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Review

Dose−response associations, physical activity intensity and mortality risk: A narrative review

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Abstract

Physical activity is consistently associated with reduced mortality, decreased risk for non-communicable diseases, and improved mental health in observational studies. Randomized controlled trials and observational Mendelian randomization studies support causal links between physical activity and health outcomes. However, the scarcity of evidence from randomized controlled trials, along with their inherent challenges like exposure contrasts, healthy volunteer biases, loss to follow-up, and limited real-world dose−response data, warrants a comprehensive approach. This review advocates synthesizing insights from diverse study designs to better understand the causal relationship between physical activity, mortality risk, and other health outcomes. Additionally, it summarizes recent research since the publication of current physical activity recommendations. Novel observational studies utilizing device-measured physical activity underscore the importance of every minute of activity and suggest that all intensity levels confer health benefits, with vigorous-intensity potentially requiring lower volumes for substantial benefits. Future guidelines, informed by device-measured physical activity studies, may offer refined age-specific recommendations, emphasize vigorous-intensity physical activity, and include daily step counts as a simple, easily assessable metric using commercial wearables.

Keywords: Accelerometers; Non-communicable diseases; Public health; Sedentary behavior

1. Introduction

Seventy years ago, Morris et al.[1] published the first scientific evidence that physical activity may be beneficially associated with health. In their classic London Transport Workers Study, the authors showed that the risk of dying from coronary heart disease was about twice as high in the “inactive” bus drivers compared with the “active” conductors. Since then, numerous observational studies have shown that physical activity is associated with both longevity[2−4] and a lower risk of developing non-communicable diseases (NCDs), including cardiovascular diseases (CVDs), type 2 diabetes, and many types of cancers.[5−7] The beneficial effects of physical activity also extend to mental health conditions and some neurological disorders (e.g., more active individuals have a lower risk for depression[8] and for dementia and Alzheimer’s disease[9]). Higher levels of physical activity appear to improve health in the general population, as well as in specific patient groups. Consequently, the most recent guidelines on physical activity for public health from the World Health Organization (WHO) provide similar recommendations for both healthy individuals and those living with chronic conditions.[10] For example, adults, older adults, and those living with chronic conditions should aim to accumulate 150−300 min of moderate-to-vigorous intensity per week, or 75−150 min of vigorous intensity per week, or an equivalent combination of both.[10]

The WHO physical activity guidelines are reflected in national guidelines as well as clinical guidelines for a range of conditions, such as cancer, diabetes, and heart disease. However, in both healthy individuals and in those living with chronic conditions, the effect of physical activity on longevity and NCDs has not been convincingly demonstrated by randomized controlled trials (RCTs).[11,12]

Further, most of the evidence underlying the current guidelines is based on observational data examining the relationship

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between self-reported physical activity and major health outcomes. Unfortunately, self-reported data may be prone to information biases due to social desirability and cognitive reporting ability. To reduce this type of bias, more recent cohort studies have included devices to measure physical activity and sedentary time. As a result, new evidence on the associations between physical activity, NCDs, and longevity is rapidly emerging.

This narrative review aimed to discuss the current understanding of the relationship between physical activity, sedentary behaviors, and health outcomes. Specifically, we will summarize the limitations of RCTs when informing public health and why physical activity guidelines primarily have to rely on observational data. We will thereafter discuss how the introduction of device-measured physical activity in observational research affects the interpretation of the dose−response associations between physical activity and health outcomes. We will also discuss how this has contributed to our understanding of how different physical activity intensities are associated with health. Finally, we will summarize the current knowledge on how different combinations of physical activity and sedentary time are associated with health.

2. Observational research *vs.* randomization within a trial

To date, few well-funded and well-executed RCTs have examined whether physical activity improves longevity and prevents NCDs.[11,13,14] While randomization within a trial is considered to provide the highest level of scientific evidence, they have so far failed to replicate the benefits consistently seen in observational research. However, there are several reasons to question whether RCTs are better placed to determine causal effects of physical activity on longevity than well-conducted observational studies. The Generation 100 Study was designed to evaluate the effect of 5 years of supervised exercise training on all-cause mortality in older Norwegian adults.[13] Despite the relatively long follow-up, intervention including supervised exercise sessions, and complete follow-up on mortality, participants randomized to exercise were at no lower risk of mortality than controls (hazard ratio = 0.94, 95% confidence interval: 0.59−1.41). The Generation 100 Study[13] was an impressive achievement; however, it can also be pointed to as an example of the inherent limitations of RCTs with respect to studying the effects of physical activity on mortality and NCD outcomes in general. Using the Generation 100 study, we exemplify here some of the limitations with randomization within a trial when examining the effect of physical activity on longevity.

2.1. Difficulties with achieving the intended exposure contrast

Generation 100 participants were randomized to moderate-intensity training, high-intensity interval training, or to follow national guidelines for physical activity (control condition). Yet, control participants had a high activity level throughout the study, and many reported doing high-intensity interval training. At the same time, many participants in the intervention arms apparently did not meet the prescribed amounts of exercise, and nearly 25% of study participants did not complete the trial. A causal interpretation of a "negative" trial outcome is thus highly uncertain if the intended and achieved exposure contrast diverge.

2.2. Healthier participants are included in the trial

Participants included in the trial were healthier and more active than excluded participants, and the death rate among control participants was half the expected rate. Given that the largest benefits of physical activity are observed among the least active, the potential for health benefits may be smaller in trial participants.

2.3. Understanding the dose−response relationship

Physical activity recommendations are based on the dose−response relationships between physical activity and health outcomes. The Generation 100 study included 2 intervention arms with different intensity components. Yet, how much activity at these intensities would be needed to observe health benefits was not addressed because this would require at least 2 additional intervention groups. Further, structured exercise training does not account for activities of daily living, such as walking for pleasure, cycling uphill, and short bursts of vigorous intensity, which may also carry significant health benefits.[15]

Given these limitations, which we assume will also be a challenge for upcoming trials, including the large 50,000-participant Women's Health Initiative Strong and Healthy (WHISH) trial,[16] we propose that no single study design is suited to determine the causal effects of physical activity on longevity and NCDs. Instead, interpretation should be based on triangulation of results from as many different study designs as possible without assigning a hierarchy.[17] For example, evidence of the beneficial effects of being sufficiently physically active on NCD risk is supported by experimental data showing the positive effects of physical activity and regular exercise on lipid and glucose metabolism, blood pressure, inflammation, and immune function.[18] Studies using genetic variants as instrumental variables, so-called mendelian randomization, indicate lower risk of mortality,[19,20] heart disease,[19] type 2 diabetes,[19,20] depression,[20] and breast cancer[21] in more active individuals. Finally, large-scale observational studies are the cornerstone of any effort to determine dose−response associations.

3. Magnitude of the dose−response associations—self-report *vs.* device-measured physical activity

3.1. Self-report physical activity and risk for mortality

A recent systematic review of 50 studies, including more than 163 million person-years of follow-up and 811,616 events, showed a non-linear, dose−response association between non-occupational, self-reported physical activity and risk for mortality.[6] The risk reduction was approximately 30% at the minimum recommended levels of physical activity, which is equivalent to 2.5 h per week of at least moderate-intensity physical activity (e.g., brisk walking), with only a marginally reduced risk at higher levels of physical activity. Similar risk reductions, between 30% and 40%, were observed by Arem et al.[22] in a pooled analysis of U.S. men and women ($n = 661,137$; 161,686 deaths); by Wen et al.[23] in East Asian men and women ($n = 416,000$; 10,780 deaths); and by Lear et al.[24] in a harmonized sample of approximately 130,000 individuals from 17 high-, middle-, and low-income countries. However, in all studies the maximal risk reduction was observed at activity levels substantially higher than the current physical activity guidelines. For example, the risk was 40% lower in those reporting 10 h of moderate-intensity physical activity compared with the inactive referent group in the US sample.[22] When analyzing physical activity across domains (i.e., transport, leisure, and occupation), Lear et al.[24] reported a maximal risk reduction of approximately 30% at activity levels close to 20 h of at least moderate-intensity per week. Notably, the shape of the dose−response association was different between high- and upper-middle-income countries compared to lower middle- and low-income countries. The magnitude of the association was stronger in higher-income countries, and there was no association between recreational physical activity and the risk of death in low-income countries. The latter is likely explained by the low prevalence and homogeneous nature of recreational activities in the studies of low-income country samples.[24] In summary, all studies are consistent, showing a marked risk reduction when comparing those who are active at levels lower than the equivalent of current physical activity guidelines with those who report "no" physical activity (i.e., the referent group). It also seems clear that high levels of physical activity are required to obtain maximal risk reduction, and this level varies according to whether physical activity is operationalized as recreational or leisure time activity compared with total physical activity covering all domains (occupation, recreation, transport, and domestic chores).

The shape of the dose−response association is similar when cardiovascular and cancer mortality is modeled as the outcome, but the maximal risk reduction may not be the same.[6,25] In a recent analysis of more than 200,000 East Asian adults, the risk for CVD mortality was 44% lower compared with a 36% lower all-cause mortality risk when comparing those who were inactive with the group meeting physical activity recommendations.[25] However, overall cancer mortality appears to be less affected by physical activity than CVD mortality, with a maximal risk reduction of approximately 10%−20%.[6]

Many prospective observational studies are limited by the exposure measurements collected at baseline. Repeated measurements of physical activity reduce within-person measurement error and lead to a better representation of long-term physical activity levels. This strengthens the magnitude of the association with leisure-time physical activity by ~20 percentage points and ~25 percentage points for all-cause and CVD mortality, respectively, when comparing the least active with the most active quartile.[25] In summary, observational data assessing physical activity by self-report suggest that the maximal risk reduction for all-cause, CVD, and cancer mortality is observed, in most studies, at higher than the lower boundary for the physical activity guidelines of at least 150 min of moderate-to-vigorous intensity physical activity (MVPA) per week.

3.2. Device-measured physical activity and risk for mortality

The most recent guidelines have removed the requirement that activity should be accumulated in bouts of at least 10 min,[10] and studies examining the association between physical activity and mortality using devices that take every minute into account are accumulating. Ekelund et al.[26] examined the association between total physical activity in a harmonized meta-analysis including approximately 36,000 men and women (2149 deaths) and observed a maximal risk reduction for all-cause mortality of 65%. The amount of physical activity needed to obtain this risk reduction was similar to that observed in US men in the National Health and Nutrition Examination Study; approximately 300 activity counts per minute. Another study[27] mapped physical activity energy expenditure (PAEE) from wrist-worn accelerometers in the UK Biobank ($n = 96,476$; 732 deaths). The authors observed a 75%−80% risk reduction for all-cause mortality at a PAEE of 40 kJ/kg/day (median in the sample and equivalent to the mean of the general UK population[28]) compared with a PAEE of 15 kJ/kg/day.

Another feature of device-based measurements of physical activity in cohort studies is the possibility of estimating the number of daily steps accumulated. This metric is easily understood by the general public, and many are monitoring their steps using smart watches or mobile phones. A harmonized meta-analysis of 15 studies ($n = 47,471$; 3013 deaths) observed a non-linear dose−response association between total daily steps and risk for mortality. Taking more steps per day was associated with a progressively lower risk for all-cause mortality of approximately 40%−50% at 6000−8000 steps per day and 8000−10,000 steps per day in those ≥60 years and <60 years, respectively, with no further risk reduction at higher levels.[29] In a follow-up study[30] including approximately 20,000 participants for which data on CVDs were available, a similar nonlinear dose−response association between total steps per day and risk for CVD was observed in older (≥60 years) but not younger (<60 years) participants. From the reference of 2000 steps/day, the risk decreased progressively and was halved at 6000 daily steps without a clear levelling off at higher step counts. Evidence is also emerging that a higher number of steps per day is associated with a lower risk of CVD, cancer incidence,[31] and risk of hospitalization.[32]

However, total physical activity measured by accelerometers, operationalized as activity counts per day,[26] PAEE,[27] or steps per day,[29−32] is not directly comparable to data obtained by self-report. This is in part because self-reports usually collect information on MVPA during leisure time. A direct comparison between accelerometer-derived MVPA and MVPA from self-report suggests a considerably larger magnitude of risk reduction at a lower level of physical activity from device-measured physical activity compared with self-report.[18,33]

4. The importance of intensity for reducing the risk of NCDs and mortality

4.1. Light- and moderate-intensity physical activity

Physical activity intensity is typically categorized into sedentary, light, moderate, vigorous, and very vigorous intensity. Self-report questionnaires are unlikely to accurately measure sedentary time and light-intensity physical activity (LPA) and cannot assess short and sporadic bouts of activity of any intensity. In recent years, evidence based on accelerometery has emerged suggesting that LPA may reduce the risk of all-cause mortality with a similar magnitude of risk reduction achievable as that observed for MVPA. However, one meta-analysis found that approximately 5 h of LPA per day are needed to obtain a 50% risk reduction compared with approximately 20−25 min of MVPA.[26] By stratifying LPA into "low-intensity" and "high-intensity" LPA, the researchers suggested that 70−80 min per day of "high-intensity" LPA (moderate walking) produced similar risk reduction for all-cause mortality as is observed for approximately 25 min of MVPA.[26] However, since many of the participants in the aforementioned meta-analysis were older, "high-intensity" LPA may be equivalent to MVPA in younger individuals. Another recent meta-analysis summarizing the association between LPA and the risk for CVD mortality showed a 20% risk reduction for every 30 min of additional daily LIPA; the nonlinear dose−response association suggested a 50% risk reduction for CVD mortality at approximately 100 min of LPA per day.[34] Thus, recent evidence reported in studies assessing physical activity by devices suggests that LPA has beneficial associations with health; however, the amount of LPA needed to reduce the risk of premature death appears to be approximately 3−4 times higher than that of MVPA. A direct comparison between LPA and MVPA and their associations with mortality risk should also consider that LPA appears to be more sensitive to bias from reverse causation as compared with MVPA.[35]

4.2. Vigorous-intensity physical activity

The physical activity guidelines suggest that a specific amount of physical activity with moderate intensity (i.e., 150 min/week) can be substituted with half the amount of vigorous-intensity physical activity (VPA) to obtain the same health benefits.[10] This notion has recently been challenged by studies that specifically examined the associations between VPA and the risk of incident diseases and mortality. For example, in analyses using data from the UK Biobank ($n = 71,893$), Ahmadi et al.[36] suggested that as little as 15−20 min of VPA per week was associated with an up to 40% lower risk of death from all-cause mortality, CVD, and cancer. The risk was further reduced with higher amounts of VPA. In a sample of non-exercisers from the UK Biobank ($n = 25,241$), as little as 4−5 min of VPA per day was associated with 26%−30% and 32%−24% reduced risk for all-cause and CVD mortality, respectively;[15] similarly, a median of 4.5 min of daily VPA was associated with an ~30% reduced risk for physical activity-related cancer incidence.[37]

Higher levels of adiposity increase the risk of mortality and NCDs, including CVD. A meta-analysis of 8 prospective cohort studies including 34,492 participants (2034 deaths) showed a lower risk of mortality irrespective of adiposity levels at higher levels of device-measured physical activity.[38] Recent data for 70,830 UK Biobank participants suggest that about 500 min of MVPA or 30−35 min of VPA per week (as measured with devices) effectively eliminated the CVD risk associated with abdominal obesity.[39] Moreover, both studies showed higher risk of death and CVD when physical activity was low in non-obese people.

In summary, the available literature suggests that light, moderate, and vigorous intensities of physical activity can be combined in different amounts to reduce the risk for NCDs and premature death. Large amounts of LPA, up to 4−6 h per day, are needed to reduce the risk of mortality to a level equivalent to that of 25 min of MVPA.[26] On the other end of the intensity spectrum, it seems that no more than about 5 min of VPA per day are needed to substantially reduce the risk of incident diseases and mortality and to eliminate the risk of major CVD associated with obesity.[39] However, the results observed for VPA need to be replicated in more heterogeneous populations with repeated measurements of exposure and confounding variables using different monitor placements (e.g., hip) and extensively validated accelerometer prediction algorithms. The general belief, on which the current physical activity recommendations are based, that a specific amount of MVPA can be substituted with half of that amount of VPA to provide the same health benefits is challenged by these recent observations. If confirmed, future physical activity public health guidelines may need to consider a stronger emphasis on VPA rather than MVPA.

4.3. Volume vs. intensity

Another pertinent issue related to the intensity of physical activity is whether a higher intensity has additional health benefits over and above that of the total volume of intensity. Again, data derived from the UK Biobank ($n = 88,412$) suggest that higher volumes of PAEE (derived from wrist-worn devices) are associated with a lower risk of incident CVD. However, if the same amount of PAEE is achieved from MVPA, the health benefits are even greater.[40] Studies examining whether the intensity of stepping (high *vs*. low cadence) has additional benefits beyond that of total steps per day are inconsistent. The Steps for Health Collaborative[29] observed a lower risk of death (33% risk reduction; 95% confidence interval: 0.56−0.83) in the most active quartile compared with the least active quartile for an intensity defined as the highest number of steps over a 30-min period (peak 30 min). However, other intensity measures were not related to lower risk when adjusted for the total number of steps. Thus, it is currently unclear whether the benefits of physical activity on health outcomes are more pronounced if the activity is performed at a higher intensity when the total amount of physical activity is identical.

5. Physical activity mitigates the detrimental association between sedentary time/behavior and health

Studies using device-measured sedentary time suggest that higher amounts appear to be associated with a higher risk for mortality,[26] and this association seems to be statistically independent of time spent in MVPA and other confounders, including body mass index. Further, the dose−response seems almost linear when sedentary time exceeds 9 h per day.[26] However, data from a harmonized meta-analysis in more than 1 million men and women showed that the detrimental association between sedentary time and risk for mortality was eliminated in those reporting 60−70 min of MVPA per day.[41] Similar analyses in approximately 36,000 men and women, in which these behaviors were measured by devices, confirmed the observations from the self-report data. Approximately 30−40 min of MVPA per day appears to attenuate or even eliminate the detrimental association observed between device-measured sedentary time and all-cause mortality.[42] It is noteworthy that the latter 2 studies examined the joint associations between physical activity and sedentary time with mortality, which is conceptually different from examining the association between sedentary time and mortality adjusted for MVPA. The joint association analyses consider the 2 exposures in combination and provide evidence that combining high levels of sedentary time with high levels of physical activity may mitigate the risk of premature mortality.

The modifying effect of MVPA was further examined in a pooled individual participation data analysis of almost 12,000 middle-aged and older men and women (Sagelv et al.[43]). Being sedentary for more than 12 h per day (median split) was associated with a 38% higher mortality risk, but only among individuals not meeting the current physical activity guidelines (operationalized as accumulating less than 22 min per day of MVPA). In those meeting the physical activity guidelines, there was no association between sedentary time and mortality (Sagelv et al.[43]). The current WHO physical activity guidelines state that, "to reduce the detrimental effects of high sedentary time on health, adults should aim to do more than the recommended levels of moderate-to-vigorous intensity physical activity".[10] If future high-quality studies support the observations discussed above, this recommendation may need to be reconsidered.

6. Summary

Due to the absence of robust evidence from RCTs, the evidence underlying current physical activity recommendations mainly relies on self-reported observational data. In contrast, the removal of the "10-minute block" from the latest recommendations is supported by data from device-measured physical activity; the current thinking is that every minute counts. This discrepancy will likely be resolved, at least in part, when the evidence for the next generation of physical activity recommendations is summarized, evidence that likely, to a large extent, will be based on observational research assessing physical activity and sedentary time with devices.

Studies incorporating device-measured physical activity in large cohorts, combining data from multiple studies in harmonized meta-analyses, and individual-participation data analyses published since the release of the current physical activity recommendations have already generated novel findings. This may result in a recommended number of steps per day, as this is a simple metric that can be easily assessed by commercial wearables and smartphones; however, we should keep in mind that wearables and research devices may differ somewhat in their measurements of steps. Furthermore, there may be a reconsideration of the current understanding of the relationship between moderate and vigorous intensity, which suggests that 150 min of physical activity at a moderate intensity is equal to 75 min of physical activity at a vigorous intensity. New data summarized in this review suggest "more bang for the buck" if activity is performed at a higher intensity, although additional research is needed to determine whether this is independent of the total volume of physical activity. Finally, more refined age-specific recommendations may be a consequence of the more precise dose−response associations observed between physical activity and health outcomes when the exposure variables are derived from devices.

Authors' contributions

UE outlined the content of the manuscript and drafted the first version; MASL, KED, and JT commented and drafted specific sections of the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

References

1. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *The Lancet* 1953;**262**:111–20.
2. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. *The Lancet* 2012;**380**:219–29.
3. Wasfy MM, Baggish AL. Exercise dose in clinical practice. *Circulation* 2016;**133**:2297–313.
4. Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the extremes: The amount of exercise to reduce cardiovascular events. *J Am Coll Cardiol* 2016;**67**:316–29.
5. Matthews CE, Moore SC, Arem H, et al. Amount and intensity of leisure-time physical activity and lower cancer risk. *J Clin Oncol* 2020;**38**:686–97.
6. Garcia L, Pearce M, Abbas A, et al. Non-occupational physical activity and risk of cardiovascular disease, cancer and mortality outcomes: A dose-response meta-analysis of large prospective studies. *Br J Sport Med* 2023;**57**:979–89.
7. Ekelund U, Palla L, Brage S, et al. Physical activity reduces the risk of incident type 2 diabetes in general and abdominally lean and obese men and women: The EPIC-Interact study. *Diabetologia* 2012;**55**:1944–52.
8. Pearce M, Garcia L, Abbas A, et al. Association between physical activity and risk for depression: A systematic review and meta-analysis. *JAMA Psych* 2022;**79**:550–9.

9. Iso-Markku P, Kujala UM, Knittle K, Polet J, Vouksimma E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: Systematic review, meta-analysis and quality assessment of cohort and case-control studies. *Br J Sport Med* 2022;**56**:701–9.
10. Bull FC, Al-Ansari S, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sport Med* 2020;**54**:1451–62.
11. Ballin M, Nordström P. Does exercise prevent major non-communicable diseases and premature mortality? A critical review based on results from randomized controlled trials. *J Int Med* 2021;**290**:1112–29.
12. Kujala UM. Is physical activity a cause of longevity? It is not as straightforward as some would believe. A critical analysis. *Br J Sports Med* 2018;**52**:914–8.
13. Stensvold D, Viken H, Steinshamn SL, et al. Effect of exercise training for five years on all cause mortality in older adults-the Generation 100 study: Randomised controlled trail. *BMJ* 2020;**371**: m3485. doi:10.1136/bmj.m3485.
14. Harris T, Limb ES, Hosking F, et al. Effect of pedometer-based walking interventions on long-term health outcomes: Prospective 4-year follow-up of two randomized controlled trials using routine primary care data. *PLoS Med* 2019;**16**: e1002836. doi:10.1371/journal.pmed.1002836.
15. Stamatakis E, Ahmadi MN, Gill JM, et al. Association of wearable device-measured vigorous intermittent lifestyle physical activity with mortality. *Nature Med* 2022;**28**:2521–9.
16. Stefanick ML, Kooperberg C, LaCroix AZ. Women's Health Initiative strong and healthy (WHISH): A pragmatic physical activity intervention trial for cardiovascular disease prevention. *Contemp Clin Trials* 2022;**119**: 106815. doi:10.1016/j.cct.2022.106815.
17. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol* 2016;**45**:1866–86.
18. Wasfy MM, Lee IM. Examining the dose−response relationship between physical activity and health outcomes. *N Engl J Med Evid* 2022;**1**:12. doi:10.1056/EVIDra2200190.
19. Sillanpää E, Palviainen T, Ripatti S, Kujala UM, Kaprio J. Polygenic score for physical activity is associated with multiple common diseases. *Med Sci Sports Exerc* 2022;**54**:280–7.
20. Wang Z, Emmerich A, Pillon NJ, et al. Genome-wide association analyses of physical activity and sedentary behaviour provide insights into underlying mechanisms and roles in disease prevention. *Nat Genet* 2022;**54**:1332–44.
21. Dixon-Suen SC, Lewis SJ, Martin RM, et al. Physical activity, sedentary time and breast cancer risk: A Mendelian randomisation study. *Br J Sports Med* 2022;**56**:1157–70.
22. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: A detailed pooled analysis of the dose−response relationship. *JAMA Intern Med* 2015;**175**:959–67.
23. Wen CP, Wai JPM, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *The Lancet* 2011;**378**:1244–53.
24. Lear SA, Hu W, Rangrajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130, 000 people from 17 high-income, middle-income, and low-income countries: The PURE study. *The Lancet* 2017;**390**:2643–54.
25. Martinez-Gomez D, Cabanas-Sanchez V, Yu T, et al. Long-term leisure-time physical activity and risk of all-cause and cardiovascular mortality: Dose−response associations in a prospective cohort study of 210,327 "Taiwanese" adults. *Br J Sports Med* 2022;**56**:919–26.
26. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose−response associations between accelerometry measured physical activity and sedentary behaviour and all cause mortality: Systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:I4570. doi:10.1136/bmj.l4570.
27. Strain T, Wijndaele K, Dempsey PC, et al. Wearable-device-measured physical activity and future health risk. *Nature Med* 2020;**26**:1385–91.
28. Brage S, Lindsey T, Venables M, et al. Descriptive epidemiology of energy expenditure in the UK: Findings from the National diet and nutrition survey 2008−15. *Int J Epidemiol* 2020;**49**:1007–21.
29. Paluch AE, Bajpal S, Bassett DR, et al. Daily steps and all-cause mortality: A meta-analysis of 15 international cohorts. *Lancet Public Health* 2022;**3**:e219–28.
30. Paluch AE, Bajpal S, Ballin M, et al. Prospective association of daily steps with cardiovascular disease: A harmonized meta-analysis. *Circulation* 2023;**147**:122–31.
31. Del Pozo Cruz B, Ahmadi M, Lee IM, Stamatakis E. Prospective associations of daily step counts and intensity with cancer and cardiovascular disease incidence and mortality and all-cause mortality. *JAMA Intern Med* 2022;**182**:1139–48.
32. Mañas A, Del Pozo Cruz B, Ekelund U, et al. Association of accelerometer-derived step volume and intensity with hospitalizations and mortality in older adults: A prospective cohort study. *J Sport Health Sci* 2022;**11**:578–85.
33. Ekelund U, Dalene KE, Tarp J, Lee IM. Physical activity and mortality: What is the dose response and how big is the effect? *Br J Sports Med* 2020;**54**:1125–6.
34. Qiu S, Cai X, Jia L, et al. Does objectively measured light-intensity physical activity reduce the risk of cardiovascular mortality? A meta-analysis. *Euro Heart J Qual Care Clin Outcomes* 2021;**7**:496–504.
35. Tarp J, Hansen BH, Fagerland MW, Steene-Johannessen J, Andersssen SA, Ekelund U. Accelerometer-measured physical activity and sedentary time in a cohort of US adults followed for up to 13 years: The influence of removing early follow-up on associations with mortality. *Int J Behav Nutr Phys Act* 2020;**17**:39. doi:10.1186/s12966-020-00945-4.
36. Ahmadi M, Clare PJ, Katzmarzyk P, del Poz Cruz B, Lee IM, Stamatakis E. Vigorous physical activity, incident heart disease and cancer: How little is enough? *Eur Heart J* 2022;**43**:4801–14.
37. Stamatakis E, Ahmadi MN, Friedenreich CM, et al. Vigorous intermittent lifestyle physical activity and cancer incidence among nonexercising adults. *JAMA Oncol* 2023;**9**:1255–9.
38. Tarp J, Fagerland MW, Dalene KE, et al. Device-measured physical activity, adiposity and mortality: A harmonised meta-analysis of eight prospective cohort studies. *Br J Sports Med* 2022;**56**:725–32.
39. Sanchez-Lastra MA, Ding D, Del Pozo Cruz B, et al. Joint associations of device-measured physical activity and abdominal obesity with incident cardiovascular disease: A prospective cohort study. *Br J Sports Med* 2023. doi:10.1136/bjsports-2023-107252.
40. Dempsey PC, Rowlands AV, Strain T, et al. Physical activity volume, intensity and incident cardiovascular disease. *Eur Heart J* 2022;**43**:4789–800.
41. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *The Lancet* 2016;**388**:1302–10.
42. Ekelund U, Tarp J, Fagerland MW, et al. Joint associations of accelerometer-measured physical activity and sedentary time with all-cause mortality: A harmonised meta-analysis in more than 44, 000 middle-aged and older individuals. *Br J Sports Med* 2020;**54**:1499–506.
43. Sagelv EH, Hopstock LA, Morseth B, et al. Device-measured physical activity, sedentary time and risk of all-cause mortality: An individual participant data analysis of four prospective cohort studies. *Br J Sports Med* 2023;**57**:1457–63.