Original Investigation

Continuous Dose-Response Association Between Sedentary Time and Risk for Cardiovascular Disease
A Meta-analysis

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IMPORTANCE Prior studies suggest that higher sedentary time is associated with a greater risk for cardiovascular disease (CVD). However, the quantitative, dose-response association between sedentary time and CVD risk is not known.

OBJECTIVE To determine the categorical and quantitative dose-response association between sedentary time and CVD risk.

DATA SOURCES Two independent investigators searched the MEDLINE and EMBASE databases for all studies published before July 6, 2015, that evaluated the association between sedentary time and incident CVD.

STUDY SELECTION Prospective cohort studies with participants 18 years or older that reported the association between sedentary time and incident CVD were included.

DATA EXTRACTION AND SYNTHESIS Two independent investigators performed the data extraction and collection using a standardized form. The study quality was assessed using the Newcastle-Ottawa Scale. The categorical dose-response association was evaluated by comparing the pooled hazard ratio (HR) for incident CVD associated with different levels of sedentary time (vs lowest sedentary time) across studies. The continuous dose-response association was assessed using random-effects generalized least squares spline models. Data were collected from April 5 to July 6, 2015.

MAIN OUTCOMES AND MEASURES Incident CVD (coronary heart disease, including nonfatal myocardial infarction, stroke, and cardiovascular mortality).

RESULTS Nine prospective cohort studies with 720 425 unique participants (57.1% women; 42.9% men; mean age, 54.5 years) and 25 769 unique cardiovascular events and a median follow-up of 11 years were included. In categorical analyses, compared with the lowest sedentary time category (median, 2.5 h/d), participants in the highest sedentary time category (median, 12.5 h/d) had an increased risk for CVD (HR, 1.14; 95% CI, 1.09-1.19). However, no apparent risk associated with intermediate levels of sedentary time (HR for 7.5 h/d, 1.02; 95% CI, 0.96-1.08) was found. In continuous analyses, a nonlinear association between sedentary time and incident CVD was found (*P* for nonlinearity < .001), with an increased risk observed for more than 10 hours of sedentary time per day (pooled HR, 1.08; 95% CI, 1.00-1.14).

CONCLUSIONS AND RELEVANCE The association between sedentary time and the risk for CVD is nonlinear with an increased risk only at very high levels. These findings could have implications for guideline recommendations regarding the risks related to sedentary behavior.

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Physical inactivity has been identified as 1 of the 4 major modifiable risk factors for cardiovascular disease (CVD).[1] The current guidelines recommend a minimum of 150 min/wk of moderate-intensity physical activity or 75 min/wk of vigorous-intensity physical activity in sessions lasting 10 minutes or more.[2] Despite these recommendations and aggressive public health promotion, less than 4% of adults (aged 20-59 years) meet these guideline recommendations for exercise.[3,4] Thus, novel preventive approaches aimed at other modifiable facets of the inactive lifestyle, such as excess sedentary or sitting time, are needed to reduce the burden of CVD.

Sedentary time is defined as time spent in activities involving low levels of energy expenditure (1.0-1.5 metabolic equivalent tasks, such as sitting, watching television, driving).[5] Several epidemiologic studies have demonstrated that prolonged sedentary time is associated with an increased risk for CVD.[6-17] Furthermore, recent studies suggest that the contributions of prolonged sedentary time toward increased CVD risk appear to be independent of the level of physical activity.[7,12,17,18] However, the quantitative risk for CVD associated with different levels of sedentary time, independent of physical activity and other risk factors for cardiovascular (CV) events, is not known, and therefore, no consensus recommendations have been issued regarding limits on the amounts of sedentary time to optimize CVD prevention. To address this knowledge gap, we performed a pooled analysis of prospective cohort studies using a well-established meta-analytical approach[19,20] to determine the categorical and quantitative dose-response association between sedentary time and CVD risk, independent of physical activity. We hypothesized that a dose-dependent association exists between sedentary time and the risk for adverse CV events independent of physical activity, particularly at higher levels of sedentary time.

Key Points

Questions What is the quantitative association between sedentary time and the risk for cardiovascular disease?

Findings In this meta-analysis of 9 prospective cohort studies with 720 425 unique participants and 25 769 unique cardiovascular events, a nonlinear association between sedentary time and incident cardiovascular events was found, with an increased risk observed for more than 10 h/d of sedentary time.

Meaning The association of sedentary time with the risk for adverse cardiovascular events is nonlinear with an increased risk only at very high levels, which could have implications for guideline recommendations regarding the risks related to sedentary behavior.

Methods

Literature Search Strategy

We followed the protocol for Meta-analysis of Observational Studies in Epidemiology (MOOSE) for performing and reporting the present meta-analysis.[21] We searched for all prospective cohort studies that examined the association between sedentary times and the risk for adverse CV events, including coronary artery disease, stroke, and CV-related mortality among adult participants (18 years or older at baseline). Systematic searches through the electronic databases (MEDLINE [OVID] and EMBASE [Elsevier Inc]) were performed with assistance from the study librarian (H.M.). Special search features, including EMTREE, explosion technique, and subheadings, were also used. We also performed additional manual searches through the reference lists of original publications and review articles. We used various combinations of the following key words and MeSH terms: *sedentary time*, *sitting*, *cardiovascular risk*, *coronary artery disease*, *stroke*, and *cardiovascular disease mortality*. The search was restricted to published English language articles that focused on human participants.

Study Selection

Prospective cohort studies that reported the association between baseline sedentary times and the risk for CVD incidence were included. Studies with all types of sedentary activity (as assessed by sitting time) were included in the initial study selection process. Because our primary aim is to quantify the risk for CVD associated with total sedentary time independent of physical activity, only studies that reported measures of total sedentary time and the associated risk for CVD adjusted for physical activity were included in the meta-analysis. If multiple articles were published from the same cohort, we included data from the study with the most detailed report of sedentary time and/or the larger sample size. The primary outcome of interest for this meta-analysis was incident atherosclerotic CVD (coronary heart disease, including nonfatal myocardial infarction, stroke, and CV-related mortality). Two independent investigators (A.P. and U.S.) conducted the initial screening of all titles or abstracts and then evaluated all potentially relevant articles based on full-text reviews. Studies were excluded if they failed to meet all the criteria detailed above. All discrepancies regarding study inclusion were adjudicated by the senior author (J.D.B.). For one study,[6] the data on association between sedentary time categories and CVD risk were obtained from a related thesis publication by the same author group archived in the University of Tampere, Finland electronic database (https://tampub.uta.fi/bitstream/handle/10024/76853/gradu06623.pdf?sequence=1). The study quality was assessed using the Newcastle-Ottawa Scale, which allowed a total score of 9 points or fewer (9 indicates the highest quality) summarizing 8 aspects of each study.[22]

Data Collection

Two of us (A.P. and U.S.) independently performed the data collection from April 5 to July 6, 2015, using a standardized form. Information recorded for each study is detailed in the eMethods in the Supplement. Disagreements between the 2 reviewers regarding extracted data were resolved by consensus, and if needed, in consultation with the senior author (J.D.B.). No personal communication with study authors was required to obtain pertinent data from the selected studies.

Table 1. Baseline Characteristics of the Studies Included in the Meta-analysis

Source	Country	No. of Participants	Mean Age, y	Female Sex, %	Follow-up Duration, y	CV Outcomes	
						Assessed	No. of Participants
Matthews et al,[14] 2014	United States	64 304	51	59	6.4	CV-related mortality	1376
Bjørk Petersen et al,[8] 2014	Denmark	58 704[a]	48	60	5.4	Incident CHD	1446
Kim et al,[13] 2013							
Women	United States	73 201	58	100	13.7	CV-related mortality	2814
Men	United States	61 395	59	0	13.7	CV-related mortality	3721
Chomistek et al,[9] 2013	United States	71 018	63	100	12.2	Incident CV event	4235
Herber Gast et al,[11] 2013	Australia	6154	52	100	9.9	Incident CV event	177
Patel et al,[16] 2010	United States	123 216	63	57	14.0	CV-related mortality	6369
Katzmarkzyk et al,[12] 2009	Canada	17 013	42	57	13	CV-related mortality	759
Borodulin et al,[6] 2015[b]	Finland	4601	47	55	8.8	Incident CV event	188
Matthews et al,[15] 2012	United States	240 819	62	44	8.5	CV-related mortality	4684

Abbreviations: CHD, coronary heart disease; CV, cardiovascular.

[a] Indicates with available data on sitting times.

[b] The data for pooled analysis for this study were obtained from a related thesis publication by the same author group archived in the electronic database of the University of Tampere, Tampere, Finland (https://tampub.uta.fi/bitstream/handle/10024/76853/gradu06623.pdf?sequence=1).

Statistical Analysis

Exposure Assessment

Dose-response meta-analysis was performed using the statistical analysis approach as previously described.[19,20] Briefly, we estimated the median sedentary duration for each sedentary time category as described in the eMethods in the Supplement and assigned it to the corresponding hazard ratio (HR) for each study. The reported ranges of sedentary time categories and estimated medians are detailed in eTable 1 in the Supplement.

Outcome Assessment

For the present meta-analysis we used the HR or relative risk as available with their 95% CIs as a measure of the effect size associated with each category of sedentary time for all studies. In articles that studied more than 1 type of sedentary activity (eg, sitting time, television time), overall sedentary time was preferentially included for analysis. We used HRs from multivariable-adjusted models with the most complete adjustment for potential baseline confounders, including the presence of baseline CVD risk factors and physical activity levels for primary analysis.[23]

Categorical Dose-Response Analysis

Categorical and continuous dose-response analysis was performed in the present study. The categorical dose-response analysis was performed with STATA software (version 10.0; StataCorp). Because most of the studies had 3 or fewer sedentary time categories (6 of 9), we used a previously described approach[19] to pool data across studies and generated 3 pooled categories of sedentary time (ie, highest, intermediate, and lowest) as described in the eMethods in the Supplement. The median durations of the pooled highest, intermediate, and lowest sedentary time categories were 2.5 (interquartile range, 1.5- 2.9), 7.5 (interquartile range, 6.6-7.6), and 12.5 (interquartile range, 9.5-13.8) hours, respectively. The pooled HRs and 95% CI for CVD associated with different categories of sedentary time were calculated by comparing the highest and intermediate with the lowest sedentary time categories using the random-effects modeling technique as described by DerSimonian and Laird.[24] Maximally adjusted HRs, when reported, were used for the primary analysis to account for confounding variables. Pooled analysis comparing highest vs lowest sedentary times included all available studies (n = 9), whereas comparisons of intermediate vs lowest sedentary time categories included 8 studies. We assessed heterogeneity using the I^2 test (I^2 > 50% was assumed to be a result of significant heterogeneity). We tested the robustness of the observed associations by performing subgroup analyses based on age of participants (>55 vs ≤55 years), geographic location (US vs non-US studies), physical activity levels (above vs below the pooled median level), multivariable adjustment strategy used in the analysis (HR associated with models with vs without adjustment for physical activity and body mass index [BMI]), and duration of follow-up (<10 vs ≥10 years). Publication bias was assessed using contour-enhanced funnel plots and the Begg's rank correlation test. All *P* values were-2 tailed. For all tests, a probability level less than .05 was considered statistically significant.

Continuous Dose-Response Analysis

The continuous dose-response association between sedentary time and risk for CVD was assessed using a generalized least squares regression model with the maximum likelihood method using SAS software (version 9.2; SAS Corporation), as previously described in the literature.[19,20,25] This method accounts for appropriate variance-covariance associations between and within studies. It uses the multiple data points available in all studies simultaneously to provide the best overall pooled dose-response estimate in a single estimation. Nonlinearity in the association between sedentary time and CVD risk was assessed by modeling sedentary time duration with the use of restricted cubic splines with 3

Table 2. Sedentary Time Categories and Associated Risk for Cardiovascular Events Across Included Studies

Source	Categories of Sedentary Times	Most Adjusted HR by Category (95% CI)	Covariates in the Most Adjusted Model
Matthews et al,[14] 2014	Overall sedentary behavior, h/d 1: >12.00 2: 8.51 to 12.00 3: 5.76-8.50 4: <5.76	Black participants: 1: 1.11 (0.93-1.33) 2: 1.08 (0.91-1.28) 3: 0.9 (0.76-1.07) 4: 1 [Reference] White participants: 1: 1.75 (1.24-2.48) 2: 1.59 (1.14-2.20) 3 1.44 (1.05-1.98) 4: 1 [Reference]	Age, sex, ethnicity,enrollment source, educational level, income, smoking, BMI, sleep duration, diabetes, employment status, physical activity[a,b]
Bjørk Petersen et al,[8] 2014	Overall sedentary behavior, h/d 1: >10 2: 6 to <10 3: 0 to <6	1: 1.07 (0.91-1.27) 2: 0.96(0.85-1.09) 3: 1 [Reference]	Age, sex, educational level, physical activity levels, smoking, BMI, alcohol consumption, diabetes, hypertension
Kim et al,[13] 2013	Total daily sitting time, h/d 1: ≥10 2: 5 to <10 3: <5	Women: 1: 1.19 (1.06-1.34) 2: 0.96 (0.85-1.07) 3: 1 [Reference] Men: 1: 1.06 (0.96-1.18) 2: 0.98 (0.90-1.07) 3: 1 [Reference]	Age, sex, educational level, ethnicity, smoking, hypertension, diabetes, alcohol consumption, energy intake, physical activity[a,b]
Chomistek et al,[9] 2013	Total daily sitting time, h/d 1: ≥10 2: 5.1 to 9.9 3: ≤5	1: 1.15 (1.05-1.25) 2: 1.02 (0.95-1.09) 3: 1 [Reference]	Age, ethnicity, educational level, income, smoking, marital status, alcohol intake, total caloric intake, sleep duration, hypertension, diabetes, BMI, HLD, depression, family history of MI, dietary pattern, physical activity
Herber Gast et al,[11] 2013	Sitting time, h/d 1: 8.4 2: 4.9 3: 2.7	1: 0.90 (0.62-1.32) 2: 1.03 (0.72-1.47) 3: 1 [Reference]	Age, educational level, smoking, alcohol consumption, physical activity, BMI
Matthews et al,[15] 2012	Total daily sitting time, h/d 1: ≥9 2: 7 to 8 3: 5 to 6 4: 3 to 4 5: <3	1: 1.16 (1.02-1.30) 2: 0.95 (0.86-1.06) 3:1.02 (0.94-1.11) 4: 0.98 (0.90-1.06) 5: 1 [Reference]	Age, sex, ethnicity, educational level, smoking, diet quality, physical activity, BMI
Patel et al,[16] 2010	Total sitting time, h/d 1: ≥6 2: 3 to 5 3: 0 to <3	Women: 1: 1.33 (1.17-1.52) 2: 1.20 (1.10-1.32) 3: 1 [Reference] Men: 1: 1.18 (1.08-1.30) 2: 1.06 (0.99-1.14) 3: 1 [Reference]	Age, sex, ethnicity, marital status, educational level, smoking status, BMI, alcohol use, total caloric intake, comorbidities score, physical activity[b]
Katzmarkzyk et al,[12] 2009	Total sitting time 1: Almost all the time 2: ¾ of the time 3: ½ of the time 4: ¼ of the time 5: Almost none of the time	1: 1.54 (1.09-2.17) 2: 1.47 (1.09-1.96) 3: 1.22 (0.94-1.60) 4: 1.01 (0.77-1.31) 5: 1 [Reference]	Age, sex, smoking, alcohol use, physical activity levels, Physical Activity Readiness Questionnaire
Borodulin et al,[6] 2015[c]	Total sitting time, h/d 1: ≥10 2: <10	1: 1.45 (0.91-2.29) 2: 1 [Reference]	Age, sex, employment status, educational level, BMI, smoking, alcohol use, hypertension or antihypertensive use, HLD or anti-HLD medication use, physical activity levels

Abbreviations: BMI, body mass index; HLD, hyperlipidemia; HR, hazard ratio; hypertension; MI, myocardial infarction.

[a] Age was used as underlying time metric.

[b] Analysis stratified based on the covariate.

[c] The data for pooled analysis for this study were obtained from a related thesis publication by the same author group archived in the electronic database of the University of Tampere, Tampere, Finland (https://tampub.uta.fi/bitstream/handle/10024/76853/gradu06623.pdf?sequence=1).

knots at fixed centiles (5%, 50%, and 95%) of the distribution. We first estimated a restricted cubic spline model with a generalized least squares regression, considering the correlation within each set of reported HRs. We then combined the study-specific estimates, using the restricted maximum likelihood method in a multivariable random-effects meta-analysis. We also performed sensitivity analyses using HRs from models without adjustment for physical activity and BMI levels to determine whether the observed dose-response association was different with vs without adjustment for these potential confounders.

Results

Characteristics of Included Studies

The study selection process and results from the literature search are shown in eFigure 1 in the Supplement. We included 9 cohort studies with 720 425 unique participants (57.1% women; 42.9% men; mean age, 54.5 years) and 25 769 unique incident CVD events during a median follow-up of 11 years. Baseline characteristics of the included studies are shown in **Table 1**. Of the 9 studies that were included,[6,8,9,11-16] 2 studies[9,11]

included only women and 7 studies[6,8,12-16] included men and women. Sedentary behavior was assessed by self-reported questionnaire in the included studies. Objective criteria (administrative database or national mortality and/or death index) were used to identify the incident CVD or associated mortality events in most studies (**Table 2**). Most studies adjusted for covariates such as age (n = 9), sex (n = 9), BMI (n = 7), smoking (n = 9), physical activity (n = 9), and CVD risk factors (diabetes and/or hypertension) (n = 6) in the most adjusted model evaluating the association between sedentary time and CVD risk (Table 2). Across most of the included studies, higher sedentary time was associated with lower levels of physical activity (eTable 2 in the Supplement).

Study Quality, Publication Bias, and Subgroup Analysis

Assessment of study quality yielded a mean score of 8.7, and all studies had a score of 8 or above (eTable 3 in the Supplement). We did not observe a significant publication bias in the present meta-analysis (*P* for Egger line regression test = .26; *P* for Begg rank correlation test = .45 [eFigure 2 in the Supplement]).

Association Between Total Sedentary Time and CVD Risk

Figure 1 shows the pooled estimates the risk for CVD associated with different sedentary time categories. No significant heterogeneity was observed in the pooled analysis comparing the highest vs lowest sedentary time categories across studies (I^2 = 39.7%; *P* = .08), whereas moderate heterogeneity was observed in the pooled comparison between intermediate vs lowest sedentary time categories (I^2 = 61.8%; *P* = .004). Compared with the lowest sedentary time category (median duration, 2.5 h/d), participants in the highest sedentary time category (median duration, 12.5 h/d) had an increased risk for CVD (pooled HR, 1.14; 95% CI, 1.09-1.19). However, the risk associated with the intermediate sedentary time category (median duration, 7.5 h/d) compared with the lowest sedentary time category was not statistically significant (pooled HR, 1.02; 95% CI, 0.96-1.08). In continuous analyses, we found a nonlinear association between sedentary time and CVD risk (*P* < .001 for nonlinearity), with a nonsignificant increased risk observed only at sedentary times more than 6.8 h/d (pooled HR, 1.01; 95% CI, 0.95-1.08), and that became statistically significant at times more than 10.04 h/d (pooled HR, 1.08; 95% CI, 1.00-1.14) (**Figure 2**).

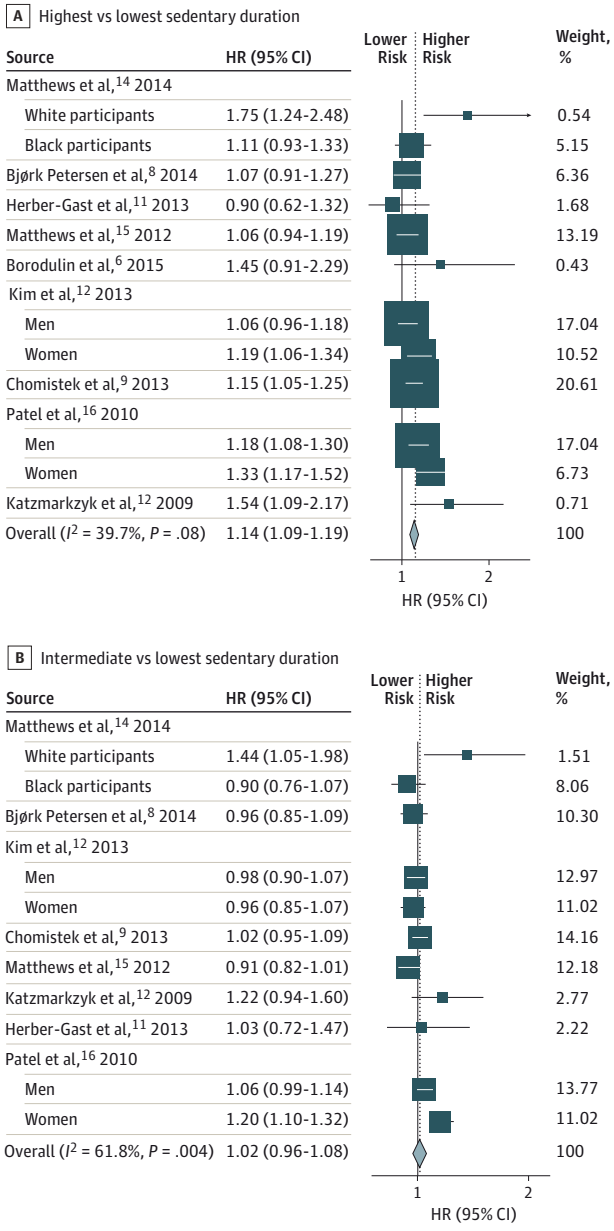
Subgroup and Sensitivity Analysis

To confirm the robustness of our study findings, we conducted additional sensitivity and subgroup analysis evaluating the association between the highest levels of sedentary time and the risk for CVD. We did not observe a significant difference in magnitude or direction of the association between high levels of sedentary time and CVD risk in subgroup analyses by age, geographic location, follow-up duration, and levels of physical activity at baseline (eTable 4 in the Supplement).

To characterize better the effect of physical activity on the observed associations between sedentary time and CVD risk, we conducted additional sensitivity analyses by pooling HRs from multivariable-adjusted models without adjustment for physical activity (4 studies[11,13-15]). We observed similar associations between the highest levels of sedentary time and CVD risk using HRs unadjusted for physical activity (eTable 4 in the Supplement). Similar findings were also observed in continuous dose-response analyses with a statistically significant risk for CVD events observed at a modestly lower sedentary time threshold of 9.2 hours compared with the primary analysis (10.04 h/d) (**Figure 3**A and B).

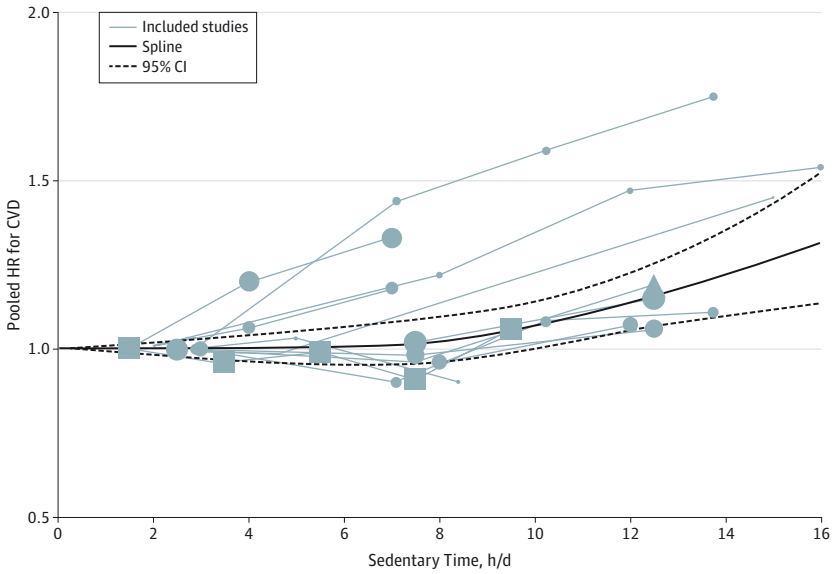
We also assessed the role of BMI as a potential contributor to the observed association between sedentary time and

Figure 1. Pooled Association Between Sedentary Time Categories and Risk for Cardiovascular Disease



Forest plots show pooled estimates of the hazard ratio (HR) for cardiovascular disease risk. Size of the data marker indicates the percentage weight of each study in the pooled analysis.

Figure 2. Dose-Response Association Between Sedentary Time Duration and Risk for Cardiovascular Disease (CVD)



Dose-response associations are reported in the included studies and observed on pooled analysis. The pooled analysis estimates are shown by spline (smoothed fit) and 95% CIs of the pooled hazard ratio (HR) for adverse cardiovascular events by duration of sedentary time. The size of each data marker indicates study size.

CVD risk by performing separate pooled analysis using HRs from models that evaluated the association between sedentary time and CVD risk with vs without adjustment for BMI. In categorical analyses, the pooled estimate was not different in studies with vs without adjustment for BMI (eTable 4 in the Supplement). Similar findings were also observed in continuous dose-response analysis using hazard ratios unadjusted for BMI (Figure 3C).

Joint Effect of Physical Activity and Sedentary Time on CVD Risk

The joint effect of physical activity and sedentary time was reported quantitatively in 3 studies.[8,9,15] We did not perform a meta-analysis to evaluate the joint effects of physical activity and sedentary time on CVD risk owing to the small number of available studies. However, we compared the relative hazard associated with higher levels of sedentary time among physically inactive vs active groups in each of the 3 studies (eTable 5 in the Supplement). Five studies[8,9,11,13,15] performed interaction testing between physical activity levels and sedentary time for CVD risk. Of these, 4 studies[8,9,11,15] observed no significant interaction between the 2 variables, whereas 1 study[13] reported a significant interaction between television viewing time and physical activity level among men for CVD risk (eTable 5 in the Supplement).

Discussion

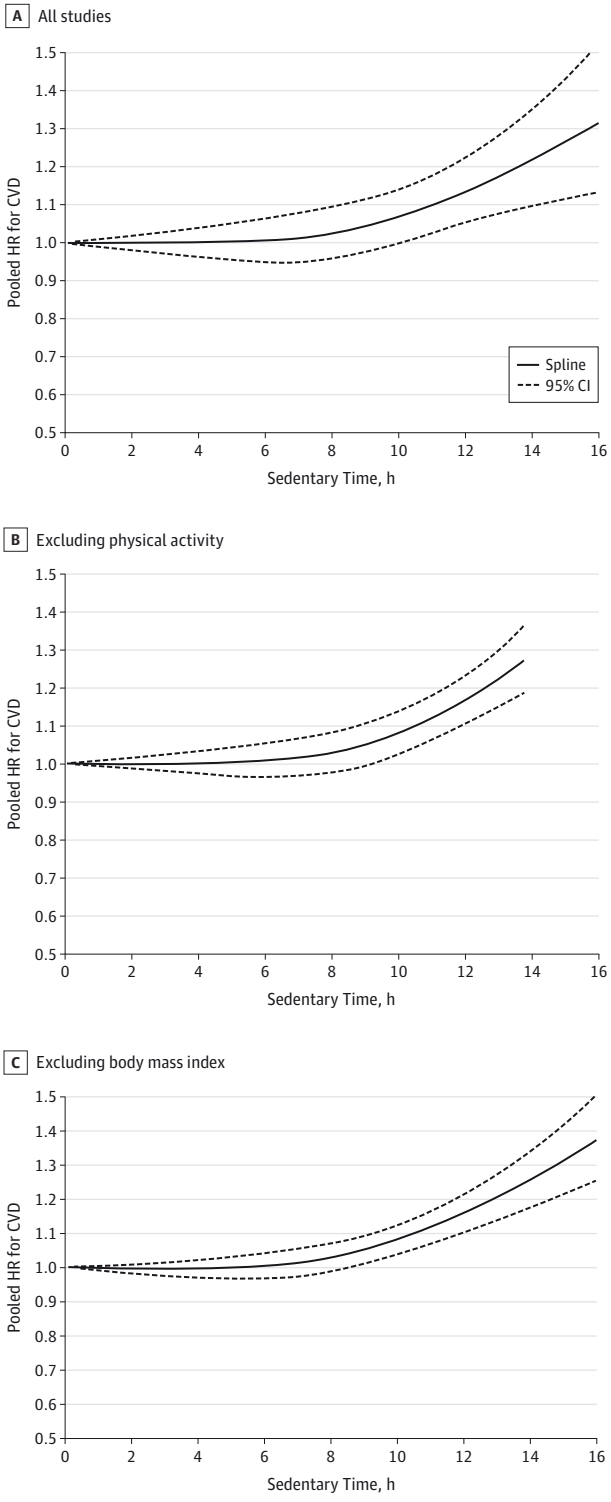
The findings from this meta-analysis, based on 720 425 participants from 9 cohort studies and including 25 769 CVD events, demonstrate a nonlinear association between sedentary time levels and CVD risk. After adjustment for physical activity and other CVD risk factors, significant risk for CVD was observed with very high levels of sedentary time (>10 h/d), with no apparent risk associated with intermediate levels of sedentary time. To our knowledge, the present study represents the largest and most comprehensive evaluation of the dose-response association between sedentary time and CVD risk in the general population.

Recent meta-analyses have evaluated the dichotomous association between sedentary time (high vs low) and the risk for adverse clinical outcomes and demonstrated an increased risk for diabetes, CVD, and incident cancer with greatest levels of sedentary time.[7,26] However, these studies were limited by lack of adjustment for physical activity in the included studies[26] or the lack of assessment of the graded dose-response association between sedentary time and CVD risk.[7] Thus, the independent contributions of different levels of sedentary time toward CVD risk were not assessed. The present study adds significantly to the existing body of literature by providing a comprehensive evaluation of the dose-response association between sedentary time and CVD risk.

We observed a nonlinear association between total sedentary duration and CVD risk, with increased risk observed only at a sedentary duration greater than 10 hours. The biological mechanism underlying this nonlinear association is not completely understood, but it appears to reflect an apparent threshold effect of sedentary time on cardiometabolic risk factors. Along these lines a recent study by Qi et al[27] demonstrated deleterious associations between objectively measured sedentary time and cardiometabolic biomarkers, with more pronounced abnormalities in triglyceride levels, glucose intolerance, insulin sensitivity, and C-reactive protein levels observed only at the highest levels of sedentary time.

The nonlinear association between total sedentary time and CVD risk observed in this study is in contrast to the linear

Figure 3. Continuous Dose-Response Association Between Total Sedentary Duration and Risk for Cardiovascular Disease (CVD)



Continuous dose-response association between total sedentary duration and risk for CVD after adjustment for all potential confounders including physical activity (9 studies); after adjustment for potential confounders excluding physical activity (4 studies); and after adjustment for potential confounders excluding body mass index (5 studies). Spline (smoothed fit) and 95% CI of pooled hazard ratio (HR) for CVD incidence by sedentary hours are shown.

association between television viewing time and CVD risk that was previously reported by Grøntved and Hu in 2012.[10] This discrepancy between the study findings could be owing to differences in the measures of sedentary behavior and pooled HRs for CVD events used in the 2 meta-analyses. Although overall sedentary time was used as a measure of sedentary behavior in the 9 cohort studies included in the present meta-analysis, Grøntved and Hu[10] included fewer studies and evaluated the association between television viewing, a less informative measure of overall sedentary behavior,[28] and the risk for CVD. As a result, the observed differences in the associations could have been related to the difference in the exposure variable of interest. Furthermore, Grøntved and Hu[10] observed a nonlinear association between television viewing and mortality in a pooled analysis, similar to our study findings.

Our study findings have important clinical and public health implications. Current public health guidelines are focused on physical activity promotion in the general population and recommend at least 30 minutes of moderate- to vigorous-intensity physical activity on most days of the week among healthy adults.[2] In contrast, no such guideline recommendations exist regarding the targets for reducing daily duration of sedentary times in the general population. This lack represents an important gap in the public health guidelines when we consider that as many as two-thirds of adult waking hours are sedentary. Our study findings provide important insights into the thresholds beyond which sedentary time may be detrimental to CV health, independent of physical activity levels. Reduction of sedentary times for CVD prevention may be particularly relevant among individuals who may not be able to tolerate guideline-recommended physical activity levels owing to comorbidities or other limitations.[15,29] Nonambulatory interventions, such as sit-stand workstations and activity-permissive desks, aimed at reducing sedentary times among these individuals with very high levels of sedentary time (>10 h/d) may help to reduce CVD risk. This finding is also supported by recent observational data that have reported significant benefits of increased standing or stepping for cardiometabolic risk biomarkers.[30]

The main strengths of our meta-analysis are inclusion of large, well-established prospective studies from a range of geographic locations; a large number of included participants and follow-up CV events; and detailed adjustment for a wide range of potential confounding risk factors that allowed us to evaluate the independent contributions of different levels of sedentary time to CVD risk. The included studies were of high quality (mean score of 8.7 of 9), and we found no significant publication bias in our included studies. We observed low to moderate degrees of heterogeneity in categorical dose-response analyses, with moderate heterogeneity only for the intermediate vs lowest sedentary time comparison. Furthermore, to confirm the robustness of our study findings, we performed several sensitivity and subgroup analyses and observed no significant change in the magnitude of the direction of the pooled effect size for the association between total sedentary duration and CVD risk.

Our study also has several important limitations. First, the study protocol was not published a priori. Second, because we

performed a meta-analysis of observational studies, the results are subject to unmeasured or residual confounding. Third, measurement errors in self-reported sedentary time and variability in the scale of sitting time across studies may have limited the analytical power of the study to determine the association between sedentary time and CVD risk, particularly at higher levels. However, owing to the large number of participants and events included in our dose-response pooled analysis, our study was well powered to detect even a very small risk for CVD associated with unit increases in sedentary time, even at the extreme levels. Future studies with objectively measured sedentary time levels using accelerometers and long-term follow-up are needed to confirm our study findings. Finally, we only included English language studies in our meta-analysis to negate culture-based heterogeneity in our study findings. Although this criterion may have led to potential language bias, previous studies have failed to demonstrate a systematic bias from use of language restriction.[31]

Conclusions

Our study findings suggest that CVD risk associated with total sedentary time is nonlinear, with an increased risk only at very high levels (>10 h/d). Furthermore, the CVD risk associated with very high levels of sedentary time is independent of the baseline CVD risk factor burden and physical activity levels. Future studies are needed to characterize the mechanisms through which high levels of sedentary time increase CVD risk and to determine whether nonambulatory sitting reduction interventions can potentially reduce the risk for adverse CVD events among individuals with very high levels of sedentary time.

ARTICLE INFORMATION

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Study concept and design: Pandey, Kulinski, Berry.
Acquisition, analysis, or interpretation of data: Pandey, Salahuddin, Garg, Ayers, Anand, Mayo, Kumbhani, de Lemos, Berry.
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Critical revision of the manuscript for important intellectual content: Pandey, Ayers, Kulinski, Kumbhani, de Lemos, Berry.
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