JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 8, 2024
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ORIGINAL RESEARCH

Sex Differences in Association of Physical Activity With All-Cause and Cardiovascular Mortality

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ABSTRACT

BACKGROUND Although physical activity is widely recommended for reducing cardiovascular and all-cause mortality risks, female individuals consistently lag behind male individuals in exercise engagement.

OBJECTIVES The goal of this study was to evaluate whether physical activity derived health benefits may differ by sex.

METHODS In a prospective study of 412,413 U.S. adults (55% female, age 44 ± 17 years) who provided survey data on leisure-time physical activity, we examined sex-specific multivariable-adjusted associations of physical activity measures (frequency, duration, intensity, type) with all-cause and cardiovascular mortality from 1997 through 2019.

RESULTS During 4,911,178 person-years of follow-up, there were 39,935 all-cause deaths including 11,670 cardiovascular deaths. Regular leisure-time physical activity compared with inactivity was associated with 24% (HR: 0.76; 95% CI: 0.73-0.80) and 15% (HR: 0.85; 95% CI: 0.82-0.89) lower risk of all-cause mortality in women and men, respectively (Wald F = 12.0, sex interaction $P < 0.001$). Men reached their maximal survival benefit of HR 0.81 from 300 min/wk of moderate-to-vigorous physical activity, whereas women achieved similar benefit at 140 min/wk and then continued to reach a maximum survival benefit of HR 0.76 also at ~300 min/wk. Sex-specific findings were similar for cardiovascular death (Wald F = 20.1, sex interaction $P < 0.001$) and consistent across all measures of aerobic activity as well as muscle strengthening activity (Wald F = 6.7, sex interaction $P = 0.009$).

CONCLUSIONS Women compared with men derived greater gains in all-cause and cardiovascular mortality risk reduction from equivalent doses of leisure-time physical activity. These findings could enhance efforts to close the "gender gap" by motivating especially women to engage in any regular leisure-time physical activity.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 17, 2023; revised manuscript received December 11, 2023, accepted December 12, 2023.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2023.12.019

ABBREVIATIONS AND ACRONYMS

CDC = Centers for Disease Control and Prevention

MPA = moderate intensity aerobic physical activity

MVPA = moderate-to-vigorous intensity aerobic physical activity

NHIS = National Health Interview Survey

PA = physical activity

VPA = vigorous intensity aerobic physical activity

Although greater amounts of physical activity (PA) are associated with well-known reductions in cardiovascular and all-cause mortality, fewer than one-quarter of all Americans meet the minimum guidelines for PA[1] as recommended by the Centers for Disease Control and Prevention (CDC),[2] and the American Heart Association/American College of Cardiology.[3] Both sets of guidelines recommend a minimum 150 min/wk of moderate PA or 75 min/wk of vigorous PA, in addition to at least 2 days of muscle strengthening activities per week. While these recommendations are the same for male and female individuals,[2] it has been long known that female individuals persistently lag behind male individuals in PA engagement—manifesting a "gender gap" that begins early in life and continues throughout adulthood.[4,5] The extent to which this gap in levels of PA engagement may translate into differences in outcomes has been unclear. There are long-established and well-recognized sex differences in the physiologic response to PA, in thresholds of exercise tolerance, and in overall exercise capacity.[6,7] Thus, it is possible that the degree of health benefit derived from PA could differ between sexes based on frequency, duration, intensity, and type of exercise. Understanding any such differences could inform efforts to close the "gender gap" and optimize PA-related outcomes for all.

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METHODS

All data and materials are publicly available from the CDC National Center for Health Statistics and are accessible online.[8] The National Center for Health Statistics Disclosure Review Board approved the National Health Interview Survey (NHIS) study.[9] Data analyses for this study were additionally approved by the Cedars-Sinai Medical Center institutional review board.

STUDY SAMPLE. The CDC and the National Center for Health Statistics have conducted the NHIS with data collected from all 50 states and the District of Columbia (Supplemental Methods).[10,11] We pooled data from a total of 646,279 adult participants of the NHIS from years 1997 to 2017 and linked their records to National Death Index records through December 31, 2019. We excluded participants with preexisting diagnoses of coronary heart disease, myocardial infarction, stroke, emphysema, chronic bronchitis, or cancer (n = 120,200), limitations in activities of daily living (n = 6,332), missing data on PA (n = 23,975), or missing data on follow-up status or key covariates (n = 63,651). We further excluded individuals with outcomes occurring within the first 2 years of follow-up (n = 19,708) to minimize the potential of reverse causation bias. The remaining 412,413 participants comprised our study sample.

PA, CLINICAL, AND OUTCOMES DATA. At each survey, a consistent set of standardized questions was used to ascertain frequency, duration, and type of regular PA engagement (Supplemental Methods).[12,13] The frequency of the activity (times/wk) was multiplied by duration of the activity to provide the minutes per week of aerobic PA. To account for intensity, total weighted moderate-to-vigorous intensity aerobic physical activity (MVPA) was obtained by summing the duration of moderate intensity plus vigorous intensity multiplied by 2.[14,15] Data were also collected on sociodemographic characteristics, medical comorbidities, and self-rated health status (Supplemental Methods). All participants were under surveillance for all-cause and cardiovascular death.[16]

STATISTICAL ANALYSES. For the primary outcomes analyses, we examined the association of PA measures with mortality using Cox proportional hazard regression models that accounted for the complex multistage sampling design of the survey (ie, using weight, primary sampling units, and strata)[17] and adjusted for covariates including age, race/ethnicity, body mass index, smoking status, hypertension, diabetes mellitus, alcohol consumption, education, income-to-poverty ratio, marriage status, access to medical care, self-reported health status, and chronic disease conditions. Before entering the model, unweighted PA measures were expanded using restricted cubic spline given potential nonlinear relationships. Sex differences in the associations between PA measures and mortality were assessed using likelihood ratio tests between models with and without parameters representing the interaction between sex and the cubic spline variables representing PA. The level of PA measure at which the maximal benefit was achieved for men was considered as the comparator referent. We secondarily assessed level of aerobic PA engagement based on frequency, duration per session, and intensity, where intensity was calculated as the proportion of vigorous PA out of total MVPA. Specifically, participants were categorized as physically inactive (<150 min/wk of MVPA) or physically active (≥150 min/wk of MVPA), per the 2018 PA guideline.[2] Physically active participants were then categorized by frequency, duration per session, and intensity of aerobic PA, and inactive

participants were considered the referent for all analyses. Similarly, participants were also categorized by muscle strengthening activity as physically inactive (<2 sessions/wk) or physically active (≥2 sessions/wk). We then repeated multivariable-adjusted Cox models, as described previously, to examine sex-specific associations for these categorized PA measures. We used the adjusted Wald test to evaluate the sex interaction by including the multiplicative terms of PA and sex.

In secondary analyses, we repeated analyses for women and men stratified by age grouped by decade or 2 decades. To account for the previously reported tendency of women to underreport PA duration compared with men,[18] we conducted secondary analyses that incorporated sex-specific PA duration weights applied to both women (ie, multiplied by 1.2) and men (ie, multiplied by 0.8) (Supplemental Methods). We also repeated analyses assessing for any sex differences in outcomes associated with aerobic and muscle strengthening activity combined. To contextualize observed PA associations with mortality, we examined associations of PA with prevalent major risk factors (ie, hypertension, diabetes) and measures of self-reported health (Supplemental Methods). In exploratory analyses, to assess whether sex-specific associations may have changed over time, we also repeated the primary analyses while considering PA data collected during 2007 (instead of 1997) as the "baseline" assessment in relation to outcomes surveillance data collected through 2017. All analyses were performed using R v4.2.1 and STATA v16. A 2-tailed *P* value <0.05 was considered significant.

RESULTS

Of the 412,413 participants in our study, 54.7% were women, 14.4% identified as Black, and 18.4% identified as Hispanic. The mean age was 43.9 ± 16.6 years and other baseline characteristics are shown in **Table 1**. Frequency and distribution of characteristics by sex were similar for participants included in our analyses when compared with those who were excluded (Supplemental Table 1). Over a total 4,911,178 person-years of follow-up, there occurred 39,935 all-cause deaths (8.1 per 1,000 person-years) including 11,670 cardiovascular deaths (2.4 per 1,000 person-years).

SEX DIFFERENCES IN AEROBIC PA ASSOCIATIONS WITH ALL-CAUSE MORTALITY. The baseline characteristics of physically active participants are shown in Supplemental Table 2. Overall, 32.5% of women and 43.1% of men regularly engaged in aerobic PA, and all major measures of PA were significantly more

TABLE 1 Characteristics of the Study Participants

	Frequency and Proportion[a]		
	Women (n = 225,689)	Men (n = 186,724)	*P* Value
Age, y			<0.001
18-44	122,559 (56.1)	106,129 (59.0)	
45-64	67,989 (31.2)	60,290 (32.2)	
65-85	35,141 (12.5)	20,305 (8.6)	
Race and ethnicity			<0.001
Hispanic	41,974 (13.7)	34,099 (14.8)	
Non-Hispanic Black	35,806 (12.6)	23,725 (11.0)	
Non-Hispanic White	135,435 (67.9)	117,985 (68.6)	
Other[b]	12,474 (5.6)	10,915 (5.4)	
Education level			0.089
<High school degree	39,731 (14.9)	32,710 (16.1)	
High school degree	53,978 (24.3)	44,833 (24.6)	
>High school degree	131,221 (60.4)	108,470 (58.8)	
Body mass index, kg/m^2			<0.001
<25	106,095 (48.7)	60,120 (32.0)	
25-29	66,069 (28.5)	83,499 (44.2)	
≥30	53,525 (22.7)	43,105 (23.7)	
Hypertension	51,741 (20.9)	40,741 (20.8)	<0.001
Diabetes	12,545 (4.9)	10,365 (5.1)	0.92
Smoking status			<0.001
Never	148,904 (66.1)	100,307 (55.1)	
Former	37,290 (16.6)	42,121 (21.9)	
Current	39,326 (17.1)	44,130 (22.8)	
Alcohol use, d/wk			<0.001
0	169,389 (74.0)	102,651 (55.7)	
1	25,796 (11.8)	32,075 (17.0)	
≥2	30,504 (14.1)	51,998 (27.1)	
Chronic conditions, n			<0.001
0	151,369 (68.7)	129,007 (69.7)	
1	59,425 (25.3)	46,717 (24.7)	
≥2	14,895 (5.9)	11,000 (5.4)	
Self-rated health			<0.001
Excellent	70,560 (33.2)	64,287 (36.1)	
Very good	77,895 (34.8)	65,037 (34.8)	
Good	58,034 (24.5)	44,102 (22.8)	
Fair/Poor	16,395 (6.3)	11,361 (5.3)	
Access to medical care[c]	198,110 (88.3)	143,277 (78.0)	<0.001
Marriage status			<0.001
Never married	49,859 (20.1)	50,983 (25.0)	
Married/living with partner	115,146 (61.8)	104,940 (64.7)	
Widowed/divorced/separated	60,237 (17.8)	30,485 (10.1)	
Unknown	447 (0.1)	316 (0.1)	
Income-to-poverty ratio[d]			<0.001
<1	33,977 (11.1)	20,311 (8.7)	
1-1.99	39,120 (15.1)	28,061 (13.6)	
≥2	122,754 (60.7)	116,877 (66.0)	
Other[e]	29,838 (12.9)	21,475 (11.6)	

Values are n (%). [a]Analyses of percent values were conducted using the adjustment of weights, primary sampling units, and strata. Variable categories may not sum to 100% because of truncation and unspecified category (ie, refused, not ascertained, or don't know). [b]This category included American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; Asian; Hispanic or Latino; mixed races; refused to respond; or race unknown. [c]Place of usual source of medical care included clinic or health center, doctor's office, hospital emergency room, hospital outpatient department, and some other places. [d]Income-to-poverty ratio was calculated by dividing top-coded total combined imputed family income by the U.S. Census Bureau's poverty thresholds. [e]This category included unknown and undefinable conditions.

BMI = body mass index; DM = diabetes mellitus.

TABLE 2 PA Type and Duration in NHIS Participants

	Frequency and Proportion[a]		
	Female	Male	*P* Value
MVPA, min/wk			
Mean value	206	353	<0.001
<150	155,978 (67.3)	107,065 (56.4)	<0.001
150-299	20,423 (9.6)	18,731 (10.3)	
≥300	49,288 (22.9)	60,928 (33.1)	
MPA, min/wk			
Mean value	53	84	<0.001
<150	203,584 (89.6)	158,610 (84.7)	<0.001
150-299	12,785 (6.0)	14,115 (7.6)	
≥300	9,320 (4.3)	13,999 (7.5)	
VPA, min/wk			
Mean value	76	135	<0.001
<75	164,914 (71.5)	115,272 (60.9)	<0.001
75-149	23,305 (10.9)	21,944 (12.1)	
≥150	37,470 (17.4)	49,508 (26.8)	
Intensity (VPA/MVPA), %[b]			
Mean value	29.3	38.7	<0.001
<25	644 (0.3)	974 (0.5)	<0.001
25-49	3,356 (1.5)	3,900 (2.1)	
50-74	27,296 (12.9)	28,031 (15.3)	
75-100	38,415 (17.8)	46,754 (25.5)	
Muscle strengthening PA, sessions/wk			
Mean value	0.85	1.25	<0.001
0	182,984 (79.9)	135,443 (72.0)	<0.001
2-3	26,574 (12.5)	27,932 (15.3)	
4-5	7,982 (3.8)	12,075 (6.5)	
≥6	8,149 (3.6)	11,274 (6.0)	

Values are n (%) or mean. [a]Analyses of percent values and mean values account for the complex multistage sample design of the survey using weights, primary sampling units, and strata. Variable categories may not sum to 100% because of truncation. [b]Only physically active participants (ie, MVPA>0 min/wk) were shown.

MPA = moderate intensity physical activity; MVPA = moderate-to-vigorous intensity physical activity; NHIS = National Health Interview Survey; PA = physical activity; VPA = vigorous intensity physical activity.

frequent in men (Table 2) (*P* for all <0.001). In particular, regular engagement for women and men was 10.3% and 15.2% for MPA (≥150 min/wk) and was 28.3% and 38.9% for VPA (≥75 min/wk), respectively. For women, regular PA compared with inactivity was associated with a 24% lower risk of all-cause mortality (HR: 0.76; 95% CI: 0.73- 0.80). For men, regular PA compared with inactivity was associated with a reduction in all-cause mortality by 15% (HR: 0.85; 95% CI: 0.82-0.89), and this magnitude of benefit was significantly less than that seen for women (Table 3) (Wald test, F = 12.0, $P < 0.001$ for interaction).

In dose-dependent analyses for the entire cohort, the benefit of PA on all-cause mortality peaked at ~300 min/wk of MVPA and then plateaued (Supplemental Figure 1). The greatest mortality benefit in men was achieved at 300 min/wk of MVPA with an 18% lower hazard in all-cause mortality. Women derived a similar magnitude of benefit at 140 min/wk of MVPA, and continued to benefit with increasing min/wk of MVPA until the greatest benefit of 24% lower hazard (HR: 0.76; 95% CI: 0.72-0.80) was achieved at ~300 min/wk (Figure 1). When examining the relationship specifically for VPA and all-cause mortality, the sex difference was also significant: the greatest benefit was seen in men who engaged in 110 min/wk of VPA, with a 19% lower hazard in all-cause mortality (HR: 0.81; 95% CI: 0.77-0.85); by comparison, women derived the same benefit from only 57 min/wk of VPA (likelihood ratio test, chi-square = 12.8, $P = 0.004$). Although the benefit of VPA reached a plateau beyond 110 min/wk in men, further benefit was derived from more min/wk of VPA in women (Supplemental Figure 2). For women, the 110 min/wk of VPA was associated with 24% lower hazard for all-cause mortality (HR: 0.76; 95% CI: 0.72-0.80) and although the absolute maximum benefit for women was reached at 120 min/wk, the corresponding risk reduction was similar at 24% lower hazard (HR: 0.76; 95% CI: 0.72-0.79). Similarly, for MPA, women appeared to derive a greater mortality benefit per unit time spent engaging in this level of PA: for men the maximal benefit was seen at 90 min/wk of MPA with a 20% reduction in all-cause mortality (HR: 0.80; 95% CI: 0.75-0.84), and for women the same magnitude of benefit was seen at 50 min/wk of MPA (HR: 0.79; 95% CI: 0.75-0.84) (Supplemental Figure 2) although the interaction term for this sex difference did not reach statistical significance (likelihood ratio test, chi-square = 3.85, $P = 0.27$). For women, 90 min/wk of MPA was associated with 24% lower hazard for all-cause mortality (HR: 0.76; 95% CI: 0.71-0.80) and although the maximum benefit for women was reached at 97 min/wk of MPA, the corresponding risk reduction was similar at 24% lower hazard (HR: 0.76; 95% CI: 0.71-0.80).

SEX DIFFERENCES IN MUSCLE STRENGTHENING ACTIVITY ASSOCIATIONS WITH ALL-CAUSE MORTALITY. Men compared with women were more likely to engage in muscle strengthening PA and with greater frequency (Table 2). Overall, 19.9 % of women and 27.8 % of men reported engaging in any regular muscle strengthening PA, with fewer sessions for women (average 0.85 sessions/wk) than men (average 1.25 sessions/wk). For men who performed regular muscle strengthening PA compared with inactivity, mortality risk was reduced by 11% (HR: 0.89; 95% CI: 0.85-0.94); for women, the mortality risk reduction was 19% (HR: 0.81; 95% CI: 0.76-0.85) and this sex difference was significant (Table 3) (Wald test, F = 7.9, $P = 0.005$ for interaction). In dose-dependent

TABLE 3 Association of PA With All-Cause Mortality by Sex

	Female		Male		
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	*P* for Interaction
Aerobic PA					
Inactive	Referent	—	Referent	—	
Active[a]	0.76 (0.73-0.80)	<0.001	0.85 (0.82-0.89)	<0.001	<0.001
Frequency, sessions/wk					
Inactive	Referent	—	Referent	—	
1-5	0.71 (0.65-0.76)	<0.001	0.84 (0.78-0.89)	<0.001	<0.001
6-9	0.74 (0.70-0.79)	<0.001	0.83 (0.78-0.88)	<0.001	
≥10	0.80 (0.76-0.85)	<0.001	0.85 (0.80-0.90)	<0.001	
Duration of session, min					
Inactive	Referent	—	Referent	—	
<15	0.80 (0.75-0.86)	<0.001	0.84 (0.79-0.89)	<0.001	0.063
15-29	0.84 (0.77-0.91)	<0.001	0.91 (0.84-0.98)	0.025	
30-59	0.73 (0.69-0.78)	<0.001	0.78 (0.74-0.83)	<0.001	
≥60	0.78 (0.73-0.83)	<0.001	0.79 (0.74-0.85)	<0.001	
Intensity (VPA/MVPA), %					
Inactive	Referent	—	Referent	—	
<25	0.65 (0.51-0.81)	<0.001	0.78 (0.64-0.96)	0.020	0.007
25-49	0.70 (0.62-0.79)	<0.001	0.81 (0.73-0.90)	<0.001	
50-74	0.75 (0.71-0.80)	<0.001	0.83 (0.78-0.88)	<0.001	
75-100	0.78 (0.75-0.82)	<0.001	0.82 (0.78-0.86)	<0.001	
Muscle strengthening activity					
Inactive	Referent	—	Referent	—	
Active[a]	0.81 (0.76-0.85)	<0.001	0.89 (0.85-0.94)	<0.001	0.005
Frequency, sessions/wk					
Inactive	Referent	—	Referent	—	
2-3	0.74 (0.69-0.80)	<0.001	0.86 (0.81-0.92)	<0.001	<0.001
4-5	0.80 (0.73-0.88)	<0.001	0.89 (0.81-0.97)	0.014	
≥6	0.91 (0.85-0.98)	0.008	0.96 (0.90-1.03)	0.27	

All models accounted for the multistaged survey sample design and were adjusted for total MVPA, muscle strengthening PA (ie, frequency), and covariates that included age, race/ethnicity, body mass index, smoking status, hypertension, diabetes mellitus, alcohol consumption, education, income-to-poverty ratio, marriage status, access to medical care, self-rated health, and chronic disease conditions. [a]Physically active adults were then stratified by frequency, duration, and intensity of PA.

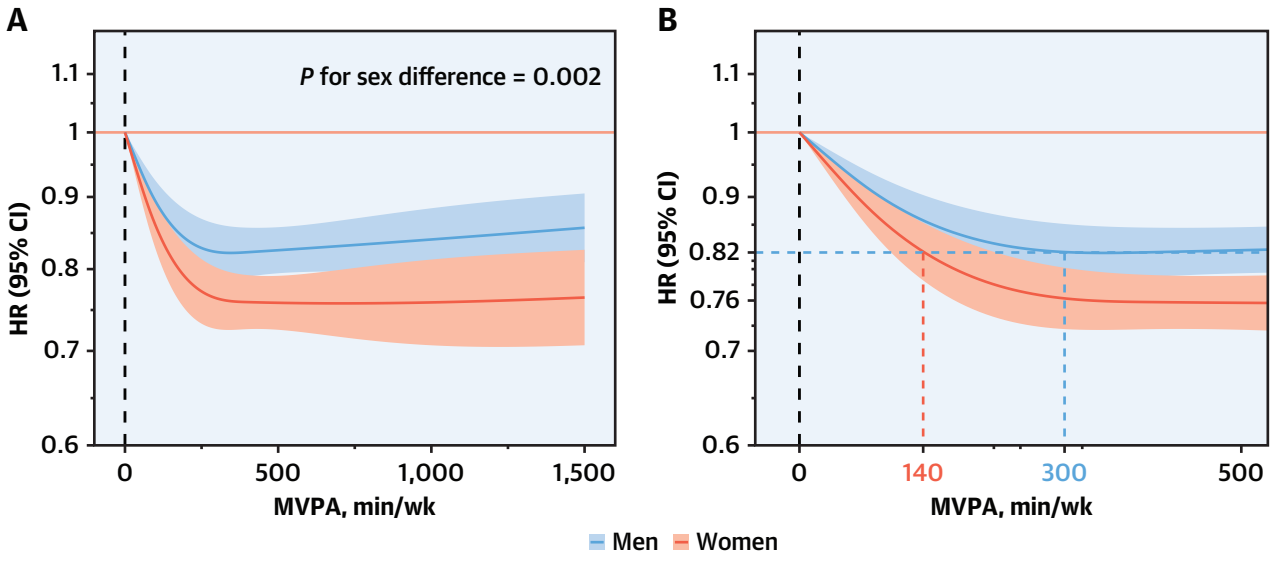
Abbreviations as in Table 2.

analyses, men derived the greatest mortality benefit from engaging in 3 sessions/wk of muscle strengthening PA with a 14% lower hazard in all-cause mortality; women derived equivalent or greater benefit by engaging in only a single muscle strengthening PA per week (**Figure 2**). For women compared with men engaging in 3 sessions/wk of muscle strengthening PA, there was ∼2-fold greater relative reduction in all-cause mortality.

SEX DIFFERENCES IN PA ASSOCIATIONS WITH CARDIOVASCULAR MORTALITY. For cardiovascular mortality, engaging in regular aerobic PA compared with inactivity was associated with a risk reduction of 14% (HR: 0.86; 95% CI: 0.80-0.93) for men and 36% (HR: 0.64; 95% CI: 0.58-0.71) for women; this sex difference was significant (Wald test, $F = 18.8$, $P < 0.001$ for interaction) (Supplemental Table 3). Similarly, engaging in regular muscle strengthening activities compared with inactivity was associated with a cardiovascular risk reduction of 11% (HR: 0.89; 95% CI: 0.80-0.98) in men and 30% (HR: 0.70; 95% CI: 0.62-0.78) in women, and this 3-fold relative sex difference was also significant (Wald test, $F = 9.9$, $P = 0.001$ for interaction) (Supplemental Table 3).

SECONDARY ANALYSES. Across measures of aerobic PA frequency, duration per session, and intensity, the relative magnitude of survival benefit was consistently higher in women than in men for all-cause and cardiovascular mortality (**Table 3**, Supplemental Table 3). Because of slight variations in the questions related to PA in the NHIS 1997 survey, compared with the surveys from subsequent years, we conducted sensitivity analyses excluding participant data from 1997 and findings remained consistent (Supplemental Table 4). In analyses that age-stratified results by decade and then by 2 decades (Supplemental Tables 5

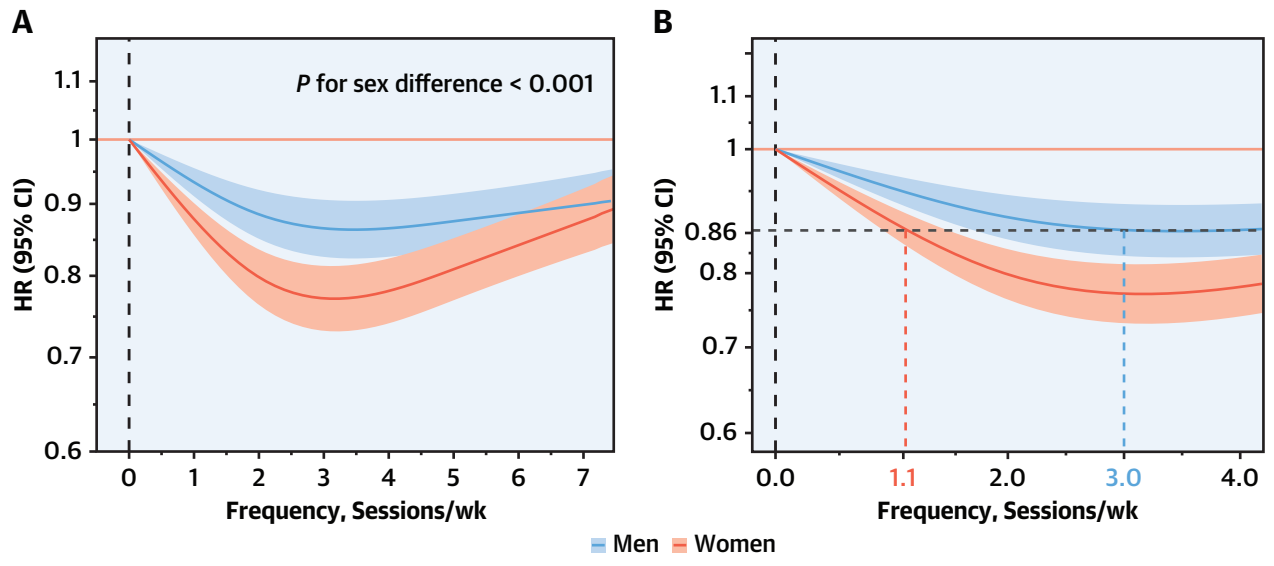
FIGURE 1 Sex-Specific Association of MVPA With All-Cause Mortality



The multivariable-adjusted association of moderate-to-vigorous intensity aerobic physical activity (MVPA) duration with all-cause mortality is shown by sex overall (A) and with focused comparison on the maximal survival benefit achieved for female compared with male individuals (B).

and 6), the magnitude of PA-related mortality risk reduction was consistently greater in women than men particularly for middle-aged individuals (ie, age 40-59 years, $P < 0.05$ for interaction); within the age <40 or ≥60-year strata, the magnitude of sex difference was attenuated ($P > 0.05$ for interaction) (Supplemental Tables 5 and 6). In secondary analyses accounting for potential underreporting of PA in

FIGURE 2 Sex-Specific Association of Muscle Strengthening Physical Activity With All-Cause Mortality



The multivariable-adjusted association of muscle strengthening frequency with all-cause mortality is shown by sex overall (A) and with focused comparison on the maximal survival benefit achieved for female compared with male individuals (B).

women compared with men, results were consistent with those of primary analyses (Supplemental Table 7, Supplemental Figure 3). When considering regular engagement in both aerobic PA and muscle strengthening activity combined, in an additive manner, we observed slightly greater risk reduction in women (HR: 0.72; 95% CI: 0.67-0.87) and men (HR: 0.76; 95% CI: 0.71-0.87) for all-cause mortality although this difference was not statistically significant (Supplemental Table 8). In analyses of PA and self-reported health status, we found that both aerobic PA and muscle strengthening PA were associated with lower odds of self-rated poorer health, indicating a positive relationship with perceived quality of life; these associations also did not significantly differ by sex (Supplemental Table 9). In cross-sectional analyses of PA and risk factors, we found that PA engagement was associated with lower odds of prevalent diabetes in both sexes, to varying degrees (Supplemental Table 10). Interestingly, PA engagement was associated with lower odds of prevalent hypertension in women but higher odds in men; notwithstanding the limitations of cross-sectional analyses, this finding may represent reverse causality (ie, men with a diagnosis of hypertension may be more motivated to exercise).

EXPLORATORY ANALYSES. To examine the extent to which sex-specific associations may have changed over time, we repeated analyses of PA measures and all-cause mortality while considering 2007 as the "baseline" year of PA data collection (instead of year 1997) with ~10 years of outcomes surveillance through 2017 (instead of ~20 years' surveillance). Results of these analyses were similar in directionality of sex difference to those of the primary analyses for both overall aerobic PA and muscle strengthening activity measures, although the magnitude of differences was attenuated in the setting of fewer events accrued per category over the shorter follow-up period (Supplemental Table 11).

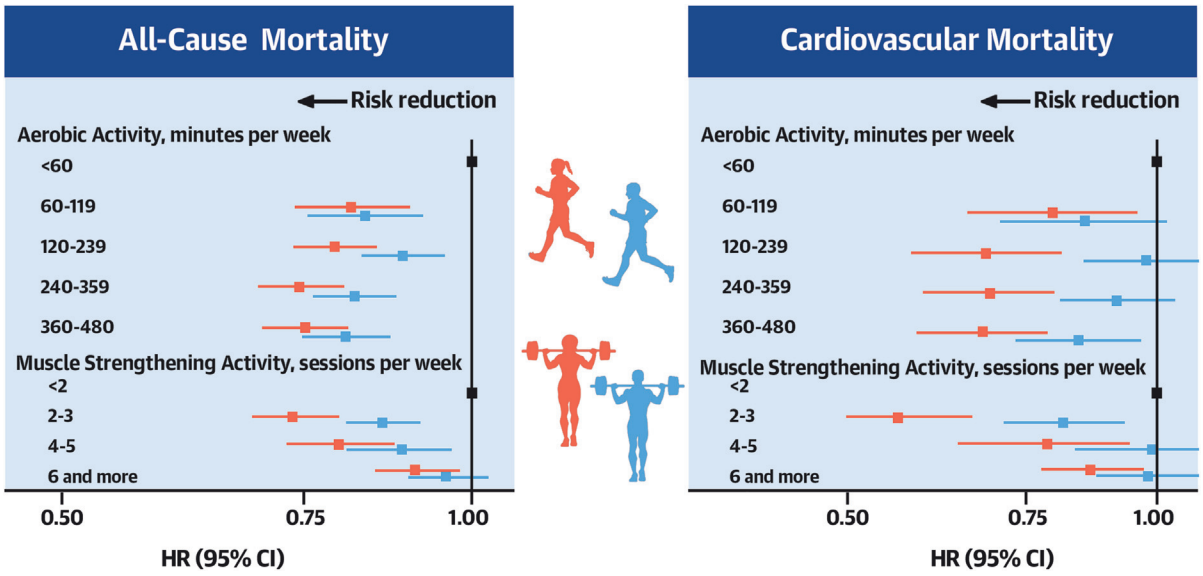
DISCUSSION

In a population-scale nationally representative cohort of U.S. adults, we observed evidence of substantial sex differences in the relations of self-reported leisure-time PA with survival benefit. Although both sexes achieved a peak survival benefit at 300 minutes of weekly aerobic MVPA, women derived a 24% mortality reduction that was substantially greater than for men who derived an 18% mortality reduction from the same degree of regular exercise; similarly, for any given dose of PA leading up to 300 min/wk, women derived proportionately greater benefits than men. These findings were evident for both all-cause and cardiovascular-specific mortality. Importantly, the greater magnitude of PA-related survival benefit in women than men was consistently found across varied measures and types of PA including frequency, duration per session, and intensity of aerobic PA, as well as frequency of muscle strengthening activities. Our results from this large representative population study not only highlight a sex differential response in health benefits from PA but suggest that women stand to especially gain in reduction of cardiovascular and all-cause mortality risk (**Central Illustration**). Such findings could be used to further motivate engagement in PA among currently less engaged segments of the female population and particularly those individuals for whom time represents a barrier to exercise.

Prior data on sex differences in PA-associated outcomes are limited. In a Taiwanese cohort study of 199,265 male and 216,910 female individuals, designed to identify the minimum amount of exercise needed to reduce all-cause mortality, both sexes derived a similar 14% risk reduction in association with as little as 15 minutes of moderate intensity activity per day or 90 min/wk.[19] Consistent with these findings, our results also showed that all-cause mortality benefit was comparable between sexes at similarly lower doses of exercise. Extending from these findings, we further found that sex differences emerged at higher doses of exercise. With respect to cardiovascular outcomes, a meta-analysis of 33 studies showed that relative risk for coronary heart disease was 2-fold lower for female individuals compared with male individuals at similar levels of PA, with a significant sex interaction.[20] Our study adds to these findings by demonstrating similar sex differences in PA-associated risk for not only incident disease but also cardiovascular mortality.

There are several potential explanations for our findings. It has long been known that male individuals have measurably greater exercise capacity than female individuals across all ages.[6,7,21] This may be in part due to attributes including on average proportionately larger hearts, wider lung airways, greater lung diffusion capacity, and larger muscle fibers in male compared with female individuals.[22-24] In particular, men have ~38% more lean body mass compared with women,[23] and so a relatively lower absolute limit to exercise-induced vasodilatory

CENTRAL ILLUSTRATION **Sex Differences in Physical Activity–Associated Mortality Risk Reduction**



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We studied 412,413 U.S. adults and found that women compared with men derived greater gains in all-cause and cardiovascular mortality risk reduction from equivalent doses of leisure-time physical activity.

capacity imposed by substantially lower lean mass and muscle mass in women may be proportionately more efficiently improved by strengthened muscle from PA and especially from muscle strengthening PA of the same dose.[25] Indeed, this phenomenon could underlie the marked sex differences in mortality risk reduction seen from equivalent frequencies of muscle strengthening activity. In fact, physiology studies have demonstrated that female individuals exhibit greater vascular conductance and blood flow during exercise, with female individuals having a higher density of capillaries per unit of skeletal muscle when compared with male individuals.[26] Accordingly, although female individuals have generally lower muscle strength at baseline, when both male and female individuals undergo strength training, female individuals experience greater relative improvements in strength, which is a stronger predictor of mortality than muscle mass.[27,28] Furthermore, sexual dimorphism at the level of muscle fiber type and muscle fiber metabolic, contractile, and dynamic function may also contribute to sex differential responses to the same dose of PA.[29] For example, male individuals have a greater proportion of type II glycolytic muscle fibers, whereas female individuals have a greater proportion of type I oxidative fibers.[30,31] These differences could contribute to not only the known greater female sensitivity to disuse atrophy[32] but also, conversely, the greater female sensitivity to PA observed in our study. We did note an age-interaction such that the female benefit appeared to be attenuated in older compared with younger age; further research may discern whether this finding is related to the menopausal transition with or without hormone replacement therapy taken by some women. Notably, in age-stratified analyses, sex differences were most pronounced for middle-aged adults (ie, ages 40 to 59 years) and this finding aligns with the wealth of prior evidence indicating that relative differences in cardiovascular risk factor burden in middle age are highly impactful on not just later but overall life-long risks for adverse outcomes.[33]

Notwithstanding the need to validate our results in separate studies and using complementary measures of PA exposure and response, our findings have several implications. The longstanding conventional assumption has been that male and female

individuals across all age groups should engage in the same amount of regular PA to gain the same benefit.[5] This assumption has motivated public health attention on the frequently observed "PA gap" between female and male individuals,[5] wherein female individuals are from childhood onward consistently found to be approximately 6% to 10% less physically active than their male counterparts.[34,35] Our findings suggest that attention to the "PA gap" may benefit from a greater emphasis on equalizing levels of engagement rather than equalizing specific dose exposures. Large studies of European children have shown that male individuals consistently perform better on tests of muscular strength, power, and endurance, as well as speed-agility and exercise capacity, whereas female individuals perform better on flexibility measures.[36] In adults, at least one study has shown that the predicted exercise capacity assessed from a Bruce protocol treadmill stress test should be adjusted lower for women than for men, in relation to all-cause as well as cardiovascular death.[7] In the context of prior studies, our findings indicate that female individuals stand to gain proportionately more than male individuals in reduction of cardiovascular and all-cause mortality risk for a given dose of regular exercise. Although existing PA guidelines currently offer sex-agnostic recommendations,[2,3] sex-specific considerations could enhance individual risk assessments and tailored exercise prescriptions in the effort to increase engagement in PA especially for female individuals.

STUDY LIMITATIONS. Several limitations of our study merit consideration. First, all PA data collected were self-reported, albeit using a standardized questionnaire that remained stable over time.[12,13] Numerous PA studies have examined the validity of similarly standardized questionnaire data and found generally acceptable reliability and moderate validity.[37] Objective measures of PA, using devices such as accelerometers or wearables, are increasingly feasible but still incur substantial costs and so the availability of such data linked to outcomes across diverse populations remain limited.[38] Fortunately, a degree of external validity for the PA data collected in the current analysis is also provided by separate studies that used accelerometry and observed the magnitude and significance of mortality associations to be consistent with our results.[39] Although our analyses considered the potential effects of sex differences in self-reported PA level, additional studies are needed to further investigate how variable recall bias may influence the extent to which benefits from PA can differ by sex. Although the primary focus of this analysis was on leisure-time PA, unmeasured variation in household or other activities that can vary by sex could yet have contributed to outcome differences. When estimating muscle strengthening activities, the only information collected was the frequency and not the duration of such activity; nonetheless, this type of reporting is consistent with the 2018 U.S. guidelines on PA that simply recommend performing muscle strengthening activities at least twice weekly without mention of duration.[2] In addition, the NHIS collects aerobic PA data based on exercise occurring for at least 10 minutes and benefits can be derived from periods of PA shorter than 10 minutes. Similarly, the NHIS data on muscle strengthening activities were limited to questions on lifting weights or doing calisthenics. Given the observational design of the study, causal relationships cannot be presumed and results should be interpreted with caution. To mitigate the effects of potential confounding, we excluded participants who were censored within the first 2 years of follow-up for initial analysis. However, unmeasured confounders could yet have influenced results including differential reporting by male and female individuals, unassessed health status factors, and variations in PA engagement over time. Although our sampling methods aimed to reduce the likelihood of reverse causation, we cannot entirely rule out its possible influence in the analyses. Although our exploratory analyses suggest that sex-specific outcomes likely persisted throughout the 2 decades of outcomes surveillance studied, trends in PA engagement continue to evolve and will warrant future additional studies.[12]

CONCLUSIONS

We found evidence of significant sex differences in association of self-reported leisure-time PA with all-cause and cardiovascular death in a large nationally representative cohort of U.S. adults followed for >4 million person-years. Overall, women compared with men derived greater gains in all-cause and cardiovascular mortality risk reduction from equivalent doses of leisure-time PA. These findings could motivate efforts to close the "gender gap" by encouraging especially women to engage in any regular leisure-time PA. Our findings extend from a continually growing body of concordant evidence from physiology and clinical studies on sexual dimorphism in exercise capacity and associated outcomes. Taken together, the results from the current study combined with those of prior investigations

suggest that PA-related risk assessments and recommendations could benefit from sex-specific considerations; in turn, sex-specific guidance could serve to motivate increased PA engagement particularly among women who stand to gain substantial health benefits. Recognizing the limitations of a one-size-fits-all approach, increasing attention to sex differences in PA-related risks and benefits could augment precision medicine efforts to improve health outcomes for all.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported in part by National Institutes of Health grants K23HL153888, K23AG058752, R21HL156132, R01HL142983, R01HL151828, R01HL131532, R01HL143227, R01AG072475, U54AG062319, and U54AG065141, and the Erika J. Glazer Family Foundation, National Key R&D Program of China (2022YFC2502800), National Natural Science Foundation of China (82103908), Shandong Provincial Natural Science Foundation (ZR2021QH014), Shuimu Scholar Program of Tsinghua University, and National Postdoctoral Innovative Talent Support Program (BX20230189). The funding sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The National Center for Health Statistics Disclosure Review Board approves the NHIS. Data analyses for this study were additionally approved by the Cedars-Sinai Medical Center Institutional Review Board. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Physiological responses to various types and intensity of PA differ between men and women, as does the associated health benefit. Although women tend to engage in less PA, the survival benefit gained from exercise is greater for women than for men.

TRANSLATIONAL OUTLOOK: Awareness of this gender gap and motivating women to engage regularly in leisure-time PA could increase their longevity.

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KEY WORDS mortality, physical activity, sex differences

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.