

# Association of Midlife Cardiorespiratory Fitness With Incident Depression and Cardiovascular Death After Depression in Later Life

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**IMPORTANCE** Cardiorespiratory fitness (hereinafter referred to as fitness) as estimated by exercise testing is a modifiable risk factor independently associated with chronic diseases, cardiovascular disease (CVD) events, and mortality, but the association of fitness at midlife with incidence of later-life depression and the risk of CVD mortality after a depression diagnosis is unknown.

**OBJECTIVE** To determine whether fitness measured in midlife would be inversely associated with later-life CVD mortality with antecedent depression.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective cohort study at a single-center, community-based preventive medicine clinic was performed as part of the Cooper Center Longitudinal Study. Data were collected from January 13, 1971, through December 31, 2009, and analyzed from October 6, 2015, through August 14, 2017. Participants included generally healthy men and women who presented for preventive medicine examinations at midlife and who were eligible for Medicare from 1999 to 2010. Those with a self-reported history of depression, myocardial infarction, or stroke at examination were excluded.

**EXPOSURES** Objective midlife fitness estimated from results of treadmill exercise testing.

**MAIN OUTCOMES AND MEASURES** Depression diagnosis from Medicare claims files using established algorithms and CVD mortality from National Death Index records.

**RESULTS** A total of 17 989 participants (80.2% men) with a mean (SD) age of 50.0 (8.7) years were included. After 117 218 person-years of Medicare follow-up, 2701 depression diagnoses, 610 deaths due to CVD without prior depression, and 231 deaths due to CVD after depression were observed. A high level of fitness in midlife was associated with a 16% lower risk of depression (hazard ratio [HR], 0.84; 95% CI, 0.74-0.95) compared with a low level of fitness. A high fitness level was also associated with a 61% lower risk of death due to CVD without depression (HR, 0.39; 95% CI, 0.31-0.48) compared with a low level of fitness. After a diagnosis of depression, a high fitness level was associated with a 56% lower risk of death due to CVD (HR, 0.44; 95% CI, 0.31-0.64) compared with a low fitness level.

**CONCLUSIONS AND RELEVANCE** Midlife fitness is associated with a lower risk of later-life depression, CVD mortality, and CVD mortality after incident later-life depression. These findings suggest the importance of midlife fitness in primary prevention of depression and subsequent CVD mortality in older age and should encourage physicians to consider fitness and physical activity in promoting healthy aging.

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Depression and depressive disorders are common conditions affecting older individuals and are associated with cardiovascular disease (CVD). In the presence of CVD events, the prevalence of depression is high, with as many as 1 in 5 patients with CVD having depression, especially after stroke.<sup>1</sup> Conversely, depression is linked with CVD mortality.<sup>2-4</sup> In fact, a 2014 American Heart Association Scientific Statement evaluated 53 studies and concluded that depression should be elevated as a risk factor for adverse outcomes in patients with acute coronary syndrome.<sup>5</sup>

Given that CVD remains a leading cause of death in the United States, primary prevention of CVD has been advocated through assessment of multiple risk factors and practice guidelines with ongoing updates.<sup>6</sup> The American Psychological Association has also encouraged engagement by psychologists in primary prevention for behavioral and mental disorders.<sup>7</sup> Considering the large health burden of depressive disorders, interventional approaches alone may be inadequate and lack cost-effectiveness, further supporting incorporation of a preventive approach.<sup>8,9</sup> Because many of the risk factors for depression, such as life events or adverse socioeconomic factors, are not easily modifiable, the specific approach to prevention may not be clear, and research specifically addressing long-term risk reduction in this area has been advocated.<sup>10</sup>

A modifiable risk factor for depressive and CVD conditions is cardiorespiratory fitness (hereinafter referred to as fitness).<sup>11-16</sup> Fitness is inversely associated with all-cause and CVD mortality<sup>11,13,17</sup> and a lower incidence of depression and physician visits concerning depression.<sup>18-21</sup>

Considering the link of depression to CVD, a modifiable risk factor such as fitness with the potential to lower the risk of depression and CVD sequelae in aging adults would be useful. However, the association between midlife fitness and later-life depression with subsequent CVD mortality has not been evaluated. We hypothesized that a higher level of fitness in middle age would be associated with a lower risk of depression in older age and a lower risk of CVD mortality after incident depression. By linking the Cooper Center Longitudinal Study (CCLS) with claims data from the Centers for Medicare & Medicaid Services, we studied the association of fitness in midlife with the subsequent risk of depression diagnosis and CVD mortality.

## Methods

### Study Population

The CCLS is an updated continuation of the Aerobics Center Longitudinal Study, an ongoing, prospective study at The Cooper Institute in Dallas, Texas, that began in 1970.<sup>11,13,22</sup> Patients evaluated at the Cooper Clinic and included as participants in the CCLS are generally well-educated, non-Hispanic white patients with access to health care. Patients receive a preventive medical examination that includes self-reported medical and lifestyle history, physician-administered physical examination, anthropometric measurements, fasting laboratory studies, and a maximal treadmill fitness assessment. Data were

### Key Points

**Question** Is higher cardiorespiratory fitness in midlife associated with a lower risk of cardiovascular mortality after incident depression past 65 years of age?

**Findings** In this cohort study of Medicare-eligible patients, higher levels of fitness in midlife were associated with a 16% lower risk of depression. In addition, after a diagnosis of depression, higher levels of fitness were associated with a 56% lower risk of cardiovascular mortality.

**Meaning** Men and women who are more physically fit at midlife have a lower risk of depression and cardiovascular mortality after a diagnosis of depression in later life, suggesting that fitness is an important part of a primary preventive strategy for cardiovascular disease and depression across the lifespan.

collected from January 13, 1971, through December 31, 2009. Participants provide written informed consent for inclusion in the research database, and the study is reviewed and approved annually by the institutional review board of The Cooper Institute.

A total of 19 241 patients enrolled in the CCLS who had complete information to determine their midlife health status and were enrolled in fee-for-service Medicare coverage from January 1, 1999, through December 31, 2009, were considered for inclusion in the study. After excluding 901 individuals with a history of depression and 351 individuals with a history of CVD, including myocardial infarction and stroke, at the time of the midlife examination, a final sample size of 17 989 was included in this analysis. Participants were followed up from the date of initiating Medicare coverage until death or the end of follow-up on December 31, 2009.

The measurements of baseline variables in the CCLS have been well described and were obtained in accordance with standard protocols.<sup>11,13</sup> Body mass index was calculated as measured weight in kilograms divided by measured height in meters squared. Seated resting blood pressure was obtained with a mercury sphygmomanometer. Fasting venous blood samples were assayed for serum cholesterol and glucose levels using standardized, automated techniques. The measurement of cardiorespiratory fitness was obtained from time to maximum effort using the modified Balke protocol.<sup>23</sup> The test time using this protocol is highly correlated with directly measured maximum oxygen uptake ( $r = 0.92$ ).<sup>24,25</sup> Each participant's treadmill time was categorized into age- and sex-specific quintiles derived from the CCLS as a whole, in accordance with a standard approach, using previously published definitions of fitness categories.<sup>11,26</sup> Quintile 1 represented low fitness; quintiles 2 and 3, moderate fitness; and quintiles 4 and 5, high fitness.

The outcome measure of depression was ascertained from Medicare administrative data obtained from the Centers for Medicare & Medicaid Services. The diagnosis was determined from the Chronic Condition Warehouse included in the Beneficiary Annual Summary File using established algorithms for research purposes.<sup>27,28</sup> Depression was defined using *International Classification of Diseases, Ninth Revision (ICD-9)* codes 296.20 to 296.36, 296.50 to 296.56, 296.60 to 296.66,

Table 1. Midlife Characteristics of CCLS Participants

Characteristic	Cardiorespiratory Fitness Category <sup>a</sup>		
	Low (n = 2959)	Moderate (n = 7230)	High (n = 7800)
Age at CCLS examination, mean (SD), y <sup>b</sup>	46.9 (8.5)	49.4 (8.7)	51.6 (8.5)
Age at Medicare entry, mean (SD), y	67.7 (4.7)	67.8 (5.0)	67.7 (4.9)
Medicare age, mean (SD), y <sup>c</sup>	74.2 (6.3)	74.5 (6.8)	74.2 (6.9)
Women, No. (%)	472 (16.0)	1306 (18.1)	1781 (22.8)
Smoking, No. (%) <sup>d</sup>	899 (30.0)	1332 (18.4)	637 (8.2)
Treadmill time, mean (SD), min	10.2 (2.9)	14.2 (3.1)	19.4 (4.3)
Fitness, mean (SD), MET	8.1 (1.4)	9.9 (1.4)	12.3 (2.1)
BMI, mean (SD)	27.9 (4.7)	26.1 (3.5)	24.4 (2.9)
Systolic blood pressure, mean (SD), mm Hg	123.6 (15.0)	121.3 (14.5)	120.8 (14.8)
Total cholesterol level, mean (SD), mg/dL	219.7 (41.2)	215.0 (39.1)	208.8 (37.0)
Fasting glucose level, mean (SD), mg/dL	103.3 (22.1)	100.6 (16.2)	98.5 (12.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCLS, Cooper Center Longitudinal Study; MET, metabolic equivalent.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

<sup>a</sup> Determined from age- and sex-adjusted CCLS quintiles as low fitness (quintile

1), moderate fitness (quintiles 2-3), and high fitness (quintiles 4-5).

<sup>b</sup> Indicates age at the time of initial assessment.

<sup>c</sup> Indicates mean of age attained during Medicare follow-up.

<sup>d</sup> Owing to missing data, denominators may be less than the column headings.

296.89, 298.0, 300.4, 309.1, and 311.<sup>29</sup> Mortality information was obtained from the National Death Index, and the underlying cause of death was defined by ICD-9 codes for deaths before 1999 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes for deaths from 1999 through 2009. Death due to CVD was defined by ICD-9 codes 410.0 to 458.9 and equivalent ICD-10 codes.

### Statistical Analyses

Data were analyzed from October 6, 2015, through August 14, 2017. Patient characteristics at midlife were summarized by fitness level, and incidence rates of depression and CVD death were compared across strata of fitness using an exponential survival model. A failure time model was used to investigate the multivariate outcomes of incident depression, CVD mortality without previous depression, and CVD mortality after the diagnosis of depression.<sup>30</sup> The model fits marginal Cox proportional hazards regression models to each outcome and uses the robust sandwich estimate of the covariance matrix to account for dependence of multiple failure times.<sup>31</sup> Models were fit to attained age and adjusted for midlife age, sex, year of examination, smoking, systolic blood pressure, cholesterol level, body mass index, and fasting glucose level. The proportional hazards assumption was tested using weighted Schoenfeld residuals, and terms for the covariate  $\times$  attained age were entered to address residual non-proportional hazards. A 2-sided *P* value of less than .05 was considered statistically significant. All analyses were programmed in SAS/STAT, version 9.4 (SAS Institute Inc). Unless otherwise indicated, data are expressed as mean (SD).

## Results

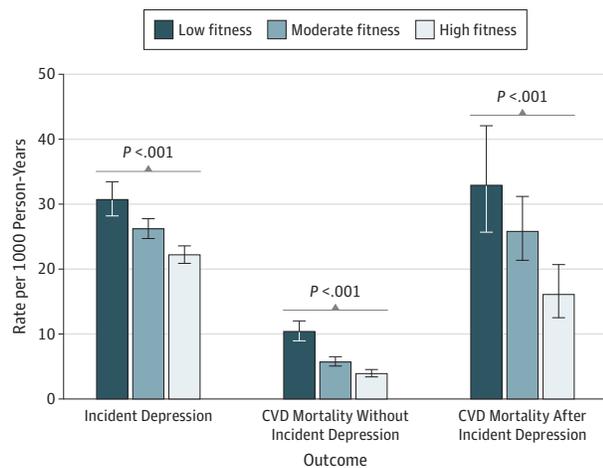
We included a total of 17 989 participants (3559 women [19.8%] and 14 430 men [80.2%]) with a mean (SD) age of 50.0 (8.7)

years at the midlife examination. Baseline midlife characteristics of the study participants by fitness category are summarized in **Table 1**. Compared with participants in the low fitness category, those in the high fitness category had a lower mean body mass index (24.4 [2.9] vs 27.9 [4.7]), lower systolic blood pressure (120.8 [14.8] vs 123.6 [15.0] mm Hg), and more favorable mean levels of total cholesterol (208.8 [37.0] vs 219.7 [41.2] mg/dL [to convert to millimoles per liter, multiply by 0.0259]) and fasting glucose (98.5 [12.3] vs 103.3 [22.1] mg/dL [to convert to millimoles per liter, multiply by 0.0555]) (Table 1).

After 117 218 person-years of follow up, we observed 2701 diagnoses of depression and 841 deaths due to CVD. Two hundred thirty-one deaths were due to CVD after incident depression and 610 without incident depression. Incidence rates of depression and CVD mortality are summarized in the **Figure**. The rates of depression diagnosis in later life as well as CVD mortality after depression and CVD mortality without incident depression showed significant declines from low to moderate to high fitness categories assessed in midlife. Compared with the low fitness category, the rate of depression in the high fitness category was 22.2 per 1000 person-years (1041 diagnoses) and 26.2 in the moderate fitness category (1136 diagnoses) vs 30.7 in the low fitness category (524 diagnoses). For CVD mortality without incident depression, the rate in the high fitness category was 3.9 deaths per 1000 person-years (184 deaths) vs 5.7 in the moderate fitness category (249 deaths) and 10.4 in the low fitness category (177 deaths); for CVD mortality after depression, the rate in the high fitness category was 16.1 deaths per 1000 person-years (61 deaths) vs 25.8 in the moderate fitness category (107 deaths) and 32.9 in the low fitness category (63 deaths) (Figure).

Multivariate analyses revealed a consistent association with higher midlife fitness and a lower risk of incident depression, CVD mortality, and CVD mortality after a diagnosis of depression (Table 2 and Table 3). In analyses stratified by midlife

**Figure. Incidence Rates of Depression, CVD Mortality Without Incident Depression, and CVD Mortality After Incident Depression by Fitness Category**



Fitness categories are determined from age- and sex-adjusted Cooper Center Longitudinal Study quintiles as low (quintile 1), moderate (quintiles 2-3), and high (quintiles 4-5). P value indicates significant difference for trend across fitness categories. Error bars represent 95% CI for rates. CVD indicates cardiovascular disease.

fitness categories and adjusted for traditional risk factors, the high fitness category was associated with a 16% lower risk of depression (hazard ratio [HR], 0.84; 95% CI, 0.74-0.95) and a 61% lower risk of CVD mortality (HR, 0.39; 95% CI, 0.31-0.48) compared with low fitness. In those with incident depression, high fitness was associated with a 56% lower risk of CVD death (HR, 0.44; 95% CI, 0.31-0.64) (Table 2). Similarly, in analyses with fitness entered as a continuous variable expressed in units of metabolic equivalent, higher fitness was associated with a lower risk of depression per metabolic equivalent (HR, 0.95; 95% CI, 0.93-0.97), lower risk of CVD mortality without incident depression (HR, 0.84; 95% CI, 0.80-0.88), and lower risk of CVD mortality after depression (HR, 0.87; 95% CI, 0.81-0.93) (Table 3).

## Discussion

In the present study, we observed 2 important findings. First, in a large, generally healthy cohort of men and women, higher midlife fitness was associated with lower risk of a depression diagnosis after 65 years of age. Second, not only was higher midlife fitness associated with a lower risk of CVD mortality, but importantly, it was also associated with a lower risk of CVD mortality when CVD death was preceded by depression. This association was notable in later life years after the fitness assessment.

Depression and CVD are the most common causes of disability in the developed nations of the world, a connection between depression and CVD has been recognized for a number of years,<sup>32</sup> and a higher prevalence of depression has been found in patients with myocardial infarction, stroke, and heart

**Table 2. Hazards for Incident Events by Fitness Categories<sup>a</sup>**

Incident Event by Fitness Category	HR (95% CI)	
	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>
Depression		
High	0.72 (0.64-0.80)	0.84 (0.74-0.95)
Moderate	0.84 (0.76-0.93)	0.92 (0.83-1.03)
Low	1 [Reference]	1 [Reference]
CVD mortality without incident depression		
High	0.33 (0.27-0.41)	0.39 (0.31-0.48)
Moderate	0.48 (0.39-0.58)	0.52 (0.43-0.64)
Low	1 [Reference]	1 [Reference]
CVD mortality after incident depression		
High	0.39 (0.27-0.56)	0.44 (0.31-0.64)
Moderate	0.69 (0.50-0.95)	0.74 (0.54-1.02)
Low	1 [Reference]	1 [Reference]

Abbreviations: CCLS, Cooper Center Logitudinal Study; CVD, cardiovascular disease; HR, hazard ratio.

<sup>a</sup> Determined from age- and sex-adjusted CCLS quintiles as low fitness (quintile 1), moderate fitness (quintiles 2-3), and high fitness (quintiles 4-5). Low fitness is the referent category for HRs.

<sup>b</sup> Adjusted for sex, age, examination year, and sex × stratum interaction.

<sup>c</sup> Adjusted for sex, age, examination year, systolic blood pressure, total cholesterol level, body mass index, smoking status, and sex × stratum interaction.

failure.<sup>33-35</sup> Reviews of published studies of depression as a risk factor for mortality in CVD and coronary heart disease<sup>3</sup> have shown considerable variation in methods, measurements, and cohorts and, in fact, some reluctance to assign depression as a risk factor for coronary heart disease because of the uncertainty as to the direction of causality. However, the preponderance of evidence supports classifying depression as a risk factor for adverse outcomes in CVD and coronary heart disease.<sup>2-5</sup> Several physiologic mechanisms that may be common to depression and CVD have been suggested to explain the observed associations. These mechanisms include inflammatory changes, platelet aggregation, hypothalamic-pituitary-adrenal axis dysregulation, and autonomic dysfunction leading to an increase in arrhythmia and myocardial ischemia.<sup>36-38</sup> Cardiorespiratory fitness has been shown to be favorably associated with risk of these proposed intermediaries, although the directionality of these associations is unclear.<sup>39-41</sup>

Higher fitness has been associated with a lower risk for all-cause and CVD mortality,<sup>11,13,42</sup> and improvement in fitness level has also been shown to be associated with lower mortality risk.<sup>26</sup> A number of studies have shown that higher fitness is associated with a lower risk of nonfatal outcomes, including myocardial infarction and heart failure, as well as depression.<sup>14,18,43,44</sup>

In an effort to intervene in CVD-associated depression from a psychological perspective, there has also been interest in depression screening among patients with CVD in different stages of disease and phases of treatment; however, screening methods and interventions are diverse, and the overall value of these efforts is inconsistent.<sup>45-47</sup> Furthermore, arguments have been presented for and against screening, referral, and treatment

Table 3. Hazards of Incident Events by Continuous Fitness

Incident Event	HR (95% CI) per MET Fitness			
	Model 1 <sup>a</sup>	P Value	Model 2 <sup>b</sup>	P Value
Depression	0.93 (0.91-0.95)	<.001	0.95 (0.93-0.97)	<.001
CVD mortality				
Without incident depression	0.82 (0.77-0.86)	<.001	0.84 (0.80-0.88)	<.001
After incident depression	0.84 (0.79-0.91)		0.87 (0.81-0.93)	

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent.

<sup>a</sup> Adjusted for sex, age, examination year, and sex × stratum interaction.

<sup>b</sup> Adjusted for sex, age, examination year, systolic blood pressure, total cholesterol level, body mass index, smoking status, and sex × stratum interaction.

of depression in patients with CVD based on current evidence and cost-effectiveness.<sup>5,45,46</sup>

Intervention studies have shown that exercise, which is known to increase fitness in individuals with depression,<sup>48</sup> has an evident antidepressant effect when used in individuals with mild to moderate depression in the short term.<sup>20</sup> A recent large cohort study of 33 908 healthy adults followed up for 11 years also showed that regular leisure time exercise of any intensity provided protection against future depression.<sup>9</sup> Prior work<sup>14,16</sup> has shown the association of higher levels of midlife fitness with a lower risk of CVD conditions in later life, such as stroke, that are associated with depression. In addition, fitness in the years before diagnosis of cancer can play a role in influencing the health outcomes after such a condition develops.<sup>49</sup>

Because effective, acute management of depression alone is not likely to relieve more than a portion of the overall burden of depressive disorders, early prevention of depression and CVD would be valuable if the primary risk modification was effective and enduring across the lifespan.<sup>6-9</sup> A new and interesting finding in this study is that higher fitness assessed in middle age is associated with a lower risk of CVD mortality even in the presence of incident depression, with the fitness effect extending many years into older age. Health care costs and use of services are greatly increased in the setting of heart disease combined with the comorbid condition of depression, and these findings suggest that lowering risk through early prevention efforts may have economic as well as health benefits.<sup>50,51</sup>

We were not able to gauge how changes in fitness would affect risk in the later years of the cohort; however, fitness<sup>50,51</sup> can be improved in most individuals by aerobic training, which need not be complicated or expensive.<sup>52,53</sup> Despite this finding, surveys indicate that only about 50% of adults meet aerobic exercise guidelines and far fewer meet muscle-strengthening and aerobic guidelines.<sup>54,55</sup>

### Strengths and Limitations

This study has several important strengths, including a large, homogeneous population and long follow-up. Although the primary racial/ethnic composition of non-Hispanic white pa-

tients and generally higher socioeconomic class may decrease generalizability, the healthy nature of this population with access to preventive health care allows evaluation of the association of fitness on a primordial basis and avoids the effect of unmeasured confounders. The association of risk factors and lifetime risk of CVD have been shown to be similar to that of the general population.<sup>42</sup> The fitness measurement is objective and hence provides a more accurate picture of midlife physical activity level than self-report would because fitness correlates well with activity level. In addition, the outcomes are based on administrative claims data provided by the health care professional and are likely more accurate than self-report, especially in older patients.<sup>56</sup>

Limitations include that diagnoses determined from Medicare claims data are not clinically adjudicated. We were not able to detect outcomes or physician visits occurring between the midlife examination and Medicare eligibility, nor were we able to determine severity of the depression. However, Medicare data has been used by other researchers with a similar approach to provide informative findings regarding the association of traditional risk factors with Medicare outcomes.<sup>57-59</sup> Of importance, information about the use of medication that could influence the presence or the absence of depression diagnosis is not available for this cohort. Finally, we cannot eliminate the possibility of depression and CVD leading to lower fitness levels. However, the relatively long mean period from fitness measure to Medicare observation makes such reverse causation less likely.

### Conclusions

This study shows that being fit at midlife is associated with a lower risk of later-life depression and subsequent CVD mortality, even in the presence of depression. These findings suggest the importance of fitness in primary prevention of heart disease and associated CVD mortality in older aging adults. This study further supports the critical need for health care professionals to consider fitness and physical activity as part of overall preventive care to promote healthy aging.

#### ARTICLE INFORMATION

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**Author Contributions:** Dr Willis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Willis, DeFina.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Willis, Martin, DeFina, Trivedi.

Critical revision of the manuscript for important

**Intellectual content:** Willis, Leonard, Barlow, DeFina. **Statistical analysis:** Willis, Leonard. **Administrative, technical, or material support:** Willis, Barlow, DeFina, Trivedi. **Supervision:** DeFina, Trivedi.

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