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Any increment in physical activity reduces mortality of primary care inactive patients

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HOW THIS FITS IN:

Active people show a reduced risk of premature mortality. However, do physically inactive primary care patients, after much of their lives in inactivity, reduce mortality risk when they move from no activity to any increment in physical activity? This research found that inactive patients who increased their physical activity even at a minimum level, below minimal recommendations, significantly reduced mortality, and those who adopted current recommendations or even a higher dose of activity had lower mortality in a curvilinear dose-response relationship. These findings could encourage primary healthcare professionals to promote physical activity and facilitate initial negotiation of objectives when prescribing a physical activity plan.
ABSTRACT

Background: It is unclear how returning to physical activity (PA) after long periods of inactivity gives expected health benefits.

Aim: To determine whether the inactive primary care population reduce their mortality by increasing PA, even in low doses.

Design and setting: Prospective cohort of 3,357 inactive patients attending 11 Spanish public primary healthcare centers.

Method: Change in PA was repeatedly measured during their participation in the ‘Experimental Program for Physical Activity Promotion’ clinical trial in 2003-2006, using the ‘7-day PA Recall’. Mortality until December 31, 2018, (312 deaths) has been recorded from national statistics and survival time from the end of the clinical trial analyzed using proportional hazard models.

Results: After 46,191 person-years follow-up, compared with individuals that remained completely inactive, the mortality of those who achieved minimal recommendations of 150-300 minutes/week (M/W) of moderate or 75-150 M/W of vigorous intensity, was reduced by 45% (adjusted Hazard Ratio –aHR= 0.55; 95% confidence interval -95%CI: 0.41 to 0.74); those who did not meet these recommendations but increased PA in low doses, i.e. 50 M/W of moderate PA, showed a 31% reduced mortality (aHR=0.69; 98%CI: 0.51 to 0.93); and those who surpassed the recommendation saw a 49% reduction in mortality (aHR= 0.51; 95%CI: 0.32 to 0.81). The inverse association between increased PA and mortality follows a continuous curvilinear dose-response relationship.

Conclusion: Inactive primary care patients reduce mortality by increasing PA even in doses below the recommended. Greater reduction is achieved through meeting PA recommendations or adopting levels of PA higher than recommended.

Keywords: exercise, mortality, primary health care, cohort studies, survival analysis, health behavior.
Introduction

The benefits of physical activity (PA) are unquestionable, and previous studies estimate that mortality of people who are active is reduced by between 30 and 60% compared to those who are not. Despite this, it is estimated that worldwide 27.5% of adults and 81% of adolescents do not meet the minimum recommendations of 150 minutes per week (M/W) of moderate physical activity or 75 M/W of vigorous activity and in more developed countries these recommendations are not met by more than 40%. If we focus specifically on the primary care (PC) consulting population, the proportion of inactive patients is even higher, close to 70%; and since inactivity is one of the most important risk factors for health, PC professionals often try to promote PA in their patients through interventions of proven effectiveness. However, many of them wonder whether primary care patients who have spent much of their lives in a state of inactivity would regain the well-known benefits associated with PA by becoming active again, and whether moving from no activity to minimum increases in PA would translate in health benefits so relevant as to substantially impact on mortality.

Some longitudinal studies have tried to clarify this unknown, although they are scarce and, to our knowledge, they are based on cohorts of convenience samples of general population or subgroups of patients with specific pathologies, not on the population of patients attended in primary care. Therefore, what is needed are long-term longitudinal studies following inactive primary care patients in which the change that some of them experience in the level of physical activity over time is validly and repeatedly measured, in order to analyze how this change is associated with mortality. The objective of this study is to evaluate the effect that has on mortality the return to PA of the inactive primary care population, even with modest increases below current recommendations.

Methods
Cohort study of 3,357 inactive primary care patients who participated in the PEPAF (Experimental Program for Physical Activity Promotion) clinical trial and did not meet current recommended levels of physical activity, from 11 primary healthcare centers in 8 Spanish autonomous regions, aged between 19 and 80 years. Patients were recruited through systematic sampling of all patients scheduled for consultation with physicians, following a random procedure\textsuperscript{11}. Their level of physical activity was repeatedly measured between 2003 and 2006, at 6, 12 and 24 months after their inclusion in the clinical trial\textsuperscript{24}. Subsequently, their mortality was recorded, after 12 years, as of December 31, 2018, using data provided by the National Institute of Statistics of Spain, and survival time was calculated from the last PA measurement in 2006.

**Exposure measurement**

The change in physical activity was measured throughout the 24-month follow-up of the PEPAF clinical trial using the semi-structured 7-day Physical Activity Recall (PAR) interview, which has highly accredited validity and reliability\textsuperscript{25,26}. The PAR counts the episodes of PA that last more than 10 minutes in the 7 days prior to the interview, and is able to calculate compliance with the PA recommendations and the activity dose in MET\textsuperscript{h}/day, multiplying the hours dedicated to activities of moderate, vigorous and very vigorous intensity, by the corresponding METs: 4, 6 and 10, respectively.

**Covariates**

In the PEPAF clinical trial, abdominal girth, body mass index and the percentage of body fat based on the thickness of cutaneous folds were measured following the protocols of the ACSM\textsuperscript{27}. Active health problems in the 12 months prior to the start of the study, subsequently grouped with the ACGs\textsuperscript{28} case mix system, and cardiovascular risk factors at study entry were reported by family doctors after reviewing the medical history. Additionally, research nurses carried out the measurement of alcohol consumption (AUDIT)\textsuperscript{29}, tobacco consumption, blood pressure, cholesterol, blood
glucose, blood pressure, educational level, and social class according to the recommendations of the Spanish Epidemiology Society\textsuperscript{30}.

**Statistical analysis**

Cox proportional-hazards models were used to estimate adjusted hazard ratios (aHR) of mortality and 95% confidence intervals (95%CI). Average increment of physical activity reported at six, 12 and 24 months after baseline measurement, weighted by time elapsed from the previous assessment, assigning a zero for missing values in single-time measurements due to patient non-attendance as the most likely outcome in inactive patients and the more conservative way to handling them, was grouped into four exposure groups that match leisure time physical activity (LTPA) doses with physical activity guidelines\textsuperscript{6}: (1) reference group including those who did not increment LTPA at all; (2) the low doses category, which included those who increased some LTPA but did not meet current minimal recommendations of 150 M/W of moderate intensity or 75 of vigorous intensity (<1 MET*h/day); (3) those who meet recommendations of 150-300 M/W of moderate or 75-150 of vigorous intensity (1-3.9 MET*h/day); and (4) the very high doses category, including those who surpassed the recommended activity doses (>= 4 MET*h/day). Statistical models were simultaneously adjusted for known factors associated to mortality and potential confounding variables, such as baseline age, sex, socioeconomic status, education level, smoking, dyslipidemia, blood pressure, obesity, alcohol consumption, diabetes, cancer, cardiovascular disease, other chronic conditions, and primary care center, based on the causal directed acyclic graph shown in Supplementary Figure 1\textsuperscript{31}. Backward, forward and stepwise selection strategies were used performing likelihood ratio tests with 0.05 significance level. The potential modification of the effect of LTPA by age and sex was evaluated by testing first and second grade interaction terms using a significance threshold of 0.01. We repeated the analysis considering LTPA as a continuous variable following a linear, quadratic or cubic function, and different transformations. Goodness of fit tests and their appropriate semi-parabolic shape led
us to select the square root transformation. Proportional hazard assumption was checked, using log-log plots, statistical tests for the interaction of time with the variables and Schoenfeld residual plots, showing no significant violations. We compared participants who died and survivors using logistic regression analysis to check the correct identification of all the variables associated with mortality to be included in the proportional hazards models. Sensitivity analyses were performed by excluding those who died within the first, second, and third year and by using a two-part regression model (accounting for the excess of zeros) imputation method for the physical activity missing values. We estimated the proportion of avoidable deaths attributable to physical inactivity among the entire population, i.e., the population attributable fraction (PAF)\textsuperscript{32}. Statistical analyses were performed using SAS version 9.4 and R version 3.5.1 software.

**Results**

Of the 3,357 primary care attendees who did not meet the minimal PA recommendations at baseline, 1,031 (30.7%) did not report any LTPA increment over the 2-year follow-up in the PEPAF clinical trial; 917 (27.3%) reported a 2-year LTPA average increment lower than one MET\text{*}h/d; 1,190 (35.4%) reported an increase of between one and four MET\text{*}h/d, which corresponds with meeting the current PA recommendations; and 219 (6.5%) reported an average increment that was higher than four MET\text{*}h/d. All of the patients have at least one physical activity measurement (at six, 12 or 24 months) recorded, 3001 (89%) at least two and 2506 (75%) all three. Of the 10,071 total expected measurements, 1,207 (12%) were missed, while from those conducted 4,484 (51%) had a value of 0 MET\text{*}h/d.

Patient baseline characteristics are shown in Supplementary Table 1. They were predominantly female (65.6%), 50.7 years old on average (sd=14.8, range=19-80), and mostly manual workers without university studies. The characteristics of the
participants were not well balanced between the four LTPA comparison groups, because while women, younger adults, those with lower educational level, lower social class, and those who had cancer and cardiovascular risk factors were more likely not to increment LTPA, those with other chronic comorbidities at baseline were more likely to increment their LTPA level over the 2-year follow-up in the PEPAF clinical trial.

During the 12-year follow-up after finishing the PEPAF clinical trial, 312 participants died, most of them due to cancer (130, 41.7%), 63 (20.2%) of cardiovascular disease, 34 (10.9%) of respiratory diseases, and 20 (6.4%) of neurological disorders. Supplementary Table 2 shows the characteristics associated with mortality, such as male sex, older age, low level of education and social class, obesity, diabetes, other risk factors and chronic diseases. The aforementioned crude associations between participants’ characteristics, LTPA, and mortality highlight the need for adjustment by all these potential confounders to estimate the causal effect of LTPA increment on mortality.

After adjustment for sociodemographic characteristics, baseline risk factors and chronic diseases, compared with individuals in the null LTPA increment group, those who increased daily LTPA less than one MET*h/day had a 31% reduced risk for all-cause mortality (aHR = 0.69; 95% CI: 0.51 to 0.93); those who increased LTPA to meet guideline recommendations reduced mortality by 45% (aHR = 0.55; 95%CI: 0.41 to 0.74); and those who surpassed these recommendations increasing LTPA by four or more MET*h/day experienced the highest mortality reduction, by approximately 50% (aHR = 0.51; 95%CI: 0.32 to 0.81). Supplementary Table 3 and Supplementary Figure 2 show these reductions in all-cause mortality associated to daily LTPA compared with those individuals who did not increase LTPA at all. When analyzing the dose-response relationship between mortality and LTPA considered quantitatively, results were consistent with the aforementioned categorical analysis, showing a steep reduction in mortality risk, close to 20%, associated with a minimum LTPA increment of 0.5 MET*h/day (equivalent to 10 minutes of moderate LTPA a day), followed by a
progressive drop to an approximately 45% decrease in mortality at 3 MET*h/day (equivalent to one hour of moderate LTPA or 25 minutes of vigorous LTPA a day), with further positive effects on mortality as LTPA incremented. We found neither significant nor meaningful modifications of the effect of LTPA on mortality in the age and sex subgroups (p > 0.28).

According to an estimated aHR of 1.51 for not meeting minimal physical activity recommendations (95%CI: 1.19 to 1.92), the population fraction of deaths attributable to inactivity is 20% (95%CI: 9.4% to 28.3%), i.e., 62 out of 312 deaths that occurred in the study population during the 12-year follow-up would have been avoided if the entire population had adopted the minimal recommendations.

Consistently with the reported survival analyses, logistic regression analyses examining the probability of dying found a 32% reduction in the odds of death associated to minimal increments of LTPA (aOR= 0.68; 95%CI: 0.46 to 0.99), a 50% reduction associated to meeting the current PA recommendations (aOR= 0.50; 95%CI: 0.35 to 0.71), and a 52% reduction for those who surpassed these recommendations (aOR= 0.48; 95%CI: 0.26 to 0.87). Restriction of the survival analyses to deaths that occurred after the first, second, and third year of follow-up did not show meaningful differences in the reported results (aHR for low LTPA doses group <1 MET*h/day = 0.70 -95%CI: 0.51 to 0.96-; aHR for those meeting recommendations of 1-3.9 MET*h/day = 0.52 -95%CI: 0.38 to 0.71-; and aHR for the very high LTPA doses group >= 4 MET*h/day = 0.46 -95%CI: 0.27 to 0.76-; when restricting analyses to deaths after the third year of follow-up). There were also not significant differences when we imputed the missing values for physical activity using the two part regression model ((aHR for low LTPA doses group <1 MET*h/day = 0.68 -95%CI: 0.49 to 0.93-; aHR for those meeting recommendations of 1-3.9 MET*h/day = 0.56 -95%CI: 0.42 to 0.76-; and aHR for the very high LTPA doses group >= 4 MET*h/day = 0.54 -95%CI: 0.34 to 0.85).

Discussion
Summary

Our results confirm that the increase in physical activity levels in an inactive population of primary care patients translates into a significant reduction in mortality. These benefits follow a clear dose-response relationship, in which mortality starts to fall even with only small increases in physical activity, for example, 10 minutes of moderate activity per day, or 50 per week, and continues to decrease progressively, so that the risk of death is approximately halved when the minimum recommendations are met. This has been observed in an inactive population, probably for many years before entering this study, after 46,191 person-years of follow-up, and, if these recommendations had been met by the whole population, it would have prevented one in every five deaths observed in this study, an impact on mortality equal to or greater than to that attributed to other risk factors, such as tobacco, hypertension, obesity or diabetes.  

Although physical activity promotion by healthcare professionals is a highly efficient intervention (NNT=12), minimum recommended threshold of 150 M/W of moderate or 75 of vigorous PA may be perceived as a barrier for long term inactive patients. Because of that, it is very important to discover in our study that minimal increases in the level of physical activity, even below the minimum recommendations established by international organizations, and observed in a totally inactive population of patients, are associated with a significant reduction in mortality. When primary healthcare professionals try to promote physical activity in patients who have been inactive for many years, it is easier to negotiate a small initial goal, such as including 10 minutes of moderate activity a day, which will benefit them and can later be increased progressively. This applies equally to men and women of all age groups, who in our results benefit equally from the increase in their levels of physical activity. This makes it a universal health promotion intervention for primary care that achieves significant health benefits, even with the most modest increments in physical activity.

Strengths and Limitations
This study is one of the first to explicitly evaluate the effect of increasing physical activity, measured over two years, in a large representative sample of inactive primary care patients. Though objective measures of physical activity levels are desirable, to avoid recall and social desirability bias, the use of structured self-reported measurements are an accepted and extensively used method in population-based epidemiological studies linking physical activity and health. Nevertheless, the 7-day PAR interview has shown a good correlation with objective measures of PA and considering that all study subjects performed the same measurement with certified nurses, measurement error is expected to be non-differential among the exposure groups\textsuperscript{26}. Missing values in some of the single time physical activity measurements can also introduce bias and threat the validity of results. However, we consider this bias to be negligible as the different conducted imputation methods both assigning a value of zero activity - being the most likely value in the repeated measurements- and using the two-part regression model provided similar results. The observational nature of the study does not preclude the possibility of residual confounding, although a significant number of possible confounding factors have been controlled. Although sensitivity analyses excluding deaths within the first 2 and 3 years of follow-up reduce the likelihood of reverse causality owing to undetected hidden diseases at baseline, we cannot completely rule out this possibility.

**Comparison with existing literature**

To our knowledge, the present study is the only one that has been carried out in primary care with inactive men and women of all ages to study the reduction in mortality associated with a change from inactive to active. Previously, Wannamethee et al. published a study in primary care in which only men participated, whose results are consistent with ours\textsuperscript{15}. Three other previous studies which have looked into the decrease in mortality associated with compliance with the minimum recommendations in the primary care population were carried out in selected subgroups, and their results are consistent with the decrease in mortality shown in our study when the minimum
recommendations are met\textsuperscript{17,21,22}. In this regard, our study adds the fact that a 31% decrease in mortality is observed even without reaching these minimum recommendations. The latter is consistent with the results of previous epidemiological studies that have shown that a minimum amount of physical activity reduces mortality\textsuperscript{2,33,34}.

**Implications for Research and/or practice**

The potential public health impact of promoting physical activity in the primary care population is estimated in 20% of deaths that could have been avoided if all participants had adopted the minimum recommendations of accumulating at least 150 M/W of moderate activity or 75 M/W of vigorous exercise. This study also shows that even without reaching this minimum level of activity, the impact on mortality is very important for women and men of all age groups. The message should be that any increase in physical activity of inactive patients is clearly better than nothing, although the greater the activity, the greater the benefits. Additionally, as other studies have shown, with respect to intensity, low-intensity Physical Activity also produces substantial benefits\textsuperscript{35}, while more benefits could be obtained at moderate intensity, and increasingly vigorous intensity physical activity is associated with additional health benefits\textsuperscript{36}.

In conclusion, ‘Exercise is Medicine’: encouraging primary care patients to abandon inactivity and adopt any amount of PA, even below the threshold of the guidelines’ recommendations, reduces all-cause mortality preventing a substantial number of deaths. Physical activity assessment and promotion in routine clinical practice is an effective and efficient medicine for helping patients to become healthier and for extending longevity. We need innovative implementation strategies to translate proven physical activity promotion interventions to practice in a sustainable and generalizable way considering the multilevel social-ecological determinants of physical activity and those related to clinical practice of health care professionals and organizations\textsuperscript{37}.
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Ethical approval: The study protocol was approved by the local clinical research ethics committee (CEIC de Euskadi PI2017171).

Competing interests: None.

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settings: systematic review and meta-analysis of randomised controlled trials. 
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