P-annotatePDF-v12

INSTRUCTIONS ON THE ANNOTATION OF PDF FILES

To view, print and annotate your content you will need Adobe Reader version 9 (or higher). This program is freely available for a whole series of platforms that include PC, Mac, and UNIX and can be downloaded from http://get.adobe.com/reader/. The exact system requirements are given at the Adobe site: http://www.adobe.com/products/reader/tech-specs.html.

Note: ***Please do NOT make direct edits to the PDF using the editing tools as doing so could lead us to overlook your desired changes.*** *Rather, please request corrections by using the tools in the Comment pane to annotate the PDF and call out the changes you are requesting. If you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file.*

PDF ANNOTATIONS

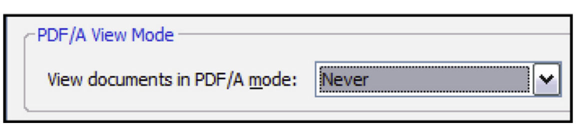
Adobe Reader version 9

When you open the PDF file using Adobe Reader, the Commenting tool bar should be displayed automatically; if not, click on 'Tools', select 'Comment & Markup', then click on 'Show Comment & Markup tool bar' (or 'Show Commenting bar' on the Mac). If these options are not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than 9 or the PDF has not been prepared properly.

(Mac)

PDF ANNOTATIONS (Adobe Reader version 9)

The default for the Commenting tool bar is set to 'off' in version 9. To change this setting select 'Edit | Preferences', then 'Documents' (at left under 'Categories'), then select the option 'Never' for 'PDF/A View Mode'.

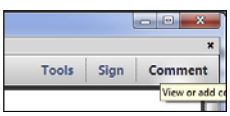


(Changing the default setting, Adobe version 9)

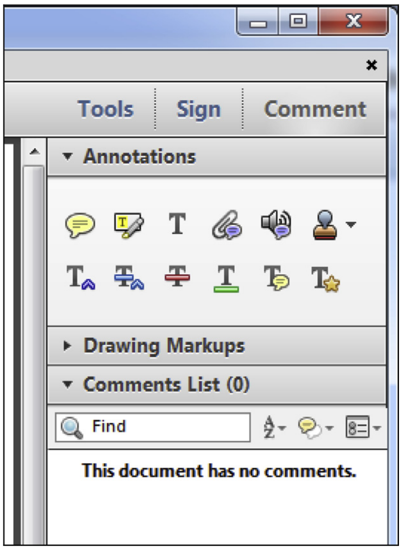
Adobe Reader version X and XI

To make annotations in the PDF file, open the PDF file using Adobe Reader XI, click on 'Comment'.

If this option is not available in your Adobe Reader menus then it is possible that your Adobe Acrobat version is lower than XI or the PDF has not been prepared properly.



This opens a task pane and, below that, a list of all Comments in the text. These comments initially show all the changes made by our copyeditor to your file.



HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Insert text	Click the 'Text Edits' button on the Commenting tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on 'x' in the top right-hand corner.	Click the 'Insert Text' icon on the Comment tool bar. Click to set the cursor location in the text and simply start typing. The text will appear in a commenting box. You may also cut-and-paste text from another file into the commenting box. Close the box by clicking on '_' in the top right-hand corner. Replace text
Replace text	Click the 'Text Edits' button on the Commenting tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).	Click the 'Replace (Ins)' icon on the Comment tool bar. To highlight the text to be replaced, click and drag the cursor over the text. Then simply type in the replacement text. The replacement text will appear in a commenting box. You may also cut-and-paste text from another file into this box. To replace formatted text (an equation for example) please Attach a file (see below).
Remove text	Click the 'Text Edits' button on the Commenting tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.	Click the 'Strikethrough (Del)' icon on the Comment tool bar. Click and drag over the text to be deleted. Then press the delete button on your keyboard. The text to be deleted will then be struck through.
Highlight text/ make a comment	Click on the 'Highlight' button on the Commenting tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.	Click on the 'Highlight Text' icon on the Comment tool bar. Click and drag over the text. To make a comment, double click on the highlighted text and simply start typing.
Attach a file	Click on the 'Attach a File' button on the Commenting tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. To make a comment, go to 'General' in the 'Properties' window, and then 'Description'. A graphic will appear in the PDF file indicating the insertion of a file.	Click on the 'Attach File' icon on the Comment tool bar. Click on the figure, table or formatted text to be replaced. A window will automatically open allowing you to attach the file. A graphic will appear indicating the insertion of a file.
Leave a note/ comment	Click on the 'Note Tool' button on the Commenting tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.	Click on the 'Add Sticky Note' icon on the Comment tool bar. Click to set the location of the note on the document and simply start typing. Do not use this feature to make text edits.

HOW TO...		
Action	**Adobe Reader version 9**	**Adobe Reader version X and XI**
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
Undo/delete change	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.	To undo any changes made, use the right click button on your mouse (for PCs, Ctrl-Click for the Mac). Alternatively click on 'Edit' in the main Adobe menu and then 'Undo'. You can also delete edits using the right click (Ctrl-click on the Mac) and selecting 'Delete'.

SEND YOUR ANNOTATED PDF FILE BACK TO ELSEVIER

Save the annotations to your file and return as instructed by Elsevier. Before returning, please ensure you have answered any questions raised on the Query Form and that you have inserted all corrections: later inclusion of any subsequent corrections cannot be guaranteed.

FURTHER POINTS

- Any (grey) halftones (photographs, micrographs, etc.) are best viewed on screen, for which they are optimized, and your local printer may not be able to output the greys correctly.
- If the PDF files contain colour images, and if you do have a local colour printer available, then it will be likely that you will not be able to correctly reproduce the colours on it, as local variations can occur.
- If you print the PDF file attached, and notice some 'non-standard' output, please check if the problem is also present on screen. If the correct printer driver for your printer is not installed on your PC, the printed output will be distorted.

Our reference: AMEPRE 5518

AUTHOR QUERY FORM

ELSEVIER	Journal: AMEPRE Article Number: 5518	Please e-mail your responses and any corrections to: E-mail: T.Person@elsevier.com

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof. It is crucial that you NOT make direct edits to the PDF using the editing tools as doing so could lead us to overlook your desired changes. Rather, please request corrections by using the tools in the Comment pane to annotate the PDF and call out the changes you would like to see. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult http://www.elsevier.com/artworkinstructions.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof.

Location in article	Query / Remark: Click on the Q link to find the query's location in text Please insert your reply or correction at the corresponding line in the proof
	If there are any drug dosages in your article, please verify them and indicate that you have done so by initialing this query.
Q1	The author names have been tagged as given names and surnames (surnames are highlighted in teal color). Please confirm if they have been identified correctly. Please also confirm if the author names have been presented in the desired order, please carefully verify the spelling of all authors' names, and confirm the accuracy and completeness of any affiliations.
Q2	Author: "PRSIMA" was added to the Figure 1 legend to specify the guidelines used.
	Please check this box or indicate your approval if you have no corrections to make to the PDF file. ☐

Thank you for your assistance.

American Journal of Preventive Medicine

REVIEW ARTICLE

Replacing Sedentary Time: Meta-analysis of Objective-Assessment Studies

Name is "Borja" and "del Pozo-Cruz" is the surname

Q1 Jesús del Pozo-Cruz, PhD,[1] Antonio García-Hermoso, PhD,[2] Rosa M. Alfonso-Rosa, PhD,[1,3] Francisco Alvarez-Barbosa, PhD,[1,4] Neville Owen, PhD,[5,6] Sebastien Chastin, PhD,[7,8] Borja del Pozo-Cruz, PhD[9,10]

Name is "Jesús" and "del Pozo-Cruz" is the surname

Context: The aim was to summarize estimates of the potential benefits for cardiometabolic risk markers and all-cause mortality of replacing time spent in sedentary behaviors with light-intensity physical activity or with moderate to vigorous physical activity, from studies using device-based measurement.

Evidence acquisition: Four databases covering the period up to December 2016 were searched and analyzed (February 2017). Data were extracted by two independent reviewers. For the meta-analyses, the estimated regression coefficients (β) and 95% CIs were analyzed for BMI, waist circumference, and high-density lipoprotein cholesterol. Pooled relative rate and 95% CIs were calculated for fasting glucose, fasting insulin, and homeostatic model assessment-insulin resistance values. Hazard ratios were extracted from studies of all-cause mortality risk.

Evidence synthesis: Ten studies (with 17,390 participants) met the inclusion criteria. Reallocation of 30 minutes of sedentary time to light-intensity physical activity was associated with reductions in waist circumference, fasting insulin, and all-cause mortality risk; and with an increase in high-density lipoprotein cholesterol. Reallocating 30 minutes of sedentary time to moderate to vigorous physical activity was associated with reductions in BMI, waist circumference, fasting glucose, fasting insulin, and all-cause mortality (not pooled) and with an increase in high-density lipoprotein cholesterol.

Conclusions: Replacing sedentary time with either light-intensity physical activity or moderate to vigorous physical activity may be beneficial, but when sedentary time is replaced with moderate to vigorous physical activity, the predicted impacts are stronger and apparent for a broader range of risk markers. These findings point to potential benefits of replacing sedentary time with light-intensity physical activity, which may benefit those less able to tolerate or accommodate higher-intensity activities, including many older adults.

Am J Prev Med 2018;▌(▌):▌▌▌–▌▌▌.

CONTEXT

The adverse health consequences of sedentary behavior (time spent sitting) have more recently been identified in relation to cardiovascular disease risk[1,2] and all-cause mortality,[3] controlling for the influence of moderate to vigorous physical activity[4] (MVPA); these adverse health consequences of sedentary behavior have been shown for a range of health outcomes.[5] Some countries have now expanded the scope of their PA guidelines, with joint recommendations on increasing PA and reducing sedentary time.[6,7]

Time spent standing or being physically active is time that is not spent sedentary. Thus, the effect of spending

From the [1]Department of Physical Education and Sports, University of Seville, Seville, Spain; [2]Laboratorio de Ciencias de la Actividad Física, el Deporte y la Salud, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Santiago de Chile, Chile; [3]Area of Human Motricity and Sport Performance, University of Seville, Seville, Spain; [4]Department of Physical Activity and Sport, Cardenal Espinola CEU, Seville, Spain; [5]Swinburne University of Technology, Melbourne, Australia; [6]The Baker Heart and Diabetes Institute, Melbourne, Australia; [7]Institute for Applied Health Research, School of Health and Life Science, Glasgow Caledonian University, Glasgow, Scotland, United Kingdom; [8]Department of Sports and Movement Sciences, Ghent University, Ghent, Belgium; [9]Institute for Positive Psychology and Education, Faculty of Health Sciences, Australian Catholic University, Sydney, Australia; and [10]Department of Exercise Sciences, University of Auckland, Auckland, New Zealand

Address correspondence to: Borja del Pozo-Cruz, PhD, Institute for Positive Psychology and Education, Faculty of Health Sciences, Australian Catholic University, P.O. Box 968, North Sydney, NSW 2059, Australia. E-mail: borja.delpozocruz@acu.edu.au.

0749-3797/$36.00
https://doi.org/10.1016/j.amepre.2018.04.042

Table 1. Pooled Effect Size of Replacing 30 Minutes of Sedentary Time With LIPA and MVPA

Outcomes of interest	Replacing sedentary time with LIPA					Replacing sedentary time with MVPA				
	n	Effect size (95% CI)	*p*-value	I^2	Egger test (*p*-value)	*n*	Effect size (95% CI)	*p*-value	I^2	Egger test (*p*-value)
BMI, β	6	−0.091 (−0.244, 0.063)	0.247	73.7	0.446	6	−1.071 (−1.796, −0.346)	0.004**	60.8	0.381
Waist circumference, β	5	−0.567 (−0.862, −0.272)	<0.001**	37.0	0.057	5	−2.955 (−3.878, −2.032)	<0.001**	83.0	<0.001
HDL-c, β	3	0.012 (0.002, 0.023)	0.022*	73.4	0.459	3	0.035 (0.021, 0.050)	<0.001**	0.0	0.650
Fasting glucose, RR	4	0.998 (0.996, 1.000)	0.058	0.0	0.505	4	0.992 (0.984, 0.999)	0.024*	0.0	0.447
Fasting insulin, RR	3	0.974 (0.964, 0.984)	<0.001**	0.0	0.718	3	0.879 (0.847, 0.911)	<0.001**	0.0	0.482
HOMA-IR, RR	2	0.994 (0.879, 1.124)	0.919	81.3	–	2	0.998 (0.877, 1.136)	0.977	97.1	–

Note: Boldface indicates statistical significance (*$p<0.05$; **$p<0.01$).
HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; LIPA, light-intensity physical activity; MVPA, moderate to vigorous physical activity; RR, risk ratio.

more or less time being either physically active or sedentary will impact outcomes in a direct way, but those outcomes will also depend at least in part on the other activities being displaced. A recent meta-analysis pointed out that although reducing total sedentary time is feasible, in most intervention studies it has not been clear to which component of time use the sedentary time has been reallocated.[8] Although there are published studies identifying potential for cardiometabolic health benefits and mortality risk reductions of replacing sedentary time with light-intensity PA (LIPA) or MVPA,[9–14] there are no meta-analysis findings available to synthesize what is known about the potential impacts of such substitutions.

A systematic review and meta-analysis is necessary to synthesize the findings of studies that have used an isotemporal substitution approach (this approach assumes that activity time in a day is finite and that performing one activity involves substitution for another; and depending on the intensity of activity that is replaced, the estimated effects on health might be different[15]) to estimate the potential cardiometabolic and all-cause mortality outcomes of reallocating objectively assessed time spent in sedentary behaviors to LIPA or to MVPA.

EVIDENCE ACQUISITION

This meta-analysis was undertaken in accordance with the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE)[16] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17] The protocol was registered with the National Institute for Health Research International prospective register of systematic reviews (PROSPERO) under the registration number CRD42016037585.

Data Sources

Electronic database searchers of Ovid Medline (through the search engine PubMed); Scopus; SPORTdiscus; and Web of Knowledge conducted in December 2016. The last search was performed on December 30, 2016. No limit on the date of publication was imposed. The following search terms and keywords were used: ([*sedentary lifestyle* or *light physical activity* or *sedentary behaviour* or *sedentary time*] or *accelerometry* or *accelerometer*) and (*isotemporal substitution* or *sedentary break* or *displac* sedentary time* or *replacing* or *displacing* or *reallocating* or *substituting*) and (*metabolic disease* or *body composition* or *cholesterol* or *mortality* or *metabolic risk* or *metabolic biomarker* or *waist circumference* or *cardiovascular disease*). The complete search strategy is shown in Appendix Table 1 (available online). Also, reference lists were examined to detect studies potentially eligible for inclusion.

Eligibility Criteria

Studies were included in the review if they met the following inclusion criteria: (1) included people aged ≥18 years; (2) reported objective measure of activity (self-report methods can under- or over-estimate the amount of PA and sedentary behavior (SB) performed, because of biases introduced by recall error, social desirability, and other issues; therefore, only studies conducted with objective methods of PA assessment were included); (3) reported, using isotemporal models, on the effects of replacing sedentary behavior with LIPA or MVPA on at least one cardiometabolic or mortality as an outcome of interest; (4) were written in English; and (5) reported primary research findings.

Two independent reviewers carried out the screening and review, with a third reviewer sought in case of disagreement. Articles were first screened and selected for eligibility based on title and abstract. The full text was then reviewed after confirming eligibility to be included and data were extracted.

Data Collection

Information extracted was as follows: characteristics of the sample, method of objective measurement of PA, the amount of sedentary time being replaced, outcomes of interest, analytical approach, and main results from each of the studies. Also, data that would assist in findings from the meta-analysis from the different studies (i.e., regression coefficient and 95% CI representing the effect of replacing SB with more active behavior on the outcome of interest) were extracted. To maximize the generalizability of the findings, when data were not available the original authors were contacted.

Risk of Bias

An assessment of each study's quality was made using an adjusted format of the Newcastle–Ottawa quality assessment scale.[18] This scale contains eight items categorized into three domains (selection, comparability, and exposure). A star system is used to enable semiquantitative assessment of study quality, such that the highest-quality studies are awarded a maximum of one star per item with the exception of the comparability domain, which allows allocating two stars. Thus, the score ranges from zero to nine stars (maximum score for cohort and cross-sectional studies was nine and seven, respectively).

Data Synthesis and Analytical Approach

A one-step individual participant data meta-analysis was conducted. All analyses were carried out using Comprehensive Meta-analysis Software, Biostat, version 3. The estimated regression coefficients (β) and 95% CIs were combined and used in the meta-analysis for BMI, body fat, waist circumference (WC), and high-density lipoprotein cholesterol (HDL-c). Assuming linear regression properties,[19] results from original studies reporting estimated β and 95% CIs for 10-minute units (n=2) were scaled up to 30 minutes (β and 95% CIs X 3) for comparison purposes. Also, the relative rate (RR) and 95% CIs were calculated for fasting glucose, fasting insulin, and homeostatic model assessment–insulin resistance (HOMA-IR) values. Finally, hazard ratios (HRs) with associated 95% CIs were extracted from studies for risk of all-cause mortality. The random effects model (DerSimonian–Laird approach) was used in all cases to summarize the pooled β and RR. All-cause mortality studies HRs were not pooled because all three studies utilized overlapping data from the National Health and Nutrition Examination Survey. In that case, the range of values was reported. The likelihood approach with random effects was used to better account for the imprecision in the estimate of between-study variance.[20] When studies presented several statistical risk-adjustment models, only values associated with the statistical models that contained the fewest number of additional covariates were considered, in order to improve comparability across studies.

The percentage of total variations across the studies because of heterogeneity (Cochran's Q-statistic) was estimated using I^2. Values I^2 of <25%, 25%–50%, and >50% were considered as small, medium, and large amounts of heterogeneity respectively.[21]

Small-study effects bias was assessed using the extended Egger's test, and funnel plots were used to graphically investigate publication bias among studies.[22,23]

Finally, a sensitivity analysis was conducted to assess the robustness of the summary estimates to determine whether or not a particular study accounted for the heterogeneity. A series of analyses were therefore conducted by sequentially omitting one study at each turn.

EVIDENCE SYNTHESIS

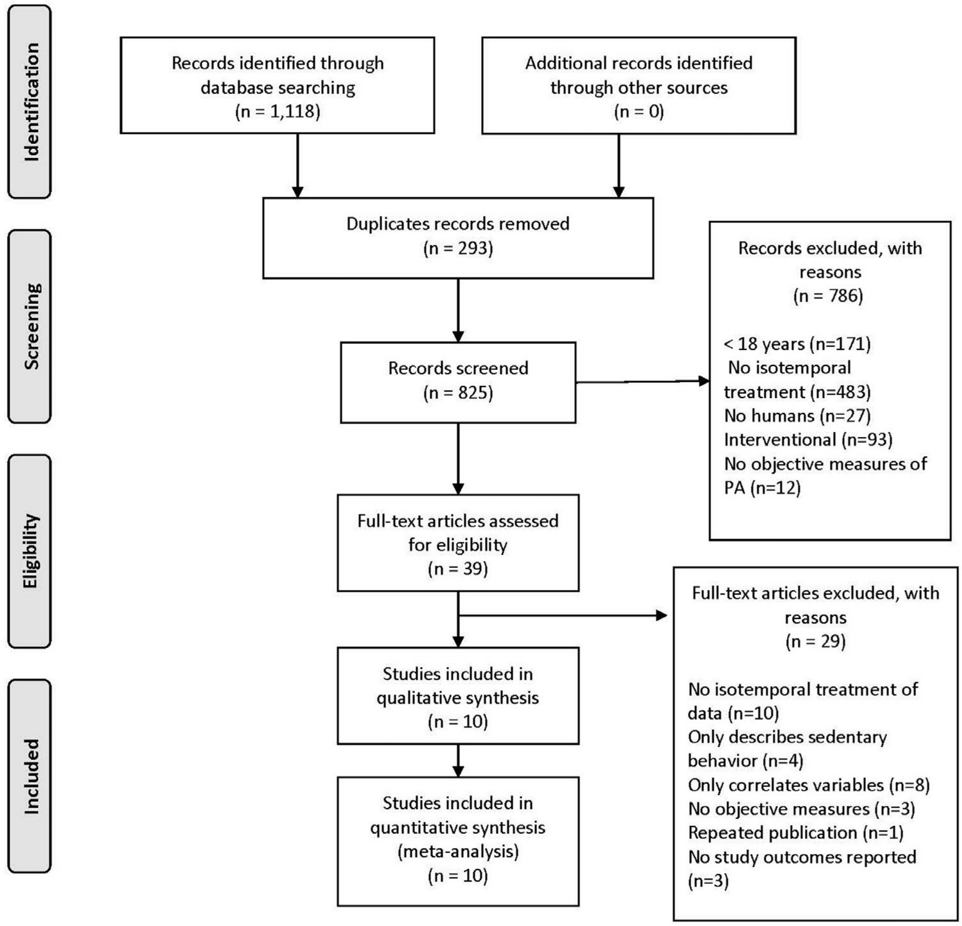
Study Selection

The search strategy initially identified 1,118 articles (Figure 1). After initial screening, 39 full articles were retrieved. Of these, 29 were rejected (ten had not used an isotemporal substitution model, four only addressed sedentary behavior, eight examined correlates of behavior, three had no accelerometer-based measures, one was a duplicated publication in different data sets, and three had no study outcomes). Finally, only ten studies were included in the systematic review and meta-analysis.

Study Characteristics

The 10 studies included a total of 17,390 participants. Sample sizes ranged from 279 to 5,377 individuals. Gender was evenly distributed (men, 50.31%) and the mean age was 55.8 years.

Seven of the studies were cross-sectional, observational investigations, and three were prospective survival analyses. The characteristics of the studies are summarized in Appendix Table 2 (available online). All used accelerometers to assess SB and PA. Definitions of SB, MVPA, and LIPA were based on previously validated counts per minute (cpm) cut-off points registered with an accelerometer. The SB cut offs that were employed varied across the studies, with <100 cpm when only data from the vertical axis of the accelerometer were used or <200 cpm when data from the vector axis of the accelerometer were used. Similarly, the LIPA cut-off criterion used was either 100–1,951 cpm (vertical-axis data) or 200–2,689 cpm. The MVPA cut offs that were >1,951 cpm when only data from the vertical axis were used and >2,690 cpm when data from the vector axis of the accelerometer were used. In one study[9] where data from the vertical axis of the accelerometer were used, the cut offs for LIPA and MVPA were ≥100 to 2,019 cpm and ≥2,020 cpm respectively. Epoch duration was similar across the studies (i.e., 1-minute). There was one study that utilized an epoch of 1 second[10] and employed a proportional to <100 cpm SB/60-second epoch cut off.



Q2 OK

Figure 1. PRISMA flow diagram of the study.

Another study[19] employed an epoch of 15 seconds and a proportional to <100 cpm SB/15-second epoch cut off. Age ranged from 20 to 89 years. Sample size and sampling strategy varied from small convenience samples to large representative samples. Isotemporal substitution modeling was reported for BMI (*n*=6); WC (*n*=5); HDL-c (*n*=3); fasting glucose (*n*=4); insulin (*n*=3); HOMA-IR (*n*=2); and all-cause mortality (*n*=3), with time blocks exchanged being 30 minutes in duration.

Risk of Bias

All of the nine cross-sectional studies and all three of the longitudinal studies were deemed to be of high quality, with a Newcastle–Ottawa score ≥6 (Appendix Table 3, available online).

Effects of Reallocating Sedentary Time to Light-Intensity Physical Activity and to Moderate to Vigorous Physical Activity

Table 1 and Appendix Figure 4 (available online) show the estimated regression coefficients (β) and RRs, and associated 95% CI of replacing 30 minutes of sedentary time with LIPA and MVPA on the selected outcomes.

Reallocation of 30 minutes of sedentary time to LIPA was predicted to be associated with reductions in WC (0.57 cm/30 minutes, β= −0.57, 95% CI= −0.86, −0.27, $p<0.001$) and fasting insulin (2.4%/30 minutes, RR=0.97, 95% CI=0.96, 0.98, $p<0.001$); and with an increase in HDL-c (0.012 mmol/L/30 minutes, β=0.012, 95% CI=0.002, 0.023, $p=0.022$). Estimates were not significant for BMI, fasting insulin, and HOMA-IR.

Reallocating 30 minutes of sedentary time to MVPA was predicted to be associated with reductions in BMI (1/30 minutes, β= −1.07, 95% CI= −1.80, −0.35, $p=0.004$); WC (2.9 cm/30 minutes, β= −2.95, 95% CI= −3.88, −2.03, $p=0.005$); fasting glucose (0.01%/30 minutes, RR=0.99, 95% CI=0.98, 0.99, $p=0.023$); and fasting insulin (1.12%/30 minutes, RR=0.88, 95% CI=0.85, 0.91, $p<0.001$); and with an increase in HDL-c (0.03 mmol/L/30 minutes, β=0.03, 95% CI=0.02, 0.05, $p<0.001$). Estimates were not significant for HOMA-IR.

Results from the all-cause mortality studies show that replacing 30 minutes of sedentary time with LIPA (with HRs ranging from 0.80 to 0.87) or MVPA (with HRs ranging from 0.19 to 0.51) is estimated to be associated with a lower risk of all-cause mortality.

Publication Bias and Sensitivity Analysis

Both funnel plot asymmetry and Egger test show no significant publication bias (Table 1 and Appendix Figure 5, available online).

The sensitivity analysis conducted showed that one particular study accounted for the majority of the heterogeneity[10] showing a nonsignificant effect of replacing SB with MVPA on BMI after removing the aforementioned study from the pooled analysis.

DISCUSSION

The main findings of this meta-analysis show that reallocating sedentary time to LIPA or MVPA may result in reductions in WC and fasting insulin, and increased HDL-c. Equal time-exchange of SB with MVPA may lead to additional reductions of fasting glucose, all-cause of mortality, and increased HDL-c levels. These findings suggest potential benefits of replacing SB with LIPA. This might provide alternative intervention strategies as it may be more feasible and less challenging than more strenuous activity (which is also more difficult than lighter activity to be fit into daily life routines, especially in particular domains, such as work or education, where SB is particularly prevalent), for enhancing cardiovascular health among the general adult population.[8] Also, LIPA could be a feasible strategy to increase the total volume of PA among those considered already active and therefore could bring additional cardiovascular benefits.[24]

There is evidence from experimental trials that breaking up sedentary time can beneficially impact cardiometabolic risk markers.[25,26] Consistent with what was found in this meta-analysis, such experimental studies have demonstrated that regular brief activity breaks during otherwise sedentary periods translate into cardiometabolic risk improvement in adults[27,28] and may have the potential of preventing mortality from, at least, cardiovascular disease.[29,30] There is evidence that interruption of sitting with short, frequent bouts of at least LIPA improves postprandial glycemia.[31,32] However, the current evidence on effectiveness of interventions targeting exclusively SB to influence biological dimensions of health risk is limited.[33]

Evidence from experimental studies suggests that SB detrimentally alters metabolic function and can be associated with chronic inflammation.[34] Observational studies and RCTs have shown that increased PA improves insulin sensitivity[35] and lowers chronic inflammation.[36] Statistically significant associations with cardiometabolic biomarkers identified in this meta-analysis (i.e., HDL-c, fasting glucose, and fasting insulin) appeared to be different, depending on the intensity of the type of PA with which sedentary time was replaced. The current findings suggest that replacing SB with MVPA may have greater beneficial effects as compared with doing so with lower-intensity activities. Also, there is other evidence to suggest benefit when time in sedentary bouts was reallocated to long PA bouts: substituting 120 minutes of sedentary time with equal LIPA may have about the same theoretic beneficial effect on HOMA-IR as would substituting 40 minutes of SB for an equal duration of MVPA.[37]

Although mechanisms underpinning the findings of this meta-analysis are not well known, some supporting evidence could be found in animal models as described by Hamilton and colleagues.[38] Even modest local muscle contractions seem to maintain lipoprotein lipase activity, which could contribute to the detected associations. Of particular interest is that total volume of PA activity appears to have stronger associations with cardiometabolic biomarkers than MVPA.[39,40] In addition, energy expenditure associated with spontaneous PA, the Non-exercise Activity Thermogenesis has been associated with human obesity markers.[41] The findings presented here need to be considered in light of the potential limitations of isotemporal substitution method.[42] Therefore, confirming these observations in experimental designs is of interest for public health authorities, in particular, identifying for how long these reallocations of time need to be sustained to achieve beneficial outcomes. Findings from a recent meta-analysis[8] suggest that it is possible to reduce sedentary time by 30 minutes per day in the short and medium term with potentially clinically relevant benefits (as shown in this meta-analysis). However, the same meta-analysis states that it is still unclear whether such behavioral change is feasible and sustainable over the long term, because of the lack of studies.

Consistently with previous findings,[43,44] reallocating 30 minutes of sedentary time to LIPA or MVPA predicted estimated reductions in WC (approximately 0.57 cm and 2.95 cm for LIPA and MVPA respectively). Similarly, replacing 30 minutes of sedentary time with MVPA was associated with reductions in BMI. However, the estimations for the reallocation of 30 minutes of sedentary time to LIPA on BMI were not significant. There seems to be evidence that the relationship between PA and WC is consistent across all intensities whereas the relationship between PA and BMI is intensity-dependent (i.e., only higher intensities seem to affect BMI).[43] Although the former could provide a plausible explanation for the findings regarding WC and BMI, one cannot rule out the possibility that heterogeneity of results with the BMI studies analyzed (I^2=73.7%) and differences in the sample population across studies could have added some uncertainty to the obtained results. There is a need for more studies experimentally investigating this issue.

A recent meta-analysis reporting on the relationship of sedentary time with mortality found that greater sedentary time was associated with higher mortality risk, after controlling for the influence of MVPA,[4] and regular PA has consistently been associated with a reduced mortality risk.[45,46] There is evidence that a greater total activity volume, regardless of time spent in any particular intensity, is a strong predictor of mortality over a long follow-up period.[47] In this context, the articles included in this meta-analysis from the National Health and Nutrition Examination Survey study[9,47,48] suggest that replacing sedentary time with an equal amount of PA (LIPA and MVPA) may play a potentially worthwhile protective role.[45] Despite MVPA bringing more benefits than LIPA for the same amount of SB time being displaced (approximately 40% and 20% reduction in risk of all-cause of mortality respectively according to this study's estimates), LIPA may nevertheless be a more feasible and relevant way for activity in contexts where MVPA is impractical (e.g., in office workplace environments); in people unable to engage in MVPA (older adults or those with physical frailties); or among those who may benefit from being more physically active.

The findings of this meta-analysis highlight the importance of considering the combined effects that movement and non-movement behaviors may have on the cardiovascular and mortality outcomes of adults (i.e., replacing sedentary time with MVPA predicts a stronger association compared with LIPA). Recently, a 24-hour analysis approach has been suggested to evaluate the codependent nature of the daily proportion of movement and non-movement behaviors on health and a novel analytical approach has been proposed (i.e., compositional analysis) to account for it.[44] Therefore, this new approach can be used on both epidemiologic observational and experimental data to provide new insights in the relationship between PA and health to develop a new 24-hour PA guideline based on compositional analysis.[6]

Limitations

This meta-analysis has limitations at the level of the individual studies examined and at the level of the review that was feasible with the data available. The cross-sectional nature of the pooled observations does not allow definitive conclusions to be drawn around the causal relationship between the variables of interest. Second, isotemporal substitution modeling has some limitations. The principle underpinning isotemporal substitution modeling, multiple regression analysis, bring some issues such as not contemplating the codependent nature of PA data, that may further limit it utility in this field.[44] And despite all studies using accelerometers, an objective method of free-living activity assessment, the cut point used for determining SB using these devices (less than 100 cpm) includes elements of misclassification.[49] Therefore, moving toward assessment of SB based on posture, for instance, using monitors that detect posture directly, has been recommended. Consistent with the findings of this meta-analysis, an Australian study[50] concluded that replacing assessed posture while sitting with more active behaviors (i.e., standing or stepping) was associated with improvements of various cardiometabolic risk biomarkers. Also, the studies assessing LIPA did not differentiate between the low and high end of that particular activity intensity, potentially missing some valuable information, particularly for cardiovascular risk factors.[38]

At the level of the current review, statistical heterogeneity was high for some of the meta-analyzed outcomes and should be interpreted with caution. One of the eligible studies was not included in the pooled analysis as when contacted, the corresponding author was unavailable and therefore data could not be retrieved to be pooled in this meta-analysis. Finally, to increase the comparability among studies, only effect sizes associated with less adjusted models were combined and analyzed, which could additionally limit the validity of the reported results. To further increase comparability among studies, the estimated β and 95% CIs of studies using 10-minute blocks as unit of exchange was scaled up to 30 minutes so all included studies would consistently show the effects of replacing 30 minutes of sedentary time with LIPA and MVPA on the selected outcome. Although these estimations conform to linearity properties of the method used (i.e., linear regression analysis), results should be interpreted with caution.

CONCLUSIONS

The findings of the current synthesis suggest that even light-intensity activities, such as walking or standing, may provide preventive benefits for cardiometabolic health. It is to be expected that MVPA will have stronger estimated effects because of the well-known dose–response effect. Also, given the potential beneficial additive effects, LIPA should be encouraged, even among those considered currently active. Future such research should move beyond observational evidence and identify more robust indications of cardiometabolic outcomes of experimentally reallocating time spent in sedentary behaviors with physical activities of different intensities.[33]

ACKNOWLEDGMENTS

Owen is supported by a National Health and Medical Research Council of Australia (NHMRC) Senior Principal Research Fellowship (No. 1003960), an NHMRC Centre for Research Excellence Grant (NHMRC 1057608) and by the Victorian Government's Operational Infrastructure Support Program.

BdPC and JdPC conceived and drafted the study. FAB and JdPC conducted the literature search. AGH conducted the statistical analysis. RAR, SC, and NO critically reviewed the manuscript.

All authors approved the final version of the manuscript. No financial disclosures were reported by the authors of this paper.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found, in the online version, at doi:10.1016/j.amepre.2018.04.042.

REFERENCES

1. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. *Int J Epidemiol.* 2012;41(5):1338–1353. https://doi.org/10.1093/ije/dys078.
2. Owen N, Healy GN, Matthews CE, et al. Too much sitting: the population health science of sedentary behavior. *Exerc Sport Sci Rev.* 2010;38(3):105–113. https://doi.org/10.1097/JES.0b013e3181e373a2.
3. Ekelund U, Steene-Johannessen J, Brown WJ, et al. 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. *Lancet.* 2016;388(10051):1302–1310. https://doi.org/10.1016/S0140-6736(16.
4. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med.* 2015;162(2):123–132. https://doi.org/10.7326/M14-1651.
5. Tremblay MS, Colley RC, Saunders TJ, et al. Physiological and health implications of a sedentary lifestyle. *App Physiol Nutr Metab.* 2010;35(6):725–740. https://doi.org/10.1139/H10-079.
6. Tremblay MS, Carson V, Chaput JP, et al. Canadian 24-hour movement guidelines for children and youth: an integration of physical activity, sedentary behaviour, and sleep. *Appl Physiol Nutr Metab.* 2016;41(6)):S311–S327. (suppl 3) https://doi.org/10.1139/apnm-2016-0151.
7. Brown WJ, Bauman A, Bull FC, et al. Development of evidence based physical activity recommendations for adults (18−64 years). Report prepared for the Australian Government Department of Health; 2012.
8. Shrestha N, Grgic J, Wiesner G, et al. Effectiveness of interventions for reducing non-occupational sedentary behaviour in adults and older adults: a systematic review and meta-analysis. *Br J Sports Med.* 2018 In press. Online January 13 https://doi.org/10.1136/bjsports-2017-098270.
9. Schmid D, Ricci C, Baumeister SE, et al. Replacing sedentary time with physical activity in relation to mortality. *Med Sci Sports Exerc.* 2016;48(7):1312–1319. https://doi.org/10.1249/MSS.0000000000000913.
10. Gupta N, Heiden M, Aadahl M, et al. What is the effect on obesity indicators from replacing prolonged sedentary time with brief sedentary bouts, standing and different types of physical activity during working days? A cross-sectional accelerometer-based study among blue-collar workers. *PLoS One.*. 2016;11(5):e0154935 https://doi.org/10.1371/journal.pone.0154935.
11. Falconer CL, Page AS, Andrews RC, et al. The potential impact of displacing sedentary time in adults with type 2 diabetes. *Med Sci Sports Exerc.* 2015;47(10):2070–2075. https://doi.org/10.1249/MSS.0000000000000651.
12. Buman MP, Winkler EA, Kurka JM, et al. Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005−2006. *Am J Epidemiol.* 2014;179(3):323–334. https://doi.org/10.1093/aje/kwt292.
13. Hamer M, Stamatakis E, Steptoe A. Effects of substituting sedentary time with physical activity on metabolic risk. *Med Sci Sports Exerc.* 2014;46(10):1946–1950. https://doi.org/10.1249/MSS.0000000000000317.
14. Healy GN, Winkler EA, Brakenridge CL, et al. Accelerometer-derived sedentary and physical activity time in overweight/obese adults with type 2 diabetes: cross-sectional associations with cardiometabolic biomarkers. *PLoS One.* 2015;10(3):e0119140 https://doi.org/10.1371/journal.pone.0119140.
15. Mekary RA, Willett WC, Hu FB, et al. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol.* 2009;170(4):519–527. https://doi.org/10.1093/aje/kwp163.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283(15):2008–2012. https://doi.org/10.1001/jama.283.15.2008.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135.
18. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses Published http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp; 2000 Published .
19. Yates T, Henson J, Edwardson C, et al. Objectively measured sedentary time and associations with insulin sensitivity: importance of reallocating sedentary time to physical activity. *Prev Med.* 2015;76:79–83. https://doi.org/10.1016/j.ypmed.2015.04.005.
20. Hardy RJ, Thompson SG. A likelihood approach to meta−analysis with random effects. *Stat Med.* 1996;15(6):619–629. https://doi.org/10.1002/(SICI)1097-0258(19960330)15:6<619::AID-SIM188>3.0.CO;2-A.
21. Higgins J, Thompson SG. Quantifying heterogeneity in a meta−analysis. *Stat Med.* 2002;21(11):1539–1558. https://doi.org/10.1002/sim.1186.
22. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629.
23. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Hoboken, NJ:: Wiley Online Library; 2008. https://doi.org/10.1002/9780470712184.
24. Kokkinos P. Physical activity, health benefits, and mortality risk. *ISRN Cardiol.* 2012;2012:718789. https://doi.org/10.5402/2012/718789.
25. Saunders TJ, Larouche R, Colley RC, et al. Acute sedentary behaviour and markers of cardiometabolic risk: a systematic review of intervention studies. *J Nutr Metab.* 2012;2012:712435. https://doi.org/10.1155/2012/712435.
26. Dempsey PC, Owen N, Biddle SJ, et al. Managing sedentary behavior to reduce the risk of diabetes and cardiovascular disease. *Current Diab Rep.* 2014;14(9):522. https://doi.org/10.1007/s11892-014-0522-0.
27. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. *Diabetes Care.* 2012;35(5):976–983. https://doi.org/10.2337/dc11-1931.

28. Larsen RN, Kingwell BA, Sethi P, et al. Breaking up prolonged sitting reduces resting blood pressure in overweight/obese adults. *Nutr Metab Cardiovasc Dis.* 2014;24(9):976–982. https://doi.org/10.1016/j.numecd.2014.04.011.
29. Blaak EE, Antoine JM, Benton D, et al. Impact of postprandial glycaemia on health and prevention of disease. *Obes Rev.* 2012;13(10):923–984. https://doi.org/10.1111/j.1467-789X.2012.01011.x.
30. O'Keefe JH, Abuannadi M, Lavie CJ, et al. Strategies for optimizing glycemic control and cardiovascular prognosis in patients with type 2 diabetes mellitus. *Mayo Clin Proc.* 2011;86(2):128–138. https://doi.org/10.4065/mcp.2010.0434.
31. Peddie MC, Bone JL, Rehrer NJ, et al. Breaking prolonged sitting reduces postprandial glycemia in healthy, normal-weight adults: a randomized crossover trial. *Am J Clin Nutr.* 2013;98(2):358–366. https://doi.org/10.3945/ajcn.112.051763.
32. Bailey DP, Locke CD. Breaking up prolonged sitting with light-intensity walking improves postprandial glycemia, but breaking up sitting with standing does not. *J Sci Med Sport.* 2015;18(3):294–298. https://doi.org/10.1016/j.jsams.2014.03.008.
33. Martin A, Fitzsimons C, Jepson R, et al. Interventions with potential to reduce sedentary time in adults: systematic review and meta-analysis. *Br J Sports Med.* 2015;49(16):1056–1063. https://doi.org/10.1136/bjsports-2014-094524.
34. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes.* 2007;56(11):2655–2667. https://doi.org/10.2337/db07-0882.
35. Mann S, Beedie C, Balducci S, et al. Changes in insulin sensitivity in response to different modalities of exercise: a review of the evidence. *Diabetes Metab Res Rev.* 2014;30(4):257–268. https://doi.org/10.1002/dmrr.2488.
36. You T, Arsenis NC, Disanzo BL, et al. Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. *Sports Med.* 2013;43(4):243–256. https://doi.org/10.1007/s40279-013-0023-3.
37. Ekblom-Bak E, Ekblom O, Bolam KA, et al. SCAPIS Pilot Study: sitness, fitness and fatness—is sedentary time substitution by physical activity equally important for everyone's markers of glucose regulation? *J Phys Act Health.* 2016;13(7):697–703. https://doi.org/10.1123/jpah.2015-0611.
38. Hamilton MT, Healy GN, Dunstan DW, et al. Too little exercise and too much sitting: inactivity physiology and the need for new recommendations on sedentary behavior. *Curr Cardiovasc Risk Rep.* 2008;2(4):292–298. https://doi.org/10.1007/s12170-008-0054-8.
39. Wolff-Hughes DL, Fitzhugh EC, Bassett DR, et al. Total activity counts and bouted minutes of moderate-to-vigorous physical activity: relationships with cardiometabolic biomarkers using 2003—2006 NHANES. *J Phys Act Health.* 2015;12(5):694–700. https://doi.org/10.1123/jpah.2013-0463.
40. Hatfield DP, Chomitz VR, Chui K, et al. Exploring new relationships between physical activity volume and intensity and cardiometabolic risk in U.S. adolescents. *J Phys Act Health.* 2015;12(9):1312–1319. https://doi.org/10.1123/jpah.2014-0418.
41. von Loeffelholz C, et al. *The Role of Non-exercise Activity Thermogenesis in Human Obesity*. In: De Groot LJ, Chrousos G, Dungan K, et al. eds. Endotext. South Dartmouth, MA: MDText.com, Inc., 2000.
42. Chastin SF, Palarea-Albaladejo J, Dontje ML, et al. Combined effects of time spent in physical activity, sedentary behaviors and sleep on obesity and cardio-metabolic health markers: a novel compositional data analysis approach. *PLoS One.* 2015;10(10):e0139984. https://doi.org/10.1371/journal.pone.0139984.
43. Howard B, Winkler EA, Sethi P, et al. Associations of low- and high-intensity light activity with cardiometabolic biomarkers. *Med Sci Sports Exerc.* 2015;47(10):2093–2101. https://doi.org/10.1249/MSS.0000000000000631.
44. Batacan RB, Jr., Duncan MJ, Dalbo VJ, et al. Effects of light intensity activity on CVD risk factors: a systematic review of intervention studies. *Biomed Res Int.* 2015;2015:596367. https://doi.org/10.1155/2015/596367.
45. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med.* 2015;175(6):959–967. https://doi.org/10.1001/jamainternmed.2015.0533.
46. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med.* 2012;9(11):e1001335. https://doi.org/10.1371/journal.pmed.1001335.
47. Fishman EI, Steeves JA, Zipunnikov V, et al. Association between objectively measured physical activity and mortality in NHANES. *Med Sci Sports Exerc.* 2016;48(7):1303–1311. https://doi.org/10.1249/MSS.0000000000000885.
48. Loprinzi PD, Loenneke JP. Mortality risk and perceived quality of life as a function of waking time in discretionary movement-based behaviors: isotemporal substitution effects. *Qual Life Res.* 2017;26(2):343–348. https://doi.org/10.1007/s11136-016-1385-4.
49. Chastin SF, Egerton T, Leask C, et al. Meta-analysis of the relationship between breaks in sedentary behavior and cardiometabolic health. *Obesity.* 2015;23(9):1800–1810. https://doi.org/10.1002/oby.21180.
50. Healy GN, Winkler EA, Owen N, et al. Replacing sitting time with standing or stepping: associations with cardio-metabolic risk biomarkers. *Eur Heart J.* 2015;36(39):2643–2649. https://doi.org/10.1093/eurheartj/ehv308.