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Research Article

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Adolescent Exercise in Association with Mortality from All Causes, Cardiovascular Disease, and Cancer among Middle-Aged and Older Chinese Women

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Abstract

Background: Little is known regarding the role of early-life exercise, a potentially modifiable factor, in long-term adult morbidity and mortality. We utilized the Shanghai Women's Health Study (SWHS) to investigate adolescent exercise in association with cancer, cardiovascular disease (CVD), and all-cause mortality among middle-aged and older women.

Methods: The SWHS is a prospective cohort of 74,941 Chinese women ages 40 to 70 years recruited from 1996 to 2000. In-person interviews at enrollment assessed adolescent and adult exercise history, medical and reproductive history, and other lifestyle and socioeconomic (SES) factors. Mortality follow-up occurs via annual linkage to the Shanghai Vital Statistics Registry. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were derived from Cox regression models.

Results: Adjusting for birth year and other adolescent factors, adolescent exercise was associated with reduced risk of cancer, CVD, and total mortality [HRs (95% CI), 0.83 (0.72–0.95), 0.83 (0.70–0.98), and 0.78 (0.71–0.85), respectively for $\leq$1.33 hours (h)/week, and 0.83 (0.74–0.93), 0.62 (0.53–0.72), and 0.71 (0.66–0.77), respectively for >1.33 h/week (reference = none)]. Results were attenuated after adjustment for adult SES and lifestyle factors. Participation in sports teams was inversely associated with cancer mortality [HR (95% CI), 0.86 (0.76–0.97)]. Joint adolescent and adult exercise was associated with reduced risk of all-cause, CVD, and cancer mortality [HRs (95% CIs), 0.80 (0.72–0.89), 0.83 (0.69–1.00), and 0.87 (0.74–1.01), respectively], adjusting for adult/adolescent factors, and adolescence exercise only was inversely associated with cancer mortality [HR (95% CI), 0.84 (0.71–0.98)].

Conclusions: Adolescent exercise participation, independent of adult exercise, was associated with reduced risk of cancer, CVD, and all-cause mortality.

Impact: Results support promotion of exercise in adolescence to reduce mortality in later life. *Cancer Epidemiol Biomarkers Prev; 24(8); 1270–6. ©2015 AACR.*

Introduction

Substantial evidence supports the protective role of physical activity in the incidence of cancer, cardiovascular disease (CVD), and overall mortality (1–5). However, much less is known for the role of early-life physical activity in association with morbidity and mortality in later life (6–11). Understanding the impact of physical activity in adolescence on long-term adult health can have important implications for cancer and other chronic disease prevention over the life course.

Epidemiologic studies of adolescence physical activity and adult cancer have largely focused on breast cancer, with some studies reporting reduced risks of breast cancer in association with adolescence physical activity (11, 12). Although there have been many studies of overweight/obesity in childhood and adolescence and later adult mortality (13, 14), virtually no studies have investigated the role of exercise participation during adolescence, a key potentially modifiable exposure that could provide critical opportunities for disease prevention (8, 15). Unhealthy lifestyle habits in adolescence, including exercise habits, may track into adulthood and exercise habits during both early life and adulthood may be particularly influential on adult health outcomes (7, 8, 11). Therefore, it is important to consider adult exercise and other adult factors when evaluating the association of adolescent exercise on adult mortality outcomes; however, few cohort studies have this information.

To address the lack of data, we utilized the Shanghai Women's Health Study (SWHS) to evaluate the association of adolescent exercise and cancer, CVD, and all-cause mortality among middle-aged and older women. The SWHS is a large population-based prospective cohort study of approximately 75,000 Chinese women ages 40 to 70 years at enrollment with detailed information on both adolescent and adult lifestyle-related factors. We further evaluated the joint effect of adolescent and adult exercise on mortality outcomes. Although exposure information is recalled at cohort enrollment, the SWHS is one of the few large prospective cohorts with data on both adolescent and adult lifestyle factors able to evaluate this

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research question (mean follow-up for outcomes is currently 12.9 years).

Materials and Methods

Shanghai Women's Health Study

The SWHS is an ongoing population-based prospective cohort study of Chinese women. The study methods and rationale have been reported in detail elsewhere (16). Briefly, participants were recruited from seven urban counties in Shanghai, China. A total of 74,941 women ages 40 to 70 years were recruited from December 1996 through May 2000 with a participation rate of 92.7%. The baseline survey included an in-person interview, self-administered questionnaire, and anthropometric measurements taken by trained interviewers using standardized protocols. Information was collected on demographics, selected lifestyle factors during adolescence, adult lifestyle habits (e.g., diet, physical activity, alcohol, smoking), menstrual and reproductive history, medical history, and occupational history. All participants, provided written informed consent. Human subjects Institutional Review Board approval, including approval of the informed consent process, was obtained by the appropriate Institutional Review Boards in China (Shanghai Cancer Institute, Shanghai, China) and the United States (Vanderbilt University, Nashville, TN, USA).

Adolescent exercise participation

Exercise participation between the ages of 13 to 19 years was assessed at the baseline interview. Women were asked if they participated in exercise activities regularly, defined as at least once a week, for more than 3 months continuously. For women who reported participating in exercise regularly during adolescence, information was collected on the number of years of participation and number of hours per week of participation. Information was also collected on participation in sports tournaments and sports teams (yes; no). The reproducibility of the SWHS physical activity questionnaire has been previously evaluated and shown to be reasonable with the kappa statistic = 0.83 for adolescent exercise participation and the intraclass coefficient = 0.83 for years of adolescent exercise (17). For adolescent exercise participation (average per year), women were classified as none, ≤1.33 (median) hours (h)/week, >1.33 h/week.

Covariates

Adolescent covariates. Dietary intake during adolescence was assessed using an abbreviated 19-item food frequency questionnaire (FFQ) for select major food items or groups. Information was collected on frequency (every day, every week, every month, every year, or not at all) and amount in Liangs (1 Liang = 50 g). Body mass index (BMI; kg/m^2) at age 20, the only measure of early-life BMI available, was calculated using weight and height at age 20 reported at the baseline interview. Total energy intake could not be estimated as the FFQ included only 19-items for select major food items or groups.

Adult covariates. A 77-item FFQ at baseline was used to assess habitual current dietary intakes of Shanghai women during a face-to-face interview. The FFQ was validated in comparison with 24-hour dietary recalls over 1 year with correlation coefficients of 0.41 to 0.66 for major food groups (18). During the baseline interview, participants were asked about regular exercise in the past five years ("regular" was defined as at least once per week, for more than three months continuously). Information was collected on type, intensity, and duration for up to three activities. The physical activity questionnaire has been shown to be valid (17). Adult height and weight were measured in-person by trained staff at study enrollment and used to calculate baseline adult BMI (kg/m^2). At the baseline interview, highest education achieved, lifetime occupational history, current family income, and medical history (including type II diabetes, hypertension, CVD, and cancer) was assessed.

Cohort follow-up and outcome ascertainment

Follow-up for participants has included in-person interviews every 2 to 3 years to collect interim health history and update exposure information. Response rates were 99.8%, 98.7%, 96.7%, and 92.0% for the first (2000–2002), second (2002–2004), third (2004–2007), and fourth (2008–2011) follow-up surveys, respectively. Data on vital status and cancer diagnoses have also been obtained by annual linkage to the population-based Shanghai cancer and vital statistics registries. The primary study outcome was deaths from all causes. Cause of death information was collected from death certificates from the Shanghai Vital Statistics Registry, which are coded using the International Classification of Diseases, Ninth Revision. Cause-specific deaths examined included deaths due to cardiovascular disease (codes: 390–459) and cancer (codes: 140–208). We also examined specific cancer-related deaths for the four most common types [lung cancer (ICD code: 162), colorectal cancer (ICD codes: 153 and 154), stomach cancer (ICD code: 151), breast cancer (ICD code: 174)]. Follow-up for vital status was >99.9% complete.

Statistical analyses

Participants who were lost to follow-up shortly after study enrollment (n = 5) or had missing information on length of physical activity participation in adolescence or adolescent dietary intake (n = 58) were excluded from all analyses, leaving 74,878 women for the current analysis. Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were derived from Cox proportional hazards models using age as the time-scale (19). Entry time was defined as age at baseline interview and exit time defined as age at death, last follow-up, or December 31, 2011, whichever came first.

Models are adjusted for three sets of covariates. First, we adjusted for birth year (continuous), adolescent dietary factors, age at menarche, and early-life BMI (model 1). We then conducted two analyses to consider adjustment for adult factors. We first additionally adjusted for adult socioeconomic (SES) factors, including latest occupation held (manual and agricultural workers/unknown, clerical, professional), education level achieved (≤elementary, junior high school, high school, >high school), and marital status (married, widowed, single/separated/divorced) as reported at baseline (model 2). We then further adjusted for adult lifestyle factors (BMI, fruit, and vegetable intake, meat intake, exercise participation) and major comorbidities reported at baseline (diabetes, hypertension, CVD, cancer; model 3). It should be noted that although many studies of early-life factors and adult health outcomes adjust for adult exposures, in an attempt to measure the independent effects of early-life exposures, this approach can bias findings due to adjustment for mediating factors in the causal pathway, and hinder interpretation of results (7, 9). Therefore, we show results before adjustment for adult factors, adjusted for adult SES only, and adjusted for adult

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SES and lifestyle factors. In addition, we conducted a joint association analysis for participation in both adolescent and adult exercise (adolescent/adult none, adolescent only, adult only, both adolescent and adult).

Linear trends were evaluated using the Wald test, treating the exposure as a continuous variable. We examined the proportional hazards assumption, both graphically and by testing the significance of interaction terms for the exposures and years of follow-up, and found no evidence for departure from the assumption of proportional hazards. To further consider potential birth cohort effects, we conducted a sensitivity analysis stratifying by birth year and results were similar (data not shown). We also conducted an analysis by approximate 10-year birth cohorts, however, the *P*-value for interaction by birth cohort was not statistically significant (data not shown). All analyses were performed using SAS version 9.4 (SAS Institute Inc.). Tests of statistical significance were based on two-sided probability and *P* values <0.05 were considered statistically significant.

Results

After a mean of 12.9 years of follow-up, 5,282 deaths were identified in the cohort, including 2,375 from cancer and 1,620 from CVD. Select age-adjusted baseline characteristics and adolescent lifestyle factors by adolescent exercise participation are shown in Table 1. Compared with women who reported not exercising during adolescence, women who exercised were younger, had lower early-life BMI and adult BMI, consumed more fruit and less vegetables, had higher education and were more likely to have professional occupations and participate in exercise regularly as an adult.

Table 2 displays associations for adolescent exercise and mortality outcomes. In models adjusted for birth year and other adolescent factors (model 1), adolescent exercise participation was associated with reduced risk of all-cause mortality [HRs (95% CI), 0.78 (0.71–0.85) for $\leq$1.33 h/week, 0.71 (0.66–0.77) for >1.33 h/week], CVD mortality [HRs (95% CI), 0.83 (0.70–0.98) for $\leq$1.33 h/week, 0.62 (0.53–0.72) for >1.33 h/week], and cancer mortality [HRs (95% CI), 0.83 (0.72–0.95) for $\leq$1.33 h/week, 0.83 (0.74–0.93) for >1.33 h/week]. Sport team/tournament participation was also inversely associated with risk of all-cause, CVD, and cancer mortality. After adjustment for adult SES factors and adult lifestyle factors and major chronic disease history (model 3), potential mediators of the associations, results were attenuated, although an inverse association remained for all-cause mortality and CVD mortality. In addition, the association of adolescent exercise and cancer mortality remained statistically significant for exercise <1.33 h/week [model 3: HR, 0.84, 95% CI, 0.72–0.99], but not exercise $\geq$1.33 h/week [model 3: HR, 0.90, 95% CI, 0.78–1.05). Sports team/tournament participation was inversely associated with cancer mortality regardless of adjustment [HR (95% CI), 0.86 (0.76–0.97)]. Associations were similar in sensitivity analyses excluding ever smokers and ever drinkers (only 3% of cohort was excluded due to low prevalence of these behaviors among middle-aged and older Shanghai women during the time of the study), after excluding first 2 years of follow-up, and among women with no baseline history of major chronic diseases (data not shown).

We also investigated associations for the top four cancer-specific deaths, including lung cancer ($n = 462$), colorectal cancer ($n = 343$), stomach cancer ($n = 285$), and breast cancer ($n = 232$) (Supplementary Table S1). Adolescent exercise was inversely associated with lung cancer mortality [adjusted HRs (95% CI), 0.63 (0.44–0.92) for $\leq$1.33 h/week, 0.84 (0.60–1.17) for >1.33 h/week]; however, associations for other cancers were not statistically significant.

We investigated the joint association of adolescent and adult exercise and risk of mortality (Table 3). Exercise participation as both an adolescent and adult was associated with 20%, 17%, and 13% reduced risks of total, CVD, and cancer, respectively. For cancer mortality, the inverse association was stronger for adolescent only exercise [HR (95% CI), 0.84 (0.71–0.98)). Results were similar after excluding the first 2 years of follow-up, whereas among women without prevalent chronic diseases reported at the baseline interview, inverse associations for all-cause and CVD mortality tended to be somewhat stronger (Table 3). The exception was the association of adolescent exercise alone and cancer mortality, which was no longer significant after exclusion of women with prevalent chronic disease, though the HR was unaltered [HRs (95% CI), 0.84 (0.67–1.06)].

Discussion

In this large population-based prospective cohort study with high baseline participation (92%) and almost complete follow-up for mortality outcomes (>99%), adolescent exercise was associated with reduced risk of adult cancer, CVD, and all-cause mortality among middle-aged and older women. Although attenuated after adjustment for adult SES and lifestyle factors, inverse associations remained. Furthermore, participation in exercise both during adolescence and recently as an adult was significantly associated with reduced risks of 20%, 17%, and 13% for all-cause, CVD, and cancer mortality, respectively. In addition, exercise participation in adolescence only, but not adult only, appeared to be more strongly associated with reduced risk of cancer mortality among all participants, however, this association was no longer statistically significant after exclusion of women with major chronic diseases reported at baseline. Findings support the importance of promoting the initiation of regular exercise participation in early life and across the life course to prevent morbidity and mortality due to cancer and other chronic diseases.

Adult physical activity has been well studied in relation to mortality (1, 2, 4, 5, 20). In a previous report in the SWHS published in 2007 (focusing on adult physical activity), both adult exercise and adult total activity (i.e., exercise and non-exercise activities such as cycling or walking for transportation) were significantly associated with reduced risk of all-cause mortality (21). The paucity of data on adolescent physical activity and adult morbidity and mortality in later life has been highlighted in a review by Hallal and colleagues (8). This review also noted the lack of data on adolescent physical activity and adult morbidity and mortality overall, and specifically for non-Western populations. We identified only one cohort study of physical activity in adolescence and adult mortality (22). However, this study was limited to information on job-related activity, and did not have information on exercise participation in adolescence, which is more likely to be modifiable. This large, well-conducted study of a mainly rural population in Iran reported no association for occupational activity at ages 15 and 30 years with mortality outcomes (22). We also identified a study reported in a *Letter to the Editor*

Table 1. Select cohort characteristics by adolescent exercise participation, Shanghai Women's Health Study, 1997 to 2011 ($n = 74{,}878$)[a]

	Adolescent exercise participation			
	No	**≤1.33 h/week**	**>1.33 h/week**	P^b
Age at baseline (years)				
40–49	8.0	68.4	56.8	
50–59	14.9	19.5	30.2	
60–70	77.1	12.1	13.0	<0.001
Early-life BMI (kg/m^2)[c]				
<17.8	18.0	19.9	20.4	
17.8–22.05	61.3	63.5	65.2	
≥22.05	20.7	16.6	14.4	<0.001
Adolescent fruit intake (g/day)				
0	53.1	34.0	26.9	
>0–<10.7	25.1	33.5	31.9	
≥10.7	21.8	32.5	41.2	<0.001
Adolescent vegetable intake (g/day)				
<126.2	25.0	28.8	32.1	
126.2–<210.4	32.1	37.4	37.3	
≥210.4	42.9	33.8	30.6	<0.001
Education level achieved				
≤Elementary	60.7	10.6	5.3	
Junior high school	23.1	68.7	29.7	
High school	12.0	14.9	41.6	
>High school	4.2	5.8	23.4	<0.001
Longest held occupation				
Manual and agricultural workers/unknown	63.6	55.8	37.1	
Clerical	23.2	23.5	18.7	
Professional	13.2	20.7	44.2	<0.001
Marital status at baseline				
Married	86.6	89.9	90.0	
Widowed	8.6	6.6	5.9	
Divorced/single/never married	4.8	3.5	4.1	<0.001
Adult exercise participation at baseline interview				
No	69.3	66.0	61.8	
<2.0 MET-h/week (about <30 min/day)	20.3	22.7	26.2	
≥2.0 MET-h/week (about ≥30 min/day)	10.4	11.3	12.0	<0.001
Adult BMI (kg/m^2) at baseline				
<18.5	3.3	3.7	3.9	
18.5–<24.99	53.4	61.0	64.4	
25.0–<29.99	35.4	30.6	27.7	
≥30.0	7.9	4.7	4.0	<0.001
Diabetes at baseline				
No	95.5	96.1	96.7	
Yes	4.5	3.9	3.3	<0.001
Hypertension at baseline				
No	75.8	78.1	78.2	
Yes	24.2	21.9	21.8	0.001
History of cancer at baseline				
No	98.1	98.2	97.7	
Yes	1.9	1.8	2.3	0.003

[a]All values (except age) were directly standardized to the age distribution of the cohort.
[b]*P*-value from chi-square test for general association.
[c]Excludes 11,082 women missing BMI at age 20.

that evaluated physical fitness during adolescence and adult mortality in a historical cohort study of 510 Japanese women (23). The authors reported results from an unadjusted descriptive analysis only, showing that cumulative all-cause mortality proportions were lower in women with a high physical fitness score (based on four performance tests). This study did not include a multivariable analysis or physical activity measures. In summary, to our knowledge, our study is the first to specifically evaluate adolescent exercise participation in association with adult cancer, CVD, and all-cause mortality.

Physical activity has many known health benefits that could explain an inverse association with CVD and cancer mortality, including improved immune function, reduced inflammatory factors, decreased insulin and insulin-like growth factors, improved lipid profiles, and reduced hypertension (24–26). Although the exact mechanisms underlying exercise in early-life and adult mortality are not well established, adolescent physical activity has been associated with lower blood pressure, improved cholesterol profiles, and improved bone density (27–30). In both adolescents and adults, physical activity has been associated with reduced adiposity, a risk factor for the development and prognosis of many cancer types and CVD (28, 31–33). Furthermore, adolescent exercise may improve adult mortality through the tracking of healthy exercise habits from adolescence into adulthood (8).

When examining the association of adolescent exercise and types of cancer deaths for the four most common cancer types, we observed an inverse association for lung cancer mortality only.

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Table 2. HRs and 95% CIs for associations of adolescent exercise participation with all-cause and cause-specific mortality, Shanghai Women's Health Study, 1997 to 2011 ($n = 74{,}878$)

	Events	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
All-cause mortality				
Adolescent exercise				
None	2,924	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤1.33 h/week	734	0.78 (0.71–0.85)	0.85 (0.77–0.95)	0.85 (0.76–0.94)
>1.33 h/week	1,624	0.71 (0.66–0.77)	0.87 (0.79–0.96)	0.86 (0.78–0.95)
P_{trend}		<0.001	0.01	0.006
Sports team/tournaments				
No	4,563	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	719	0.80 (0.74–0.87)	0.90 (0.82–0.98)	0.91 (0.84–1.00)
CVD mortality				
Adolescent exercise				
None	1,058	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤1.33 h/week	200	0.83 (0.70–0.98)	0.95 (0.79–1.15)	0.95 (0.79–1.14)
>1.33 h/week	362	0.62 (0.53–0.72)	0.84 (0.70–1.01)	0.82 (0.69–0.99)
P_{trend}		<0.001	0.065	0.04
Sports team/tournaments				
No	1,455	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	165	0.79 (0.66–0.93)	0.96 (0.80–1.15)	0.98 (0.82–1.18)
Cancer mortality				
Adolescent exercise				
None	1,084	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤1.33 h/week	375	0.83 (0.72–0.95)	0.84 (0.72–0.99)	0.84 (0.72–0.99)
>1.33 h/week	916	0.83 (0.74–0.93)	0.91 (0.78–1.05)	0.90 (0.78–1.05)
P_{trend}		0.003	0.349	0.312
Sports team/tournaments				
No	1,977	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	398	0.82 (0.73–0.92)	0.86 (0.76–0.96)	0.86 (0.76–0.97)

[a]Model 1: Adjusted for birth year, adolescent dietary factors (fruit intake, vegetable intake, soy protein intake, total meat intake), age at menarche, and early-life BMI.
[b]Model 2: Additionally adjusted for adult SES factors reported at baseline (education level achieved, longest occupation, and marital status at baseline interview).
[c]Model 3: Additionally adjusted for adult leisure-time physical activity, adult fruit intake, adult vegetable intake, adult meat intake, adult BMI, and baseline major chronic disease history.

Although no previous study has reported on adolescent exercise and cancer mortality, we did find one large, recent cohort study of adult exercise and cancer-specific mortality. In this report, which used the NIH-AARP Diet and Health Study cohort, exercise was associated with reduced risk of lung cancer mortality (34). A recent meta-analysis of adult exercise and risk of lung cancer reported evidence for inverse associations in both men and women (35). Potential mechanisms for the inverse association of physical activity and lung cancer include reduced oxidative stress, improved cardiopulmonary function and reduction of carcinogens in the airways, and improved immune function (36, 37).

Table 3. HRs and 95% CIs[a] for the joint association of adolescent and adult exercise[b] with all-cause and cause-specific mortality, Shanghai Women's Health Study, 1997 to 2011 ($n = 74{,}878$)[a]

	All-cause mortality		CVD mortality		Cancer mortality	
Exercise	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
All participants						
None	1,539	1.00 (reference)	564	1.00 (reference)	549	1.00 (reference)
Adolescence only	1,357	0.82 (0.73–0.91)	297	0.82 (0.67–1.00)	751	0.84 (0.71–0.98)
Adult only	1,385	0.87 (0.81–0.94)	494	0.84 (0.74–0.95)	535	0.93 (0.83–1.05)
Both	1,001	0.80 (0.72–0.89)	265	0.83 (0.69–1.00)	540	0.87 (0.74–1.01)
Exclude first 2 years of follow-up ($n = 74{,}411$)						
None	1,395	1.00 (reference)	520	1.00 (reference)	492	1.00 (reference)
Adolescence only	1,222	0.81 (0.73–0.91)	263	0.78 (0.63–0.95)	681	0.84 (0.71–1.00)
Adult only	1,278	0.88 (0.82–0.95)	462	0.85 (0.75–0.96)	487	0.94 (0.83–1.07)
Both	920	0.81 (0.73–0.90)	251	0.83 (0.68–1.00)	489	0.86 (0.73–1.02)
Healthy women[c] ($n = 52{,}577$)						
None	659	1.00 (reference)	196	1.00 (reference)	283	1.00 (reference)
Adolescence only	769	0.76 (0.65–0.90)	112	0.70 (0.49–0.99)	475	0.84 (0.67–1.06)
Adult only	470	0.83 (0.74–0.94)	123	0.70 (0.56–0.88)	218	0.90 (0.75–1.07)
Both	420	0.71 (0.60–0.84)	70	0.61 (0.43–0.88)	271	0.85 (0.68–1.07)

[a]Adjusted for birth year, adolescent dietary factors (fruit intake, vegetable intake, soy protein intake, total meat intake), age at menarche, BMI at age 20, adult SES factors reported at baseline (education level achieved, occupation, and marital status), adult leisure-time physical activity, adult fruit intake, adult vegetable intake, adult meat intake, adult BMI, and baseline major chronic disease history.
[b]Includes leisure-time physical activity (i.e., exercise) only. Nonexercise physical activity during adolescence was not collected.
[c]Excludes women with a history of cancer, CHD, stroke, diabetes, or hypertension at baseline.

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Studies of early-life exposures and adult health outcomes commonly adjust for adult exposures in multivariable models, in an attempt to determine the independent contributions of early-life factors. However, this approach can bias findings and hinder interpretations (7, 9). For example, adult lifestyle factors are potential mediators, and adjusting for a mediator in the pathway between exposure and disease can lead to attenuation of a true association, or even artifactual associations (38). Due to this concern, we presented findings adjusted for adult SES and adult lifestyle factors, separately. Regardless, the inverse association for all-cause mortality and adolescent exercise remained after adjustment. Further, we present results for adolescent participation alone, adult exercise participation alone, and both adolescent and adult participation, which generally show inverse associations for each exercise category.

A limitation of our physical activity measure was that we did not have data on non–leisure-time physical activity during adolescence, including walking or biking to and from school or occupational activities, which would increase the total amount of activity. Lack of this information may tend to bias total physical activity and mortality associations towards the null (39). Therefore, our results may underestimate the association of adolescent physical activity and mortality in later life. Another limitation is that the SWHS questionnaire defined regular exercise as $\geq$1/week for $\geq$3 months continuously, thereby including in the exposure some women with low levels of exercise averaged over one year. We conducted a sensitivity analysis to examine the influence of excluding women who reported <1 hour per week of activity over one year (3.6% of cohort), and the associations were similar to those presented (data not shown). Given the limited data in this area, future studies with more detailed adolescent physical activity assessments and studies in other populations are needed.

Another important limitation to consider is that the adolescent exercise information was based on recalled data. However, reliability data were available for the adolescent exercise measures, which were found to have good reproducibility (17). Although there are known limitations with recall of past exposures, and in particular exposures many years prior to the assessment, prospective studies that begin in adolescence and follow participants 30 to 50 years to middle and old age are time-consuming, costly and not feasible in all populations. Therefore, recall of adolescent exposures in adulthood is an important approach to enable the study of early-life exposures and later adult health. It should be noted that the SWHS could not include women who died between adolescence and when study recruitment began among women ages 40 to 70 years. This should be taken into account when considering the external generalizability of our results. However, the SWHS did not exclude women with prevalent chronic disease at study recruitment, which should increase generalizability of findings. Furthermore, the SWHS is a population-based prospective cohort representative of the urban Shanghai population during the study period, with a high baseline response rate (92%) and almost complete follow-up for mortality outcomes. Finally, another limitation to consider was that we could not adjust for total energy intake in adolescence.

We conducted sensitivity analyses to consider potential bias by (1) excluding the first 2 years of follow-up and (2) limiting our results to women with no history of major chronic diseases. For the joint effects analysis of both adolescent and adult exercise, results were stronger for total and CVD mortality when these exclusions were applied. In addition, the association for cancer mortality and exercise in adolescence alone was no longer statistically significant after the exclusion. The HR was the same magnitude, however, and the resulting change in significance could be due to the reduction in sample size. A limitation of this joint effects analysis was the lack of detail beyond a binary yes/no variable. With continued follow-up of the cohort for outcomes, we will be able to evaluate the joint association in more detail in the future.

In summary, adolescent exercise participation was associated with reduced risk of cancer, CVD, and all-cause mortality in later life, regardless of adjustment for adult lifestyle and SES factors. Although measurement error cannot be ruled out as adolescence exercise participation was recalled by middle-aged and older women at cohort enrollment, our result support that participation in adolescent exercise may influence adult mortality outcomes in middle-aged and older women, and both adolescent and adult exercise may significantly affect cancer, CVD, and total mortality in later life.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: X.O. Shu
Development of methodology: X.O. Shu, G. Yang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X.O. Shu, G. Yang, H. Cai, Y.-T. Gao, H.-L. Li, Y.-B. Xiang, W. Zheng
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.J. Nechuta, X.O. Shu, H. Cai
Writing, review, and/or revision of the manuscript: X.O. Shu, G. Yang, Y.-T. Gao, Y.-B. Xiang, W. Zheng
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X.O. Shu, H. Cai, Y.-T. Gao, H.-L. Li, Y.-B. Xiang, W. Zheng
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