Midlife Fitness and the Development of Chronic Conditions in Later Life

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Background: The association between cardiorespiratory fitness and mortality is well described. However, the association between midlife fitness and the development of nonfatal chronic conditions in older age has not been studied.

Methods: To examine the association between midlife fitness and chronic disease outcomes in later life, participant data from the Cooper Center Longitudinal Study were linked with Medicare claims. We studied 18,670 healthy participants (21.1% women; median age, 49 years) who survived to receive Medicare coverage from January 1, 1999, to December 31, 2009. Fitness estimated by Balke treadmill time was analyzed as a continuous variable (in metabolic equivalents [METs]) and according to age- and sex-specific quintiles. Eight common chronic conditions were defined using validated algorithms, and associations between midlife fitness and the number of conditions were assessed using a modified Cox proportional hazards model that stratified the at-risk population by the number of conditions while adjusting for age, body mass index, blood pressure, cholesterol and glucose levels, alcohol use, and smoking.

Results: After 120,780 person-years of Medicare exposure with a median follow-up of 26 years, the highest quintile of fitness (quintile 5) was associated with a lower incidence of chronic conditions compared with the lowest quintile (quintile 1) in men (15.6 [95% CI, 15.0-16.2] vs 28.2 [27.4-29.0] per 100 person-years) and women (11.4 [10.5-12.3] vs 20.1 [18.7 vs 21.6] per 100 person-years). After multivariate adjustment, higher fitness (in METs) was associated with a lower risk of developing chronic conditions in men (hazard ratio, 0.95 [95% CI, 0.94-0.96] per MET) and women (0.94 [0.91-0.96] per MET). Among decedents (2406 [12.9%]), higher fitness was associated with lower risk of developing chronic conditions relative to survival (compression hazard ratio, 0.90 [95% CI, 0.88-0.92] per MET), suggesting morbidity compression.

Conclusions: In this cohort of healthy middle-aged adults, fitness was significantly associated with a lower risk of developing chronic disease outcomes during 26 years of follow-up. These findings suggest that higher midlife fitness may be associated with the compression of morbidity in older age.


Healthy aging has been well studied, with multiple reports describing an association of traditional cardiovascular risk factors, such as smoking and hypertension. Although physical activity (PA) likely represents an important determinant of healthy aging, studies have reported inconsistent results; therefore, the incremental contribution of PA to healthy aging beyond other healthy lifestyle characteristics remains unclear. The inverse association between cardiorespiratory fitness and mortality after adjustment for other risk factors is well established. In addition, compared with self-reported measures of PA, fitness levels are more strongly associated with mortality, reflecting, at least in part, the objective nature of their measurement.

See Invited Commentary at end of article

Therefore, we hypothesized that higher midlife fitness levels would be strongly associated with healthy aging as defined by a low burden of chronic condition (CC) outcomes. To test this hypothesis, we merged individual-level data from the Cooper Center Longitudinal Study (CCLS) with Medicare claims files from the Center for Medicare and Medicaid Services (CMS).
STUDY SAMPLE
The study sample was derived from the CCLS, which is a large cohort of individuals who have completed a preventive medicine examination at the Cooper Clinic in Dallas, Texas, from 1970 to 2009. Patients seen at the Cooper Clinic are generally well-educated non-Hispanic whites from middle to upper socioeconomic strata. Patients who are part of the CCLS receive a comprehensive clinical examination that includes self-reported personal and family history, standardized medical examination by a physician, anthropometric measurements, fasting laboratory studies, and a maximal treadmill exercise test. Participants provide written informed consent for inclusion in the research database. The study was reviewed and approved annually by the institutional review board of The Cooper Institute.

Among 73,439 participants in the CCLS who had complete data for analysis, 24,809 became 65 years or older between January 1, 1999, and December 31, 2009, and were eligible to receive Medicare coverage. After excluding 2,973 participants (12.0%) lacking traditional Medicare fee-for-service coverage (ie, Medicare Advantage participants lacking claims files), we excluded an additional 2,593 participants (10.3%) with a self-reported history of myocardial infarction, stroke, cancer, chronic lung disease, or diabetes mellitus as defined by self-report or fasting blood glucose level of 126 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555) at study entry. An additional 807 individuals (2.4%) whose CCLS examination occurred after enrollment into a Medicare fee-for-service plan or were receiving early (younger than 65 years) eligibility coverage because of disability or renal dialysis were excluded, leaving a study sample of 18,670 (21.1% women) CCLS participants for the present analysis.

CLINICAL VARIABLES
Fitness was assessed by maximal effort using the modified Balke protocol, as previously described.17 The test time using this protocol correlates highly with directly measured maximal oxygen uptake (r=0.92).18,19 In accordance with standard approaches to the analysis of fitness data,8,9 each participant’s treadmill time was classified into age- and sex-specific quintiles of fitness, with low fitness represented as quintile 1. Details of the treadmill times across fitness quintiles are reported by age and sex groups in eTable 1 (http://www.archinternmed.com). Using well-characterized regression equations, treadmill times from the Balke protocol also allow for estimation of fitness level in metabolic equivalents (METs).18,20

The measurement of other baseline variables in the CCLS has been well described.8,9,21 Body mass index (calculated as weight in kilograms divided by height in meters squared) was determined using a standard clinical scale and stadiometer. Seated resting blood pressure was obtained with a mercury sphygmomanometer. Venous blood obtained when the participant was seated was used for laboratory studies, and a maximal treadmill exercise test. Participants provide written informed consent for inclusion in the research database. The study was reviewed and approved annually by the institutional review board of The Cooper Institute.

We determined the overall burden of CCs at ages 70, 75, 80, and 85 years by classifying all participants alive at these ages into different strata according to the presence of each of the 8 CCs. This required that the earliest indication of the condition occurred before or at the attained age among survivors. We calculated the incidence of CCs by dividing the number of diagnoses by the total observation time. Because patients could develop more than 1 CC during the surveillance period, a modified multivariate failure time model was used.26,27 Death during the surveillance period and survival to the end of the surveillance period were considered censoring events. We used attained age as the time scale, relegateing all age effects to the baseline hazard characterizing each event stratum. Midlife fitness was entered as a continuous variable (in METs). Men and women were modeled separately. We accommodated possible departures from proportional hazards by testing for and retaining significant covariate by attained age effects. Main effects were estimated at the mean attained age.

To assess the association between fitness and (1) the development of a CC or (2) death, we conducted additional analyses among the subset of participants who died during the observation period, using a similar modeling approach.26,29 In this model, we treated death as an outcome of interest rather than a censoring event. This model therefore allowed transitions to death as well as to higher CC states. The estimates for the effect of fitness on the transition to (1) an additional CC or (2) death were compared using the Wald $\chi^2$ statistic. This comparison takes the form of a ratio of relative risks in which each relative risk is for CCs relative to death, and the numerator is evaluated at 1-MET higher fitness than the denominator. We refer to this ratio as the morbidity compression ratio; values significantly less than 1 offer evidence of compression of morbidity. Finally, to compare descriptively the association between fitness and CC burden at the end of life, for each level of fitness we partitioned the remaining years of follow-up according to the time spent at each level of CC burden.

$P<.05$ (2-sided) was considered statistically significant. All statistical analyses were performed using commercial software (SAS for Windows, release 9.2; SAS Institute, Inc).
Baseline characteristics for 14,726 men and 3944 women in the study sample are reported in Table 1, demonstrating low levels of traditional risk factors at study entry. As expected, fitness levels were higher in men compared with women, with higher levels of traditional risk factors in the lower fitness strata. After 120,780 person-years of Medicare follow-up, there was considerable variation in the prevalence of CC burden by attained age and across conditions (Figure).

The association between midlife fitness and the incidence of CCs is provided in Table 2, demonstrating a higher incidence of CCs across levels of fitness measured in midlife. The highest level of midlife fitness (quintile 5) was associated with a lower incidence of CCs compared with low midlife fitness (quintile 1) in men (15.6 [95% CI, 15.0-16.2] vs 28.2 [27.4-29.0] per 100 person-years) and women (11.4 [10.5-12.3] vs 20.1 [18.7 vs 21.6] per 100 person-years). After multivariate adjustment, higher fitness was associated with a lower risk of developing CCs (men: hazard ratio [HR], 0.95 [0.94-0.96] per MET; women: HR, 0.94 [0.91-0.96] per MET; P < .001 for all comparisons) (Table 3). In men, higher blood pressure, higher total cholesterol, higher body mass index, higher glucose, and smoking prevalence were associated with a higher risk of developing CC outcomes (Table 3). Overall, a comparable pattern of results was observed for women but with wider CIs.

When each of the 8 CCs was removed from the list of CCs in separate sensitivity analyses, the association between lower fitness and the risk of CC outcomes re-
mained unchanged, suggesting that our findings are insensitive to any particular set of CCs (eTable 2). In an additional sensitivity analysis, when these data were stratified by the median age (49 years) at examination, we observed a similar pattern of results for fitness levels measured in younger participants (men: HR, 0.94 [0.92-0.95]; women: 0.92 [0.88-0.96]) and older participants (men: HR, 0.95 [0.93-0.96]; women: 0.94 [0.91-0.97]; P < .001 for all comparisons).

By the end of the follow-up period, there were 2406 deaths (12.9%) with 13 759 person-years of Medicare follow-up, representing approximately 5 years of fol-
In the present study, higher fitness measured in midlife was strongly associated with a lower incidence of CCs decades later. Furthermore, higher midlife fitness was more strongly associated with a delay in the onset of CCs than with overall survival, suggesting that higher fitness in midlife is associated with the compression of morbidity in later life.

We observed clinically significant associations between midlife fitness levels and chronic disease burden in later life. At lower fitness levels, where the association was strongest (Table 2), our data suggest that a modest increase in fitness could translate into marked reduction of CCs in older age. For example, a 1- to 2-MET improvement in fitness resulting in promotion from the first to the second fitness quintile at age 50 years was associated with a 20% reduction in the incidence of CCs at ages 65 and older. Previous PA intervention studies30-32 have achieved mean fitness gains of this magnitude using a 6-month program of 150 minutes per week of moderate-intensity exercise.

Studies have examined the association between risk factors in midlife and healthy aging,14-6,7,27 demonstrating consistent associations between obesity, smoking, and hypertension and subsequent healthy aging decades later. However, the association between midlife PA patterns and healthy aging has been inconsistent.1,4,6,7,27 To our knowledge, the association between midlife fitness and healthy aging has not been reported. In contrast to the more inconsistent associations with PA, we observed that higher midlife fitness was strongly and consistently associated with a lower rate of CC outcomes in later life in men and women. This discordance between PA and fitness is not unexpected given reports15,16,35 demonstrating stronger associations between fitness and mortality compared with PA.

The inverse association between fitness and mortality has been well studied,8,10,12,14,21 but less is known regarding the association between midlife fitness and CCs

Table 3. Risk for Developing a Chronic Condition by Fitness and Risk Factor Levels Measured in Midlife

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 14 726)</th>
<th>Women (n = 3 994)</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>χ²b P Value</td>
<td>χ²b P Value</td>
</tr>
<tr>
<td>Fitness, per 1 METc</td>
<td>0.95 (0.94-0.96)</td>
<td>0.94 (0.91-0.96)</td>
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<tr>
<td>BMI, per 3 U</td>
<td>1.36 (1.13-1.63)</td>
<td>1.63 (1.15-2.31)</td>
</tr>
<tr>
<td>SBP, per 20 mm Hgd</td>
<td>1.09 (1.07-1.11)</td>
<td>1.05 (1.00-1.10)</td>
</tr>
<tr>
<td>Total cholesterol level, per 40 mg/dLd</td>
<td>1.68 (1.38-2.04)</td>
<td>1.53 (1.02-2.30)</td>
</tr>
<tr>
<td>Smoking, no vs yesd</td>
<td>0.84 (0.80-0.87)</td>
<td>0.76 (0.68-0.85)</td>
</tr>
<tr>
<td>Glucose level, per 1 mg/dL</td>
<td>1.05 (1.03-1.07)</td>
<td>1.03 (0.99-1.08)</td>
</tr>
<tr>
<td>Alcohol intake, per 1 drink/wk</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.01)</td>
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</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; MET, metabolic equivalent; SBP, systolic blood pressure.

1SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

2All models were adjusted for all covariates listed in the table as well as follow-up entry age, year of examination, and time-dependent interaction terms (see “Methods” section for details).

3One MET equals 3.50 mL of oxygen per kilogram per minute.

4Status at baseline.

Table 4. Proportion of Final 5 Years of Life Spent With Chronic Conditions, Stratified by Midlife Fitness Level

<table>
<thead>
<tr>
<th>Chronic Conditions, % (95% CI)a</th>
<th>Fitness Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 or 1</td>
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<tr>
<td>Men</td>
<td>(n = 14 726)</td>
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<tr>
<td>1337</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>(n = 3 994)</td>
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<tr>
<td>1237</td>
<td></td>
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<td></td>
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Abbreviation: Q, quintile.

aData represent the proportion (given as the percentage [95% CI]) of follow-up time based on person-years spent at each level of chronic condition burden according to strata of midlife fitness levels.

low-up in each fitness group before death. Among decedents with higher levels of midlife fitness, the morbidity compression ratio comparing CC development relative to that of death was significantly lower (0.90 [0.88-0.92] per MET). Thus, higher midlife fitness is associated with the delay in the development of CCs to a greater extent than the extension of the lifespan, suggesting the compression of morbidity nearer the end of life. The association of fitness with the compression of CC burden can also be seen in the proportion of time spent with different numbers of CCs before death. Compared with participants with lower midlife fitness, those with higher midlife fitness appeared to spend a greater proportion of their final 5 years of life with a lower burden of CCs (Table 4).
later in life. This reflects limited available data for nonfatal clinical events among established fitness cohorts with long-term follow-up. In the present study, we combined Medicare administrative claims data with a large cohort of healthy men and women with objectively measured fitness levels, providing an efficient strategy to examine the association between midlife fitness and the development of a diverse set of CCs decades later. Our findings support the hypothesis that fitness in midlife is associated with a lower burden of chronic disease in later life.

In addition to reducing the burden of CCs, we also observed that higher midlife fitness was associated more strongly with the delay in the onset of CCs than with survival, suggesting that higher midlife fitness may promote the compression of morbidity in later life. Because of the strong correlation between morbidity and mortality, lifestyle patterns that equally delay the onset of both morbidity and mortality could result in more years of life lived with chronic disease. In contrast, lifestyle characteristics that delay the onset of chronic disease to a greater extent than they prolong the lifespan could theoretically compress life-years lived with chronic disease and hence increase the years with improved quality of life and lower health care expenditures. Several studies suggested the importance of physical exercise as a potential source of morbidity compression. However, most were relatively small with few overall deaths, limiting the ability to test for the presence of this phenomenon. In a cohort of middle-aged runners and control individuals monitored for 21 years (N = 961), runners were found to have less disability as assessed by the Health Assessment Questionnaire Disability Index, suggesting that regular physical exercise might delay the onset of disability. However, the authors were not able to assess for the presence or absence of morbidity compression because of the overall small number of deaths in the study sample (n = 225). In the present study, we included 18,670 participants with 2,406 deaths, allowing a comparison of the associations between fitness, CCs, and mortality in the final 5 years of life.

Several limitations of this study should be noted. First, outcome data were derived from administrative data from the CMS rather than adjudicated clinical diagnoses. Nevertheless, Medicare data have been shown to be a reliable source of information across multiple clinical outcomes. Furthermore, Medicare data represent a unique and cost-effective resource, providing an opportunity to assess the association between midlife fitness levels and long-term chronic disease outcomes that would be prohibitively expensive, if not impossible, to replicate in a prospective cohort study of comparable size and duration.

Second, we linked individual-level data with Medicare claims files to compare the association between fitness and chronic disease outcomes at age 65 years or older. We were not able to capture outcomes that occurred between study entry and the onset of Medicare eligibility. For example, participants who died before achieving Medicare eligibility were not included in the present analysis. However, merging individual-level data with Medicare claims files has been used by other investigators in a parallel context, providing novel insight into the contribution of traditional risk factors and other Medicare outcomes. We observed a similar pattern of results for fitness levels measured in earlier life (ie, age ≤49 years) as well as in later life (ie, age >49 years) and closer to Medicare eligibility.

Third, we created an a priori panel of CCs across multiple organ systems and in accordance with definitions of healthy aging defined by others. Although this may have influenced our findings, we observed a similar pattern of results after multiple sensitivity analyses that sequentially excluded one of these CCs (eTable 2). Therefore, we believe that our findings are insensitive to the choice of CC panel and reflect a reasonable estimate of the association between midlife fitness and CC outcomes in older age.

Fourth, the CCLS is a unique cohort with a higher socioeconomic and educational status and a lower prevalence of traditional risk factors when compared with the general population. However, although the level of risk factors is lower than in the general population, prior work suggests that the effects are similar.

Finally, additional factors, such as life stress and dietary patterns, were not included in our analyses because these data are limited in the CCLS. Additional covariates could alter the observed associations of CCs and fitness. Follow-up data on fitness and PA are not uniformly available in the CCLS; therefore, we are not able to estimate the effect of changes in fitness with chronic disease burden in older age. However, our primary purpose was to determine the contribution of a single measure of midlife fitness with surrogates for healthy aging decades later. Furthermore, although fitness measures more proximate to the outcome would be of interest, it would also raise concerns regarding the possibility of reverse causation, in which low fitness reflected undiagnosed chronic disease burden. The healthy nature of our cohort and the long duration of follow-up make the presence of undiagnosed CCs at study entry unlikely and further support the hypothesis that greater midlife exercise is associated with a lower burden of chronic disease across the life span.

In summary, midlife fitness was associated with a lower risk of common chronic health conditions in men and women older than 65 years enrolled in Medicare. The finding that higher fitness was more strongly associated with CCs than with overall survival suggests that higher midlife fitness may be associated with the compression of morbidity in older age.

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Author Contributions: Dr Willis had full access to all the data in the study and takes responsibility for the integ-
rity of the data and the accuracy of the data analysis. Dr Berry had final responsibility for the decision to submit for publication. All authors have read and agree to the manuscript as written. Study concept and design: Willis, DeFina, and Berry. Acquisition of data: Willis, Gao, Leonard, DeFina, and Berry. Drafting of the manuscript: Willis and Berry. Critical revision of the manuscript for important intellectual content: Willis, Gao, Leonard, DeFina, and Berry. Statistical analysis: Willis, Gao, and Leonard. Obtained funding: Berry. Administrative, technical, and material support: Willis and DeFina. Study supervision: Willis and Berry.

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REFERENCES

Thriving of the Fittest

In 1980, James F. Fries, MD, published his seminal thesis on the limit of the average human life span—which he pinpointed at 85 years—and the compression morbidity into the final period of life, which he offered as both observation of a societal trend and a public health goal.¹ He whimsically invoked this ideal by citing a poem by Oliver Wendell Holmes Sr about a “one-hoss shay,” a carefully constructed carriage that functions beautifully and then breaks down “to pieces all at once” after exactly 100 years. Fries contrasts this vision to the notion that ever-increasing life span afforded by improvements in public health and medicine would lead to increasing proportions of the population spending many of their final years with significant infirmity. Fries and his colleagues² have continued to find evidence for the compression of morbidity and the “rectangularization” of the survival curve.

The concept of healthy or “successful” aging, once considered almost an oxymoron, was introduced in the 1960s and 1970s and has since been an area of active investigation. Healthy aging has been found to be related to several lifestyle factors, including abstinence from smoking, physical activity, maintenance of weight within normal ranges, and moderate alcohol consumption.³ In recent years, clues to the genetics of longevity have begun to emerge,⁴ and genetics undoubtedly plays an important role in maintaining good health as well as avoiding disease. Several studies⁵ have also found that cardiorespiratory fitness measured at a single time is strongly associated with both longevity and reduced risk of chronic disease, particularly cardiovascular disease, and is a better predictor than physical activity levels, likely, in part, because of the objectivity of the measurement and ability to capture the cumulative effects of exercise.

Willis and colleagues⁶ provide further evidence for physical fitness as a contributor to healthy aging and the compression of morbidity. By linking the large clinical database comprising men and women who visited the Cooper Clinic from 1970 to 2009 and underwent standardized treadmill fitness testing to Medicare claims when they reached age 65 years or older, the authors identified 18,670 persons who were free from chronic disease at the time of their examinations and were covered by Medicare from 1999 to 2009. After adjusting for age, body mass index, systolic blood pressure, total cholesterol level, smoking, fasting blood glucose level, and alcohol intake, there was a strong graded relationship of fitness to the rate of development of a set of common chronic conditions, including ischemic heart disease, congestive heart failure, stroke, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, Alzheimer disease, and colon or lung cancer. The authors found an approximate 6% reduction in the risk of a chronic disease for every MET achieved, with a range of 5 to 6 METs across quintiles of fitness or an approximate doubling of risk between quintiles 1 and 5. This relationship was robust and similar when individual diseases were eliminated from the common set of conditions. Fitness appeared strongly protective against each condition, and there were similar relationships in men and women.

Furthermore, in an analysis of 2,406 decedents, there was a clear relationship between fitness and the proportion of the final 5 years of life spent with a chronic condition. The highest of 3 fitness groups spent approximately 50% as much time with 4 or more chronic diseases as the lowest fitness group and 34% more time with no or 1 chronic disease.