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CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Cardiorespiratory Fitness Is Associated With Early Death Among Healthy Young and Middle-Aged Baby Boomers and Generation Xers

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ABSTRACT

BACKGROUND: Increased mortality associated with low cardiorespiratory fitness has shown to take effect during late adulthood in previous generations. A recent rise in early death was observed in the United States. We investigated the impact of low cardiorespiratory fitness during young and middle adulthood on premature death in healthy adults from recent generations.

METHODS: A prospective cohort study of a nationally representative sample of US Baby Boomers and Generation Xers (born 1945-1980). Between 1999 and 2004, 3242 adults ages 20 to 49 years (weighted N = 59,888,450; mean age, 33.8 ± 0.2 years) underwent submaximal treadmill exercise test in the National Health and Nutrition Examination Survey study. Weighted Cox proportional hazards regression were used to evaluate the association of cardiorespiratory fitness with premature death at 65 years or younger.

RESULTS: During a mean follow-up of 13.8 years, 104 deaths (weighted deaths N =1,326,808) occurred. Low cardiorespiratory fitness was associated with an increased risk of premature death as a result of all-cause (hazard ratio [HR], low vs high: 2.26; 95% confidence interval [CI], 1.10 to 4.64, *P* for trend = 0.036) and cancer mortality (HR low vs moderate/high: 6.53; 95% CI, 2.38 to 17.9). Further, this association was stronger in adults ages 35 to 49 years at baseline (HR, 4.17 [95% CI, 1.19 to 9.11]).

CONCLUSION: We observed an inverse association between cardiorespiratory fitness during middle adulthood and premature death, which was not detected in preceeding generations. These findings suggested that low cardiorespiratory fitness might be emerging as a new risk factor for early death among US Baby Boomers and Generation Xers.

 • The American Journal of Medicine (2020) 000:1−8

KEYWORDS: Baby Boomers; Cardiorespiratory fitness; Early death; Generation Xers; Middle-aged adults; Young adults

Funding: None.

Conflict of Interests: None.

Authorship: Mr. Cao and Dr. Yang contributed equally. All authors had access to the data and a role in writing this manuscript.

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https://doi.org/10.1016/j.amjmed.2019.12.041

BACKGROUND

Increasing epidemiological evidence demonstrate a rising trend in early death among young and middle-age US Baby Boomers (born 1946-1964) and Generation Xers (born 1965-1980) compared to their preceding generations.[1] With estimated 76 million Boomers and 55 million Gen Xers currently residing in the United States, this trend affects nearly half of its total population.[2] Several studies[3,4] have attempted to elucidate the etiologic factors associated with elevated premature mortality and have identified several potential risk factors, including the obesity epidemic,[5] drug poisoning,[6] suicide led by mental health issues,[7] chronic obstructive pulmonary disease and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS),[1] many of which may operate through increasing human body's physical stress.

However, as a strong determinant of physical stress tolerance, cardiorespiratory fitness has not yet been investigated in association with premature death among young and middle-aged (20-49 years) adults in the contemporary generations. Cardiorespiratory fitness is defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity and reflects physical fitness.[8] Previous studies have provided considerable evidence supporting a long-term protective effect of cardiorespiratory fitness on risks for coronary heart disease, cardiovascular disease,[9] respiratory disease,[10] cancer outcomes,[11,12] and all-cause mortality among older adults.[13] Several plausible mechanisms support the inverse association between cardiorespiratory fitness and risk of death or disease; the relatively poor cardiovascular function, indicated by the low cardiorespiratory fitness, may lead to a low tolerance of physical stress.[14] Excessive physical stress (eg, high blood pressure) negatively effects tissue adaptation,[15,16] which may cause inflammation, injury, and death. Therefore, the detrimental effect of low cardiorespiratory fitness was primarily attributable to the reduced physical tolerance caused by aging in previous studies.[16]

Only one study specifically examined the association of cardiorespiratory fitness and mortality in adults younger than 40 years.[17] In their study, an association of cardiorespiratory fitness with mortality was not detected in those 20-49 years (born before 1950s). Cohorts born since 1945 have lifestyle behaviors that are distinct from preceding generations, such as lower levels of physical activity,[18] excessive sedentary behavior,[19] and suboptimal dietary patterns,[20] resulting in elevated physical stress and early cluster of disease risk factors at younger age.[21−23]

To date, a comprehensive evaluation of the effect of cardiorespiratory fitness on premature mortality among young and middle-age Baby Boomers and GenX adults has not been conducted because of a lack of study with large sample size with cardiorespiratory fitness measurement and long follow-up. Moreover, despite a considerable body of literature indicating an association among high levels of sedentary behavior with lower levels of cardiorespiratory fitness,[24] unfavorable health outcomes, and earlier mortality,[25] no prior study has examined sedentary behavior as an effect modifier in associations between cardiorespiratory fitness and mortality. Therefore, the present study evaluated associations of cardiorespiratory fitness during early and middle adulthood with all-cause premature mortality in a nationally representative sample of the healthy US population, as well as within population subgroups defined by several sociodemographic and behavioral factors.

CLINICAL SIGNIFICANCE

- Early death rate in recent US generations is increasing.
- In a national sample of US contemporary population, lower levels of young and middle-age adulthood cardiorespiratory fitness, as assessed by a submaximal treadmill test, were associated with higher risk of premature and all-cancer mortality.
- Low cardiorespiratory fitness might be emerging to a new risk factor for early death among US Baby Boomers and Generation Xers.

METHODS

Study Design and Population

The National Health and Nutrition Examination Survey (NHANES) study, conducted by the US National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), has collected information on the health and nutritional status of a nationally representative, complex, stratified, clustered, multistage probability sample of the civilian noninstitutionalized US population continuously in 2-year cycles since 1999. Participants provided informed consent and underwent both an in-person interview at home and a physical examination in a mobile examination center.[26] Data on sociodemographic characteristics, measured weight and height, and lifestyle behaviors in participants who completed a cardiorespiratory fitness test in 3 cycles in 1999-2000, 2001-2002, and 2003-2004 were included in this study. To ensure the safety and validity of the test, participants were excluded from cardiorespiratory fitness based on medical conditions (eg, heart diseases), medications, physical limitations, limits on heart rate and blood pressure, and irregular heart rates.[27] In light of the strict exclusion criteria, only healthy individuals were included in present analysis. Approximately 70% of the eligible NHANES participants were tested and approximately 12% of the participants prematurely terminated treadmill test without their VO_{2max} because of excessive blood pressure and heart rate.[27]

Cardiorespiratory Fitness Test

Cardiorespiratory fitness was assessed by a submaximal treadmill exercise test performed by trained health technicians.[28] Participants were assigned to 1 of 8 treadmill test protocols based on their estimated maximum rate of oxygen consumption (VO_{2max}), which was predicted from sex, age, body mass index (BMI), and self-reported level of physical activity using the formula developed by Jackson et al.[29] Each protocol included a 2-minute warm-up, 3-minute exercise stages, and a 2-minute cool down period. Each protocol aimed to elicit a heart rate that was approximately

80% of the age-predicted maximum (220-age) by the end of the second exercise stage.[27]

Heart rate was monitored continuously via an automated monitor with 4 electrodes connected to the participant's chest and abdomen. Heart rate was recorded at the end of the warm-up period and each exercise stage and each minute of recovery. Blood pressure was assessed at the end of each stage by an automated sphygmomanometer. At the end of the warm-up and each exercise stage, participants were asked to rate their perceived exertion using the Borg scale.[30]

VO_{2max} (mL/kg/min) was estimated by extrapolation using measured heart rate responses to 2 exercise stages assuming a linear relationship between heart rate and oxygen consumption up to the age-predicted max heart rate. Cardiorespiratory fitness was categorized into 3 levels: low (<20th percentile), moderate (20th-59th percentile), or high (≥60th percentile) based on the widely used gender- and age-specific cutoff points of estimated VO_{2max} from the Aerobics Center Longitudinal Study (ACLS).[31]

Assessment of Premature Death

The NCHS provided mortality data that was linked to the National Death Index through December 31., 2015. The International Classification of Diseases, 10th Revision (ICD-10) was used to record causes of death.[32] Follow-up length was defined as the interval in months from the examination date to the date of death or to December 31, 2015, for those who were censored. In the present study, all deaths are considered as premature deaths because all occurred before age 65.[33] To reduce the probability of reverse causation, deaths occurring during the first 2 years of follow-up were excluded.[34]

Sociodemographic Characteristics, Lifestyle Factors, and Comorbid Conditions

Self-reported sociodemographic characteristics included gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and others), and educational attainment (less than high school, high school, and beyond high school). Lifestyle factors included leisure-time physical activity, sedentary behaviors, and smoking status. Participants reported whether engaging in recreational moderate and vigorous physical activities over the past 30 days.[35] No vs. any moderate-to-vigorous physical activities (MVPA) at leisure time was used to define inactive and active participants. Participants were asked to report daily hours for sitting watching television/videos or computer use outside of work and were further categorized into less sedentary (≤2 h/d) and sedentary (>2 h/d). These cutoffs, previously used in other studies,[19,36,37] also reflect the median values in the present study population. Smoking status was classified into never smokers (did not smoke >100 cigarettes and do not smoke now), former smokers (smoked >100 cigarettes in life and do not smoke now), or current smokers (smoked 100 cigarettes in life and smoke now). Dietary covariates including total energy intake (kcal/d) and total alcohol intake (g/d) were derived from 24-h recall interview.[38]

Three comorbid conditions related to cardiorespiratory fitness were included in the analyses: hypertension, diabetes, and high cholesterol. Hypertension was determined by a previous diagnosis by a health profession or NHANES measured blood pressure value of ≥130 mm Hg systolic or ≥ 80 mm Hg diastolic.[39] High blood cholesterol was determined by self-report diagnosis by a health professional or an NAHENS measured total cholesterol level ≥6.2 mmol/L (240 mg/dL).[40] Participants were considered as having diabetes based on the self-reported questionnaire.[41]

Statistical Analysis

Baseline characteristics were summarized by levels of cardiorespiratory fitness by sex. Weighted mean ± 95% confidence interval (CI) was used for continuous variables and weighted percentage for categorical variables. Further, the distribution of sociodemographic characteristics, lifestyle factors, and comorbid conditions were compared among 3 levels of cardiorespiratory fitness using linear regression for continuous variables and χ^2 tests for categorical variables.

All analyses used sample weights that accounted for the stratified multistage probability design of the survey. Cox proportional hazard models were used to calculate adjusted hazard ratios (HRs) and 95% CIs according to levels of cardiorespiratory fitness. Three multivariable models were conducted. First, the baseline model was adjusted for age, sex, and race/ethnicity. Secondly, smoking status, alcohol intake, and total energy intake were additionally adjusted in the multivariable model. Third, in the fully adjusted model, BMI, sedentary behavior, physical activity, hypertension, diabetes, and high cholesterol were further adjusted. All 3 models generated results for the overall sample and for males and females separately. Linear trends were tested by modeling cardiorespiratory fitness level (low, moderate, or high) as an ordinal variable in Cox proportional hazard models. Finally, subgroup analyses were conducted based on age (<35 vs ≥35 years), BMI (<25 vs ≥25 kg/m^2), sedentary behavior (≤2 vs >2 h/d), any MVPA (Yes vs No), and smoking status (never vs ever smoker). In addition, a series of sensitivity analyses were performed by: 1) excluding death as a result of accidents; 2) using alternative cutoff published by Wang et al to categorize cardiorespiratory fitness. All analyses were done using Stata, version 15.1 (StataCorp, Texas, USA). All statistical tests were 2-sided and statistical significance was set at P <0 .05.

RESULTS

A total of 3302 adults ages 20 to 49 years (born in 1950 to 1983) completed the submaximal treadmill exercise test with valid data on cardiorespiratory fitness level. Participants with a history of cancer (n = 45), or died in the first 2 years of follow-up (n = 15) were excluded. The final analyzed sample consisted of 3242 adults (weighted N = 59,888,450; mean [standard error, SE] age, 33.8 [0.2]

Table 1 Baseline Characteristics by Cardiorespiratory Fitness Level Among US Adults Ages 20-49 Years, NHANES 1999-2004*,†

	All	Male					Female				
		All male	Low	Moderate	High	*P* Value	All female	Low	Moderate	High	*P* Value
N	3242	1707	246	598	863		1535	293	512	730	
Weighted, N	59,888,450	31,533,263	4,381,672	11,197,310	15,954,281		28,355,187	4,914,828	9,520,874	13,919,484	
Estimated VO_{2max}, mL/kg/min	40 ± 0.6	43.6 ± 0.6	32.5 ± 0.4	39.0 ± 0.2	49.9 ± 0.7	<0.001	36.0 ± 0.6	26.4 ± 0.4	31.9 ± 0.3	42.2 ± 0.6	<0.001
Age, y	33.8 ± 0.4	33.6 ± 0.5	32.6 ± 1.3	33.4 ± 0.8	34.1 ± 0.8	0.053	34.0 ± 0.6	32.8 ± 1.1	33.3 ± 1	34.9 ± 0.9	0.002
Race, %											
Non-Hispanic white	70.1	70.2	58.9	71.4	72.4	0.003	70.0	60.8	67.3	75.1	<0.001
Non-Hispanic black	10.4	9.6	11.9	9.7	8.8		11.3	19.2	12.4	7.7	
Hispanic	15.3	15.8	21.3	14	15.6		14.6	14.6	15.4	14	
Other	4.3	4.4	8.0	4.9	3.1		4.1	5.4	4.8	3.2	
BMI, kg/m^2	27.1 ± 0.3	27.2 ± 0.3	29.8 ± 0.8	27.3 ± 0.4	26.3 ± 0.3	<0.001	26.9 ± 0.5	29.7 ± 1.1	26.9 ± 0.6	26.0 ± 0.7	<0.001
Smoking Status, %											
Never	56.2	52.1	55.7	51.8	51.3	0.30	60.9	64.2	60.2	60.1	0.74
Former	16.7	17.7	16.9	15.2	19.7		15.6	15.0	17.0	14.9	
Current	27.1	30.2	27.4	33	29.1		23.5	20.8	22.8	25.1	
Hypertension, %	22.1	26.6	26.2	31	23.5	0.03	17.2	22.7	14.3	17.3	0.04
Diabetes, %	1.3	0.9	1.0	1.3	0.6	0.34	1.6	4.0	0.6	1.5	0.011
High cholesterol, %	19.7	22.3	21.2	25.1	20.7	0.26	16.7	17.6	18.7	15	0.38
Physical active, %‡	73.5	73.4	62.7	71.3	77.8	<0.001	73.7	64.5	75.2	76	0.007
Sedentary, %§	43.2	45.8	53	48.3	42.1	0.02	40.4	47.0	46.7	33.7	<0.001
Follow-up, y	13.8 ± 0.1	13.7 ± 0.1	13.3 ± 0.4	13.7 ± 0.2	13.8 ± 0.2		13.8 ± 0.2	13.8 ± 0.3	13.8 ± 0.2	13.9 ± 0.2	

BMI = body mass index; NHANES = National Health and Nutrition Examination Survey.

*All estimates were weighted to be nationally representative.

†Low cardiorespiratory fitness is defined as an estimated VO_{2max} below the 20th percentile of the Aerobics Center Longitudinal Study (ACLS) data of the same sex and age group; moderate cardiorespiratory fitness is defined as a value between the 20th and 59th percentile; and high cardiorespiratory fitness is defined as at or above the 60th percentile.

‡Physical active was defined as engaging in moderate or vigorous recreational physical activity over the past 30 days.

§Sedentary was defined as TV watching or PC use >2 h/d outside of work.

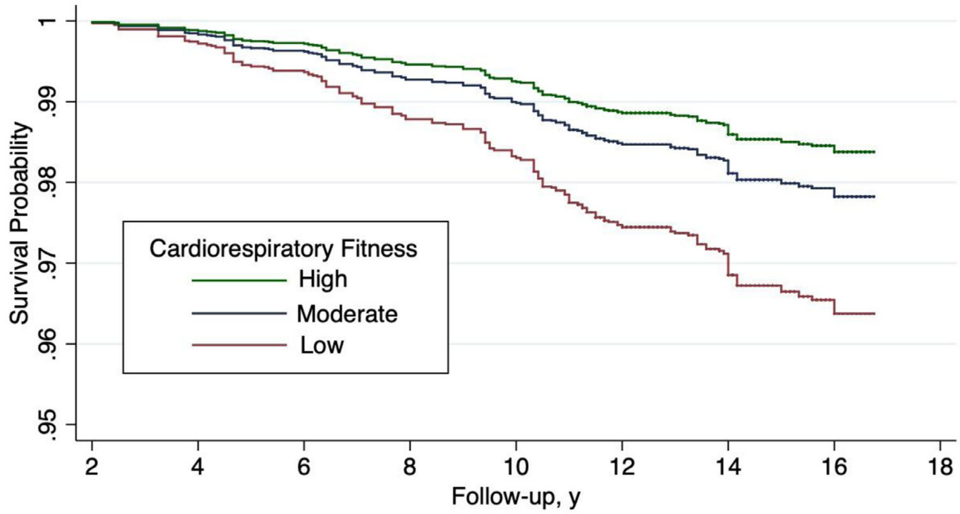

Figure 1 Survival curve by cardiorespiratory fitness level. Survival curves illustrating the association between cardiorespiratory fitness and premature death. Survival curves are adjusted for age, sex, race/ethnicity, smoking status, alcohol intake, total energy intake, body mass index (BMI), sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.

years; 1535 [47.4%] female). Baseline characteristics by cardiorespiratory fitness levels are presented in Table 1 for males and females, respectively. In summary, 70.1% of participants were white and 27.1% were current smokers. Mean estimated VO_{2max} was 40.0 mL/kg/min, and mean BMI was 27.1 kg/m^2. A potential racial/ethnical difference was observed: A larger portion of non-Hispanic black and Hispanic adults were classified in the low cardiorespiratory fitness level compared with non-Hispanic white participants (all P <0.005). Positive associations between levels of cardiorespiratory fitness and leisure-time physical activity were observed among both male (P <0.001) and female ($P = 0.002$). Notably, adults with high cardiorespiratory fitness are less likely to be sedentary compared with those with low cardiorespiratory fitness (all P <0.05).

During a mean follow-up of 13.8 years (range, 2.0-16.8 years) and 533,548 person-years of observation, 104 participants died (weighted death = 1,326,808) from any cause; of these 23 participants died as a result of accidents. Overall, survival curves of all-cause mortality stratified by cardiorespiratory fitness levels illustrated incremental reduction in all-cause mortality associated with increasing cardiorespiratory fitness (Figure 1). Specifically, lower cardiorespiratory fitness level was associated with high risk of all-cause mortality (Table 2) in both crude (HR, 2.15; 95% CI, 1.13 to 4.09) and fully adjusted (HR, 2.26; 95% CI, 1.10 to 4.64) models, particularly among men. Compared with a high level of cardiorespiratory fitness, the adjusted HRs for all-cause mortality in the low cardiorespiratory fitness groups were 2.72 (1.10 to 6.74) in males and 1.55 (0.56 to 4.26) in females. In addition, the relationship between levels of cardiorespiratory fitness and premature mortality appeared to be linear (P for trend = 0.036) in the overall population. Statistically significant trends were seen in both males ($P = 0.071$) and females ($P = 0.030$) in baseline models. However, in the fully adjusted model, such trend was more prominent among males (P for trend = 0.076) compared with females (P for trend = 0.181). Moreover, low cardiorespiratory fitness was associated with higher risk for cancer mortality (HR, 6.53; 95% CI, 2.38 to 17.9) and cardiovascular disease mortality (HR, 1.84; 95% CI, 0.59 to 5.68) (eTable 1, available online).

Figure 2 illustrated results from subgroup analyses by age, BMI, sedentary behavior, physical activity and smoking status (eTable 2, available online). Notably, cardiorespiratory fitness during 35-49 years was inversely associated with premature mortality (low vs high: adjusted HR, 4.49; 95% CI, 2.19 to 9.20). Further, the association of cardiorespiratory fitness on premature mortality appeared to be stronger (P for interaction = 0.33) among those with normal BMI (P for trend = 0.023) compared with those with BMI categoriezed as overweight or obese (P for trend = 0.251). Finally, stronger associations appeared among adults who reported lack of MVPA (low vs high: HR, 2.36; 95% CI, 1.00 to 6.79) or sedentary (low vs high: HR, 2.60; 95% CI, 1.00 to 6.79) compared with their counterparts with no evidence of statistically significant interaction (P for interaction >0.05).

The number of deaths as a result of accidents is presented in eTable 3, available online. Findings from sensitivity analyses were similar when excluding accidental deaths (eTable 4, available online) or categorizing levels of cardiorespiratory fitness using alternative cutoff (eTable 5, available online).

DISCUSSION

In this large representative sample of US adults, cardiorespiratory fitness were assessed during their young and middle adulthood between 1999 and 2004. During 13.8 years of

Table 2 Hazard Ratios and 95% CIs for All-Cause Mortality by Cardiorespiratory Fitness Level and Sex*

	Mortality		Hazard Ratio (95% CI)		
	No./Total No.	Weighted death (%)	Baseline model[†]	Multivariable model[‡]	Multivariable model[§]
All					
High	46/1593	505,322 (1.7)	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	35/1110	488,384 (2.4)	1.39 (0.70 to 2.79)	1.41 (0.70 to 2.80)	1.35 (0.67 to 2.71)
Low	23/539	333,102 (3.6)	2.15 (1.13 to 4.09)	2.33 (1.23 to 4.41)	2.26 (1.10 to 4.64)
P for trend			0.026	0.016	0.036
Men					
High	34/863	399,945 (2.5)	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	23/598	318,886 (2.9)	1.13 (0.52 to 2.44)	1.11 (0.53 to 2.33)	1.11 (0.50 to 2.46)
Low	14/246	261,453 (6.0)	2.27 (1.06 to 4.87)	2.50 (1.18 to 5.28)	2.72 (1.10 to 6.74)
P for trend			0.071	0.048	0.076
Women					
High	12/730	105,377 (0.8)	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	12/512	169,497 (1.8)	2.49 (0.87 to 7.08)	2.52 (0.88 to 7.22)	2.57 (0.86 to 7.74)
Low	9/293	71,649 (1.5)	2.08 (0.86 to 5.06)	1.89 (0.69 to 5.15)	1.55 (0.56 to 4.26)
P for trend			0.030	0.086	0.181

ACLS = Aerobics Center Longitudinal Study; CI = confidence interval.

*Low cardiorespiratory fitness is defined as an estimated VO_{2max} below the 20th percentile of the ACLS data of the same gender and age group; moderate cardiorespiratory fitness is defined as a value between the 20th and 59th percentile; and high cardiorespiratory fitness is defined as at or above the 60th percentile.

†Adjusted for age, gender (overall only), and race/ethnicity.

‡Additionally adjusted for smoking status, alcohol intake, and total energy intake.

§Additionally adjusted for sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.

follow-up, higher cardiorespiratory fitness levels were associated with lower risk of all-cause mortality, independent from sociodemographic factors, diet, adiposity, sedentary behavior, and comorbidities. In age group-specific analyses, this association was observed in the middle-aged (35-49 years) but not in young (20-34 years) adults.

To our knowledge, this is the first study to prospectively investigate the association of cardiorespiratory fitness with premature mortality risk in a nationally representative sample of healthy young to middle-aged adults residing in contemporary United States. The heightened risk of premature mortality associated with low cardiorespiratory fitness was

Subgroup	Weighted (Death/Total Population)	Low vs. High Adjusted HR (95% CI)[a]
Age, yrs		
20-34	712,916/31,436,651	1.39 (0.49 to 3.89)
35-49	613,892/28,451,799	4.17 (1.91 to 9.11)
	P for interaction=.007	
BMI, kg/m²		
<25	515,929/25,132,734	4.72 (1.69 to 13.2)
≥25	810,879/34,755,716	1.70 (0.67 to 4.35)
	P for interaction=.33	
Sedentary behavior, h/d		
≤2	588,989/34,618,968	1.86 (0.59 to 5.82)
>2	737,819/25,269,482	2.60 (1.00 to 6.79)
	P for interaction=.83	
Physical Activity		
Inactive	583,479/15,844,674	2.36 (1.02 to 5.45)
Active	743,329/44,043,776	2.17 (0.67 to 6.98)
	P for interaction=.99	
Ever smoking		
No	459,886/33,668,447	2.34 (0.83 to 6.57)
Yes	866,922/26,220,003	2.24 (0.88 to 5.71)
	P for interaction=.75	

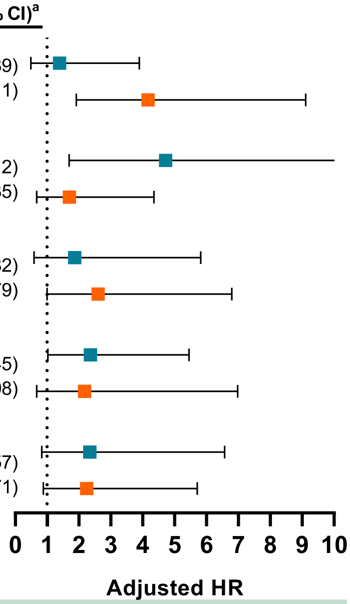

Figure 2 Stratified hazard ratios and 95% confidence intervals (CIs) for all-cause premature death according to cardiorespiratory fitness level.
[a]Adjusted for age, sex, race/ethnicity, smoking status, alcohol intake, total energy intake, body mass index (BMI), sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.

previously found only among older adults.[10] This study provides new insights on contributing factors to the recent increasing premature mortality rates in US Baby Boomers and Generation Xers. The presence of an association of cardiorespiratory fitness and mortality risk at an age younger than previously observed in studies of older adults[10] suggests a physical tolerance impairment that resembles aging occurs already during middle-age adulthood, which might be attributable to the contemporary unhealthy lifestyle. Similarly, King et al found that the Baby Boomers are at significantly higher risk of developing lifestyle-related chronic conditions such as hypertension, hypercholesterolemia, diabetes, and obesity compared with previous generations.[42]

Moreover, these negative effects associated with low cardiorespiratory fitness might be further worsened and shifted to a younger age by coexisting unfavorable lifestyle behaviors. In support, previous studies suggested stronger risks on mortality from a combination of poor health behaviors than that from a single behavior,[43] including low cardiorespiratory fitness.[44] Findings from the current study corroborate this point and reveal a potential stronger negative effect of low cardiorespiratory fitness among physical inactivity or sedentary participants than their counterparts. Although little data have been available in previous studies, sedentary behavior and physical activity seem to act independently in their relationship with cardiorespiratory fitness, such that physical activity may not overcome the deleterious influence of prolonged sitting on cardiorespiratory fitness.[24]

The second edition of *Physical Activity Guidelines for Americans* (2018) encourages adults to participant in at least 150 minutes MVPAs per week.[35] However, only two-thirds of US population are currently meeting these recommendations.[45] More importantly, although the prevalence of sedentary behaviors is high and rising, which puts more negative effects on cardiorespiratory fitness, evidence-based strategies shaping US adults' sitting and screen time is lacking. Hence, findings from the present study provide timely and important knowledge informing targeted interventions in these birth cohorts who are facing an increasing morality rate.

A clear strength of this study is the large representative sample of the healthy US population, the use of a treadmill exercise test to determine cardiorespiratory fitness, the inclusion of young and middle-aged adults from the Baby Boom and generation X era, and the assessment of important risk factors as potential confounders and effect modifiers. This study also had several limitations because it is an observational study that may be influenced by residual confounding. We attempt to mitigate the possibility of residual confounding adjusting for various confounding factors, excluding participants with cardiovascular disease or a history of cancer, excluding those who died within the first 2 years of follow-up, and conducting a range of sensitivity analyses. Second, although this is the largest study with objectively measured cardiorespiratory fitness, our study had small number of deaths in subgroup analyses, which produced a wide 95% CI.

CONCLUSION

In conclusion, cardiorespiratory fitness is inversely associated with premature death among healthy young and middle-aged US adults of recent generations. These findings provide insights on the contribution of low cardiorespiratory fitness to the rising mortality rate among Baby Boomers and Generation Xers.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2019.12.041.

eTable 1 Hazard Ratios and 95% CIs for CVD and Cancer Mortality by Cardiorespiratory Fitness Level and Sex*

	Mortality		Hazard Ratio (95% CI)		
	(No./Total No.)	Weighted (%)	Baseline model†	Multivariable model‡	Multivariable model§
Cardiovascular disease					
Moderate/High	8/2703	0.2	1 [Reference]	1 [Reference]	1 [Reference]
Low Fit	4/539	0.4	2.03 (0.70 to 5.89)	2.11 (0.67 to 6.65)	1.84 (0.59 to 5.68)
P for trend			0.187	0.195	0.283
Cancer					
Moderate/High	18/2703	0.4	1 [Reference]	1 [Reference]	1 [Reference]
Low Fit	7/539	1.4	4.41 (1.44 to 13.5)	4.70 (1.57 to 14.1)	6.53 (2.38 to 17.9)
P for trend			0.011	0.007	0.001

BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease.

*Low cardiorespiratory fitness is defined as an estimated VO_{2max} below the 20th percentile of the ACLS data of the same gender and age group; moderate cardiorespiratory fitness is defined as a value between the 20th and 59th percentile; and high cardiorespiratory fitness is defined as at or above the 60th percentile.

†Adjusted for age, gender (overall only), and race/ethnicity.

‡Additionally adjusted for smoking status, alcohol intake, and total energy intake.

§Additionally adjusted for BMI, sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.

eTable 2 Stratified Hazard Ratios and 95% CIs for All-Cause Premature Death by Cardiorespiratory Fitness Level*

	Mortality		Hazard Ratio (95% CI)		
	(No./Total No.)	Weighted (%)	Baseline model†	Multivariable model‡	Multivariable model§
Age 20-34, y					
High	26/832	2.2	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	16/632	2.0	0.91 (0.44 to 1.90)	0.89 (0.41 to 1.90)	0.85 (0.38 to 1.90)
Low	12/345	2.9	1.32 (0.57 to 3.03)	1.40 (0.58 to 3.39)	1.39 (0.49 to 3.89)
P for trend			0.639	0.604	0.704
Age 35-49, y					
High	20/761	1.2	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	19/478	2.8	2.38 (0.93 to 6.11)	2.44 (0.97 to 6.14)	2.31 (0.92 to 5.79)
Low	11/194	4.7	4.36 (1.92 to 9.91)	4.47 (2.11 to 9.47)	4.17 (1.91 to 9.11)
P for trend			<0.001	<0.001	<0.001
BMI <25					
High	20/732	1.5	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	14/424	2.2	1.56 (0.65 to 3.74)	1.48 (0.61 to 3.59)	1.47 (0.59 to 3.67)
Low	6/129	5.0	4.2 (1.28 to 13.81)	4.12 (1.44 to 11.82)	4.72 (1.69 to 13.2)
P for trend			0.040	0.031	0.023
BMI ≥25					
High	26/861	1.9	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	21/686	2.5	1.3 (0.51 to 3.35)	1.33 (0.48 to 3.65)	1.32 (0.48 to 3.61)
Low	17/393	3.1	1.68 (0.7 to 4.05)	1.81 (0.77 to 4.23)	1.70 (0.67 to 4.35)
P for trend			0.242	0.173	0.251
Sitting ≤2 h/d					
High	28/970	1.4	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	18/578	2.0	1.36 (0.59 to 3.11)	1.43 (0.61 to 3.35)	1.42 (0.58 to 3.48)
Low	10/269	2.7	1.72 (0.62 to 4.79)	2.03 (0.7 to 5.9)	1.86 (0.59 to 5.82)
P for trend			0.264	0.178	0.259
Sitting >2 h/d					
High	18/623	2.3	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	17/532	2.8	1.28 (0.53 to 3.08)	1.27 (0.53 to 3.03)	1.22 (0.51 to 2.93)
Low	13/270	4.5	2.17 (0.94 to 5.04)	2.29 (1.00 to 5.27)	2.60 (1.00 to 6.79)

eTable 2 (*Continued*)

	Mortality		Hazard Ratio (95% CI)		
	(No./Total No.)	Weighted (%)	Baseline model[†]	Multivariable model[‡]	Multivariable model[§]
P for trend			0.089	0.073	0.078
No MVPA					
High	16/464	2.8	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	18/346	3.9	1.52 (0.55 to 4.23)	1.48 (0.51 to 4.27)	1.43 (0.51 to 4.06)
Low	15/214	5.2	2.12 (0.9 to 4.99)	2.30 (0.98 to 5.38)	2.36 (1.02 to 5.45)
P for trend			0.082	0.061	0.053
Any MVPA					
High	30/1129	1.4	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	17/764	1.8	1.3 (0.55 to 3.05)	1.24 (0.52 to 2.98)	1.17 (0.45 to 3.04)
Low	8/325	2.6	2.04 (0.7 to 5.99)	2.24 (0.72 to 6.95)	2.17 (0.67 to 6.98)
P for trend			0.207	0.202	0.264
Never smoking					
High	21/894	1.1	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	15/638	1.3	1.26 (0.43 to 3.7)	1.28 (0.44 to 3.73)	1.25 (0.46 to 3.42)
Low	10/335	2.4	2.13 (0.76 to 5.95)	2.21 (0.78 to 6.28)	2.34 (0.83 to 6.57)
P for trend			0.172	0.153	0.123
Ever smoking					
High	25/699	2.5	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	20/472	3.7	1.46 (0.68 to 3.09)	1.51 (0.71 to 3.2)	1.37 (0.61 to 3.10)
Low	13/204	5.4	2.36 (1.1 to 5.07)	2.51 (1.18 to 5.37)	2.24 (0.88 to 5.71)
P for trend			0.039	0.026	0.111

BMI = body mass index; CI = confidence interval; MVPA = moderate to vigorous physical activity.

*Low cardiorespiratory fitness is defined as an estimated VO_{2max} below the 20th percentile of the Aerobics Center Longitudinal Study (ACLS) data of the same sex and age group; moderate cardiorespiratory fitness is defined as a value between the 20th and 59th percentile; and high cardiorespiratory fitness is defined as at or above the 60th percentile. All estimates were weighted to nationally representative.

[†]Adjusted for age, sex (overall only), and race/ethnicity.

[‡]Additionally adjusted for smoking status, alcohol intake, and total energy intake.

[§]Additionally adjusted for BMI, sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.

eTable 3 Underlying Cause of Death By Cardiorespiratory Fitness Level

	Low	Moderate	Hight
Accident			
N	5	9	9
Weighted, N	59,153	165,330	117,779
Weighted, %	17.8	33.9	23.8
Non-accident	18	26	37
Weighted, N	273,948	323,053	387,542
Weighted, %	82.2	66.1	76.2

eTable 4 Hazard Ratios and 95% CIs for Non-Accident Premature Death by Cardiorespiratory Fitness Level and Sex*

	Mortality		Hazard Ratio (95% CI)		
	(No./Total No.)	Weighted (%)	Baseline model†	Multivariable model‡	Multivariable model§
All					
High	37/1593	1.7	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	26/1110	2.4	1.23 (0.59 to 2.54)	1.27 (0.62 to 2.6)	1.2 (0.57 to 2.53)
Low	18/539	3.6	2.35 (1.13 to 4.89)	2.59 (1.24 to 5.42)	2.54 (1.13 to 5.7)
P for trend			0.038	0.022	0.040
Male					
High	27/863	2.5	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	16/598	2.9	1.07 (0.43 to 2.66)	1.1 (0.46 to 2.62)	1.05 (0.43 to 2.56)
Low	11/246	6.0	2.53 (1.08 to 5.94)	2.88 (1.26 to 6.6)	3.06 (1.24 to 7.53)
P for trend			0.078	0.042	0.054
Female					
High	10/730	0.8	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	10/512	1.8	1.72 (0.56 to 5.32)	1.71 (0.58 to 5.05)	1.94 (0.57 to 6.66)
Low	7/286	1.5	2.05 (0.78 to 5.38)	1.8 (0.6 to 5.37)	1.75 (0.61 to 5.02)
P for trend			0.107	0.221	0.202

BMI = body mass index; CI = confidence interval.

*Low cardiorespiratory fitness is defined as an estimated VO_{2max} below the 20th percentile of the Aerobics Center Longitudinal Study (ACLS) data of the same sex and age group; moderate cardiorespiratory fitness is defined as a value between the 20th and 59th percentile; and high cardiorespiratory fitness is defined as at or above the 60th percentile.

†Adjusted for age, sex (overall only), and race/ethnicity.

‡Additionally adjusted for smoking status, alcohol intake, and total energy intake.

§Additionally adjusted for BMI, sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.

eTable 5 Hazard Ratios and 95% CIs for All-Cause Premature Death by Cardiorespiratory Fitness Level (Alternative Cutoff) and Sex*

	Mortality		Hazard Ratio (95% CI)		
	(No./Total No.)	Weighted (%)	Baseline model†	Multivariable model‡	Multivariable model§
All					
High	25/712	1.9	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	50/1846	1.9	1.02 (0.48 to 2.17)	1.10 (0.53 to 2.30)	1.07 (0.52 to 2.22)
Low	29/684	3.4	1.71 (0.91 to 3.22)	1.95 (1.02 to 3.73)	1.86 (0.97 to 3.57)
P for trend			0.088	0.044	0.073
Male					
High	19/370	2.6	1 [Reference]	1 [Reference]	
Moderate	33/983	2.6	0.99 (0.41 to 2.39)	1.06 (0.46 to 2.44)	1.03 (0.43 to 2.48)
Low	19/354	5.1	1.91 (0.87 to 4.16)	2.26 (1.04 to 4.87)	2.41 (1.04 to 5.57)
P for trend			0.091	0.042	0.052
Female					
High	6/342	1.1	1 [Reference]	1 [Reference]	
Moderate	17/863	1.2	1.14 (0.31 to 4.20)	1.19 (0.30 to 4.67)	1.28 (0.29 to 5.70)
Low	10/330	1.4	1.25 (0.36 to 4.33)	1.17 (0.31 to 4.46)	1.01 (0.27 to 3.75)
P for trend			0.716	0.806	0.991

BMI = body mass index; CI = confidence interval.

*Low cardiorespiratory fitness is defined as an estimated VO_{2max} below the 20th percentile of the same gender and age group; moderate cardiorespiratory fitness is defined as a value between the 20th and 79th percentile; and high cardiorespiratory fitness level is defined as at or above the 80th percentile.

†Adjusted for age, sex (overall only), and race/ethnicity.

‡Additionally adjusted for smoking status, alcohol intake, and total energy intake.

§Additionally adjusted for BMI, sedentary behavior, physical activity, hypertension, diabetes, and hypercholesterolemia.