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Hypogonadism, Testosterone Replacement Therapy and Risk of Depression in Middle Aged and Older Men in the US

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Hypogonadism, Testosterone Replacement Therapy and Risk of Depression in Middle Aged and Older Men in the US

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas Medical Branch

June, 2019

Dedication

This dissertation is dedicated to the hope that it serves as a foundation for greater understanding of the role of testosterone and other novel pharmacotherapeutic interventions in reducing the burden of depression and other leading mental illnesses at a local, national and global level.

Acknowledgements

I will forever be indebted to my mentor, Dr. Baillargeon for teaching me not just the fundamentals of epidemiological research but also the values of scientific integrity. I consider myself extremely fortunate to have had such amazing role models as Dr. Kristen Peek who was always there to guide me and ensure that I was taking all the right steps in order to succeed.

This dissertation or none of the associated work would have been possible without the loving presence of my mom *Fatima* and my dad *Mahmood,* who brought me into this world and made me what I am today. I can never thank my wife *Fatima* enough for her love, support and understanding throughout the various phases of my training and for being an amazing mom to our son Khizer-who came into our lives 2 years and a day before I defended this dissertation and gave me the courage and focus I never thought I could get.

Hypogonadism, Testosterone Replacement Therapy and Risk of Depression in Middle Aged and Older Men in the US

Publication No._____

Zulqarnain Javed, Ph.D.

The University of Texas Medical Branch, 2019

Supervisor: Jacques Baillargeon

Hypogonadism is posited as a risk factor for depression. Limited evidence from randomized controlled trials (RCTs) suggests that testosterone replacement therapy (TRT) may improve depressive symptoms in hypogonadal men. However, evidence from real world, population-based studies is lacking. Moreover, TRT prescription increased by over three-fold for middle aged and older men in the past decade; however little is known about TRT prescribing patterns in men with depression. To the best of our knowledge, this is the first large-scale, real-world, nationally representative study of middle aged and older men to examine: a) TRT prescribing patterns, by depression status b) the association between untreated hypogonadism and incident depression and c) the risk of depression in hypogonadal men exposed to TRT. This dissertation used data from Clinformatics Data Mart-one of the nation's largest commercial health insurance programs. The association between hypogonadism and depression was tested using a case-control study design. The effects of TRT on risk of depression were assessed using nested case control and retrospective cohort study designs. In order to examine TRT prescribing patterns, annual incident TRT use was calculated for each year from 2002-2016 and stratified by age and hypogonadal status. Separate conditional logistic regression models tested whether a) hypogonadism is associated with increased odds of incident depression and b) exposure to TRT in hypogonadal men is associated with reduced odds of incident depression. Cox proportional hazards regression analyses assessed whether exposure to TRT in hypogonadal men is associated with reduced risk of depression. For each given calendar year from 2002-2016, TRT prescription rates were higher among depressed men, compared to their counterparts; the overall increase was similar for the two groups. After adjusting for relevant covariates, we did not find a consistent association between hypogonadism and depression. No association was observed between TRT and depression. This dissertation will add significantly to current knowledge of TRT prescription patterns in depressed men. Contrary to our hypothesis, we did not find an association between TRT and depression. Our results will improve current knowledge regarding the link between hypogonadism, TRT and depression, and inform future research in light of methodological challenges discussed herein.

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List of Abbreviations

ADAM	Androgen Deficiency in the Aging Male
ADT	Androgen Deprivation Therapy
AMS	Aging Males' Symptoms
BDI	Beck Depression Inventory
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPT	Current Procedural Terminology
CRP	C-Reactive Protein
DHT	Dihydrotestosterone
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GDS	Geriatric Depression Scale
GnRH	Gonadotropin Releasing Hormone
HAM-D	Hamilton Depression Rating Scale
HCPCS	Healthcare Common Procedure Coding System
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal Axis
ICD	International Classification of Disease
IL	Interleukins
LDL	Low Density Lipoprotein
LH	Luteinizing Hormone
NDC	National Drug Classification
PFC	Pre-Frontal Cortex
POMS	Profile of Mood States
TCC	Therapeutic Classification Code
TNF	Tumor Necrosis Factor
TRT	Testosterone Replacement Therapy
VA	Veterans Affairs

Chapter 1: Introduction

Hypogonadism affects approximately 2.4 million middle aged and older Americans.[1,2] Prior population based studies have reported hypogonadism prevalence rates of 6 to as high as 20% in middle aged and older men.[1–3] Hypogonadism is associated with poor psychological health including low libido, fatigue, anxiety, mood changes, sleep disturbances, etc., and is posited as a risk factor for depression.[4–15]

In this context, testosterone has become one of the most widely prescribed medications in the US with the use of testosterone products increasing exponentially in recent years.[16,17] Testosterone replacement therapy (TRT) prescription in men≥40 years of age increased by over three-fold in the past decade,[18,19] and is associated with improved overall physical and psychological well-being.[20–23] A large body of literature focuses on TRT associated improvements in libido, energy levels, bone density, muscle mass, and muscle strength however relatively few studies have investigated mental health effects of TRT in middle aged and older hypogonadal men.[6,7,20,24–27] Results from the largest RCT to date suggest that TRT may lower the risk of depression in older men.[28] This finding is supported by results from recent systematic reviews and meta-analyses reporting an overall beneficial effect of TRT on depression.[23,29]

While the link between TRT and improved psychological health is biologically plausible,[9,13,30,31] current evidence is primarily based on a relatively small number of RCTs. Evidence from real-world, large-scale, population-based studies is lacking. To the best of our knowledge, no prior real-world, population-based study has assessed the effects of TRT on incident depression in a nationally representative sample of middle

aged and older men. Moreover, little is known about TRT prescribing patterns in men with history of depression. In addition, relatively few large-scale studies have assessed the risk of depression in a nationally representative sample of middle aged and older men. We hypothesize that TRT prescription rates were higher for depressed men as compared to non-depressed men during the past 15 years. We further hypothesize that hypogonadism is associated with increased risk of depression and that TRT is associated with reduced risk of depression.

1.1 Aims and Hypotheses

In order to address aforementioned gaps in current knowledge of the subject and to test the above stated hypotheses, the following aims are proposed:

Aim 1: Among middle aged and older men enrolled in CDM during 2002-2016:

1A) Assess incident TRT prescribing patterns over time, by depression status.

1B) Assess whether TRT prescribing patterns in depressed men vary by age.

1C) Assess whether TRT prescribing patterns in depressed men vary by hypogonadal status.

Aim 2: Among middle aged and older men enrolled in CDM during 2012-2016:

2A) Assess whether untreated hypogonadism is associated with increased odds of incident depression.

2B) Assess whether exposure to TRT in hypogonadal men is associated with reduced odds of incident depression.

Aim 3: Among middle aged and older hypogonadal men enrolled in CDM during 2012-2016:

3A) Assess whether exposure to TRT is associated with reduced risk of depression.

3B) Assess the effects of sociodemographic and clinical factors on the TRT-depression association.

3C) Assess whether the effect of TRT on risk of depression varies by duration of exposure to TRT.

Chapter 2: Background

2.1 Hypogonadism: Etiology, Diagnosis and Prevalence

The metabolic and physiologic effects of testosterone are often perceived as restricted to its role as *sex hormone*. However, the role of testosterone transcends far beyond reproduction. It exerts important effects on musculoskeletal system including muscle mass, muscle strength, bone strength and bone mineral density; body mass index and body composition and overall sexual function.[20,27,32] The effects of testosterone on male reproductive system begin as early as the prenatal period.[31] Prior research on the effects of testosterone on human physiology have shown that hypogonadism, i.e., testosterone deficiency is linked to adverse physical and psychological health outcomes[8,20,32–36] while testosterone supplementation is linked to various measure of physical and psychological wellbeing.[20,27,29,31,37–39] It is associated with reduced risk of cognitive impairment, protective effects on cardiovascular system, improved metabolic functions such as reduced risk of diabetes and metabolic syndrome and improved mood.[20,21,32,40,41]

TRT prescription rates have increased by over three fold in middle aged and older over the past decade; however, effects on mental health broadly and depression specifically are not well understood. Given the tremendous increase in testosterone therapy prescriptions in the US over the past decade, it is important to understand the etiology, physical and mental sequelae and prevalence of hypogonadism in order to better understand its association with depression.

2.1.1 Etiology

Testosterone is secreted by the Leydig cells of male testes as a result of neuroendocrine signals from the central nervous system (CNS). The hypothalamus secretes the Gonadotropin Releasing Hormone (GnRH), which signals the pituitary gland to secrete Luteinizing Hormone (LH). In turn, LH stimulates the Leydig cells of testes to produce testosterone. Testosterone may act directly on target organs and cells or it may act after being converted to Dihydrotestosterone (DHT) by the enzyme 5α Reductase.[31] GnRH also stimulates the pituitary to release Follicle Stimulating Hormone (FSH), which acts on the Sertoli cells of testes to produce sperms. Testosterone, FSH and LH levels help determine the type of hypogonadism (primary or secondary).[35]

The etiology of hypogonadism is multifactorial. It might occur as a result of abnormalities at various levels of the Hypothalamic-Pituitary-Gonadal Axis. Hypogonadism can be either primary or secondary. Rarely, hypogonadism can be mixed or result from androgen insensitivity.[42]

A. Primary

Primary hypogonadism occurs when there is insufficient testosterone production as a result of testicular failure. Klinefelter syndrome is the most common form of primary hypogonadism and the most common cause of male hypogonadism. Other causes of primary hypogonadism include testicular tumors, undescended testis, mumps, hemochromatosis, trauma, chemotherapy and aging.[43]

B. Secondary

Secondary hypogonadism occurs as a result of disturbance of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which might involve disorders of the pituitary or the

hypothalamus. It involves altered GnRH secretion from the hypothalamus, resulting in impaired LH (and FSH) secretion from the pituitary, ultimately resulting in decreased testosterone release from the testes. Major causes of secondary hypogonadism include Kallman syndrome, pituitary disorders including tumors, surgery, radiation therapy and certain inflammatory conditions such as sarcoidosis, histiocytosis and tuberculosis etc.[43]

C. Other

Rare causes of hypogonadism include mixed (primary and secondary) and androgen insensitivity. Mixed hypogonadism involves defects at both the level of the hypothalamus-pituitary and the testes i.e., combined primary and secondary hypogonadism. Androgen insensitivity is another rare form of hypogonadism, which involves failure of target organs to respond to testosterone.

2.1.2 Diagnosis

Clinical diagnosis of hypogonadism involves both laboratory testing and evaluation of a patient's signs and symptoms. Various criteria have been used to define hypogonadism in prior studies including hormone assays, self-reported signs and symptoms and a combination of the two approaches.

A. ***Hormone Assays***

Normal range of testosterone in the human body is 300 ng/dl-1000 ng/dl. A cut-off of 300 ng/dl is generally used to define testosterone deficiency.[35] However, there are considerable variations in the definition of hypogonadism including differences by type of testosterone measured (free vs total), age (young vs middle vs old age

group) and units of measurement (ng/dl vs nmol/l). Prior studies have defined hypogonadism as total testosterone<300 ng/dl and free testosterone<5 ng/dl or 10.4 nmol/l and 0.17 nmol/l, respectively.[44] However, in conjunction with clinical presentation, it has also been defined as total testosterone <8 nmol/l and bioavailable testosterone<2.5 nmol/l.[45]

B. Hypogonadal Signs and Symptoms

Various clinical signs and symptoms have been used to define hypogonadism, in combination with laboratory tests for testosterone levels. One population based study used two sets of self-reported symptoms i.e. specific (libido, erectile dysfunction, osteoporosis) and non-specific (lethargy, sleep disturbance, depressed mood and low physical performance) to define hypogonadism.[1] Another population-based study used eight different self-reported symptoms including loss of libido, erectile dysfunction, depression, lethargy, inability to concentrate, sleep disturbance, irritability and depressed mood.[2]

Other measures have been developed to measure androgen deficiency including the Androgen Deficiency in the Aging Male (ADAM) questionnaire, which consists of 10 questions to assess libido, energy, strength, height, enjoyment, sadness, erections, ability to play sports, sleepiness after dinner and recent deterioration in work performance.[46]

C. Symptomatic Hypogonadism

Hypogonadal signs and symptoms are paired with testosterone laboratory values to define *symptomatic hypogonadism*. Different criteria have been used for this purpose. One study defined symptomatic hypogonadism as a) ≥1 specific (libido,

erectile dysfunction, osteoporosis) or ≥2 non-specific (lethargy, sleep disturbance, depressed mood and low physical performance) symptoms and b) total testosterone<300 ng/dl (10.4 nmol/liter) and free testosterone<5 ng/dl (0.17 nmol/liter).[1] Another study used the following criterion: ≥3 hypogonadal symptoms and total testosterone <200 ng/dl (or 6.94 nmol/liter) or ≥3 symptoms and total testosterone 200–400 ng/dl (6.94–13.88 nmol/liter) and free testosterone <8.91 ng/dl (0.3092 nmol/liter). In the latter study, men were not considered androgen deficient if they met one of these conditions: a) <3 signs/ symptoms, b) ≥3 signs/symptoms and total testosterone more than 400 ng/dl (13.88 nmol/liter) or c) ≥3 signs/symptoms and total testosterone 200–400 ng/dl (6.94–13.88 nmol/liter) and free testosterone ≥8.91 ng/dl (0.3092 nmol/liter).[2]

*D. **Hyoogonadism and ICD-Based Diagnostic Criteria***

The definition of hypogonadism used in this study is based on the International Classification of Disease (ICD), 9th and 10th Edition-the most commonly used disease classification system. ICD codes have been used for a variety of clinical, administrative and research purposes. Major uses of ICD codes include health insurance claims processing, reimbursement, health outcomes and health services research and a variety of epidemiological and population health research applications. This classification system is based on a unique ICD code given to a specific medical condition or set of conditions. The process of allocation of ICD code(s) includes multiple checkpoints that include evaluation of clinical signs and symptoms by a physician, results of laboratory tests/imaging and/or other relevant clinical investigation, documentation of diagnosis/diagnoses by a physician based on

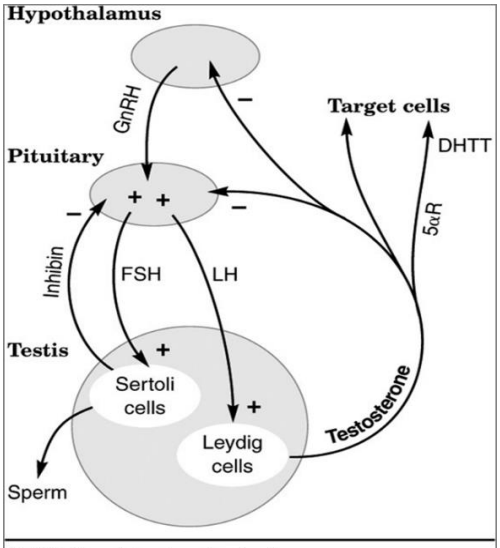
information from clinical examination and laboratory tests and ultimate allocation of codes by professional coders. [47]

2.1.3 Prevalence

Hypogonadism affects approximately 2.4 million middle aged and older Americans.[1,2] Prior population based studies have reported considerable variation in the prevalence of hypogonadism based on study setting, definition of hypogonadism, age and other clinical and sociodemographic factors.[1,48,49] Three large, population based studies of men aged 40-79 years operationally defined hypogonadism using both clinical symptoms and hormone assays, and reported prevalence rates of 5.6-6%.[1,2,50] In contrast, another study of men aged 40-79 years used only hormone assays as criterion for hypogonadism and reported 20.4% prevalence in this population.[3]

Risk of hypogonadism increases substantially with age,[2,51] with a reported incidence rate of 12.3 per 1000 person-years[2] and a rate of decline of 1.6-3% in total testosterone levels per year.[52] Testosterone levels start to decline in men in their 30s.[39] Levels are reported to drop approximately 3.2 ng/dl (0.11 nmol/l) each year after the age of 30[51]. These findings are corroborated by other studies that found hypogonadism incidence rate of 12% in men in their 50s and approximately 20% in men in their 60s.[51] In addition, a study of over 2000 men aged ≥45 years with considerably high comorbidity rate presenting to 130 primary care practices across the US reported hypogonadism prevalence rate of 38.7% in this population.[49]

Fig. 1. Testosterone Synthesis



(Source: Zarrouf et al., 2009)[31]

2.2 Hypogonadism and Health Outcomes

Hypogonadism is associated with various adverse physical health outcomes. It is associated with adverse changes in body composition including increased body mass index, reduced muscle mass, loss of bone density, sexual dysfunction and is linked to overall poor physical function and increased risk of various chronic medical conditions.[38,53–58] Results from prior studies suggest hypogonadism might act as a risk factor for diabetes, metabolic syndrome,[59–62] rheumatic disease,[56] osteoporosis and bone fractures,[63,64] frailty and other chronic medical conditions.[65] While considerable research has focused on the physical health effects of hypogonadism, few studies have assessed the relationship between hypogonadism and mental health in general, and depression specifically in middle aged men in the US.

2.2.1 Hypogonadism and Depression: Biologic Pathways and Conceptual Models

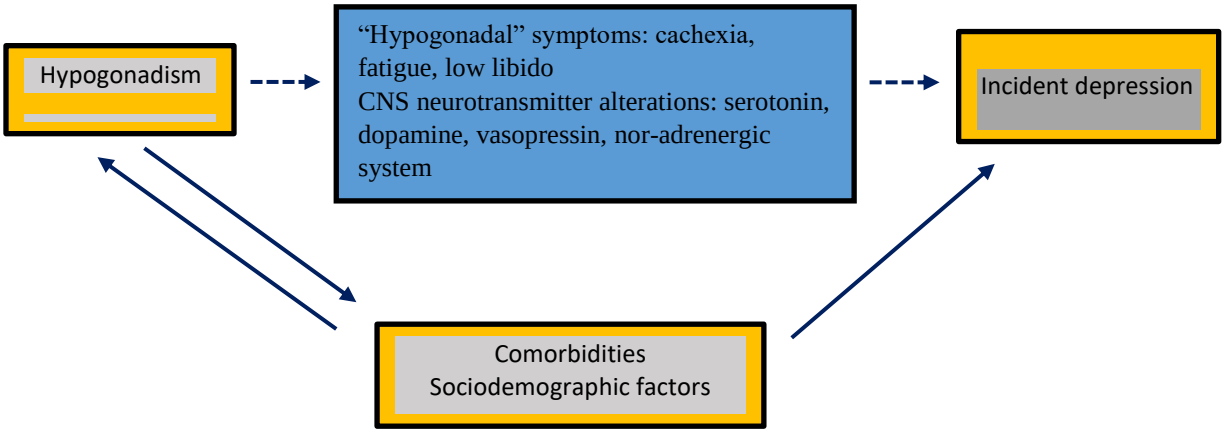
Various pathophysiological pathways have been proposed to explain the link between hypogonadism and depression. Hypogonadism might increase the risk of depression via CNS neurotransmitter alterations including serotonin,[30,66,67] dopamine,[30,68,69] vasopressin[70] and the nor-adrenergic system.[30,71] Other proposed CNS effects include decreased neurogenesis[10,30,72] and androgen receptor expression,[30,73] and alterations of the HPA axis including hyperactive HPA-mediated stress response.[10,30,74–76]

Evidence from animal models suggests testosterone upregulates CNS serotonin 2A receptor densities-which are implicated in the pathophysiology of depression; hence, deficiency of testosterone may cause depression via decreased serotonin receptor density.[9,77] These findings are further supported by animal studies demonstrating anxiety-like behavior associated with intrahippocampal administration of flutamide-an androgen receptor antagonist.[73] Testosterone has also been shown to modulate CNS dopaminergic activity including dopamine metabolism in striatal neurons in mice, which suggests deficiency of testosterone might increase risk of depression or depressive symptoms through alterations of central dopamine metabolism.[69] One unique study of preadolescent male rats demonstrated neonatal androgen antagonism inhibited neuronal growth and development in the hippocampus and dendritic spine formation with a resultant increase in depressive behaviors.[72]

In addition, various adverse physical health sequelae of hypogonadism including loss of muscle mass, decreased bone strength and bone mineral density, increased body mass index, sexual dysfunction and overall poor physical function might contribute directly or indirectly to depression.[58,78–85] In addition, it is proposed that hypogonadism might precipitate depressive symptoms similar to hypothyroidism.[9]

Existing evidence from the literature suggests an increased risk of depression associated with hypogonadism,[4,8,9,11,13] and an inverse relationship between testosterone levels and depression.[86–89] Testosterone levels start to decline in men in their 40s.[52] A greater understanding of the association between hypogonadism and depression might help inform policies and practices to treat potential adverse effects of hypogonadism on mental health in general and depression specifically, especially as men start to experience andropause.[28,31,90] In this context, evidence from large-scale, population based observational studies of middle-aged men is lacking.

Figure 2. Hypogonadism and Depression: Conceptual Model



2.2.2 Hypogonadism, Mental Health and Risk of Depression: Current Knowledge and Implications for Future Research

Hypogonadism is associated with poor psychological health in general including low libido, fatigue, anxiety, mood changes, sleep disturbances, etc., and is posited as a risk factor for depression.[4,8,9,11,13,15] The association between hypogonadism and depression is seen across depression measures, study designs, and age groups.[7,8,31] Existing evidence

demonstrates an inverse relationship between testosterone levels and risk of depression using a variety of self-reported depression symptom scales including Beck Depression Inventory,[7,14,91] Hamilton Rating Scale,[92–94] Center for Epidemiologic Studies Depression Scale.[7,88] Similarly, the association between low testosterone levels and risk of depression is seen across study designs.[86,87,89,95,96] Further, two RCTs demonstrated increased risk of depression associated with androgen deprivation therapy (ADT).[4,13]

Findings from observational studies present a similar picture. In a retrospective cohort study of 278 men ≥45 years of age, Shores et al[9] found a 2-year depression incidence of 21.7% in hypogonadal men vs 7.1% in eugonadal men, with an adjusted hazard ratio of 4.2 (95%CI=1.5-12.0). Similarly, in a study of 157 men with erectile dysfunction, Makhlouf et al[88] reported that men with hypogonadism have nearly 3 times increased risk of depression, compared to eugonadal men (adjusted OR=3.13; p=0.005). Another study of 116 men from the Finnish National Population Register reported nearly 5 times increased risk of clinically significant depression in hypogonadal men compared with other men.[91] Results from two population based studies of older men[86,95] found an inverse association between testosterone levels and depressive symptoms. One large, population-based study of 78,000 older US men found 23% increased risk of depression in ADT recipients compared to the unexposed group.[4] Further, the association between hypogonadism and depression is seen among both middle aged[89,97] and older men.[86,95] While the underlying pathophysiologic link between low testosterone and depression is supported by existing evidence in general, relatively few studies have assessed the potential effects of TRT on depression in middle aged and older hypogonadal men[6,15,23,24,28,29,31,98,99]

Majority of current evidence is based on studies of small samples of men, specific subpopulations of hypogonadal men or correlations between testosterone levels (i.e. not clinically defined hypogonadism) and depression. Further, there is considerable variation in inclusion/exclusion criteria including age range and definition of hypogonadism among existing studies. To the best of our knowledge, no study to date has assessed the hypothesized association in a large, nationally representative sample of middle aged and older men in the US.

2.3 TRT and Improved Physical and Psychological Well Being: Implications for Treating and Preventing Depression

2.3.1 Testosterone Replacement Therapy (TRT): Prevalence and Recent Trends

Testosterone has become one of the most widely prescribed medications in the US in recent years.[16,17,100] In a study analyzing global testosterone sales trends in 41 countries, the US observed the second largest increase in sale of testosterone products in the past decade.[16] During the same period, TRT prescription in men≥40 years of age increased by over 3 fold overall while a five-fold increase was observed for topical gel prescriptions.[18,101] One study of commercially insured men≥18 years found an almost four-fold increase in TRT initiation rate between 2000 and 2011.[102] More recent analyses of national prescription sales data suggest an approximate doubling in number of men receiving TRT between 2010 and 2013.[19,103] Another large-scale study of men ≥30 years of age found an over 6 fold increase in TRT prescribing overall and nearly 4.5 fold increase in new TRT prescription from 2002-2013.[104]

In the backdrop of such significant increase in use of TRT in recent years, it is important to examine the effects of TRT on mental health in hypogonadal men. In spite

of a tremendous increase in TRT prescription in recent years, evidence regarding prescription patterns in middle aged and older men with depression is lacking, and must be investigated.

TABLE 1. Recent Increase in TRT in the US

Baillargeon et al., 2018	Commercial insurance	≥30 y	9,962,538	2002-2016	221
Nguyen et al., 2015	Outpatient pharmacy	All ages	7,246,013	2010-2013	183
Layton et al., 2014	Commercial insurance	>18 y	410,019	2000-2010	374
Baillargeon et al., 2013	Commercial insurance	>40 y	10,739,815	2001-2011	359

(Source: Gabrielsen et al., 2016)[19]

2.3.2 Testosterone as an Important Regulator of Physical and Mental Health

The widespread effects of testosterone range from sexual function to muscle mass and strength, body mass index and the cardiovascular, skeletal and nervous system.[20,32] TRT has been associated with improvements in a variety of physical and mental health outcomes and has been shown to improve muscle mass, muscle strength, bone mineral density, lean muscle mass, lipid metabolism and body mass index.[20,27,32,105,106] In addition, evidence from prior experimental and observational studies suggests an association between TRT and improved cardiovascular health, including reductions in Low Density Lipoprotein (LDL) and total cholesterol in hypogonadal men.[21,105,107] Current evidence suggests that TRT might also have an immunosuppressive effect, as shown by an inverse association between TRT and a variety of inflammatory markers including Tumor Necrosis Factor (TNF)-α, Interleukins (ILs), C-Reactive Protein (CRP).[108,109] Other studies have shown an association between TRT and reduced risk of diabetes and/or improved glycemic index and reduced risk of hypertension.[105,110]

A recent population based study of over 83,000 men investigated the potential link between TRT and a variety of cardiovascular outcomes and found that TRT-associated normalization of testosterone levels was associated with reduced risk of myocardial infarction and mortality in men.[21] Similarly, a randomized controlled trial of hypogonadal men with type-2 diabetes showed that TRT is associated with reduced insulin resistance, improved glycemic control, and reduced visceral adiposity and cholesterol.[105] Further, evidence from the largest RCT to date on the effects of TRT on a variety of physical and mental health outcomes suggests TRT is associated with improvements in a variety of physical health functions including improved sexual function and overall physical function. This RCT also showed an improvement in mood and reduced severity of depression in men receiving TRT compared to placebo.[28] A possible beneficial effect of TRT on depression is supported by two recent systematic reviews that found significant reduction in depressive symptoms associated with TRT.[23,29]

While considerable research has investigated the physical health effects of TRT, few studies in comparison have evaluated the effects of TRT on mental health. Fewer still have assessed the association between TRT and depression in middle aged and older hypogonadal men. Current evidence on the association between TRT and depression is primarily based on results from a limited number of RCTs which suggest that TRT might help reduce the severity or risk of depression, especially in hypogonadal men. However, evidence from large-scale, population-based, nationally representative studies is absent.

2.4 Effects of TRT on Depression: Current Evidence and Knowledge Gaps

This section presents evidence from RCTs, animal studies and a few observational studies regarding the link between TRT and depression.

2.4.1 Evidence from RCTs.

The effects of TRT on mood overall and depression specifically have been investigated by a few RCTs in recent years. Current evidence from these RCTs suggests that TRT is associated with improvement in a variety of depression states including major depressive disorder,[93] subsyndromal depression or dysthymia,[26,111] treatment-resistant depression[92] and overall mood.[112] Results from the largest published clinical trial to date of TRT in hypogonadal men[21] showed improvements in depressive symptoms in 796 older men after receipt of TRT (effect size=0.18, $p<0.01$). These findings are further reinforced by prior RCTs reporting improvements in depressive symptoms with TRT using a variety of measuring instruments including Hamilton Depression Rating Scale (HAM-D),[24,26,111] Beck Depression Inventory (BDI)[6,93,112] and Profile of Mood States (POMS).[96] However, a recent meta-analysis of RCTs presented mixed results.[31] While the meta-analysis found an overall positive effect of TRT on depression in hypogonadal men, two RCTs failed to show improvements in eugonadal men.[113,114]

In general, a possible positive effect of TRT on depression is supported by results from two recent systematic reviews and meta-analyses examining the link between TRT and depressive symptoms. One systematic review and meta-analysis of 12 RCTs found protective effects of TRT and reduced risk of depression associated with TRT use in hypogonadal men.[23] Another large meta-analysis of 27 RCTs found significant improvements in depression associated with TRT compared to placebo, with a clinically

meaningful reduction in depressive symptoms comparable to or even better than efficacy of pharmacologic agents for treatment of depression.[29] The meta-analysis also reported a dose-response relationship between TRT and depression, with greater improvements in depressive symptoms associated with larger doses of TRT.[29] These results are further reinforced by a large, multi-center trial by Snyder et al,[28] which found significant improvements in depressive symptoms associated with TRT.

While current evidence predominantly supports a beneficial effect of TRT on depression, few RCTs failed to show such effects. One study of 90 adults with HIV/AIDS found improvements in mood associated with TRT; however, the differences were not statistically significant compared to placebo.[114] Another study of 26 healthy adult men reported TRT-associated improvements in depression; however, the study did not find statistically significant differences between TRT and placebo groups.[113] Similarly, a study of 22 men aged 30-65 years with treatment-resistant depression found improvements in depressive symptoms associated with TRT on the HAM-D scale but not on the BDI scale.[24] Significant differences in the effects of TRT between hypogonadal and eugonadal men and possible variation by severity of depressive symptoms and comorbid medical conditions is supported by results from other RCTs[96,115] and lends support to our hypothesis.

Limitations of RCT Evidence

RCTs are a great source of evidence for possible use of TRT in treating or preventing depression in hypogonadal men. However, it is important to acknowledge certain limitations inherent to RCT design, including generally small sample size, strict inclusion/exclusion criteria, restricted/unrepresentative target population (clinic, hospital

etc.), short follow-up times, issues of adherence and contamination, and lack of generalizability to the US population.[116,117] Findings from two recent meta-analyses of RCTs investigating the effects of TRT on depressive symptoms suggest substantial variation in target population, baseline testosterone levels, duration/dose of TRT and length of follow-up.[29,31] Further, the sample size for the largest RCT included in these meta-analyses was 464 older men, which further highlights the issue of lack of generalizability.[28] In this context, it is important to address these and similar RCT limitations, and examine the hypothesized relationship in a large, real world, population-based sample of middle aged and older men.

2.4.2 Evidence from Animal Models.

A possible beneficial effect of TRT on depression, mood and overall psychological health is reinforced by results from animal studies that have demonstrated anti-depressant effects of testosterone and its metabolites in both male and female mice.[118–121] One study of adult male mice found testosterone administration was associated with decreased immobility behavior, suggestive of anti-depressant effects of testosterone[121] In another mouse depression model testing the effects of testosterone, Bernardi et al[122] demonstrated that castration was associated with a substantial increase in duration of immobility in behavior despair and tail-suspension tests, suggesting increased depressive behavior in hypogonadism. Conversely, the authors were able to show that testosterone propionate reduced the duration of immobility in castrated mice, supporting evidence for potential anti-depressant effects of testosterone.

One animal study of aged male and female mice investigated the effects of testosterone in a similar depression model, and reported that testosterone and its metabolites were associated with decreased immobility time and increased struggling time in the forced swim test, suggestive of anti-depressant actions of testosterone and its metabolites DHT, 3α diol, 17β diol and 5α-androstane.[120] Similarly, a study of young, middle and old aged male rats reported that 3α-androstanediol-a testosterone metabolite was associated with improvements in a variety of cognitive, anxiety and depressive outcomes, as measured by avoidance, water maze, forced swim, and defensive freezing tests.[119] In a unique study, Carrier and Kabbaj[123] used a chronic social isolation model to induce a depression and anxiety-like state in castrated male and female rats and tested the effects of testosterone and imipramine-an antidepressant on these behaviors. The authors found that testosterone exhibited anxiolytic and antidepressant effects in male rats. Further, testosterone amplified the effects of imipramine on cell proliferation in the hippocampus of male rats-a key brain region involved in the etiology and pathogenesis of depression. Hippocampal neurogenesis is further suggestive of antidepressant effects of testosterone.

It is also important to note that a beneficial effect of TRT is not unequivocal. Few studies failed to find a positive effect of TRT on depression/depressive symptoms. One study of male and female rats failed to find an effect of testosterone on learned helplessness-an animal model of depression.[124] Another study found a beneficial effect of testosterone metabolites on depressive behavior; however, the authors were not able to find a beneficial effect of testosterone on depressive symptoms.[119] Overall, evidence from

animal studies complements evidence from human studies regarding a possible beneficial effect of testosterone on depression specifically and mental health broadly.

2.4.3 Evidence from Observational Studies

Few observational studies have investigated the link between testosterone replacement therapy and depression. Fewer still have assessed the association in middle aged and older men. Khera et al[39] tested the potential association using data from a prospective observational registry-TRiUS (Testim Registry in the US). The study, which included data for 849 hypogonadal men showed high prevalence of depressive symptoms in the cohort. The authors further reported that after a 12-month exposure to TRT, moderate to severe depressive symptoms dropped significantly from 17.3% to 2.1%, with an overall improvement shown by mean scores on the Patient Health Questionnaire (PHQ-9)-the depression measurement instrument used in the study. The same study also reported clinically meaningful improvement in depression symptoms scores in patients <60 years of age and those taking anti-depressants.[39]

In another study using TRiUS data, Miner et al[125] reported significant improvements in mood, depressive symptoms at 3, 6 and 12 months after initiation of TRT, compared to baseline. The latter study also found significant improvements in a variety of metabolic and anthropometric parameters associated with TRT use, including BMI, fasting blood glucose and blood pressure, which might reduce the risk of adverse psychological outcomes in general.

A multinational observational study of 1053 men presenting to community clinical practices in eight different countries assessed the effects of TRT on symptoms of

aging and hypogonadism (including depression) as measured by the Aging Males' Symptoms (AMS) scale, physical and mental fatigue a variety of sexual and anthropometric outcomes. This study reported significant improvements in hypogonadal symptoms associated with TRT use, in particular among adults <50 years of age.[126]

However, none of the above mentioned studies used a nationally representative sample of middle aged and older men to tests the effects of TRT. Further, neither study used a separate, clearly defined clinical diagnosis of depression as an outcome. While current evidence from observational studies implies a positive association between TRT and antidepressant effects, large-scale, nationally representative studies of middle aged and older men are needed to address limitations of current studies and to better the hypothesized association.

2.5 TRT and Depression: Biologic Pathways and Conceptual Models

TRT is associated with improved psychological well-being.[20,23,31] Various biologic pathways have been proposed to explain the potential effects on depression. Depressed individuals might experience low interhemispheric cortico-cortical coherence; TRT is posited to improve depressive symptoms by improving cerebral neuronal communication between left prefrontal (PFC) and right parietal cortex.[127] Specifically, testosterone-induced changes in steroid- responsive networks in the limbic system lead to a series of biochemical alterations that result in improved functional connectivity between left prefrontal and right parietal cortex.[128] Results from a double blind, placebo controlled trial of women demonstrated a significant increase in functional connectivity in the left PFC and right parietal cortex depression circuit.[127] Another RCT of healthy

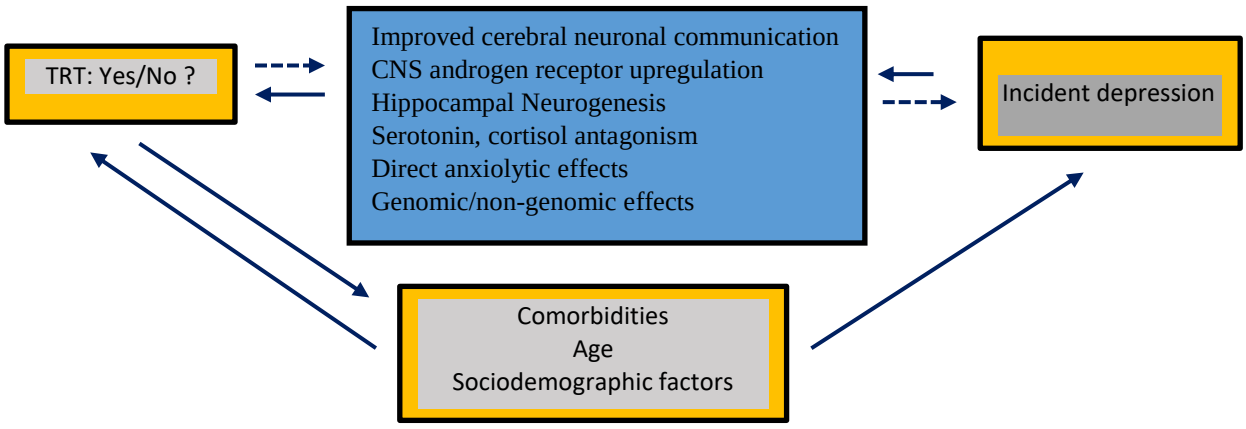
female volunteers aged 19-26 years, testosterone administration was associated with associated with reduced vigilant emotional response to fear, which suggests potential fear-reducing and anti-depressant effects of testosterone in the CNS.[129]

One study of middle aged and older hypogonadal men showed TRT administration was associated with improved cerebral perfusion in midbrain and superior frontal gyrus.[130] This finding is reinforced by prior studies proposing testosterone as an important regulator of neurogenesis and androgen-receptor up-regulation in the hippocampus and amygdala, key regions of the brain affected in depression.[30,127] Testosterone is hypothesized to improve depression outcomes by antagonizing 5HT serotonin receptor activity and influencing dopaminergic activity in the CNS-both of which play important roles in the pathophysiology of depression.[30,66,68] TRT has also been shown to exert inhibitory effect on stimulation and release of the "stress hormone" cortisol which might improve depressed mood.[30]

Results from animal studies support potential anti-anxiety and anti-depressive effects of testosterone. One study of gonadectomized male rats demonstrated that testosterone administration was associated with anti-anxiety effects, in part via effects of its metabolite DHT on dorsal hippocampus-a critical brain region involved in health behaviors and pathophysiology of various psychological disorders, including depression.[131] To support this finding, another study of gonadectomized male rats treated with intrahippocampal flutamide-an androgen receptor antagonist exhibited increased anxiety symptoms compared with control group. The latter study further suggests important influence of testosterone on CNS regions involved in depression, anxiety and other adverse mental health outcomes. Similarly, another study of Female European Eel

tested the effects of testosterone and DHT on dopaminergic activity in CNS regions involved in dopamine metabolism and demonstrated that both androgens were associated with increased dopaminergic activity, which provides further evidence of potential anti-depressant effects of testosterone.[68] Further, TRT has been shown to improve various physical and mental health indices including sexual desire, fatigue, lean body mass etc., which might, in turn, help improve ameliorate symptoms of depression.[30,31]

Figure 3. TRT and Depression: Conceptual Model



2.6 Hypogonadism, TRT and Depression: Knowledge Gaps

Testosterone levels start to decline in men in their 40s.[52] A greater understanding of the association between hypogonadism and depression might help inform policies and practices to treat potential adverse effects of hypogonadism on mental health in general and depression specifically, especially as men start to experience andropause.[28,31,90] In this context, evidence from large scale, population based observational studies of middle-aged men and older men is lacking.

Current guidelines for TRT do not warrant a trial of TRT for psychiatric outcomes.[132,133] While the weight of current evidence suggests there may be an overall beneficial effect of TRT on depression, substantial variation is observed in current evidence of the effects of TRT on mental health in general and depression specifically, and might be attributed to differences in gonadal status,[25,96,113] presence of comorbidities,[94,113] duration of therapy,[29,134] measurement of depression symptoms,[23,31] prior psychiatric disorders and study design.[25,135,136] Further, patients' socioeconomic or comorbidity status might affect both the probability of receiving TRT[21,137–140] and the risk of depression.[141–145]

Existing evidence regarding the effects of TRT on depression is based on RCTs with small sample sizes and considerable variation in inclusion/exclusion criteria, definition of gonadal status, duration of TRT, target population and measurement of depression. Evidence from real world, population based observational studies is lacking. Further, very few large-scale studies have tested the link between hypogonadism and depression, and TRT and depression in middle aged and older men in the US. In addition, TRT prescribing patterns over the past 15 years in depressed men have not been examined. To the best of our knowledge, this is the first large scale, population-based study of middle aged and older men in the US to assess: a) TRT prescribing patterns in middle aged and older men by depression status b) the association between hypogonadism and depression and c) the effects of TRT on incident depression.

2.7 Summary

Current evidence from RCTs, observational studies and animal studies suggests an increased risk of depression associated with hypogonadism, and an overall beneficial effect of TRT on mood and depression, particularly in hypogonadal men. However, further research is required to explore the link between hypogonadism, TRT and depression in a large, population-based, real-world samples of middle-aged and older hypogonadal men and . It is also important to better understand trends in prevalence of TRT prescription in middle aged and older men with depression, given recent increase in TRT prescription in the US and globally. This study aims to address these gaps in current literature and provide the first piece of evidence from a nationally representative sample of middle aged and older adults in the US.

Chapter 3: Methods

3.1 Data Source

This dissertation used administrative claims data from Clinformatics Data Mart (CDM; Optum Insight), a database of one of the nation's largest commercial health insurance programs. CDM is a diverse data source with data from over 30 million members across 50% of the nation's hospitals.[56,146] Enrollees are included either in a fee-for-service or a managed care plan including health maintenance organizations, preferred provider organizations and exclusive provider organizations. Health plans provide coverage for outpatient, inpatient and other professional health services. CDM data have been used previously to investigate a broad range of health outcomes and health services including drug exposure and toxicity. [56,147–149] Numerous large-scale, pharmacoepidemiological studies have used CDM data to analyze medication prescription trends and the impact of clinical and pharmacological exposures on a wide array of physical and mental health outcomes in a variety of target populations.[18,56,138,150] CDM is an excellent source of inpatient, outpatient and pharmacy claims data and relevant demographic information including age, race and zip code based income and education quartiles.

From the CDM database, medical file provided inpatient and outpatient claims data, which were utilized to define hypogonadism and depression using International Classification of Disease, Ninth Revision (ICD-9) and ICD-10 and Current Procedure Terminology (CPT) codes. Pharmacy claims were used to obtain relevant prescription information, including name, formulation, days of supply and dates of fill.[18] Relevant

prescription variables included TRT, antidepressant drugs and any psychotropic prescription. TRT was defined using National Drug Codes (NDC) and Healthcare Common Procedure Coding System (HCPCS-J) codes. Antidepressant and psychotropic prescription drugs were defined using NDC codes. Member file provided information regarding sociodemographic variables and enrollment.

3.2 Sample size.

Based on incidence rates of depression in hypogonadal men in prior claims based observational studies,[4,9] we expect 12-month incidence of approximately 7-10% for the primary outcome of interest i.e., depression. We used effect size estimates, criteria for minimal clinical efficacy (e.g., ≥50% change in HAM-D scores) and TRT response rates (e.g., relative risk reduction) from prior RCTs to estimate sample size for our study.[4,24,26,28,31] In order to detect a 50% relative risk reduction in depression incidence[31] in TRT group (e.g., 5%) v/s control (e.g., 10%) using two-sided alpha=0.05 and power=80%, a sample size of approximately 600 per group was required (n≈1200). Chi-squared statistic to compare proportions of dichotomous variables was used to determine sample size per group.[151] The sample size used in this dissertation was significantly larger than the sample size required to detect such differences, which ensured the analyses had sufficient power to detect such differences in depression incidence between the two groups.

Table 2. Study Variables

Variable	Definition	Measurement
Hypogonadism	Low blood testosterone levels: Testicular dysfunction/hypofunction, Klinefelter's syndrome	ICD-9 codes: 257.xx, 758.7 ICD-10 codes: E89.5, E29.0-29.1, E29.8, E29.9, Q98.4
Testosterone Replacement Therapy (TRT)	Days of supply of testosterone: Formulation: intramuscular, oral, transdermal, topical	NDC and HCPCS-J codes: Appendix: Table 1
Depression	Depression diagnoses: Major depressive disorder; dysthymic disorder; depression associated with personality disorder; adjustment disorder with depression; adjustment disorder with mixed anxiety and depressed mood; depressive psychoses; depressive disorder not elsewhere classified	ICD-9 codes: 296.2x; 296.3x; 296.82; 298.0; 300.4; 301.12; 309.0; 309.1; 309.28; 311 ICD-10 codes: F32.x; F33.x; F34.1; F43.21; F43.23
Elixhauser Index	Index measure of comorbidity	Various comorbidities (Appendix: Fig. 1)
Age	Categorical	40-49; 50-59; 60-65
Education	Zip code level educational attainment, categorized into quartiles[152]	Quartile 1, 2, 3, 4
Income	Zip code level median income, categorized into quartiles[152]	Quartile 1, 2, 3, 4
Outpatient Visits	Categorical	1-3, 4-9, ≥10
Antidepressant Use	Therapeutic Classification Codes (TCC); Yes/No	TCC=28.16.04x (Appendix: Table 2)
Other Mental Disorders	Any/None	ICD Codes (Appendix: Table 3)
Prescription Drugs	Count of different classes of prescription drugs	Therapeutic Class Codes (Red Book TM[153,154]; Appendix Table 4)

3.3 Specific Aim 1

3.3.1 Conceptual Framework

Prior studies examined TRT prescribing patterns in the general population[18,19,102,103] and the VA[155] however ours is be the first population based study to assess incident TRT prescription patterns by depression status and potential variation in TRT prescription by age and gonadal status in middle aged and older men with depression enrolled in a large commercial health insurance program. Hypogonadism is a risk factor for depression,[9] and is the primary indication for TRT prescription.[133] Further, risk of hypogonadism increases with age[2] and patient's age might affect both the probability of receiving TRT[18] and the risk of depression-both overall and in hypogonadal men.[8,156] To the best of our knowledge, evidence regarding use of TRT in men-both hypogonadal and eugonadal-with depression is lacking. We hypothesize that TRT prescribing patterns in this cohort of middle aged and older men vary by depression status. In order to assess TRT prescribing patterns in this cohort of middle aged and older men, following aims are proposed:

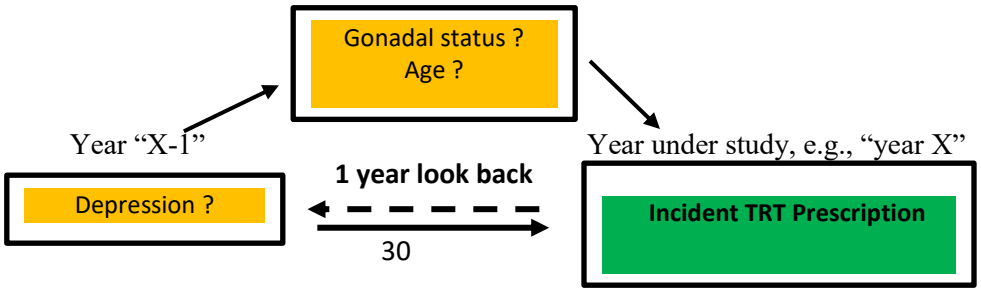
Among middle aged and older men enrolled in CDM during 2002-2016:

1A) Assess incident TRT prescribing patterns over time, by depression status.

1B) Assess whether TRT prescribing patterns in depressed men vary by age.

1C) Assess whether TRT prescribing patterns in depressed men vary by hypogonadal status.

Figure 4. TRT Prescribing Patterns: Analytic Strategy



3.3.2 Study Design and Cohort

This descriptive study used claims data for each year from 2002-2016 in order to analyze TRT prescription trends in middle aged and older men with depression. For each calendar year of interest (2002-2016), a separate cohort was created as a denominator file of participants. Each cohort comprised men aged 40-65 years enrolled in CDM during the given study calendar year. Each participant was allowed to contribute to multiple cohorts. We first examined TRT prescription trends overall and subsequently assessed trends by depression status (depressed vs non-depressed). In addition, we conducted stratified analysis by age and hypogonadal status in men with depression.

Inclusion/exclusion criteria.

Male gender, age 40-65 years and continuous enrollment during and 12 months prior to a given calendar year (look-back) was the primary inclusion criteria. In order to calculate incident TRT use, all men with a TRT prescription within the 12 month look back period were excluded. Participants were required to have a new prescription for TRT in the calendar year of interest and have had continuous enrollment with no TRT use in the prior 12 months. For stratified analyses restricted to men with depression, we further required that each eligible participant have a diagnosis of depression in the look-back period. We only included data for participants with complete information for each calendar year.

3.3.3 Variables

Testosterone Replacement Therapy (TRT)

Incident TRT users were defined as men who received at least one new TRT prescription in a given calendar year and did not receive a prescription within the prior 12 months. TRT was assessed as a binary variable (TRT vs no TRT). All formulations of TRT including intramuscular, oral, transdermal and topical were included in the analyses and were determined using the relevant National Drug Codes (NDC) and Healthcare Common Procedure Coding System (HCPCS-J) codes[101] (Table 1; Appendix: Table 1).

Depression

A person was considered depressed if he had ≥2 outpatient (30 days apart) or ≥1 inpatient ICD-9/ICD-10 codes for diagnosis of depression within 12 months prior to a given calendar year of interest.[157–159] (Table 1). Depression was analyzed as a binary variable (depressed vs not depressed). Following diagnoses were included in the definition of depression: major depressive disorder (ICD9 codes: 296.2x & 296.3x; ICD-10 codes: F32.0-F32.5, F32.9, F33.x), atypical depressive disorder (ICD-9: 296.82; ICD10: F32.89), depressive type psychosis (ICD-9: 298.0; ICD-10: F32.3, F33.3), dysthymic disorder (ICD-9: 300.4; ICD-10: F34.1), chronic depressive personality disorder (ICD-9: 301.12; ICD-10: F34.1), adjustment disorder with depressed mood (ICD-9: 309.0; ICD-10: F43.21), prolonged depressive reaction (ICD-9: 309.1, ICD-10: F34.1, F43.21), adjustment disorder with mixed anxiety and depressed mood (ICD-9: 309.28; ICD-10: F43.23) and depressive disorder not elsewhere classified (ICD-9: 311; ICD-10: F32.9)

Hypogonadism

Hypogonadism was defined using relevant ICD-9 codes[56,138,149] (Table 1) and analyzed as a binary variable (hypogonadal vs not hypogonadal).

Age.

Age was measured as a categorical variable (40-49; 50-59; 60-65). Stratified analyses examined TRT prescription overall and in men with depression for each age category.

3.3.4 Statistical Analysis

Descriptive Characteristics

Descriptive characteristics of the sample were expressed as frequencies (N) and percentages (%). Incident TRT use was calculated as total number of men with at least one new TRT prescriptions (*numerator*) in a given calendar year over all men enrolled in CDM in that year who did not receive TRT within the prior calendar year (*denominator: "at risk"*). Incidence was calculated separately for each year of interest and stratified by depression status (depressed vs not depressed). Each participant was allowed to contribute to multiple years during the study period. TRT prescription patterns were assessed overall and in men with depression. In addition, stratified analyses were restricted to men with depression, and assessed prescription patterns by age and hypogonadal status.

Stratified Analyses

In order to assess potential variation in incident TRT use over time, TRT use was stratified by age: 40-49, 50-59, 60-65 and gonadal status (hypogonadal vs eugonadal), respectively for a given calendar year.

Trend Analysis

We tested for differences in TRT prescription trends between depressed and non-depressed groups by creating two interaction terms between depression and time. First, the time variable “year” was centered around the mean to create a mean-centered time variable “yearctr”=year-mean (year). Then, a quadratic term was created for the mean-centered time variable “yearctr2”= [(year-mean year)*(year-mean year)] to test for difference in the observed curve (pre 2012/13, post 2012) for both groups. Subsequently, two interaction terms were created. First, an interaction term “depyearctr” was created between depression and mean-centered year variable. A second interaction term- “depyrctr2” was created between depression and higher order (quadratic) term for time. Creation of second interaction term was informed by shape of TRT prescription curve.

The interaction terms were entered into a multivariable logistic regression model, which also included variables for depression, time (mean-centered and quadratic year) and the covariates age and hypogonadal status. We then tested whether the combined effect of the two interaction terms was statistically significant using a logistic regression model with a contrast statement. The combined effect was based on chi-square statistic with 2 degrees of freedom and determined whether prescription trends were statistically different for depressed vs non-depressed men.

3.4 Specific Aim 2

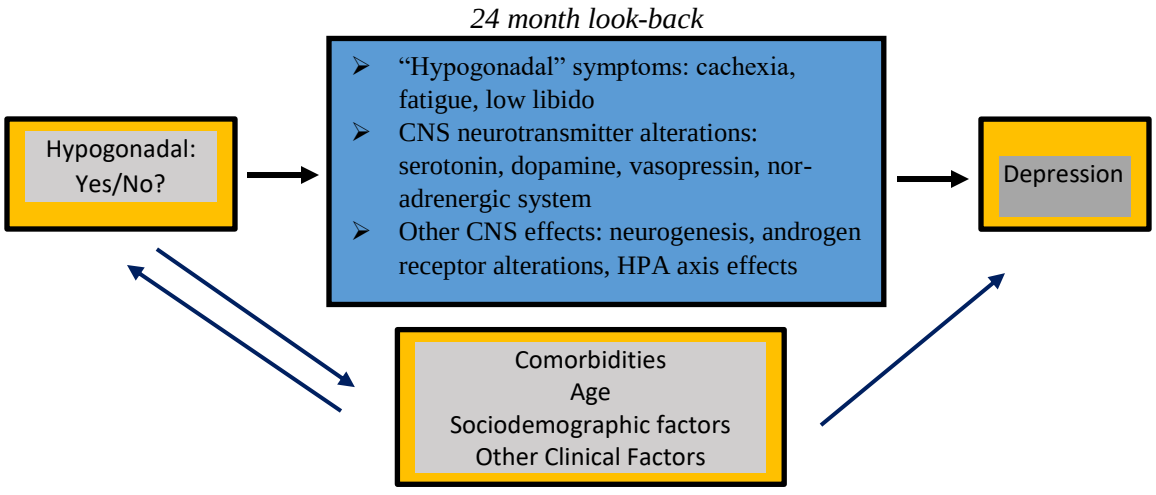
3.4.1 Conceptual Framework

Conceptual Model 2A

Hypogonadism is associated with adverse mental health outcomes including low libido, fatigue, mood changes, sleep disturbances etc., and is posited as a risk factor for depression.[7–9,89,91] In addition to hypogonadal symptoms which might be directly or indirectly associated with depression, various physiologic pathways might explain the potential association including serotonin, dopamine, vasopressin and nor-adrenergic system alterations.[9,30,31] Other proposed CNS effects associated with hypogonadism include decreased neurogenesis, alterations in androgen receptor physiology and HPA axis disturbances.[9,10,31,91]

Aim 2A tested whether untreated hypogonadism is associated with increased odds of incident depression in middle aged and older men (Fig. 5). Relevant statistical models were used to adjust for potential confounders of the hypogonadism-depression relationship including socioeconomic, demographic and clinical factors which might affect both the risk of hypogonadism[37,160] and/or the risk of depression.[141–143,161]

Figure 5. Hypogonadism and Depression: Conceptual Model

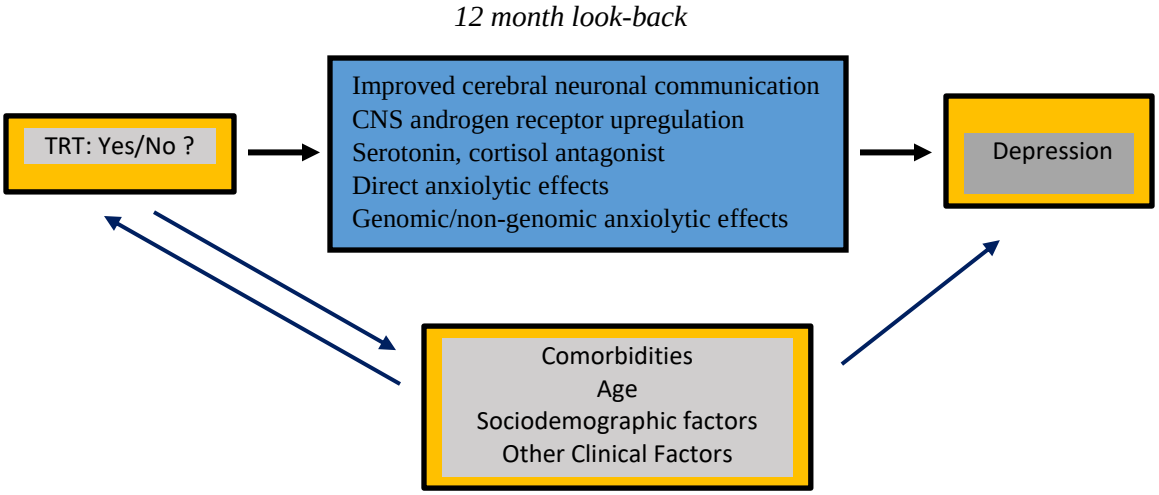


Conceptual Model 2B

Evidence from RCTs, animal models and few observational studies suggests TRT is posited to improve overall psychological wellbeing and decrease risk or severity of depression in hypogonadal men.[23,28,31] Proposed mechanisms of TRT action include improved cerebral neuronal communication, CNS androgen receptor upregulation, dopamine agonistic, serotonin (5HT receptor) antagonistic activity and direct and indirect anxiolytic effects.[30,66–68]

Aim 2B tested whether middle aged and older men with incident depression are less likely to have been exposed to TRT compared to men without depression (Fig. 2B). A patient's comorbidity status (diabetes, COPD, HIV, neurological disorders, etc.) might affect both his probability of receiving TRT[133,138,139,162] and/or the risk of depression.[141–143] Similarly, socioeconomic status is an important determinant of access to healthcare overall and might account for variation in receipt of TRT.[135,137,162] Appropriate statistical techniques were used to adjust for potential confounders of the TRT-depression relationship.

Figure 6. TRT and Depression: Conceptual Model



To restate, following aims were tested:

Among middle aged and older men enrolled in CDM during 2012-2016:

2A) Assess whether untreated hypogonadism is associated with increased odds of incident depression.

2B) Assess whether TRT in hypogonadal men is associated with reduced odds of incident depression.

3.4.2 Study Design and Cohorts

A matched case control study of men aged 40-65 years was conducted using Clinformatics Data Mart™ (CDM) (Optum Insight, Eden Prairie, MN), a database of one of the nation's largest commercial health insurance programs. Two different cohorts were developed. Aim 2A used a traditional case control design whereas Aim 2B used a nested case control design.

3.4.2-I Aim 2A Cohort

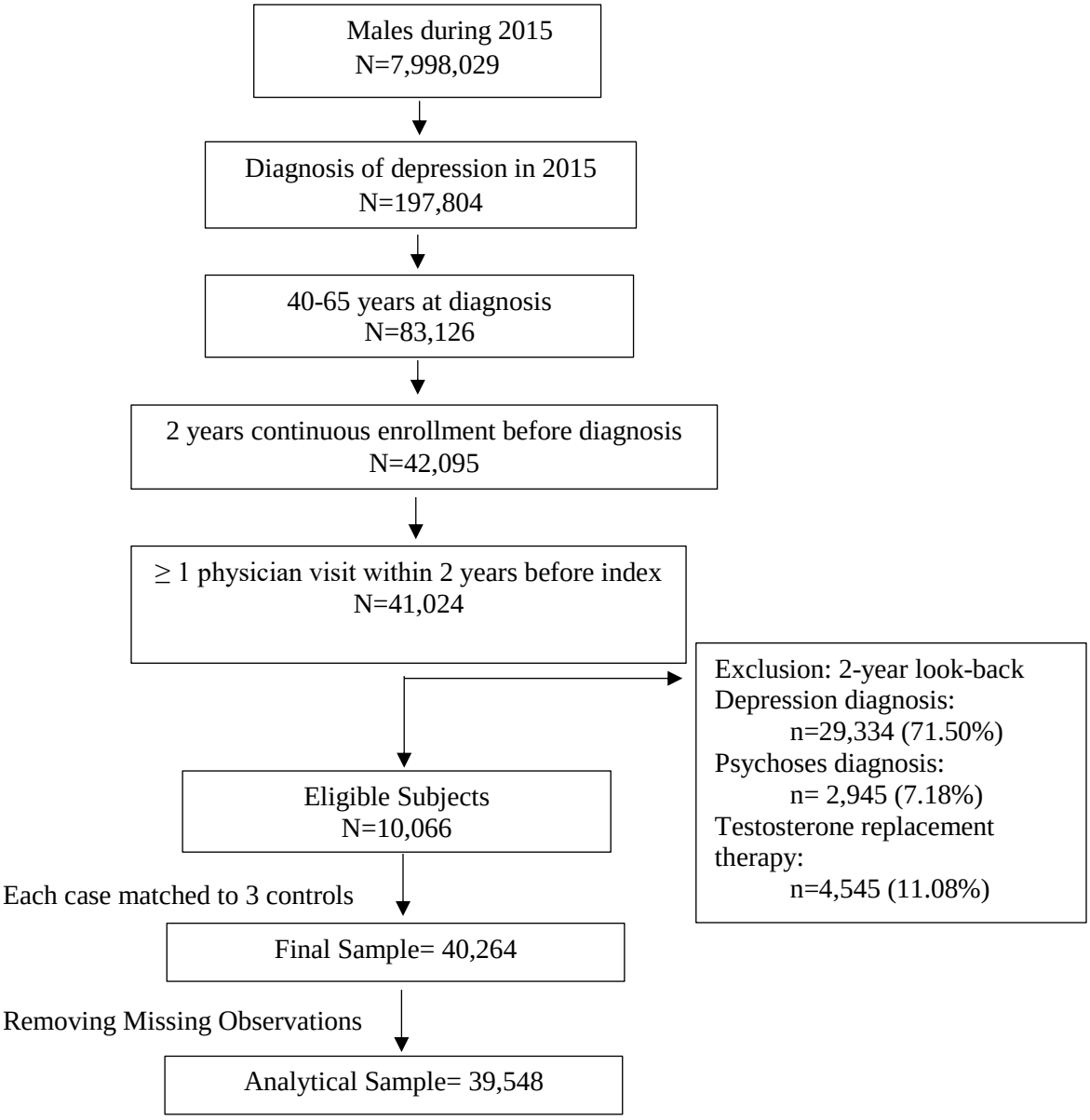
Cases

Cases were defined as participants with a primary diagnosis of incident depression, measured as ≥2 outpatient (≥30 days apart) or ≥1 inpatient ICD-9/ICD-10 codes for diagnosis of depression during Jan. 1, 2015-Dec. 31, 2015.

Controls

Controls were defined as participants without diagnosis of depression during the study period.

Fig. 7. Aim 2A Case Selection



Matching

Using a 3:1 matching criterion, each case was matched to three controls on month of diagnosis/index month, age at index date and Elixhauser comorbidity score. Based on number of comorbid medical conditions, comorbidity index was categorized into three categories, i.e., 0, 1, 2, ≥3.

Inclusion/Exclusion Criteria

Male gender and age 40-65 years were the primary inclusion criteria. All participants were required to be continuously enrolled in CDM within 24 months prior to index date (i.e. look-back period) and have at least one physician visit within this period. Participants younger than 40 years or older than 65 years of age and those who received a diagnosis of depression or psychoses within the look back period were excluded from the final sample. In order to reduce potential effects of prior exposure to TRT, we excluded participants who received a TRT prescription, as defined by relevant NDC and HCPCS-J codes (Appendix: Table 1) in the look back period. In order to avoid potential selection bias resulting from differences in characteristics of men who had no physician visit in the look back period versus those who had at least one visit, we excluded men without a physician visit in the 24 month look back period.

Variables

Exposure

Diagnosis of hypogonadism (ICD-9-CM=257.xx, 758.7; ICD-10-CM=E89.5, E29.0-29.1, E29.8, E29.9, Q98.4) within 1 year prior to the index date was the primary exposure of interest. An ICD code for diagnosis of hypogonadism was confirmed with a CPT code (84402, 84403) for a laboratory evaluation of blood testosterone levels prior to ICD code date. Hypogonadism was operationalized as a dichotomous (yes/no) variable; no hypogonadism served as the referent category.

Covariates

Age

Age was measured as a categorical variable (40-49; 50-59; 60-65). Participant age at index date was used as a matching variable for cases and controls.

Elixhauser Comorbidity Score

In order to examine TRT prescription by comorbidity status, an aggregate measure of comorbidity, Elixhauser Comorbidity Index was used. This measure has been used widely in prior studies assessing the effects of various pharmacological interventions including TRT[138] and includes various cardiovascular, neurological, respiratory, gastrointestinal, psychiatric and other medical conditions.[138,163] Comorbidity score was categorized as 0, 1, 2, ≥3 for number of comorbidities, as used in prior studies[101] and used as a matching variable for cases and controls (Appendix: Fig. 1).

Income

Income was measured as zip code level median income and categorized into quartiles, based on the level of income reported for each zip code: quartile 1 (bottom quartile or lowest income level); quartile 2; quartile 3; quartile 4 (top quartile or highest income level) as used in previous studies.[152]

Education

Education was measured using zip code level educational attainment, i.e. percentage of persons with less than college education. For each zip code, the proportion of persons aged ≥ 25 years in the neighborhood with at least a high school education was calculated and categorized into quartiles: quartile 1 (lowest educational attainment); quartile 2; quartile 3; quartile 4 (highest educational attainment), as used in prior studies.[152,164]

Region

Region of residence was defined using census bureau divisions for geographic region (Northeast, Midwest, South, West).

Antidepressants

Multivariable regression models further adjusted for prior antidepressant use, which was measured using Therapeutic Class Codes (TCC: 28.16.04x; Appendix: Table 2) for any antidepressant prescription in the look-back period. Antidepressant use was analyzed as a binary (yes/no) variable.

Physician visits

In order to account for possible effects of access and utilization of healthcare, multivariable models adjusted for number of outpatient visits in the look back period. This variable was operationalized as 1-3, 4-9, ≥10 visits in the look-back period.

Additional Covariates: Sensitivity Analyses

We performed additional sensitivity analyses to adjust for prior prescription drug use and other mental health conditions by including each of the following variables as separate covariates in multivariable regression models.

Other Mental Health Conditions.

Other mental health conditions were defined using relevant ICD-9 and ICD-10 codes for a diagnosis of mood disorders, dementias and other mental disorders not included in the Elixhauser index in the look back period (Appendix: Table 3) and categorized as any mental health condition from the above stated categories vs none.

Prescription Drugs

Prescription drug use was defined using relevant Therapeutic Classification Codes (TCC) for any prescription drug in the look-back period, which included 36 major classes of prescription drugs (Appendix: Table 4). For this purpose, pharmacy claims were linked to RedBook™ Select database, which provided a 10-digit Therapeutic Class Code for each unique prescription drug category.[153,154]

3.4.2-II Aim 2B Cohort

Cases

Cases were defined as participants with a primary diagnosis of depression, measured as ≥2 outpatient (at least 30 days apart) or ≥1 inpatient ICD-9/ICD-10 codes for diagnosis of depression during Jan. 1, 2014-Dec. 31, 2016.

Controls

Controls were defined as participants without diagnosis of depression during the study period.

Matching

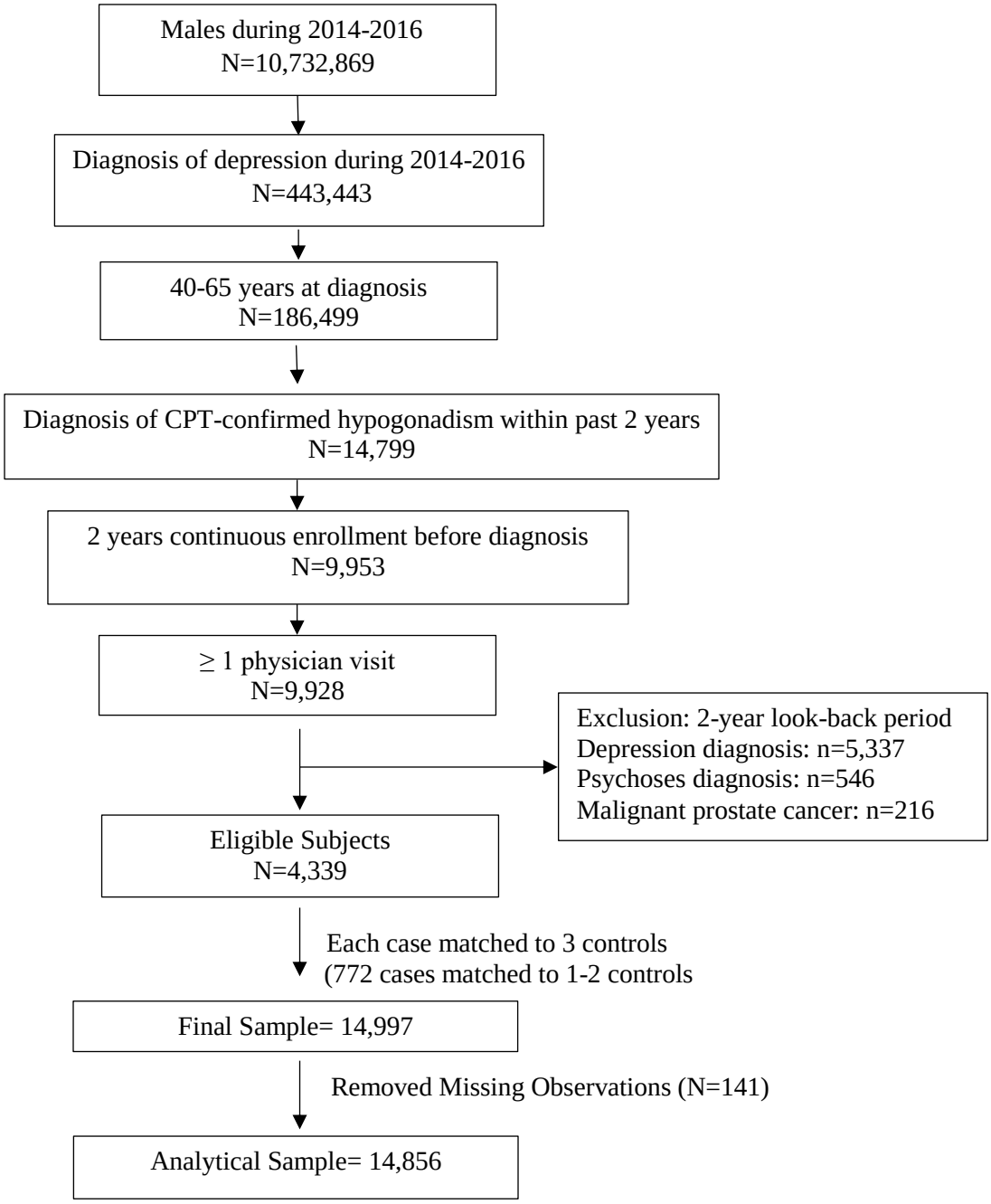
Using a 3:1 matching criterion, each case was matched to three controls on month of diagnosis/index month, age at index date and Elixhauser comorbidity score. Based on number of comorbid medical conditions, comorbidity index was categorized into three categories, i.e., 0, 1, 2, ≥3.

Inclusion/Exclusion Criteria

Male gender and age 40-65 years were the primary inclusion criteria. All participants were required to have a diagnosis of hypogonadism within 24 months prior to the

depression diagnosis/index date in order to be included into the study ("nested" within a cohort of hypogonadal men), with a CPT code for a testosterone laboratory test preceding ICD code for diagnosis of hypogonadism.

Fig. 8 Aim 2B Case Selection



Participants were further required to have not had a diagnosis of depression or psychoses, and have at least 1 physician visit within the 24 months look-back period. Participants with diagnoses of depression or malignant prostate cancer (ICD-9=185, 222.2, 600.2, 600.21) within the look-back period were excluded.

Variables

Exposure

TRT was the primary exposure of interest. TRT was measured using relevant NDC and HCPCS-J codes. Men were considered exposed if their most recent TRT prescription overlapped by >=1 days within the 30 day period prior to index date. For sensitivity analyses, additional exposure windows of TRT were used.

Covariates

Age, comorbidity status and zip code based income and education quartiles were included as covariates. Additional analyses adjusted for physician visits and antidepressant use in the look-back period, as for Aim 2A. Physician visits were categorized as 1-3, 4-9, ≥10. Antidepressant use was defined as a binary (yes/no) variable. Sensitivity analyses adjusted for other mental health conditions and prior prescription drug use. Other mental health conditions included mood disorders, anxiety disorders, dementias and other mental disorders not included in the Elixhauser index and categorized as any vs none (Appendix: Table 3). Prior prescription drugs included a count of the different classes of prescription drugs used, based on unique Therapeutic Class Codes and National Drug Classification Codes.

3.4.3 Statistical Analysis

Descriptive Analysis

Descriptive characteristics of the sample were expressed as frequencies (N) and percentages (%). Age, income, education, region, comorbidity status, outpatient visits and antidepressant use were stratified by depression status. Frequencies and proportions of any individual comorbidities that were unbalanced across cases and controls were also compared. Differences in distribution of covariates across the two groups were assessed using conditional logistic regression.

Multivariable Models

Aim 2A

Two separate models were tested. Model 2A-I tested the independent association between untreated hypogonadism and incident depression. Fully adjusted, multivariable model, i.e., model 2A-II tested the association between hypogonadism and incident depression, accounting for sociodemographic, clinical, pharmacological and healthcare factors including any comorbidities that were unbalanced across cases and controls. The association between hypogonadism and incident depression in each model was analyzed using conditional logistic regression analyses which generated estimates of odds ratio (OR) and 95% CI for incident depression.

Aim 2B

Two separate models were tested. Model 2B-I tested the independent association between TRT and incident depression. Fully adjusted, multivariable model, i.e., model 2B-II tested the association between TRT and incident depression, accounting for

sociodemographic, clinical, pharmacological and healthcare factors including any comorbidities that were unbalanced across cases and controls. The association between TRT and incident depression in each model was analyzed using conditional logistic regression analyses which generated estimates of odds ratio (OR) and 95% CI for incident depression.

Sensitivity Analysis

Three different sensitivity analyses were performed.

Sensitivity Analysis-2A

For Aim 2A, sensitivity analyses included additional variables in the multivariable models. Specifically, sensitivity analyses tested for the effects of other mental health conditions and any prescription drug use on the hypogonadism-depression association.

Sensitivity Analysis 2B

For Aim 2B, two sensitivity analyses were performed. First sensitivity analysis tested for potential effects of other mental health conditions and prior prescription drug use on the TRT-depression association. A second sensitivity analysis examined the effect of additional exposure windows of TRT. Two different exposure definitions were used. For the first definition, men were considered exposed if they met the criteria for primary exposure definition and had >=1 TRT prescriptions within each 6 month period prior to the index date, up to 1 year prior to index date. For the second definition, men were considered exposed if they met the criteria for the primary definition and had >=1 TRT prescriptions within each 3 month period prior to the index date, up to 1 year prior to index date.

3.5 Specific Aim 3

3.5.1 Conceptual Framework

Hypogonadism is associated with increased risk of depression and other adverse psychiatric outcomes.[8,9,91] TRT is posited to improve psychological wellbeing overall and decrease risk or severity of depression in hypogonadal men.[7,23,28,29,31] Results from prior RCTs, systematic reviews and meta-analyses suggest that TRT might reduce depressive symptoms, depression severity and improve overall psychological well-being.[23,29,31] We hypothesize that exposure to TRT in middle aged and older hypogonadal men is associated with decreased risk of depression (Fig. 9). Further, effects of TRT on mental health might vary by duration of exposure to TRT.[134] However, the association between TRT and incident depression has not been evaluated in a large, real-world sample of middle aged and older men.

Prior research suggests risk of hypogonadism and likelihood of receiving TRT increases with age.[2,51] Existing evidence from the literature suggests that the effects of TRT on depression might vary by age.[8] Similarly, a patient's comorbidity status (diabetes, COPD, HIV, neurological disorders, etc.) might affect both his probability of receiving TRT[28,133,138,139,162] and/or the risk of depression. This study assessed whether the effects of TRT on depression vary by age or comorbidity status. In addition, socioeconomic status is an important determinant of access to healthcare overall and might account for variation in receipt of TRT.[137,165,166] Evidence from prior studies suggests existence of an inverse relationship between socioeconomic status and

depression.[165–167] Multivariable models adjusted for relevant sociodemographic and clinical covariates.

In order to address the above stated gaps in current knowledge of the subject, and to test the proposed hypotheses, the following specific aims are proposed:

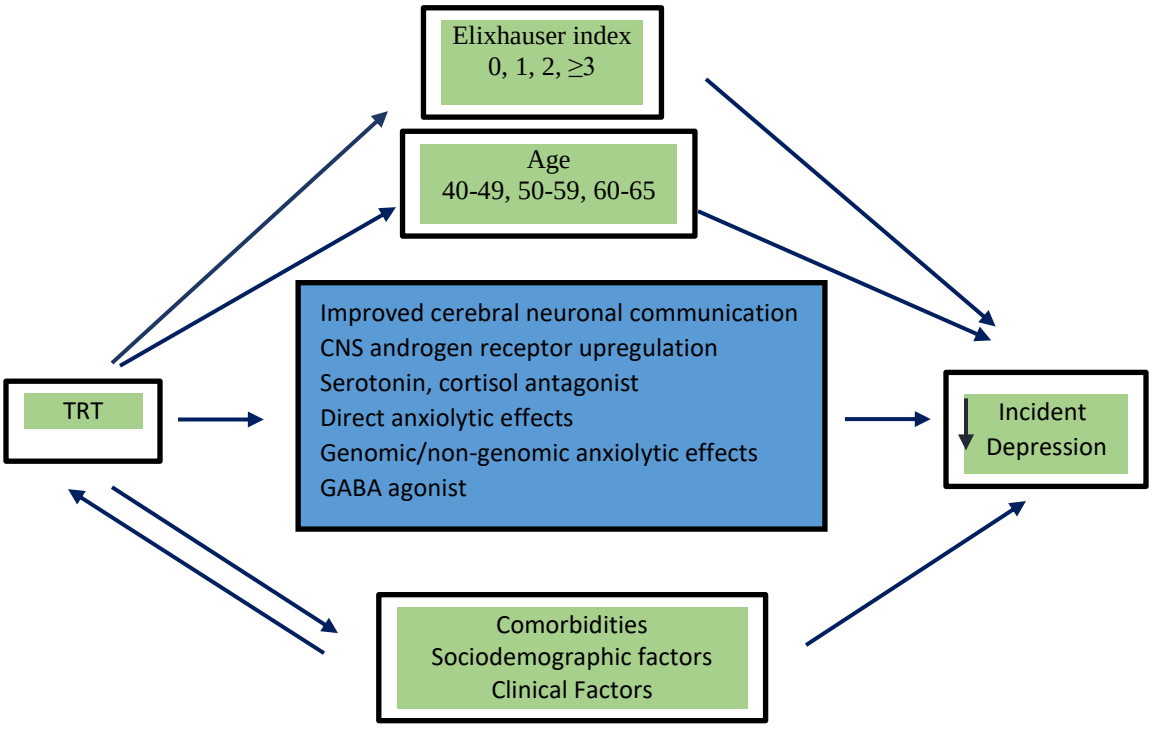
Among middle aged and older hypogonadal men enrolled in CDM during 2012-2016:

3A) Assess whether exposure to TRT is associated with reduced incidence of depression.

3B) Assess the effects of sociodemographic and clinical factors on the TRT-depression association.

3C) Assess whether the effect of TRT on incident depression varies by duration of exposure to TRT.

Fig. 9. TRT and Depression: Conceptual Model



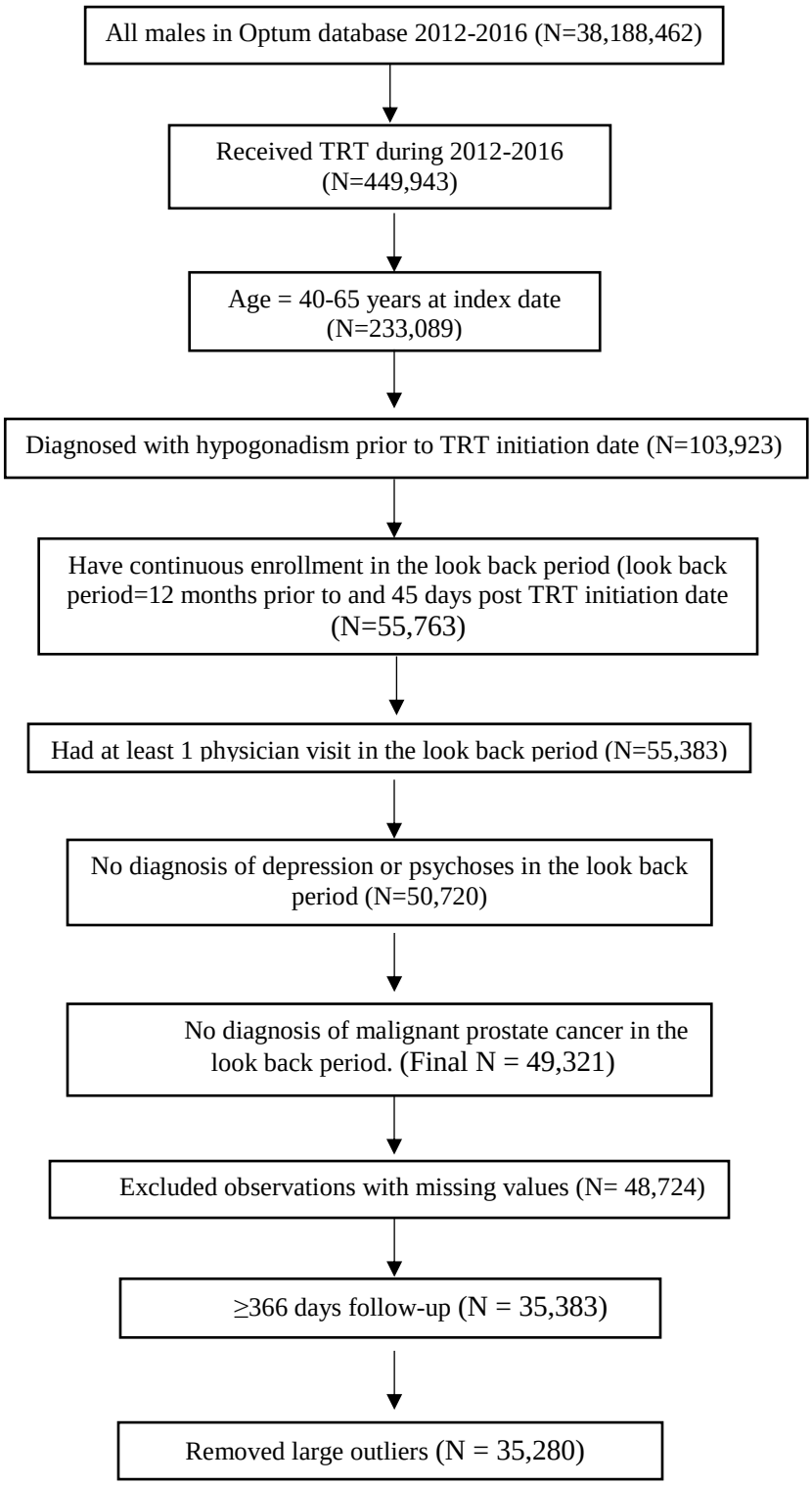
3.5.2 Study Design and Cohort

This study included men aged 40-65 years who were enrolled in CDM from 2012-2016. In order to test the association between TRT and incident depression, a retrospective cohort design was used. TRT was the primary exposure of interest whereas diagnosis of depression was the primary outcome of interest.

Inclusion/Exclusion Criteria

Male gender and age 40-65 years at index (TRT initiation/study entry) date during 2012 through 2016 were the primary inclusion criteria. We required that each participant be continuously enrolled within one year prior to and 45 days after initiation of TRT (look-back period), have a diagnosis of hypogonadism and at least 1 physician visit within the look-back period. In order to assess incident depression, participants were required to have not had a diagnosis of depression within the look-back. We restricted our analysis to participants who had a minimum of 366 days of follow-up and did not experience the outcome within the first year of follow-up. Participants with diagnoses of depression, psychoses or malignant prostate cancer (ICD-9=185, 222.2, 600.2, 600.21) within the look-back period, and those with ≤365 days of follow-up were excluded from the final analytic sample.

Fig. 10. Specific Aim 3 Cohort Selection


All males in Optum database 2012-2016 (N=38,188,462)
Received TRT during 2012-2016 (N=449,943)
Age = 40-65 years at index date (N=233,089)
Diagnosed with hypogonadism prior to TRT initiation date (N=103,923)
Have continuous enrollment in the look back period (look back period=12 months prior to and 45 days post TRT initiation date (N=55,763)
Had at least 1 physician visit in the look back period (N=55,383)
No diagnosis of depression or psychoses in the look back period (N=50,720)
No diagnosis of malignant prostate cancer in the look back period. (Final N = 49,321)
Excluded observations with missing values (N= 48,724)
≥366 days follow-up (N = 35,383)
Removed large outliers (N = 35,280)

3.5.3 Variables

Exposure

Exposure to TRT was the primary independent variable. TRT was assessed as a binary variable: >30 days exposure. Unexposed group was defined as ≤30 days of exposure to TRT. Sensitivity analyses were conducted using different exposure windows, i.e., 31-90, 91-180, 181-366 days of TRT. For all analyses, exposure was restricted to within the first 366 days of follow-up, i.e., 366 days after index/TRT initiation date (HSPCS-J and NDC Codes; Appendix: Table 1). All formulations of testosterone were included in this analysis.

Outcome

Incident depression, i.e. time to first occurrence of depression was the event time variable. Patients were censored at loss of coverage, or end of study date. Depression was defined as ≥2 outpatient (at least 30 days apart) or ≥1 inpatient ICD-9/ICD-10 codes for diagnosis of depression within a given calendar year.

Covariates

We tested for the effects of a variety of sociodemographic and clinical covariates in this analysis. Age, education, income, geographic region of residence, Elixhauser comorbidity index, outpatient physician visits and antidepressant use were included as covariates in the primary analysis.

Age

Participant age was measured at the index date, and analyzed as a categorical variable (40-49, 50-59, ≥60 years). Prior research suggests risk of hypogonadism and likelihood of receiving TRT increases with age.[2,51] In addition, the association between TRT and depression might vary by age.[8] Age was used as a covariate in multivariable regression models in order to assess its effects on the TRT-depression association. In addition, age was analyzed as an effect modifier to assess whether the effects of TRT on depression vary by different age categories.

Income

Income was reported as median household income for each zip code and categorized into quartiles.

Education

Education was reported as percentage of individuals in a zip code with high school education or higher, and categorized into quartiles.

Region

Region of residence was defined using census bureau divisions for geographic region (Northeast, Midwest, South, West).

Comorbidity Score

In order to account for comorbid medical conditions, Elixhauser comorbidity index-an aggregate measure of comorbidity was used. This measure has been used widely in prior studies assessing the effects of various pharmacological interventions including TRT.[138,163] Comorbidity score was categorized as 0, 1, 2, ≥3. In addition, individual

comorbidities were analyzed to see distribution across the two groups. Multivariable models adjusted for overall comorbidity score and any comorbidities that were unevenly distributed across the two groups.

Antidepressants

Multivariable regression models further adjusted for prior antidepressant use, which was measured using Therapeutic Class Codes (28.16.04x; Appendix: Table 2) for any antidepressant prescription in the look-back period. Antidepressant use was analyzed as a binary (yes/no) variable.

Outpatient Visits

In order to account for possible effects of access and utilization of care, number of outpatient visits was included as a covariate in multivariable models and operationalized as 0, 1-3, 4-9, ≥10 visits in the look-back period.

Additional Covariates

We performed additional sensitivity analyses to adjust for prior prescription drug use and other mental health conditions by including each of these variables as separate covariates in multivariable regression models.

Prescription Drugs.

Prescription drug use was defined using relevant Therapeutic Classification Codes (TCC) for any prescription drug in the look-back period and measured as count of the different types of prescription drugs used (Appendix: Table 4). For this purpose,

pharmacy claims were linked to RedBook™ Select database, which provided a 10-digit TCC code for each unique prescription drug category.[153,154]

Other Mental Health Conditions.

Other mental health conditions were defined using relevant ICD-9 and ICD-10 codes for a diagnosis of mood disorders, anxiety disorders, dementia and other mental disorders not included in the Elixhauser index. Mental health conditions were identified in the look back period (Appendix: Table 3). Additional sensitivity analyses adjusted for mental health conditions both in the look-back and follow-up period.

3.5.4 Statistical Analysis

Descriptive Characteristics

Descriptive characteristics of the sample were expressed as frequencies (N) and percentages (%). Age, income, education, region, Elixhauser comorbidity score, antidepressant use and outpatient visits at baseline were stratified by TRT exposure. Frequencies and proportions of any individual comorbidities that were unbalanced across the exposed and unexposed groups were also compared. Differences in baseline characteristics by TRT exposure category were assessed using chi-square tests for categorical variable and t-tests for continuous variables. Kaplan Meier survival curves were generated to compare time to depression incidence and event-free survival between the two exposure categories.

Tied Data

A frequency count of survival times suggested nearly 43% of event times were tied. In order to handle a relatively large number of ties, the *exact* method was used.

Testing Proportionality

The assumption of proportionality in multivariate Cox models was tested by analysis of Martingale residuals and assessing whether the logarithm of the baseline cumulative hazard rate and the Schoenfield residuals are proportional to the follow-up time. We further tested for the proportional hazards assumption by creating interaction terms between the primary predictor variable (TRT) and time and identifying significant interaction effects. Analysis of Schoenfeld residuals suggested no major variable violated the proportional hazard assumption. However, variable "fluid and electrolyte disorders" violated the assumption and was excluded from subsequent models (Appendix: Table 5). This variable is neither a potential confounder of the TRT-depression association nor clinically relevant in the context of the hypothesized relationship. Based on results of proportionality testing and clinical relevance, this variable was not included in the final analytic model. No significant interaction effects were observed between TRT and time, which suggested the primary predictor variable TRT did not violate the assumption of proportionality. Similarly, analysis of Martingale Residuals and supremum test for proportional hazard assumption suggested the primary exposure variable (TRT) did not violate the assumption of proportionality.

Outlier Analysis

Outlier analysis was performed to detect outliers and potential influential observations using a variety of approaches. Martingale residual plot did not reveal any large outliers; however, analysis of deviance residuals revealed a few relatively large

outliers (n=503; deviance residual>2.5). 103 observations had relatively large ld (likelihood displacement) and lmax (maximum Eigenvalue) values compared to the rest of the sample, i.e., ld>0.02 and lmax>0.05 which suggested a potential influential effect.

Model Fit and Final Model Selection

Final model selection was based on comparing model fit with and without identified outliers. using Cox-Snell residuals. Three different models were assessed. First model included all observations. Second model was examined after deleting observations with large residuals while a third model was tested after removing the identified potential influential observation (ld>0.02 or lmax>0.05). Comparison of the three models for model fit suggested model without the potential influential observations was the best fit (Appendix: Table 6). Comparison of the TRT-depression association between models with and without potential influential observations suggested the association was similar for both models. Model without potential influential observations had the best fit and was selected for final statistical analyses, with a sample size of 35,280.

Cox Proportional Hazard Regression Analysis

Cox proportional hazard regression analysis was performed to test the association between TRT and incident depression. Participants were censored at loss of coverage or if they were depression free by the end of the study period.

Two separate models were tested. Model 3A tested the independent association between exposure to TRT and time to incident depression. Two fully adjusted, multivariable models were generated: model 3B included all variables in model 3A + age, income, education, region, comorbidity status, outpatient visits and prior antidepressant

use. Elixhauser comorbidity index was analyzed as a score; however, individual comorbidities were also analyzed separately and entered into multivariable models if the distribution of an individual comorbidity differed between the exposed and unexposed groups. Four comorbidities-HIV, liver disease, peripheral vascular disease and uncomplicated diabetes were unevenly balanced across the two groups; multivariable models adjusted for these comorbidities.

In each model, the association between exposure to TRT and incident depression was analyzed using multivariable cox proportional hazards regression analyses which generated estimates of hazard ratio (HR) and 95% CI for risk of depression. Each model subsequently adjusted for additional covariates. Adjusted survival curves were generated to analyze the association between depression and the two TRT categories, adjusting for relevant covariates. In order to assess whether the effect of TRT on depression is modified by age or comorbidity status, two interaction terms were created for: i) TRT*age, and ii) TRT*comorbidity status to check for possible effect modification. And inform further stratification of regression models by age or comorbidity score.

Sensitivity Analysis

Three sensitivity analyses were conducted to account for additional covariates and to assess to assess the effect of additional TRT exposure windows on risk of depression. First sensitivity analysis adjusted for additional covariates including any prescription drug use and other mental health diagnoses in the look-back period. A second sensitivity analysis was conducted in order to assess the robustness of our findings and to assess the association between duration of exposure to TRT and depression. The latter analysis was conducted using different TRT exposure windows, i.e., 31-90, 91-180, 181-366 days of

TRT. This analysis also adjusted for any mental health conditions during the follow-up period.

A third sensitivity analysis tested whether the association between TRT and depression varies by age or comorbidity status. In order to assess potential effect modification by age or comorbidity status, interaction terms were created between TRT*Age and TRT*Comorbidity Score. Each interaction term was entered into a regression model for test of statistical significance and to inform possible model stratification for further analyses.

Chapter 4: Results

4.1 Specific Aim-1 Results

Specific Aim-1 assessed TRT prescription trends in middle aged and older men with depression enrolled in CDM between the years 2002-2016. Descriptive characteristics are presented in two separate sections. First section (4.1.1) presents descriptive characteristics for all men enrolled in CDM during the study period who met the primary inclusion/exclusion criteria. A second section (4.1.2) presents study sample characteristics by depression status (depressed vs non-depressed). A third section (4.1.3) presents prescription trends stratified by age and hypogonadal status in men with depression. The last section (4.1.4) presents results from trend analysis to assess differences in prescription trends in depressed vs non-depressed men.

4.1.1 Descriptive Characteristics & Prescription Trends: Overall Study Population

We identified 5,565,649 men 40-65 years of age enrolled in CDM between 2002-2016. The minimum sample size for a given calendar year was 907,530 men. Overall, incident TRT prescription increased from 2002-2012/2013 and decreased thereafter from 2012-2016. For each calendar year, prescription rates were higher in men ≥50 years of age, compared to men <50 years of age. TRT prescription trends overall and by age group are presented in Figures 11 and 12.

As shown in Fig. 11, TRT prescription rates increased overall by nearly two-fold from 2002-2016 in this population of men. However, the increase was most prominent between 2002 and 2012/2013. Thereafter, prescription rates decreased from 2012-2016.

The increase within the 2002-2012 period was greater than 4.5 fold. The pattern observed in these findings is consistent with prior studies demonstrating a drop in TRT prescription rates around 2013-2014, which might in part be due to increased FDA communications and regulations including greater scrutiny of testosterone prescribing practices and push for increased awareness regarding potential adverse events associated with irrational use of testosterone therapy.[19,168]

As shown in Fig. 12, men aged 50-59 and 60-65 years had higher prescription rates compared to men aged 40-49 years for most years; however, the latter group saw the sharpest increase in prescription rates across the three age groups-nearly six-fold between 2002 and 2012 and nearly 2.5 fold overall from 2002-2016. The overall increase in prescription rates was minimal for the other two age groups. Further, in the 2014-2016 period the age groups 40-49 and 50-59 had comparable prescription rates, which were higher compared to the 60-65 year age group.

Fig. 11. TRT Prescription Trends in Middle Aged and Older Men

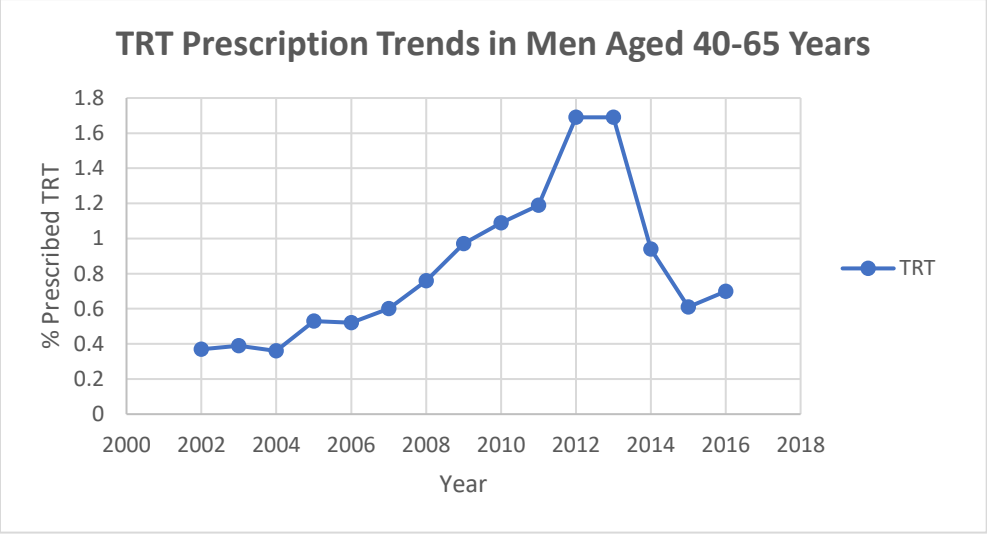
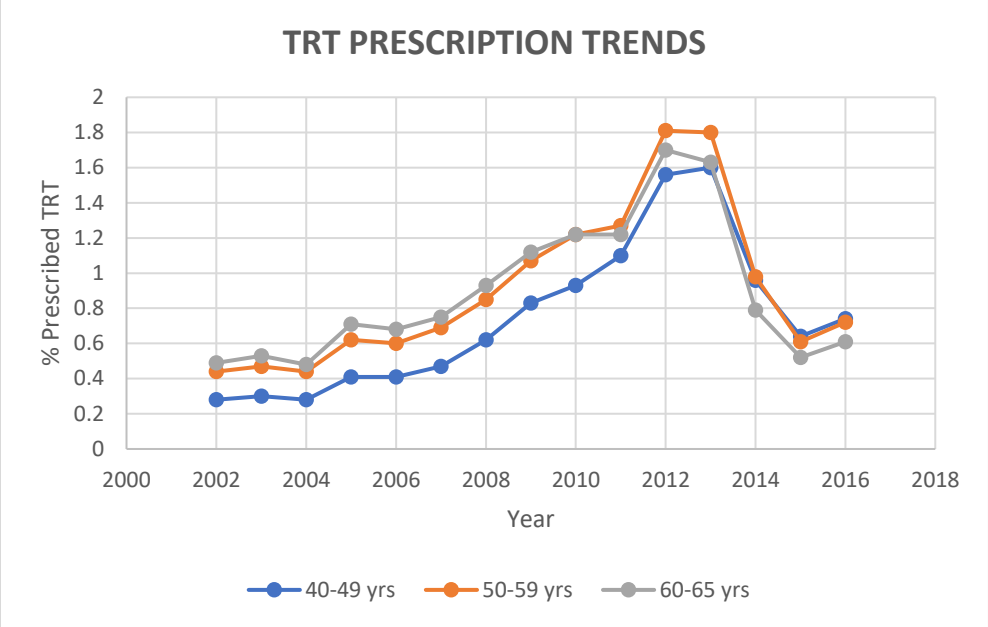


Fig. 12. TRT Prescription Trends in Middle Aged and Older Men by Age



4.1.2 Descriptive Characteristics & Prescription Trends by Depression Status

Prevalence of depression in this cohort of men ranged from 1.55% in 2002 to 3.42% in 2016. Descriptive characteristics, by depression status are presented in Tables 3 and 4. Table 3 presents prescribing patterns overall and in depressed vs non-depressed men. Table 4 presents prescribing patterns specifically for men with depression. In general, TRT prescription rates were higher for depressed men vs non-depressed men for each calendar year from 2002-2016. Similar to prescription trends presented above for the overall study population, TRT prescription for both groups increased substantially from 2002 to 2012 and decreased thereafter to 2016. For both groups, an increasing trend was observed from 2002-2012 and a decreasing trend thereafter from 2012 to 2016. Fig. 13 presents TRT prevalence trends in depressed vs non-depressed men.

Table 3. TRT Prescribing Patterns: 2002-2016: All Men

	2002	2003	2004	2005	2006	2007	2008
All Men							
Received TRT (%)	0.37	0.39	0.36	0.53	0.52	0.60	0.76
Eligible Men (n)	907530	1005998	1071270	1141228	1207178	1238553	1279785
Age Range							
40-49							
Received TRT (%)	0.28	0.30	0.28	0.41	0.41	0.47	0.62
Eligible Men (n)	463428	505879	531653	556705	567324	565847	568888
50-59							
Received TRT (%)	0.44	0.47	0.44	0.62	0.60	0.69	0.85
Eligible Men (n)	335569	374642	402613	436796	476724	496272	516778
60-65							
Received TRT (%)	0.49	0.53	0.48	0.71	0.68	0.75	0.93
Eligible Men (n)	108533	125477	137004	147727	163130	176434	194119
Depressed							
No							
Received TRT (%)	0.35	0.37	0.35	0.51	0.50	0.57	0.72
Eligible Men (n)	893457	987628	1051129	1116820	1179330	1206753	1245976
Yes							
Received TRT (%)	1.13	1.28	1.23	1.37	1.30	1.64	2.03
Eligible Men (n)	14073	18370	20141	24408	27848	31800	33809

Table 3 (Contd.)	2009	2010	2011	2012	2013	2014	2015	2016
All Men								
Received TRT (%)	0.97	1.09	1.19	1.69	1.69	0.94	0.61	0.70
Eligible Men (n)	1273472	1269086	1279370	1321987	1353241	1225563	1258792	1326997
Age Range								
40-49								
Received TRT (%)	0.83	0.93	1.10	1.56	1.60	0.96	0.64	0.74
Eligible Men (n)	556120	548494	538605	542819	541157	482121	488957	506142
50-59								
Received TRT (%)	1.07	1.22	1.27	1.81	1.80	0.98	0.61	0.72
Eligible Men (n)	515406	516367	527927	549214	566961	517588	532104	560773
60-65								
Received TRT (%)	1.12	1.22	1.22	1.70	1.63	0.79	0.52	0.61
Eligible Men (n)	201946	204225	212838	229954	245123	225854	237731	260082
Depressed								
No								
Received TRT (%)	0.93	1.05	1.14	1.62	1.63	0.90	0.58	0.68
Eligible Men (n)	1238506	1232651	1241283	1280382	1309412	1185798	1217016	1281576
Yes								
Received TRT (%)	2.34	2.69	2.79	3.63	3.53	1.92	1.38	1.52
Eligible Men (n)	34966	36435	38087	41605	43829	39765	41776	45421

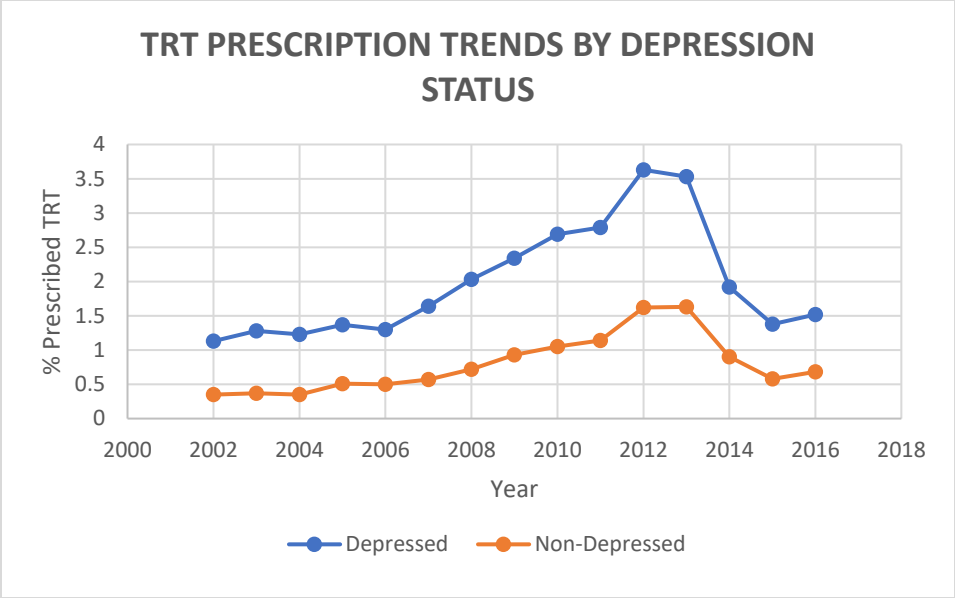
TRT Prescribing patterns by age and hypogonadal status in men with depression are presented in Table 4.

Table 4. TRT Prescribing Patterns: 2002-2016: Men with Depression

	2002	2003	2004	2005	2006	2007	2008
Depressed Men							
Received TRT (%)	1.13	1.28	1.23	1.37	1.30	1.64	2.03
Eligible Men (n)	14073	18370	20141	24408	27848	31800	33809
Age Range							
40-49							
Received TRT (%)	0.93	1.03	0.97	1.13	1.22	1.36	1.63
Eligible Men (n)	7488	9549	10239	12140	13361	14390	14558
50-59							
Received TRT (%)	1.22	1.49	1.58	1.52	1.36	1.80	2.31
Eligible Men (n)	5330	7037	7789	9711	11333	13267	14278
60-65							
Received TRT (%)	1.91	1.85	1.23	1.96	1.46	2.15	2.37
Eligible Men (n)	1255	1784	2113	2557	3154	4143	4973
Hypogonadal Status							
No							
Received TRT (%)	1.02	1.15	1.07	1.17	1.12	1.46	1.74
Eligible Men (n)	13976	18183	19897	24067	27462	31293	33182
Yes							
Received TRT (%)	16.49	13.90	14.34	15.84	14.25	13.21	17.38
Eligible Men (n)	97	187	244	341	386	507	627

	2009	2010	2011	2012	2013	2014	2015	2016
Depressed Men								
Received TRT (%)	2.34	2.69	2.79	3.63	3.53	1.92	1.38	1.52
Eligible Men (n)	34966	36435	38087	41605	43829	39765	41776	45421
Age Range								
40-49								
Received TRT (%)	2.19	2.42	2.60	3.41	3.43	1.93	1.34	1.73
Eligible Men (n)	14693	15162	15154	16003	16083	14141	14382	15003
50-59								
Received TRT (%)	2.38	3.02	3.01	3.99	3.83	2.08	1.55	1.60
Eligible Men (n)	14672	15185	16130	17600	18791	16899	17885	19513
60-65								
Received TRT (%)	2.64	2.53	2.69	3.27	3.07	1.62	1.10	1.09
Eligible Men (n)	5601	6088	6803	8002	8955	8725	9509	10905
Hypogonadal Status								
No								
Received TRT (%)	2.01	2.41	2.40	3.10	2.79	1.43	0.99	1.01
Eligible Men (n)	34309	35616	37025	40174	41872	37784	39659	42704
Yes								
Received TRT (%)	19.48	14.90	16.48	18.52	19.37	11.26	8.69	9.61
Eligible Men (n)	657	819	1062	1431	1957	1981	2117	2717

Fig. 13. TRT Prescription Trends: Depressed vs Non-Depressed Men



Differences in TRT prescription rates in depressed vs non-depressed men were wider during 2006-2012, compared to years prior to and following this time period. At any given year, TRT prescription rates in depressed men were at least 2-fold higher compared to men without depression. Both groups saw the highest prescription rates during 2012-2013. From 2002-2012, the depressed group experienced a 3.2-fold increase in TRT prescription rates, compared to 4.62-fold increase for non-depressed group. The overall increase in prescription rates from 2002-2016 was less remarkable for both groups, with 1.35-fold and 1.94-fold increase for the depressed and non-depressed group, respectively.

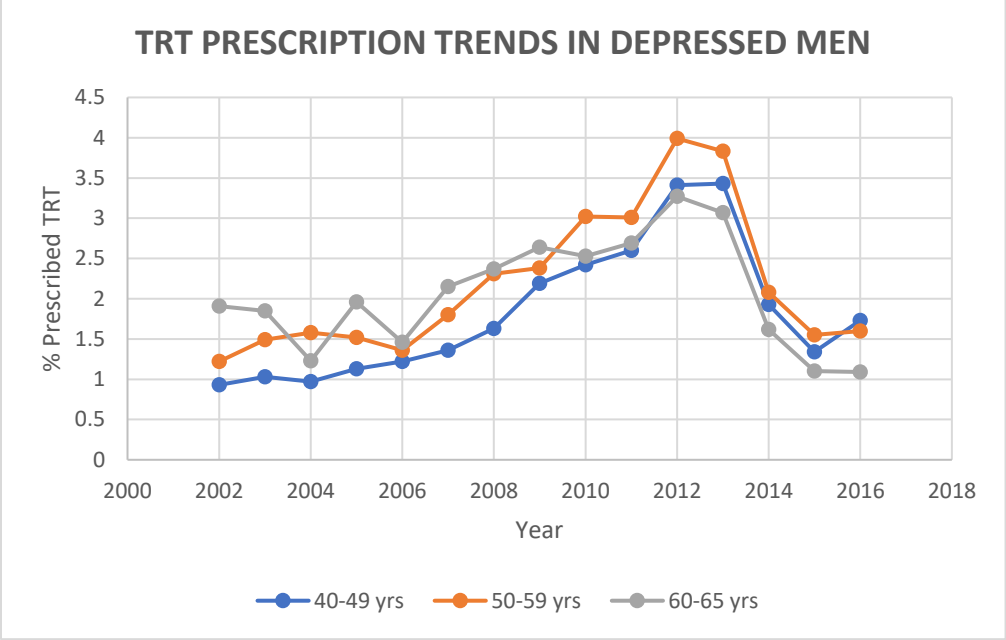
4.1.3 TRT Prescription Trends in Depressed Men: Stratified Analyses

We further examined TRT prescription trends by age and hypogonadal status in depressed men.

4.1.3-I Prescription Trends in Depressed Men: Age-Stratified Analysis

Analysis of prescription trends in depressed men by age revealed patterns similar to the earlier analysis (Section 4.1.1). For each year from 2002-2011, TRT prescription rates were higher for older men compared to men in their 40s. However, prescription rates were lower for the oldest age group (60-65) years during 2012-2016 while prescription rates during the same period were comparable among the other two age groups. Interestingly, men aged 40-45 years experienced the sharpest increase in TRT prescription rates-both from 2002-2016 and overall, with a 3.67-fold increase in prescription rates from 2002-2012 and 1.86-fold increase overall. These trends are depicted in Fig. 14.

Fig. 14. TRT Prescription Trends in Depressed Men: Age Stratification

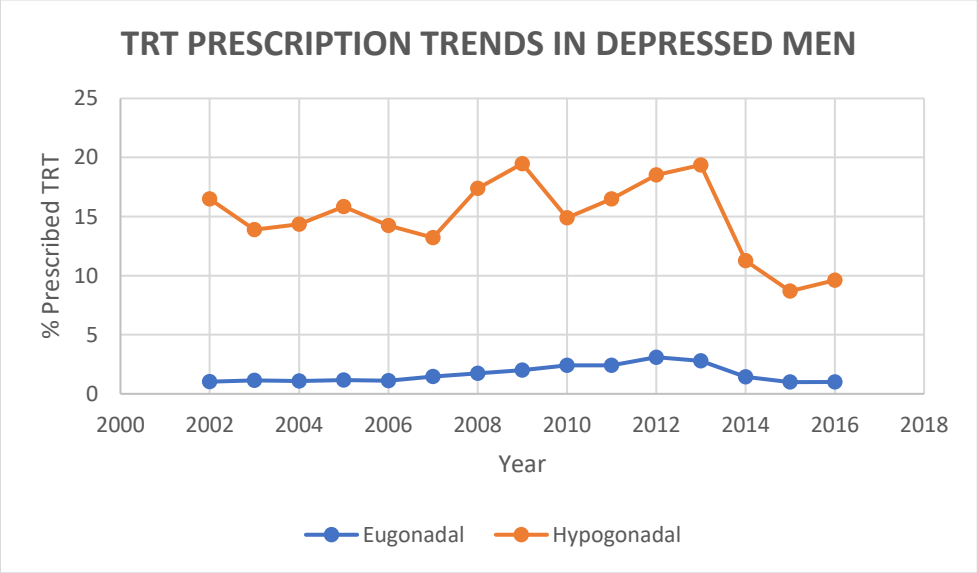


4.1.3-II Prescription Trends in Depressed Men: Stratification by Hypogonadal Status

TRT prescription trends were further analyzed by hypogonadal status in depressed men (Fig. 15). For each year from 2002-2016, TRT prescription rates were higher among depressed hypogonadal men, compared to depressed eugonadal men. Prescription rates among hypogonadal men peaked twice at 2009 and 2013, whereas prescription rate among eugonadal men peaked around 2012. Similar to trends observed earlier in the section, prescription rates increased overall from 2002-2012/2013 and decreased thereafter.

Overall, prescription rates dropped from 16.49% in 2002 to 9.61% in 2016 for the depressed hypogonadal group and remained somewhat similar for the eugonadal group during the same period. For the entire study period, TRT prescription rates for depressed, hypogonadal men were at least 9 times higher at any given time point, compared to their counterparts.

Fig. 15. TRT Prescription Trends in Depressed Men, by Hypogonadal Status



4.1.4 Trend Analysis

In order to assess possible differences in prescription patterns between depressed and non-depressed groups, trend tests using multivariable logistic regression analyses were performed. Trend tests were adjusted for age and hypogonadal status. Results from trend analysis are presented in Table 5.

Results from trend analyses show a statistically significant depression*time (mean-centered year) interaction term, suggesting possible differences in TRT prescription patterns between the depressed and non-depressed groups (Table 5). Test for combined effect of the two interaction terms suggested that the overall trend was statistically significant between the two comparison groups over time (contrast test results: Wald Chi-Square=64.57; $p<0.0001$). As outlined in the preceding section, the depressed group had considerably higher prescription rates for each year from 2002-2016; however, the increase for the non-depressed group was slightly greater from 2002-2012 and overall from 2002-2016, compared to the depressed group. The statistically significant result for the combined interaction term suggested that prescription patterns over time were statistically different between the two groups. However, the statistically insignificant interaction term between depression and quadratic time (Table 5) suggests that both groups experienced a relatively similar curve in prescription rates i.e., a decreasing trend from 2012-2016.

A closer look at the prescription patterns between the two groups suggests both depressed and non-depressed men experienced a somewhat similar increase in prescription rates between 2002-2012 and a nearly identical decline from 2012 onward. It is possible that the study's large sample size amplified the statistical association to a certain extent. Overall, both depressed and non-depressed groups followed a similar

trajectory over time and trend differences observed in this analysis should be interpreted in light of large sample size.

Table 5. Trend Analysis

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.8728	0.00789	132617.365	<.0001
Depressed	1	1	0.4195	0.00730	3306.2956	<.0001
yearctr		1	0.0799	0.000850	8830.6823	<.0001
yearctr2		1	-0.0221	0.000198	12476.6860	<.0001
depyrctr		1	-0.0407	0.00351	134.1707	<.0001
depyrctr2		1	-0.00109	0.000808	1.8254	0.1767
hypogonadal	1	1	1.3717	0.00377	132188.668	<.0001
Agecat (50-59)	1	1	0.0740	0.00357	428.6321	<.0001
Agecat (60-65)	2	1	0.0140	0.00455	9.4164	0.0022

4.1.5 Summary

TRT prescription rates increased substantially by nearly 4.5 fold during the 10 year period from 2002-2016 and declined thereafter from 2012-2016. Overall, prescription rates were higher among depressed men relative to non-depressed men. Prescription rates were higher among older depressed, compared to men 40-49 years of age, in general. Further, as expected depressed men with a diagnosis of hypogonadism were more likely to receive TRT compared to their counterparts. These results suggest a high incidence of TRT prescription in depressed men overall and within specific sub-populations of depressed men. Prescription trends for all analyses suggest an increasing trend from 2002-2012 and decreasing trend from 2012-2016, regardless of depression status. Future research should focus on sociodemographic and other determinants of TRT use. In addition, further research is required to better understand the possible effects of FDA warnings/communications and policies on TRT prescription and use.

4.2 Specific Aim 2 Results

The results for Specific Aim 2 are divided into two sections and six sub-sections. The first section and first two sub-sections include descriptive characteristics and findings from multivariable regression for Aim 2A while the third subsection presents results from sensitivity analysis. The second section and sub-sections three and four include descriptive characteristics and multivariable regression results for Aim 2B. The last subsection presents results for sensitivity analyses for Aim 2B.

4.2.1 Specific Aim 2A Results

4.2.1-I Descriptive Characteristics

Aim 2A examined whether untreated hypogonadism was associated with increased odds of incident depression. Descriptive characteristics of the sample are presented in Table 6. Final sample consisted of 39,548 men aged 40 to 65 years. Total number of cases was 9,887 whereas the total number of controls was 29,661. Overall, 1,416 (3.58%) men had a diagnosis of hypogonadism during the study period. Comparison of hypogonadism diagnosis among cases and controls suggested prevalence of hypogonadism was higher among cases, compared to their counterparts. Specifically, 4.01% of cases had a diagnosis of hypogonadism in the look-back period compared to 3.44% for controls. Nearly 42% of participants in the final study sample were in the 50-59 age range whereas approximately 22% were in the 60-65 age group.

Age and Elixhauser comorbidity score (matching variables) were distributed evenly across cases and controls. Cases had greater number of physician visits, (>3 visits: 80.57% cases vs 72.13% controls), higher rates of antidepressant prescription (42.45% cases vs 9.58% controls) and were more prevalent in the Midwest and Northeast

compared to controls. Overall, controls had lower educational attainment compared to cases (Table 6). Examination of individual Elixhauser comorbidities revealed some imbalance among cases and controls. Cases had higher prevalence of congestive heart failure, arrhythmias, pulmonary circulation disorders, valvular disease, peripheral vascular disorders, paralysis, chronic pulmonary disease, other neurological disorders, diabetes, hypertension, renal failure, hypothyroidism, liver disease, rheumatoid arthritis, HIV, peptic ulcer disease, lymphoma, solid tumor, metastatic cancer, alcohol/drug abuse, coagulopathy, fluid and electrolyte disorders, weight loss and anemias. Multivariable regression models accounted for all comorbidities that were unbalanced across cases and controls.

For purposes of sensitivity analyses, rates of other mental health conditions and prescription drug use between the two groups were compared. Compared to controls, cases had higher rates of prior prescription drug use (mean for types of prescription drugs: 10 for cases vs 7 for controls) and other mental health conditions (34.45% cases vs 16.27% controls).

Table 6. Descriptive Characteristics: Depressed vs Non-Depressed Men

	No Depression (%)	Depression (%)	p
All men	29661 (100)	9887 (100)	
Age*			
40-49	10749 (36.24)	3583 (36.24)	
50-59	12324 (41.55)	4108 (41.55)	
60-65	6588 (22.21)	2196 (22.21)	
Elixhauser Comorbidity Score*			
0	6756 (22.78)	2252 (22.78)	
1	6027 (20.32)	2009 (20.32)	
2	4845 (16.33)	1615 (16.33)	
≥3	12033 (40.57)	4011 (40.57)	
Income			0.09
Quartile 1	7403 (24.96)	2491 (25.19)	
Quartile 2	7334 (24.73)	2547 (25.76)	
Quartile 3	7434 (25.06)	2453 (24.81)	

Quartile 4	7490 (25.25)	2396 (24.23)	
Education			<0.0001
Quartile 1	7752 (26.14)	2272 (22.98)	
Quartile 2	7270 (24.51)	2506 (25.35)	
Quartile 3	7359 (24.81)	2538 (25.67)	
Quartile 4	7280 (24.54)	2571 (26)	
Region			<0.01
MW	7879 (26.56)	2924 (29.57)	
NE	3071 (10.35)	1304 (13.19)	
So	12839 (43.39)	3859 (39.03)	
We	5872 (19.80)	1800 (18.21)	
Physician visits			<0.0001
1-3	8266 (27.87)	1921 (19.43)	
4-9	12156 (40.98)	3448 (34.87)	
>=10	9239 (31.15)	4518 (45.70)	
Prior Antidepressant Prescription	2843 (9.58)	4197 (42.45)	<0.01
Other Mental Health Diagnoses	6325 (21.32)	4922 (49.78)	<0.0001
Prescription Drugs *(mean; SD)*	7.45 (5.99)	10.19 (7.83)	<0.0001
Hypogonadism	1020 (3.44)	396 (4.01)	0.01
Elixhauser Comorbidities:			
Congestive Heart Failure	1486 (5.01)	826 (8.35)	<0.0001
Cardiac Arrhythmia	3839 (12.94)	1684 (17.03)	<0.0001
Valvular Disease	2118 (7.14)	831 (8.40)	<0.0001
Pulmonary Circulation Disorders	498 (1.68)	326 (3.30)	<0.0001
Peripheral Vascular Disorders	1901 (6.41)	940 (9.51)	<0.0001
Hypertension Uncomplicated	16504 (55.64)	5238 (52.98)	<0.0001
Hypertension Complicated	1780 (6)	708 (7.16)	<0.0001
Paralysis	230 (0.78)	285 (2.88)	<0.0001
Other Neurological Disorders	865 (2.92)	770 (7.79)	<0.0001
Chronic Pulmonary Disease	4805 (16.20)	2081 (21.05)	<0.0001
Diabetes Uncomplicated	7630 (25.72)	2326 (23.53)	<0.0001
Diabetes Complicated	2558 (8.62)	1001 (10.12)	<0.0001
Hypothyroidism	3170 (10.69)	957 (9.68)	0.003
Renal Failure	1585 (5.34)	730 (7.38)	<0.0001
Liver Disease	2345 (7.91)	1048 (10.60)	<0.0001
Peptic Ulcer Disease	271 (0.91)	135 (1.37)	<0.0001
HIV/AIDS	244 (0.82)	143 (1.45)	<0.0001
Lymphoma	203 (0.68)	111 (1.12)	<0.0001
Metastatic Cancer	278 (0.94)	226 (2.29)	<0.0001
Solid Tumor Without Mets	1741 (5.87)	715 (7.23)	<0.0001
Rheumatoid Arthritis/collagen	1203 (4.06)	558 (5.64)	<0.0001
Coagulopathy	749 (2.53)	479 (4.84)	<0.0001
Weight Loss	700 (2.36)	623 (6.30)	<0.0001
Fluid and Electrolyte Disorders	2218 (7.48)	1420 (14.36)	<0.0001
Blood Loss Anemia	204 (0.69)	104 (1.05)	0.0004
Deficiency Anemia	1153 (3.89)	538 (5.44)	<0.0001
Alcohol Abuse	803 (2.71)	769 (7.78)	<0.0001
Drug Abuse	593 (2)	635 (6.42)	<0.0001

**Matching variable*

4.2.1-II Multivariable Models

Multivariable models tested the association between hypogonadism and depression, both independently and after adjusting for a variety of sociodemographic, clinical, pharmacological and healthcare factors. Three different models were tested. First model tested the independent association between hypogonadism and incident depression. Second model adjusted for region, education, income, physician visits and prior antidepressant use. The latter model also accounted for any Elixhauser comorbidities that were unevenly balanced across cases and controls. Sensitivity analyses subsequently adjusted for other mental health conditions and any prescription drugs in the look-back period. Results from multivariable logistic regression are presented in Table 7.

Untreated hypogonadism was independently associated with 17% increased odds of incident depression (Model 2A-1: OR=1.17; 95%CI=1.04 1.32). This finding is consistent with current literature on the topic. However, the observed association between hypogonadism and depression was not statistically insignificant after adjusting for covariates included in Model 2A-II. While the direction of effect was still indicative of increased risk of depression, the association was no longer statistically meaningful. We also assessed the odds of depression associated with other covariates. Higher income was associated with lower risk of depression whereas higher education quartiles were linked to an increased risk of depression. Men were more likely to be diagnosed with depression in the Northeast and less likely in the South and West, relative to men in the Midwest. Greater number of physician/outpatient visits was linked to an increased risk of depression.

Table 7. Conditional Logistic Regression Analysis

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Model 2A-I		
Hypogonadism	1.17 (1.04 1.32)	1.15 (0.99 1.32)
(Referent=No Hypogonadism)		
Model 2A-II		
Income		
(Referent=Quartile 1)		
Quartile-2		0.98 (0.90 1.06)
Quartile-3		0.88 (0.80 0.96)
Quartile-4		0.79 (0.71 0.88)
Education		
(Referent=Quartile 1)		
Quartile-2		1.18 (1.09 1.28)
Quartile-3		1.31 (1.19 1.44)
Quartile-4		1.45 (1.30 1.61)
Region		
(Referent=Midwest)		
Northeast		1.22 (1.12 1.34)
South		0.81 (0.75 0.86)
West		0.84 (0.77 0.91)
Elixhauser Comorbidities:		
Congestive Heart Failure		1.30 (1.14 1.48)
(Referent=No Congestive Heart Failure*)*		
Cardiac Arrhythmia		1.25 (1.15 1.37)
(Referent=No Cardiac Arrhythmia*)*		
Valvular Disease		1.00 (0.89 1.12)
(Referent=No Valvular Disease*)*		
Pulmonary Circulation Disorders		1.19 (0.98 1.44)
(Referent=No Pulmonary Circulation Disorders*)*		
Peripheral Vascular Disorders		1.26 (1.13 1.41)
(Referent=No Peripheral Vascular Disorders*)*		
Hypertension Uncomplicated		1.03 (0.95 1.11)
(Referent=No Hypertension*)*		
Hypertension Complicated		1.02 (0.89 1.17)
(Referent=No Hypertension Complicated*)*		
Paralysis		3.01 (2.41 3.78)
(Referent=No Paralysis*)*		
Other Neurological Disorders		1.74 (1.52 1.98)
(Referent=No Neurological Disorders*)*		
Chronic Pulmonary Disease		1.25 (1.16 1.36)
(Referent=No Chronic Pulmonary Disease*)*		
Diabetes Uncomplicated		0.97 (0.89 1.05)

(Referent=No Diabetes Uncomplicated*)*	
Diabetes Complicated	1.23 (1.09 1.38)
(Referent=No Diabetes Complicated*)*	
Hypothyroidism	1.02 (0.93 1.12)
(Referent=No Hypothyroidism*)*	
Renal Failure	1.08 (0.94 1.24)
(Referent=No Renal Failure*)*	
Liver Disease	1.12 (1.01 1.24)
(Referent=No Liver Disease*)*	
Peptic Ulcer Disease	1.06 (0.81 1.38)
(Referent=No Peptic Ulcer Disease*)*	
HIV/AIDS	1.48 (1.15 1.92)
(Referent=No HIV/AIDS*)*	
Lymphoma	1.17 (0.87 1.56)
(Referent=No Lymphoma*)*	
Metastatic Cancer	1.97 (1.54 2.52)
(Referent=No Metastatic Cancer*)*	
Solid Tumor Without Mets	0.99 (0.87 1.12)
(Referent=No Solid Tumor Without Mets*)*	
Rheumatoid Arthritis/collagen	1.23 (1.08 1.40)
(Referent=No Rheumatoid Arthritis*)*	
Coagulopathy	1.25 (1.07 1.47)
(Referent=No Coagulopathy*)*	
Weight Loss	1.83 (1.58 2.12)
(Referent=No Weight Loss*)*	
Fluid and Electrolyte Disorders	1.59 (1.44 1.76)
(Referent=No Fluid and Electrolyte Disorders*)*	
Blood Loss Anemia	0.77 (0.56 1.06)
(Referent=No Blood Loss Anemia*)*	
Deficiency Anemia	0.89 (0.77 1.02)
(Referent=No Deficiency Anemia*)*	
Alcohol Abuse	2.54 (2.22 2.90)
(Referent=No Alcohol Abuse*)*	
Drug Abuse	2.10 (1.81 2.43)
(Referent=No Drug Abuse*)*	
Outpatient Visits	
(Referent=1-3)	
4-9	1.31 (1.22 1.41)
≥10	1.96 (1.80 2.12)
Antidepressant Prescription	6.39 (5.99 6.82)
(Referent=No Antidepressant)	

Similarly, having a prescription for an antidepressant drug in the look-back was associated with over 6 times increased risk of depression (OR=6.39; 95%CI=5.99 6.82).

While cases and controls were matched on Elixhauser comorbidity score, multivariable model 2A-II adjusted for any comorbidities that were unbalanced between the two groups. Our findings suggest that congestive heart failure, arrhythmias, peripheral vascular disorders, paralysis, chronic pulmonary disease, other neurological disorders, diabetes (complicated), liver disease, rheumatoid arthritis, metastatic cancer, alcohol/drug abuse, coagulopathy, fluid and electrolyte disorders and weight loss were associated with increased risk of depression. Overall, no association was observed between hypogonadism and depression after adjusting for relevant sociodemographic, clinical, pharmacological and healthcare factors.

4.2.1-III Sensitivity Analysis

Results from sensitivity analysis are presented in Table 8. Sensitivity analysis adjusted for other mental health conditions and any prescription drug use in the look-back. Hypogonadism was associated with 18% increased odds of incident depression (OR=1.18; 95%CI=1.04 1.34) after adjusting for all covariates in Model 2A-II and prior mental health conditions. Sensitivity analyses further tested the potential effect of prior prescription drug use on the hypogonadism-depression association. In the fully adjusted model accounting for all covariates in Model 2A-II and both prior mental health conditions and prescription drug use, the association between hypogonadism and incident depression was attenuated to near non-significance with a small, borderline risk of depression (OR=1.15; 95%CI=1.00 1.31; p=0.04). Diagnosis of other mental health conditions was associated with over 2 fold increased odds of depression (OR=2.13; 95%CI=2.01 2.26). Similarly, one additional prescription drug type was linked to a 6% increased odds of incident depression (OR=1.06; 95%CI=1.06 1.07).

Table 8. Sensitivity Analysis

	Adjusted OR* (95% CI)	**Adjusted OR*** (95% CI)
Hypogonadism *(Referent=No Hypogonadism)*	1.18 (1.04 1.34)	1.15 (1.00 1.31)**
Any Other Mental Health Diagnosis *(Referent=No Other Mental Health Diagnosis)*	2.21 (2.08 2.34)	2.13 (2.01 2.26)
Any Prescription Drug Use *(Referent=No Prescription Drug Use)*		1.06 (1.06 1.07)

*Adjusted for all covariates in Model 2A-II
**95%CI=1.004 1.307; *p=0.04*

4.2.2 Specific Aim 2B Results

4.2.2-I Descriptive Characteristics

Aim 2B examined the association between TRT and incident depression. Descriptive characteristics of the sample are presented in Table 9. Final sample consisted of 14,856 men aged 40 to 65 years. Total number of cases was 3,824 whereas the total number of controls was 11,032. Overall, 3,560 (23.96%) men met the criteria for primary definition of TRT exposure (most recent prescription overlapping by >=1 day within 30 days prior to index/depression diagnosis date) and were defined as "exposed." Comparison of TRT exposure among cases and controls suggested prevalence of TRT was higher among cases, compared to their counterparts. Specifically, 26.80% of cases received TRT in the look-back period compared to 22.98% for controls. Nearly 45% of participants in the final study sample were in the 50-59 age range whereas approximately 36% were in the 40-49 year age group.

Age and Elixhauser comorbidity score (matching variables) were distributed evenly across cases and controls. Cases had greater number of physician visits, (>3 visits: 94.09% cases vs 88.88% controls) and higher rates of antidepressant prescription (54.39% cases vs 13.88% controls). Cases were more prevalent in the Midwest, West and Northeast compared to controls. Overall, cases and controls had similar educational attainment; however, controls had lower income compared to cases (Table 9). Examination of individual Elixhauser comorbidities revealed some imbalance among cases and controls. Cases had higher prevalence of congestive heart failure, cardiac arrhythmia, pulmonary circulation disorders, peripheral vascular disorders, paralysis, chronic pulmonary disease, other neurological disorders, complicated diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease, rheumatoid arthritis, HIV, solid tumor, metastatic cancer, lymphoma, rheumatoid arthritis, alcohol/drug abuse, coagulopathy, fluid and electrolyte disorders, weight loss and deficiency anemia, compared to controls. Multivariable regression models accounted for all comorbidities that were unbalanced across cases and controls.

For purposes of sensitivity analyses, rates of mental health conditions and prescription drug use between the two groups were compared. Compared to controls, cases had higher rates of prior prescription drug use (mean for types of prescription drugs: 14 for cases vs 10 for controls) and other mental health conditions (38% cases vs 20.77% controls).

Table 9. Descriptive Characteristics: Depressed vs Non-Depressed Men

	No Depression (%)	Depression (%)	p
All men	11032 (100)	3824 (100)	
Age*			
40-49	3992 (36.19)	1388 (36.30)	
50-59	5028 (45.58)	1729 (45.21)	
60-65	2012 (18.24)	707 (18.49)	
Elixhauser Comorbidity Score*			
0	1726 (15.65)	583 (15.25)	
1	2425 (21.98)	821 (21.47)	
2	2025 (18.36)	716 (18.72)	
≥3	4856 (44.02)	1704 (44.56)	
Income			<0.0001
Quartile 1	2662 (24.13)	1057 (27.64)	
Quartile 2	2764 (25.05)	950 (24.84)	
Quartile 3	2793 (25.32)	918 (24.01)	
Quartile 4	2813 (25.50)	899 (23.51)	
Education			0.42
Quartile 1	2778 (25.18)	971 (25.39)	
Quartile 2	2776 (25.16)	1001 (26.18)	
Quartile 3	2727 (24.72)	917 (23.98)	
Quartile 4	2751 (24.94)	935 (24.45)	
Region			<0.01
MW	1487 (13.48)	651 (17.02)	
NE	638 (5.78)	259 (6.77)	
So	7062 (64.01)	2232 (58.37)	
We	1845 (16.72)	682 (17.83)	
Physician visits			<0.0001
1-3	1227 (11.12)	226 (5.91)	
4-9	4274 (38.74)	999 (26.12)	
>=10	5531 (50.14)	2599 (67.97)	
Prior Antidepressant Prescription	1531 (13.88)	2080 (54.39)	<0.0001
Other Mental Health Diagnoses	2291 (20.77)	1453 (38)	<0.0001
Prescription Drugs *(mean; SD)*	9.96 (6.57)	13.80 (8.70)	<0.0001
TRT	2535 (22.98)	1025 (26.80)	<0.0001
Elixhauser Comorbidities:			
Congestive Heart Failure	407 (3.69)	214 (5.60)	<0.0001
Cardiac Arrhythmia	1278 (11.58)	518 (13.55)	0.002
Pulmonary Circulation Disorders	155 (1.41)	98 (2.56)	<0.0001
Peripheral Vascular Disorders	715 (6.48)	355 (9.28)	<0.0001
Paralysis	40 (0.36)	49 (1.28)	<0.0001
Other Neurological Disorders	226 (2.05)	226 (5.91)	<0.0001
Chronic Pulmonary Disease	1794 (16.26)	799 (20.89)	<0.0001
Diabetes Complicated	1115 (10.11)	472 (12.34)	<0.0001
Hypothyroidism	2226 (20.18)	742 (19.40)	0.003
Renal Failure	545 (4.94)	251 (6.56)	0.0001
Liver Disease	885 (8.02)	406 (10.62)	<0.0001
Peptic Ulcer Disease	95 (0.86)	61 (1.60)	0.0004
HIV/AIDS	180 (1.63)	102 (2.67)	<0.0001
Lymphoma	89 (0.81)	44 (1.15)	0.04
Metastatic Cancer	65 (0.59)	54 (1.41)	<0.0001

Solid Tumor Without Mets	360 (3.26)	177 (4.63)	0.0001
Rheumatoid Arthritis/collagen	535 (4.85)	280 (7.32)	<0.0001
Coagulopathy	263 (2.38)	160 (4.18)	<0.0001
Weight Loss	272 (2.47)	158 (4.13)	<0.0001
Fluid and Electrolyte Disorders	838 (7.60)	426 (11.14)	<0.0001
Deficiency Anemia	683 (6.19)	305 (7.98)	0.0002
Alcohol Abuse	224 (2.03)	175 (4.58)	<0.0001
Drug Abuse	268 (2.43)	293 (7.66)	<0.0001

**Matching variable*

4.2.2-II Multivariable Models

Multivariable models tested the association between TRT and incident depression, both independently and after adjusting for sociodemographic, clinical, pharmacological and healthcare factors. Three different models were tested. First model tested the independent association between TRT and incident depression. Second model adjusted for region, education, income, physician visits and prior antidepressant use and any Eixhauser comorbidities that unevenly balanced across the two groups. Sensitivity analyses subsequently adjusted for other mental health conditions and any prescription drugs in the look-back period. Results from multivariable logistic regression are presented in Table 10.

Table 10. Conditional Logistic Regression Analysis

	Unadjusted OR (95% CI)	**Adjusted OR** (95% CI)
Model 2B-I		
>30 days TRT *(Referent=≤30 days TRT)*	1.22 (1.13 1.33)	1.07 (0.97 1.18)

Model 2B-II	
Income	
(Referent=Quartile 1)	
Quartile-2	0.83 (0.73 0.95)
Quartile-3	0.82 (0.70 0.95)
Quartile-4	0.75 (0.63 0.90)
Education	
(Referent=Quartile 1)	
Quartile-2	1.14 (0.99 1.30)
Quartile-3	1.14 (0.98 1.33)
Quartile-4	1.18 (0.98 1.42)
Region	
(Referent=Midwest)	
Northeast	1.04 (0.84 1.29)
South	0.71 (0.63 0.80)
West	0.91 (0.78 1.06)
Elixhauser Comorbidities:	
Congestive Heart Failure	1.09 (0.86 1.38)
(Referent=No Congestive Heart Failure*)*	
Cardiac Arrhythmia	1.09 (0.94 1.26)
(Referent=No Cardiac Arrhythmia*)*	
Pulmonary Circulation Disorders	1.12 (0.80 1.58)
(Referent=No Pulmonary Circ. Disorders*)*	
Peripheral Vascular Disorders	1.24 (1.03 1.48)
(Referent=No Periph. Vascular Disorders*)*	
Paralysis	2.40 (1.43 4.04)
(Referent=No Paralysis*)*	
Other Neurological Disorders	2.25 (1.76 2.87)
(Referent=No Neurological Disorders*)*	
Chronic Pulmonary Disease	1.22 (1.08 1.38)
(Referent=No Pulmonary Disease*)*	
Diabetes Complicated	1.46 (1.24 1.71)
(Referent=No Diabetes Complicated*)*	
Hypothyroidism	1.07 (0.95 1.20)
(Referent=No Hypothyroidism*)*	
Renal Failure	1.11 (0.90 1.36)
(Referent=No Renal Failure*)*	
Liver Disease	1.27 (1.08 1.49)
(Referent=No Liver Disease*)*	
Peptic Ulcer Disease	1.26 (0.83 1.91)
(Referent=No Peptic Ulcer Disease*)*	
HIV/AIDS	1.46 (1.08 1.98)
(Referent=No HIV/AIDS*)*	
Lymphoma	1.03 (0.65 1.63)

(Referent=No Lymphoma*)*	
Metastatic Cancer	1.49 (0.90 2.48)
(Referent=No Metastatic Cancer*)*	
Solid Tumor Without Mets	1.18 (0.92 1.52)
(Referent=No Solid Tumor Without Mets*)*	
Rheumatoid Arthritis/collagen	1.13 (0.94 1.37)
(Referent=No Rheumatoid Arthritis*)*	
Coagulopathy	1.38 (1.07 1.79)
(Referent=No Coagulopathy*)*	
Weight Loss	1.10 (0.85 1.43)
(Referent=No Weight Loss*)*	
Fluid and Electrolyte Disorders	1.26 (1.07 1.49)
(Referent=No Fluid Electrolyte Disorders*)*	
Deficiency Anemia	1.15 (0.96 1.38)
(Referent=No Deficiency Anemia*)*	
Alcohol Abuse	1.71 (1.32 2.21)
(Referent=No Alcohol Abuse*)*	
Drug Abuse	2.15 (1.74 2.67)
(Referent=No Drug Abuse*)*	
Outpatient Visits	
(Referent=1-3)	
4-9	1.30 (1.09 1.55)
≥10	2.19 (1.84 2.62)
Antidepressant Prescription	6.86 (6.23 7.56)
(Referent=No Antidepressant)	

In the unadjusted model, exposure to >30 days of TRT was associated with 22% increased risk of incident depression (Model 2B-I: OR=1.22; 95%CI=1.13 1.33). However, no association between TRT and incident depression was observed after adjusting for additional covariates included in Model 2B-II, i.e., income, education, region, Elixhauser comorbidities, outpatient visits and antidepressant prescription. Analysis of covariates suggested higher income was associated with relatively lower risk of depression whereas educational attainment had no effect on risk of depression. Men were less likely to be diagnosed with depression in the South, relative to men in the

Midwest region. Greater number of physician/outpatient visits was linked to an increased risk of depression (OR for ≥10 visits = 2.19; 95%CI=1.84 2.62). Similarly, having a prescription for an antidepressant drug in the look-back was associated with nearly 7 times increased risk of depression (OR=6.86; 95%CI=6.23 7.56). While cases and controls were matched on Elixhauser comorbidity score, multivariable model 2B-II accounted for any such comorbidities. As shown, peripheral vascular disorders, paralysis, other neurological disorders, chronic pulmonary disease, complicated diabetes, liver disease, HIV, coagulopathy, fluid and electrolyte disorders, alcohol and drug abuse were associated with increased risk of depression.

Overall, we did not find an association between TRT and depression after adjusting for relevant sociodemographic, clinical, pharmacological and healthcare factors. Sensitivity analyses explored this association further.

4.2.2-III Sensitivity Analysis

Two different sensitivity analyses were performed. First sensitivity analysis adjusted for other mental health conditions and any prescription drug use in the look-back period. For this sensitivity analysis, the primary definition of TRT was used.

A second sensitivity analysis examined the effect of additional exposure windows of TRT on risk of depression. Two exposure windows were used, with subsequently greater exposure to TRT: TRT *definition 2*: men were considered exposed if they met the criteria for primary exposure definition and had >=1 TRT prescriptions within each 6 month period prior to the index date, up to 1 year prior to index date; TRT *definition 3*: men were considered exposed if they met the criteria for the primary definition and had

>=1 TRT prescriptions within each 3 month period prior to the index date, up to 1 year prior to index date).

As shown in Table 11 below, no association was observed between TRT and incident depression after adjusting for all covariates in Model 2B-II and prior mental health conditions (OR=1.07; 95%CI=0.97 1.19). This sensitivity analyses further tested the potential effect of prior prescription drug use on the TRT-depression association. In the fully adjusted model accounting for all covariates in Model 2B-II and both prior mental health conditions and prescription drug use, no association was observed between TRT and incident depression (OR=1.04; 95%CI=0.94 1.14). Diagnosis of other mental health conditions in the look-back was associated with nearly 2 fold increased risk of depression (OR=1.99; 95%CI=1.81 2.19). Similarly, use of an additional prescription drug type was linked to a 7% increased risk of depression (OR=1.07; 95%CI=1.06 1.07).

Table 11. Sensitivity Analysis-I

	Adjusted OR* (95% CI)	**Adjusted OR*** (95% CI)
TRT *(Referent=≤30)*	1.07 (0.97 1.19)	1.04 (0.94 1.14)
Any Other Mental Health Diagnosis *(Referent=No Other Mental Health Diagnosis)*	1.99 (1.81 2.19)	2.60 (2.38 2.83)
Any Prescription Drug Use *(Referent=No Prescription Drug Use)*		1.07 (1.06 1.07)

**Adjusted for all covariates in Model 2B-II*

Results from second sensitivity analysis are presented in Table 12. As shown, none of the additional TRT exposure windows were associated with incident depression.

These results suggest that after accounting for relevant social, demographic, clinical and healthcare factors, TRT was not associated with depression. These results should be interpreted with caution given potential limitations associated with an observational study design, including selection bias.

Table 12. Sensitivity Analysis-II

	Adjusted OR* (95% CI)
TRT-Definition 2 **(***Referent=Not Meeting Definition 2 Criterion)*	1.02 (0.92 1.13)
TRT-Definition 3 *(Referent=Not Meeting Definition 3 Criterion)*	1.01 (0.89 1.14)

**Adjusted for all covariates in Model 2B-II+other mental health conditions + any prescription drugs*

4.2.3 Summary

Specific Aim 2 tested two hypotheses. First hypothesis examined the link between untreated hypogonadism and incident depression using a case-control study design. We did not find an association between hypogonadism and depression in the fully adjusted, multivariable models. Sensitivity analyses adjusted for additional clinical and pharmacologic factors and showed a small, borderline significant increased odds of depression. Overall, our findings are contrary to our original hypothesis of potential adverse effects of hypogonadism on mental health broadly and increased risk of depression specifically. We accounted for a variety of social, demographic, clinical, pharmacologic and healthcare factors in this study and did not find a strong, statistically robust link between hypogonadism and odds of depression. Future research should explore the association with consideration for severity of hypogonadism and depression, and possibly greater follow-up times in order to establish causality.

Second hypothesis tested the association between TRT and incident depression in hypogonadal men, using a nested case control study design. We adjusted for a variety of social, demographic, clinical, pharmacologic and healthcare factors to explore the link between exposure to TRT and odds of depression. Further, we required that all men in the final cohort have a diagnosis of hypogonadism. In the fully adjusted, multivariable models, we did not find an association between TRT and incident depression. Our finding is contrary to our original hypothesis, which postulated that TRT might have a beneficial effect on depression and/or depressive symptoms. Sensitivity analyses accounted for other clinical conditions, including other mental health diagnoses and prior prescription drug use however, no association was observed between TRT and depression in these

analyses. These results should be interpreted with caution, given potential design biases including lack of causality, selection bias, information bias and relatively short look-back period. Potential limitations and implications of our findings are discussed further in Chapter 5 (Discussion).

4.3 Specific Aim 3 Results

Results for this specific aim are organized into three sections. First section presents descriptive characteristics and results from Kaplan-Meier analysis. Second section presents results from cox proportional hazard models. Third section presents results from sensitivity analyses.

4.3.1 Descriptive Characteristics

The final sample consisted of 35,280 participants. Of these 5,064 (14.35%) were in the exposed group (>30 days TRT) whereas 30216 (85.65%) were in the unexposed group (<=30 days TRT). Descriptive characteristics of study population by TRT exposure are presented in Table 13.

Men in the exposed group were more likely to reside in the Midwest, be relatively younger and have higher income and education. Further, men in the TRT-exposed group were more likely to receive a prescription for antidepressants in the look-back period and had a greater number of outpatient visits in the look-back period. Elixhauser comorbidity score was evenly distributed across the two groups. However, some differences were found in the distribution of individual comorbidities across the two groups. Specifically, men in the exposed group were more likely to have HIV and less likely to have uncomplicated diabetes, liver disease and peripheral vascular disorders compared to the unexposed group. Analysis of variables included in the sensitivity analysis suggested men in the exposed group received a greater number of prescription medications in the look-back period, compared to their counterparts. No differences were found by mental health

diagnoses between the two groups.

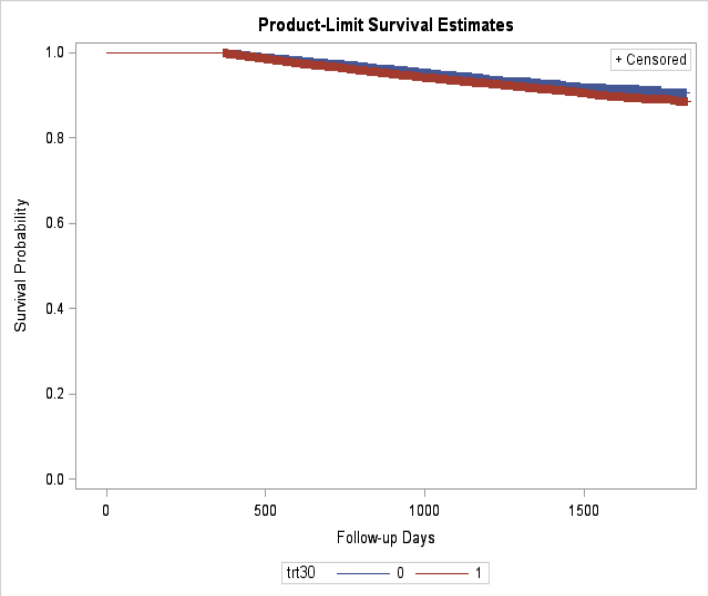
Table 13. Descriptive Characteristics of Study Sample, by TRT Exposure

	Unexposed (%)	Exposed (%)	p
All men	5064 (100)	30216 (100)	
Age			0.02
40-49	1829 (36.12)	11489 (38.02)	
50-59	2271 (44.85)	13333 (44.13)	
60-65	964 (19.04)	5394 (17.85)	
Elixhauser Comorbidity Score			0.19
0	1316 (25.99)	8033 (26.59)	
1	1458 (28.79)	8936 (29.57)	
2	1117 (22.06)	6636 (21.96)	
3+	1173 (23.16)	6611 (21.88)	
Income			<0.0001
Quartile 1	1382 (27.29)	7433 (24.60)	
Quartile 2	1298 (25.63)	7528 (24.91)	
Quartile 3	1199 (23.68)	7633 (25.26)	
Quartile 4	1185 (23.40)	7622 (25.23)	
Education			<0.0001
Quartile 1	1403 (27.71)	7444 (24.64)	
Quartile 2	1342 (26.50)	7578 (25.08)	
Quartile 3	1238 (24.45)	7550 (24.99)	
Quartile 4	1081 (21.35)	7644 (25.30)	
Region			<0.0001
MW	681 (13.45)	4802 (15.89)	
NE	253 (5.00)	1344 (4.45)	
So	3264 (64.46)	18951 (62.72)	
We	866 (17.10)	5119 (16.94)	
Prior Antidepressant Prescription	797 (15.74)	5575 (18.45)	<0.0001
Physician visits			0.01
0	2221 (43.86)	12986 (42.98)	
1-3	1902 (37.56)	10999 (36.40)	
4-9	645 (12.74)	4261 (14.10)	
≥10	296 (5.85)	1970 (6.52)	
Elixhauser Comorbidities:			
Other Mental Health Diagnoses	1166 (23.03)	6919 (22.90)	0.84
Prescription Drugs *(mean; SD)*	7.16 (4.94)	7.57 (5.14)	<0.0001
Diabetes (Uncomplicated)	1008 (19.91)	5287 (17.50)	<0.0001
HIV	39 (0.77)	332 (1.10)	0.04
Liver Disease	242 (4.78)	1234 (4.08)	0.02
Peripheral Vascular Disorders	193 (3.81)	934 (3.09)	0.02

4.3.2 Kaplan-Meier Analysis

Results from Kaplan-Meier analysis are presented in Fig. 16. Over a maximum of 5 year follow-up period, there were a total of 2004 (5.68%) cases of incident depression. 237 (4.68%) patients in the unexposed group developed depression whereas 1767 (5.85%) patients in the exposed group developed depression. The total number of observations censored were 33,276. 14,298 participants were lost to follow-up over the 5 year period.

Fig. 16. Kaplan-Meier Analysis



Test of Equality over Strata		
Test	**Chi-Square**	**Pr > Chi-Square**
Log-Rank	8.0777	0.0045
Wilcoxon	7.7966	0.0052
-2Log(LR)	9.0945	0.0026

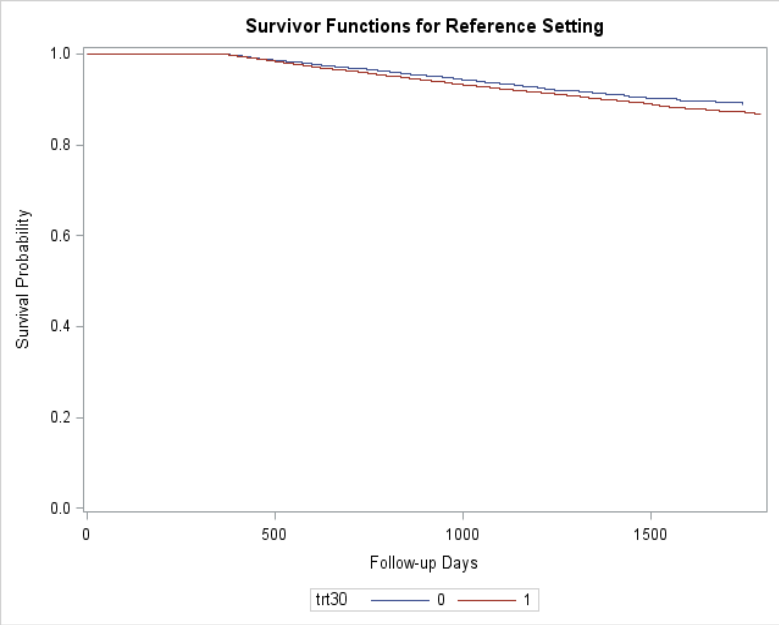
Mean depression free survival time was 1704 days (SE= 2.00). Kaplan Meier curves showed differences in survival rate between TRT users and non-users (Fig. 16). The mean and median survival rate for TRT-exposed group (mean=0.94; median=0.94) was similar to the unexposed group (mean=0.96; median=0.96). The 5-year depression-free survival rate was 0.91 (95%CI=0.89 0.92), i.e., 92% for the unexposed group and 0.89 (95%CI=0.88 0.89), i.e., 89% for the exposed group. As shown by results of Log-

Rank and Wilcoxon statistics, the exposed group had a lower probability of survival, compared to the unexposed group. This finding is examined further in multivariable models. We also assessed failure rates at several different time points during the course of follow-up. The failure rates for the unexposed and exposed groups were 0.03 (95%CI=0.02 0.03) and 0.03 (95%CI=0.03 0.04), 0.07 (95%CI=0.06 0.08) and 0.08 (95%CI=0.07 0.08), 0.09 (95%CI=0.08 0.11) and 0.11 (95%CI=0.11 0.12) at 2 years (730 days), 3.5 years (1278 days) and 5 years (1825 days), respectively. In general, at each follow-up time point, failure probability was higher for the TRT-exposed group, compared to the unexposed group, which corresponds with survival rates for the two groups reported earlier in this section.

4.3.3 Multivariable Cox Proportional Hazard Regression Analysis

Multivariable models adjusted for a variety of sociodemographic, clinical and healthcare factors using cox proportional hazard models. Adjusted survival curves are shown in Fig. 17. Adjusted survival curves exhibited differences in survival probability between the two groups, with a lower probability of survival for the exposed group. Multivariable cox proportional models and sensitivity analyses further explored the relationship with particular attention to the effects of other comorbidities, mental health conditions, prescription drug use and effect of duration of TRT exposure on risk of depression.

Fig. 17. Adjusted Survival Curves



Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	607.7522	23	<.0001
Score	688.5477	23	<.0001
Wald	672.2238	23	<.0001

Primary Analysis

Cox proportional hazard regression models were used to test the association between TRT and depression. Cox models tested for the effects of TRT both with and without covariates. In the unadjusted model, exposure to >30 days of TRT was associated with an increased risk of depression (Unadjusted OR=1.22; 95%CI=1.06 1.39). However, no association between TRT and depression was observed after adjusting for relevant sociodemographic and clinical covariates including age, region, income, education, Elixhauser comorbidities, outpatient visits and prior antidepressant use (Adjusted HR=1.12; 95%CI=0.98 1.28).

Analysis of covariates showed a decreased hazard of depression for the older age group, relative to participants 40-49 years of age. Higher income was associated with decreased risk of depression whereas higher education was associated with slightly higher hazard of depression compared to men with lower income and lower education, respectively. Higher comorbidity scores were associated with increased hazard of

depression (HR for ≥3 comorbidities=1.29; 95% CI=1.12 1.49). Relative to the Midwestern states, there was lower hazard of depression in the southern and western states. Prior antidepressant use was associated with increased hazard of depression (HR=5.54; 95%CI=5.06 6.05); similarly, greater number of outpatient visits was associated with higher hazard of incident depression. Results of multivariable cox regression analysis are presented in Table 14.

Table 14. Multivariable Cox Proportional Hazard Models

	Unadjusted HR (95% CI)	**Adjusted HR (95% CI)**
TRT	1.22 (1.06 1.39)	1.12 (0.98 1.28)
(Referent ≤30 days TRT)		
Age		
(Referent=40-49)		
50-59		0.87 (0.78 0.96)
60-65		0.84 (0.74 0.96)
Income		
(Referent=Quartile 1)		
Quartile-2		0.97 (0.85 1.11)
Quartile-3		0.87 (0.75 1.02)
Quartile-4		0.81 (0.68 0.96)
Education		
(Referent=Quartile 1)		
Quartile-2		1.11 (0.97 1.27)
Quartile-3		1.16 (0.99 1.35)
Quartile-4		1.21 (1.01 1.44)
Region		
(Referent=Midwest)		
Northeast		1.06 (0.85 1.31)
South		0.77 (0.69 0.87)
West		0.85 (0.73 0.98)
Comorbidity Score		
(Referent=0)		
1		1.00 (0.88 1.13)
2		1.09 (0.95 1.26)
≥3		1.29 (1.12 1.49)
Other Comorbidities:		
Diabetes (Uncomplicated)		0.90 (0.79 1.01)
(Referent=No Diabetes)		
HIV		0.07 (0.02 0.27)

(Referent=No HIV)	
Liver Disease	0.91 (0.74 1.12)
(Referent=No Liver Disease)	
Peripheral Vascular Disease	0.86 (0.68 1.10)
(Referent=No Peripheral Vascular Disease)	
Antidepressant Prescription	5.54 (5.06 6.05)
(Referent=No)	
Outpatient Visits	
(Referent=0)	
1-3	1.25 (1.13 1.39)
4-9	1.35 (1.19 1.54)
≥10	1.34 (1.12 1.59)

4.3.4 Sensitivity Analysis

Sensitivity Analysis-I

Sensitivity analysis-I assessed the effects of additional covariates including prior prescription drug use and other mental health conditions on the TRT-depression association. Results from this sensitivity analysis are presented in Table 15.

As in the previous analysis, no association was observed between TRT and depression after adjusting for other mental health conditions (HR= 1.13; 95% CI=0.98 1.29). We subsequently adjusted for prior prescription drug use and found no association between TRT and depression (HR=1.15; 95%CI=1.00 1.31; p=0.05). Both prior mental health conditions and prescription drug use were associated with increased hazard of depression (HR=1.87; 95%CI=1.70 2.05 and HR=1.08; 95%CI=1.07 1.09, respectively). Subsequent analyses analyzed this finding further by examining the effect of different TRT exposure windows on risk of depression.

Sensitivity Analysis-II

Evidence from prior studies suggests ≥90 days of exposure to TRT might be required to achieve clinically meaningful effects on health in general and mental health in particular.[134] In order to assess possible variation in effects of TRT by duration of exposure, the following categories of exposure were used: 31-90, 91-180, 181-366 days (referent=≤30 days). Results from the analysis are presented in Table 16. This analysis also adjusted for other mental health conditions both during look-back period and during study follow-up.

Overall, no association between TRT and depression was observed at lower windows of exposure (HR for 31-90 days=1.07; 95%CI=0.91 1.25 and HR for 91-180 days=1.14; 95%CI=0.97 1.33) of TRT. However, a small, borderline significant increased hazard of depression was observed for the 181-366 day exposure category, which is contrary to our original hypothesis (HR=1.19; 95%CI=1.03 1.38).

Our finding might be attributed to issues related to study design which are discussed in detail in the discussion section. First, we did not assess TRT dosage. Second, in this study exposure to TRT was restricted to within the first year after TRT initiation. It is possible that a relatively short exposure window contributed to the observed finding. It is also possible that some men did not take TRT for a continuous period during the exposure window or discontinued TRT prior to achieving eugonadal testosterone levels, which is a pre-requisite for observing beneficial effects on physical or mental health.

Current evidence from the literature suggests a minimum duration of exposure to TRT for beneficial effects on depressive symptoms. This exposure window has been reported as a minimum of 3-6 weeks whereas 18-30 weeks exposure has been suggested for maximal improvements in depressive symptoms.[134] However, one small RCT of older

men (60-75 years) failed to find an effect of higher doses of TRT on mood. Similarly, a meta-analysis of 27 RCTs demonstrated a dose-response relationship between TRT and improvement in depressive symptom, with higher doses achieving greater change in depressive symptoms.[29] In the same meta-analysis, the authors failed to find an association between TRT duration and depressive symptoms. Further research is required to explore TRT as a time-dependent covariate and examine the association using longer exposure windows and longer follow-up times.

Table 15. Sensitivity Analysis-I

	Adjusted HR* (95% CI)	**Adjusted HR**** (95% CI)
TRT *(Referent=≤30 days)*	1.13 (0.98 1.29)	1.15 (1.00 1.31)[±]
Any Other Mental Health Diagnosis *(Referent=No Other Mental Health Diagnosis)*	1.40 (1.27 1.54)	1.87 (1.70 2.05)
Any Prescription Drug Use *(Referent=No Prescription Drug Use)*		1.08 (1.07 1.09)

Table 16. Sensitivity Analysis-II

	Adjusted HR**	**95% CI**
TRT		
(Referent≤30 days)	1.07	0.91 1.25
31-90	1.14	0.97 1.33
91-180	1.19	1.03 1.38
181-366		

**Adjusted for age, education, income, region, comorbidity score, outpatient visits, antidepressant use, other mental health conditions*
**Adjusted for age, education, income, region, comorbidity score, outpatient visits, antidepressant use, other mental health conditions, any prescription drug use*
[±]p=0.05

4.3.5 TRT & Depression: Variation by Age or Comorbidity Status

We further tested for potential variation in the effects of TRT on depression by age or comorbidity status. In order to test for this, interaction terms were created for TRT*Age and TRT*Comorbidity Score. Each interaction terms was subsequently and separately added to a regression model with TRT as the primary exposure variable and depression as the outcome. Results from this analysis are presented in Tables 19 and 20.

As shown in the tables below, none of the tested interaction terms were statistically significant, which suggested that the effect of TRT on depression does not vary by either age or patient's comorbidity status. Since neither interaction term was statistically significant, regression models were not stratified for further analysis.

Table 17. TRT*Age Interaction*

Analysis of Maximum Likelihood Estimates			
Parameter	DF	Chi-Square	*p*
TRT	1	4.07	0.04
Age	2	0.32	0.85
TRT*Age	2	1.99	0.37

Table 18. TRT*Comorbidity Score Interaction**

Analysis of Maximum Likelihood Estimates			
Parameter	DF	Chi-Square	*p*
TRT	1	3.60	0.06
Elixhauser Score	3	0.67	0.88
TRT*Elixhauser Score	3	1.42	0.70

**Adjusted for education, income, region, unbalanced Elixhauser comorbidities, outpatient visits, other mental health conditions, any prescription drugs*
***Adjusted for education, income, region, unbalanced Elixhauser comorbidities, outpatient visits, other mental health conditions, any prescription drugs*

4.3.6 Summary

In this study, we tested the association between TRT and depression using a retrospective cohort study design. We adjusted for a variety of social, demographic, clinical and healthcare factors to explore the link between exposure to TRT and risk of depression and ensured that all men in the final cohort were hypogonadal. However, in the fully adjusted model, we did not find an association between TRT and depression. Our finding is contrary to our original hypothesis, which postulated that TRT might have a beneficial effect on depression and/or depressive symptoms. A variety of sensitivity analyses explored possible effects of other clinical conditions, including other mental health conditions and prescription drug use. We also examined additional TRT exposure windows. No association was observed between TRT and depression in our main analysis; however, we observed a small increased risk of depression associated with TRT in the sensitivity analysis which was limited to >180 day exposure category and might be attributed to several design issues and potential selection bias. Our results should be interpreted with caution, given methodological challenges discussed in the preceding section. In spite of the limitations, we present the first piece of evidence from a large, nationally representative, real-world sample of middle-aged and older men in the US. Our findings and the highlighted methodological issues pertaining to TRT research will further the understanding of the link between TRT and depression, and inform future research on the topic to achieve greater understanding of the effects of TRT on these and related health outcomes.

Chapter 5

Discussion

This dissertation presents the first piece of evidence of TRT prescription trends and the association between hypogonadism, TRT and depression from a large, population-based, nationally representative sample of middle aged and older adults in the US. This dissertation used data from one of the nation's largest commercial insurance databases and adds to current knowledge of the risk of depression associated with hypogonadism and TRT. Further, this dissertation adds to a growing body of literature evaluating recent trends in TRT prescription and, to the best of our knowledge, presents the first piece of evidence assessing TRT prescription patterns in depressed men over the past 15 years.

5.1 TRT Prescription Trends in Middle Aged and Older Men with Depression

Major Findings in the Context of Existing Research

This study assessed TRT prescription trends in middle aged and older men from 2002-2016. This study assessed TRT prescription trends overall and in men with depression. Further, prescription trends were analyzed by age in the overall sample and in depressed men, and by hypogonadal status in depressed men. In line with our hypothesis, we found that for each given calendar year, TRT prescription rates were higher for depressed men, compared to non-depressed men. The increase was greatest in the 2002-2012 period, after which a decline in prescription rates was observed. Further, TRT prescription rates increased by nearly 2.5 fold overall from 2002-2016 while the increase during the same period was less remarkable for depressed men-TRT prescription rates increased by 1.35 fold for depressed men. We further observed considerable variation in

TRT prescription by age and hypogonadal status. Our results confirmed our hypotheses that TRT prescription patterns vary by age and hypogonadal status in depressed men.

Overall, our findings support current evidence on TRT prescription patterns in the US and globally. The US has seen one of the sharpest increases in TRT prescription rates overall in the industrialized world over the past decade.[31] During the same period, TRT prescription rates have increased by 2-4 fold in middle aged and older men in the US.[18,33-37] However, to the best of our knowledge this is the first large-scale, population-based study to assess TRT prescription trends in middle aged and older men with depression.

Relatively few studies have assessed TRT use in men with mental health diagnoses. One large study of over 63,000 men aged ≥18 years enrolled in a large commercial health plan and Medicare Supplemental Insurance reported 7.4% of men receiving TRT had a prior diagnosis of depression.[45] Another study of men ≥20 years enrolled in the Veterans Administration (VA) reported 23% of men initiating TRT had a diagnosis of major depression while 8.4% had a diagnosis of anxiety.[46] However, both these studies used data for 2-3 years in order to examine TRT predictors in the respective study populations. Similarly, prior studies have assessed TRT prescription trends in middle aged and older men;[18] however, to the best of our knowledge, no large-scale study has assessed TRT prescription using in middle aged and older depressed men over a period of nearly 15 years.

The trends in TRT prescription reported in this study are similar to reports from prior studies. Baillargeon et al.[18] reported an over 3 fold increase in TRT prescription rates in men ≥40 years from 2001-2011, which is similar to the 3.2 fold increase observed in our study from 2002-2012. However, the overall increase in TRT prescription over the

entire study period was relatively smaller compared to findings from some of the other studies,[18,102] which can be attributed to different time period and different study populations, i.e., men aged 40-65 years in this study vs men≥30 years,[104] ≥40 years[18] or men≥18 years.[102] We assessed TRT patterns both before and after increased FDA surveillance of testosterone products and communication/warnings (issued in 2014) regarding possible adverse cardiovascular effects of TRT, which might have impacted our results. Evidence from prior research suggests TRT prescription rates declined on/after 2014.[104,168] One study of men ≥30 years reported that TRT prescription rates declined by 48% and 62% in established and new users, respectively from 2013-2016, [104] which is similar to the 57% relative decrease in TRT prescription in depressed men observed in our study. However, the increase from 2002-2012/13 observed in our study was relatively smaller compared to that reported by the authors in the aforementioned study (3.2 vs 4.5 fold), which might be attributed to differences in cohort age (40-65 yr vs ≥30 yr) and inclusion/exclusion criteria, including diagnosis of depression.

Our results were comparable to findings from other studies that examined TRT prescription patterns during similar time periods. Two studies assessed TRT prescription trends in broad age groups of US adults during 2009-2013 using VA and outpatient pharmacy data, respectively and reported 78-183% increase in TRT prescription during this period, which is comparable to our findings.[103,155] Similarly, another study using VA data analyzed TRT prescription trends from 2008-2016 and found less than 1.5% increase in TRT prescription overall during this period.[168] We also reported a significant increase in TRT prescription from 2002-2012 and a considerable decrease from 2012-2016, which is similar to patterns observed in other studies-both in terms of a considerable increase in

the first half of the study period (2002-2012)[18] and the drop in the second half (2012-2016).[168]

This study presents the first piece of evidence regarding TRT prescription patterns in middle aged men with depression. Few studies have assessed prevalence of mental disorders and other comorbidities in TRT users; however no study to date has assessed TRT prescription trends over time in men with depression. Two studies of men ≥18 years using commercial insurance and VA data examined TRT prescription practices and reported approximately 7-8% prevalence of depression in TRT users.[155,169] Another study of male veterans reported 23.4% prevalence of major depression in men initiating TRT.[155] However, none of these studies assessed incident TRT prescription patterns in depressed men. The prevalence of depression in our study (1.55% to 3.42%) was lower compared to prevalence reported in the aforementioned studies which might be attributable to several reasons. First, our study population included a much narrower age range i.e. 40-65 years compared to the much broader age range in the above mentioned studies. Second, we used a strict definition for diagnosis of depression (≥1 inpatient or ≥2 inpatient diagnoses of depression within a 12 month period) and only included conditions where depression was the primary diagnosis, which might have impacted the final sample size for depressed men. Third, we used data from a population-based sample of middle aged and older men, in contrast to other target populations which are not generalizable to the entire US population, such as VA.

We found that for each given calendar year, TRT prescription rates were considerably higher among depressed men, compared to non-depressed men. This finding is expected, given the overlap between “depressive” and “hypogonadal” symptoms and

subsequent likelihood of initiating TRT. Further, our finding resonates with prior research showing an increased risk of TRT use associated with poor psychological health.[170] This finding has several policy implications. First, it highlights substantially higher prescription rates in men with a leading mental illness with subsequent implications for greater monitoring of health effects in this population. Second, it underlines the importance of greater understanding of mental health effects of TRT on depression as well as other mental health conditions since depression might co-occur with other physical and mental illnesses. Similar to prior reports, we found a significant increasing prescription trend from 2002-2012 and a decreasing trend thereafter. This pattern was observed for both depressed and non-depressed men. However, the increase overall was slightly greater for the non-depressed group. As reported previously, the sharp drop in TRT prescription rates around 2013-2014 might be associated with FDA communications regarding greater monitoring of TRT prescription, use and health effects.

5.1.1 TRT Prescription Patterns by Age and Hypogonadal Status in Depressed Men

Major Findings in the Context of Existing Research

We also analyzed TRT prescription trends by age and hypogonadal status and found considerable variation in prescription patterns based on these variables. While we observed a similar increasing-decreasing trend for all age groups as observed in earlier analyses, we found that prescription rates were higher for older men in general and in particular for men aged 50-59 years, compared to men in their 40s for each year from 2002-2011 while a nearly paradoxical trend was observed from 2012-2016 with lower rates for the 60-65 age group and higher rates for the younger age groups. The age

differences in TRT prescription reported here are similar to previous reports, at least in the 2002-2011 period. Other studies that assessed prescription patterns beyond 2010-2011 did not assess differences by sub-categories within the 40-65 year range.[171] We also observed that prescription rates increased most dramatically for the 40-49 year age group overall, with a nearly 4-fold increase from 2002-2012. However, prescription rates were higher overall for the 50-59 age group for each given year. It is to be pointed out that men start to experience "andropause" in their 40s and testosterone levels decline thereafter. In lieu of this, our results suggest an increasing trend in TRT use in men in their 40s and 50s- a time when men start to experience symptoms of testosterone deficiency. This finding highlights the need for greater monitoring of TRT use and effects on mental health in men in this age group, particularly in men who have a diagnosis of depression.

We also assessed TRT prescription patterns by hypogonadal status in depressed men and as expected, we found that for each given calendar year prescription rates were considerably higher among hypogonadal vs eugonadal depressed men and varied from a maximum of 19% to a low of 9% across study years. This finding is consistent with prior research that suggests men who initiate TRT are likely to have other comorbid medical conditions including sexual and psychological dysfunction.[102,155]

Ours is the first large-scale study to assess prescription trends by hypogonadal status in depressed men which adds to limited evidence regarding TRT initiation and use by prior hypogonadal status. Walsh et al. (2014) examined TRT treatment trends in male veterans aged 40-89 years in the Pacific Northwest by hypogonadal status and reported that percentage of men treated with testosterone decreased from 31% in 2002 to 28% in 2011.[172] In our study, TRT prescription rates in depressed men with a diagnosis of

hypogonadism men saw a similar decreasing trend from 2002-2016; however, prescription rates in our study were lower, which might be attributed to a narrower age range and a much broader target population, as compared to veteran population. Similarly, Canup et al[149] used data from the Department of Defense Pharmacy Data Transaction Service to report that between 2007 and 2011 both testicular hypofunction diagnosis and testosterone prescriptions increased considerably in male recipients, however testosterone prescriptions per hypogonadism diagnosis decreased during the same period. These findings, coupled with the overall increased in TRT use in depressed men reported earlier suggest possible prescription and use of TRT without documenting a laboratory test or clinical diagnosis for testosterone deficiency. It is also possible that these results reflect a possible increased caution and awareness regarding TRT prescription in hypogonadal men with comorbidities.

Results from recent studies suggest that a significant proportion of men receiving TRT might not have a laboratory-confirmed diagnosis of hypogonadism[102] Using VA data for 111,631 male veterans from 2009-2012, Jasuja et al. (2015) reported that nearly 60% of TRT initiators did not have an ICD-9 code for diagnosis of hypogonadism.[155] Future research should examine testosterone/hormone testing practices to establish a diagnosis of hypogonadism prior to initiating TRT in men with depression or other mental health conditions.

5.1.2 Limitations and Strengths

This study presents the first piece of evidence of TRT prescription trends in a large, real-world, population-based sample of middle aged and older men with

depression. This study had several notable strengths including large sample size for each year of study, data from over a decade and assessment of variation in TRT patterns by age and hypogonadal status over time. While there is considerable research on the effects of TRT on physical health, much less is known about the effects of TRT on mental health, especially in middle aged and older hypogonadal men. This study highlights a high prevalence of TRT use in men with depression, which in turn underline the importance of better understanding of the effects of TRT on depression in this population.

Our findings should be interpreted in light of a few limitations. First, we assessed TRT prescription trends over time, we did not account for additional covariates such as other medical conditions that might have impacted TRT prescription for a given year and/or over time. However, we adjusted for hypogonadism and age when testing for differences in trend between the depressed and non-depressed groups over time. Second, this study used data from a commercial health insurance database, which is prone to errors, omissions and possible under-reporting of mental health conditions. Third, this study only includes data for men 40-65 years of age and results cannot be generalized to other age groups. Future studies should assess trends in TRT prescription in men with co-occurring mental health conditions and explore other sociodemographic predictors of TRT.

5.2 Hypogonadism and Depression

Major Findings in the Context of Current Research

This study assessed the association between untreated hypogonadism and incident depression in a large, nationally representative sample of middle aged and older men. In this matched case control study of 39,548 men aged 40-65 years, we did not find a consistent association between hypogonadism and depression. While no association was observed in the fully adjusted main model, sensitivity analyses showed hypogonadism was associated with a weak, borderline significant increased odds of depression; however, we did not observe a strong, statistically robust odds of depression in hypogonadal men. These finding are in contrast to our original hypothesis of increased risk of depression associated with hypogonadism.

In this study, we adjusted for a variety of sociodemographic and clinical risk factors that might confound the relationship between hypogonadism and depression. Sensitivity analyses further accounted for additional pharmacologic and clinical risk factors including prior prescription drug use and other mental health conditions. In order to ensure comparability of cases and controls, we matched the two groups on age, comorbidity status and index date. No association was observed between hypogonadism and incident depression in the fully adjusted primary model (2A-II) that accounted for income, education, region of residence, physician visits and prior antidepressant use. After adjusting for additional covariates including other mental health conditions and prescription drug use in the sensitivity analyses, a weak, statistically borderline association was observed. Overall, hypogonadism was not consistently associated with increased odds of depression. To the best of our knowledge, this is the first large scale

study of a nationally representative sample of middle-aged men to investigate the association between hypogonadism and depression.

Our findings are in contrast to prior studies on this topic. In a retrospective cohort analysis of 278 men ≥45 years of age, Shores et al.[9] found a 2-year depression incidence of 21.7% in hypogonadal men vs 7.1% in eugonadal men, with an adjusted hazard ratio of 4.2 (95%CI=1.5-12.0). Similarly, in a study of 157 men with erectile dysfunction, Makhlouf et al.[88] reported that men with hypogonadism have nearly 3 times increased risk of depression, compared to eugonadal men (adjusted OR=3.13; p=0.005).[88] Another study of 116 men from the Finnish National Population Register reported nearly 5 times increased risk of clinically significant depression in hypogonadal men compared with other men.[91] Results from two population based studies of older men[86,95] found an inverse association between testosterone levels and depressive symptoms. However, majority of current evidence is based on studies of small samples of men, specific subpopulations of hypogonadal men or correlations between testosterone levels (i.e. not clinically defined hypogonadism) and depression. Further, there is considerable variation in inclusion/exclusion criteria including age range and definition of hypogonadism among existing studies. To the best of our knowledge, no study to date has assessed the hypothesized association in a large, nationally representative sample of middle aged men in the US.

In spite of the contrasting findings reported above, our findings are similar to a few studies that did not find an increased risk of depression in men with hypogonadism or low testosterone levels.[7] One large study of nearly 3,000 men and women aged 70-79 years reported that free testosterone levels had an inverse relationship with depression in

women but not men. Similar to our findings, the authors reported a borderline significant inverse association between total testosterone and depression in men.[95] Similarly, another study (n=236) of men ≥70 years found no association between free testosterone levels and depression, as measured by the Geriatric Depression Scale (GDS).[173] One small study of elderly men (n=108 for men) and women with a chronic stable condition receiving nursing and rehabilitation care did not find an association between either free testosterone or total testosterone, and depressive symptoms (as measured by the GDS).[174] However, as pointed out these studies included elderly men above 70 years of age. It is important to point out that the potential link between hypogonadism and depression can be confounded by a variety of clinical factors in the elderly, including disability, frailty and other medical comorbidities in this age group, compared to a younger population. Further, results from this age group specifically cannot be extrapolated to middle aged and older men. Halabi et al. (2011)[175] investigated the link between hypogonadism and depression in men with COPD and reported that after adjusting for a variety of clinical and sociodemographic factors, no association was observed between a diagnosis of hypogonadism and depression. However, the authors only included 104 men and all had a diagnosis of COPD, which suggests that results from a small sample of COPD patients cannot be generalized to middle aged or older men in the US.

This study adds to current evidence on the topic by addressing some of the limitations of available studies. We used a rigorous matching criteria to ensure comparability of cases and controls and adjusted for a variety of risk factors that might act as potential confounders of the hypogonadism-depression association. In addition, we used a clear ICD and CPT code based definition for both cases and controls. This study

adds significantly to current literature by presenting the first piece of evidence regarding the association between hypogonadism and depression in a nationally representative sample of middle aged men in the US and the first large scale, population based study of middle aged men to test the hypothesized association using a strict ICD and CPT code based criteria for clinical diagnosis of hypogonadism and depression. Prior studies have investigated the hypogonadism-depression link in older men or across broad age ranges. However, ours is the first large scale study to assess the potential association in middle aged men specifically. As men start to experience andropause, it is important to better understand the effects of hypogonadism on mental health.[90] Prior studies have shown beneficial effects of testosterone replacement therapy on mental health. If detected early and appropriately treated, some of the adverse effects of hypogonadism might be potentially prevented or reversed, including its effects on depression.[23,24,31]

This study used a variety of statistical techniques including matching on key demographic and clinical factors to control for potential confounders and reduce covariate imbalance among cases and controls. Multivariable regression models adjusted for a number of sociodemographic and clinical factors including socioeconomic status, comorbidities, healthcare utilization. Sensitivity analyses further adjusted for additional risk factors such as other mental health conditions and prescription drug use. Overall, our results did not show a strong association between hypogonadism and depression.. Sensitivity analysis showed a weak association with a small increased odds of depression; however, the effect size estimates reported in these analyses are smaller compared to some of the previously published studies on this topic.[9,88]

In this context, it is important to acknowledge important differences in study design, age group, inclusion/exclusion criteria and other methodological techniques that might have contributed to such differences. First, we used a strict matching criteria to reduce potential covariate imbalance between cases and controls and make the two groups comparable. Second, we adjusted for a variety of sociodemographic, clinical, pharmacologic and healthcare utilization variables which attenuated the association in the multivariable models. Third, this study only included men within a narrow age range, i.e., 40-65 years. Since severity of hypogonadism increases with age, pathological effects of hypogonadism might be less severe for middle vs older age groups. Fourth, we excluded men with prior diagnosis of depression or psychosis, which reduced the overall sample size for cases. Fifth, we confirmed the diagnosis of hypogonadism with a CPT code for laboratory test for testosterone levels. However, we did not include laboratory values to determine severity of hypogonadism. It is evident from prior studies on this topic that greater severity of hypogonadism or deficiency of testosterone is linked to an increased risk or severity depression.[7,86] However, given our study design, we were not able to account for hypogonadism severity. Sixth, these results must be interpreted in light of potential selection bias, especially given observational study design. Men might either choose to or undergo a laboratory test for testosterone levels for a variety of reasons other than mental health issues. Further, these men might have different clinical and sociodemographic profiles compared to men who choose not to. These and other issues might increase the risk of selection bias, which might have impacted our findings.

While we adjusted for a variety of medical conditions, multivariable models did not adjust for anxiety disorders. Evidence from prior studies suggests that anxiety might

co-occur with depression.[176] Further, anxiety disorders have been shown to be associated with hypogonadism. One study of hypogonadal men found increased risk of anxiety disorders associated with hypogonadism.[11] Similarly, anxiety disorders might increase the risk of depression.[177,178] Hence, anxiety might fall in the causal pathway between hypogonadism and depression, and act as a mediator of the hypothesized association. Since the original intention of this study was to test the association between hypogonadism and depression, we restricted our analysis to testing the primary hypothesis of an association between hypogonadism and depression. While we did not adjust for anxiety, we accounted for other major mental health conditions. Future research should assess anxiety and depression possibly as a combined outcome. Further, future studies should examine the potential role of anxiety as a mediator of the hypogonadism-depression association.

We adjusted for a variety of potential confounders of the hypogonadism-depression association, including socioeconomic, demographic, clinical, pharmacologic and healthcare factors. It is possible that more than one covariates included in the multivariable models were measuring the same (or similar) underlying construct and as a result, were collinear. For example, in this study we adjusted for both income and education, which are both markers for socioeconomic status. Similarly, we matched our cases and controls on Elixhauser comorbidity score and also adjusted for any other comorbidities that were unbalanced across the two groups, which might have resulted in collinearity issues since the sicker patients are more likely to have "other" comorbidities. Further, we adjusted for other mental health conditions and prior prescription drug use. It is possible that men with other mental health conditions were more likely to receive

medication for other conditions, resulting in possible collinearity issues between the two variables. It is also possible that a diagnosis of hypogonadism correlated with other factors such as physician visits or antidepressant use (i.e., men more likely to see a physician were more likely to receive a diagnosis), which might have diluted the effect of one of these variables on the dependent variable (depression). While collinearity might inflate parameter variance, it might also make parameter estimates less accurate and possibly unstable.[179] While the assessment of the magnitude of collinearity and its potential impact on parameter estimates was beyond the scope of this dissertation, future epidemiological studies should explore possible collinearity effects, especially when simultaneously adjusting for a relatively large number of covariates.

As discussed above, the observed association between hypogonadism and depression was attenuated significantly after adjusting for relevant covariates in the main model and any prescription drug use in the sensitivity analyses. In separate analyses (Appendix: Table 7), we found that the observed association was no longer statistically meaningful after inclusion of antidepressant use in the main model. This finding suggests a potential mediating role of antidepressant use and any prescription drug use in the hypogonadism-depression association. It is possible that men with greater severity of hypogonadism were more likely to receive antidepressant prescription due to "depression-like" symptoms, compared to eugonadal men or men with relatively mild hypogonadism. Further, men with more severe hypogonadism might have more severe or treatment-resistant depression; in turn, antidepressant use in this group of men might be associated with little or no resolution in depressive symptoms;[180] hence, antidepressant use might appear as a mediating factor in the hypogonadism-depression pathway.

Further, hypogonadal men might be more likely to receive other prescription drugs due to hypogonadism- associated comorbidities,[53,61] compared to eugonadal men. Certain prescription drugs might increase the risk of depression and it is likely that a few prescription drugs worsened depressive symptoms in men included in this study through potential adverse events.[181,182] Further, it is known that certain drugs including immunosuppressives, antipsyhcotics and few antidepressants have adverse effects on sexual function and spermatogenesis.[183–185] Men receiving these and other drugs with potential negative effects on sexual function might worsen hypogonadal symptoms and in turn, increase the risk of depression. Future studies should investigate potential adverse events and drug-drug interactions in hypogonadal men.

5.2.1 Limitations and Strengths.

Our study has a few limitations. First, it is a case control study and cannot establish causality. Second, we confirmed the ICD-based diagnosis of hypogonadism with a CPT code for a laboratory test for testosterone levels. Hence, there might be potential selection bias resulting from differences in proportion of cases and controls who undergo such testing. Third, patients might self-select into getting a laboratory test or they might undergo a laboratory test for a different condition. However, we tried to minimize the latter by ensuring patients underwent testosterone laboratory testing prior to receiving an ICD code for diagnosis of hypogonadism. Fourth, this study used administrative claims data, which might suffer from errors, omissions, misreporting and under-reporting, in particular for mental health conditions. Fifth, this study only focused

on middle-aged men. Hence, our findings cannot be generalized to older or younger hypogonadal men.

It is also important to acknowledge the limitation of the zip code variable included in this dissertation. We used 5-digit residential zip codes to create four distinct regions for CDM enrollees (Northeast, Midwest, South, West). However, some subjects had >=1 residential zip codes, which were concatenated randomly without a logical sequence, making the resulting zip code difficult to use and interpret. Later, CDM released a look-up table to identify the most populous zip code for the concatenated zip codes. Subsequently, we updated our data with the most populous zip code. We used the most current approach to address this issue; however, the most populous zip code might not necessarily be an enrollee's most current zip code and hence it might not be an accurate representation of an enrollee's residential location. Zip code/region was not a primary predictor in our models and was used as a covariate in multivariable models. However, studies analyzing region as a primary predictor should pay particular attention to coding/classification of this variable, including implications for any observed variation in the measured outcome. This is an inherent limitation of the CDM dataset and must be acknowledged by future studies using this variable.

In spite of the limitations, our study has a number of strengths including large sample size, nationally representative cohort of middle-aged men, strict matching criteria, adjustment for a number of potential confounding factors and well defined criteria for definition of hypogonadism and depression. This study provides the first piece of evidence of the potential link between hypogonadism and depression in a large, representative sample of middle aged men.

5.3 TRT and Depression

This dissertation analyzed the association between TRT and depression using two different study designs i.e., nested case control and retrospective cohort. This section presents an overview of major findings and relevant limitations separately for the two study designs and subsequently discusses major implications and future directions.

5.3.1 Nested Case Control Design (Specific Aim 2B)

Major Findings in the Context of Current Research

This study analyzed the association between TRT and incident depression in a large, nationally representative sample of middle aged and older men. We found that TRT was not associated with incident depression after adjusting for relevant sociodemographic, clinical and healthcare factors. Our results were in contrast to our original hypothesis of protective effect of TRT on depression in hypogonadal men. This is the first large-scale, population-based study to study this relationship in middle aged and older men, accounting for nearly 30 medical conditions and a variety of sociodemographic and healthcare factors. While prior evidence from the literature suggests a possible protective influence of testosterone on depression and depressive symptoms, we did not find such an association in this study. In order to assess the robustness of our findings, we performed a variety of sensitivity analyses. In addition, we adjusted for a variety of covariates in our primary model (2B-II). First, in addition to sociodemographic variables and a variety of Elixhauser comorbidities, we adjusted for healthcare (outpatient visits) and prior antidepressant use. Second, we adjusted for other mental health conditions and prior prescription drug use in the look-back period. Third,

we examined potential effects of duration of TRT using different TRT exposure windows. However, none of the analyses showed a statistically meaningful relationship between TRT and depression.

Our findings are in contrast to evidence from prior studies that showed a positive effect of TRT on depressive symptoms. Predominant evidence from prior RCTs suggests a beneficial impact of TRT on depressive symptoms.[23,29,31] One systematic review and meta-analysis of 12 RCTs found protective effects of TRT and reduced risk of depression associated with TRT use.[23] Similarly, a large meta-analysis of 27 RCTs found significant improvements in depression associated with TRT compared to placebo, with a clinically meaningful reduction in depressive symptoms comparable to or even better than efficacy of pharmacologic agents for treatment of depression.[29] The meta-analysis also reported a dose-response relationship between TRT and depression, with greater improvements in depressive symptoms associated with larger doses of TRT. Another meta-analysis of TRT in hypogonadal men reported an overall beneficial effect of TRT on depression.[31] Our results must be interpreted with caution in light of potential selection bias and other limitations inherent to study design which might have impacted our results.

First, ours was an observational study design and results should be interpreted in light of potential selection bias. It is possible that a certain proportion of men either "self-selected" into receiving TRT or were selected to receive testosterone by their clinician. These men might be sicker or have more severe depressive symptoms compared to men who did not receive TRT. Further, these men might have opted for TRT for other intended outcome such as improvements in muscle mass/strength or energy which might have impacted their decision to continue or stop therapy. It is also possible that a

significant percentage of men might have initiated TRT possibly for improvements in physical health or "hypogonadal symptoms" in general and not necessarily for intended improvements in depression or other specific mental health outcomes. In the absence of stringent guidelines for TRT prescription and the definition of an ideal candidate for TRT, some of the null findings might be attributed to selection bias. It is also possible that a proportion of men did not receive TRT based on other clinical conditions or concerns regarding effects of TRT on mental or physical health. It is also possible that some men with mild hypogonadism did not receive TRT to help with "andropause," which might have affected some of our findings.

Second, we did not take into account the number of days of continuous TRT use prior to depression diagnosis. It is possible that men took TRT for a certain period and then discontinued it before possibly taking it again. Third, we did not include laboratory values for testosterone levels in our definition of hypogonadism. It is possible that at least a few men with borderline hypogonadism stopped TRT after improvements in testosterone levels shortly after initiating TRT. Fourth, we did not compare endogenous testosterone levels for the exposed and unexposed groups. It is possible that a certain proportion of men who received TRT experienced some improvement in testosterone levels but failed to achieve eugonadal status. Fourth, we did not account for severity of hypogonadism in our cohort. It is possible that any improvements in depressive symptoms were more prominent in men with relatively less severe hypogonadism, compared to more extreme testosterone deficiency.

In this context, Khera et al. (2012)[39] assessed the effects of TRT on depressive symptoms in 849 hypogonadal men over a 12 month period using data from a

prospective, observational registry-Testim Registry in the United States (TRiUS)-one of the few observational studies to assess the relationship between TRT and depression in hypogonadal men. This study reported significant improvements in depressive symptoms with TRT; however, certain differences need to be pointed out. First, the authors used laboratory values to define hypogonadism and categorize hypogonadism by severity based on testosterone levels. Second, the authors monitored changes in testosterone levels over time and demonstrated that improvements in reported depressive symptoms corresponded with improvements in measured testosterone levels over time, including a statistically significant negative correlation between testosterone levels and depressive symptoms. Third, the authors reported that clinically meaningful improvements in depressive symptoms were seen only in men with low-normal to normal testosterone levels and men who were taking antidepressants and were not seen in men with lower testosterone levels (<250 ng/dl). In our study, we did not include laboratory values for testosterone levels, which limits our ability to comment on the association between hypogonadism severity. Further, case control study design did not allow for monitoring of testosterone levels after initiation of TRT i.e., normalization of testosterone levels; hence, the association between testosterone normalization and risk of depression cannot be established.

In spite of the challenges noted above, our results are similar to findings from a few RCTs that did not find an association between TRT and depression. Zarrouf et al. (2009) conducted a meta-analysis of RCTs assessing the effects of TRT on depression and reported that while the overall effect of TRT on depression was protective in hypogonadal men, few RCTs did not find an association.[31] One study of men with

refractory depression failed to find a statistically significant association between TRT and depression, using Beck Depression Inventory (BDI) scale.[24] Another RCT of hypogonadal men did not find statistically meaningful differences between the effects of TRT or placebo on depression, as measured by the HAM-D (Hamilton) scale.[25] However, both these studies had very small sample sizes and included men with refractory depression. Further, the meta-analysis reported considerable differences in the effects of TRT by route of administration, reporting a reduced risk of depression in men receiving testosterone gel but no overall effect in men receiving testosterone injections. It is possible that the effects of TRT in our study varied by route, however we included all doses and formulations in our TRT variable definition and were not able to identify any such differences. Similarly, another RCTs showed an overall beneficial effect of TRT on sexual health but the authors did not find an association between TRT and either energy or mood.[186] However, the authors did not include a discrete measure for depression as an outcome; hence, results cannot be generalized to depression outcomes more broadly. It is possible that the effects of TRT differ by specific depression sub-categories. However, we did not analyze this in our study.

Future large-scale studies should explore potential differences by route of administration. Current evidence supports TRT effects across a wide age range, including middle aged men,[29,31] however possible variation by age is possible and must be explored. This hypothesis is tested further in Section 6.3.1-B. Future research should also assess possible differences in effects of TRT by severity of depressive symptoms, i.e., effects on major depressive disorder vs dysthymia etc.

Limitations and Strengths

Our findings need to be interpreted in light of various limitations. First, this was a case control study design; hence causality cannot be established. Second, as discussed in detail in the preceding section, we did not include laboratory values of testosterone to establish a diagnosis of hypogonadism. Third, this study did not assess the severity of hypogonadism. Fourth, this study did not assess the effect of TRT on sub-classes of depression. Fourth, we did not assess differences by route of administration. Fifth, case control study design does not allow for monitoring of testosterone levels over time to assess testosterone normalization, i.e., eugonadal status. Sixth, this study only men 40-65 years of age; hence generalizability to the adult US population is not possible. Seventh, this study used administrative claims data, which is prone to errors, omissions and potential under-reporting of mental health conditions.

In spite of these limitations, this study presents the first piece of evidence of the link between TRT and incident depression in middle aged and older men using data from one of the nation's largest commercial health insurance databases. Major strengths include large sample size, nationally representative sample of middle aged and older adults, real-world, population-based sample and statistical techniques to reduce bias and confounding. While our results do not show an association between TRT and depression, future studies should continue to investigate the potential link, taking in to account the limitations highlighted in this section.

5.3.2 Retrospective Cohort Design (Specific Aim-3)

Major Findings in the Context of Current Research

This study analyzed risk of depression in a large, nationally representative sample of middle aged and older hypogonadal men receiving TRT. Similar to results reported for Specific Aim 2B, we found no association between exposure to >30 days of TRT and depression in our main analytical model. We adjusted for a variety of sociodemographic, clinical and healthcare factors in order to test this association. In order to assess the robustness of our results, we performed a variety of sensitivity analyses. First, we adjusted for outpatient visits and prior antidepressant use in our main model, in addition to accounting for sociodemographic factors and comorbid medical conditions. Second, we adjusted for other mental health conditions and prior prescription drug use in the sensitivity analyses. Third, we assessed the effect of additional exposure windows on risk of depression using different cut-offs for duration of TRT. Contrary to our hypothesis, TRT was not associated with depression in the fully adjusted models. Sensitivity analyses showed a small increased risk of depression associated with >180 days of TRT exposure; however no association was observed for any of the other exposure categories. Overall, contrary to our hypothesis we did not find an association between TRT and depression.

While existing evidence predominantly supports potential antidepressant effects of TRT, few studies reported no association between TRT and depression or psychological health more broadly. Results from a meta-analysis of four RCTs showed an overall beneficial effect of TRT on psychosexual health; however, the meta-analysis did not find a beneficial effect of TRT specifically on energy or mood.[186] There is evidence that TRT might not be as efficacious in men with major depression specifically,

compared to men with other types of depressive or mood disorders.[187] This idea is supported by two relatively small RCTs that failed to find a positive influence of TRT in men diagnosed with major depressive disorder.[25,180]

Null association between TRT and depression is also reported by few other RCTs. In an RCT of older men above 65 years of age, Vaughan et al[188] found no effect of TRT on depression, as assessed by the Beck Depression Inventory. However, the study only included older men and results cannot be generalized to middle aged men. Similarly, Spitzer et al. (2013)[189] assessed the effects of TRT on psychological health in an RCT of 140 men 40-70 years of age and did not find a significant impact of TRT on either depressed mood or psychological well-being overall. However, this trial only included men with erectile dysfunction and does not represent the general middle aged and older US population. Further, erectile dysfunction might complicate a person's depressive symptomatology and require more vigorous TRT treatment and monitoring for potential mental health benefits. In our study, we did not capture erectile dysfunction and it is possible that results might vary in men with and without this disorder. Further, we included an umbrella definition for depression outcome and did not assess the effects on specific depression diagnoses such as major depressive disorder, dysthymia. We also did not stratify depression by severity, i.e., treatment resistant depression etc. It is possible that statistically and clinically meaningful differences are relatively harder to achieve for these groups compared to men with less severe depressive symptoms. Conversely, even small improvements in depressive symptoms in severely depressed men might be statistically significant but not clinically meaningful. In a large RCT of diabetic men, Kim et al[190] did not find a statistically meaningful effect of TRT on depressive

symptoms. However, the authors excluded men with relatively severe depressive symptoms and the study was restricted to men with diabetes, which can directly interact with endogenous testosterone levels and might directly and indirectly increase the risk of depression.

In general, our findings are in contrast to majority of evidence from prior RCTs and few observational studies that reported improvements in depressive symptoms with TRT.[23,39,125] A systematic review and meta-analysis of 12 RCTs found protective effects of TRT and reduced risk of depression associated with TRT use.[23] Similarly, a large meta-analysis of 27 RCTs found significant improvements in depression associated with TRT compared to placebo, with a clinically meaningful reduction in depressive symptoms comparable to or even better than efficacy of pharmacologic agents for treatment of depression. The meta-analysis also reported a dose-response relationship between TRT and depression, with greater improvements in depressive symptoms associated with larger doses of TRT.[29] In our study, we did not account for TRT dose, which combined with total number of days can be an excellent measure to assess dose-response. These results are further reinforced by a large, multi-center trial by Snyder et al. (2016) which found significant improvements in depressive symptoms associated with TRT.[28] Our results are contrary to our original hypothesis and evidence from prior RCTs and limited number of observational studies. These findings should be interpreted in light of various design issues and limitations.

First, this is an observational study and is prone to selection bias. The risks and possible effects of selection bias on study outcomes have been discussed in detail in the previous section. Second, we did not include testosterone laboratory values in this study;

hence, identification of possible improvements in testosterone levels over time was not possible. Hence, we cannot claim that men who were exposed to TRT did, in fact, experience improvements in testosterone levels over time. This is an important issue, especially in lieu of observing beneficial effects of testosterone on mental health outcomes as a result of improved endogenous testosterone levels and a possible transition from hypogonadal to eugonadal state. Fourth, we did not account for adherence to TRT prescription over time. While our primary exposure window for TRT was relatively short- with the intention of reducing possible variability in TRT over longer time periods- variability in TRT prescription and use is still possible over a period of one year. It is possible that a certain proportion of men stopped taking TRT after observing beneficial effects on mood and/or energy after a short period. In addition, a short exposure window limited our ability to assess exposure to TRT over longer periods of time with subsequent mental health outcomes.

In this context, Miner et al[125] conducted a unique, 12-month observational study of US adults aged 21-85 years and evaluated the association between TRT and a variety of anthropometric, cardiometabolic and psychological outcomes. The authors reported a significant improvement in depressive symptoms, as measured by the PHQ-9 scale with exposure to TRT at 3, 6 and 12 months. The authors also monitored testosterone levels over time and examined whether normal levels were attained in addition to monitoring variations in testosterone levels over time. Further, the study reported correlations between improvements in testosterone levels and improvements in depressive symptoms at different time points and found significant correlation between the two constructs at 6 months of follow-up, as men achieved eugonadal status. In our study, we did not include

a measure of laboratory values for testosterone levels, which presents three major challenges. First, it does not allow us to assess potential improvements in testosterone levels over time, which is essential to observing any beneficial effects of TRT in hypogonadal men. Second, it does not allow for identification of men who initiated TRT but never achieved eugonadal levels, which presents an important complication since these men might be at a particularly increased risk of depression and other adverse mental health outcomes. Third, it does not allow for assessment of men who achieved supraphysiologic levels of testosterone. Although the latter is a rare possibility in this study, it is still possible especially if men were only narrowly below the cut-off for normal testosterone levels but continued TRT without adequate monitoring. Supraphysiologic doses or endogenous levels of TRT have been associated with adverse psychiatric outcomes such as mania and particular attention must be paid to adequate monitoring of TRT receipients to avoid such adverse events.

Similarly, another observational study of over 700 hypogonadal men assessed the effects of TRT on sexual function, body composition and psychological health over a 6 month period.[126] The authors found significant improvements in Aging Males' Symptoms scale, including its psychological domains. It is important to point out that the authors also assessed variation in TRT dosing, adherence to TRT prescription and transition to eugonadal status during the study period. This way they were able to document variation in TRT prescription and use over time, thereby reducing bias resulting from absence of this information. However, the study did not include a standard measure of depression diagnosis as used in other studies. Nevertheless, it underlines an important methodological issue when following TRT recipients over time. Future studies should

include a measure of adherence to TRT and possibly, assessment of testosterone levels to make more accurate comparison between exposed and unexposed groups and to reduce bias resulting from lack of information on adherence and normalization.

We used a unique definition for our exposure variable. We used men with 30 days or less of TRT as the referent category and used additional exposure windows for comparison. It is possible that men with no exposure to TRT at all might represent a very different population compared to men with >90 or >180 days of exposure to TRT. Hence, we used the lowest category of exposure as the reference group to examine the effects of >30 days and higher duration of TRT exposure on depression. It is also possible that men with no exposure to TRT had a different depression severity profile compared to men with longer exposures to TRT. However, we used the cut-offs based on current evidence regarding clinical efficacy of TRT.[134]

It has been reported that a >120 day exposure to TRT might be required to observe maximum effects on depressive symptoms.[134] However, in this study we did not find a dose-response relationship between TRT and depression. In contrast, we found a small risk of depression associated with the longest duration of exposure to TRT in our sensitivity analyses. Few prior studies have reported adverse psychiatric effects of TRT in eugonadal men or men receiving supra-physiologic doses of TRT, including men taking anabolic steroids.[97,191–193] However, we minimized that risk by requiring a diagnosis of hypogonadism for all men receiving TRT. We suspect that the minor adverse effects of TRT on depression observed in our sensitivity analysis represent potential issues related to selection bias, variation in TRT use over time (on-off) and lack of testosterone laboratory data to monitor variation/improvement in testosterone levels over

time. Further, this effect was observed only for men with the longest duration of exposure to TRT. While this is contrary to prior evidence, it is possible that men who received TRT for longer periods of time had either more severe hypogonadism or more severe depressive symptoms. It is also possible that these men were still hypogonadal after receiving TRT or continued to take TRT for other intended outcomes such as muscle mass/strength and/or improved body habitus. Future studies should assess both adherence to TRT prescription and long-term follow-up to correlate changes in endogenous testosterone levels with mental health outcomes using appropriate statistical techniques, including assessment of TRT as a time-varying covariate.

We used relevant statistical techniques to minimize the effects of selection bias, including multivariable regression and matching on key variables such as age, index date and comorbidity score. However, it is possible that some of our models had unmeasured and potentially unobserved confounding, leading to biased estimates. Other statistical approaches are available, and might help address this issue. Instrumental variables are one such tool and are widely used in epidemiologic studies to account for both measured and unmeasured confounding. In the context of this dissertation, one possible underlying factor contributing to selection bias might be the supply of physicians including endocrinologists, psychiatrists or primary care physicians around an individual patient's residential zip code, which might in turn influence the likelihood of receiving TRT. Hence, men might be more likely to have received a prescription for TRT if they lived in an area with high physician supply, compared to men living in a low supply area. In this case, one possible instrument might be physician supply per capita around patients' residential zip code. This might be calculated by first estimating the total number of

practicing physicians within each zip code that falls within a 15-mile radius of each patient's residential zip code and then dividing the total number of physicians (summed across zip codes within 15 miles) by total population (summed across zip codes). The resulting IV can be analyzed as both a binary and ordinal variable, by dividing men into "high supply area" vs "low supply area," using median number of physicians per capita in the overall sample and grouping men into four categories, based on quartiles of physician supply. Two stage, least squares regression models can be used for this IV analysis. Similar approaches might help address the issue of unmeasured confounding and selection bias and must be assessed in future studies.

In the context of the above discussion, it is possible that our findings are attributable, at least in part, to issues such as selection bias, lack of information on testosterone laboratory values, adherence to TRT prescription and dosage of TRT and possible variation in TRT use over time. Future studies should take these factors into account when evaluating the effects of TRT on depression.

Limitations and Strengths

This study has several limitations. First, we used administrative claims data, which is prone to errors and omissions resulting in potential information bias. Second, while we used a short exposure window for TRT, we did not account for potential variation in TRT use over time. Third, as discussed in the preceding section, this study did not use laboratory values to monitor changes in testosterone levels over time, thereby limiting our ability to assess potential mental health effects of testosterone normalization. Fourth, this is an observational study design and is prone to selection bias (discussed in detail in

detail in Section 5.3.1). Fourth, this study only used first year of follow-up for TRT exposure, which restricted our ability to monitor TRT use over longer time periods. Fifth, this study did not assess differences in the hypothesized association by different depression diagnoses e.g., treatment-resistant, major depression etc. Sixth, the exposed and unexposed groups were not matched, which might have affected our findings through residual confounding and other possible differences between the two groups.

In spite of these limitations, this study has several notable strengths. First, this study presents the first piece of evidence from a large, real-world, population-based sample of middle aged and older adults in the US. Major strengths of this study include large sample size, nationally representative sample of commercially insured middle aged and older adults, multivariable models to adjust for a variety of confounding factors, assessment of effect of duration of TRT and establishment of causality. This study, and the methodological issues and challenges it highlights will inform future research on the topic and help improve current knowledge and understanding of the link between TRT and depression.

Chapter 6

Conclusions and Future Directions

This dissertation examined three outstanding clinical and public health issues. We report a) TRT prescription trends in men with depression b) the association between hypogonadism and depression and c) the effect of TRT on depression in middle aged and older men in the US.

Our results present the first piece of evidence of incident TRT prescribing practices in middle aged and older men with depression. We found significantly higher rates of TRT prescription in depressed men, compared to non-depressed men and considerable variation in TRT prescription patterns by age and hypogonadal status. Future research should examine variation in hypogonadism diagnosis practices using laboratory tests for testosterone levels, and the impact of these practices on TRT prescription, initiation and use over time-overall and in men with depression. Future studies should also assess the impact of FDA rulings/communication with possible increased monitoring of testosterone products on TRT prescribing practices in the general population and in men with physical and mental comorbidities. Researchers should further explore adherence to TRT after initiation, particularly in men with major mental health conditions such as depression. Last, further research is required to assess TRT prescribing patterns in men with other mental health conditions such as anxiety, mood disorders and other major psychiatric disorders.

This dissertation also assessed the link between hypogonadism and depression. Overall, we did not find an increased risk of depression associated with a diagnosis of

hypogonadism. This finding is in contrast to prior evidence from the literature. We assessed the robustness of our finding by adjusting for a variety of sociodemographic, clinical, pharmacologic and healthcare utilization factors and observed a small, borderline significant increased risk of depression associated with hypogonadism. Future research should examine the effect of severity and duration of hypogonadism on risk of depression and similar major mental health outcomes, and the potential role of relevant pharmacotherapeutic interventions in mitigating some of the adverse mental health effects of hypogonadism. Further research is required to explore potential mediating pathways, including the role of other psychiatric disorders and prescription drugs. Large scale, longitudinal studies are needed to establish a causal link between hypogonadism and depression. Our findings will improve current understanding of the link between hypogonadism and depression by providing the first piece of evidence from a nationally representative sample of middle aged and older men. Our results will inform future research and practice with regard to timely diagnosis, appropriate treatment and potential prevention of the adverse mental health effects of hypogonadism, in particular the risk of depression.

Last, this dissertation analyzed the effect of TRT on depression in a large, real-world, population-based sample of middle aged and older men. The association was examined using two unique study designs. After controlling for a variety of clinical and sociodemographic factors, no association was observed between TRT and depression. We observed a small increased risk of depression in one sensitivity analysis; however, it might be attributed to study design issues and challenges. Overall, we reported a null association between TRT and depression, which is contrary to our original hypothesis.

TRT prescription, use and follow-up presents a unique challenge for researchers, given the risk of self-selection, non-adherence, initiation for reasons other than improvements in depressive symptoms and the challenges of including the results of laboratory tests in administrative claims data. Our study highlights these and other challenges that need to be properly addressed and accounted for when studying the effects of TRT on depression. These results and the methodological challenges underlined by our findings add significantly to current research on this topic and will inform future research in order to minimize bias resulting from these and related challenges.

Appendix

Fig. 1 Elixhauser Comorbidity Index

Table 1. Testosterone Replacement Therapy Therapeutic Class, National Drug Classification and HCPCS-J Codes

Therapeutic Class Code	Therapeutic Class Description
4012040120	Calcium Phosphate Dibasic
6808010025	Fluoxymesterone
6808010050	Methyltestosterone
6808010090	Testosterone
6808010095	Testosterone/Estradiol
8828100001	Vitamins W/Minerals, Misc Prep
9201010153	Homeopathic Prep & Comb.

NDC	Product Name	Therapeutic Class Description
456100410	ANDRO 100	Testosterone
456060410	ANDRO L.A. 200	Testosterone
588507670	ANDRO-CYP 100	Testosterone
588507770	ANDRO-CYP 200	Testosterone
418657141	ANDRO/FEM	Testosterone/Estradiol
52544007654	ANDRODERM	Testosterone
52544007660	ANDRODERM	Testosterone
52544007730	ANDRODERM	Testosterone
52544007754	ANDRODERM	Testosterone
52544046954	ANDRODERM	Testosterone
52544046960	ANDRODERM	Testosterone
52544047030	ANDRODERM	Testosterone
52544047054	ANDRODERM	Testosterone
54868370400	ANDRODERM	Testosterone
54868603200	ANDRODERM	Testosterone
51842501	ANDROGEL	Testosterone
51842530	ANDROGEL	Testosterone
51845001	ANDROGEL	Testosterone
51845030	ANDROGEL	Testosterone
51846230	ANDROGEL	Testosterone

51846231	ANDROGEL	Testosterone
51846233	ANDROGEL	Testosterone
51848833	ANDROGEL	Testosterone
51848888	ANDROGEL	Testosterone
16590071930	ANDROGEL	Testosterone
21695011230	ANDROGEL	Testosterone
35356037605	ANDROGEL	Testosterone
54569533800	ANDROGEL	Testosterone
54569533900	ANDROGEL	Testosterone
54569533901	ANDROGEL	Testosterone
54569633700	ANDROGEL	Testosterone
54868479200	ANDROGEL	Testosterone
54868481000	ANDROGEL	Testosterone
54868581400	ANDROGEL	Testosterone
68115080930	ANDROGEL	Testosterone
187090201	ANDROID	Methyltestosterone
187031106	ANDROID-10	Methyltestosterone
187049906	ANDROID-25	Methyltestosterone
418655141	ANDRONATE	Testosterone
418656141	ANDRONATE	Testosterone
832008600	ANDROXY	Fluoxymesterone
67979051143	AVEED	Testosterone
2197590	AXIRON	Testosterone
10116100101	BOCASAL	Calcium Phosphate Dibasic
217680608	DELATEST	Testosterone
217680708	DELATESTADIOL	Testosterone/Estradiol
54396032816	DELATESTRYL	Testosterone
54396032840	DELATESTRYL	Testosterone
54569462000	DELATESTRYL	Testosterone
54569541600	DELATESTRYL	Testosterone
54868501600	DELATESTRYL	Testosterone
67979050140	DELATESTRYL	Testosterone
456101910	DEP ANDRO 100	Testosterone
456060310	DEP ANDRO 200	Testosterone
456102010	DEP ANDROGYN	Testosterone/Estradiol
52604025706	DEPATESOGEN	Testosterone/Estradiol
9025302	DEPO-TESTADIOL	Testosterone/Estradiol
403379718	DEPO-TESTADIOL	Testosterone/Estradiol
54569419900	DEPO-TESTADIOL	Testosterone/Estradiol
9034702	DEPO-TESTOSTERONE	Testosterone
9041701	DEPO-TESTOSTERONE	Testosterone

9041702	DEPO-TESTOSTERONE	Testosterone
403300918	DEPO-TESTOSTERONE	Testosterone
403304918	DEPO-TESTOSTERONE	Testosterone
35356005810	DEPO-TESTOSTERONE	Testosterone
54569141100	DEPO-TESTOSTERONE	Testosterone
54569530100	DEPO-TESTOSTERONE	Testosterone
54868021600	DEPO-TESTOSTERONE	Testosterone
54868021601	DEPO-TESTOSTERONE	Testosterone
54868079600	DEPO-TESTOSTERONE	Testosterone
55045302902	DEPO-TESTOSTERONE	Testosterone
55175500701	DEPO-TESTOSTERONE	Testosterone
63874106101	DEPO-TESTOSTERONE	Testosterone
9008510	DEPO-TESTOSTERONE NOVAPLUS	Testosterone
9008601	DEPO-TESTOSTERONE NOVAPLUS	Testosterone
9008610	DEPO-TESTOSTERONE NOVAPLUS	Testosterone
314081570	DEPOTEST	Testosterone
314083570	DEPOTEST	Testosterone
314087570	DEPOTESTOGEN	Testosterone/Estradiol
684020210	DUO SPAN	Testosterone
588504770	DUO-CYP	Testosterone/Estradiol
684010210	DUO-SPAN II	Testosterone
298630561	DUOGEN L.A.	Testosterone/Estradiol
298663561	DUOGEN L.A.	Testosterone/Estradiol
43797002212	DURA-DUMONE	Testosterone/Estradiol
59441058710	DURATEST-100	Testosterone
59441058810	DURATEST-200	Testosterone
59441058910	DURATESTRIN	Testosterone/Estradiol
59441059010	DURATHATE-200	Testosterone
418050141	ESTRA-TESTRIN	Testosterone/Estradiol
182307363	ESTRADIOL VALERATE TESTOSTERONE ENA	Testosterone/Estradiol
402036010	ESTRADIOL VALERATE TESTOSTERONE ENA	Testosterone/Estradiol
54569301300	ESTRADIOL VALERATE TESTOSTERONE ENA	Testosterone/Estradiol
54569301400	ESTRADIOL VALERATE TESTOSTERONE ENA	Testosterone/Estradiol
49072072710	ESTRADIOL W/TESTOSTERONE CYPIONATE	Testosterone
182306963	ESTRADIOL/TESTOSTERONE CYPIONATE	Testosterone/Estradiol
364661154	ESTRADIOL/TESTOSTERONE CYPIONATE	Testosterone/Estradiol

402025710	ESTRADIOL/TESTOSTERONE CYPIONATE	Testosterone/Estradiol
54569178201	ESTRADIOL/TESTOSTERONE CYPIONATE	Testosterone/Estradiol
314065070	EVERONE	Testosterone
314065270	EVERONE	Testosterone
65628002001	FIRST-TESTOSTERONE	Testosterone
65628002101	FIRST-TESTOSTERONE MC	Testosterone
182153801	FLUOXYMESTERONE	Fluoxymesterone
223097001	FLUOXYMESTERONE	Fluoxymesterone
223097101	FLUOXYMESTERONE	Fluoxymesterone
223097201	FLUOXYMESTERONE	Fluoxymesterone
302302001	FLUOXYMESTERONE	Fluoxymesterone
349826701	FLUOXYMESTERONE	Fluoxymesterone
364065901	FLUOXYMESTERONE	Fluoxymesterone
536382601	FLUOXYMESTERONE	Fluoxymesterone
603364521	FLUOXYMESTERONE	Fluoxymesterone
677093401	FLUOXYMESTERONE	Fluoxymesterone
781160801	FLUOXYMESTERONE	Fluoxymesterone
814324014	FLUOXYMESTERONE	Fluoxymesterone
904121860	FLUOXYMESTERONE	Fluoxymesterone
51432018303	FLUOXYMESTERONE	Fluoxymesterone
63481018316	FORTESTA	Testosterone
9001401	HALOTESTIN	Fluoxymesterone
9001906	HALOTESTIN	Fluoxymesterone
9003603	HALOTESTIN	Fluoxymesterone
9003604	HALOTESTIN	Fluoxymesterone
59441060210	HISTERONE-100	Testosterone
43797002012	HISTERONE-50	Testosterone
52349011510	MEDITEST	Testosterone
181061200	METESTONE	Methyltestosterone
181061300	METESTONE	Methyltestosterone
115703701	METHITEST	Methyltestosterone
115703801	METHITEST	Methyltestosterone
115140801	METHYLTESTOSTERONE	Methyltestosterone
115398201	METHYLTESTOSTERONE	Methyltestosterone
115398203	METHYLTESTOSTERONE	Methyltestosterone
115398403	METHYLTESTOSTERONE	Methyltestosterone
115398603	METHYLTESTOSTERONE	Methyltestosterone
182018501	METHYLTESTOSTERONE	Methyltestosterone
182058201	METHYLTESTOSTERONE	Methyltestosterone
182058301	METHYLTESTOSTERONE	Methyltestosterone

302412001	METHYLTESTOSTERONE	Methyltestosterone
302412010	METHYLTESTOSTERONE	Methyltestosterone
302412101	METHYLTESTOSTERONE	Methyltestosterone
349209401	METHYLTESTOSTERONE	Methyltestosterone
349211201	METHYLTESTOSTERONE	Methyltestosterone
349239601	METHYLTESTOSTERONE	Methyltestosterone
364017001	METHYLTESTOSTERONE	Methyltestosterone
364017101	METHYLTESTOSTERONE	Methyltestosterone
364017201	METHYLTESTOSTERONE	Methyltestosterone
463612201	METHYLTESTOSTERONE	Methyltestosterone
463612210	METHYLTESTOSTERONE	Methyltestosterone
463612301	METHYLTESTOSTERONE	Methyltestosterone
463612310	METHYLTESTOSTERONE	Methyltestosterone
463612401	METHYLTESTOSTERONE	Methyltestosterone
463612410	METHYLTESTOSTERONE	Methyltestosterone
527107801	METHYLTESTOSTERONE	Methyltestosterone
527107810	METHYLTESTOSTERONE	Methyltestosterone
527114001	METHYLTESTOSTERONE	Methyltestosterone
527114010	METHYLTESTOSTERONE	Methyltestosterone
536463001	METHYLTESTOSTERONE	Methyltestosterone
536463401	METHYLTESTOSTERONE	Methyltestosterone
536463410	METHYLTESTOSTERONE	Methyltestosterone
536463801	METHYLTESTOSTERONE	Methyltestosterone
536463810	METHYLTESTOSTERONE	Methyltestosterone
677008501	METHYLTESTOSTERONE	Methyltestosterone
677008601	METHYLTESTOSTERONE	Methyltestosterone
677008701	METHYLTESTOSTERONE	Methyltestosterone
814478514	METHYLTESTOSTERONE	Methyltestosterone
814478814	METHYLTESTOSTERONE	Methyltestosterone
814479014	METHYLTESTOSTERONE	Methyltestosterone
839142506	METHYLTESTOSTERONE	Methyltestosterone
839142516	METHYLTESTOSTERONE	Methyltestosterone
839142906	METHYLTESTOSTERONE	Methyltestosterone
839142916	METHYLTESTOSTERONE	Methyltestosterone
839508806	METHYLTESTOSTERONE	Methyltestosterone
839508816	METHYLTESTOSTERONE	Methyltestosterone
904080760	METHYLTESTOSTERONE	Methyltestosterone
904080860	METHYLTESTOSTERONE	Methyltestosterone
904080960	METHYLTESTOSTERONE	Methyltestosterone
904080980	METHYLTESTOSTERONE	Methyltestosterone
51432028403	METHYLTESTOSTERONE	Methyltestosterone

51432028603	METHYLTESTOSTERONE	Methyltestosterone
51432028803	METHYLTESTOSTERONE	Methyltestosterone
54569083300	METHYLTESTOSTERONE	Methyltestosterone
54569084100	METHYLTESTOSTERONE	Methyltestosterone
63481023901	NATESTO	Testosterone
85097006	ORETON METHYL	Methyltestosterone
187031206	ORETON METHYL	Methyltestosterone
9052001	PREMIERPRO RX DEPO-TESTOSTERONE	Testosterone
9052010	PREMIERPRO RX DEPO-TESTOSTERONE	Testosterone
52083053010	PRIMOTEST FORTE	Methyltestosterone
47649012705	SHOTEST	Testosterone
47649012805	SHOTEST	Testosterone
47649012905	SHOTEST	Testosterone
52244003060	STRIANT	Testosterone
55056306001	STRIANT	Testosterone
25332003910	T-CYPIONATE	Testosterone
25332005110	T-E CYPIONATE	Testosterone/Estradiol
536947070	TEST-ESTRO-CYPIONATE	Testosterone/Estradiol
298683561	TESTA-C	Testosterone
217681208	TESTAMONE-100	Testosterone
684015210	TESTASPAN	Testosterone
418085110	TESTEX	Testosterone
16590085330	TESTIM	Testosterone
35356075830	TESTIM	Testosterone
54569559500	TESTIM	Testosterone
54868498900	TESTIM	Testosterone
66887000105	TESTIM	Testosterone
17314283603	TESTODERM	Testosterone
17314460803	TESTODERM	Testosterone
17314460903	TESTODERM	Testosterone
54569394400	TESTODERM	Testosterone
54569394500	TESTODERM	Testosterone
17314471703	TESTODERM TTS	Testosterone
418078110	TESTOLIN	Testosterone
418079141	TESTOLIN	Testosterone
76420065001	TESTONE CIK	Testosterone
298621561	TESTONE L.A.	Testosterone
298679761	TESTONE L.A.	Testosterone
10116100102	TESTOPEL PELLETS	Testosterone
10116100103	TESTOPEL PELLETS	Testosterone

43773100102	TESTOPEL PELLETS	Testosterone
43773100103	TESTOPEL PELLETS	Testosterone
43773100104	TESTOPEL PELLETS	Testosterone
66887000401	TESTOPEL PELLETS	Testosterone
66887000410	TESTOPEL PELLETS	Testosterone
66887000420	TESTOPEL PELLETS	Testosterone
10116100101	TESTOPEL PELLETS	Testosterone
182071463	TESTOSTERONE	Testosterone
223058010	TESTOSTERONE	Testosterone
223858130	TESTOSTERONE	Testosterone
223859010	TESTOSTERONE	Testosterone
223859130	TESTOSTERONE	Testosterone
223860010	TESTOSTERONE	Testosterone
223860130	TESTOSTERONE	Testosterone
314008310	TESTOSTERONE	Testosterone
314077170	TESTOSTERONE	Testosterone
364660754	TESTOSTERONE	Testosterone
364660756	TESTOSTERONE	Testosterone
395652056	TESTOSTERONE	Testosterone
395652059	TESTOSTERONE	Testosterone
395652062	TESTOSTERONE	Testosterone
402008310	TESTOSTERONE	Testosterone
402008330	TESTOSTERONE	Testosterone
402008410	TESTOSTERONE	Testosterone
402008430	TESTOSTERONE	Testosterone
536890070	TESTOSTERONE	Testosterone
536950070	TESTOSTERONE	Testosterone
536950075	TESTOSTERONE	Testosterone
574046000	TESTOSTERONE	Testosterone
574046005	TESTOSTERONE	Testosterone
574046025	TESTOSTERONE	Testosterone
574091610	TESTOSTERONE	Testosterone
588506370	TESTOSTERONE	Testosterone
591292102	TESTOSTERONE	Testosterone
591292118	TESTOSTERONE	Testosterone
591321617	TESTOSTERONE	Testosterone
591321630	TESTOSTERONE	Testosterone
591321726	TESTOSTERONE	Testosterone
591321730	TESTOSTERONE	Testosterone
603783188	TESTOSTERONE	Testosterone
677031021	TESTOSTERONE	Testosterone

684012610	TESTOSTERONE	Testosterone
781309270	TESTOSTERONE	Testosterone
781309370	TESTOSTERONE	Testosterone
814768840	TESTOSTERONE	Testosterone
832112005	TESTOSTERONE	Testosterone
832112035	TESTOSTERONE	Testosterone
832112065	TESTOSTERONE	Testosterone
832112089	TESTOSTERONE	Testosterone
832112142	TESTOSTERONE	Testosterone
904087410	TESTOSTERONE	Testosterone
904087510	TESTOSTERONE	Testosterone
904087610	TESTOSTERONE	Testosterone
17317056702	TESTOSTERONE	Testosterone
17317056703	TESTOSTERONE	Testosterone
17317056708	TESTOSTERONE	Testosterone
25332003010	TESTOSTERONE	Testosterone
38779004703	TESTOSTERONE	Testosterone
38779004704	TESTOSTERONE	Testosterone
38779004705	TESTOSTERONE	Testosterone
38779004708	TESTOSTERONE	Testosterone
38779004709	TESTOSTERONE	Testosterone
38779016300	TESTOSTERONE	Testosterone
38779016303	TESTOSTERONE	Testosterone
38779016304	TESTOSTERONE	Testosterone
38779016305	TESTOSTERONE	Testosterone
38779016308	TESTOSTERONE	Testosterone
38779016309	TESTOSTERONE	Testosterone
38779253600	TESTOSTERONE	Testosterone
38779253602	TESTOSTERONE	Testosterone
38779253603	TESTOSTERONE	Testosterone
38779253604	TESTOSTERONE	Testosterone
38779253605	TESTOSTERONE	Testosterone
38779253606	TESTOSTERONE	Testosterone
38779253607	TESTOSTERONE	Testosterone
38779253608	TESTOSTERONE	Testosterone
38779253609	TESTOSTERONE	Testosterone
38779259805	TESTOSTERONE	Testosterone
38779259809	TESTOSTERONE	Testosterone
45802011602	TESTOSTERONE	Testosterone
45802011639	TESTOSTERONE	Testosterone
45802011665	TESTOSTERONE	Testosterone

45802061001	TESTOSTERONE	Testosterone
49452765001	TESTOSTERONE	Testosterone
49452765002	TESTOSTERONE	Testosterone
49452765003	TESTOSTERONE	Testosterone
49452765201	TESTOSTERONE	Testosterone
49452765202	TESTOSTERONE	Testosterone
49452765203	TESTOSTERONE	Testosterone
49884041848	TESTOSTERONE	Testosterone
49884041872	TESTOSTERONE	Testosterone
49884051063	TESTOSTERONE	Testosterone
49884051072	TESTOSTERONE	Testosterone
51432077510	TESTOSTERONE	Testosterone
51552002910	TESTOSTERONE	Testosterone
51552002925	TESTOSTERONE	Testosterone
51552002999	TESTOSTERONE	Testosterone
51552056402	TESTOSTERONE	Testosterone
51552056404	TESTOSTERONE	Testosterone
51552056405	TESTOSTERONE	Testosterone
51552056407	TESTOSTERONE	Testosterone
51552056410	TESTOSTERONE	Testosterone
51552056425	TESTOSTERONE	Testosterone
51552056499	TESTOSTERONE	Testosterone
51927102600	TESTOSTERONE	Testosterone
54569220500	TESTOSTERONE	Testosterone
54569300300	TESTOSTERONE	Testosterone
63275989804	TESTOSTERONE	Testosterone
63275989805	TESTOSTERONE	Testosterone
63275989808	TESTOSTERONE	Testosterone
63275989809	TESTOSTERONE	Testosterone
66993093430	TESTOSTERONE	Testosterone
66993093454	TESTOSTERONE	Testosterone
66993096389	TESTOSTERONE	Testosterone
143965901	TESTOSTERONE CYPIONATE	Testosterone
143972601	TESTOSTERONE CYPIONATE	Testosterone
182071263	TESTOSTERONE CYPIONATE	Testosterone
182071363	TESTOSTERONE CYPIONATE	Testosterone
223863510	TESTOSTERONE CYPIONATE	Testosterone
223863610	TESTOSTERONE CYPIONATE	Testosterone
364660954	TESTOSTERONE CYPIONATE	Testosterone
364661054	TESTOSTERONE CYPIONATE	Testosterone
402025510	TESTOSTERONE CYPIONATE	Testosterone

402025610	TESTOSTERONE CYPIONATE	Testosterone
403301018	TESTOSTERONE CYPIONATE	Testosterone
409655701	TESTOSTERONE CYPIONATE	Testosterone
409656201	TESTOSTERONE CYPIONATE	Testosterone
409656220	TESTOSTERONE CYPIONATE	Testosterone
536948070	TESTOSTERONE CYPIONATE	Testosterone
536949070	TESTOSTERONE CYPIONATE	Testosterone
574082001	TESTOSTERONE CYPIONATE	Testosterone
574082010	TESTOSTERONE CYPIONATE	Testosterone
574082710	TESTOSTERONE CYPIONATE	Testosterone
591322379	TESTOSTERONE CYPIONATE	Testosterone
591412879	TESTOSTERONE CYPIONATE	Testosterone
677098021	TESTOSTERONE CYPIONATE	Testosterone
703612101	TESTOSTERONE CYPIONATE	Testosterone
703612501	TESTOSTERONE CYPIONATE	Testosterone
781307370	TESTOSTERONE CYPIONATE	Testosterone
781307470	TESTOSTERONE CYPIONATE	Testosterone
781307471	TESTOSTERONE CYPIONATE	Testosterone
781309670	TESTOSTERONE CYPIONATE	Testosterone
781309770	TESTOSTERONE CYPIONATE	Testosterone
814773340	TESTOSTERONE CYPIONATE	Testosterone
23490634301	TESTOSTERONE CYPIONATE	Testosterone
49072071110	TESTOSTERONE CYPIONATE	Testosterone
54569213100	TESTOSTERONE CYPIONATE	Testosterone
54569302500	TESTOSTERONE CYPIONATE	Testosterone
54868361800	TESTOSTERONE CYPIONATE	Testosterone
54868361801	TESTOSTERONE CYPIONATE	Testosterone
54868366900	TESTOSTERONE CYPIONATE	Testosterone
55045209202	TESTOSTERONE CYPIONATE	Testosterone
55175501801	TESTOSTERONE CYPIONATE	Testosterone
62756001540	TESTOSTERONE CYPIONATE	Testosterone
62756001640	TESTOSTERONE CYPIONATE	Testosterone
62756001740	TESTOSTERONE CYPIONATE	Testosterone
223861310	TESTOSTERONE CYPIONATE W/ESTRADIOL	Testosterone
143975001	TESTOSTERONE ENANTHATE	Testosterone
223860810	TESTOSTERONE ENANTHATE	Testosterone
223860910	TESTOSTERONE ENANTHATE	Testosterone
364661654	TESTOSTERONE ENANTHATE	Testosterone
364661754	TESTOSTERONE ENANTHATE	Testosterone
402035510	TESTOSTERONE ENANTHATE	Testosterone

402035610	TESTOSTERONE ENANTHATE	Testosterone
536167070	TESTOSTERONE ENANTHATE	Testosterone
574082105	TESTOSTERONE ENANTHATE	Testosterone
591322126	TESTOSTERONE ENANTHATE	Testosterone
677031321	TESTOSTERONE ENANTHATE	Testosterone
781310570	TESTOSTERONE ENANTHATE	Testosterone
814770540	TESTOSTERONE ENANTHATE	Testosterone
904245510	TESTOSTERONE ENANTHATE	Testosterone
51309042910	TESTOSTERONE ENANTHATE	Testosterone
54569301200	TESTOSTERONE ENANTHATE	Testosterone
223861010	TESTOSTERONE ENANTHATE ESTRADIOL VA	Testosterone/Estradiol
223861102	TESTOSTERONE ENANTHATE ESTRADIOL VA	Testosterone/Estradiol
182119763	TESTOSTERONE PROPIONATE	Testosterone
223866010	TESTOSTERONE PROPIONATE	Testosterone
223866130	TESTOSTERONE PROPIONATE	Testosterone
314077270	TESTOSTERONE PROPIONATE	Testosterone
364668654	TESTOSTERONE PROPIONATE	Testosterone
402038310	TESTOSTERONE PROPIONATE	Testosterone
402038330	TESTOSTERONE PROPIONATE	Testosterone
463107310	TESTOSTERONE PROPIONATE	Testosterone
574046105	TESTOSTERONE PROPIONATE	Testosterone
574046125	TESTOSTERONE PROPIONATE	Testosterone
574091910	TESTOSTERONE PROPIONATE	Testosterone
588506870	TESTOSTERONE PROPIONATE	Testosterone
677030921	TESTOSTERONE PROPIONATE	Testosterone
719338187	TESTOSTERONE PROPIONATE	Testosterone
781310270	TESTOSTERONE PROPIONATE	Testosterone
802395717	TESTOSTERONE PROPIONATE	Testosterone
802395719	TESTOSTERONE PROPIONATE	Testosterone
802395721	TESTOSTERONE PROPIONATE	Testosterone
904086810	TESTOSTERONE PROPIONATE	Testosterone
904086830	TESTOSTERONE PROPIONATE	Testosterone
17317056802	TESTOSTERONE PROPIONATE	Testosterone
17317056803	TESTOSTERONE PROPIONATE	Testosterone
17317056808	TESTOSTERONE PROPIONATE	Testosterone
38779005403	TESTOSTERONE PROPIONATE	Testosterone
38779005404	TESTOSTERONE PROPIONATE	Testosterone
38779005405	TESTOSTERONE PROPIONATE	Testosterone
38779016502	TESTOSTERONE PROPIONATE	Testosterone
38779016503	TESTOSTERONE PROPIONATE	Testosterone

38779016504	TESTOSTERONE PROPIONATE	Testosterone
38779016505	TESTOSTERONE PROPIONATE	Testosterone
38779016506	TESTOSTERONE PROPIONATE	Testosterone
38779016508	TESTOSTERONE PROPIONATE	Testosterone
49072071710	TESTOSTERONE PROPIONATE	Testosterone
49452001101	TESTOSTERONE PROPIONATE	Testosterone
49452001102	TESTOSTERONE PROPIONATE	Testosterone
49452001103	TESTOSTERONE PROPIONATE	Testosterone
49452001104	TESTOSTERONE PROPIONATE	Testosterone
49452767001	TESTOSTERONE PROPIONATE	Testosterone
49452767002	TESTOSTERONE PROPIONATE	Testosterone
49452767003	TESTOSTERONE PROPIONATE	Testosterone
51309043310	TESTOSTERONE PROPIONATE	Testosterone
51552003001	TESTOSTERONE PROPIONATE	Testosterone
51552003002	TESTOSTERONE PROPIONATE	Testosterone
51552003003	TESTOSTERONE PROPIONATE	Testosterone
51552003004	TESTOSTERONE PROPIONATE	Testosterone
51552003005	TESTOSTERONE PROPIONATE	Testosterone
51552003006	TESTOSTERONE PROPIONATE	Testosterone
51552003008	TESTOSTERONE PROPIONATE	Testosterone
51552003009	TESTOSTERONE PROPIONATE	Testosterone
51552003025	TESTOSTERONE PROPIONATE	Testosterone
51552003099	TESTOSTERONE PROPIONATE	Testosterone
54569236300	TESTOSTERONE PROPIONATE	Testosterone
63370098525	TESTOSTERONE PROPIONATE	Testosterone
63370098535	TESTOSTERONE PROPIONATE	Testosterone
63370098545	TESTOSTERONE PROPIONATE	Testosterone
63370098550	TESTOSTERONE PROPIONATE	Testosterone
187090101	TESTRED	Methyltestosterone
58016096700	TESTRED	Methyltestosterone
58016096730	TESTRED	Methyltestosterone
58016096760	TESTRED	Methyltestosterone
58016096790	TESTRED	Methyltestosterone
187020010	TESTRED CYPIONATE 200	Testosterone
418043141	TESTRIN-P.A.	Testosterone
463106910	TESTRO AQ	Testosterone
463107010	TESTRO-L.A.	Testosterone
314078670	VALERTEST NO. 1	Testosterone/Estradiol
12539010601	VIGOREX	Methyltestosterone
12539012701	VIGOREX	Testosterone
12539012710	VIGOREX	Testosterone

61098010010	VIGOREX	Vitamins W/Minerals, Misc Prep
12539005060	VIGOREX	Homeopathic Prep & Comb.
76030103	VIRILON	Methyltestosterone
76030104	VIRILON	Methyltestosterone
76030110	VIRILON IM	Testosterone
245087105	VOGELXO	Testosterone
245087135	VOGELXO	Testosterone
245087165	VOGELXO	Testosterone
245087189	VOGELXO	Testosterone
245087240	VOGELXO	Testosterone
245087242	VOGELXO	Testosterone

HCPCS Codes	
J0900, J1070, J1080, J1090, J3120, J3130, J3140, J3150, S0189	Injectable testosterone formulations

Table 2. Antidepressant Treatment Therapeutic Class Codes (TCC)

TCC Code	**Antidepressant Medication**
2816040000	Antidepressants
2816040010	Agomelatine
2816040040	Citalopram
2816040043	Desvenlafaxine
2816040045	Duloxetine HCl
2816040050	Escitalopram
2816040054	Esketamine
2816040120	Fluoxetine
2816040130	Fluvoxamine Maleate
2816040134	Levomilnacipran
2816040135	Nefazodone HCl
2816040139	Selegiline
2816040140	Sertraline
2816040155	Venlafaxine HCl
2816040420	Isocarboxazid
2816040450	Phenelzine
2816040455	Reboxetine
2816040465	Tranylcypromine
2816040805	Amitriptyline & Comb.

2816040810	Amoxapine
2816040812	Clomipramine
2816040815	Desipramine
2816040820	Doxepin (2816040820)
2816040830	Imipramine
2816040840	Maprotiline
2816040843	Mirtazapine
2816040845	Nortriptyline
2816040847	Paroxetine
2816040850	Protriptyline
2816040855	Trazodone
2816040860	Trimipramine
2816040910	Bupropion
2816049300	Vilazodone

Table 3. Other Mental Health Conditions

Mental Health Condition	**ICD Codes**	
	ICD-9	**ICD-10**
Dementias	2900	F0390
	29010	F0390
	29011	F0390
	29012	F0390
	29012	F05
	29013	F0390
	29020	F0390
	29020	F05
	29021	F0390
	2903	F0390
	2903	F05
	29040	F0150
	29041	F0151
	29042	F0151
	29043	F0151
	2940	F04
	29410	F0280
	29411	F0281
	29420	F0390
	29421	F0391
	3310	G309
	G300	
	G301	
	G308	
	33111	G3101
	33119	G3109
	3312	G311

	3317 G94 33182 33183 33189 797 R4181
Mood Disorders	29600 F3010 29601 F3011 29602 F3012 29603 F3013 29605 F303 29606 F304 29610 F3010 29611 F3011 29612 F3012 29613 F3013 29615 F303 29616 F304 29640 F3110 29641 F3111 29642 F3112 29643 F3113 29645 F3173 29646 F3174 29650 F3130 29651 F3131 29652 F3132 29653 F314 29655 F3175 29656 F3176 29660 F3160 29661 F3161 29662 F3162 29663 F3163 29664 F3164 29665 F3177 29666 F3178 2967 F319 29680 F319 29681 F308 29689 F3181 29690 F39 29699 F3481 29699 F3489
Anxiety Disorders	30000 F419 30001 F410 30002 F411 30009 F418 30010 F449 30020 F409 30021 F4001 30022 F4002

	30023 F4010 30029 F40218 30029 F40240 30029 F40241 30029 F408 30921 F930 30924 F4322
Other Mental Health Conditions	2930 F05 2931 F05 F06.1 2939 F068 2948 F060 2948 F068 2949 F068 29900 F840 29901 F840 29910 F843 29911 F843 29980 F845 29980 F848 29981 F845 29981 F848 29990 F849 29991 F849 30011 F444 30011 F446 30012 F440 30013 F441 30014 F4481 30015 F449 30016 F4489 30016 F6811 30019 F688 3003 F422 3003 F423 3003 F428 3003 F429 3005 F488 3006 F481 3007 F4521 3007 F4522 30081 F450 30082 F451 30082 F459 30089 F458 30089 F488 3009 F489 3009 F99 3010 F600 30110 F340 30111 F6089

	30113 F340 30120 F601 30121 F601 30122 F21 3013 F603 3014 F605 30150 F604 30151 F6812 30159 F604 3016 F607 3017 F602 30181 F6081 30182 F606 30183 F603 30184 F6089 30189 F6089 3019 F609 3020 F66 3021 F6589 3022 F654 3023 F651 3024 F652 30250 F640 30250 Z87890 30251 F640 30252 F640 30253 F640 3026 F642 30270 R37 30271 F520 30272 F5221 30272 F528 30273 F5231 30274 F5232 30275 F524 30276 F526 30279 F521 30279 F528 30281 F650 30282 F653 30283 F6551 30284 F6552 30285 F641 30289 F6581 30289 F6589 30289 F66 3029 F659 3060 F458 3061 F458 3062 F458 3063 F424

	3063 F458 3064 F458 30650 F458 30651 F525 30652 F458 30653 F458 30659 F458 3066 F458 3067 F458 3068 F458 3068 F59 3069 F459 3070 F985 3071 F5000 30720 F959 30721 F950 30722 F951 30723 F952 3073 F984 30740 F519 30741 F5102 30741 F5109 30742 F5101 30742 F5103 30742 F5109 30743 F5119 30744 F5111 30744 F5112 30744 F5119 30745 F518 30746 F513 30747 F518 30748 F518 30749 F518 30750 F509 30751 F502 30752 F983 30753 F9821 30754 F5089 30759 F5081 30759 F5082 30759 F5089 30759 F9829 3076 F980 3077 F981 30780 F4541 30781 G44209 30789 F4542 3079 F633 3079 R451 3080 F430

	3081 F430 3082 F430 3083 F430 3084 F430 3089 F430 3089 R457 30922 F948 30923 F948 30929 F4329 30929 F948 3093 F4324 3094 F4325 30981 F4310 30981 F4312 30982 F438 30983 F438 30989 F438 3099 F4320 3100 F070 3101 F070 3102 F0781 31081 F482 31089 F0789 3109 F09 31200 F911 31201 F911 31202 F911 31203 F911 31210 F918 31211 F918 31212 F918 31213 F918 31220 F912 31221 F912 31222 F912 31223 F912 31230 F639 31231 F630 31232 F632 31233 F631 31234 F6381 31235 F6381 31239 F633 31239 F6389 3124 F918 31281 F911 31282 F912 31289 F918 3129 F919 3130 F938 3131 F938

	31321 F938 31322 F938 31323 F940 3133 F938 31381 F913 31382 F938 31383 F938 31389 F938 31389 F941 31389 F988 3139 F939 3139 F948 3139 F989 31400 F900 31400 F909 31401 F901 31401 F902 31401 F909 3141 F908 3142 F908 3148 F908 3149 F909 31500 F810 31501 R480 31502 F810 31509 F8181 3151 F812 3152 F8181 3152 F8189 31531 F801 31532 F802 31532 H9325 31534 F804 31535 F8081 31539 F800 31539 F8082 31539 F8089 3154 F82 3155 F82 3158 F88 3159 F819 3159 F89 316 F54 317 F70 3180 F71 3181 F72 3182 F73 319 F79 2910 2914 3051 F17200

Table 4. Prescription Drugs

Therapeutic Class Code	Therapeutic Class Description
0000000000	Unspecified (0000000000)
0200000000	Alternative Pharmacotherapy Agents
0400000000	Allergy Immunotherapy & Antihistamines
0800000000	Anti-Infective Agents
1000000000	Antineoplastic Agents
1200000000	Autonomic Drugs
1600000000	Blood Derivatives
2000000000	Blood Form./Coagulation Agents
2400000000	Cardiovascular Agents
2600000000	Cellular Therapy
2800000000	Central Nervous System Agents
3200000000	Contraceptive Cream/Foam/Dev.
3400000000	Dental Agents
3600000000	Diagnostic Agents
3800000000	Disinfectants
4000000000	Electrolytic,Caloric,Water Bal
4400000000	Enzymes
4500000000	Enzyme Inhibitors
4800000000	Respiratory Agents
5200000000	Eye, Ear, Nose, & Throat Prep.
5600000000	Gastrointestinal Drugs
5700000000	Genitourinary Agent
6000000000	Gold Compounds
6400000000	Heavy Metal Antagonists
6800000000	Hormones & Synthetic Subst.
7000000000	Immunosuppressants
7200000000	Anesthetics, Local (Parenteral)
7601000000	Unspecified (7601000000)
7800000000	Radioactive Agents
8000000000	Serums, Toxoids, Vaccines
8400000000	Skin & Mucous Membrane Agents
8600000000	Smooth Muscle Relaxants
8800000000	Vitamins & Comb.
9200000000	Misc. Pharmacotherapy Agents
9400000000	Devices & Non-Drug Items
9600000000	Pharmaceutical Aids/Adjuvants
9999999999	Blank

Table 5. Testing Proportionality: Schoenfeld Residuals

Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations							
	schtrt30	**schage_cat**	**schinc**	**schedu**	**schregion**	**schelix_ cat**	**schatp**
time Follow-up days	0.006 0.776 2105	-0.017 0.442 2105	0.017 0.431 2105	0.004 0.838 2105	0.0349 0.110 2105	-0.032 0.144 2105	-0.012 0.591 2105
logtime	0.007 0.756 2105	-0.016 0.454 2105	0.018 0.421 2105	0.011 0.624 2105	0.034 0.124 2105	-0.040 0.066 2105	-0.009 0.675 2105
time2	0.005 0.835 2105	-0.015 0.479 2105	0.015 0.499 2105	-0.001 0.975 2105	0.035 0.112 2105	-0.024 0.277 2105	-0.013 0.561 2105

Pearson Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations						
	schvisits	**schhiv**	**schld**	**schpvd**	**schfluid**	**schdiab_nc**
Time Follow-up days	-0.020 0.367 2105	0.027 0.215 2105	-0.025 0.254 2105	-0.012 0.591 2105	0.037 0.087 2105	0.016 0.473 2105
logtime	-0.020 0.353 2105	0.025 0.253 2105	-0.028 0.196 2105	-0.009 0.666 2105	0.043 0.049 2105	0.001 0.791 2105
time2	-0.021 0.347 2105	0.028 0.200 2105	-0.022 0.308 2105	-0.015 0.488 2105		0.026 0.238 2105

Table 6. Cox-Snell Residuals: Final Model Fit

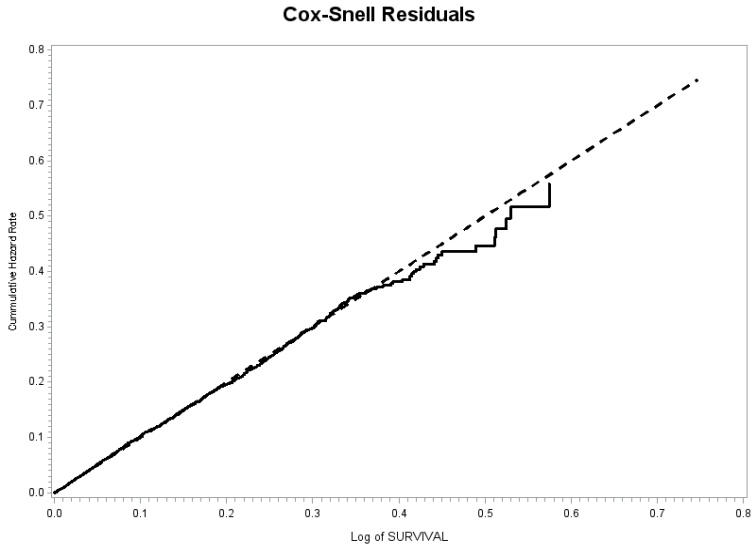


Table 7. Aim 2A: Conditional Logistic Regression Model (potential mediation effect)

	Model 2A-I (A)* **Adjusted OR (95% CI)**	**Model 2A-I (B)**** **Adjusted OR (95% CI)**	**Model 2A-I (C)***** **Adjusted OR (95% CI)**
Hypogonadism (*Referent=No Hypogonadism)*	1.32 (1.16 1.49)	1.19 (1.05 1.35)	1.15 (0.99 1.32)

*Adjusted for income, education, region, unbalanced comorbidities

**Adjusted for income, education, region, unbalanced comorbidities, physician visits

***Adjusted for income, education, region, unbalanced comorbidities, physician visits, antidepressant use

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