

Weight Loss: Mediator or Modifier?

Its role may depend on the relationship we are trying to understand

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September 9, 2026



Disclosure

- Robin Mogg & Becky Taub are Madrigal employees

Overview

Background:

- Weight loss (WL) has been shown to reduce liver stiffness and collagen markers in patients without significant fibrosis who have obesity/metabolic risk
- These markers (VCTE, ELF, others) have been proposed as reasonably likely surrogate endpoints (RLSEs) for MASH trials as measures of liver fibrosis improvement
- In MASH trials, fibrosis improvement (FI) is assessed by serial liver biopsy based on a one stage improvement in fibrosis, as assessed by pathologists

AIM: To assess the independent associations of WL and FI with changes in non-invasive tests (NITs), and explore how WL may impact the ability of NIT changes to reflect FI

Methods:

- Changes in WL, FI, and NITs were examined at Week 52 in resmetirom and placebo treated patients with MASH and F2-F3 fibrosis from the MAESTRO-NASH pivotal trial, of which 17% (80 mg resmetirom), 22% (100 mg resmetirom) and 12% (placebo) had $\geq 5\%$ WL
- Linear and logistic regression models were used to explore associations

Resmetirom: Phase 3 Program, Pivotal Trial MAESTRO-NASH

KEY ELIGIBILITY CRITERIA

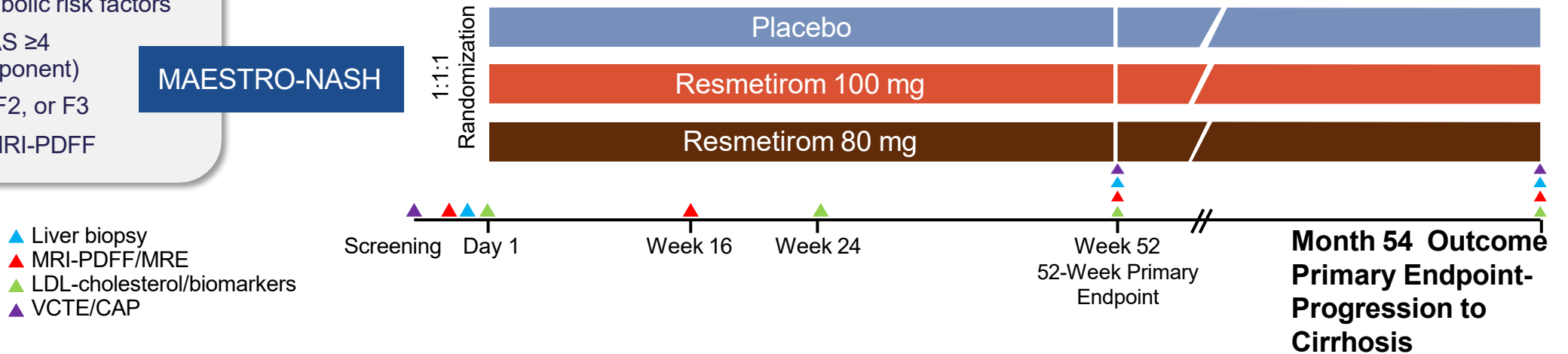
Presence of ≥ 3 metabolic risk factors

NASH on biopsy: NAS ≥ 4
(with ≥ 1 in each component)

Fibrosis stage F1B, F2, or F3

$\geq 8\%$ hepatic fat by MRI-PDFF

MAESTRO-NASH



DUAL PRIMARY ENDPOINT AT WEEK 52

MASH resolution (ballooning score=0, inflammation score=0/1, and ≥ 2 -point reduction in NAS) with no worsening of fibrosis

≥ 1 -stage improvement in fibrosis with no worsening of NAS

MRE: magnetic resonance enterography; MRI: magnetic resonance imaging; NAS: NAFLD activity score; PDFF: proton density fat fraction; VCTE/CAP: vibration-controlled transient elastography with controlled attenuation parameter.
Harrison S, et al. *N Engl J Med*. 2024;390:497-509. Reproduced for educational purposes only

Weight Loss as a Potential Mediator

Mediator

Helps explain *how* or *why* one thing leads to another, part of the pathway from *cause to effect*



Treatment with a drug may cause weight loss, which may lead to fibrosis improvement
Treatment with a drug may also improve fibrosis through pathways independent of weight loss

- A statistical mediation analysis helps determine how much of the treatment effect may be mediated through weight loss versus pathways independent of weight loss

Resmetirom's treatment effect on fibrosis improvement is largely independent of weight loss, although weight loss is associated with improved outcomes

Effects of Resmetirom on Metabolic-Dysfunction Associated Steatohepatitis in Patients With Weight Loss and/or Diabetes Taking Glucagon-Like Peptide-1 Receptor Agonists and Other Diabetes Therapies: A Secondary Analysis of the MAESTRO-NASH Trial

Mazen Nouredin^{1,2} | Mary Rinella³ | Rebecca Taub⁴ | Dominic Labriola⁴ | Raul C. Camacho⁴ | Naim Alkhouri⁵ | Rohit Loomba⁶ | Meena B. Bansal⁷

<https://pmc.ncbi.nlm.nih.gov/articles/PMC12646629/pdf/APT-62-1089.pdf>

- Weight loss is associated with greater fibrosis improvement, but does not explain resmetirom's treatment effect on fibrosis

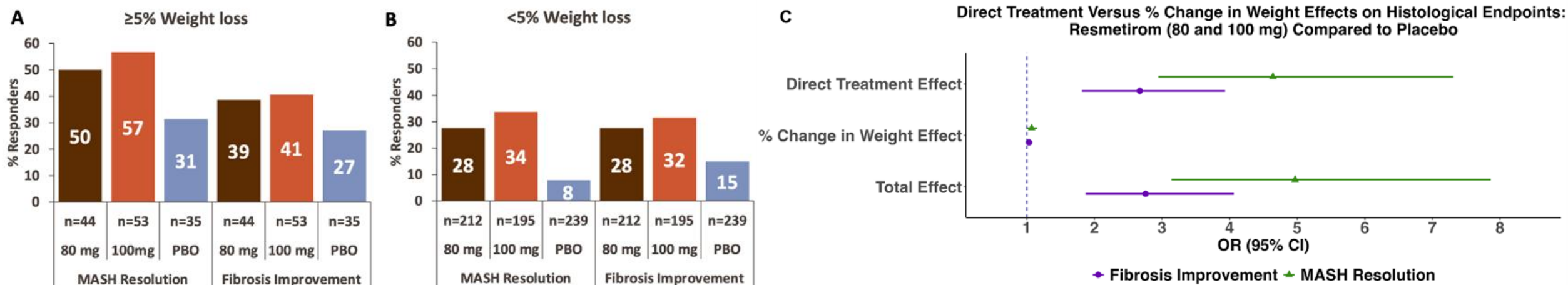
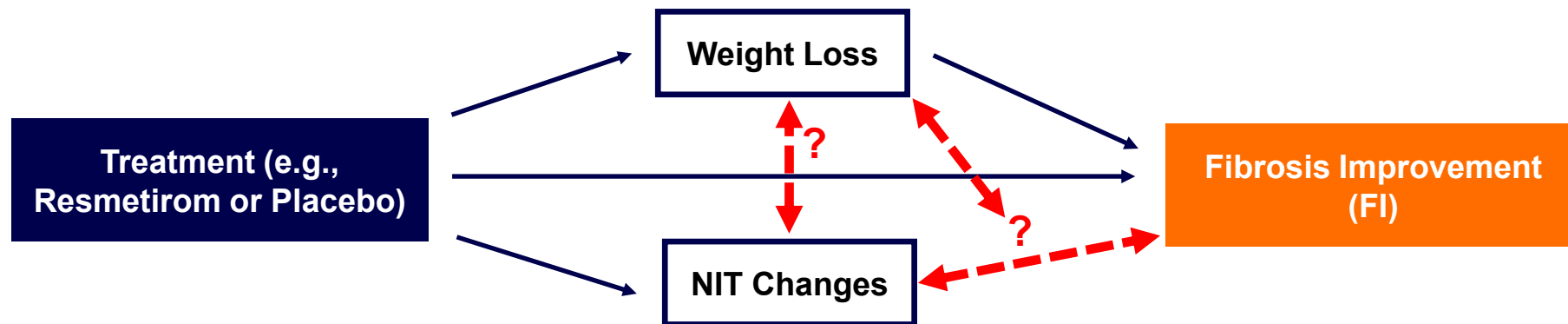


FIGURE 3 | MASH resolution with no worsening of fibrosis and fibrosis improvement (reduction by at least one stage with no worsening of MASH) in patients with (A) or without (B) $\geq 5\%$ weight loss, and mediation analysis: Odds ratios (OR) with 95% confidence intervals for the total effect of resmetirom versus placebo, as well as the direct treatment effect and the indirect effect mediated through the percent change in weight at Week 52 on both MASH resolution and fibrosis improvement (C). CI, confidence interval; OR, odds ratio; Pbo, placebo.

Weight Loss as a Potential Effect Modifier

Effect Modifier

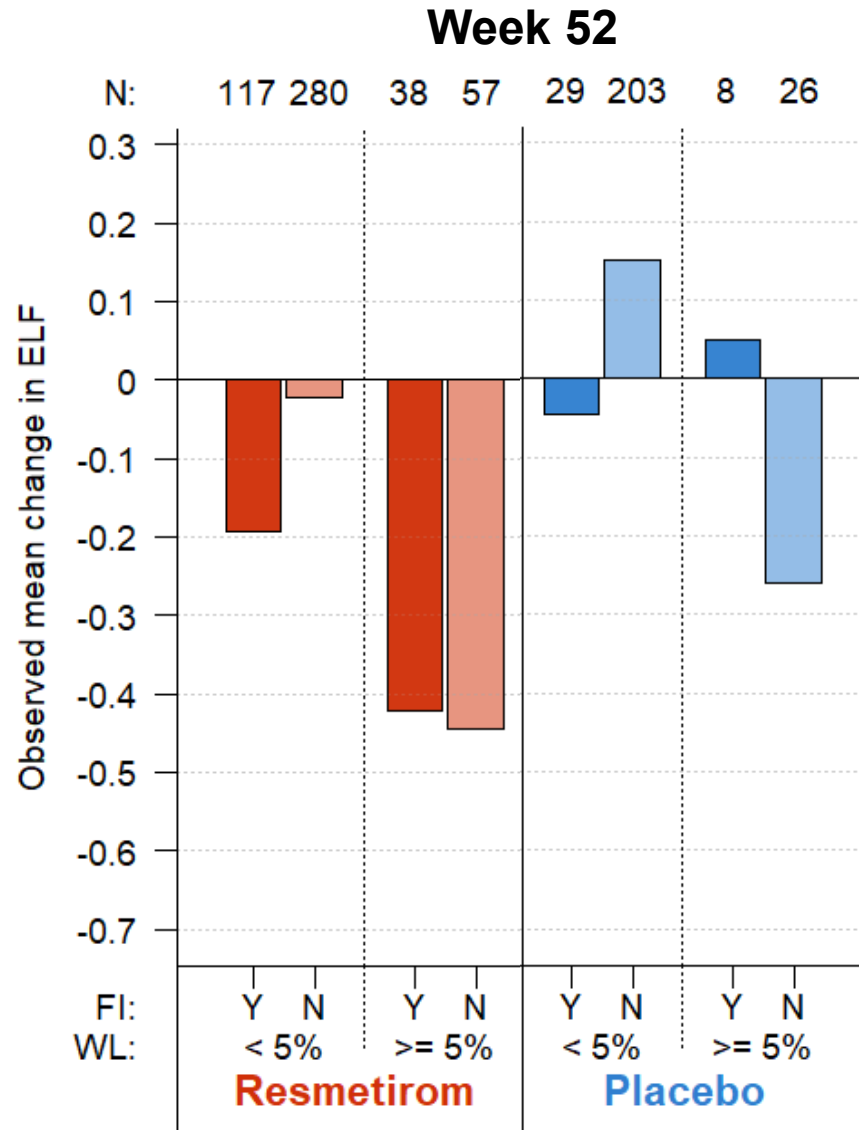
Changes how *strongly* one thing is related to another; the relationship *differs* depending on the modifier



Treatment with a drug can cause changes in non-invasive tests (NITs) that may or may not reflect FI
Weight loss may also be associated with NIT changes – and may **MODIFY** the relationship between those NIT changes and fibrosis improvement

- We further evaluate these associations – and whether weight loss modifies the NIT change–FI relationship – using linear and logistic regression models

Observed mean changes in ELF at Week 52 by treatment group, weight loss (WL) and fibrosis improvement (FI)

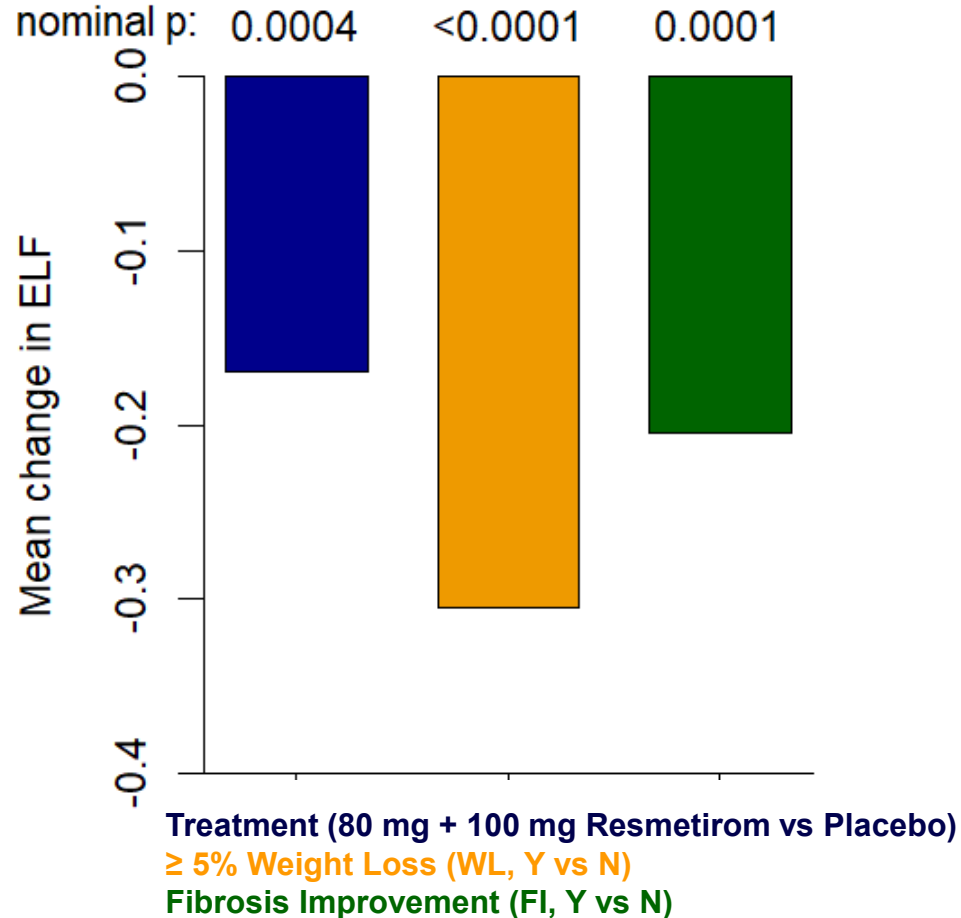


Data subgrouped by treatment (resmetirom vs placebo), weight loss (WL, < / ≥ 5%) and fibrosis improvement (FI, yes / no)

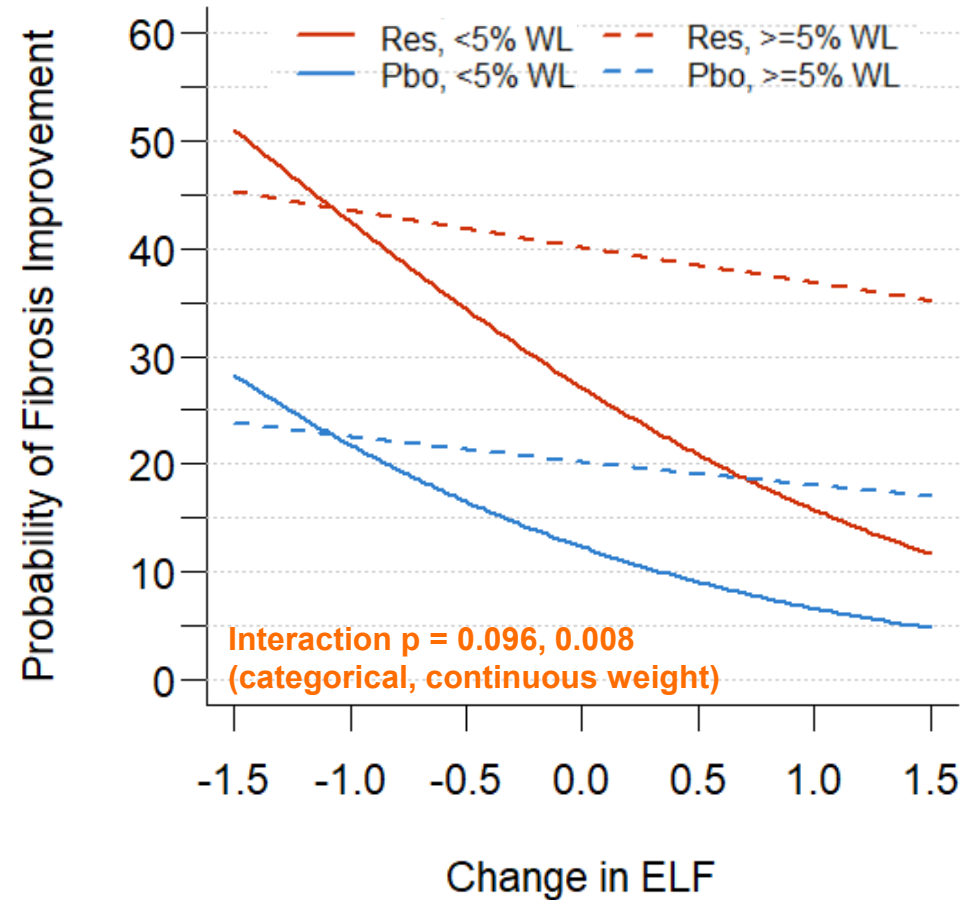
- Mean reductions in ELF are larger in patients who received resmetirom vs placebo
- Mean reductions in ELF are larger in the subgroup of patients with ≥ 5% WL vs < 5% (for both resmetirom and placebo groups)
- In subgroup of patients with < 5% WL, mean reductions in ELF are larger for those who had FI vs those who did not have FI (for both resmetirom and placebo groups)
- In the subgroup of resmetirom treated patients with ≥ 5% WL, mean reduction in ELF is similar for those who did and did not have FI
- In the subgroup of placebo treated patients with ≥ 5% WL, mean reduction in ELF is larger for those who did not have FI

Linear and logistic regression model fits: ELF changes at Week 52

Linear regression results: Are there independent associations with ELF changes?



Logistic regression results: Does weight loss modify the relationship between ELF changes and FI?

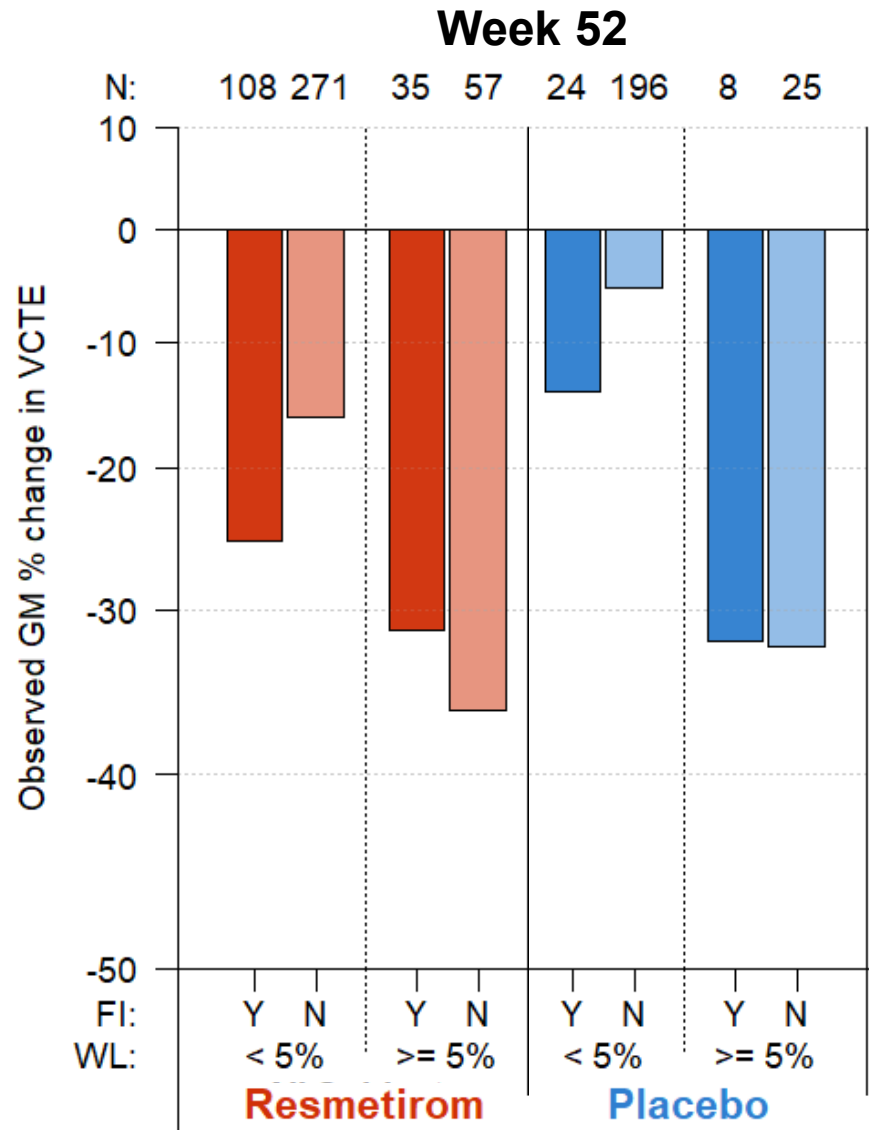


Effects estimated by multivariable regression using complete Baseline and Week 52 weight, ELF, and fibrosis data

Linear regression: $\Delta \text{ELF} \sim \text{Treatment} + \text{Baseline ELF} + \text{Baseline Weight} + \geq 5\% \text{ WL} + \text{FI}$

Logistic regression: $\text{Prob}(\text{FI}) \sim \text{Treatment} + \text{Baseline ELF} + \text{Baseline Weight} + \Delta \text{ELF} + \geq 5\% \text{ WL} + (\Delta \text{ELF} \times \geq 5\% \text{ WL})$

Observed mean changes in VCTE at Week 52 by treatment group, weight loss (WL) and fibrosis improvement (FI)

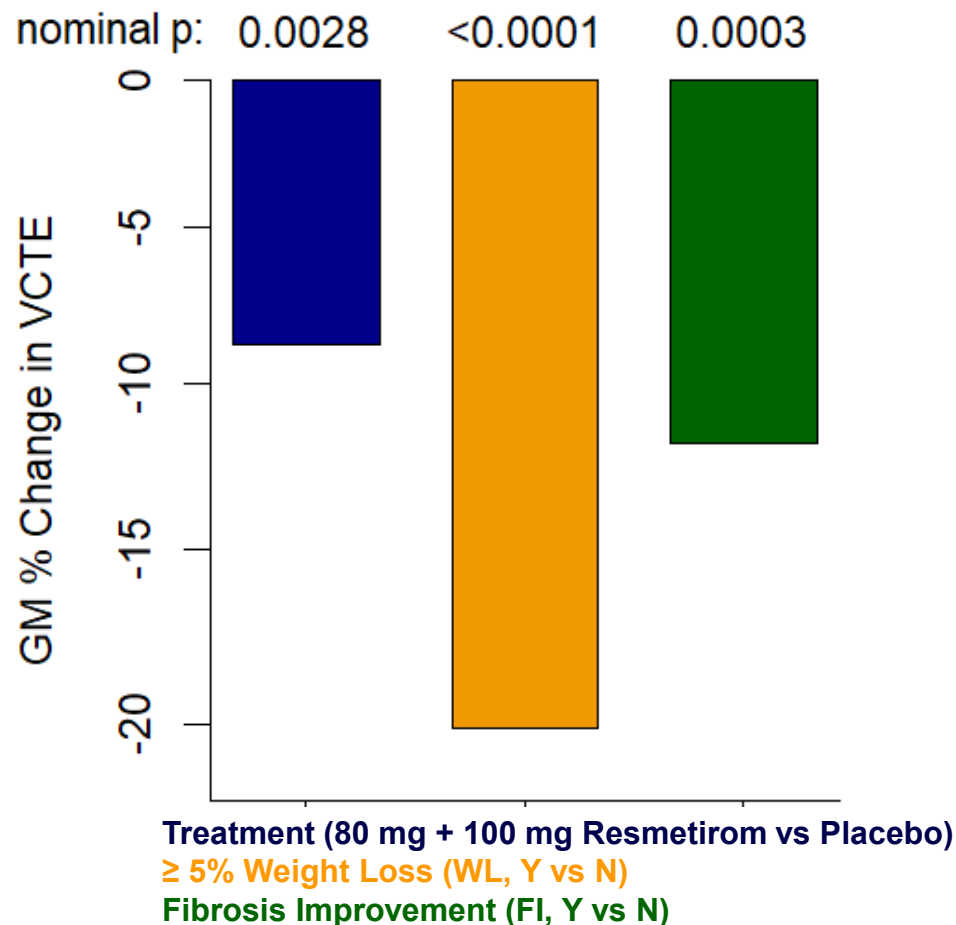


Data subgrouped by treatment (resmetirom vs placebo), weight loss (WL, < / ≥ 5%) and fibrosis improvement (FI, yes / no)

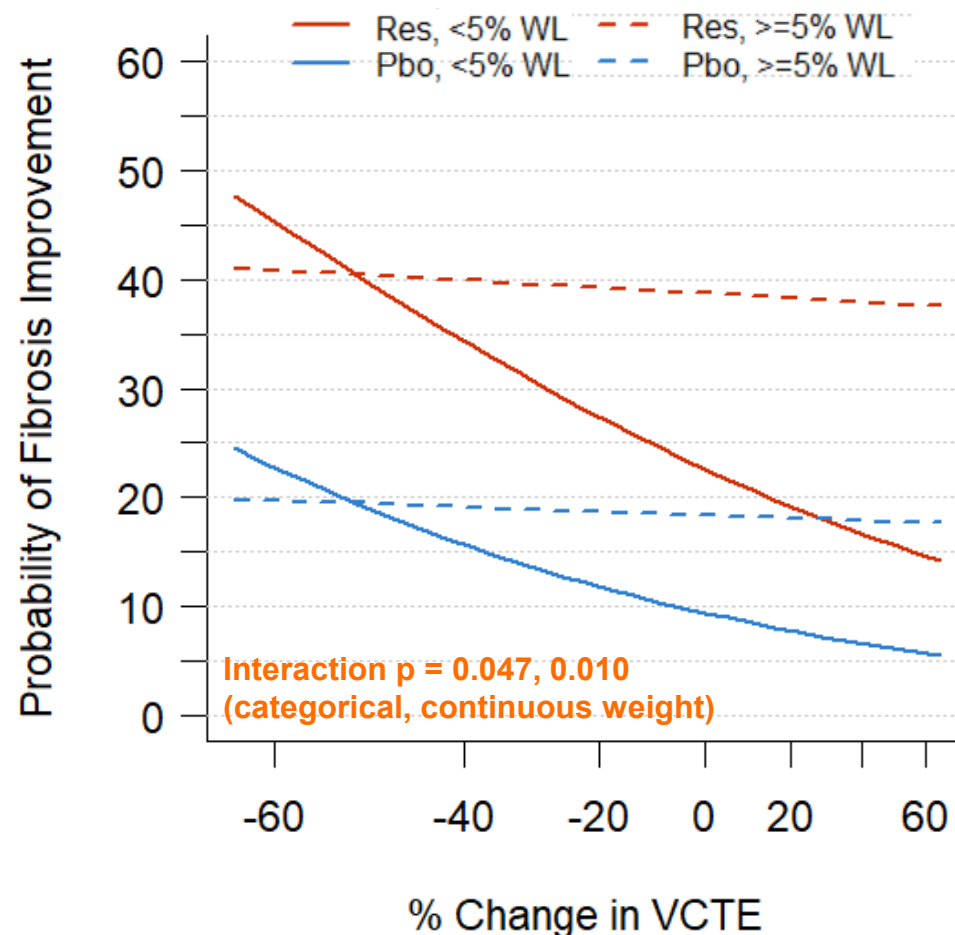
- Geometric mean (GM) % reductions in VCTE are larger in patients who received resmetirom vs placebo
- GM % reductions in VCTE are larger in the subgroup of patients with ≥ 5% WL vs < 5% (for both resmetirom and placebo groups)
- In subgroup of patients with < 5% WL, GM % reductions in VCTE are larger for those who had FI vs those who did not have FI (for both resmetirom and placebo groups)
- In the subgroup of patients with ≥ 5% WL, GM % reduction in VCTE is similar for those who did and did not have FI (for both resmetirom and placebo groups)

Linear and logistic regression model fits: VCTE changes at Week 52

Linear regression results: Are there independent associations with VCTE changes?



Logistic regression results: Does weight loss modify the relationship between VCTE changes and FI?



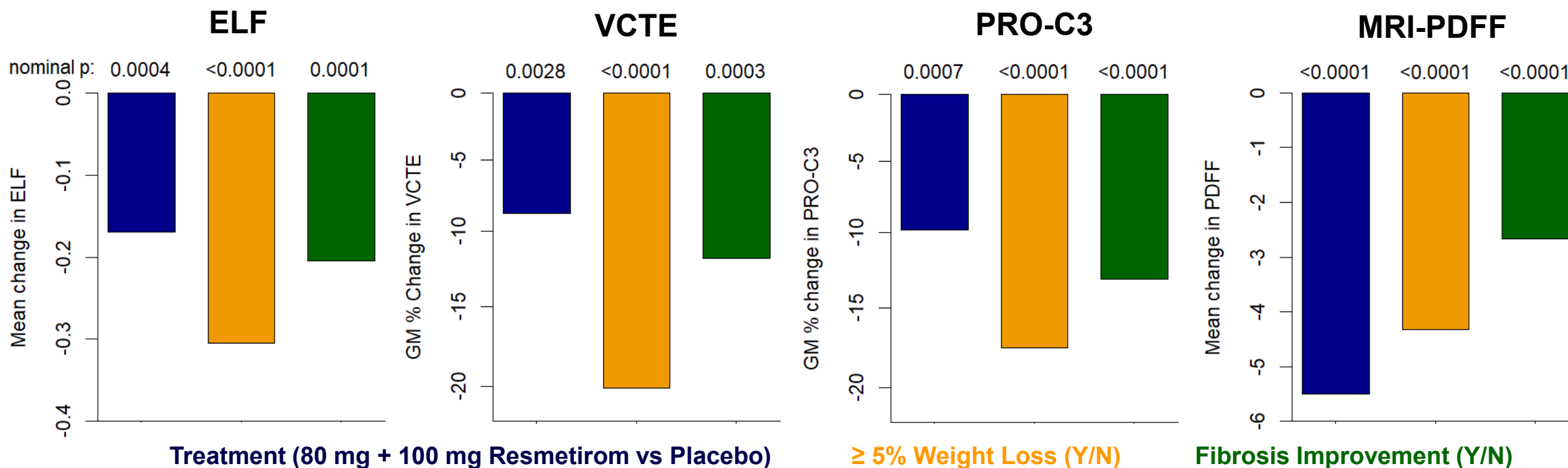
Effects estimated by multivariable regression using complete Baseline and Week 52 weight, VCTE, and fibrosis data

Linear regression: $\% \Delta \text{VCTE} \sim \text{Treatment} + \text{Baseline VCTE} + \text{Baseline Weight} + \geq 5\% \text{ WL} + \text{FI}$

Logistic regression: $\text{Prob}(\text{FI}) \sim \text{Treatment} + \text{Baseline VCTE} + \text{Baseline Weight} + \% \Delta \text{VCTE} + \geq 5\% \text{ WL} + (\% \Delta \text{VCTE} \times \geq 5\% \text{ WL})$

“Interaction term” allows the VCTE–FI association to differ by WL category

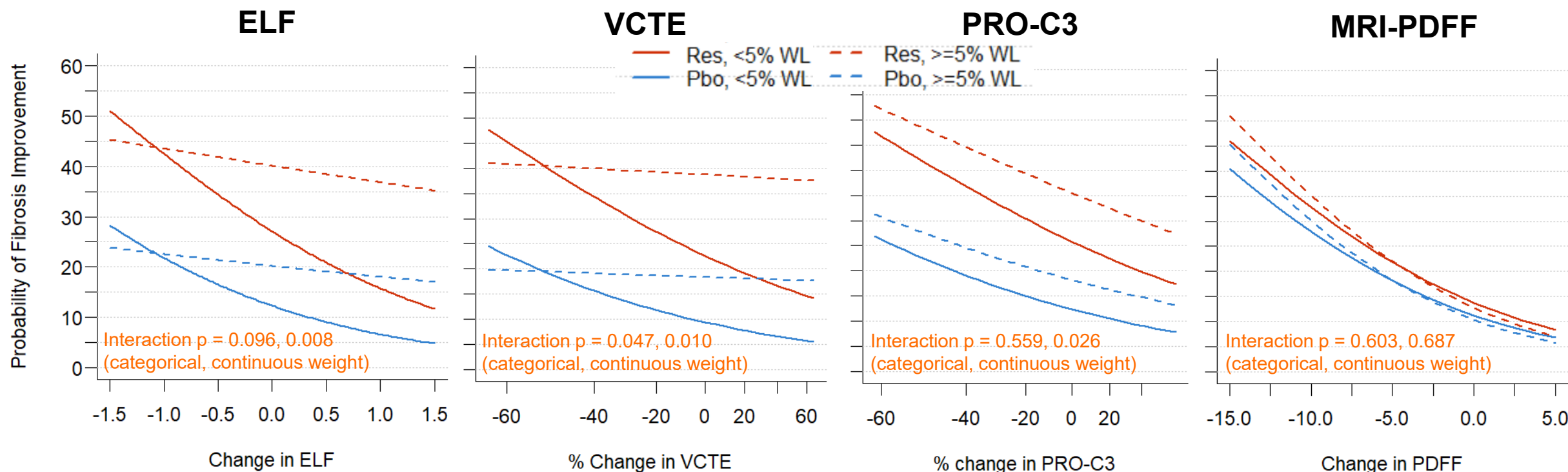
Resmetirom treatment, weight loss, and fibrosis improvement are independently associated with NIT changes in MAESTRO-NASH



** Effects estimated by multivariable linear regression using complete Baseline and Week 52 weight, biomarker, and fibrosis data:
 $\Delta \text{Biomarker} \sim \text{Treatment} + \text{Baseline Biomarker} + \text{Baseline Weight} + \geq 5\% \text{ Weight Loss} + \text{Fibrosis Improvement}$

- Resmetirom treatment, weight loss and fibrosis improvement are each independently associated with changes in ELF, VCTE, PRO-C3, and MRI-PDFF
- Across all evaluated biomarkers, weight loss is more strongly associated with NIT changes than fibrosis improvement – even when both are included in the same model

Exploring weight loss as a modifier of NIT-fibrosis improvement relationships in MAESTRO-NASH



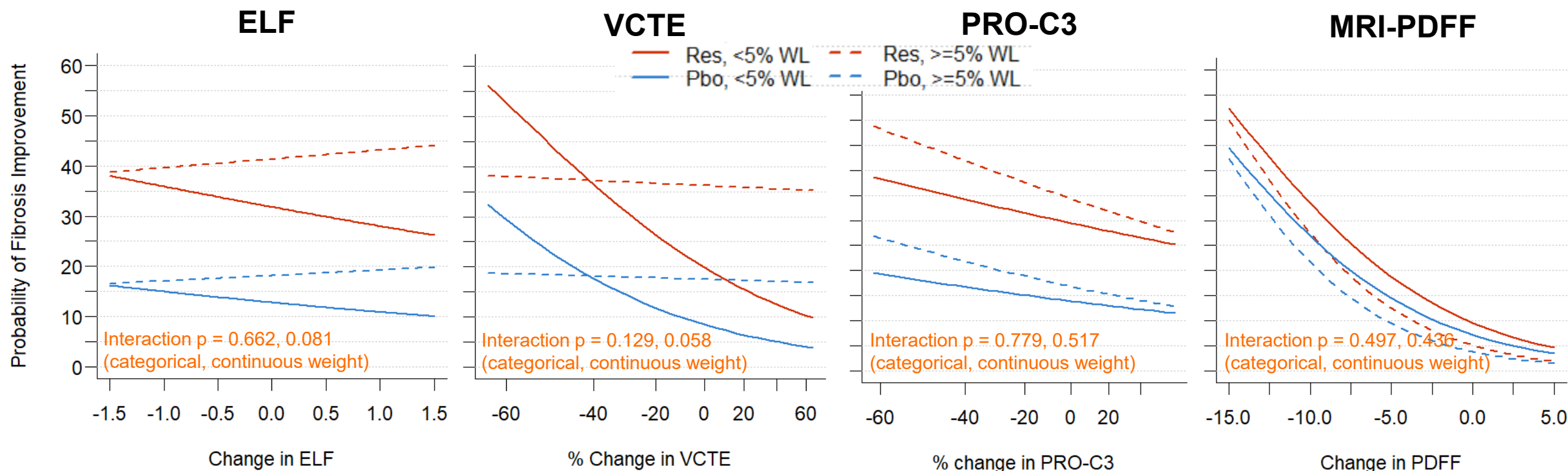
** Associations estimated by multivariable logistic regression using complete Baseline and Week 52 weight, biomarker, and fibrosis data:
 $\text{Prob}(\text{Fibrosis Improvement}) \sim \text{Treatment} + \text{Baseline Biomarker} + \text{Baseline Weight} + \Delta \text{Biomarker} + \geq 5\% \text{ Weight Loss} +$

$(\Delta \text{Biomarker} \times \geq 5\% \text{ Weight Loss})$

“Interaction term” allows the biomarker – fibrosis association to differ by weight loss category

- Weight loss appears to modify the associations between ELF, VCTE and PRO-C3 changes with fibrosis improvement; MRI-PDFF minimally impacted

Exploring weight loss as a modifier of NIT-fibrosis improvement relationships in MAESTRO-NASH F2 patients



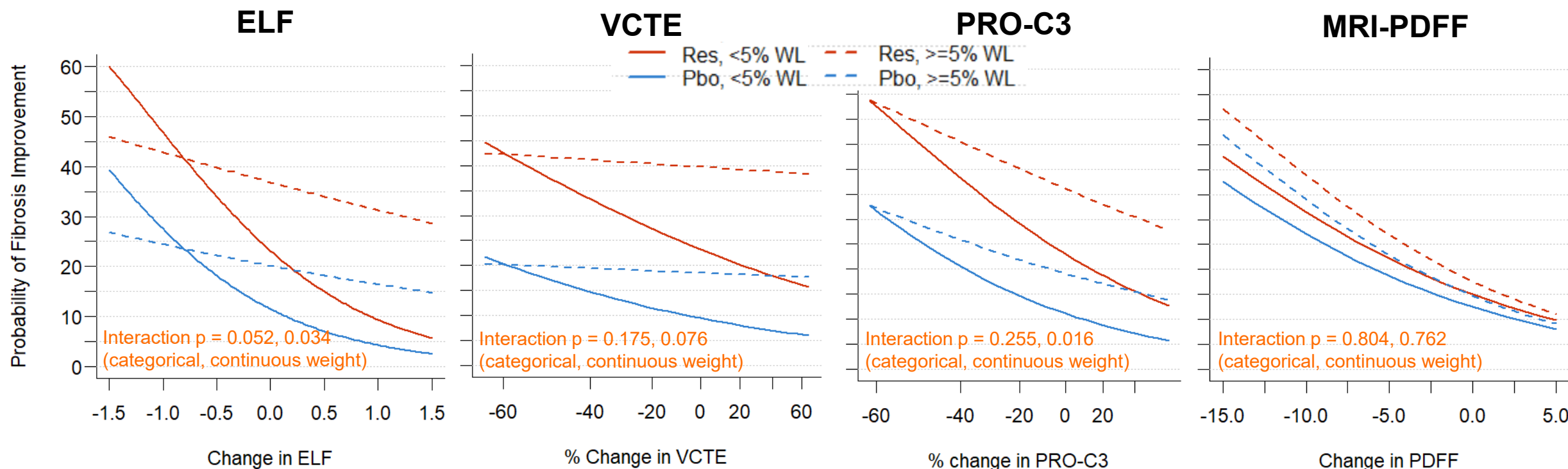
** Associations estimated by multivariable logistic regression using complete Baseline and Week 52 weight, biomarker, and fibrosis data:
 $\text{Prob}(\text{Fibrosis Improvement}) \sim \text{Treatment} + \text{Baseline Biomarker} + \text{Baseline Weight} + \Delta \text{Biomarker} + \geq 5\% \text{ Weight Loss} +$

$(\Delta \text{Biomarker} \times \geq 5\% \text{ Weight Loss})$

“Interaction term” allows the biomarker – fibrosis association to differ by weight loss category

- Weight loss appears to modify the association between VCTE changes with fibrosis improvement; VCTE associations stronger in F2 patients and ELF, PRO-C3 associations weaker; MRI-PDFF minimally impacted

Exploring weight loss as a modifier of NIT-fibrosis improvement relationships in MAESTRO-NASH F3 patients



** Associations estimated by multivariable logistic regression using complete Baseline and Week 52 weight, biomarker, and fibrosis data:
 $\text{Prob}(\text{Fibrosis Improvement}) \sim \text{Treatment} + \text{Baseline Biomarker} + \text{Baseline Weight} + \Delta \text{Biomarker} + \geq 5\% \text{ Weight Loss} +$

$(\Delta \text{Biomarker} \times \geq 5\% \text{ Weight Loss})$

“Interaction term” allows the biomarker – fibrosis association to differ by weight loss category

- Weight loss appears to modify the associations between ELF, VCTE and PRO-C3 changes with fibrosis improvement; ELF, PRO-C3 associations stronger in F3 patients; MRI-PDFF minimally impacted

Wrap-Up

- Resmetirom's effect on fibrosis improvement is largely independent of weight loss
- Weight loss nevertheless has a substantial, independent association with changes in multiple NITs
- For some NITs, weight loss also appears to modify how strongly NIT change is associated with fibrosis improvement
- Therefore, the interpretation of NIT change as a marker of fibrosis improvement may depend on the presence and magnitude of weight loss
- The NIT-fibrosis relationships, and their modification by weight loss, appear more pronounced for ELF and PRO-C3 in F3 patients than F2 patients
- These are secondary, hypothesis-generating analyses from MAESTRO-NASH