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ABSTRACT

Background Previous epidemiological studies examining the association between physical activity (PA) and mortality risk have measured absolute PA intensity using standard resting metabolic rate reference values which fail to consider individual differences. Our study compared risk of all-cause and cardiovascular mortality between absolute and corrected estimates of PA volume.

Methods We included 49,982 adults aged ≥ 40 years who participated in the Health Survey for England and Scottish Health Survey in 1994-2008. Physical activity was classified as absolute or corrected MET-hours/week taking into account participant's weight, height, age, and sex. We used Cox regression models to examine the association between absolute and corrected PA volumes and all-cause and cardiovascular mortality.

Results We found no difference in the association between levels of PA and risk of all-cause and cardiovascular mortality for absolute and corrected MET-hours/week, although there was a consistent decrease in mortality risk with increasing PA. There was no difference in mortality when analyses were stratified by sex, age and body mass index.

Conclusions The association between PA volume and risk of mortality was similar regardless of whether PA volume was estimated using absolute or corrected METs. There is no empirical justification against the use of absolute METs to estimate PA volume from questionnaires.

TEXT

Engaging in regular physical activity (PA) improves cardiometabolic health, and reduces risk of chronic disease and mortality.[1,2] Over recent decades, PA guidelines have evolved from a primary focus on aerobic exercise to a multimodal approach incorporating strength-promoting exercise and other activities (e.g. balance and flexibility training) as an adjunct to aerobic exercise.[1,3] Performing regular bouts of vigorous intensity PA is important for optimal health benefits.[4]

A common measure of PA intensity involves metabolic equivalents (METs), defined as multiples of resting metabolic rate (RMR).[5] PA intensity is classified as light (1.6 to < 3.0 METs), moderate (3.0 to < 6.0 METs) and vigorous (≥ 6.0 METs).[5] The standard 1-MET reference value for RMR is 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ and most likely traces back to a medical textbook from 1890 which published data of a single 70-kg, 40-year-old man.[6,7] Multiple studies that have re-evaluated RMR in large heterogeneous samples report substantially lower mean RMR of 2.51-3.30,[8-11] questioning the use of 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ as the standard 1-MET reference.

Generally, absolute METs measure the total amount of energy expended during PA, without considering individual characteristics.[1] While, METs corrected for RMR take into account variation in individual characteristics, such as age, gender, height and weight when calculating the amount of energy needed to complete a given PA task.[9] The Compendium of Physical Activities provides a comprehensive list of absolute METs which determines intensity-weighted PA volume.[5] However, use of absolute METs may underestimate the true effort needed by overweight and obese, older and female persons to perform PA; the subgroups of the population that are least likely to meet PA guidelines.[9,11] This can lead to considerable misclassification of PA intensity as individuals from these subgroups may engage in more vigorous PA than estimated from absolute METs.[9,11] Corrected METs may offer a more accurate estimate of intensity-weighted PA volume.

Epidemiological studies examining links between PA and mortality risk have predominantly used absolute measures of PA intensity,[12-15] which may lead to PA level misclassification and potential attenuation of the observed associations. Although one study considered the relative intensity of PA using a generic question about perceived effort during sports, they did not measure PA volume.[16] To our knowledge, no study has compared mortality risk estimates derived from absolute and corrected METs. The aim of this study was to compare these two intensity-weighted PA volume estimation methods (absolute vs. corrected METs) on the direction and magnitude of PA-mortality associations using an established pooled dataset of population cohorts.[15]

METHODS

Participants

We used data collected from the Health Survey for England (HSE) and the Scottish Health Survey (SHS). The HSE and SHS are household-based population surveillance studies in which a multistage, stratified probability design was used to select households representative of the target populations of England and Scotland, respectively.[17,18] The HSE surveys were conducted in 1994, 1997, 1998, 1999, 2003, 2004, 2006 and 2008, and the SHS in 1995, 1998 and 2003. Interview response rates ranged from 58-71% for the HSE[17] and 60-81% for the SHS.[18] All participants provided written informed consent, but for this study, only adults aged ≥ 40 years were included. Ethical approval was granted by relevant local research ethics committees.

Mortality Outcomes

The primary outcome was risk of all-cause and cardiovascular disease (CVD) mortality. Surviving participants were censored on December 31, 2009 (SHS) and March 31, 2011 (HSE). Primary cause of death was diagnosed and coded according to the International Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9) or Tenth Revision (ICD-10). CVD deaths were recorded using the ICD-9 codes: 390.0-459.9 and ICD-10 codes: I01-I99. Length of survival was calculated based on the time to death or censoring at the end of the study period. Participants with physician-diagnosed CVD or cancer at baseline, and/or who died during the first 24 months of follow-up, were excluded in order to reduce the possibility of reverse causation.

Physical Activity Assessment

Non-occupational PA was assessed using an established questionnaire[19] which asked participants to report the frequency and duration of their participation in three categories of PA in the four weeks prior to the interview: domestic PA (e.g., housework and gardening); walking; and sports and exercise. We calculated the absolute MET-hours/week of each participant by multiplying the absolute MET per activity with the number of hours the activity was performed per week, using the standard 1-MET reference of 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. Corrected MET-hours/week were calculated using the same method, except we used the corrected 1-MET reference from the Harris-Benedict prediction equation for RMR[20] rather than the standard 1-MET reference. Previous work reported that the Harris-Benedict equation is a valid measure of energy expenditure with a minimal difference of 391 kcal/day compared to gas exchange values using indirect calorimetry.[21]

Corrected MET intensity = mean absolute MET per activity × (3.5/Harris-Benedict predicted RMR).[11]

where Harris-Benedict predicted RMR = 10 × weight (kg) + 6.25 × height (cm) - 5 × age (years) + 5 for males; and 10 × weight (kg) + 6.25 × height (cm) - 5 × age (years) - 161 for females.[20]

We grouped participants by MET-hours/week into four categories based on recent PA guidelines:[1] inactive (0 MET-hours/week); insufficiently active (< 7.5 MET-hours/week, excluding 0 MET-hours/week); sufficiently active (7.5 to < 15 MET-hours/week); and highly active (≥ 15 MET-hours/week). Domestic-related PA was excluded from calculations of total MET-hours/week because its recall is often imprecise due to its incidental nature and generally is not associated with CVD mortality[22] or risk factors.[23] In a sensitivity analysis, participants were grouped into inactive (0 MET-hours/week) or tertiles of PA according to their total MET-hours/week. Participants whose total MET-hours/week was > 5 standard deviations above the mean were treated as outliers and excluded from all analyses, similar to previous research.[24]

Covariates

Trained interviewers measured height and weight using standard protocols[17,18] to calculate body mass index (BMI). In stratified analyses, we classified a BMI score < 25 as indicative of underweight or normal weight, 25 to < 30 as overweight, and ≥ 30 as obese. Additional survey items assessed age, sex, presence of long-standing physical or mental illness, and age finished full-time education. Smoking habits were categorised as current smoker or non-current smoker, and alcohol consumption was classified as drinking alcohol less than, or greater than or equal to, five times per week. Scores from the 12-item General Health Questionnaire (GHQ) were used to assess psychological distress with a GHQ score ≥ 4 indicating psychological distress.[25]

Statistical Analysis

PA levels and participant characteristics were described in relation to absolute and corrected METs. We used Cox proportional hazards regression models to examine associations between PA and risk of all-cause and CVD mortality using absolute and corrected METs. Model 1 was partially adjusted for age and sex. Model 2 was fully adjusted including age, sex, BMI, long-standing illness, smoking habits, alcohol consumption, psychological distress and education level. We also ran additional fully adjusted models stratified by sex, age and BMI. We generated ROC curves with corresponding areas under the curve (AUC) to examine whether corrected MET-hours/week is a better predictor of mortality outcomes than absolute MET-hours/week. We examined the proportional hazards assumption through Kaplan Mayer plots and no apparent violations were evident. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows Version 22.0 (IBM, Chicago, IL, USA).

RESULTS

The core analytic sample included 49,982 adults from England and Scotland aged ≥ 40 years and was predominately white (93.5%). Baseline characteristics are presented in Table 1. Over an average follow-up time of 9.1 ± 4.5 years (corresponding to 452,335 person-years), 5227 all-cause and 1513 CVD deaths were recorded. When shifting from absolute to corrected METs, 6.2% fewer participants were classified as insufficiently active, 1.1% fewer participants were classified as sufficiently active, and 7.3%

more participants were classified as highly active. Supplementary eFigure 1 presents the distribution of the absolute and corrected MET-hours/week in the analytic sample.

Tables 2 and 3 show the partially and fully adjusted multivariate associations between levels of PA and all-cause and CVD mortality risk, respectively. In both models using absolute and corrected METs, compared to the inactive participants, participation in any amount of PA was associated with a significantly reduced risk of all-cause and CVD mortality, although, there was a slight attenuation in HR estimates for fully adjusted models. The pattern of risk reduction in all-cause and CVD mortality between the four PA levels did not differ between the use of absolute or corrected METs. In a sensitivity analysis where we replicated these Cox regression models using insufficiently active as the reference group no appreciable differences were found (data not shown).

Supplementary eTables 1 and 2 show the fully adjusted multivariate associations between PA levels and risk of all-cause and CVD mortality, respectively, stratified by sex, age and BMI. Using corrected METs slightly attenuated the association between PA levels and all-cause mortality in adults aged > 60 years and with obesity (BMI > 30). We found modest differences in CVD mortality associations between absolute and corrected METs in certain population subgroups, including highly active females, sufficiently active adults aged 50-59 years, and overweight adults (BMI: 25 to < 30) who were sufficiently or highly active. Overall, differences in stratified mortality risk estimates between absolute and corrected METs were not consistent in direction or magnitude. For results from the sensitivity analysis where we grouped participants into tertiles based on MET-hours/week, PA-mortality risks were also similar between absolute and corrected METs (Supplementary eTables 3 and 4). The AUC did not differ between absolute and corrected METs, indicating a comparable predictive ability for mortality outcomes (Supplementary eTable 5).

DISCUSSION

To our knowledge, this study is the first to compare the impact of using absolute vs. corrected METs on the direction and magnitude of PA-mortality associations. In accordance with previous studies using comparable large, heterogeneous cohorts, we found that any amount of PA was associated with a reduced risk of all-cause and CVD mortality.[14,15] Our results showed that correcting intensity-weighted PA volume (MET-hours/week) for variations in RMR did not materially change PA-mortality associations, compared to using absolute MET-hours/week. We also did not find consistent differences in mortality risk estimates between absolute and corrected METs when stratified by the RMR correction parameters, sex, age and BMI.

There are several explanations for our results. One possibility is that the use of absolute METs led to little misclassification in this sample compared to the corrected METs. Supplementary eFigure 1 shows a similar frequency distribution of absolute and corrected MET-hours/week, indicating that correcting MET-hours/week using the Harris-Benedict equation led to minimal reclassification of the sample. In particular, the population subgroups most likely to have PA intensity misrepresented by absolute METs (overweight and obese, older and female persons)[9,11] are also more likely to be inactive and may not have therefore been reclassified from correcting MET-hours/week. Further, an absence of differences in mortality rates at the group level does not necessarily imply that there is no impact of using absolute vs. corrected MET-hours/week at the individual level. Our findings might simply show that there are no differences at the group level.

Previous research also suggested that the Harris-Benedict equation may overestimate RMR in Caucasians, relative to measured RMR.[26,27] This potential overestimation of RMR may have attenuated the magnitude of difference in PA-mortality associations between absolute and corrected METs, possibly explaining, at least in part, the observed null difference. There is evidence that the Mifflin-St Jeor equation is more accurate at predicting RMR than the Harris-Benedict equation[27] and offers an alternative prediction equation. Finally, the questionnaire used in our study to estimate PA enquires about bouts lasting for at least 10-15 minutes;[28] a convention that contradicts the most recent US guidelines which acknowledge that PA of any duration is health enhancing.[1] Questionnaires cannot capture incidental PA of higher intensity and the capacity of incidental PA to reach relative vigorous intensity is often underappreciated,[29] especially when considering the relative intensity of PA in population subgroups with lower RMR.[30] It is possible that estimating levels of incidental PA more accurately (e.g., using accelerometers) could have shifted more of the distribution of corrected MET-hours/week, and would have contributed to more pronounced differences in PA-mortality associations.

This is the first study, to our knowledge, to compare intensity-weighted PA volume corrected for RMR. Strengths of our study included the large, population-based sample, and our comprehensive and data-driven analytic approach. We reduced the possibility of reverse causation by removing early deaths and participants with underlying diseases at baseline. Nonetheless, our study had a number of limitations. First, 93.5% of the sample was white which limits the generalizability of our results to other racial groups. Second, the data sources HSE and SHS were cross-sectional surveys which only assessed PA at baseline. As a result, it is unknown whether levels of PA changed from baseline to follow-up. Third, PA was self-reported using a questionnaire of mostly leisure-time PA,[15] which may have led to recall and social desirability bias.

In summary, we found no evidence of different associations between PA levels and risk of all-cause and CVD mortality between absolute and corrected METs. Future research should re-examine differences in mortality risk estimates derived from absolute METs using different correction methods, such as accelerometer or heart rate data.

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Table 1: Baseline Characteristics of Participants[a]

Characteristic	Physical activity level[b]							
	Absolute MET-hours/week				Corrected MET-hours/week			
	Inactive (n = 10,162)	Insufficiently active (n = 17,169)	Sufficiently active (n = 8747)	Highly active (n = 13,904)	Inactive (n = 10,163)	Insufficiently active (n = 14,086)	Sufficiently active (n = 8179)	Highly active (n = 17,554)
Age, years[c]	59.3 (12.7)	56.5 (11.7)	55.7 (11.1)	54.6 (10.6)	59.3 (12.7)	56.3 (11.7)	55.6 (11.2)	55.2 (10.8)
Female sex	5882 (57.9)	10,000 (58.2)	5042 (57.6)	6801 (48.9)	5883 (57.9)	7956 (56.5)	4705 (57.5)	9181 (52.3)
White ethnicity	9499 (93.5)	15 958 (93.0)	8158 (93.3)	13,099 (94.3)	9500 (93.5)	13,071 (92.9)	7633 (93.4)	16,510 (94.2)
Body mass index[c,d]	28.0 (5.3)	27.6 (4.8)	27.1 (4.4)	26.7 (4.2)	28.0 (5.3)	27.4 (4.8)	27.2 (4.5)	27.0 (4.3)
Long-standing illness	5982 (58.9)	8443 (49.2)	3855 (44.1)	5627 (40.5)	5980 (58.8)	6930 (49.2)	3665 (44.8)	7332 (41.8)
Current smoker	3095 (30.5)	3976 (23.2)	1728 (19.8)	2438 (17.5)	3094 (30.4)	3368 (23.9)	1729 (21.1)	3046 (17.4)
Frequent alcohol consumption (≥ 5 days/week)	1888 (18.6)	3725 (21.7)	1905 (21.8)	3444 (24.8)	1887 (18.6)	3110 (22.1)	1757 (21.5)	4208 (24.0)
Psychological distress (GHQ Score ≥ 4)	1870 (18.4)	2297 (13.4)	945 (10.8)	1317 (9.5)	1871 (18.4)	1908 (13.5)	967 (11.8)	1683 (9.6)
Finished full-time education at age ≥ 19 years	920 (9.1)	2716 (15.8)	1635 (18.7)	3022 (21.7)	921 (9.1)	2218 (15.7)	1484 (18.1)	3670 (20.9)
Total MET-hours/week[e]	N/A	3.0 (3.5)	10.5 (3.6)	25.6 (19.2)	N/A	3.3 (3.5)	10.9 (3.7)	29.3 (23.1)

Abbreviations: GHQ, General Health Questionnaire; N/A, not applicable.

[a] Sample includes 11 cohorts of 49,982 adults aged ≥ 40 years who responded to the Health Survey for England or Scottish Health Survey.

[b] Physical activity levels were classified into four categories: inactive (0 MET-hours/week); insufficiently active (< 7.5 MET-hours/week, but not inactive); sufficiently active (7.5 to < 15 MET-hours/week); and highly active (≥ 15 MET-hours/week).

[c] Values are expressed as mean (standard deviation).

[d] Body mass index (BMI) = weight (kg) / height (m^2).

[e] Values are expressed as median (IQR).

Table 2: Associations between physical activity and risk of all-cause mortality using absolute and corrected MET-hours/week[a]

Physical activity level[b]	No. of deaths	n	Model 1[c]		Model 2[d]	
			HR	95% CI	HR	95% CI
Absolute MET-hours/week						
Inactive	1850	10,162	1.00 [reference]	N/A	1.00 [reference]	N/A
Insufficiently active	1751	17,169	0.70	0.65-0.75	0.77	0.72-0.83
Sufficiently active	728	8747	0.63	0.58-0.69	0.73	0.67-0.80
Highly active	898	13,904	0.54	0.50-0.58	0.64	0.59-0.70
Total	5227	49,982	N/A	N/A	N/A	N/A
Corrected MET-hours/week						
Inactive	1851	10,163	1.00 [reference]	N/A	1.00 [reference]	N/A
Insufficiently active	1461	14,086	0.71	0.67-0.76	0.78	0.73-0.84
Sufficiently active	703	8179	0.64	0.59-0.70	0.73	0.67-0.79
Highly active	1212	17,554	0.56	0.52-0.60	0.66	0.61-0.71
Total	5227	49,982	N/A	N/A	N/A	N/A

Abbreviations: HR, hazard ratio; N/A, not applicable.

[a] Sample includes 11 cohorts of 49,982 adults aged ≥ 40 years who responded to the Health Survey for England or Scottish Health Survey.

[b] Physical activity levels were classified into four categories: inactive (0 MET-hours/week); insufficiently active (< 7.5 MET-hours/week, but not inactive); sufficiently active (7.5 to < 15 MET-hours/week); and highly active (≥ 15 MET-hours/week).

[c] Adjusted for age and sex.

[d] Adjusted for age, sex, BMI, long-standing illness, alcohol consumption, smoking, psychological distress and education.

Table 3: Associations between physical activity and risk of cardiovascular mortality using absolute and corrected MET-hours/week[a]

Physical activity level[b]	No. of deaths	n	Model 1[c]		Model 2[d]	
			HR	95% CI	HR	95% CI
Absolute MET-hours/week						
Inactive	546	10,162	1.00 [reference]	N/A	1.00 [reference]	N/A
Insufficiently active	494	17,169	0.68	0.61-0.77	0.77	0.68-0.87
Sufficiently active	217	8747	0.66	0.56-0.77	0.79	0.67-0.92
Highly active	256	13,904	0.55	0.47-0.64	0.68	0.58-0.80
Total	1513	49,982	N/A	N/A	N/A	N/A
Corrected MET-hours/week						
Inactive	547	10,163	1.00 [reference]	N/A	1.00 [reference]	N/A
Insufficiently active	407	14,086	0.69	0.60-0.78	0.77	0.68-0.88
Sufficiently active	203	8179	0.65	0.55-0.77	0.76	0.64-0.89
Highly active	356	17,554	0.58	0.50-0.66	0.71	0.62-0.82
Total	1513	49,982	N/A	N/A	N/A	N/A

Abbreviations: HR, hazard ratio; N/A, not applicable.

[a] Sample includes 11 cohorts of 49,982 adults aged ≥ 40 years who responded to the Health Survey for England or Scottish Health Survey.

[b] Physical activity levels were classified into four categories: inactive (0 MET-hours/week); insufficiently active (< 7.5 MET-hours/week, but not inactive); sufficiently active (7.5 to < 15 MET-hours/week); and highly active (≥ 15 MET-hours/week).

[c] Adjusted for age and sex.

[d] Adjusted for age, sex, BMI, long-standing illness, alcohol consumption, smoking, psychological distress and education.