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Semaglutide reduces proteomic organ-specific biological age across randomized clinical trials

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ABSTRACT

Semaglutide confers cardiovascular and kidney benefits and reduces all-cause mortality in high-risk populations. Whether biological-age metrics capture these effects and provide mechanistic insight remains unclear. We analyzed proteomics from 10,052 participants across five placebo-controlled semaglutide trials using externally trained organ-specific mortality clocks, proteomic frailty scores and disease-risk models. Semaglutide reduced heart biological age by approximately 2 to 4 years versus placebo, with reductions of 1 to 4 years across kidney, brain, pancreas, lung and multiorgan clocks. Proteomic frailty and cardiometabolic disease-risk scores improved during up to 156 weeks of follow-up. Effects were not fully mediated by weight loss, glycated hemoglobin or C-reactive protein. Exploratory mediation analyses suggested that heart biological-age changes may account for 34% to 49% of effects on selected outcomes. These findings demonstrate reproducible remodeling of mortality-associated proteomic signatures across populations and durations, supporting their potential as treatment-response readouts without establishing biological rejuvenation, causal mediation or surrogate validity.

INTRODUCTION

Aging is a major shared risk factor for chronic disease and mortality, motivating efforts in geroscience to identify molecular signatures associated with biological processes that accompany age-related decline across organ systems[1,2]. However, many such signatures have not been established as causal drivers of aging or as validated surrogate endpoints for clinical benefit. This raises a central question[1,2]: are molecular signatures associated with aging biology responsive to interventions that reduce all-cause mortality and improve clinically relevant manifestations of age-related decline? Semaglutide, a long-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) available as once-weekly subcutaneous and once-daily oral formulations, provides an opportunity to address this question[3]. Although most therapies are developed for individual diseases or syndromes, semaglutide has benefits across obesity, cardiovascular disease, chronic kidney disease (CKD) and metabolic dysfunction-associated steatohepatitis[3–9]. Semaglutide promotes weight loss primarily by reducing appetite and energy intake through distributed neural pathways[10], creating a pharmacologically induced negative energy balance. Caloric restriction is a well-established intervention for extending lifespan and healthspan across mammalian species[11], and the CALERIE trial reduced DunedinPACE, a DNA-methylation measure of the pace of biological aging[11,12]. Semaglutide also lowers circulating inflammatory biomarkers,with anti-inflammatory effects shown in preclinical cardiovascular and neuroinflammation models[13–15]. Together, these observations provide a basis for testing whether molecular measures associated with aging biology respond to semaglutide and whether their changes parallel—or potentially help characterize—semaglutide's established effects on mortality and other clinically relevant outcomes. Semaglutide has therefore been proposed as a longevity therapeutic[13–15], but geroprotective claims require validated biomarkers[16] that predict clinically relevant aging outcomes. Whether these effects reflect weight loss, glycemic control or other mechanisms remains a separate question[17].

Testing whether semaglutide modifies aging biology requires biomarkers that are biologically anchored, clinically relevant and responsive over trial timescales. Second-generation biological-age clocks are prognostic models defined by selected plasma proteins and fitted weights[18,21]; applying a clock model to an individual's proteomic profile yields a participant-level biological-age score. Recent UK Biobank Olink models provide organ-specific biological-age estimates[18,19], a proteomic frailty score[20] and proteomic disease-risk scores[21]. These "proteomic clocks" predict mortality and organ-specific diseases in the large cohorts in which they were developed[18,21], but their relevance to clinical populations and responsiveness to drug treatments are unknown. We analyzed Olink Explore HT proteomics from five semaglutide randomized

placebo-controlled clinical trials with adjudicated cardiovascular, kidney and mortality endpoints: SELECT[5], STEP-HFpEF (heart failure with preserved ejection fraction)[22], STEP-HFpEF DM (diabetes mellitis)[23], FLOW[8] and SOUL[7]. For each clock model, we derived a biological-age score (expressed in years) and an age-deviation score (the residual from regression of biological age on chronological age). Biological-age scores were used for age comparison and longitudinal treatment-effect analyses; age deviations were used for baseline association analyses (online Methods). We first tested whether baseline organ-specific age deviations were associated with tissue-relevant disease history and predicted incident outcomes. We then tested whether semaglutide modified these scores, if changes were explained by concurrent changes in glycemic control, body weight and inflammation, whether semaglutide modified proteomic frailty and disease-risk scores, and if organ-specific score changes showed statistical mediation of selected clinical outcomes. We therefore tested whether externally trained organ-specific proteomic mortality clocks retained clinical relevance when applied to randomized trial populations, if they were responsive to pharmacological intervention, and whether treatment-associated changes related to systemic vulnerability and clinical outcomes.

RESULTS

Organ-specific mortality clocks predict relevant outcomes across five semaglutide trial populations

Baseline characteristics of participants with Olink proteomic data differed across trials (Table 1). SELECT enrolled participants with overweight or obesity and cardiovascular disease, but without diabetes; STEP-HFpEF enrolled participants with obesity and HFpEF; STEP-HFpEF DM included participants with obesity, HFpEF and type 2 diabetes (T2D); FLOW enrolled participants with T2D and established CKD, and SOUL enrolled participants with T2D and high cardiovascular risk. Participants with Olink data were demographically similar to the full trial populations (Supplementary Table 1), including in SELECT, in which protein profiling was performed in a case-enriched subset (online Methods).

Applying each clock to baseline proteomic profiles yielded biological-age scores that strongly correlated with chronological age across all five trials (Fig. 1a)[18]. Age deviation was defined as the residual from within-trial regression of biological age on chronological age. Because the clocks were trained in UK Biobank and applied to multinational trial populations, absolute agreement between biological and chronological age should not be interpreted as calibration; the analyses focused on relative associations and change. Multiorgan, conventional and organismal age

deviations were most strongly correlated across trials, whereas adrenal, salivary and pituitary age deviations were less coupled to the main cluster and were based on fewer proteins (Fig. 1b). Across the three diabetes trials, higher baseline glycated hemaglobin (HbA_{1c}) was associated with several age-deviation scores, although the direction and magnitude of organ-specific associations varied (Supplementary Fig. 1a).

To assess whether age-deviation scores behaved as expected in the trial populations, we examined their cross-sectional associations with prevalent clinical conditions and biomarkers. In SELECT, CKD, microalbuminuria and heart failure with reduced ejection fraction (HFrEF) were positively associated with multiple organ-specific age deviations, whereas HFpEF and prediabetes showed fewer associations (Supplementary Fig. 1b). Current smoking status was associated with higher age deviation across several systems, and low high-density lipoprotein cholesterol was associated with age deviation across multiple organs. These findings indicate that the scores broadly behaved as expected after chronological-age adjustment, although they do not establish whether associations reflect organ-specific disease biology, systemic illness or altered circulating protein handling.

Integrative clock-derived scores showed the broadest associations with poorer patient-reported health status (Supplementary Fig. 1c, d), while brain and muscle age deviations showed the broadest organ-specific associations.

Medication associations were descriptive and were used to identify potential covariates for sensitivity analyses. Furosemide use was positively associated with multiple organ-age deviations, whereas metformin showed negative associations in diabetic populations (Fig. 1c, d, e, f, g). Because medication use is non-randomized, medication variables were included as covariates in the sensitivity analyses rather than interpreted causally.

Having established their cross-sectional clinical relevance, we next tested whether baseline age-deviation scores predicted future clinical outcomes independently of chronological age. In SELECT participants receiving placebo, higher baseline organ-specific age deviation was associated with all-cause mortality, hospitalization for heart failure and major adverse cardiovascular event/s (MACE) in Cox proportional hazards models with chronological age modeled as a linear covariate (Fig. 1h and Supplementary Fig. 1e). For kidney outcomes—including macroalbuminuria, nephropathy and estimated glomerular filtration rate decline—the largest hazard ratios per 1-year higher biological-age score, adjusted for chronological age, were observed for the kidney score; for cardiovascular outcomes—including heart-failure hospitalization, cardiovascular death and MACE—the largest hazard ratios were observed for the

heart score (Fig. 1i). Similar patterns were observed in SOUL (Supplementary Fig. 1f, g). These analyses support the prognostic relevance of organ-specific age-deviation scores in trial populations.

In placebo-treated participants, median age deviations generally increased over the follow-up period, with the largest changes observed in FLOW, which had the longest follow-up and a high CKD burden (Fig. 1j). Having characterized longitudinal changes under placebo, we next tested whether semaglutide changed clock-derived biological-age scores relative to placebo.

Semaglutide is associated with lower organ-specific biological-age scores across cardiometabolic trial populations

We next tested whether semaglutide changed organ-specific biological age from baseline versus placebo. Heart biological age was reduced across all five trials (Fig. 2a and Supplementary Fig. 2a). Across diverse cardiometabolic trial populations (including people living with established cardiovascular disease without diabetes, HFpEF, CKD or T2D at high cardiovascular risk) reductions were observed at the earliest sampled post-baseline timepoint and persisted or recurred during follow-up of up to 156 weeks (Fig. 2a, b, c). Kidney and artery biological age also decreased in some trials, particularly FLOW and SOUL. Broader score reductions emerged with longer follow-up in SOUL, whereas early liver and immune score increases suggested transient organ-specific responses. Because trial populations, doses, sampling schedules and proteomic matrices differed, effects were estimated separately rather than pooled. Overall, heart biological age showed the most consistent response, whereas other organ-specific effects varied by trial and timepoint.

Because the SELECT proteomic sub-study was event-enriched, it included a higher proportion of participants with MACE than the full SELECT trial: 781 of 1,641 participants in the Olink sub-study versus 1,270 of 17,604 participants in the full trial. We therefore used sampling weights to estimate treatment effects that were more representative of the parent SELECT population (online Methods). Weighted analyses reduced the number of statistically significant organ-level changes compared with the unweighted analysis, but the direction of semaglutide effects was broadly consistent (Supplementary Fig. 2b). We assessed robustness to concomitant glucose-lowering therapy by adjusting for baseline metformin use in trials including participants with T2D (STEP-HFpEF DM: 71.0%; FLOW: 52.4%; SOUL: 74.9%); semaglutide -associated, biological-age reductions were largely preserved after metformin adjustment (Fig. 2c). Interaction analyses indicated that most organ-specific biological-age scores responded similarly across participants

with different baseline age deviations, with selected exceptions in STEP-HFpEF DM and FLOW where greater improvements were observed in participants with greater baseline age deviations for pituitary, pancreas, adipose and brain scores (Supplementary Fig. 2d).

To identify proteins contributing to significant treatment-associated changes in biological age, we estimated semaglutide effects for each protein included in the corresponding clock model using the same change-from-baseline regression framework. We then compared each protein treatment effect with its clock coefficient. Protein changes contributed to a lower biological-age score when the product of the treatment-effect estimate and clock coefficient was negative, and to a higher score when this product was positive (Fig. 2d). Lower heart biological-age scores were supported by changes in proteins including NPPB, PXDNL and BMP10, and lower kidney scores by changes including HAVCR1, PDZK1, ITGB6 and UMOD. Adipose biological age showed a time-dependent pattern (Fig. 2c). In the protein-level decomposition, semaglutide-associated leptin lowering increased the adipose biological-age score because leptin has a negative coefficient in the model. This coefficient may partly reflect observational associations between lower leptin concentrations and poorer outcomes in older populations rather than intentional fat loss during treatment[24]. The apparent early pro-aging signal was not sustained, and later timepoints showed lower adipose biological age. Changes in FABP4 and CD300LG were also observed across trials, but their interpretation during dynamic weight loss remains uncertain because cross-sectional associations may not apply to intervention-induced change (Fig. 2c, d).

To test whether these effects extended beyond disease-enriched populations, we performed supportive analyses using SomaScan proteomic data from the semaglutide trials STEP 1[4] and STEP 2[25] in participants with overweight or obesity. After cross-platform harmonization, treatment effects were directionally consistent with the main Olink analysis (Supplementary Fig. 2e; online Methods).

Semaglutide-associated clock changes are not fully explained by weight loss, glycemic improvement or high-sensitivity C-reactive protein (hsCRP) reduction

To test whether reductions in organ-specific biological age were statistically mediated by semaglutide-associated weight loss, improved glycemic control or reduced inflammation, we performed exploratory mediation analyses using changes in body weight, HbA_{1c} and hsCRP as candidate mediators. Across trials, most changes in heart and kidney biological age were not statistically mediated by concurrent changes in body weight, HbA_{1c} or hsCRP (Fig. 3a, b, c, d, e). By contrast, the increase in adipose biological age was largely mediated by weight change, consistent with the weight-related behavior of the model described above.

Semaglutide improves proteomic frailty and predicted disease-associated risk

We next explored whether the effect of semaglutide also modified proteomic signatures of systemic vulnerability. For this, we included the proteomic frailty score (PFS)[20] as a complementary whole-body readout to reflect integrated physiological reserve and biological vulnerability across systems. Baseline PFS correlated positively with chronological age across all trials (r = 0.15–0.26) (Supplementary Fig. 3a). Among organ clocks, PFS showed the strongest cross-sectional correlation with the stomach clock (r ~0.48–0.62), followed by conventional and multiorgan clocks (Supplementary Fig. 3b). After adjustment for age, race and smoking status, PFS was higher in women than in men, consistent with the sex pattern observed in UK Biobank[20] (Supplementary Fig. 3c).

Semaglutide significantly reduced PFS in STEP-HFpEF and STEP-HFpEF DM at week 52, with no significant change at week 20 in either trial (Fig. 4a). FLOW showed a biphasic pattern, with a significant early increase at week 12 followed by significant progressive reductions at weeks 52 and 156. In SOUL, PFS was not significantly changed at week 13 but was significantly reduced by week 104. SELECT showed no significant effect at week 20. These findings indicate that the effects of semaglutide on systemic biological frailty are time-dependent, with substantial reductions emerging beyond the first year of treatment. Baseine frailty deviations did not significantly modify the treatment effect of semaglutide on frailty change in any trial (Fig. 4b).

To evaluate the impact of semaglutide on disease susceptibility beyond established endpoints, we applied validated UK Biobank-derived proteomic risk models for 15 conditions[21]. Across trials, semaglutide showed predominantly beneficial or neutral effects on predicted disease risk (Fig. 4c). Significant reductions were most evident for T2D proteomic risk scores, cardiovascular condition risk scores and risk scores for selected respiratory diseases (including chronic obstructive pulmonary disease, asthma, primary pulmonary hypertension), whereas increases in proteomic risk scores were uncommon and transient. Together, these analyses support the view that the proteomic effects of semaglutide extend beyond individual organ clocks to a broader reduction in systemic biological vulnerability.

Changes in biological-age signatures show statistical mediation of selected clinical outcomes

Finally, we tested whether treatment-associated changes in organ-specific biological age statistically mediated the effects of semaglutide on clinical outcomes. In SELECT, mediation models were used to decompose the semaglutide treatment effect into direct effects and indirect effects operating through changes in each biological-age score. Changes in the heart

biological age showed the largest favorable mediated proportion, accounting for an estimated 36% of the semaglutide effect on all-cause death and 40% of the semaglutide effect on cardiovascular death (Fig. 5a). In contrast, the adipose biological age showed negative mediated proportions, attenuating 48% of the treatment effect on all-cause death and 54% on cardiovascular death. At the protein level, NPPB showed the strongest favorable signal for all-cause death; associations for MACE and cardiovascular death were not statistically significant (Fig. 5b).

In SOUL, change in heart biological age showed the largest positive mediated proportions across MACE, all-cause death and CKD outcomes, accounting for 49%, 36% and 34% of the semaglutide treatment effect, respectively (Fig. 5c). The artery biological-age score showed positive mediated proportions of 11–16% across these endpoints, whereas immune and liver biological-age scores showed negative mediated proportions. At the protein level, NPPB contributed most strongly to the heart-clock mediation estimates, whereas LTBP^{2}, TNFRSF11B, CRLF^{1} and THBS^{2} contributed to artery-clock estimates (Fig. 5d). Heart-score changes showed the most consistent positive statistical mediation estimates across the selected outcomes.

DISCUSSION

Organ-specific proteomic models trained to predict mortality provide a framework for quantifying organ-level biological aging from circulating proteins. Here, we applied these models across five disease-enriched semaglutide randomized clinical trials, involving patients with heart failure, CKD, high-cardiovascular-risk and diabetes. The resulting scores retained associations with clinically relevant phenotypes across trial populations and were reproducibly modified by semaglutide. The most consistent response was lower heart biological age across populations with obesity without diabetes, obesity-related HFpEF, CKD and high-risk T2D. The direction of these biomarker changes was concordant with cardiovascular benefits observed in the parent trials. Together, these findings provide proteomic evidence relevant to the hypothesis that semaglutide may have gerotherapeutic effects, while emphasizing that rigorous testing is needed to distinguish direct effects on aging biology from indirect benefits mediated through cardiometabolic risk factors[26,27]. More broadly, the results support a precision-geromedicine framework in which interventions are evaluated not simply by whether they “slow aging,” but by which organ systems respond, in which populations, over what timescale and whether those molecular responses predict preserved function or reduced disease burden[28].

Frailty and disease-risk scores provided complementary systems-level readouts of physiological reserve[29]. This is clinically relevant in older adults with cardiometabolic disease, where frailty, sarcopenic obesity and concerns about lean-mass loss influence treatment decisions[30]. Semaglutide reduced PFS despite substantial weight loss. There is currently no convincing evidence that semaglutide increases frailty or causes an average deterioration in physical function, but evidence remains limited in very old, sarcopenic or already-frail individuals. In people with reduced mobility such as those with knee osteoarthrosis and HF, semaglutide improved physical function[24]. However, PFS is a proteomic biomarker, and these analyses do not demonstrate improvement in clinically measured frailty or physical function.

The adipose-clock signal highlights an important limitation of mortality-trained clocks in interventional studies. Leptin reduction during intentional fat loss appeared as adipose aging acceleration because the model was trained in an observational population in which low leptin may reflect unintentional weight loss associated with frailty, cachexia or active disease[24]. Thus, beneficial treatment-induced remodeling can conflict with risk patterns learned from weight-stable cohorts.

An important consideration when interpreting individual clocks, including the adipose and heart clocks, is the small number of proteins accounting for much of their predictive power. Absolute calibration may differ when UK Biobank-trained models are applied to multinational, disease-enriched trial populations, although within-trial associations and treatment contrasts may remain informative. SELECT included a case-enriched proteomic sub-study; Olink Normalized Protein eXpression (NPX) values are relative rather than absolute measures, complicating cross-trial comparisons, and missing organ-specific protein measurements introduced a small degree of uncertainty. A central limitation is that proteomic biological-age models are predictive biomarkers rather than established mechanistic measures of biological aging or disease progression. Accordingly, treatment-induced, biological-age reductions should be interpreted as favorable remodeling of mortality-associated proteomic signatures, not as proof of biological rejuvenation.

Few interventional studies have examined organ-specific biological-age responsiveness to pharmacologic treatment, partly because these biomarkers were developed recently and have rarely been evaluated in interventional studies. Prior randomized interventions, including diet and exercise studies, have largely focused on organismal DNA-methylation clocks rather than organ-specific proteomic aging signatures[12,31,32].

In conclusion, semaglutide improves several clinically relevant outcomes associated with age-related. Organ-specific proteomic clocks provide a testable framework of: which molecular aging signatures respond to treatment, whether those responses are organ-specific, and whether they predict clinical benefit. In this framework, organ-specific proteomic biological-age readouts are not yet surrogate endpoints, but they may serve as candidate translational biomarkers for prioritizing mechanisms, populations and treatment windows.

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Data availiabilty

An authorized researcher can request access to clinical study data by submitting a research proposal for review and approval by Novo Nordisk and an internal independent review panel. Requests are usually considered after the research is finished and the main results have been published. If the research supports a regulatory application, requests will be considered after the product and its intended use are approved in both the EU and the USA. Participants' clinical data will be anonymized, following an approved internal process, before data are shared to external third parties. For details on how to request access to clinical data, visit novonordisk-trials.com.

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Author Contributions

M.D., A.A.-O., and L.B.K. conceived and supervised the analysis, with M.D. and S.A.C.V responsible for data curation.. M.D., D.B.-R., S.A.C.V., L.J.E.G., and V.N.G. designed and performed the experiments. M.D. and S.A.C.V. analyzed the data, with clinical interpretation provided by H.M.C., K.A., K.J.K., and F.K.K. M.D., A.A.-O., K.A., K.J.K., D.B.-R. and S.A.C.V. wrote the first draft of the manuscript, edited all subsequent drafts and incorporated the input of all co-authors. All authors approved the submission of the manuscript.

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Competing interests

M.D. is an employee of and holds shares in Novo Nordisk Research and Development UK Limited.

H.M.C. declares serving on advisory panels for Bayer, Novo Nordisk and Roche; receiving research funding from IQVIA, Sanofi and Roche; receiving grants from the Chief Scientist Office, Diabetes UK, European Commission, Juvenile Diabetes Research Foundation and Medical Research Council; and holding stock in Eli Lilly and Roche.

L. J. E. G. declares no conflicts of interest.

D.R. declares having received consulting honoraria from AbbVie, Altimmune, Amgen, AstraZeneca, Biohaven, Boehringer Ingelheim, Calibrate, Carmot Therapeutics/Roche/Genentech, CinRx Pharma, Eli Lilly, eMed, Epitomee, Fractyl Health, i2o Therapeutics, Kailera Therapeutics, Novo Nordisk, Pfizer, Regeneron, Regor, Rhythm Pharmaceuticals, Souffle Therapeutics, Source BioScience, Structure Therapeutics, Tenvie Therapeutics, Viking Therapeutics, Wondr Health, WW and Zealand Pharma; and stock options from Calibrate, Epitomee and Ro.

K.A., D.B.-R., K.J.K., F.K.K., S.A.C.V. and A.A.-O. are employees of and hold shares in Novo Nordisk A/S.

V.N.G. declares serving on advisory panels for Dior, LongeVC, Retro Biosciences and Thorne, and was supported by grants from Hevolution and NIH.

L.B.K. was an employee of and holds shares in Novo Nordisk A/S.

Supplementary information

The online version contains supplementary material available at: https://doi.org/10.1038/xxxxxxxxxxxx.

Table 1 | Baseline characteristics by trial and treatment in participants with Olink proteomic data

	SELECT		STEP-HFpEF		STEP-HFpEF DM		FLOW		SOUL	
Characteristic	**Placebo (*n* = 867)**	**Semaglutide 2.4 mg† SC (*n* = 774)**	**Placebo (*n* = 208)**	**Semaglutide 2.4 mg† SC (*n* = 208)**	**Placebo (*n* = 235)**	**Semaglutide 2.4 mg† SC (*n* = 234)**	**Placebo (*n* = 1,143)**	**Semaglutide 1.0 mg† SC (*n*= 1,128)**	**Placebo (*n* = 2,604)**	**Oral semaglutide 14 mg† (*n* = 2,651)**
Proteomics origin	Serum	Serum	Serum	Serum	Serum	Serum	Plasma	Plasma	Serum	Serum
Age, years	63.0±9.1	62.6±8.9	68.3±9.8	68.6±9.6	69.1±8.7	68.8±8.3	67.3±9.0	67.1 ±8.7	66.7±7.5	66.7±7.6
Female sex	217 (25)	192 (25)	119 (57)	118 (57)	113 (48)	91 (39)	360 (31)	335 (30)	743 (29)	710 (27)
White race	763 (88)	680 (88)	201 (97)	207 (100)	221 (94)	212 (91)	801 (70)	788 (70)	1934 (74)	1966 (74)
Body weight, kg	98.4±18.5	98.9±18.5	107.6±23.0	108.7±22.9	106.9±21.6	108.6±20.7	92.0±21.9	91.5±19.8	90.9±20.1	90.1±19.7
BMI, kg/m²	33.7±5.2	33.7±5.3	38.2±6.5	38.5±6.7	38.2±6.4	38.3±5.7	32.6±6.7	32.4±6.2	31.7±6.0	31.4±5.8
Current smoker	166 (19)	159 (21)	19 (9)	19 (9)	26 (11)	25 (11)	138 (12)	143 (13)	335 (13)	299 (11)
SBP, mmHg	130.9±15.0	131.9±15.8	131.3±15.4	132.2±15.2	135.2±14.5	132.5±14.0	138.1±15.6	139.3±16.5	134.9±16.6	134.9±16.6
DBP, mmHg	78.4±10.4	79.8±10.4	79.2±10.2	77.7±10.2	76.5±10.1	78.2±9.5	75.5±10.0	76.3±10.3	76.5±10.4	76.5±10.5
T2D	0 (0)	0 (0)	1 (0)	1 (0)	235 (100)	234 (100)	1,143 (100)	1,128 (100)	2,604 (100)	2,651 (100)
eGFR, ml/min/1.73 m²	79.8±18.5	80.1±18.0	Not performed	Not performed	67.4±22.7	69.5±22.3	47.9±15.0	47.0±15.5	73.8±22.2	74.4±22.3

HbA_{1c}, %	5.76±0.35	5.79±0.34	Not performed	Not performed	7.08±1.07	6.96±1.16	7.77±1.27	7.76±1.24	7.91±1.12	7.99±1.18
Median (IQR) hsCRP, mg/l	1.9 (0.9–4.7)	2.0 (1.0–4.7)	3.9 (2–7.9)	3.7 (1.9–7.1)	3.2 (1.5–8.5)	3.2 (1.8–7.5)	2.5 (1.1–6)	2.4 (1.1–5.6)	2.1 (0.9–4.5)	1.9 (0.9–4.2)

Data are presented as mean±s.d. or *n* (%) unless otherwise indicated.

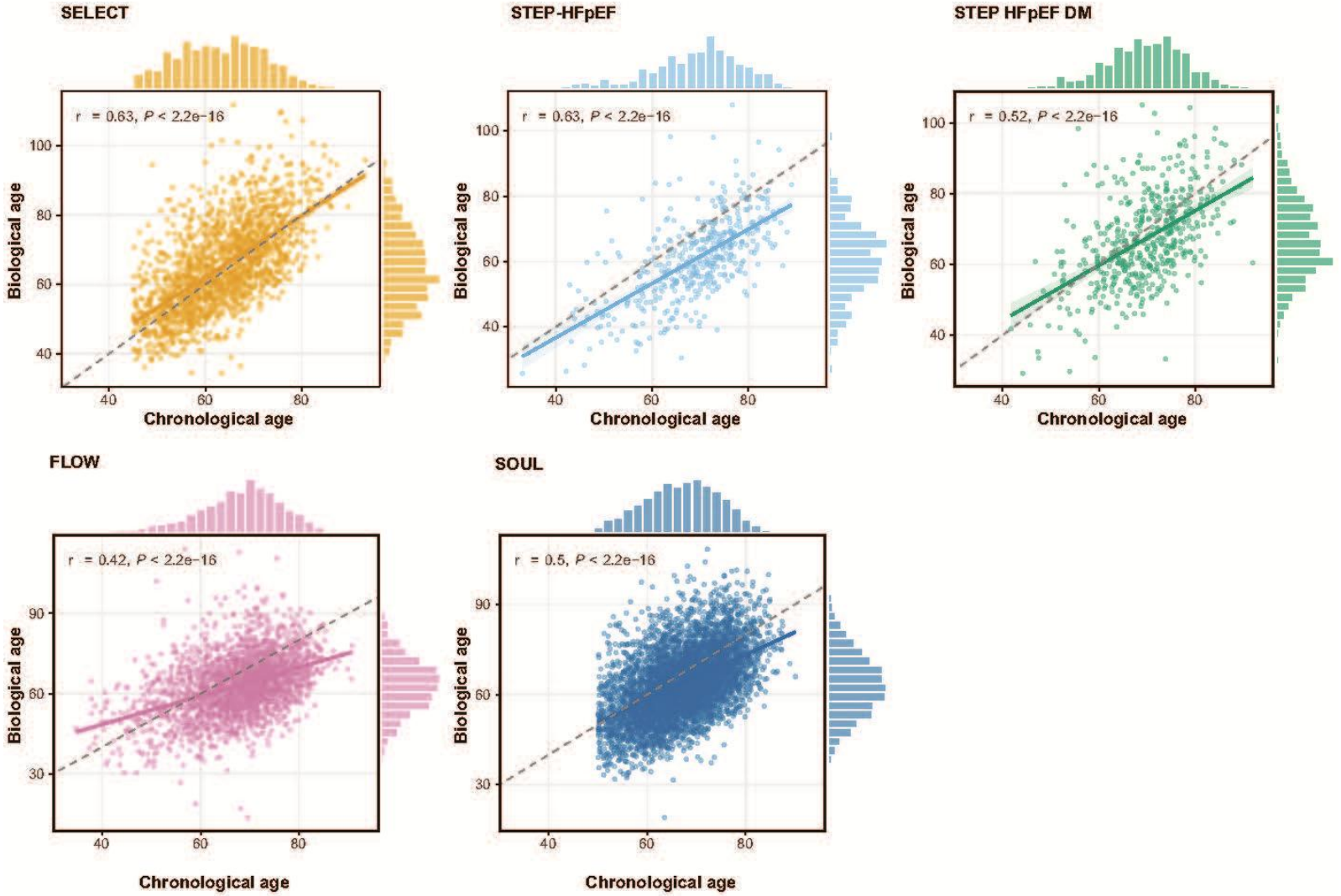
[†]Maximum dose.

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein; IQR: interquartile range; *n*, number of participants; SBP, systolic blood pressure; SC, subcutaneous; s.d., standard deviation; T2D, type 2 diabetes.

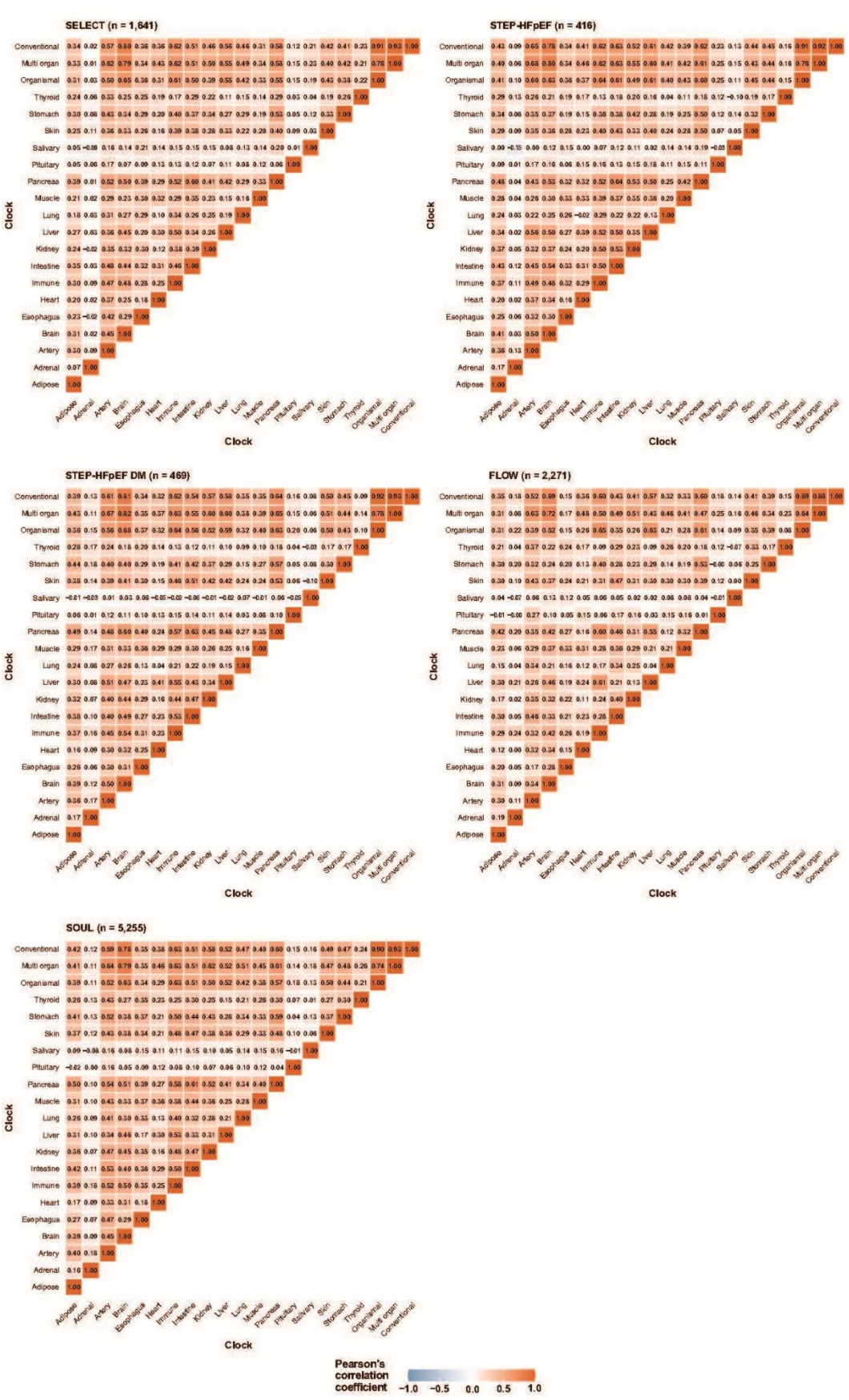
Figures

Fig. 1 | Clinical validation of organ-specific biological aging biomarkers in randomized controlled trials. **a**, Relation between predicted biological age and chronological age. Scatterplots show that predicted biological age from the conventional clock described by Goeminne , L. J. E. *et al*[20] has a positive association with chronological age. The black dashed line indicates the line of identity (y = x), representing equality between predicted biological age and chronological age. Trial-specific fitted lines show the observed linear relationships. r = Pearson correlation coefficient. **b**, Correlations among age-deviation scores across trials. Heatmaps show pairwise Pearson correlation coefficients between organ-specific and composite age-deviation scores after regressing biological age on chronological age in SELECT (n = 1,641), STEP-HFpEF (n = 416), STEP-HFpEF DM (n = 469), FLOW (n = 2,271) and SOUL (n = 5,255). **c–g**, Associations between concomitant medication use at randomization and baseline organ-specific or composite age-deviation scores in SELECT, STEP-HFpEF, STEP-HFpEF DM, FLOW and SOUL. Heatmaps show regression coefficients from models adjusted for chronological age, sex, the interaction between age and sex, smoking status and race. Only medications used by at least 2.5% of participants within each trial were included. Holm–Bonferroni-adjusted $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. **h**, Associations between baseline organ-specific age-deviation scores and time-to-event outcomes in SELECT participants receiving placebo. The heatmap shows log hazard ratios per 1-s.d. higher baseline age-deviation score from Cox proportional hazards models adjusted for chronological age. **i**, Associations of baseline kidney and heart biological-age scores with selected time-to-event outcomes in SELECT participants receiving placebo. Estimates are log hazard ratios per 1-year higher biological-age score from Cox proportional hazards models adjusted for chronological age; whiskers denote 95% confidence intervals. **j**, Percentage changes from baseline in age-deviation scores among participants receiving placebo across the five trials. The longitudinal timepoints for which we have proteomics data after baseline measurements are: week 20 in SELECT; weeks 20 and 52 in STEP-HFpEF and STEP-HFpEF DM; weeks 12, 52 and 156 in FLOW; and weeks 13 and 104 in SOUL. Points represent the median percentage change from baseline and error bars represent standard error. Significance asterisks indicate within-placebo changes from baseline. * Holm–Bonferroni-adjusted < 0.05; ** Holm–Bonferroni-adjusted < 0.01; *** Holm–Bonferroni-adjusted < 0.001.

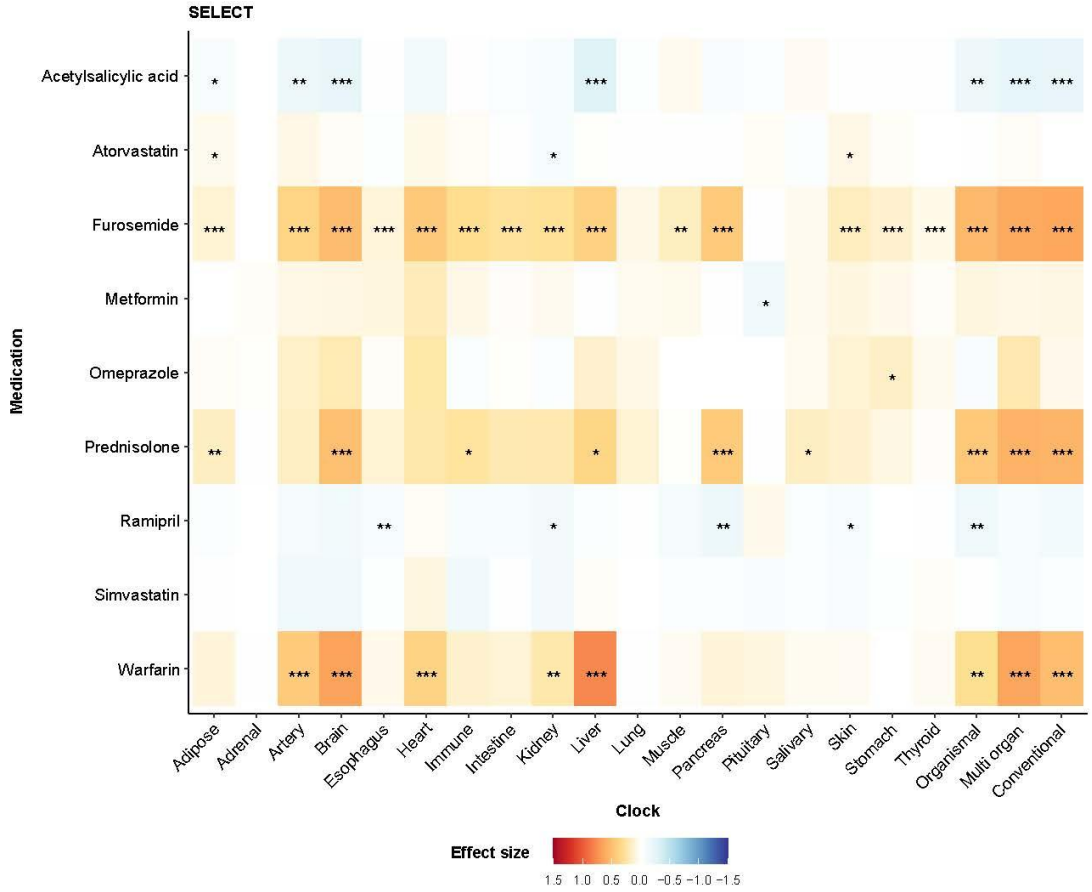
a.


SELECT
r = 0.63, P < 2.2e−16
STEP-HFpEF
r = 0.63, P < 2.2e−16
STEP HFpEF DM
r = 0.52, P < 2.2e−16
FLOW
r = 0.42, P < 2.2e−16
SOUL
r = 0.5, P < 2.2e−16
Biological age
Chronological age

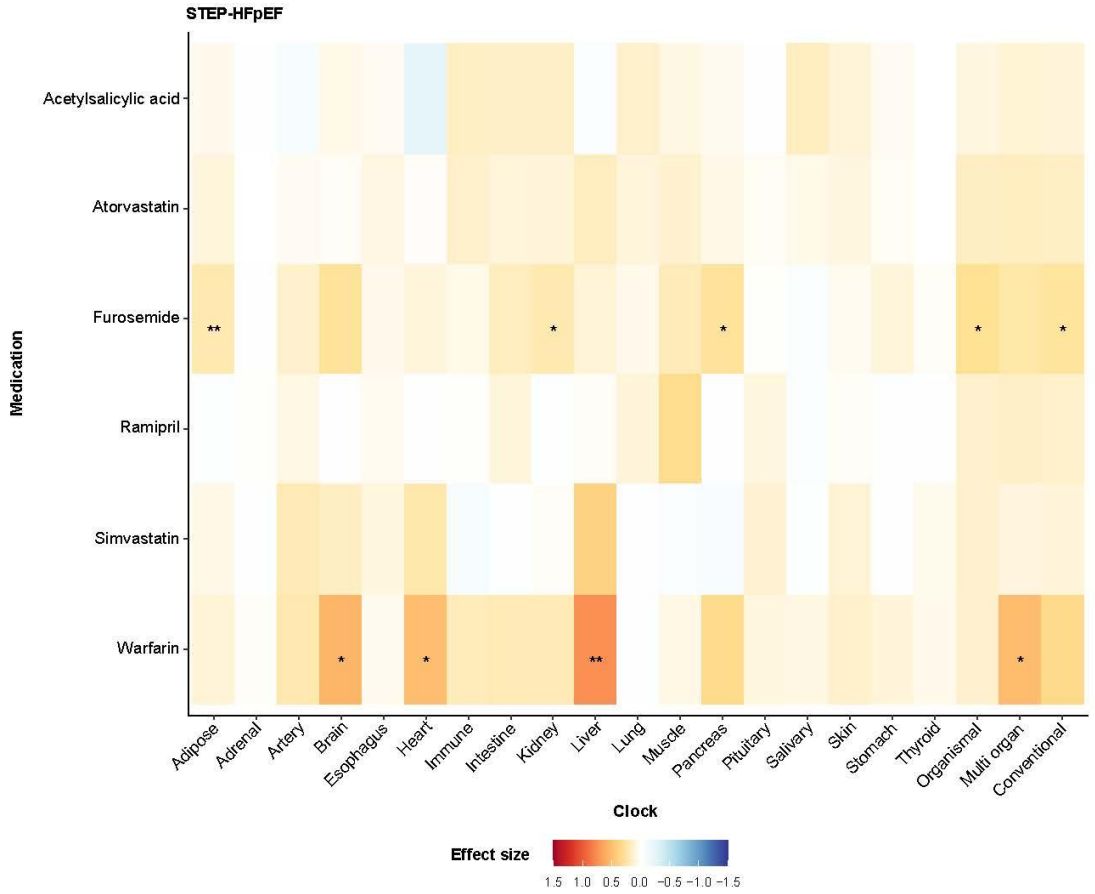
b.


SELECT (n = 1,641)
STEP-HFpEF (n = 416)
STEP-HFpEF DM (n = 469)
FLOW (n = 2,271)
SOUL (n = 5,255)
Clock
Adipose
Adrenal
Artery
Brain
Esophagus
Heart
Immune
Intestine
Kidney
Liver
Lung
Muscle
Pancreas
Pituitary
Salivary
Skin
Stomach
Thyroid
Organismal
Multi organ
Conventional
Pearson's correlation coefficient
−1.0
−0.5
0.0
0.5
1.0

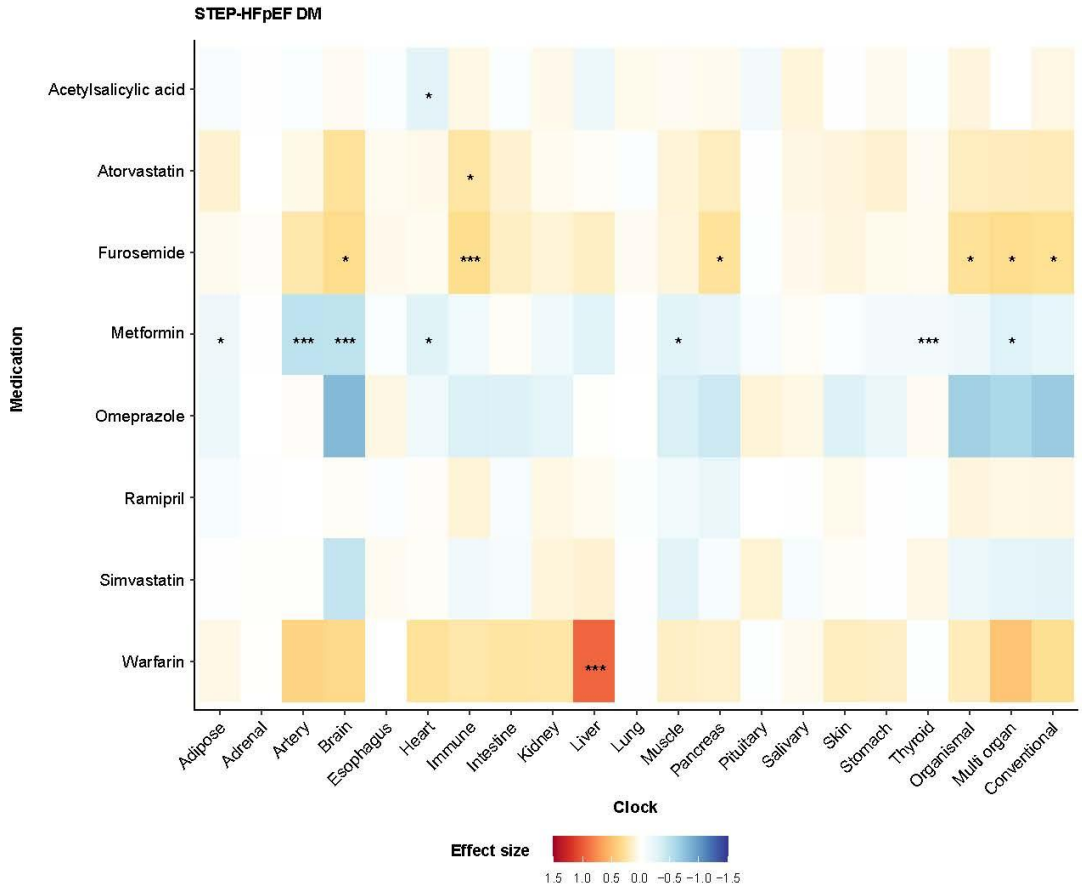
c.


SELECT
Medication
Acetylsalicylic acid
Atorvastatin
Furosemide
Metformin
Omeprazole
Prednisolone
Ramipril
Simvastatin
Warfarin
Adipose
Adrenal
Artery
Brain
Esophagus
Heart
Immune
Intestine
Kidney
Liver
Lung
Muscle
Pancreas
Pituitary
Salivary
Skin
Stomach
Thyroid
Organismal
Multi organ
Conventional
Clock
Effect size
1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5

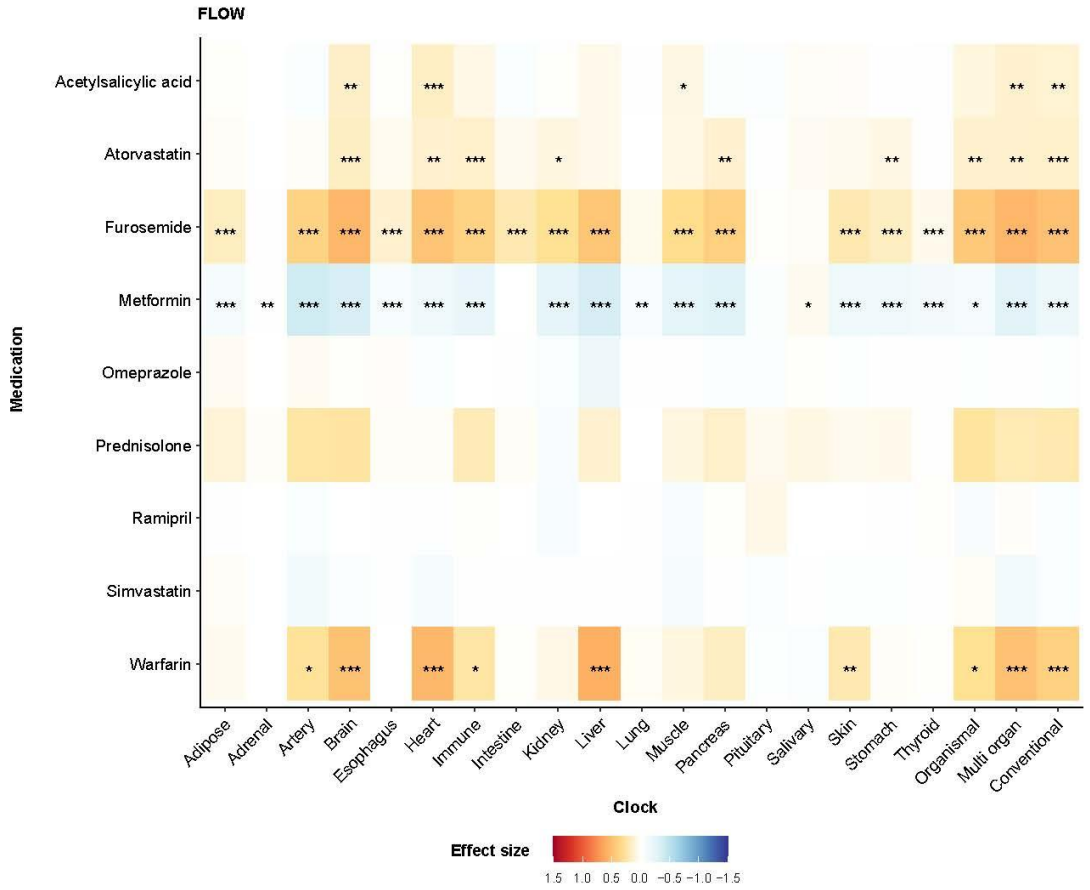
d.


STEP-HFpEF
Medication
Acetylsalicylic acid
Atorvastatin
Furosemide
Ramipril
Simvastatin
Warfarin
Adipose
Adrenal
Artery
Brain
Esophagus
Heart
Immune
Intestine
Kidney
Liver
Lung
Muscle
Pancreas
Pituitary
Salivary
Skin
Stomach
Thyroid
Organismal
Multi organ
Conventional
Clock
Effect size
1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5

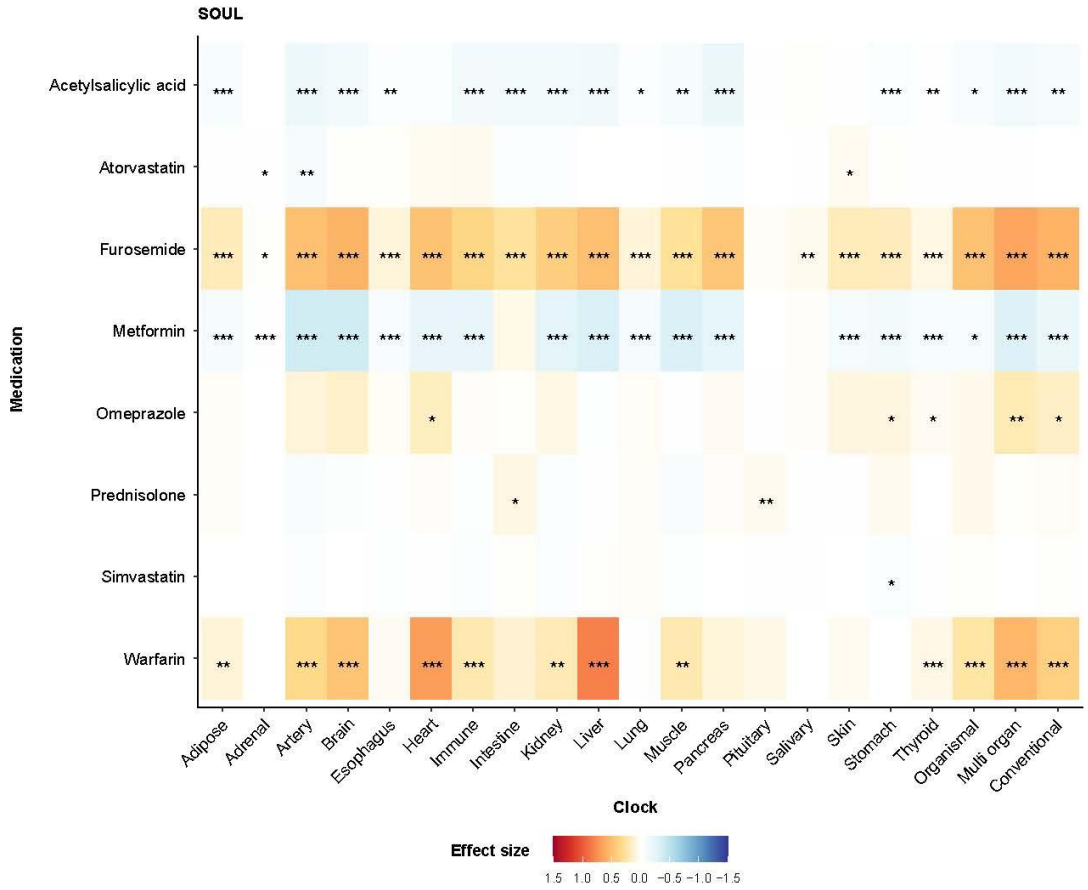
e.


STEP-HFpEF DM
Medication
Acetylsalicylic acid
Atorvastatin
Furosemide
Metformin
Omeprazole
Ramipril
Simvastatin
Warfarin
Adipose
Adrenal
Artery
Brain
Esophagus
Heart
Immune
Intestine
Kidney
Liver
Lung
Muscle
Pancreas
Pituitary
Salivary
Skin
Stomach
Thyroid
Organismal
Multi organ
Conventional
Clock
Effect size
1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5

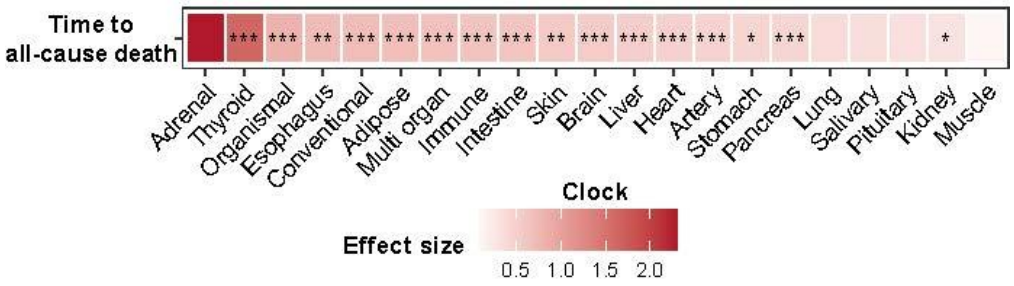
f.


FLOW
Medication
Acetylsalicylic acid
Atorvastatin
Furosemide
Metformin
Omeprazole
Prednisolone
Ramipril
Simvastatin
Warfarin
Adipose
Adrenal
Artery
Brain
Esophagus
Heart
Immune
Intestine
Kidney
Liver
Lung
Muscle
Pancreas
Pituitary
Salivary
Skin
Stomach
Thyroid
Organismal
Multi organ
Conventional
Clock
Effect size
1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5

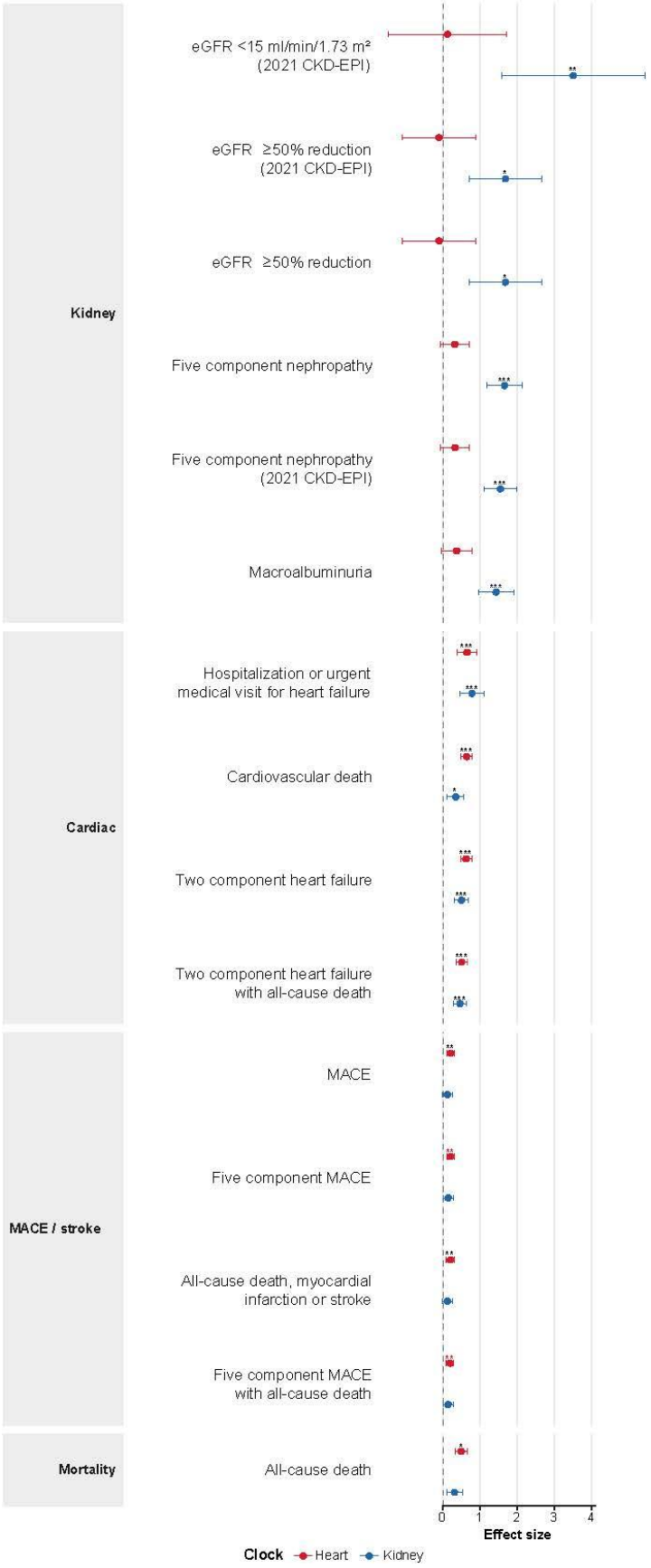
g.


SOUL
Medication
Acetylsalicylic acid
Atorvastatin
Furosemide
Metformin
Omeprazole
Prednisolone
Simvastatin
Warfarin
Adipose
Adrenal
Artery
Brain
Esophagus
Heart
Immune
Intestine
Kidney
Liver
Lung
Muscle
Pancreas
Pituitary
Salivary
Skin
Stomach
Thyroid
Organismal
Multi organ
Conventional
Clock
Effect size
1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5

h.


Time to
all-cause death
Adrenal
Thyroid
Organismal
Esophagus
Conventional
Adipose
Multi organ
Immune
Intestine
Skin
Brain
Liver
Heart
Artery
Stomach
Pancreas
Lung
Salivary
Pituitary
Kidney
Muscle
Clock
Effect size
0.5 1.0 1.5 2.0

i.


Kidney
eGFR <15 ml/min/1.73 m² (2021 CKD-EPI)
eGFR ≥50% reduction (2021 CKD-EPI)
eGFR ≥50% reduction
Five component nephropathy
Five component nephropathy (2021 CKD-EPI)
Macroalbuminuria
Cardiac
Hospitalization or urgent medical visit for heart failure
Cardiovascular death
Two component heart failure
Two component heart failure with all-cause death
MACE / stroke
MACE
Five component MACE
All-cause death, myocardial infarction or stroke
Five component MACE with all-cause death
Mortality
All-cause death
0
1
2
3
4
Effect size
Clock
Heart
Kidney

j.

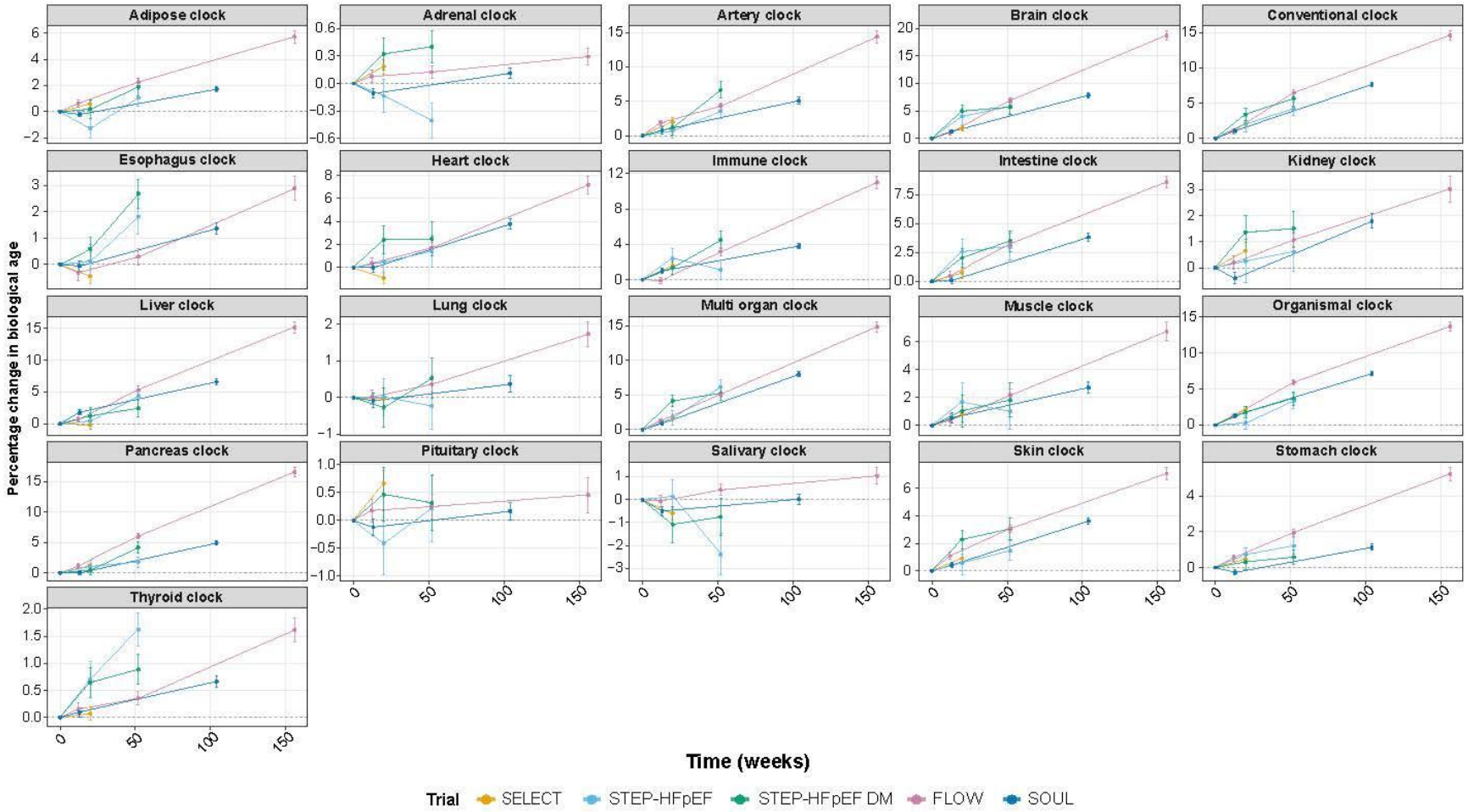
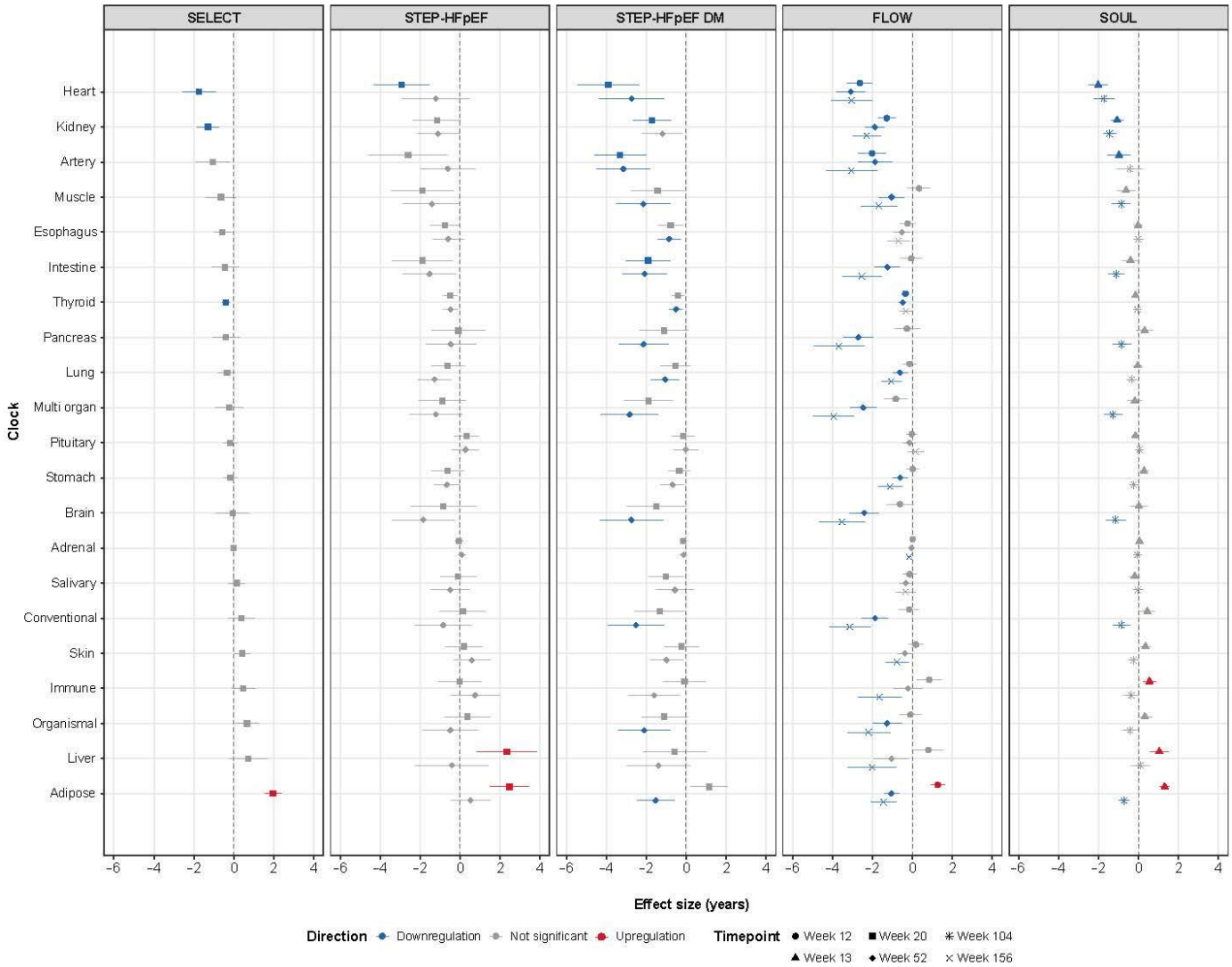
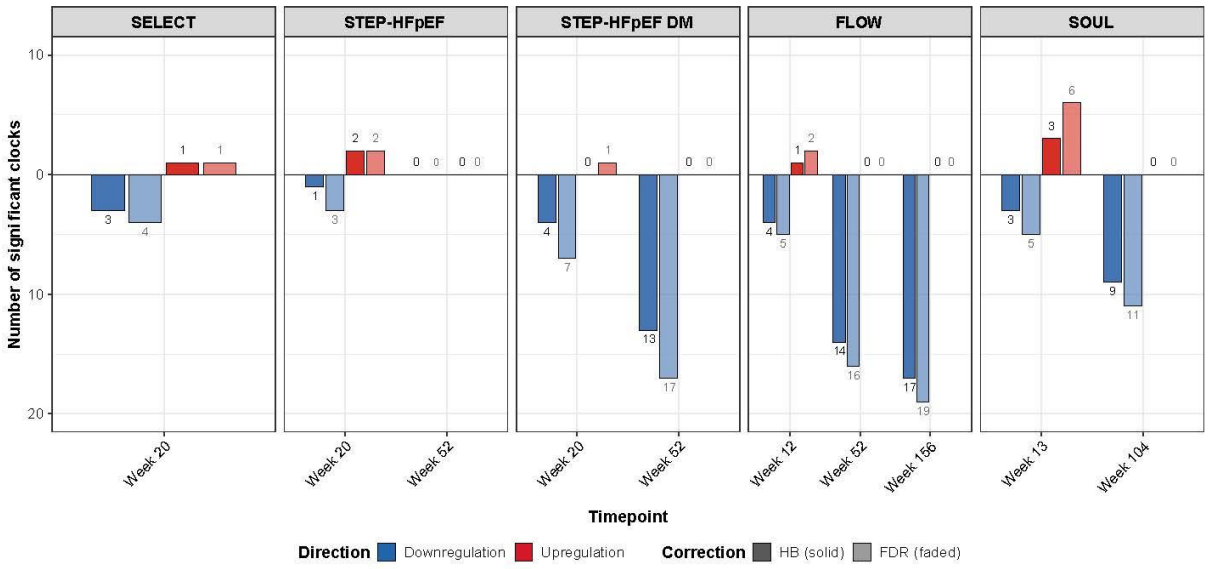

Adipose clock
Adrenal clock
Artery clock
Brain clock
Conventional clock
Esophagus clock
Heart clock
Immune clock
Intestine clock
Kidney clock
Liver clock
Lung clock
Multi organ clock
Muscle clock
Organismal clock
Pancreas clock
Pituitary clock
Salivary clock
Skin clock
Stomach clock
Thyroid clock
Percentage change in biological age
Time (weeks)
Trial
SELECT
STEP-HFpEF
STEP-HFpEF DM
FLOW
SOUL

Fig. 2 | Effects of semaglutide on organ-specific biological-age scores across multiple trials. **a**, Effect sizes represent the between-group difference in change from baseline in estimated biological age between semaglutide and placebo at each timepoint. Active treatments were subcutaneous semaglutide 2.4 mg in SELECT, STEP-HFpEF and STEP-HFpEF DM, subcutaneous semaglutide 1.0 mg in FLOW and oral semaglutide 14 mg in SOUL. Negative values indicate a reduction in predicted biological age (i.e. a younger clock estimate), whereas positive values indicate an increase in predicted biological age. Each timepoint is represented by a distinct point shape (circle, week 12; triangle, week 13; square, week 20; diamond, week 52; asterisk, week 104; cross, week 156). Error bars denote 95% confidence intervals. *P* values were corrected for multiplicity using Holm–Bonferroni. Colors indicate significance and direction after *P* value correction: blue, significantly downregulated; red, significantly upregulated; gray, non-significant. **b**, Number of significantly affected organ biological-age clock models by trial, timepoint, adjustment method and direction. Bar plots showing the count of organ-specific biological-age models significantly affected by semaglutide versus placebo across five clinical trials (SELECT, STEP-HFpEF, STEP-HFpEF DM, FLOW and SOUL). Within each panel, bars represent significance counts under two multiple-testing correction methods: Holm–Bonferroni (HB, solid; more conservative) and FDR (faded; less restrictive). Significance threshold: adjusted $P < 0.05$ for either adjustment method. **c**, Line plots showing the change in adipose, heart, kidney and thyroid-clock biological age in placebo and semaglutide across five clinical trials. **d**, Scatter plots displaying individual proteins that contribute to each significant clock. Points represent treatment-effect estimates on the x-axis and protein weights in organ-specific biological-age clock models on the y-axis for heart, kidney and adipose tissue at week 20 in SELECT, STEP-HFpEF and STEP-HFpEF DM, week 12 in FLOW, and week 13 in SOUL. Each point represents a single protein, with color coding indicating statistical significance and direction: blue dots denote significant downregulation, red dots denote significant upregulation, and gray dots represent non-significant changes. Significance corrected for multiplicity.

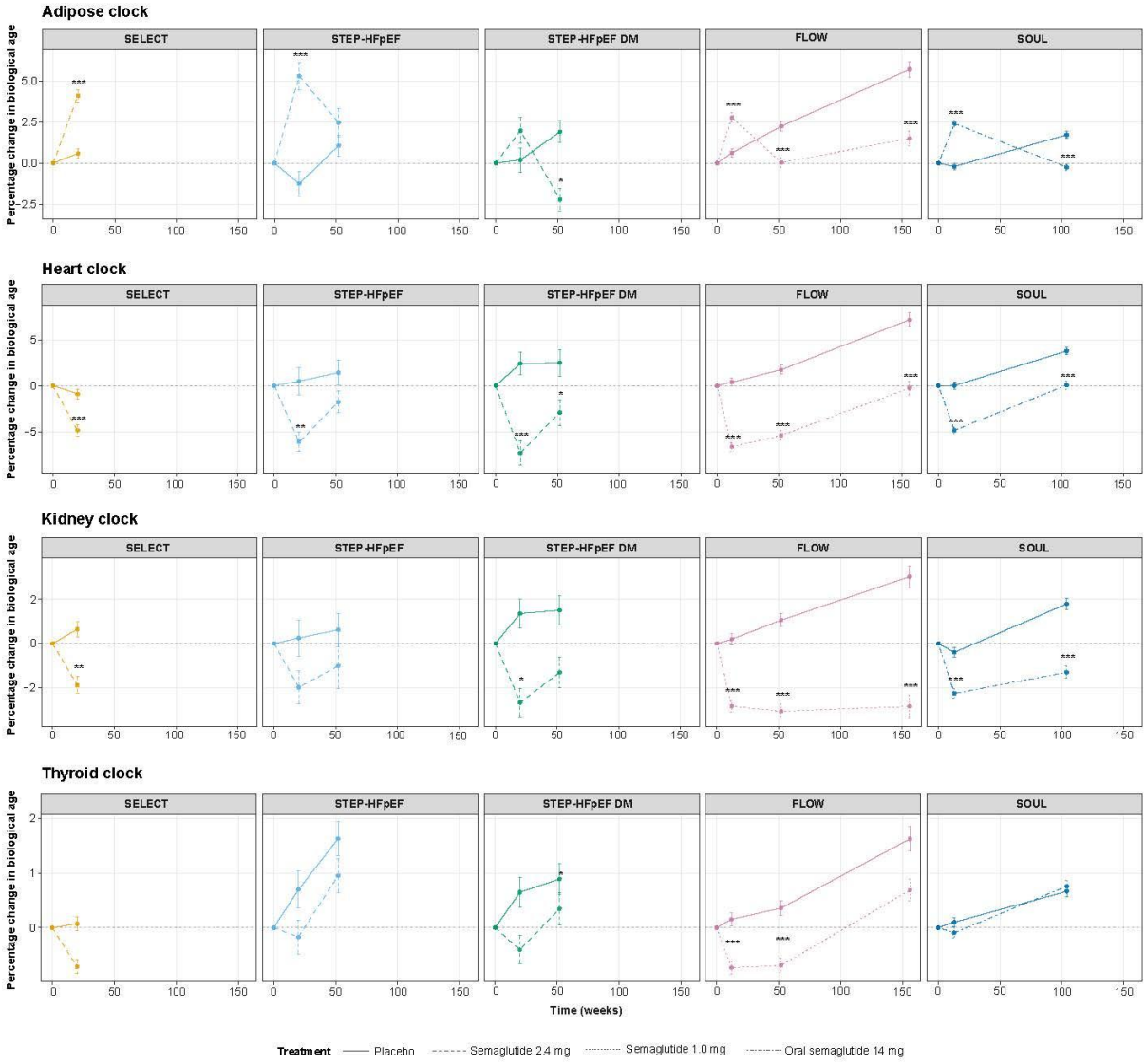
a.


SELECT
STEP-HFpEF
STEP-HFpEF DM
FLOW
SOUL
Clock
Heart
Kidney
Artery
Muscle
Esophagus
Intestine
Thyroid
Pancreas
Lung
Multi organ
Pituitary
Stomach
Brain
Adrenal
Salivary
Conventional
Skin
Immune
Organismal
Liver
Adipose
-6
-4
-2
0
2
4
Effect size (years)
Direction
Downregulation
Not significant
Upregulation
Timepoint
Week 12
Week 13
Week 20
Week 52
Week 104
Week 156

b.


SELECT
STEP-HFpEF
STEP-HFpEF DM
FLOW
SOUL
Number of significant clocks
10
0
10
20
3
4
1
1
1
3
2
2
0
0
0
0
4
7
0
1
13
17
0
0
4
5
1
2
14
16
0
0
17
19
0
0
3
5
3
6
9
11
0
0
Week 20
Week 20
Week 52
Week 20
Week 52
Week 12
Week 52
Week 156
Week 13
Week 104
Timepoint
Direction
Downregulation
Upregulation
Correction
HB (solid)
FDR (faded)

c.


Adipose clock
Heart clock
Kidney clock
Thyroid clock
SELECT
STEP-HFpEF
STEP-HFpEF DM
FLOW
SOUL
Percentage change in biological age
Time (weeks)
Treatment
Placebo
Semaglutide 2.4 mg
Semaglutide 1.0 mg
Oral semaglutide 14 mg

d.

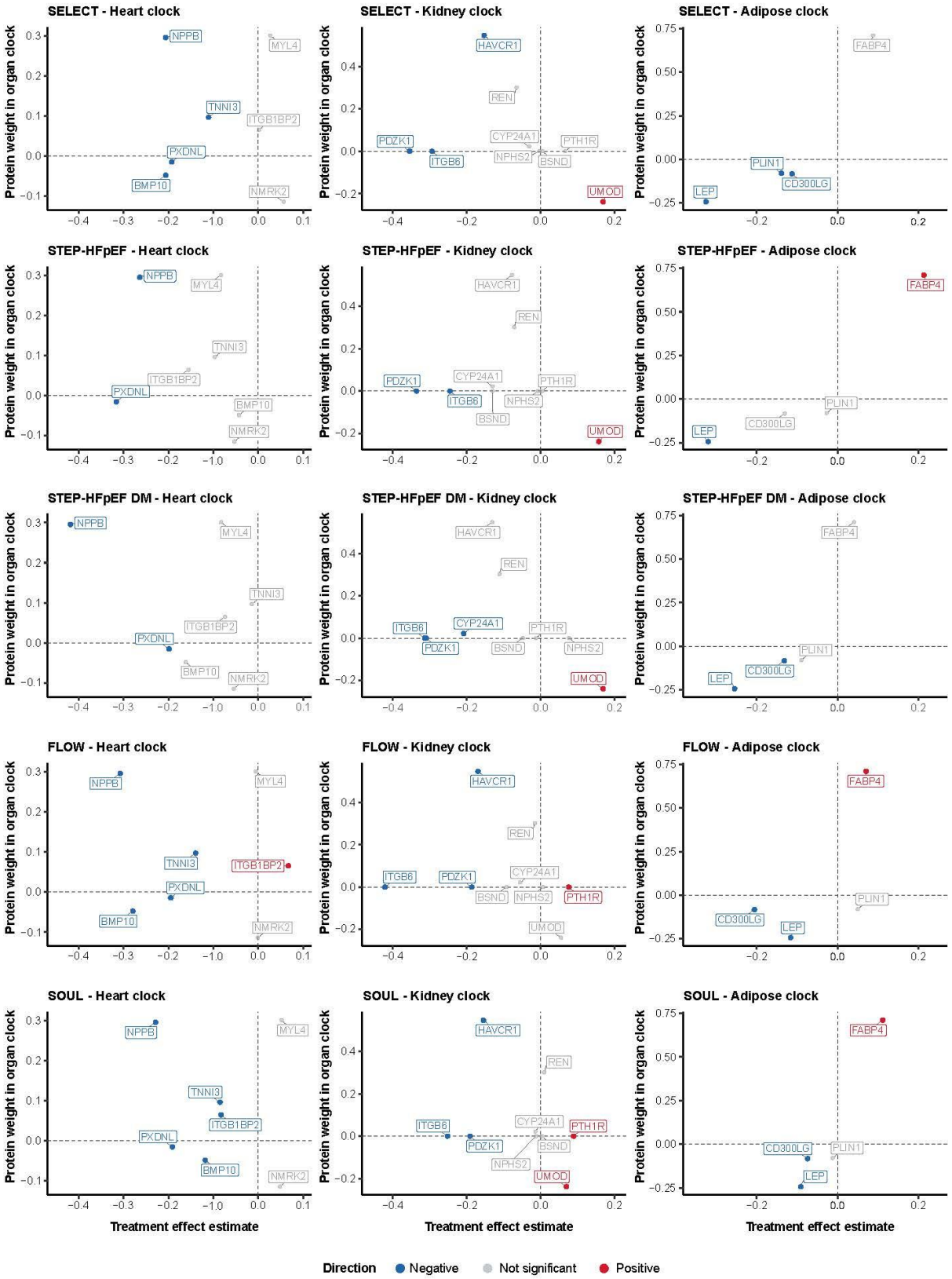
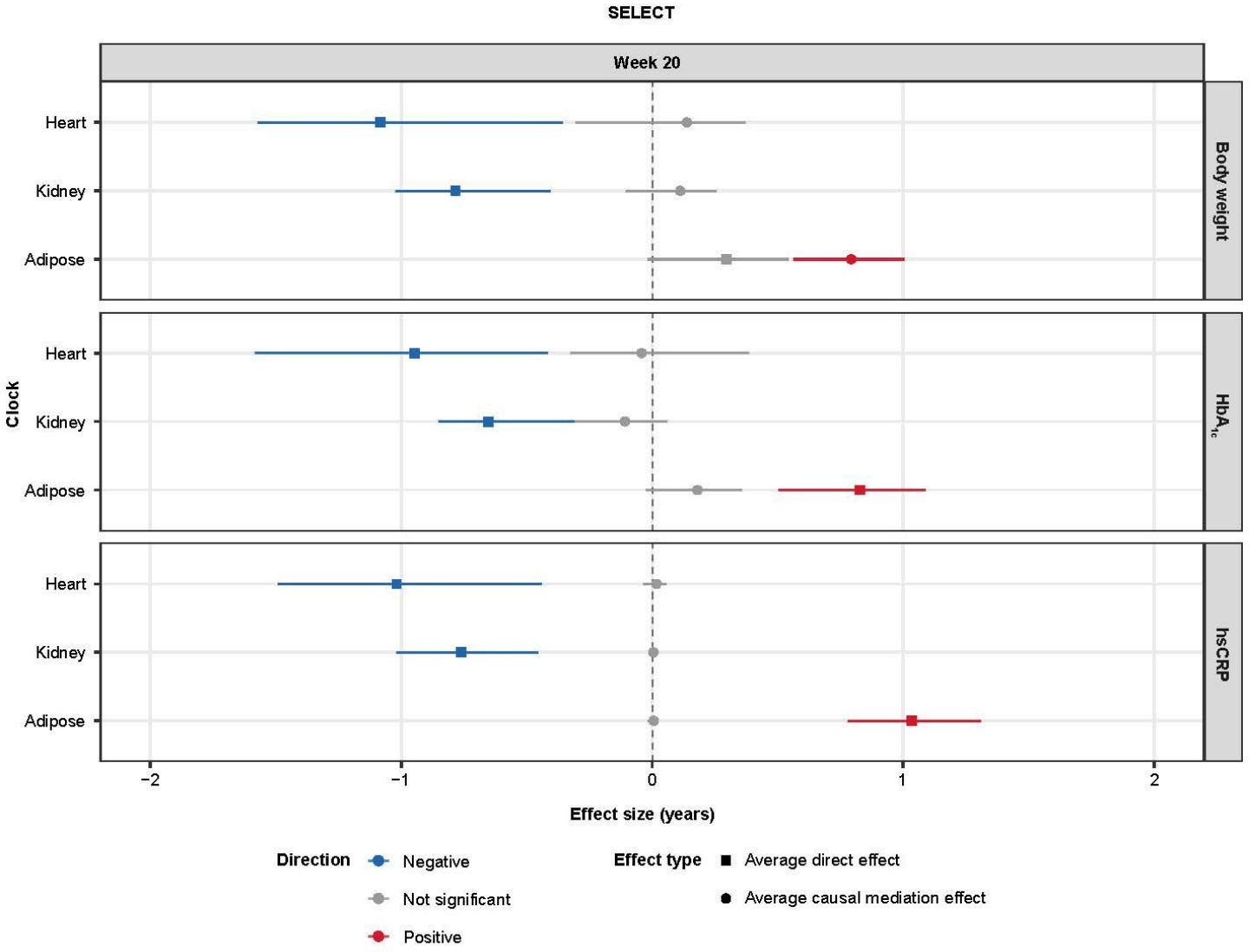
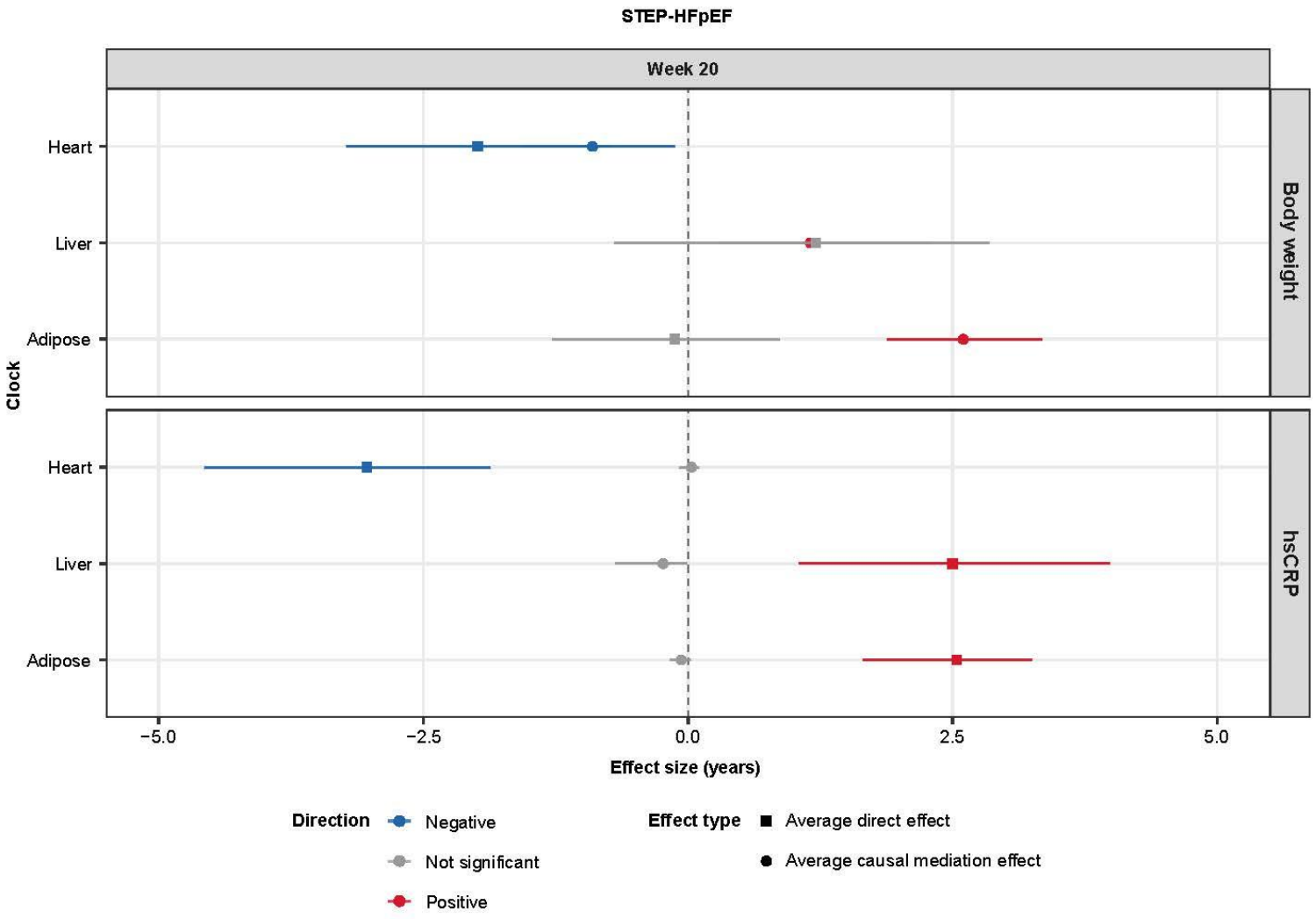

SELECT - Heart clock
SELECT - Kidney clock
SELECT - Adipose clock
STEP-HFpEF - Heart clock
STEP-HFpEF - Kidney clock
STEP-HFpEF - Adipose clock
STEP-HFpEF DM - Heart clock
STEP-HFpEF DM - Kidney clock
STEP-HFpEF DM - Adipose clock
FLOW - Heart clock
FLOW - Kidney clock
FLOW - Adipose clock
SOUL - Heart clock
SOUL - Kidney clock
SOUL - Adipose clock
Protein weight in organ clock
Treatment effect estimate
NPPB
MYL4
TNNI3
ITGB1BP2
PXDNL
BMP10
NMRK2
HAVCR1
REN
PDZK1
CYP24A1
PTH1R
ITGB6
NPHS2
BSND
UMOD
FABP4
PLIN1
CD300LG
LEP
Direction
Negative
Not significant
Positive

Fig. 3 | Semaglutide-associated changes in biological-age scores are not fully explained by changes in body weight, glycemic control or systemic inflammation. a–e, Mediation analyses of the effects of semaglutide on organ-specific biological-age scores in **a**, SELECT, **b**, STEP-HFpEF, **c**, STEP-HFpEF DM, **d**, FLOW and **e**, SOUL. Forest plots show the average direct effect (ADE; squares) and average causal mediation effect (ACME; circles) of semaglutide on organ-specific biological-age scores for each candidate mediator: change in body weight, change in glycated hemoglobin (HbA1c) and change in high-sensitivity C-reactive protein (hsCRP), where available. The ADE represents the estimated effect of semaglutide on biological age that was not statistically explained by the specified mediator, whereas the ACME represents the estimated indirect effect through that mediator. Effect sizes are expressed in years. Negative values indicate a semaglutide-associated reduction in biological age, whereas positive values indicate an increase. Error bars denote 95% confidence intervals estimated using bootstrap resampling. Colors indicate significance and direction: blue, significant negative effect; red, significant positive effect; gray, non-significant. Significance was assessed at $P < 0.05$ after Holm–Bonferroni correction for multiple comparisons across organs and timepoints within each trial.

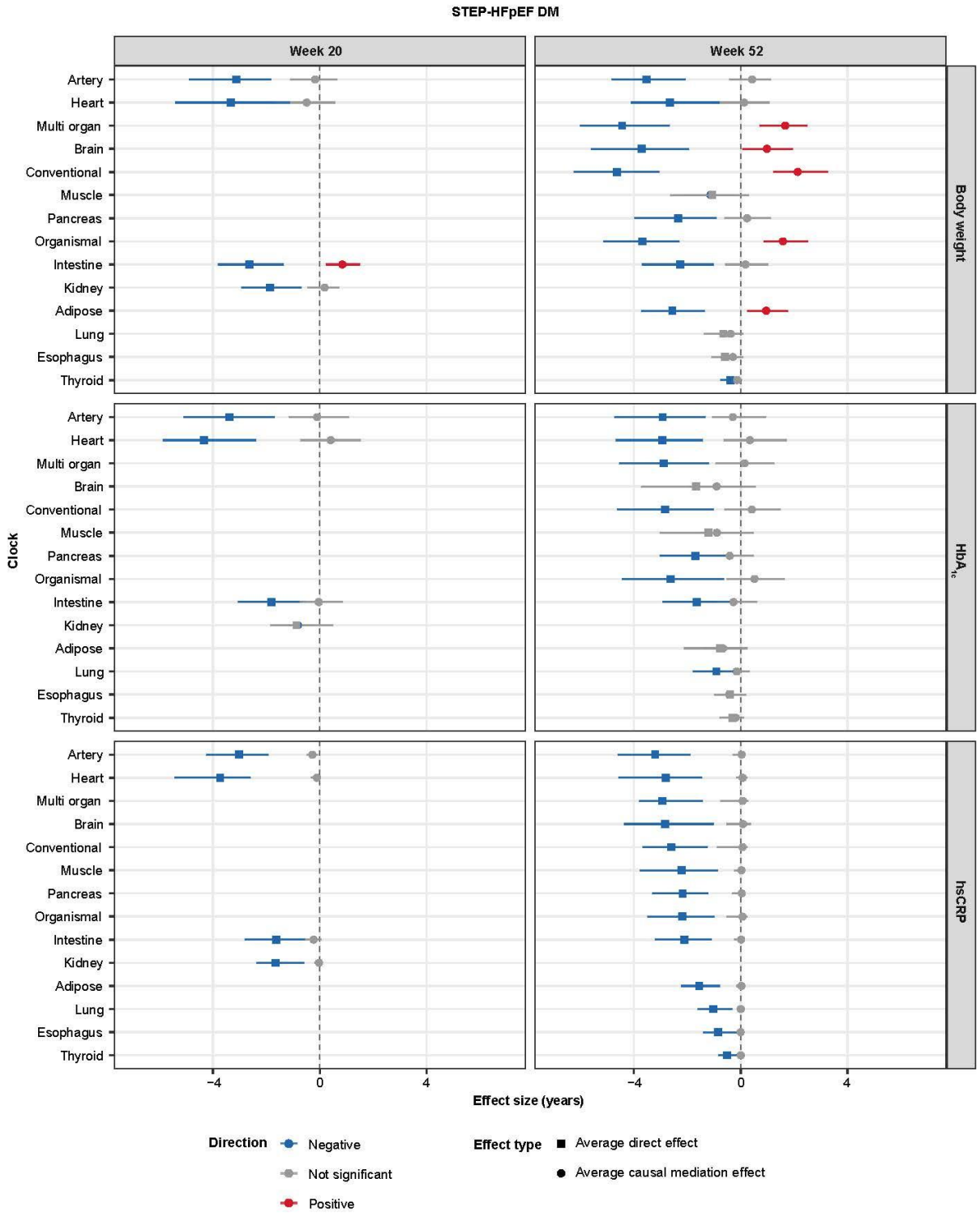
a.


SELECT
Week 20
Heart
Kidney
Adipose
Body weight
HbA1c
hsCRP
Clock
−2
−1
0
1
2
Effect size (years)
Direction
Negative
Not significant
Positive
Effect type
Average direct effect
Average causal mediation effect

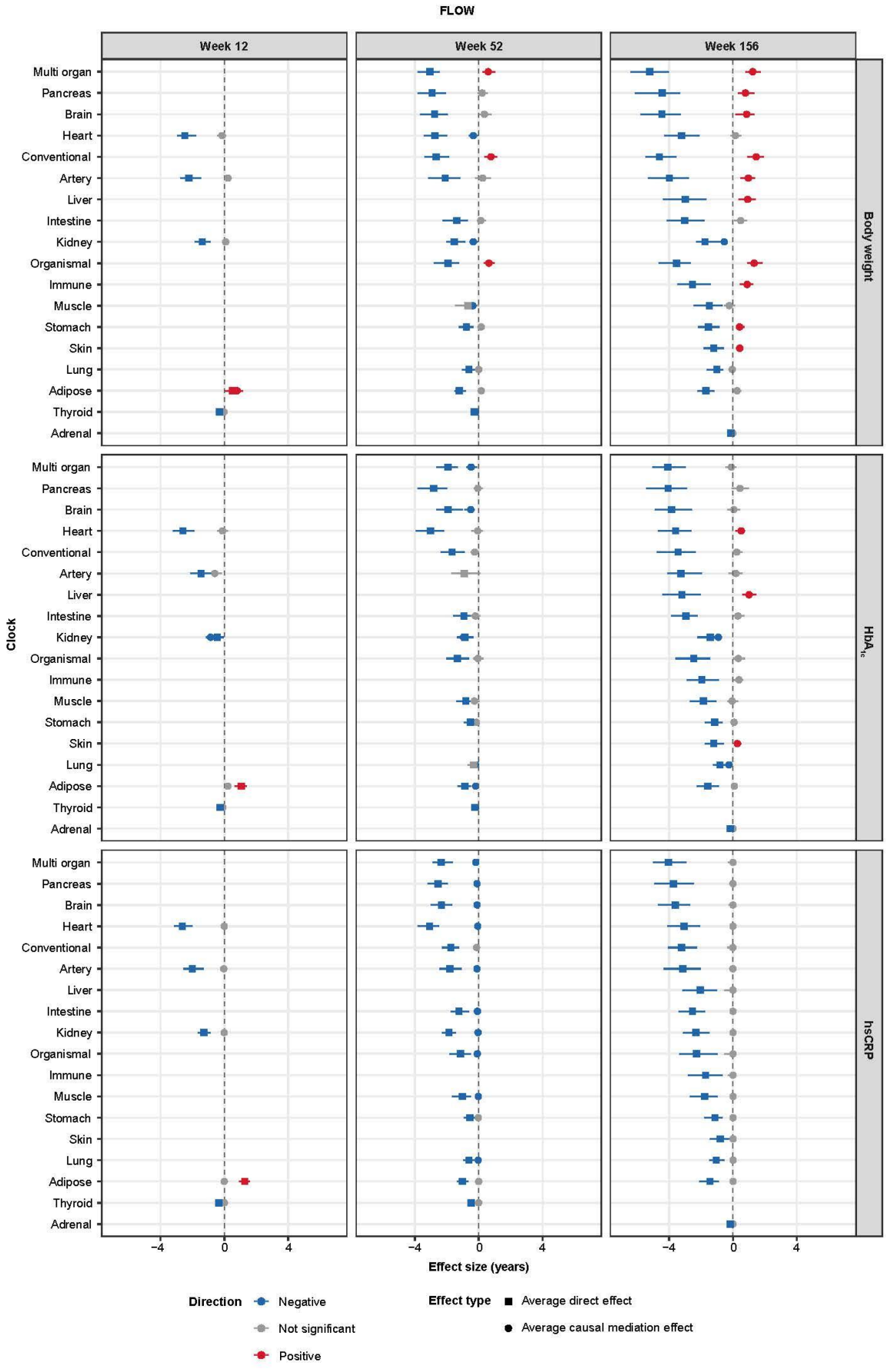
b.


STEP-HFpEF
Week 20
Heart
Liver
Adipose
Clock
Body weight
hsCRP
−5.0
−2.5
0.0
2.5
5.0
Effect size (years)
Direction
Negative
Not significant
Positive
Effect type
Average direct effect
Average causal mediation effect

c.


STEP-HFpEF DM
Week 20
Week 52
Body weight
HbA1c
hsCRP
Clock
Artery
Heart
Multi organ
Brain
Conventional
Muscle
Pancreas
Organismal
Intestine
Kidney
Adipose
Lung
Esophagus
Thyroid
−4
0
4
Effect size (years)
Direction
Negative
Not significant
Positive
Effect type
Average direct effect
Average causal mediation effect

d.


FLOW
Week 12
Week 52
Week 156
Body weight
HbA1c
hsCRP
Clock
Multi organ
Pancreas
Brain
Heart
Conventional
Artery
Liver
Intestine
Kidney
Organismal
Immune
Muscle
Stomach
Skin
Lung
Adipose
Thyroid
Adrenal
−4
0
4
Effect size (years)
Direction
Negative
Not significant
Positive
Effect type
Average direct effect
Average causal mediation effect

e.

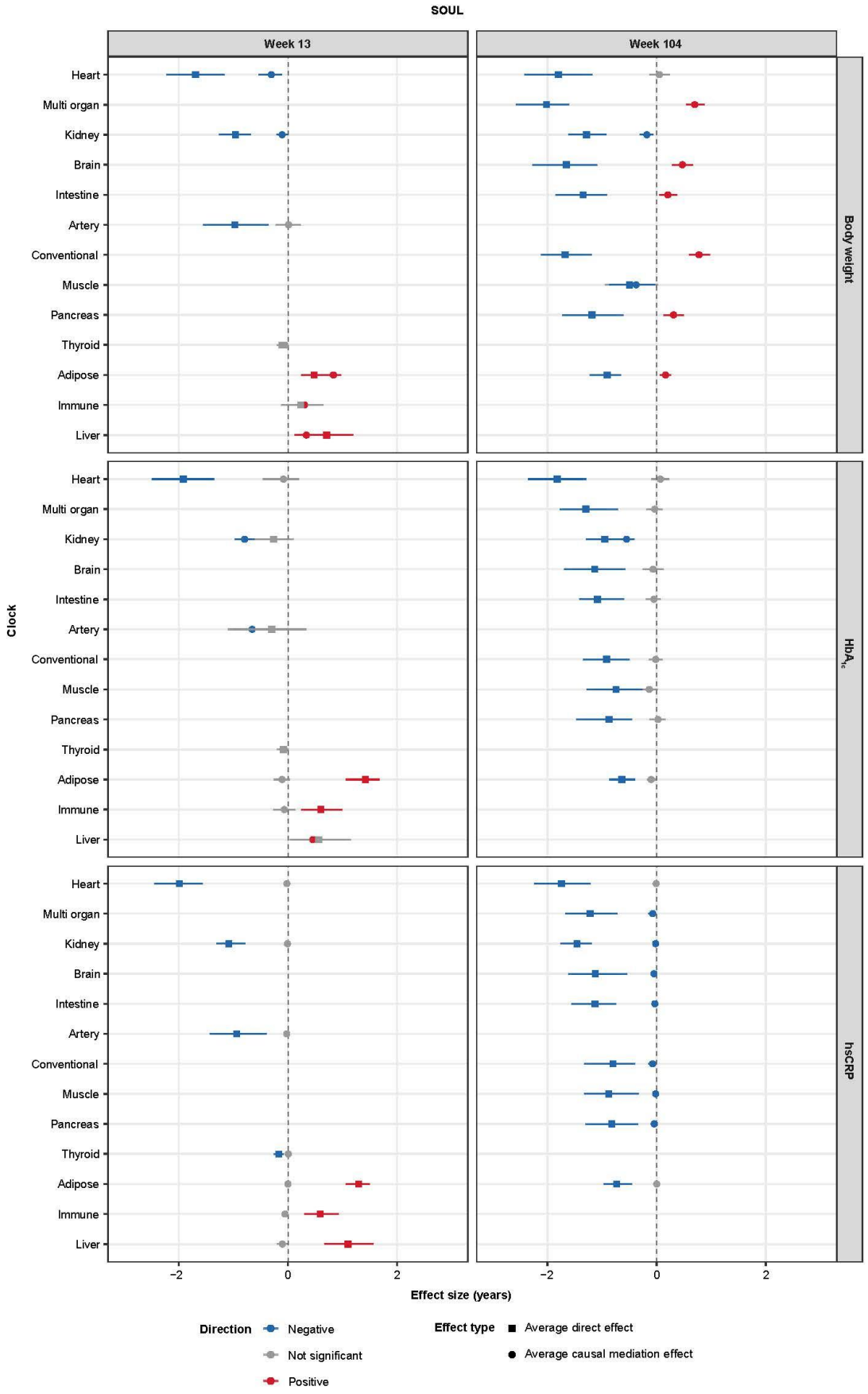
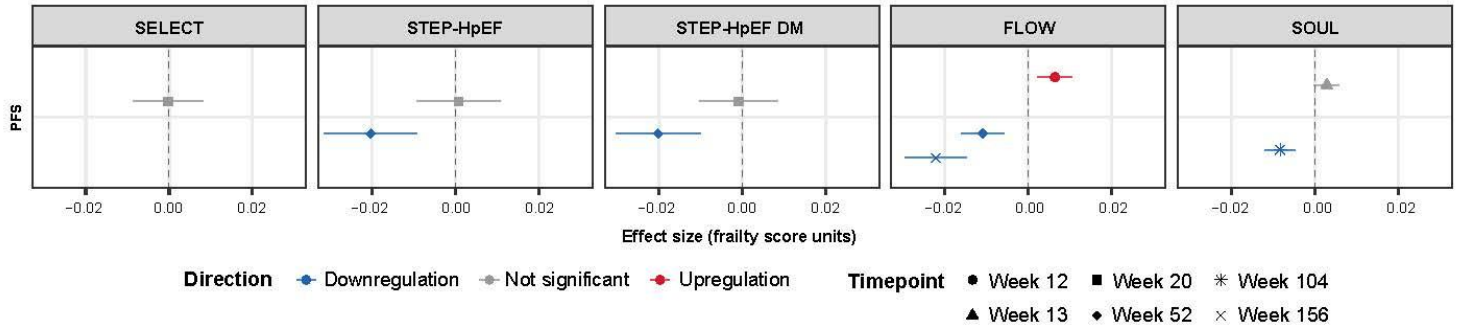
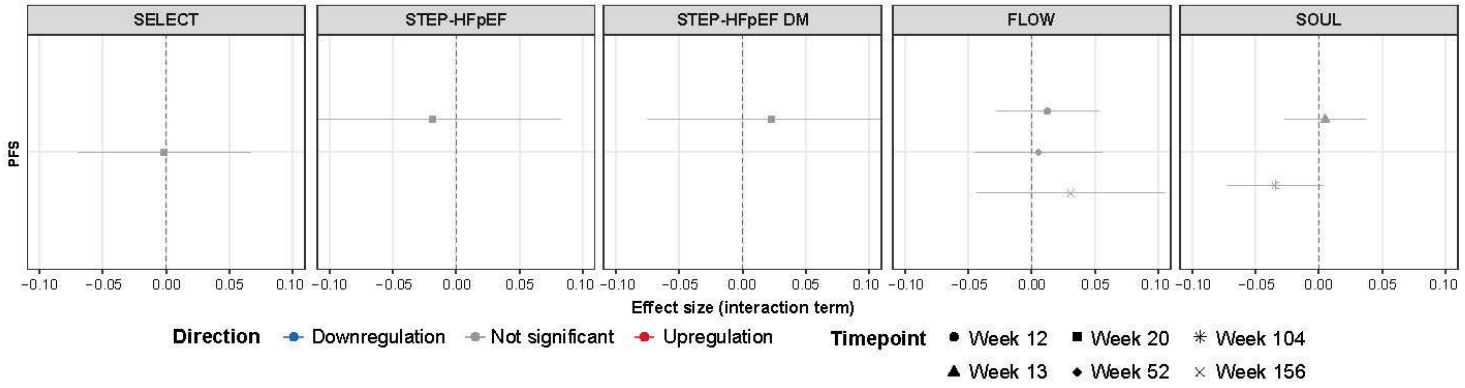

SOUL
Week 13
Week 104
Body weight
HbA1c
hsCRP
Clock
Heart
Multi organ
Kidney
Brain
Intestine
Artery
Conventional
Muscle
Pancreas
Thyroid
Adipose
Immune
Liver
−2
0
2
Effect size (years)
Direction
Negative
Not significant
Positive
Effect type
Average direct effect
Average causal mediation effect

Fig. 4 | Semaglutide reduces proteomic frailty scores and disease-associated risk across multiple trials. a, Effect of semaglutide on the proteomic frailty score (PFS). Forest plots show the between-group difference in PFS change from baseline between semaglutide and placebo across SELECT, STEP-HFpEF, STEP-HFpEF DM, FLOW and SOUL. Negative values indicate a reduction in PFS, whereas positive values indicate an increase. Active treatments were subcutaneous semaglutide 2.4 mg in SELECT, STEP-HFpEF and STEP-HFpEF DM, subcutaneous semaglutide 1.0 mg in FLOW and oral semaglutide 14 mg in SOUL. Error bars denote 95% confidence intervals. **b**, Interaction between baseline PFS and the semaglutide treatment effect on PFS change. Forest plots show the interaction term between treatment assignment and baseline PFS across the five trials. Negative values indicate a greater semaglutide-associated reduction in PFS among participants with higher baseline PFS, whereas positive values indicate the reverse. Error bars denote 95% confidence intervals. Colors indicate direction and significance. **c**, Effects of semaglutide on disease-associated risk scores. Forest plots showing the semaglutide treatment-associated change in predicted disease-risk scores across five clinical trials: SELECT, STEP-HFpEF, STEP-HFpEF DM, FLOW and SOUL. Effect sizes represent the difference in disease-risk change from baseline between semaglutide and placebo at each timepoint. Negative values indicate a reduction in predicted disease risk (i.e. beneficial effect), whereas positive values indicate an increase in disease risk. Each timepoint is represented by a distinct point shape (circle, week 12; triangle, week 13; square, week 20; diamond, week 52; asterisk, week 104; cross, week 156). Error bars denote 95% confidence intervals. Significance was assessed at $P < 0.05$ after Holm–Bonferroni false-discovery-rate correction for multiple comparisons. Colors indicate direction and significance after correction: blue, significantly downregulated (beneficial); red, significantly upregulated (harmful); gray, non-significant. Disease-risk scores calculated using UK Biobank-derived proteomic models[21].

a.


SELECT
STEP-HpEF
STEP-HpEF DM
FLOW
SOUL
PFS
−0.02
0.00
0.02
Effect size (frailty score units)
Direction
Downregulation
Not significant
Upregulation
Timepoint
Week 12
Week 20
Week 104
Week 13
Week 52
Week 156

b.


SELECT
STEP-HFpEF
STEP-HFpEF DM
FLOW
SOUL
PFS
−0.10
−0.05
0.00
0.05
0.10
Effect size (interaction term)
Direction
Downregulation
Not significant
Upregulation
Timepoint
Week 12
Week 20
Week 104
Week 13
Week 52
Week 156

c.

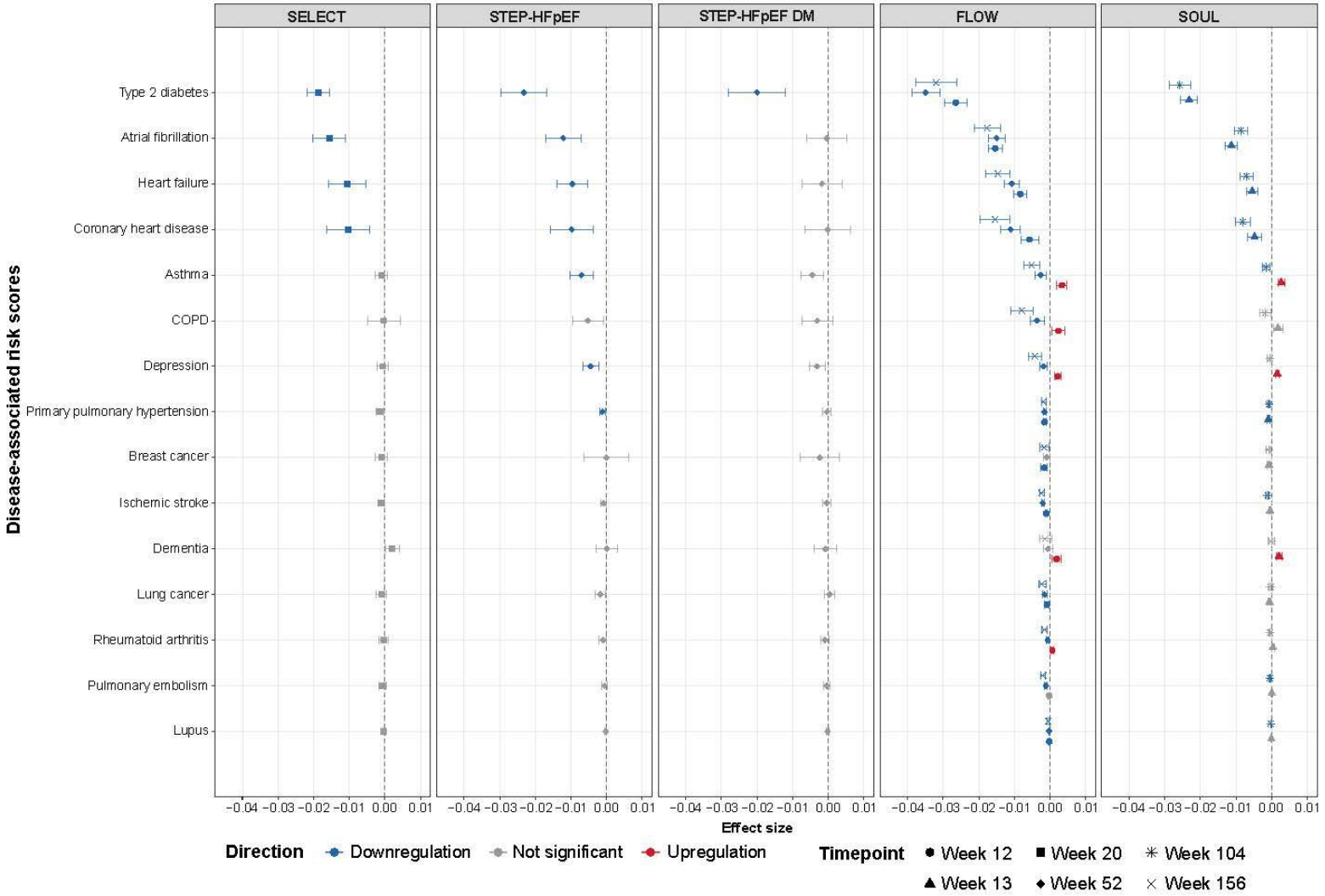
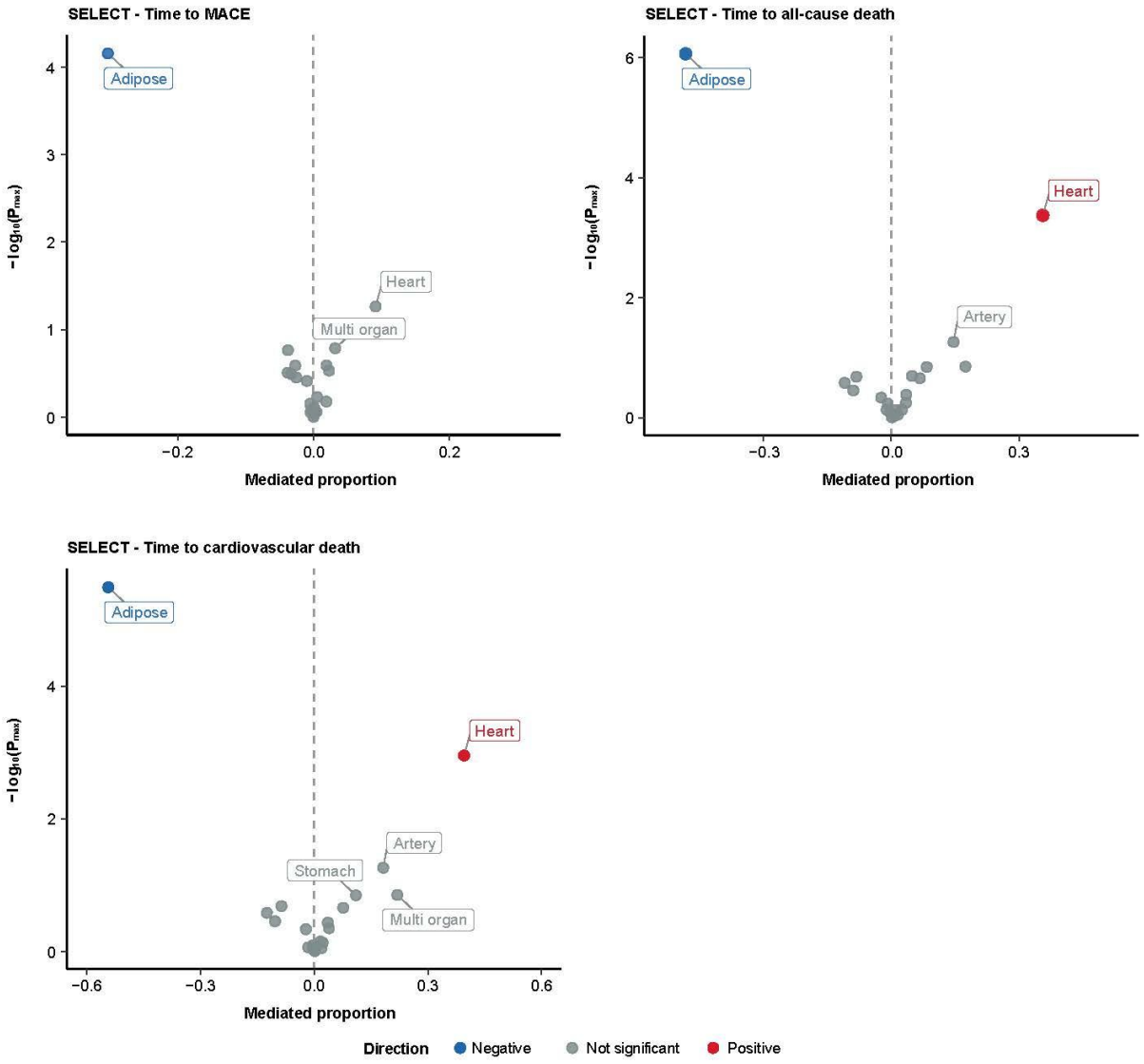
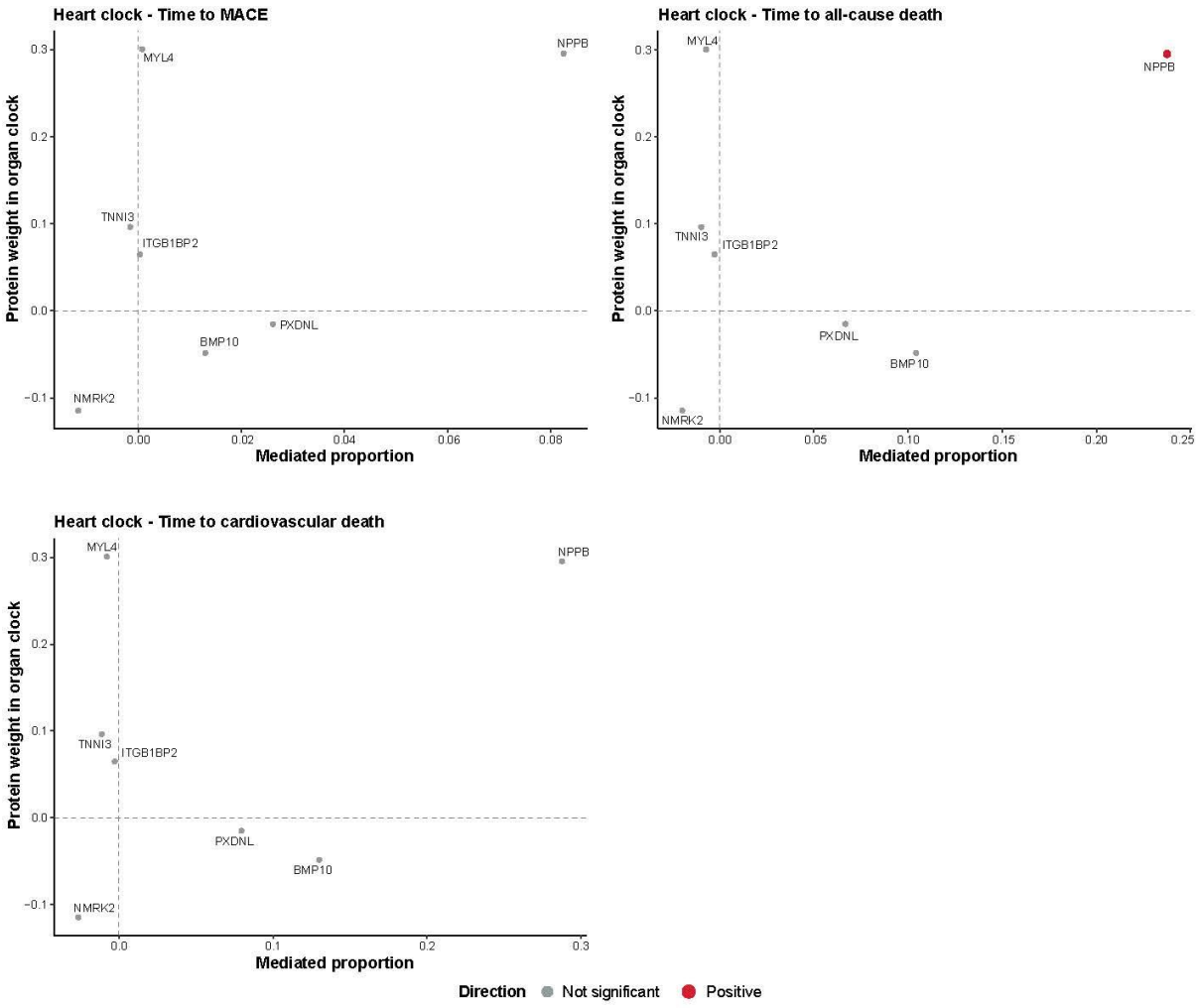

SELECT
STEP-HFpEF
STEP-HFpEF DM
FLOW
SOUL
Disease-associated risk scores
Type 2 diabetes
Atrial fibrillation
Heart failure
Coronary heart disease
Asthma
COPD
Depression
Primary pulmonary hypertension
Breast cancer
Ischemic stroke
Dementia
Lung cancer
Rheumatoid arthritis
Pulmonary embolism
Lupus
−0.04 −0.03 −0.02 −0.01 0.00 0.01
Effect size
Direction
Downregulation
Not significant
Upregulation
Timepoint
Week 12
Week 20
Week 104
Week 13
Week 52
Week 156

Fig. 5 | Organ-specific biological-age clock models mediate the effects of semaglutide on cardiovascular outcomes and mortality. a, Mediation of the effect of semaglutide on organ-relevant clinical outcomes through organ-specific biological-age clock models in SELECT. Volcano plots showing the results of causal mediation analyses for each clock-outcome pair. The x-axis represents the estimated mediated proportion, reflecting the extent to which each organ clock accounts for the treatment effect on time-to-event outcomes. Positive values indicate that the clock mediates an enhancement of the treatment effect, whereas negative values indicate attenuation. The y-axis represents the -log10 *P* value derived from the mediated clock. Points further from the center indicate greater mediation effect size. Red: positive mediated proportion; blue: negative mediated proportion; gray: non-significant. , significance determined using the high-dimensional mediation testing procedure with muti-testing control. Results are shown unadjusted and adjusted for change in body weight and change in waist circumference. **b**, Scatter plots displaying mediation proportion on either time to MACE, time to all-cause death or time to cardiovascular death for individual proteins that make up the heart clock. Points represent mediation proportion estimates on the x-axis and heart-clock weights values on the y-axis. Each point represents a single protein, with color coding indicating statistical significance and direction: blue dots denote significant negative mediation proportion, red dots denote significant positive mediation proportion and gray dots represent non-significant changes. **c**, Mediation of the effect of semaglutide on organ-relevant clinical outcomes through organ-specific biological-age clock models in SOUL. Volcano plots showing the results of causal mediation analyses for each clock-outcome pair. The x-axis represents the estimated mediated proportion, reflecting the extent to which each organ clock accounts for the treatment effect on time-to-event outcomes. Positive values indicate that the clock mediates an enhancement of the treatment effect, whereas negative values indicate attenuation. The y-axis represents the –log10 *P* value derived from the mediated clock. Points further from the center indicate greater mediation effect size. Red: positive mediated proportion; blue: negative mediated proportion; gray: non-significant. Significance was determined using the high-dimensional mediation testing procedure for multi-testing control. **d**, Scatter plots displaying mediation proportion on either time to MACE, time to all-cause death or major kidney disease event outcome in SOUL for individual proteins that make up the heart and artery clocks. Points represent mediation proportion estimates on the x-axis and heart-clock weights values on the y-axis. Each point represents a single protein, with color coding indicating statistical significance and direction: blue dots denote significant negative mediation proportion, red dots denote significant positive mediation proportion and gray dots represent non-significant changes.

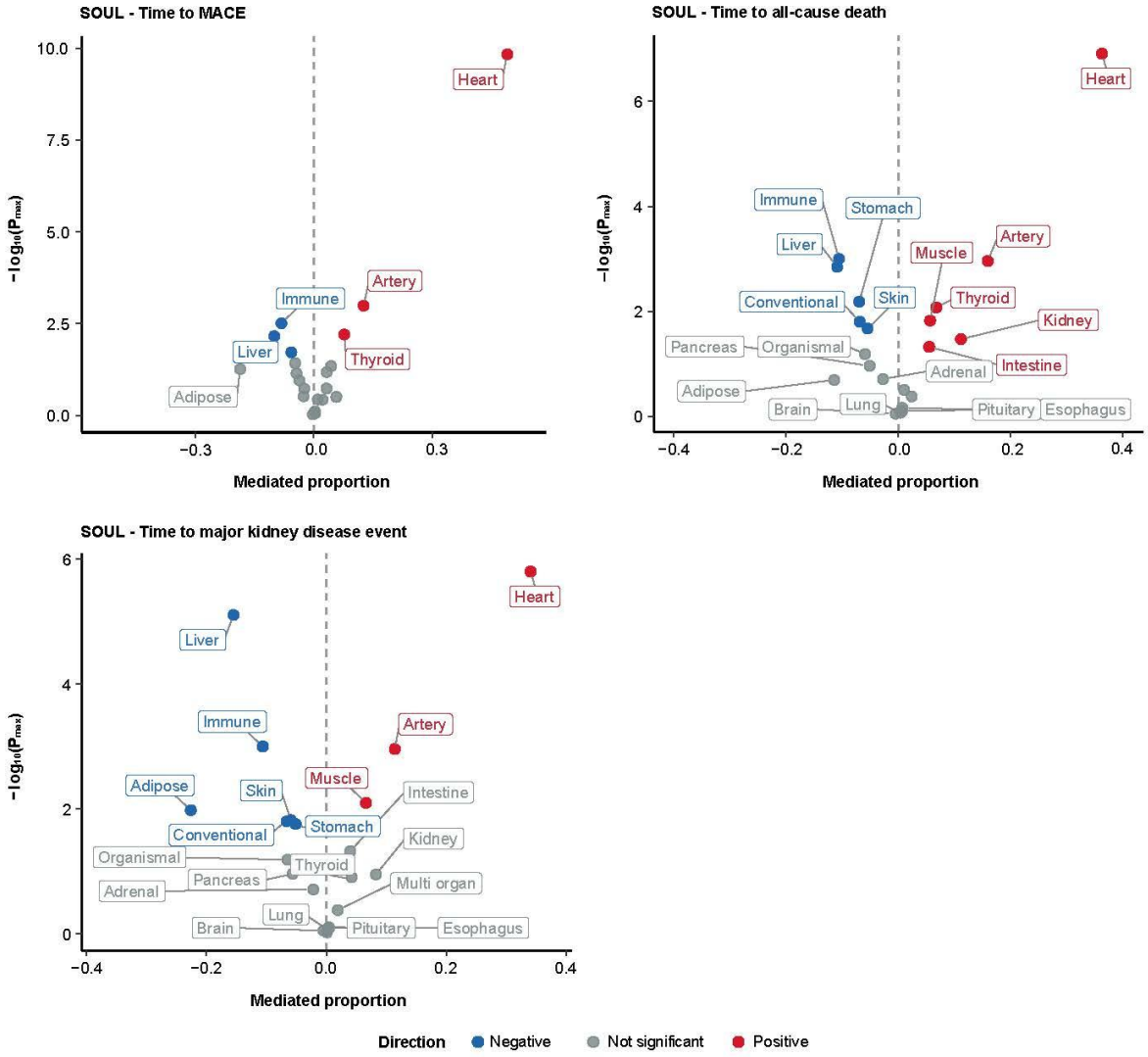
a.


SELECT - Time to MACE
Adipose
Heart
Multi organ
−log10(Pmax)
Mediated proportion
SELECT - Time to all-cause death
Adipose
Heart
Artery
SELECT - Time to cardiovascular death
Adipose
Heart
Artery
Stomach
Multi organ
Direction
Negative
Not significant
Positive

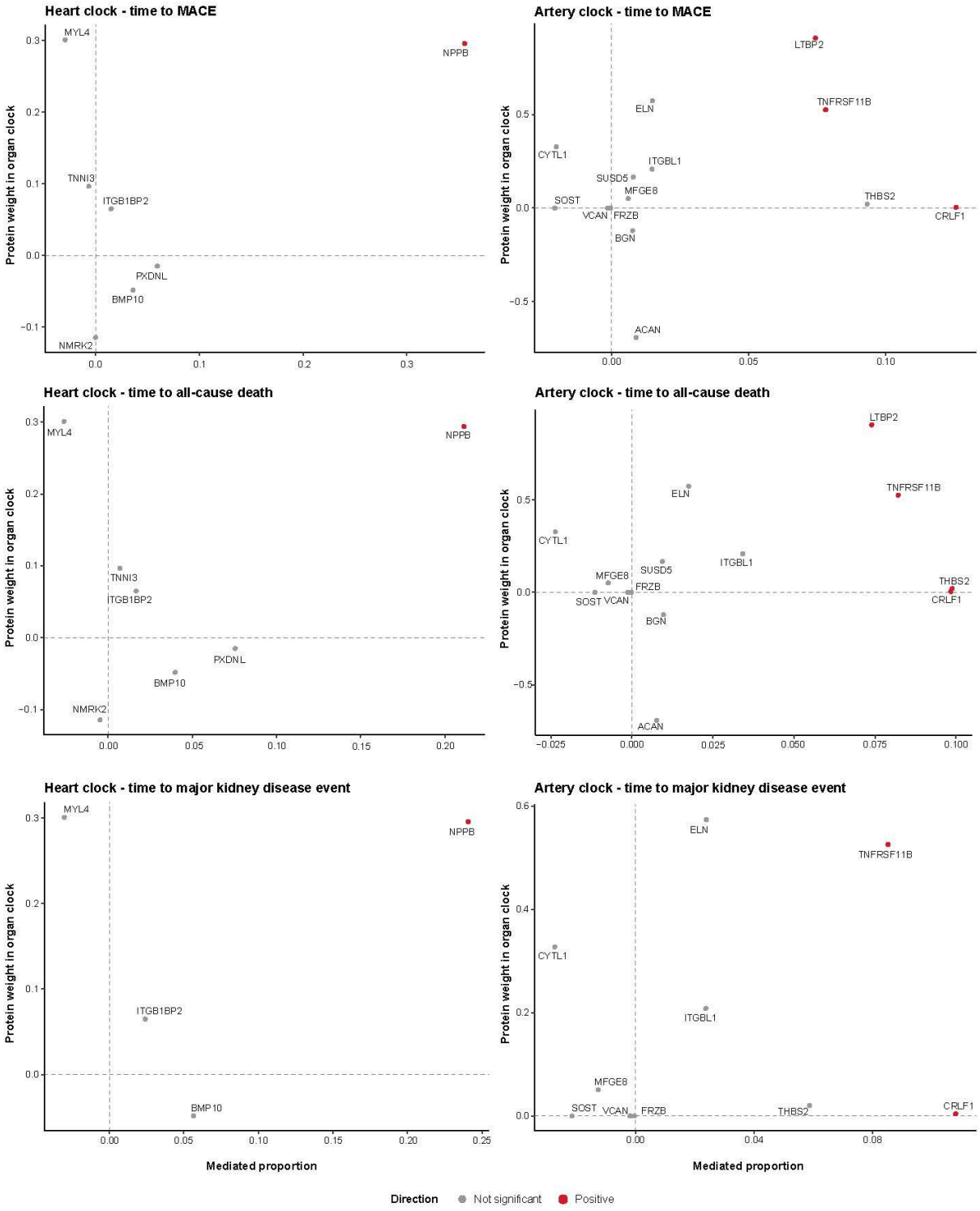
b.


Heart clock - Time to MACE
Protein weight in organ clock
Mediated proportion
MYL4
NPPB
TNNI3
ITGB1BP2
PXDNL
BMP10
NMRK2
Heart clock - Time to all-cause death
Heart clock - Time to cardiovascular death
Direction
Not significant
Positive

c.


SOUL - Time to MACE
SOUL - Time to all-cause death
SOUL - Time to major kidney disease event
Mediated proportion
Direction
Negative
Not significant
Positive

d.


Heart clock - time to MACE
Artery clock - time to MACE
Heart clock - time to all-cause death
Artery clock - time to all-cause death
Heart clock - time to major kidney disease event
Artery clock - time to major kidney disease event
Protein weight in organ clock
Mediated proportion
MYL4
NPPB
TNNI3
ITGB1BP2
PXDNL
BMP10
NMRK2
LTBP2
ELN
TNFRSF11B
CYTL1
ITGBL1
SUSD5
MFGE8
SOST
VCAN
FRZB
THBS2
CRLF1
BGN
ACAN
Direction
Not significant
Positive

Supplementary Files

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

- DermitLongevitymsOnlinecontent26Aug2026Submitted.pdf