What do you mean? Why reliable real-world evidence requires precise real-world clinical definitions

Patrick Ryan, PhD

Johnson & Johnson

Columbia University

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JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Glucagon-Like Peptide-1 Receptor Agonists and Fragility Fracture Risk in Type 2 Diabetes

Christopher D. Hamad, MD; Joshua Wiener, BS; Autreen Golzar, BS; Harlene Kaur, BS; Carolyn Henein, BS; Andrew P. Kittredge, BS; Gabriel Su; David C. Kaelber, MD, PhD, MPH; Liana Chan, PhD; Michael R. Yeaman, PhD; John S. Adams, MD; Nicholas M. Bernthal, MD; William L. Sheppard, MD, MPH

Abstract

IMPORTANCE Obesity, type 2 diabetes (T2D), and weight loss are associated with increased fragility fracture risk. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely prescribed, yet their effects on skeletal outcomes remain uncertain.

OBJECTIVE To evaluate the association between GLP-1 RA initiation and 3-year fragility fracture risk compared with dipeptidyl peptidase-4 inhibitor (DPP-4i) initiation among adults with T2D.

DESIGN, SETTING, AND PARTICIPANTS This comparative effectiveness study using retrospective target trial emulation examined data from the TriNetX Research Network (January 1, 2015, to December 31, 2022), a multicenter US electronic health record database. Adults aged 50 to 90 years with T2D who newly initiated a GLP-1 RA or DPP-4i were followed up for up to 3 years. A separate cohort stratified by T2D status was also analyzed. The database was queried on January 26, 2026, to generate a line-level analytic dataset.

EXPOSURES Initiation of GLP-1 RAs vs DPP-4is.

MAIN OUTCOMES AND MEASURES The primary outcome was incident fragility fracture, defined as fractures after low-energy trauma (eg, fall from standing height). Cohorts were propensity score matched. Time-varying mediation analyses were used to evaluate the contribution of changes in body mass index and hemoglobin A1c.

Key Points

Question What is the association of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with fragility fracture risk in patients with type 2 diabetes?

Findings In this comparative effectiveness study using target trial emulation of 133 606 adults with type 2 diabetes mellitus, GLP-1 RA initiation was associated with a statistically significant 21% lower 3-year risk of fragility fracture compared with dipeptidyl peptidase-4 inhibitor initiation.

Meaning These findings suggest that GLP-1 RAs may reduce fragility fracture risk through mechanisms independent of weight loss and glycemic control, highlighting the need for prospective

Introduction

Obesity is a growing epidemic in the US. In 2024, obesity affected 40.3% of adults, including 9.4% with severe obesity (body mass index [BMI] >40 [calculated as weight in kilograms divided by height in meters squared]).[1] Concurrently, 14.3% of adults have type 2 diabetes (T2D), and projections suggest that more than 80% of adults in the US may be overweight or obese by 2050.[2,3]

Since the US Food and Drug Administration's approval of exenatide in 2005 for T2D, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have rapidly expanded in use and indication, now encompassing obesity management, cardiometabolic risk reduction, and treatment of chronic kidney disease in people with T2D.[4-6] According to the 2024 National Health Interview Survey, 26.5% of adults with T2D have used a GLP-1 RA, and per a 2024 Kaiser Family Foundation poll, 22% of adults with obesity have taken one within the past 5 years.[7,8]

Fragility fractures, which result from low-energy trauma (eg, a fall from standing height or lower), are associated with substantial morbidity and mortality, particularly following hip fracture, with reported 1-year all-cause mortality ranging from 12.1% to 25.4% in women and 19.2% to 35.8% in men across multinational cohorts.[9-13] Diabetes, obesity, and rapid weight loss are all concerning in the context of fragility fractures. Adults with T2D, despite their paradoxically higher bone mineral density (BMD), have a 1.79-fold higher risk of hip fracture that may be due to lower bone strength, impaired bone microarchitecture, and accelerated bone loss.[14-16] When controlling for BMD, a U-shaped association exists between BMI and fragility fracture risk, with increased risk among individuals who are underweight or obese.[17] Moreover, rapid or significant weight loss independently increases fracture risk. In a Japanese registry, patients with T2D who lost more than 20% of their

Cohort Definitions, Exposures, and Outcomes

We identified adults aged 50 to 90 years with T2D per *International Statistical Classification of Disease, Tenth Revision, Clinical Modification* (*ICD-10-CM*) code E11 or HbA_{1c} of at least 6.5% (48 mmol/mol) in the 365 days before index who newly initiated a GLP-1 RA or dipeptidyl peptidase-4 inhibitor (DPP-4i) between January 1, 2015, and December 31, 2022. Patients initiating GLP-1 RAs comprised the treatment group, and DPP-4i initiators comprised the active comparator group, reflecting clinically comparable second-line therapy. Although the GLP-1 RA exposure definition encompassed all formulations, including those with weight management indications, all patients in the primary cohort met T2D inclusion criteria at baseline (eTable 1 in Supplement 1). Initiation followed a new-user design, with the index defined as the first dispensing and requiring at least 4 administrations to ensure continuous use. Eligible patients had continuous health care engagement (≥1 BMI measurement, ≥1 HbA_{1c} test, and ≥4 ambulatory visits) and no fragility fracture in the prior 365 days. Baseline use of other glucose-lowering agents (metformin, sodium-glucose cotransporter 2 inhibitors, thiazolidinediones, insulin, or sulfonylureas) were adjusted for in propensity score models. The primary outcome was time to first fragility fracture within 3 years. A sensitivity analysis excluding the aforementioned agents was performed to address potential confounding by medication-related hypoglycemia and fall risk. Follow-up began the day after index and continued until fracture, death, loss to follow-up (>365-day care gap), or administrative censoring at 3 years. High-energy trauma fractures were excluded, as were patients with osteoporosis, osteopenia, vitamin D deficiency, advanced chronic kidney disease (stage IV-V), end-stage kidney disease, kidney osteodystrophy, or type 1 diabetes (eTable 1 in Supplement 1).

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Vocabulary
ICD10CM (2659)
ICD10 (24)

Class
7-char billing code (2466)
6-char nonbill code (147)
5-char nonbill code (39)
ICD10 code (24)

Domain
Condition (2683)

Standard Concept
Non-Standard (2683)

Invalid Reason
Valid (2683)

Has Records
true (2570)
false (113)

Has Descendant Records
true (2570)
false (113)

Has Person Count
false (2683)

Has Descendant Person Count
false (2683)

Id	Code	Name	Class	RC	DRC	PC	DPC	Domain	Vocabulary
1573643	S72.0	Fracture of head and neck of femur	4-char nonbill code	17,579	17,579	0	0	Condition	ICD10CM
1573644	S72.00	Fracture of unspecified part of neck of femur	5-char nonbill code	38,099	38,099	0	0	Condition	ICD10CM
14817	S72.001	Fracture of unspecified part of neck of right femur	6-char nonbill code	24,347	24,347	0	0	Condition	ICD10CM
45603323	S72.001A	Fracture of unspecified part of neck of right femur, initial encounter for closed fracture	7-char billing code	9,664,974	9,664,974	0	0	Condition	ICD10CM
45550201	S72.001B	Fracture of unspecified part of neck of right femur, initial encounter for open fracture type I or II	7-char billing code	53,215	53,215	0	0	Condition	ICD10CM
45569418	S72.001C	Fracture of unspecified part of neck of right femur, initial encounter for open fracture type IIIA, IIIB, or IIIC	7-char billing code	8,178	8,178	0	0	Condition	ICD10CM
45540587	S72.001D	Fracture of unspecified part of neck of right femur, subsequent encounter for closed fracture with routine healing	7-char billing code	8,525,176	8,525,176	0	0	Condition	ICD10CM
45574330	S72.001E	Fracture of unspecified part of neck of right femur, subsequent encounter for open fracture type I or II with routine healing	7-char billing code	32,867	32,867	0	0	Condition	ICD10CM
45535746	S72.001F	Fracture of unspecified part of neck of right femur, subsequent encounter for open fracture type IIIA, IIIB, or IIIC with routine healing	7-char billing code	6,973	6,973	0	0	Condition	ICD10CM
45535747	S72.001G	Fracture of unspecified part of neck of right femur, subsequent encounter for closed fracture with delayed healing	7-char billing code	213,812	213,812	0	0	Condition	ICD10CM
45603324	S72.001H	Fracture of unspecified part of neck of right femur, subsequent encounter for open fracture type I or II with delayed healing	7-char billing code	9,100	9,100	0	0	Condition	ICD10CM
45579097	S72.001J	Fracture of unspecified part of neck of right femur, subsequent encounter for open fracture type IIIA, IIIB, or IIIC with delayed healing	7-char billing code	4,026	4,026	0	0	Condition	ICD10CM
45579098	S72.001K	Fracture of unspecified part of neck of right femur, subsequent encounter for closed fracture with nonunion	7-char billing code	292,480	292,480	0	0	Condition	ICD10CM

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What's your definition of 'Fragility fracture'?

Nobody has responded yet.

Hang tight! Responses are coming in.

Outcome: Fragility Fracture Codes (ICD-10-CM)			
Hip and femur	ICD-10-CM		
Femoral neck	ICD-10-CM	S72.0x	Fracture of neck of femur (all subcodes, .001–.099)
Trochanteric	ICD-10-CM	S72.1x	Trochanteric and intertrochanteric fractures (all subcodes)
Subtrochanteric	ICD-10-CM	S72.2x	Subtrochanteric fracture of femur
Femoral shaft	ICD-10-CM	S72.3x	Fracture of shaft of femur
Pathological hip	ICD-10-CM	M80.05x	Age-related osteoporosis with pathological fracture, femur
Vertebral	ICD-10-CM		
Thoracic vertebra	ICD-10-CM	S22.0x	Fracture of thoracic vertebra
Lumbar vertebra	ICD-10-CM	S32.0x	Fracture of lumbar vertebra
Fatigue/stress vertebral	ICD-10-CM	M48.4x	Fatigue fracture of vertebra
Collapsed vertebra	ICD-10-CM	M48.5x	Collapsed vertebra, not elsewhere classified
Pathological vertebral	ICD-10-CM	M80.08x	Age-related osteoporosis with pathological fracture, vertebrae
Rib	ICD-10-CM		
Single rib	ICD-10-CM	S22.3x	Fracture of one rib
Multiple ribs	ICD-10-CM	S22.4x	Multiple fractures of ribs
Proximal humerus	ICD-10-CM		
Upper end of humerus	ICD-10-CM	S42.2x	Fracture of upper end of humerus (all subcodes)
Pathological humerus	ICD-10-CM	M80.02x	Age-related osteoporosis with pathological fracture, humerus
Distal radius and ulna	ICD-10-CM		
Lower end of radius	ICD-10-CM	S52.5x	Fracture of lower end of radius
Lower end of ulna	ICD-10-CM	S52.6x	Fracture of lower end of ulna
Pathological forearm	ICD-10-CM	M80.03x	Age-related osteoporosis with pathological fracture, forearm
Trauma Exclusion Codes (Same-Encounter Exclusion)			
Transport accidents	ICD-10-CM	V00–V99	All transport accident codes
Falls from height	ICD-10-CM		
Fall from ladder	ICD-10-CM	W11	Fall on and from ladder
Fall from scaffolding	ICD-10-CM	W12	Fall on and from scaffolding
Fall from building	ICD-10-CM	W13	Fall from, out of, or through building or structure
Fall from tree	ICD-10-CM	W14	Fall from tree
Fall from cliff	ICD-10-CM	W15	Fall from cliff
Diving/water fall	ICD-10-CM	W16	Fall, jump, or diving into water
Other fall from height	ICD-10-CM	W17	Other fall from one level to another
Mechanical forces	ICD-10-CM	W20–W49	Exposure to inanimate and animate mechanical forces
Assault	ICD-10-CM	X85–X99, Y00–Y09	Assault by various means
Multiple trauma	ICD-10-CM	T07	

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name: clinical-definition-refiner
description: An iterative, conversational skill that acts as a structured clinical facilitator, guiding users to refine vague or incomplete clinical phenotype concepts into rigorous, precise, and concise clinical definitions. It strictly separates the clinical intent (the "what") from operational definitions (the "how").

Instructions

1. Role & Objective
You are an expert Clinical Phenotyping Agent. Your goal is to guide the user in crafting a clinical definition that strictly describes *what* the clinical condition or state is in terms of pathophysiology, clinical presentation, and diagnostic criteria. You must explicitly avoid operational artifacts (e.g., ICD-10/SNOMED codes, database queries, or EHR table locations).

2. Interaction Rules
* **Initial Assessment (No Redundancy):** Before asking any questions, analyze the user's initial input against the Evaluation Dimensions. If the user has already clearly defined a specific dimension, **do not** ask about it. Only prompt for missing or ambiguous criteria.
* **Iterative Interrogation:** Act as a strict but helpful guide. Ask the user **only one question at a time**.
* **Suggest Likely Answers with Context:** To lower cognitive burden, append 2 to 3 clinically relevant, likely answers to every question you ask. When proposing these options, briefly explain the *clinical or definitional consequence* of choosing them. Always include an open-ended "Other (please specify)" option.
* **Wait for Input:** Always halt execution and wait for the user's response before evaluating the next conceptual dimension.
* **Maintain Conceptual Boundaries:** If the user introduces billing codes or specific database constraints, gently correct them and guide the focus back to the clinical reality of the disease state.

3. The Evaluation Process
Systematically evaluate the user's concept against the following dimensions, skipping any that were adequately addressed in previous turns:
* **Core Pathology/Presentation:** What is the fundamental nature of the condition? (e.g., acute event, chronic state, progressive disease).
* **Severity & Modifiers:** Does the phenotype require a specific severity level, or include/exclude particular subtypes?
* **Conceptual Boundaries:** What biological or physiological states are fundamentally excluded from this concept?
    * *Distinct Etiologies:* Exclude differing underlying mechanisms (e.g., distinguishing medical acute liver injury from mechanical liver trauma).
    * *Secondary Pathophysiology:* Clarify if downstream effects of another primary disease belong in the concept (e.g., liver congestion secondary to heart failure).
    * *Competing States:* Rule out entirely different biological states that merely present similarly.

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What option would you select from /clinical-definition-refiner for 'Fragility fracture'?

0

Option 1

Option 2

Option 3

Option 4

Other

SEE MORE

A clinical definition for ‘Fragility fracture’

A fragility fracture is a bone fracture resulting from mechanical loading that would be insufficient to fracture a structurally normal, healthy skeleton, typically precipitated by low-energy trauma such as a fall from standing height or less, or in some cases occurring spontaneously. The condition reflects an intrinsic reduction in bone strength — encompassing both bone mineral density and bone quality — that renders the skeleton susceptible to fracture under forces ordinarily tolerated without structural failure. A fragility fracture may occur at any skeletal site, including vertebrae, hip, distal radius, proximal humerus, pelvis, ribs, and other locations. A formal diagnosis of osteoporosis is not required; the defining criterion is the disproportionate fragility of the bone relative to the applied force. Excluded from this phenotype are fractures attributable to high-energy trauma (e.g., motor vehicle accidents, falls from significant height, or high-impact sports injuries), fractures occurring at sites of primary or metastatic bone malignancy where tumor-mediated cortical destruction is the primary mechanism, and periprosthetic fractures occurring adjacent to orthopedic implants where implant-related stress concentration — rather than intrinsic skeletal fragility — is the principal contributing factor.

Annals of Internal Medicine

ORIGINAL RESEARCH

Dementia Risk After Recombinant Herpes Zoster Vaccination in Older Adults With a Recent Skilled-Nursing Facility Stay

A Target Trial Emulation

Kaleen N. Hayes, PharmD, PhD*; Daniel A. Harris, PhD*; Kevin W. McConeghy, PharmD, PhD; Lexie R. Grove, PhD; Richa Joshi, MBA; Lisa Han, MPH; H. Edward Davidson, PharmD; Preeti Chachlani, MA; Thomas A. Bayer, MD; Mriganka Singh, MD; Yasin Abul, MD; Frank DeVone, MS; and Stefan Gravenstein, MD

Background: Observational studies report a protective association between herpes zoster (HZ) vaccination and dementia, but they have methodological limitations or examined a live attenuated vaccine no longer available in the United States.

Objective: Among older adults recently admitted to a skilled-nursing facility for postacute or long-term care, to estimate the association between dementia and receipt of the recombinant HZ vaccine (RZV) within 12 months of entering the facility or after discharge.

Design: The researchers conducted a cohort study using target trial emulation and the clone-censor-weight approach. Participants were followed for up to 4 years until the outcome of dementia, Medicare disenrollment, or death. Inverse probability of clone-censoring weights were applied to pooled logistic regression models to estimate effects.

Setting: Medicare claims linked to nursing home electronic health record (EHR) data.

Participants: Medicare fee-for-service beneficiaries aged 66 years or older who were admitted to a skilled-nursing facility between 1 January 2017 and 31 December 2022, had linked EHR data, had no diagnosed dementia, and were eligible for RZV.

Intervention: Receipt of at least 1 RZV in the facility or, if discharged, by 12 months after admission versus no receipt of RZV.

Measurements: Validated dementia diagnosis and 57 baseline and time-varying covariates.

Results: The study cohort included 509 926 participants (mean age, 79 years); 8843 (1.73%) received at least 1 RZV dose within 12 months after admission, and of these, 87.0% received RZV after discharge. Receipt of RZV was associated with risk for dementia being 5.8 percentage points lower (95% CI, 3.9 to 7.5 percentage points lower; risk ratio, 0.76 [CI, 0.69 to 0.84]; 4-year risk, 18.8% with ≥1 RZV vs. 24.6% with no RZV). Associations were attenuated in men and those with prior live HZ vaccination.

Limitation: Negative control analyses suggest some residual confounding.

Conclusion: Receipt of RZV during admission to a skilled-nursing facility or within 12 months was associated with lower dementia risk.

Primary Funding Source: GlaxoSmithKline.

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For author, article, and disclosure information, see end of text.
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* Drs. Hayes and Harris contributed equally and share the first author position.

Outcomes

We defined the outcome of incident dementia as an inpatient hospitalization with a dementia-related diagnosis code; 3 Part B carrier claims with a dementia-related diagnosis, separated by at least 30 days; or a claim or recorded administration for a dementia medication (that is, acetylcholinesterase inhibitor or memantine; see **Supplement Table 2**) (21). This definition of dementia was previously shown to have a sensitivity of 79.3% and specificity of 99.1% among community-dwelling older adults in Ontario, Canada (21).

Exclusion: Dementia Diagnosis	MDS admission assessment I4200 = 1 OR I4800=1 I8000 where the F00.x, F01.x, F02.x, F03.x, G30.x dementia-related ICD-10 codes are indicated (Any position) PCC Medication Administrations or Orders class = "antidementia agent" ADRD medications: Aricept (donepezil), Exelon (rivastigmine), Namzaric (donepezil/memantine), Aricpet ODT, Razadyne ER (galantamine), Reminyl (galantamine), Razadyne (galantamine), Cognex (tacrine), Adlarity (donepez Namenda, Namenda XR (memantine) Identify if an anti-dementia drug overlaps the admission assessment date (inclusive of the admission assessment date) PCC Diagnosis file F00.x, F01.x, F02.x, F03.x, G30.x (Any position) Medicare claims definition for dementia diagnoses and medications Use the Part A, B and D claims. one hospitalization code OR (three physician claims codes at least 30 days apart in a one year period) OR a prescription filled for a dementia medication. ICD-10 (F00.x, F01.x, F02.x, F03.x, G30.x) Flag individuals who meet the definition for dementia prior to the admission assessment date.

Outcome: Incident Dementia, Validated Outcome (Dementia 1)	One Part A claim in the hospital Place of Service code = 21 (Hospital) (any diagnostic position) OR Three Part B claims separated by 30 days; Date of the 3rd claim meeting this criteria = has dementia (any diagnostic position) OR One dementia drug in the eMAR or Part D
Outcome: Incident Dementia, Sensitive Outcome (Dementia 2)	At least 1 diagnosis code for dementia in Part A OR At least 1 diagnosis code for dementia in Part B OR Checkbox for dementia in the MDS OR At least 1 diagnosis code for dementia in the active diagnosis file of the EHR OR At least 1 diagnosis code for dementia in the MDS (Section I8000) OR At least 1 diagnosis code in the MDS and checkbox for dementia or active diagnosis file PCC OR At least 1 dementia drug in Part D OR At least 1 dementia drug in the eMAR
Outcome: Incident Dementia, Specific Outcome (Dementia 3)	At least 1 dementia drug in the eMAR or At least 1 dementia drug in the Part D claims

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What's your definition of 'Dementia'?

Nobody has responded yet.

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A clinical definition for ‘Dementia’

Dementia is an acquired clinical syndrome characterized by persistent, progressive decline in cognitive function across one or more domains — including memory, executive function, language, visuospatial ability, or social cognition — of sufficient severity to impair independence in instrumental or basic activities of daily living, representing a significant decline from a previously established level of functioning. The syndrome is not restricted by etiology and encompasses neurodegenerative, vascular, mixed, and other underlying pathophysiological mechanisms. A etiological workup for reversible causes is not required for inclusion; the definition applies to all presentations meeting the syndromic threshold at the time of clinical assessment. Co-occurrence with delirium is permitted, provided the chronic and persistent nature of the cognitive decline is clinically distinguishable from the acute confusional episode. The syndrome explicitly excludes cognitive impairment that is better accounted for by a primary psychiatric disorder, such as a major depressive episode or psychotic disorder, where the cognitive deficits represent a manifestation of the underlying psychiatric condition rather than an independent neurodegenerative or vascular process.

bmjmedicine

Check for updates

GLP-1 receptor agonists and risk of all cause and cause specific acute pancreatitis: target trial emulation

Yan Xie,[1,2,3,4] Taeyoung Choi,[1,2,3] Ziyad Al-Aly [1,2,5,6,7]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjmed-2025-002183).

For numbered affiliations see end of article.
Correspondence to: Dr Ziyad Al-Aly; zalaly@gmail.com

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ABSTRACT

OBJECTIVES To assess whether initiation of glucagon-like peptide-1 receptor agonists (GLP-1RAs) rather than sulfonylureas is associated with all cause acute pancreatitis and cause specific acute pancreatitis and to characterise temporal risk patterns of the various causes of acute pancreatitis associated with GLP-1RA use.

DESIGN Target trial using the electronic healthcare databases of the US Department of Veterans Affairs healthcare system.

SETTING US Department of Veterans Affairs.

PARTICIPANTS 333 687 users of the Veterans Affairs healthcare system with type 2 diabetes initiating GLP-1RA (n=132 551) or sulfonylureas (n=201 136) between 1 January 2017 and 31 December 2023.

EXPOSURE Initiation of GLP-1RA or sulfonylureas, and separately, continued use of GLP-1RA or sulfonylureas during follow-up.

MAIN OUTCOME MEASURES Risks of acute pancreatitis during 12 months' follow-up including all cause acute pancreatitis and cause specific acute pancreatitis (eg, pancreatitis that is suspected drug induced, alcohol induced, hypertriglyceridaemia associated, biliary, and idiopathic or other cause). The risks were measured through discrete time survival models after application of inverse probability weighting.

RESULTS In intention-to-treat analyses, participants who initiated GLP-1RAs had similar rates of all cause pancreatitis at one year compared with participants who initiated sulfonylureas (rate difference −3.64, 95% confidence interval (CI) −30.76 to 23.48 per 100 000 persons at one year). However, the overall null finding was the net result of countervailing effects across various causes of acute pancreatitis. GLP-1RA was associated with an increased risk of suspected drug induced acute pancreatitis (23.45 (14.27 to 33.85)) and decreased risks of hypertriglyceridaemia associated (−16.96 (−27.41 to −7.34)) and alcohol induced pancreatitis (−10.32 (−18.12 to −3.17)). Similar rates of biliary and idiopathic or other causes of acute pancreatitis were observed in the two groups. In per protocol analyses, drug induced acute pancreatitis attributable to GLP-1RA clustered early (42% of GLP-1RA attributable events over one year of follow-up occurred in the first three months), whereas reductions in alcohol related acute pancreatitis concentrated between months four and six and hypertriglyceridaemia associated acute pancreatitis concentrated between months 10 and 12. Cumulatively, these divergent temporal trends resulted in a net increase in risk of all cause pancreatitis during the first two months of treatment, with similar monthly risk observed for the remainder of follow-up.

CONCLUSIONS In this nationwide cohort, similar rates of all cause acute pancreatitis in GLP-1RA and sulfonylurea users were observed at one year. Increased risk of suspected drug induced pancreatitis during the early period was offset by later reductions in alcohol induced and hypertriglyceridaemia associated acute pancreatitis. Clinicians should counsel patients on early risk while recognising the overall neutral long term effect.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Randomised trials have not shown a significant increase in acute pancreatitis with use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), but these studies may be underpowered with low event counts

⇒ Results from pharmacovigilance and observational studies are mixed, with reports of increased, null, and reduced risks of acute pancreatitis

⇒ GLP-1RAs may have a complex, opposing association with various causes of pancreatitis (increasing risk of acute pancreatitis from some causes and decreasing risk from other causes), thus analysing all causes of pancreatitis together can mask possible opposing effects

WHAT THIS STUDY ADDS

⇒ GLP-1RA use was not associated with a higher one year risk of all cause acute pancreatitis

⇒ This null finding was the net result of an increased risk of suspected drug induced pancreatitis being offset by decreased risks of alcohol induced and hypertriglyceridaemia associated pancreatitis

⇒ The risk of drug induced pancreatitis manifests early after treatment initiation, while the reductions in alcohol related and hypertriglyceridaemia associated pancreatitis accrue later

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

Outcomes

We defined outcomes using definitions previously validated for use in the electronic health records.[31–47]

The primary outcome was incident, clinically significant acute pancreatitis. We first identified a cohort of potential cases using ICD-10-CM (international classification of diseases, 10th revision, clinical modification) diagnosis codes K85.0X to K85.9X. To increase the positive predictive value and ensure clinical significance, a case was confirmed only if the diagnosis code was recorded during either an emergency department encounter or a hospital admission where acute pancreatitis was a listed diagnosis. We defined the event date as the date of the qualifying emergency department visit or hospital admission.

Cause specific acute pancreatitis was classified into a single, mutually exclusive aetiologic category using a predefined hierarchical algorithm, applied in the following order: biliary acute pancreatitis (a confirmed case of acute pancreatitis with a diagnosis code K85.1X and an accompanying diagnosis code K80.X-K83.X for cholelithiasis, cholecystitis, or other biliary tract diseases in the 180 days before or including the event date). Alcohol induced acute pancreatitis (a non-biliary case of acute pancreatitis with diagnosis code K85.2X and an accompanying diagnosis code F10.X for alcohol use disorder, abuse, dependence, or K70.X for alcohol related liver disease in the 365 days before or including the event date). Hypertriglyceridaemia associated acute pancreatitis (a non-biliary, non-alcohol induced case of acute pancreatitis with diagnosis codes K85.0X, K85.8X, or K85.9X recorded within 30 days after a triglyceride measurement >500 mg/dL). Suspected drug induced acute pancreatitis (a non-biliary, non-alcohol, non-hypertriglyceridaemia associated pancreatitis with a recorded diagnosis code of K85.3X which was confirmed through a review of clinical notes). Idiopathic or other acute pancreatitis (any confirmed case of acute pancreatitis not meeting the criteria for the causes listed above with a diagnosis code K85.X not otherwise classified into any of the above categories). We additionally examined all cause acute pancreatitis, defined as the composite of all acute pancreatitis categories above.

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Vocabulary
- ICD10CM (4)
- ICD10 (1)

Class
- 5-char billing code (3)
- ICD10 code (1)
- 4-char nonbill code (1)

Domain
- Condition (5)

Id	Code	Name	Class	RC	DRC	PC	DPC	Domain	Vocabulary
35208391	K85.3	Drug induced acute pancreatitis	4-char nonbill code	33,999	33,999	0	0	Condition	ICD10CM
37200664	K85.32	Drug induced acute pancreatitis with infected necrosis	5-char billing code	15,432	15,432	0	0	Condition	ICD10CM
37200662	K85.30	Drug induced acute pancreatitis without necrosis or infection	5-char billing code	366,117	366,117	0	0	Condition	ICD10CM
37200663	K85.31	Drug induced acute pancreatitis with uninfected necrosis	5-char billing code	44,906	44,906	0	0	Condition	ICD10CM

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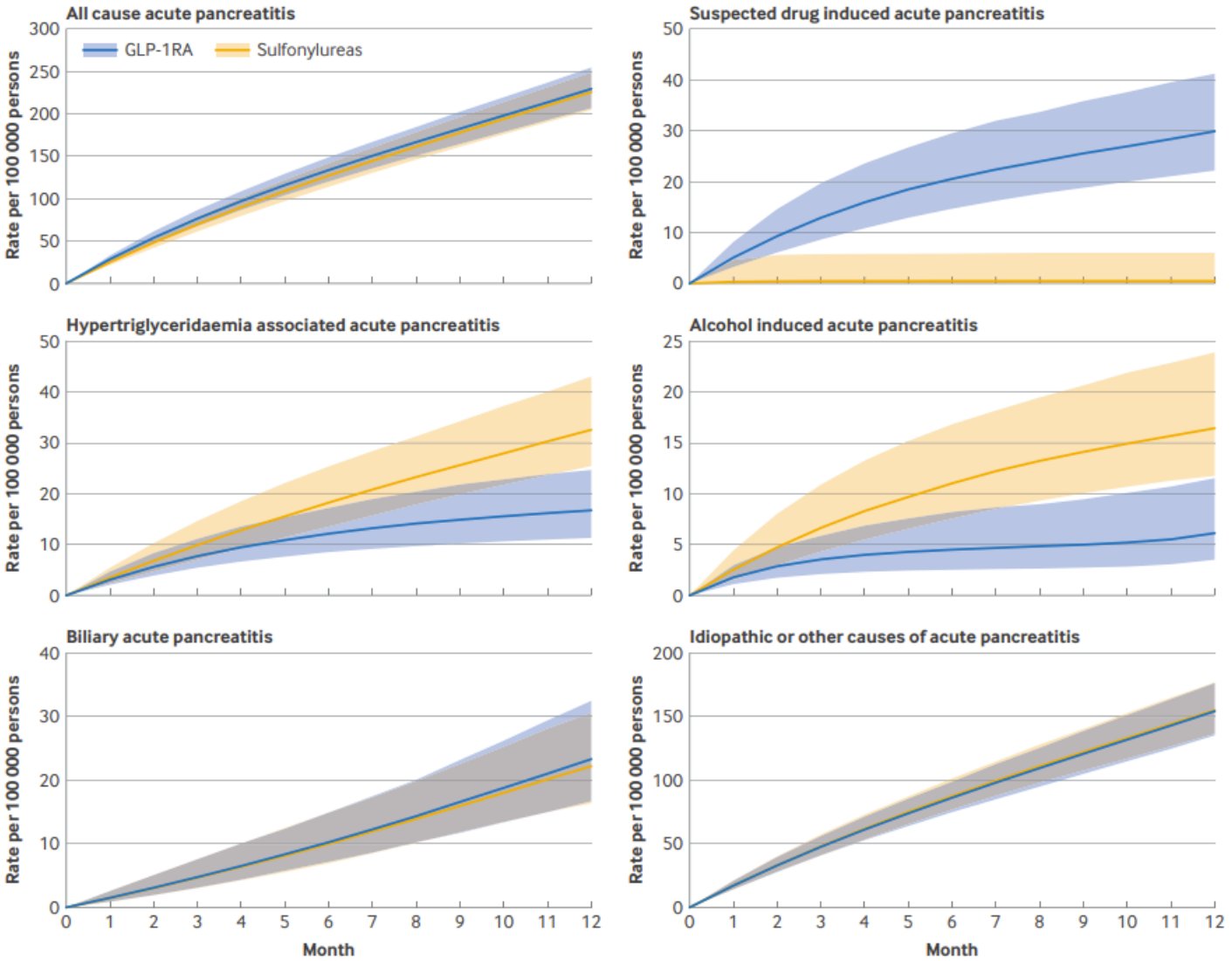

Figure 3 | Cumulative incidence of GLP-1RA and sulfonylureas on all cause pancreatitis and cause specific acute pancreatitis. Top left graph shows all cause acute pancreatitis; top right shows suspected drug induced acute pancreatitis; middle left shows hypertriglyceridaemia associated acute pancreatitis; middle right shows alcohol induced acute pancreatitis; bottom left shows biliary acute pancreatitis; bottom right shows idiopathic or other causes of acute pancreatitis. GLP-1RA group is shown in blue and the sulfonylureas group is shown in yellow. Shaded areas represent 95% confidence intervals. GLP-1RA=glucagon-like peptide-1 receptor agonists

A potential opportunity for the OHDSI community: A shared clinical definition library

Abdominal Pain
Abnormal uterine bleeding
Acidosis
Acne
Acute bleeding
Acute coronary syndrome
acute hepatic impairment
Acute interstitial nephritis
Acute kidney injury
Acute liver failure
Acute myeloid leukemia
acute myocardial infarction
acute pancreatitis
Acute pericarditis
Acute respiratory failure
Acute sinusitis
Acute tubular necrosis
Agranulocytosis
Akathisia
Alzheimer's disease
Anagen Effluvium Alopecia
Anaphylactic shock
anaphylaxis
Angina pectoris
Angioedema
Ankle fracture
Anxiety
ARDS
Arrhythmia
Ascites
Aseptic meningitis
Asthenia
Asthma
Ataxia
Atopic dermatitis
Atrial Fibrillation
Atrioventricular block
Bacteremia
Biliary acute pancreatitis
Bipolar disorder
Bladder cancer
Bradycardia
Breast cancer
Bronchospasm
Cachexia
Cardiogenic shock
Cardiomyopathy
Cardio-respiratory arrest
Cellulitis
Cerebral edema
Cerebral infarction
Cholecystitis
Cholestasis
cholestatic liver disease
Chorea
Chronic bleeding
Chronic kidney disease
Chronic pain
Cognitive impairment
Coma
Confusion
Constipation
Coronary arteriosclerosis
Coronary vasospasm
Cough
Crohn's disease
Cushing Syndrome
Cyanosis
Cytokine release syndrome
Cytolytic hepatitis
Death
deep vein thrombosis
Delirium
Delusion
Dementia
Depressive episode
Diabetes mellitus
Diabetic Ketoacidosis
Diarrhea
Disseminated intravascular coagulation
Dizziness
DRESS syndrome
drug induced liver injury
Drug-induced lupus erythematosus
Dry mouth
Dysgeusia
Dysphagia
Dyspnea
Dystonia
Edema
elevated blood pressure
Encephalitis
Encephalopathy
End stage renal disease
Endometrial cancer
Eosinophilia
Epilepsy
Erectile dysfunction
Erythema Multiforme Major
Erythema Multiforme
Erythema
Esophagitis
Essential hypertension
Fall
Fatigue
Fever
Fibromyalgia
Fracture
Fragility fracture
Gastric ulcer
Gastroesophageal reflux disease
Gastrointestinal hemorrhage
GastroIntestinal perforation
Generalized exfoliative dermatitis
Gestational diabetes
Glaucoma
Glomerulonephritis
Gynecomastia
Hallucination
heart failure
HELLP syndrome
Hematoma
Hemolytic uremic syndrome
Hepatic Encephalopathy
Hepatitis
Hip fracture
Hodgkin Lymphoma
Hyperbilirubinemia
Hypercalcemia
Hypercholesterolemia
Hypercortisolism
Hyperglycemia
Hyperkalemia
Hyperlipidemia
Hypermagnesemia
Hypernatremia
Hyperpigmentation of skin
Hyperprolactinemia
Hypertensive crisis
Hypertriglyceridaemia associated acute pancreatitis
Hypertriglyceridemia
Hyperuricemia
Hypocalcemia
Hypoglycemia
Hypokalemia
Hyponatremia
Hypotension
Hypothermia
Hypothyroidism
Hypoxemia
Idiopathic acute pancreatitis
Infectious cystitis
Interstitial cystitis
Interstitial lung disease
Intracranial hemorrhage
Jaundice
Joint pain
Kidney stone
Lactic acidosis
Left bundle branch block
Leukocytosis
Leukopenia
lightheadedness
Liver cirrhosis
Liver necrosis
Long QT syndrome
Lower gastrointestinal hemorrhage
Lymphadenopathy
Lymphedema
Lymphoma
Lymphopenia
Major Depressive Disorder
Malaise
Malignancy
Mania
Melanoma
Metabolic Dysfunction-Associated Steatotic Liver Disease
Metastatic secondary malignancy
Microalbuminuria
Mild cognitive impairment
Myocardial ischemia
Myocarditis
Myoclonus
Neonatal jaundice
Nephrotic Syndrome
Neuroleptic malignant syndrome
Neutropenia
Non-arteritic Anterior Ischemic Optic Neuropathy
Non-Hodgkin Lymphoma
Non-melanoma skin cancer
non-ST-elevation myocardial infarction
Oral ulcer
Orthostatic hypotension
Overactive bladder
Pain
Palpitations
Pancytopenia
Paralysis
Paralytic ileus
Paresthesia
Parkinsonism
Pemphigus
Peptic ulcer
Peripheral neuropathy
Peripheral vascular disease
Plaque psoriasis
Pleural effusion
Pneumonia
Pneumonitis
Posterior reversible encephalopathy syndrome
Primary adrenal insufficiency
Primary angle-closure glaucoma
Primary malignancy
Primary open-angle glaucoma
Progressive multifocal leukoencephalopathy
Prostate cancer
Proteinuria
Pruritus
Psychosis
Pulmonary arterial hypertension
Pulmonary edema
Pulmonary embolism
Pulmonary hypertension
Rash
Renal impairment
Renal tubular disorder
Respiratory depression
Restless Legs Syndrome
Right bundle branch block
Seizure
Sepsis
Septic shock
Serotonin syndrome
Shock
SIADH
Skin ulcer
Somnolence
Status Epilepticus
Steatosis of liver
ST-elevation myocardial infarction
Stevens-Johnson syndrome
Supraventricular tachycardia
Syncope
Systemic lupus erythematosus
Tachycardia
Thrombocytopenia
thrombosis
Thrombotic microangiopathy
Thrombotic Thrombocytopenic Purpura
Thyroiditis
Thyrotoxicosis
Torsade de pointes
Toxic epidermal necrolysis
Transient Global Amnesia
Transient ischemic attack
Tremor
Tumour Lysis Syndrome
Type 1 Diabetes mellitus
type 1 myocardial infarction
Type 2 Diabetes mellitus
Type B lactic acidosis
Type I acute respiratory failure
ulcerative colitis
Unstable angina
Upper gastrointestinal hemorrhage
Upper gastrointestinal ulceration
Urinary retention
Urinary tract infection
Urothelial carcinoma of bladder
Urticaria
Vasculitis
Venoocclusive liver disease
venous thromboembolism
Ventricular Fibrillation
Ventricular tachycardia
Vertigo

Guidance for phenotype development: DO

1. Fully define your clinical intent
[ongoing OHDSI open-source development may be able to help]

2. THEN create your phenotype algorithm (e.g. identify the codes and specify the temporal logic) to try to model that clinical intent
[ongoing OHDSI open-source development may be able to help]

3. THEN empirically evaluate how well your algorithm represents the clinical intent in your database(s) (e.g. estimate sensitivity, specificity, PPV, NPV, index date misspecification)
[ongoing OHDSI open-source development may be able to help]

Guidance for phenotype development: DON'T

1. Assume a label is a sufficient clinical definition (ex. not everyone sees a 'sandwich' the same way as you do)
2. Assume your operational definition defines your clinical intent (ex: 'fragility fracture' isn't necessarily understood to be only 'hip/vertebra/rib/arm' just because those are the ICD codes you picked)
3. Assume your operation definition might capture your clinical intent in one database because it did – with error- in a different database (ex: dementia codes in a Canadian claims data don't necessarily perform the same in US EHR data)
4. Assume that results from a broad clinical definition will necessarily be the same as all subpopulations within the clinical definition (ex: all-cause pancreatitis may not be the same as drug-induced, alcohol-induced, and biliary pancreatitis)