Physical Activity and Long-Term Mortality Risk in Older Adults with and without Cardiovascular Disease: A Nationwide Cohort Study

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Keywords

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Abstract

Aims: To evaluate the association between physical activity (PA) levels and mortality among older adults, to determine whether it differs according to cardiovascular disease (CVD) status, and to assess the optimal weekly duration of PA associated with subsequent survival. **Methods:** Participants ($n = 1,799$) were drawn from a national survey conducted from 2005 to 2006, constituting Israeli adults aged ≥ 65 years. Sociodemographic, clinical, behavioral, and psychosocial data were collected via interview at study entry. Based on a detailed PA questionnaire and according to published guidelines, participants were classified as sufficiently active, insufficiently active, and inactive. CVD status was self-reported. Mortality data (last follow-up, December 2016) were obtained from the Israeli Ministry of Health. Using Cox models, inverse probability weighted hazard ratios (HRs) for mortality, based on propensity score, were estimated for PA categories. **Results:** Among the participants at baseline (mean age, 74.6 years), 559 (31.1%) were sufficiently active, 506

(28.1%) were insufficiently active, and 734 (40.8%) were inactive. During follow-up (mean, 9.0 years), 684 participants (38.0%) died. PA was inversely associated with mortality, with propensity score-adjusted HRs (95% confidence intervals) of 0.84 (0.71–1.01) in insufficiently and 0.73 (0.61–0.88) in sufficiently active participants ($p_{\text{trend}} < 0.001$). No PA-by-CVD interaction was detected on multiplicative scale ($p = 0.36$) or additive scale ($p = 0.58$). A monotonic survival benefit was observed until ~ 150 min of PA per week, beyond which no further gain was apparent. **Conclusions:** In a nationwide cohort of older adults, nearly 70% did not meet the guideline for PA. PA engagement was inversely associated with long-term mortality risk, similarly in individuals with and without CVD. A maximum survival advantage was achieved at around 150 min of exercise per week.

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Introduction

Over the years, observational studies have consistently demonstrated a strong, dose-response inverse association between physical activity (PA) and mortality across different countries and populations, including older adults

(aged ≥ 65 years) [1]. The association was also shown among patients with cardiovascular disease (CVD) [2, 3]. The older adult population is characterized by a high prevalence of chronic illnesses, functional disabilities, cognitive decline, and decreased psychological functioning [4]. These characteristics correlate both with one's likelihood of being physically active and his/her survival [5–8]. However, these parameters were not adequately taken into consideration in many of the previous studies examining the association between PA and survival in the elderly [9].

PA can improve CVD risk factor profiles, prevents primary and secondary cardiovascular events in both young and older adults [10]. Cardiovascular pathophysiology and physiology of aging share common biological pathways, such as insulin resistance and inflammation [11], which may result in alterations in the cardiovascular system as well as in muscles, bones, and nerves, all of which tend to erode exercise capacity and to increase susceptibility to CVD [12]. Taken together, CVD status may modify the potential benefits of PA, marking the importance of quantifying the association between PA and survival in older adults with and without CVD. To date, only a few studies have addressed this issue. Bembom et al. [13], studying a cohort of older adults from Sonoma, CA (median age, 70 years), showed that the mortality-sparing effect of PA is independent of the presence or absence of underlying CVD. In contrast, Jeong et al. [14], studying a large population-based cohort from the Republic of Korea (median age, 59.5 years), concluded that individuals with CVD may benefit from PA to a greater extent than do healthy subjects without CVD. Notably, both studies used a relatively short follow-up duration of up to 5 years which makes them particularly prone to “healthy exerciser bias,” a special type of selection bias where healthy and relatively fit elderly individuals are more likely to participate in vigorous PA [9]. Hence, further investigation in this field is warranted. In addition, as PA was more strongly associated with survival in elderly than younger subjects [1], the optimal weekly duration of PA among the elderly is yet to be clear [15].

We utilized an extensive dataset of 1,799 Israeli older adults aged ≥ 65 years followed-up over nearly a decade to examine the long-term association between PA and all-cause mortality in a nationwide cohort, while appropriately accounting for a wide range of potential confounders and assessing the modifying role of CVD on the association. Further, we attempted to identify the cumulative weekly duration of PA associated with subsequent survival in this population.

Materials and Methods

Study Design and Setting

The cohort comprised all participants interviewed in the first National Health and Nutrition Survey of the Elderly in Israel (“Mabat Zahav”), carried out between 2005 and 2006 by the Israel Center for Disease Control and the Nutrition Department of the Israel Ministry of Health [16]. The survey population constituted a random sample of Israeli citizens aged 65 years or older, with the sampling framework provided by the 2 major health maintenance organizations in Israel (Clalit Health Services and Maccabi Health Services), representing approximately 86% of all elderly individuals in Israel. The final sample included 1,852 community-dwelling participants residing in Israel for at least 1-year. Data were obtained via a personal interview in the interviewee's place of residence (own home or retirement home) using a structured questionnaire. Among the participants interviewed, 53 were excluded because of severe cognitive impairment ($n = 46$) or incomplete questionnaires ($n = 7$), yielding 1,799 participants (for whom survey data are available online at the Ministry of Health government website [17]).

Assessment of PA

Leisure-time PA was self-reported during the baseline interview, based on a standard questionnaire (for full questionnaire see Ministry of Health website – English version available [18]), as previously described in detail [19]. In 2 sets of questions, participants were asked about their PA habits. One set referred to vigorous-intensity activity and another set addressed any type of moderate PA that lasted at least 10 min. Participants reported the frequency (times per week) and average time they devoted to each specific activity, as follows: walking outdoors or on a treadmill, jogging, swimming, bike riding or stationary cycling, light exercise (such as yoga, the Feldenkrais Method, the Alexander technique, and light gymnastics), body shaping, and strength training; an “other activity” option was also offered. Based on the reported total weekly time of PA and intensity, participants were classified into 3 PA categories according to the official American College of Sports Medicine (ACSM) guideline [20]: sufficiently active, insufficiently active, or inactive. Individuals who performed moderate PA for at least 150 min per week or a vigorous-intensity activity for at least 75 min per week or a combination of the 2 were classified as sufficiently active; those who engaged in PA but in a lesser amount than these definitions were classified as insufficiently active; and those who reported no activity or activity less than once a week were classified as inactive.

Cardiovascular Status Assessment

Cardiovascular morbidity was self-reported during the baseline interview. Participants were classified as having CVD if they answered “Yes” to one of the following questions: “Did a doctor tell you in the past that you have: myocardial infarction/heart failure/other heart disease?” or reported having undergone coronary artery bypass grafting or percutaneous coronary intervention.

Mortality Assessment

Data on all-cause mortality (from study entry throughout December 31, 2016) were obtained by linking the cohort (via national identification numbers) to the nationwide database of death, managed by the Ministry of Health.

Table 1. Selected characteristics of study cohort by physical activity categories before and after inverse probability of treatment weighting^a

	Observed cohort				Weighted cohort ^a			
	PA categories			<i>p</i> value	PA categories			<i>p</i> value
	inactive (<i>n</i> = 734)	insufficiently active (<i>n</i> = 506)	sufficiently active (<i>n</i> = 559)		inactive (<i>n</i> = 730)	insufficiently active (<i>n</i> = 505)	sufficiently active (<i>n</i> = 532)	
Age, mean (SD), years	75.1 (6.6)	74.8 (6.0)	73.9 (5.8)	<0.01	74.8 (6.7)	75.0 (5.9)	74.8 (6.1)	0.91
Female sex, <i>n</i> (%)	439 (59.8)	284 (56.1)	235 (42.0)	<0.01	399 (54.7)	258 (51.1)	266 (50.0)	0.32
Perceived good/very good health, <i>n</i> (%)	296 (40.3)	281 (55.5)	409 (73.2)	<0.01	381 (52.5)	272 (53.9)	296 (55.6)	0.58
CVD, <i>n</i> (%)	296 (40.3)	171 (33.8)	180 (32.2)	0.01	268 (36.7)	182 (36.0)	196 (36.9)	0.97
Hypertension, <i>n</i> (%)	288 (40.1)	209 (41.6)	254 (45.7)	0.13	308 (42.8)	207 (41.6)	229 (43.4)	0.87
Perceived health trajectories, <i>n</i> (%) ^b								
Better	50 (6.8)	54 (10.7)	54 (9.7)		60 (8.3)	46 (9.1)	45 (8.5)	
Similar	294 (40.1)	252 (49.8)	338 (60.5)	<0.01	349 (47.8)	241 (47.9)	278 (52.3)	0.63
Worse	390 (53.1)	200 (39.5)	167 (29.9)		320 (43.9)	217 (43.0)	209 (39.2)	
Comorbidities, <i>n</i> (%)								
0	75 (10.2)	68 (13.4)	82 (14.7)		93 (12.7)	64 (12.8)	79 (14.9)	
1–3	538 (73.3)	366 (72.3)	435 (77.8)	<0.01	545 (74.6)	377 (74.6)	396 (74.4)	0.78
≥4	121 (16.5)	72 (14.2)	42 (7.5)		93 (12.7)	64 (12.6)	57 (10.7)	
MMSE score, mean (SD)	30.6 (4.5)	30.6 (3.3)	30.9 (2.8)	0.29	30.6 (3.6)	30.5 (3.7)	30.4 (3.3)	0.68
Functional limitations, <i>n</i> (%) ^c								
Full function	470 (64.0)	426 (84.2)	514 (91.9)		566 (77.5)	403 (79.8)	437 (82.1)	
Moderate impairment	215 (29.3)	66 (13.0)	43 (7.7)	<0.01	138 (18.9)	83 (16.5)	91 (17.1)	0.11
Severe impairment	49 (6.7)	14 (2.8)	2 (0.4)		26 (3.6)	18 (3.7)	4 (0.8)	
GHQ score, mean (SD)	2.2 (2.2)	1.8 (2.1)	2.2 (2.6)	0.03	2.2 (2.3)	2.1 (2.3)	2.0 (2.3)	0.66
Smoking status, <i>n</i> (%)								
Current	97 (13.2)	50 (9.9)	49 (8.8)		82 (11.3)	58 (11.5)	63 (11.8)	
Past	240 (32.7)	168 (33.2)	213 (38.1)	0.04	262 (35.9)	183 (36.3)	197 (37.0)	0.99
Never	397 (54.1)	288 (56.9)	297 (53.1)		386 (52.9)	263 (52.1)	273 (51.3)	
Pack-years, mean (SD)	23.5 (41.0)	15.8 (29.8)	18.4 (36.0)	<0.01	18.7 (32.4)	15.9 (30.2)	21.0 (43.8)	0.74
BMI, kg/m ² , mean (SD)	30.3 (5.4)	29.1 (4.5)	28.0 (4.0)	<0.01	29.2 (5.0)	29.1 (4.8)	28.8 (4.4)	0.51
Married, <i>n</i> (%)	427 (58.5)	310 (61.6)	403 (73.1)	<0.01	459 (63.2)	320 (64.1)	348 (65.8)	0.72
Arab ethnicity, <i>n</i> (%)	213 (29.0)	35 (6.9)	52 (9.3)	<0.01	121 (16.6)	84 (16.6)	67 (12.6)	0.27
Employment, <i>n</i> (%) ^d	631 (86.0)	377 (74.5)	396 (70.8)	<0.01	572 (78.4)	395 (78.2)	404 (76.0)	0.63
Education, mean (SD), years	8.7 (5.5)	11.1 (4.7)	12.5 (4.5)	<0.01	11.2 (5.3)	10.6 (4.9)	11.7 (4.7)	0.05
Steady partner, <i>n</i> (%)								
Living alone	182 (24.8)	120 (23.7)	122 (21.8)		175 (23.9)	120 (23.7)	129 (24.2)	
Living with a spouse	421 (57.4)	313 (61.9)	399 (71.4)	<0.01	457 (62.6)	319 (63.3)	345 (64.8)	0.87
Living with a kin/companion/caregiver/other	131 (17.8)	73 (14.4)	38 (6.8)		99 (13.5)	65 (13.0)	59 (11.1)	
Personal income, <i>n</i> (%)								
Low	538 (82.3)	316 (70.1)	301 (59.8)		478 (73.4)	315 (70.0)	336 (70.1)	
Intermediate	101 (15.4)	108 (23.9)	157 (31.2)	<0.01	147 (22.5)	111 (24.7)	114 (23.8)	0.65
High	15 (2.3)	27 (6.0)	45 (8.9)		27 (4.2)	24 (5.3)	29 (6.1)	
Household income category, <i>n</i> (%)								
Low	381 (69.1)	201 (51.5)	189 (40.5)		319 (56.2)	207 (52.5)	222 (52.7)	
Intermediate	126 (22.9)	121 (31.0)	178 (38.1)	<0.01	176 (31.0)	126 (32.0)	129 (30.5)	0.58
High	44 (8.0)	68 (17.4)	100 (21.4)		72 (12.7)	61 (15.5)	71 (16.8)	

ADL, activities of daily living; BMI, body mass index; GHQ, General Health Questionnaire; MMSE, Mini-Mental State Examination; SD, standard deviation; CVD, cardiovascular disease. ^a Weighted by inverse probability of treatment, as described in the Statistical Analyses section. ^b Perceived health at the time of the interview in comparison to preceding year. ^c Evaluated via ADL score, as described in the Statistical Analyses section. ^d Including salaried/un-salaried/volunteer.

Additional Covariates

Comprehensive information on sociodemographic variables, health conditions, disabilities, mental health, cognitive function, anthropometric measures, and nutritional status was obtained at the baseline interview [16]. Baseline covariates included age, sex, multimorbidity index, smoking status and pack-years, current perceived health, perceived health compared to the year

preceding the interview, CVD, hypertension, functional status, mental health, cognitive status, body mass index, ethnicity, marital status, living with a steady partner, employment, education, personal income, and household income. Full description of baseline covariates is available in online suppl. material; see www.karger.com/doi/10.1159/000518169 for all online suppl. material.

Fig. 1. Distribution of PA categories in the entire cohort and by CVD status. $p = 0.01$ for the comparison of distributions between CVD and non-CVD individuals. CVD, cardiovascular disease, PA, physical activity.

Statistical Analysis

A propensity score was constructed using a multinomial logistic regression, through which the probability of being classified into a specific PA category (inactive, insufficiently active, or sufficiently active), conditional on measured baseline covariates, was estimated. Inverse probability weights were calculated using the propensity score [21], by weighting each participant in each PA category inverse to her/his probability of being classified into that specific PA category. In this manner, we created a pseudopopulation in which the distribution of measured baseline covariates is independent of PA category; thus, accounting for differences between the individuals in PA categories that could influence the outcome. Because of the instability that can be induced by extreme weights, stabilized weights were used to preserve the original sample size [22]. Truncation was additionally applied by resetting observations with weights below the 1st percentile and above the 99th percentile to the values of the 1st and 99th percentiles, respectively [21, 23]. Mortality rates in PA categories, stratified by CVD status, were estimated according to inverse probability weights based on the propensity score. Subsequently, weighted Cox proportional hazards regression models with age as the time scale were constructed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality in PA categories. HRs were further estimated for each PA category stratified by CVD status. Linear trend across PA categories was tested by treating PA categories as a continuous variable in the regression model. We repeated the main analysis by using a conventional Cox model adjusted for selected baseline covariates. Effect modification of baseline CVD on the PA-mortality association was examined by testing a two-way interaction term of PA-by-CVD in a regression model which included PA and CVD status as the main effects. Additive interaction was tested by comparing adjusted risk differences as estimated through stratified proportional hazards models. In addition, we calculated the total time (minutes) of PA summing all the activities reported. We then applied spline methodology using a penalized spline term to assess the relationship between total time of PA and

mortality in a Cox regression model. The proportional hazards assumption was tested using the Schoenfeld residuals, with no violations found in any of the models. Analyses were performed using R software, version 3.4.1 (R Development Core Team).

Results

At study entry, the mean (standard deviation) age of the 1,799 participants was 74.6 (6.2) years, and 958 (53.3%) were women. Overall, 817 participants (45.4%) were current or past smokers, 813 (45.2%) perceived their health as poor, and 389 (21.6%) had some level of functional impairment. At baseline, 734 participants (40.8%) did not engage in any type of PA, 506 (28.1%) engaged in PA below the ACSM guideline, and 559 (31.1%) met the guideline. Baseline characteristics distributed differently across PA categories. Compared with sufficiently active participants, inactive participants were slightly older and more likely to be female, with higher body mass index, current smokers and of lower socioeconomic status (SES) as measured by years of education, personal income, and household income. Sufficiently active participants reported better general health, with lower CVD prevalence than insufficiently active and inactive participants. Weighting using the inverse propensity score resulted in balanced PA groups with regard to baseline characteristics (Table 1).

At baseline, 647 (36.0%) participants reported a history of CVD. Among the latter group, 180 (27.9%) were

Fig. 2. Adjusted mortality rate across PA categories among individuals with and without CVD. Rates are weighted according to inverse of propensity score for PA category. CVD, cardiovascular disease; PA, physical activity.

Table 2. HRs and 95% CIs for mortality associated with physical activity category

PA	Number of subjects	Unadjusted	Multivariable adjustment ^a	Inverse probability weighting ^b
All cohort (<i>n</i> = 1,799; number of cases = 684)				
Inactive	734	1	1	1
Insufficiently active	506	0.64 (0.54, 0.77)	0.80 (0.66, 0.97)	0.84 (0.71, 1.01)
Sufficiently active	559	0.52 (0.43, 0.63)	0.69 (0.56, 0.86)	0.73 (0.61, 0.88)
<i>p</i> value for trend		<0.001	<0.001	<0.001
CVD (<i>n</i> = 647; number of cases = 306)				
Inactive	296	1	1	1
Insufficiently active	171	0.70 (0.54, 0.93)	0.91 (0.67, 1.23)	0.90 (0.69, 1.18)
Sufficiently active	180	0.61 (0.46, 0.82)	0.77 (0.55, 1.07)	0.76 (0.58, 1.00)
<i>p</i> value for trend		<0.001	0.1	<0.05
Non-CVD (<i>n</i> = 1,152; number of cases = 378)				
Inactive	438	1	1	1
Insufficiently active	335	0.62 (0.49, 0.79)	0.70 (0.54, 0.91)	0.81 (0.64, 1.02)
Sufficiently active	379	0.48 (0.37, 0.62)	0.61 (0.45, 0.82)	0.71 (0.56, 0.91)
<i>p</i> value for trend		<0.001	<0.001	0.005

SD, standard deviation; CVD, cardiovascular disease; BMI, body mass index; HRs, hazard ratios; CIs, confidence intervals; PA, physical activity. ^aCox proportional hazards regression model adjusting for age, sex, CVD, comorbidity index, smoking status, pack-years, perceived general health, perceived health 1 year before interview, hypertension, activities of daily living score, general health questionnaire score, mini-mental state examination score, BMI, ethnicity, marital status, living alone, employment, education, personal income, and household income. ^bWeighted Cox proportional hazards regression model based on the propensity score for PA category.

sufficiently active, 171 (26.4%) were insufficiently active, and 296 (45.7%) were inactive; among the 1,152 non-CVD subjects, the PA distribution was 379 (32.9%), 335 (29.1%), and 438 (38.0%), respectively (*p* = 0.01) (Fig. 1).

The mean (25th–75th percentile) follow-up period was 8.8 (7.6–10.8) years. During that period, 684 (38.0%) participants died. The mean age (standard deviation) of the decedents was 83.4 (6.9) years. Propensity score-adjusted cumulative mortality rates across PA categories and CVD status are presented in Figure 2. In general, non-CVD participants had lower mortality rates than

CVD participants. In addition, PA was associated with lower mortality rates, in a dose-response fashion, in both CVD and non-CVD groups. Notably, the adjusted mortality rate in inactive non-CVD participants was comparable to that of sufficiently active CVD participants, particularly during the later follow-up stage. In relative terms, the unadjusted HRs for mortality in the entire cohort were 0.64 (95% CI, 0.54–0.77) in insufficiently active and 0.80 (95% CI, 0.66–0.97) in sufficiently active participants, compared with inactive individuals (*p* for trend <0.001). In the propensity score-weighted model, the

HRs were 0.84 (95% CI, 0.71–1.01) and 0.73 (95% CI, 0.61–0.88), respectively (p for trend <0.001). Similar results were obtained using a traditional multivariable adjustment (Table 2). Among participants with CVD, the HRs in the propensity score-weighted model were 0.90 (95% CI, 0.69–1.18) in insufficiently active and 0.76 (95% CI, 0.58–1.00) in sufficiently active participants, compared with inactive individuals (p for trend <0.05); among non-CVD participants, the HRs were 0.81 (95% CI, 0.64–1.02) and 0.71 (95% CI, 0.56–0.91), respectively (p for trend = 0.005) (Table 2). The association between PA and mortality did not differ statistically between participants with and without underlying CVD, on neither multiplicative scale (p for interaction = 0.36) nor additive scale (p for interaction = 0.58).

Applying spline interpolation technique, a nonlinear relationship between the total time of PA (minutes per week) and mortality was detected (Fig. 3). As the total weekly minutes increased, the risk for mortality decreased, with a maximal protective effect observed around 150 PA min per week. Beyond 150 PA min per week, no further improvement in survival was found.

Discussion

In a nationwide cohort of Israeli individuals with an average age of 75 years, over 40% were physically inactive and another 30% were insufficiently active. PA was inversely associated with propensity score-adjusted long-term mortality risk. The association was similar between individuals with and without CVD at study entry. Remarkably, CVD patients who performed sufficient PA had a comparable mortality risk to inactive individuals free of CVD. To our knowledge, this is among the first studies to specifically explore long-term mortality in relation to PA among older adults aged ≥ 65 years while adequately accounting for a wide range of potential confounders. Furthermore, whether the weekly amount of PA recommended by the ACSM for healthy adults aged 18–65 years should be similarly applied to older age-groups needed clarification. In the present study, we were able to show a survival benefit starting at virtually any amount of weekly PA.

In a multinational panel database that included representative samples of community-based populations from 19 countries in Europe, the overall prevalence of inactivity among individuals aged 55 or older was 12.5%, geographically ranging from 4.9% (Sweden) to 29% (Portugal) [24]. Using data from 3 leading national sur-

Fig. 3. Spline-based HRs and 95% CIs for mortality associated with the total time of PA (minutes per week). Spline-based HRs (95% CIs) for mortality associated with total time of PA (minutes per week) derived from unadjusted (blue) and multivariable-adjusted (purple) Cox models. The latter is adjusted for age, sex, comorbidity index, smoking, perceived general health, perceived health 1 year preceding the baseline interview, hypertension, ADL score, MMSE score, BMI, ethnicity, marital status, employment, education, and household income. The total amount of PA was calculated as the sum of all leisure activities reported at the baseline interview, based on duration and frequency of each activity. The histogram at the bottom shows the distribution of PA total time. The highest 5% of total time has been trimmed for visualization purposes. HRs, hazard ratios; CIs, confidence intervals; BMI, body mass index; PA, physical activity.

veys in the USA, the estimated prevalence of adults aged 65 and over not meeting the PA guideline was higher but differed by survey, ranging from 36.1 to 60.9% [25]. In our nationally representative sample of adults aged ≥ 65 years, 68.9% did not meet the PA guideline (including 40.8% who did not engage in any PA). These proportions were even higher for participants with prevalent CVD.

Several previous studies have evaluated the possible health benefits of PA among participants with a variety of different morbidities [26, 27]. To this end, there is a lack of consensus regarding tailored PA guidelines for specific patient populations [27]. In particular, the modifying role of pre-existing CVD in the association between PA and mortality remains unclear, with only a few studies that are directly addressing this question [13, 14]. Bembo et al. [13] investigated 2,074 persons aged 54 years and older living in and around Sonoma, CA, and showed that the association between PA and mortality was independent of the presence or absence of underlying CVD. However, this study has several limitations, including a short follow-up period of 2-years and relatively “young”

older adults who were, on average, better educated and more health-conscious relative to the community from which they were drawn. This led to a low mortality rate. From a methodological point of view, the inactive participants were analyzed together with the insufficiently active participants, thereby limiting generalizability. In contrast to the Sonoma study, an analysis utilizing data from the National Health Insurance Services-Health Screening Cohort in Korea recently suggested that individuals with CVD may benefit from PA to a greater extent than healthy subjects without CVD [14]. Again, some methodological issues are important to mention in this context. First, the study had a short median follow-up time of 5.9 years, with relatively young median age of <60 years. Also, functional status, mental health, and cognitive performance were not adjusted for. Moreover, CVD participants were, on average, 6 years older than non-CVD participants, calling into question this interaction finding.

A recent meta-analysis showed that among adults aged ≥ 60 years, even a lower than recommended amount of PA was associated with a 22% mortality risk reduction, compared with 28% reduction in those meeting the recommendations [28]. Our results extend this finding by showing a graded relationship between PA and long-term survival in elderly people with and without pre-existing CVD. The possible benefits of PA can be attributed to reverse causation, when inactivity is the result of the presence of advanced disease or disability at the time of the survey [9, 29]. Studies of older adults are particularly vulnerable to reverse causation [29] because older individuals who are healthy enough to preform PA are more likely to experience a reduced mortality risk irrespective of their PA level, a concept referred to as a “healthy exerciser bias” [9]. This issue pertains also to the question of whether or not the presence of CVD influences the engagement in PA. In order to minimize this bias, we used a propensity score adjustment approach [30]. In this context, the wealth and diversity of social and health-related information available in our dataset constitute a major methodological strength of this study. Specifically, attributes of aging, such as poor self-rated health, functional limitations, cognitive impairment, and decreased psychological functioning [4], may serve as important confounders because they are strongly associated with both PA engagement [5, 8, 31] and mortality [7]. SES constitutes another important confounder in this context, being related to both exposure [31] and outcome [32]. Nevertheless, many previous investigations conducted among older adults did not address these potential key con-

founders in their analyses. For example, a few studies on the association between PA and mortality in the elderly population have incorporated measures of mental health [33, 34], self-rated health [33, 35], functional limitations, or any additional SES aspects beyond education [14], which may result in substantial residual confounding [36, 37].

Some limitations of our study should be acknowledged. We relied on self-reported data on both PA and CVD that likely resulted in some exposure misclassification. Although objectively measured PA appears to provide slightly more consistent results than self-reported PA [38], the latter was previously found to be reasonably valid, including among aged individuals [39]. Nonetheless, it is advised that future studies shall use both self-reported and objectively measured PA to gain the most complete PA information [38]. Regarding self-reported CVD in our study, cardiovascular events are unlikely to be missed when those are self-reported. Indeed, an Australian study showed a high accuracy of self-reported CVD events in comparison to medical record adjudication and a statewide hospital morbidity database [40]. Exposure data in our study were reported only once, at baseline, and changes in PA levels and/or CVD status over the course of the follow-up period were not captured. This may result in underestimation of the true associations [3]. Generally, PA can be divided into leisure-time PA and nonexercise activity thermogenesis, such as transportation, occupational, and household activities. Only the former was assessed in our study, and we did not address the different modalities of PA performed (e.g., walking, cycling, swimming, etc.). Further research, adequately powered to assess specific PA domains, such as frequency, duration, intensity, and activity type, is therefore warranted.

Conclusions

In this nationwide survey of older adults, close to half of the participants were inactive and $\sim 70\%$ did not meet the guideline for PA. Our survival analysis supports the importance of performing PA, even below the recommended threshold, by showing an inverse relationship with long-term mortality risk among adults aged 65 years and over. Elderly people, regardless of their CVD status, can benefit from any amount of PA, with a maximum survival advantage supposedly achieved at around 150 min of exercise per week. These findings support the importance of PA as part of healthy aging.

Statement of Ethics

All aspects of the study were conducted according to the World Medical Association Declaration of Helsinki and approved by the Institutional Ethics Committees at both Sheba Medical Center (3546-16-SMC) and Tel Aviv University (No. 362); written informed consent was obtained for every participant.

Conflict of Interest Statement

The authors report no competing interests.

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Author Contributions

O.S., G.C., and Y.G. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Contributions in conception or design of the work provided by O.S., G.C., and Y.G.; contributions in the acquisition, analysis, or interpretation of data for the work given to all authors; statistical analysis performed by O.S., G.C., and Y.G.; drafting of the work done by O.S., G.C., and Y.G.; revising the draft critically for important intellectual content done by all authors; final approval of the version to be published given by all authors.

Data Availability Statement

Anonymized data and materials have been made publicly available at the Israel Ministry of Health website (https://www.health.gov.il/UnitsOffice/ICDC/mabat/Pages/Mabat_Gold.aspx).

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