

# Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study

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## Summary

**Background** Statins are commonly prescribed for management of dyslipidaemia and cardiovascular disease. Increased fitness is also associated with low mortality and is recommended as an essential part of promoting health. However, little information exists about the combined effects of fitness and statin treatment on all-cause mortality. We assessed the combined effects of statin treatment and fitness on all-cause mortality risk.

**Methods** In this prospective cohort study, we included dyslipidaemic veterans from Veterans Affairs Medical Centers in Palo Alto, CA, and Washington DC, USA, who had had an exercise tolerance test between 1986, and 2011. We assigned participants to one of four fitness categories based on peak metabolic equivalents (MET) achieved during exercise test and eight categories based on fitness status and statin treatment. The primary endpoint was all-cause mortality adjusted for age, body-mass index, ethnic origin, sex, history of cardiovascular disease, cardiovascular drugs, and cardiovascular risk factors. We assessed mortality from Veteran's Affairs' records on Dec 31, 2011. We compared groups with Cox proportional hazard model.

**Findings** We assessed 10043 participants (mean age 58·8 years, SD 10·9 years). During a median follow-up of 10·0 years (IQR 6·0–14·2), 2318 patients died, with an average yearly mortality rate of 22 deaths per 1000 person-years. Mortality risk was 18·5% (935/5046) in people taking statins versus 27·7% (1386/4997) in those not taking statins ( $p < 0·0001$ ). In patients who took statins, mortality risk decreased as fitness increased; for highly fit individuals ( $>9$  MET;  $n=694$ ), the hazard ratio (HR) was 0·30 (95% CI 0·21–0·41;  $p < 0·0001$ ) compared with least fit ( $\leq 5$  METs) patients (HR 1;  $n=1060$ ). For those not treated with statins, the HR for least fit participants ( $n=1024$ ) was 1·35 (95% CI 1·17–1·54;  $p < 0·0001$ ) and progressively decreased to 0·53 (95% CI 0·44–0·65;  $p < 0·0001$ ) for those in the highest fitness category ( $n=1498$ ).

**Interpretation** Statin treatment and increased fitness are independently associated with low mortality among dyslipidaemic individuals. The combination of statin treatment and increased fitness resulted in substantially lower mortality risk than either alone, reinforcing the importance of physical activity for individuals with dyslipidaemia.

**Funding** None.

## Introduction

Results of several clinical trials have shown that statin treatment substantially reduces morbidity and mortality of individuals with coronary heart disease.<sup>1–3</sup> On the basis of these findings, the Adult Treatment Panel 3 and other expert panels have issued guidelines<sup>4</sup> for statin treatment of patients with established coronary heart disease.<sup>5</sup> Trials also suggest that statin treatment provides health benefits for individuals with high risk of cardiovascular disease who do not have coronary heart disease.<sup>6–9</sup>

Expert panels on management of lipids have also emphasised the importance of lifestyle changes for reduction of cardiovascular risk.<sup>4,5</sup> These recommendations are based on evidence from large epidemiological studies. Data from these studies show inverse, graded, independent, and robust associations between physical activity (fitness) and mortality risk in apparently healthy participants<sup>10–16</sup> and in patients with cardiovascular disease, irrespective of age, sex, or comorbidities.<sup>14,17–20</sup> Mortality risk is highest for patients with low fitness; risk decreases as fitness increases irrespective of sex, presence of other risk factors, or age.<sup>14,15,17,19–21</sup>

Although a healthy lifestyle—including physical activity and fitness—is promoted as an essential component for prevention and management of coronary heart disease, little data are available regarding the combined health benefits of fitness and statin treatment. Furthermore, for dyslipidaemic patients who cannot take statins, whether increased mortality risk can be abated by increased fitness is unclear. We assessed the separate and combined effects of statin treatment and exercise capacity on all-cause mortality risk in veterans with dyslipidaemia.

## Methods

### Study design and patients

This prospective cohort study included patients from the Veterans Affairs Medical Centers in Washington, DC, USA and Palo Alto, CA, USA. The cohort was taken from a database of more than 20000 veterans who had dyslipidaemia (defined by the International Classification of Diseases) and who had a symptom-limited exercise tolerance test between 1986, and 2011. The test was administered either as part of a routine assessment or to assess exercise-induced ischaemia. This information, along with the patient's medical history, was electronically stored.

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Exclusion criteria were: history of an implanted pacemaker; development of left bundle branch block during the test; inability to complete the test because of musculoskeletal pain or impairments; exercise capacity less than 2 metabolic equivalents (MET); instability or need for emergency intervention; body-mass index less than 15.5 kg/m<sup>2</sup>; impaired chronotropic response to exercise; HIV/AIDS; and missing data.

The study was approved by the institutional review board at each institution, and all participants gave written informed consent.

### Procedures

Clinical characteristics and demographic and drug information were obtained from the patients' electronic medical record before the exercise tolerance test. Each individual was asked to verify the information, including history of chronic disease, current treatments, and smoking habits. Bodyweight and height were assessed by a standardised scale and recorded before the test.

Duration of statin treatment was based on the first and last date that statins were prescribed for each patient. Individuals were judged to be on statin treatment if these

two dates were more than 3 months apart. The most recent assessments of lipid and lipoprotein concentrations represent post-statin treatment values. For patients not taking statins, the lipid assessment values before diagnosis of dyslipidaemia represent the first assessment and the most recent lipid assessment represents the final value.

Exercise capacity was assessed by a standard treadmill test with the Bruce protocol at the centre in Washington DC, and by an individualised ramp protocol<sup>22</sup> at the Palo Alto centre. Peak exercise time was recorded in minutes. Peak exercise capacity (in MET) was estimated with standardised equations on the basis of peak speed and grade for the ramp protocol<sup>22</sup> and peak exercise time for the Bruce protocol.<sup>23</sup> One MET was defined as the energy expended at rest, which is roughly equivalent to an oxygen consumption of 3.5 mL per kg of bodyweight per min. Participants were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.<sup>24</sup> Use of handrails was allowed only if necessary for balance and safety. Age-predicted peak exercise heart rate was evaluated with a population-specific equation.<sup>25</sup> Drug regimens were not altered before testing.

	Entire cohort (n=10 043)	Taking statins (n=5033)	Not taking statins (n=5010)	p value
Age (years)	58.8 (10.9)	59.4 (10.4)	57.6 (11.3)	<0.0001
Weight (kg)	90.5 (17.7)	92.4 (17.8)	88.5 (17.3)	<0.0001
Body-mass index (kg/m <sup>2</sup> )	29.2 (5.2)	29.7 (5.3)	28.7 (5.2)	<0.0001
Resting heart rate (beats per min)	71 (13)	71 (13)	71 (13)	0.76
Resting systolic blood pressure (mm Hg)	131 (20)	130 (20)	131 (21)	0.11
Resting diastolic blood pressure (mm Hg)	79 (12)	79 (12)	79 (12)	0.25
Peak MET	7.4 (2.6)	6.9 (1.9)	7.8 (3.0)	<0.0001
Ethnic origin				
African-American	5192 (52%)	3346 (66%)	1846 (37%)	<0.0001
White	4425 (44%)	1624 (32%)	2801 (56%)	<0.0001
Other	426 (4%)	63 (1%)	363 (7%)	<0.0001
History of cardiovascular disease	4198 (42%)	2980 (59%)	1218 (24%)	<0.0001
Family history of cardiovascular disease	1687 (17%)	609 (12%)	1078 (22%)	<0.0001
Current smoker	2222 (22%)	1266 (25%)	956 (19%)	<0.0001
Hypertension	5500 (55%)	3032 (60%)	2468 (49%)	<0.0001
Type 2 diabetes mellitus	3775 (38%)	2075 (41%)	1700 (34%)	<0.0001
Drug treatments				
β blocker	1489 (15%)	860 (17%)	629 (13%)	<0.0001
Calcium channel blockers	1773 (18%)	963 (19%)	810 (16%)	<0.0001
Angiotensin-converting enzyme inhibitors	1869 (19%)	1249 (25%)	620 (12%)	<0.0001
Angiotensin receptor blockers	232 (2%)	200 (4%)	32 (1%)	<0.0001
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	1973 (20%)	1336 (26%)	637 (13%)	<0.0001
Diuretics	1271 (13%)	1025 (20%)	246 (5%)	<0.0001
Nitrates or vasodilators	546 (5%)	185 (4%)	361 (7%)	<0.0001
Aspirin	668 (7%)	480 (10%)	188 (4%)	<0.0001

Data are mean (SD) or n (%). p value calculated by Z test for ethnic origin, by  $\chi^2$  test for drug treatments and medical history (cardiovascular disease, hypertension, and diabetes mellitus), and by t test for of the remaining variables. MET=metabolic equivalents.

**Table 1: Baseline characteristics**

	Patients treated with statins				Patients not treated with statins			
	Before statin treatment (n=2959)	After statin treatment (n=2959)	Mean difference (95% CI)	p value	Initial (n=1433)	At follow-up (n=1433)	Mean difference (95% CI)	p value
Total cholesterol (mmol/L)	6.1 (0.8)	4.4 (1.2)	1.7 (1.6 to 1.7)	<0.0001	6.0 (0.8)	5.1 (1.1)	0.9 (0.8 to 0.9)	<0.0001
Triglycerides (mmol/L)	1.6 (0.9)	1.5 (1.0)	0.2 (0.1 to 0.2)	<0.0001	1.5 (0.9)	1.5 (0.8)	0.1 (0.0 to 0.2)	0.03
HDL cholesterol (mmol/L)	1.2 (0.3)	1.2 (0.3)	0.1 (0.0 to 0.1)	<0.0001	1.2 (0.4)	1.2 (0.4)	0.0 (0.0 to 0.0)	0.22
LDL cholesterol (mmol/L)	4.2 (0.7)	2.6 (1.0)	1.6 (1.5 to 1.6)	<0.0001	4.0 (0.8)	3.6 (0.9)	0.4 (0.4 to 0.5)	<0.0001

Data are mean (SD) unless stated otherwise. p values calculated by paired t test.

**Table 2: Lipid and lipoprotein concentrations**

We created four fitness categories on the basis of peak MET. Patients with a peak MET value of 5.0 or less (the lowest 25th percentile of the MET values achieved) were classed as least fit; those with a peak MET value of 5.1–7.0 (26th–50th percentile) were classed as moderately fit; those with a peak MET value of 7.1–9.0 (51st–75th percentile) were classed as fit; and those with a peak MET value of more than 9.0 (>75th percentile) were classed as highly fit. We formed two groups (treated with statins and not treated with statins) within each fitness category, giving eight categories in total.

The primary endpoint was death from any cause. Dates of death were first assessed from the database and verified from the Veterans Affairs Beneficiary Identification and the Record Locator System File. This system is used to calculate benefits for relatives of deceased veterans and is 95% complete and accurate.<sup>26</sup> Mortality was assessed on 31 Dec 31, 2011.

### Statistical analysis

Follow-up time is presented as median with IQRs. We calculated mortality rate as the ratio of events to person-years of follow-up. Continuous variables are presented as means and SDs and categorical variables as relative frequencies. We tested baseline associations between categorical variables with  $\chi^2$  or Z tests. We did one-way ANOVA and t tests to evaluate mean differences of normally distributed variables between individuals taking and not taking statins. We tested the assumption of equality of variances between groups by Levene's test, and the assumption of normality with probability–probability plots. We calculated hazard ratios (HRs) for all-cause mortality for the four fitness categories, the two statin treatment categories, and the eight fitness–statin categories with Cox proportional hazard models. We also assessed first order interactions between statin treatment and fitness groups. For the four fitness categories, the least fit category was the reference group. For the statin treatment categories, no statin treatment was the reference group. For the eight fitness–statin categories, the least fit, treated with statins category was the reference group. We also used Cox proportional hazard models to assess risk in the eight fitness–statin categories. We adjusted analyses for age, body-mass index, ethnic origin, sex, history of cardiovascular disease, cardiovascular medications

	Patients (n)	Deaths (n; %)	Unadjusted HR (95% CI)	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)*	p value†
<b>Whole cohort (n=10 043)</b>						
≤5.0 MET	2084	920 (44%)	1	1	1	..
5.1–7.0 MET	2727	726 (27%)	0.61 (0.55–0.67)	0.68 (0.62–0.75)	0.70 (0.63–0.77)	<0.0001
7.1–9.0 MET	3040	443 (15%)	0.34 (0.31–0.38)	0.48 (0.43–0.54)	0.50 (0.45–0.57)	<0.0001
>9.0 MET	2192	229 (10%)	0.22 (0.19–0.25)	0.35 (0.30–0.40)	0.38 (0.32–0.44)	<0.0001
<b>Patients taking statins (n=5032)</b>						
≤5.0 MET	1060	389 (37%)	1	1	1	..
5.1–7.0 MET	1573	329 (21%)	0.56 (0.49–0.65)	0.64 (0.55–0.74)	0.64 (0.55–0.74)	<0.0001
7.1–9.0 MET	1705	173 (10%)	0.28 (0.23–0.33)	0.40 (0.33–0.48)	0.41 (0.34–0.49)	<0.0001
>9.0 MET	694	39 (6%)	0.17 (0.12–0.23)	0.29 (0.21–0.41)	0.32 (0.23–0.45)	<0.0001
<b>Patients not taking statins (n=5011)</b>						
≤5.0 MET	1024	531 (52%)	1	1	1	..
5.1–7.0 MET	1154	397 (34%)	0.65 (0.57–0.74)	0.72 (0.64–0.82)	0.74 (0.65–0.84)	<0.0001
7.1–9.0 MET	1335	270 (20%)	0.40 (0.34–0.46)	0.56 (0.48–0.65)	0.57 (0.49–0.66)	<0.0001
>9.0 MET	1498	190 (13%)	0.22 (0.18–0.25)	0.35 (0.29–0.41)	0.37 (0.31–0.44)	<0.0001
<b>Excluding people in the least fit category (≤5.0 MET) who died within 2 years of follow-up (n=9797)</b>						
≤5.0 MET	1968	804 (41%)	1	1	1	..
5.1–7.0 MET	2662	661 (25%)	0.64 (0.57–0.70)	0.70 (0.64–0.76)	0.70 (0.63–0.77)	<0.0001
7.1–9.0 MET	2997	400 (13%)	0.35 (0.31–0.40)	0.50 (0.44–0.56)	0.50 (0.45–0.57)	<0.0001
>9.0 MET	2170	207 (10%)	0.22 (0.19–0.26)	0.35 (0.30–0.41)	0.38 (0.32–0.44)	<0.0001

HR=hazard ratio. MET=metabolic equivalents. \*Adjusted for age, body-mass index, ethnic origin, sex,  $\beta$  blockers, calcium channel blockers, angiotensin-converting enzymes, angiotensin receptor blockers, aspirin, diuretics, history of smoking, history of cardiovascular disease, hypertension, and diabetes mellitus. †For fully adjusted HR.

**Table 3: Mortality risk by fitness**

(angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$  blockers, calcium channel blocker, diuretics, vasodilators), and cardiovascular disease risk factors (hypertension, type 2 diabetes mellitus, smoking). We tested assumption of proportionality for all Cox proportional hazard analyses graphically, by plotting the cumulative hazards of the logarithms of the covariates; the proportionality assumption was fulfilled for each model. All hypotheses were two sided and p less than 0.05 was deemed statistically significant. We did all statistical analyses with SPSS (version 19.0).

### Role of the funding source

There was no funding source for this study. The corresponding author had full access to all data in the study and had final responsibility to submit it for publication.

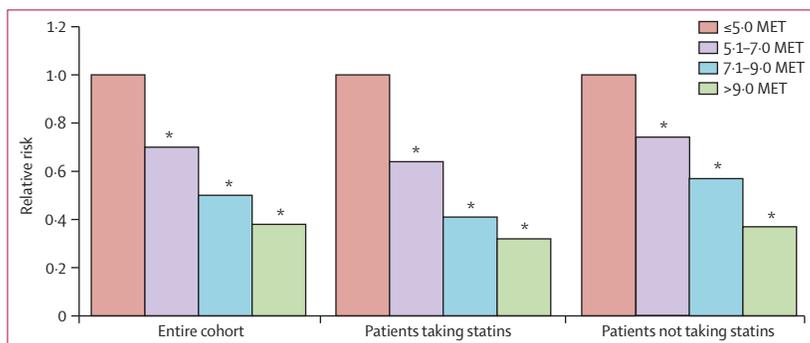


Figure: Relative mortality risk by fitness category

\*Significantly different from reference group. MET=metabolic equivalent.

	Deaths (n; %)	Unadjusted HR	Age-adjusted HR	Fully adjusted HR*	p value†
Least fit, statins (n=1060)	389 (37%)	1	1	1	..
Least fit, no statins (n=1024)	531 (52%)	1.22 (1.07-1.39)	1.22 (1.07-1.38)	1.35 (1.17-1.54)	<0.0001
Moderately fit, statins (n=1573)	329 (21%)	0.57 (0.49-0.66)	0.64 (0.56-0.75)	0.65 (0.56-0.75)	<0.0001
Moderately fit, no statins (n=1154)	397 (34%)	0.81 (0.70-0.93)	0.89 (0.77-1.02)	1.02 (0.88-1.12)	0.81
Fit, statins (n=1705)	173 (10%)	0.28 (0.23-0.33)	0.40 (0.33-0.48)	0.41 (0.34-0.49)	<0.0001
Fit, no statins (n=1335)	270 (20%)	0.50 (0.43-0.58)	0.69 (0.59-0.81)	0.81 (0.69-0.96)	0.01
Highly fit, statins (n=694)	39 (6%)	0.16 (0.12-0.22)	0.27 (0.19-0.38)	0.30 (0.21-0.41)	<0.0001
Highly fit, no statins (n=1498)	190 (13%)	0.27 (0.22-0.32)	0.42 (0.35-0.51)	0.53 (0.44-0.65)	<0.0001

\*Adjusted for age, body-mass index, β blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aspirin, diuretics, history of smoking, history of cardiovascular disease, hypertension, and diabetes mellitus. †For fully adjusted model.

Table 4: Mortality risk for the combined fitness and statin categories

## Results

We assessed 20023 people for eligibility. We enrolled 10043 veterans (9700 men and 343 women). 5192 were African-American (mean age 57.8 years, SD 10.7), 4425 were white (mean age 59.5 years, SD 10.9), and 426 were other (mean age 57.6 years, SD 11). Median follow-up was 10.0 years (IQR 6.0-14.2); providing 105 334 person-years. 2318 (23.1%) patients died (no data were missing), with an average yearly mortality of 22 deaths per 1000 person-years (95% CI 13-31). Patients not treated with statins had significantly higher mortality than did patients treated with statins (1386/4997 vs 935/5046 died; 27.7% vs 18.5%; p<0.0001). No interaction existed between site and METs (p=0.66) or ethnic origin and METs (p=0.40).

Individuals taking statins tended to be older and had a higher body-mass index and lower exercise capacity than those not taking statins (table 1). The prevalences of cardiovascular disease, smoking, hypertension, type 2 diabetes mellitus, and use of β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors,

angiotensin receptor blockers, diuretics, and aspirin were also higher in patients taking statins than in those not taking statins. Family history of cardiovascular disease, and use of nitrates or vasodilators was higher in patients not taking statins than in those taking statins.

Median duration of statin treatment was 70 months. For patients not treated with statins, median duration between the first and final lipid assessments was 51 months. Patients treated with statins had a significantly greater reduction in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides than did those not taking statins (table 2).

Significant predictors of all-cause mortality were: age (HR 1.05, 95% CI 1.04-1.05; p<0.0001), hypertension (1.22, 1.12-1.34; p<0.0001), smoking (1.26, 1.15-1.39; p<0.0001); type 2 diabetes (1.39, 1.27-1.51; p<0.0001), body-mass index (0.98, 0.97-0.99; p=0.001), and exercise capacity. For each 1 MET increase in exercise capacity, adjusted mortality decreased (HR 0.88, 95% CI 0.86-0.89; p<0.0001). Adjusted mortality risk was also significantly lower for patients taking statins than those not taking statins (0.65, 0.59-0.71; p<0.0001).

The effect of exercise capacity was stronger in the statin treatment group. For each 1 MET increase in exercise capacity, the HR for adjusted mortality was 0.83 (95% CI 0.80-0.87; p<0.0001) for those taking statins compared with 0.89 (95% CI 0.87-0.91; p<0.0001) for those not taking statins. The interaction between fitness categories and statin treatment also significantly affected mortality risk (p=0.007).

Table 3 and the figure show mortality risk across fitness categories. For the entire cohort in the final adjusted model, mortality risk progressively decreased as exercise capacity increased (table 3). Similarly, the adjusted risks for individuals treated with statins were progressively lower with increased exercise capacity.

To account for the possibility that the higher mortality rates in the low fitness categories were caused by underlying diseases (such as cachexia or musculoskeletal or peripheral vascular conditions) and not low fitness per se (reverse causality), patients who died within the first 2 years of follow-up (n=246) were excluded and the analyses were repeated. The association between exercise capacity and mortality risk remained (p<0.0001 for all comparisons) and the risk reduction did not change substantially from that in the entire cohort (table 3).

To test whether individuals treated with β blockers had lower exercise capacity and were consequently aggregated into a lower fitness category, we investigated the association between exercise capacity and mortality risk in patients treated and not treated with β blockers. Exercise capacity was slightly higher in participants not treated with β blockers than in those who were (mean 7.4 MET [SD 2.6] vs 7.1 MET [SD 2.4]; p=0.007). However, mortality risk trends between the fitness categories did not differ substantially for those treated and not treated with β blockers (data not shown).

To further explore the combined effect of fitness and statins, we did additional analyses to assess possible differences in mortality risk between those on statin treatment and those not on statin treatment. We used the least fit individuals on statins as the reference group, adjusting for age, body-mass index, hypertension, smoking, diabetes, sex, ethnic origin, cardiovascular disease, and cardiac drugs. Mortality risk was significantly higher for the least fit individuals not treated with statins (HR 1.35, 95% CI 1.17–1.54;  $p < 0.0001$ ). Mortality risk for moderately fit patients not taking statins did not differ from the reference group, but risk was lower for those in the next two fitness categories (table 4). For individuals taking statins, risk decreased progressively as fitness increased (table 4).

## Discussion

Our findings support the notion that both statin treatment and increased fitness lower mortality significantly and independently from other clinical characteristics. Our findings accord with previous reports regarding statin treatment for primary or secondary prevention of premature mortality in individuals at high risk of cardiovascular mortality.<sup>1–4</sup> Previous studies have also shown an inverse and graded association between fitness and mortality risk in apparently healthy individuals<sup>10,11,14,15</sup> and in those with hypertension,<sup>17</sup> diabetes mellitus,<sup>21,27,28</sup> and cardiovascular disease.<sup>13,20</sup> However, the present study offers some unique and clinically relevant information.

Combination of statin treatment and an exercise capacity of more than 5 MET lowers mortality risk substantially more than either alone, which is evident when assessing the effect of fitness on mortality risk in patients treated and not treated with statins (table 3). The combined effect of fitness and statin treatment on mortality risk is further shown by combining fitness and statin treatment status and using the least fit, statin group as the reference group (table 4). The most unfavourable combination was low exercise capacity and lack of statin therapy. Conversely, outcomes associated with high fitness and statin treatment were much more favourable. Collectively, these findings suggest that statin treatment combined with moderate fitness offers additional protection against premature mortality in individuals with dyslipidaemia. The absence of fitness, statin treatment, or both significantly increases the risk of mortality. Muscle complaints caused by statin treatment affect 25% of statin users, but can be easily dismissed by the patient and their doctor.<sup>29</sup> For patients who cannot be prescribed statins, achieving moderate fitness (7.1–9.0 MET) offers modest protection against premature mortality. For those with an exercise capacity of more than 9 MET, protection against premature mortality is at least as much (if not greater) as that for individuals in the moderate or fit range (5.1–9.0 METs) who take statins. Thus, physical activity, which improves fitness, is an efficacious and cost-effective means to prevent premature mortality and therefore should be promoted by health-care providers.

## Panel: Research in context

### Systematic review

A Medline search using the terms “exercise capacity or fitness”, “statin therapy”, “dyslipidemia”, and “mortality” in all combinations, produced no results. Several studies have examined the associations between exercise and mortality risk and between statin treatment and mortality risk, independently. We are unaware of any studies of the combined contribution of exercise capacity (fitness) and statin treatment on mortality risk.

### Interpretation

We report that both statin treatment and increased fitness lower all-cause mortality significantly and independently of other clinical characteristics in dyslipidaemic individuals. Additionally, the combination of statin treatment and fitness lowers mortality more than do either alone. The exercise capacity necessary to achieve protection that is much the same as or even greater than that achieved by statin treatment in unfit individuals is moderate and achievable for many middle-aged and older adults. This finding suggests that improved fitness is an attractive adjunct treatment to statins or an alternative when statins cannot be taken.

To our knowledge, this study is the only assessment of the combination of statin treatment and fitness for treatment of dyslipidaemic individuals (panel). We included the largest clinically referred cohort of dyslipidaemic individuals. Access to care was independent of a patient's financial status because it was provided by the Veterans Health Administration, which enabled epidemiological assessment while minimising the effect of disparities in medical care.<sup>30,31</sup> Equal access to care, along with the existence of electronic health records within the Veterans Health Administration system, enables history and alterations in health status to be analysed in detail. These factors, coupled with the similar trends when we excluded least fit individuals who died during the first 2 years of follow-up, reduce the effect of pre-existing disease on our findings. Reverse causality is unlikely and our findings support the validity of the association between fitness and statin treatment and mortality risk.

This work has several limitations because of its design. Mainly male veterans were included, which limits our ability to generalise the findings to women. We only had information for all-cause mortality, and did not have data for cardiovascular interventions or cardiovascular mortality. We have no data regarding adverse effects of statins to discern whether statin treatment interfered with exercise capacity. In this regard, use of statins was similar for the least fit (51%), fit (58%), and moderately fit (56%) patients, whereas highly fit participants used statins the least (38%).

We did not assess onset of chronic diseases, their severity, or duration of treatment. Our records also lacked dietary information. The two different exercise protocols used to assess fitness are also a potential limitation. Our previous work<sup>14</sup> suggests that the ramp protocol is more accurate measurement of MET. However, separate analyses from the two locations yielded similar results, suggesting that the differences in protocols had little effect. Fitness levels were based on the initial assessment and follow-up

data on fitness status were not available. Since the initial fitness assessment is likely to underestimate fitness status, the effect of fitness on mortality risk in our cohort is likely to be underestimated.

Finally, factors that influence a person's decision to take part in physical activity (and therefore likely to have increased fitness) or take statins are also likely to affect all-cause mortality. The present study was not designed to account for the effect of such covariates on mortality risk. Only randomised controlled trials can make such assessments. However, a randomised controlled trial of statin treatment and exercise would be too costly and ethically questionable. In this regard, our findings provide clinically relevant information with a substantial contribution to public health.

Our findings suggest that combination of statin treatment and fitness lowers all-cause mortality in dyslipidaemic individuals than do either alone. Improved fitness is an attractive adjunct treatment to statins or an alternative when statins cannot be prescribed. The low exercise capacity (roughly 7 MET) associated with the aforementioned health benefits is clinically significant and reinforces the importance of physical activity for individuals with dyslipidaemia.

#### Contributors

PK conceived and designed the study, collected, analysed, and interpreted the data, wrote the report, and directed the study. CF conceived and designed the study and assisted with interpretation of the data and writing of the report. JM collected data and assisted with interpretation of the data and writing of the report. DP oversaw analysis and interpretation of the data and writing of the report. MD assisted with interpretation of the data and writing of the report.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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