

# **Objectively measured physical activity and all cause mortality: a systematic review and meta-analysis**

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## **ABSTRACT**

Current physical activity recommendations have been based on evidence from systematic reviews of questionnaire-based data. Questionnaire-based physical activity data are subject to both random and non-random error. If the estimated association between physical activity and health outcomes was different when a more accurate, objective measure was used, this would have important health policy implications for physical activity. We conducted a systematic review and meta-analysis of published cohort studies that investigated the association between an objective measure of physical activity and all cause mortality. We searched PubMed, Scopus, Embase, Cochrane library, and SPORTDiscus for prospective cohort studies that examined the association between objectively measured (accelerometer, pedometer, or doubly labeled water method) physical activity and mortality in adults aged  $\geq 18$  years, of either sex. Summary hazard ratios and 95% confidence interval [CI]s were computed using random-effects models. Thirty-three articles from 15 cohort studies were identified that together ascertained 3,903 deaths. The mean years of follow-up ranged from 2.3–14.2 years. Individuals in the highest category of light, moderate-to-vigorous, and total physical activity had 40% (95%CI 20% to 55%), 56% (95%CI 41% to 67%), and 67% (95%CI 57% to 75%), respectively, lower risk for mortality compared to individuals in the lowest category of light, moderate-to-vigorous, and total physical activity. The summary hazard ratio for objectively measured physical activity and all cause mortality is lower than previously estimated from questionnaire based studies. Current recommendations for physical activity that are based on subjective measurement may underestimate the true reduction in mortality risk associated with physical activity.

**Keywords:** accelerometry; mortality; exercise; objectively measured; meta-analysis; systematic review

## INTRODUCTION

Leisure time physical activity (PA) is inversely associated with mortality, and with incidence of non-communicable diseases, but with most of the potential benefit gained from relatively modest amounts of activity. In a meta-analysis, Woodcock et al<sup>1</sup> estimated that if a sedentary individual increased light to moderate activity in leisure time from none to only 11 metabolic equivalent (MET) hours/ week, or 2.5 hours/week of activity with an intensity equivalent to brisk walking, they would reduce their mortality risk by 19%. A further increase to 31 MET hours/week, or 7 hours per week would only reduce risk of death by a further five percentage points.<sup>1</sup> Samitz et al<sup>2</sup> similarly found hazard ratio (HR)s of 0.86 and 0.74, respectively, for 2½ hours and five hours of moderate-to-vigorous PA (MVPA) per week compared to the lowest level of activity (median 11 min/week).

The results from these systematic reviews underpin the population PA targets recommended by the U.S. Department of Health and Human Services and the Chief Medical Officer, UK— that is, at least, 2½ hours of moderate PA such as brisk walking per week.<sup>3,4</sup> However, the validity of these recommendations depends on the accuracy of the measurement used to capture PA in the studies included in the systematic reviews – in each case, questionnaires. While questionnaires capture this exposure to some extent, they have been shown to be affected by a material level of both random and non-random error<sup>5,6</sup> which can be minimised using an objective measure of PA such as doubly labeled water, accelerometer, or pedometer.

A meta-analysis of 12 articles from 11 cohort studies among adults aged ≥60 years of age found device-measured light PA, MVPA, and total PA to be associated with 1.93, 2.66, and 3.43 higher risk for all cause mortality among participants who were least active compared with the most active group.<sup>7</sup> A systematic review of five studies found 6%-36% reduction in risk for mortality for each 1,000 increase in daily step count measured by pedometer or accelerometer.<sup>8</sup> An individual participant data (IPD) meta-analysis that examined accelerometer measured PA and all cause mortality using data from eight studies (six published and two unpublished) found 73%, 62%, and 48% lower risk when comparing the highest to lowest category of total, light, and MVPA, respectively,<sup>9</sup> which is much lower than what has been found for questionnaire-based studies. To add to this evidence, we conducted a systematic review and meta-analysis of published cohort studies that reported the association between an objective measure of PA and all cause mortality among adults ≥18 years of age. This study that included the largest number of published studies on this topic till

date had no restrictions to type of device used to measure PA, unit of measurement, or age group among adults.

## METHODS

In this systematic review and meta-analysis, we followed the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Five electronic databases, Medline via PubMed, Scopus, Embase via Ovid, Cochrane library, and SPORTDiscus, were searched up to and including August 31, 2020 with no language restrictions. We searched the bibliographies of included records to identify additional studies. We did not contact the corresponding authors of papers because we did not require any additional information/clarification. The search terms for all the databases included, accelerometry, accelero\*, actigraphy, actigra\*, objectively assessed physical activity, objectively measured physical activity, pedometer, doubly labelled water, doubly labeled water, and mortality. Details of the search strategy are given in Supplementary Table 1.

Studies were considered eligible for inclusion if i) they were prospective cohort studies that measured PA objectively by accelerometer, pedometer, or the doubly labeled water method, ii) they investigated the association between objectively assessed light, moderate, vigorous, or moderate-to-vigorous, or as steps, and mortality from any cause, and iii) the participants were adults aged 18 years and older. We excluded studies that examined the association in specific disease populations (for example, patients with cancer, type 2 diabetes, or chronic heart failure). Only original research articles were included; consequently, editorials, commentaries, reviews, conference abstracts, letters, or research briefs were excluded.

We used a data extraction form in Microsoft Excel that had been developed *a priori* by RR. The information extracted were: study name, study design and population, country, sample size, mean age, percentage of male participants, length and person-years of follow-up, mortality rate, number of deaths, PA measurement instrument, unit of measurement, PA definition, mean PA at baseline, PA categories, early deaths included (yes/no), adjustment factors, subgroup analysis (yes/no), the grouping variable for subgroup analysis, and the point estimate (hazard ratio[HR]/odds ratio/relative risk) with its lower and upper 95% confidence limits. Most of the studies reported the estimates in quantiles (tertiles, quartiles, and quintiles), few treated PA as a continuous measure. If a study reported relative risk<sup>10</sup> we treated it as HR. The only study that reported log odds ratio<sup>11</sup> did not have data that could be harmonised. If, instead of HRs, the observed and logrank expected events were reported in

each exposure category,<sup>12</sup> then the method/s reported by Tierney et al<sup>13</sup> was used to compute the HRs. For studies that reported only p-values for statistical significance,<sup>11,14</sup> the confidence intervals were computed using the Altman and Bland method.<sup>15</sup> For each PA category (light, moderate-to-vigorous, and total), if there were multiple publications from the same cohort, we selected the one with the longest follow-up; if two studies had the same length of follow-up then the one with the largest sample size or had data that could be harmonized was included in the meta-analysis. If a study reported separate estimates for low and high light PA then the latter was chosen for the analyses. If there were discrepancies in the estimates in the text and tables, the numbers in tables were included in the review and analysis. One reviewer (RR) selected and extracted the ~~data~~data, and a second reviewer (JH) checked the data for accuracy; inconsistencies were resolved through discussions.

Two reviewers (RR and JH) independently evaluated the quality of included studies using the Newcastle Ottawa Scale. For cohort studies, this scale has a high inter-rater reliability, 0.94.<sup>16</sup> In this scale, the quality of a study is assessed using three domains – selection of exposed and non-exposed cohort, comparability of cohorts based on design/analysis, and outcome assessment. A star is awarded for each item within the selection and outcome domains and a maximum of two stars are awarded for comparability.<sup>17</sup> For the comparability domain, we considered comorbidities/self-rated health status to be the most important confounder due to its association with both mortality and PA. The maximum number of stars that a single study could accomplish was nine. We rated the quality of studies as high, medium, or low based on 8–9, 5–7, and <5 stars, respectively. Any discrepancy in rating was resolved through discussions between the reviewers (RR and JH). Details of evaluation of measures of quality are given in the Supplementary text.

Light, moderate-to-vigorous, and total PA were defined as reported in the studies. If the study reported steps/day, or total accelerometer counts, then these totals were used to define total PA. For each category of PA (light, moderate-to-vigorous, and total), we compared HRs for the highest to that of the lowest category (Supplementary Table 2). For studies that compared the lowest to the highest category, we took the reciprocal of the point estimate and used that for the meta-analysis.

We used the DerSimonian and Laird random-effects model<sup>18</sup> to pool estimates for the association between light, moderate-to-vigorous, and total PA and mortality and for dose-response, subgroup, and sensitivity analyses. We conducted separate analysis for five studies that measured total PA in steps/day as a continuous measure.<sup>12,19–22</sup> We examined the dose-response association between MVPA and all cause mortality by restricted cubic spline

analysis wherein three knots were specified at 0.2, 0.4, and 1.0 hour/day of MVPA. The Wald test was used to assess for non-linearity by testing the point estimate of the second spline was equal to zero.<sup>23</sup> We assessed statistical heterogeneity among studies included in the analysis using the  $I^2$  statistic. For the calculation of the  $I^2$  statistic, we used the natural log of HR and 95% CI in a random-effects model. The degree of heterogeneity was categorised as low, moderate, and high based on  $I^2$  values of 25%, 50%, and 75%, respectively.<sup>24</sup> Publication bias and small study effects were assessed through funnel plot and Egger's test for funnel plot asymmetry for exposure category with at least ten studies.

We conducted sensitivity analysis to assess the impact of outliers (extreme values for the reference category) on the estimates and studies with different definitions of exposure categories: for example, to examine the association between total PA and mortality, we excluded studies that defined the exposure as steps/day and only studies that measured minutes/day were included. We also assessed sensitivity of the estimates to exclusion of early deaths through analysis of studies that reported hazard ratios/relative risks after excluding these participants. Finally, we investigated if the estimates varied by sex, age (>60 years vs ≤60 years), study quality, and years of follow-up (<5 years vs ≥5 years).

All analyses were conducted using STATA version 14.0 (StataCorp, College Station, TX, USA).

## RESULTS

We retrieved 1,129 records from a search of studies published up until June 17, 2018 from PubMed, Scopus, Embase through Ovid, the Cochrane library, and SPORTSdiscus. An updated search up until August 31, 2020 unearthed additional 367 records appending the total to 1,496. Exclusion of duplicate records resulted in 1,256 records for further assessment. Screening of the title and abstract resulted in 51 articles. Eighteen articles were excluded after full texts of the studies were examined resulting in 33 articles<sup>10–12,14,19–22,25–49</sup> from 15 cohort studies for the systematic review and meta-analyses (Supplementary Figure 1). Out of 33 articles, 18 were from the National Health and Nutrition Examination Survey (NHANES) (2003–2006 and 2003–2004) study alone<sup>14,27–29,33–46</sup> and two were from the Swedish Attitude Behaviour and Change study<sup>31,47</sup> Though we included these studies for the systematic review, for the meta-analysis we included only two NHANES studies<sup>27,28</sup> – one for light PA and MVPA and another for total PA– and one paper from the Swedish Attitude Behaviour and Change study<sup>31,47</sup>. We included only these studies because they had exposures that could be

categorized into highest versus lowest category and had longer follow-up periods followed by larger sample size.

The descriptive information for 33 articles from 15 cohort studies is presented in Table 1. The 15 studies included 141,582 participants with mean age at baseline ranging from 48.4<sup>27</sup> years to 85 years.<sup>11</sup> Two studies were each conducted exclusively among men<sup>20,30</sup> and women<sup>10,22</sup> whereas in the remaining studies there was a preponderance of female participants. Out of the 15 studies, six were conducted in the US,<sup>10,14,22,25,27–30,33–46,48</sup> three in the UK,<sup>19,20,32</sup> and one each in Australia,<sup>12</sup> Brazil,<sup>49</sup> Canada,<sup>11</sup> Japan,<sup>21</sup> Norway,<sup>26</sup> and Sweden.<sup>31,47</sup> The mean/median follow-up fell within the range 2.3 years–14.2 years, whereas the mortality rate ranged from 5 per 10,000 person-years<sup>32</sup> to 850 per 10,000 person-years.<sup>12</sup>



**Table 1. Characteristics of the cohort studies included in the systematic review**

Study	Author	Country	Sample size	Age (years)	Male%	Mean: Follow-up length (years)	Mortality rate per 10,000 PY	Physical Activity Measurement Instrument	Mean PA (baseline)	Covariates
70-years olds in Niigata city, Japan in 1998	Yamamoto, 2018 <sup>21</sup>	Japan	419	71	54.4	9.8	185	Pedometer	6,470 steps/day	Sex, body mass index, cigarette smoking, alcohol intake, and medication use
Baltimore Longitudinal Study of Aging	Wanigatunga, 2019 <sup>48</sup>	USA	548	75.8	52.2	4.4	253	Accelerometer	Total PA: 5.6 hours/day	Age, sex, race/ethnicity, body mass index, smoking history, currently working for pay, self-reported health, grip strength, usual gait speed, comorbidities, and activity monitor wear days.
Como Vai study	Bielemann, 2020 <sup>49</sup>	Brazil	971	60-69 years: 51.1%, 70-79 years: 34.7%, ≥80 years 14.2%	37.8	2.6	300	Accelerometer	Light PA: 132 min/day, MVPA: 10.8 min/day	Age, skin color, schooling, economic level, smoking, self-perceived health, number of morbidities, and functional capability.
Health ABC study	Manini, 2006 <sup>25</sup>	USA	302	74.8	49.7	6.2	296	Doubly labelled water	1.7 kcal/day	Age, sex, race study site, weight, height,

										percentage of body fat, sleep duration, self-rated health, education, smoking status and history, cardiovascular disease, lung disease, diabetes, hip or knee osteoarthritis, osteoporosis, cancer, and depression.
Multicenter Norwegian study	Hansen, 2020 <sup>26</sup>	Norway	2,183	57	47.0	9.1	60	Accelerometer	Median: 8,002 steps/day	Sex, wear time, VPA, education, body mass index, smoking, alcohol intake, and number of medical conditions.
NHANES (2003-2006) <sup>a</sup>	Borgundvaag, 2016 <sup>27</sup>	USA	5,562	48.4	49.2	6.7	158	Accelerometer	<sup>b</sup> Light PA: 200.4 min/day, MVPA: 15.2 min/day	Age, sex, race/ethnicity, poverty-to-income ratio, education, smoking, alcohol, dietary fat, dietary saturated fat, dietary sodium, accelerometer wear time, and other physical activity intensity
	Saint-Maurice, 2018 <sup>28</sup>	USA	4,840	57.0	49.7	6.6	219	Accelerometer	Light PA: 4.1 hour/day, MVPA: 1.3hour/day	Age, sex, race/ethnicity, body mass index, education, smoking, alcohol consumption, diabetes mellitus, stroke, chronic heart failure, reduced mobility, cancer/ malignancy, and either light PA or MVPA

OPACH Study, an ancillary study to the Women's Health Initiative	Lamonte, 2017 <sup>10</sup>	USA	6,382	78.6	0.0	3.1	218	Accelerometer	Total PA: 334.1 min/day (light PA: 284.3 min/day, MVPA: 49.8 min/day)	Age, race and ethnicity, education, current smoking, alcohol intake in past 3 months, age at menopause, self-rated general health, number of comorbid conditions, accelerometer wear time (h/d), and Short Physical Performance Battery score/MVPA/light PA
OPAL (Older People and Active Living)	Fox, 2015 <sup>19</sup>	UK	208	≥70	51.2	4.2	378	Accelerometer	64 took <3,196 steps/day, 67 took 3,196–5,170 steps/day, and 70 took >5,170 steps/day	Age, sex, educational attainment, Index of Multiple Derivation, weight status, GP Management System, number of self-reported chronic illnesses at baseline, and lower limb function.
Osteoporotic Fractures in Men Study (MrOS)	Ensrud, 2014 <sup>30</sup>	USA	2,918	79.0	100.0	4.5	311	SenseWear Pro Armband	Light PA: 67.7 min/day, at least moderate PA: 82.3 min/day	Age, race, site, season, education, marital status, health status, smoking, comorbidity burden, depressive symptoms, cognitive function, number of instrumental activity of daily living impairments, percentage body fat, PA scale for the elderly, gait speed, and time spent asleep
Study of Everyday Physical Activity, a	Chipperfield, 2008 <sup>11</sup>	Canada	191	85.0	36.9	2.0	393	Accelerometer	17.7% were moderately	Age, functional status (health-related

satellite study of the Aging in Manitoba Longitudinal Project									active and 10.1% were extremely active	restriction), physical status (severity of chronic conditions), and psychological status (positive affect).
Sweden Attitude Behaviour and Change study	Dohrn, 2017 <sup>31</sup>	Sweden	851	66.7	44.1	14.2	65	Accelerometer	Light PA: 5h 44 min/day, MVPA: 31 min/day	Education, smoking status, and presence of hypertension, heart disease, cancer, and diabetes at baseline and stratified by sex and age tertiles.
Tasped	Dwyer, 2015 <sup>12</sup>	Australia	2,576	58.8	47.6	90% for 10 years	850	Pedometer	8,856 steps/day	Age, sex, body mass index at baseline, total energy intake from all sources (kJ) at baseline, current smoking status at baseline, alcohol consumption (g/day) at baseline, education at baseline and study cohort
The British Regional Heart Study	Jefferis, 2018 <sup>20</sup>	UK	1,274	78.4	100.0	5.0 <sup>b</sup>	344	Accelerometer	Light PA: 199 min/day, MVPA: 40 min/day, mean steps/day: 4938	Age, region of residence, season of wear, accelerometer wear time, social class, alcohol use, smoking, sleep time, living alone, body mass index, and mobility disability.
UK Biobank	Chudasama, 2019 <sup>32</sup>	UK	95,616	63 <sup>b</sup>	43.7	6.9 <sup>b</sup>	5	Accelerometer	Median: 27.1 average acceleration in mg/day	Age, sex, ethnicity, socioeconomic status, employment status, education level, body mass index, smoking

Women's Health Study	Lee, 2019 <sup>22</sup>	USA	16,741	72.0	0.0	4.3	70	Accelerometer	5,499 steps/day	status, alcohol consumption, fruit and vegetable, oily fish, non-oily fish, processed meat, red meat intake, and sedentary time. Age, wear time, smoking status, alcohol use, intakes of saturated fat, fiber, fruits, and vegetables, hormone therapy, parental history of myocardial infarction, family history of cancer, general health, history of cardiovascular disease, history of cancer, cancer screening, BMI, history of hypertension, high cholesterol, and diabetes.
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<sup>a</sup> Out of 18 studies based on NHANES data only two studies were included in the meta-analysis (Borgundvaag, 2016<sup>27</sup> for light physical activity and moderate-to-vigorous physical activity; Saint-Maurice, 2018<sup>28</sup> for total physical activity). Out of the two papers<sup>31,47</sup> based on the Swedish Attitude Behaviour and Change study, Dohrn, 2017<sup>31</sup> was included.

<sup>b</sup>Median

Abbreviations: PY=person-years, PA= physical activity, MVPA=moderate-to-vigorous physical activity

Out of 33 articles included in the review, only 15 were of high quality<sup>10,12,19,22,25,26,28,29,31,32,38,42,45–47</sup> and the rest were moderate (Table 2).<sup>11,14,</sup>

20,21,27,30,33–37,39–41,43,44,48,49, Out of 33 articles only 16 adjusted for comorbidities/self-rated health status or accounted for these in the

analysis,<sup>10,11,19,22,25,26,28–32,45–49</sup> the confounder that we deemed most important for quality assessment.

**Table 2. Quality of Studies Included in the Systematic Review (Newcastle Ottawa Scale)**

Study	Selection			Comparability		Outcome		Total stars	
	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Adjusted for comorbidities/self-rated health status and other important covariates	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up	
Beddhu, 2015 <sup>14</sup>	*	*	*	*	*	*		*	7
Bielemann, 2020 <sup>49</sup>	*	*	*	*	**	*			7
Borgundvaag, 2016 <sup>27</sup>		*	*	*	*	*	*	*	7
Chipperfield, 2008 <sup>11</sup>		*	*	*	**	*		*	7
Chudasama, 2019 <sup>32</sup>	*	*	*	*	**	*	*	*	9
Dohrn, 2017 <sup>31</sup>		*	*	*	**	*	*	*	8
Dwyer, 2015 <sup>12</sup>	*	*	*	*	*	*	*	*	8
Edwards, 2016 <sup>33</sup>		*	*	*	*	*	*	*	7
Ensrud, 2014 <sup>30</sup>		*	*	*	**	*		*	7
Evenson, 2017 <sup>34</sup>		*	*	*	*	*	*	*	7
Evenson, 2016 <sup>35</sup>		*	*	*	*	*	*	*	7
Fishman, 2016 <sup>36</sup>		*	*	*	*	*	*	*	7
Fox, 2015 <sup>19</sup>	*	*	*	*	**	*		*	8
Hansen, 2020 <sup>26</sup>	*	*	*	*	**	*	*	*	9
Jefferis, 2018 <sup>20</sup>		*	*	*	*	*	*	*	7
Koster, 2012 <sup>37</sup>		*	*	*	*	*		*	6
Lamonte, 2017 <sup>10</sup>	*	*	*	*	**	*		*	8
Lee, 2016 <sup>38</sup>	*	*	*	*	*	*	*	*	8
Lee, 2019 <sup>22</sup>	*	*	*	*	**	*		*	8
Loprinzi & Crush, 2016 <sup>40</sup>		*	*	*	*	*	*	*	7
Loprinzi, 2017 <sup>39</sup>		*	*	*	*	*	*	*	7
Loprinzi, 2016 <sup>41</sup>		*	*	*	*	*	*	*	7
Manini, 2006 <sup>25</sup>		*	*	*	**	*	*	*	8
Matthews, 2016 <sup>42</sup>	*	*	*	*	*	*	*	*	8
Saint-Maurice, 2018 <sup>28</sup>	*	*	*	*	**	*	*	*	9
Saint-Maurice, 2020 <sup>29</sup>	*	*	*	*	**	*	*	*	9
Schmid, 2015 <sup>43</sup>		*	*	*	*	*		*	6

Schmid, 2016 <sup>44</sup>		*	*	*	*	*	*	*	7
Shiroma, 2019 <sup>45</sup>	*	*	*	*	**	*	*	*	9
Tarp, 2020 <sup>46</sup>	*	*	*	*	**	*	*	*	9
von Rosen, 2020 <sup>47</sup>	*	*	*	*	**	*	*	*	9
Wanigatunga, 2019 <sup>48</sup>		*	*	*	**	*		*	7
Yamamoto, 2018 <sup>21</sup>		*	*	*	*		*		5

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Notes: Representativeness of the exposed cohort: One star=Truly/somewhat representative of the general population

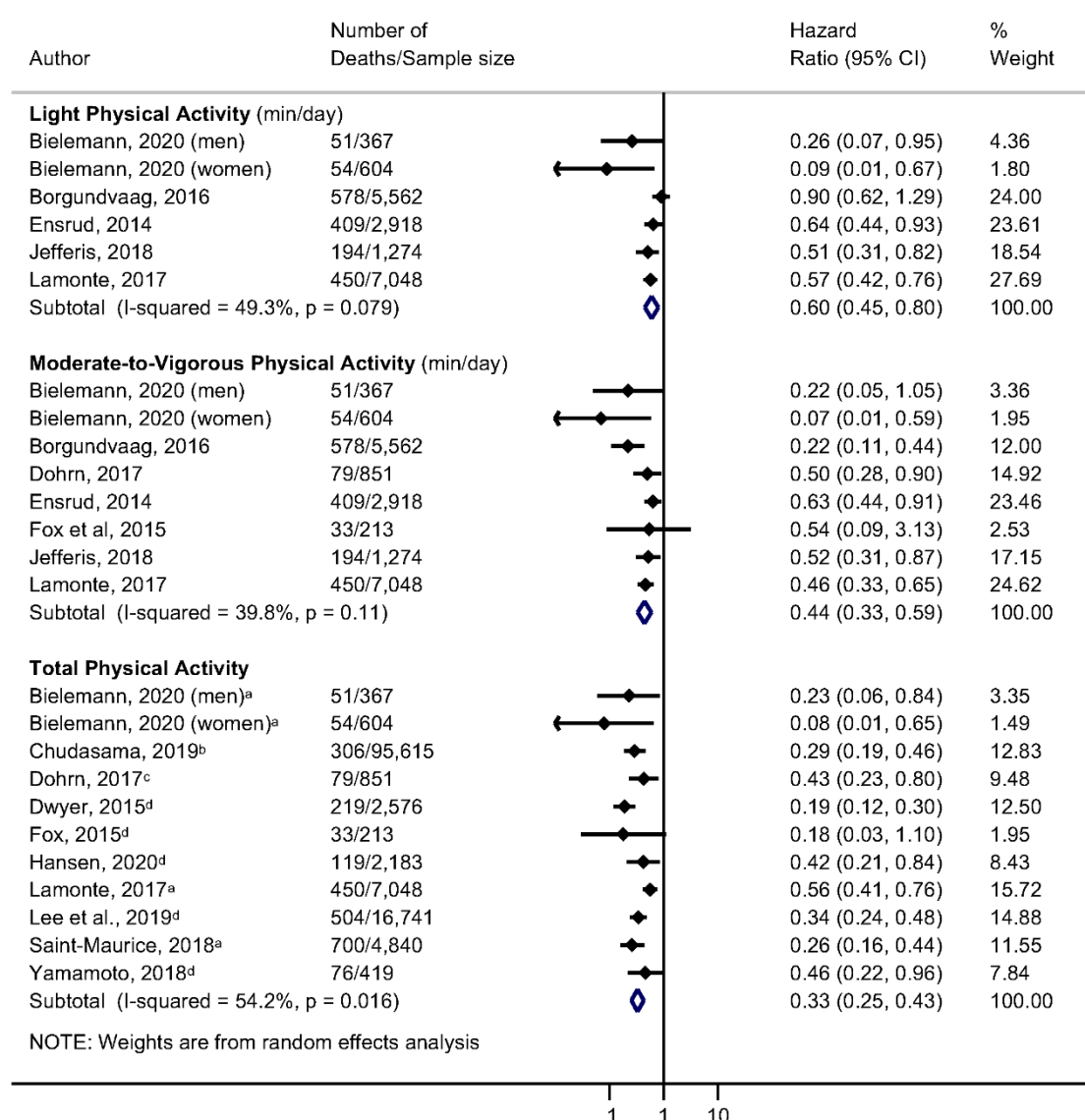
Selection of the non-exposed cohort: One star = Drawn from the same community as the exposed cohort

Comparability: One star= Study controls for comorbidities/self-rated health status, 2<sup>nd</sup> star= Study controls for other confounders

Follow-up long enough for outcomes to occur: One star=  $\geq 5$  years

Adequacy of follow up: Complete follow up/all groups had similar loss to follow-up/less than 5% of total lost to follow-up

Three<sup>11,25,48</sup> out of the 15 cohort studies were not included in the meta-analyses because the dose of exposure could not be harmonised because they were defined differently. Manini et al<sup>25</sup> reported a 57% lower risk for all cause mortality for individuals in highest compared with the lowest tertile (95%CI, 0.21 to 0.88). Chipperfield<sup>11</sup> found moderately active individuals to have 49% lower odds of mortality compared to moderately inactive individuals. Likewise, extremely active individuals were found to have 70% lower odds of mortality compared to extremely inactive individuals. The Baltimore Longitudinal Study of Aging found every hour/day increase in total physical activity associated with 13% decreased risk for all cause mortality.<sup>48</sup>



**Figure 1. Hazard ratio of all cause mortality for highest versus lowest category of light physical activity, moderate-to-vigorous physical activity, and total physical activity. Arrow indicates that the confidence interval extends beyond the width shown.**

<sup>a</sup>Unit=min/day; <sup>b</sup>milli-gravitational units (mg); <sup>c</sup>Unit=counts/day; <sup>d</sup>Unit=steps/day



There was moderate degree of heterogeneity in the studies included in the meta-analysis. Relatively high levels of light, moderate-to-vigorous, and total PA were each associated with reduced risk for all cause mortality (Figure 1). Total PA was found to be protective of all cause mortality with a pooled HR of 0.33 (95% CI, 0.25 to 0.43). Furthermore, compared to individuals who engaged in the lowest category of light PA, individuals in the highest category had 40% lower risk for all cause mortality. After including the outlier study for minutes/day of light PA,<sup>31</sup> the mortality risk was reduced from an HR of 0.60 to 0.55 (Supplementary Figure 2). For MVPA, we observed a non-linear dose response association with all cause mortality ( $P_{\text{nonlinearity}} < 0.001$ ); the summary HR was lower at 0.44 (Figure 1) with no appreciable additional benefits beyond 40 minutes per day (Supplementary Figure 3).

The adjusted pooled HR of the sensitivity analysis for total PA by excluding five studies that measured steps/day<sup>12,19,21,22,26</sup> instead of minutes/day was 0.34 (95% CI, 0.23 to 0.51) (Supplementary Figure 4). When we analysed steps/day as a continuous measure, the pooled estimate showed that an extra 1,000 steps/day would reduce the risk of mortality by 13% (Supplementary Figure 5). Minimal change to the results for studies that reported the estimates after exclusion of early deaths illustrates the robustness of the pooled HR for MVPA and total PA (Supplementary Figure 6).

Subgroup analyses showed that light PA was associated with 45% and 36% lower risk for mortality among women and men, respectively (p-value = 0.634). For MVPA, these estimates were 63% and 51%, respectively (p-value = 0.626) (Supplementary Figures 7 and 8). For light and moderate-to-vigorous PA, there was only one study that included participants with a mean age  $\leq 60$  years. Therefore, we were unable to conduct analyses for this age group (Supplementary Figure 9). However, for total PA we found 74% reduced risk for all cause mortality in participants with a mean age  $\leq 60$  years; the corresponding risk was 60% in participants with a mean age greater than 60 years of age (p-value = 0.21) (Supplementary Figure 10). For light PA, a lone study was of high quality and the rest were of moderate quality. Subgroup analysis by study quality did not differ substantially from the overall estimate for MVPA (p-value = 0.92) (Supplementary Figure 11) and for total PA (p-value = 0.95) (Supplementary Figure 12). Estimates for  $< 5$  years versus  $\geq 5$  years of follow-up did not differ much from the overall estimates especially for MVPA and total PA (Supplementary Figures 13, 14, and 15). We were able to assess publication bias for only MVPA (number of studies: 10). We found insufficient evidence for publication bias and small study effects (Egger's test p-value: 0.20) (Supplementary Figure 16).

## DISCUSSION

In this systematic review and meta-analysis of published cohort studies irrespective of the device (accelerometer, pedometer) and unit (minutes or hours/day, counts/minute, steps/day, or milli-gravitational units (mg)) used to measure PA, we found high versus low: light, moderate-to-vigorous, and total PA, were each associated with lower risk for all cause mortality. The findings from this systematic review of studies that used an objective measurement of PA are considerably lower than the pooled estimates obtained from the questionnaire-based studies.<sup>1,2</sup>

In addition to the six published studies that contributed data to the IPD meta-analysis by Ekelund et al<sup>9</sup> we were able to synthesise evidence from nine additional studies. The results from the meta-analysis are consistent with that of Ekelund et al<sup>9</sup> especially for total and moderate-to-vigorous PA, but that study included only accelerometer studies whereas for total PA we also included studies that used a pedometer to measure PA. A difference found in our meta-analysis was that the summary hazard ratio for MVPA was lower than for light PA when the highest category was compared to lowest category that warrants further investigation. Our results for light PA and MVPA are consistent with the results from a meta-analysis by Rojer et al.<sup>7</sup>

Woodcock et al<sup>1</sup> in their systematic review based on questionnaires, reported 19% reduction in risk of mortality for 30 minutes daily of moderate intensity activity undertaken five days a week and a 24% reduction in risk for one hour/day. Samitz et al<sup>2</sup> estimated risk reductions of 14% (30 min/day) and 26% (one hour/day) for MVPA. In contrast, we found no evident additional benefits beyond 40 minutes of MVPA per day with a relatively stable hazard ratio around 0.50.

For the highest compared to the lowest level of total PA, Samitz et al<sup>2</sup> estimated an HR of 0.65 (95%CI, 0.60 to 0.71) for all cause mortality. In our analysis of studies using objective measurement of PA, we found a pooled HR of 0.33 (95%CI, 0.25 to 0.43) when comparing highest to lowest levels of total PA, that is a halving of the HR found in the questionnaire-based systematic review which reported the lowest HR for very high levels of PA. This finding is close to that reported by Ekelund et al<sup>9</sup> wherein the hazard ratio was 0.27 when the highest quarter was compared to lowest quarter of accelerometer measured total PA expressed in counts/minute. The finding of a greater risk reduction in association with total PA versus MVPA when accelerometry is used is consistent with the view that total energy

expenditure is the key determinant of reduced risk of mortality. Alternatively, the participants who undertake the highest quantity of total PA might be those who also are in the highest category for MVPA and who also take additional amounts of light activity.

Though only a modest number of studies were included in this review and meta-analysis, the sample size of most of the studies was reasonably large and the number of events in the meta-analysis was large ( $n=3,903$ ). A limitation of this study was the variability in the duration of PA across cohorts within the categories being compared, i.e. light, or moderate-to-vigorous PA. This, however, should not bias the key comparison made here between objective and subjective measurement of PA as such variability in duration of exposure within the different categories of PA must have been present in the questionnaire-based studies even if the instrument did not capture it fully. Another limitation is the use of different objective measures of PA across studies. The meta-analysis for total PA included studies that used either accelerometer or pedometer. This should not be a major limitation as there is a high correlation ( $r=0.80$ ) between accelerometers and pedometers in estimating total PA.<sup>50</sup> Pedometers are unable to measure different intensities of PA<sup>50</sup> and therefore only accelerometry data was available for studies that estimated light and moderate-to-vigorous PA. Even so, the definitions of PA intensity levels varies according to the cut-points used and the populations studied.<sup>51</sup> Another limitation is that we included studies that measured steps/day either using pedometer or accelerometer that could be a source of measurement bias. However, two separate studies conducted among free living individuals (age range: 18-60 years) found strong correlation between steps/day measured via accelerometer and pedometer.<sup>52</sup>

The comparison between results from cohorts using questionnaire and accelerometer could be criticised based on the grounds that they come from a different set of cohorts, involving potentially a different distribution of confounders, and variation in the prevalence of PA. However, given the similarity of the findings across both the studies using objective measurement and those using questionnaires, it is unlikely that the difference in estimates compared to the questionnaire-based studies could be explained by a form of sampling bias such as this. It is more likely that the difference in the overall magnitude of association observed between the objectively measured and questionnaire measured PA is real and can be accounted for by the use of a more accurate form of measurement.<sup>53</sup> While we could not compare questionnaire-based estimates of risk to those estimated using objective measures in most of the studies included here, one of the studies based on NHANES data that was included in this systematic review<sup>35</sup> reported an HR of 0.44 for accelerometer-assessed

MVPA and all cause mortality when comparing the highest to lowest quartile. The corresponding estimate for self-reported MVPA was 0.63. Even though we did not present the data in our meta-analysis, the finding from a cohort study using doubly labelled water of a greater than 50% reduction in mortality risk further supports the conclusion that when objective measures are used a lower HR is likely to be seen.<sup>25</sup>

Another criticism might be that most of the studies in the current review used 7-day accelerometer data, while the questionnaire-based studies attempted to capture habitual activity and this might affect estimated associations. Arguing against this being an important cause of the differences observed is data from the Dwyer et al study<sup>12</sup> which was able to examine associations using both baseline and repeat assessment with pedometer 3.7 years later. They found only a 4% difference in magnitude of the risk estimate for all cause mortality if the later measure was used rather than baseline, suggesting that one point of time measurement of PA reflects habitual activity reasonably well when used in cohort studies of this kind.

The protective effect in the studies using objective measurement appears to extend further into the upper range of PA than is seen with questionnaires. This could be due to greater measurement error at higher levels of PA with questionnaires. Supporting this possibility, a multi-centre study in Norway found participants reported more vigorous activity and less sedentary time in questionnaires than when PA was measured with an accelerometer.

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Estimates of lower risk of death associated with PA in reviews based on both questionnaires and objective measures could be due to reverse causation. That is, individuals who were at a higher risk of death because of the presence of detectable or undetectable serious illness were less likely to engage in PA. This concern has been addressed in both study settings by the demonstration that removal of early deaths did not substantially affect the estimates of risk reduction especially for MVPA. However, it will require further investigation through more in-depth examination of health status at the time of assessment of PA in future cohorts. Mendelian randomisation, using PA as the exposure of interest might also become more feasible in the future and provide further insight into causality.<sup>55</sup>

## CONCLUSION

The beneficial effect of PA estimated from cohort studies using objective measurement of PA is considerably higher than that obtained from the questionnaire-based studies. Although the focus of current guidelines is on moderate/vigorous PA it is apparent in this systematic

review that the beneficial effect of PA extends across the spectrum of intensity levels. Newer cohort studies that have PA data measured by both accelerometer (with standardised cutpoints for intensity of PA) and questionnaire can potentially confirm the findings from this study. Examining not only mortality but also other outcomes such as cardiovascular diseases, type 2 diabetes, cancer, metabolic health, and mental health will be an important next step.

## **AUTHOR CONTRIBUTORSHIP**

RR acquired, analysed, and interpreted the data, drafted and revised the work critically for important intellectual content, and approved the final version. TD conceived the study, interpreted the data, drafted and revised the work critically for important intellectual content, and approved the final version. JH checked data abstractions and quality of the study, revised the work critically for important intellectual content, and approved the final version. AP, MW, KR, and SB interpreted the data, revised the work critically for important intellectual content, and approved the final version.

## **DECLARATION OF INTERESTS**

All authors with the exception of KR declare no support from any organisation 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. KR reports receipt of grants from the NIHR Biomedical Research Centre, Oxford Martin School, and RCUK (ESRC) during the conduct of the study, but declares no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

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