Preventive Medicine 179 (2024) 107812

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Review Article

Association of sedentary time with risk of cardiovascular diseases and cardiovascular mortality: A systematic review and meta-analysis of prospective cohort studies

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ARTICLE INFO

Keywords:
Sedentary behaviour
Cardiovascular risk
Cardiovascular mortality
Systematic review
meta-analysis
Cohort studies

ABSTRACT

Given the high prevalence of cardiovascular disease (CVD), we meta-analysed CVD relative risk (RR) in relation to high vs. low categories of self-reported and objectively assessed sedentary behaviours from cohort studies; in a sub-sample ($n = 4$ studies), the theoretical substitution of one hour spent sedentary with the same amount of time spent in light-intense physical activity was evaluated. Based on 19 studies (60,526 fatal and non-fatal CVD, 1,473,354 individuals and 13,559,139 persons-year) we estimated a 30% increased CVD risk for high vs. low categories of sedentary behaviour (RR = 1.29, confidence interval (CI) = 1.22;1.37). Every hour spent sedentary corresponds to a 5% increased fatal and non-fatal CVD risk (RR = 1.05, CI = 1.02;1.07). Dose-response meta-analysis revealed that sedentary behaviour is statistically significantly associated to fatal and non-fatal CVD risk following a J-shaped relation. Substituting one hour spent sedentary with physical activity of light intensity reduced the risk of fatal and non-fatal CVD events by one-fifth (RR =0.84, CI = 0.73;0.97). In meta-regression analysis, potential influential factors such as age, sex, and medical condition did not essentially alter the results.

1. Introduction

Cardiovascular disease (CVD) continues to be a major public health concern as it is the leading cause of morbidity and mortality, worldwide (Roth et al., 2020). An estimated 18.6 million deaths are reported, yearly (Roth et al., 2020). The overall prevalence of CVD has doubled from 271 million in 1990 to 523 million in 2019 (Roth et al., 2020). Reducing sedentary behaviours, such as sitting, reclining positions, watching TV, and having a sedentary job has been proposed to be an effective strategy among others to reduce or prevent CVD (Carter et al., 2017; Lavie et al., 2019). According to available literature based on self-reported and objectively assessed measures, a high level of sedentary behaviour is associated with approximately 15% increased risk of CVD (Biswas et al., 2015). Although evidence about the relation of sedentary behaviour to the risk of CVD incidence and mortality is constantly rising, high-quality studies on the association between sedentary behaviour and the risk of CVD are needed. Results from prospective cohort studies on sedentary behaviour and the risk of CVD may provide stronger scientific evidence of higher methodological quality compared to findings from retrospective and cross-sectional studies (Grimes and Schulz, 2012; Choi and Noseworthy, 1992; Kopec and Esdaile, 1990). It is important to provide continuous updates on current scientific evidence about the relationship of sedentary behaviour with risk of CV and related mortality based on prospective cohort studies. In addition, it is important to investigate specific CVD outcomes, such as stroke and coronary heart disease (CHD), and to employ the use of advanced statistical tools, such

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https://doi.org/10.1016/j.ypmed.2023.107812
Received 27 April 2023; Received in revised form 6 December 2023; Accepted 6 December 2023
Available online 9 December 2023

as non-linear meta-regression analysis to investigate the shape of the relationship between sedentary behaviour and CVD risk. Moreover, it would be of great public health interest to provide a meta-analytic estimate of CVD risk reduction by substituting sedentary time with light physical activity (Keadle et al., 2017). The World Health Organisation (WHO) recommends substituting time spent in sedentary activities with some physical activity. (World Health Organization, 2020) The aim of this systematic review and meta-analysis is to provide an update of the association between time spent in sedentary behaviour, and the risk of CVD, including specific CVD outcomes, such as stroke, CHD and related mortality. This meta-analysis is based on prospective studies. Our first objective is to investigate the determinants of heterogeneity in the association between CVD risks and CVD-related mortality by focusing on the target population and other methodological factors. A second objective is to investigate the shape of the relation between time spent in sedentary activities and CVD risk using non-linear dose-response meta-regression. Finally, the third objective is to investigate the association between time spent in sedentary activity and the risk of specific cardiovascular outcomes. We further evaluated the public health impact of sedentary behaviour in relation to CVD burden and mortality by conducting a meta-analysis of results from isotemporal substitution analysis.

2. Methods

2.1. Eligibility criteria

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The paper selection was conducted according to the PECO(ST) approach (Mintzker et al., 2022). The target Population (P) was apparently healthy adults of both sexes. Studies based on CVD survivors were excluded. As some studies may have included participants having a CVD diagnosis at baseline, we stratified for studies that adjusted for baseline CVD in a sensitivity analysis. Studies were included if they considered time spent in any sedentary activities, such as TV watching and sitting (exposure (E) and provided risk estimates for the comparison of high vs. low categories of time spent in sedentary activities or for sedentariness coded as a continuous variable. Any CVD outcome or CVD-related mortality was considered as outcome (O). Finally, we included observational studies with a prospective study design (S) published in peer-reviewed journals after 1st January 2010 (T). The systematic literature database search was conducted using MEDLINE, COCHRANE, EMBASE, CINAHL, and Web of Science. In addition, the reference list of included studies and previous systematic reviews and meta-analyses were hand-searched for eligible studies. The risk of bias and overall study quality was assessed by two independent authors using the New castle Ottawa Scale (NOS) (Evenson et al., 2016). Studies with an NOS score greater than six were of moderate to high quality (Peterson et al., 2011). Any discussion about a study's quality was solved by consulting a third senior author.

2.2. Statistical analyses

We meta-analysed multivariable-adjusted RRs of high vs. low categories of sedentary time in relation to CVD incidence and mortality using a random effect model with the study's weight defined by inverse variance. All studies contributed to the meta-analysis with one risk estimate only. If more than one risk estimate was provided by a study (for example for sex, or specific types of CVD), we pooled these risks using a fixed effect meta-analytic approach. Moreover, if different articles provided data from the same cohort, we chose the study with the highest number of CVD cases. The between-study heterogeneity was calculated and reported using the Cochrane Q test (if at least 10 studies were available) and I^2 statistic. Stratification analyses and linear meta-regression were conducted to ascertain potential sources of variation. Publication bias was investigated by visual inspection of the funnel plot and by Egger's test (Peters et al., 2006). Sensitivity analyses were conducted by omitting one study at a time. Finally, non-linear dose-response meta-regression analyses of time spent in sedentary time and CVD incidence and mortality risk were carried out using restricted cubic splines with 5th, 35th,65th and 95th percentiles of time spent in sedentary time (hours) as knots (Orsini et al., 2006). We conducted a meta-analysis of results from isotemporal substitution analysis to estimate the CVD risk reduction due to the substitution of one hour of time spent sedentary with time spent in physical activities of light intensity.

All statistical analyses were conducted using STATA version. 14.

3. Results

The literature search yielded 27 articles to be included in the systematic review and meta-analysis (Liu et al., 2020; Stamatakis et al., 2019; Jefferis et al., 2019; Garcia et al., 2019; Bellettiere et al., 2019; Dohrn et al., 2018; Celis-Morales et al., 2018; Grace et al., 2017; Schmid et al., 2016; McDonnell et al., 2016; Evenson et al., 2016; Matthews et al., 2015; Keadle et al., 2015; Ikehara et al., 2015; Young et al., 2014; Seguin et al., 2014; Matthews et al., 2014; Ensrud et al., 2014; Kim et al., 2013; Chomistek et al., 2013; Matthews et al., 2012; Ford, 2012; Wijndaele et al., 2011a; Wijndaele et al., 2011b; Stamatakis et al., 2011; Warren et al., 2010; Dunstan et al., 2010) (Fig. 1).

Among the included articles, 16 studies were conducted in the USA, six in the European region and five studies in the Pacific-Asian region. Among studies from the Pacific-Asian region, three studies were from Australia, while China and Japan contributed with one study each. The median age of the participants was 58.6 years (range = 45.3 to 79 years) and 44.3% were men. Four studies included only men (Jefferis et al., 2019; Young et al., 2014; Ensrud et al., 2014; Warren et al., 2010) and three studies only women (Bellettiere et al., 2019; Seguin et al., 2014; Chomistek et al., 2013). The median sample size was n = 22,257 participants (range = 851 to 502,655), with a median follow-up time of 7.1 years (range = 2.1 to 21.0), resulting in a median number of persons-year of 158,025 (range = 12,084 to 3,122,107). The median number of non-fatal CVD reported by the included studies was 1738 (range = 42 to 7420) and the median number of CVD deaths was 432 (range = 24 to 22,210). The methodological quality of the included studies was high to excellent. Most of the included studies used self-reports to assess sedentary time; however, six studies assessed time spent in sedentary time using accelerometer (Jefferis et al., 2019; Bellettiere et al., 2019; Dohrn et al., 2018; Schmid et al., 2016; Evenson et al., 2016; Ensrud et al., 2014) (Supplementary Table 1).

3.1. Meta-analysis of RRs of high vs. low category of time spent sedentary

We summarized the risk estimates for both fatal and non-fatal CVD risk in a meta-analysis of 19 studies, resulting in 60,526 fatal and non-fatal CVD cases, 1,473,354 individuals and 13,559,139 persons-year (Liu et al., 2020; Stamatakis et al., 2019; Jefferis et al., 2019; Garcia et al., 2019; Bellettiere et al., 2019; Dohrn et al., 2018; Celis-Morales et al., 2018; Grace et al., 2017; Schmid et al., 2016; McDonnell et al., 2016; Keadle et al., 2015; Ikehara et al., 2015; Young et al., 2014; Matthews et al., 2014; Ensrud et al., 2014; Kim et al., 2013; Chomistek et al., 2013; Stamatakis et al., 2011; Warren et al., 2010). We observed a 29% increased RR of fatal or non-fatal CVD for sedentary individuals compared to those with low sedentary time (RR = 1.29, 95% CI = 1.22; 1.37, Fig. 2), with a statistically significant between-study heterogeneity (I^2 = 48.9%, $P_{Cochrane}$ = 0.009).

We performed a meta-analysis of fatal CVD based on 13 studies, resulting in 42,919 fatal CVD cases, 1,366,427 individuals, and 12,883,670 persons-year (Liu et al., 2020; Stamatakis et al., 2019; Dohrn et al., 2018; Celis-Morales et al., 2018; Grace et al., 2017; Schmid et al., 2016; Keadle et al., 2015; Ikehara et al., 2015; Seguin et al., 2014; Matthews et al., 2014; Ensrud et al., 2014; Kim et al., 2013; Warren

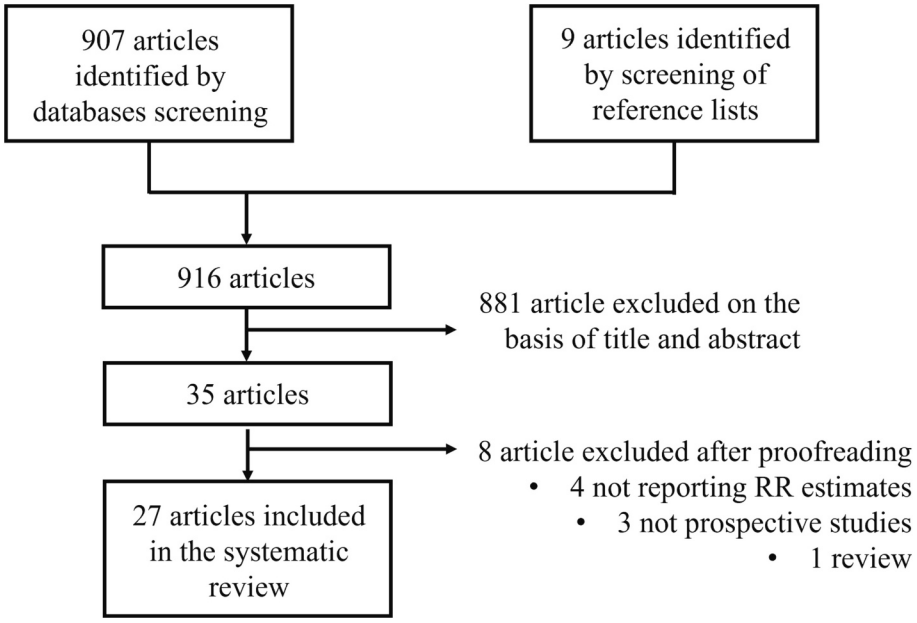

Fig. 1. Flowchart of paper selection.

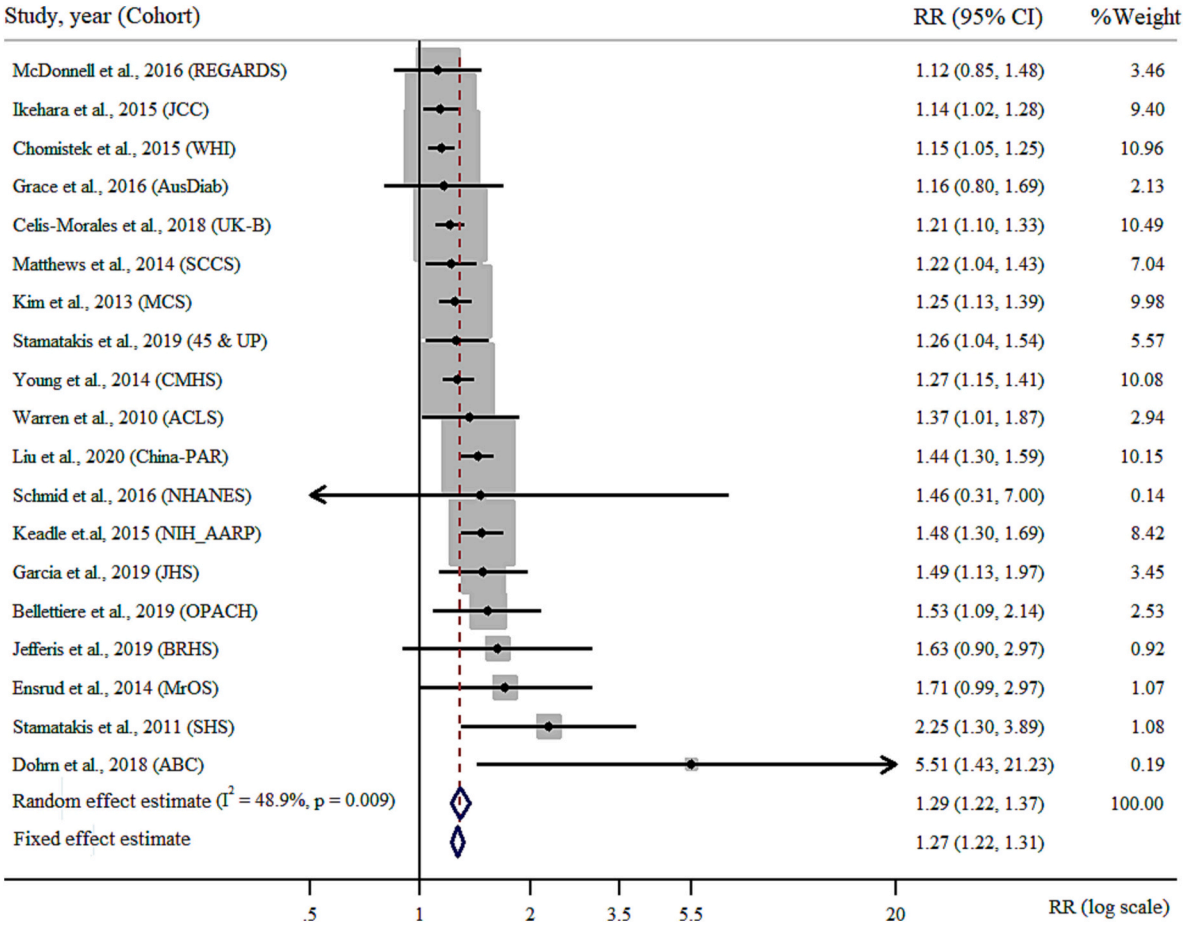

Fig. 2. Overall meta-analysis of fatal and non-fatal CVD outcomes. Relative risks were performed considering the higher category of time spent in sedentary activity vs. the lower category of time spent in sedentary activity.

et al., 2010). We observed a random effect estimate corresponding to a 27% increased risk of CVD mortality (RR = 1.27, 95% CI = 1.19; 1.36) for high vs. low levels of sedentary behaviour with a low, non-significant between-study heterogeneity (I^2 = 25%, $P_{Cochrane}$ = 0.103). Finally, nine studies (21,200 non-fatal CVD cases, 794,926 individuals, and 4,854,208 persons-year) yielded a 30% increased non-fatal CVD

mortality risk (RR = 1.30, 95% CI = 1.18; 1.43) for high vs. low sedentary behaviours (Liu et al., 2020; Jefferis et al., 2019; Garcia et al., 2019; Bellettiere et al., 2019; Celis-Morales et al., 2018; McDonnell et al., 2016; Young et al., 2014; Chomistek et al., 2013; Stamatakis et al., 2011) (Fig. 3) with a relevant between-study heterogeneity (I^2 = 65%).

3.2. Meta-analysis of fatal and non-fatal stroke and coronary heart disease

Five studies provided data for the meta-analysis of fatal and non-fatal stroke (Liu et al., 2020; McDonnell et al., 2016; Keadle et al., 2015; Ikehara et al., 2015; Chomistek et al., 2013). Three of them reported

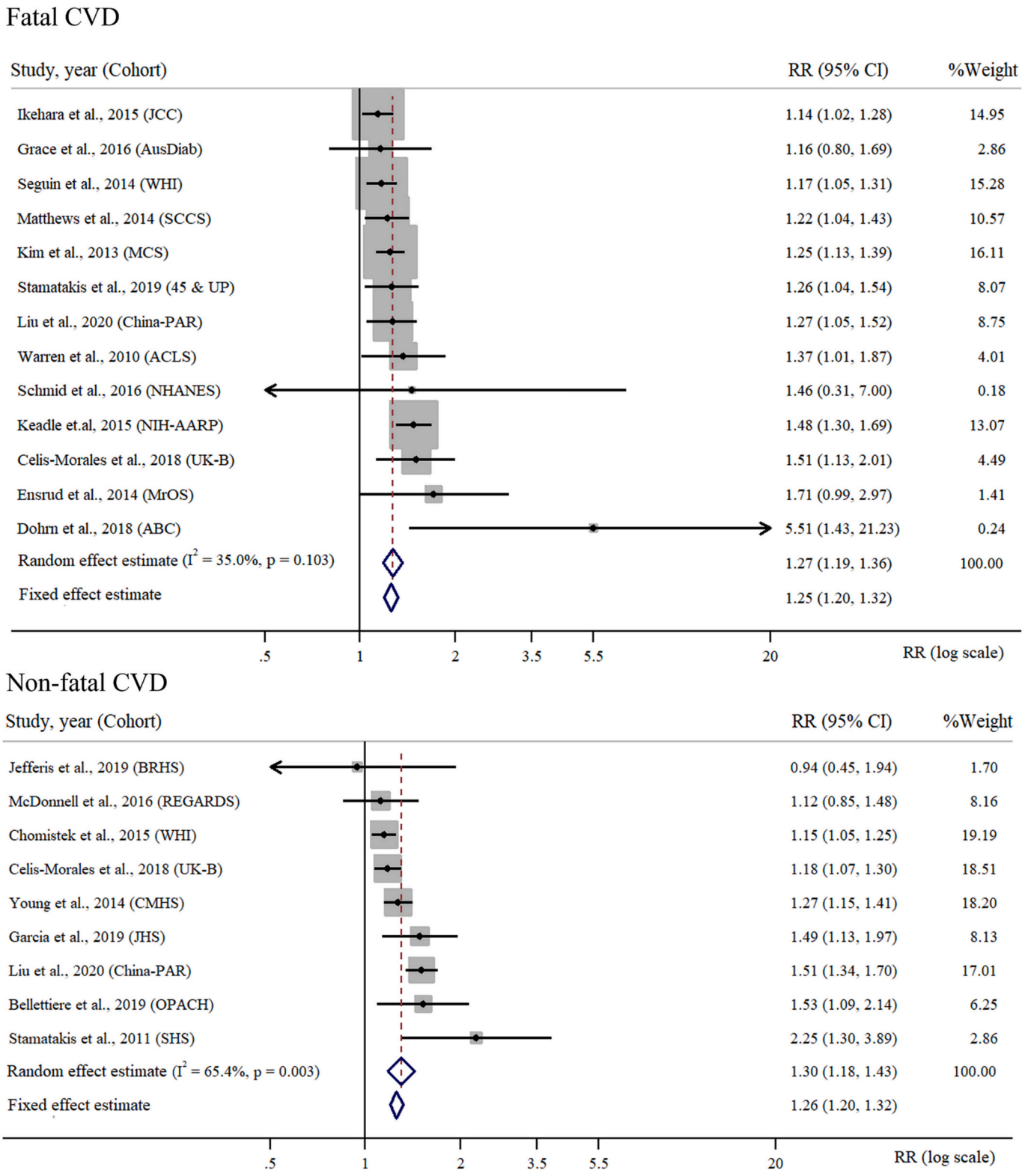

Fig. 3. Meta-analysis by fatal and non-fatal CVD outcomes. Relative risks performed considering higher category of time spent in sedentary activity vs. lower category of time spent in sedentary activity.

non-fatal stroke (Liu et al., 2020; McDonnell et al., 2016; Chomistek et al., 2013) while two reported about fatal stroke (Keadle et al., 2015; Ikehara et al., 2015). The overall number of fatal and non-fatal strokes was 9424 (54.4% non-fatal), with an overall sample size of 493,710 participants and 6,335,850 persons-year. The meta-analysis of fatal and non-fatal stroke resulted in a 15% increased risk of stroke for sedentary vs. non-sedentary individuals (RR = 1.15, 95% CI = 1.06; 1.24, $I^2 = 0\%$). Four studies provided data for the meta-analysis of fatal and non-fatal CHD (Liu et al., 2020; Keadle et al., 2015; Ikehara et al., 2015; Chomistek et al., 2013) of which two of them provided data on non-fatal CHD (Liu et al., 2020; Chomistek et al., 2013) and two on fatal CHD (Keadle et al., 2015; Ikehara et al., 2015). Overall, these studies had 11,871 CHD cases (28% non-fatal), a sample size of 471,453 and a 6,177,825 persons-year. An estimated 47% increased risk of fatal and non-fatal CHD was observed for sedentary vs. non-sedentary individuals (RR = 1.47, 95% CI = 1.12; 1.93, $I^2 = 89.5\%$).

3.3. Meta-analysis of one hour increase of time spent in sedentary activity

Eight studies reported risk estimates for the association between one hour increase in time spent in sedentary behaviours and the risk of cardiovascular fatal or non-fatal event (Stamatakis et al., 2019; Bellettiere et al., 2019; Celis-Morales et al., 2018; Grace et al., 2017; Keadle et al., 2015; Ikehara et al., 2015; Chomistek et al., 2013; Wijndaele et al., 2011b). In this meta-analysis a 5% increase in fatal and non-fatal cardiovascular risk was observed for each hour increase in time spent sedentary (RR = 1.05, 95% CI = 1.02; 1.07, $I^2 = 84\%$).

3.4. Non-linear dose-response meta-regression analysis

Sixteen studies (Liu et al., 2020; Stamatakis et al., 2019; Jefferis et al., 2019; Garcia et al., 2019; Bellettiere et al., 2019; Dohrn et al., 2018; McDonnell et al., 2016; Keadle et al., 2015; Ikehara et al., 2015; Young et al., 2014; Kim et al., 2013; Chomistek et al., 2013; Ford, 2012; Stamatakis et al., 2011; Warren et al., 2010; Dunstan et al., 2010) provided a mixture of self-reported and objectively assessed data for a non-linear dose-response meta-analysis, with a cumulative number of 33,903 cases and 8,825,687 persons-year. In our dose-response meta-analysis (Fig. 4), we observed a J-shaped relation of time spent in sedentary behaviours with risk of fatal and non-fatal CVD (Pvalue for non-linearity = 0.0012).

3.5. Stratified meta-analyses and investigation of heterogeneity determinants

Details of stratified analyses and meta-regression were reported on Table 1.

Studies with a mean or median age above the overall median (58.6 years) yielded a risk estimate of 1.37 (95% CI = 1.16; 1.62, $I^2 = 62.2\%$). In younger participants, we observed a 27% increased risk of fatal and non-fatal CVD for sedentary vs. non-sedentary individuals (RR = 1.27, 95% CI = 1.20; 1.35, $I^2 = 40.1\%$). The meta-analyses stratified by sex provided a summary risk estimate of 41% (RR = 1.41, 95% CI = 1.17; 1.70, $I^2 = 88.1\%$) and 34% (RR = 1.34, 95% CI = 1.16; 1.54, $I^2 = 77.5\%$) for women and men, respectively. The meta-analysis of objectively assessed sedentariness yelded 65% increased risk of fatal and non-fatal CVD for sedentary vs. non-sedentary individuals (RR = 1.65, 95% CI = 1.29; 2.13, $I^2 = 0\%$). The meta-analysis based on self-reported sedentariness yielded a 27% increased CVD risk (RR = 1.27, 95% CI = 1.20; 1.35, $I^2 = 51.2\%$). For studies with a NOS score below or equal to six, a 57% increased CVD risk was observed (RR = 1.57, 95% CI = 1.25; 1.97, $I^2 = 27.5\%$). The exclusion of studies with a NOS score below or equal to six resulted in a 28% increased risk of fatal and non-fatal CVD for sedentary vs. non-sedentary individuals (RR = 1.28, 95% CI = 1.21; 1.36, $I^2 = 49\%$). Based on studies conducted in the US, we observed 28% increased risk of fatal and non-fatal CVD with no significant between-study heterogeneity (RR = 1.28, 95% CI = 1.20; 1.37, $I^2 = 34\%$). We observed a substantial between study heterogeneity for studies conducted in Europe (RR = 1.77, 95% CI = 1.10; 2.86, $I^2 = 70.8\%$) and in the Pacific-Asian region (RR = 1.27, 95% CI = 1.10; 1.46, $I^2 = 68.4\%$). We observed 26% increased fatal and non-fatal CVD risk for sedentariness (RR = 1.26, 95% CI = 1.19; 1.34, $I^2 = 61.2\%$) after excluding studies with an overall number of persons-year below the median. When considering the meta-analysis of RR estimates adjusted for physical activity, we observed a RR of 1.31 (95% CI = 1.19; 1.43, $I^2 = 61.2\%$). A similar result of 25% increased fatal and non-fatal CVD risk was observed for the meta-analysis conducted on studies adjusting for physical functioning (RR = 1.25, 95% CI = 1.15; 1.36, $I^2 = 0\%$). Finally, 27% increased risk of fatal or non-fatal cardiovascular event was observed for the meta-analysis conducted on RR estimates adjusted for

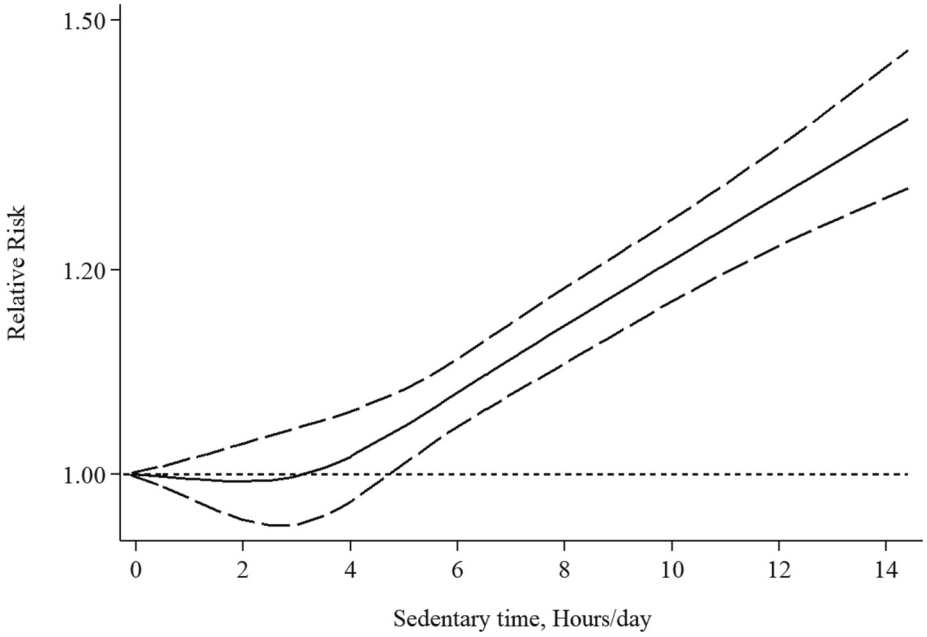

Fig. 4. Non-linear dose-response meta-regression of fatal and non-fatal CVD outcomes by time spent in sedentary time.

Table 1
Stratified analyses and meta-regression.

		RR (95% CI)	I_1^2 (%)	I_2^2 (%)	Pvalue
Age*	≥58.6 years	1.37 (1.16; 1.62)	62.2	50.4	0.891
	<58.6 years	1.27 (1.20; 1.35)	40.1		
Sex	Women	1.41 (1.17; 1.70)	88.1	82.3	0.751
	Men	1.34 (1.16; 1.54)	77.5		
Assessment of sedentariness	Accelerometry (objective)	1.62 (1.29; 2.13)	0.00	43.3	0.070
	Questionnaire (self-reported)	1.27 (1.20; 1.35)	51.2		
New-Castle Ottawa scale	NOS ≤ 6	1.57 (1.25; 1.97)	27.5	50.2	0.593
	NOS > 6	1.28 (1.21; 1.36)	49.0		
Region	USA	1.28 (1.20; 1.37)	34.0	52.9	0.844
	Europe	1.77 (1.10; 2.86)	70.8		
	Asian-Pacific	1.27 (1.10; 1.46)	68.4		
Sample size*	≥158,025 pers-year	1.26 (1.19; 1.34)	61.2	45.6	0.145
	<158,025 pers-year	1.44 (1.24; 1.67)	21.5		
Adjusting factors	Physical activity	1.31 (1.19; 1.43)	61.2	–	–
	Physical functioning	1.25 (1.15; 1.36)	0.00		
	Baseline T2D or CVD	1.27 (1.20; 1.34)	27.5%		

I_1^2: Heterogeneity within stratification; I_2^2: Residual heterogeneity after meta-regression; Pvalue from regression omnibus statistical test.
* Stratification performed by median number.

CVD at baseline or type-2 diabetes (RR = 1.27, 95% CI = 1.20; 1.34, I^2 = 27.5).

3.6. Meta-analysis of substitution of one hour spent in sedentary time with an equal amount of time spent in light physical activity

Four studies performed isotemporal substitution analysis to estimate the risk of CVD events in relation to the substitution of one hour spent in sedentary time with same amount of time spent in light physical activity.[15, 16, 23, 26] Here, we observed a significant one fifth reduced risk of fatal and non-fatal CVD events for the substitution of our hour of time spent in sedentary activity with same amount of time spent in light physical activity (RR = 0.84, 95% CI = 0.73; 0.97, I^2 = 77%).

3.7. Sensitivity analyses and publication bias assessment

Excluding one study at the time from the initial meta-analysis of fatal and non-fatal CVD risk resulted in RRs between 1.27 (95% CI = 1.20; 1.34, when excluding the study of Liu et al., 220) and 1.31 (95% CI = 1.23; 1.39, when excluding the study of Chomistek et al., 2013). A supplementary analysis conducted for high vs low TV watching categories resulted in 36% increased fatal and non-fatal CVD risk (RR = 1.36, 95% CI = 1.23; 1.52, I^2 = 73.4%). When excluding studies that only used TV watching as a measure of sedentary time, we observed a 39% increased fatal and non-fatal CVD risk (RR = 1.39, 95% CI = 1.25; 1.54, I^2 = 81%). The visual inspection of funnel plot (Supplementary Fig. 1a) for CVD risk showed an asymmetric distribution of the study points around the summary risk estimate pointing towards a possible publication bias. The possible presence of a publication bias in the fatal and non-fatal CVD meta-analysis was confirmed by the Egger test (Pvalue = 0.040). After the exclusion of the study of Dohrn et al., 2018, the funnel plots showed a symmetric distribution and non-statistically significant Egger test.

4. Discussion

We report that sedentary individuals had 30% increased risks of fatal and non-fatal CVD compared to their non-sedentary counterparts. Our result reinforces findings from previous meta-analyses where 14% to 15% increased risks of CVD incidence and mortality were reported for being sedentary, respectively (Biswas et al., 2015; Patterson et al., 2018). There are certain reasons for the discrepancies between our results and those of previous meta-analyses (Biswas et al., 2015; Patterson et al., 2018). First, we only included prospective studies which may result in a more accurate estimate of the CVD risk while retrospective and cross-sectional studies may bear different types of biases (Grimes and Schulz, 2012; Choi and Noseworthy, 1992; Kopec and Esdaile, 1990). Second, our meta-analysis includes more recent studies than previous meta-analyses. Moreover, inclusion of the most updated data from historical large cohorts in our meta-analysis resulted in larger number of CVD cases and larger observational time, which may have generated some discrepancies between our results and those of previous meta-analyses (Biswas et al., 2015; Patterson et al., 2018). Finally, there could be a possible problem of residual confounding in previous meta-analyses, because when results from more than one adjusted model were reported they only considered the RR ratios associated with the one that contained the fewest number of additional covariates (Biswas et al., 2015). In our study, we confirmed the results from the study of Patterson et al., as we observed a 5% increased risk for every hour spent sedentary (Patterson et al., 2018). When comparing our non-linear meta-regression to the one of Patterson, we also observed a small but relevant difference. On the one hand, we observed a monotone nonlinear increasing relation between the time spent sedentary and CVD risk. According to our work, a 62% increased CVD risk was observed for t prolonged sedentary behaviour based on objectively assessed measures as compared to self-reported measures with an increased CVD risk of 29%. This result is impressive, but it is somehow expected because self-reported measures of time spent in sedentary time may be negatively biased with respect to the ones objectively assessed (Bauman et al., 2018; Chastin et al., 2018). Notably, and for the first time, using a meta-analysis we reported that the RRs due to sedentariness were higher for fatal and non-fatal CHD risks than for stroke. Another novel result of our meta-analysis is the finding that substitution of one hour spent in sedentary time with an equal amount of light physical activity corresponded to a 20% reduced risk of fatal and non-fatal CVD. Finally, our results agree with the recent WHO recommendation on physical activity and sedentary behaviour (World Health Organization, 2020). In general, sedentary behaviours should be limited, this is particularly recommendable for older adults. Replacing sedentary time with physical activity of any intensity, even light intensity physical activity, seems like a key to improve the CVD health.

4.1. Strengths and limitations

The present meta-analysis has numerous strengths. First, to our knowledge this is the most comprehensive meta-analysis investigating CVD risk in relation to sedentary behaviour. Second, based on prospective cohort studies of high methodological quality, we used sophisticated methods to ensure robustness of our results including stratified analyses, meta-regression, sensitivity analysis, and non-linear dose-response meta-analysis. We also need to highlight some weaknesses of our meta-analysis. First, only a few studies provided data on specific CVD outcomes. Furthermore, we acknowledge some between-study heterogeneity which may have affected the precision of our estimates; however, we were able to minimize such heterogeneity by evaluating potential influential factors such as geographical area or study quality or by considering factors related to the target population such as age, physical functioning, and prevalent CVD and Type-II diabetes.

5. Conclusions

We estimated a 30% increased CVD risk for sedentary people compared to their non-sedentary peers with 5 % increased CVD risk for each hour spent in sedentary activities. Moreover, we reported that the substitution of one hour spent in sedentary activities with an equal amount of time spent in light physical activity would reduce CVD risk by one fifth.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2023.107812.

Ethical compliance statement

Authors have no conflict of interest or any ethical issue to declare. None of the authors received any funding or supplementary compensation. The current work should be considered as a spontaneous scientific contribution.

CRediT authorship contribution statement

S. Onagbiye: Writing – review & editing, Investigation, Data curation. **A. Guddemi:** Writing – review & editing, Data curation. **O.J. Baruwa:** Writing – review & editing, Data curation. **F. Alberti:** Writing – review & editing, Data curation. **A. Odone:** Writing – review & editing, Supervision, Data curation. **H. Ricci:** Writing – review & editing, Data curation. **M. Gaeta:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **D. Schmid:** Writing – review & editing, Supervision, Data curation, Conceptualization. **C. Ricci:** Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No financial support was obtained for this work.

Data availability

Data will be made available on request.

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