Male	1.08	< 0.001	183.97	< .001	[1.083, 1.085]
Race ^c					

White	1.03	0.001	34.72	< .001	[1.033, 1.037]
Black	1.09	0.001	76.68	< .001	[1.08, 1.09]
Hispanic	0.93	0.001	-51.99	< .001	[0.93, 0.94]
Asian\Pac. Islander	0.91	0.001	-49.57	< .001	[0.913, 0.919]
Native American	1.11	0.003	36.10	< .001	[1.10, 1.12]
Other	0.95	0.001	-29.67	< .001	[0.94, 0.95]
Median income ^d					
\$1 - \$38,999	1.05	0.001	34.02	< .001	[1.04, 1.05]
\$39,000 - \$47,999	1.02	0.001	17.95	< .001	[1.02, 1.03]
\$48,000 - \$62,999	1.01	0.001	10.28	< .001	[1.012, 1.018]
\$63,000 or more	0.98	0.001	-12.11	< .001	[0.97, 0.98]
Constant	4.42	0.008	805.19	< .001	[4.40, 4.43]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.8e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 1,126,523.21$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of diagnoses, $IRR = 1.03$, 95% CI [0.92, 1.16], $z = 0.64$, $p = .520$ (Table 94).

Table 94

Multivariate NBRM of Diagnoses in Cohort VI (2015)

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.03	0.059	0.64	.520	[0.92, 1.16]
Age	1.01	< 0.001	1050.26	< .001	[1.01364, 1.01369]
Sex ^b					
Male	1.08	< 0.001	163.81	< .001	[1.084, 1.086]
Race ^c					
White	1.01	0.001	12.30	< .001	[1.011, 1.016]
Black	1.06	0.001	51.55	< .001	[1.06, 1.07]
Hispanic	0.92	0.001	-59.18	< .001	[0.920, 0.925]
Asian\Pac. Islander	0.91	0.001	-43.22	< .001	[0.91, 0.92]
Native American	1.10	0.003	27.97	< .001	[1.09, 1.10]
Other	0.93	0.001	-35.93	< .001	[0.930, 0.937]
Median income ^d					
\$1 - \$38,999	1.04	0.001	21.92	< .001	[1.03, 1.04]
\$39,000 - \$47,999	1.02	0.001	11.09	< .001	[1.01, 1.02]
\$48,000 - \$62,999	1.01	0.001	7.20	< .001	[1.00, 1.01]
\$63,000 or more	0.98	0.001	-7.77	< .001	[0.982, 0.989]
Constant	4.69	0.010	713.48	< .001	[4.67, 4.71]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.4e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, diagnoses, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 8,464,261.87$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of diagnoses, $IRR = 1.18$, 95% CI [1.12, 1.23], $z = 7.19$, $p < .001$, hence, the null hypothesis was rejected (Table 95).

Table 95

Multivariate NBRM of Diagnoses in the Combined Cohort

Diagnoses	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	1.18	0.027	7.19	< .001	[1.12, 1.23]
Age	1.01	4.78e-06	2884.90	< .001	[1.0136, 1.0137]
Sex ^b					
Male	1.07	0.0001	413.26	< .001	[1.078, 1.079]
Race ^c					
White	1.03	0.0003	107.29	< .001	[1.038, 1.039]
Black	1.08	0.0004	205.14	< .001	[1.08, 1.09]
Hispanic	0.95	0.0004	-110.03	< .001	[0.94, 0.95]
Asian\Pac. Islander	0.93	0.0006	-94.54	< .001	[0.930, 0.933]
Native American	1.07	0.001	58.49	< .001	[1.073, 1.079]

Other	0.96	0.0006	-52.91	< .001	[0.964, 0.967]
Median income ^d					
\$1 - \$38,999	1.04	0.0006	64.47	< .001	[1.03, 1.04]
\$39,000 - \$47,999	1.02	0.0006	33.72	< .001	[1.020, 1.022]
\$48,000 - \$62,999	1.01	0.0006	18.38	< .001	[1.010, 1.012]
\$63,000 or more	0.97	0.0006	-33.14	< .001	[0.97, 0.98]
Constant	4.13	0.003	1918.95	< .001	[4.12, 4.13]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

External cause of injury results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 9.5e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, external causes of injury, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 66,658.51$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of external causes of injury, $IRR = 4.95$, 95% CI [2.76, 8.86], $z = 5.38$, $p < .001$, hence, the null hypothesis was rejected (Table 96).

Table 96

Multivariate NBRM of External Causes of Injury in Cohort I (2010)

Ecodes	IRR	SE	z	p	95% CI
Androgen toxicity ^a					

Yes	4.95	1.472	5.38	< .001	[2.76, 8.86]
Age	1.00	< 0.001	148.08	< .001	[1.0080, 1.0082]
Sex ^b					
Male	1.36	0.002	145.99	< .001	[1.36, 1.37]
Race ^c					
White	1.53	0.005	114.70	< .001	[1.52, 1.54]
Black	1.28	0.005	55.20	< .001	[1.27, 1.30]
Hispanic	1.34	0.006	58.64	< .001	[1.33, 1.35]
Asian\Pac. Islander	1.37	0.011	37.62	< .001	[1.34, 1.39]
Native American	1.22	0.017	14.28	< .001	[1.19, 1.25]
Other	1.33	0.010	37.08	< .001	[1.31, 1.35]
Median income ^d					
\$1 - \$38,999	0.97	0.006	-4.29	< .001	[0.95, 0.98]
\$39,000 - \$47,999	0.99	0.006	-0.78	.436	[0.98, 1.00]
\$48,000 - \$62,999	1.07	0.007	10.56	< .001	[1.06, 1.09]
\$63,000 or more	1.07	0.007	10.60	< .001	[1.06, 1.09]
Constant	0.10	< 0.001	-278.68	< .001	[0.103, 0.107]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.0e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis.

An adjusted NBRM was conducted to examine the relationship between androgen toxicity,

external causes of injury, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2 (12) = 77,295.09, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of external causes of injury, $IRR = 5.04, 95\% \text{ CI } [3.25, 7.80], z = 7.27, p < .001$, hence, the null hypothesis was rejected (Table 97).

Table 97

Multivariate NBRM of External Causes of Injury in Cohort II (2011)

Ecodes	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	5.04	1.122	7.27	< .001	[3.25, 7.80]
Age	1.00	< 0.001	179.14	< .001	[1.0094, 1.0096]
Sex ^b					
Male	1.31	0.002	130.64	< .001	[1.30, 1.31]
Race ^c					
White	1.56	0.006	113.59	< .001	[1.55, 1.57]
Black	1.25	0.005	47.29	< .001	[1.24, 1.26]
Hispanic	1.34	0.006	57.10	< .001	[1.32, 1.35]
Asian\Pac. Islander	1.31	0.011	31.63	< .001	[1.29, 1.34]
Native American	1.73	0.025	37.81	< .001	[1.68, 1.78]
Other	1.26	0.009	31.93	< .001	[1.25, 1.28]
Median income ^d					
\$1 - \$38,999	0.93	0.006	-8.53	< .001	[0.92, 0.95]

\$39,000 - \$47,999	0.97	0.007	-4.03	< .001	[0.95, 0.98]
\$48,000 - \$62,999	0.99	0.007	-0.32	.752	[0.98, 1.01]
\$63,000 or more	1.05	0.007	6.97	< .001	[1.03, 1.06]
Constant	0.10	< 0.001	-259.44	< .001	[0.104, 0.107]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.5e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, external causes of injury, and covariates in cohort three. The log likelihood ratio chi-square test statistic for five-predictor model, $LR \chi^2(12) = 50,710.13$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of external causes of injury, $IRR = 5.67$, 95% CI [3.50, 9.20], $z = 7.04$, $p < .001$, hence, the null hypothesis was rejected (Table 98).

Table 98

Multivariate NBRM of External Causes of Injury in Cohort III (2012)

Ecodes	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	5.67	1.40	7.04	< .001	[3.50, 9.20]
Age	1.01	< 0.001	164.82	< .001	[1.00, 1.01]
Sex ^b					
Male	1.27	0.003	100.02	< .001	[1.26, 1.27]

Race ^c					
White	1.26	0.006	42.45	< .001	[1.24, 1.27]
Black	1.03	0.006	5.78	< .001	[1.02, 1.04]
Hispanic	0.99	0.007	-0.09	.925	[0.98, 1.01]
Asian\Pac. Islander	0.88	0.011	-9.14	< .001	[0.86, 0.91]
Native American	1.20	0.022	9.86	< .001	[1.15, 1.24]
Other	1.07	0.009	8.61	< .001	[1.05, 1.09]
Median income ^d					
\$1 - \$38,999	0.99	0.008	-0.70	.484	[0.97, 1.01]
\$39,000 - \$47,999	0.98	0.008	-2.24	.025	[0.96, 0.99]
\$48,000 - \$62,999	1.00	0.008	1.06	.291	[0.99, 1.02]
\$63,000 or more	1.02	0.008	3.19	.001	[1.01, 1.04]
Constant	0.11	0.001	-209.30	< .001	[0.112, 0.116]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 8.6e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, external causes of injury, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 69,039.01$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a

significant effect on the incidence of external causes of injury, $IRR = 4.71$, 95% CI [3.17, 6.99], $z = 7.70$, $p < .001$, hence, the null hypothesis was rejected (Table 99).

Table 99

Multivariate NBRM of External Causes of Injury in Cohort IV (2013)

Ecodes	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	4.71	0.949	7.70	< .001	[3.17, 6.99]
Age	1.01	< 0.001	201.77	< .001	[1.0111, 1.0114]
Sex ^b					
Male	1.31	0.002	125.12	< .001	[1.30, 1.31]
Race ^c					
White	1.21	0.006	39.38	< .001	[1.20, 1.22]
Black	1.02	0.005	3.74	< .001	[1.01, 1.03]
Hispanic	1.13	0.006	21.25	< .001	[1.12, 1.14]
Asian\Pac. Islander	1.06	0.009	6.67	< .001	[1.04, 1.07]
Native American	1.30	0.019	17.74	< .001	[1.27, 1.34]
Other	1.05	0.008	6.81	< .001	[1.04, 1.07]
Median income ^d					
\$1 - \$38,999	0.92	0.006	-10.82	< .001	[0.91, 0.93]
\$39,000 - \$47,999	0.94	0.006	-8.10	< .001	[0.92, 0.95]
\$48,000 - \$62,999	0.98	0.007	-2.53	.012	[0.96, 0.99]
\$63,000 or more	1.00	0.007	0.75	.455	[0.99, 1.02]

Constant	0.11	0.001	-233.84	< .001	[0.11, 0.12]
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Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 8.5e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, external causes of injury, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 76,227.71$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of external causes of injury, $IRR = 4.76$, 95% CI [3.30, 6.87], $z = 8.36$, $p < .001$, hence, the null hypothesis was rejected (Table 100).

Table 100

Multivariate NBRM of External Causes of Injury in Cohort V (2014)

Ecodes	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	4.76	0.890	8.36	< .001	[1.011, 1.012]
Age	1.01	< 0.001	216.66	< .001	[1.011, 1.012]
Sex ^b					
Male	1.31	0.002	127.68	< .001	[1.31, 1.32]
Race ^c					
White	1.19	0.006	35.36	< .001	[1.18, 1.20]
Black	1.01	0.005	2.94	.003	[1.00, 1.02]

Hispanic	0.12	0.006	19.86	< .001	[1.11, 1.14]
Asian\Pac. Islander	1.08	0.009	8.91	< .001	[1.06, 1.09]
Native American	1.28	0.019	16.62	< .001	[1.24, 1.31]
Other	1.05	0.008	6.80	< .001	[1.04, 1.07]
Median income ^d					
\$1 - \$38,999	0.91	0.006	-12.49	< .001	[0.89, 0.92]
\$39,000 - \$47,999	0.92	0.006	-10.55	< .001	[0.91, 0.93]
\$48,000 - \$62,999	0.97	0.007	-4.09	< .001	[0.95, 0.98]
\$63,000 or more	0.99	0.007	-0.25	.802	[0.98, 1.01]
Constant	0.12	0.001	-231.00	< .001	[0.11, 0.12]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 6.4e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, external causes of injury, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 56,750.99$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of external causes of injury, $IRR = 4.50$, 95% CI [2.93, 6.91], $z = 6.89$, $p < .001$, hence, the null hypothesis was rejected (Table 101).

Table 101

Multivariate NBRM of External Causes of Injury in Cohort VI (2015)

Ecodes	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	4.50	0.985	6.89	< .001	[2.93, 6.91]
Age	1.01	< 0.001	185.73	< .001	[1.0115, 1.0118]
Sex ^b					
Male	1.31	0.003	113.98	< .001	[1.31, 1.32]
Race ^c					
White	1.09	0.006	15.58	< .001	[1.07, 1.10]
Black	0.93	0.005	-11.18	< .001	[0.91, 0.94]
Hispanic	1.05	0.007	8.02	< .001	[1.04, 1.06]
Asian\Pac. Islander	0.97	0.009	-2.25	.025	[0.96, 0.99]
Native American	1.25	0.020	13.67	< .001	[1.21, 1.29]
Other	0.97	0.009	-2.58	.010	[0.95, 0.99]
Median income ^d					
\$1 - \$38,999	0.88	0.007	-13.87	< .001	[0.87, 0.90]
\$39,000 - \$47,999	0.89	0.007	-12.43	< .001	[0.88, 0.90]
\$48,000 - \$62,999	0.93	0.008	-7.26	< .001	[0.92, 0.95]
\$63,000 or more	0.97	0.008	-2.68	.007	[0.96, 0.99]
Constant	0.13	0.001	-187.98	< .001	[0.13, 0.14]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 5.0e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, external causes of injury, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 386,333.53$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of external causes of injury, $IRR = 4.88$, 95% CI [4.08, 5.83], $z = 17.45$, $p < .001$, hence, the null hypothesis was rejected (Table 102).

Table 102

Multivariate NBRM of External Causes of Injury in the Combined Cohort

Ecodes	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	4.88	0.443	17.45	< .001	[4.08, 5.83]
Age	1.01	2.34e-05	446.49	< .001	[1.0103, 1.0104]
Sex ^b					
Male	1.31	0.001	305.67	< .001	[1.31, 1.32]
Race ^c					
White	1.35	0.002	163.93	< .001	[1.35, 1.36]
Black	1.13	0.002	56.61	< .001	[1.12, 1.13]
Hispanic	1.22	0.002	86.07	< .001	[1.21, 1.23]
Asian\Pac. Islander	1.18	0.004	45.15	< .001	[1.17, 1.19]
Native American	1.38	0.008	51.41	< .001	[1.36, 1.39]

Other	1.16	0.003	46.86	< .001	[1.16, 1.17]
Median income ^d					
\$1 - \$38,999	0.93	0.002	-21.14	< .001	[0.93, 0.94]
\$39,000 - \$47,999	0.95	0.002	-15.11	< .001	[0.94, 0.95]
\$48,000 - \$62,999	0.99	0.003	-0.31	.759	[0.99, 1.00]
\$63,000 or more	1.02	0.003	9.01	< .001	[1.02, 1.03]
Constant	0.11	0.0004	-587.37	< .001	[0.111, 0.113]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Procedure results. Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.4e+05$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 34,137.39$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of medical procedures, $IRR = 0.93$, 95% CI [0.65, 1.32], $z = -0.37$, $p = .709$ (Table 103).

Table 103

Multivariate NBRM of Procedures in Cohort I (2010)

Procedures	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	0.93	0.166	-0.37	.709	[0.65, 1.32]

Age	0.99	< 0.001	-72.87	< .001	[0.9980, 0.9981]
Sex ^b					
Male	1.09	0.001	94.50	< .001	[1.09, 1.10]
Race ^c					
White	1.05	0.001	35.11	< .001	[1.05, 1.06]
Black	1.00	0.001	2.34	.019	[1.000, 1.008]
Hispanic	1.10	0.002	44.43	< .001	[1.09, 1.10]
Asian\Pac. Islander	1.18	0.004	45.30	< .001	[1.17, 1.18]
Native American	1.03	0.006	5.14	< .001	[1.01, 1.04]
Other	1.19	0.004	52.46	< .001	[1.18, 1.20]
Median income ^d					
\$1 - \$38,999	0.81	0.002	-69.26	< .001	[0.80, 0.81]
\$39,000 - \$47,999	0.84	0.002	-55.88	< .001	[0.83, 0.84]
\$48,000 - \$62,999	0.86	0.002	-46.79	< .001	[0.86, 0.87]
\$63,000 or more	0.93	0.002	-21.40	< .001	[0.93, 0.94]
Constant	2.05	0.007	205.14	< .001	[2.03, 2.06]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.6e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the

five-predictor model, $LR \chi^2(12) = 30,640.46$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of medical procedures, $IRR = 0.82$, 95% CI [0.62, 1.08], $z = -1.39$, $p = .164$ (Table 104).

Table 104
Multivariate NBRM of Procedures in Cohort II (2011)

Procedures	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.82	0.114	-1.39	.164	[0.62, 1.08]
Age	0.99	< 0.001	-88.30	< .001	[0.9977, 0.9978]
Sex ^b					
Male	1.09	0.001	90.74	< .001	[1.091, 1.096]
Race ^c					
White	1.04	0.001	26.88	< .001	[1.04, 1.05]
Black	0.99	0.002	-1.76	.079	[0.99, 1.00]
Hispanic	1.09	0.002	39.09	< .001	[1.08, 1.09]
Asian\Pac. Islander	1.23	0.004	55.28	< .001	[1.22, 1.24]
Native American	0.97	0.006	-3.27	.001	[0.96, 0.99]
Other	1.17	0.003	50.55	< .001	[1.17, 1.18]
Median income ^d					
\$1 - \$38,999	0.95	0.003	-13.12	< .001	[0.94, 0.96]
\$39,000 - \$47,999	1.01	0.003	3.50	< .001	[1.00, 1.01]

\$48,000 - \$62,999	1.03	0.003	10.44	< .001	[1.02, 1.04]
\$63,000 or more	1.07	0.003	21.57	< .001	[1.07, 1.08]
Constant	1.78	0.006	147.75	< .001	[1.77, 1.79]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.8e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 27,615.68$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of medical procedures, $IRR = 0.61$, 95% CI [0.44, 0.86], $z = -2.80$, $p = .005$, hence, the null hypothesis was rejected (Table 105).

Table 105
Multivariate NBRM of Procedures in Cohort III (2012)

Procedures	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.61	0.105	-2.80	.005	[0.44, 0.86]
Age	0.99	< 0.001	-86.74	< .001	[0.9974, 0.9975]
Sex ^b					
Male	1.10	.001	86.64	< .001	[1.103, 1.108]
Race ^c					

White	1.00	0.002	3.32	.001	[1.00, 1.01]
Black	0.99	0.002	-3.16	.002	[0.98, 0.99]
Hispanic	1.03	0.003	11.29	< .001	[1.02, 1.04]
Asian\Pac. Islander	1.20	0.006	35.02	< .001	[1.19, 1.22]
Native American	0.96	0.008	-3.86	< .001	[0.94, 0.98]
Other	1.22	0.004	52.08	< .001	[1.21, 1.22]
Median income ^d					
\$1 - \$38,999	0.90	0.003	-26.90	< .001	[0.89, 0.90]
\$39,000 - \$47,999	0.95	0.003	-12.48	< .001	[0.94, 0.95]
\$48,000 - \$62,999	0.98	0.003	-4.00	< .001	[0.97, 0.99]
\$63,000 or more	1.03	0.004	7.82	< .001	[1.02, 1.03]
Constant	1.92	0.009	138.90	< .001	[1.91, 1.94]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.2e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 32,498.60$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of medical procedures, $IRR = 0.94$, 95% CI [0.73, 1.19], $z = -0.50$, $p = .618$ (Table 106).

Table 106

Multivariate NBRM of Procedures in Cohort IV (2013)

Procedures	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.94	0.115	-0.50	.618	[0.73, 1.19]
Age	0.99	< 0.001	-99.86	< .001	[0.9973, 0.9974]
Sex ^b					
Male	1.10	0.001	93.57	< .001	[1.100, 1.105]
Race ^c					
White	1.02	.002	11.83	< .001	[1.02, 1.03]
Black	1.00	.002	0.55	.581	[0.99, 1.00]
Hispanic	1.07	.002	25.60	< .001	[1.06, 1.07]
Asian\Pac. Islander	1.17	.004	41.59	< .001	[1.16, 1.18]
Native American	1.03	.007	4.51	< .001	[1.01, 1.04]
Other	1.21	.004	52.38	< .001	[1.20, 1.21]
Median income ^d					
\$1 - \$38,999	0.93	.003	-19.49	< .001	[0.92, 0.94]
\$39,000 - \$47,999	0.97	.003	-7.41	< .001	[0.96, 0.98]
\$48,000 - \$62,999	1.01	.003	4.79	< .001	[1.00, 1.02]
\$63,000 or more	1.07	.003	19.88	< .001	[1.06, 1.07]
Constant	1.87	.007	151.13	< .001	[1.86, 1.89]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' *IRR* = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 3.3e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 30,766.60$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of medical procedures, $IRR = 0.87$, 95% CI [0.69, 1.09], $z = -1.16$, $p = .248$ (Table 107).

Table 107

Multivariate NBRM of Procedures in Cohort V (2014)

Procedures	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.87	0.103	-1.16	.248	[0.69, 1.09]
Age	0.99	< 0.001	-105.03	< .001	[0.9971, 0.9972]
Sex ^b					
Male	1.10	0.001	94.95	< .001	[1.103, 1.107]
Race ^c					
White	1.10	0.002	7.17	< .001	[1.01, 1.02]
Black	1.01	0.002	4.61	< .001	[1.00, 1.01]
Hispanic	1.05	0.002	19.23	< .001	[1.04, 1.06]
Asian\Pac. Islander	1.17	0.004	41.46	< .001	[1.16, 1.18]
Native American	1.02	0.007	3.46	.001	[1.01, 1.03]

Other	1.19	0.004	47.55	< .001	[1.18, 1.20]
Median income ^d					
\$1 - \$38,999	0.93	0.003	-18.22	< .001	[0.93, 0.94]
\$39,000 - \$47,999	0.97	0.003	-8.10	< .001	[0.96, 0.97]
\$48,000 - \$62,999	1.00	0.003	1.93	.053	[0.99, 1.01]
\$63,000 or more	1.06	0.003	17.17	< .001	[1.05, 1.07]
Constant	1.91	0.008	151.67	< .001	[1.90, 1.93]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 2.6e+06$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis.

An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(12) = 24,273.80$, $p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, did not have a significant effect on the incidence of medical procedures, $IRR = 0.94$, 95% CI [0.72, 1.24], $z = -0.37$, $p = .711$ (Table 108).

Table 108

Multivariate NBRM of Procedures in Cohort VI (2015)

Procedures	IRR	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	0.94	0.132	-0.37	.711	[0.72, 1.24]

Age	0.99	< 0.001	-103.11	< .001	[0.9967, 0.9968]
Sex ^b					
Male	1.10	0.001	82.02	< .001	[1.102, 1.108]
Race ^c					
White	0.99	0.002	-1.90	.057	[0.98, 1.00]
Black	0.99	0.003	-1.89	.059	[0.98, 1.00]
Hispanic	1.01	0.003	5.99	< .001	[1.01, 1.02]
Asian\Pac. Islander	1.15	0.005	32.18	< .001	[1.14, 1.16]
Native American	1.01	0.008	1.62	.105	[0.99, 1.02]
Other	1.18	0.005	38.00	< .001	[1.17, 1.19]
Median income ^d					
\$1 - \$38,999	0.98	0.004	-4.55	< .001	[0.97, 0.98]
\$39,000 - \$47,999	1.00	0.004	2.09	.036	[1.00, 1.01]
\$48,000 - \$62,999	1.03	0.004	8.43	< .001	[1.02, 1.04]
\$63,000 or more	1.10	0.004	22.01	< .001	[1.09, 1.11]
Constant	1.89	0.009	124.42	< .001	[1.87, 1.91]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
IRR = rate ratio, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Overdispersion test results showed significant evidence of dispersion, $G^2 = 1.9e+07$, $p < .001$, thus, the overdispersion assumption was met and NBRM was deemed ideal for the analysis. An adjusted NBRM was conducted to examine the relationship between androgen toxicity, procedures, and covariates in the combined cohort. The log likelihood ratio chi-square test

statistic for the five-predictor model, $LR \chi^2(12) = 173,395.96, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure, upon an adjustment of covariates, had a significant effect on the incidence of medical procedures, $IRR = 0.86, 95\% \text{ CI } [0.77, 0.96], z = -2.61, p = .009$, hence, the null hypothesis was rejected (Table 109).

Table 109
Multivariate NBRM of Procedures in the Combined Cohort

Procedures	<i>IRR</i>	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.86	0.049	-2.61	.009	[0.77, 0.96]
Age	0.99	1.1e-05	-226.84	< .001	[0.9974, 0.9975]
Sex ^b					
Male	1.10	0.0004	221.31	< .001	[1.100, 1.102]
Race ^c					
White	1.02	0.0008	35.24	< .001	[1.02, 1.03]
Black	1.00	0.0009	3.49	< .001	[1.001, 1.005]
Hispanic	1.06	0.001	63.20	< .001	[1.06, 1.07]
Asian\Pac. Islander	1.19	0.001	106.07	< .001	[1.18, 1.19]
Native American	1.01	0.002	4.30	< .001	[1.00, 1.01]
Other	1.20	0.001	125.06	< .001	[1.19, 1.20]
Median income ^d					
\$1 - \$38,999	0.90	0.001	-66.61	< .001	[0.90, 0.91]
\$39,000 - \$47,999	0.94	0.001	-35.89	< .001	[0.94, 0.95]

\$48,000 - \$62,999	0.97	0.001	-13.93	< .001	[0.97, 0.98]
\$63,000 or more	1.03	0.001	23.88	< .001	[1.032, 1.038]
Constant	1.91	0.003	382.84	< .001	[1.91, 1.92]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,'
 IRR = rate ratio, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. =
 pacific, Constant = baseline incidence rate.

Bivariate and multivariate point estimates of inpatient variables in the combined cohort are compared in Figure 21.

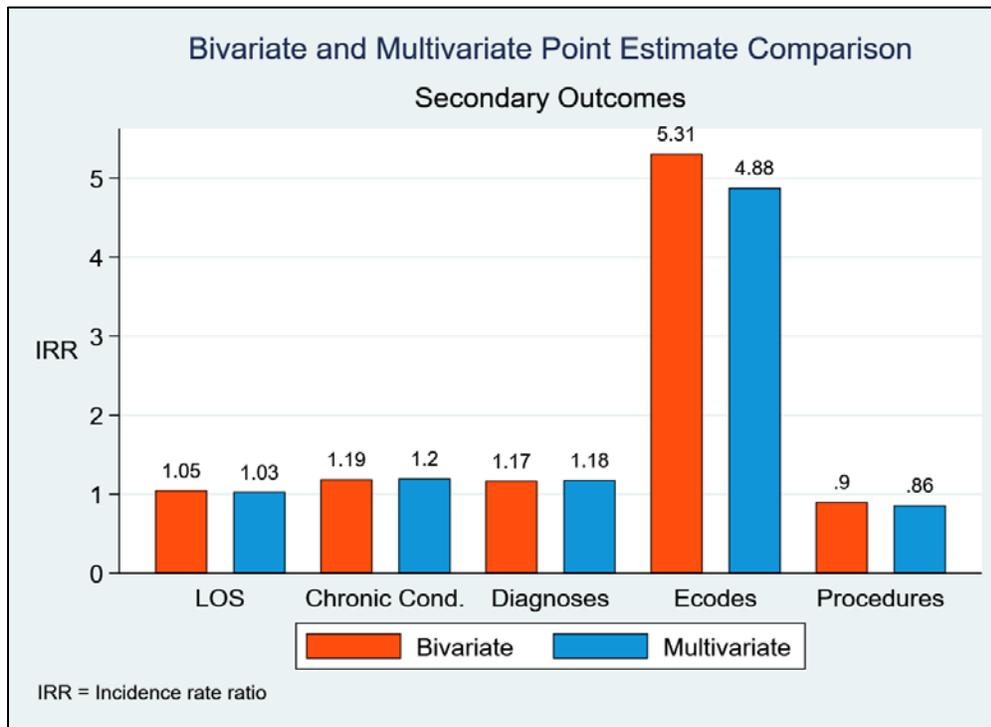


Figure 21. Bivariate and multivariate point estimates of inpatient variables.

Aim 2 [RQ 3]. What is the relationship between androgen toxicity and healthcare costs?

H₀₃. There is no relationship between androgen toxicity and healthcare costs.

H_{a3}. There is a relationship between androgen toxicity and healthcare costs.

Log-gamma generalized linear model analysis was conducted to determine the multivariate relationship between androgen toxicity and healthcare costs. The study design assumptions of the log-gamma GLM were (a) a dependent variable measured on the ratio or interval scale, (b) statistical independence of observations, (c) correct specification of variance function $v(\mu)$, and (d) correct specification of the link function (Hardin & Hilbe, 2012). The data assumptions of the log-gamma GLM were (a) non-negative dependent variable values, (b) positively skewed dependent variable values, and (c) variance held nearly constant on the log-scale (Hardin & Hilbe, 2012). Prior to the analysis, the assumptions of non-negative values, positive skew, and nearly constant variance on the log-scale were assessed.

Non-negative and positively skewed values. Long format tabulation and detailed summary statistics were conducted to determine the data characteristics of the healthcare cost variable. The results of visual inspection of the tabulation showed non-negative values and positive skew for each cohort. The minimum values for healthcare costs were (≥ 100) for each yearly cohort and the combined cohort. The skewness and kurtosis statistics were ($Sk = 7.43$; $Ku = 100.83$) cohort one, ($Sk = 12.47$; $Ku = 388.79$) cohort two, ($Sk = 12.01$; $Ku = 387.59$) cohort three, ($Sk = 12.55$; $Ku = 384.79$) cohort four, ($Sk = 11.42$; $Ku = 311.58$) cohort five, ($Sk = 11.52$; $Ku = 316.88$) cohort six, and ($Sk = 11.64$; $Ku = 341.54$) combined cohort. The summary results suggested that the log-gamma model was superior to the specification of Gaussian regression with a log-transformed response. Therefore, the log-gamma GLM was considered preferable and suitable for the analysis.

Near constant variance. Anscombe residuals were generated using the method by Hardin and Hilbe (2012) to determine whether the variance was held near constant on the log-

scale by the estimated scale parameter ensuring log-transformed normality. The plotted results confirmed that the Anscombe residuals were within the range of constant variance and showed a good approximation of log normality. The Anscombe residual plots for the cohorts (I-VI) and the combined cohort were presented previously in the bivariate analysis section (Figure 17; Figure 18).

Healthcare cost results. An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in cohort one. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 31,392.64, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.15, 95\% \text{ CI } [-0.59, 0.28], z = -0.70, p = .486$. The predicted margins of healthcare costs by androgen toxicity exposure (no = 36,147.33, $p < .001$) and (yes = 30,924.82, $p < .001$) indicated a significant marginal difference (MD = 5,222.51) in healthcare cost difference between the two levels of exposure (Table 110).

Table 110

Multivariate GLM Regression of Total Healthcare Costs in Cohort I (2010)

Healthcare costs	β	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	-0.15	0.223	-0.70	.486	[-0.59, 0.28]
Age	0.01	< 0.001	316.17	< .001	[0.0103, 0.0105]
Sex ^b					
Male	0.26	0.001	211.68	< .001	[0.261, 0.266]
Race ^c					

White	0.11	0.001	55.85	< .001	[0.10, 0.11]
Black	0.20	0.002	83.17	< .001	[0.20, 0.21]
Hispanic	0.30	0.002	113.36	< .001	[0.30, 0.31]
Asian\Pac. Islander	0.32	0.004	70.09	< .001	[0.32, 0.33]
Native American	0.20	0.007	26.99	< .001	[0.19, 0.22]
Other	0.24	0.004	55.05	< .001	[0.23, 0.24]
Median income ^d					
\$1 - \$38,999	0.02	0.003	6.07	< .001	[0.01, 0.03]
\$39,000 - \$47,999	0.06	0.003	17.06	< .001	[0.05, 0.07]
\$48,000 - \$62,999	0.15	0.003	39.75	< .001	[0.14, 0.16]
\$63,000 or more	0.20	0.003	52.09	< .001	[0.19, 0.21]
Constant	9.52	0.004	2109.70	< .001	[9.51, 9.53]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline cost.

An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in cohort two. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 13,417.38, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.22, 95\% \text{ CI } [-0.57, 0.12], z = -1.26, p = .209$. The predicted margins of healthcare costs by androgen toxicity exposure (no = 38,832.15, $p < .001$) and (yes = 30,997.71, $p < .001$) indicated a significant marginal difference ($MD = 7,834.44$) in healthcare cost difference between the two levels of exposure (Table 111).

Table 111

Multivariate GLM Regression of Total Healthcare Costs in Cohort II (2011)

Healthcare costs	β	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	-0.22	0.179	-1.26	.209	[-0.57, 0.12]
Age	0.01	< 0.001	292.26	< .001	[0.0100, 0.0102]
Sex ^b					
Male	0.26	0.002	198.82	< .001	[0.25, 0.26]
Race ^c					
White	0.21	0.002	95.93	< .001	[0.21, 0.22]
Black	0.29	0.002	106.85	< .001	[0.28, 0.29]
Hispanic	0.37	0.002	126.58	< .001	[0.37, 0.38]
Asian\Pac. Islander	0.39	0.005	75.58	< .001	[0.38, 0.40]
Native American	0.04	0.009	5.32	< .001	[0.03, 0.06]
Other	0.28	0.004	64.30	< .001	[0.27, 0.29]
Median income ^d					
\$1 - \$38,999	-0.04	0.004	-10.66	< .001	[-0.05, -0.04]
\$39,000 - \$47,999	-0.02	0.004	-4.46	< .001	[-0.02, -0.01]
\$48,000 - \$62,999	0.04	0.004	10.04	< .001	[0.03, 0.05]
\$63,000 or more	0.06	0.004	13.59	< .001	[0.05, 0.07]
Constant	9.61	0.005	1823.98	< .001	[9.60, 9.62]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline cost.

An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in cohort three. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 9,954.89, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.13, 95\% \text{ CI } [-0.52, 0.24], z = -0.71, p = .479$. The predicted margins of healthcare costs by androgen toxicity exposure (no = 37,002.98, $p < .001$) and (yes = 32,199.77, $p < .001$) indicated a significant marginal difference ($MD = 4,803.21$) in healthcare cost difference between the two levels of exposure (Table 112).

Table 112

Multivariate GLM Regression of Total Healthcare Costs in Cohort III (2012)

Healthcare costs	β	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	-0.13	0.196	-0.71	.479	[-0.52, 0.24]
Age	0.009	< 0.001	241.91	< .001	[0.0091, 0.0093]
Sex ^b					
Male	0.24	0.001	172.01	< .001	[0.24, 0.25]
Race ^c					
White	0.14	0.003	47.18	< .001	[0.14, 0.15]
Black	0.26	0.003	74.79	< .001	[0.25, 0.27]
Hispanic	0.28	0.003	72.57	< .001	[0.28, 0.29]
Asian\Pac. Islander	0.16	0.007	23.68	< .001	[0.15, 0.18]
Native American	0.06	0.010	5.54	< .001	[0.03, 0.08]

Other	0.28	0.004	58.20	< .001	[0.27, 0.29]
Median income ^d					
\$1 - \$38,999	0.03	0.004	6.59	< .001	[0.02, 0.04]
\$39,000 - \$47,999	0.04	0.005	8.63	< .001	[0.03, 0.05]
\$48,000 - \$62,999	0.10	0.005	19.96	< .001	[0.09, 0.11]
\$63,000 or more	0.14	0.005	28.86	< .001	[0.13, 0.15]
Constant	9.61	0.006	1592.84	< .001	[9.60, 9.62]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline cost.

An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in cohort four. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 22,653.49, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = -0.07, 95\% \text{ CI } [-0.24, 0.40], z = 0.48, p = .631$. The predicted margins of healthcare costs by androgen toxicity exposure (no = 42,848.69, $p < .001$) and (yes = 46,355.69, $p < .001$) indicated a significant marginal difference ($MD = -3,507.00$) in healthcare cost difference between the two levels of exposure (Table 113).

Table 113

Multivariate GLM Regression of Total Healthcare Costs in Cohort IV (2013)

Healthcare costs	β	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.07	0.163	0.48	.631	[-0.24, 0.40]

Age	0.009	< 0.001	265.24	< .001	[0.0095, 0.0097]
Sex ^b					
Male	0.26	0.001	191.41	< .001	[0.261, 0.266]
Race ^c					
White	0.20	0.002	67.52	< .001	[0.19, 0.20]
Black	0.29	0.003	86.24	< .001	[0.28, 0.30]
Hispanic	0.39	0.003	110.79	< .001	[0.38, 0.40]
Asian\Pac. Islander	0.38	0.005	72.47	< .001	[0.37, 0.39]
Native American	0.30	0.009	32.42	< .001	[0.28, 0.32]
Other	0.33	0.004	67.01	< .001	[0.32, 0.34]
Median income ^d					
\$1 - \$38,999	-0.03	0.004	-6.87	< .001	[-0.04, -0.02]
\$39,000 - \$47,999	-0.01	0.004	-3.79	< .001	[-0.025, -0.008]
\$48,000 - \$62,999	0.05	0.004	11.96	< .001	[0.04, 0.06]
\$63,000 or more	0.13	0.004	28.61	< .001	[0.12, 0.14]
Constant	9.71	0.005	1731.60	< .001	[9.70, 9.72]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline cost.

An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in cohort five. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 15,008.99, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure had a significant effect

on healthcare cost, $\beta = 0.36$, 95% CI [0.07, 0.66], $z = 2.42$, $p = .015$, hence, the null hypothesis was rejected. The predicted margins of healthcare costs by androgen toxicity exposure (no = 54,181.83, $p < .001$) and (yes = 65,333.56, $p < .001$) indicated a significant marginal difference ($MD = -20,151.73$) in healthcare cost difference between the two levels of exposure (Table 114).

Table 114

Multivariate GLM Regression of Total Healthcare Costs in Cohort V (2014)

Healthcare costs	β	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	0.36	0.152	2.42	.015	[0.07, 0.66]
Age	0.009	< 0.001	269.91	< .001	[0.0096, 0.0098]
Sex ^b					
Male	0.27	0.001	198.93	< .001	[0.26, 0.27]
Race ^c					
White	0.18	0.003	60.40	< .001	[0.17, 0.19]
Black	0.27	0.003	79.61	< .001	[0.26, 0.28]
Hispanic	0.37	0.003	102.31	< .001	[0.36, 0.37]
Asian\Pac. Islander	0.37	0.005	71.72	< .001	[0.36, 0.38]
Native American	0.13	0.009	14.63	< .001	[0.11, 0.15]
Other	0.34	0.004	69.39	< .001	[0.33, 0.34]
Median income ^d					
\$1 - \$38,999	-0.03	0.004	-8.61	< .001	[-0.04, -0.03]
\$39,000 - \$47,999	-0.02	0.004	-6.13	< .001	[-0.03, -0.01]

\$48,000 - \$62,999	0.02	0.004	5.66	< .001	[0.01, 0.03]
\$63,000 or more	0.09	0.004	20.89	< .001	[0.08, 0.10]
Constant	9.79	0.005	1733.62	< .001	[9.78, 9.80]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, SE = standard error, z = Wald z statistic, p = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline cost.

An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in cohort six. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 9,532.06, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = 0.04, 95\% \text{ CI } [-0.30, 0.40], z = 0.27, p = .784$. The predicted margins of healthcare costs by androgen toxicity exposure (no = 47,257.54, $p < .001$) and (yes = 49,643.55, $p < .001$) indicated a significant marginal difference ($MD = -2,386.01$) in healthcare cost difference between the two levels of exposure (Table 115).

Table 115

Multivariate GLM Regression of Total Healthcare Costs in Cohort VI (2015)

Healthcare costs	β	SE	z	p	95% CI
Androgen toxicity ^a					
Yes	0.04	0.179	0.27	.784	[-0.30, 0.40]
Age	0.009	0.001	233.51	< .001	[0.0095, 0.0097]
Sex ^b					
Male	0.26	0.001	171.52	< .001	[0.263, 0.269]
Race ^c					

White	0.15	0.003	43.96	< .001	[0.145, 0.158]
Black	0.24	0.003	62.18	< .001	[0.235, 0.251]
Hispanic	0.34	0.004	83.38	< .001	[0.334, 0.351]
Asian\Pac. Islander	0.34	0.005	58.76	< .001	[0.334, 0.358]
Native American	0.14	0.010	13.67	< .001	[0.12, 0.16]
Other	0.35	0.005	61.93	< .001	[0.34, 0.36]
Median income ^d					
\$1 - \$38,999	-0.05	0.005	-9.52	< .001	[-0.06, -0.04]
\$39,000 - \$47,999	-0.04	0.005	-8.92	< .001	[-0.06, -0.03]
\$48,000 - \$62,999	-0.001	0.005	-0.19	< .001	[-0.011, 0.009]
\$63,000 or more	0.07	0.005	12.54	< .001	[0.05, 0.08]
Constant	9.89	0.006	1489.30	< .001	[9.88, 9.90]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific, Constant = baseline cost.

An adjusted log-gamma GLM regression was conducted to examine the relationship between androgen toxicity, healthcare cost, and covariates in the combined cohort. The log likelihood ratio chi-square test statistic for the five-predictor model, $LR \chi^2(4) = 93,417.68, p < .0001$, indicated that the model fit was significant. Androgen toxicity exposure did not have a significant effect on healthcare cost, $\beta = 0.09, 95\% \text{ CI } [-0.46, 0.24], z = 1.33, p = .185$. The predicted margins of healthcare costs by androgen toxicity exposure (no = 40,957.98, $p < .001$) and (yes = 45,136.51, $p < .001$) indicated a significant marginal difference ($MD = -4,178.53$) in healthcare cost difference between the two levels of exposure (Table 4.96).

Table 116

Multivariate GLM Regression of Total Healthcare Costs in the Combined Cohort

Healthcare costs	β	<i>SE</i>	<i>z</i>	<i>p</i>	95% CI
Androgen toxicity ^a					
Yes	0.09	0.073	1.33	.185	[-0.04, 0.24]
Age	0.009	1.5e-05	660.05	< .001	[0.0098, 0.0099]
Sex ^b					
Male	0.26	5.65e-04	465.89	< .001	[0.262, 0.264]
Race ^c					
White	0.19	0.001	174.98	< .001	[0.18, 0.19]
Black	0.28	0.001	220.50	< .001	[0.27, 0.28]
Hispanic	0.37	0.001	273.83	< .001	[0.37, 0.38]
Asian\Pac. Islander	0.38	0.002	173.48	< .001	[0.380, 0.389]
Native American	0.18	0.003	48.02	< .001	[0.17, 0.19]
Other	0.32	0.001	166.30	< .001	[0.322, 0.329]
Median income ^d					
\$1 - \$38,999	-0.01	0.001	-8.11	< .001	[-0.019, -0.011]
\$39,000 - \$47,999	0.005	0.001	2.79	.005	[0.001, 0.009]
\$48,000 - \$62,999	0.06	0.001	25.99	< .001	[0.06, 0.07]
\$63,000 or more	0.12	0.001	64.02	< .001	[0.120, 0.128]
Constant	9.66	0.002	4281.75	< .001	[9.65, 9.66]

Note. a = base category 'no', b = base category 'female,' c = base category 'missing,' d = base category 'missing,' β = coefficient, *SE* = standard error, *z* = Wald *z* statistic, *p* = significance level, CI = confidence interval, Pac. = pacific.

Comparison of bivariate and multivariate marginal healthcare cost estimates of the combined cohort are shown in Figure 22.

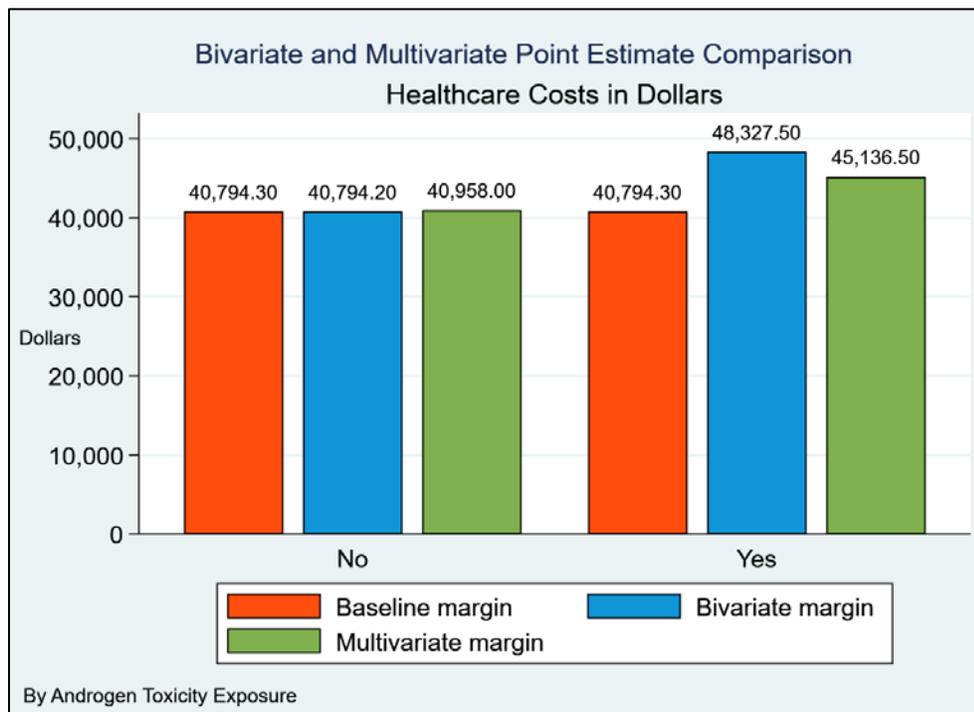


Figure 22. Bivariate and multivariate point estimates of healthcare costs.

Aim 3 [RQ 4]. What is the relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and total healthcare costs over the study period?

H₀₄. There is no relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and healthcare costs over the study period.

H_{a4}. There is a relationship between androgen toxicity and annual trends in health outcomes, inpatient variables, and healthcare costs over the study period.

Graphical methods were used to generate plots of annual trends in relative risks, incidence rate ratios, and marginal estimates for the health outcomes, inpatient variables, and total healthcare costs.

Health outcome results. The relative risk trends for each health outcome are shown in

Figure 23.

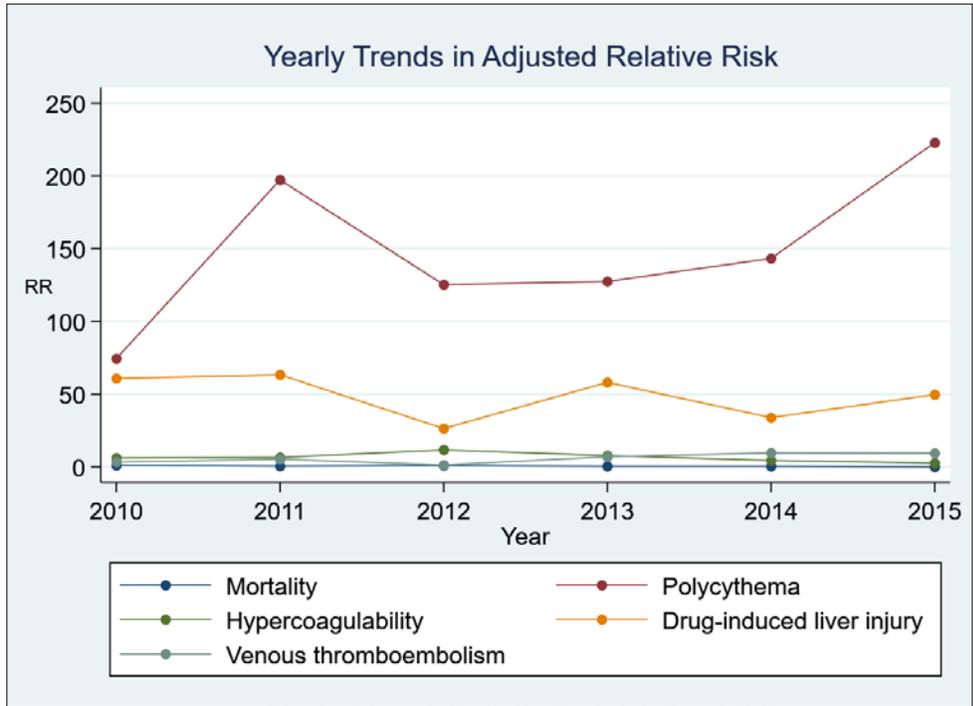


Figure 23. Annual trends in relative risk for each health outcome.

Inpatient variable results. The incidence rate ratio trends for each inpatient variable are shown in Figure 24.

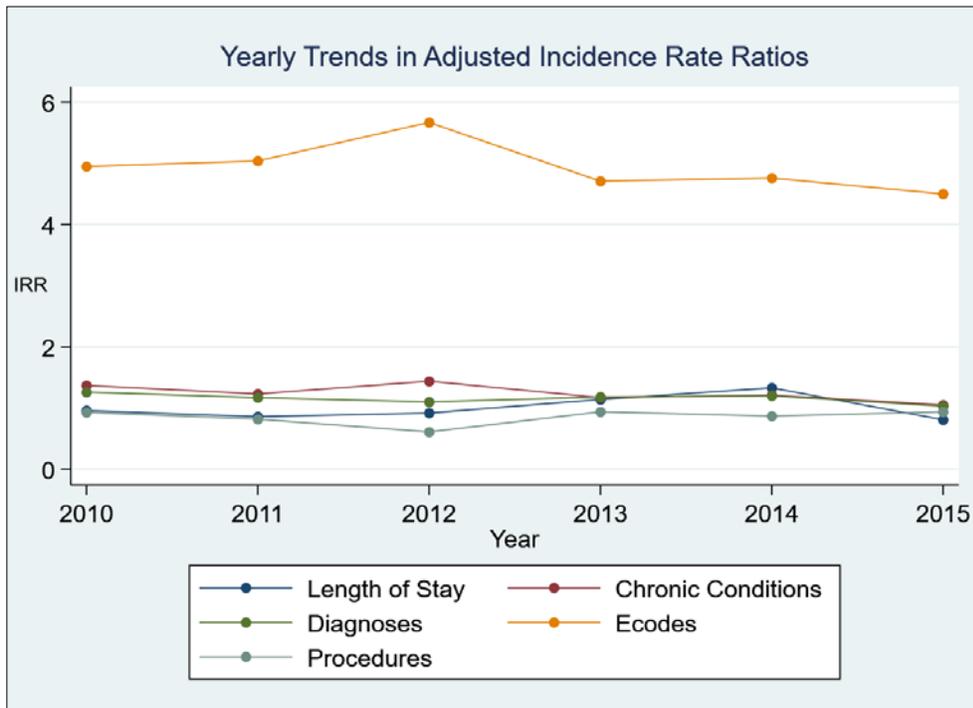


Figure 24. Annual trends in incidence rate ratios for each inpatient variable.

Healthcare cost results. Mean healthcare costs dropped 14.24% from 2010 to 2011, trended upwards 52.55% from 2011 to 2014, and dropped 24.01% from 2014 to 2015. The marginal trends in total healthcare costs are presented in Figure 25.

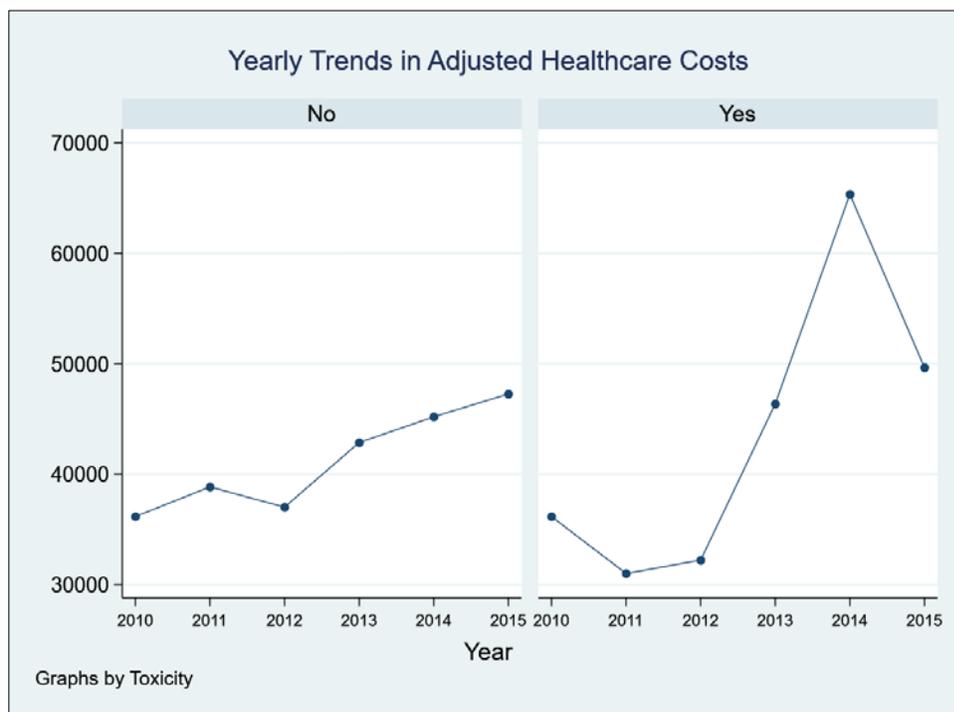


Figure 25. Annual trends in total healthcare costs by exposure.

Aim 4 [RQ 5]. What is the relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied?

H₀₅. There is no relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied.

H_{a5}. There is a relationship between androgen toxicity, health outcome variables, and inpatient variables when propensity score methods are applied.

Odds weighted (IP), inverse probability of treatment weighted (IPT), and propensity score (PS) weighted noncanonical generalized linear binomial regression and NBRM were conducted to examine and replicate the multivariate relationships found between androgen toxicity, health outcomes, and inpatient variables in the main analyses of this study. The selected PS methods were chosen to allow a straightforward comparison and interpretation of the

findings. The effects resulting from the IP analyses were interpreted as the average treatment effect in the treated (ATT), which is the difference between inpatients actually exposed and their counterfactuals Guo (S. Guo & Fraser, 2015; Hernán & Robins, 2019). The ATT is the average exposure effect, in terms of risk, that would be expected if each inpatient in the exposed (treated) index cohorts received exposure (treatment) compared to if no inpatients in the index cohorts received the exposure (Lee & Little, 2017). In contrast, the results from the IPT analyses were interpreted as the average treatment effect (ATE) or the average exposure effect, in terms of risk, expected if each inpatient in the exposed index cohorts and non-exposed reference cohorts received the exposure (treatment) compared to if no inpatients received exposure (Lee & Little, 2017). The propensity score weighted effects were interpreted as adjusted results for each analysis. The study design assumptions for IP, IPT, and PS weighted analysis were (a) independent and identically distributed subjects, (b) exogenous selection of subjects, and (c) no unmeasured confounding (ignorability). The data assumptions of IP and IPT weighting analysis were (a) correct model specification, (b) data positivity, and (c) balanced covariates.

Model specification. A saturated model was specified for IP and IPT analysis using all covariates, a non-linear term, and an interaction term for each yearly cohort analysis, thus satisfying the model specification assumption (S. Guo & Fraser, 2015; Thoemmes & Ong, 2016). An unsaturated model was specified for PS analysis, since saturation was not required (S. Guo & Fraser, 2015).

Positivity. Detailed summary analysis was conducted on the stabilized IP and IPT weights and each covariate. The results returned values greater than zero in the stabilized weights for all covariates satisfying the positivity assumption. A separate PS analysis confirmed

positivity in the propensity scores generated from an unsaturated model satisfying the positivity assumption for each covariate.

Covariate balance. For each cohort, eight simple IP and IPT weighted regressions were conducted after estimation of the IP and IPT weights in a saturated model to examine covariate balance. The covariate balance models included:

1. Weighted ordinary least squares regression with age as the interval dependent variable and androgen toxicity as the nominal dichotomous independent variable (exposure):
 - a. Model one = [age] by [androgen toxicity] + [pweight = sw_a].
 - b. Model two = [age] by [androgen toxicity] + [pweight = sw_b].
2. Weighted logistic regression with sex as the nominal dichotomous dependent variable and androgen toxicity as the nominal dichotomous independent variable (exposure):
 - a. Model one = [sex] by [androgen toxicity] + [pweight = sw_a].
 - b. Model two = [sex] by [androgen toxicity] + [pweight = sw_b].
3. Multinomial logistic regression with race as the nominal dependent variable and androgen toxicity as the nominal dichotomous independent variable (exposure):
 - a. Model one = [race] by [androgen toxicity] + [pweight = sw_a].
 - b. Model two = [race] by [androgen toxicity] + [pweight = sw_b].
4. Ordinal logistic regression with median income as the ordinal dependent variable and androgen toxicity as the nominal dichotomous independent variable (exposure):
 - a. Model one = [median income] by [androgen toxicity] + [pweight = sw_a].
 - b. Model two = [median income] by [androgen toxicity] + [pweight = sw_b].

Each of the model results showed nonsignificant coefficients indicating that the covariates were balanced. A separate balance assessment for PS analysis confirmed that each of the covariates was also balanced.

Mortality results. An IP, IPT, and PS weighted GLM binomial regression was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the risk of mortality in the main multivariate binomial regression model of the combined cohort. The IP weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the risk of death, $RR = 0.24$, 95% CI [0.09, 0.66], $z = -2.79$, $p = .005$, hence, the null hypothesis was rejected. The IPT weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect on the risk of death, $RR = 0.23$, 95% CI [0.08, 0.63], $z = -2.87$, $p = .004$, hence, the null hypothesis was rejected. The PS weighted binomial regression results indicated that androgen toxicity exposure did not have a significant effect on the average risk of death, $RR = 0.44$, 95% CI [0.16, 1.17], $z = -1.64$, $p = .101$. A comparison of mortality point estimates for each statistical method used in the binomial regression models is presented in Figure 26.

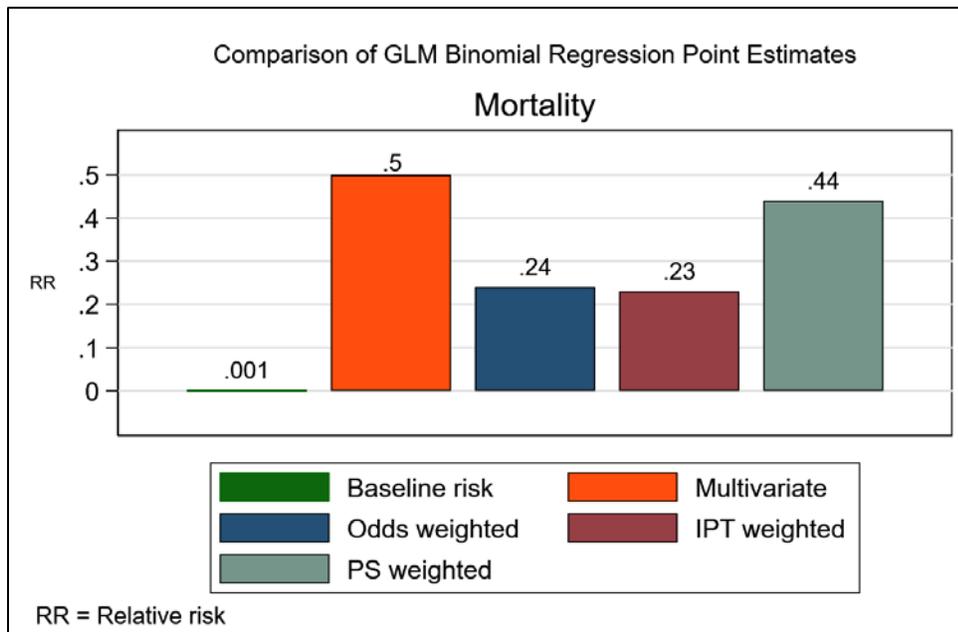


Figure 26. Comparison of mortality point estimates.

Polycythemia results. An IP, IPT, and PS weighted GLM binomial regression was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the risk of polycythemia in the main multivariate binomial regression model of the combined cohort. The IP weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the risk of polycythemia, $RR = 97.59$, 95% CI [57.57, 165.43], $z = 17.01$, $p < .001$, hence, the null hypothesis was rejected. The IPT weighted binomial regression results indicated that androgen toxicity exposure had some average exposure effect on the risk of polycythemia, $RR = 88.21$, however, significance level and confidence intervals could not be estimated due to high singular of variance matrix. The PS weighted binomial regression results indicated that androgen toxicity exposure had a significant effect on the average risk of polycythemia, $RR = 152.64$, 95% CI [117.82, 197.76], $z = 38.06$, $p < .001$, hence, the null hypothesis was rejected. A comparison of

polycythemia point estimates for each statistical method used in the binomial regression models is presented in Figure 27.

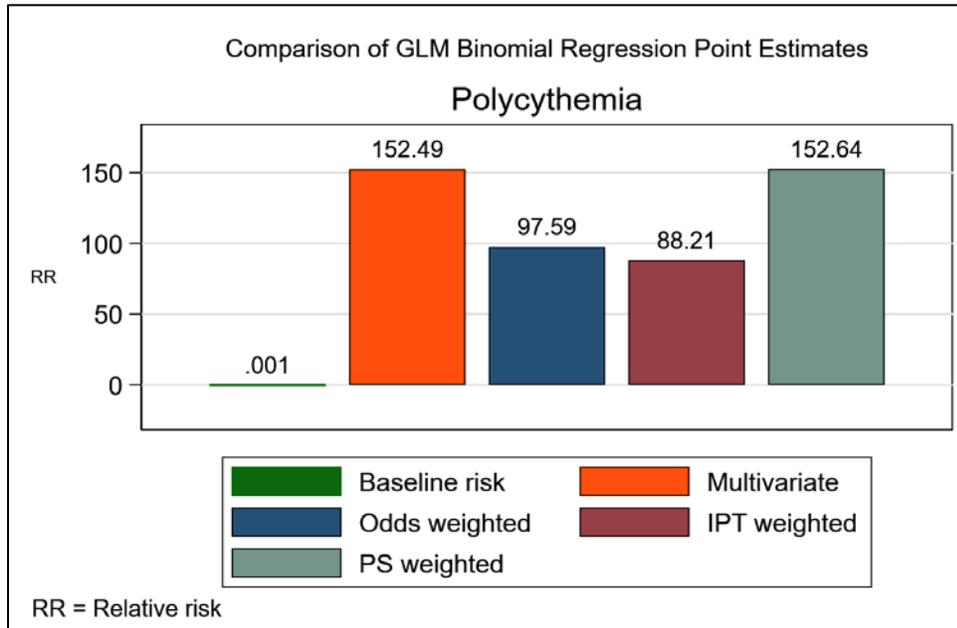


Figure 27. Comparison of polycythemia point estimates.

Hypercoagulability results. An IP, IPT, and PS weighted GLM binomial regression was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the risk of hypercoagulability in the main multivariate binomial regression model of the combined cohort. The IP weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the risk of hypercoagulability, $RR = 7.78$, 95% CI [1.99, 30.44], $z = 2.95$, $p = .003$, hence, the null hypothesis was rejected. The IPT weighted binomial regression results indicated that androgen toxicity exposure had some exposure effect on the risk of hypercoagulability, $RR = 6.13$, however, significance level and confidence intervals could not be estimated due to high singular of variance matrix. The PS weighted binomial regression results indicated that androgen toxicity

exposure had a significant effect on the average risk of hypercoagulability, $RR = 6.43$, 95% CI [3.44, 12.05], $z = 5.82$, $p < .001$, hence, the null hypothesis was rejected. A comparison of hypercoagulability point estimates for each statistical method used in the binomial regression models is presented in Figure 28.

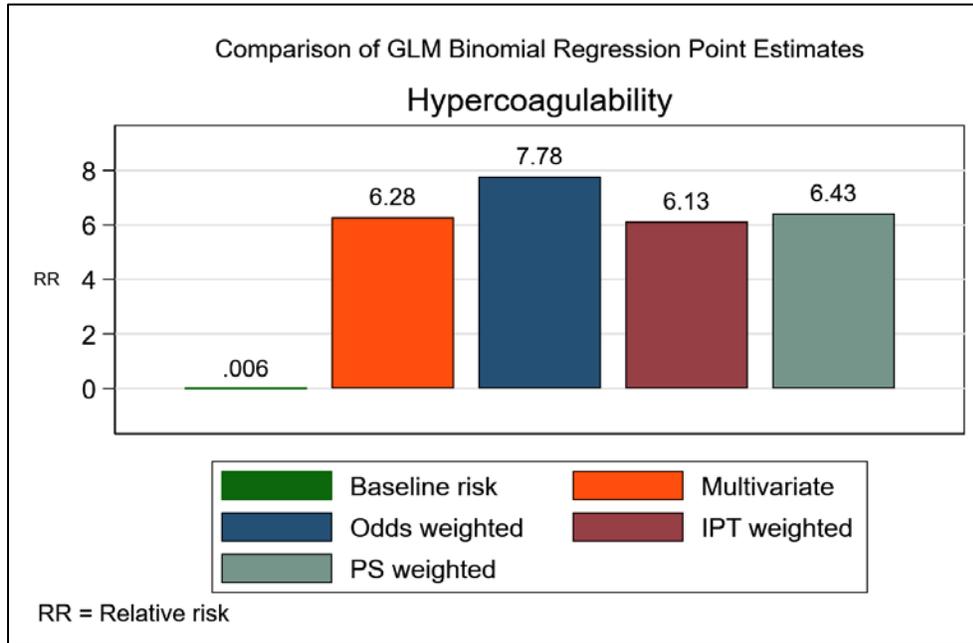


Figure 28. Comparison of hypercoagulability point estimates.

Drug-induced liver injury results. An IP, IPT, and PS weighted GLM binomial regression was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the risk of drug-induced liver injury in the main multivariate binomial regression model of the combined cohort. The IP weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the risk of drug-induced liver injury, $RR = 37.13$, 95% CI [16.54, 83.35], $z = 8.76$, $p < .001$, hence, the null hypothesis was rejected. The IPT weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect on the risk of

drug-induced liver injury, $RR = 39.33$, 95% CI [17.89, 86.50], $z = 9.13$, $p < .001$, hence, the null hypothesis was rejected. The PS weighted binomial regression results indicated that androgen toxicity exposure had a significant effect on the average risk of drug-induced liver injury, $RR = 49.73$, 95% CI [27.86, 88.74], $z = 13.22$, $p < .001$, hence, the null hypothesis was rejected. A comparison of drug-induced liver injury point estimates for each statistical method used in the binomial regression models is presented in Figure 29.

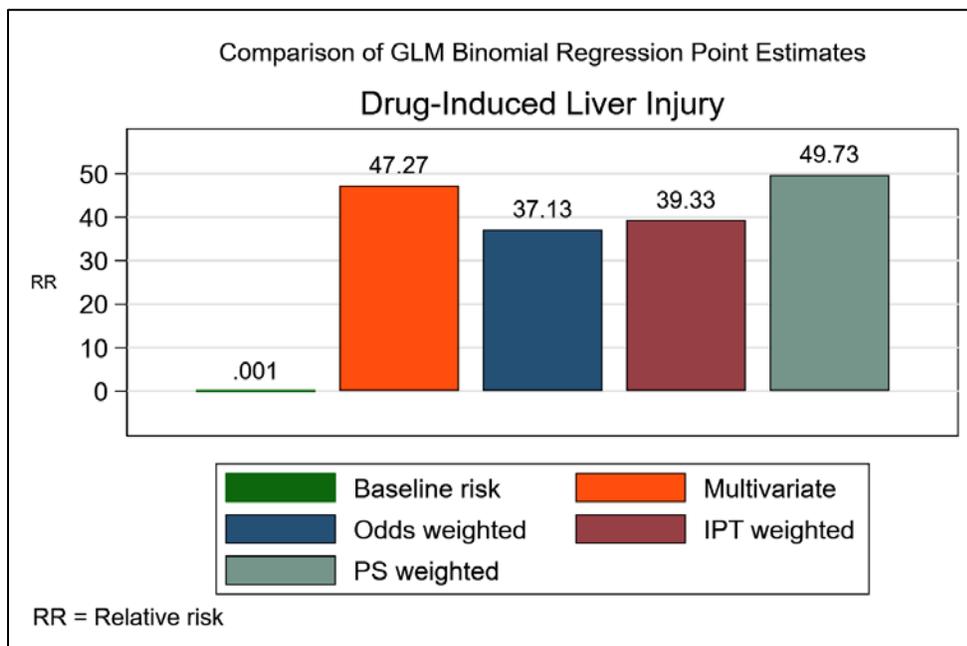


Figure 29. Comparison of drug-induced liver injury point estimates.

Venous thromboembolism results. An IP, IPT, and PS weighted GLM binomial regression was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the risk of venous thromboembolism in the main multivariate binomial regression model of the combined cohort. The IP weighted binomial regression results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the risk of venous thromboembolism, $RR = 2.83$, 95% CI [1.72, 4.66], $z = 4.11$, $p <$

.001, hence, the null hypothesis was rejected. The IPT weighted binomial regression results indicated that androgen toxicity exposure had some average exposure effect on the risk of venous thromboembolism, $RR = 2.96$, however, significance level and confidence intervals could not be estimated due to high singular of variance matrix. The PS weighted binomial regression results indicated that androgen toxicity exposure had a significant effect on the average risk of venous thromboembolism, $RR = 7.55$, 95% CI [5.53, 10.30], $z = 12.75$, $p < .001$, hence, the null hypothesis was rejected. A comparison of venous thromboembolism point estimates for each statistical method used in the binomial regression models is presented in Figure 30.

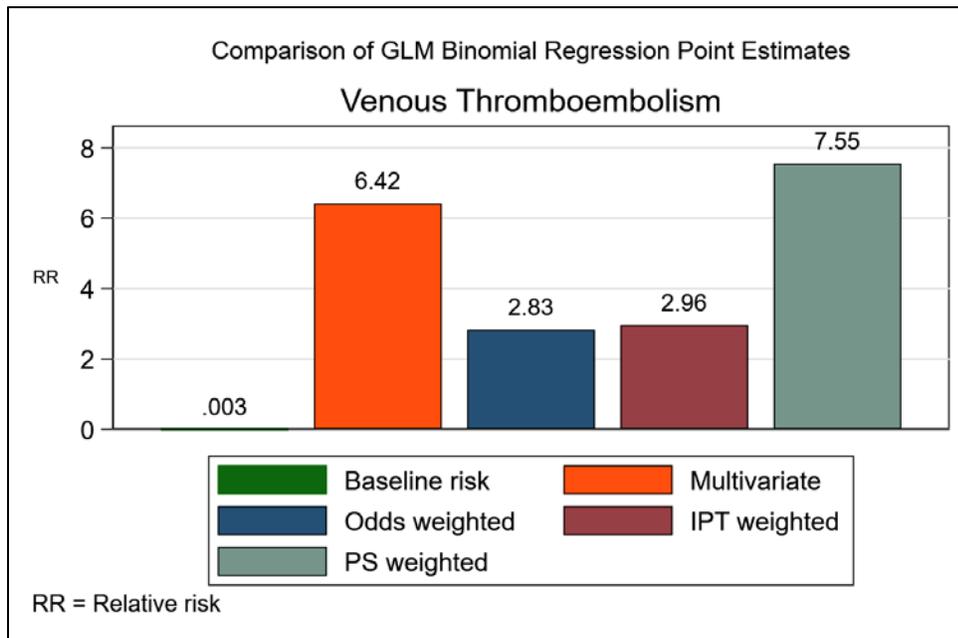


Figure 30. Comparison of venous thromboembolism point estimates.

Length of stay results. An IP, IPT, and PS weighted NBRM was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the incidence of length of stay in the main multivariate NBRM of the combined cohort. The IP weighted NBRM results indicated that androgen toxicity exposure did not have a significant

average exposure effect in the exposed on the incidence of length of stay, $IRR = 1.26$, 95% CI [0.97, 1.63], $z = 1.75$, $p = .080$. The IPT weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect on the incidence of length of stay, $IRR = 1.28$, 95% CI [1.01, 1.63], $z = 2.05$, $p = .041$, hence, the null hypothesis was rejected. The PS weighted NBRM results indicated that androgen toxicity exposure had a significant effect on the average incidence of length of stay, $IRR = 1.02$, 95% CI [0.81, 1.30], $z = 0.24$, $p = .807$, hence, the null hypothesis was not rejected. A comparison of length of stay point estimates for each statistical method used in the negative binomial regression models is presented in Figure 31.

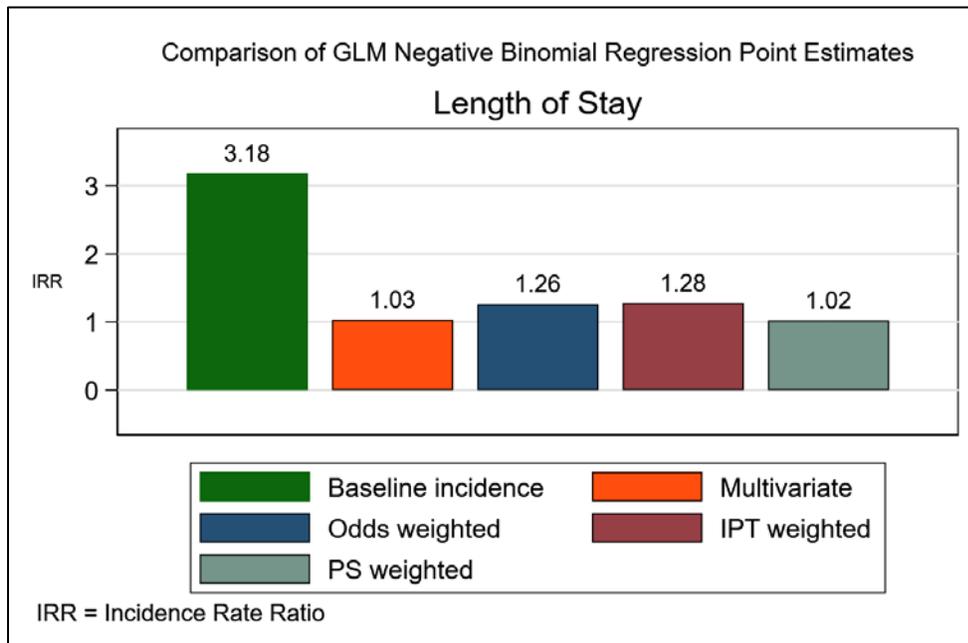


Figure 31. Comparison of length of stay point estimates.

Chronic condition results. An IP, IPT, and PS weighted NBRM was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the incidence of chronic conditions in the main multivariate NBRM of the combined cohort.

The IP weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the incidence of chronic conditions, $IRR = 1.25$, 95% CI [1.15, 1.35], $z = 5.63$, $p < .001$, hence, the null hypothesis was rejected. The IPT weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect on the incidence of chronic conditions, $IRR = 1.25$, 95% CI [1.16, 1.34], $z = 6.16$, $p < .001$, hence, the null hypothesis was rejected. The PS weighted NBRM results indicated that androgen toxicity exposure had a significant effect on the average incidence of chronic conditions, $IRR = 1.13$, 95% CI [1.06, 1.19], $z = 4.13$, $p < .001$, hence, the null hypothesis was rejected. A comparison of chronic condition point estimates for each statistical method used in the negative binomial regression models is presented in Figure 32.

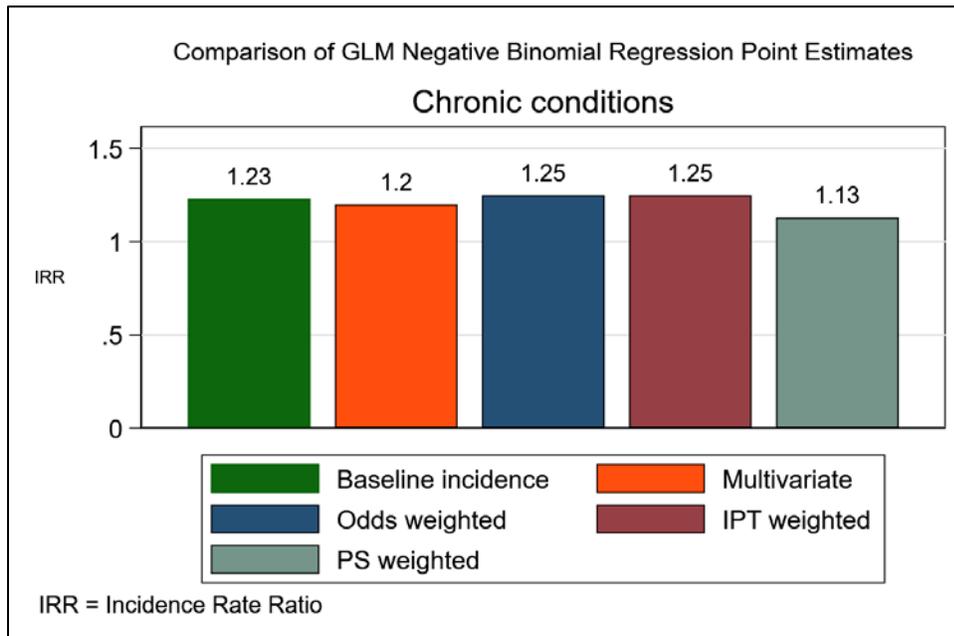


Figure 32. Comparison of chronic condition point estimates.

Diagnosis results. An IP, IPT, and PS weighted NBRM was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the

incidence of diagnoses in the main multivariate NBRM of the combined cohort. The IP weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the incidence of diagnoses, $IRR = 1.23$, 95% CI [1.15, 1.33], $z = 5.79$, $p < .001$, hence, the null hypothesis was rejected. The IPT weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect on the incidence of diagnoses, $IRR = 1.25$, 95% CI [1.17, 1.34], $z = 6.49$, $p = .007$, hence, the null hypothesis was rejected. The PS weighted NBRM results indicated that androgen toxicity exposure had a significant effect on the average incidence of diagnoses, $IRR = 1.14$, 95% CI [1.09, 1.20], $z = 5.47$, $p < .001$, hence, the null hypothesis was rejected. A comparison of diagnosis point estimates for each statistical method used in the negative binomial regression models is presented in Figure 33.

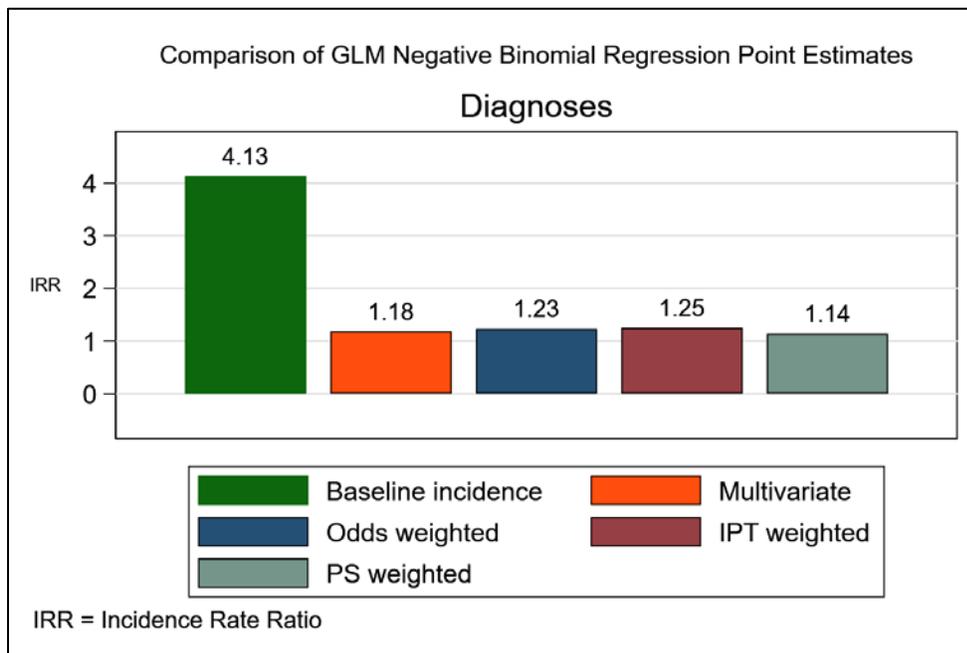


Figure 33. Comparison of diagnosis point estimates.

External cause of injury results. An IP, IPT, and PS weighted NBRM was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the incidence of external causes of injury in the main multivariate NBRM of the combined cohort. The IP weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect in the exposed on the incidence of ecodes, $IRR = 6.16$, 95% CI [5.34, 7.11], $z = 24.90$, $p < .001$, hence, the null hypothesis was rejected. The IPT weighted NBRM results indicated that androgen toxicity exposure had a significant average exposure effect on the incidence of external causes of injury, $IRR = 5.79$, 95% CI [5.21, 6.44], $z = 32.54$, $p < .001$, hence, the null hypothesis was rejected. The PS weighted NBRM results indicated that androgen toxicity exposure had a significant effect on the average incidence of external causes of injury, $IRR = 4.21$, 95% CI [4.01, 4.42], $z = 57.39$, $p < .001$, hence, the null hypothesis was rejected. A comparison of external causes of injury point estimates for each statistical method used in the negative binomial regression models is presented in Figure 34.

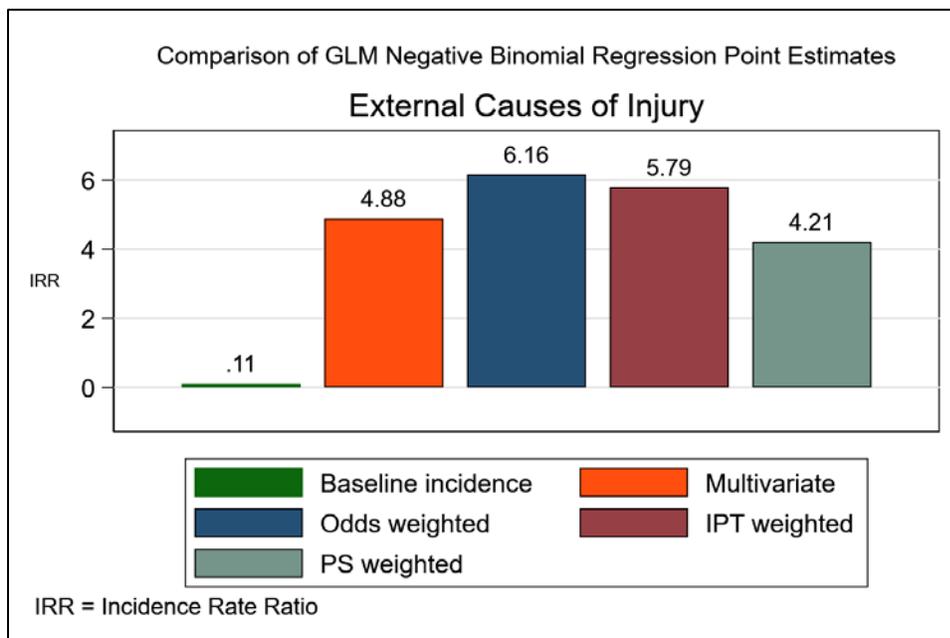


Figure 34. Comparison of external cause of injury point estimates.

Procedure results. An IP, IPT, and PS weighted NBRM was conducted to examine, replicate, and compare the multivariate relationship found between androgen toxicity and the incidence of procedures in the main multivariate NBRM of the combined cohort. The IP weighted NBRM results indicated that androgen toxicity exposure did not have a significant average exposure effect in the exposed on the incidence of procedures, $IRR = 1.00$, 95% CI [0.78, 1.27], $z = 0.02$, $p = .988$. The IPT weighted NBRM results indicated that androgen toxicity exposure did not have a significant average exposure effect on the incidence of procedures, $IRR = 0.96$, 95% CI [0.77, 1.21], $z = -0.28$, $p = .780$. The PS weighted NBRM results indicated that androgen toxicity exposure did not have a significant effect on the average incidence of procedures, $IRR = 0.92$, 95% CI [0.78, 1.08], $z = -0.98$, $p = .326$. A comparison of procedure point estimates for each statistical method used in the negative binomial regression models is presented in Figure 35.

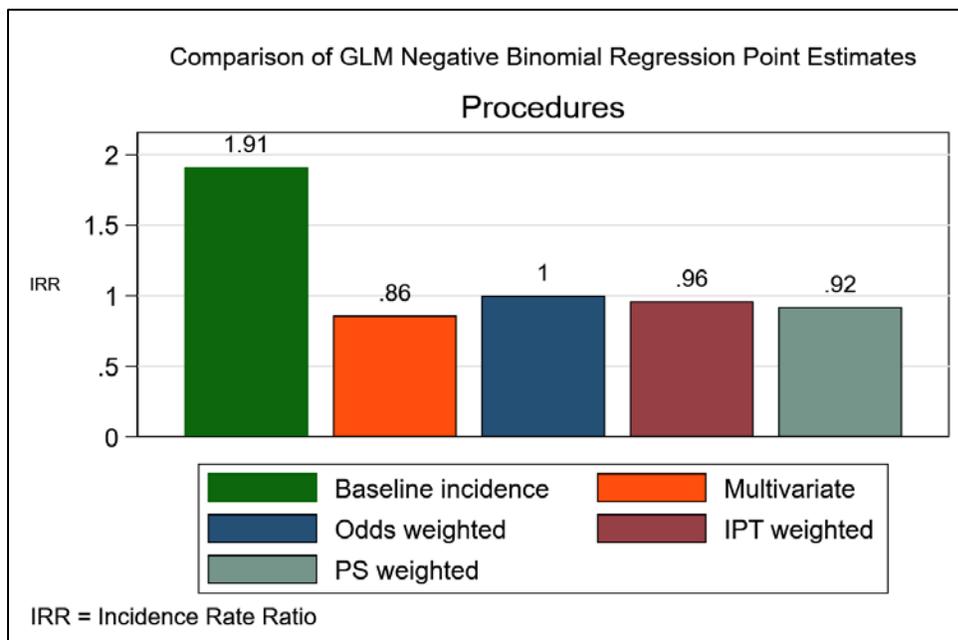


Figure 35. Comparison of procedure point estimates.

Evaluation of Findings

Aim 1 [RQ 1]. What is the relationship between androgen toxicity and risk of health outcomes?

Mortality evaluation. The mortality findings among each of the cohorts in all bivariate, multivariate, and replication analyses showed a *decreased* risk of mortality associated with androgen toxicity exposure. The findings are inconsistent with androgen toxicity theory in some existing literature and were unexpected given the randomized controlled trial by Shehzad Basaria et al. (2010) that was stopped by a safety monitoring board finding greater risk of adverse cardiovascular events and the retrospective cohort by Vigen et al. (2013a) reporting higher risk of myocardial infarction, ischemic stroke, and mortality counter to the results of the current study. The findings were expected given the randomized controlled trial by Srinivas-Shankar et

al. (2010) showing no influence of androgen therapy and increased mortality at six months in older intermediate-frail and frail men but rather improvements in factors associated with improved survival. Almost all androgen therapies are associated with improvements in increased lean body mass, reduced body fat mass, greater muscular strength, and favorable metabolic profiles. Hence, the mechanisms underlying these favorable characteristics may explain the discrepancy in the decreased mortality findings of this study.

Polycythemia evaluation. Polycythemia findings among each of the cohorts in all bivariate, multivariate, and replication analyses showed *extreme* risk of polycythemia associated with androgen toxicity exposure. The findings are consistent with the existing literature and were expected given nearly all the studies reviewed in Chapter II reported increases in secondary erythrocytosis, hence, hematotoxicity was the most common form of androgen toxicity in the literature. The findings align to the seminal study by Andrea D. Coviello et al. (2008) that established the fundamental dose-response relationship between testosterone and capacity to induce differentiation of red marrow hematopoietic stem cells directly to increase red blood cell number in healthy men.

Hypercoagulability evaluation. The hypercoagulability findings among each of the cohorts in all bivariate, multivariate, and replication analyses showed *a moderate* risk of hypercoagulability associated with androgen toxicity exposure. The findings were expected given the randomized controlled trial by Ajayi Ajayi et al. (1995) showing increased thromboxane A₂ receptor density and aggregation responses with androgen administration as likely requisite mechanisms for hypercoagulable states.

Drug-induced liver injury evaluation. The drug-induced liver injury findings among each of the cohorts in all bivariate, multivariate, and replication analyses showed *extreme* risk of DILI associated with androgen toxicity exposure. The study findings were expected given the multitude of case reports reporting severe morphological changes such as benign liver adenoma, hepatocellular carcinoma, direct hepatocellular and cholestatic cellular injury, and non-alcoholic fatty liver disease following long-term DILI by 17AA androgens (Gupta et al., 2016; Kato et al., 2018; Leone, G. Santos, Finan, E. Alsina, & S. Franco, 2016; Romano et al., 2017; Takahashi et al., 2017). The findings of the present study may represent first-stage liver disease and dysfunction leading to more serious conditions like hepatocellular carcinoma which could express decades after chronic exposure.

Venous thromboembolism evaluation. The venous thromboembolism findings among each of the cohorts except for cohort three in all bivariate, multivariate, and replication analyses showed *low-to-moderate* risk of VTE associated with androgen toxicity exposure. The findings were expected given the risk window for VTE after starting androgen therapy reported by Martinez et al. (2016). In addition, the variation in VTE from year-to-year was also expected since the results of C. J. Glueck et al. (2016) and C. J. Glueck et al. (2011) suggested undiagnosed thrombophilia were responsible for VTE after initiating androgen therapy.

Aim 1 [RQ 2]. What is the relationship between androgen toxicity and incidence of inpatient variables?

Length of stay evaluation. Length of stay findings were nonsignificant in the first four cohorts and the combined cohort in all bivariate, multivariate, and replication analyses. In cohort five and six, there were both significant *low decreased* and significant *modest increased*

incidence of inpatient stay associated with androgen toxicity exposure for cohort five and cohort four, respectively. The study findings were unexpected given the research by Baillargeon et al. (2016) showing decreased risk of hospitalizations and unplanned readmissions among older men treated with androgen therapy.

Chronic condition evaluation. Chronic condition findings among cohorts one, two, four, five, and combined in all bivariate, multivariate, and replication analyses showed *modest increased* incidence of chronic conditions associated with androgen toxicity exposure. The findings were expected given the research by Tse et al. (2017) showing up to a 28% increase in comorbidities in hereditary angioedema patients treated with 17AA androgens.

Diagnosis evaluation. Diagnosis findings among cohorts one, two, four, five, and combined in all bivariate, multivariate, and replication analyses showed low-to-modest increased incidence of diagnosed diseases associated with androgen toxicity exposure. The incidence of diagnoses served as a proxy measure of comorbidity in the present study. Therefore, the findings were expected given the research by Tse et al. (2017) demonstrating increased comorbidity in patients exposed to chronic 17AA androgen exposure.

External cause of injury evaluation. The findings of external causes of injury among each cohort in all bivariate, multivariate, and replication analyses showed *high increased* incidence of external causes of injury associated with androgen toxicity exposure. The findings were expected given that the external cause of injury coded (E932.1) was used to identify androgen toxicity exposure and to establish assignment to index and reference cohorts. Although inpatients with androgen toxicity had a greater burden of disease indirectly expressed by both

increased chronic diseases and diagnoses, the increase in external causes of injury characterizes the severity of disease which was unexpected.

Procedure evaluation. Procedure findings among each yearly cohort except cohort three in all bivariate, multivariate, and replication analyses showed *null effects* on the incidence of procedures associated with androgen toxicity exposure. In the combined cohort bivariate analysis, the incidence of procedures was not significant but became significant upon adjustment and could not be replicated with PS methods. The procedure results were unexpected given the findings of Vigen et al. (2013a), Finkle et al. (2014), and Shehzad Basaria et al. (2010) showing increased risk for major cardiovascular events that often necessitate the need for medical procedures. The main mechanism to explain the lack of effect on procedure number may simply be that androgen toxicity in the assessed cohorts caused disease not leading to or independent from diseases that often necessitate the need to medical procedure-based interventions.

Aim 2 [RQ 3]. What is the relationship between androgen toxicity and healthcare costs?

Healthcare cost evaluation. Healthcare cost findings among each of the yearly cohorts except cohort five in all bivariate, multivariate, adjusted, and replication analyses showed *overall null effects* of androgen toxicity exposure on healthcare costs. In cohorts one, two, and three, androgen toxicity exposure had a significant marginal effect between the two levels of exposure (no or yes) evidenced with higher healthcare costs in unexposed inpatients. In contrast, cohorts four, five, and six showed significantly higher healthcare costs in exposed inpatients. In the combined cohort, androgen toxicity exposure was significantly associated with increased health care costs, but upon adjustment significance did not persist. The disparity in healthcare costs

was not expected given the study by Tse et al. (2017) demonstrating considerably greater healthcare costs and economic burden of disease resulting from 17AA androgen therapy.

Summary

The current epidemiologic study examined the relationships between androgen toxicity, risk of primary health outcomes, incidence of inpatient variables, and marginal total healthcare costs among inpatients. A population-based retrospective cohort design using National Inpatient Sample data spanning six years from 2010 to 2015 was employed to meet the study purpose. Androgen toxicity exposure was associated with a higher risk for the primary health outcomes of polycythemia, hypercoagulability, drug-induced liver injury, and venous thromboembolism, but not for mortality. Higher incidence of chronic conditions, diagnoses, and external causes of injury, and a lower incidence of procedures were also found to be associated with exposure with no effect on the duration of inpatient stay. A higher economic burden of disease measured in total healthcare costs was not found in relation to androgen toxicity exposure although marginal differences between exposure and non-exposure were found. Yearly trends in health outcomes risk were stable and consistent for each health outcome except polycythemia, whereas all incidence trends were consistent over each year of the analysis. Healthcare cost trended upwards consistently from 2011 to 2014 for the exposures contrasted with a less pronounced but gradual increase in healthcare costs for all but 2012 in the non-exposures. Odds weighted, inverse probability of treatment weighted, and propensity score weighted analysis allowed successful replication of each of the main analysis results for the health outcomes and inpatient variables except for procedures.

Chapter V: Discussion

The thesis of this study was *the therapeutic use of androgens in the overall inpatient population among U.S. hospitals is associated with health and economic consequences*. As such, the problem addressed by this study was a lack of knowledge and meaningful data in an inpatient population regarding the effect of androgen toxicity exposure on the risk of primary health outcomes and the economic burden of disease. The *primary purpose* of the study was to characterize the epidemiology of androgen toxicity by determining the relationship between androgen toxicity exposure and the risk of inpatient health outcomes in nationally representative cohorts of inpatients. The *secondary study purpose* was to further characterize the epidemiology of androgen toxicity by determining the relationship between androgen toxicity exposure, incidence of inpatient variables, and the economic burden of disease among inpatient cohorts. A population-based quantitative retrospective cohort design using secondary data was used in the investigation to assess the risk of health outcomes, incidence of inpatient variables, and total healthcare costs associated with androgen toxicity.

The study did not require informed consent, participant assent forms, recruitment documents, or study site endorsements for Institutional Review Board approval given the use of secondary NIS data. The NIS data used in this study was not analyzed until Institutional Review Board approval was granted upon the submission of a HIPAA waiver request and complete Institutional Review Board application (Appendix A).

In this nationally representative cohort study, several key risk associations between androgen toxicity exposure, health outcomes, inpatient variables, and total healthcare costs were found. Androgen toxicity exposure was associated with:

1. Health outcomes:
 - a. Decreased risk of mortality;
 - b. Extreme increased risk of polycythemia;
 - c. Moderate increased risk of hypercoagulable states;
 - d. Extreme increased risk of drug-induced liver injury; and
 - e. Low-to-moderate risk of venous thromboembolism.
2. Inpatient variables:
 - a. Both low decreased and modest increased incidence of length of stay;
 - b. Modest increased incidence of chronic conditions;
 - c. Low-to-moderate increased incidence of diagnoses;
 - d. High increased incidence of external causes of injury; and
 - e. Null effects on the incidence of procedures.
3. Healthcare costs:
 - a. Overall null effects on healthcare costs for each of the cohorts;
 - b. Decreased marginal effects on healthcare costs in cohorts (1-3); and
 - c. Increased marginal effects on healthcare costs in cohorts (4-6).

The limitations of the study were:

1. A lack of NIS data on pharmacologic properties of androgens and explicit reasons for hospitalization.
2. Possible NIS data inaccuracies relating to misclassification bias of health outcome variables.
3. Relatively low diagnosed androgen toxicity exposure in the sample.

4. Possible existence of androgen-treated inpatients without diagnosed androgen toxicity.
5. A lack of adjustment for confounding factors existing outside of the NIS data.
6. Measures of association for risk and incidence were inherently non-causal and confined by the study design.

The discussion of Chapter V addresses the implications of the study organized around each dependent variable, drawing conclusions and offering explanations for the study findings. Study strengths and limitations are discussed in the context of the study problem, purpose, significance, and contribution to the existing literature. Chapter V presents and discusses the recommendations for clinical practice and future research elucidating how researchers may use and build upon the study findings to improve existing knowledge and gain deeper understanding of the androgen research literature.

Implications

Health outcomes. The present investigation represents the first large-scale population-based study examining the association of androgen toxicity exposure with theory-based health outcomes. The reduction of risk factors linked to unfavorable health outcomes and increased inpatient stay, comorbidity, and disease severity represents a U.S. health priority and consequently, a major focus of healthcare reform measures nationwide (Chokshi, Chang, & Wilson, 2016). The literature on androgen toxicity theory is almost equally divided with either increased risk or decreased risk and protective effects for identical health outcomes. Most of the literature detailing greater health risk is based on illicit androgen use by athletes and

bodybuilders, whereas the predominance of the therapeutic androgen literature noted lower risk potential.

Mortality. In the present study, inpatients exposed to androgen toxicity had a lower risk of death in a combined sample size > 33 million inpatients. The mortality findings imply that inpatients with an androgen toxicity diagnosis experienced a protective effect that decreased mortality risk. Although the age of inpatients with androgen toxicity exposure was considerably higher than most published studies, the mortality findings were unexpected given the randomized controlled trial of androgen therapy by Shehzad Basaria et al. (2010) of older men with limited mobility and hypogonadism that was stopped by a safety monitoring board finding greater risk of adverse cardiovascular events commonly associated death and disadvantaged survival. The retrospective cohort by Vigen et al. (2013a) also found a higher risk of myocardial infarction, ischemic stroke, and mortality in stark contrast to the findings of this study. In addition, the present study findings were expected given the randomized controlled trial by Srinivas-Shankar et al. (2010) demonstrating no effect of androgen therapy to increase mortality at six months in older intermediate-frail and frail men but rather favorable protective factors associated with improved survival. The studies by Muraleedharan, Marsh, Kapoor, Channer, and Jones (2013), Hankey et al. (2014), and R. Sharma et al. (2015) showed androgen deficiency was associated with an increased risk of all-cause mortality, whereas androgen treatment to restore optimal androgen levels was associated with improved survival and substantially lower all-cause mortality in older men. The randomized controlled trial by Peter J. Snyder et al. (2016) showed therapeutic testosterone increased lean body mass, reduced body fat mass, and increased physical function in older men, while the meta-analysis by Cai et al. (2014) demonstrated exert a

favorable influence on metabolic profile in older hypogonadal men with type two diabetes mellitus. Therefore, these mechanisms may explain the discrepancy in mortality findings of this study and those in the literature. The implication of mortality findings is important because counter research, such found in the study by Vigen et al. (2013a) was used as scientific evidence by the FDA to warrant pharmaceutical labeling mandates in 2014.

Polycythemia. In the present study, androgen toxicity was associated with an increased risk of blood diseases. Inpatients exposed to androgen toxicity had an extreme risk of polycythemia, an expected finding since hematotoxicity is the most frequently reported adverse effect associated with androgens in the literature. Current evidence suggests two mechanisms for androgen-induced secondary erythrocytosis including stimulation of erythropoietin and direct stem cell stimulation (Burns et al., 2016). The seminal research by Andrea D. Coviello et al. (2008) showed the capacity of androgens to directly induce the differentiation of red marrow hematopoietic stem cells. Although findings of elevated risk were expected, the effect sizes for polycythemia found in this study ($RR = 74.39$ to $RR = 222.86$, $p < .001$) were not since the term “polycythemia” is usually specified in the literature to denote polycythemia vera which is a form of blood cancer (Burns et al., 2016). Burns et al. (2016), in the most concise and authoritative textbook of hematology, explicitly states the term secondary erythrocytosis is the most appropriate term for dramatic erythropoiesis induced by androgens increasing hemoglobin levels in the polycythemic range (p. 879). The implication of extreme risk of secondary erythrocytosis in inpatients is that some unknown salient characteristic or condition may predispose this population for greater hematotoxicity than other populations.

Hypercoagulability. A moderate risk of hypercoagulability and low-to-moderate risk of VTE were also found to be associated with androgen toxicity exposure in the present study. The finding of increased hypercoagulability risk ($RR = 2.63$ to $RR = 11.65$) aligns to the increased thromboxane A₂ receptor density and aggregation responses found by Ajayi Ajayi et al. (1995). Hypercoagulable states are similar to hereditary thrombophilias evidenced in the study by Charles J. Glueck, Goldenberg, and Wang (2018) since thrombophilias often coincide or lead to thrombotic conditions representing one aspect of vascular toxicity.

Venous thromboembolism. The present study findings of both hypercoagulability and VTE were expected given the initial risk window for VTE after starting androgen therapy, a six-month time-to-event reported by Charles J. Glueck et al. (2018), was confirmed by the six-month time-to-event VTE risk window ($RR = 1.63$) reported by Martinez et al. (2016). Unexpectedly, the risk estimates for VTE of the present study ($RR = 1.24$ to $RR = 9.57$) were considerably higher than those reported by Martinez et al. (2016) ($RR = 1.00$ to $RR = 1.88$). The highest rate ratio estimate of the present study was nearly five times greater in magnitude and only one out of six estimates was lower than the highest rate ratio reported by Martinez et al. (2016). The present study findings contrast with the reported risk estimates of Baillargeon et al. (2015) showing slightly elevated VTE risk with intramuscular androgen administration in one analysis subgroup. Although the present study findings conflict with Baillargeon et al. (2015), the findings may not support the addition of a general warning for risk of venous thromboembolism with androgen products by the FDA as recommended by Martinez et al. (2016). Although Martinez et al. (2016) characterized the transient nature of VTE, it is unclear whether this holds

in the population assessed by this study or whether some salient factor is common with androgen toxicity exposure.

Androgen-related mechanisms leading to VTE are complex, however, the overarching medical consensus points to either hypercoagulable states or hereditary thrombophilias coupled with increased thromboxane A₂ receptor density and aggregation response ultimately leading to venous thromboembolism or other thrombotic outcomes like pulmonary embolism as demonstrated in the case-series study by Charles J. Glueck et al. (2018). The discrepancies between studies reporting VTE risk associated with androgen therapy may be explained by the rarity of certain diseases like familial thrombophilia or hypercoagulable states in healthy populations versus comorbid populations. An association between undiagnosed thrombophilia and the initiation of androgen therapy was found in the research by C. J. Glueck et al. (2011). Therefore, undiagnosed familial thrombophilia could not be ruled out in the present study. The general implication for increased risk of hypercoagulability, venous thromboembolism, and secondary erythrocytosis lies in the notion that hypercoagulability (vasculotoxicity) and secondary erythrocytosis into the polycythemic range (hematotoxicity), together, set the ideal physiologic conditions needed for thrombotic events to occur.

Drug-induced liver injury. Hepatotoxicity has been well-established since the initial synthesis of testosterone from cholesterol by Ruzicka and Wettstein (1935) yielding highly liver toxic 17AA methyltestosterone. In the present study, an extreme risk of drug-induced liver injury was found. The DILI findings were expected and coincide with numerous case reports reporting severe morphological changes such as benign liver adenoma, hepatocellular carcinoma, liver dysfunction, and non-alcoholic fatty liver disease following long-term exposure to 17AA

androgens (Gupta et al., 2016; Hardt et al., 2012; Kato et al., 2018; Leone, G. Santos, Finan, E. Alsina, & S. Franco, 2016; Romano et al., 2017; Solbach et al., 2015; Takahashi et al., 2017). The effect magnitude range of DILI risk in the present study ($RR = 26.29$ to $RR = 63.31$, $p < .001$) was not expected given the findings of a randomized trial by Supasyndh et al. (2013) that showed only low-to-moderate changes consistent with liver dysfunction and direct liver tissue injury. A possible reason to explain this discrepancy is that an acute exposure was assessed by Supasyndh et al. (2013) versus the likely long-term chronic exposure involved in the findings of the present study.

Liver damage caused by 17AA androgens occurs over long periods of consistent exposure even with low dosages. The present study findings imply that inpatients exposed to androgen toxicity may be in first-stage liver disease and dysfunction leading up to more serious conditions like hepatocellular carcinoma which might express decades after chronic androgen exposure periods. Although there was evidence suggesting that 17AA androgens were involved with hepatotoxicity in the results, it cannot be confirmed that methylated androgens were used. As stated previously, most of the androgen toxicity literature has focused on illicit androgen use by athletes and bodybuilders. The present study had two possible androgen-related toxicity outcomes: illicit androgen use outcomes and therapeutic androgen use outcomes. As such, illicit use, although unlikely in an inpatient setting, is distinct from the clinical outcomes assessed in this study. The findings offered no suggestion that any inpatients with androgen toxicity exposure were abusing illicit androgens given the mean age of exposures was nearly 65 years old. Illicit users are more likely to be younger 20 to 39 years of age and present with a misleading external image of health during medical encounters which often hinders

comprehensive diagnostic testing (H. G. Pope et al., 2014; D. Sagoe et al., 2014). The findings of this study suggest that exposed inpatients experienced greater clinical hepatotoxicity from prescribed androgens due to greater disease severity as evidenced by the frequency of various cancers and rare anemias that were found.

Inpatient variables. Androgen toxicity exposure was expected to increase the incidence of inpatient variables considering the large body of evidence that was used to develop androgen toxicity theory in Chapter II. Given the health risks found in the literature and those found in this study, there was an additional expectation that there would be higher incidence rates in each of the inpatient variables.

Length of stay. The present study findings showed unexpected low decreases and modest increases in the incidence of length of stay in contrast to the findings of Baillargeon et al. (2016) that reported decreased hospitalizations and unplanned readmissions with therapeutic androgen replacement. Since inpatients of greater age, by the mere fact of hospitalization, can be assumed to be at a greater predisposition for comorbidity, the differences in comorbidity of the present study and the comorbidity of the population assessed by Baillargeon et al. (2016) may explain some of these inconsistencies.

Chronic conditions and diagnoses. Similar to length of stay, the incidence of chronic conditions and diagnoses found in this study were modestly higher and low-to-modestly higher among inpatients exposed to androgen toxicity. Chronic conditions and diagnoses were considered an indirect surrogate measure of comorbidity since the incidence of chronic diseases and diagnoses provides an approximate picture of overall inpatient health. Chronic conditions often develop simultaneously throughout the lifespan, therefore, the present study findings were

expected and aligned to the research by Tse et al. (2017) showing up to a 28% increase in comorbidities in hereditary angioedema patients treated with 17AA androgens. In four cohorts, the incidence rate ratios reported in the present study were similar in magnitude than those reported by Tse et al. (2017), whereas, the incidence rate ratios in two cohorts of the present study were greater ($IRR = 1.37$ and $IRR = 1.44$) than those noted by Tse et al. (2017). One likely reason for the discrepancy in these effect estimates could be the age of the study populations. Although Tse et al. (2017) assessed patients with average ages (30.4-48.7) years, the present study assessed an inpatient population with average ages (> 55) years. Possible reasons for the inconsistency in effect estimates beyond the influence of age may be attributed to methodology and sample size. Tse et al. (2017) used a case-control sampling methodology of an insurance database matching five controls (180) to each hereditary angioedema case (36) in contrast to the yearly cohorts, each with sample sizes from approximately 4.4 to 6.5 million inpatients in the present study. Increases in age tend to increase comorbidity even in healthy populations, therefore, the findings of increased incidence of chronic conditions could also reflect the natural history of age-related disease progression (Jaul & Barron, 2017).

External causes of injury. Androgen toxicity exposure was associated with a high incidence of external causes of injury in each of the study cohorts. The findings were anticipated given that the external cause of injury coded (E932.1) was used to identify exposure and establish cohorts for analysis, although the magnitude of effect was not expected with the finding of adjusted incidence rate ratios (≥ 4.50) in each cohort. The average number of external causes of injury for unexposed inpatients among each cohort was (0.3), whereas the mean number of external causes of injury for exposed inpatients was (≥ 1.5) representing a ($\geq 500\%$) increase in

external causes of injury comparing unexposed to exposed. One probable mechanism underlying the differential incidence of external causes of injury is the sub-forms of androgen exposure experienced by inpatients. That is, although androgen toxicity exposure in this study was explicit, meaning androgen toxicity was diagnosed, inpatients could have experienced any of the six forms of androgen toxicity identified in Chapter II or combinations of the androgen toxicity forms simultaneously. Therefore, inpatients with androgen toxicity were expected to have a greater burden of disease indirectly expressed by an increased number of external causes of injury, length of stay, chronic conditions, diagnoses, and procedures although other unknown lifestyle factors may reside outside of the data. Here, it is also notable that the increased incidence of external causes of injury might be due, in part, to the extreme comorbidity and severity of disease found in the primary diagnoses of the exposed inpatients.

Procedures. In the present study, androgen toxicity exposure had no effect on the incidence of procedures among each of the study cohorts. The null procedure findings were unexpected given the large body of evidence by Vigen et al. (2013a), Finkle et al. (2014), Shehzad Basaria et al. (2010), Charles J. Glueck et al. (2018), and Martinez et al. (2016) that demonstrated an increased risk for major health outcomes such as AMI, stroke, VTE, pulmonary embolism, and cardiovascular events which often necessitate inpatient medical procedures. Given the present study findings of increased chronic conditions and diagnoses, the expected decrease in the incidence of procedures was not evidenced by the data.

Healthcare cost. The economic burden of disease among inpatients of the present study was measured by total healthcare costs. Androgen toxicity exposure unexpectedly had no effect on the economic burden of disease in the adjusted analysis. However, marginal subgroup

analysis showed androgen toxicity exposure had a significant marginal effect between the two levels of exposure (no or yes) evidenced with higher healthcare costs in unexposed inpatients in cohorts one, two, and three. The significant marginal effect in the unexposed inpatients was reversed in cohorts four, five, and six showing androgen toxicity exposure level significantly increased healthcare costs in exposed inpatients with the analysis of cohort five showing the largest difference in healthcare costs ($MD = 20,151.73$). The unanticipated healthcare costs findings in the unexposed failed align with the findings of Tse et al. (2017) that showed considerably greater healthcare costs as a result of 17AA androgen exposure. However, three cohort analyses showed an increase in average healthcare costs in exposures which aligned to the findings of Tse et al. (2017). The consequence of these differential findings may be due to the high number of missing values for the healthcare cost variable that were subsequently dropped in the data cleaning stage to enable the analysis. Still, another explanation for some of the conflicting healthcare cost findings may be related to the use of only three quarters of the NIS data for 2015. However, since all exposed inpatients did not have missing healthcare cost values and the findings in 2015 were increased, not decreased, it is unclear why the differential findings exist. Most of the cohorts from 2010 to 2015 showed slight increases in the number of E932.1 diagnoses, although the overall number relative to the sample size was extremely small. Given the rare occurrence of androgen toxicity and unknown guidelines for applying the diagnosis in practice, many cases of androgen toxicity may go undiagnosed except for certain hospitals with physicians familiar with the diagnosis. Hospital-level factors may have played a role in the discrepant findings, but given the a priori focus on health outcomes, inpatient variables, and

healthcare costs, and inconsistent hospital-level data from year-to-year, hospital characteristics were not assessed in this study.

Limitations and delimitations. Several data limitations were evident in the execution of this study. Due to NIS data inconsistencies among the six years of data assessed in the study many variables such as hospitalization type, hospital location, hospital division, and hospital region were dropped from the analysis. Major operating room procedure, elective admission, mortality likelihood, disease severity, patient residence, and 13 created variables were dropped from the analysis as a delimitation to narrow the scope of the study. For the nominal variables race, median income, and patient residence data fidelity was preserved by creating another variable level termed “missing” to hold missing values. With healthcare costs, only three quarters of the data in 2015 were used, but the estimates from that year were still higher than three other years among the exposures. In addition, healthcare cost was recoded to the average of the median healthcare cost estimate between two exposure levels (exposure and non-exposure) of the independent variable androgen toxicity instead of multiple imputation since observations of androgen toxicity (E932.1) were small in each year and dropping all missing values for healthcare costs would also drop observations of the independent variable. The effect on the management of missing healthcare cost values was expected to result in bias towards only the null. Although the method was deemed appropriate for the analysis, the healthcare costs for androgen toxicity exposure should be interpreted with caution as the true estimate is likely higher than estimated in this study.

The main limitations of this study are those that are detected or undetected in all observational studies, including unmeasured confounding, residual confounding, and hidden

bias, among others. One limitation of the study and possible selection bias was the use of the external cause of injury code E.932.1 to assign exposure status among the cohort. The assignment solitarily demonstrates that an inpatient has experienced androgen toxicity from an unknown androgen therapy, which may or may not be the reason for hospitalization. It is possible that inpatients with this exposure have common negative health behaviors that increase the risk of the outcomes that were assessed. In addition, the E932.1 assignment confirm that inpatients were treated with androgens and experienced a consequence of the therapy but does not provide any information on pharmacologic properties such as androgen type, dose, duration, or mode of administration. Although, pharmacological properties are critical to understand the mechanisms of androgen toxicity, the focus of the study was to obtain valid estimates of health outcomes risk resulting from androgen toxicity diagnosis in a nationally representative inpatient population. Therefore, the study findings from the large data analysis adequately provide valid estimates of risk in an inpatient setting without pharmacological information. The primary diagnose of inpatients with androgen toxicity exposure did offer possible clues to characterize the reasons for androgen therapy but could not confirm the actual disease that androgen therapy was intended to treat. Exposed inpatients were older White males with an unusually high number of diagnoses for cancer and different anemias, the latter of which suggest anemias were the intended target of treatment for most exposures.

Another limitation was possible inaccuracies of the NIS data. Misclassification bias of health outcomes based on diagnosis codes was an inevitable consequence of the use of secondary data. The accuracy and completeness of diagnoses in the NIS data cannot be measured. It is possible that health outcomes and androgen toxicity exposures in each year were mis-classified;

however, due to the sample size, this tendency may be more or less dampened. The number of androgen toxicity exposures was another limiting aspect of the study. Of the 33,996,356 observations, there were only 488 androgen toxicity exposures from 2010 to 2015. Information bias and confounding cannot be ruled out, given the existence of androgen toxicity alone, does not exclude the existence of androgen-treated inpatients without resultant androgen toxicity. Finally, due to the inclusive nature of the sample and limited variables, unmeasured confounding through factors lying outside of the data could not be adjusted in the analysis.

A delimitation of the study was the choice of NIS data over other secondary data sources to allow analysis over the entire length of inpatient stay. Another delimitation was the assessment of yearly index and reference cohorts for health outcomes, inpatient variables, and healthcare cost analysis in separate analyses while also merging all the study cohorts for an overall analysis. Given the study sample sizes for each yearly cohort, the health outcome, inpatient variable, and healthcare costs analysis for each year retained comparability and validity of statistical inference with the combined cohort analysis. Lastly, comorbidity measures were excluded from the analysis due to the number of comorbidity measures in the NIS data. Instead, the incidence of chronic conditions and diagnoses were used as an indirect surrogate measure of comorbidity, although, the true characterization of comorbidity, although important, was not feasible in this study.

Study strengths. Despite the limitations, the strengths of this study are several fold. The main strength of the study was that multiple levels of analysis were conducted encompassing descriptive statistics, health outcome risk, risk trends, and replication analysis through the use of propensity score methods. An additional primary strength of the study was the large sample size

($n = 33,996,356$ observations), racially and socioeconomically diverse cohorts, and representative coverage of all geographic regions of the United States. There is no known study with a larger sample size and diversity than the current study sample that has been assessed in the published androgen literature. The closest sample size was < 2.22 million as reported in the population-based case-control study by Martinez et al. (2016) that assessed VTE associated with androgen therapy in men aged 20-89 years old and exposure defined from filled androgen prescriptions. A retrospective cohort design was chosen to allow a valid estimation of rate ratios, in contrast to the mis-specified rate ratios reported by Martinez et al. (2016). In addition, the retrospective cohort design was also selected to permit a focus on theory-based assessments of many primary health outcomes including mortality, polycythemia, hypercoagulability, drug-induced liver injury, and venous thromboembolism instead of a sole assessment of VTE.

In the present study, the effects of androgen toxicity were mapped in the only assessment of the entire duration of stay in an inpatient population using a population-based design unaligned to insurance records, health records, or the government-linked databases like those used by Baillargeon et al. (2014), Baillargeon et al. (2015), Baillargeon et al. (2016), Martinez et al. (2016), and Prince et al. (2016). An additional strength was the use of one data source instead of utilizing outcome algorithms on multiple data sources, as seen in much of the published literature. In the present study, specific ICD-9-CM code-defined outcomes from one data source were used to counter information bias. Finally, to guard against several biases and unmeasured confounding, three replication analyses were incorporated using odds weighting, inverse probability of treatment weighting, and propensity score weighting on all health outcomes and inpatient variables. Given the large sample size, multivariate analyses, and replication analyses,

the results of this study are robust and valid estimates of health outcome risk in an inpatient population.

Recommendations

The results of this investigation suggest that androgen toxicity exposure exerts protective effects on mortality, extreme risk on secondary erythrocytosis into the polycythemic range, moderate risk on hypercoagulable states, fair-to-moderate risk on venous thromboembolism, and extreme risk on drug-induced liver injury. The investigation findings further suggest that androgen toxicity exposure exerts substantial increases on the incidence of external causes of injury, fair-to-moderate increases on the incidence of chronic conditions and diagnoses, differential effects on the incidence of length of stay, and null effects on the incidence of procedures. Finally, this investigation submits that androgen toxicity exposure exerts inconsistent differential effects on the economic burden of disease of inpatients.

The comparisons made by this study offer key meaningful data that may be used for efforts to reduce risk and healthcare costs in an inpatient setting given the differential effects and disparities that were found for the covariates of age, sex, race, and median income. Standardized androgen screening for rare blood disorders such as familial thrombophilia and other coagulation disorders known to increase the propensity to develop thrombotic events may be useful and routinely incorporated with inpatients with severe cancer. Clinicians should explore other non-17AA androgens for conditions such as hereditary angioedema and diverse anemias reassessing the risk-to-benefit of using long-term 17AA treatments. Upon the decision to use 17AA androgens, greater emphasis on continual therapeutic monitoring is warranted and should be applied.

Rare familial thrombophilias or acquired thrombophilias coupled with increases in secondary erythrocytosis into the polycythemic range along with increases in thromboxane A2 receptor density may set the ideal, but infrequent, conditions for thrombotic events in a subset of inpatients. Future research is needed to confirm how androgens influence the risk of venous thromboembolism and other thrombotic events in those with familial or acquired thrombophilias.

The hepatotoxic effects of 17 alpha-alkylated androgens have been well-established for 60 or more years after the methylated synthesis of testosterone from cholesterol by Ruzicka, Goldberg, and Rosenberg (1935). Although 17AA androgens have important utility in the treatment of anemias and hereditary angioedema, the findings of this investigation suggest an extreme risk of drug-induced liver injury and initial-stage liver disease possibly by the therapeutic use of methylated androgens. Liver damage caused by 17AA androgens is insidious over chronic exposure even with low doses. Current evidence by Robles-Diaz et al. (2015) indicates that a distinct DILI phenotype with primary hepatocellular injury concurrently with cholestasis leading to jaundice is associated with 17AA exposure, whereas other evidence by Peter Bond, William Llewellyn, and Peter Van Mol (2016) indicates recurring chronic oxidative stress leading to neoplastic transformation ultimately resulting in hepatocellular carcinoma as a consequence of methylated androgens. Future research is needed to map the process by which androgen-related DILI leads to serious austere health outcomes such as liver cancer.

Conclusions

Androgen toxicity exposure increased the risk for secondary erythrocytosis, hypercoagulable states, venous thromboembolism, and drug-induced liver injury among inpatients. These findings persisted across a series of propensity score weighting methods.

Given the importance of reducing risk factors for health outcomes in U.S. hospital admissions among inpatients, further exploration of diagnosed androgen toxicity has extensive clinical and public health relevance.

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Appendices

Appendix A: IRB Approval Letter



TRIDENT
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INTERNATIONAL

Office of Institutional Research
Institutional Review Board
5757 Plaza Drive, Suite 100, Cypress, CA 90630
Office: (714) 816-0388 ext. 2518 | Fax: (714) 226-9844

Memo
From Simcha Pollard, Ph.D.
Chair, Institutional Review Board of Trident College
Re: IRB approval IRB # 1072

Protocol and Study Information	
Date Submitted to IRB: Submitted 5/22/2019 Approved 5/24/2019	
Principal Investigator: Scottie Howell	Research Advisor: Dr. Ryan Dwight
Proposal Title: Risk of Primary Health Outcomes among Inpatients with Androgen Toxicity: A Retrospective Cohort Study of the National Inpatient Sample.	
Investigator Information	
Name	Department
Scottie Howell CHHS	
Co-Investigator	
Co-Investigator	

I am pleased to inform you that Trident University IRB has approved your project: Exempt. Exemption is based upon Research involves collection or study of existing data, which does not contain identifiers linked to human subjects (CFR 46.0101(b)(4)), which is being evaluated. You will need to upload your approval letter into the IRB Approval Folder in your 800 Drop Box. Reapplication is not required in a year if the study is still being conducted. Please feel free to start your study at any time.

Best wishes and good luck,

Simcha (Stephen) Pollard, Ph.D.

Simcha (Stephen) Pollard Ph.D.