Midlife Fitness and the Development of Chronic Conditions in Later Life

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Background: The association between cardiorespiratory fitness (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 (2,406 [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 reports1-7 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, studies3-7 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 (fitness) and mortality after adjustment for other risk factors is well established.8-10 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.15

See also Invited Commentary

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 medical 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 2973 participants (12.0%) lacking traditional Medicare fee-for-service coverage (ie, Medicare Advantage participants lacking claims files), we excluded an additional 2599 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. The test time using this protocol correlates highly with directly measured maximal oxygen uptake \((r = 0.92)\). In accordance with standard approaches to the analysis of fitness data, 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). A summary measure of the burden of CCs, the combined number was used as the outcome measure (eg, 0 CCs, 1 CC).

OUTCOME MEASURES

Medicare inpatient claims data were obtained from the CMS for surviving participants who were 65 years or older and were thus eligible for Medicare benefits from 1999 through 2009. The CMS data contain 100% of claims paid by Medicare for covered health care services. Chronic condition diagnoses used in this study were determined from the Chronic Condition Warehouse included in the Beneficiary Annual Summary File. Chronic conditions are defined within the Chronic Condition Warehouse from well-established algorithms for research purposes. A panel of 8 CCs was used for the present analysis: congestive heart failure, ischemic heart disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, Alzheimer disease, and colon or lung cancer. These conditions were chosen from the Chronic Condition Warehouse in an effort to define a broad panel across multiple organ systems in accordance with definitions of healthy aging as defined by others. Minor conditions (ie, cataracts) and sex-specific outcomes (ie, breast or prostate cancer) were excluded to define a consistent set of conditions between men and women. To create a summary measure of the burden of CCs, the combined number was used as the outcome measure (eg, 0 CCs, 1 CC).

STATISTICAL ANALYSIS

We determined the overall burden of CCs at ages 70, 75, 80, and 85 years by classifying all participants alive at these age thresholds according to the presence or absence 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. 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, relegating 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. In this model, we treated death as an outcome of interest rather than 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.)
RESULTS

Baseline characteristics for 14,726 men and 3,944 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 [18.7-21.6] 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-

### Table 2. Rate of CC Burden by Midlife Fitness Measurement in Men and Womena

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>2632</td>
<td>2986</td>
<td>3209</td>
<td>3033</td>
<td>2866</td>
</tr>
<tr>
<td>Rate of CC burden (95% CI)</td>
<td>28.2 (27.4-29.0)</td>
<td>22.4 (21.7-23.1)</td>
<td>20.1 (19.5-20.7)</td>
<td>17.8 (17.2-18.4)</td>
<td>15.6 (15.0-16.2)</td>
</tr>
<tr>
<td>No. of conditions</td>
<td>4797</td>
<td>4376</td>
<td>4263</td>
<td>3466</td>
<td>2856</td>
</tr>
<tr>
<td>Person-years</td>
<td>17002</td>
<td>19506</td>
<td>21256</td>
<td>19483</td>
<td>18300</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>552</td>
<td>767</td>
<td>730</td>
<td>944</td>
<td>951</td>
</tr>
<tr>
<td>Rate of CC burden (95% CI)</td>
<td>20.1 (18.7-21.6)</td>
<td>16.6 (15.6-17.8)</td>
<td>14.3 (13.2-15.4)</td>
<td>12.3 (11.4-13.3)</td>
<td>11.4 (10.5-12.3)</td>
</tr>
<tr>
<td>No. of conditions</td>
<td>747</td>
<td>876</td>
<td>673</td>
<td>713</td>
<td>652</td>
</tr>
<tr>
<td>Person-years</td>
<td>3724</td>
<td>5251</td>
<td>4721</td>
<td>5793</td>
<td>5744</td>
</tr>
</tbody>
</table>

Abbreviations: CC, chronic condition; Q, quintile.

a Rates per 100 person-years reported in age- and sex-specific quintiles of fitness based on Balke treadmill times, with Q1 being low fitness and Q5 being high fitness.
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 studies have observed 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, 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. 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. 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 studies have observed mean fitness gains of this magnitude using a 6-month program of 150 minutes per week of moderate-intensity exercise.

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Fitness, per 1 METc</td>
<td>0.95 (0.94-0.96)</td>
<td>.001</td>
</tr>
<tr>
<td>BMI, per 3 U</td>
<td>1.36 (1.13-1.63)</td>
<td>.001</td>
</tr>
<tr>
<td>SBP, per 20 mm Hg</td>
<td>1.09 (1.07-1.11)</td>
<td>.001</td>
</tr>
<tr>
<td>Total cholesterol level, per 40 mg/dLd</td>
<td>1.68 (1.38-2.04)</td>
<td>.001</td>
</tr>
<tr>
<td>Smoking, no vs yesd</td>
<td>0.84 (0.80-0.87)</td>
<td>.001</td>
</tr>
<tr>
<td>Glucose level, per 1 mg/dL</td>
<td>1.05 (1.03-1.07)</td>
<td>.001</td>
</tr>
<tr>
<td>Alcohol intake, per 1 drink/wk</td>
<td>1.00 (1.00-1.00)</td>
<td>.19</td>
</tr>
</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.

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

a All 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).

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

c Status at baseline.

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

<table>
<thead>
<tr>
<th>Fitness Level</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronic Conditions, % (95% CI)a</td>
<td>0 or 1</td>
</tr>
<tr>
<td>D1 (n = 649), 3399 person-years before death</td>
<td>43.5 (41.8-45.2)</td>
<td>38.1 (36.5-38.7)</td>
</tr>
<tr>
<td>D2-D3 (n = 1046), 6242 person-years before death</td>
<td>51.0 (49.8-52.2)</td>
<td>35.7 (34.5-36.9)</td>
</tr>
<tr>
<td>D4-D5 (n = 711), 4118 person-years before death</td>
<td>58.3 (56.8-59.8)</td>
<td>32.1 (30.7-33.5)</td>
</tr>
</tbody>
</table>

Abbreviation: Q, quintile.

a Data 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.
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 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. Our findings have important implications for public health and prevention practice by extending our knowledge of the health benefits of exercise in midlife.

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 2406 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.

Accepted for Publication: May 30, 2012.
Published Online: August 27, 2012. doi:10.1001/archinternmed.2012.3400
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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.

Financial Disclosure: Dr Berry has received financial compensation from Merck for being a member of its speakers’ bureau.

Funding/Support: The Cooper Institute is a 501(c)(3) nonprofit research institute and provided internal funding for this study. Dr Berry receives funding from the Dedman Family Scholar in Clinical Care endowment at The University of Texas Southwestern Medical Center; grant K23 HL092229 from the National Heart, Lung, and Blood Institute; and grant 10BG1A4280091 from the American Heart Association.

Role of the Sponsors: The University of Texas Southwestern Medical Center; the National Heart, Lung, and Blood Institute; and the American Heart Association made no contribution to the design of the study. In addition, the sponsors made no contribution to the collection, management, analysis, or interpretation of the data, or preparation, review, or approval of the manuscript.


Additional Contributions: The authors thank Kenneth H. Cooper, MD, MPH, for establishing the Cooper Center Longitudinal Study in 1970 and the Cooper Clinic physicians and staff for data collection.

References