Madrigal analysis of multivariable NIT associations with fibrosis improvement in MAESTRO-NASH

Robin Mogg, PhD

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Disclosure

- Robin Mogg is a Madrigal employee

Overview

Background:

- In MASH trials, fibrosis improvement (FI) is assessed by serial liver biopsy based on a one stage improvement in fibrosis, as assessed by pathologists
- Non-invasive tests (NITs, e.g., VCTE, ELF, others) have been proposed as reasonably likely surrogate endpoints (RLSEs) for MASH trials as measures of liver fibrosis improvement
- Weight loss (WL) appears to modify the change in NIT-fibrosis relationship, with strong univariate associations observed in patients without WL (< 5% WL)

AIM: To explore which NIT changes are independently associated with fibrosis improvement when evaluated together in MAESTRO-NASH patients with < 5% weight loss, and whether these relationships differ by fibrosis stage

Methods:

- Changes in NITs and FI were examined at Week 52 in resmetirom and placebo treated patients with MASH, F2-F3 fibrosis and < 5% WL at Week 52 from the MAESTRO-NASH pivotal trial (~80% of overall population)
- Multivariable logistic regression models were used to explore associations

Resmetirom: Phase 3 Program, Pivotal Trial MAESTRO-NASH

KEY ELIGIBILITY CRITERIA

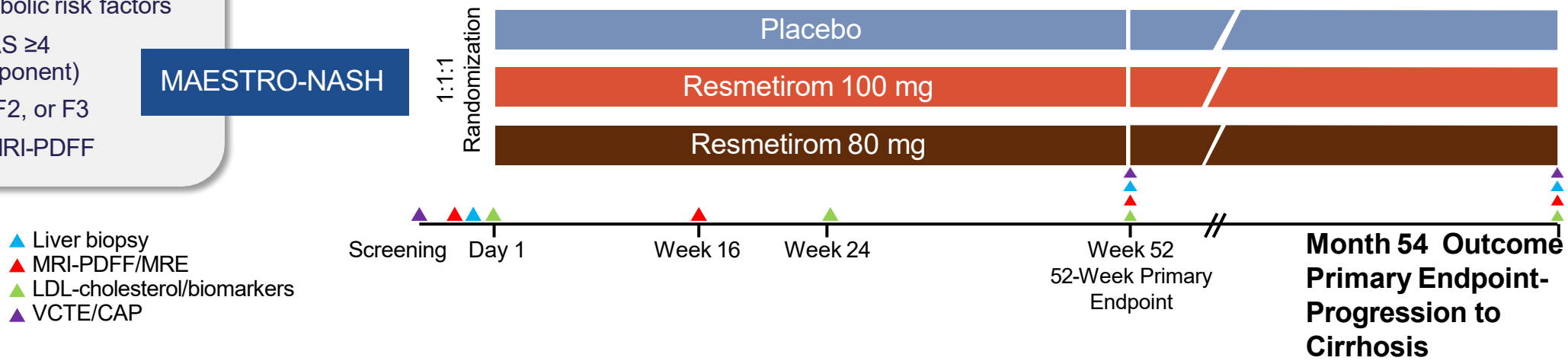
Presence of ≥3 metabolic risk factors

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

Fibrosis stage F1B, F2, or F3

≥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

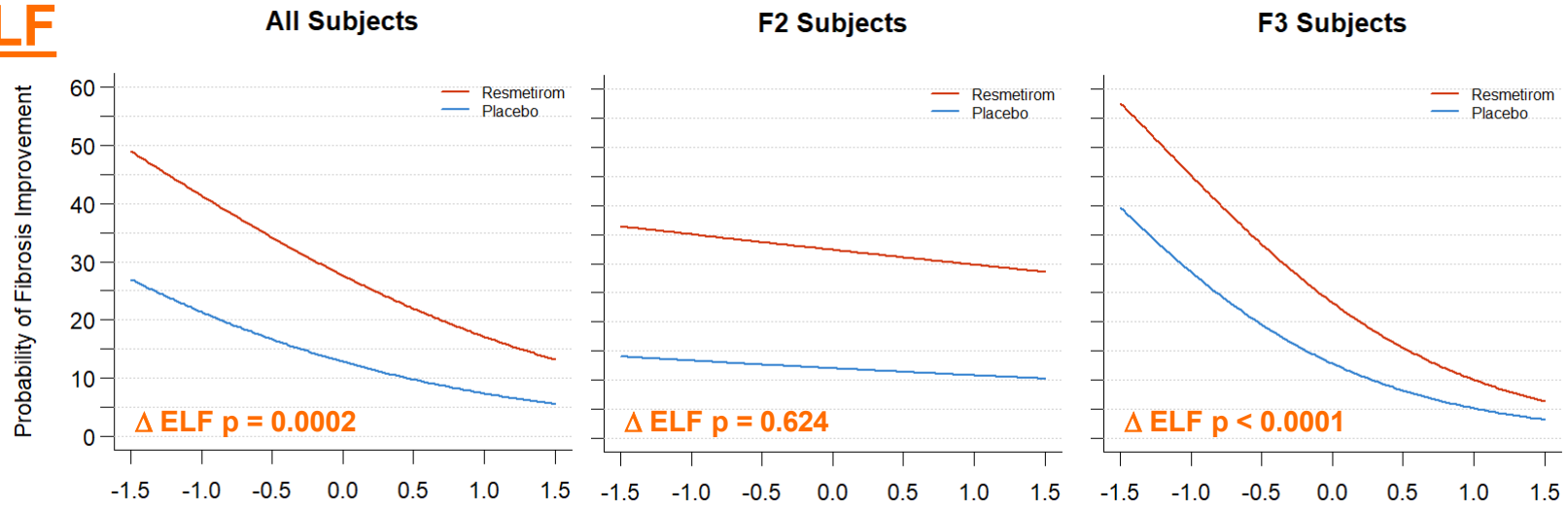
≥1-stage improvement in fibrosis with no worsening of NAS

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

Associations of individual NIT changes with fibrosis improvement (FI), in the subset of MAESTRO-NASH patients with < 5% weight loss

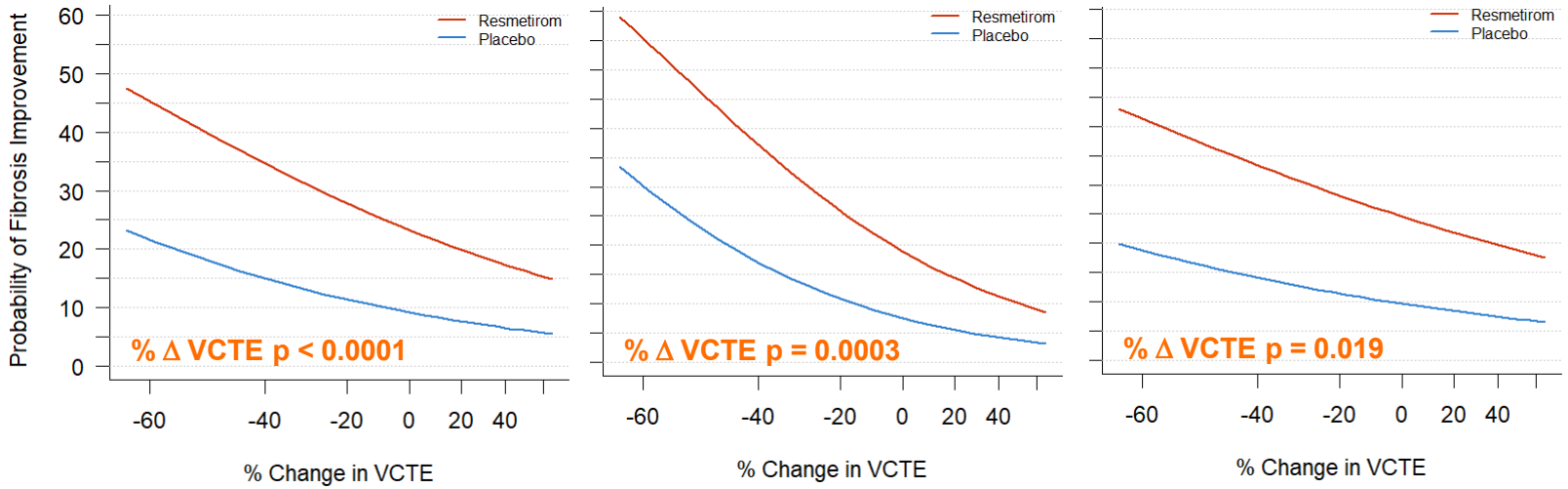
Associations of individual NIT changes with fibrosis improvement (FI) in patients with < 5% weight loss (WL): ELF, VCTE

ELF



Changes in ELF are strongly associated with FI in F3, no apparent association in F2

VCTE



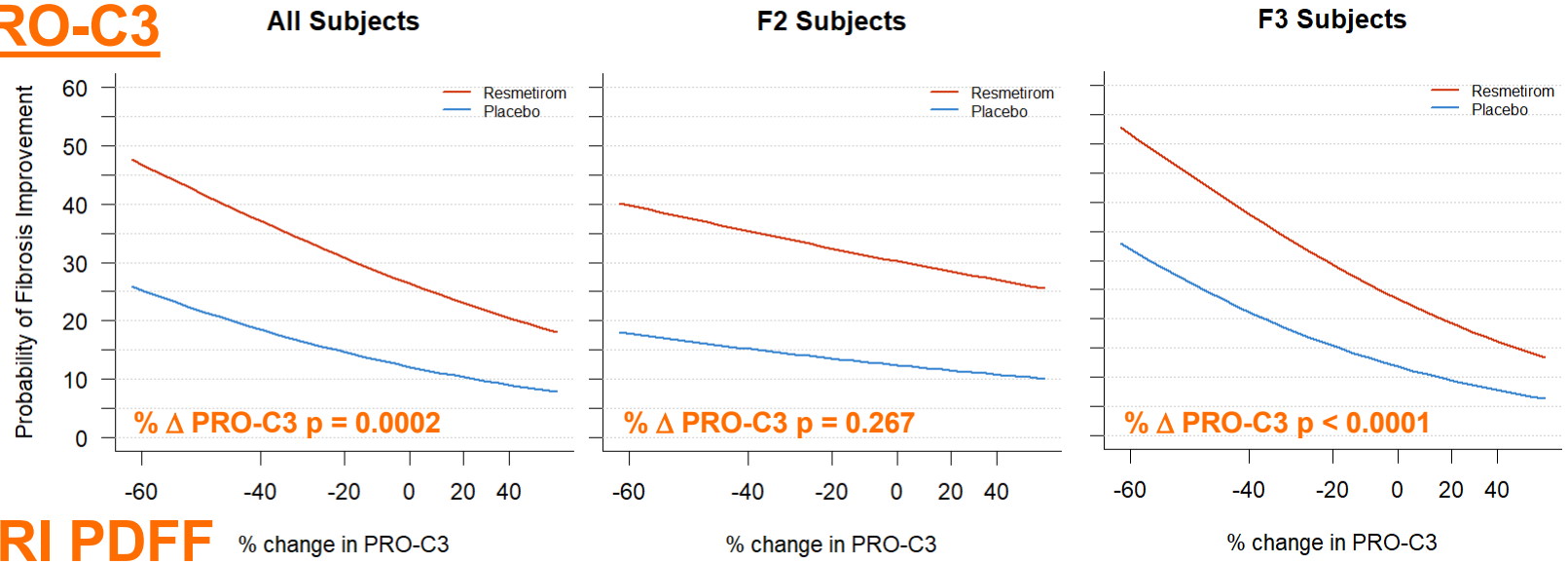
% changes in VCTE are strongly associated with FI in both F2 and F3

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker + Δ Biomarker

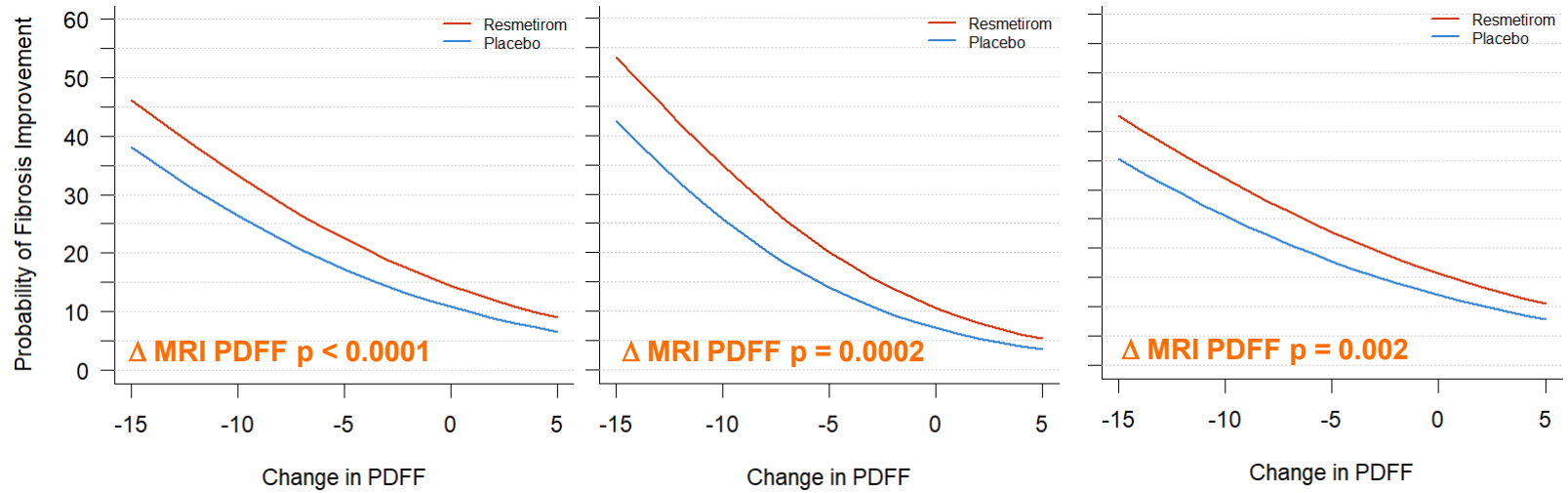
Associations of individual NIT changes with fibrosis improvement (FI) in patients with < 5% weight loss (WL): PRO-C3, MRI PDFF

PRO-C3



% changes in PRO-C3 are strongly associated with FI in F3, no clear association in F2

MRI PDFF



Changes in MRI PDFF are strongly associated with FI in both F2 and F3

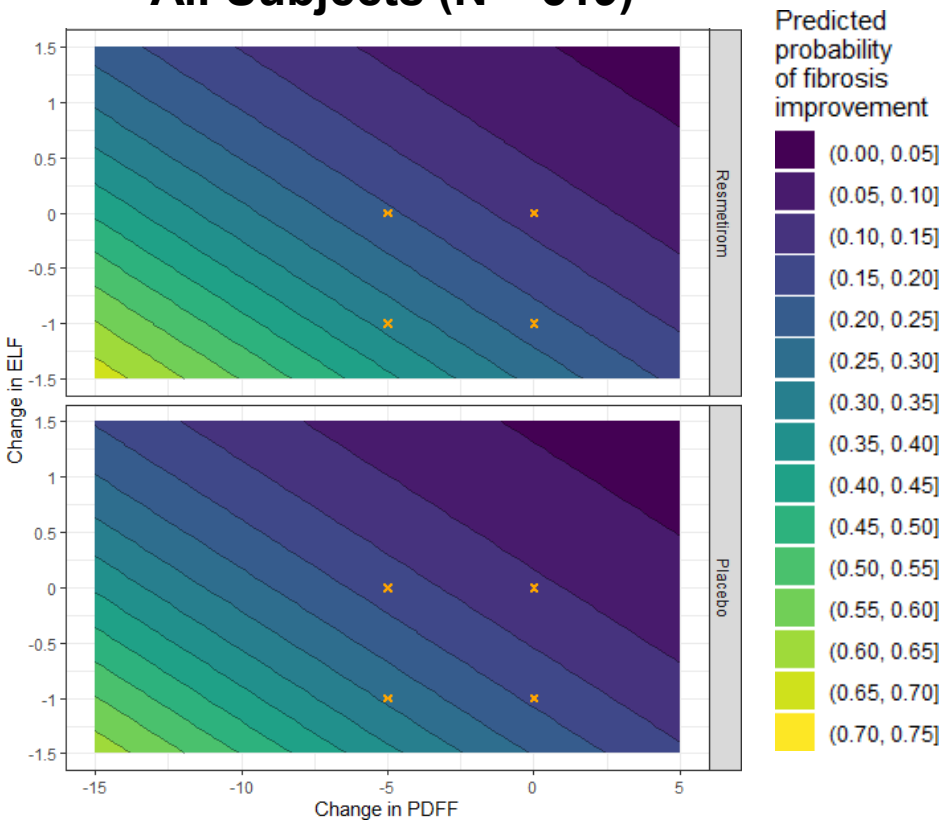
Effects estimated by multivariable logistic regression using complete Baseline and Week 52 weight, biomarker, and fibrosis data

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker + Δ Biomarker

Associations of pairwise NIT changes with fibrosis improvement (FI), in the subset of MAESTRO-NASH patients with < 5% weight loss

Associations of pairwise NIT changes with fibrosis improvement (FI): Δ MRI PDFF + Δ ELF (in subset of MAESTRO-NASH patients with < 5% weight loss)

All Subjects (N = 519)

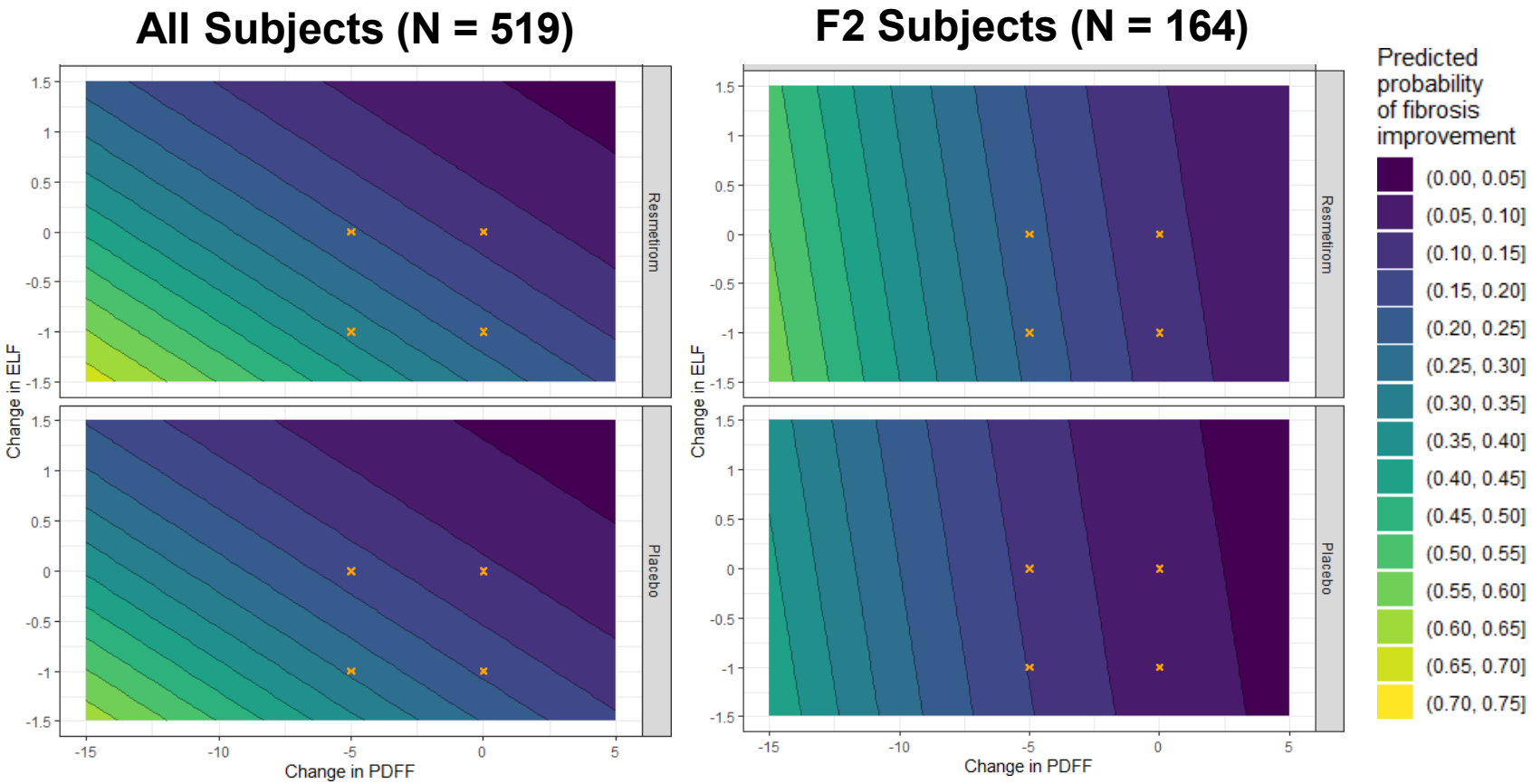


Nominal p-values	Treatment	Δ MRI PDFF	Δ ELF
All Subjects	0.490	< 0.0001	0.001

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI):
Δ MRI PDFF + Δ ELF (in subset of MAESTRO-NASH patients with < 5% weight loss)

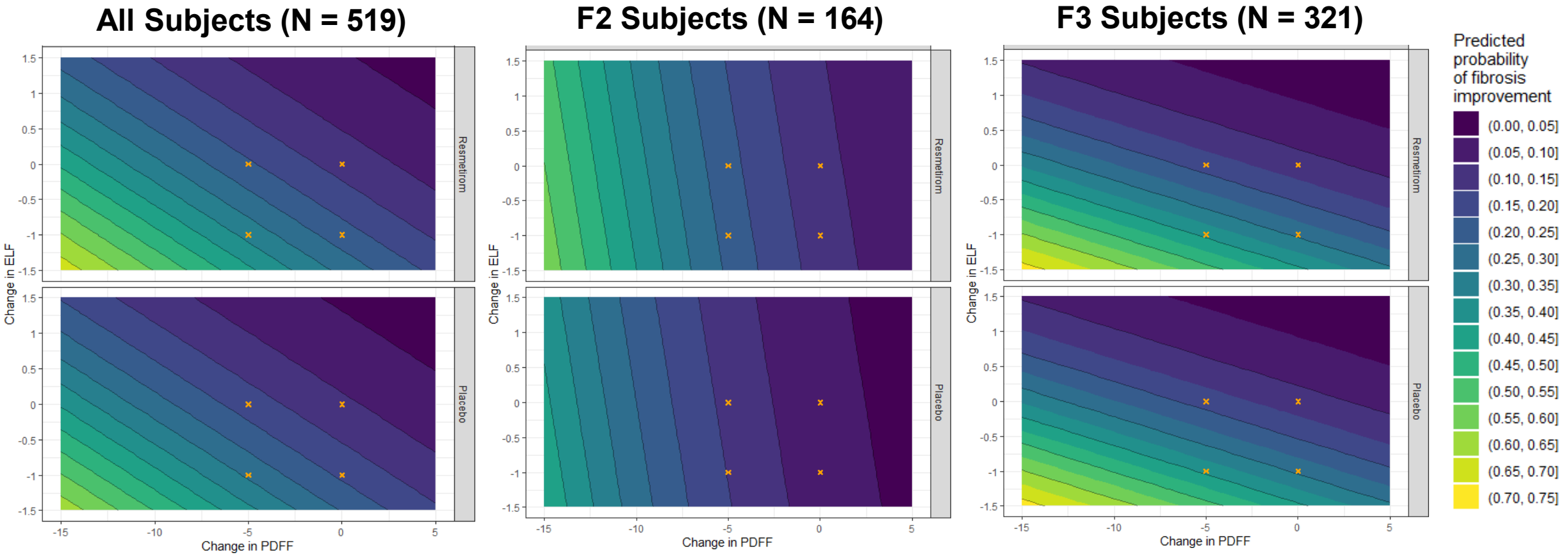


Nominal p-values	Treatment	Δ MRI PDFF	Δ ELF
All Subjects	0.490	< 0.0001	0.001
F2 Subjects	0.314	0.001	0.786

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI):
Δ MRI PDFF + Δ ELF (in subset of MAESTRO-NASH patients with < 5% weight loss)



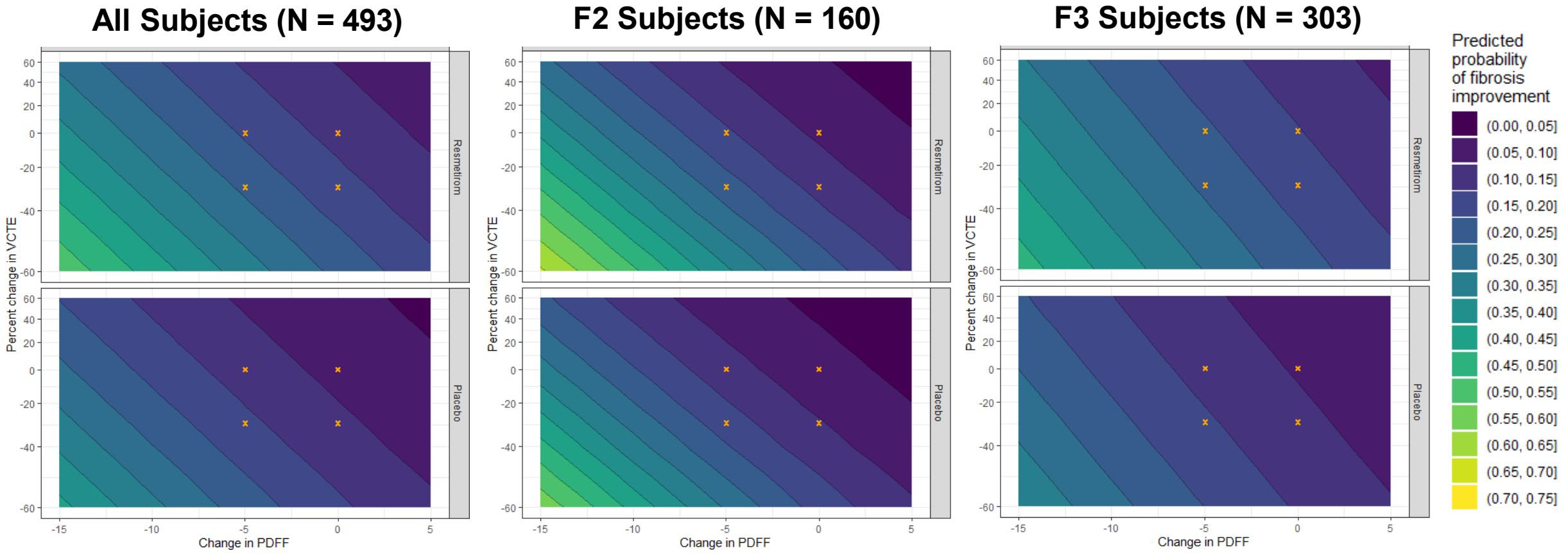
Nominal p-values	Treatment	Δ MRI PDFF	Δ ELF
All Subjects	0.490	< 0.0001	0.001
F2 Subjects	0.314	0.001	0.786
F3 Subjects	0.999	0.005	0.0001

MRI-PDFF remains independently associated with FI in both F2 and F3; ELF provides additional information primarily in F3

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI): Δ MRI PDFF + % Δ VCTE (in subset of MAESTRO-NASH patients with < 5% weight loss)



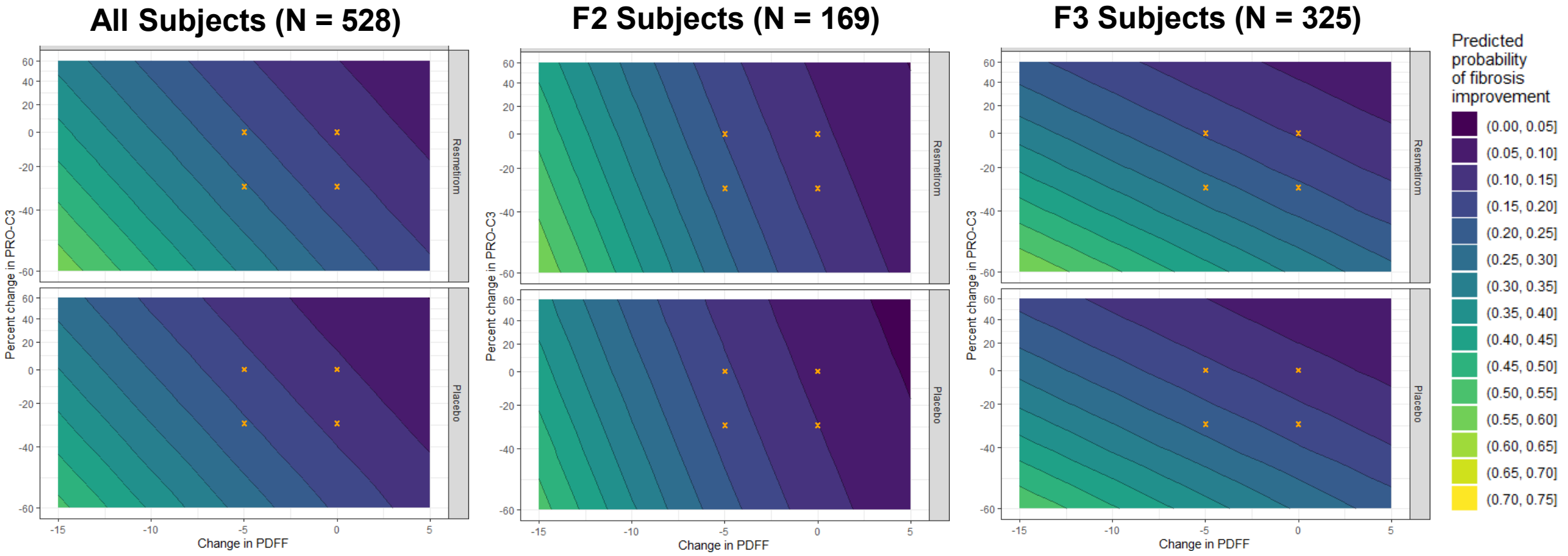
Nominal p-values	Treatment	Δ MRI PDFF	% Δ VCTE (log)
All Subjects	0.113	**0.0005**	**0.012**
F2 Subjects	0.593	**0.007**	**0.023**
F3 Subjects	0.178	**0.015**	0.189

MRI-PDFF and VCTE provide independent information overall; VCTE appears more informative in F2

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI): Δ MRI PDFF + % Δ PRO-C3 (in subset of MAESTRO-NASH patients with < 5% weight loss)



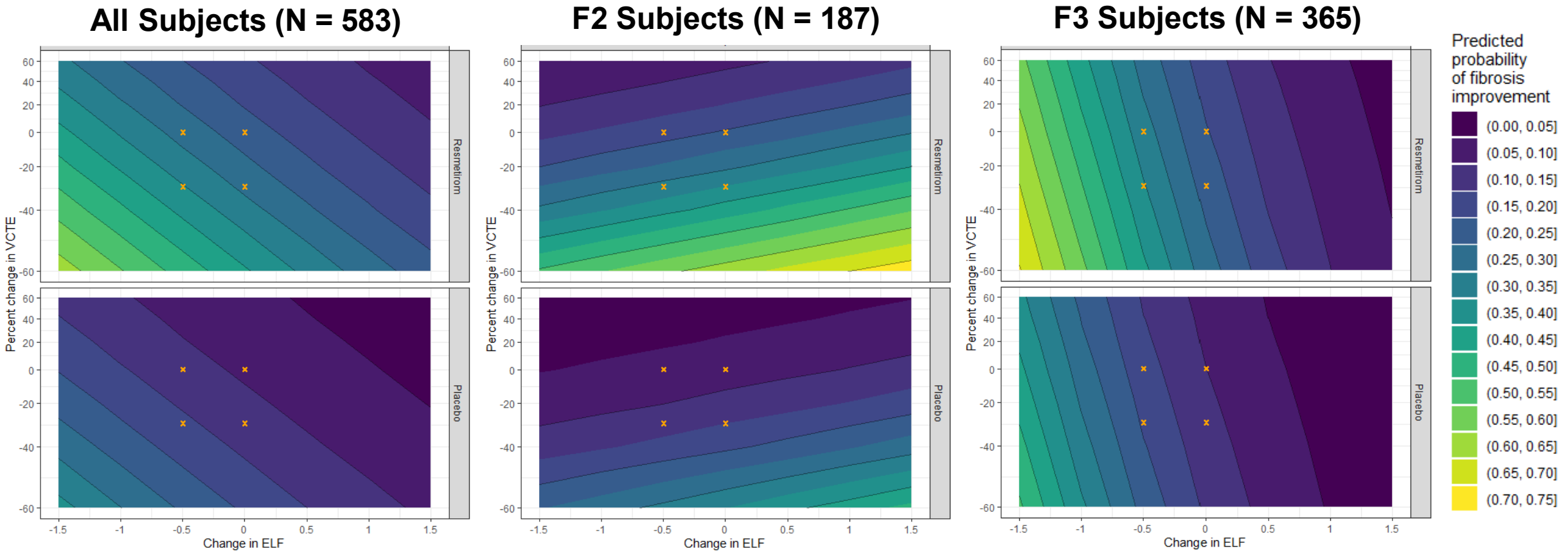
Nominal p-values	Treatment	Δ MRI PDFF	% Δ PRO-C3 (log)
All Subjects	0.342	< 0.0001	0.014
F2 Subjects	0.623	0.002	0.416
F3 Subjects	0.562	0.023	0.004

MRI-PDFF remains independently associated across stages; PRO-C3 provides additional information primarily in F3

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI): Δ ELF + % Δ VCTE (in subset of MAESTRO-NASH patients with < 5% weight loss)



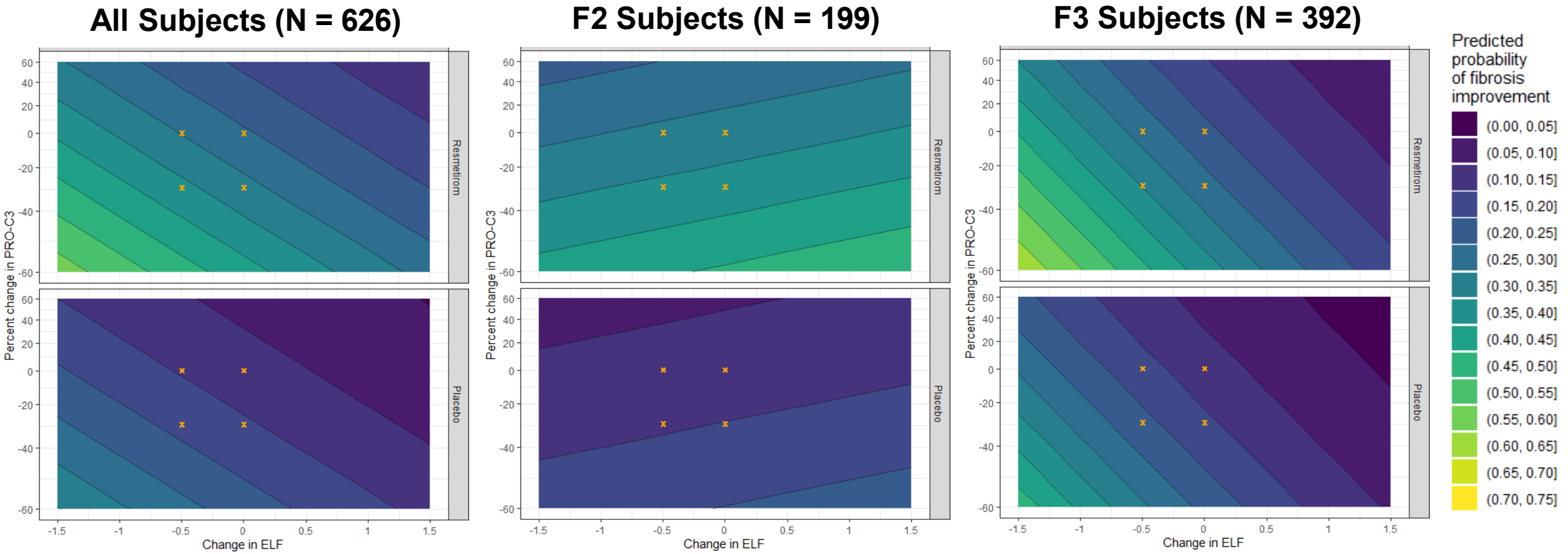
Nominal p-values	Treatment	Δ ELF	% Δ VCTE (log)
All Subjects	< 0.0001	0.002	0.001
F2 Subjects	0.009	0.314	0.0002
F3 Subjects	0.013	< 0.0001	0.261

VCTE appears more informative in F2, whereas ELF appears more informative in F3

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI): Δ ELF + % Δ PRO-C3 (in subset of MAESTRO-NASH patients with < 5% weight loss)



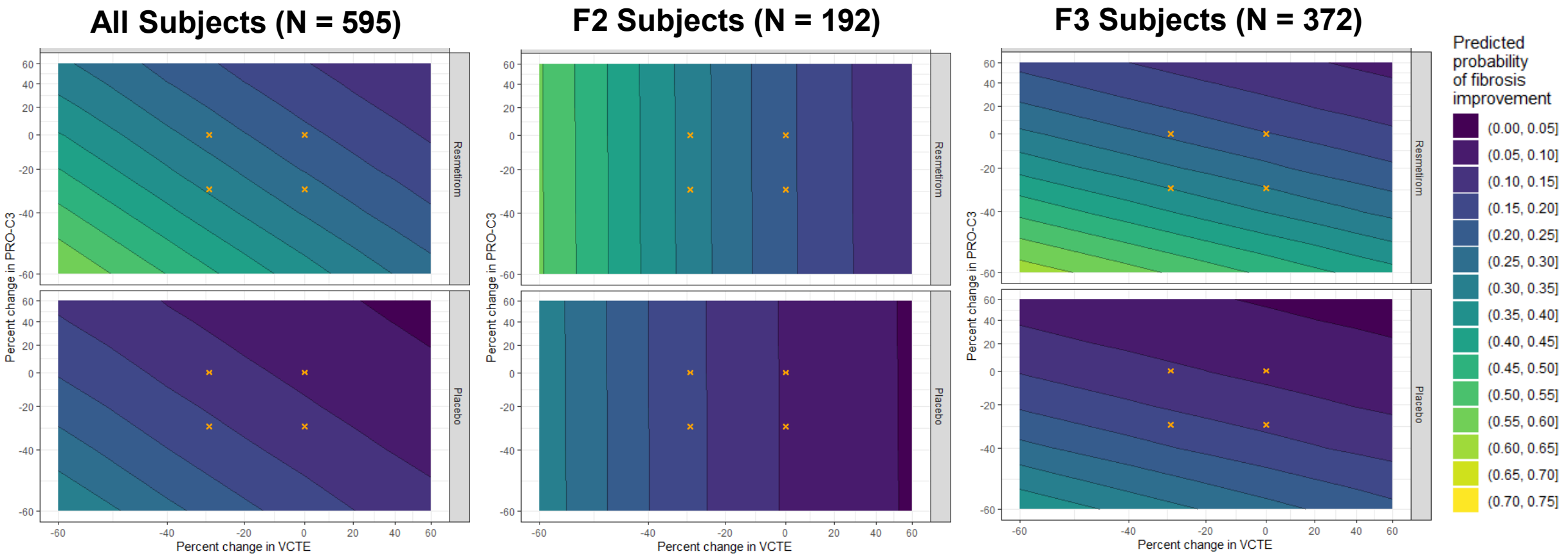
Nominal p-values	Treatment	Δ ELF	% Δ PRO-C3 (log)
All Subjects	0.0001	0.020	0.004
F2 Subjects	0.003	0.719	0.181
F3 Subjects	0.028	0.005	0.021

ELF and PRO-C3 provide independent information overall and in F3, but neither shows an independent association in F2

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

Associations of pairwise NIT changes with fibrosis improvement (FI): % Δ VCTE + % Δ PRO-C3 (in subset of MAESTRO-NASH patients with < 5% weight loss)



Nominal p-values	Treatment	% Δ VCTE (log)	% Δ PRO-C3 (log)
All Subjects	0.0001	0.0005	0.002
F2 Subjects	0.027	0.001	0.991
F3 Subjects	0.003	0.104	0.0001

VCTE appears more informative in F2, whereas PRO-C3 appears more informative in F3

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

Logistic regression: Prob(FI) ~ Treatment + Baseline Biomarker 1 + Δ Biomarker 1 + Baseline Biomarker 2 + Δ Biomarker 2

A qualitative synthesis of the strength of the association of changes in NITs with fibrosis improvement

	Overall	F2	F3
MRI PDFF	✓✓✓	✓✓✓	✓✓✓
VCTE	✓✓✓	**✓✓✓**	weaker
ELF	✓✓✓	weak	**✓✓✓**
PRO-C3	✓✓✓	weak	**✓✓✓**

Wrap-Up

In MAESTRO-NASH:

- Multiple NIT changes are independently associated with fibrosis improvement in patients with < 5% weight loss
- MRI PDFF provides information about FI across both F2 and F3 disease
- VCTE appears particularly informative in F2
- ELF and PRO-C3 provide stronger independent information in F3
- These findings suggest that the NITs providing information about fibrosis improvement may differ by fibrosis stage
- These are secondary, hypothesis-generating analyses from MAESTRO-NASH