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

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Summary

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

Methods We did a systematic review, searching six databases (PubMed, PsycINFO, Embase, Web of Science, Sport Discus, and Scopus) from database inception until October, 2015, for 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 for all-cause mortality, cardiovascular disease mortality, or breast, colon, and colorectal cancer mortality. We included data from 16 studies, of which 14 were identified through a systematic review and two were additional unpublished studies where pertinent data were available. All study data were analysed according to a harmonised protocol, which categorised reported daily sitting time and TV-viewing time into four standardised groups each, and physical activity into quartiles (in metabolic equivalent of task [MET]-hours per week). We then combined data across all studies to analyse the association 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 Of the 16 studies included in the meta-analysis, 13 studies provided data on sitting time and all-cause mortality. These studies included 1 005 791 individuals who were followed up for 2–18·1 years, during which 84 609 (8·4%) died. Compared with the referent group (ie, those sitting <4 h/day and in the most active quartile [>35·5 MET-h per week]), mortality rates during follow-up were 12–59% higher in the two lowest quartiles of physical activity (from HR=1·12, 95% CI 1·08–1·16, for the second lowest quartile of physical activity [<16 MET-h per week] and sitting <4 h/day; to HR=1·59, 1·52–1·66, for the lowest quartile of physical activity [<2·5 MET-h per week] and sitting >8 h/day). Daily sitting time was not associated with increased all-cause mortality in those in the most active quartile of physical activity. Compared with the referent (<4 h of sitting per day and highest quartile of physical activity [>35·5 MET-h per week]), there was no increased risk of mortality during follow-up in those who sat for more than 8 h/day but who also reported >35·5 MET-h per week of activity (HR=1·04; 95% CI 0·99–1·10). By contrast, those who sat the least (<4 h/day) and were in the lowest activity quartile (<2·5 MET-h per week) had a significantly increased risk of dying during follow-up (HR=1·27, 95% CI 1·22–1·31). Six studies had data on TV-viewing time (N=465 450; 43 740 deaths). Watching TV for 3 h or more per day was associated with increased mortality regardless of physical activity, except in the most active quartile, where mortality was significantly increased only in people who watched TV for 5 h/day or more (HR=1·16, 1·05–1·28).

Interpretation High levels of moderate intensity physical activity (ie, about 60–75 min per day) seem 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. These results provide further evidence on the benefits of physical activity, particularly in societies where increasing numbers of people have to sit for long hours for work and may also inform future public health recommendations.

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Introduction

In a seminal 1953 *Lancet* paper, J N Morris and colleagues[1] reported an increased risk of coronary heart disease in London bus drivers compared with conductors. Since then, many observational studies have shown that lack of physical activity is a major risk factor for morbidity and premature mortality.[2–4] Indeed, estimates from 2012 indicated that not meeting physical activity recommendations is responsible for more than 5 million deaths globally each year.[4]

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Research in context

Evidence before this study

Compelling evidence from many observational studies shows that lack of physical activity increases the risks of many non-communicable diseases such as type 2 diabetes, cardiovascular disease, stroke, some cancers, and premature mortality. Sedentary behaviour, on the other hand, has emerged as a potential risk factor for many chronic conditions and mortality during the last decade. A recent meta-analysis suggested that prolonged TV-viewing time was associated with increased risk for type 2 diabetes, cardiovascular disease, and all-cause mortality. Two other meta-analyses had examined the associations of sitting time with non-communicable disease incidence and mortality. One of these concluded that prolonged sitting time was associated with increased risks of deleterious health outcomes regardless of physical activity level, whereas the other concluded that physical activity (no details on the amount of activity were provided) seemed to attenuate the increased risk of all-cause mortality due to high sitting. No previous systematic review had directly compared the joint effects of different, specified levels of physical activity and sitting time, to investigate the associations of different amounts of sitting time and physical activity in relation to all-cause mortality. Such information is required for the development of public health guidelines targeting sedentary behaviour.

We performed a systematic literature search in six databases (PubMed, PsycINFO, Embase, Web of Science, Sport Discus, and Scopus) from database inception until October, 2015, following the PRISMA guidelines. We identified 8381 articles, of which 16 were identified as eligible for inclusion. We also identified two studies in which the pertinent data were available but unpublished. We then contacted the principal author/investigator of these 18 studies and asked whether they were willing to reanalyse their data according to a harmonised protocol. In total, 16 studies were analysed according to a predefined protocol and included in this harmonised meta-analyses (details on the two excluded studies are provided in the text).

Added value of this study

This is the first meta-analysis to use a harmonised approach to directly compare mortality between people with different levels of sitting time and physical activity. Examining the joint effects of these two behaviours is important, because most people engage in both behaviours every day, so the effects of both should be considered in public health guidelines.

Implications of all the available evidence

These results provide further evidence on the benefits of physical activity, particularly in societies where increasing numbers of people have to sit for long hours for work or transport. Our findings indicate that increased sitting time is associated with increased all-cause mortality; however, the magnitude of increased risk with increased sitting time is mitigated in physically active people. Indeed, those belonging to the most active quartile and who are active about 60–75 min per day of moderate intensity physical activity seem to have no increased risk of mortality, even if they sit for more than 8 h a day.

See **Online** for appendix

Nowadays, sedentary behaviours are highly prevalent, and data from adults in high-income countries suggest the majority of time awake is spent being 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 did 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 that 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 database inception until Oct 30, 2014, updating the search up to Oct 10, 2015 (a detailed search description is provided in the appendix). We also obtained data from two additional studies,[27,28] when the pertinent data were available but not published. Authors or principal investigators were contacted and asked about their willingness to participate in a harmonised meta-analysis. One study[11] did not respond to our request to participate and one additional study[12] 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, we analysed individual data from 16 studies[11–25,29] according to a predefined protocol and included these data 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 [HRs], odds ratios [ORs], or relative risks [RRs] with 95% CIs) for all-cause mortality, cardiovascular disease mortality, or breast, colon, and colorectal cancer mortality. This review protocol is registered with the PROSPERO database.

For the **study protocol** see http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015023870

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Data extraction and harmonisation

One author (JS-J) 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 of participants; number of men and women; years of follow-up; number of deaths from all causes, cancer, and cardiovascular disease; and methods of ascertainment; assessment details for physical activity and sitting time; and covariates included in adjusted models.

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 (appendix). Of the remaining two studies, one[13] used five categories that we collapsed into four by combining the two highest categories, whereas the other study[14] used only three categories of sitting time (appendix). Data for TV-viewing time from six studies[16,20,22–25] could be combined into four common groups (appendix). We reanalysed data from each study using predefined categories of sitting time in four groups (0–<4 h/day, 4–<6 h/day, 6–8 h/day, >8 h/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) since this information was available from all studies (appendix). 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 metabolic equivalent of task (MET)-hours per week (MET-h per 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 conventionally accepted intensity levels (3·3 METs for walking, 4 METs for moderate intensity activity, 7 METs for vigorous intensity activity, and 7·2 METs for strenuous sports).[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 physical activity in MET-h per week in its continuous form in four studies.[14,17,22,27] In these studies, we asked contributing studies to calculate MET-h per week in three[14] or four[17,22,27] categories that were assumed to reflect the quartiles derived from the other studies (appendix).

The median MET-h per week across studies for the upper boundary for the first (lowest) quartile was 2·5 MET-h per week (equivalent to about 5 min of moderate intensity activity per day). Corresponding values for the second and third quartiles were 16 MET-h per week (about 25–35 min of moderate intensity activity per day) and 30 MET-h per week (about 50–65 min of moderate intensity activity per day), and the lower boundary for the fourth (top) quartile was 35·5 MET-h per week (about 60–75 min of moderate intensity activity per day; appendix). Examples of moderate intensity activities are brisk walking at 5·6 km/h, and bicycling for pleasure at 16 km/h.[30]

Data analyses and syntheses

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

Principal authors or investigators for all studies except one[29] 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,[26] we used publicly available individual level data to perform the analyses.[29]

All studies apart from three[17–19] either excluded all participants with major chronic diseases at baseline or excluded deaths occurring within at least 1 year in

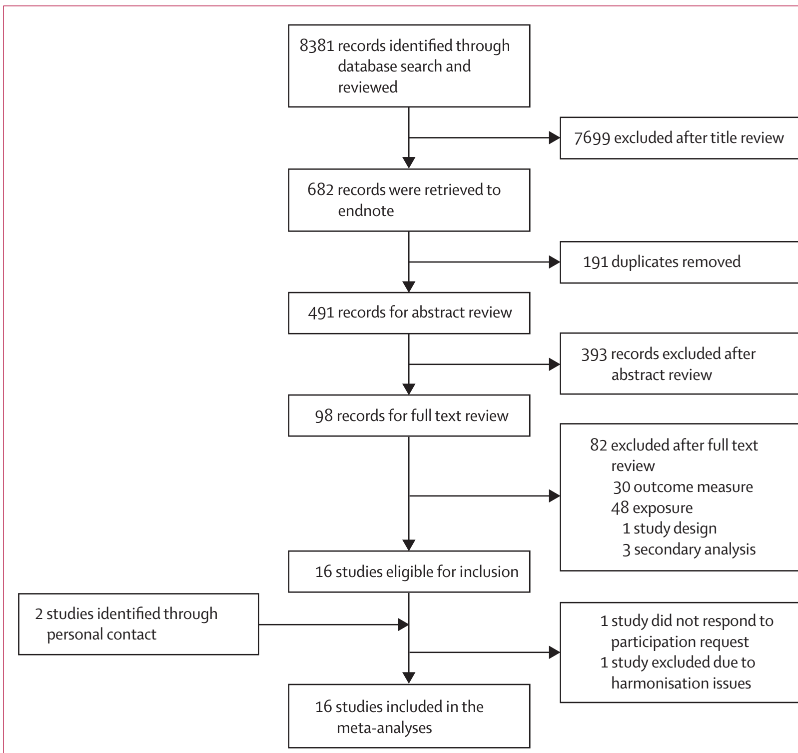

Figure 1: **Study selection**

	Country; study name; participant characteristics	Years of follow-up	Mortality outcome(s), number of cases	Method of case ascertainment	Variables the covariates were adjusted for	Quality
Sitting						
Katzmarzyk et al, 2009[13]	Canada; Canada Fitness Survey (CFS); 17 013 men and women aged 18–90 years	12·9 years (maximum)	All-cause, 1832; CVD, 759; cancer, 547	Canadian Mortality Database	Age, sex, smoking, and alcohol consumption	0·85
Inoue et al, 2008[14]	Japan; Japan Public Health Center-based Prospective Study; 83 034 men and women aged 45–74 years	8·7 years	All-cause, 4564; CVD, 974; cancer, 2044	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]	USA; American Cancer Society Cancer Prevention Study II Nutrition Cohort (CPS-II); 123 216 men and women aged 50–74 years	14 years (maximum)	All-cause, 19 230; CVD 6369; cancer, 6989	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]	USA; NIH-AARP Diet and Health Study; 240 814 men and women aged 50–71 years	8·5 years	All-cause, 17 044; CVD, 4684; cancer, 7652	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 aged ≥45 years	2·8 years	All-cause, 5405	New South Wales Registry of Births, Deaths, and Marriages	Age, sex, education, urban or 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 Study on Women's Health; 6656 women aged ≥75 years	9 years (maximum) 6 years (median)	All-cause, 2003	Australian National Death Index	Age, education, marital status, area, smoking, alcohol consumption, BMI, number of chronic conditions, self-rated health, and assistance with daily tasks	0·90
León-Munoz et al, 2013[19]	Spain; 2635 men and women aged ≥60 years	2 years	All-cause, 846	National Death Index	Age, sex, education, BMI, smoking, alcohol consumption, weight, BMI, chronic lung disease, ischaemic 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]	USA; Multiethnic Cohort Study; 134 596 men and women aged 45–75 years	13·7 years	All-cause, 19 143; CVD, 6535; cancer, 6697	Death certificate linked to National Death Index and classified using International Classification of Diseases	Age, sex, race or ethnic origin, 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 aged 18–99 years	5·4 years	All-cause, 1074; CVD, 308	Danish Civil Registration system	Age, sex, educational level, smoking habits, BMI, alcohol consumption, and hypertension	0·95
Matthews et al, 2014[22]	USA; Southern Community Cohort Study; 63 308 men and women aged 40–79 years	6·4 years	All-cause, 5007; CVD, 1376; cancer, 1227	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; 4513 men and women aged 35–66 years	7·5 years	All-cause, 112	Danish registry of causes of death	Age, sex, socioeconomic 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 aged 19–99 years	18·1 years	All-cause, 5004; CVD, 1537; cancer, 1536	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]*	USA; Women's Health Initiative; 92 234 women aged 50–79 years	10·2 years	All-cause 10 800; CVD 3206; cancer 4338	Hospital records, autopsy records, death certificates, and National Center for Health Statistics' National Death Index	Age, race or ethnic origin, 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; 8800 men and women aged ≥25 years	6·6 years	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 or ex-smoker), total energy intake, alcohol, waist circumference, hypertension, total cholesterol, high-density lipoproteins, 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 aged 45–79 years	9·5 years	All-cause 1270; 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 dyslipidaemia, baseline history of diabetes, family history of CVD, and cancer	0·90
Ford et al, 2012[25]	USA; National Health and Nutrition Examination Survey; 7350 men and women aged ≥20 years	5·8 years	All-cause, 542	National Death Index and classified using International Classification of Diseases	Age, sex, race education, smoking, and Healthy Eating Index score	0·90

(Table 1 continues on next page)

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	Country; study name; participant characteristics	Years of follow-up	Mortality outcome(s), number of cases	Method of case ascertainment	Variables the covariates were adjusted for	Quality
(Continued from previous page)						
Matthews et al, 2012[16]	USA; NIH-AARP Diet and Health Study; 240 814 men and women aged 50–71 years	8·5 years	All-cause, 17 044; CVD, 4684; cancer, 7652	Social Security Administration and the National Death Index	Age, sex, race, education, BMI, smoking, and diet	0·95
Kim et al, 2013[20]	USA; Multiethnic Cohort Study; 134 596 men and women aged 45–75 years	13·7 years	All-cause, 19 143; CVD, 6535; cancer, 6697	Death certificate linked to National Death Index and classified using International Classification of Diseases	Age, sex, race or ethnic origin, education, smoking history, history of diabetes or hypertension, energy intake, and alcohol consumption	0·95
Matthews et al, 2014[22]	USA; Southern Community Cohort Study; 63 308 men and women aged 40–79 years	6·4 years	All-cause, 5007; CVD, 1376; cancer, 1227	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 the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

Table 1: **Characteristics of studies included in the meta-analysis, data extracted from original publications**

sensitivity analyses. Two of the remaining three studies,[18,19] which included older participants, provided analyses for this meta-analysis in which they excluded deaths within the first 2 years. The remaining study,[17] which had a short follow-up period (mean 2·8 years), analysed their data excluding those with baseline cardiovascular disease, 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 on the basis of questionnaire categories) and also those who had the most physical activity (top quartile >35·5 MET-h per week; ie, referent). We calculated effect estimates using Cox regression analyses and presented as HRs with their associated 95% CIs. 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 association between sitting and mortality differed between people with different activity levels, to address whether physical activity modified the detrimental effect of prolonged sitting. That is, we separately investigated the association between sitting time and all-cause mortality 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 cardiovascular disease and cancer mortality as the outcomes. We also tested whether the HRs differed between extreme groups (ie, 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 effect 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).

For the **BioLINCC website** see https://biolincc.nhlbi.nih.gov/home/

Role of the funding source

The study had no sponsors. UE, JS-J, and MWF had full access to the harmonised data provided by study partners.

Results

We identified 8381 articles by searching six different databases. We retrieved 98 papers for full text review, of which 16 studies[11–26] were identified as eligible for inclusion (figure 1). We also obtained data from two additional studies.[27,28] We used publicly available data[29] for the follow-up of one of the studies.[26] Therefore, we analysed individual data from 16 studies[13–25,27–29] according to a predefined protocol and included these data in the harmonised meta-analyses. Quality scores were high (≥0·85 in all studies; table 1).

Of the 16 studies included in the meta-analysis, 13 studies[13–22,27–29] provided data on sitting time and all-cause mortality. These studies included 1005791 individuals who were followed up for 2–18·1 years, during which 84609 (8·4%) died, and whom we 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 cardiovascular disease 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). The number of participants and deaths refer to those provided by the individual studies and included in the harmonised meta-analysis.

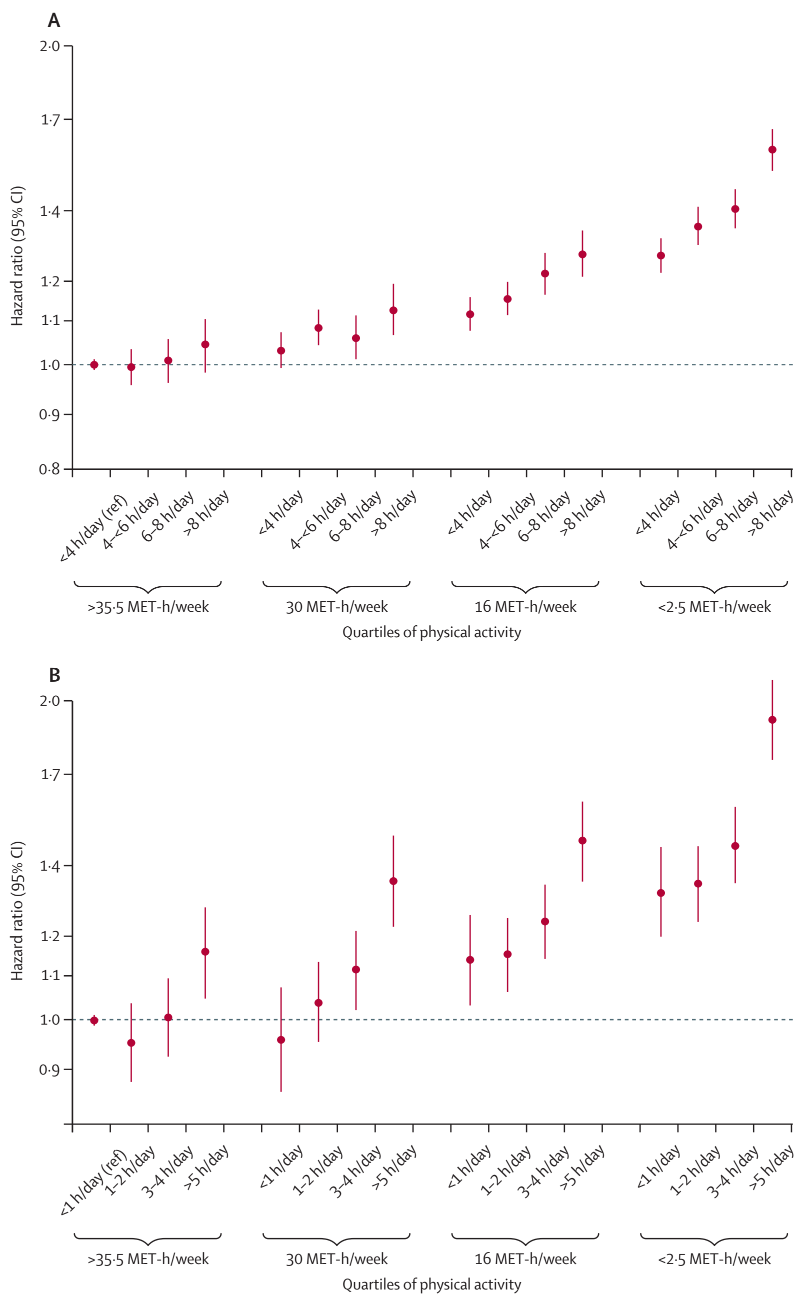

Figure 2: **Meta-analyses of the joint associations of sitting time and physical activity with all-cause mortality (A) and of TV-viewing time and physical activity with all-cause mortality (B)**
(A) Sitting time analysis, N=1 005 791. (B) TV-viewing time analysis, N=465 450. The reference categories are the groups with the highest levels of physical activity (>35·5 MET-h per week) in combination with <4 h/day of sitting (A) or <1h/day of TV-viewing (B). The median MET-h per week for the upper boundary for the first (lowest) quartile was 2·5 MET-h per week (equivalent to about 5 min of moderate intensity activity per day). Corresponding values for the second and third quartiles were 16 MET-h per week (about 25–35 min of moderate intensity activity per day) and 30 MET-h per week (about 50–65 min of moderate intensity activity per day), and the lower boundary for the fourth (top) quartile was 35·5 MET-h per week (about 60–75 min of moderate intensity activity per day).

The appendix shows the summary HRs for the joint associations of sitting time and physical activity with all-cause mortality. 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 (figure 2A). Compared with the referent group (ie, those sitting <4 h/day and in the most active quartile), mortality during follow-up was 12–59% higher in the two lowest quartiles of physical activity (HR 1·12, 95% CI 1·08–1·16, for the second lowest quartile of physical activity and <4 h/day; HR 1·59, 1·52–1·66, for the lowest quartile of physical activity and >8 h/day of sitting time; appendix).

However, in the third quartile of physical activity (ie, the second most active group), only those sitting 4 h/day or more had higher mortality than the reference group. 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 (appendix).

Since we did not have access to individual level data from all studies, we estimated whether HRs between groups differed significantly, as described in the appendix. Those in the most active quartile, but who also reported the most sitting time (>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 did the least active who also sat the least (<4 h/day; HR 1·27, 1·22–1·30).

We then repeated these analyses with TV-viewing time instead of sitting time. Similar findings were observed, although the effect estimates were less precise, possibly because of smaller sample sizes (figure 2B, appendix). In those who watched TV for 5 h or more per day, the hazard for all-cause mortality was markedly increased by between 16% and 93% across activity quartiles (appendix). Among the most active quartile, only this amount of TV-viewing time (≥5 h/day) was significantly associated with an increased hazard of mortality (HR 1·16, 95% CI 1·05–1·28). In comparison, people in the least active quartile who watched TV for only less than 1 h/day had a significantly higher mortality risk (HR 1·32, 1·20–1·46; $p=0·007$).

In a subsample of studies with available data, we examined mortality due to cardiovascular disease and cancer. The results for cardiovascular disease mortality were similar to those observed for all-cause mortality (appendix). Compared with those sitting less than 4 h a day in the most active quartile, cardiovascular disease mortality rates were 23–74% higher in the two lowest quartiles of physical activity (appendix). For cancer mortality, increased hazards of between 12% and 22% with more sitting time were observed only for people in the least active quartile (appendix). Using TV-viewing time instead of sitting time did not materially change the results for cardiovascular disease, and the association between cancer mortality and TV-viewing time was not significant for all levels of physical activity (appendix).

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 more than 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 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 less than 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, 3 h or more per day of TV-viewing time was associated with increased risk among all, except for the most active quartile. In the most active quartile, TV-viewing time of 5 h or more per day was associated with an increased hazard of all-cause mortality (HR 1·15; 95% CI 1·05–1·27).

	<4 h/day of sitting time	4–<6 h/day of sitting time	6–8 h/day of sitting time	>8 h/day of sitting time
≤2·5 MET-h per week	1 (ref) (N=76 212; 6646)	1·08 (1·04–1·12) (N=48 613; 5224)	1·09 (1·05–1·14) (N=66 839; 5820)	1·27 (1·22–1·32) (N=60 730; 6018)
16 MET-h per week	1 (ref) (N=77 651; 7221)	1·04 (1·00–1·07) (N=73 444; 7873)	1·06 (1·02–1·10) (N=51 263; 5322)	1·12 (1·07–1·17) (N=60 838; 5012)
30 MET-h per week	1 (ref) (N=75 365; 5387)	1·05 (1·01–1·10) (N=63 959; 5489)	1·03 (0·98–1·08) (N=48 292; 3504)	1·10 (1·04–1·16) (N=52 576; 3487)
>35·5 MET-h per week	1 (ref) (N=90 762; 6208)	1·00 (0·96–1·04) (N=65 976; 5268)	1·01 (0·97–1·06) (N=49 715; 3565)	1·04 (0·98–1·10) (N=43 856; 2717)

The reference categories are the groups with <4 h/day of sitting for all quartiles of physical activity. *Median upper boundary for Q1–3 and lower boundary for Q4 in MET-h per week. The equivalent amount of time spent in moderate intensity activity are ≈5 min/day (Q1); 25–35 min/day (Q2); 50–65 min/day (Q3); and 60–75 min/day (Q4).

Table 2: **Meta-analyses of the associations between sitting time and all-cause mortality (N=1 005 791; 84 609 deaths) stratified by quartiles of physical activity***

	<1 h/day of TV-viewing time	1–2 h/day of TV-viewing time	3–4 h/day of TV-viewing time	≥5 h/day of TV-viewing time
≤2·5 MET-h per week	1 (ref) (N=10 609; 1064)	1·00 (0·94–1·08) (N=33 411; 3382)	1·10 (1·02–1·18) (N=40 688; 4702)	1·44 (1·34–1·56) (N=22 779; 3533)
16 MET-h per week	1 (ref) (N=12 280; 984)	1·00 (0·93–1·08) (N=45 493; 4098)	1·08 (1·01–1·15) (N=51 917; 5576)	1·29 (1·19–1·39) (N=21 365; 2870)
30 MET-h per week	1 (ref) (N=11 232; 613)	1·08 (0·98–1·18) (N=39 807; 2589)	1·17 (1·07–1·27) (N=43 699; 3675)	1·41 (1·28–1·56) (N=17 563; 1925)
>35·5 MET-h per week	1 (ref) (N=12 478; 752)	0·96 (0·88–1·04) (N=40 642; 2738)	(0·93–1·10) (N=44 018; 3551)	1·15 (1·05–1·27) (N=17 469; 1688)

The reference categories are the groups with <1 h/day of TV viewing across quartiles of physical activity. *Median upper boundary for Q1–3 and lower boundary for Q4 in MET-h per week. The equivalent amount of time spent in moderate intensity activity are; ≈5 min/day (Q1); 25–35 min/day (Q2); 50–65 min/day (Q3); and 60–75 min/day (Q4).

Table 3: **Meta-analyses of the associations between TV-viewing time, and all-cause mortality (N=465 450; 43 740 deaths) stratified by quartiles of physical activity***

Discussion

These analyses, including data from more than 1 million individuals, indicate that high levels of physical activity, equivalent to 60–75 min of moderate intensity physical activity per day, seem to eliminate the increased mortality risks associated with high total sitting time. Indeed, those in the highest physical activity quartile (about 60–75 min/day) who sat for more than 8 h daily had a significantly lower risk of dying during follow-up than did those who sat for less than 4 h in the least active quartile (about 5 min/day). In the middle two quartiles of physical activity (which encompass current physical activity guideline levels[34]), the mortality risks associated with increased 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 for 5 h or more a day.

Our harmonised meta-analytical approach allowed us to examine associations betweeen 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 was 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 mortality due to cardiovascular disease and cancer. 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 60–75 min of moderate intensity activity per day or more. This amount 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” (1 h a day of moderate intensity activity). Notably, 60–75 min of moderate intensity activity is congruent with the level of physical activity showing maximum mortality benefit in a large meta-analysis from 2015.[37] In the present study, this amount of activity (reported by a quarter of the participants), was required to eliminate the increased hazard associated with sitting for more than 8 h/day. However, even those in the second quartile of physical activity (about 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 (about 5 min 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 h/day and were also least active, is similar to that of smoking[38] and obesity.[39]

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 seemed to be stronger in magnitude. This difference is congruent with previous observations[20] and might 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.[40] It is also plausible that individuals break up their sitting time more frequently during work than when viewing TV, and breaking up sedentary time seems to be beneficial for various cardio-metabolic risk factors.[40] Another explanation for the difference observed could be that TV-viewing might be accompanied by snacking behaviours[41] and food advertising on TV might affect eating behaviour.[42] Thus, associated dietary behaviours may explain some of the differences observed.

Our meta-analysis has several 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" *vs* "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 subgroup 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 might eliminate the detrimental association between daily sitting time and mortality is biologically plausible. There is evidence that 1 h of moderate intensity activity positively influences postprandial lipid metabolism following 8 h of sitting,[43] and that 45 min of cycling at moderate intensity following more than 10 h of sitting has beneficial effects on glucose metabolism in type 2 diabetes.[44]

The study has also some limitations; first, the majority of studies included participants older than 45 years and all but one study was conducted in the USA, western Europe, or Australia. Thus, the results may not be generalisable 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 might have distorted our results. Fourth, although we did not find any evidence for publication bias, we cannot rule out that publication bias could exist, because of the low number of studies in some analyses. Fifth, we attempted to minimise bias from reverse causation (ie, illness causing individuals to become sedentary) by including apparently healthy participants; however, we cannot fully rule this bias out. Sixth, all studies asked participants to self-report sedentary behaviour and physical activity at one point in time. This measure increases the chance of random measurement error, which would attenuate true associations.

In conclusion, high levels of moderate intensity physical activity (ie, about 60–75 min per day) seem 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 (eg, for work or transport), it is important also to be physically active.

Contributors

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. JS-J and UE did the literature search. MWF analysed the data. MWF, JS-J, and UE had full access to study level data from all contributing studies.

Declaration of interests

We declare no competing interests.

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