Ekelund, U., Steene-Johannessen, J., Brown, W. J., Fagerland, M. W., Owen, N., Powell, K. E., Bauman, A., Lee, I. (2016). Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *The Lancet*, 388, s. 1302-1310.

Does physical activity attenuate, or even eliminate the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than one million men and women

Ulf Ekelund [1,2], Jostein Steene-Johannessen [1], Wendy J Brown [3], Morten Wang Fagerland [1,4], Neville Owen [5], Kenneth E Powell [6], Adrian Bauman [7], I-Min Lee [8,9]

for The Lancet Physical Activity Series Working Group* and the Lancet Sedentary Behaviour Working Group**

[1] Department of Sport Medicine, Norwegian School of Sport Sciences, Oslo, Norway
[2] MRC Epidemiology Unit, University of Cambridge, Cambridge, UK
[3] Centre for Research on Exercise, Physical Activity and Health, School of Human Movement and Nutrition Sciences, University of Queensland, Australia
[4] Oslo Centre for Biostatistics and Epidemiology Research Support Services Oslo University Hospital Norway
[5]Baker IDI Heart and Diabetes Institute, Melbourne, Australia
[6] Atlanta, GA, USA
[7] School of Public Health, Sydney University, Australia
[8] Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[9] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
*, ** Listed at end of manuscript

Address for correspondence:
Ulf Ekelund
Department of Sports Medicine, Norwegian School of Sports Sciences,
PO Box 4014, Ullevål Stadion, 0806, Oslo, Norway
E-mail: Ulf.ekelund@nih.no
Phone: +4723262239
Word count; 329 (abstract); 3425 (main text)

Abstract

Background

High amounts of sedentary behaviour have been associated with increased risks for several chronic conditions and mortality. However, it is unclear whether physical activity attenuates or even eliminates the detrimental effects of prolonged sitting.

Methods

We included data from 16 studies, of which 14 were identified through a systematic review of six databases from database inception until October 2015 and two were additional unpublished studies where pertinent data were available. All study data were analysed according to a harmonised protocol, which categorized reported daily sitting time and TV-viewing time into four standardised groups each, and physical activity into quartiles. We then combined data across all studies (N=1,005,791) to analyse the joint and stratified associations of daily sitting time and physical activity with all-cause mortality, and estimated summary hazard ratios using Cox regression. We repeated these analyses using TV-viewing time instead of daily sitting time.

Findings

Daily sitting time was not associated with higher all-cause mortality rates among those in the most active quartile. Compared with the referent (<4 h of sitting per day and highest quartile of physical activity [>35.5 MET-hour/week]), there was no increased risk of dying during follow up in those who sat for more than 8h/day but who also reported >35.5 MET-hour/week of activity (HR=1.04; 95% CI, 0.99, 1.10). In contrast, those who sat the least (<4 h/day) and were in the lowest (<2.5 MET-hour/week) activity quartile had a significantly increased risk of dying during follow-up (HR=1.27, 95% CI, 1.22, 1.31). For TV viewing time, >3 hours/day was associated with higher mortality rates regardless of physical activity, except in the most active quartile, where mortality rates were significantly higher only in the >5 hours/day group.

Interpretation

High levels of moderate intensity physical activity (i.e. about 60 to 75 minutes per day) appear to eliminate the increased risk of death associated with high sitting time. However, this high activity level attenuates, but does not eliminate the increased risk associated with high TV viewing time.

Funding

None

INTRODUCTION

In a seminal 1953 Lancet paper, Morris and colleagues demonstrated an increased risk of coronary heart disease (CHD) in London bus drivers compared with conductors.[1] Since then, numerous observational studies have shown that lack of physical activity is a major risk factor for morbidity and premature mortality.[2-4] Indeed, recent estimates indicate that not meeting physical activity recommendations is responsible for more than 5 million deaths globally each year. [4]

Today, sedentary behaviours are highly prevalent and data from adults in high-income countries suggest the majority of time awake is spent sedentary. [5,6] Further, high amounts of sedentary behaviour, usually assessed as daily sitting time or time spent viewing TV, have been associated with increased risks for several chronic conditions and mortality. [7-9] A crucial question is: if one is active enough, will this attenuate or even eliminate the detrimental association of daily sitting time with mortality? [8,9]

We therefore conducted a systematic review and meta-analysis to examine the joint and stratified associations of sedentary behaviour and physical activity with all-cause mortality, using data from studies which were analysed according to a standard protocol.

METHODS

Data Sources, Literature Search and Study Selection

Following PRISMA guidelines,[10] we identified 16 published [11-26] studies through a systematic review of six databases (PubMed, PsycINFO, EMBASE, Web of Science, Sport Discus and Scopus) from data base inception until October 30th 2014, updating the search up to October 10th 2015 (a detailed search description is provided in the appendix). We also obtained data from two additional studies where the pertinent data were available but not published. [27,28] Authors/principal investigators were contacted and asked about their willingness to participate in a harmonised meta-analysis. One study[12] did not respond to our request to participate and one additional study was excluded as it measured physical activity by accelerometry, which could not be harmonised with self-report data. For one other study, the Women's Health Initiative Observational Study (WHIOS)[26] investigators did not agree to participate but data for a shorter follow-up were publicly available.[29] Thus, individual data from 16 studies were analysed according to a pre-defined protocol and included in the harmonised meta-analyses. We included English-language, prospective cohort studies that had individual level exposure and outcome data, provided data on both daily sitting or TV-viewing time and physical activity, and reported effect estimates (hazard ratios, odds ratios or relative risks with 95% CIs) for all-cause, cardio-vascular disease (CVD), breast, colon and colorectal cancer mortality. This review protocol is registered with the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015023870).

Data extraction

One author (JSJ) extracted, and all other authors confirmed, the following information from each eligible study: name of the first author, study location, source and number of participants, age, number of men and women, years of follow-up, number of deaths from all-causes, cancer, and cardio-vascular disease (CVD) and methods of ascertainment, assessment details for physical activity and sitting time, and covariates included in adjusted models (Table 1).

Data Harmonisation

To reduce heterogeneity we first reviewed the questionnaires used to assess sedentary behaviour and physical activity, then determined whether it was possible to define these exposures using the same metric across all studies. All but two studies[13,14] asked about sitting time using an open-ended format or categories that could be collapsed into four or five common groups (Supplementary Table 1). Of the remaining two studies, one[13] used five categories (almost none, 1/4 of the time, 1/2 of the

time, 3/4 of the time and almost all) that were collapsed into four by combining the two highest categories, while another used only three categories of sitting time[14] (see Appendix). Data on TV-time from six studies [16,20,22-25] could be combined into four common groups (Supplementary Table 2). Data from each study were reanalysed using predefined categories of sitting time in four groups (0-<4h/day, 4-<6 h/day, 6-8h/day, >8h/day) and TV-viewing time in four groups (<1 h/day, 1-2 h/day, 3-4 h/day and >5 h/day).

Physical activity was assessed by different validated self-report questionnaires in all studies. To reduce heterogeneity in the assessment of physical activity, we only included information on walking and leisure time and recreational physical activities (including exercise and sports) as this information was available from all studies (Supplementary table 1). We asked each contributing study to recalculate their estimated physical activity energy expenditure by multiplying the reported duration by the intensity, and expressing physical activity in MET-hours per week (MET-h/week). We used the same MET-values for intensity as in the original publications. For those studies that simply reported duration of specific physical activities [14,19,22] we assigned the following conventionally accepted intensity levels: walking, 3.3 METs; moderate intensity activity, 4 METs; vigorous intensity activity, 7 METs; and strenuous sports, 7.2 METs. [30] Therefore, our estimate of physical activity reflects participation in moderate and vigorous intensity activity (MVPA). Due to the design of the questions used for assessing physical activity it was not possible to calculate MET-h/week in its continuous form in four studies. [14,17,22,27] In these studies, we asked contributing studies to calculate MET-h/week in three [14] or four [17,22,27] categories which were assumed to reflect the quartiles derived from the other studies (Supplementary Table 2).

The median MET-h/week across studies for the upper boundary for the 1st (lowest) quartile was 2.5 MET-h/week (equivalent to about 5 minutes of moderate intensity activity per day). Corresponding values for the 2nd and 3rd quartiles were 16 MET-h/week (about 25-35 min of moderate intensity activity per day) and 30 MET-h/week (about 50-65 min of moderate intensity activity per day), and the lower boundary for the 4th (top) quartile was 35.5 MET-h/week (about 60-75 min of moderate intensity activity per day) (Supplementary Table 2). Examples of moderate intensity activities are brisk walking at 5.6 km/h, and bicycling for pleasure at 16 km/h. [30]

Quality assessment

Using the study quality checklist proposed by Kmet et al [31] two authors (JSJ and UE) independently assessed the studies and any disagreements were resolved by consensus. Studies were scored (0- No, 1- Partial, 2-Yes) on 14 criteria. The sum of all scores was then divided by the highest possible score (28), giving quality scores ranging from 0 (worst) to 1 (best).

Data analyses and syntheses

Principal authors/investigators for all studies except one reanalysed their data according to a harmonised protocol using minimally adjusted models (adjusted for sex and age) and in models that adjusted for the same covariates as in their original publications. For the WHIOS study we used publicly available individual level data to perform the analyses. [29]

All studies except for three [17-19] either excluded all participants with major chronic diseases at baseline or excluded deaths occurring within at least one year in sensitivity analyses. Two of the remaining three studies, [18,19] which included older participants, provided analyses for this meta-analysis in which deaths within the first two years were excluded. The remaining study [17], which had a short follow-up period (mean, 2.8 years), analysed their data excluding those with baseline cardiovascular disease (CVD), diabetes and cancer. Thus, all studies in this meta-analysis included, for the most part, apparently healthy participants at baseline.

We first performed joint analyses of the associations of daily sitting time, physical activity and all-cause mortality, to directly compare groups with different amounts of sitting time and physical activity against those who sat the least (<4 h/day; arbitrarily chosen based on questionnaire categories) and also had the most physical activity (top quartile >35.5 MET-h/week) (i.e., referent). Effect estimates were calculated using Cox regression analyses and presented as hazard ratios (HRs) with their associated 95% confidence intervals. We estimated summary HRs across studies with a fixed effect inverse variance method. [32] We then repeated these analyses, but used TV-viewing time instead of sitting time.

Next, in stratified analyses (stratification by physical activity), we assessed whether the dose-response relationship between sitting and mortality differed among persons with different activity levels, to address whether physical activity modified the detrimental effect of prolonged sitting. That is, we separately investigated the relationship between sitting time and all-cause mortality rates for each quartile of physical activity, with those sitting the least serving as referent. We then repeated these analyses using TV time instead.

In secondary analyses we repeated all analyses but used CVD and cancer mortality as the outcomes. We also tested whether the HRs differed between extreme groups (i.e. the group who sat the most and also had the most activity, compared with the group who sat the least and were least active). We performed sensitivity analyses and separated the highest category for sedentary time into two (8-10 h/day and >10 h/day) and repeated the analyses; we estimated the impact of each individual study by repeating the meta-analysis for all-cause mortality, excluding one study at a time, and we also examined publication bias[33] and heterogeneity; these findings are reported in the Appendix. Finally, we reanalysed our data and estimated summary HRs across studies with random effect models and the main findings were unchanged (data not shown). All meta-analyses were performed using Matlab (R2014a, The Mathworks, Inc.).

Role of the Funding Source
The funders of each study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. UE, JSJ and MWF had full access to the harmonised data provided by study partners.

RESULTS

Study Selection and characteristics

The literature search, study selection and reasons for study exclusion are summarised in Figure 1. In total, 8,381 articles were identified by searching six different databases. Ninety-eight papers were retrieved for full text review, of which 16 were identified as eligible for inclusion. Quality scores were high, exceeding 0.85 in all studies (Table 1).

Thirteen studies [13-22,27-29] including 1,005,791 individuals who were followed between 2 and 14 years, during which 84,609 (8.4%) died, were included in the meta-analysis of the associations of sitting time and physical activity with all-cause mortality. Nine studies [13-16,20-22,28-29] also had data on CVD mortality and eight [13-16,20,22,28-29] on cancer mortality. Three [16,20,22] of the 13 studies also had data on TV-viewing time, and with three additional studies [23-25], contributed to the meta-analysis of the joint associations of TV-viewing time and physical activity with all-cause mortality (N=465,450; 43,740 deaths).

Joint association analyses

The summary HRs for the joint associations of sitting time and physical activity with all-cause mortality are shown in Figure 2a and supplementary Table 4. A clear dose-response association was observed, with an almost curvilinear augmented risk for all-cause mortality with increased sitting

time in combination with lower levels of activity. Compared with the referent group (i.e. those sitting <4 h/day and in the most active quartile), mortality rates during follow up were 12 to 59% higher in the two lowest quartiles of physical activity, even when sitting time was lowest.

However, in the third quartile of physical activity (i.e., the second most active group), only those sitting 4 or more h/day had higher mortality rates. Among the most active, there was no significant relation between amount of sitting and mortality rates, suggesting that high physical activity eliminated the increased risk of prolonged sitting on mortality. Indeed, this observation was confirmed in sensitivity analyses using five categories for sitting time (Supplementary Table 5). Since we did not have access to individual level data from all studies, we estimated whether hazard ratios between groups differed significantly, as described in the appendix. Those in the most active quartile, but who also reported the most sitting (>8 h/day), had a significantly lower risk ($p<0.0001$) of dying during follow-up (HR=1.04, 95%CI, 0.99, 1.10) than the least active who also sat the least (<4 h/day) (HR=1.27, 95% CI, 1.22, 1.30).

We then repeated these analyses with TV-viewing time instead of sitting time. Largely parallel findings were observed, although the effect estimates were less precise, possibly because of smaller sample sizes (Figure 2b and Supplementary Table 4). In those who watched TV >5h/day, the hazard for all-cause mortality was markedly increased by between 16% and 93% across activity quartiles. Among the most active quartile, only this amount of TV-viewing time (>5 h/day) was significantly associated with an increased hazard (HR=1.16, 95% CI, 1.05, 1.28). In comparison, persons in the least active quartile who watched only <1 h/day of TV experienced a statistically significantly higher risk (HR 1.32, 95% CI, 1.20, 1.46; [p=0.007]).

In a subsample of studies with available data, we examined CVD and cancer mortality. The results for CVD mortality were similar to those observed for all-cause mortality (Supplementary Table 6). For cancer mortality, increased hazards of between 12% and 22% with more sitting time were observed only for persons in the least active quartile (Supplementary Table 7). Using TV-viewing time instead of sitting time did not materially change the results for CVD and cancer mortality (Supplementary Table 8 and 9).

Stratified analyses

The associations between sitting time and all-cause mortality are shown separately for individuals in four levels (quartiles) of physical activity in Table 2. Among the three least active quartiles, increased all-cause mortality rates were observed with increased sitting time, compared with the referent categories (<4 h/day). The hazard of sitting >8 h/day was much higher in the least active quartile (27%) than in the second (12%) and third (10%) activity quartiles. In the most active quartile, there was no statistically significant association between daily sitting time and all-cause mortality.
We then analysed TV-viewing time instead of sitting time, using as referent those who watched TV for <1 h/day (Table 3). TV viewing for up to 2 h/day did not significantly increase the risk of mortality during follow-up in any activity strata; however, three or more h/day of TV-viewing time was associated with increased risk among all, except for the most active quartile. Among this group, >5 h/day of TV viewing was associated with an increased hazard (HR=1.15; 95% CI, 1.05, 1.27) for all-cause mortality.

DISCUSSION

These analyses, including data from more than 1 million individuals, indicate that high levels of physical activity, equivalent to 60 to 75 minutes of moderate intensity physical activity per day, appear to eliminate the increased mortality risks associated with high total sitting time. Indeed, those in the highest physical activity quartile (~60-75 minutes/day) who sat for more than 8 hours daily had a significantly lower risk of dying during follow up than those who sat for less than four

hours in the least active quartile (~5 minutes/day). In the middle two quartiles of physical activity (which encompass current physical activity guideline levels[34]), the mortality risks associated with more sitting time were attenuated compared with those seen in the least active quartile. For TV viewing time, the results were similar, except that high physical activity attenuated, but did not eliminate the risk, in those viewing TV ≥5 h/day.

Our harmonised meta-analytical approach allowed us to examine associations among sedentary behaviours, physical activity and all-cause mortality with greater precision and a more uniform classification of sedentary behaviour and physical activity than has previously been possible. The results suggest that high levels of physical activity attenuate the harmful effects of prolonged sitting time. Across sitting time categories, all-cause mortality rates were considerably reduced at higher levels of physical activity, and eliminated in those who were the most active. These results were consistent in joint and stratified analyses and in analyses of CVD and cancer mortality. By combining the results of a larger number of studies, and using a harmonised approach to reduce heterogeneity in the exposure variables, we were able to reduce statistical uncertainty in the results and also estimate levels of sitting time and physical activity for informing public health policy.
The amount of physical activity in the top quartile equated to approximately 60 to 75 minutes of moderate intensity activity per day or more. This is beyond the basic level of most physical activity recommendations for public health [34, 35] but only slightly greater than the upper amount recommended in the Australian Physical Activity Guidelines [36] and the level recommended by the US guidelines [35] for "even greater health benefits" (one hour a day of moderate intensity activity). Notably, 60 to 75 minutes of moderate intensity activity is congruent with the level of physical activity showing maximum mortality benefit in a recent large meta-analysis.[37] In the present study, this amount of activity (reported by one quarter of the participants), was required to eliminate the increased hazard associated with sitting for more than 8 hours per day. However, even those in the second quartile of physical activity (~25-35 min of moderate intensity activity per day, which is congruent with the basic level recommended), there were smaller increases in mortality risks associated with high sitting time than were seen in the least active group (~5 minutes per day), even though the risks were not completely eliminated. In comparison with other risk factors for poor health, the increased mortality risk (58%) in those who sat for more than 8 hours per day and were also least active, is similar to that of smoking [39] and obesity. [40]

If daily sitting time and TV viewing time capture similar aspects of sedentary behaviour, we expected broadly similar magnitudes of associations from both exposures. Yet the effect of TV viewing on all-cause mortality appeared to be stronger in magnitude. This difference is congruent with previous observations [20] and may be partly due to differences in the accuracy of reporting these behaviours. However, other explanations are also plausible. TV viewing typically occurs in the evenings (at least, for the generation represented in the included studies), usually after dinner, and prolonged postprandial sedentary time may be particularly detrimental for glucose and lipid metabolism. [41] It is also plausible that individuals break up their sitting time more frequently during work than when viewing TV, and breaking up sedentary time appears to be beneficial for various cardio-metabolic risk factors. [41] Another explanation for the difference observed could be that TV viewing may be accompanied by snacking behaviours [42] and food advertising on TV may affect eating behaviour. [43] Thus, associated dietary behaviours may explain some of the differences observed.

Our meta-analysis has considerable strengths. Most important, all original study data were reanalysed in a harmonised manner. This approach substantially reduced heterogeneity between studies for measures of sedentary behaviour and physical activity, and allowed direct interpretation of levels of sitting time and physical activity (beyond comparing "high" versus "low"). The large sample size allowed detailed joint analyses of the dose-response associations among sedentary behaviours, physical activity, and mortality, providing precise effect estimates with narrow confidence intervals. We performed sub-group analyses to examine possible bias from any single

study by reanalysing all data, excluding each study one at a time and the results were essentially unchanged (data available on request). Mortality ascertainment varied across studies but all used official national or regional registers, likely to be high or complete. Our observation that physical activity may eliminate the detrimental association between daily sitting time and mortality is biologically plausible. There is evidence that one hour of moderate intensity activity positively influences postprandial lipid metabolism following 8 hours of sitting [44], and that 45 minutes of cycling at moderate intensity following more than 10 hours of sitting has beneficial effects on glucose metabolism in type 2 diabetes.[45]

There also are limitations; first, the majority of studies included participants older than 45 years and all but one study was conducted in the US, western Europe or Australia. Thus, the results may not be generalizable beyond these populations. Second, all except two studies combined data from men and women, which precluded specific analyses. Third, residual confounding may exist. A priori, we required contributing studies to control for the same covariates included in their original publication. However, unmeasured or poorly measured confounders may have distorted our results. Fourth, although we did not find any evidence for publication bias, we cannot rule out that publication bias may exist, due to the low number of studies in some analyses. Fifth, we attempted to minimise bias from reverse causation (i.e., illness causing individuals to become sedentary) by including apparently healthy participants; however, we cannot fully rule this out. Sixth, all studies asked participants to self-report sedentary behaviour and physical activity at one point in time. This increases the chance of random measurement error, which would attenuate true associations.

In conclusion, high levels of moderate intensity physical activity (i.e. about 60 to 75 minutes per day) appear to eliminate the increased risk of death associated with high sitting time. However, this high activity level attenuates, but does not eliminate the increased risk associated with high TV viewing time. If long periods of sitting time each day are unavoidable (e.g. for work or transport), it is important also to be physically active.

Declaration of interest
We declare no competing interests.

Author Contribution
All authors contributed to the design of the study, generated hypotheses, interpreted the data, and wrote and critically reviewed the report. UE wrote the first draft of the report. JSS and UE did the literature search. MWF analysed the data. MWF, JSS and UE had full access to study level data from all contributing studies.

Acknowledgements
Members of The Lancet Physical Activity Series II steering group are; Adrian Bauman, School of Public Health, Sydney University, Australia; Ding Ding, Sydney School of Public Health University of Sydney, Sydney, Australia; Ulf Ekelund, Norwegian School of Sports Sciences, Oslo, Norway and Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK; Gregory Heath, Department of Health & Human Performance, University of Tennessee, Chattanooga, US; Pedro C Hallal, Postgraduate Programme in Epidemiology, Federal University of Pelotas, Pelotas, Brazil; Harold W. Kohl III, University of Texas School of Public Health, Austin, US; I-Min Lee, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA and Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; Kenneth E Powell, Atlanta, GA, US; Michael Pratt, National Center for Chronic Disease Prevention and Health Promotion, Emory University, Atlanta, Georgia, USA; Rodrigo Reis, Pontiff Catholic University of Paraná in Brazil and Federal University of Parana, Parana, Brazil; Jim Sallis, Division of Behavioural Medicine, University of California, San Diego, US

Members of The Lancet Sedentary Working Group are;
Mette Aadahl, Department of Public Health, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; William J. Blot, Department of Medicine, Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; Tien Chey, Sydney School of Public Health, University of Sydney, Sydney Australia; Anusila Deka, Epidemiology Research Program, American Cancer Society, Atlanta, USA; David Dunstan, Baker IDI Heart and Diabetes Institute, Melbourne, Australia; Earl S Ford, Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, USA; Kristine Færch Steno Diabetes Center, Gentofte, Denmark; Manami Inoue Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan; Peter T Katzmarzyk, Pennington Biomedical Research Center, Baton Rouge, USA; Sarah Kozey Keadle, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA; Charles E Matthews, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA; David Martinez, Preventive Medicine and Public Health School of Medicine Universidad Autónoma de Madrid, Spain; Alpa V Patel, Epidemiology Research Program, American Cancer Society, Atlanta, USA; Toby Pavey, School of Human Movement and Nutrition Sciences, The University of Queensland, Brisbane, Australia; Christina Bjørk Petersen, National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; Hidde Van Der Ploeg, Department of Public & Occupational Health, VU University Medical Center Amsterdam, Netherlands; Vegar Rangul, HUNT Research Centre, Faculty of Health Science Nord-Troendelag University College Levanger; Parneet Sethi, Baker IDI Heart and Diabetes Institute, Melbourne, Australia; Erik R. Sund, HUNT Research Centre, Faculty of Health Science Nord-Troendelag University College Levanger; Kate Westgate, MRC Epidemiology Unit, University of Cambridge, Cambridge, UK; Katrien Wijndaele, MRC Epidemiology Unit, University of Cambridge, Cambridge, UK; Song Yi-Park, Cancer Epidemiology Program, University of Hawaii Cancer Center, Honululu, USA;

In addition to data from all the contributing studies, this manuscript was prepared using WHIOS Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the WHIOS or the NHLBI.

Figure Legends

Figure 1. Study selection.

Figure 2. Meta-analyses of the joint associations of sitting time and physical activity with all-cause mortality (Figure 2a; N=1,005,791) and of TV-viewing time and physical activity with all-cause mortality (Figure 2b; N=465,450). The reference categories are the groups with the highest levels of physical activity (>35.5 MET-/week) in combination with <4 h/day of sitting (Figure 2a) or <1h/day of TV-viewing (Figure 2b). The median MET-h/week for the upper boundary for the 1st (lowest) quartile was 2.5 MET-h/week (equivalent to about 5 minutes of moderate intensity activity per day). Corresponding values for the 2nd and 3rd quartiles were 16 MET-h/week (about 25 to 35 min of moderate intensity activity per day) and 30 MET-h/week (about 50 to 65 min of moderate intensity activity per day), and the lower boundary for the 4th (top) quartile was 35.5 MET-h/week (about 60 to 75 min of moderate intensity activity per day).

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Table 1. Characteristics of studies included in the meta-analysis

Author, Year (ref)	Country; Study Name; Participant Characteristics	Years of follow-up	Mortality Outcome(s), No. of Cases	Method of Case Ascertainment	Covariates Adjusted For	Quality
Sitting						
Katzmarzyk et al, 2009 (13)	Canada; Canada Fitness Survey (CFS); 17,013 men and women; 18-90 y	12.9 y (maximum)	All-cause, 1,832; CVD, 759; Cancer, 547	Canadian Mortality Database	Age, sex smoking, alcohol consumption	0.85
Inoue et al, 2008 (14)	Japan; Japan Public Health Center-based Prospective Study; 83, 034 men and women; 45-74 y	8.7 y	All-cause, 4,564; CVD, 974; Cancer, 2,044	Death certificate provided by Ministry of Health, Labour, and Welfare and classified using International Classification of Diseases	Age, sex, geographical area, occupation, history of diabetes, smoking, alcohol consumption, BMI and total energy intake	0.95
Patel et al, 2010 (15)	United States; American Cancer Society Cancer Prevention Study II Nutrition Cohort (CPS-II); 123,216 men and women; 50-74 y	14 y (maximum)	All-cause, 19,230; CVD 6,369; Cancer, 6,989	National Death Index and classified using International Classification of Diseases	Age, sex, race, education, BMI, alcohol consumption, smoking status, marital status, total energy intake and comorbidity	0.95
Matthews et al, 2012 (16)	United States; NIH-AARP Diet and Health Study; 240,814 men and women; 50-71 y	8.5 y	All-cause, 17,044; CVD, 4,684; Cancer, 7,652	Social Security Administration and the National Death Index	Age, sex, race, education, BMI, smoking, and diet	0.95
Van der Ploeg et al, 2012 (17)	Australia; 45 and Up Study; 222,497 men and women; ≥45 y	2.8 y	All-cause, 5,405	New South Wales Registry of Births, Deaths, and Marriages	Age, sex, education, urban/rural residence, BMI, marital status, smoking, self-rated health and receiving help with daily task for long time, illness or disability.	0.95
Pavey et al, 2012 (18)	Australia; The Australian Longitudinal	9 y (maximum)	All-cause, 2,003	Australian National Death Index	Age, education, marital status, area, smoking,	0.90

	Study on Women's Health; 6,656 women; ≥75 y	6 y (median)			alcohol consumption, BMI, number of chronic conditions, self-reported health, assistance with daily tasks	
León-Munoz et al, 2013 (19)	Spain; 2,635, men and women; ≥60 y	2 y	All-cause, 846	National Death Index	Age, sex, education, BMI, smoking, alcohol consumption, weight, BMI, chronic lung disease, ischemic heart disease, stroke, diabetes mellitus, osteomuscular disease, cancer. Morbidity, health-related quality of life, mobility limitations and agility limitations	0.85
Kim et al, 2013 (20)	United States; Multiethnic Cohort Study; 134,596 men and women; 45-75 y	13.7y	All-cause, 19,143; CVD, 6,535; Cancer, 6,697	Death certificate linked to National Death Index and classified using International Classification of Diseases	Age, sex race/ethnicity, education, smoking history, history of diabetes or hypertension, energy intake and alcohol consumption	0.95
Petersen et al, 2014 (21)	Denmark; Danish Health Examination Survey; 71,363 men and women; 18-99 y	5.4 y	All-cause, 1,074; CVD, 308	Danish Civil Registration system	Age, sex, educational level, smoking habits, BMI, alcohol consumption and hypertension	0.95
Matthews et al, 2014 (22)	United States; Southern Community Cohort Study, 63,308 men and women; 40-79 y	6.4 y	All-cause, 5,007; CVD, 1,376; Cancer, 1,227	Social Security Administration and the National Death Index and classified using International Classification of Diseases	Age, sex, source of enrolment, race, education, income, marital status, occupational status, comorbid conditions, alcohol intake, smoking history, BMI, and sleep duration	0.95

Jørgensen et al, 2003 (27)	Denmark; INTER99; 4,513 men and women; 35-66 y	7.5 y	All-cause, 112	Danish registry of causes of death	Age, sex, socio-economic status, smoking, BMI, alcohol, diabetes and hypertension	0.90
Krokstad et al, 2013 (28)	Norway; The Nord-Trøndelag Health Study (HUNT); 40,752 men and women; 19-99 y	18.1 y	All-cause, 5,004; CVD, 1,537; Cancer, 1,536	Norwegian Causes of death Registry and classified using International Classification of Diseases	Age, sex, BMI, smoking, alcohol, blood pressure and medication	0.95
WHIOS (29)*	United States; Women's health Initiative; 92,234 women; 50-79 y	10.2 y	All-cause 10,800; CVD 3,206; Cancer 4,338	Hospital records, autopsy records, death certificates and National Center for Health Statistic`s National Death Index	Age, race/ethnicity, education, marital status, BMI, smoking, alcohol consumption, number of chronic diseases, number of falls in the past year, hormone use, depressed mood, living alone and activities of daily living disability	0.95
TV-viewing						
Dunstan et al, 2010 (23)	Australia; The Australian Diabetes, obesity and Lifestyle Study; 8,800 men and women; ≥25 y	6.6 y	All-cause, 284; CVD, 87 and Cancer,125	Australian National Death Index and classified using International Classification of Diseases	Age, sex, education, BMI, smoking (current/ex-smoker), total energy intake, alcohol, waist circumference, hypertension, total cholesterol, HDL, triglycerides, glucose tolerance and undiagnosed and known diabetes	0.90
Wijndaele et al, 2010 (24)	UK, European Prospective Investigation into cancer and Nutrition Study; 13,197 men and women; 45-79 y	9.5 y	All-cause 1,270; CVD, 323; Cancer, 570	Office of National Statistics (UK) and classified using International Classification of Diseases	Age, sex, education, smoking, alcohol consumption, anti-hypertensive medication, medication for dyslipidemia, baseline history	0.90

					of diabetes, family history of CVD and cancer	
Ford et al, 2012 (25)	United States; National Health and Nutrition Examination Survey; 7,350 men and women; ≥20 y	5.8 y	All-cause, 542	National Death Index and classified using International Classification of Diseases	Age, gender, race education, smoking, Healthy Eating Index score	0.90
Matthews et al, 2012 (16)	United States; NIH-AARP Diet and Health Study; 240,814 men and women; 50-71 y	8.5 y	All-cause, 17,044; CVD, 4,684; Cancer, 7,652	Social Security Administration and the National Death Index	Age, sex, race, education, BMI, smoking, and diet	0.95
Kim et al, 2013 (20)	United States; Multiethnic Cohort Study; 134,596 men and women; 45-75 y	13.7 y	All-cause, 19,143; CVD, 6,535; Cancer, 6,697	Death certificate linked to National Death Index and classified using International Classification of Diseases	Age, sex race/ethnicity, education, smoking history, history of diabetes or hypertension, energy intake and alcohol consumption	0.95
Matthews et al, 2014 (22)	United States; Southern Community Cohort Study; 63,308 men and women; 40-79 y	6.4 y	All-cause, 5,007; CVD, 1,376; Cancer, 1,227	Social Security Administration and the National Death Index and classified using International Classification of Diseases	Age, sex, source of enrolment, race, education, income, marital status, occupational status, comorbid conditions, alcohol consumption, smoking history, BMI, and sleep duration	0.95

BMI, body mass index; CVD, cardiovascular disease; HDL, High density lipoprotein; PAR-Q, Physical Activity Readiness Questionnaire;

*data downloaded from https://biolincc.nhlbi.nih.gov/home/ (Accessed January 7th 2016)

Table 2. Meta-analyses of the associations between sitting time and all-cause mortality (N=1,006,091; 84,659 deaths) stratified by quartiles of physical activity**.** The reference categories are the groups with <4 h/day of sitting for all quartiles of physical activity.

Quartiles of PA * (MET-h/w)	Sitting time (h/day)			
	<4	4-<6	6-8	>8
≤2.5	1 (REF) (N=76,212; 6,646)	1.08 (1.04, 1.12) (N=48,613; 5,224)	1.09 (1.05, 1.14) (N=66,839; 5,820)	1.27 (1.22, 1.32) (N=60,730; 6,018)
16	1 (REF) (N=77,651; 7,221)	1.04 (1.00, 1.07) (N=73,444; 7,873)	1.06 (1.02, 1.10) (N=51,263; 5,322)	1.12 (1.07, 1.17) (N=60,838; 5,012)
30	1 (REF) (N=75,365; 5,387)	1.05 (1.01, 1.10) (N=63,959; 5,489)	1.03 (0.98, 1.08) (N=48,292; 3,504)	1.10 (1.04, 1.16) (N=52,576; 3,487)
>35.5	1 (REF) (N=90,762; 6,208)	1.00 (0.96, 1.04) (N=65,976; 5,268)	1.01 (0.97, 1.06) (N=49,715; 3,565)	1.04 (0.98, 1.10) (N=43,856; 2,717)

*median upper boundary for Q1-3 and lower boundary for Q4 in MET-h/w. The equivalent amount of time spent in moderate intensity activity are; ≈5 min/d (Q1); 25-35 min/d (Q2); 50-65 min/d (Q3) and 60-75 min/d (Q4).

Table 3. Meta-analyses of the associations between TV-viewing time, and all-cause mortality (N=465,450) stratified by quartiles of physical activity**.** The reference categories are the groups with <1h/day of TV-viewing across quartiles of physical activity.

Quartiles of PA * (MET-h/w)	TV-viewing time (h/day)			
	<1	1-2	3-4	≥5
≤2.5	1 (REF) (N=10,609; 1,064)	1.00 (0.94, 1.08) (N=33,411; 3,382)	1.10 (1.02, 1.18) (N=40,688; 4,702)	1.44 (1.34, 1.56) (N=22,779; 3,533)
16	1 (REF) (N=12,280; 984)	1.00 (0.93, 1.08) (N= 45,493; 4,098)	1.08 (1.01, 1.15) (N=51,917; 5,576)	1.29 (1.19, 1.39) (N=21,365; 2,870)
30	1 (REF) (N=11,232; 613)	1.08 (0.98, 1.18) (N=39,807; 2,589)	1.17 (1.07, 1.27) (N=43,699; 3,675)	1.41 (1.28, 1.56) (N=17,563; 1,925)
>35.5	1 (REF) (N= 12,478; 752)	0.96 (0.88, 1.04) (N=40,642; 2,738)	1.01 (0.93, 1.10) (N=44,018; 3,551)	1.15 (1.05, 1.27) (N=17,469; 1,688)

*median upper boundary for Q1-3 and lower boundary for Q4 in MET-h/w. The equivalent amount of time spent in moderate intensity activity are; ≈5 min/d (Q1); 25-35 min/d (Q2); 50-65 min/d (Q3) and 60-75 min/d (Q4