GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS AND OBSTRUCTIVE SLEEP APNEA RISK USING MEDICARE DATA 2007 - 2019

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Contents

Abbreviations

Abbreviation	Full term
ACNU	Active-Comparator New User
AHI	Apnea-Hypopnea Index
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CCW	Chronic Conditions Data Warehouse
CDW-H	Carolina Data Warehouse
CMS	Centers for Medicare & Medicaid Services
CPAP	Continuous Positive Airway Pressure
CPT	Current Procedural Terminology
DAG	Directed Acyclic Graph
EHR	Electronic Medical Record
FFS	Fee-for-Service
GLP-1RA	Glucagon-Like Peptide 1 Receptor Agonist
HCPCS	Healthcare Common Procedure Coding System
ICD-9	International Classification of Disease, 9th Revision
ICD-10	International Classification of Disease, 10th Revision
ICD-9-CM	International Classification of Disease, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Disease, 10th Revision, Clinical Modification
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
NDC	National Drug Code
NDI	National Death Index
NPV	Negative Predictive Value
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PPV	Positive Predictive Value
PTCA	Percutaneous Transluminal Coronary Angioplasty
QBA	Quantitative Bias Analysis
RD	Risk Difference
RSC	Reference Standard in CDW-H
SGLT-2	Sodium-Glucose Co-Transporter-2
T2D	Type 2 Diabetes
T2DM	Type 2 Diabetes Mellitus
UNC	University of North Carolina

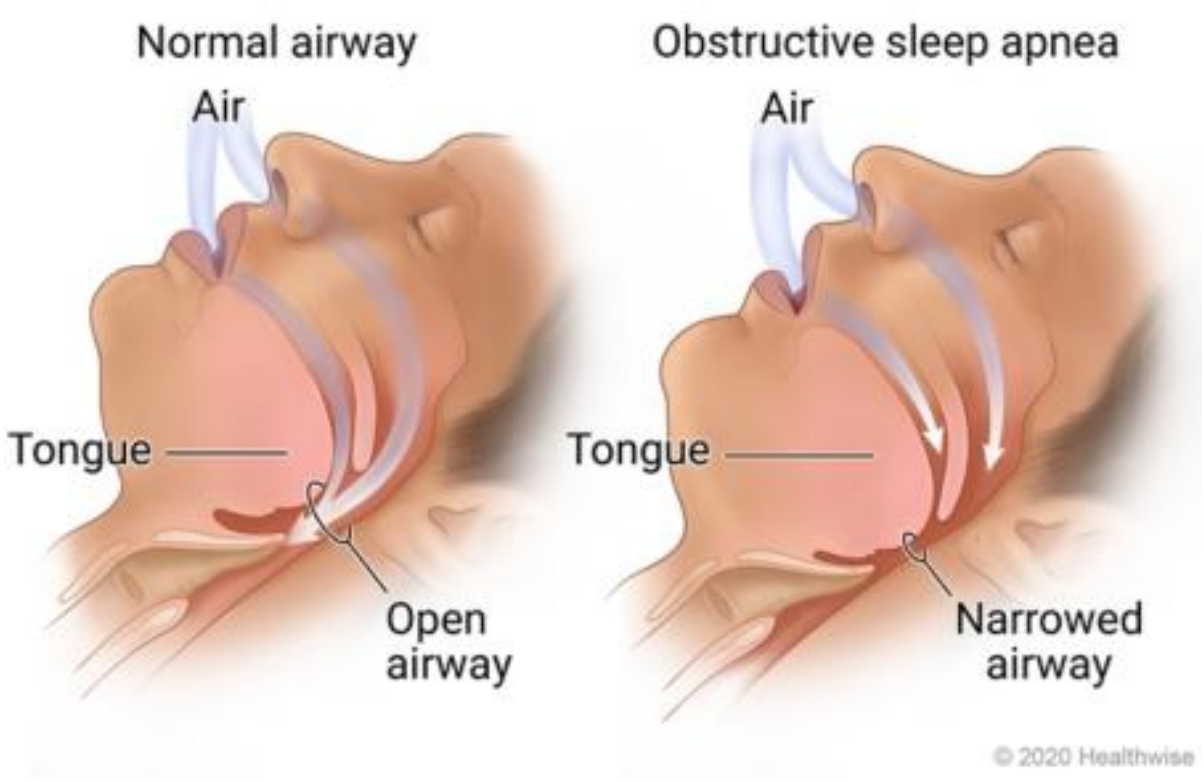
1. Introduction

1.1. Disease overview

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a prevalent chronic disorder characterized by complete or partial upper airway closure which causes patients to temporarily stop or decrease their breathing repeatedly during sleep.[1,2] (Error! Reference source not found.) OSA occurs when the soft tissues in the lower portion of the throat fail to keep the airway open during sleep resulting in markedly reduced (hypopnea) or absent (apnea) airflow at the pharyngeal airway which is usually accompanied by oxyhemoglobin desaturation and is typically terminated by a brief micro-arousal.[3] OSA symptoms may include daytime sleepiness, impaired concentration and mood, morning headaches, snoring, and witnessed breathing pauses during sleep observed by the bed partner.[4] Left untreated, the condition is associated with an increased risk for cardiovascular disease such as hypertension, coronary artery disease, stroke, diabetes and cancer.[5–7] It also has significant psychosocial implications, impacting cognitive function, social interactions, and quality of life.[8]

Figure 1 The development of OSA through complete or partial airway closure



Source: Ignite Healthwise, LLC (2024)[9]

Etiology

The etiology of OSA involves structural anatomy related and nonstructural factors. Structural factors related to craniofacial bony anatomy including retrognathia and micrognathia, maxillo-mandibular hypoplasia, macroglossia, adenotonsillar hypertrophy, particularly in children and young adults, and high, arched palate (particularly in women) predispose patients with OSA to pharyngeal collapse during sleep.[10,11] Nonstructural risk factors for OSA include obesity, central fat distribution, male sex, increasing age, menopause, alcohol use, sedative use and smoking.[12] Among the nonstructural risk factors for OSA, obesity is the most modifiable. It has been estimated that 58% of moderate to severe OSA is attributable to obesity.[13]

Pathophysiology

The pathophysiological causes of OSA vary substantially between individuals. Important components include upper airway anatomy, the ability of the upper airway dilator muscles to respond to respiratory challenge during sleep, the propensity to wake from increased respiratory drive during sleep (arousal threshold), and the stability of the ventilatory control system (loop gain).[14] The upper airway in humans is a collapsible tube of soft tissue and little bony or rigid support. Decreased muscle tone throughout the body, including relaxation of upper airway dilator muscles, leads to a relative narrowing of the air passage during normal sleep. In healthy individuals, this physiological phenomenon does not cause significant symptoms.[15] However, in patients with sleep disorders, upper airway narrowing creates marked airflow turbulence and repetitive partial or complete obstruction of the pharynx during sleep.[16] Despite increased breathing efforts, upper airway collapse results in episodes of obstructive hypopneas or apneas, disrupting sleep architecture. In patients with OSA, neuromuscular activity in the upper airway, including reflex activity, decreases more significantly during sleep. The reduced ventilatory motor output to upper airway muscles is considered the critical initiating event for upper airway obstruction. This effect is most pronounced in individuals with anatomical predispositions to upper airway collapse.[17]

Epidemiology and disease burden

OSA is the most common sleep-related breathing disorder.[18] The global prevalence of OSA, defined broadly as an apnea-hypopnea index (AHI) greater than five events per hour of sleep, in 2019 was estimated to range from 9% to 38% (nearly a billion people).[19] Applying the same broad OSA definition, the estimated prevalence is approximately 15 to 30 percent in males and 10 to 15 percent in females in the United States.[20,21] However, when a more stringent definition is used (AHI ≥5 events per hour plus symptoms or AHI ≥15 events per hour), the estimated prevalence reduces to approximately 15 percent in males and 5 percent in females.[20–22] OSA prevalence increases with age, male sex, and obesity, and is notably higher among individuals with comorbidities such as hypertension, cardiovascular disease, and type 2 diabetes.[6,23] Additionally, racial and ethnic disparities in OSA prevalence have been documented, with African American populations exhibiting a higher burden of

disease independent of body weight.[24] Over the past 30 years, obesity levels in the US adult population have risen dramatically. The percentage change in the age-standardized prevalence of obesity (BMI ≥ 30 kg/m^2) increased by 123.6% (112.4 – 136.4) in males and 99.9% (88.8 – 111.1) in females, partly explaining the increase in OSA prevalence.[25,26]

Diagnosis and Treatment

The presence of OSA may be assessed by formal polysomnography studies. A common measurement of OSA severity in these studies is the AHI. AHI is an average that represents the combined number of apneas and hypopneas that occur per hour of sleep. AHI levels of 5 to 14, 15 to 29, and 30 or greater have been used to classify OSA as mild, moderate and severe respectively.[27–29] Treatment of OSA include lifestyle modifications such as behavioral changes with diet and exercise programs, continuous positive airway pressure (CPAP) therapy, medications (tirzepatide, modafinil, and armodafinil), mandibular advancement devices, jaw or tongue retraining devices, and surgical procedures to address or bypass airway obstruction.[30] Furthermore, weight loss is an integral part of the management of OSA. Indeed, weight loss by either medical or surgical approaches can significantly alleviate OSA symptoms by improving the airway's size and function, potentially even leading to remission (AHI < 5 events/h) in some cases.[31,32]

Research Gaps

Overall, there remain limited effective pharmacological treatments for OSA. Although CPAP and weight loss are the primary interventions for OSA, adherence to CPAP therapy is suboptimal, and weight loss can be challenging for many patients.[33] GLP-1RAs represent a promising therapeutic option, offering both weight loss and metabolic benefits. Limited evidence suggests a potential role for glucagon-like peptide-1 receptor agonists (GLP-1RAs) in OSA management in patients with type 2 diabetes mellitus (T2DM), but rigorous studies are needed to confirm this relationship. Understanding the effects of GLP-1RAs on OSA risk is important to inform treatment strategies for individuals newly diagnosed with T2DM, potentially reducing the burden of comorbid OSA and improving patients' quality of life.

Furthermore, while the cardiovascular benefits of GLP-1RAs in T2DM are well-documented, it remains unclear whether OSA modifies these effects. Biologically, it is plausible OSA could modify the cardiovascular effects of GLP-1RAs through pathophysiologic mechanisms that independently promote inflammation, atherogenesis, endothelial dysfunction, hypertension, and arrhythmogenesis.[3,14] These mechanisms have been shown in research studies to amplify cardiovascular risk beyond traditional metabolic drivers and are linked with progression of subclinical atherosclerosis and adverse cardiovascular outcomes.[34–36]Investigating this interaction could therefore refine our understanding of how to optimize treatment strategies for patients with T2DM and comorbid OSA.

1.2. Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide (GIP) Receptor Agonists

GLP-1RAs are a class of incretin-based antihyperglycemic drugs which are commonly used as second-line in the treatment of patients with T2DM.[37] These agents mimic the action of the incretin hormone GLP-1 by stimulating insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety. Notably, GLP-1RAs have demonstrated substantial benefits in weight reduction and cardiovascular health, including improved glycemic control, reduced blood pressure, and decreased inflammation.[38]

In recent years, GLP-1RAs such as semaglutide and liraglutide and the dual GIP/GLP-1RA, tirzepatide have been approved for weight management in individuals with obesity, even in the absence of diabetes.[39] Studies have shown that these agents can lead to significant weight loss, primarily through appetite suppression and reduced caloric intake.[40–44] Tirzepatide, in particular, demonstrated unprecedented weight loss in the SURPASS and SURMOUNT trials. In SURPASS-1, tirzepatide induced a dose-dependent bodyweight loss ranging from 7.0 to 9.5kg in people with T2DM after 40 weeks compared to placebo while in SURMOUNT-1, 50% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants in the 10mg and 15mg tirzepatide groups achieved body weight reductions of 20% or more compared with 3% in the placebo group at 72 weeks.[42,43]

Given the strong association between obesity and OSA, it is hypothesized that GLP-1RAs may influence OSA by reducing weight and visceral fat, potentially alleviating upper airway obstruction.[45] Early evidence supporting this hypothesis emerged from randomized trials of liraglutide. In the SCALE Sleep Apnea trial, Blackman et al. (2016) randomized adults with obesity and moderate-to-severe OSA who were unwilling or unable to use continuous positive airway pressure (CPAP) to liraglutide 3.0 mg or placebo for 32 weeks. Liraglutide produced significantly greater weight loss (−5.7% vs −1.6%) and a larger reduction in apnea–hypopnea index (AHI) compared with placebo (−12.2 vs −6.1 events/hour), demonstrating that GLP-1RA therapy can directly improve objective measures of OSA severity.[46] More recently, semaglutide has been evaluated in populations with overweight or obesity, although OSA was not always a prespecified endpoint. In the STEP-1 trial, once weekly semaglutide 2.4 mg plus lifestyle modifications induced a change in body weight from baseline to 68 weeks of −15.3kg in the semaglutide group compared with −2.6kg in the placebo group (estimated treatment difference, −12.7kg; 95% CI, −13.7 to −11.7).[44] The development of dual GIP/GLP-1RA such as tirzepatide has further advanced this evidence. In both pivotal studies (SURPASS and SURMOUNT trials), tirzepatide significantly reduced AHI and improved oxygen desaturation indices compared with placebo, alongside substantial weight loss, establishing the first large-scale evidence that dual incretin agonists can directly modify OSA severity.[42,43]

Despite these advances, important gaps remain. Most trials have focused on OSA severity among prevalent cases rather than incident disease, and evidence in older, high-risk populations is limited.

This protocol details the scope and methodology of the dissertation.

2. Objectives

Aim 1: To estimate the comparative effect of GLP-1RA versus sodium-glucose co-transporter-2 (SGLT-2) inhibitors on the incidence of OSA in older adults with type 2 diabetes.

Aim 2: To investigate whether comorbid OSA at baseline modifies the comparative effect of GLP-1RA (vs. SGLT-2 inhibitors) on the incidence of adapted major adverse cardiovascular events (MACE) defined as stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or all-cause mortality in older adults with type 2 diabetes.

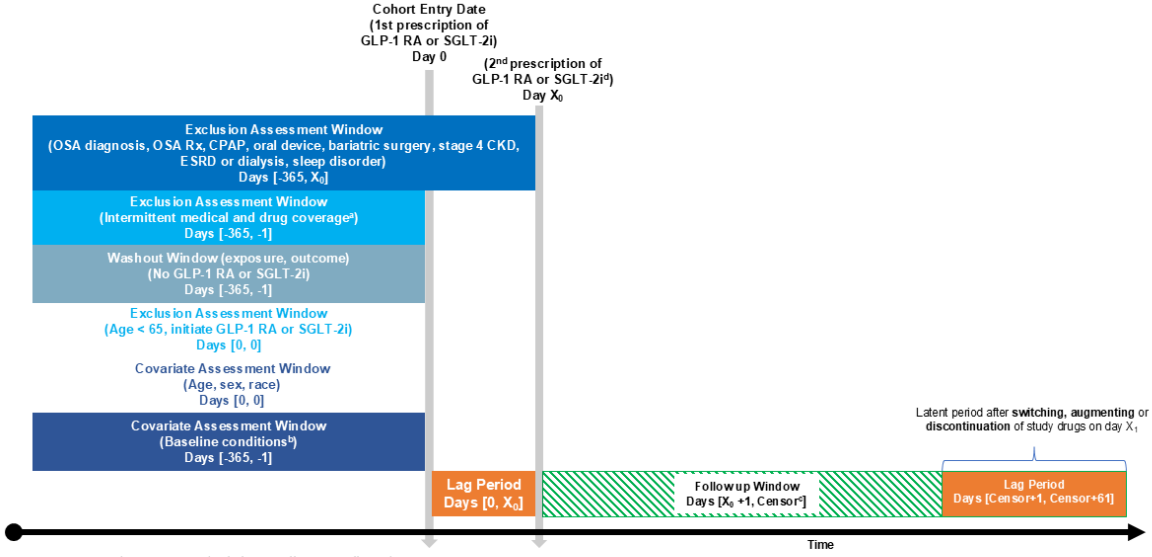
3. Study design

We will implement an active-comparator, new user (ACNU) retrospective cohort study design to identify new users of GLP-1RA and new users of SGLT-2 inhibitors after a washout period of 12 months without any dispensed prescriptions for the two drug classes compared. This emulates a head-to-head trial comparing patients assigned to treatment with GLP-1RA versus SGLT-2 inhibitors. By enrolling only new users and following subjects from the start of treatment, time-varying hazards, including lag times, can be assessed, and described, while preserving the temporality of covariate assessment. The rationale behind choosing an active comparator (a guideline treatment alternative for GLP-1 agonists) is to minimize the impact of confounding by indication and other unmeasured patient characteristics (such as healthy initiator bias or frailty).[47]

Index Drug	**Comparator Drug**
GLP-1 receptor agonists	SGLT-2 inhibitors

Figure 2. Overview of study design and new user cohort for as treated analysis

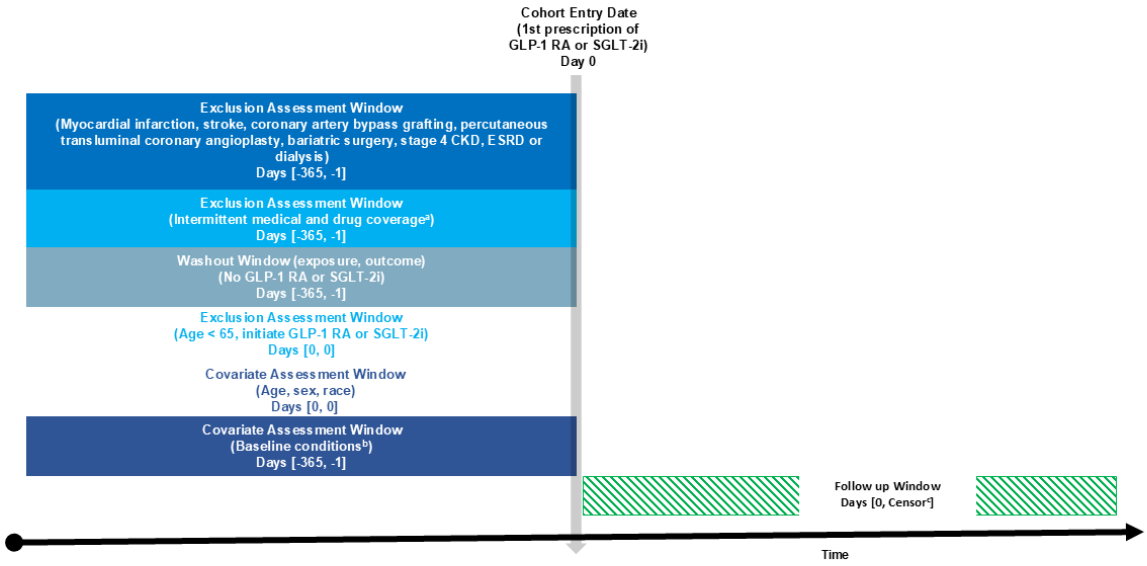
Aim 1:



a. Up to 30-day gaps in medical plan enrollment or allowed
b. Baseline conditions included: Diabetes mellitus, Hypertension, Hyperlipidemia, Chronic obstructive pulmonary disease, Congestive heart failure, Myocardial infarction, Chronic kidney disease, Depression, Thyroid disorders (Hypothyroidism, Hyperthyroidism, Goiter), Pancreatic disorders (Pancreatic disease, Acute Pancreatitis, Chronic Pancreatitis), Diabetic complications (neuropathy, nephropathy, cataract, retinopathy), Obesity
c. Earliest of: outcome of interest (obstructive sleep apnea [OSA]), disenrollment, death, end of the study period
d. 2nd prescription of initial drug class within days supply of 1st prescription and 30-day grace period allowing for switching within drug class

GLP-1 RA = Glucagon-like peptide 1 receptor agonist
SGLT-2i = Sodium-glucose cotransporter-2 inhibitor
CPAP = Continuous positive airway pressure
CKD = Chronic kidney disease
OSA Rx = Prescriptions for modafinil, and armodafinil
ESRD = End-stage renal disease

Aim 2:



a. Up to 30 day gaps in medical or pharmacy enrollment allowed
b. Baseline conditions included: Diabetes mellitus, Hypertension, Hyperlipidemia, Chronic obstructive pulmonary disease, Congestive heart failure, Chronic kidney disease, Depression, Thyroid disorders (Hypothyroidism, Hyperthyroidism, Goiter), Pancreatic disorders (Pancreatic disease, Acute Pancreatitis, Chronic Pancreatitis), Diabetic complications (neuropathy, nephropathy, cataract, retinopathy), Obesity, obstructive sleep apnea
c. Earliest of: outcome of interest (stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty or all-cause mortality), switching, augmenting or discontinuation of study drugs, disenrollment, end of the study period

GLP-1 RA = Glucagon-like peptide 1 receptor agonist
SGLT-2i = Sodium-glucose cotransporter-2 inhibitor
CKD = Chronic kidney disease
ESRD = End-stage renal disease

4. Data Source

Medicare Fee-for-Service (FFS) Database (Parts A, B, and D) 2007-2019 (or additional years of data if available). This US federal database contains deidentified individual-level, longitudinal information on demographics, diagnoses, and procedures, and outpatient prescription dispensations recorded during billing of all health care encounters.

The Medicare data available at UNC comprises a randomly selected 20% national sample of all Medicare FFS beneficiaries aged 65 years and older who were simultaneously enrolled in Medicare Part A (inpatient services), B (physician and outpatient services), and D (prescription drugs) plans for a minimum of one calendar month from 2007 to 2019. Once selected into the sample, all future claims become part of the database.

5. Study population

The base population for the analysis will consist of all fee-for-service Medicare beneficiaries aged 66 years or older with at least one prescription dispensing claim for GLP-1RA or SGLT-2 inhibitors between January 1, 2008, and December 31, 2018.

5.1. Inclusion criteria

We will include an active comparator new user cohort where GLP-1 agonists are compared with SGLT-2 inhibitors. New users are defined as individuals who initiate the drugs of interest or their active comparator after a preceding washout period of at least 12 months without a prescription for the drug classes compared. Participants are allowed to have other anti-hyperglycemic drugs during the washout period except the drugs being compared. Study subjects are required to have 2 diagnosis codes for T2DM and at least 12 months of continuous part A, B, and D coverage before the first prescription date. Since SGLT2 inhibitors were approved in March 2013[48], the earliest possible first prescription date for this study will be January 1, 2014, allowing for adoption and uptake in clinical practice and mitigating channeling bias immediately after approval.[49]

5.2. Exclusion criteria

We will exclude all patients who do not refill the same drug class within the days supply and a grace period of 30 days after the first prescription. Requiring two prescriptions increases the probability that patients actually started therapy. We will describe the patients who do not meet the refill criterion to assess the potential selection imposed by requiring a refill. Patients with evidence of pre-existing OSA (diagnosis of OSA, prescriptions for modafinil and armodafinil, prior use of continuous positive airway pressure (CPAP) therapy, oral device) and adapted Major Adverse Cardiovascular Events (MACE) (see outcome section) within all the available lookback period prior to the first prescription or between the first and 2nd prescription will be excluded from the analysis for Aim 1 and Aim 2 respectively. For both Aims 1 and 2, we will also exclude patients with a history of bariatric surgery, stage 4 chronic kidney disease,

end-stage renal disease or dialysis during the lookback period prior to the first prescription. Additionally, for Aim 1, we will exclude patients with any sleep disorder, tracheostomy and current home oxygen therapy within the lookback period prior to the first prescription.

6. Exposure

Exposure will be defined by at least two same drug class prescription dispensing claims of either GLP-1 agonists or SGLT-2 inhibitors (active comparator) for Aim 1 and at least one prescription dispensing claim of either GLP-1 agonists or SGLT-2 inhibitors for Aim 2 between January 1, 2014, and December 31, 2018, identified using Anatomical Therapeutic Chemical (ATC) classification codes and National Drug Codes (NDCs). We will identify an active comparator cohort where GLP-1 agonists are compared with SGLT-2 inhibitors.

Table 1. Anatomical Therapeutic Chemical (ATC) classification codes used to identify exposure

Drug class	**ATC code**
GLP-1 agonists	
Exenatide	A10BJ01
Exenatide Extended Release	A10BJ01
Liraglutide	A10BJ02
Insulin degludec and Liraglutide	A10AE56
Lixisenatide	A10BJ03
Insulin glargine and Lixisenatide	A10AE54
Albiglutide	A10BJ04
Dulaglutide	A10BJ05
Semaglutide	A10BJ06
SGLT-2 inhibitors	
Dapagliflozin	A10BK01

Dapagliflozin and metformin	A10BD15
Dapagliflozin and saxagliptin	A10BD21
Canagliflozin	A10BK02
Canagliflozin and metformin	A10BD16
Empagliflozin	A10BK03
Empagliflozin and linagliptin	A10BD19
Empagliflozin and metformin	A10BD20
Ertugliflozin	A10BK04
Ertugliflozin and metformin	A10BD23
Ertugliflozin and sitagliptin	A10BD24

7. Outcome

7.1. Aim 1

The outcome of interest for Aim 1 is incident obstructive sleep apnea (OSA). The American Academy of Sleep Medicine (AASM) guidelines recommend ordering sleep studies (in-lab polysomnography or technically adequate home sleep apnea tests) only when there is clinical suspicion of moderate-to-severe OSA and note that repeat testing after a negative result is uncommon unless symptoms persist or the initial test was inconclusive.[50] OSA will therefore be defined if there are both a polysomnography and least one diagnosis code for OSA (ICD-9 code 327.23 or ICD-10 code G47.33) within 60 days after the polysomnography (Healthcare Common Procedure Coding System 95808, 95810, 95811, G0398-G0400) in line with Sterling et al..[51] Date of diagnosis will be assigned at the first OSA claim associated with polysomnography. However, because this algorithm was used for cohort definition and has not been validated in Medicare claims data, we will implement four other algorithms for defining OSA: 1) A polysomnography and at least one procedure code for OSA treatment (positive airway pressure (PAP) therapy or oral device) or diagnosis code for OSA within 60 days after the polysomnography.[52] 2) A polysomnography and at least one diagnosis code for unspecified sleep apnea plus one procedure code for OSA treatment (positive airway pressure (PAP) therapy or oral device) within 60 days after the polysomnography. 3) At least two diagnosis codes of OSA within 60 days.[53] 4) At least

one procedure code for OSA treatment (positive airway pressure (PAP) therapy or oral device). The detailed list of codes for implementing the specified algorithms for identifying incident OSA is provided in Table 3. The performance of all five algorithms will be assessed in a validation study using linked Medicare and EHR data (details in section on validation study).

Table 2. Codes used to identify obstructive sleep apnea outcome

Code Type	Code	Outcome
ICD-9-CM Diagnosis code*	327.20, 327.23, 780.51, 780.57, 780.53	Obstructive sleep apnea (adult) (pediatric), organic sleep apnea, unspecified, unspecified sleep apnea, insomnia with sleep apnea, unspecified, hypersomnia with sleep apnea, unspecified
ICD-10-CM Diagnosis code†	G47.30, G47.33	Sleep apnea , unspecified, Obstructive sleep apnea (adult) (pediatric)
CPT§/HCPCS‡	E0485, E0486, E0601, E0470, E0471, 94660, 95808, 95810, 95811, G0398, G0399, G0400	Oral device/appliance, Continuous airway pressure device, Respiratory assist device, bi-level pressure capability, without backup rate feature, used with noninvasive interface, sleep test

*ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification
†ICD-10-CM International Classification of Disease, Tenth Revision, Clinical Modification
‡HCPCS Healthcare Common Procedure Coding System
§CPT Current Procedural Terminology

7.2. Aim 2

The outcome for **Aim 2** is adapted MACE, a composite of myocardial infarction (MI), stroke, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), and all-cause mortality.[54] We use an adapted definition that substitutes all-cause mortality for cardiovascular death because Medicare claims

data do not reliably distinguish cause-specific mortality. Adapted MACE will be defined by the first occurrence of any of these outcomes. MI, stroke, CABG and PTCA will be determined from insurance claims using ICD codes described in **Table 3**. All-cause mortality will be defined by the presence of a death date in Medicare summary file. Research suggests strong concordance between death dates as recorded by Centers for Medicare & Medicaid Services (CMS) enrollment data and the National Death Index (NDI) in the entire Medicare population (kappa score of 0.98).[55]

Table 3. Codes used to identify Adapted MACE outcomes

Code Type	Code and Position	Outcome (Discharge Diagnosis)
ICD-9-CM Diagnosis code*	410.xx (except 410.x2, subsequent episode of care) in any of first 5 discharge code positions	Hospitalization for acute myocardial infarction
ICD-10-CM Diagnosis code†	I21.xx in any of first 5 discharge code positions	
ICD-9-CM Diagnosis code	433.x1, 434.x1, or 436 (excluding 434.x0) in the primary diagnosis position on an inpatient claim	Hospitalization for ischemic stroke
ICD-10-CM Diagnosis code	I63.xxx in the primary diagnosis position on an inpatient claim	
ICD-9-CM Diagnosis code	V45.81, 414.02, 414.03, 414.04, 414.05 in any position	Coronary Artery Bypass Grafting (CABG) procedures
ICD-9 Procedure code	36.1x in any position	
ICD-10-CM Diagnosis code	Z95.1, T82.21x, I25.7x (except I25.75x), I25.810, I25.812 in any position	
ICD-10 Procedure code	0210 – 0213 in any position	

CPT§/HCPCS‡	33510 – 33536, 4110F in any position	
ICD-9-CM Diagnosis code	V45.82 in any position	Percutaneous transluminal coronary angioplasty (PTCA)
ICD-9 Procedure code	36.0x, 00.6x, 00.4x in any position	
ICD-10-CM Diagnosis code	Z95.5, Z98.61 in any position	
ICD-10 Procedure code	02703ZZ in any position	
CPT/HCPCS	92920 - 92928 in any position	
Medicare Summary File data	Death date	All-cause mortality

*ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification
†ICD-10-CM International Classification of Disease, Tenth Revision, Clinical Modification
‡HCPCS Healthcare Common Procedure Coding System
§CPT Current Procedural Terminology

8. Follow-up

The analysis of both Aims 1 and 2 will employ an "as-treated" approach. Follow-up will begin after the second prescription date for Aim 1 or after the first prescription date for Aim 2 and will continue until the occurrence of the outcome of interest or any censoring event. Censoring events include treatment discontinuation, switching to comparator, or augmentation with comparator, death from any cause (with the exception of an analysis treating death as a competing event, see below) for Aim 1 only, termination of enrollment in Medicare Part A, B, or D claims data, or December 31, 2019, whichever comes first. Patients who develop OSA between the 1st prescription and start of follow up in Aim 1 will be described and excluded from the study.

Treatment discontinuation will be defined as the absence of a prescription of the cohort drug class within the days of supply plus a 30-day grace period following the

last prescription. Switching to and augmenting with the other drug class will be defined as first dispensed prescription of the other drug class.

9. Covariates

Covariates determined by means of a directed acyclic graph (DAG; see appendix C) for **Aim 1** and **Aim 2** will be assessed during the 1 year before the first prescription date except for age, sex and race/ethnicity which will be assessed on the first prescription date. We will examine the following baseline covariates:

9.1. Aim 1

Demographics:

- Age, sex, race/ethnicity, year of cohort entry, available measures of socioeconomic status

Codes for Comorbidities:

- Diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, congestive heart failure, ischemic heart disease, myocardial infarction, chronic kidney disease, depression, thyroid disorders (hypothyroidism, hyperthyroidism, goiter), pancreatic disorders (pancreatic disease, acute pancreatitis, chronic pancreatitis), diabetic complications (neuropathy, nephropathy, cataract, retinopathy), depression, obesity

Codes for Health Behaviors:

- Tobacco use, alcohol use

Comedications:

- Insulin (long and short acting separately), metformin, thiazolidinediones, sulfonylureas, DPP4-I, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, loop diuretics, other diuretics, beta blockers, calcium channel blockers, NSAIDs, hormone therapy, CPAP, modafinil, and armodafinil

Healthcare utilization:

- Number of hospital admissions, duration of hospital admissions, number of outpatient visits, number of emergency department visits, number of surgical procedures, number of HbA1c tests, lipid panel, flu vaccination, endocrinology visit

9.2. Aim 2

Demographics:

- Age, sex, race/ethnicity, year of cohort entry, available measures of socioeconomic status

Codes for Comorbidities:

- Diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, congestive heart failure, ischemic heart disease, chronic kidney disease, depression, thyroid disorders (hypothyroidism, hyperthyroidism, goiter), pancreatic disorders (pancreatic disease, acute pancreatitis, chronic pancreatitis), diabetic complications (neuropathy, nephropathy, cataract, retinopathy), depression, obesity, obstructive Sleep Apnea (defined based on the most specific definition of OSA out of the five algorithms)

Codes for Health Behaviors:

- Tobacco use, alcohol use

Comedications:

- Insulin (long and short acting separately), metformin, thiazolidinediones, sulfonylureas, DPP4-I, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, loop diuretics, other diuretics, beta blockers, calcium channel blockers, NSAIDs, hormone therapy, CPAP, modafinil, and armodafinil

Healthcare utilization:

- Number of hospital admissions, duration of hospital admissions, number of outpatient visits, number of emergency department visits, number of surgical procedures, number of HbA1c tests, lipid panel, flu vaccination, endocrinology visit

See Appendix for the complete list of covariate definitions and DAG.

10. Statistical analysis

10.1. Aim 1

Propensity Score (PS) methods will be used to control for measured confounders. Specifically, logistic regression will be utilized to estimate propensity scores - the probability of initiating GLP-1RA compared to SGLT-2 inhibitors, conditional on baseline covariates. Our primary aim is to estimate the counterfactual scenario of what would have happened to the initiators of GLP-1RA if they had initiated SGLT-2 inhibitors instead. To achieve this goal, we will estimate the average treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS)) (Standardized Morbidity Ratio Weighting).[56] The adequacy of covariate balance will be evaluated based on standardized absolute mean differences (SAMD), with a threshold of less than 0.1 indicating satisfactory balance.[57]

We will implement Cox models overall and stratified by calendar year of initiation.[58] Standardized Morbidity Ratio (SMR) weighted Kaplan-Meier survival functions will be compared between our cohorts, adjusted for the same baseline covariates. The primary effect measure estimate will be weighted cumulative incidence differences (CID). We will estimate CID at various times (e.g. 1, 2, and 3 years) after drug

initiation and generate cumulative incidence plots with the assumption that there is no unmeasured confounding. To estimate the CID and generate corresponding plots, we will use the Cox model as computational tool to derive model-based survival probabilities from which cumulative incidence functions will be computed.

As secondary analyses, first, we will stratify our analysis by age at cohort entry (≥66 – 75 years and ≥76 years), sex , and race/ethnicity (depending on sample size). Additionally, when estimating the risk of health outcomes in older Medicare patients, censoring those who died before hypothetically experiencing the outcome of interest, as commonly done, could introduce bias in the risk estimation.[59,60] Therefore, because death is a competing risk in this older population, we will also employ Aalen-Johansen (AJ) estimators to assess the impact of this potential bias on our primary risk estimates. First, we will estimate the overall survival function and hazard function for each event type (outcome of interest as well as death) in the SMR weighted population. Next, we will compute the AJ estimators by multiplying the hazard function of the outcome of interest at each event time by the overall survival at the previous time point. This approach effectively treats death as a competing event by assigning patients a risk of 0 for incident OSA after death.[61] Finally, we will estimate SMR weighted hazard ratios (HRs) as secondary effect measure estimates using the Cox model without accounting for competing risks. This analysis will assume proportional hazards and potential non-proportionality will be assessed by graphical examination of hazard curves to confirm they do not cross.[62]

10.2. Aim 2

The analysis will follow all the details described for Aim 1 except for treating death as a competing risk since death is a component of the outcome. Thus, the primary estimand remains the ATT in the overall study population. Additionally, for Aim 2, the effect estimate of initiating GLP-1RA versus SGLT-2 inhibitor on the incidence of adapted MACE across levels of OSA status will be compared to assess effect measure modification by baseline comorbid OSA on the absolute scale. To evaluate effect modification by baseline comorbid OSA (defined based on the most specific definition of OSA out of the five algorithms), we will re-estimate propensity scores separately within each OSA stratum (OSA present vs. OSA absent) and apply SMR weighting so that, in each stratum, the SGLT-2 inhibitor group is standardized to the covariate distribution of GLP-1RA initiators to achieve optimal covariate balance. This stratified propensity score approach allows us to account for potential differences in the distribution of effect modifiers and confounders across OSA strata, providing the best non-parametric estimate of the treatment effect within each stratum. To formally test for effect modification, we will fit a weighted additive Poison model including all patients from both OSA strata, with an interaction term between exposure and baseline OSA status. The outcome model will include a prespecified, parsimonious set of covariates chosen a priori based on clinical relevance and constraints imposed by the number of observed adapted MACE events (approximately 10-15 events per covariate).[63] Statistical tests of homogeneity (Wald test and the log likelihood ratio test using a = 0.20) will be used to assess evidence of statistical interaction between incident rate differences of adapted MACE among initiators of GLP-1RA versus SGLT-2 inhibitor across levels of OSA. In the event the Poison model fails to converge, a Cox model with an

interaction term between exposure and baseline OSA status will be used instead to compare hazard ratios of adapted MACE among initiators of GLP-1RA versus SGLT-2 inhibitor across levels of OSA.

11. Sensitivity analyses

To examine the robustness of our primary results to changes in study population and condition definitions, we plan to perform the following sensitivity analyses:

1. We will repeat the primary analysis using initial treatment analysis (IT) (no censoring for drug discontinuation, switching, or augmentation).
2. We will repeat the IT analysis above without requiring part D data during follow-up and will thus censor for loss of parts A or B coverage only.
3. Since it takes substantial weight loss to impact OSA, we will repeat the analysis restricting to patients who initiate semaglutide, the most effective GLP-1RA for weight loss prior to tirzepatide's approval in 2022.
4. Repeat primary analysis excluding individuals with diagnosis for chronic obstructive pulmonary disease (COPD), depression and hypothyroidism at baseline.
5. Repeat primary analysis excluding individuals with a cancer diagnosis (except non-melanoma skin cancer) or cancer related procedures during the lookback period.
6. We will repeat the primary analysis but include individuals with only 1 prescription for a study drug.
7. We will vary the grace period from 30 days to 15, and 60 days.
8. We will vary the length of the lag-period (both after initiation and after stopping, switching, or augmenting) from 60 days to 0 and 90 days for Aim 1 and from zero to 60, and 90 days for Aim 2 to assess the robustness of the primary analysis results to the length of these periods.
9. We will repeat the analyses using the other algorithms for the definition of OSA incidence.
10. We will perform asymmetric trimming of propensity scores (1%, 2.5%, and 5% cut-points) to assess the significance of any populations treated contrary to expectation (i.e. populations treated with GLP-1RA despite low PS, or treated with SGLT2i despite high PS) and the effect they have on the overall weighting and the effect measure estimate [64].
11. Restrict analysis to 1st new use period.
12. Repeat analysis restricting to patients with baseline metformin use. This approach has been shown to improve confounding control and covariate balance by restricting to populations that are using study drugs as second-line therapies following initial metformin use.
13. Include patients initiating GLP-1RA or SGLT-2 inhibitors in 2019 with less than one year of follow-up.

12. Quantitative bias analysis

12.1. Overview

Quantitative bias analysis (QBA) comprises the methods used to estimate the direction, magnitude, and uncertainty of bias arising from systematic errors that

impact an estimate from epidemiologic research.[65] Uncontrolled confounding is a key source of systematic error or bias in observational studies. It occurs when variables (*U*) that are not mediators of the observed exposure-outcome association, and that can explain part or all of the observed effect, are not measured and controlled for during study design or analysis.[66,67] QBA techniques to adjust for uncontrolled confounding fall largely under simple sensitivity analysis, multidimensional analysis, probabilistic analysis (summary level and record level), direct bias modeling and missing data methods, Bayesian bias analysis, and multiple bias modeling.[68] Applications of these methods include bias formulas, direct specification of the bias factor,[69] simulation or imputation of *U* using external information,[70–72] propensity score calibration using validation data,[73–75] intensity scores,[76] the use of negative controls,[77] and bounding techniques,[78–81] among others.

Observational studies leveraging claims data often inadequately adjust for obesity, a key confounder in the GLP-1RA - OSA relationship, due to lack of body mass index (BMI) measurements and the underuse and poor validity of weight-related diagnosis codes.[82–85] BMI is a statistical index using a person's weight and height to provide an estimate of body fat in adult males and females. It is calculated by taking a person's weight, in kilograms, divided by their squared height, in meters.[86] Unmeasured confounding by BMI may bias effect estimates, as GLP-1RAs are known to significantly reduce weight whereas SGLT-2is have minimal weight loss effect, making it likely that patients with high BMI will be preferentially prescribed GLP-1RAs and high BMI is a strong risk factor for OSA (and, to a lesser extent, MACE).[12,23] Consequently, failure to adjust for BMI would likely inflate the observed risk of OSA among GLP-1RA compared with SGLT-2i initiators and underestimate the true protective effect of GLP-1RAs (or overestimate harm). It is therefore important to quantify how the adjusted cumulative incidence differences comparing the incidence of obstructive sleep apnea among Medicare beneficiaries initiating GLP-1 receptor agonists versus SGLT-2 inhibitors in our primary analysis may be biased by an unmeasured confounder – BMI. Using BMI as a continuous variable, instead of a binary obesity classification (BMI ≥30 kg/m²), offers critical advantages for confounding adjustment in observational studies. Continuous BMI preserves granularity by capturing the full spectrum of adiposity, from underweight to severe obesity, rather than dichotomizing individuals into "obese" or "non-obese" categories, especially in patients with T2D with a very high prevalence of obesity.

12.2. Objective

To assess the potential influence of unmeasured BMI on the estimated adjusted 3-year cumulative incidence difference of OSA comparing initiators of GLP-1RA versus SGLT-2 inhibitors.

12.3. Data source

Patient data will be obtained from Medicare Fee-for-Service (FFS) Database (Parts A, B, and D) 2007-2019 maintained by UNC-Chapel Hill's Cecil G. Sheps Center for Health Services Research (Sheps Center) linked with data from the Carolina Data Warehouse for Health (CDW-H) 2014-2019.

Individuals who had at least one in-person health encounter in the electronic health record of the University of North Carolina Health (UNCH) system, and a documented, Medicare issued, Health Insurance Claim number (HIC) or Medicare Beneficiary Identifier (MBI) between April 4th 2014 and December 31st 2021 were linked to their Medicare Fee-for-service (FFS) claims between January 1st 2015 and December 31st 2019 (inclusive).

The Carolina Data Warehouse for Health (CDW-H) is a central data repository containing EHR data sourced from the University of North Carolina (UNC) Health Care System which comprises 16 hospitals across 20 campuses and more than 900 clinics in North Carolina (NC).[87,88] The data covers a wide range of patient demographic, clinical, and administrative data with data elements as far back as 2014.

12.4. Data linkage process

Linkage to Medicare administrative claims data was performed deterministically by the Centers for Medicare & Medicaid Services using the unique Medicare identifier (HIC/MBI). UNC received a crosswalk with the encrypted EHR medical record number and encrypted Medicare ID that is consistent across all Medicare data provided to UNC, with additional flags documenting whether the sex and date of birth variables were also an exact match.

12.5. Inclusion criteria

Linked Medicare FFS beneficiaries who meet the following claims data-based criteria will be included:

- Flagged as having exact matching sex and date of birth values
- A diagnosis of T2DM and aged ≥66 years
- New users of GLP-1RA or SGLT-2 inhibitors between January 1, 2014, and December 31, 2018, after a preceding washout period of at least 12 months
- Have at least 12 months of continuous insurance coverage (Parts A, B, and D) before the first prescription date

12.6. Exclusion criteria

Linked Medicare FFS beneficiaries who meet the following claims data-based criteria will be excluded:

- Flagged as having mismatching sex and date of birth values
- Non-T2DM patients
- Patients aged <66 years
- Patients who do not refill the same drug class within the days' supply plus a grace period of 30 days after the first prescription.
- Patients with a pre-existing sleep apnea diagnosis, prescriptions for modafinil, and armodafinil, prior use of continuous positive airway pressure (CPAP) therapy or oral device within all the available lookback period prior to the first prescription or between the first and 2nd prescription.

- Patients with a history of bariatric surgery, any sleep disorder, stage 4 chronic kidney disease, end-stage renal disease or dialysis, tracheostomy and current home oxygen therapy during the lookback period.

To understand the selection introduced by applying these inclusion and exclusion criteria, we will compare the distribution of baseline covariates across three progressively restricted cohorts: (1) all GLP-1RA and SGLT2i initiators in the national 20% random sample of Medicare FFS enrollees (Cohort I); (2) all GLP-1RA and SGLT2i initiators in the linked Medicare FFS sample (Cohort II); and (3) Cohort II subsample with non-missing BMI values (Cohort III). Additionally, we will quantify the proportion of linked beneficiaries with missing BMI data between April 4, 2014, and December 31, 2019, describe their characteristics, and assess potential differences from those with non-missing BMI. This comparison will inform the potential for selection bias when conducting analyses requiring BMI or implementing quantitative bias analysis using BMI distributions derived from linked EHR data.

12.7. Derivation of observed BMI

BMI will be derived from CDW-H data as follows:

Step 1: Identification of height and weight measurements

Since adult stature remains largely stable over time, we will use any height measurement in the data irrespective of whether it was recorded before or after index date to maximize completeness without substantial misclassification of stature.[89] For weight, which may fluctuate, we will extract all available weight measurements within 365 days before index and calculate the median weight for each patient for simplicity and to reduce the number of missing values.

Step 2: Data cleaning and plausibility checks

All height and weight values will be standardized to meters and kilograms, respectively, using standard conversion factors (1in = 0.0254m; 1lb = 0.4536kg). Height values outside the range of 1.2 to 2.2 meters and weights outside 30 kilograms and 300 kilograms, which encompasses typical adult anthropometric reference ranges will be excluded as implausible.[90]

Step 3: Calculate BMI

Cleaned height (m) and weight (kg) values will be combined to calculate BMI as:

$$\text{BMI} = \frac{\text{weight (kg)}}{[\text{height (m)}]^2}$$

To evaluate the possibility of confounding by BMI, we will follow the approach described by Stürmer *et al.*,[91] to test whether BMI predicts treatment choice independently of measured covariates. Specifically, we will estimate the association between BMI and choice between initiating GLP-1RA versus SGLT-2 inhibitor

independent of other covariates, by fitting a PS model equivalent to the one in the main cohort using linked Medicare FFS claims data and adding BMI values from the electronic health record (CDW-H) where information on BMI is available (complete case analysis). To do so, we will fit a PS model with the same variables in the claims-based PS model in addition to BMI using Cohort III. If BMI does not predict treatment choice independent of claims data covariates, this means that it is well balanced between initiators of GLP-1RA and SGLT-2 inhibitor conditionally on these covariates and cannot confound a comparison of OSA outcomes for which BMI is a strong risk factor.

If the analysis described above, as expected, provides evidence for BMI being associated with treatment choice independent of other covariates (and hence a confounder of the GLP-1RA vs. SGLT2i effect estimate on OSA), we will assess the potential influence of unmeasured BMI on the effect estimate. Our primary approach will be a QBA using bias formulas. As a secondary approach, contingent on the number of outcome events, we will implement multiple imputation.

12.8. Probabilistic bias analysis

Unmeasured confounding due to obesity (BMI categories)

To explore the impact of dichotomization of BMI versus continuous BMI on confounding control, we will classify individuals in cohort III with BMI measurements greater than or equal to 30kg/m^2 as obese and those with BMI measurements lesser than 30kg/m^2 as non-obese.[86] If obesity prevalence is unbalanced between initiators of GLP-1RA and SGLT-2 inhibitor, we will use probabilistic bias analysis to investigate the influence of unmeasured obesity on the estimated effect of GLP-1RA versus SGLT-2 inhibitors initiation on incident OSA in an exploratory analysis. To do so, we will follow the following steps:

Step 1: Identify the bias parameters

We will leverage the linked claims-EHR data (cohort III) to obtain plausible estimates of obesity prevalences among initiators of GLP-1RA (p_1) as well as initiators of SGLT-2 inhibitor (p_0). An estimate the association between being obese and incident OSA (independent of exposure) (RD_{conf}) will be obtained from published literature (Table 5) and equation 1.

Table 5. Association of obesity with obstructive sleep apnea

Study Name	Year	Study Design	Population	Measure (95% CI)	Adjustment Variables
Esmaeili et al[106]	2025	Meta-analyses	Adults ≥ 65 years (56.2% had OSA; 25.7% were obese;	BMI ≥30 vs. BMI<25kg/m^2; OR = 4.84 (3.09, 6.00)	age, sex, race

			P(OSA/obese) was 74.3%)		
Lee, S., Ryu, S., Lee, G.E. et al[107]	2024	Cross-sectional	Chinese and Korean participants aged 50–75 (12.4% at high risk of OSA; 6.4% were obese; P(OSA/obese) was 12.2%)	BMI ≥30 vs. BMI<30kg/m^2; PR = 2.19 (0.90, 5.32)	age, sex, Asian subgroup, marital status, education, income, and employment status
Chen et al[108]	2015	Longitudinal	US adults aged 54–93 years in the Multi-Ethnic Study of Atherosclerosis (MESA) (9.8% had OSA)	NA	NA

To convert the odds ratio (OR) to an approximate risk ratio (RR), we would first estimate baseline OSA prevalence among non-obese (p_0) using the formula by Owusu-Edusei et al.[109]

$$p_0 \approx \frac{overall\ OSA\ prevalence - (p_{obese} \times p_{OSA|obese})}{1 - p_{obese}}$$

Next, we would obtain the RR using the formula below proposed by Zhang and Yu[110]

$$RR \approx \frac{OR}{(1-p_0) + (p_0 \times OR)}$$

The absolute risk difference for the outcome-confounder association would then be estimated using the equation proposed by Newcombe and Bender.[111]

$$RD_{conf} = P_0 \times (RR - 1) \qquad \textbf{(equation 1)}$$

RD_{conf} is the assumed RD for the outcome-confounder association
RR is the assumed RR for the outcome-confounder association (based on prior knowledge)
p_0 is the assumed prevalence of exposure to the confounder among those without the main exposure, based on prior knowledge.

Step 2: Assign probability distributions to each bias parameters

Now, we will assign trapezoidal probability distributions to each of the three bias parameters (p_1, p_0, and RD_{conf}). For each bias parameter, we will center the modes approximately on the values of the three bias parameters and choose a reasonable range for the mode and then extend the trapezoidal distribution to

lower and upper bounds such that the width of the trapezoid is approximately twice the width of the range between modes.

Step 3: Randomly sample from the bias parameter distributions

From the assigned trapezoidal distributions of each of the three bias parameters, I will randomly sample initial values for p_1, p_0, and RD_{conf}.

Step 4: Use simple bias analysis to correct for the bias

Using these bias parameters (p_1, p_0, and RD_{conf}.), we will apply a simple QBA (equation 2) to estimate the adjusted cumulative incidence difference (RD_{adj}) that would be observed after accounting for unmeasured confounding by obesity status. This simple method (adapted from methods and tool described in Lash, Fox, and Fink, 2009, (https://sites.google.com/site/biasanalysis/Home)) assumes that estimates are constant across strata of the confounder.[68]

$$RD_{adj} = RD_{obs} - (P_1 - P_0) \times RD_{conf} \quad \textbf{(equation 2)}$$

RD_{adj} is the risk difference estimate after "adjusting" for uncontrolled confounding given the specified assumptions.
RD_{obs} is the observed risk difference estimate for the main exposure-outcome association
RD_{conf} is the assumed RD for the outcome-confounder association (based on prior knowledge)
p_1 is the assumed prevalence of exposure to the confounder among those with the main exposure, based on prior knowledge.
p_0 is the assumed prevalence of exposure to the confounder among those without the main exposure, based on prior knowledge.

The observed crude estimate will be compared with the adjusted estimate to assess potential bias due to obesity. The observed estimate (RD_{obs}) is biased up if the $RD_{obs} > RD_{adj}$; down if the $RD_{obs} < RD_{adj}$; away from the null if the RD_{obs} is farther from the null than the RD_{adj}; toward the null if the RD_{obs} is closer to the null than the RD_{adj}; and unbiased if $RD_{obs} = RD_{adj}$.

Step 5: Resample, save and summarize

We will repeat steps 3 and 4 above several times, each time saving the effect estimate adjusted for obesity and summarize the results. The median of the simulation interval is the corrected estimate for the unmeasured confounding conditional on the accuracy of the distributions assigned to the bias parameters and the corresponding 2.5th and 97.5th percentiles as the 95% "bias correction interval".

12.9. Multiple imputation

Multiple imputation involves the creation of complete datasets, in which missing values have been replaced by plausible values generated using an imputation model.[92] To mitigate unmeasured confounding by BMI, we will use multiple imputation to generate predicted BMI values for all study participants. These imputed values will be incorporated as covariates in propensity score models to estimate propensity scores, enabling confounding control through SMR weighting. If multiple imputation proves infeasible (e.g., due to very few outcome events or convergence issues), we will instead perform a generalized bias analysis using a plasmode simulation approach, as described by Arah (2017).[93]

Overview of strategy

We will employ a two-phase multiple imputation approach to address unmeasured BMI in our primary Medicare FFS cohort. Phase 1 involves developing a BMI prediction model using the linked Medicare-CDW-H data where BMI is observed (Cohort III). Phase 2 involves applying this prediction model within a multiple imputation framework to impute missing BMI values for eligible beneficiaries in the broader national Medicare population with missing BMI measurements (Cohort I). For the regression model coefficients estimated in Cohort III to be validly transported to Cohort I, we assume that within levels of included predictors, the absence of BMI in Cohort I does not depend on its unobserved value. Thus, BMI is missing at random (MAR) conditional on measured covariates.

This approach follows the principle that adjusting for predicted BMI as a proxy confounder is superior to complete omission of BMI adjustment when the missingness mechanism is administrative (i.e., BMI is not captured in claims data for billing purposes).

Phase 1: Development of BMI prediction model

Study population

The BMI prediction model will be developed using Cohort III applying the inclusion and exclusion criteria outlined in sections 12.5 and 12.6 respectively. As in the primary analysis using claims data, baseline covariates will be assessed during the 1 year before the first prescription date except for age, sex and race/ethnicity which will be assessed on the first prescription date.

Derivation of observed BMI (outcome variable)

BMI values will be obtained from the linked EHR data within 90 (or 180 depending on missingness) days preceding the index date (i.e. second prescription date). These BMI values will be used as the outcome variable of the BMI prediction model. We will follow the steps outlined under section 12.7 ‘Derivation of observed BMI’ to obtain BMI values.

Predictor variables

We will leverage the predictor variables (including OSA) used by Suissa et al. in their validated Medicare claims-based BMI prediction algorithm, which demonstrated reasonable predictive performance (R^2 = 0.32, AUC = 0.75 for BMI ≥30).[94] Additionally, we will include the treatment group (GLP-1RA vs. SGLT-2i), outcome of interest (3-year risk of OSA) and calendar year of index date.

Key claims data predictors of BMI from Suissa et al. (97 variables total):

- Demographics: Age, sex, race/ethnicity
- Obesity-related ICD codes: Obesity (E66.x), morbid obesity (E66.01), overweight (E66.3), sleep apnea
- Comorbidities: Type 2 diabetes, hypertension, hyperlipidemia, heart failure, COPD, GERD, depression, osteoarthritis, CKD, NAFLD
- Medications: ACE inhibitors, ARBs, beta-blockers, CCBs, diuretics, statins, insulin, other antidiabetics, PPIs, NSAIDs, opioids
- Comorbidity scores: Combined comorbidity score, $CHADS_2$-VASc score, frailty index
- Healthcare utilization: ED visits, office visits, inpatient days, nursing facility days, screening tests

Model development

Step 1: Distribution assessment and transformation of BMI

After deriving BMI in the linked Medicare-CDW-H data, we will inspect its empirical distribution (histogram, kernel density, skewness and kurtosis statistics, Q–Q plots). If the BMI distribution is non-normal, we will evaluate transformations such as a logarithmic transformation (e.g., *log*(BMI), *SQRT*(BMI)) to approximate normality, since standard imputation models assume conditional normality for continuous variables. The transformed variable (e.g. *log*(BMI)) will be used as the target variable in the imputation regression model.

Step 2: Model specification for BMI

Using the predictor variables, we will fit a standard linear regression model with the transformed continuous BMI as the dependent variable:

(Transformed) BMI (continuous) = $\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p + \varepsilon$

Where:

- $X_1, X_2, ..., X_p$ are the predictor variables
- $\beta_0, \beta_1, \beta_2, ..., \beta_p$ are regression coefficients estimated without regularization
- ε is the error term

From this estimated regression model, the estimated regression coefficients ($\hat{\beta}_0$, $\hat{\beta}_1$, $\hat{\beta}_2$, …, $\hat{\beta}_p$) and their variance-covariance matrix $\sigma^2 V$, (where V is the X'X matrix from the intercept and variables $X_1, X_2, ..., X_p$) and the estimated variance of the residual distribution will be extracted.[95]

Step 3: Model performance assessment

Model performance in the development cohort (Cohort III) will be assessed using R^2 (Proportion of variance in observed BMI explained by the model).

Phase 2: Multiple imputation implementation

Target population for imputation

Multiple imputation will be applied to Cohort I: National 20% random sample of Medicare FFS beneficiaries who meet all other eligibility criteria but have missing BMI measurements in the EHR during the relevant time window.

Multiple imputation procedure

We will implement multiple imputation, using SAS's PROC MI with the FCS statement. In each imputation cycle, missing (transformed) BMI will be imputed using the specified linear regression model from phase 1, assuming a conditionally normal distribution. Broadly, with one missing covariate, the multiple imputation procedure proceeds by iteratively fitting the specified univariate conditional model for the missing variable, updating parameter estimates, and drawing stochastic imputations.[96–98] For continuous BMI, in each iteration of *m* imputations (here, *m* = 20), the algorithm:

1. Draws a new set of regression coefficients (and residual variance) from their posterior distribution. That is, they are simulated from ($\hat{\beta}_0$, $\hat{\beta}_1$, $\hat{\beta}_2$, …, $\hat{\beta}_p$), σ^2, and V, and

2. Imputes the missing BMI value for each person by a linear combination of the parameters drawn in step 1 multiplied by the individual covariate values of the predictor variables.

3. After imputation, we will back-transform the imputed values to the original BMI scale, ensuring interpretability in downstream propensity scores-based analyses.

We will thus generate *m* = 20 imputed datasets where every individual will have a BMI value, either the actual BMI value (internal validation sample) or an imputed one (everybody else).

Phase 3: Analysis using multiply-imputed datasets

Primary analysis with imputed BMI

After generating M = 20 complete datasets with imputed BMI values, we will conduct our primary comparative effectiveness analysis (GLP-1RA vs. SGLT-2i for incident OSA) separately in each imputed dataset using the methods specified in Section 10.

Pooling results across imputed datasets

Results from the M = 20 analyses will be combined using Rubin's rules through the PROC MIANALYZE procedure in SAS to obtain pooled point estimates, pooled standard errors and 95% Confidence intervals.

13. Validation of claims-based OSA algorithms

13.1. Overview

Administrative claims data presents a convenient source data for research on healthcare utilization and outcomes, particularly among patients excluded from trials such as older adults. The validity of these studies relies upon the ability of claims data to accurately capture treatment(s) of interest, study outcome(s), and other important design and clinical issues.[67] Claims-based algorithms using International Classification of Diseases (ICD) codes and procedure codes are commonly used in administrative data, such as Medicare FFS, to identify OSA cases. However, their accuracy needs validation against clinical evidence, especially when linked with EHR data, to ensure reliability.

13.2. Objectives

Aim 1: To validate claims-based algorithms for identifying obstructive sleep apnea in Medicare Fee-for-Service beneficiaries by leveraging clinical evidence from linked electronic health record data.

Aim 2: Compare algorithm performance to determine the optimal claims-based definition for OSA.

13.3. Data source

This study will use data 2014-2019 Carolina Data Warehouse for Health (CDW-H) linked to Medicare Fee-for-Service (FFS) Database (Parts A, B, and D), i.e., cohort II. Medicare FFS is a US federal database which contains deidentified individual-level, longitudinal information on demographics, diagnoses, and procedures, and outpatient prescription dispensations recorded during billing of all health care encounters. The Medicare data available at UNC comprises a randomly selected

20% sample of Medicare FFS beneficiaries aged 65 years and older who were simultaneously enrolled in Medicare Part A (inpatient services), B (physician and outpatient services), and D (prescription drugs) plans for a minimum of one calendar month from 2007 to 2019. Once selected into the sample, all future claims become part of the database. The CDW-H is a central data repository containing EHR data sourced from the University of North Carolina (UNC) Health Care System which comprises 16 hospitals across 20 campuses and more than 900 clinics in North Carolina (NC).[87,88] The data covers a wide range of patient demographic, clinical, and administrative data with data elements as far back as 2014 and will serve as a source of physician-confirmed OSA diagnoses and polysomnography reports. OSA events defined using algorithms in Medicare FFS Database (Parts A, B, and D) (test source) will be validated against medical records from CDW-H (reference standard).

13.4. Inclusion criteria

Medicare FFS beneficiaries in the linked Medicare sample (cohort II) who meet the following criteria will be included:

- A diagnosis of T2DM and aged ≥66 years
- Meet the definition of at least one of the four claims-based OSA algorithms
- Have non-missing OSA diagnosis data in CDW-H linked data between April 4, 2014, and December 31, 2019.

13.5. Exclusion criteria

Linked Medicare FFS beneficiaries (cohort II) who meet the following criteria will be excluded:

- Non-T2DM patients aged <66 years
- Patients with a pre-existing sleep apnea diagnosis, prescriptions for modafinil, and armodafinil, prior use of continuous positive airway pressure (CPAP) therapy or oral device within at least 12 months prior to first OSA defining code (all available lookback period).
- Patients with a history of bariatric surgery, any sleep disorder, end-stage renal disease or dialysis (all available lookback period).

The selection introduced by applying these inclusion and exclusion criteria will be assessed by comparing the distribution of baseline covariates of patients with OSA between all beneficiaries initiating GLP-1RA or SGLT2i in the national 20% random sample of Medicare FFS enrollees (cohort I) and the linked Medicare data (cohort II).

13.6. Event definition

We will include linked Medicare FFS beneficiaries (cohort II) that have evidence of a definite or probable OSA in Medicare FFS after a washout period of at least 12 months without an OSA defining code.

OSA definition – Medicare FFS

OSA will be identified in Medicare FFS by International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM), International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM), Healthcare Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT) codes from inpatient and outpatient insurance claims. Specifically, potential OSA events will be identified using the five algorithms listed under section 7.1.

OSA definition – linked CDW-H (reference standard)

The reference standard for true OSA status will be derived from CDW-H data for those patients with OSA outcomes that can be linked. The ideal approach is to use polysomnography results via a medical chart review, if available in structured form, with an Apnea-Hypopnea Index (AHI) > 5 as a threshold for OSA diagnosis, as this is the clinical gold standard. However, if polysomnography results are unavailable in structured form, clinical notes or attachments, we will rely on the presence of at least two OSA diagnosis codes in CDW-H, as a proxy. This is supported by Keenan et al. (2020), who found appreciable positive predictive values (PPV) and negative predictive values (NPV) for EHR-based OSA ICD codes compared to polysomnography chart reviews (Figure 4), although by design their study raised the prevalence to 55%.[112] It is therefore expected that the performance in our setting (low incidence) will be quite different. However, the expected sensitivity and specificity for various prevalences shown in **Figure 4** are somewhat reassuring overall.

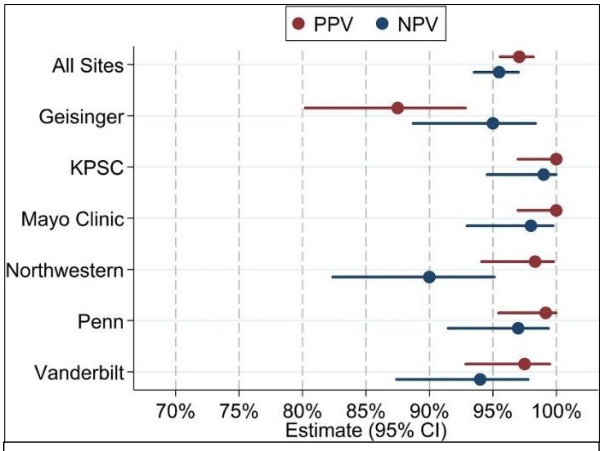


Figure 3. Performance characteristics (PPV and NPV) against gold-standard clinical chart review for an EHR-based OSA case definition of two or more ICD-9/ICD-10 diagnostic codes related to OSA is shown overall and at each participating site. CI = confidence interval, EHR = electronic health record, ICD = International Classification of Diseases, KPSC = Kaiser Permanente Southern California, NPV = negative predictive value, OSA = obstructive sleep apnea, Penn = University of Pennsylvania, PPV = positive predictive value.

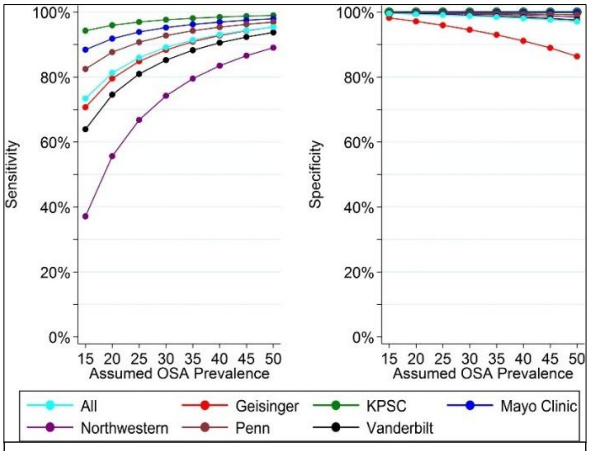


Figure 4. Sensitivity and specificity of the EHR-based OSA case definition of two or more ICD-9/ICD-10 diagnostic codes related to OSA is shown overall and at each participating site as a function of PPV, NPV and assumed prevalence. EHR = electronic health record, ICD =, International Classification of Diseases, KPSC = Kaiser Permanente Southern California, NPV = negative predictive value, OSA = obstructive sleep apnea, Penn = University of Pennsylvania, PPV = positive predictive value.

13.7. Validation

We will first describe the patient characteristics of patients with OSA outcomes in cohort I and in cohort II (linked to CDW-H data). Concordance between potential OSA events from each claims-based algorithm and events from the reference standard in CDW-H will be used to determine true positives and false positives (Table 6: Validation Study 2x1). A true positive is defined as instances in which the algorithm and the reference standard both flag the event as OSA. A false positive is defined as instances in which the algorithm flags the event as OSA, but the reference standard flags the event as otherwise. This evaluation of concordance will be performed for each algorithm separately.

Table 6: Validation study 2x1

	Reference* Positive	Reference Negative	Reference Unknown
Algorithm Positive	True Positive	False Positive	Not enough information

*Polysomnography or at least two OSA diagnosis codes in CDW-H

13.8. Statistical analysis

The validation will compare the potential OSA events identified using claims-based algorithms with the OSA events confirmed using CDW-H-based reference standard, to calculate a positive predictive value performance metric (PPV). The PPV is the proportion of cases identified by claims-based algorithms that are correctly classified as OSA cases in CDW-H.

Although sensitivity and specificity provide a more complete characterization of algorithm performance, their estimation typically requires sampling both algorithm-positive and algorithm-negative individuals and performing detailed medical record review, which is often infeasible in large administrative databases. Consequently, in many pharmacoepidemiologic validation studies, PPV alone is reported as a conservative and informative metric because it directly reflects outcome misclassification among identified cases.

Equation for validation parameter:

$$\text{Positive Predictive Value (PPV)} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}}$$

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Appendix A: Codes used to identify covariates

Comorbidities		
Code Type	**Code**	**Covariate**
ICD-9-CM Diagnosis code	CCW	Diabetes mellitus
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	CCW	Hypertension
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	CCW	Hyperlipidemia
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	CCW	Chronic obstructive pulmonary disease
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9	Congestive heart failure
ICD-10-CM Diagnosis code	I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9	
ICD-9-CM Diagnosis code	CCW	Ischemic Heart Disease
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code		Myocardial infarction
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	CCW	Chronic kidney disease
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	CCW	Acquired Hypothyroidism
ICD-10-CM Diagnosis code	CCW	
ATC code	H03AA	
ICD-9-CM Diagnosis code	243	Congenital Hypothyroidism
ICD-10-CM Diagnosis code	E00, E00.X	
ATC code	H03AA	
ICD-9-CM Diagnosis code	242.X, 242.0X, 242.1X, 242.2X, 242.3X, 242.4X, 242.8X, 242.9X	Hyperthyroidism
ICD-10-CM Diagnosis code	E05, E05.X, E05.XX	

ATC code	H03B	
ICD-9-CM Diagnosis code	240, 240.X, 241, 241.X	Goiter
ICD-10-CM Diagnosis code	E01, E01.X, E04, E04.X	
ICD-9-CM Diagnosis code	245, 245.X	Thyroiditis
ICD-10-CM Diagnosis code	E06, E06.X	
ICD-9-CM Diagnosis code	246, 246.X	Other disorders of thyroid
ICD-10-CM Diagnosis code	E07	
ICD-9-CM Diagnosis code	CCW	Depression
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	577, 577.X	Pancreatic disorders
ICD-10-CM Diagnosis code	K85, K85.X, K85.0X, K85.1X, K85.2X, K85.3X, K85.8X, K85.9X, K86, K86.X, K86.8X	
ICD-9-CM Diagnosis code	249.6X, 250.6X, 357.2	Diabetes neuropathy
ICD-10-CM Diagnosis code	E08.4X, E09.4X, E10.4X, E11.4X, E13.4X	
ICD-9-CM Diagnosis code	249.4X, 250.4X	Diabetes nephropathy
ICD-10-CM Diagnosis code	E08.21, E09.21, E10.21, E11.21, E13.21	
ICD-9-CM Diagnosis code	CCW	Cataract
ICD-10-CM Diagnosis code	CCW	
ICD-9-CM Diagnosis code	249.5X, 250.5X, 362.0X	Diabetes retinopathy
ICD-10-CM Diagnosis code	E08.3X, E09.3X, E10.3X, E11.3X, E13.3X	
ICD-9-CM Diagnosis code	278.0, 278.0X, V85.3X, V85.4X	Obesity
ICD-10-CM Diagnosis code	E66.X, Z68.3XX, Z68.4XX	
Health Behaviors		
Code Type	Code	Covariate
ICD-9-CM Diagnosis code	305.1, 649.0, 649.0X, 989.84, V15.82	Tobacco use
ICD-10-CM Diagnosis code	F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, O99.330, O99.331, O99.332, O99.333, O99.334, O99.335, T65.211A, T65.212A, T65.213A, T65.214A, T65.221A, T65.222A, T65.223A, T65.224A, T65.291A, T65.292A, T65.293A, T65.294A, Z87.891	
ICD-9-CM Diagnosis code	265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.X, V11.3	Alcohol use

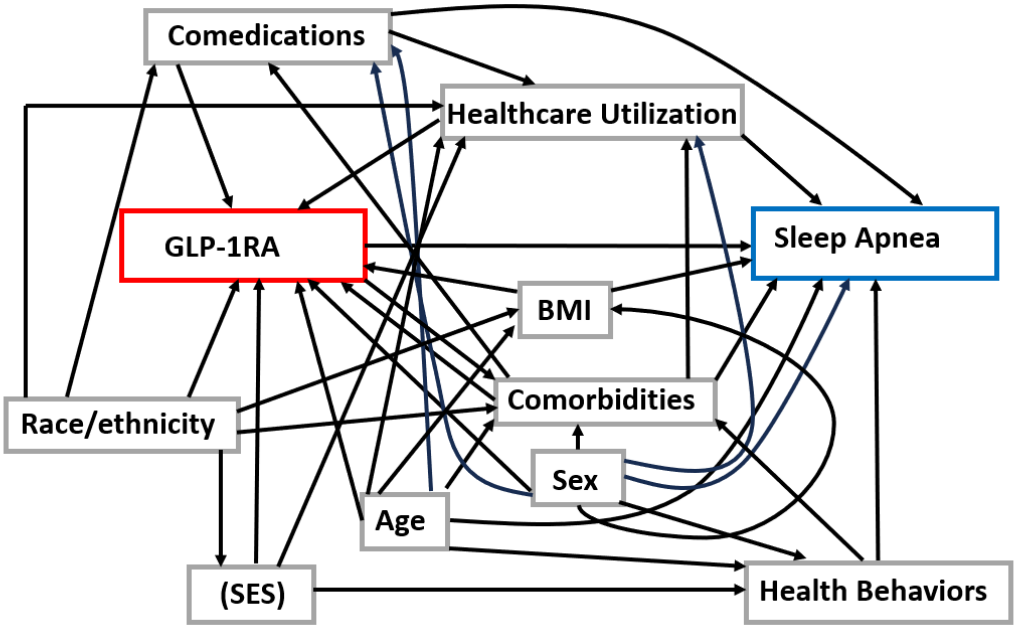
ICD-10-CM Diagnosis code	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1	
CPT-4	99363, 99364, 85610, 3555F, G0248, G0249, G0250	
Comedications		
Code Type	**Code**	**Covariate**
ATC code	A10AE, A10AC	Long-Acting Insulin
ATC code	A10AB	Short-Acting Insulin
ATC code	A10AD	Insulin Combinations
ATC code	A10BA02	Metformin
ATC code	A10BG	Thiazolidinediones
ATC code	A10BB	Sulfonylureas
ATC code	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
ATC code	C09A, C09B	Angiotensin converting enzyme inhibitors
ATC code	C09C, C09D	Angiotensin II receptor blockers (ARBs)
ATC code	C10AA	Statins
ATC code	C03C	Loop diuretics
ATC code	C03A, C03B, C03D, C03E, C03X	Other diuretics
ATC code	C07	Beta blockers
ATC code	C08	Calcium channel blockers
ATC code	M01A	NSAIDs
ATC code	L02	Hormone therapy
ATC code	N06BA07, N06BA13	Modafinil and armodafinil
Healthcare utilization		
Code Type	**Code**	**Covariate**
CPT code	83036, 86037, 3044F, 3045F, 3046F	Hba1c test
CPT code	80061, 83704, 3048F, 3049F, 3050F	Lipid test
CPT code	G0008, G9141, G9142, G8108, 90470, 90471, 90660, 90663, 90658, 90630, 90653, 90654, 90655, 90656, 90657, 90662, 90672, 90673, 90674, 90682, 90685, 90686, 90687, 90688, 90689, 90694, 90756, Q2034, Q2035, Q2036, Q2037, Q2038, Q2039	Flu Vaccination
ICD-9-CM code	V04.81, 99.52	
ICD-10-CM code	Z23	
CPT code	99201, 99202, 99203, 99204, 99205	Office/Outpatient visit, new patient
CPT code	99211, 99212, 99213, 99214, 99215	Office/Outpatient visit, established patient
CPT code	99202 - 99215	Endocrinology visit

Appendix B: Codes used to identify prevalent cancer at baseline

ICD-9-CM diagnosis codes*: 140.0–208.92 (except 173.X), 209.00–209.36, 209.70-209.79, 230.X, 231.X, 233.X, 234.X, 235.X, 236.X, 237.0-237.1, 237.3, 237.5-237.6, 237.7, 237.9, 238.4, 238.6, 238.7 (all but 238.78), 239.6, 239.7, 273.2, 273.3, 277.89, 288.4, 795.06, 795.16, 796.76, V10.X, V87.41, V66.1, V66.2, V67.1, V67.2, V71.1
ICD-10-CM diagnosis codes†: C00–D49 (except C44)
HCPCS codes‡: G8371, G8372, G8377, J9999, G0355, G0356, G8376, G8377, G8380, G8381, G8464, G8465, G8518, G8519, G8520, G9050-G9054, G9063-G9067, G9069-G9117, G9131-G9133, G9118-G9130, G9134-G9139, G9714-G9715, G9726, G0256, G0261
CPT§: 49220, 3271F, 3272F, 3273F, 3274F, 3300F – 3318F, 3321F, 3370F, 3372F, 3374F, 3376F, 3378F, 3380F, 3382F, 3384F, 3386F, 3388F, 3390F, 4163F, 4164F, 4180F, 4201F

*ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification
†ICD-10-CM International Classification of Disease, Tenth Revision, Clinical Modification
‡HCPCS Healthcare Common Procedure Coding System
§CPT Current Procedural Terminology

Appendix C: Directed Acyclic Graph



KEY

Exposure

Outcome

Confounder

( )Unmeasured confounder