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# Falls, fractures, lean mass and age with GLP-1receptor agonists and tirzepatide: meta-analysis of 162 placebo-controlled trials andage-subgroup data for adults aged 75 years orolder

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**Systematic Review**

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## Abstract

# Background.

Weight loss with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and tirzepatide includes loss of lean mass, raising concern about falls and fractures in older adults. Whether harm increases with participant age, and whether benefit persists at 75 years or older, has not been examined systematically.

# Methods.

We extracted serious adverse events coded as "Fall", any fracture, and hip/femur fracture from all placebo-controlled, parallel-group randomised trials of GLP-1 RAs or tirzepatide in adults (treatment ≥ 12 weeks) with results posted on ClinicalTrials.gov (searched 31 October 2026), and searched PubMed (1 November 2026) for placebo-controlled trials reporting lean mass by dual-energy X-ray absorptiometry (DXA). Risk ratios (RR) and mean differences (MD) were pooled by random-effects models (REML, Hartung-Knapp), and effect modification by trial mean age was tested by meta-regression. Post hoc, we extracted results by participant age from FDA review documents and published subgroup analyses, and pooled placebo-controlled trials reporting 6-minute walk distance (6MWD) and bone-turnover markers.

# Results.

In 162 trials (83,571 participants on GLP-1 RA or tirzepatide, 62,962 on placebo; trial mean ages up to 74 years), serious falls (k = 30; RR 0.91, 95% CI 0.77–1.07), any serious fracture (k = 76; RR 0.90, 0.80–1.01) and hip/femur fracture (k = 22; RR 1.04, 0.80–1.36) were not increased, and meta-regression showed no association with trial mean age (falls: RR per 10 years 0.92, 0.55–1.54; p = 0.75). Lean mass fell by 2.76 kg more than with placebo (9 trials, mean age 29–53 years; −3.78 to − 1.74), and by 4.12 kg in the four semaglutide or tirzepatide trials. Within SELECT (semaglutide 2.4 mg, n = 17,604), the fracture RR rose across age bands from 0.47 (0.25–0.91) at < 55 years to 1.30 (0.75–2.26) at ≥ 75 years (ratio per band 1.44, 1.11–1.87; p = 0.006); at ≥ 75 years, hip and pelvis fractures occurred in 17/703 vs 4/663 participants (RR 4.01, 1.36–11.85). At about 75 years or older (subgroups ≥ 70 to ≥ 75 years) in type 2 diabetes, HbA1c was lowered by 0.6–0.7 percentage points and the pooled hazard ratio for major adverse cardiovascular events was 0.80 (0.61–1.06); any serious adverse event was not more frequent with treatment in SELECT, LEADER or STEP-HFpEF. 6MWD improved by 15.2 m (8.6–21.9; k = 6). No placebo-controlled trial reported grip strength, gait speed or the Short Physical Performance Battery.

# Conclusions.

Across trials, GLP-1 RAs and tirzepatide reduced lean mass without increasing serious falls or fractures, with no evidence that trial mean age modified this. Within the largest trial, however, the fracture RR

increased with participant age, and hip and pelvis fractures were more frequent with semaglutide at 75 years or older. In adults with type 2 diabetes aged about 75 years or older, HbA1c is lowered and cardiovascular estimates point in the same direction as in younger adults without reaching significance. Trials in this age group that measure efficacy together with fat mass, lean mass, muscle strength, physical function and fractures are needed.

## Introduction

GLP-1 RAs and the GIP/GLP-1 receptor co-agonist tirzepatide produce weight losses of 10–20% in people with obesity and are increasingly prescribed to older adults. Part of the weight lost is lean mass. In placebo-controlled DXA studies, about 25–30% of the weight lost with these agents was lean mass [1, 2], and a 2026 systematic review found lean-mass loss above a 25% benchmark in about two thirds of incretin trials [3].

In older adults, loss of muscle mass could plausibly translate into weakness, falls and fractures, and gastrointestinal adverse effects or volume depletion could add to fall risk. Clinicians therefore ask whether there is an age above which the harms of drug-induced weight loss outweigh its benefits.

Previous meta-analyses pooled lean mass [1, 4] or bone outcomes [4, 5], mostly in trials of middle-aged adults (mean ages 20–64 years in the 35 trials reviewed by Batsis et al. [3]). They did not test whether falls or fractures vary with participant age. Falls are rarely a prespecified trial outcome, but they are recorded as adverse events, and ClinicalTrials.gov results list serious adverse events completely.

We therefore asked three questions: (1) do GLP-1 RAs or tirzepatide change the risk of serious falls and fractures compared with placebo, and does that effect vary with trial mean age; (2) how much DXA-measured lean mass do they remove, and at which ages has this been measured; and (3) what do results reported by participant age within trials show for adults aged about 75 years or older, for benefit as well as harm, and for muscle function and bone turnover?

## Methods

# Protocol

The question, eligibility criteria, outcomes and analysis plan for the trial-level analyses (falls, fractures, lean mass) were written down on 1 November 2026, before data extraction. The protocol was not prospectively registered; it was registered retrospectively on OSF Registries after the analyses were completed (https://doi.org/10.17605/OSF.IO/YCDBH). The protocol listed results restricted to participants aged ≥ 65 or ≥ 75 years as a secondary source where available; the use of FDA review documents for this purpose, and the muscle-function and bone-turnover analyses, were added after the trial-level analyses showed that no trial had a mean age of 75 years or more, and are post hoc. Deviations from the protocol: risk ratios were pooled by inverse-variance REML rather than Mantel-Haenszel random effects (Mantel-Haenszel fixed effect is reported as a sensitivity analysis), and

analyses were run in Python validated against the R package metafor rather than in R. Planned analyses that were not performed (falls of any seriousness, lean mass as a proportion of weight lost, risk difference including double-zero trials, funnel plot, RoB 2) are listed with all other deviations in the registration. Reporting follows PRISMA 2020 where applicable.

## Eligibility

- **Design**: parallel-group randomised trials, treatment ≥ 12 weeks; crossover and non-randomised studies excluded.
- **Participants**: adults (trials with a paediatric or adolescent population excluded), with or without diabetes.
- **Intervention**: a GLP-1 RA (semaglutide subcutaneous or oral, liraglutide, dulaglutide, exenatide, lixisenatide, albiglutide, efpeglenatide) or tirzepatide.
- **Comparator**: placebo on the same background therapy. Arms that also received another investigational drug (e.g. cagrilintide, bimagrumab) and multi-agonists other than tirzepatide were excluded.

**Outcomes**

1. Participants with ≥ 1 serious adverse event coded as MedDRA preferred term "Fall".
2. Serious adverse events whose term contains "fracture" (any site), and the subset at the hip or femur.
3. Between-group difference in change of DXA total lean mass (or fat-free mass), kg.

Serious events were used because ClinicalTrials.gov reports them without a frequency threshold, whereas non-serious events are usually listed only above 5%.

## Data sources and extraction

**Falls and fractures.** ClinicalTrials.gov (API v2 [9]) was queried on 31 October 2026 (UTC) for studies with posted results whose interventions included any of the drugs above and whose record contained "placebo". For each record, adverse-event groups were classified from their titles as GLP-1 RA, placebo or other; multiple GLP-1 RA dose arms were combined. Classifications for every trial contributing events were reviewed by hand, and two trials whose groups double-counted participants (AWARD-1, SURMOUNT-4) were corrected to their randomised double-blind period. Participants at risk and participants affected were taken from the serious adverse-event tables. Mean age came from the baseline table, or from the primary publication when missing (SUSTAIN-6, SURMOUNT-OSA, NCT03987451). For fractures, counts were summed across fracture terms, so a participant with two fracture types is counted twice.

**Lean mass.** PubMed was searched on 1 November 2026 with drug terms (tirzepatide, semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide, albiglutide, efpeglenatide, or GLP-1 receptor agonists),

body-composition terms (body composition, lean mass, lean body mass, fat-free mass, DXA/DEXA, absorptiometry) and trial terms (randomized controlled trial, randomi*, placebo). The reference list of a previous meta-analysis [1] and the registry records above were also checked. Mean differences with standard errors were taken from registry results or the primary report where accessible; otherwise from the tabulation in Beavers et al. [1]. Medians with interquartile ranges were converted to means and SDs [6]. Three trials reported only pre- and post-treatment values; their change SDs were imputed with a correlation of 0.9 [7] and they were used in a sensitivity analysis only.

**Age-subgroup data (post hoc).** For participants aged about 75 years or older, we text-searched the FDA review documents of the trials and programmes contributing most participants (SELECT, NDA 215256 supplement 11 [11]; PIONEER phase 3a, NDA 213051 [12]; LEADER, NDA 022341 [13]) for age-subgroup tables, and searched PubMed for post hoc or prespecified age analyses of cardiovascular and heart-failure outcome trials. We extracted event counts or hazard ratios by age group for major adverse cardiovascular events (MACE), all-cause death, any serious adverse event, falls and fractures, and placebo-adjusted HbA1c differences. Where reports gave percentages only, denominators were derived from group sizes.

**Muscle function and bone turnover (post hoc).** From the trials above, ClinicalTrials.gov results and PubMed, we extracted placebo-controlled differences in 6MWD, grip strength, gait speed, Short Physical Performance Battery (SPPB) and muscle strength, and in serum C-terminal telopeptide of type I collagen (CTX) and procollagen type 1 N-terminal propeptide (P1NP). This was a targeted rather than a fully systematic search.

# Statistical analysis

Risk ratios were pooled on the log scale with a random-effects model (REML estimate of $\tau^2$, Hartung-Knapp confidence intervals). Trials with no events in either arm were excluded; trials with a zero cell received a 0.5 continuity correction. Sensitivity analyses used the Mantel-Haenszel fixed-effect RR, the Peto odds ratio, restriction to semaglutide and tirzepatide trials, restriction to trials with ≥ 3,000 participants, and leave-one-out. Lean mass was pooled as a mean difference with the same model.

Effect modification by age was tested by random-effects meta-regression with trial mean age as a continuous covariate (Hartung-Knapp), and by a split at a trial mean age of 65 years, tested as a meta-regression on a ≥ 65-year indicator (Hartung-Knapp). Small-study effects were assessed with Egger's regression test for outcomes with ≥ 10 trials. The predicted RR at given ages was reported only within the observed age range. Heterogeneity is reported as $\tau^2$ and $I^2$.

Within SELECT, the trend in log RR across the four ordered age bands was estimated by inverse-variance weighted regression on band order (fixed effect), and the RR at ≥ 75 years was compared with the fixed-effect pooled RR of the three younger bands. Hazard ratios for MACE at about 75 years or older from two analyses in type 2 diabetes were pooled on the log scale (REML with a Wald interval, because a Hartung-

Knapp interval with two studies is uninformative). 6MWD and CTX were pooled as mean differences (REML, Hartung-Knapp).

Analyses were written in Python (NumPy, SciPy). The code reproduced the reference results of the metafor package for the BCG vaccine dataset (pooled log RR − 0.7145, SE 0.1798, $\tau^2$ 0.3132; meta-regression slope − 0.0291) [8]. Data and code are provided as supplementary files.

## Risk of bias

Of the 79 trials contributing events, 78 were double-blind or more (ClinicalTrials.gov masking field) and 76 were industry-sponsored. Formal outcome-level RoB 2 assessment was not performed; this is a limitation.

## Results

# Included trials

The registry search returned 282 records; 162 trials met the criteria (83,571 participants at risk on a GLP-1 RA or tirzepatide, 62,962 on placebo; Fig. 1A). Among the 156 trials reporting age, trial mean ages ranged from 23 to 74 years, and 13 had a mean age of 65 years or more. Seventy-nine trials reported ≥ 1 serious fall or fracture (Table S1). Only two trials had a mean age of 70 years or more (GetGoal-O, 74.2 years, n = 350; PIONEER 5, 70 years, n = 324), and none had a mean age of 75 years or more. The lean-mass search identified 12 trials (9 in the primary analysis; Fig. 1B).

## Serious falls

Thirty trials recorded ≥ 1 serious fall: 355 of 56,019 participants on a GLP-1 RA or tirzepatide and 372 of 49,661 on placebo. The pooled RR was 0.91 (95% CI 0.77–1.07; $\tau^2$ 0.022; $I^2$ 10%; Fig. 2). Results were similar with the Mantel-Haenszel RR (0.93, 0.81–1.08), the Peto OR (0.93, 0.80–1.08) and leave-one-out analysis (RR range 0.87–0.97). The largest single-trial estimates went in opposite directions: SELECT, RR 1.46 (0.95–2.24), and SOUL, RR 0.57 (0.35–0.93).

# Age and serious falls

In meta-regression, the RR did not change with trial mean age: RR per 10 years 0.92 (0.55–1.54), p = 0.75 (Fig. 3). Predicted RRs were 0.94 (0.72–1.23) at a mean age of 60 years and 0.87 (0.62–1.23) at 70 years. In the prespecified split, the RR was 0.76 (0.60–0.95; k = 9) in trials with mean age ≥ 65 years and 1.08 (0.89–1.30; k = 21) in younger trials (test for subgroup difference p = 0.025). This difference was not present when age was treated as continuous, and the older subgroup consisted mainly of cardiovascular and kidney outcome trials in type 2 diabetes. Restricted to the 12 trials with ≥ 3,000 participants, the RR was 0.91 (0.72–1.16) and the subgroup difference was p = 0.095. Restricted to semaglutide and

tirzepatide trials (k = 12), the RR was 0.80 (0.58–1.11), and 0.63 (0.47–0.83) in the six with mean age ≥ 65 years.

# Fractures

Serious fracture events were reported in 76 trials: 838 among 73,196 participants on a GLP-1 RA or tirzepatide and 840 among 57,901 on placebo. The pooled RR was 0.90 (0.80–1.01; $I^2$ 11%), with no association with trial mean age (RR per 10 years 0.90, 0.72–1.11; p = 0.31) and no subgroup difference at 65 years (0.91 vs 0.88; p = 0.86). Restricted to semaglutide and tirzepatide trials (k = 41), the RR was 0.80 (0.71–0.90; $I^2$ 0%). Egger's test showed no small-study asymmetry for falls (p = 0.58) or fractures (p = 0.62); for hip/femur fractures p = 0.07.

Hip or femur fractures were reported in 22 trials (195/51,104 vs 192/47,800; RR 1.04, 0.80–1.36; Figure S1). The meta-regression slope was not significant (p = 0.59). The split at 65 years gave RR 1.27 (0.97–1.66) in younger trials and 0.82 (0.53–1.27) in older trials (p = 0.027), again with the older trials having the lower estimate.

# Lean mass

In the nine primary trials (mean age 29–53 years), GLP-1 RAs or tirzepatide reduced DXA lean mass by 2.76 kg more than placebo (95% CI − 3.78 to − 1.74; $I^2$ 82%; Fig. 4; Table S2). In the four semaglutide or tirzepatide trials the difference was − 4.12 kg (− 4.59 to − 3.65; $I^2$ 0%). Adding the three trials with imputed change SDs gave − 2.17 kg (− 3.30 to − 1.03). The slope against mean age was − 0.66 kg per 10 years (− 2.24 to 0.92; p = 0.35; k = 8), estimated over an age range that did not include older adults. In the SURMOUNT-1 DXA substudy, the share of weight lost as lean mass with tirzepatide was 26% overall and 24% in the small subgroup aged ≥ 65 years [2].

# Age gradient within SELECT

The FDA clinical review of SELECT (semaglutide 2.4 mg in adults with obesity and cardiovascular disease without diabetes; 17,604 randomised [10]) tabulated selected serious fracture events by age, in a post hoc response to an FDA information request [11] (Fig. 5). The RR was 0.47 (0.25–0.91) at < 55 years, 0.55 (0.33–0.92) at 55 to < 65 years, 0.89 (0.60–1.34) at 65 to < 75 years and 1.30 (0.75–2.26) at ≥ 75 years. The RR increased by a factor of 1.44 per age band (1.11–1.87; p = 0.006), and the RR at ≥ 75 years was 1.91 times that of the three younger bands combined (1.03–3.56; p = 0.041). At ≥ 75 years, hip and pelvis fractures occurred in 17 of 703 participants on semaglutide and 4 of 663 on placebo (RR 4.01, 1.36–11.85); this finding is stated in the US prescribing information [25]. The FDA's fracture definition differs from the registry count used in the trial-level analysis (108 vs 139 events in the age table; 128 vs 159 in the registry). In the pooled PIONEER phase 3a programme of oral semaglutide, falls in participants older than 75 years were reported in 7 on semaglutide (adjusted proportion 3.5%) and 1 on comparator (1.2%); denominators were not given [12].

# Participants aged about 75 years or older

In type 2 diabetes, the hazard ratio (HR) for MACE was 0.70 (0.48–1.01) with albiglutide at ≥ 75 years in Harmony Outcomes (n = 1,140) [14] and 0.93 (0.63–1.36) with semaglutide at > 70 years (mean 75.1 years) in pooled SUSTAIN-6 and PIONEER 6 (n = 1,554) [15]; the pooled HR was 0.80 (0.61–1.06; $I^2$ 8%; Fig. 6; Table S4). In SELECT, the MACE HR at ≥ 75 years was 0.92 (0.67–1.25) [11]. In LEADER, all-cause death at 75–84 years occurred in 54 of 401 participants on liraglutide and 70 of 393 on placebo (RR 0.76, 0.55–1.05) [13]. HbA1c was lowered by 0.7 percentage points with semaglutide at > 70 years [15] and by 0.64 (0.46–0.81) with lixisenatide in GetGoal-O (mean age 74.2 years) [24].

Any serious adverse event was not more frequent with treatment at about 75 years or older: RR 0.94 (0.84–1.05) in SELECT, 0.58 (0.40–0.84) in the pooled STEP-HFpEF trials [16] and 1.00 (0.90–1.11) at 75–84 years in LEADER. Both sources that reported fractures or bone injuries at ≥ 75 years gave RRs above 1 with wide intervals (SELECT 1.30, 0.75–2.26; STEP-HFpEF serious bone and joint injuries 4/136 vs 3/156, RR 1.53, 0.35–6.71).

# Muscle function and bone turnover

We found no placebo-controlled trial of a GLP-1 RA or tirzepatide that reported grip strength, gait speed or SPPB. Six trials reported 6MWD (Table S3; [17–19, 22]): the pooled difference was + 15.2 m (8.6–21.9; $I^2$ 0%), and + 17.6 m (10.7–24.5) in the three trials in heart failure with preserved ejection fraction and obesity (STEP-HFpEF, STEP-HFpEF DM and SUMMIT; mean or median age 65–70 years) [17–19]. In the prespecified pooled age analysis of STEP-HFpEF, in which 292 participants were aged ≥ 75 years, the effect on 6MWD did not differ across age groups [16]. In S-LiTE, knee-extension torque after diet-induced weight loss did not differ between liraglutide 3.0 mg and placebo (+ 1.9 Nm, − 7.8 to 11.6) [23].

In a 52-week trial of semaglutide 1.0 mg in adults with increased fracture risk (mean age 63 years), CTX increased by 166 ng/L (26–307) relative to placebo, while P1NP did not differ (+ 3.8 ng/mL, − 5.6 to 13.3) [20]. Pooled with two smaller trials in type 2 diabetes ([21]; NCT02020616), the CTX difference was + 0.049 µg/L (− 0.060 to 0.159; p = 0.19; k = 3).

## Discussion

Across 162 placebo-controlled trials, GLP-1 RAs and tirzepatide did not increase serious falls (RR 0.91) or serious fractures (RR 0.90), and meta-regression showed no association of either risk with trial mean age (trial mean ages up to 74 years). In separate DXA trials, the same drug classes reduced lean mass by 2.8 kg relative to placebo on average, and by about 4 kg in semaglutide or tirzepatide trials. Within SELECT, however, the fracture RR increased with participant age, and at 75 years or older hip and pelvis fractures were about four times as frequent with semaglutide as with placebo.

The split at 65 years pointed towards fewer falls in older trials (RR 0.76). We do not interpret this as protection. The continuous meta-regression showed no age gradient, the split was one of several

analyses, and the older trials were mostly large cardiovascular or kidney outcome trials in type 2 diabetes, which differ from obesity trials in background treatment, weight loss and event ascertainment. Trial mean age is also a weak proxy for the age of individual participants, so these are ecological associations. The same pattern for hip and femur fractures (lower RR in older trials) has the same limits.

The between-trial and within-trial results differ, and for the question of age the within-trial result is the more informative. Meta-regression on trial mean age compares trials that differ in population, drug and event ascertainment, with trial mean ages no higher than 74 years; it cannot detect a gradient that exists among individuals within trials (ecological bias). The SELECT analysis compares randomised groups of one trial across age bands. It is nonetheless a post hoc analysis of a single trial, prepared in response to a regulatory request, with wide confidence intervals and only 21 hip or pelvis fractures at 75 years or older. It is a signal that needs confirmation, not an established effect.

Data for the oldest adults remain sparse. No placebo-controlled trial with posted results had a mean age of 75 years or more, DXA lean mass had not been measured in any trial with a mean age above 53 years, and no trial reported grip strength, gait speed or SPPB. The age-subgroup data that exist show that, in type 2 diabetes, HbA1c is lowered at about 75 years or older and cardiovascular estimates point in the same direction as in younger participants (pooled HR 0.80, 0.61–1.06), and that serious adverse events overall were not increased. 6MWD improved by 14 to 20 m in trials in heart failure with obesity, and in STEP-HFpEF the effect did not differ between age groups, including participants aged 75 years or older; lean mass was not measured in these trials, so they show that walking capacity was not reduced, not that lean-mass loss is harmless. This does not exclude effects on strength, falls or fractures in frail adults or adults with sarcopenic obesity, who are rarely enrolled.

Our results agree with pooled analyses that found reduced lean mass [1, 4] without a detectable effect on fractures across trials [4]. They add the complete serious adverse-event tables of 162 trials, an explicit test of effect modification by trial mean age, and age-subgroup results from regulatory reviews. The increase in CTX in the one trial in people at increased fracture risk [20] is consistent with increased bone resorption during weight loss, but the pooled CTX difference was not significant, and no trial has linked bone-marker changes to fractures.

# Limitations

- Falls were not prespecified outcomes in any trial; they were collected as adverse events, and only serious falls are reported completely on ClinicalTrials.gov. Non-serious falls, the majority of falls, could not be analysed.
- Fracture counts were summed across MedDRA terms, so participants with more than one fracture type were counted more than once.
- Age was analysed at the trial level; individual-participant data would be needed to estimate risk for people aged 75 years or more.

- Trials without posted results, mainly academic trials, are missing from the falls and fracture analysis.
- Lean-mass trials were small and heterogeneous ($I^2$ 82%); for six trials (three in the primary analysis) data came from a published tabulation rather than the primary report, and three needed imputed SDs.
- Risk of bias was not formally assessed with RoB 2, and the protocol was not prospectively registered.
- The age-subgroup, muscle-function and bone-marker analyses were post hoc and used a targeted search. The SELECT age data come from one trial, through a regulatory review, with a sponsor-selected fracture definition.
- Results at about 75 years or older come from different trials, populations, age cut-offs (≥ 75, > 70, 75–84 years) and outcome definitions, and were pooled only for MACE in type 2 diabetes.

# Conclusions

Across placebo-controlled trials, GLP-1 RAs and tirzepatide reduced lean mass without increasing serious falls or fractures, with no evidence that trial mean age modified this. Within SELECT, the fracture risk ratio rose with participant age, and hip and pelvis fractures were more frequent with semaglutide at 75 years or older. In adults with type 2 diabetes aged about 75 years or older, HbA1c is lowered and cardiovascular estimates point in the same direction as in younger adults (HR 0.80, 0.61–1.06), and serious adverse events overall were not increased. Trials in adults aged 75 years or older are needed that measure efficacy together with fat mass, lean mass, muscle strength, physical function and fractures, and that test protein and resistance-exercise co-interventions.

# Declarations

**Funding.** None.

**Competing interests.** The author declares no competing interests.

**Ethics.** Not required; the study used published, aggregate data.

**Use of AI tools.** Claude (Anthropic) was used to retrieve registry and PubMed records, write and run the analysis code, draw the figures and draft the text. The author checked the protocol, data extraction and interpretation and is responsible for the content.

**Data and code availability.** Trial-level data (ctgov_event_trials.tsv, leanmass_trials.tsv), age-subgroup and function/bone extracts (fda_age75.tsv, efficacy_age75.tsv, function_bone.tsv), the analysis code (metalib.py, analysis_ae.py, analysis_lean.py, analysis_age75.py), figure scripts (figures.py, figure5.py, prisma.py), the validation script and the protocol are provided as supplementary files. **Registration.** Registered retrospectively on OSF Registries on 1 November 2026, after data extraction and analysis:

https://doi.org/10.17605/OSF.IO/YCDBH (https://osf.io/ycdbh). The registration lists all deviations from the protocol.

**Author contributions.** KO conceived the question, supervised the analysis and approved the manuscript.

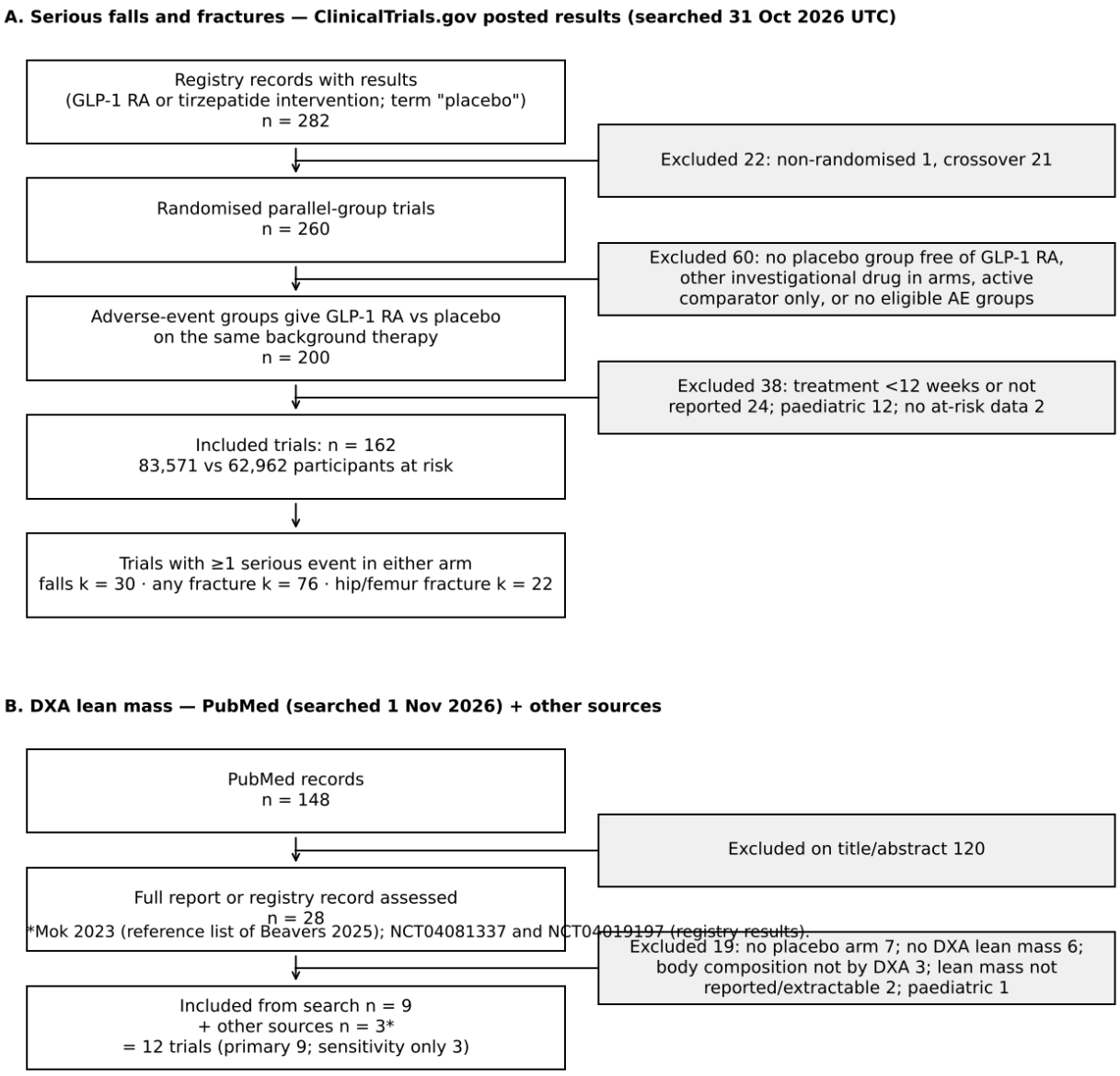
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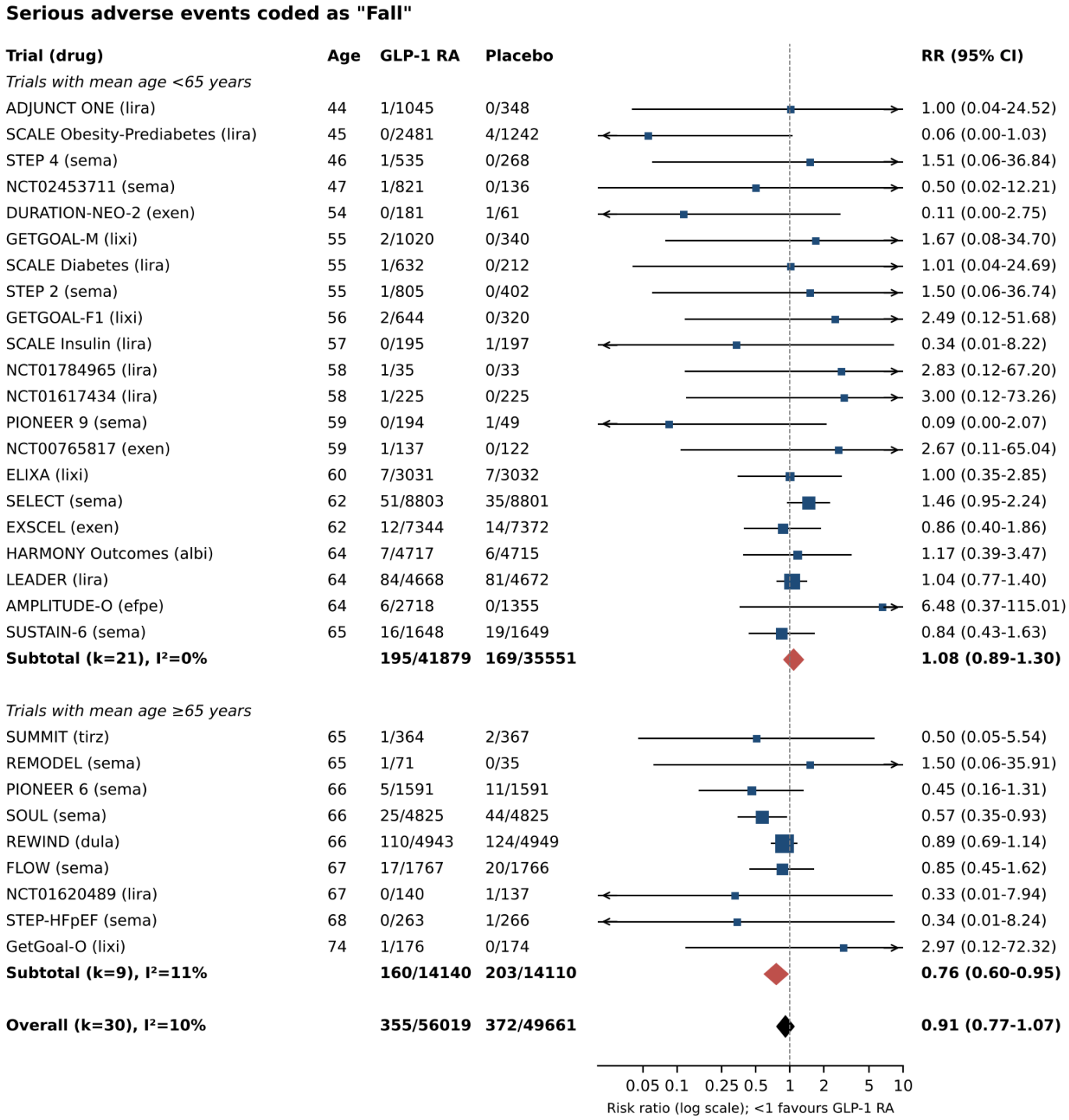
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# Figures




## Figure 1

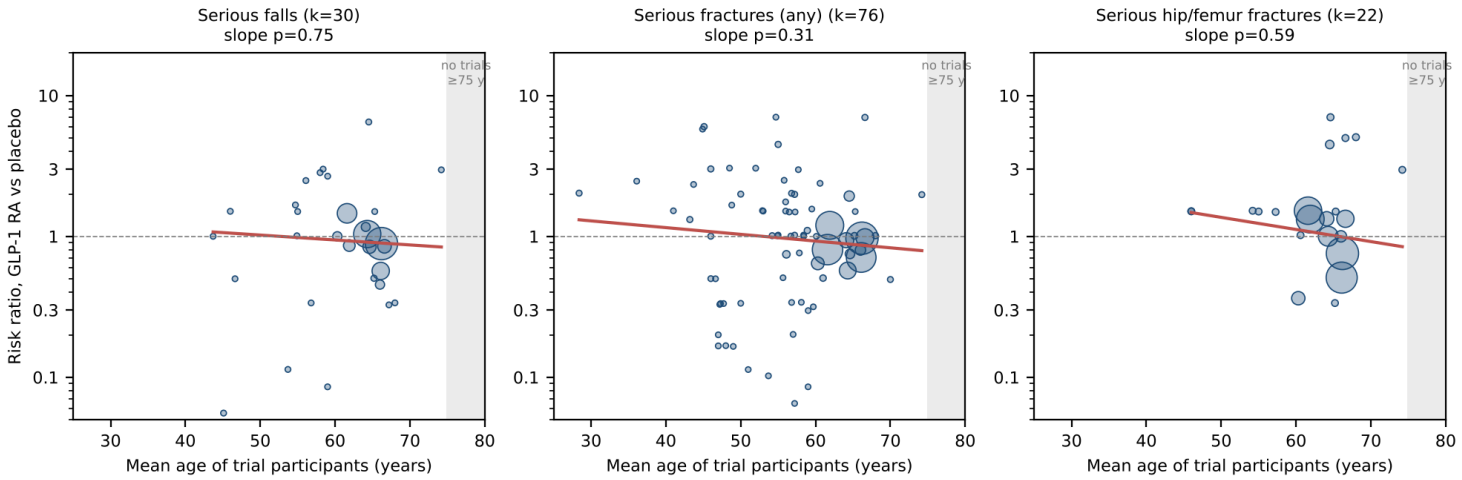
Study selection. (A) Placebo-controlled trials of GLP-1 receptor agonists or tirzepatide with adverse-event results posted on ClinicalTrials.gov (searched 31 October 2026). (B) Placebo-controlled trials reporting lean mass by dual-energy X-ray absorptiometry (DXA), identified in PubMed (searched 1 November 2026) and other sources.




Random effects (REML, Hartung-Knapp). Test for subgroup difference p=0.025.
Meta-regression on mean age: RR per +10 years 0.92 (0.55-1.54), p=0.75.
Single-zero trials: 0.5 continuity correction.

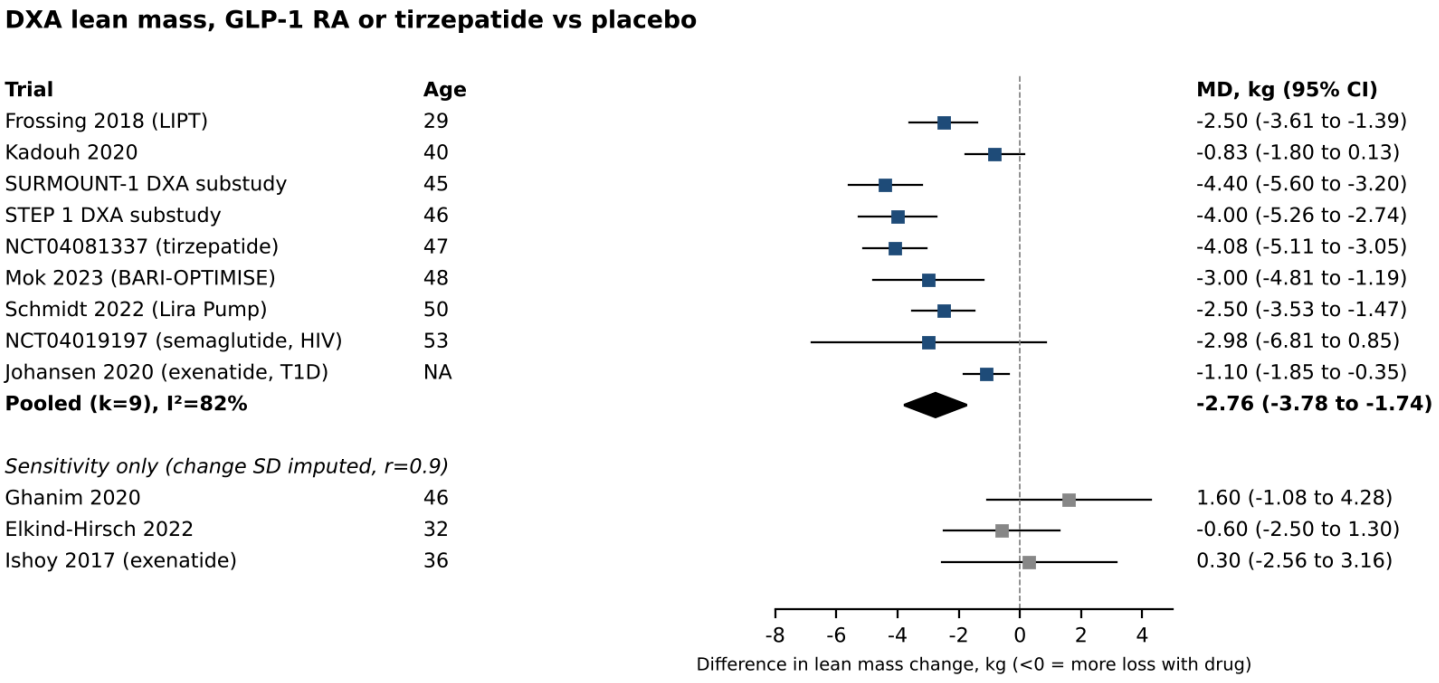
## Figure 2

Serious adverse events coded as "Fall", by trial, ordered by trial mean age and grouped by mean age <65 or ≥65 years. Risk ratios (GLP-1 receptor agonist or tirzepatide vs placebo) with 95% confidence intervals; pooled by random-effects meta-analysis (REML, Hartung-Knapp). Trials with a zero cell received a 0.5 continuity correction.




## Figure 3

Trial-level risk ratios against trial mean age for serious falls, any serious fracture and serious hip/femur fracture. Circle area is proportional to inverse variance; the line is the random-effects meta-regression. No trial had a mean age of 75 years or more (shaded area).



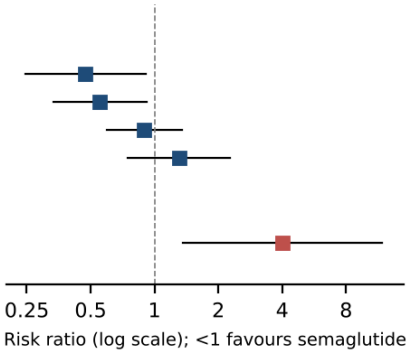

Random effects (REML, Hartung-Knapp). Meta-regression on mean age (k=8, range 29-53 y): -0.66 kg per +10 years (-2.24 to 0.92), p=0.35.
No trial had a mean age ≥60 years.

## Figure 4

Difference in change of DXA lean mass (kg), GLP-1 receptor agonist or tirzepatide minus placebo, with 95% confidence intervals. Primary analysis (9 trials) pooled by random-effects meta-analysis (REML, Hartung-Knapp); three trials with imputed change SDs are shown separately and were used in sensitivity analysis only.

**SELECT (semaglutide 2.4 mg vs placebo): fracture risk by age**

| Age group | Drug | Placebo | RR (95% CI) |
|---|---|---|---|
| *Selected serious fracture events* | | | |
| <55 y | 13/2057 | 28/2094 | 0.47 (0.25-0.91) |
| 55 to <65 y | 23/3387 | 41/3338 | 0.55 (0.33-0.92) |
| 65 to <75 y | 43/2656 | 49/2706 | 0.89 (0.60-1.34) |
| ≥75 y | 29/703 | 21/663 | 1.30 (0.75-2.26) |
| *Hip and pelvis fractures* | | | |
| ≥75 y | 17/703 | 4/663 | 4.01 (1.36-11.85) |



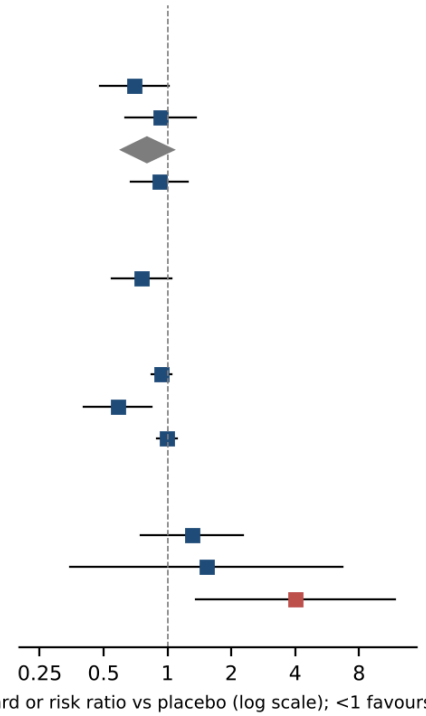

Source: FDA clinical review of NDA 215256 S-011 (Tables 85 and p.225; post hoc response to an FDA information request).
Trend across the four age bands (log RR on band order, fixed effect): ratio 1.44 per band (1.11-1.87), p = 0.006.
≥75 vs <75 years (fixed-effect pool of the three younger bands): ratio of risk ratios 1.91 (1.03-3.56), p = 0.041.

## Figure 5

Selected serious fracture events by age group in SELECT (semaglutide 2.4 mg vs placebo), from the FDA clinical review of NDA 215256 supplement 11. Squares are risk ratios with 95% confidence intervals; the lower row shows hip and pelvis fractures in participants aged ≥75 years. Trend across age bands by inverse-variance weighted regression of log risk ratio on band order.

**Benefits and harms in participants aged about 75 years or older**

| Trial and age group | n | Drug | Placebo | Estimate (95% CI) |
|---|---|---|---|---|
| *Cardiovascular events (MACE), HR* | | | | |
| Harmony Outcomes (T2D), ≥75 y | 1140 | | | 0.70 (0.48-1.01) |
| SUSTAIN-6 + PIONEER 6 (T2D), >70 y | 1554 | | | 0.93 (0.63-1.36) |
| **Pooled, T2D** | | | | **0.80 (0.61-1.06)** |
| SELECT (no diabetes), ≥75 y | 1366 | | | 0.92 (0.67-1.25) |
| *All-cause death, RR* | | | | |
| LEADER (T2D), 75-84 y | 794 | 54/401 | 70/393 | 0.76 (0.55-1.05) |
| *Any serious adverse event, RR* | | | | |
| SELECT, ≥75 y | 1366 | 337/703 | 338/663 | 0.94 (0.84-1.05) |
| STEP-HFpEF pooled, ≥75 y | 292 | 31/136 | 61/156 | 0.58 (0.40-0.84) |
| LEADER, 75-84 y | 794 | 252/401 | 248/393 | 1.00 (0.90-1.11) |
| *Fractures and bone injuries, RR* | | | | |
| SELECT, ≥75 y, selected fractures | 1366 | 29/703 | 21/663 | 1.30 (0.75-2.26) |
| STEP-HFpEF, ≥75 y, bone/joint injury | 292 | 4/136 | 3/156 | 1.53 (0.35-6.71) |
| SELECT, ≥75 y, hip and pelvis | 1366 | 17/703 | 4/663 | 4.01 (1.36-11.85) |




Pooled T2D estimate: random effects (REML), z-based CI, $I^2$ 8%. SUSTAIN-6 + PIONEER 6 subgroup >70 y had mean age 75.1 y.
STEP-HFpEF denominators derived from published percentages. Sources: Harmony post hoc 2024; Bain 2025; FDA reviews of NDA 215256 S-011 (SELECT) and NDA 022341 (LEADER); Pandey 2025 (STEP-HFpEF).

## Figure 6

Benefit and harm estimates for participants aged about 75 years or older, by trial and outcome: major adverse cardiovascular events (hazard ratios), all-cause death, any serious adverse event, and fractures or bone injuries (risk ratios). The pooled type 2 diabetes estimate is from a random-effects model (REML) with a Wald interval.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS1.png
- Supplementarymaterial.docx