

Supplemental Online Content

Vaccarino V, Alumuwaqqat Z, Kim JH, et al. Association of mental stress–induced myocardial ischemia with cardiovascular events in patients with coronary heart disease. *JAMA*. doi:10.1001/jama.2021.17649

eFigure 1. Flow chart for cohort construction

eFigure 2. Distribution of first and subsequent events for each of the study endpoints

eFigure 3. Cumulative incidence of the secondary study endpoint (cardiovascular death, MI, or hospitalizations for heart failure)

eFigure 4. Pooled estimates and plots for the association of mental stress–induced myocardial ischemia with the secondary endpoint of cardiovascular death, MI, or hospitalizations for heart failure

eFigure 5. Cumulative incidence of secondary study endpoint (cardiovascular death, MI, or hospitalizations for heart failure) for separate ischemia phenotypes in the pooled sample

eTable 1. Association of ischemia provoked by mental stress and by conventional (pharmacological or exercise) stress with the primary study endpoint in the pooled sample

eTable 2. Association of ischemia phenotypes with the primary and the secondary endpoints in the pooled sample

This supplemental material has been provided by the authors to give readers additional information about their work.

SUPPLEMENTAL MATERIAL

Supplemental Figures and Tables.

eFigure 1

Flow chart for cohort construction.

eFigure 2

Distribution of first and subsequent events for each of the study endpoints in the two study populations, by mental stress-induced myocardial ischemia status.

eFigure 3.

Cumulative incidence of the secondary study endpoint (cardiovascular death, MI, or hospitalizations for heart failure) in each of the two study populations, by mental stress-induced myocardial ischemia status. Because of the repeated events analysis, patients were removed from the risk set at each timepoint only if they died or were censored. In the Mental Stress Ischemia Prognosis Study, the median observation period was 72.3 (interquartile range, 70.2-72.3) months in patients with mental stress ischemia, and 72.3 (interquartile range, 67.8-72.3) months in patients without mental stress ischemia. In the Myocardial Infarction and Mental Stress Study, the median observation period was 56.7 (interquartile range, 46.0-68.7) months in patients with mental stress ischemia, and 55.5 (interquartile range, 46.2-63.4) months in patients without mental stress ischemia.

eFigure 4

Pooled estimates and plots for the association of mental stress induced myocardial ischemia with the secondary endpoint of cardiovascular death, MI, or hospitalizations for heart failure, overall and in subgroups. The two study populations were pooled using individual patient data meta-analysis. For the overall sample, both unadjusted and fully adjusted estimates are shown. For the subgroups, the estimates shown are unadjusted.

eFigure 5

Cumulative incidence of the secondary study endpoint (cardiovascular death, MI, or hospitalizations for heart failure) for separate ischemia phenotypes in the pooled sample. Because of the repeated events analysis, patients were removed from the risk set at each timepoint only if they died or were censored. The median observation period was 72.3 (interquartile range, 56.5-72.3) months in patients with both mental stress and conventional stress ischemia; 68.6 (interquartile range, 53.9-72.3) months in patients with mental stress ischemia only; 72.3 (interquartile range, 58.8-72.3) months in patients with conventional stress ischemia only; and 70.7 (interquartile range, 55.8-72.3) months in patients with no ischemia.

eTable 1

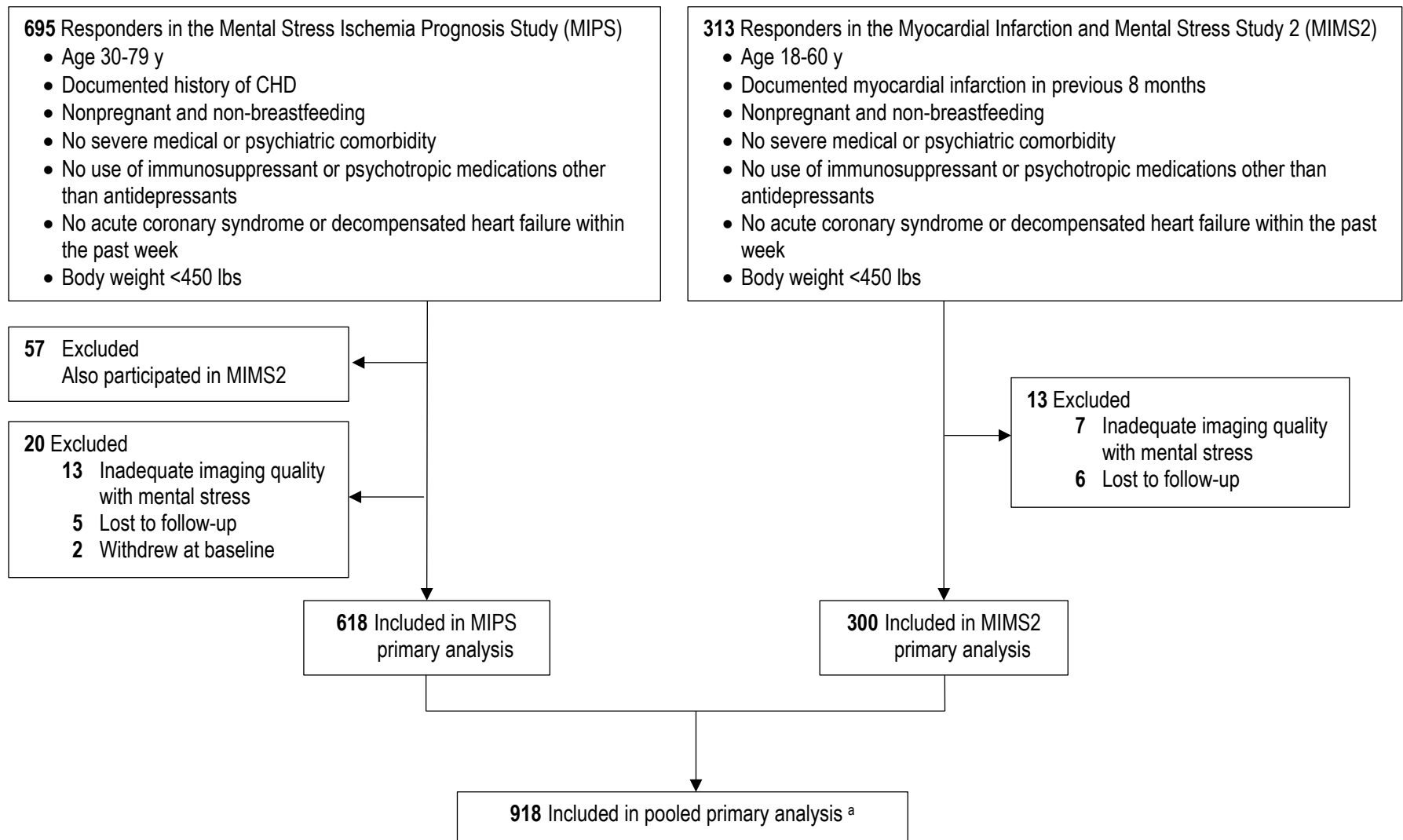
Association of ischemia provoked by mental stress and by conventional (pharmacological or exercise) stress with the primary study endpoint in the pooled sample, using the summed difference score (SDS) as a continuous variable and a cut point of ≥ 4 as a definition of ischemia.

eTable 2

Association of ischemia phenotypes with the primary and the secondary endpoints in the pooled sample.

eFigure 1

Flow chart for cohort construction.

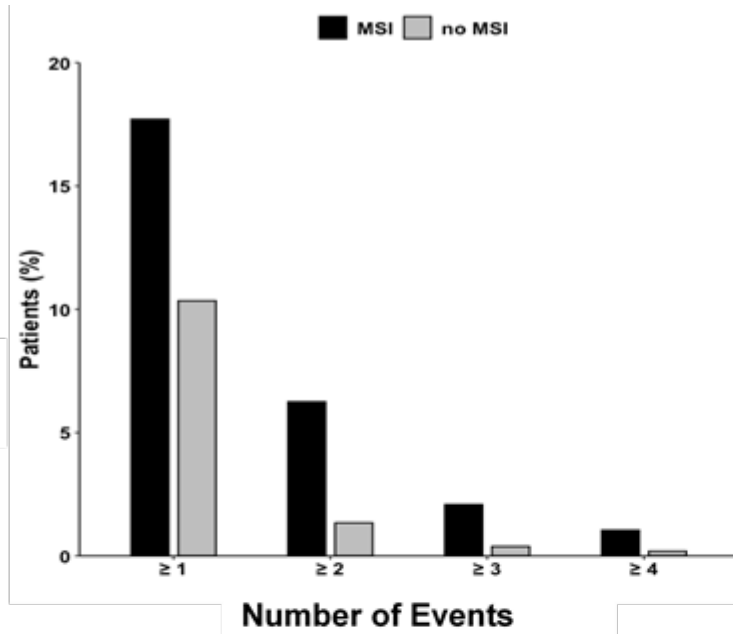


^a 19 patients with inadequate imaging quality with conventional stress where further excluded in analyses of conventional stress (N=899)

eFigure 2

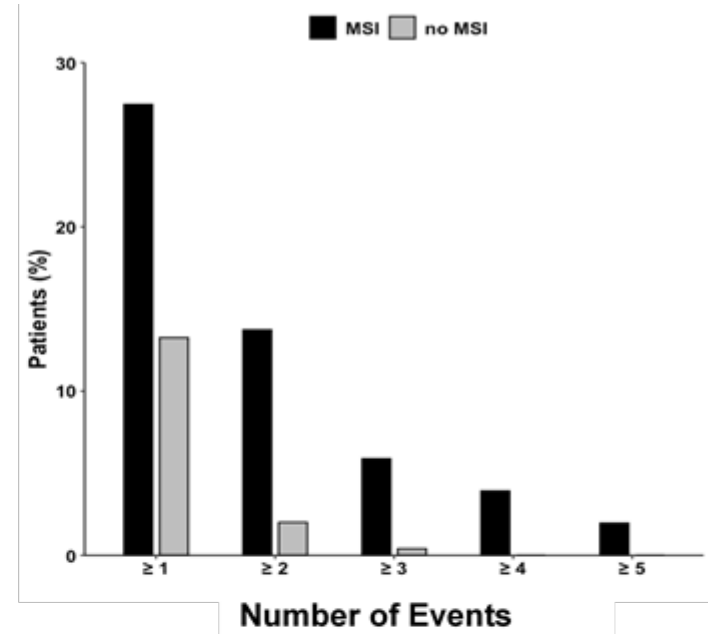
Distribution of first and subsequent events for each of the study endpoints in the two study populations, by mental stress-induced myocardial ischemia (MSI) status.

Mental Stress Ischemia Prognosis Study

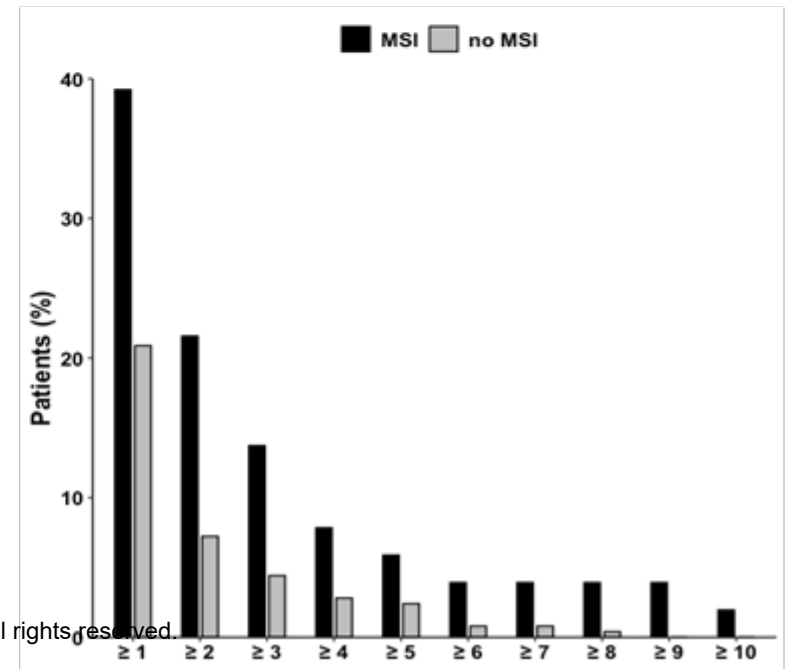
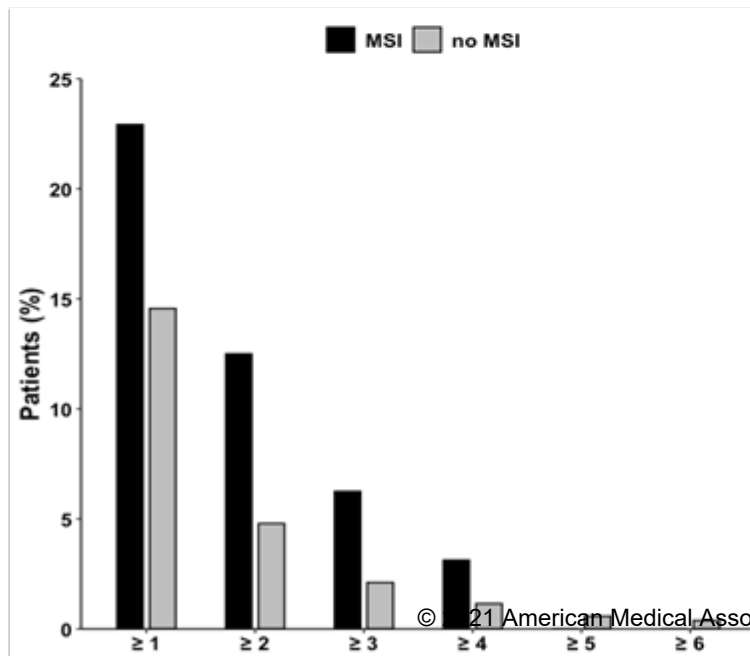


Cardiovascular
Death or MI

Myocardial Infarction and Mental Stress Study 2

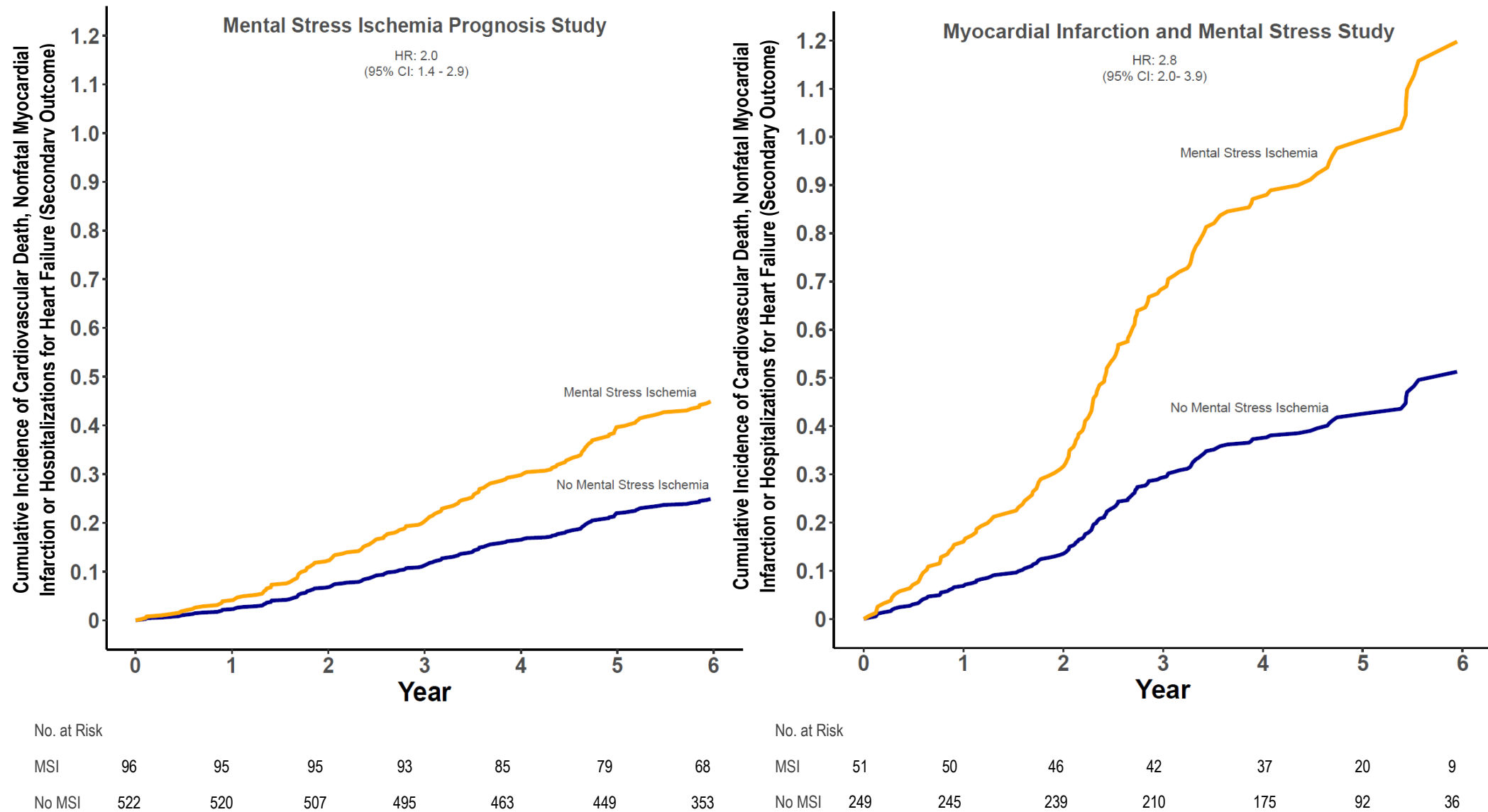


Cardiovascular
Death, MI or
Heart Failure

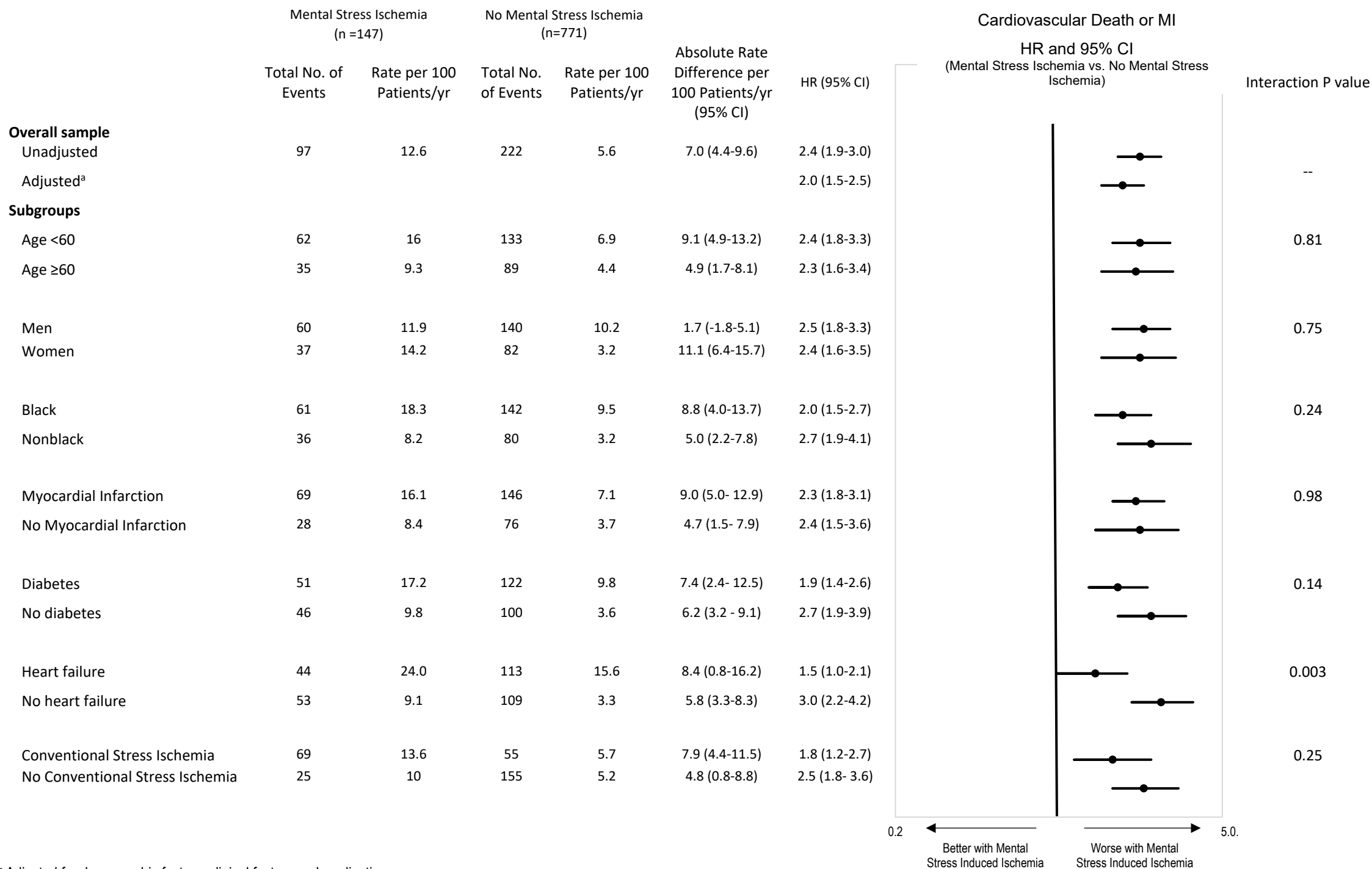


eFigure 3

Cumulative incidence of the secondary study endpoint (cardiovascular death, MI, or hospitalizations for heart failure) in each of the two study populations, by mental stress-induced myocardial ischemia (MSI) status. Because of the repeated events analysis, patients were removed from the risk set at each timepoint only if they died or were censored.



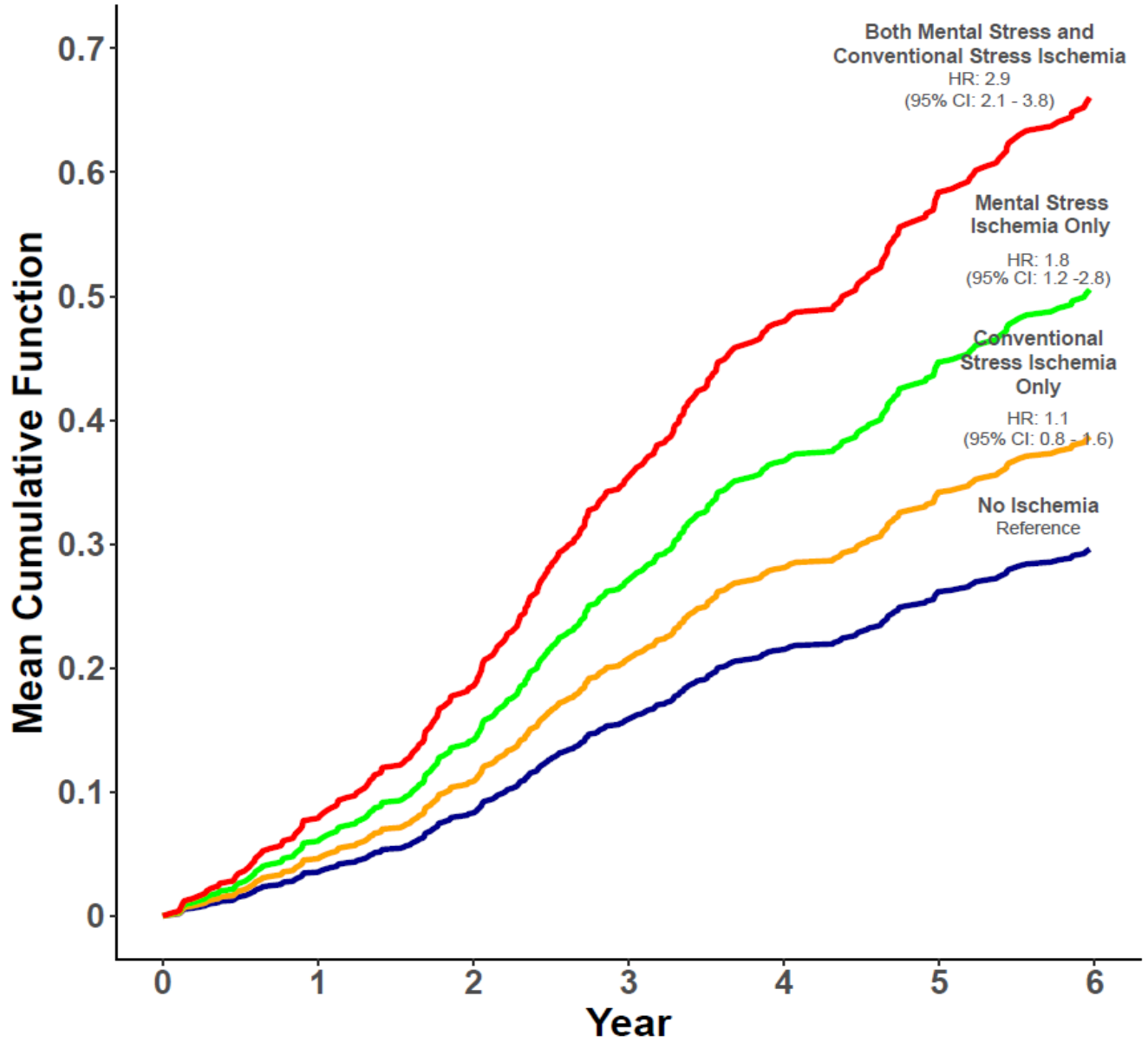
eFigure 4
Pooled estimates and plots for the association of mental stress induced myocardial ischemia with the secondary endpoint of cardiovascular death, MI, or hospitalizations for heart failure, overall and in subgroups.



^a Adjusted for demographic factors, clinical factors and medications.

eFigure 5

Cumulative incidence of the secondary study endpoint (cardiovascular death, MI, or hospitalizations for heart failure), for separate ischemia phenotypes in the pooled sample. Because of the repeated events analysis, patients were removed from the risk set at each timepoint only if they died or were censored.



No. at Risk

Both Mental Stress and Conventional Stress Ischemia	96	95	91	88	79	67	56
Mental Stress Ischemia Only	49	48	47	45	41	30	19
Conventional Stress Ischemia Only	185	184	180	172	158	137	102
No Ischemia	569	564	549	518	469	396	280

eTable 1

Association of ischemia provoked by mental stress and by conventional (pharmacological or exercise) stress with the primary study endpoint in the pooled sample, using the summed difference score as a continuous variable and a cut point of ≥ 4 as a definition of ischemia.

	CVD death or MI	
	Summed Difference Score, Per Score Point Increase	SDS ≥ 4 HR (95% CI)
Mental Stress Test (n=918)		
Unadjusted	1.15 (1.09, 1.21)	2.48 (1.69, 3.64)
Adjusted for demographic and clinical risk factors ^a	1.14 (1.08, 1.21)	2.29 (1.55, 3.38)
Conventional Stress Test (n=899)		
Unadjusted	1.07 (1.04, 1.10)	1.95 (1.40, 2.70)
Adjusted for demographic and clinical risk factors ^a	1.07 (1.04, 1.10)	1.84 (1.32, 2.57)

^a 4 patients were excluded due to missing values.

Demographic and clinical risk factors adjusted for in these models are the same as in models of Table 2.

Abbreviations:

SDS: Summed difference score

HR: Hazards ratio

CI: Confidence interval

CVD: cardiovascular disease

MI: Myocardial infarction

eTable 2

Association of ischemia phenotypes with the primary and the secondary endpoints in the pooled sample.

Ischemia Phenotype	Primary Outcome (CV Death/MI)			Secondary Outcome (CV Death/MI/HF)		
	Total No. of Events	Rate per 100 Patient/yr	HR (95%CI)	Total No. of Events	Rate per 100 Patient/yr	HR (95%CI)
No Ischemia	68	2.3	reference	155	5.3	reference
Only CSI	30	3.1	1.4 (0.9, 2.1)	55	5.6	1.1 (0.8, 1.6)
Only MSI	12	4.8	2.0 (1.1, 3.7)	25	10.0	1.8 (1.2, 2.8)
Both MSI and CSI	41	8.1	3.8 (2.6, 5.6)	69	13.7	2.9 (2.1, 3.8)

Abbreviations:

MSI: Mental stress-induced myocardial ischemia

CSI: Conventional stress-induced ischemia