Is running associated with a lower risk of all-cause, cardiovascular and cancer mortality, and is the more the better? A systematic review and meta-analysis

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ABSTRACT

Objective To investigate the association of running participation and the dose of running with the risk of all-cause, cardiovascular and cancer mortality.

Design Systematic review and meta-analysis.

Data sources Journal articles, conference papers and doctoral theses indexed in Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, PsycINFO, PubMed/MEDLINE, Scopus, SPORTDiscus and Web of Science.

Eligibility criteria for selecting studies Prospective cohort studies on the association between running or jogging participation and the risk of all-cause, cardiovascular and/or cancer mortality in a non-clinical population of adults were included.

Results Fourteen studies from six prospective cohorts with a pooled sample of 232 149 participants were included. In total, 25 951 deaths were recorded during 5.5–35 year follow-ups. Our meta-analysis showed that running participation is associated with 27%, 30% and 23% lower risk of all-cause (pooled adjusted hazard ratio (HR)=0.73; 95% confidence interval (CI) 0.68 to 0.79), cardiovascular (HR=0.70; 95% CI 0.49 to 0.98) and cancer (HR=0.77; 95% CI 0.68 to 0.87) mortality, respectively, compared with no running. A meta-regression analysis showed no significant dose–response trends for weekly frequency, weekly duration, pace and the total volume of running.

Conclusion Increased rates of participation in running, regardless of its dose, would probably lead to substantial improvements in population health and longevity. Any amount of running, even just once a week, is better than no running, but higher doses of running may not necessarily be associated with greater mortality benefits.

INTRODUCTION

Global and national public health authorities recommend that adults take part in 150 min of moderate to vigorous physical activity (MVPA) each week.[1–5] The epidemiological literature strongly supports the beneficial associations of the total amount of MVPA with health outcomes.[6–10] Several systematic reviews and meta-analyses have summarised the evidence for the association between MVPA and the risk of disease-specific and all-cause mortality.[11–16] For example, one meta-analysis found that insufficient MVPA (defined as not meeting the current World Health Organization (WHO) guidelines for MVPA[1]) is associated with a 28% higher risk of all-cause mortality, compared with sufficient MVPA.[15] Considering the high levels of physical inactivity globally, Lee and colleagues estimated that more than 5 million premature deaths a year would be prevented if physically inactive people became sufficiently active.[15] Considerable interest has also been shown in the effects of different types of physical activity (eg, walking, cycling, running, swimming) on health and risk of premature mortality.[17–24] In other words, for a given amount of MVPA, does the type of physical activity matter?

Running is among the most popular types of physical activity. It has been estimated that each month around 3.7 million (8.5%) English adults take part in running as a sport or recreational activity.[25] Other countries, such as Australia[26] and the USA,[27] also have high participation rates. The 2017 Physical Activity Council's survey ranked running in the top 10 preferred activities in which inactive 25–44-year-old US adults wished to take part.[28] Given its popularity, running has great potential for improving population health. The Royal College of General Practitioners (RCGP) has acknowledged this potential by partnering with the *parkrun UK* initiative, to promote the uptake of running and walking among general practitioners and their patients.[29]

In a systematic review, Oja *et al*[17] concluded that the evidence for health benefits is scarce for participation in all sports except for running and football. The authors concluded that there is (i) moderate evidence for the associations between running and improved aerobic fitness, cardiovascular function and running performance; (ii) limited evidence for associations of running with improvements in metabolic fitness, adiposity status and postural balance; and (iii) inconclusive evidence for the associations of running with cardiac adaptation, muscular strength and disease-specific and all-cause mortality.[17] Oja *et al*[17] identified only one study on running participation and the risk of mortality. A subsequent, comprehensive narrative review summarised the evidence for the association of running and a range of health outcomes, including major cardiometabolic outcomes, bone and respiratory health, disability and disease-specific and all-cause mortality.[22] The strength of the association between running participation and the risk of all-cause and disease-specific mortality varied

across different studies.[22] To date, no meta-analysis has synthesised evidence on the association between running participation and the risk of mortality.

To enable evidence-based prescribing of running as a health-enhancing physical activity, it is crucial to identify its optimal dose. The 'dose' of running is usually defined by its frequency (eg, two times a week), overall duration in a given period (eg, 40 min/week), pace (eg, 10 km/h) and the total volume (eg, expressed as the product of the overall weekly duration of running and the metabolic equivalent (MET) of running at a given pace; 800 MET-min/week).[30 31] It might be expected that higher running doses would lead to better health outcomes, such as improved physical and metabolic fitness.[32] However, contrary to this assumption, Schnohr *et al*[31] suggested there may be a U-shaped relationship between the dose of running and the risk of all-cause mortality. Compared with 'sedentary' non-runners, those who ran <2.5 hours a week, those who ran less than four times a week and those who ran at a slow or average pace had significantly lower risks of all-cause mortality.[31] No statistically significant adjusted hazard ratios (HRs) were found for those who ran ≥2.5 hours a week, those who ran four or more times a week and those who ran at a fast pace.[31] The U-shaped relationship may be explained by possible pathological changes in cardiovascular tissues induced by extreme doses of endurance sports over a long term—for example, the development of patchy myocardial fibrosis, creating a substrate for heart arrhythmias.[33] However, a relatively small number of participants in the study of Schnohr *et al*[31] were classified as "strenuous" runners and only a few deaths were registered in this group, limiting the statistical power of the analysis. The finding has sparked much discussion among researchers.[22 30 34–40] To date, the available evidence on the dose–response relationship between running and the risk of mortality has not been synthesised in a meta-analysis.

The aim of this systematic review and meta-analysis was, therefore, to synthesise available evidence on the association of running participation and the dose of running with the risk of all-cause, cardiovascular and cancer mortality.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[41] The review protocol has been registered in the International Prospective Register of Systematic Reviews—PROSPERO (registration id: CRD42016049965).

Literature search

We systematically searched PubMed/MEDLINE, Scopus, EBSCOHost (including Academic Search Ultimate, CINAHL, Health Source: Nursing/Academic Edition, MasterFILE Complete, PsycINFO and SPORTDiscus), and Web of Science for journal articles and conference papers published from the database inception to February 2019. Additionally, we searched for doctoral and master theses through the Networked Digital Library of Theses and Dissertations and Open Access Theses and Dissertations databases. The searches were performed by combining the keywords "running", "jogging", "runner*" and "jogger*" with the keywords "mortalit*", "death*" and "fatal*". The search syntax can be found in online supplementary file 1. The reference lists of all included studies were checked to identify any titles that were not considered for inclusion in the primary literature search. The discrepancies of the literature search from the registered protocol are specified in online supplementary file 2.

Study selection

Two authors (ZP and NS) independently assessed the identified publications for relevance. When needed, disagreement was resolved by discussion with a third author (JG). Studies meeting the following criteria were included in this review: (1) a prospective cohort study; (2) adult sample (≥18 years of age); (3) non-clinical study population (ie, a population not defined by the presence of a disease or a health condition); and (4) reporting an association between participation in running or jogging and the risk of all-cause, cardiovascular and/or cancer mortality.

Data extraction

Using a predefined form, two authors (ZP and NS) independently extracted the following data from the included studies: (1) study date and location; (2) type of sample, sample size and gender distribution; (3) age of study participants (range and mean±SD); (4) duration of follow-up; (5) number of person-years; (6) number of runners and non-runners in the sample; (7) number of deaths in the total sample, among non-runners and among runners; (8) the method of running assessment; (9) the mode of outcome assessment; (10) adjustments for potential confounding variables; (11) type of statistical analysis; and (12) key results for the association of running participation and the dose of running with the risk of all-cause, cardiovascular and cancer mortality (online supplementary tables 1 and 2). Discrepancies in the extracted data were resolved by discussion with a third author (JG). Where needed, we also asked the authors of the included studies to provide unpublished data.

Assessment of study and evidence quality

Two authors (NL and SJHB) independently assessed the quality of included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.[42] Details of the scale items and the scoring system can be found elsewhere.[42] The appraised studies were classified based on their overall score on the NOS scale as "poor quality" (0–3 points), "fair quality" (4–6 points) or "good quality" (7-9) points. Discrepancies in the results of the two independent quality assessments were resolved by a third author (JG).

Assessment of adjustments for confounding

The appropriateness of adjustments for confounding in each study was assessed against directed acyclic graphs (DAGs).[43] A possible representation of the directions of relationships is presented in figure 1. According to this DAG, to estimate the effect of running (through subsequent health status) on mortality risk, it would be necessary to adjust for sociodemographic factors, unhealthy lifestyle (eg, smoking, alcohol intake and dietary habits), adiposity, health status and physical activity other than running.

Data analysis

If several analyses had been conducted on the same cohort and published separately, our meta-analyses included estimates from the publication with the longest follow-up. We pooled individual HRs from the models that satisfied (or were the closest to satisfying) the adjustment requirements specified according to the DAG in figure 1; which is likely to provide conservative estimates. We did this using a random-effects meta-analysis, separately for all-cause, cardiovascular and cancer mortality. We carried out the following additional analyses for all-cause mortality:

1. A subgroup analysis by gender;
2. A sensitivity analysis in which we included only studies classified as "good quality";

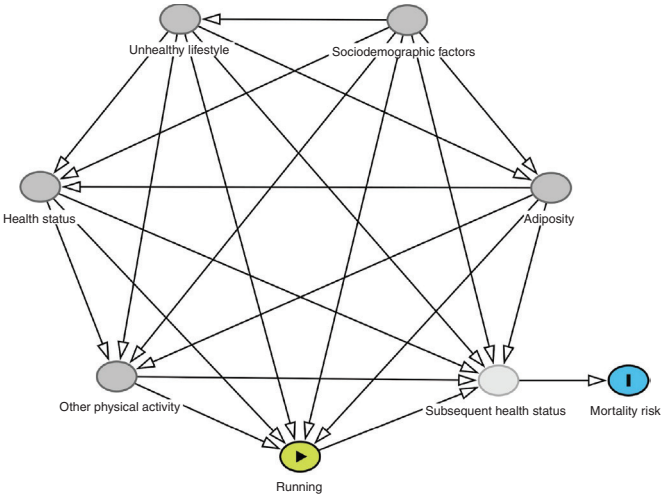

Figure 1 Directed acyclic graph for the relationship between running participation and mortality risk. Green circle, exposure; blue circle, outcome; light grey circle, unobserved variable; dark grey circle, other variable; arrow, direction of the causal relationship.

3. A sensitivity analysis in which we included the most recent study from the Copenhagen City Heart Study cohort[44] instead of the study with the longest follow-up and the largest sample size;[45]
4. A sensitivity analysis in which we included HRs from an alternative model in the study of Lee *et al*[46] (see description of model 2 in online supplementary table 1);
5. A sensitivity analysis in which, additionally, we replaced HRs from the study of Oja *et al*[18] with estimates from the study of Stamatakis *et al*[19]—that is, a subsequent analysis of the same data with further adjustments for social class and household income.

We also carried out the same sensitivity analyses as (4) and (5) above for cardiovascular disease mortality. We assessed statistical heterogeneity of the HRs using the I^2 statistic, where I^2 values of 0–40%, 30–60%, 50–90% and 75–100% were considered to represent low, moderate, substantial and high heterogeneity, respectively.[47] We could not assess publication bias using Egger's asymmetry test, owing to the small number of included studies.[48]

The dose–response relationships from individual studies were pooled using a random-effects meta-regression analysis with restricted maximum likelihood estimation. Before the meta-regression analysis, the doses reported in individual studies were harmonised according to the closest midpoint by one author (ZP). The results of the process were checked for consistency and accuracy by another author (ST). If several studies presented data on dose–response relationships for the same cohort, we included the study with the most detailed classification of dose. The categories of dose can be found in online supplementary table 2. We considered linear, quadratic, log-linear and log-quadratic models when examining the dose–response curves. The model selection was based on the Akaike information criterion (AIC). The model with the smallest AIC statistic was considered to have the best balance between simplicity and goodness of fit. All analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria), using the 'metafor' package.[49]

RESULTS

Search and study selection results

The primary search resulted in a total of 19 315 references (figure 2). After removing 4912 duplicates, we assessed 14 403 references against the inclusion criteria. Of these, 13 publications[18 30 31 44–46 50–56] met all the inclusion criteria. Additionally, one eligible publication[19] was identified in the secondary search, from the reference lists of the included papers. This resulted in a total of 14 included publications, reporting results from the following cohort studies: the Aerobics Center Longitudinal Study (USA);[30 46 50] the Copenhagen City Heart Study (Denmark);[31 44 45 56] the Health Survey for England and the Scottish Health Survey (UK; hereinafter referred to as a single study, as their data were pooled);[18 19] the National Health and Nutrition Examination Survey (USA);[54] the Shanghai Men's Health

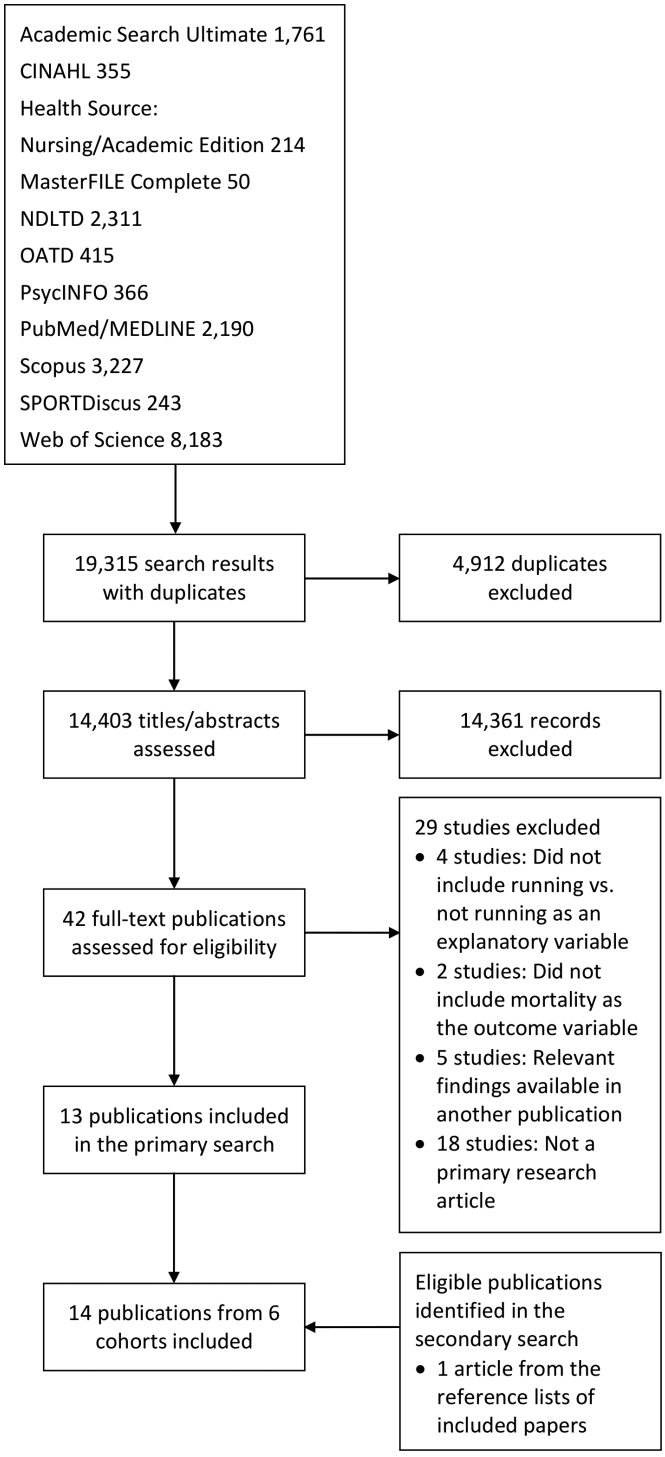

Figure 2 Flow diagram of the search and study selection process.

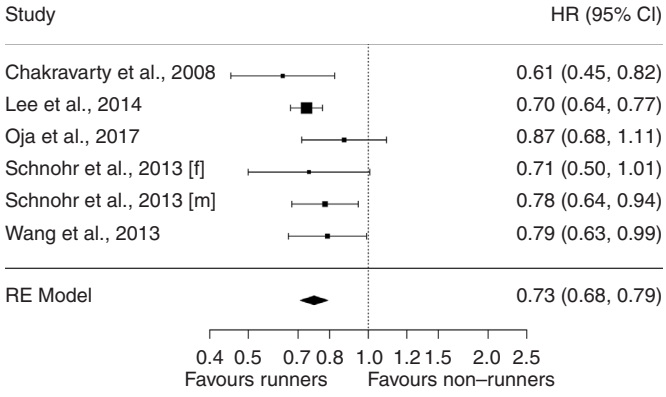

Figure 3 Running participation and all-cause mortality risk: a meta-analysis of hazard ratios. HR, adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI, 95% confidence interval for HR; f, female subsample; m, male subsample; RE Model, pooled effect size from a random-effects meta-analysis model.

Study (China);[51] and a cohort of runners from the 50+Runners Association with controls from the Stanford University Lipid Research Clinics Prevalence Study (USA).[52 53 55]

Study characteristics

The study of Wang *et al*[51] included only men, while the other studies included both sexes (online supplementary table 1). Four study samples were population-representative,[18 45 51 54] while two studies used convenience samples.[46 55] The pooled sample size from the studies included in this review is 232 149, with individual study samples ranging from 961 to 80 306 participants. In all included studies, the data on running participation were collected using self-reports, and the participants classified as runners (ie, the exposure group) comprised around 10% of the pooled sample. The mortality data in all studies were obtained from national death registers, with follow-up across individual studies ranging from 5.5 to 35 years. In total, 25 951 deaths were recorded in the study samples during follow-up.

Adjusted HRs suitable for meta-analysis of the association between running participation and the risk of all-cause mortality were available from all cohorts except the National Health and Nutrition Examination Survey[54] (online supplementary table 1). Three studies reported adjusted HRs suitable for inclusion in the meta-analysis of the association between running participation and the risk of cardiovascular mortality.[18 46 51] Adjusted HRs suitable for the meta-analysis of the association between running participation and the risk of cancer mortality were available in three studies[30 45 51] and obtained upon request from the authors of one additional study.[18]

Findings on the relationship between the dose of running and the risk of all-cause mortality were available in five publications from three cohort studies (online supplementary table 2).[18 30 31 45 46] Analyses of dose–response relationships using the data from the Aerobics Center Longitudinal Study were conducted by Lee *et al*.[30 46] The study of Lee *et al*[30] includes a more detailed classification of weekly duration, weekly frequency and total volume of running, but in this study they did not analyse the relationship between running pace and mortality risk as they did in their earlier study.[46] Analyses of dose–response relationships from the Copenhagen City Heart Study data were conducted by Schnohr *et al*.[31 45] The later study by Schnohr *et al*[31] presented a more detailed analysis. Furthermore, findings on the relationship between the dose of running and the risk of cardiovascular mortality were available in three publications from two cohort studies.[18 30 46] The relationship between the dose of running and the risk of cancer mortality was analysed in one study.[50]

The studies by Fries *et al*,[52] Wang *et al*[53] and Schnohr *et al*[56] were conducted using data from shorter follow-ups and with fewer deaths than more recent studies from the respective cohorts.[45 55] Schnohr *et al*[44] was the most recent publication from the Copenhagen City Heart Study reporting the association between running and mortality. However, they included only participants of the third examination (1991–1994), which resulted in a shorter follow-up, a smaller sample size and fewer deaths than in a previous study from the same cohort.[45] Furthermore, in the study of Stamatakis *et al*,[19] a large amount of missing data for the two additional variables included in the model (added on top of the original set of variables used in the Oja *et al*[18] study) resulted in a significantly reduced sample size compared with the original study.[18]

Methodological quality of the included studies

The included studies were given overall scores ranging from four to nine points out of the maximum of nine points on the NOS (online supplementary table 3). Based on the overall scores, one study[55] was classified as being of "fair quality", while all other studies were classified as being of "good quality".

Adjustments for confounding

Models in the Oja *et al*,[18] Stamatakis *et al*,[19] Schnohr *et al*[45] and Wang *et al*[51] studies, satisfied all the requirements for causal effect identification specified in figure 1. The other studies did not adjust for all the variables. For example, Chakravarty *et al*[55] presented HRs adjusted for age, gender and initial disability. Lee *et al*[46] calculated HRs adjusted for age, sex, examination year, smoking status, alcohol consumption and other physical activities except running in one model and HRs adjusted for age, sex, examination year, smoking status, overweight/obesity, parental cardiovascular disease, abnormal electrocardiogram, hypertension, diabetes and hypercholesterolaemia in another.

Results of meta-analyses

Running participation and the risk of all-cause mortality

The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of all-cause mortality of 27% over the follow-up periods (figure 3; HR=0.73; 95% confidence interval (CI) 0.68 to 0.79; $p<0.001$). No significant heterogeneity in the effect sizes was found across the five studies ($I^2=8.54\%$). Similar results were obtained in all four sensitivity analyses (online supplementary figures 1-4).

A subgroup meta-analysis by sex showed similar results to those of the main analysis (online supplementary figures 5 and 6). The analysis for women included HRs from two studies[45 46] and for men from three studies.[45 46 51] The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of all-cause mortality of 34% for women (HR=0.66; 95% CI 0.52 to 0.83; $p<0.001$) and 27% for men (HR=0.73; 95% CI 0.67 to 0.79; $p<0.001$). No significant heterogeneity was found between the effect sizes from different studies ($I^2<0.001\%$ for both analyses).

Running participation and the risk of cardiovascular mortality

The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk

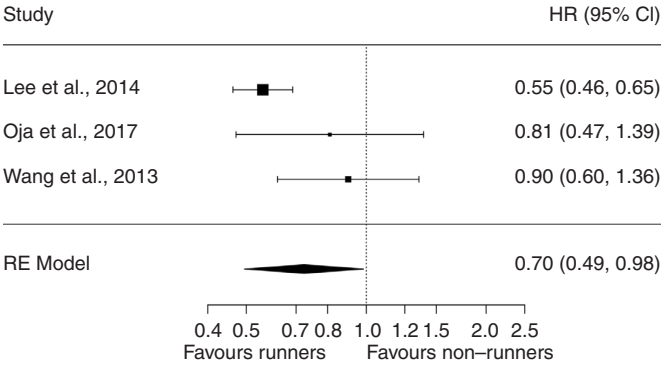

Figure 4 Running participation and cardiovascular mortality risk: a meta-analysis of hazard ratios. HR, adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI, 95% confidence interval for HR; RE Model, pooled effect size from a random-effects meta-analysis model.

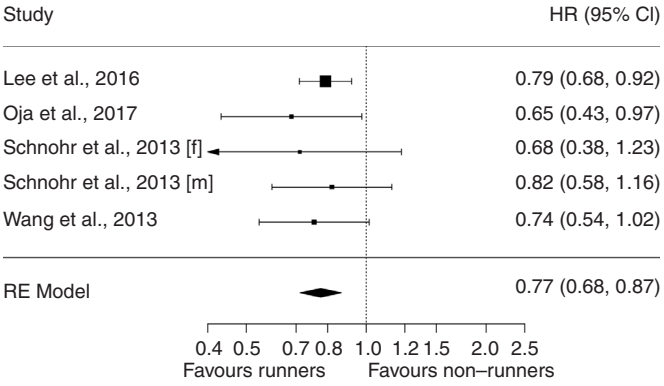

Figure 5 Running participation and cancer mortality risk: a meta-analysis of hazard ratios. HR, adjusted hazard ratio (the list of variables that were adjusted for in each study is available in online supplementary table 1); 95% CI, 95% confidence interval for HR; f, female subsample; m, male subsample; RE Model, pooled effect size from a random-effects meta-analysis model; the meta-analysis included the adjusted HR from the study of Lee *et al*.[50]

of cardiovascular mortality of 30% over the follow-up periods (figure 4; HR=0.70; 95% CI 0.49 to 0.98; p=0.040). Substantial heterogeneity in the effect sizes was found across the three studies (I^2=63.44%). Similar pooled HRs were obtained in both sensitivity analyses (online supplementary figures 7 and 8).

Running participation and the risk of cancer mortality

The random-effects meta-analysis of adjusted HRs showed running participation was associated with a reduction in the risk of cancer mortality of 23% over the follow-up periods (figure 5; HR=0.77; 95% CI 0.68 to 0.87; p<0.001). There was no significant heterogeneity between the effect sizes from the four individual studies (I^2<0.001%).

Dose of running and the risk of mortality

We conducted meta-regression analyses only for the dose–response relationship between running and all-cause mortality (figure 6), because insufficient data from individual studies were available for cardiovascular and cancer mortality as outcome variables. In all four meta-regression analyses, the linear model had the lowest AIC value (12.36, 2.76, 7.41 and 13.95 in the analysis for frequency, duration, pace and volume, respectively) compared with the other models. This suggested that the most parsimonious representation of the dose–response data was provided by a linear fit. However, no significant trends for dose–response were found (p>0.05 for all). There was moderate heterogeneity between the studies included in the meta-regression analyses for frequency, duration and pace of running. The I^2 values were 47.62%, 32.88% and 41.25%, respectively. We found substantial heterogeneity between the studies included in the meta-regression for the total volume of running (I^2=62.57%). The meta-regression coefficients for the linear trend are presented in online supplementary table 4. They can be used to calculate the estimated pooled HR from the three analysed cohorts for a given dose of running. For example, the estimated pooled HR for the total volume of running of 675 MET-min/week (ie, roughly equivalent to the recommended weekly minimum of MVPA[1]) is 0.68 (95% CI 0.51 to 0.78).

DISCUSSION

Key findings

This systematic review synthesised results of 14 studies from six prospective cohorts with a pooled sample of more than 230 000 participants. The main finding is that running participation is associated with 27%, 30% and 23% reduced risk of all-cause, cardiovascular and cancer mortality, respectively. A meta-regression analysis combining results from three cohort studies showed no significant dose–response trends. Even the smallest doses of running that were examined in the available studies (i.e. ≤1 time a week, <50 min a week, <6 mph and <500 MET-min/week) were found to confer significant all-cause mortality benefits. We found no evidence that mortality benefits increase with greater amounts of running.

Comparison with other studies

The systematic review by Oja and colleagues[17] included only one study on running participation and mortality risk. Two articles presented findings of more recent literature searches on health outcomes of running,[22 57] but they were both narrative reviews and did not conduct meta-analyses to quantitatively estimate the pooled associations of running with health outcomes. To our knowledge, the current study is the first meta-analysis of the association between running participation and the risk of mortality.

A meta-analysis by Kelly and colleagues[21] found that 675 MET-min/week of walking and cycling (ie, roughly equivalent to the current WHO MVPA recommendations[1]) is associated with a reduction in the risk of all-cause mortality by 11% (95% CI 4% to 17%) and 10% (95% CI 6% to 13%), respectively. In the sample of three cohort studies included in our meta-regression analysis, we found that the same weekly volume of running conferred significantly greater mortality benefit (32%; 95% CI 22% to 49%). However, the difference between mortality benefits for running, walking and cycling seems to disappear at moderate and high total volumes of these activities. The ratios of metabolic rates of walking, cycling and running to the resting metabolic rate (ie, METs) vary significantly between and within individuals, depending greatly on the pace of activity.[58] We speculate that during short exercise/activity sessions, the intensity (expressed in METs) is, on average, higher for running than for walking and cycling. This would explain the observed difference between mortality benefits,[21] given that greater reductions in mortality risk are associated with participation in vigorous-intensity sports and exercise than with participation in activities of lower intensities.[14] This finding warrants further research,

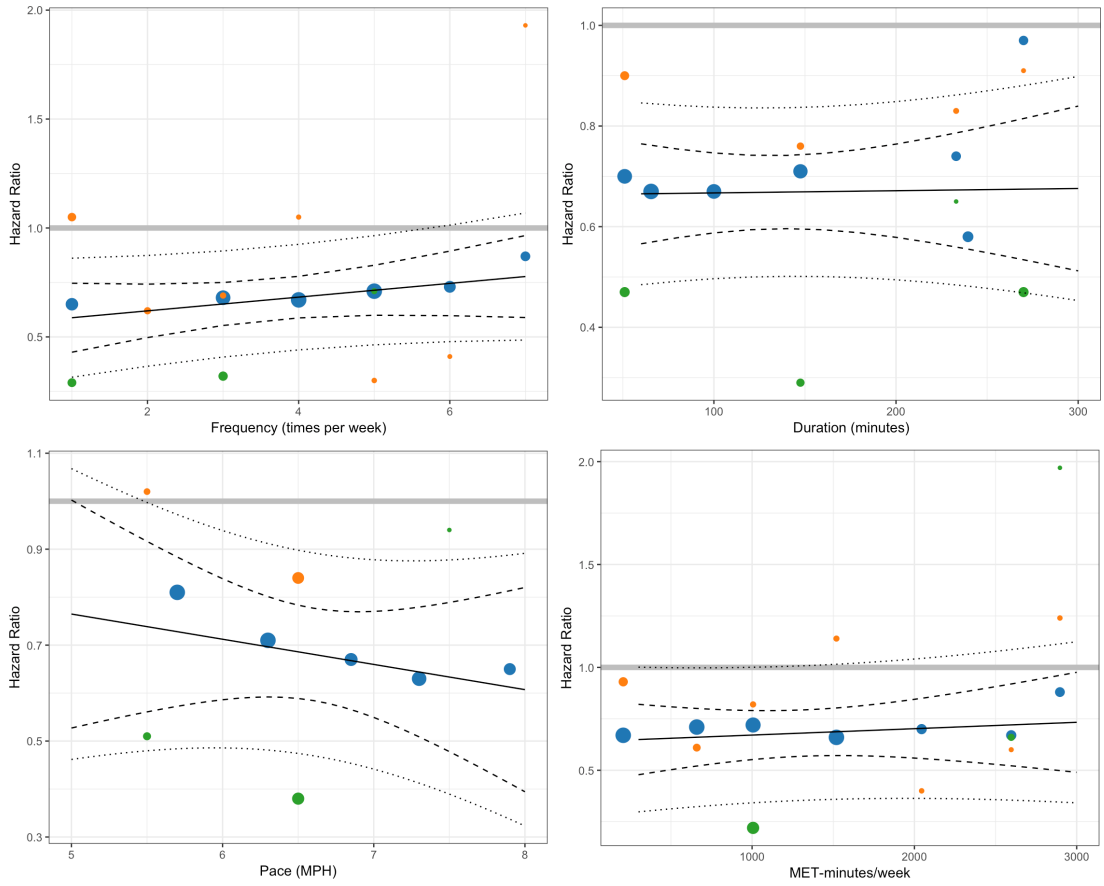

Figure 6 Dose of running and all-cause mortality risk: a meta-regression of hazard ratios. Blue circle, an adjusted hazard ratio (HR) from Lee *et al*[46] for "pace" and Lee *et al*[30] for "frequency","duration" and "volume"; orange circle, HR from Oja *et al*[18] ; green circle, HR from Schnohr *et al*;[31] The size of a circle is proportional to the precision of each study's estimated HR at the specified dose.

to directly compare the associations of running, walking and cycling with the risk of mortality in the same study sample(s).

A recent meta-analysis summarised the results of 35 running interventions (randomised controlled trials) among a total sample of more than 2000 otherwise physically inactive adults.[59] Running roughly 3–4 times and 2–3 hours a week at an intensity of 60–90% of the maximum heart rate for 1 year reduced body fat on average by 2.7%, resting heart rate by 6.7 bpm and triglycerides by 16.9 mg/dL. At the same time, it increased the average maximal oxygen uptake (VO_{2max}) by 7.1 mL/min·kg and high-density lipoprotein cholesterol by 3.3 mg/dL. These findings may explain some of the underlying causal pathways linking running participation and lower mortality risk. In support of this notion, Lee *et al*[46] found no association between running and mortality after adjusting for cardiorespiratory fitness. Although all studies in this review excluded participants with a history of severe illness at baseline and/or adjusted their analysis for health status, the possibility of reverse causation between running participation and health cannot be ruled out. In other words, the association between running and mortality may partially be explained by assuming that sick participants (who are more likely to die) were less likely to participate in running.

Implications for clinicians and policymakers

Some clinicians and public health stakeholders may have been discouraged from promoting running as a part of "lifestyle medicine" among their patients and communities, because vigorous exertion has been linked with sudden cardiac death.[60] Our results provide meta-analytic evidence that, in the general population, the mortality benefit of running outweighs the risk. Previous studies have suggested that this also holds true for some clinical populations.[22 57] However, running might not be a suitable activity for all clinical populations, and a clinician may need to make an informed decision about whether or not to prescribe it on a case-by-case basis. Furthermore, participation in running is also associated with an increased injury risk, and the risk increases with increasing daily duration of the activity.[61] If there is an increased risk of running-related overuse injuries,[62] clinicians may consider recommending walking or a lower dose of running. Our findings support such a recommendation by highlighting the probable mortality benefits of low running doses.

The WHO guidelines and national physical activity recommendations in many countries (including the UK) suggest that adults should take part in at least 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity a week.[1 3] Seventy-five minutes a week of physical activity at the lower threshold for vigorous-intensity (ie, 6 METs) is equal to 450 MET-min/week. Dose–response analyses from both the Aerobics Center Longitudinal Study[30] and the Health Survey for England/Scottish Health Survey[18] showed that even <506 MET-min/week of running are associated with a significant mortality benefit. These findings support the physical activity recommendation. However, >80% of runners seem to run at the pace faster than 6 mph,[46] which is associated with an energy cost of >9.8 METs.[58] This means that many runners could achieve mortality benefits with <50 min a week—that is, in 25 min less than the recommended minimum amount of vigorous-intensity physical activity. This may be encouraging for people who struggle to find the time to exercise, given

that a perceived lack of time has been consistently identified as a key barrier to physical activity participation.[63] Furthermore, the national physical activity recommendations in many countries suggest that more physical activity may confer additional health benefits, often referring to ≥300 min/week of moderate-intensity or ≥150 min/week of vigorous-intensity physical activity.[3] In terms of running behaviour and mortality risk, the results of our dose–response analysis do not support this recommendation.

Strengths and limitations of the review and included studies

The key strength of this study was the rigorous methodological protocol, following PRISMA guidelines for systematic reviews.[41] We searched for eligible publications in a large number of bibliographic databases using broad search terms, which ensured that relevant studies were unlikely to be missed. Additionally, we contacted authors of four included studies[18 45 54 55] in an attempt to obtain unpublished data, and we obtained additional data from one study,[18] which improved the comprehensiveness of our analyses. A limitation of this review is that, owing to the small number of included studies, we could not assess publication bias. Moreover, one of the included studies[54] reported a non-significant association between running participation and the risk of all-cause mortality, but it did not present results suitable for our meta-analysis. It might, therefore, be that the pooled HR for the association between running and mortality is somewhat overestimated.

All included studies were of good methodological quality, except for one study that was of fair quality. Despite their high scores on the methodological quality checklist, the studies had some limitations.

First, although the analyses in all studies were adjusted for a range of variables, their results might have been affected by residual confounding. For example, one study[55] did not adjust for physical activities other than running. Higher physical activity levels are associated with a lower risk of mortality.[15] Not adjusting for this variable might have led to an incorrect estimation of the effects of running—that is, an overestimation, if physical activity other than running was higher among runners than among non-runners, or an underestimation, if physical activity other than running was higher among non-runners than among runners. It is worth noting that Chakravarty *et al*[55] considered aerobic exercise as a covariate, but they decided not to include it in the final model, because it did not significantly alter the results. Only four studies[18 19 45 51] satisfied all the requirements for causal effect identification specified in figure 1. However, it is possible that some causal relationships are in the opposite direction than those assumed in the DAG in figure 1. According to a less 'conservative' DAG (online supplementary figure 9), it would only be necessary to adjust for sociodemographic factors, unhealthy lifestyle and health status. According to this 'less conservative' DAG, further adjustments for either adiposity or physical activity other than running would lead to overadjustment.

Second, the criteria for excluding participants in the included studies were usually limited to a history of cardiovascular disease or cancer. Other diseases and debilitating conditions might prevent people from running while at the same time increasing their risk of dying prematurely.

Third, results of some individual studies might have been affected by selection bias. For example, in one study,[55] the exposure group and the controls were not drawn from the same source, which was reflected in significant baseline differences between the groups. However, the exclusion of this study from the meta-analysis for all-cause mortality resulted in no significant change in the pooled HR. In the dose–response analysis from another study,[31] those included in the reference group were defined as "sedentary non-runners". This might have led to an overestimation of mortality benefits of running, as it is likely that lower mortality rates in the exposure group were partially attributable to physical activity other than running. Owing to the small number of studies that reported dose–response relationships, we could not conduct a sensitivity analysis by excluding this study.

Fourth, although it generally seems that running is a relatively stable habit,[45] individuals may change their running behaviour over the years of follow-up. Only two included studies examined the association between persistence in running behaviour over time and mortality.[46 56]

Fifth, although distance is a potentially useful measure of running dose, it was assessed in one cohort study only.[46]

Sixth, the included studies used self-reports to collect data on running participation. Potential problems with the validity and reliability of such self-reported data[64] might have resulted in attenuated associations between running participation and mortality. It is reasonable to assume that the shape of the observed dose–response curves might have been affected by such limitations of the measurement. Additionally, the questions about running varied across the cohorts, which might have reduced the between-study comparability of exposure data.

Seventh, in the meta-analyses, we could not account for the fact that the weekly frequency, weekly duration and pace of running were probably co-dependent. A future meta-analysis of individual-level data would be needed to deal with these concerns.[65]

Finally, the number of participants in the included studies and, consequently, the precision of estimates, tended to be lower for higher doses of running. Although our meta-regression accounted for the varying precision of estimates across doses, a larger number of participants with high doses of running would have improved the pooled estimates.

Conclusions and recommendations for future research

Running participation is associated with a significantly lower risk of all-cause, cardiovascular and cancer mortality, compared with no running. Any amount of running, even just once a week, is better than no running, while higher doses of running may not necessarily be associated with greater mortality benefits. Increased rates of participation in running, regardless of its dose, would probably lead to substantial improvements in population health and longevity.

More studies are needed to examine how sustained running behaviour, rather than sporadic participation, is associated with mortality risk. Future studies should also consider

What is already known?

- It is unclear how running participation and the dose of running are associated with the risk of all-cause, cardiovascular and cancer mortality.

What are the new findings?

- Running participation is associated with 27%, 30% and 23% reduced risk of all-cause, cardiovascular and cancer mortality, respectively.
- Significant reductions in mortality risk can be expected for any dose of running, even just once a week or 50 min a week.
- We found no evidence that mortality benefits increase with higher amounts of running.

assessing running habits using activity trackers, as these devices may provide more detailed and accurate insights into running behaviour.

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REFERENCES

1 World Health Organization. *Global recommendations on physical activity for health*. Geneva, CH: World Health Organization, 2010.
2 Oja P, Titze S. Physical activity recommendations for public health: development and policy context. *EPMA J* 2011;2:253–9.
3 Kahlmeier S, Wijnhoven TMA, Alpiger P, *et al*. National physical activity recommendations: systematic overview and analysis of the situation in European countries. *BMC Public Health* 2015;15:133.
4 US Department of Health and Human Services. *Physical activity guidelines for Americans*. 2nd edn. Washington, DC: US Department of Health and Human Services, 2018.
5 Chief Medical Office (CMO). *Physical activity guidelines for adults (19-64 years)*. London: Department of Health and Social Care, Government of the United Kingdom, 2011.
6 Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. *J Sci Med Sport* 2004;7(1 Suppl):6–19.
7 Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *Can Med Assoc J* 2006;174:801–9.
8 Reiner M, Niermann C, Jekauc D, *et al*. Long-term health benefits of physical activity--a systematic review of longitudinal studies. *BMC Public Health* 2013;13:813.
9 Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol* 2017;32:541–56.
10 St George A, Kite J, Hector D, *et al*. *Beyond overweight and obesity – HEAL targets for overweight and obesity and the six HEAL objectives: a rapid review of the evidence*. Sydney: NSW Ministry of Health, 2014.
11 Nocon M, Hiemann T, Müller-Riemenschneider F, *et al*. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil* 2008;15:239–46.
12 Diep L, Kwagyan J, Kurantsin-Mills J, *et al*. Association of physical activity level and stroke outcomes in men and women: a meta-analysis. *J Womens Health* 2010;19:1815–22.
13 O'Rorke MA, Cantwell MM, Cardwell CR, *et al*. Can physical activity modulate pancreatic cancer risk? A systematic review and meta-analysis. *Int J Cancer* 2010;126:2957–68.
14 Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose–response meta-analysis of cohort studies. *Int J Epidemiol* 2011;40:1382–400.
15 Lee I-M, 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.
16 de Rezende LFM, de Sá TH, Markozannes G, *et al*. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. *Br J Sports Med* 2018;52:826–33.
17 Oja P, Titze S, Kokko S, *et al*. Health benefits of different sport disciplines for adults: systematic review of observational and intervention studies with meta-analysis. *Br J Sports Med* 2015;49:434–40.
18 Oja P, Kelly P, Pedisic Z, *et al*. Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults. *Br J Sports Med* 2017;51:812–7.
19 Stamatakis E, Kelly P, Titze S, *et al*. The associations between participation in certain sports and lower mortality are not explained by affluence and other socioeconomic factors. *Br J Sports Med* 2017;51:1514–5.
20 Oja P, Titze S, Bauman A, *et al*. Health benefits of cycling: a systematic review. *Scand J Med Sci Sports* 2011;21:496–509.
21 Kelly P, Kahlmeier S, Götschi T, *et al*. Systematic review and meta-analysis of reduction in all-cause mortality from walking and cycling and shape of dose response relationship. *Int J Behav Nutr Phys Act* 2014;11:132.
22 Lavie CJ, Lee D-C, Sui X, *et al*. Effects of running on chronic diseases and cardiovascular and all-cause mortality. *Mayo Clin Proc* 2015;90:1541–52.
23 Krustrup P, Krustrup BR. Football is medicine: it is time for patients to play! *Br J Sports Med* 2018;52:1412–4.
24 Oja P, Kelly P, Murtagh EM, *et al*. Effects of frequency, intensity, duration and volume of walking interventions on CVD risk factors: a systematic review and meta-regression analysis of randomised controlled trials among inactive healthy adults. *Br J Sports Med* 2018;52:769–75.
25 Stamatakis E, Chaudhury M. Temporal trends in adults' sports participation patterns in England between 1997 and 2006: the health survey for England. *Br J Sports Med* 2008;42:601–8.
26 Eime RM, Harvey JT, Charity MJ, *et al*. The contribution of sport participation to overall health enhancing physical activity levels in Australia: a population-based study. *BMC Public Health* 2015;15:806.
27 National Sporting Goods Association Research Department. *Sports participation: 2017 edition (sport)*. Mount Prospect, IL: National Sporting Goods Association, 2017.
28 Physical Activity Council. *2018 participation report: the Physical Activity Council's annual study tracking sports, fitness, and recreation participation in the US*. Jupiter, FL: Physical Activity Council, 2018.
29 Reece LJ, Quirk H, Wellington C, *et al*. Bright spots, physical activity investments that work: Parkrun; a global initiative striving for healthier and happier communities. *Br J Sports Med* 2019;53:326–7.
30 Lee D-C, Lavie CJ, Sui X, *et al*. Running and mortality: is more actually worse? *Mayo Clin Proc* 2016;91:534–6.
31 Schnohr P, O'Keefe JH, Marott JL, *et al*. Dose of jogging and long-term mortality: the Copenhagen City heart study. *J Am Coll Cardiol* 2015;65:411–9.
32 Schnohr P. Physical activity in leisure time: impact on mortality. risks and benefits. *Dan Med Bull* 2009;56:40–71.
33 O'Keefe JH, Patil HR, Lavie CJ, *et al*. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clin Proc* 2012;87:587–95.
34 Andersen LB. Light and moderate joggers do not have lower mortality rates than strenuous joggers. *J Am Coll Cardiol* 2015;65:2670–1.
35 Burtscher M, Pesta D. Absolute or relative jogging PACE: what makes the difference? *J Am Coll Cardiol* 2015;65:2671–2.
36 Charansonney OL, Cohen-Solal A. Sex, jogging, and mortality: the Copenhagen City heart study. *J Am Coll Cardiol* 2015;65:2672.
37 Maessen MFH, Hopman MTE, Verbeek ALM, *et al*. Dose of jogging: mortality versus longevity. *J Am Coll Cardiol* 2015;65:2672–3.
38 Sanchis-Gomar F, Pareja-Galeano H, Santos-Lozano A, *et al*. Strenuous exercise worse than sedentarism? *J Am Coll Cardiol* 2015;65:2673–4.
39 Schnohr P, Marott JL, O'Keefe JH. Reply: exercise and mortality reduction: recurring reverse J- or U-curves. *J Am Coll Cardiol* 2015;65:2674–6.
40 Temporelli PL. Jogging and mortality: is there a U-shaped curve? *J Cardiovasc Med* 2017;18:e177–9.
41 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
42 Wells GA, Shea B, O'Connel D, *et al*. *The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa, ON: Ottawa Hospital Research Institute, 2011.
43 Textor J. *Drawing and analyzing causal DAGs with DAGitty*. Leeds: Institute of Genetics, Healthand Therapeutics at Leeds University, 2015.
44 Schnohr P, O'Keefe JH, Holtermann A, *et al*. Various leisure-time physical activities associated with widely divergent life expectancies: the Copenhagen City Heart Study. *Mayo Clin Proc* 2018;93:1775–85.
45 Schnohr P, Marott JL, Lange P, *et al*. Longevity in male and female joggers: the Copenhagen City Heart Study. *Am J Epidemiol* 2013;177:683–9.
46 Lee D-C, Pate RR, Lavie CJ, *et al*. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol* 2014;64:472–81.
47 Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions, version 5.1.0*. The Cochrane Collaboration, 2011. Available: https://handbook-5-1.cochrane.org/
48 Egger M, Smith GD, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
49 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010;36:1–48.
50 Lee D-C, Lavie CJ, Church TS, *et al*. Leisure-Time running and all-cause cancer mortality. *Med Sci Sports Exerc* 2016;48:514.
51 Wang N, Zhang X, Xiang Y-B, *et al*. Associations of tai chi, walking, and jogging with mortality in Chinese men. *Am J Epidemiol* 2013;178:791–6.
52 Fries JF, Singh G, Morfeld D, *et al*. Running and the development of disability with age. *Ann Intern Med* 1994;121:502–9.
53 Wang BWE, Ramey DR, Schettler JD, *et al*. Postponed development of disability in elderly runners: a 13-year longitudinal study. *Arch Intern Med* 2002;162:2285–94.

54 Loprinzi PD. Dose-response association of moderate-to-vigorous physical activity with cardiovascular biomarkers and all-cause mortality: considerations by individual sports, exercise and recreational physical activities. *Prev Med* 2015;81:73–7.
55 Chakravarty EF, Hubert HB, Lingala VB, *et al*. Reduced disability and mortality among aging runners: a 21-year longitudinal study. *Arch Intern Med* 2008;168:1638–46.
56 Schnohr P, Parner J, Lange P. Mortality in joggers: population based study of 4658 men. *BMJ* 2000;321:602–3.
57 Lee D-C, Brellenthin AG, Thompson PD, *et al*. Running as a key lifestyle medicine for longevity. *Prog Cardiovasc Dis* 2017;60:45–55.
58 Ainsworth BE, Haskell WL, Herrmann SD, *et al*. Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;2011:1575–81.
59 Hespanhol Junior LC, Pillay JD, van Mechelen W, *et al*. Meta-analyses of the effects of habitual running on indices of health in physically inactive adults. *Sports Med* 2015;45:1455–68.
60 Marijon E, Tafflet M, Celermajer DS, *et al*. Sports-related sudden death in the general population. *Circulation* 2011;124:672–81.
61 Hootman JM, Macera CA, Ainsworth BE, *et al*. Association among physical activity level, cardiorespiratory fitness, and risk of musculoskeletal injury. *Am J Epidemiol* 2001;154:251–8.
62 Hreljac A. Impact and overuse injuries in runners. *Med Sci Sports Exerc* 2004;36:845–9.
63 Downs DS, Hausenblas HA. Elicitation studies and the theory of planned behavior: a systematic review of exercise beliefs. *Psychol Sport Exerc* 2005;6:1–31.
64 Shephard RJ, Aoyagi Y. Measurement of human energy expenditure, with particular reference to field studies: an historical perspective. *Eur J Appl Physiol* 2012;112:2785–815.
65 Ioannidis J. Next-Generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. *Br J Sports Med* 2017;51:1456–8.