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Relation of Age and Health-related Quality of Life to Invasive Versus Ischemia-guided Management of Patients with Non-ST Elevation Myocardial Infarction

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Abstract

In older patients with non ST-elevation myocardial infarction (NSTEMI), an initial invasive strategy reduces cardiovascular events compared to an ischemia-guided approach, however its association with health status outcomes is unknown. Among patients with NSTEMI from 2 multicenter US AMI registries, health status was assessed at baseline and at 1, 6 and 12 months after AMI using the Seattle Angina Questionnaire (SAQ) and Short Form-12 (SF-12). Routine invasive management was defined as coronary angiography within 72 hours of admission without a preceding stress test. Among 3559 patients with NSTEMI, 2455 (69.0%) were treated with routine invasive treatment, which was more common in younger patients. In propensity-adjusted analyses, invasive treatment was associated with higher SAQ physical limitation, angina frequency, and summary scores over the year following AMI, however the differences were small (<5 points, all $p < 0.05$). While there was a trend towards worse health status in patients aged 85 years treated with an initial invasive treatment, the interaction between age and treatment for any

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Drs. Patel and Spertus had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Patel, Arnold, Jones, Qintar, Alexander, Spertus.

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health status measure (all $p = 0.09$) was not significant, except for SF-12 PCS score ($p=0.02$), where worse scores were observed with invasive treatment in patients 85 years or older. In conclusion, an initial invasive treatment for patients with NSTEMI is associated with a small benefit in health status of marginal clinical significance, mainly in younger patients. The oldest old group trended towards less health status benefit from a routine invasive strategy—results that will need to be confirmed in a larger study.

Keywords

geriatrics; acute coronary syndrome; quality of life

Acute coronary syndromes are a leading cause of morbidity and mortality in older adults.¹ Accordingly, the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology guidelines recommend a routine invasive strategy for high-risk patients, both to improve survival and quality of life.^{2,3} Older adults with NSTEMI, given their age and co-morbidities, are all high-risk patients^{4,5} and would therefore be recommended, by guidelines, to be treated with an early invasive strategy. However, the data supporting this recommendation are sparse, as older patients are underrepresented in trials^{6,7} and, when included, tend to be healthier than the overall older population.¹ Older adults would be expected to derive a greater benefit from invasive management, given their higher risk, but they are also at higher risk of complications with invasive management.¹ The balance between these potential risks and benefits of invasive management underscore the need for more data in this population, particularly in relation to health status (symptoms, function and quality of life) in older patients with NSTEMI, who place a greater emphasis on functional status and quality of life than absolute survival.⁸ To address this gap in knowledge, we examined health status after routine invasive versus ischemia-guided (conservative) treatment, stratified by age, in patients presenting with NSTEMI enrolled in 2 large multicenter, prospective MI registries.

METHODS

We included all patients presenting with NSTEMI enrolled in 2 multicenter observational prospective AMI studies in United States: Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER)⁹ and the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH)¹⁰ study. Details regarding study design, enrollment criteria, site characteristics and outcomes collected on follow-up have been described previously.^{9,10} Briefly, PREMIER enrolled 2498 patients across 19 US sites from January 1, 2003 to June 28, 2004 and TRIUMPH enrolled 4340 patients across 24 US sites from April 11, 2005 to December 31, 2008 (31 total sites, as 12 hospitals participated in both registries). Both registries enrolled adult patients with a diagnosis of AMI (EKG, biomarker, and clinical criteria) who were admitted to or were transferred to an enrolling hospital within 24 hours of presentation. All patients underwent standardized telephone interviews by a central follow-up center at 1, 6, and 12 months after AMI to prospectively assess health status through standardized questionnaires. The study protocol was approved by Institutional Review Boards at all

participating institutions. All participants provided written informed consent for enrollment, data collection, and follow-up.

The primary independent variables for the study included age and treatment. Patients were divided into 4 groups based on age: <65, 65-74, 75-84 and 85 years. Treatment was determined based on chart abstraction by local site coordinators and categorized as initial invasive or ischemia-guided based on guidelines.^{2,3} Initial invasive treatment was defined as coronary angiography within 72 hours of presentation without a preceding stress testing. Ischemia-guided (or conservative) treatment was defined as stress testing prior to coronary angiogram, coronary angiogram >72 hours after presentation, coronary angiogram after recurrent symptoms or recurrent myocardial infarction during the admission, or no coronary angiogram during index admission.

Disease-specific and generic health status was assessed using the Seattle Angina Questionnaire (SAQ) and 12-item Short-Form Health survey (SF-12), respectively. The SAQ is a 19-item validated, disease-specific instrument measuring health status in patients with coronary artery disease across 5 domains: physical limitation (PL), angina stability (AS), angina frequency (AF), treatment satisfaction (TS) and quality of life (QoL).¹¹ All domain scores and a summary score (SS) (derived from PL, AF and QoL domains) range from 0 to 100, with higher scores indicating less angina, fewer physical limitations due to angina, and better quality of life. A mean difference of 5 points in domain scores and summary scores is considered clinically significant.^{11,12} The SF-12 is a generic health status measure and provides a physical component (PCS) and a mental component (MCS) summary score using a norm-based scoring system standardized to a mean (SD) of 50 (10) with higher scores indicating better health status.¹³ A mean difference greater than 2-2.5 points in SF-12 summary scores has been suggested to be clinically significant.¹⁴

Baseline patient and treatment characteristics were compared between the 4 age subgroups using one-way analysis of variance (ANOVA) and chi-square tests for continuous and categorical variables, respectively. We estimated mean SAQ and SF-12 scores over the year after AMI, as quantified by 1, 6 and 12 month follow-up assessments for both the treatment groups within each of the 4 age subgroups. Means were calculated by maximum likelihood estimation using general linear mixed models with fixed effects for treatment, time and treatment by time interaction, and unstructured within-patient covariance matrices. Because patients selected for an initial invasive treatment may be quite different from those treated with an ischemia-guided approach, we used propensity scores methods to adjust for potential confounders between the association of treatment with health status. We created a non-parsimonious logistic regression model to estimate a patient's likelihood of receiving routine invasive treatment using the covariates listed in Supplemental Table 1. Missing values of the covariates were imputed using chained equations.¹⁵ While there were marked differences in patients characteristics between the two groups prior to the propensity match (propensity model c-index=0.79), there was substantial overlap of propensity scores for ~98% of patients, suggesting a good balance of covariates between the 2 groups after the propensity match (Supplemental Figure 1). Balance of patient characteristics before and after adjustment for propensity scores was assessed by standardized differences (differences >10% are typically considered significant).¹⁶ We then used linear mixed-effect models to

estimate the association of treatment on health status outcomes at 1, 6 and 12 months after patients' NSTEMI admission. Models included effects for age group, treatment group, propensity score (on the logit scale), patients' baseline health status score, and an unstructured within-patient covariance matrix, with nonlinear effects accommodated using restricted cubic splines. All two- and three-way interactions with age group and time were also examined (no three-way interactions were significant, so they were dropped for simplification of the results). We conducted various sensitivity analyses to evaluate robustness of associations. We used inverse probability weighting (IPW) methods¹⁷ to examine the potential impact of missing data among patients who completed no follow-up assessments with similar results. We also repeated the above analyses excluding the 2% of patients with non-overlapping propensity scores and including adjustment for two covariates with propensity-adjusted standardized differences >10% with similar results to primary analysis. We recategorized invasive management as patients who received initial catheterization at any time during index hospitalization (not only first 72 hours) to compare "overall invasive" management to ischemia-guided management. To address survival bias, we used pattern mixture models, which stratify effect of treatment on patients' observed health status outcomes by time of death. All analyses were conducted with SAS version 9.4 (SAS Institute, NC) and R version 3.3.1.¹⁸

RESULTS

Among 3,641 patients who were admitted to 31 US hospitals with a NSTEMI from 2003-2008, we excluded 82 patients for whom treatment group could not be determined (e.g., time of catheterization unknown), resulting in an analytic cohort 3559 patients. Mean age of the patients was 61.0 years, 63.1% were men, and 64.1% were white. There were 2223 patients (62.5%) who were <65 years, 715 (20.1%) between 65-74 years, 501 (14.0%) between 75-84 years, and 120 (3.4%) 85 years or older (Table 1 and Supplemental Table 2). A total of 2455 patients (69.0%) were treated with an initial invasive management (1235 (50.3%) within first 24 hours; 1763 (71.8%) underwent revascularization), it was more common in younger patients (72.4% (1610/2223) of patients <65 years, 66.6% (476/715) of those 65-74 years, 63.1% (316/501) of those 75-84 years, and 44.2% (53/120) of those 85 years treated with a routine invasive management ($p<0.001$)). Among 1104 patients who received ischemia-guided treatment, 172 (15.6%) had a stress test, 295 (26.7%) had no catheterization or stress test during the initial admission while 675 (61.1%) had a catheterization (catheterization after 72 hours in 472, after recurrent symptoms in 214 and after stress test in 49) and 398 (36.1%) underwent revascularization during the initial admission. After propensity-score adjustment, both the treatment groups were well-matched (Supplemental Table 1).

For the analysis of health status outcomes, we excluded 502 patients (14%) who did not complete any follow-up health status assessments. While patients < 65 had significantly higher SAQ summary score (higher scores=better health status) with invasive treatment at baseline and throughout 1 year of follow-up, the magnitude and duration of improvement in health status decreased with increasing age. There was a statistically non-significant trend towards worse SAQ summary scores with invasive treatment on follow-up in patients 85 years or older. (Figure 1, Supplemental Figure 2). In propensity-adjusted analyses, a routine

invasive treatment was associated with higher SAQ physical limitation, angina frequency, and summary scores (indicating less physical limitation, less angina and better health status) over the year following NSTEMI, although the magnitude of these differences was small. (<4 points for all domains; Table 2). These benefits appeared to be greatest early on, with significant interactions of treatment*time for the SAQ quality of life domain and the SAQ summary score. Although patients aged ≥ 85 years had worse health status (measured by SAQ) when treated with a routine invasive compared to ischemia-guided treatment, there was no significant interaction between age (assessed either as a continuous or categorical variable) and treatment for any of the SAQ outcomes ($p > 0.14$ [categorical], $p > 0.39$ [continuous]). There was no significant improvement in mean general health status measures SF-12 PCS and SF-12 MCS over a year of follow-up with routine invasive treatment, however there was a significant interaction of invasive treatment with age for SF-12 PCS scores with patients older than 85 years having a clinically significant, worse SF-12 PCS scores (=worse health status; mean difference = -4.1 (-7.9, -0.3)) with invasive compared to ischemia-guided treatment. Sensitivity analyses recategorizing invasive management as patients receiving catheterization as the first test during index hospitalization regardless of time (Supplement Table 4) showed similar results to the main analysis, with a interaction of age * treatment for SAQ QoL and Summary score scales along with SF-12 PCS ($p = 0.02$) suggesting that patients 85 years or older have worse angina-specific quality of life, angina-specific health status and general physical limitation with overall invasive treatment. Sensitivity analyses addressing potential survival bias suggested the effect of invasive treatment on health status did not vary by survival time in our study (Supplement Tables 5 and 6).

DISCUSSION

TRIUMPH and PREMIER registries are large multicenter registries of patients presenting with MI with rich characterization of patient characteristics and health status assessments at baseline and throughout the year after AMI. These studies offer a unique opportunity to examine serial health status outcomes associated with treatment and increasing age in patients with NSTEMI in a real world setting. We found that a routine invasive management was used less often in older adults and higher-risk patients with greater cardiac and non-cardiac comorbidities and poorer health status at baseline. After propensity adjustment for these differences in characteristics of the patients undergoing both treatments, initial invasive treatment was associated with a small average benefit in disease-specific health status over the year following the MI which was not clinically meaningful, as compared with an ischemia-guided treatment. The health status benefit was mainly accounted for by the younger patients, even though it was not above the 5-point threshold of clinical significance for the SAQ, and was most notable early during follow-up. While there was no significant interaction of treatment with age on SAQ, perhaps due to limitations in sample size and power, the patients 85 years or older appeared to derive no health status benefit with routine invasive treatment. Patients older than 85 years also appeared to have worse general health status with significantly lower SF-12 PCS scores on follow-up with invasive treatment. Although these high risk patients may still have a survival advantage with a routine invasive

strategy¹⁹ that was not evaluated in this study, our results do not support a health status benefit for the very old patients with NSTEMI.

Prior work testing different treatment strategies in older adults presenting with NSTEMI has predominantly focused on assessing cardiovascular and mortality outcomes, and the results have been mixed. In subgroup analyses of 4 large trials with >3500 patients aged ≥ 65 years, a routine invasive strategy was associated with a significant reduction in death or MI;^{20,21} however, the vast majority of these patients were <75 years of age.^{22,23} The Italian Elderly ACS study found no significant benefit of invasive vs. conservative treatment in patients ≥ 75 years of age, although it may have been underpowered.²⁴ The After Eighty trial of 457 patients ≥ 80 years found that an invasive strategy was safe with low bleeding rates and reduced the rate of major adverse cardiovascular events over 1.5 years of follow up compared to conservative strategy, however there was a signal of harm in those ≥ 90 years.¹⁹

In contrast, there are sparse data for the effect of different treatment strategies on health status in older patients with NSTEMI. The RITA 3 and FRISC II trials showed better health status scores at one year in patients with NSTEMI treated with routine invasive versus conservative strategy, however less than a quarter of these patients were ≥ 75 years.^{25,26} The role of invasive treatment and health status in older NSTEMI patients is particularly important to examine, as they tend to value improvements in functional status and quality of life more than younger patients, and at times even more than survival benefits.⁸ Furthermore, while a clinical trial is ideal to reduce selection biases that exist with the different treatment strategies, examining this question in a real world population, with the full extent of comorbidities and risk, also provides important insights that are more difficult to identify in trial populations.^{19,24}

Our data have important implications that could help facilitate patient-centered decision making. The selection of treatment strategy after NSTEMI in older patients requires balancing the potential risks and benefits, which is more complicated in older patients who have greater peri-procedural risks than younger patients.^{27,28} The guidelines recommend routine invasive management in high-risk patients, which could be applicable to nearly all older patients, but the results from this study suggest that there is no benefit in symptoms, function and quality of life in those over 85. As such, understanding these trade-offs can help patients make an informed decision about the treatment they receive based on their individual preferences.

Our study results should be interpreted in the context of the following potential limitations. We used extensive propensity-adjustment strategies to minimize selection biases, however there is still a risk of residual unmeasured confounding. Second, 60% of patients who had ischemia-guided management had a catheterization procedure later in the course of the admission. However, a sensitivity analysis comparing “overall invasive approach” regardless of time of catheterization to ischemia-guided management showed similar results to our primary analysis. Third, although this cohort is representative of a real-world AMI population who survive to hospital discharge and includes patients with a high degree of comorbidities, we still only had 120 patients ≥ 85 years of age. As such, while we had a suggestion of less health status benefit in this oldest group, the smaller number of patients

limit our ability to make firm conclusions about the benefit (or lack thereof) of invasive management in this group. Finally, our study cohort was enrolled between years 2003-2008, changes in catheterization especially radial approach and revascularization since then could generate different results. However, our data is the first analysis examining health status outcomes according to age and treatment strategies in NSTEMI and raises an important question regarding the potential for worse health status outcomes with invasive strategy in very old patients, which should be prospectively studied in larger cohorts.

In conclusion, in the setting of a NSTEMI, there was an early trend to benefit with invasive treatment on disease-specific health-related QOL which narrowed with time and was mostly present in younger patients. The oldest old group appeared to have a trend towards worse general health status with an initial invasive strategy—results that will need to be confirmed in a larger study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Unadjusted health status scores at 1, 6 and 12 months of follow-up for patients with NSTEMI treated with routine invasive management compared to ischemia-guided management according to the patient age.

Table 1

Baseline characteristics of the study population

Variable	Ages (years)				p-value
	<65 (n=2223)	65-74 (n=715)	75-84 (n=501)	85 (n=120)	
Men	1479 (66.5%)	447 (62.5%)	274 (54.7%)	44 (36.7%)	<0.001
White	1297 (58.6%)	507 (71.0%)	382 (76.6%)	88 (73.3%)	<0.001
High school education	1728 (78.4%)	518 (73.3%)	352 (72.1%)	72 (61.0%)	<0.001
Self-Pay	605 (28.0%)	34 (4.9%)	12 (2.5%)	1 (0.9%)	<0.001
Avoids health care due to cost	662 (30.5%)	82 (11.7%)	43 (8.7%)	11 (9.3%)	<0.001
Finances at end of the month					<0.001
Some left over	755(34.7%)	362 (52.7%)	285 (58.6%)	58 (50.9%)	
Just enough	833 (38.3%)	245 (35.7%)	158 (32.5%)	46 (40.4%)	
Not enough	587 (27.0%)	80 (11.6%)	43 (8.8%)	10 (8.8%)	
Current smoker	996 (45.2%)	137 (19.3%)	31 (6.2%)	3 (2.5%)	<0.001
Hypertension	1525 (68.6%)	564 (78.9%)	398 (79.4%)	91 (75.8%)	<0.001
Diabetes Mellitus	747 (33.6%)	296 (41.4%)	189 (37.7%)	33 (27.5%)	<0.001
Prior percutaneous coronary intervention	464 (20.9%)	169 (23.6%)	131 (26.1%)	22 (18.3%)	0.033
Prior Coronary artery bypass	263 (11.8%)	169 (23.6%)	132 (26.3%)	21 (17.5%)	<0.001
Prior Myocardial Infarction	528 (23.8%)	226 (31.6%)	147 (29.3%)	36 (30.0%)	<0.001
Peripheral arterial disease	108 (4.9%)	79 (11.0%)	58 (11.6%)	21 (17.5%)	<0.001
Prior cerebrovascular accident	161 (7.2%)	82 (11.5%)	66 (13.2%)	12 (10.0%)	<0.001
Heart failure	264 (11.9%)	113 (15.8%)	84 (16.8%)	32 (26.7%)	<0.001
Chronic lung disease	205 (9.2%)	109 (15.2%)	68 (13.6%)	23 (19.2%)	<0.001
Cancer (other than skin)	106 (4.8%)	98 (13.7%)	84 (16.8%)	19 (15.8%)	<0.001
Body mass index (kg/m ² , mean $\pm$ SD)	30.5 $\pm$ 7.1	29.4 $\pm$ 6.3	27.3 $\pm$ 5.2	25.3 $\pm$ 4.3	<0.001
PHQ-9 Depression Score (mean $\pm$ SD)	6.1 $\pm$ 5.8	4.8 $\pm$ 5.0	4.5 $\pm$ 4.6	4.8 $\pm$ 4.7	<0.001
Heart Rate (bpm, mean $\pm$ SD)	84.3 $\pm$ 21.4	83.7 $\pm$ 25.1	83.5 $\pm$ 21.2	88.6 $\pm$ 26.1	0.137
Systolic Blood Pressure (mmHg)	145.4 $\pm$ 31.1	142.9 $\pm$ 30.7	144.8 $\pm$ 30.2	146.3 $\pm$ 32.2	0.286
Hematocrit (% , mean $\pm$ SD)	41.0 $\pm$ 5.9	38.9 $\pm$ 6.0	37.9 $\pm$ 5.8	36.5 $\pm$ 5.4	<0.001
Estimated glomerular filtration rate (ml/min/m ² , mean $\pm$ SD)	78.9 $\pm$ 31.2	65.6 $\pm$ 25.6	59.6 $\pm$ 25.3	51.0 $\pm$ 21.3	<0.001
Peak Troponin (ng/ml, mean $\pm$ SD)	16.0 $\pm$ 52.4	19.2 $\pm$ 73.1	19.8 $\pm$ 77.8	29.5 $\pm$ 165.0	0.120

Variable	Ages (years)					p-value
	<65 (n=2223)	65-74 (n=715)	75-84 (n=501)	85 (n=120)		
GRACE mortality risk score (mean $\pm$ SD)	128.8 $\pm$ 33.1	165.0 $\pm$ 30.6	182.5 $\pm$ 30.6	204.5 $\pm$ 34.3		<0.001
Seattle Angina Questionnaire score (mean $\pm$ SD)						
Physical Limitation	81.5 $\pm$ 25.1	82.7 $\pm$ 23.2	81.1 $\pm$ 24.6	72.3 $\pm$ 30.3		0.020
Angina Frequency	82.8 $\pm$ 22.5	83.5 $\pm$ 23.0	83.0 $\pm$ 23.4	80.6 $\pm$ 24.8		0.615
Quality of Life	58.4 $\pm$ 24.3	64.9 $\pm$ 24.0	65.7 $\pm$ 23.0	66.5 $\pm$ 24.5		<0.001
Summary Score	73.9 $\pm$ 19.7	76.5 $\pm$ 19.1	76.0 $\pm$ 19.3	73.7 $\pm$ 21.3		0.006
Short-Form 12 score (mean $\pm$ SD)						
Physical Component Summary	41.3 $\pm$ 12.8	40.1 $\pm$ 12.5	38.7 $\pm$ 12.3	35.8 $\pm$ 10.9		<0.001
Mental Component Summary	47.6 $\pm$ 12.1	51.1 $\pm$ 10.2	53.0 $\pm$ 10.3	53.2 $\pm$ 10.7		<0.001

Table 2

Mean difference in health status outcomes over follow-up between patients with NSTEMI treated with initial invasive versus ischemia-guided management

Seattle Angina Questionnaire						Short Form-12	
	Physical Limitation Estimate (95% CI)	Angina Frequency Estimate (95% CI)	Quality of Life Estimate (95% CI)	Summary Score Estimate (95% CI)	Physical Component Summary Estimate (95% CI)	Mental Component Summary Estimate (95% CI)	
Overall effect of invasive treatment	3.7 (1.8, 5.5) p<0.001	1.4 (0.2, 2.7) p=0.02	1.5 (-0.1, 3.0) p=0.06	1.6 (0.4, 2.9) p=0.008	0.7 (-0.1, 1.5) p=0.07	0.7 (-0.0, 1.5) p=0.06	
Effect of treatment by month							
Month 1	4.0 (1.5, 6.6)	1.7 (-0.4, 3.8)	1.3 (-1.5, 4.2)	2.0 (-0.2, 4.1)	0.9 (-0.1, 1.9)	0.9 (-0.0, 1.9)	
Month 6	3.5 (1.2, 5.7)	0.5 (-1.6, 2.7)	0.5 (-2.2, 3.3)	1.1 (-1.1, 3.3)	0.4 (-0.6, 1.4)	0.9 (-0.1, 1.9)	
Month 12	3.5 (1.4, 5.7)	-0.8 (-2.8, 1.3)	-1.0 (-3.7, 1.7)	-1.0 (-3.1, 1.1)	0.8 (-0.3, 1.8)	0.3 (-0.6, 1.3)	
Treatment*month interaction	p=0.70	p=0.15	p=0.04	p<0.001	p=0.83	p=0.27	
Effect of invasive treatment by age group							
<65 years	3.4 (1.1, 5.6)	1.7 (0.2, 3.3)	1.8 (-0.3, 3.8)	1.9 (0.3, 3.5)	0.5 (-0.5, 1.5)	1.1 (0.1, 2.0)	
65-74 years	4.7 (1.0, 8.3)	0.8 (-1.5, 3.2)	2.2 (-1.0, 5.5)	2.3 (-0.2, 4.9)	1.6 (0.1, 3.2)	0.3 (-1.1, 1.7)	
75-84 years	3.4 (-1.6, 8.4)	2.0 (-0.8, 4.8)	1.3 (-2.6, 5.2)	1.0 (-2.0, 4.0)	1.0 (-0.8, 2.8)	0.7 (-1.0, 2.4)	
85 years	5.3 (-8.5, 19.1)	-2.6 (-8.3, 3.2)	-4.2 (-12.3, 3.9)	-2.5 (-8.8, 3.7)	-4.1 (-7.9, -0.3)	-2.3 (-5.9, 1.3)	
Treatment*age interaction	p=0.83	p=0.21	p=0.15	p=0.15	p=0.02	p=0.09	

Adjusted estimates derived using propensity-matched linear mixed effect models matched for baseline SAQ, demographic, socioeconomic, psychosocial, laboratory and medication information.