Table B.2.a. All-cause and cause-specific mortality: Association between sedentary behaviour and all-cause mortality among adults (in alphabetical order by author)

See the Supplementary materials for description of evidence of US PAGAC *(24)* by outcome

Systematic review evidence Review credibility	No. of studies/ Study design No. of participants	Quality Assessment					Description of evidence Summary of findings	Certainty
		Risk of bias	Inconsistency	Indirectness †	Imprecision	Other		
Berger 2019 *(5)* Moderate	3 prospective cohort studies N=277,763	Serious risk of bias	Serious inconsistency	Serious indirectness	No serious imprecision	None	Most studies used self-report sedentary behaviour (one study combined self-report and job title assignment). Mean follow-up was not reported. No significant association was found between high versus low ST and risk of **prostate cancer-related mortality** (RR = 1.14 [95% CI 0.94 to 1.38], 3 studies).	VERY LOW[a]
del Pozo-Cruz *(8)* Moderate	3 prospective cohort studies N=12,108	No serious risk of bias	Serious inconsistency[b]	No serious indirectness	Serious imprecision[b]	None	Included adults aged mean age ranged 49 to 61 years; mean follow-up time not reported. All studies used accelerometers to measure ST with <100 cpm (from the vertical axis of the accelerometer) used to define ST. The review reported that all 3 studies found that replacing 30 minutes of ST with LIPA or MVPA was associated with significantly lower risk of **all-cause mortality**. One study found that replacing ST with LIPA also had a significant beneficial association with risks of **CVD-** and **cancer-**related mortality and that "MPVA had an even better significant association with risks of mortality from **any cause** and **CVD." "**Hazards ratios ranged from 0.80 to 0.87 for LIPA and from 0.19 to 0.51 for MVPA", no data given by study including variance for effect estimates.	LOW[c]

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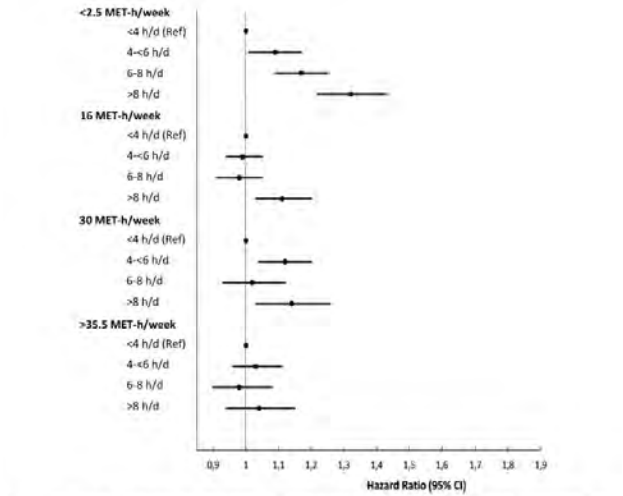
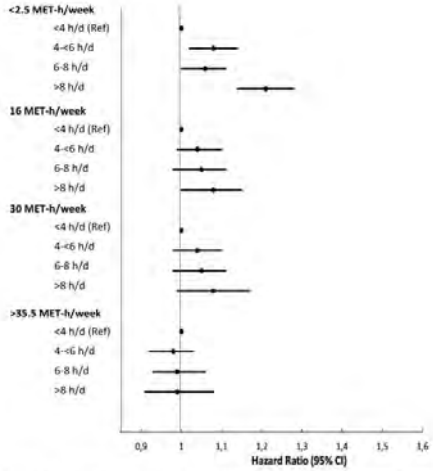
		Risk of bias	Inconsistency	Indirectness †	Imprecision	Other		
Ekelund 2018 *(9)* Moderate	11 prospective cohort studies N=888,327	No serious risk of bias	NA[d]	No serious indirectness	No serious impression	Dose-response relationship[e]	Secondary data analysis of 2016 review on the relationship between sitting time and all-cause mortality. Sitting time was categorized into four groups (0 to <4 hrs/day, 4 to < 6 hrs/day, 6-8 hrs/day, and >8 hrs/day) and TV-viewing time into four groups (<1 hr/day, 1-2 hrs/day, 3-4 hrs/day, and >5 hrs/day). Nine studies had data on the relationship between **sitting time** and **CVD mortality** (n=850,060; median follow-up 10.2 years). A significant dose-response relationship was found between sitting time and CVD mortality for the lowest quartile of PA (<2.5 MET-hrs/week): the HR for CVD mortality was 1.32 (p for trend <0.001, 95% CI only reported in figure) for those who sat for more than 8 hrs/day compared with the reference group (<4 hrs/day). There was no clear dose-response association in any of the other quartiles of PA, but significantly increased hazards were observed in those with sitting time <8 hrs/day vs. <4 hrs/day for those in the 2nd quartile (16 MET-hrs/week) (HR = 1.11 [95% CI, 1.03 to 1.20]) and 3rd quartile (30 MET-hrs/week) (HR = 1.14 [95% CI, 1.03 to 1.26]) of PA. There was no increased risk for CVD mortality in the most active quartile of PA (>35.5 MET-hrs/week) in any category of sitting time.  **Figure 1** Meta-analysis of the stratified associations between sitting time (n=850 060; 25 703 deaths) and CVD mortality. The reference categories are the groups with <4 hour/day of sitting or <1 hour/day of TV-viewing for all quartiles of physical activity. Median upper boundary for Q1–Q3 and lower boundary for Q4 in MET-hour/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).	HIGH[f]

							Five studies had data on the relationship between **TV-viewing time** and **CVD mortality** (n=458,127, median follow-up 8.5 years). Patterns were similar with those seen for sitting time. In the 'inactive' group (lowest PA quartile, <2.5 MET-hrs/week) the hazard of CVD mortality was 1.59 (95% CI only shown in figure) in those who watched TV for >5 hrs/day compared with those who watched TV for <1 hr/day) (p for trend <0.001). For the other quartiles of PA, the hazard estimates were only significantly increased in the 2nd quartile (HR=1.28, 95% CI not reported) and 3rd quartile (HR=1.41, 95% CI not reported) of PA when comparing >5 hrs/day of TV time vs. <1 hr/day of TV time. There was no increased risk of CVD mortality in the most active quartile of PA for any level of TV viewing time. Eight studies (n=777,696, median follow-up 11.5 years) had data on the relationship between **sitting time** and **cancer mortality**. There was no clear dose response relationship between sitting time and cancer risk by level of PA. In both the lowest quartile of PA (<2.5 MET-hrs/week) and the 2nd quartile of PA (16 MET-hrs/week), there was a significantly higher risk of cancer mortality in the highest sitting category (>8 hrs/day) vs. lowest (<4 hrs/day) (HR=1.21 [95% CI, 1.14 to 1.29] for the lowest PA quartile and HR=1.08 [95% CI, 1.00 to 1.15] for the 2nd PA quartile).  Figure 3 Meta-analysis of the stratified associations between sitting time (n=777 696; 30 851 deaths) and cancer mortality. The reference categories are the groups with <4 hour/day of sitting or <1 hour/day of TV viewing for all quartiles of physical activity. Median upper boundary for Q1–Q3 and lower boundary for Q4 in MET-hour/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). Five studies (n=458,091 median follow-up=8.5 years) had data on the relationship between **TV-viewing time** and **cancer mortality**. There was no significantly increased risk of cancer mortality by TV time among those in the inactive or most active PA quartiles, but there was a significantly increased hazards in the 2nd PA quartile (HR=1.18 [95% CI, 1.04 to 1.34) and 3rd PA quartile (HR=1.29 [95% CI, 1.10 to 1.51]) when comparing TV viewing time of >5 hrs/day vs. <1 hr/day.	

Systematic review evidence Review credibility	No. of studies/ Study design No. of participants	Quality Assessment					Description of evidence Summary of findings	Certainty
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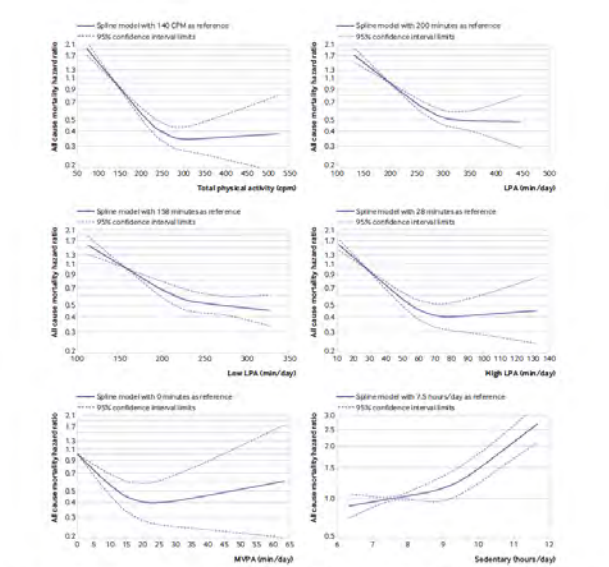
Ekelund 2019 *(10)* Moderate	8 prospective cohort studies N=36,383	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Dose--response relationship	Harmonized meta-analysis from eight prospective cohort studies, including data from 3 large surveillance systems and 2 from unpublished data. Mean age in studies was 63 years with median follow-up of 5.8 years (range 3 to 14.5 years). All 8 studies used accelerometers to measure ST (sedentary ≤100 cpm). Data was categorized into quartiles with the least active quartile as the referent. Increasing time spent in sedentary behaviour was significantly associated with **all-cause mortality.** Hazard ratios for increasing quarters of ST were 1.28 (95% CI, 1.09 to 1.51) for the 2nd quartile, 1.71 (95% CI, 1.36 to 2.15) for the 3rd quartile, and 2.63 (95% CI, 1.94 to 3.56) for the highest quartile of ST, after adjustment for potential confounders including time spent in MVPA (table below). **Table 2 | Meta-analysis for associations between total physical activity, intensities of physical activity or sedentary time by quarters and all cause mortality** Hazard ratios (95% CI) for all cause mortality*; No of participants; No of deaths Variables | First quarter (least active) | Second quarter | Third quarter | Fourth quarter (most active) Model B† Total physical activity (cpm) | 1 (ref) (n=9096; 1187) | 0.48 (0.43 to 0.54) (n=9105; 483) | 0.34 (0.26 to 0.45) (n=9096; 265) | 0.27 (0.23 to 0.32) (n=9086; 214) Physical activity intensity Light (min/d) | 1 (ref) (n=9073; 1089) | 0.60 (0.54 to 0.68) (n=9101; 511) | 0.44 (0.38 to 0.51) (n=9090; 320) | 0.38 (0.28 to 0.51) (n=9119; 229) Low light (min/d) | 1 (ref) (n=9066; 1010) | 0.66 (0.56 to 0.77) (n=9106; 518) | 0.47 (0.38 to 0.58) (n=9112, 353) | 0.42 (0.34 to 0.52) (n=9099; 268) High light (min/d) | 1 (ref) (n=9054; 1159) | 0.55 (0.49 to 0.63) (n=9120; 483) | 0.38 (0.30 to 0.48) (n=9088; 278) | 0.37 (0.32 to 0.46) (n=9113; 229) Moderate to vigorous (min/d) | 1 (ref) (n=9002; 1139) | 0.64 (0.55 to 0.74) (n=9153; 468) | 0.55 (0.40 to 0.74) (n=9123; 305) | 0.52 (0.43 to 0.61) (n=9105; 237) Sedentary (min/d) | 1 (ref) (n=9102; 327) | 1.28 (1.09 to 1.51) n=9105; 417) | 1.71 (1.36 to 2.15) (n=9096; 562) | 2.63 (1.94 to 3.56) (n=9080; 843) cpm=counts per minute. Model A adjusted for sex (when applicable), age, and wear time (n=36852, 2304 deaths). Model B adjusted for sex (when applicable), age, body mass index, socioeconomic position, and wear time (n=36383, 2149 deaths). Model C additionally adjusted for covariates listed in table 1 (n=35932, 2047 deaths). *By Cox regression. †Moderate-to-vigorous physical activity and sedentary time are mutually adjusted. Differences in min/day between the referent (least sedentary) and 2nd quarter were broadly equal to 70 min/day of sedentary time. The dose-response relationship between ST and mortality increased gradually from about 7.5 to 9 hrs/day and were more pronounced at >9.5 hrs/day (see figure below).	HIGH[g]

							 Fig 2	Dose-response associations between total physical activity (top left), light intensity physical activity (LPA) (top right), low LPA (middle left), high LPA (middle right), moderate-to-vigorous intensity physical activity (MVPA) (bottom left), and sedentary time (bottom right, data from REGARDS (Reasons for Geographic and Racial Differences in Stroke)[9] and FHS (Women's Health Study)[10] are only included for MVPA) and all cause mortality. Modelling performed using restricted cubic splines with knots at 25th, 50th, and 75th centiles of exposure specific distribution from medians of quarters (least to most active). The exposure reference is set as the median of the medians in the reference group (least active) (see supplementary table 3). Knot locations are available in supplementary table 8. cpm=counts per minute	
Ku 2018 *(13)* Moderate	19 prospective cohort studies N=1,250,482	No serious risk of bias	Serious inconsistency	Serious indirectness	No serious imprecision	Potential overlap in 6 of 7 studies of device-based measures	Analysis of the relationship between sedentary time and **all-cause mortality** in adults. Mean follow-up was 7.8 years (range 2.8 to 15.7 years). Mean age of participants ranged from 40 to 64 years. 12/19 included subjective measures of sedentary time and 7/19 used objective device-based measures. Cut-off points for categories of sedentary time were inconsistent across studies. A linear dose-response relationship was found between daily sedentary time and risk (log-linear) of **all-cause mortality**. A significant relationship was found when limited to both subjective measures (regression coefficient = 0.03 [SE, 0.01], p<0.01) and device-based measures (regression coefficient = 0.09 [SE, 0.03], p<0.01). The regression line and upper and lower 95% CI bounds showed that increased hazards of all-cause death became significant when total sedentary time exceeded approximately 7.5 hrs/day (7 hrs/day when looking at only subjective measures and 9 hrs/day when looking only at objective measures). Studies with longer follow-ups had weaker associations between daily sedentary time and mortality risks.	LOW[h]

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Ku 2019 *(14)* Moderate	11 prospective cohort studies N=36,341	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Potential overlap in 3 of 11 studies	Analysis of the relationship between sedentary time and all-cause mortality in older adults (≥65 years). Mean follow-up was 7.8 years (range 2.3 to 14.2 years). Mean age of participants ranged from 67 to 79 years. All studies used accelerometers to measure ST; 6 studies defined ST as <100 counts/min, 2 studies defined ST as <200 counts/min, 1 used <50 counts/min, and 2 studies did not report the cut point used to define ST. There was no significant dose-response association between ST and **all-cause mortality** among older adults (regression coefficient = 0.04 [SE, 0.03], p=0.15). Removing 3 studies that did not adjust for accelerometer wear time resulted in a significant dose response relationship between ST and all-cause mortality (regression coefficient = 0.08 [SE, 0.03], p=0.02). Within this model, the regression line and upper and lower 95% CI bounds showed that increased hazards of (log-transformed) all-cause death became significant when total sedentary time exceeded approximately 9 hrs/day.	MODERATE[i]
Patterson 2018 *(19)* Low	34 prospective cohort studies N=1,331,468	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	None	Mean follow-up was 8.9 years (range, 2 to 31 years). Most studies assessed sedentary behaviour via self-report, 3 included objective measurement via accelerometer. Categories used by the study authors to define levels of sedentary behaviour varied considerably across studies. For **total sitting time**, the PA-adjusted relationship was not significantly linear for **all-cause mortality** or **CVD mortality.** In PA-adjusted analysis, the RR was 1.01 (95% CI 1.00 to 1.01) for each additional hr/day below 8 hrs/day and 1.04 (95% CI, 1.03 to 1.05) for each hr/day above 8 hr/day for **all-cause mortality**. For **CVD mortality** the adjusted RR per 1 hr/day was 1.01 (95% CI, 0.99 to 1.02) when total exposure was ≤6 hrs/day and RR=1.04 (95% CI, 1.03 to 1.04) when >6 hrs/day. For **cancer mortality**, the adjusted RR was 1.01 (95% CI, 1.00 to 1.02) with no evidence of non-linearity.	MODERATE[i]

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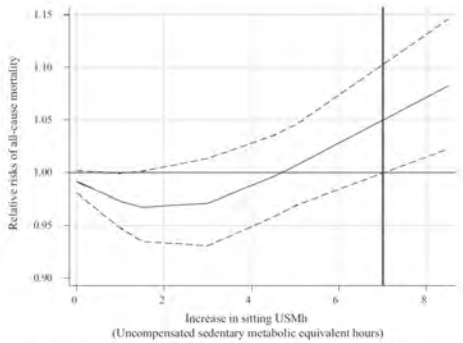
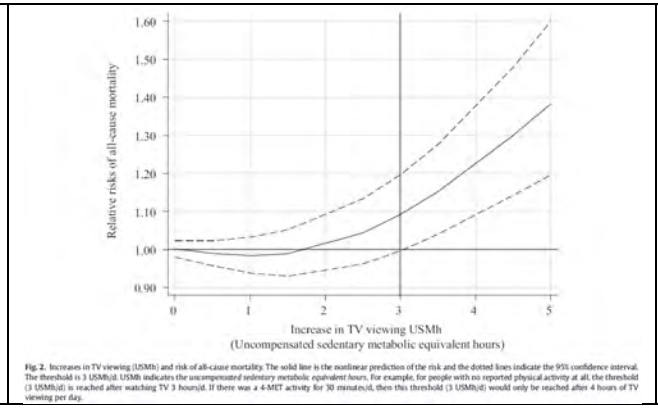
Xu 2019[j] *(22)* Low	7 prospective cohort studies N=284,161	No[d]	No[d]	No[d]	No[d]	Dose-response relationship Does not include all available and eligible cohort studies Does not account for LIPA	Examination of the relationship between sedentary activity and all-cause mortality according to PA level using individual participant level data. All measures of ST and PA were self-reported. Mean follow-up ranged from 6.6 to 13.7 years. Sedentary activity was defined by a measure that takes into account both time spent in specific activities and the intensity of those activities by computing a "net uncompensated sedentary behaviour metabolic equivalent hours" (USMh) (where USMh = [MET x hr on SB] – [MET x hr on MVPA]). Data from 5 cohort studies (n=258,688) were pooled to examine the relationship between **<u>sitting</u>** and **all-cause mortality**. The predicted dose-response RRs of sitting were 0.97 (95% CI, 0.95 to 1.00) at 1 USMh, 0.97 (95% CI, 0.93 to 1.01) at 3 USMh, 1.01 (95% CI, 0.97 to 1.05) at 5 USMh, 1.05 (95% CI, 1.00 to 1.10) at 7 USMH, and 1.08 (95% CI, 1.02 to 1.15) at 8.5 USMh. The threshold for risk started to 7 USMh, and on average, between 0 and the maximum of 8.5 USMh of 8.5 hrs, the increase in mortality was 1% (RR=1.01 [95% CI, 1.00 to 1.02]).  Fig. 1. Increase in sitting (USMh) and risk of all-cause mortality. The solid line is the nonlinear prediction of the risk and the dotted lines indicate the 95% confidence interval. The threshold is 7 USMh. USMh indicates the *uncompensated sedentary metabolic equivalent hours*. For example, for people with no reported physical activity at all, the threshold (7 USMh/d) is reached after sitting 7 hours/d. If there was a 4-MET activity for 30 minutes/d, then this threshold (7 USMh/d) would only be reached after 9 hours of sitting per day. Data from 4 cohort studies (n=156,593) were pooled to examine the relationship between **<u>TV viewing</u>** and **all-cause mortality.** The predicted dose-specific RRs of TV viewing were 0.98 (95% CI, 0.94 to 1.03) at 1 USMH, 1.09 (95% CI, 1.00 to 1.20) at 3 USMh, and 1.38 (95% CI, 1.20 to 1.60) at 5 USMh. The threshold for risk started at 3 USMh and the average increase in risk of death between 0 and the maximum value of 5 USMh was an increase of 7% (RR 1.07 [95% CI, 1.04 to 1.10]).	LOW[k]

							 Fig. 2. Increases in TV viewing (USMh) and risk of all-cause mortality. The solid line is the nonlinear prediction of the risk and the dotted lines indicate the 95% confidence interval. The threshold is 3 USMh/d. USMh indicates the *uncompensated sedentary metabolic equivalent hours*. For example, for people with no reported physical activity at all, the threshold (3 USMh/d) is reached after watching TV 3 hours/d. If there was a 4-MET activity for 30 minutes/d, then this threshold (3 USMh/d) would only be reached after 4 hours of TV viewing per day.	

Abbreviations: CI = confidence interval; cpm = counts per minute; CVD = cardiovascular disease; HR = hazard ratio; hrs =hours; min = minutes; LIPA = light intensity physical activity; MET = metabolic equivalents of task; MVPA = moderate-to-vigorous intensity physical activity; NA = not assessed; PA = physical activity; RR = risk ratio; SE = standard error; ST = sedentary time; USMh = net uncompensated sedentary behaviour metabolic equivalent hours

† Serious indirectness indicates measurement of intermediate/indirect outcomes or heterogeneity in exposures and comparisons assessed; certainty of evidence was not always downgraded for indirectness if it was not judged to impact the certainty in the findings for the outcome evaluated in the review

[a] Certainty of evidence not upgraded given serious risk of bias of most studies (generally lack of adjustment for potential confounding variables) and downgraded due to serious inconsistency in direction of effects and high statistical heterogeneity
[b] Unable to assess given data presented in article and supplemental material (i.e., qualitative results only, no effect estimates or measures of variance)
[c] Certainty of evidence not upgraded given unknown consistency and precision of effects
[d] Not able to assess given data presented in article and supplemental materials
[e] For the relationship between sitting time and CVD mortality and TV-viewing time and CVD mortality only. No dose response relationship was found according to level of PA for cancer mortality.
[f] Certainty of evidence upgraded given no serious limitations of included evidence and indication of dose-response relationship
[g] Certainty of evidence upgraded given no serious limitations in the body of evidence, individual participant-level data meta-analysis, and evidence of a dose response relationship
[h] Certainty of evidence not upgraded given serious inconsistency in pooled effects and serious indirectness given the variability in measurement and cut points defining sedentary time
[l] Certainty of evidence upgraded given no major study limitations. The potential overlap in study populations was not judged as being significant enough to warrant downgrading.
[j] Individual participant data meta-analysis
[k] Certainty of evidence not upgraded here given lack of detail about individual studies; however, all data comes from existing systematic reviews that serve as the basis for several secondary data analysis presented in this evidence profile. Main limitation is that it does not include all available and eligible cohort studies that could have contributed to this analysis.