# Semaglutide reduces multi-organ proteomic-based biological age across cohorts

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# Presenter disclosures

- Alejandro Aguayo-Orozco is an employee of Novo Nordisk

# Introduction

- Semaglutide has shown benefits for multiple clinical endpoints, including reductions in all-cause mortality and MACE, as well as improvements in kidney outcomes, knee osteoarthritis, and heart failure outcomes in adults with overweight or obesity[1–6]
- In the SELECT trial, adults with overweight or obesity (BMI of ≥27 kg/m$^2$) and CV disease but no history of diabetes were randomized to once-weekly s.c. semaglutide 2.4 mg or placebo[1]
- Goeminne et al. (2025)[7] developed organ aging models trained to predict time to death using Olink® proteomic data from the UK Biobank
  - Chronological age, mortality, and longitudinal proteome data were used to train organ-specific and conventional aging models
  - The models predict organ/system-specific disease and reflect physiologic deterioration

In this analysis, the effect of semaglutide on biological age in populations with obesity was investigated using mortality-based proteomic aging clocks

*BMI, body mass index; CV, cardiovascular; MACE, major adverse cardiovascular events; s.c., subcutaneous.*

*1. Lincoff AM et al. N Engl J Med 2023;389:2221–2232; 2. Colhoun HM et al. Nat Med 2024;30:2058–2066; 3. Wilding JPH et al. N Engl J Med 2021;384:989–1002; 4. Davies M et al. Lancet 2021;397:971–984; 5. Bliddal H et al. N Engl J Med 2024;391:1573–1583; 6. Kosiborod M et al. N Engl J Med 2023;389:1069–1084; 7. Goeminne LJE et al. Cell Metab 2025;37:205–222.*

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# Methods

Organ-specific proteomic aging clocks from Goeminne et al. (2025)[1] were applied to Olink® Explore HT proteomic data from SELECT patients, capturing the **biological age** of specific organs (**multi-organ** clock) alongside composite systemic clocks (**organismal** clock)

Organ clocks particularly relevant to the SELECT cardiometabolic population were assessed (**heart**, **kidney**, and **adipose clocks**) in association with relevant **outcomes** from the **SELECT** trial[2], including MACE†, hospitalization for HF, and all-cause mortality

- Causal mediation analysis assessed whether the effects of semaglutide on biological age were dependent or independent of changes in body weight
- Complementary evidence was drawn from the STEP 1[3] and STEP 2[4] trials (using the SomaScan® assay [v4.1]), extending findings to populations with overweight or obesity, without or with T2D, respectively

- The **treatment effect** of **semaglutide** was assessed for the organismal and multi-organ clocks
- Changes in organ clocks were also assessed for their impact on the effect of semaglutide on **mortality**

*†Composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.*
*CV, cardiovascular; HF, heart failure; HT, high-throughput; MACE, major adverse cardiovascular events; T2D, type 2 diabetes.*
*1. Goeminne LJE et al. Cell Metab 2025;37:205–222; 2. Lincoff AM et al. N Engl J Med 2023;389:2221–2232; 3. Wilding JPH et al. N Engl J Med 2021;384:989–1002; 4. Davies M et al. Lancet 2021;397:971–984.*

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SELECT proteomic clocks subset

# Baseline characteristics

| | **Male \| Female,** % | **Age,** years | **Current/former smoker,** % | **SBP \| DBP,** mmHg |
|---|---|---|---|---|
| **Semaglutide** (n=791) | 75% \| 25% | 62.5 (8.9) | 21 | 131.9 (15.9) \| 79.9 (10.4) |
| **Placebo** (n=885) | 75% \| 25% | 62.9 (9.2) | 19 | 130.8 (15.0) \| 78.3 (10.4) |

| | **Body weight,** kg | **BMI,** kg/m$^2$ | **hsCRP,** mg/L Median (IQR) | **History of hypertension,** % | **CAD,** % | **eGFR,** mL/min/1.73 m$^2$ |
|---|---|---|---|---|---|---|
| **Semaglutide** (n=791) | 98.9 (18.6) | 33.7 (5.3) | 2.0 (1.0–4.7) | 85 | 83 | 80.0 (17.9) |
| **Placebo** (n=885) | 98.5 (18.5) | 33.7 (5.2) | 1.9 (0.9–4.7) | 83 | 86 | 79.8 (18.5) |

*Data are mean (standard deviation), unless otherwise stated.*
*BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; SBP, systolic blood pressure.*

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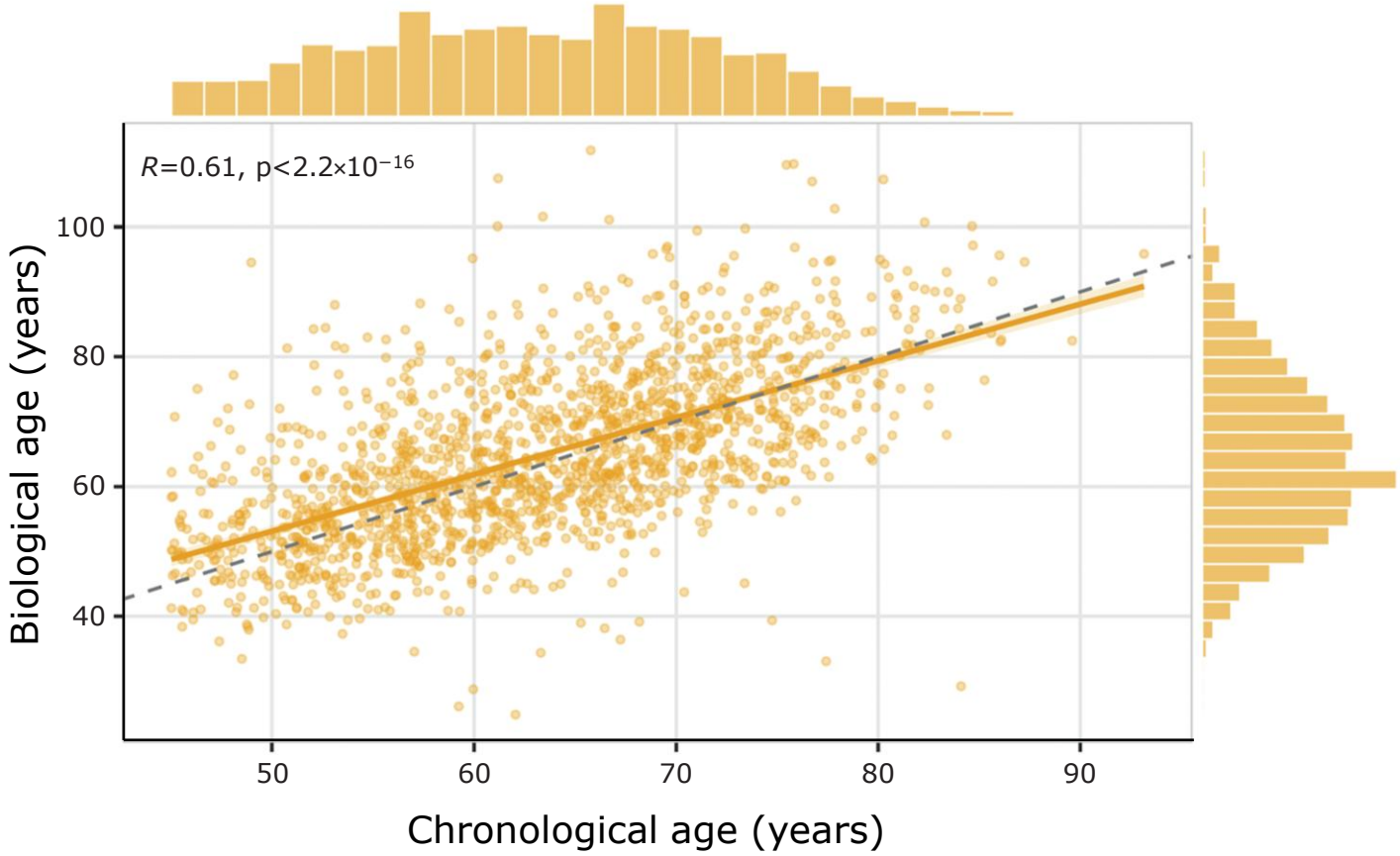
# Biological versus chronological age in SELECT




Proteomic biological age showed a strong positive correlation with chronological age

*Substantial inter-individual spread around the regression line indicates meaningful divergence between biological (conventional model) and chronological age at every age group, with some patients appearing substantially older or younger biologically than their chronological peers.*

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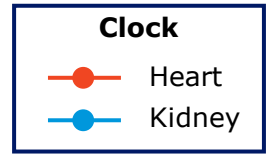
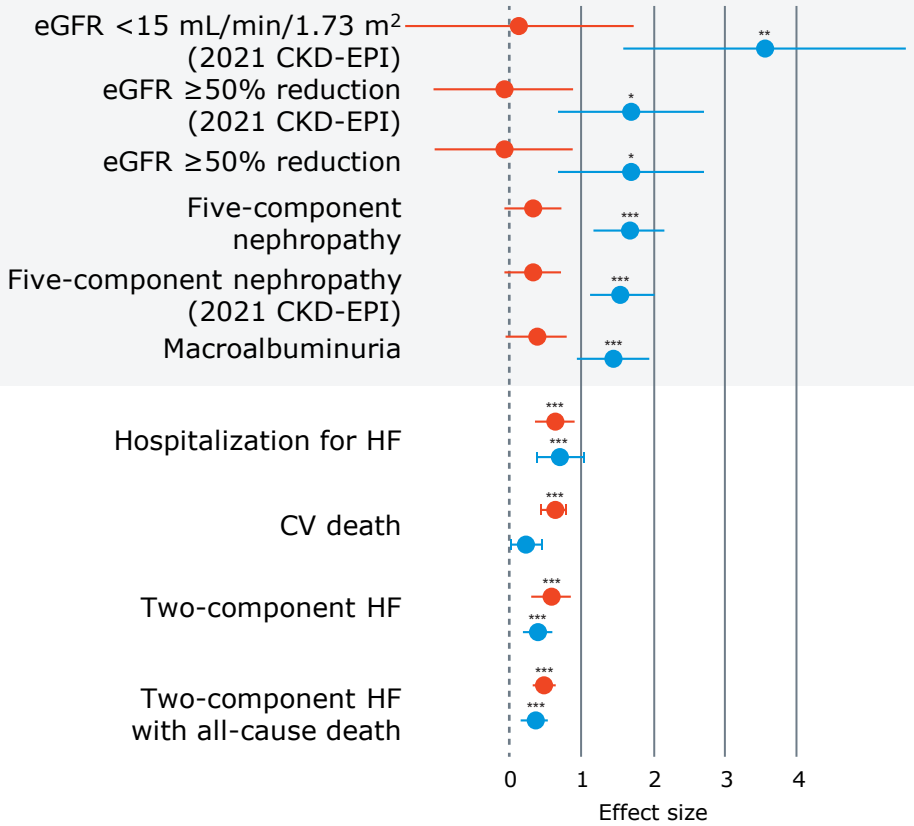
SELECT proteomic clocks subset

# Organ aging clocks predict clinical outcomes in SELECT

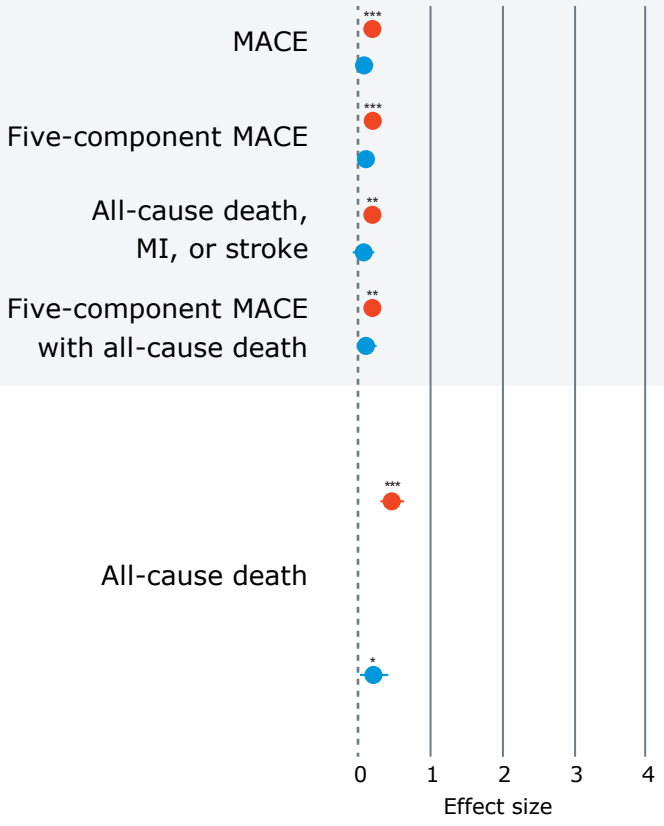



## Kidney

Largest effect sizes for macroalbuminuria and nephropathy endpoints, with effect sizes notably exceeding those for all-cause death




## MACE/stroke




## Heart

Strongest associations with hospitalization for HF and CV death, followed by MACE composites and all-cause death




## Mortality




*The heart clock consists of seven proteins (top contributors: MYL4, NPPB, NMRK2, TNNI3, and ITGB1BP2), reflecting myocardial stress, contractile integrity, and metabolic adaptation. The kidney clock consists of nine proteins (top contributors: HAVCR1, REN, UMOD, CYP24A1, and BSND), reflecting tubular injury, renal filtration, and collecting duct function. The adipose clock consists of five proteins (FABP4, LEP, CD300LG, PLIN1, and ADIPOQ), comprising canonical adipokines and lipid-handling proteins reflecting high tissue specificity. Expanded five-component MACE included CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. The HF composite included first occurrence of death from CV causes, or hospitalization or an urgent medical visit for HF. The main five-component kidney composite endpoint included death from kidney causes, initiation of chronic kidney replacement therapy (dialysis or transplantation), onset of persistent eGFR <15 mL/min/1.73 m², persistent ≥50% reduction in eGFR compared with baseline, or onset of persistent macroalbuminuria.*
*Significance levels: *p<0.05, **p<0.01, ***p<0.001. Error bars represent 95% CI.*
*CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction.*

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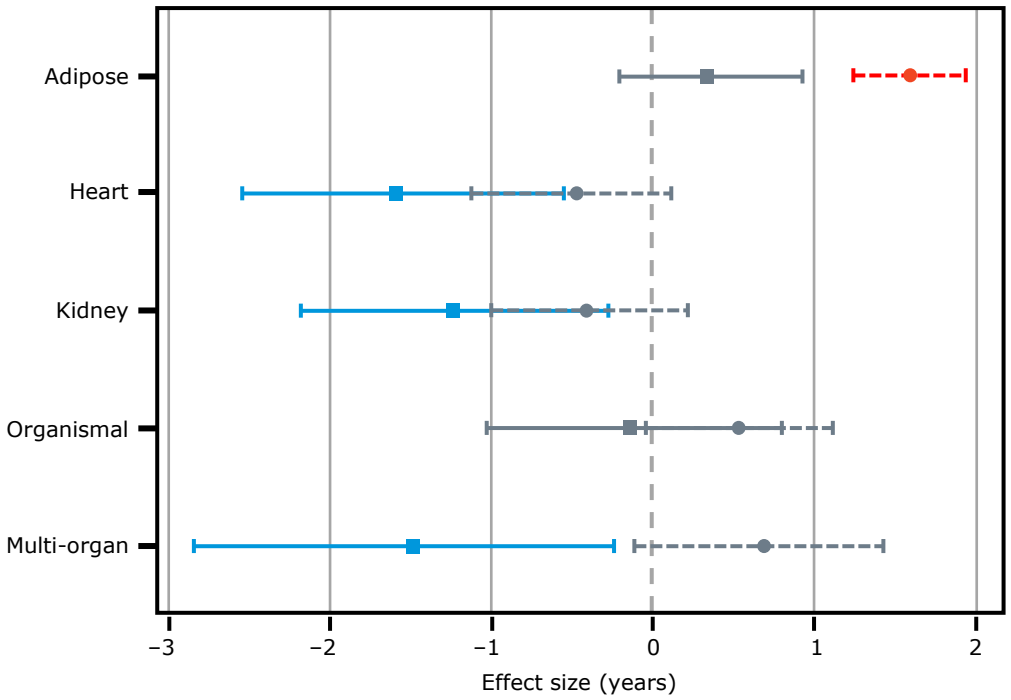
SELECT, STEP 1, and STEP 2 proteomic clocks subset

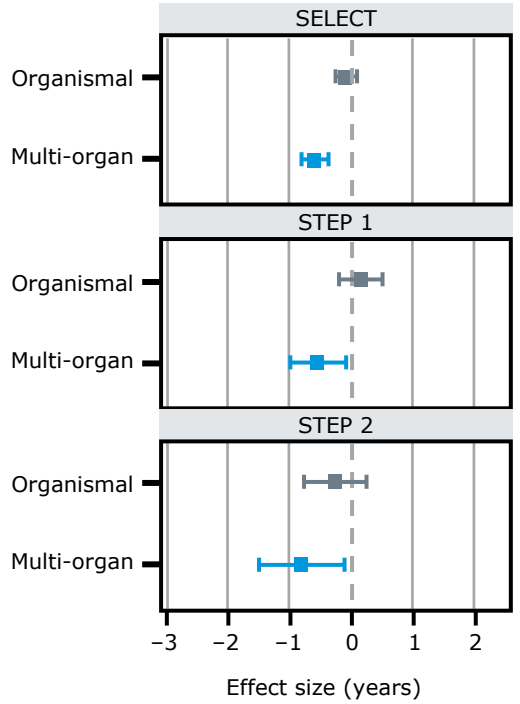
# Semaglutide reduces organ biological age in SELECT, STEP 1, and STEP 2

**Effect direction** Negative Positive Not significant **Effect type** ADE (direct effect) ACME (mediation effect)

**Olink® – SELECT**




**SomaScan® – SELECT, STEP 1, STEP 2**




- Semaglutide significantly reduced heart and kidney biological age at week 20 (vs placebo)
- For both organs, the effect was driven by the ADE, suggesting direct biological aging deceleration beyond what can be explained by weight loss alone

- Using SomaScan®, which extends to later time points and includes STEP 1 and STEP 2 (week 68) alongside SELECT (week 104), the multi-organ clock was significantly reduced across all three trials

*Mediation analysis was performed using the mediation R package. Effect sizes are expressed in biological age (years). ACME captures the proportion of the effect of semaglutide attributable to weight loss; ADE reflects the remaining direct effect. STEP 1 and STEP 2 data represent week 68; SELECT SomaScan® data represent week 104, following platform harmonization. Error bars represent 95% CI. ACME, average causal mediation effect; ADE, average direct effect; CI, confidence interval.*

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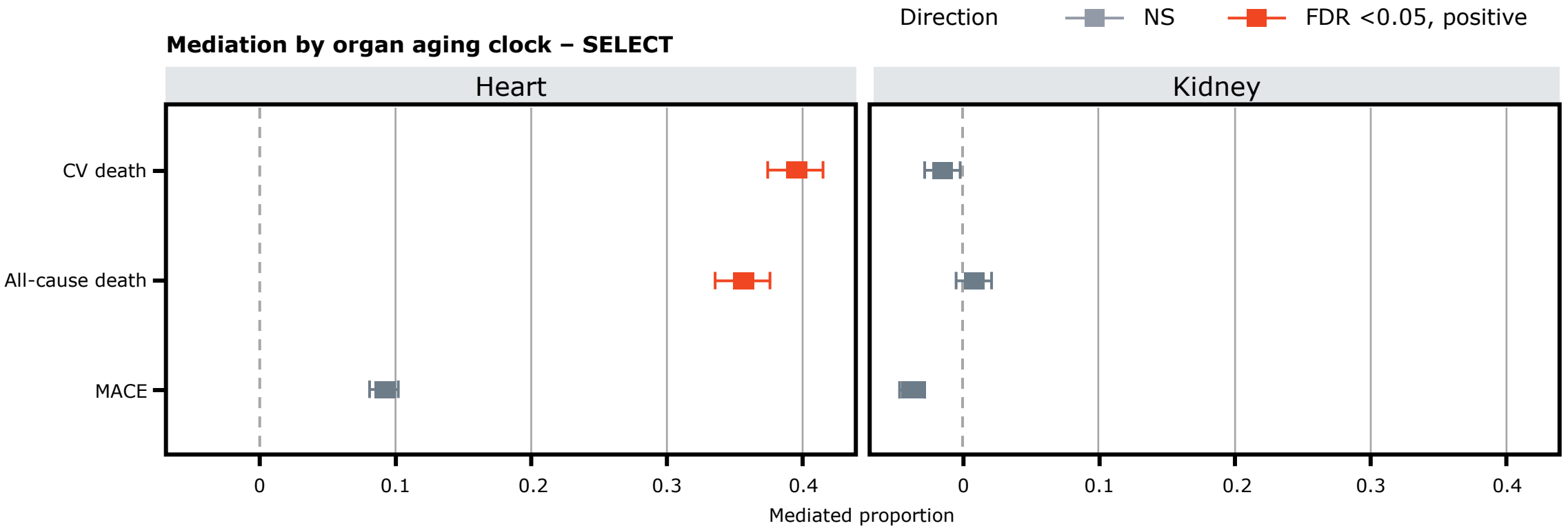
SELECT proteomic clocks subset

# Organ clock changes mediate the effect of semaglutide on mortality




- Heart clock changes significantly mediated the effect of semaglutide on all-cause death and CV death (red, FDR <0.05), accounting for approximately 36% of the all-cause mortality benefit

- Kidney clock changes did not significantly mediate any outcome, consistent with its primary prognostic specificity for kidney rather than CV endpoints

*Mediation analysis was performed using an Imai/Dai framework. Semaglutide-induced changes in heart and kidney organ aging clock scores at week 20 in SELECT were modeled as mediators of treatment effects on CV and mortality outcomes. The mediated proportion represents the fraction of the total effect of semaglutide on each outcome attributable to clock score change. Significance was assessed using FDR-corrected p<0.05. Error bars represent 95% CI.*
*CI, confidence interval; CV, cardiovascular; FDR, false discovery rate; MACE, major adverse cardiovascular events; NS, not significant.*

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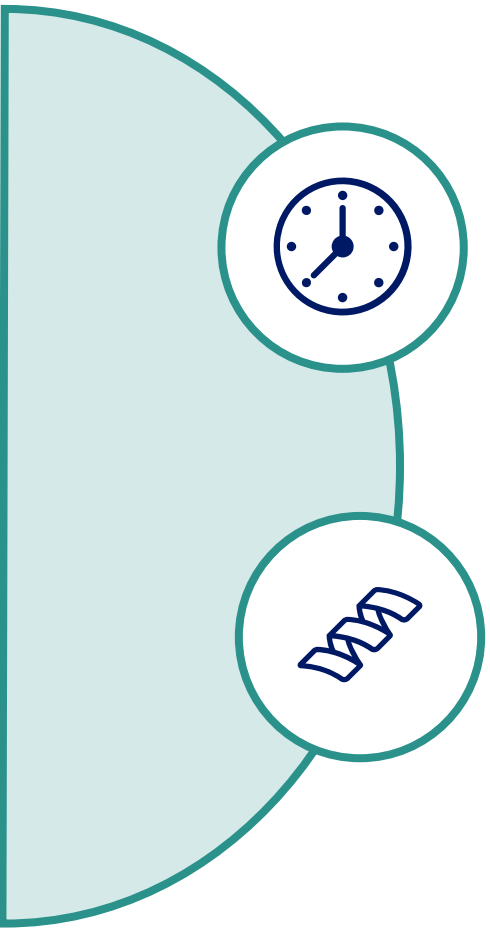
# Conclusions



**Semaglutide** consistently **reduced mortality-trained proteomic multi-organ biological age** across patients with obesity and different comorbidities, whereas organismal clocks were unchanged

These findings suggest that **semaglutide modifies proteomic signatures linked to mortality risk**

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