Physical activity trajectories and mortality:

a population-based cohort study

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ABSTRACT

Objective

To assess the prospective associations of baseline and long-term trajectories of physical activity on mortality from all-causes, cardiovascular disease, and cancer.

Design: Population-based prospective cohort study with repeated exposure assessments.

Setting: Adults from the general population in the United Kingdom.

Participants: 14,599 men and women (aged 40 to 79 years) from the European Prospective Investigation into Cancer and Nutrition – Norfolk cohort, assessed at baseline (1993 to 1997) up to 2004 for lifestyle and other risk factors; then followed till 2016 for mortality (median of 12.5 years of follow-up, after the last exposure assessment).

Main exposure

Physical activity energy expenditure (PAEE) derived from questionnaires, calibrated against combined movement and heart-rate monitoring.

Main outcome measures

Mortality from all-causes, cardiovascular disease and cancer. Multivariable proportional hazards regression models were adjusted for age, sex, socio-demographics; and time-updated medical history, overall diet quality, body mass index, blood -pressure, -triglycerides, LDL- and HDL-cholesterol levels.

Results

During 171,277 person-years of follow-up, 3,148 deaths occurred. Long-term increases in PAEE were inversely associated with mortality, independent of baseline PAEE. For each 1 *kJ/kg/day* per year increase in PAEE (equivalent to a trajectory of being inactive at baseline and subsequently meeting the World Health Organization minimum physical activity guidelines of 150 minutes/week of moderate-intensity physical activity, five years later), hazard ratios (95% CI) were: 0.76 (0.71 to 0.82) for all-cause mortality; 0.71 (0.62 to 0.82) for cardiovascular mortality; and 0.89 (0.79 to 0.99) for cancer mortality, adjusted for baseline PAEE, and established risk factors. Similar results were observed when stratified for prevalent cardiovascular disease and cancer. Joint analyses with baseline and trajectories of physical activity demonstrate that, compared to consistently inactive individuals, those with increasing physical activity trajectories over time experienced lower risks of mortality from all causes, with hazard ratios of: 0.76 (0.65 to 0.88); 0.62 (0.53 to 0.72); and 0.58 (0.43 to 0.78) at low, medium and high baseline physical activity, respectively. At the population level, meeting and maintaining at least the minimum activity recommendations would potentially prevent 46% of deaths associated with physical inactivity.

Conclusions

Middle-aged and older adults can gain substantial longevity benefits by becoming more physically active, irrespective of past physical activity levels, established risk factors, and existing cardiovascular disease or cancer. Considerable population impacts can be realised with consistent engagement in physical activity during mid-to-late life.

SUMMARY BOXES

What is already known on this topic

- It is well-established that physical activity assessed at a single time-point is associated with lower risks of mortality from all-causes, cardiovascular disease, and cancer
- Imprecision in population-level assessments and within-individual variation of physical activity levels over time may partly explain heterogeneity in observed epidemiological associations among the preponderance of studies that have examined physical activity at a single time-point on mortality
- Few studies have quantified the population health impact of different physical activity trajectories on overall mortality

What this study adds

- This study examined associations of long-term trajectories of physical activity on mortality, using repeated measures of physical activity calibrated against energy expenditure from combined movement and heart rate monitoring
- Middle-aged and older adults, including those with existing cardiovascular disease and cancer, stand to gain substantial longevity benefits by becoming more physically active, regardless of past activity levels, and changes in established risk factors, including overall diet quality, bodyweight, blood pressure, triglycerides, and cholesterol
- At the population level, meeting and maintaining at least the minimum physical activity guidelines (equivalent to 150 minutes per week of moderate-intensity physical activity) would potentially prevent 46% of deaths associated with physical inactivity
- In addition to shifting the population towards meeting at least the minimum physical activity recommendations, public health strategies should also focus on preventing declines in physical activity over middle and late adulthood

INTRODUCTION

It is well-established that physical activity is associated with lower risks of overall mortality, cardiovascular disease and certain cancers.[1–3] However, much of the epidemiology arises from observational studies assessing physical activity at a single point in time (at baseline), on subsequent mortality and chronic disease outcomes. From 1975 to 2016, over 90% of these epidemiological investigations on physical activity and mortality have used a single exposure assessment of physical activity at baseline.[4] Relating mortality risks to baseline physical activity levels does not account for within-person variation over the long term, potentially diluting the epidemiological relationship. As physical activity behaviours are complex and vary over the life-course, [5] assessing within-person trajectories of physical activity over time would better characterise the association between physical activity and mortality.

Far fewer studies have assessed physical activity trajectories over time and subsequent risks of mortality.[6–11] Some of these investigations have only included small samples of older adults, in either men or women. Importantly, most existing studies have been limited by crude categorisations of physical activity patterns, without calibration of physical activity assessments using objective measures with established validity. Many studies also do not adequately account for concurrent changes in other lifestyle risk factors—such as overall diet quality and body mass index—which may potentially confound the relationship between physical activity and mortality. This is important, as some studies have shown that associations between physical activity and weight gain are weak or inconsistent, positing that being overweight or obese may instead predict physical inactivity rather than the reverse.[12,13]. Previous investigations have also not quantified the population impact of different physical activity trajectories over time on mortality.

We examined associations of baseline and long-term trajectories of within-person changes in physical activity on all-cause, cardiovascular and cancer mortality in a population-based cohort study and quantified the number of deaths preventable from the observed physical activity trajectories.

METHODS

Study population

The data for this investigation were from the European Prospective Investigation into Cancer and Nutrition (EPIC) – Norfolk Study, comprising a baseline assessment and three repeated follow-up assessments. The EPIC-Norfolk study is a population-based cohort study of 25,639 men and women aged 40 to 79 years, resident in Norfolk in the United Kingdom, and recruited between 1993 to 1997 from community general practices as previously described.[14]

Following the baseline clinic assessment (1993 to 1997), the first follow-up (postal questionnaire) was conducted between 1995 and 1997 at a mean (standard deviation, SD) of 1.7 (0.1) years after baseline, the second follow-up (clinic visit) took place 3.6 (0.7) years after baseline, and the third and final follow-up (postal questionnaire) was initiated 7.6 (0.9) years after the baseline clinic visit. All participants with repeated measures of physical activity (at least baseline and final follow-up assessments) were included, resulting in an analytical sample of 14,599 men and women. The study was approved by the Norfolk District Health Authority Ethics Committee and adhered to the World Medical Association's Declaration of Helsinki. All participants gave written informed consent before enrolment in the study.

Assessment of physical activity

Habitual physical activity was assessed with a validated questionnaire, with a reference time frame of the past year.[15,16] The first question inquired about occupational physical activity, classified as five categories: unemployed, sedentary (e.g. desk job), standing (e.g. shop assistant, security guard), physical work (e.g. plumber, nurse), and heavy manual work (e.g. construction

worker, bricklayer). The second open-ended question asked about time spent in hours per week on cycling, recreational activities, sports or physical exercise, separately for winter and summer.

The validity of this instrument has previously been examined in an independent validation study, using individually-calibrated combined movement and heart rate monitoring as the criterion method; Physical Activity Energy Expenditure (PAEE) increased through each of four increasing categories of self-reported physical activity comprising both occupational and leisure-time physical activity.[15] In the present study, this index of total physical activity was disaggregated into its original two domain-specific variables and a calibration to PAEE was conducted in the validation dataset, in which this exact same instrument had been used (n=1747, omitting one study centre which had used a different instrument). Specifically, quasi-continuous and marginalised values of PAEE in units of *kJ/kg/day* were derived from 3 levels of occupational activity (unemployed or sedentary occupation; standing occupation; physical occupation or manual labour) and 4 levels of leisure-time physical activity (none; 0.1 to 3.5 hours; 3.6 to 7 hours; and >7 hours per week). This regression procedure allows the domain-specific levels of occupational and leisure-time physical activity to have independent PAEE coefficients, while assigning a value of 0 *kJ/kg/day* to individuals with a sedentary (or no) occupation and reporting no leisure-time physical activity (LTPA). The resulting calibration equation was:

PAEE (*kJ/kg/day*) = 0 [sedentary or no job] + 5.61 [standing job] + 7.63 [manual job]
+ 0 [no LTPA] + 3.59 [LTPA of 0.1 to 3.5 hours per week] + 7.17 [LTPA of 3.6 to 7 hours per week] + 11.26 [LTPA >7 hours per week].

Assessment of covariates

Information about participants' lifestyle and clinical risk factors were obtained at both clinic visits, carried out by trained nurses at baseline and 3.6 years later. Information collected during clinic visits included: age; height; weight; blood pressure; habitual diet; alcohol intake (units consumed per week); smoking status (never, former, and current smokers); physical activity; social class (unemployed, non-skilled workers, semi-skilled workers, skilled workers, managers, and professionals); education level (none, General Certificate of Education [GCE] Ordinary Level, GCE Advanced Level, bachelor's degree and above); medical history of heart disease, stroke, cancer, diabetes, fractures (wrist, vertebral, and hip), asthma, and other chronic respiratory conditions (bronchitis and emphysema). Additionally, time-updated information on heart disease, stroke and cancer up to the final physical activity assessment (3rd follow-up) were also collected using objective data from hospital episode statistics. This is a database containing details of all admissions, including accident and emergency attendances and outpatient appointments at National Health Service hospitals in England. Non-fasting blood samples were collected and refrigerated at 4ºC until transported within a week of sampling to be assayed for serum triglycerides, total cholesterol, and HDL cholesterol using standard enzymatic techniques. LDL cholesterol was derived using the Friedewald equation.[17]

Habitual dietary intake during the previous year was assessed using validated 130-item food-frequency questionnaires (FFQ) administered at baseline and at the second clinic visit. Validity of this FFQ for major foods and nutrients was previously assessed against 16-day weighed diet records, 24-hour recall, and selected biomarkers in a sub-sample of this cohort.[18,19] We created a comprehensive diet quality score for each participant, separately for baseline and at follow-up,

incorporating eight dietary components known to influence health and chronic disease risk.[20] The composite diet quality score included: 1) wholegrains, 2) refined grains, 3) sweetened snacks and beverages, 4) fish, 5) red and processed meat, 6) fruit and vegetables, 7) sodium, and 8) the ratio of unsaturated-to-saturated fatty acids from dietary intake. Tertiles were created for each dietary component and then scored as -1, 0, or 1 with directionality dependent on whether the food or nutrient was detrimental or beneficial for health.[20] Scores from the eight dietary components were summed into an overall diet quality score which ranged from -8 to 8, with higher values representing a healthier dietary pattern. Updated information on body weight and height were also collected from the two postal assessments (1st and 3rd follow-up).

Mortality ascertainment

All participants were followed-up for mortality by the Office of National Statistics until the most recent censor date of March 31st, 2016. Causes of death were confirmed by death certificates which were coded by nosologists according to the International Classification of Diseases (ICD). Causes of death were defined using ICD codes as follows: cancer mortality (ICD9, 140-208 or ICD10 C00-C97), and cardiovascular disease mortality (ICD9 400-438 or ICD10 I10-I79).

Statistical analysis

Cox proportional-hazards regression models were used to derive hazard ratios and 95% confidence intervals (CI). Individuals contributed person-time from the date of the last physical activity assessment (third follow-up) until date of death or censoring. To better represent long-term habitual physical activity, all available assessments of physical activity were used to derive an overall physical activity trajectory (ΔPAEE) for each individual, by linear regression against

elapsed time. The resulting coefficient of the calibrated ΔPAEE values in *kJ/kg/day/year*, together with baseline PAEE, were used as mutually-adjusted exposure variables in the Cox regression models.

To investigate joint effects of baseline and time-trajectories of physical activity, categories reflecting approximate tertiles of both baseline PAEE and the observed physical activity trajectories (ΔPAEE) were created. Categories of baseline PAEE were defined as: 1) low (PAEE= 0 *kJ/kg/day*); 2) medium (0 < PAEE < 8.4 *kJ/kg/day*) and 3) high (PAEE ≥ 8.4 *kJ/kg/day*). Categories of the observed physical activity trajectories over time were defined as: 1) *decreasers* (PAEE≤ -0.20 *kJ/kg/day/year*); 2) *maintainers* (-0.20 < PAEE < 0.20 *kJ/kg/day/year*); and 3) *increasers* (PAEE ≥ 0.20 *kJ/kg/day/year*). Joint exposure categories were then created by cross-classifying the 3-level baseline by the 3-level trajectory categories, resulting in 8 categories with the reference group being individuals with consistently low physical activity (by definition, there would be no exposure category with individuals decreasing from low baseline physical activity). Potential deaths averted at the population level by shifting the consistently inactive individuals to each of the observed exposure trajectories were estimated using the absolute difference in adjusted mortality rates between the reference and each joint exposure category, multiplied by the person-years observed in the corresponding joint exposure category. Adjusted mortality rates were derived using multivariable exponential regression, adjusting for the covariates used in the most comprehensively adjusted analytical model.

Cox-regression models were adjusted for: a) general demographics: age, sex, socioeconomic status, education level, and smoking status; b) dietary factors: total energy intake, overall diet quality, alcohol consumption; and c) medical history: asthma, chronic respiratory conditions, bone fractures, diabetes, heart disease, stroke, and cancer **(Model 1)**. Age, energy and alcohol intake, and diet quality were continuous variables. Changes in the above covariates were accounted for by further inclusion of time-updated variables at the second clinic visit (3.6 years later), as well as updated status of cardiovascular disease and cancer from hospital episode statistics up till the final physical activity assessment **(Model 2)**. Changes in body mass index were further accounted for by including into the model, continuous values of body mass index at baseline and at the final physical activity assessment **(Model 3)**. Finally, changes in blood pressure and serum lipids were accounted for by further including into the model, continuous values of systolic and diastolic blood pressure, serum triglycerides, LDL-, and HDL-cholesterol at baseline and at the second clinic visit **(Model 4)**.

Clinically-measured height and weight at both the baseline and second clinic visit were used to calibrate self-reported height and weight provided through the postal questionnaires. Self-reported values were multiplied by the ratio of mean clinically-measured values and self-reported values. Missing values of covariates at follow-up were imputed using regression on their baseline values. A complete case analysis was conducted as a sensitivity analysis. Reverse causation due to undiagnosed disease was mitigated by excluding participants dying within one year of the final physical activity assessment in all analyses. Predefined subgroups were age, sex, weight status by body mass index, and history of cardiovascular disease and cancer. We performed additional sensitivity analyses by excluding individuals with any period-prevalent disease (heart

disease, stroke and cancer) up to the final physical activity assessment, as well as excluding deaths occurring within 2 years of the final physical activity assessment. All analyses were performed using Stata/SE 14.2.

Patient and public involvement

Patients and members of the public were not formally involved in the design, analysis or interpretation of this study. Nonetheless, the research question in this article is of broad public health interest. The results of this study will be disseminated to study participants and the general public through the study websites, participant engagement events, seminars and conferences.

RESULTS

Study population

Among 14,599 participants with a mean (SD) baseline age of 58.0 (8.8) years, followed for a median (interquartile range) of 12.5 (11.9 to 13.2) years after the final physical activity assessment, there were 3,148 deaths (950 from cardiovascular disease and 1,091 from cancer) during 171,277 person-years of follow-up. Table 1 shows the study population characteristics at the four assessment time-points. On average, dietary factors such as total energy intake, alcohol consumption, and overall diet quality were similar at baseline and at the second clinic visit. The prevalence of diabetes, cardiovascular disease, cancer, and respiratory conditions increased over time. From baseline to the final follow-up assessment, mean body mass index increased from 26.1 to 26.7 kg/m^2, and mean physical activity energy expenditure (PAEE) declined by 17% from 5.9 *kJ/kg/day* to 4.9 *kJ/kg/day*. The Pearson correlation coefficients were r=0.57 for PAEE at baseline and 1.7 years later; and r=0.45 between PAEE at baseline and at the final assessment, 7.6 years later.

Associations of baseline and trajectories of physical activity with mortality

For each 1 *kJ/kg/day/year* increase in PAEE over time (ΔPAEE), the hazard ratios (95% confidence intervals) were: 0.78 (0.73 to 0.84) for all-cause mortality; 0.75 (0.66 to 0.86) for cardiovascular mortality; and 0.88 (0.79 to 0.98) for cancer mortality (Table 2, Model 1). Progressive adjustments for: time-updated covariates (Model 2); changes in body mass index (Model 3); changes in blood pressure, and blood lipids (Model 4), did not attenuate the strength of associations. In these models, baseline PAEE was also independently associated with lower mortality; for each 10 *kJ/kg/day* difference between individuals, hazard ratios (95% CI) were

0.70 (0.64 to 0.78) for all-cause mortality; 0.69 (0.57 to 0.83) for cardiovascular mortality; and 0.83 (0.70 to 0.98) for cancer mortality (Table 2, Model 4). There was no evidence of an interaction between baseline PAEE and ΔPAEE for all mortality outcomes (P= 0.62 to 0.87 from likelihood-ratio tests). The effect of PAEE averaged across all assessments on overall mortality, was 0.70 (0.62 to 0.78) for each 10 *kJ/kg/day* difference between individuals. For single time-point exposure assessments, the association of PAEE with mortality at the most recent assessment was stronger than that for baseline PAEE; hazard ratios (95% CI) of 0.68 (0.62 to 0.75) and 0.87 (0.80 to 0.94) per 10 *kJ/kg/day*, respectively.

Sensitivity analyses excluding individuals with any period-prevalent disease (heart disease, stroke and cancer) occurring up to the final physical activity assessment, as well as any deaths occurring within 2 years of this final assessment, showed similar associations with mortality for baseline PAEE and ΔPAEE, hazard ratios (95% CI) of 0.72 (0.63 to 0.81) per 10 *kJ/kg/day* and 0.78 (0.71 to 0.86) per 1 *kJ/kg/day/year*, respectively. Sensitivity analysis using complete cases did not materially change the strength of associations (attenuation<5% for ΔPAEE estimates for all outcomes), but it attenuated the statistical significance for cancer mortality (Supplementary Table 1). Adjustments for occupational physical activity categories (sedentary, standing, physical, and heavy manual) (Supplementary Table 2) slightly strengthened and attenuated associations of ΔPAEE with cardiovascular and cancer mortality, respectively.

Stratified analyses

In stratified analyses based on the most comprehensively-adjusted analytical model (Model 4), significant inverse associations for baseline and ΔPAEE on all-cause mortality persisted in all

subgroups of age, sex, adiposity, and chronic disease status (Figure 1). Although tests for interaction were not statistically significant for any subgroup, the benefit of baseline PAEE on all-cause mortality tended to be stronger in women than men, hazard ratios (95% CI) of: 0.63 (0.53 to 0.74) vs 0.76 (0.66 to 0.87) per 10 *kJ/kg/day*, respectively (P=0.08). Baseline PAEE and ΔPAEE were not associated with cardiovascular mortality for obese individuals. In stratified analyses for cancer mortality, the survival benefits of both baseline PAEE and ΔPAEE were only significant in older adults.

Joint associations of baseline and trajectories of physical activity with mortality

Compared with individuals who were consistently inactive (*low-maintainers*), individuals with medium and high baseline physical activity who maintained these levels (i.e. *medium-maintainers* and *high-maintainers*) had significantly lower risks of all-cause mortality, 28% and 33% respectively (Figure 2). Individuals with increasing physical activity trajectories experienced additional benefit, including those with low or high baseline physical activity. A dose-response gradient was observed within and between strata of baseline physical activity levels. Within strata of low, medium and high baseline physical activity, the risk of mortality was lower through ordinally increasing trajectory levels of: *decreasers*, *maintainers*, and *increasers*. Between strata of baseline physical activity, *low-increasers* experienced 24% lower risk of mortality; 38% for *medium-increasers*; and 42% for *high-increasers*. *Medium-decreasers* and *high-decreasers* had 10% and 20% lower risk of mortality, compared to the reference group of *low-maintainers*.

Estimation of population impact

Had the entire cohort remained inactive over time, an additional 24% of deaths (678 more than the observed 2840 deaths) would have potentially occurred (Figure 2). At the population level, the greatest number of potential deaths averted were in the *medium-increasers* and *medium-maintainers*, preventing 169 (25%) and 143 (21%) of the preventable deaths, respectively. All physical activity trajectories that culminated with meeting at least the minimum physical activity guidelines (equivalent to 5 *kJ/kg/day*) potentially prevented 93% of deaths associated with physical inactivity at the population-level.

DISCUSSION

Principal findings

In this prospective cohort study with repeated assessments, we found significant protective associations for increasing physical activity trajectories against mortality from all-causes, cardiovascular disease and cancer, irrespective of past physical activity levels. These associations were also independent of levels and changes in several established risk factors such as overall diet quality, body mass index, medical history including diabetes and chronic respiratory conditions, blood pressure, triglycerides and cholesterol. Both higher physical activity levels at baseline and increasing trajectories over time were protective against mortality. Notably, the strength of associations was similar in individuals with and without cardiovascular disease and cancer. These results are encouraging, not least for middle-aged and older adults with existing cardiovascular disease and cancer, who can still gain substantial longevity benefits by becoming more active, lending further credence to the broad public health benefits of physical activity.

Independent and joint effects of baseline and trajectories of physical activity

The absence of an interaction between baseline physical activity levels and long-term trajectories on mortality suggests that the relative benefit of increasing physical activity is consistent, irrespective of baseline levels. Increasing PAEE by 1 *kJ/kg/day* per year—equivalent to a trajectory of being inactive at baseline and then subsequently increasing physical activity to 5 and 10 *kJ/kg/day*, five and ten years later, respectively—was associated with a 24% lower risk of all-cause mortality. This gain in longevity from increasing physical activity over time, is in addition to the benefits already accrued from baseline physical activity, i.e. a 30% lower risk of mortality for a between-individual difference of 10 *kJ/kg/day*. For reference, 5 *kJ/kg/day*

corresponds to the World Health Organization (WHO) minimum physical activity guidelines of 150 minutes per week of moderate-intensity physical activity, and 10 *kJ/kg/day* corresponds to the WHO recommendations of 300 minutes per week of moderate-intensity physical activity, which is recommended for additional health benefits. These volumes of physical activity can be achieved in any number of ways during leisure-time and at work, with the required duration depending on relative intensities of the physical activities performed (Figure 3).

The joint analyses of physical activity trajectories beginning from different baseline levels showed that adults who were already meeting at least the minimum physical activity recommendations (i.e. 150 minutes per week of moderate physical activity), experience substantial longevity benefits by either maintaining or further increasing physical activity levels. This is evidenced by *medium-maintainers* and *high-maintainers* experiencing 28% and 33% lower mortality risks, and an additional ~10% lower risk for *increasers* in both these baseline groups. It is noteworthy that adults already meeting the equivalent of the higher WHO physical activity recommendations (i.e. 300 minutes per week of moderate physical activity) still gain further longevity benefits by increasing physical activity levels up to a mean of 14 *kJ/kg/day*. This energy expenditure corresponds to approximately three times the recommended minimum (i.e. a volume equivalent of 450 minutes per week of moderate physical activity). The joint analyses also revealed that some, but not all, of the longevity benefits from past physical activity is lost when previously active individuals decrease their activity levels. Compared to the consistently inactive, *medium-decreasers* and *high-decreasers* experienced 10% and 20% lower mortality risks, respectively. However, these effects appear modest, compared to the 28% and 33% lower mortality risks for *medium-* and *high-maintainers*, respectively. The *low-increasers*

also experienced slightly lower mortality risks than the *high-decreasers* (24% vs 20% lower than the consistently-inactive reference group, respectively) but both had higher mortality risks than the *medium-maintainers* (28% lower risk), despite all these three groups ending up at approximately the same physical activity level at the last exposure assessment. There may be several explanations for this, including: 1) relative importance of past versus more recent physical activity; 2) differential factors that may have caused these specific physical activity trajectories in the first place, beyond differences in period-prevalent disease status; and 3) the degree to which physical activity levels were maintained or continued to change beyond the last exposure assessment until the final censor date.

Population impact

Although mortality benefits were greatest in the *high-increasers* (hazard ratio of 0.58), the fraction of potential deaths averted at the population-level were greatest for the *medium-increasers* (25%) and the *medium-maintainers* (21%), in contrast to 10% for the *high-increasers*. This is due to the combination of a moderately strong aetiological association (hazard ratio of 0.72) and a greater prevalence of *medium-maintainers* (23,032 person-years, 15% of total person-years), compared to *high-increasers* (6,988 person-years, 4% of total). All physical activity trajectories during middle-to-late adulthood that culminate with meeting at least the minimum physical activity guidelines could potentially prevent 93% of deaths attributable to physical inactivity. The last 7% were the 48 deaths potentially prevented by the *medium-decreasers*, who as a group did not meet the minimum physical activity guidelines at the most recent assessment. Had this group maintained their baseline physical activity levels, an additional 136 deaths (nearly three times as many) could have been potentially prevented. Comparatively

fewer, yet still an extra 119 deaths (two times as many) could have been prevented if *high-decreasers* had maintained their baseline physical activity levels. These two *decreaser* groups were also the most prevalent in the cohort. Thus, in addition to shifting the population toward meeting the minimum physical activity recommendations, public health efforts should also focus on the maintenance of physical activity levels, specifically preventing declines over middle and late adulthood. The WHO minimum physical activity guidelines of 150 minutes per week of moderate-intensity physical activity appears to be a realistic public health target, given that these levels were observed to be attainable at the population-level. Individuals with existing chronic conditions such as cardiovascular disease and cancer, for whom our study has also demonstrated longevity benefits in, may choose to engage in commensurably lower-intensity activities but for a longer duration (Figure 3). Further research is however needed to specifically ascertain the health benefits of lower-intensity physical activities[21] in both healthy individuals and those with major chronic diseases.

Comparisons with existing studies

The present study also showed that the longevity benefits of increasing physical activity are independent of intermediary changes in several established risk factors, including body mass index, blood triglycerides and cholesterol, as well as blood pressure. These results are interesting, relative to other studies that have demonstrated considerable attenuation of the strength of associations when adjusted for similar cardio-metabolic biomarkers.[2,22] In our study, it is somewhat surprising that the protective associations of physical activity with cardiovascular mortality were not attenuated, but rather strengthened after adjusting for established cardiometabolic risk factors. These findings support research into other potential mechanisms,

including vascular function,[23] novel lipids,[24] and restoration of autonomic nervous system activity,[25] through which physical activity may protect against cardiovascular disease outcomes. In our study, the protective associations of physical activity were stronger for cardiovascular mortality than for cancer mortality, suggesting that longevity benefits were primarily driven through the prevention of cardiovascular-related deaths. Adjustment for occupational physical activity strengthened the associations with cardiovascular mortality; and also had a stronger effect for baseline physical activity, but the opposite for increasing physical activity over time on cancer mortality. The existing body of evidence, from a meta-analysis in nine international cohort studies also reported stronger inverse associations for cardiovascular mortality, compared to cancer mortality.[26,27] The weaker associations with cancer mortality may reflect the notion that cancers are a collection of neoplastic diseases, which may be aetiologically diverse and characterised by separate pathophysiologies.[1]

Our results for the association of baseline physical activity with mortality were broadly similar to those reported in the literature, although our estimates have accounted for changes in physical activity over time, which to some degree would correct for regression dilution bias.[28] In a pooled analysis of data from high-income countries within the Prospective Urban Rural Epidemiologic (PURE) study,[29] medium baseline physical activity (150 to 750 minutes per week of moderate-intensity activity) was associated with a 31% lower risk of mortality. This is similar to our estimates of a 30% lower risk of mortality for a 10 *kJ/kg/day* difference between individuals (equivalent to 300 minutes per week of moderate-intensity physical activity). Another pooled analysis examining the dose-response relationship between baseline leisure-time physical activity and mortality also reported lower mortality risks of between 31 to 37% at a comparable

368 volume of physical activity.[30] Comparisons with previous studies, examining specifically the
369 changes and patterns of physical activity over time on mortality, are difficult due to
370 methodological and analytical heterogeneity between studies, precluding the synthesis of
371 published results using meta-analytic methods. There was considerable variation in the
372 operationalisation of changes in physical activity. Some classified changes as increases and
373 decreases, compared with unchanged physical activity irrespective of baseline levels[31]; others
374 grouped varying activity levels over time as "mixed patterns"[4], potentially obscuring the benefits
375 for individuals who improved physical activity levels over time; yet others used a reference
376 group of the "consistently-active".[6,9] Furthermore, the time periods for studying these physical
377 activity trajectories were also variable, with some studies examining one to two year
378 changes,[32,33] yet others examining changes over ten years.[6,10,11] Nonetheless, the relative risks of
379 our "*high-maintainer*" and "*medium-maintainer*" groups (with hazard ratios of 0.67 and 0.72,
380 respectively) were broadly in the ranges of the "consistently-active" groups reported in previous
381 studies.[7,8,11] Future work examining physical activity trajectories over time on health outcomes
382 could consider pooling of individual-level data from compatible studies with repeated follow-up
383 assessments, ideally combined with external calibration; this would enable standardisation of
384 exposure definitions and analytical approaches.
385
386 **Strengths and limitations of the study**
387 On balance, we present a comprehensive analysis, examining longitudinal physical activity
388 trajectories in a large cohort with long follow-up for mortality, and quantified the population
389 health impact from different physical activity trajectories. To overcome limitations in the existing
390 literature which have predominantly examined mortality associations with single time-point

assessed exposures, we incorporated repeated measures of physical activity calibrated against objective measurements of individually-calibrated combined movement and heart rate monitoring. The use of longitudinal, within-individual trajectories of physical activity over time also precludes any confounding by time-invariant factors such as genetics. Our approach offers a stronger operationalisation of physical activity exposures, representing a methodological advance which may have utility in future longitudinal studies investigating the associations between physical activity and subsequent health outcomes. Our study demonstrated robust protective associations between physical activity and mortality, even after controlling for established risk factors, such as overall diet quality, body mass index, blood pressure and serum lipids. Some limitations of our study are that the analytical sample comprised of individuals who were available for follow-up approximately a decade after initial recruitment. Thus, a healthy cohort effect cannot be excluded. This however, would only serve to render our findings more conservative. As the study was observational, residual confounding due to unmeasured factors may still be possible. However, it would be virtually impossible to study the effects of habitual physical activity on mortality in a randomised controlled trial, and the observational nature of this study broadly demonstrates the attainable longevity benefits of physical activity trajectories observed in the real-world.

Conclusion

We demonstrate that middle-aged and older adults, including those with cardiovascular disease and cancer, stand to gain substantial longevity benefits by becoming more physically active, irrespective of past physical activity levels and established risk factors—including overall diet quality, body mass index, blood -pressure, -triglycerides and -cholesterol. Maintaining or

increasing physical activity from a level equivalent to meeting the minimum public health guidelines has the greatest population health impact, with these trajectories being responsible for preventing nearly 1 in 2 deaths associated with physical inactivity. In addition to shifting the population toward meeting the minimum physical activity recommendations, public health efforts should also focus on the maintenance of physical activity levels, specifically preventing declines over mid- to late life.

Table 1. Study population characteristics at baseline and follow-up assessments

Characteristic	**Baseline** (1993-1997)	**1st follow-up** (1995-1999)	**2nd follow-up** (1998-2000)	**3rd follow-up** (2002-2004)
Sample size of follow-up (n)	14,599	11,889	11,408	14,599
Follow-up duration from baseline (years)	-	1.7 (0.1)	3.6 (0.7)	7.6 (0.9)
Demographics (%)				
Age (years)	58.0 (8.8)	60.1 (8.8)	62.0 (8.8)	65.5 (9.0)
Women (%)	56.6	56.6	56.6	56.6
Job classification				
Unemployed to semi-skilled workers	15.1			
Skilled workers	38.1			
Managers & Professionals	46.7			
Diet and other Lifestyle Factors				
Energy intake (kcal/day)	2055 (593)		1961 (554)	
Overall diet quality score (range -8 to 8)	0.2 (2.9)		0.38 (2.5)	
Alcohol (units/week) 1unit = 8g	7.1 (9.1)		6.9 (9.0)	
Current smoker	9.4		6.3	
Former smoker	41.0		35.9	
Comorbidities (%)				
Diabetes	1.7		3.2	
Heart disease	2.3		3.0	5.3
Stroke	0.9		2.2	3.4
Cancer	4.9		7.6	9.6
Asthma	8.3		10.5	
Chronic obstructive pulmonary disease	8.5		10.7	
Bone fractures	6.6		6.8	
Moderate-to-poor self-rated health	15.8		15.9	
Risk Factors				
Body mass index (kg/m^2)	26.1 (3.8)	26.3 (3.8)	26.6 (3.9)	26.7 (4.2)
Systolic blood pressure (mmHg)	134.1 (17.8)		134.5 (17.9)	
Diastolic blood pressure (mmHg)	82.0 (11.0)		81.8 (11.1)	
Blood lipids (mmol/L)				
Triglycerides	1.76 (1.09)		1.86 (1.07)	
Total Cholesterol	6.14 (1.15)		6.06 (1.15)	
HDL-Cholesterol	1.43 (0.42)		1.50 (0.46)	
LDL-Cholesterol	3.94 (1.02)		3.76 (1.04)	
Physical Activity Energy Expenditure				
PAEE (kJ/kg/day)	5.9 (4.7)	5.0 (4.6)	-†	4.9 (4.8)
ΔPAEE over time (kJ/kg/day/year)	-	-	-	-0.11 (0.66)

Data are presented as mean (standard deviation), unless otherwise specified. ΔPAEE = Trajectory of physical activity energy expenditure (PAEE) over time (annual rate of change), derived from within-individual regression of PAEE across all available physical activity assessments. †Physical activity at the second follow-up was not included in this analysis, as a different questionnaire was used.

Table 2. Associations of mutually-adjusted baseline physical activity energy expenditure (PAEE) and trajectories of physical activity (ΔPAEE) with mortality

	Exposures **Baseline PAEE** (per 10 *kJ/kg/day*) **Δ PAEE** (per 1 *kJ/kg/day/year*)	**Model 1:** Adjustment for **baseline covariates & diet** n= 14,599 171, 277 person-years	**Model 2:** Additional adjustments **for changes in covariates & diet** n= 14,599 171,277 person-years	**Model 3:** Additional adjustments **for changes in body mass index** n= 14,587 171,138 person-years	**Model 4:** Additional adjustments **for changes in blood pressure and lipids** n= 13,360 156,075 person-years
All-cause Mortality		3,148 deaths	3,148 deaths	3,145 deaths	2,840 deaths
	Baseline PAEE	0.70 (0.63 to 0.77)***	0.71 (0.65 to 0.79)***	0.72 (0.65 to 0.79)***	0.70 (0.64 to 0.78)***
	Δ PAEE	0.78 (0.73 to 0.84)***	0.78 (0.73 to 0.84)***	0.78 (0.73 to 0.84)***	0.76 (0.71 to 0.82)***
CVD Mortality		950 deaths	950 deaths	949 deaths	850 deaths
	Baseline PAEE	0.72 (0.60 to 0.86)***	0.73 (0.61 to 0.88)***	0.75 (0.62 to 0.89)**	0.69 (0.57 to 0.83)***
	Δ PAEE	0.75 (0.66 to 0.86)***	0.76 (0.66 to 0.86)***	0.76 (0.67 to 0.87)***	0.71 (0.62 to 0.82)***
Cancer Mortality		1,091 deaths	1,091 deaths	1,090 deaths	977 deaths
	Baseline PAEE	0.80 (0.69 to 0.94)**	0.82 (0.70 to 0.96)*	0.83 (0.70 to 0.97)*	0.83 (0.70 to 0.98)*
	Δ PAEE	0.88 (0.79 to 0.98)*	0.89 (0.79 to 0.99)*	0.89 (0.79 to 0.99)*	0.89 (0.79 to 1.00)*

All hazard ratios (HRs) and 95% confidence intervals (CIs) are for 10 kJ/kg/day differences in baseline PAEE; and for 1 kJ/kg/day per year increase in ΔPAEE.

ΔPAEE = Trajectory of physical activity energy expenditure (PAEE) over time (annual rate of change), derived from within-individual regression of PAEE across all available physical activity assessments. CVD = cardiovascular disease.

Model 1 is adjusted for age, sex, smoking status, education level, social class, self-rated health, alcohol intake, energy intake, overall diet quality (comprising fruit & vegetables, red & processed meat, fish, wholegrains, refined grains, sugar-sweetened snacks and beverages, ratio of unsaturated-to-saturated fat intake, and sodium) as well as for medical history at baseline (cardiovascular disease, cancer, diabetes, asthma, chronic obstructive pulmonary diseases, and bone fractures).

Model 2 is adjusted for covariates in Model 1 + time-updated variables for smoking, alcohol intake, energy intake, diet quality and medical history at the 2nd clinic visit, as well as period-prevalent heart disease, stroke and cancer from hospital episode statistics up to the final physical activity assessment (3rd follow-up).

Model 3 is adjusted for covariates in Model 2 + body mass index at baseline and at the final physical activity assessment

Model 4 is adjusted for covariates in Model 3 + systolic and diastolic blood pressure, serum triglycerides, LDL-cholesterol, and HDL-cholesterol at baseline and at the 2nd clinic visit.

There was no evidence of an interaction between baseline PAEE and ΔPAEE: p=0.74, p=0.62, and p=0.87 for all-cause, cardiovascular and cancer mortality, respectively (based on likelihood ratio tests using Model 4). Asterisks indicate level of statistical significance: *p<0.05; **p≤0.01; ***p≤0.001.

Fig 1. Associations of baseline and long-term trajectories of physical activity energy expenditure (PAEE) with all-cause, cardiovascular disease (CVD) and cancer mortality, stratified by age-group, sex, body mass index (BMI), and disease status. Left panel shows hazard ratios (HR) and 95% confidence intervals (95% CIs) for each 10 *kJ/kg/day* difference in baseline physical activity energy expenditure (PAEE); Right panels shows HRs (95% CIs) for each 1 *kJ/kg/day* per year increase in PAEE (ΔPAEE). Hazard ratios are mutually adjusted for both baseline PAEE and ΔPAEE, and are based on the most comprehensively adjusted model for changes in covariates, including overall diet quality, body mass index, blood -pressure and -lipids (Model 4 from Table 2).

Fig 2. **Association of joint categories of baseline and trajectories of physical activity with all-cause mortality.** PAEE = physical activity energy expenditure. Hazard ratios (HR) are based on the most comprehensively adjusted model for changes in covariates, including overall diet quality, body mass index, blood -pressure and -lipids (Model 4 from Table 2). Potential deaths averted for each exposure category were calculated using the absolute adjusted mortality rate difference between the reference group and each specific exposure category, multiplied by person-years observed in the corresponding exposure category. WHO = World Health Organization.

Fig 3. **Physical activity energy expenditure (PAEE) of common activities performed during leisure-time and at work.** Examples of activities with varying intensities and durations to expend 5 *kJ/kg/day*, equivalent to meeting the World Health Organization (WHO) minimum physical activity guidelines (Panel A). Examples for expending 10 *kJ/kg/day*, equivalent to meeting the WHO physical activity recommendations for additional health benefits (Panel B). MET = metabolic equivalent of task

Contributors

AM and SB conceptualised the design of the study and are guarantors. KTK, RL, and NW contributed to the design of the EPIC-Norfolk study. AM and SB analysed the data, and AM wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and critically reviewed, revised and approved the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any additional organisations for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Participant consent

All participants gave written informed consent before enrolment in the study.

Ethical Approval

The study was approved by the Norfolk District Health Authority Ethics Committee and adhered to the World Medical Association’s Declaration of Helsinki.

Data sharing

Data requests can be made to the EPIC-Norfolk study team, providing reasonable justification.

Transparency

The lead author (AM) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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PRINT ABSTRACT

Study question

While physical activity assessed at a single time-point has been associated with lower risks of mortality, fewer studies have examined the association of within-person changes in physical activity over the long-term on mortality. We examined associations of baseline and long-term changes of physical activity on mortality.

Methods

In a UK population-based cohort of 14,599 men and women (aged 40 to 79 years), Physical Activity Energy Expenditure (PAEE, in kJ/kg/day) was derived from questionnaires and calibrated against objective data from combined movement and heart-rate monitoring. Survival analysis was conducted with multivariable adjustments for socio-demographics, comorbidities, diet quality, body mass index, blood-pressure and -lipids.

Study answer and limitations

After controlling for baseline physical activity and established risk factors, the hazard ratio (95% CI) for all-cause mortality was 0.76 (0.71 to 0.82) for each 1kJ/kg/day/year increase (an equivalent trajectory of being inactive at baseline and subsequently achieving the recommended 150 minutes/week of moderate-intensity physical activity, five years later). Joint analyses with baseline and long-term physical activity trajectories demonstrate that, compared to consistently inactive individuals, those with increasing physical activity trajectories experienced lower risks of mortality, with hazard ratios of: 0.76 (0.65 to 0.88); 0.62 (0.53 to 0.72); and 0.58 (0.43 to 0.78) at low, medium and high baseline activity, respectively. At the population level, meeting and maintaining at least the recommended physical activity level potentially prevented 46% of deaths attributable to physical inactivity. As the study was observational, some residual confounding cannot be excluded.

What this study adds

Middle-aged and older adults, including those with existing cardiovascular disease and cancer, can gain substantial longevity benefits by becoming more physically active, regardless of past activity levels, and changes in diet, bodyweight, blood pressure, triglycerides, and cholesterol.

Competing interests, funding, and data sharing

The study was funded by the Medical Research Council and Cancer Research UK. No competing interests. Data available on request.

*accompanying figure for the print abstract: **Figure-2**

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