

Supplementary Appendix

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

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Supplementary Methods

Linear Mixed Modeling of Longitudinal Patient-Reported Outcomes

To compare longitudinal change for the various patient reported outcomes (PRO), VR-12 Physical Component Summary Score (PCS), VR-12 Mental Component Summary Score (MCS), and PHQ-9) between the treatment groups, we estimated a linear mixed model assuming linear mean change over time within each treatment group. The model for Y_{ij} (j^{th} PRO measurement for i^{th} participant measured at time t_{ij} (in years)) is as follows:

$$Y_{ij} = \beta_0 + \beta_1 \text{Intensive}_i + \beta_2 t_{ij} + \beta_3 \text{Intensive}_i t_{ij} + b_{1i} + b_{2,c_i} + \varepsilon_{ij}$$

Where Intensive_i is the randomization assignment for the i^{th} participant (1=Intensive-treatment; 0=Standard-treatment), c_i denotes the clinic site for the i^{th} participant (participants were randomized at 102 clinic sites), b_{1i} is a subject specific random effect, b_{2,c_i} is a clinic-specific random effect, and ε_{ij} denotes the residual error component. Modeling was carried out using SAS PROC MIXED (SAS v9.4, Cary, NC). We utilized minimum variance quadratic unbiased estimation (method=MIVQUE0) and the denominator degrees of freedom for hypothesis tests of fixed effects were computed using the between-within method (ddfm=bw) (1).

Multiple Imputation Procedure for Missing Data

We examined the influence of missing data on inference for the VR-12 PCS and MCS using multiple imputation. For these analyses, we excluded N=20 participants where the VR-12 was never completed at any point during the study. For the remaining participants, we imputed VR-12 scores where PRO assessments theoretically could have been collected. We therefore did not impute VR-12 scores subsequent to a participant's death, and we only imputed missing VR-

12 scores for annual visits scheduled to occur on or before the decision to stop the SPRINT intervention (target visit date + 45 days \leq 8/20/2015, see Supplementary Table 1).

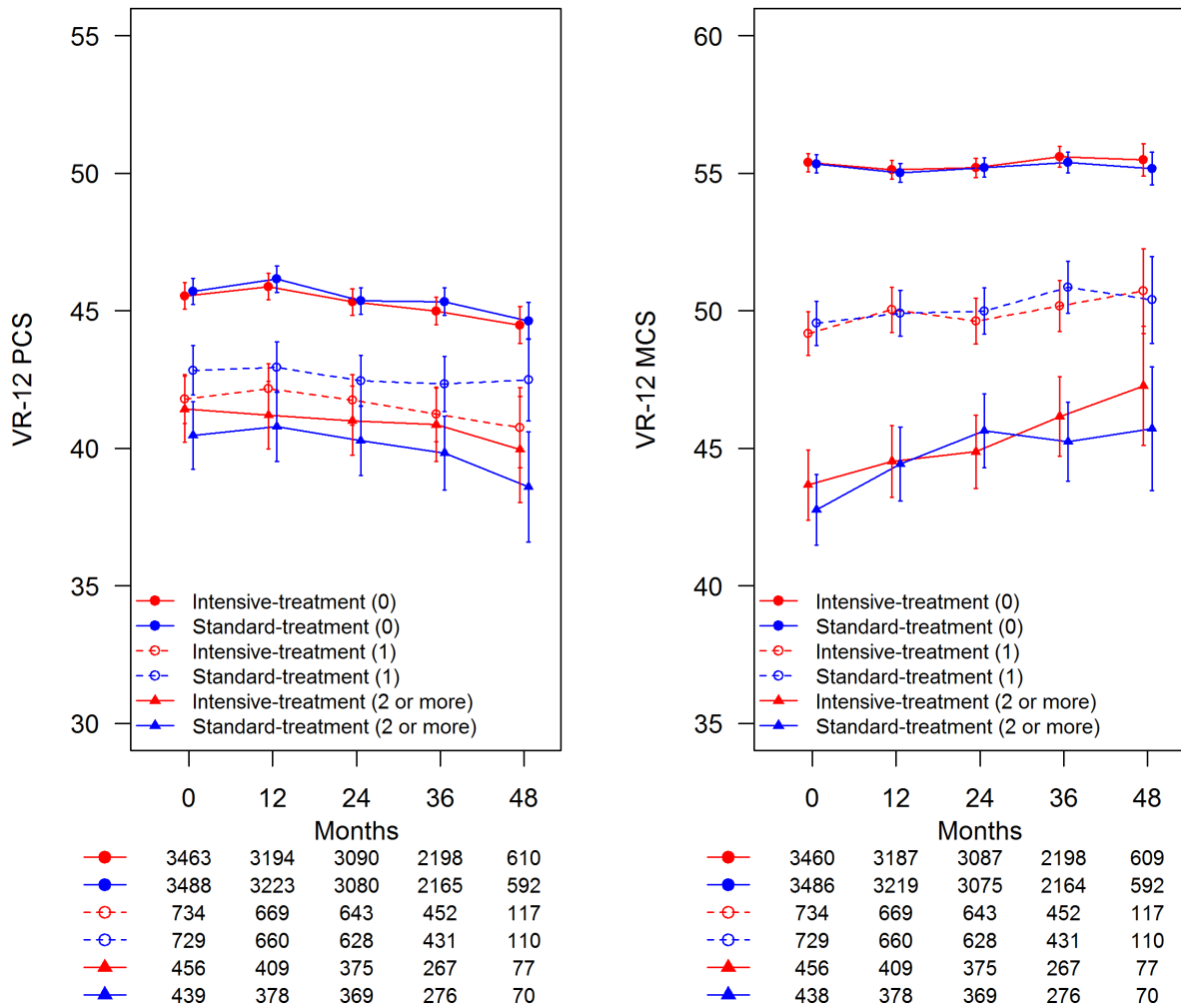
The multiple imputation procedure was implemented using *proc mi* and *proc mianalyze* in SAS v9.4 (SAS, Cary, NC), based on 100 imputed datasets. We used a two-step procedure for imputation due to the presence of both monotone and non-monotone missing data patterns. We first partially imputed missing PCS and MCS scores by treatment group using Markov Chain Monte Carlo, assuming multivariate normality (jointly for both PCS and MCS scores) and using Jeffrey's priors for the prior distribution of the mean and variance-covariance matrix. For this step, we used the *impute=monotone* option in *proc mi* so as to only impute enough data to produce monotone missing data patterns.

We then used a series of linear regression models to impute the remaining missing PCS and MCS scores, including treatment group, age, age by treatment group, sex, sex by treatment group, race/ethnicity (White, Black, Hispanic, or Other), number of antihypertensive agents at randomization (0, 1, 2, 3, or 4+), Montreal Cognitive Assessment (MoCA) Score at randomization (2), smoking status (Current, Former, or Never smoker), Body Mass Index (<25 kg/m², 25 to <30 kg/m², 30 kg/m² or greater), eGFR (<60 ml/min/1.73m² versus 60 ml/min/1.73m² or greater), systolic blood pressure at randomization, diastolic blood pressure at randomization, whether the PRO assessment followed a non-fatal primary cardiovascular event (Yes versus No, for post-baseline measurements), and PCS and MCS scores at the previous annual visit (for post-baseline measurements) as predictors. Non-fatal cardiovascular events included myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, or acute decompensated heart failure. Similar to previous work with the SPRINT cohort, we categorized MoCA scores as <10th percentile, 10th percentile to <25th percentile, \geq 25th

percentile, or missing (N=65) using normative data by age, sex, and education from the Irish Longitudinal Study on Ageing, with an adjustment for race/ethnicity (3,4).

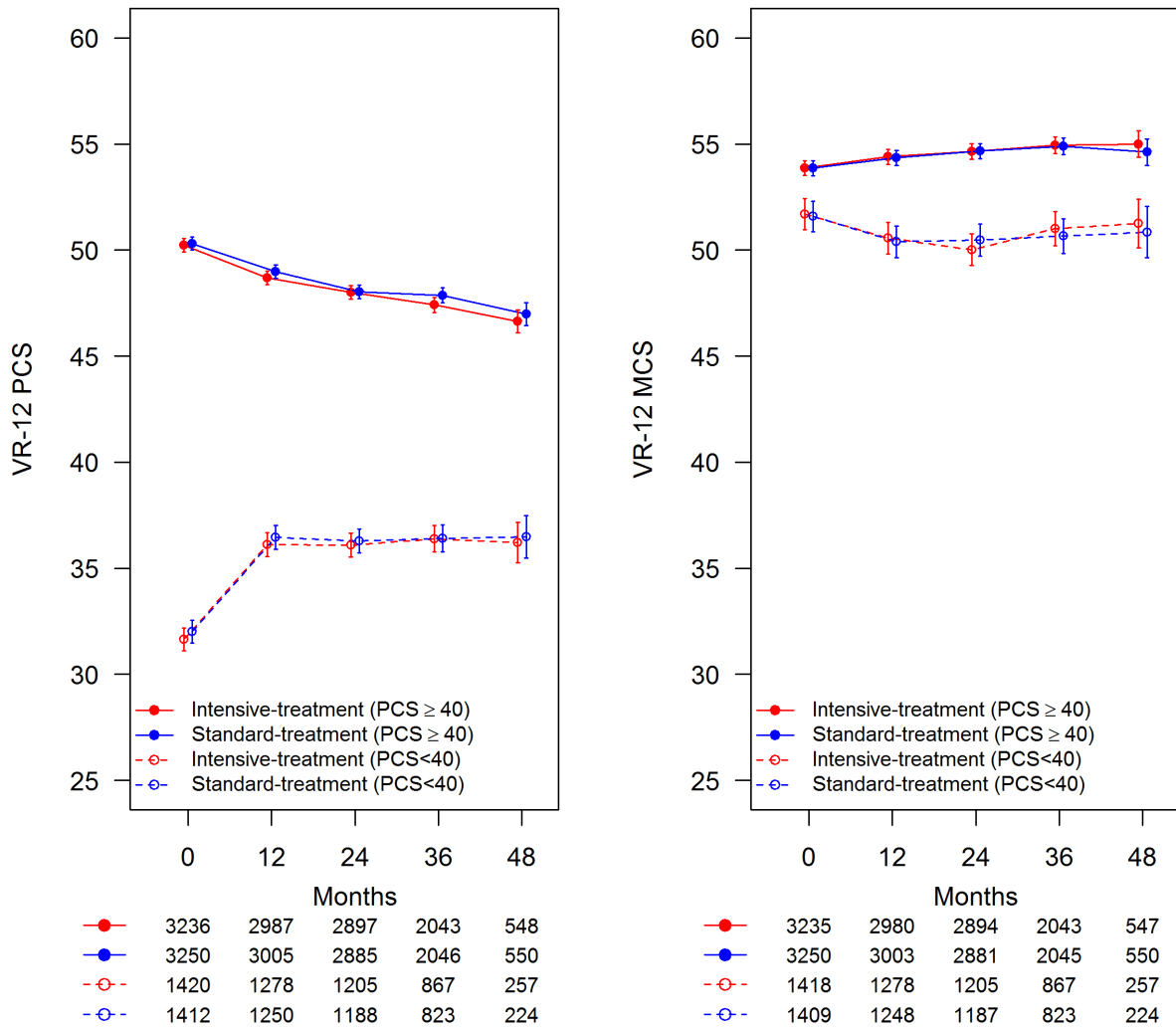
The above imputation procedure entails the common assumption that any missing VR-12 scores are missing at random (MAR), conditional on the factors included in the imputation models. We evaluated sensitivity to the MAR assumption by deterministically shifting the imputed PCS and MCS scores for participants in the intensive-treatment group. Conceptually, this sensitivity analysis was designed to examine how sharply VR-12 scores would have needed to decline for participants in the intensive-treatment with missing data in order to suggest an overall deterioration in VR-12 scores due to intensive treatment. If we let Y_{ij} denote the imputed PCS or MCS score for the i^{th} participant missing that measure at time point j (based on the same imputation model described above under the MAR assumption), then this analysis simply defined a new imputed value, $Y_{ij}^* = Y_{ij} - \delta$, with δ ranging from 1 to 4 points. Supplementary Figure 5 graphically depicts the implied trajectory of mean VR-12 scores for 1) participants with complete data, 2) participants with missing data under the MAR assumption, and 3) participants in the intensive-treatment group with shifted imputed values. When we assumed strong differential decreases in PCS and MCS scores for participants with missing data randomized to intensive therapy, we did observe statistically significant decreases on these measures for the intensive-treatment group (Supplementary Table 12). However, these assumptions for missing data still implied small differences in mean scores overall (<1 point over three years), and so are unlikely to be clinically meaningful.

FIGURE S1. Veterans RAND 12 Item Health Survey (VR-12) scores over the course of follow-up by treatment group and Mental Comorbidity Category



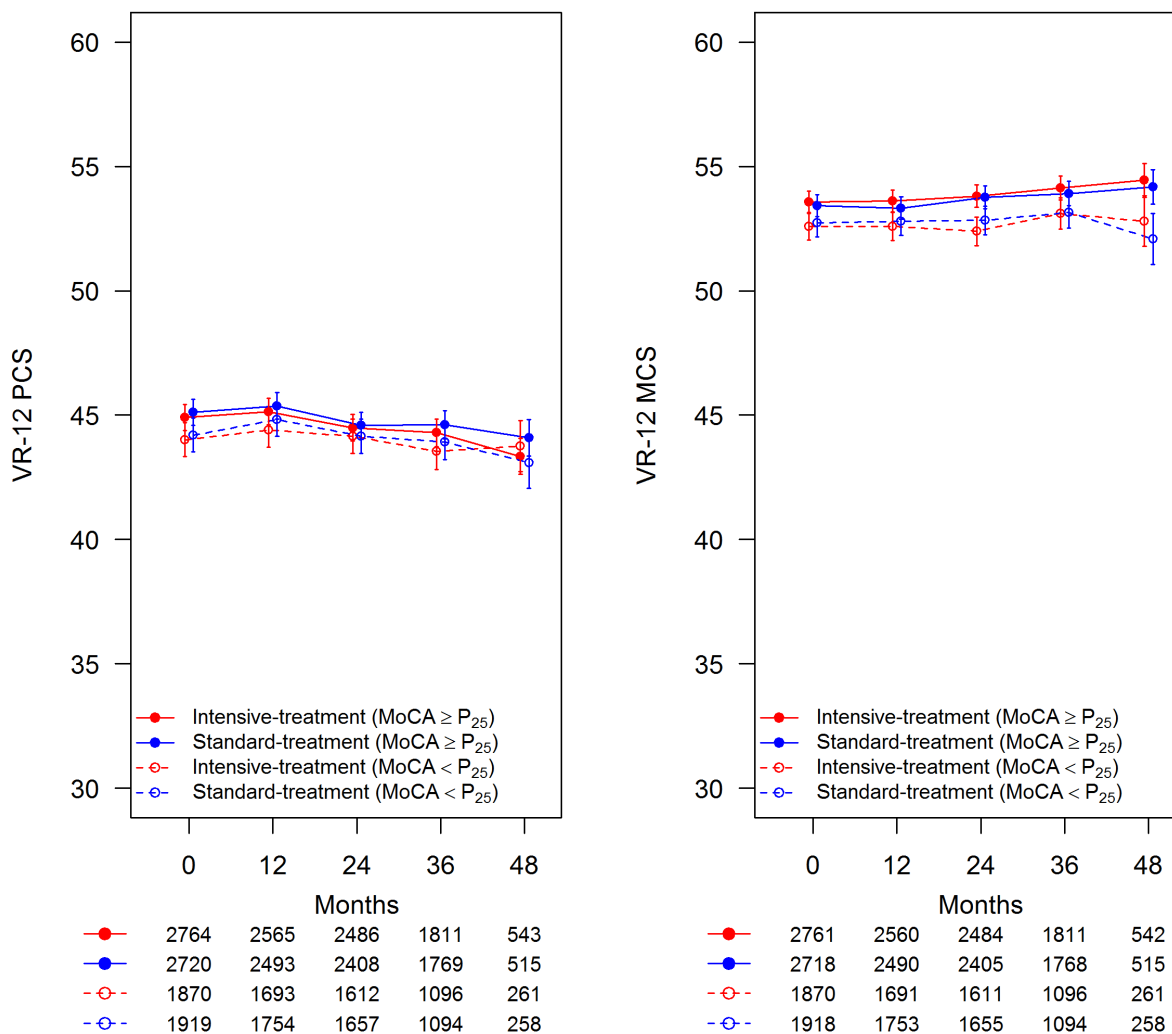
Mental comorbidity burden was categorized as 0, 1, or 2 or more comorbidities. Points represent estimated mean based on mixed model, with bars denoting 95% Confidence Intervals. Counts below figures denote number of participants assessed at each study visit within each treatment group and comorbidity subgroup. PCS denotes Physical Component Summary Score and MCS Mental Component Summary Score.

FIGURE S2. Veterans RAND 12 Item Health Survey (VR-12) scores over the course of follow-up by treatment group and baseline Physical Component Summary Score (PCS)



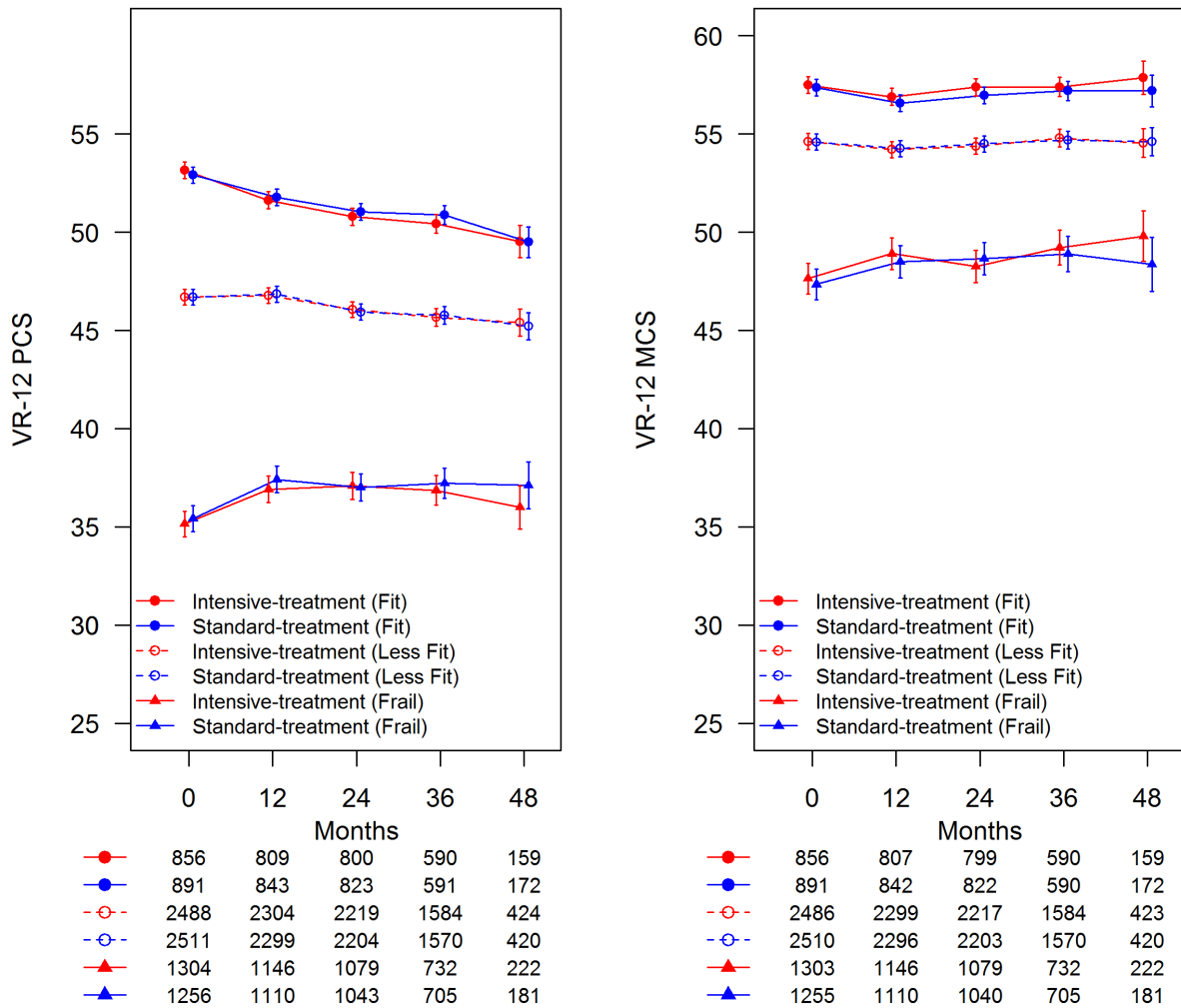
Points represent estimated mean based on mixed model, with bars denoting 95% Confidence Intervals. Counts below figures denote number of participants assessed at each study visit within each treatment group and comorbidity subgroup. MCS denotes Mental Component Summary Score.

FIGURE S3. Veterans RAND 12 Item Health Survey (VR-12) scores over the course of follow-up by treatment group and cognitive status



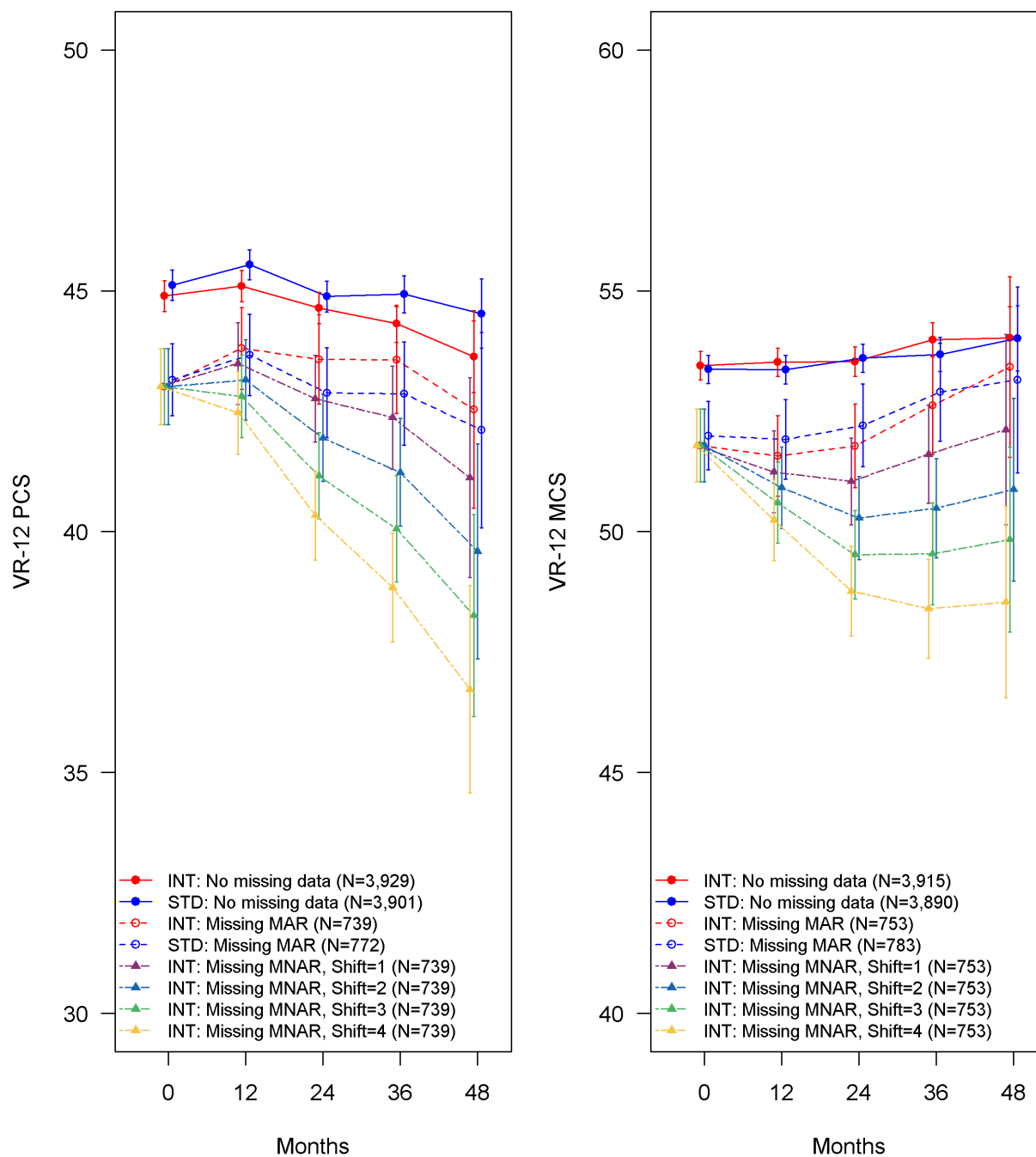
Points represent estimated mean based on mixed model, with bars denoting 95% Confidence Intervals. Counts below figures denote number of participants assessed at each study visit within each treatment group and comorbidity subgroup. PCS denotes Physical Component Summary Score, MCS Mental Component Summary Score, MoCA Montreal Cognitive Assessment, and P₂₅ Age and education specific normative 25th percentile from the Irish Longitudinal Study of Ageing (two points added to the scores of Black and Hispanic participants in SPRINT).

FIGURE S4. Veterans RAND 12 Item Health Survey (VR-12) scores over the course of follow-up by treatment group and frailty status



Points represent estimated mean based on mixed model, with bars denoting 95% Confidence Intervals. Counts below figures denote number of participants assessed at each study visit within each treatment group and comorbidity subgroup. PCS denotes Physical Component Summary Score, MCS Mental Component Summary Score, and FI Frailty Index. FI scores range from 0 to 1, with higher scores denoting greater frailty.

FIGURE S5. Mean scores on the Veteran's RAND 12-Item Survey (VR-12) for participants with complete data versus those with missing data



INT denotes Intensive-treatment, STD Standard-treatment, MAR Missing at Random, MNAR Missing Not at Random, PCS Physical Component Summary Score, and MCS Mental Component Summary Score. Points represent estimated mean based on mixed model, with bars denoting 95% Confidence Intervals. For participants with missing data, mean scores reflect values averaged over 100 imputed datasets.

TABLE S1. Completion of Veterans RAND 12 Item Health Survey (VR-12) by study visit

	Visit	Follow-up through 8/20/2015		Follow-up through 12/01/2015	
		Intensive-treatment no. / total no. (%)	Standard-treatment no. / total no. (%)	Intensive-treatment no. / total no. (%)	Standard-treatment no. / total no. (%)
VR-12 Physical Component Summary Score	Baseline	4657 / 4678 (99.6)	4662 / 4683 (99.6)	4657 / 4678 (99.6)	4662 / 4683 (99.6)
	12M	4276 / 4641 (92.1)	4266 / 4640 (91.9)	4276 / 4641 (92.1)	4266 / 4640 (91.9)
	24M	4112 / 4594 (89.5)	4083 / 4583 (89.1)	4112 / 4594 (89.5)	4083 / 4583 (89.1)
	36M	2919 / 3305 (88.3)	2877 / 3289 (87.5)	3491 / 3971 (87.9)	3434 / 3938 (87.2)
	48M	805 / 919 (87.6)	774 / 880 (88.0)	1287 / 1482 (86.8)	1278 / 1463 (87.4)
	Visit	no. / total no. (%)	no. / total no. (%)	no. / total no. (%)	no. / total no. (%)
VR-12 Mental Component Summary Score	Baseline	4654 / 4678 (99.5)	4659 / 4683 (99.5)	4654 / 4678 (99.5)	4659 / 4683 (99.5)
	12M	4269 / 4641 (92.0)	4262 / 4640 (91.9)	4269 / 4641 (92.0)	4262 / 4640 (91.9)
	24M	4109 / 4594 (89.4)	4078 / 4583 (89.0)	4109 / 4594 (89.4)	4078 / 4583 (89.0)
	36M	2919 / 3305 (88.3)	2876 / 3289 (87.4)	3491 / 3971 (87.9)	3433 / 3938 (87.2)
	48M	804 / 919 (87.5)	774 / 880 (88.0)	1286 / 1482 (86.8)	1277 / 1463 (87.3)

M denotes months. Total no. reflects the number of annual VR-12 assessments scheduled to occur on or before follow-up cutoff date (target visit date + 45 days ≤ follow-up cutoff date), removing scheduled visits following a participant's death.

TABLE S2. Additional baseline characteristics of study participants

	Intensive-treatment	Standard-treatment
Characteristic	N=4678	N=4683
Female sex - no. (%)	1684 (36)	1648 (35.2)
Age - years	67.9 ± 9.4	67.9 ± 9.5
Systolic blood pressure - mm Hg	139.7 ± 15.8	139.7 ± 15.4
Diastolic blood pressure - mm Hg	78.2 ± 11.9	78.0 ± 12.0
Antihypertensive agents - no./patient	1.8 ± 1.0	1.8 ± 1.0
Taking ≥1 antihypertensive agent - no. (%)	4246 (90.8)	4233 (90.4)
Race or ethnic group - no. (%)†		
Non-Hispanic white	2698 (57.7)	2701 (57.7)
Non-Hispanic black	1379 (29.5)	1423 (30.4)
Hispanic	503 (10.8)	481 (10.3)
Other	98 (2.1)	78 (1.7)
Body-mass index - kg/m²	29.9 ± 5.8	29.8 ± 5.7
Education - no. (%)		
<High School	431 (9.2)	445 (9.5)
High School graduate	2447 (52.3)	2386 (51.0)
College graduate	1024 (21.9)	1065 (22.7)
Graduate degree	767 (16.4)	779 (16.6)
Missing data	9 (0.2)	8 (0.2)
Smoking status - no. (%)		
Never smoker	2050 (43.8)	2072 (44.2)
Former smoker	1977 (42.3)	1996 (42.6)
Current smoker	639 (13.7)	601 (12.8)
Missing data	12 (0.3)	14 (0.3)
Alcohol use - no. (%)‡		
Non-drinker	2072 (44.3)	2069 (44.2)
Light drinker	938 (20.1)	981 (20.9)
Moderate drinker	890 (19.0)	858 (18.3)

Heavy drinker	538 (11.5)	553 (11.8)
Missing data	240 (5.1)	222 (4.7)
History of cardiovascular disease - no. (%)	940 (20.1)	937 (20.0)
Serum creatinine - mg/dl, median (IQR)	1 (0.9 to 1.2)	1.0 (0.9 to 1.2)
Estimated GFR - ml/min/1.73 m²	71.8 ± 20.7	71.7 ± 20.5
Estimated GFR <60 ml/min/1.73 m² - no. (%)	1330 (28.6)	1316 (28.3)
Estimated GFR <45 ml/min/1.73 m² - no. (%)	445 (9.6)	444 (9.5)
Ratio of urinary albumin (mg) to creatinine (g) - median (IQR)	9.6 (5.7 to 21.1)	9.4 (5.6 to 21.8)
Fasting total cholesterol - mg/dl	190.2 ± 41.4	190.0 ± 40.9
Fasting HDL cholesterol - mg/dl	52.9 ± 14.3	52.8 ± 14.6
Fasting total triglycerides - mg/dl, median (IQR)	106.5 (76.0 to 148.0)	107.0 (77.0 to 152.0)
Fasting plasma glucose - mg/dl	98.8 ± 13.7	98.8 ± 13.4
Statin use - no./total no. (%)	1978 / 4645 (42.6)	2076 / 4640 (44.7)
Aspirin use - no/total no. (%)	2406 / 4661 (51.6)	2350 / 4666 (50.4)
Antidepressant use - no. (%)	588 (12.7)	605 (13.0)

Plus-minus values are means ± SD. There were no significant differences (p-value<0.05) between the two treatment groups except for statin use (p=0.04). To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.0551. IQR denotes interquartile range, GFR glomerular filtration rate, HDL high-density lipoprotein.

† Race and ethnic group were self-reported.

‡ Non-drinker denotes <1 drink per month, light drinker 1-2 drinks per week, moderate drinker ≥3 drinks per weeks but <1 drink per day, and heavy drinker (≥1 drink per day).

TABLE S3. Mean annual change in score on the Veterans RAND 12-item Health Survey (VR-12) Physical Component Summary Score (PCS) overall and by subgroups.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	-0.234 (-0.313, -0.155)	-0.227 (-0.306, -0.147)	-0.008 (-0.120, 0.105)	0.90	
Medical comorbidity index					0.18
Two or less	-0.407 (-0.545, -0.269)	-0.252 (-0.386, -0.117)	-0.155 (-0.348, 0.037)	0.11	
Three or four	-0.148 (-0.288, -0.009)	-0.294 (-0.436, -0.151)	0.145 (-0.054, 0.345)	0.15	
Five or six	-0.194 (-0.366, -0.022)	-0.244 (-0.423, -0.066)	0.051 (-0.197, 0.298)	0.69	
Seven or more	-0.181 (-0.385, 0.022)	-0.068 (-0.268, 0.133)	-0.114 (-0.399, 0.172)	0.43	
Mental comorbidity index					0.90
Zero	-0.237 (-0.326, -0.148)	-0.226 (-0.316, -0.136)	-0.011 (-0.138, 0.116)	0.86	
One	-0.207 (-0.417, 0.003)	-0.170 (-0.383, 0.044)	-0.038 (-0.337, 0.262)	0.81	
Two or more	-0.245 (-0.529, 0.040)	-0.303 (-0.590, -0.016)	0.058 (-0.346, 0.462)	0.78	
Baseline VR-12 PCS					0.29
≥40	-0.915 (-0.998, -0.832)	-0.850 (-0.934, -0.767)	-0.065 (-0.182, 0.053)	0.28	
<40	1.341 (1.185, 1.497)	1.280 (1.120, 1.440)	0.061 (-0.162, 0.284)	0.59	
Age					0.44
<75 years	-0.145 (-0.237, -0.053)	-0.159 (-0.252, -0.066)	0.014 (-0.116, 0.145)	0.83	
75 years or older	-0.522 (-0.681, -0.364)	-0.433 (-0.591, -0.274)	-0.089 (-0.313, 0.135)	0.43	
Cognitive status†					0.38
MoCA≥normative 25 th percentile	-0.303 (-0.401, -0.205)	-0.256 (-0.356, -0.157)	-0.046 (-0.186, 0.093)	0.51	
MoCA<normative 25 th percentile	-0.121 (-0.255, 0.013)	-0.179 (-0.312, -0.046)	0.058 (-0.13, 0.247)	0.54	
Frailty status ‡					0.49
Fit (FI≤0.10)	-0.910 (-1.046, -0.774)	-0.744 (-0.878, -0.610)	-0.166 (-0.357, 0.024)	0.09	
Less Fit (0.10<FI≤0.21)	-0.369 (-0.474, -0.264)	-0.381 (-0.486, -0.275)	0.011 (-0.137, 0.160)	0.88	
Frail (FI>0.21)	0.461 (0.289, 0.633)	0.488 (0.311, 0.666)	-0.028 (-0.275, 0.219)	0.83	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S4. Mean annual change in score on the Veterans RAND 12-item Health Survey (VR-12) Mental Component Summary Score (MCS) overall and by subgroups.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	0.154 (0.069, 0.239)	0.137 (0.051, 0.222)	0.017 (-0.104, 0.137)	0.79	
Medical comorbidity index					0.49
Two or less	0.207 (0.049, 0.365)	0.266 (0.112, 0.421)	-0.059 (-0.281, 0.162)	0.60	
Three or four	0.267 (0.119, 0.415)	0.304 (0.153, 0.455)	-0.037 (-0.249, 0.174)	0.73	
Five or six	0.174 (-0.007, 0.354)	-0.015 (-0.203, 0.173)	0.188 (-0.072, 0.449)	0.16	
Seven or more	-0.179 (-0.389, 0.032)	-0.203 (-0.41, 0.004)	0.024 (-0.271, 0.319)	0.87	
Mental comorbidity index					0.76
Zero	0.045 (-0.046, 0.137)	0.004 (-0.088, 0.095)	0.042 (-0.088, 0.171)	0.53	
One	0.281 (0.040, 0.521)	0.329 (0.084, 0.574)	-0.048 (-0.391, 0.295)	0.78	
Two or more	0.792 (0.459, 1.125)	0.850 (0.514, 1.186)	-0.058 (-0.530, 0.415)	0.81	
Baseline VR-12 PCS					0.98
≥40	0.325 (0.230, 0.420)	0.296 (0.201, 0.391)	0.029 (-0.105, 0.164)	0.67	
<40	-0.245 (-0.419, -0.072)	-0.267 (-0.445, -0.088)	0.021 (-0.228, 0.270)	0.87	
Age					0.29
<75 years	0.268 (0.169, 0.367)	0.292 (0.193, 0.392)	-0.025 (-0.165, 0.116)	0.73	
75 years or older	-0.178 (-0.345, -0.011)	-0.299 (-0.466, -0.132)	0.121 (-0.115, 0.357)	0.31	
Cognitive status†					0.79
MoCA≥normative 25 th percentile	0.197 (0.093, 0.300)	0.191 (0.086, 0.296)	0.005 (-0.142, 0.152)	0.94	
MoCA<normative 25 th percentile	0.085 (-0.061, 0.232)	0.045 (-0.101, 0.191)	0.040 (-0.167, 0.247)	0.70	
Frailty status ‡					0.91
Fit (FI≤0.10)	0.049 (-0.093, 0.191)	-0.028 (-0.168, 0.112)	0.077 (-0.122, 0.276)	0.45	
Less Fit (0.10<FI≤0.21)	0.030 (-0.082, 0.142)	0.033 (-0.079, 0.145)	-0.002 (-0.160, 0.156)	0.98	
Frail (FI>0.21)	0.426 (0.232, 0.621)	0.428 (0.226, 0.629)	-0.001 (-0.281, 0.279)	0.99	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, PCS Physical Component Summary Score, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S5. Mean annual change in score on the Patient Health Questionnaire (PHQ-9) overall and by subgroups.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	-0.030 (-0.062, 0.001)	-0.034 (-0.066, -0.003)	0.004 (-0.041, 0.049)	0.86	
Medical comorbidity index					0.59
Two or less	-0.025 (-0.082, 0.032)	-0.038 (-0.094, 0.017)	0.014 (-0.066, 0.093)	0.73	
Three or four	-0.098 (-0.153, -0.043)	-0.067 (-0.123, -0.010)	-0.032 (-0.110, 0.047)	0.43	
Five or six	-0.019 (-0.085, 0.047)	-0.015 (-0.084, 0.054)	-0.004 (-0.100, 0.091)	0.93	
Seven or more	0.076 (-0.008, 0.160)	0.016 (-0.066, 0.099)	0.060 (-0.058, 0.178)	0.32	
Mental comorbidity index					0.66
Zero	0.020 (-0.011, 0.051)	0.027 (-0.004, 0.058)	-0.007 (-0.051, 0.037)	0.75	
One	-0.088 (-0.186, 0.009)	-0.116 (-0.215, -0.017)	0.027 (-0.111, 0.166)	0.70	
Two or more	-0.336 (-0.490, -0.182)	-0.386 (-0.541, -0.230)	0.050 (-0.170, 0.269)	0.66	
Baseline VR-12 PCS					0.59
≥40	0.019 (-0.014, 0.051)	0.022 (-0.010, 0.054)	-0.004 (-0.049, 0.042)	0.87	
<40	-0.142 (-0.214, -0.069)	-0.165 (-0.239, -0.091)	0.023 (-0.080, 0.127)	0.66	
Age					0.68
<75 years	-0.089 (-0.128, -0.051)	-0.089 (-0.128, -0.051)	0.000 (-0.054, 0.054)	1.00	
75 years or older	0.146 (0.090, 0.201)	0.123 (0.068, 0.179)	0.022 (-0.056, 0.101)	0.58	
Cognitive status†					0.70
MoCA≥normative 25 th percentile	-0.039 (-0.077, -0.001)	-0.034 (-0.073, 0.004)	-0.005 (-0.059, 0.050)	0.87	
MoCA<normative 25 th percentile	-0.018 (-0.073, 0.037)	-0.031 (-0.086, 0.023)	0.013 (-0.064, 0.091)	0.73	
Frailty status ‡					0.69
Fit (FI≤0.10)	0.082 (0.040, 0.125)	0.113 (0.071, 0.155)	-0.030 (-0.090, 0.030)	0.32	
Less Fit (0.10<FI≤0.21)	0.036 (-0.001, 0.073)	0.024 (-0.013, 0.061)	0.012 (-0.04, 0.065)	0.65	
Frail (FI>0.21)	-0.224 (-0.308, -0.141)	-0.255 (-0.342, -0.169)	0.031 (-0.089, 0.151)	0.61	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, PCS Physical Component Summary Score, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S6. Sensitivity analysis for the Veterans RAND 12-item Health Survey (VR-12) Physical Component Summary Scores (PCS) overall and by subgroups with follow-up through December 1st, 2015 instead of August 20th, 2015.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	-0.227 (-0.299, -0.154)	-0.250 (-0.323, -0.177)	0.023 (-0.080, 0.126)	0.66	
Medical comorbidity index					0.05
Two or less	-0.440 (-0.565, -0.315)	-0.266 (-0.389, -0.143)	-0.174 (-0.349, 0.001)	0.05	
Three or four	-0.115 (-0.243, 0.012)	-0.267 (-0.396, -0.138)	0.152 (-0.030, 0.334)	0.10	
Five or six	-0.148 (-0.304, 0.008)	-0.308 (-0.471, -0.145)	0.160 (-0.066, 0.386)	0.17	
Seven or more	-0.215 (-0.404, -0.025)	-0.143 (-0.329, 0.042)	-0.071 (-0.336, 0.194)	0.60	
Mental comorbidity index					0.67
Zero	-0.224 (-0.306, -0.142)	-0.272 (-0.354, -0.189)	0.048 (-0.068, 0.164)	0.42	
One	-0.237 (-0.428, -0.046)	-0.214 (-0.407, -0.020)	-0.023 (-0.295, 0.249)	0.87	
Two or more	-0.218 (-0.475, 0.039)	-0.117 (-0.379, 0.144)	-0.100 (-0.467, 0.266)	0.59	
Baseline VR-12 PCS					0.39
≥40	-0.856 (-0.933, -0.779)	-0.827 (-0.904, -0.750)	-0.029 (-0.138, 0.080)	0.60	
<40	1.224 (1.081, 1.368)	1.160 (1.013, 1.307)	0.065 (-0.140, 0.27)	0.54	
Age					0.42
<75 years	-0.136 (-0.22, -0.051)	-0.180 (-0.265, -0.096)	0.045 (-0.075, 0.164)	0.46	
75 years or older	-0.515 (-0.66, -0.371)	-0.463 (-0.608, -0.318)	-0.052 (-0.257, 0.153)	0.62	
Cognitive status†					0.72
MoCA≥normative 25 th percentile	-0.282 (-0.372, -0.192)	-0.291 (-0.383, -0.200)	0.009 (-0.119, 0.137)	0.89	
MoCA<normative 25 th percentile	-0.135 (-0.258, -0.012)	-0.183 (-0.304, -0.062)	0.048 (-0.125, 0.221)	0.59	
Frailty status ‡					0.68
Fit (FI≤0.10)	-0.855 (-0.981, -0.730)	-0.755 (-0.879, -0.632)	-0.100 (-0.276, 0.076)	0.27	
Less Fit (0.10<FI≤0.21)	-0.380 (-0.476, -0.283)	-0.396 (-0.493, -0.299)	0.017 (-0.120, 0.153)	0.81	
Frail (FI>0.21)	0.474 (0.316, 0.633)	0.452 (0.290, 0.613)	0.023 (-0.203, 0.249)	0.84	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S7. Sensitivity analysis for the Veterans RAND 12-item Health Survey (VR-12) Mental Component Summary Scores overall and by subgroups with follow-up through December 1st, 2015 instead of August 20th, 2015.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	0.172 (0.094, 0.25)	0.109 (0.031, 0.187)	0.063 (-0.047, 0.173)	0.26	
Medical comorbidity index					0.54
Two or less	0.227 (0.082, 0.371)	0.235 (0.093, 0.376)	-0.008 (-0.210, 0.194)	0.94	
Three or four	0.271 (0.136, 0.406)	0.268 (0.132, 0.405)	0.003 (-0.189, 0.195)	0.98	
Five or six	0.180 (0.015, 0.345)	-0.007 (-0.180, 0.166)	0.187 (-0.052, 0.426)	0.13	
Seven or more	-0.126 (-0.323, 0.070)	-0.255 (-0.447, -0.063)	0.129 (-0.146, 0.404)	0.36	
Mental comorbidity index					0.70
Zero	0.068 (-0.016, 0.152)	-0.018 (-0.102, 0.067)	0.086 (-0.034, 0.205)	0.16	
One	0.306 (0.087, 0.525)	0.340 (0.118, 0.562)	-0.034 (-0.346, 0.278)	0.83	
Two or more	0.791 (0.489, 1.093)	0.699 (0.391, 1.006)	0.093 (-0.338, 0.523)	0.67	
Baseline VR-12 PCS					0.72
≥40	0.318 (0.230, 0.405)	0.256 (0.169, 0.343)	0.062 (-0.062, 0.185)	0.33	
<40	-0.168 (-0.327, -0.008)	-0.269 (-0.433, -0.105)	0.101 (-0.128, 0.330)	0.39	
Age					0.12
<75 years	0.274 (0.183, 0.364)	0.263 (0.172, 0.355)	0.010 (-0.118, 0.139)	0.88	
75 years or older	-0.118 (-0.271, 0.034)	-0.330 (-0.483, -0.176)	0.211 (-0.005, 0.427)	0.06	
Cognitive status†					0.53
MoCA≥normative 25 th percentile	0.193 (0.098, 0.287)	0.159 (0.063, 0.255)	0.034 (-0.101, 0.169)	0.62	
MoCA<normative 25 th percentile	0.138 (0.003, 0.273)	0.030 (-0.103, 0.163)	0.108 (-0.081, 0.297)	0.26	
Frailty status ‡					0.88
Fit (FI≤0.10)	0.029 (-0.103, 0.160)	-0.040 (-0.169, 0.090)	0.068 (-0.117, 0.253)	0.47	
Less Fit (0.10<FI≤0.21)	0.054 (-0.048, 0.156)	0.017 (-0.085, 0.120)	0.037 (-0.108, 0.182)	0.62	
Frail (FI>0.21)	0.471 (0.291, 0.651)	0.369 (0.186, 0.553)	0.102 (-0.155, 0.358)	0.44	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, PCS Physical Component Summary Score, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S8. Sensitivity analysis for the Patient Health Questionnaire (PHQ-9) scores overall and by subgroups with follow-up through December 1st, 2015 instead of August 20th, 2015.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	-0.042 (-0.071, -0.013)	-0.028 (-0.057, 0.001)	-0.014 (-0.055, 0.027)	0.51	
Medical comorbidity index					0.65
Two or less	-0.046 (-0.098, 0.005)	-0.027 (-0.077, 0.023)	-0.019 (-0.091, 0.053)	0.60	
Three or four	-0.093 (-0.143, -0.043)	-0.066 (-0.116, -0.015)	-0.027 (-0.098, 0.044)	0.46	
Five or six	-0.049 (-0.110, 0.012)	-0.014 (-0.077, 0.050)	-0.035 (-0.124, 0.053)	0.43	
Seven or more	0.076 (-0.003, 0.154)	0.033 (-0.044, 0.109)	0.043 (-0.067, 0.153)	0.44	
Mental comorbidity index					0.68
Zero	0.006 (-0.022, 0.035)	0.032 (0.003, 0.060)	-0.025 (-0.065, 0.015)	0.22	
One	-0.100 (-0.189, -0.011)	-0.119 (-0.208, -0.029)	0.019 (-0.107, 0.145)	0.77	
Two or more	-0.334 (-0.475, -0.192)	-0.341 (-0.485, -0.198)	0.008 (-0.194, 0.209)	0.94	
Baseline VR-12 PCS					0.92
≥40	0.008 (-0.021, 0.038)	0.023 (-0.006, 0.053)	-0.015 (-0.057, 0.027)	0.49	
<40	-0.155 (-0.222, -0.089)	-0.146 (-0.214, -0.077)	-0.010 (-0.105, 0.086)	0.84	
Age					0.61
<75 years	-0.098 (-0.133, -0.063)	-0.079 (-0.114, -0.044)	-0.019 (-0.069, 0.031)	0.45	
75 years or older	0.124 (0.074, 0.175)	0.119 (0.068, 0.170)	0.005 (-0.066, 0.077)	0.89	
Cognitive status†					0.45
MoCA≥normative 25 th percentile	-0.051 (-0.086, -0.016)	-0.024 (-0.059, 0.012)	-0.027 (-0.077, 0.022)	0.28	
MoCA<normative 25 th percentile	-0.027 (-0.078, 0.024)	-0.031 (-0.081, 0.019)	0.004 (-0.067, 0.076)	0.90	
Frailty status ‡					0.85
Fit (FI≤0.10)	0.077 (0.038, 0.116)	0.108 (0.070, 0.147)	-0.032 (-0.087, 0.023)	0.26	
Less Fit (0.10<FI≤0.21)	0.027 (-0.007, 0.061)	0.026 (-0.008, 0.060)	0.001 (-0.047, 0.049)	0.97	
Frail (FI>0.21)	-0.248 (-0.325, -0.170)	-0.233 (-0.312, -0.154)	-0.014 (-0.125, 0.096)	0.80	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, PCS Physical Component Summary Score, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S9. Sensitivity analysis for the Veterans RAND 12-item Health Survey (VR-12) Physical Component Summary Scores (PCS) overall and by subgroups, censoring participants after the occurrence of non-fatal cardiovascular events with follow-up through August 20th, 2015.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	-0.228 (-0.309, -0.148)	-0.177 (-0.258, -0.095)	-0.052 (-0.166, 0.062)	0.37	
Medical comorbidity index					0.25
Two or less	-0.382 (-0.521, -0.244)	-0.208 (-0.344, -0.072)	-0.174 (-0.369, 0.020)	0.08	
Three or four	-0.149 (-0.289, -0.008)	-0.241 (-0.385, -0.097)	0.092 (-0.109, 0.294)	0.37	
Five or six	-0.204 (-0.378, -0.030)	-0.200 (-0.383, -0.017)	-0.004 (-0.256, 0.249)	0.98	
Seven or more	-0.191 (-0.397, 0.016)	-0.018 (-0.222, 0.187)	-0.173 (-0.463, 0.118)	0.24	
Mental comorbidity index					0.91
Zero	-0.235 (-0.325, -0.144)	-0.169 (-0.260, -0.077)	-0.066 (-0.195, 0.062)	0.31	
One	-0.192 (-0.405, 0.021)	-0.183 (-0.400, 0.034)	-0.009 (-0.313, 0.295)	0.95	
Two or more	-0.221 (-0.508, 0.065)	-0.213 (-0.507, 0.081)	-0.008 (-0.419, 0.403)	0.97	
Baseline VR-12 PCS					0.15
≥40	-0.912 (-0.995, -0.829)	-0.789 (-0.873, -0.706)	-0.122 (-0.240, -0.004)	0.04	
<40	1.372 (1.213, 1.530)	1.320 (1.157, 1.483)	0.052 (-0.175, 0.279)	0.65	
Age					0.11
<75 years	-0.136 (-0.229, -0.043)	-0.134 (-0.228, -0.040)	-0.002 (-0.134, 0.130)	0.98	
75 years or older	-0.537 (-0.698, -0.376)	-0.317 (-0.480, -0.154)	-0.22 (-0.448, 0.009)	0.06	
Cognitive status†					0.59
MoCA≥normative 25 th percentile	-0.287 (-0.386, -0.188)	-0.212 (-0.313, -0.110)	-0.076 (-0.217, 0.066)	0.30	
MoCA<normative 25 th percentile	-0.131 (-0.267, 0.005)	-0.122 (-0.258, 0.014)	-0.009 (-0.201, 0.183)	0.93	
Frailty status ‡					0.62
Fit (FI≤0.10)	-0.900 (-1.036, -0.764)	-0.708 (-0.842, -0.573)	-0.192 (-0.384, -0.001)	0.05	
Less Fit (0.10<FI≤0.21)	-0.372 (-0.477, -0.266)	-0.327 (-0.433, -0.220)	-0.045 (-0.195, 0.105)	0.56	
Frail (FI>0.21)	0.479 (0.304, 0.655)	0.540 (0.357, 0.723)	-0.061 (-0.314, 0.193)	0.64	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S10. Sensitivity analysis for the Veterans RAND 12-item Health Survey (VR-12) Mental Component Summary Scores overall and by subgroups, censoring participants after the occurrence of non-fatal cardiovascular events with follow-up through August 20th, 2015.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	0.171 (0.085, 0.257)	0.164 (0.077, 0.251)	0.007 (-0.116, 0.129)	0.91	
Medical comorbidity index					0.51
Two or less	0.225 (0.065, 0.384)	0.262 (0.105, 0.419)	-0.037 (-0.261, 0.186)	0.74	
Three or four	0.267 (0.117, 0.417)	0.333 (0.179, 0.487)	-0.066 (-0.281, 0.149)	0.55	
Five or six	0.188 (0.006, 0.371)	0.007 (-0.184, 0.198)	0.181 (-0.083, 0.446)	0.18	
Seven or more	-0.140 (-0.354, 0.075)	-0.138 (-0.351, 0.074)	-0.002 (-0.303, 0.300)	0.99	
Mental comorbidity index					0.94
Zero	0.059 (-0.033, 0.152)	0.040 (-0.053, 0.133)	0.019 (-0.112, 0.150)	0.77	
One	0.315 (0.070, 0.560)	0.332 (0.082, 0.582)	-0.017 (-0.367, 0.333)	0.92	
Two or more	0.803 (0.468, 1.139)	0.823 (0.479, 1.168)	-0.020 (-0.501, 0.461)	0.94	
Baseline VR-12 PCS					0.70
≥40	0.339 (0.243, 0.435)	0.309 (0.212, 0.406)	0.030 (-0.107, 0.166)	0.67	
<40	-0.234 (-0.411, -0.056)	-0.207 (-0.39, -0.025)	-0.026 (-0.281, 0.228)	0.84	
Age					0.26
<75 years	0.268 (0.168, 0.368)	0.304 (0.203, 0.406)	-0.036 (-0.179, 0.106)	0.62	
75 years or older	-0.111 (-0.281, 0.059)	-0.236 (-0.408, -0.064)	0.125 (-0.117, 0.367)	0.31	
Cognitive status†					0.84
MoCA≥normative 25 th percentile	0.210 (0.106, 0.314)	0.212 (0.105, 0.319)	-0.002 (-0.151, 0.147)	0.98	
MoCA<normative 25 th percentile	0.109 (-0.040, 0.259)	0.085 (-0.063, 0.234)	0.024 (-0.187, 0.234)	0.82	
Frailty status ‡					0.77
Fit (FI≤0.10)	0.047 (-0.095, 0.189)	-0.048 (-0.189, 0.093)	0.096 (-0.105, 0.296)	0.35	
Less Fit (0.10<FI≤0.21)	0.039 (-0.074, 0.153)	0.045 (-0.069, 0.159)	-0.006 (-0.166, 0.155)	0.94	
Frail (FI>0.21)	0.460 (0.262, 0.659)	0.509 (0.302, 0.716)	-0.049 (-0.336, 0.238)	0.74	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, PCS Physical Component Summary Score, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S11. Sensitivity analysis for the Patient Health Questionnaire (PHQ-9) scores overall and by subgroups, censoring participants after the occurrence of non-fatal cardiovascular events with follow-up through August 20th, 2015.

Group	Intensive-treatment Mean change/yr (95% CI)*	Standard-treatment Mean change/yr (95% CI)*	Intensive - Standard Difference (95% CI)*	p-value	Interaction p-value
All	-0.036 (-0.068, -0.004)	-0.051 (-0.083, -0.018)	0.015 (-0.031, 0.061)	0.52	
Medical comorbidity index					0.38
Two or less	-0.033 (-0.090, 0.025)	-0.051 (-0.107, 0.006)	0.018 (-0.063, 0.099)	0.66	
Three or four	-0.104 (-0.160, -0.049)	-0.080 (-0.137, -0.022)	-0.025 (-0.105, 0.055)	0.54	
Five or six	-0.014 (-0.081, 0.053)	-0.018 (-0.088, 0.052)	0.004 (-0.093, 0.101)	0.93	
Seven or more	0.072 (-0.013, 0.157)	-0.024 (-0.108, 0.061)	0.095 (-0.024, 0.215)	0.12	
Mental comorbidity index					0.65
Zero	0.016 (-0.015, 0.047)	0.012 (-0.020, 0.043)	0.004 (-0.040, 0.048)	0.85	
One	-0.098 (-0.196, 0.001)	-0.131 (-0.232, -0.031)	0.034 (-0.107, 0.174)	0.64	
Two or more	-0.34 (-0.496, -0.183)	-0.408 (-0.568, -0.247)	0.068 (-0.156, 0.292)	0.55	
Baseline VR-12 PCS					0.55
≥40	0.014 (-0.018, 0.047)	0.007 (-0.026, 0.040)	0.007 (-0.039, 0.053)	0.76	
<40	-0.147 (-0.221, -0.073)	-0.185 (-0.261, -0.109)	0.038 (-0.068, 0.144)	0.48	
Age					0.34
<75 years	-0.092 (-0.131, -0.054)	-0.096 (-0.135, -0.057)	0.004 (-0.052, 0.059)	0.90	
75 years or older	0.137 (0.081, 0.193)	0.082 (0.025, 0.139)	0.055 (-0.025, 0.135)	0.18	
Cognitive status†					0.54
MoCA≥normative 25 th percentile	-0.047 (-0.085, -0.009)	-0.049 (-0.088, -0.009)	0.002 (-0.053, 0.057)	0.95	
MoCA<normative 25 th percentile	-0.018 (-0.074, 0.038)	-0.049 (-0.104, 0.007)	0.031 (-0.049, 0.110)	0.45	
Frailty status ‡					0.42
Fit (FI≤0.10)	0.081 (0.038, 0.124)	0.114 (0.071, 0.156)	-0.033 (-0.093, 0.028)	0.29	
Less Fit (0.10<FI≤0.21)	0.030 (-0.007, 0.067)	0.010 (-0.028, 0.047)	0.020 (-0.033, 0.073)	0.45	
Frail (FI>0.21)	-0.227 (-0.312, -0.141)	-0.288 (-0.377, -0.199)	0.061 (-0.063, 0.184)	0.33	

*Estimates from linear mixed model assuming linear change over time. † Based on age and education specific normative data from the Irish Longitudinal Study of Ageing, with two points added to the scores of Black and Hispanic participants. ‡ Frailty Index scores

range from 0 to 1, with higher scores denoting greater frailty. CI denotes Confidence Interval, PCS Physical Component Summary Score, MoCA Montreal Cognitive Assessment, and FI Frailty Index

TABLE S12. Sensitivity analyses for Veterans RAND 12 Item Health Survey (VR-12) scores based on multiple imputation

Outcome	Imputation Scenario	Shift (δ)	Intensive-treatment Mean Change/yr (95% CI)*	Standard-treatment Mean Change/yr (95% CI)*	Intensive - Standard Difference (95% CI)	p-value
VR-12 Physical Component Summary Score	Observed data	NA	-0.23 (-0.31, -0.16)	-0.23 (-0.31, -0.15)	-0.01 (-0.12, 0.11)	0.90
	MAR	0	-0.23 (-0.31, -0.15)	-0.23 (-0.31, -0.14)	0.00 (-0.12, 0.11)	0.95
	MNAR	1	-0.30 (-0.38, -0.22)	-0.23 (-0.31, -0.14)	-0.07 (-0.19, 0.04)	0.21
	MNAR	2	-0.37 (-0.45, -0.29)	-0.22 (-0.30, -0.14)	-0.15 (-0.26, -0.03)	0.014
	MNAR	3	-0.44 (-0.52, -0.35)	-0.22 (-0.31, -0.14)	-0.21 (-0.33, -0.10)	<0.001
	MNAR	4	-0.51 (-0.59, -0.43)	-0.23 (-0.31, -0.14)	-0.28 (-0.40, -0.17)	<0.001
Outcome	Imputation Scenario	Shift (δ)	Mean Change/yr (95% CI)*	Mean Change/yr (95% CI)*	Difference (95% CI)	p-value
VR-12 Mental Component Summary Score	Observed data	NA	0.15 (0.07, 0.24)	0.14 (0.05, 0.22)	0.02 (-0.10, 0.14)	0.79
	MAR	0	0.17 (0.08, 0.26)	0.14 (0.05, 0.23)	0.03 (-0.09, 0.15)	0.64
	MNAR	1	0.11 (0.02, 0.20)	0.14 (0.05, 0.23)	-0.03 (-0.16, 0.09)	0.63
	MNAR	2	0.04 (-0.04, 0.13)	0.14 (0.05, 0.22)	-0.09 (-0.22, 0.03)	0.14
	MNAR	3	-0.01 (-0.10, 0.07)	0.14 (0.05, 0.23)	-0.16 (-0.28, -0.03)	0.013
	MNAR	4	-0.08 (-0.17, 0.01)	0.14 (0.05, 0.23)	-0.22 (-0.34, -0.10)	0.001

MAR denotes missing at random, MNAR missing not at random, and CI Confidence Interval. *Estimates from mixed model assuming linear change over time.

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