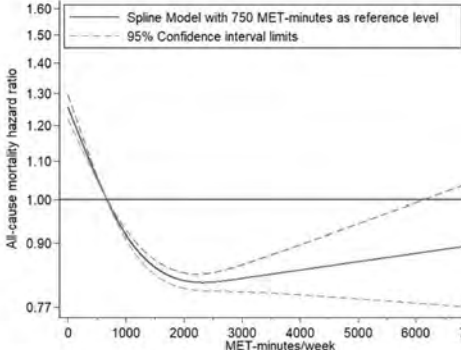


Table B.1.a. All-cause mortality: Association between physical activity and all-cause mortality among adults (in alphabetical order by author)

[See the Supplementary materials](#) for description of evidence of US PAGAC by outcome

Systematic review evidence	No. of studies/ Study design	Quality Assessment					Description of evidence Summary of findings	Certainty
		Risk of bias	Inconsistency	Indirectness†	Imprecision	Other		
Amagasa 2018 (2) Low	4 cohort studies N=17,133	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	All four cohort studies used data from NHANES 2003 to 2004 and 2005 to 2006; age range 50 to 80 years and compared replacing SB with LPA (3/4 studies) or quintiles of LPA (1/4 study). 3/4 studies reported replacing 30-60 min of SB with LPA was associated with lower all-cause mortality risk after adjustment for MVPA (HR range, 0.80 to 0.88 [95% CI range, 0.73 to 0.92]). 1/4 only found an effect among women with low MVPA when comparing modest to high levels of LPA vs. very low LPA.	MODERATE ^a

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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Blond 2019 (11) Moderate	48 prospective cohort studies N=NR	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Dose-response relationship	<p>Five studies used accelerometers to measure PA while all other studies used self-reported PA. Eight measures included occupational PA. Most studies focused on MVPA or leisure-time PA.</p> <p>A curvilinear relationship was found between total PA and all-cause mortality (p non-linearity <0.001). Compared with 750 MET min/week, those participating in 2000 MET min/week (4 hrs/week) had a statistically significantly lower risk of all-cause mortality (HR = 0.82 [95% CI, 0.81 to 0.84]) with an ARD = -16 deaths per 10,000 person years [95% CI, -17 to -14 deaths). Other comparisons presented below.</p>  <p>Figure 2 Dose-response relationship between physical activity and all cause mortality. Dose-response relation between metabolic equivalent of task (MET) min/week (with 750 MET min/week as the reference) and mortality risk estimated with restricted cubic spline regression and generalised least square trend estimation for summarised dose-response data.</p> <table border="1"> <caption>Table 1 Mortality HRs with 750 metabolic equivalent of task (MET) min/week as reference and estimated absolute rate differences per 10000 person years</caption> <thead> <tr> <th>MET min/week</th> <th>0</th> <th>500</th> <th>1000</th> <th>2000</th> <th>3000</th> <th>4000</th> <th>5000</th> <th>6000</th> </tr> </thead> <tbody> <tr> <td>Running (5 mph)^a</td> <td>0 hours/week</td> <td>1 hour/week</td> <td>2 hours/week</td> <td>4 hours/week</td> <td>6 hours/week</td> <td>8 hours/week</td> <td>10 hours/week</td> <td>12 hours/week</td> </tr> <tr> <td>All cause mortality</td> <td>Studies: 30</td> <td>35</td> <td>33</td> <td>34</td> <td>37</td> <td>5</td> <td>2</td> <td>3</td> </tr> <tr> <td>Participants^b</td> <td>812,489</td> <td>964,339</td> <td>358,878</td> <td>485,615</td> <td>225,616</td> <td>78,220</td> <td>4436</td> <td>37,856</td> </tr> <tr> <td>pp^c</td> <td>10,324,343</td> <td>9,522,179</td> <td>4,007,856</td> <td>5,235,829</td> <td>1,910,230</td> <td>686,649</td> <td>65,073</td> <td>48,6671</td> </tr> <tr> <td>Total cases^d</td> <td>47,141</td> <td>104,927</td> <td>36,201</td> <td>43,861</td> <td>12,342</td> <td>3634</td> <td>246</td> <td>2962</td> </tr> <tr> <td>HR (95% CI)</td> <td>1.26 (1.22 to 1.29)</td> <td>1.06 (1.05 to 1.06)</td> <td>0.92 (0.91 to 0.93)</td> <td>0.82 (0.81 to 0.84)</td> <td>0.83 (0.80 to 0.85)</td> <td>0.84 (0.79 to 0.90)</td> <td>0.86 (0.78 to 0.94)</td> <td>0.88 (0.78 to 0.99)</td> </tr> <tr> <td>ARD (95% CI)^e</td> <td>23 (19 to 25)</td> <td>5 (4 to 5)</td> <td>-7 (-8 to -6)</td> <td>-16 (-17 to -14)</td> <td>-15 (-18 to -13)</td> <td>-14 (-18 to -8)</td> <td>-12 (-19 to -5)</td> <td>-11 (-19 to -1)</td> </tr> </tbody> </table>	MET min/week	0	500	1000	2000	3000	4000	5000	6000	Running (5 mph) ^a	0 hours/week	1 hour/week	2 hours/week	4 hours/week	6 hours/week	8 hours/week	10 hours/week	12 hours/week	All cause mortality	Studies: 30	35	33	34	37	5	2	3	Participants ^b	812,489	964,339	358,878	485,615	225,616	78,220	4436	37,856	pp ^c	10,324,343	9,522,179	4,007,856	5,235,829	1,910,230	686,649	65,073	48,6671	Total cases ^d	47,141	104,927	36,201	43,861	12,342	3634	246	2962	HR (95% CI)	1.26 (1.22 to 1.29)	1.06 (1.05 to 1.06)	0.92 (0.91 to 0.93)	0.82 (0.81 to 0.84)	0.83 (0.80 to 0.85)	0.84 (0.79 to 0.90)	0.86 (0.78 to 0.94)	0.88 (0.78 to 0.99)	ARD (95% CI) ^e	23 (19 to 25)	5 (4 to 5)	-7 (-8 to -6)	-16 (-17 to -14)	-15 (-18 to -13)	-14 (-18 to -8)	-12 (-19 to -5)	-11 (-19 to -1)	MODERATE ^b
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		Risk of bias	Inconsistency	Indirectness†	Imprecision	Other		
Chastin 2019 (14) Moderate	12 prospective cohort studies N=127,724	No serious risk of bias	Serious inconsistency	Serious indirectness	No serious imprecision	None	<p>Studies compared high vs. low levels of physical activity (as defined by each study, and inconsistent between studies). Of the 5/12 prospective cohort studies that were pooled two studies used self-report of light PA whereas 3 studies used accelerometer-measured light PA. Light PA was defined variably including 100-2019 counts/min, 100-1040 counts/min, using Freedson cutpoints, MET>1.5 – 2.99, or self-report light activity (e.g., very easy). Most studies were among adults ≥50 years.</p> <p>A pooled analysis of 5 studies reporting all-cause mortality found a statistically significant reduced risk of all-cause mortality for the highest vs. lowest levels of light intensity physical activity (HR = 0.71 [95% CI 0.62 to 0.83], 5 studies).</p>	LOW ^c
Dinu 2019 (19) Low	11 prospective cohort studies N=231,259	No serious risk of bias	Serious inconsistency	Serious indirectness	No serious imprecision	None	<p>All studies evaluated the effects of active commuting (cycling 5 studies, walking 3 studies, mixed mode 3 studies) on health outcomes. Exposure levels of active commuting were variably reported as minutes spent walking or cycling for transportation per day, as dichotomized variables (yes or no), or as METs with the reference category as no active commuting in most studies. Follow-up ranged from 4 to 25 years.</p> <p>Persons engaged in active commuting had a significantly lower risk of all-cause mortality compared with those participating in no active commuting (RR = 0.92 [95% CI 0.85 to 0.98], 11 studies). When the 3 studies that had the largest estimates of effects were removed from the analysis, the heterogeneity was reduced (I² of 67% to 11%) and the direction of effect changed (RR = 1.00 [95% CI, 0.96 and 1.04], 8 studies).</p>	LOW ^d

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 (20) 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	<p>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 PA and SB; exposure variables differed within each study including total volume of PA (cpm), min/day spend in intensity-specific variables (sedentary ≤100 cpm, light 101-1951 cpm, moderate to vigorous ≥1952 cpm, vigorous ≥5725 cpm), bouts of MVPA (10 or more minutes of consecutive readings ≥1952 cpm). Data was categorized into quartiles with the least active quartile as the referent.</p> <p>Compared with the lowest levels of PA, any level of PA regardless of intensity (i.e., total PA) was associated with a lower risk of mortality. The magnitude of risk for increasing quarter of total PA was least active (referent, 1.00), 2nd quarter (adjusted HR = 0.48 [95% CI, 0.43 to 0.54]), 3rd quarter (adjusted HR = 0.34 [95% CI, 0.26 to 0.45]), and 4th quarter (adjusted HR = 0.27 [95% CI, 0.23 to 0.32]). Higher levels of light intensity PA, low light intensity PA, and high light intensity PA were also significantly associated with reduced risk of death during follow-up as was MVPA (including when controlling for SB time) (table below).</p> <table border="1"> <caption>Table 2 Meta-analysis for associations between total physical activity, intensities of physical activity or sedentary time by quarters and all cause mortality</caption> <thead> <tr> <th rowspan="2">Variables</th> <th colspan="4">Hazard ratios (95% CI) for all cause mortality*. No of participants: No of deaths</th> </tr> <tr> <th>First quarter (least active)</th> <th>Second quarter</th> <th>Third quarter</th> <th>Fourth quarter (most active)</th> </tr> </thead> <tbody> <tr> <td>Model B†</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Total physical activity (cpm)</td> <td>1 (ref) (n=9096, 1187)</td> <td>0.48 (0.43 to 0.54) (n=9105, 483)</td> <td>0.34 (0.26 to 0.45) (n=9096, 265)</td> <td>0.27 (0.23 to 0.32) (n=9086, 214)</td> </tr> <tr> <td>Physical activity intensity</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Light (min/d)</td> <td>1 (ref) (n=9073, 1089)</td> <td>0.60 (0.54 to 0.68) (n=9101, 511)</td> <td>0.44 (0.38 to 0.51) (n=9090, 320)</td> <td>0.38 (0.28 to 0.51) (n=9119, 229)</td> </tr> <tr> <td>Low light (min/d)</td> <td>1 (ref) (n=9066, 1010)</td> <td>0.66 (0.56 to 0.77) (n=9106, 518)</td> <td>0.47 (0.38 to 0.58) (n=9112, 353)</td> <td>0.42 (0.34 to 0.52) (n=9099, 268)</td> </tr> <tr> <td>High light (min/d)</td> <td>1 (ref) (n=9054, 1159)</td> <td>0.55 (0.49 to 0.63) (n=9120, 483)</td> <td>0.38 (0.30 to 0.46) (n=9088, 278)</td> <td>0.37 (0.32 to 0.44) (n=9111, 229)</td> </tr> <tr> <td>Moderate to vigorous (min/d)</td> <td>1 (ref) (n=9003, 1139)</td> <td>0.64 (0.55 to 0.74) (n=9113, 468)</td> <td>0.51 (0.40 to 0.74) (n=9113, 305)</td> <td>0.32 (0.43 to 0.41) (n=9105, 227)</td> </tr> <tr> <td>Sedentary (min/d)</td> <td>1 (ref) (n=9152, 327)</td> <td>1.28 (1.09 to 1.51) (n=9105, 417)</td> <td>1.71 (1.36 to 2.15) (n=9096, 562)</td> <td>2.63 (1.94 to 3.58) (n=9080, 841)</td> </tr> </tbody> </table> <p>cpm=counts per minute Model A adjusted for sex before applications; age, and wear time (n=34812, 2304 deaths); Model B adjusted for sex (after applications; age, body mass index, socioeconomic position, and wear time (n=34383, 2349 deaths); Model C, additionally adjusted for covariates listed in table 1 (n=35932, 2047 deaths). *By Cox regression. †Multivariable regression physical activity and sedentary time are mutually adjusted.</p> <p>Differences in min/day between the referent (least active) and 2nd quarter were broadly equal to 60 min/day of light intensity PA, 35 min/day of low light intensity PA, 25 min/day of high light intensity PA, and 5 min/day of MPVA.</p> <p>A non-linear, dose-response association was found between all exposure variables and mortality ($p < 0.02$ for all exposure variables) (figure below). The maximal risk reduction for total PA was observed at about 300 cpm (adjusted HR = 0.34 [95% CI 0.27 to 0.43]). Maximal risk reductions for light intensity PA was ~375 min/day, low light intensity PA at ~325 min/day, high light intensity PA at ~80 min/day, and MVPA at ~24 min/day. No further risk reductions occurred with higher levels of activity except for low light intensity PA where the risk appeared to reduce further.</p>	Variables	Hazard ratios (95% CI) for all cause mortality*. No of participants: No of deaths				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 0.46) (n=9088, 278)	0.37 (0.32 to 0.44) (n=9111, 229)	Moderate to vigorous (min/d)	1 (ref) (n=9003, 1139)	0.64 (0.55 to 0.74) (n=9113, 468)	0.51 (0.40 to 0.74) (n=9113, 305)	0.32 (0.43 to 0.41) (n=9105, 227)	Sedentary (min/d)	1 (ref) (n=9152, 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 3.58) (n=9080, 841)	HIGH ^e
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							<p>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) and FHS (Women's Health Study) 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 4. cpm=counts per minute</p>	
O'Donovan 2017 ¹ (51) Good quality ⁹	Pooled cohort analysis N=37,059	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Compared with those who met PA guidelines^h and whose HDL-C was normal, all-cause mortality risk was elevated in those who did not meet PA guidelines and whose HDL-C was normal (adjusted HR = 1.37 [95% CI, 1.16 to 1.61]) and in those who did not meet PA guidelines and whose HDL-C was low (adjusted HR = 1.65 [95% CI 1.37 to 1.98]).	MODERATE ⁱ

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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Siahpush 2019 ^l (63) Good quality ^g	Pooled cohort analysis N=68,706	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	Smokers who reported meeting aerobic and strengthening PA guidelinesⁿ had significantly lower risk of all-cause mortality (adjusted HR = 0.71 [95% CI, 0.62 to 0.81]) than those not meeting either recommendation as did those meeting aerobic PA recommendations (adjusted HR = 0.81 [95% CI 0.75 to 0.88]) versus those not meeting either recommendation. There was no association between all-cause mortality and meeting strength recommendations (and not aerobic PA recommendations) vs. meeting neither recommendation (HR = 0.90 [95% CI, -.76 to 1.07]).	MODERATE ⁱ
Stamatakis 2018 ^k (65) Good quality ^g	Pooled cohort analysis N=80,306	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Dose-response relationship ^l	Adherence to both aerobic and strengthening PA guidelinesⁿ vs. not adhering to either (adjusted HR = 0.71 [95% CI 0.57 to 0.87]) and adherence to the strength exercise guideline ^m vs. not adhering (HR = 0.80 [95% CI, 0.70 to 0.91]) was associated with significantly reduced risk of all-cause mortality Additionally, participation in any strength-promoting exercise vs. no strength-promoting exercise (adjusted HR = 0.77 [95% CI, 0.69 to 0.87]), as well as own-body-weight strength activities vs. none and gym-based strength activities vs. none were associated with a significantly reduced risk of all-cause mortality.	MODERATE ⁿ

Abbreviations: ARD = absolute rate difference; CI = confidence interval; cpm = counts per minute; HDL-C = high-density lipoprotein cholesterol; HR = hazards ratio; LPA = light physical activity; MET =metabolic equivalent of task; min = minutes; MVPA = moderate-to-vigorous intensity PA; NR = not reported; PA = physical activity; RR = risk ratio; SB = sedentary behaviour

† 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 upgraded given no serious limitations in included evidence

^b Certainty of evidence upgraded given no serious risk of bias of included studies and evidence of dose-response relationship; however, serious inconsistency (high between study variance, $I^2 > 77\%$) present

^c Certainty of evidence not upgraded given serious inconsistency in effects between studies and statistical heterogeneity and indirectness in comparisons of exposures

^d Certainty of evidence not upgraded given serious risk of bias (not appropriately adjusting for confounding), serious inconsistency (heterogeneity) and indirectness in comparisons of exposures

^e 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

^f Not a systematic review. Pooled analysis of nine cohorts of the Health Survey for England and the Scottish Health Survey and linked to the British National Health Service Central Registry for data on mortality

^g Quality rated based on the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (77)

^h 150 min/week of moderate-intensity leisure time PA, or at least 75 min/week of vigorous-intensity leisure-time PA, or an equivalent combination and performing strengthening exercises ≥ 2 times/week

ⁱ Certainty of evidence upgraded given no serious limitations in included evidence

^j Not a systematic review. Pooled analysis of 1998-2009 National Health Index Survey and linked National Death Index

^k Not a systematic review. Pooled analysis of 11 cohorts of the Health Survey for England and the Scottish Health Survey and linked to the British National Health Service Central Registry for data on mortality

^l There was evidence of a trend for greater reduced risk for all-cause mortality when comparing high, low, and no weekly volume of any strength exercise and own-body-weight strength activity

^m Performing strengthening exercises ≥ 2 times/week

ⁿ Certainty of evidence upgraded given no serious limitations in included evidence; some evidence of dose-response relationship but not judged to warrant further upgrading