American Journal of
Preventive Medicine

REVIEW ARTICLE

Sitting Time and Risk of Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis

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Context: Whether physical activity attenuates the association of total daily sitting time with cardiovascular disease and diabetes incidence is unclear. This systematic review and meta-analysis examined the association of total daily sitting time with cardiovascular disease and diabetes with and without adjustment for physical activity.

Evidence acquisition: PubMed, Web of Science, BASE, MEDLINE, Academic Search Elite, and ScienceDirect were searched for prospective studies, published between January 1, 1989, and February 15, 2019, examining the association of total daily sitting time with cardiovascular disease or diabetes outcomes. Data extraction and study quality assessments were conducted by 2 independent reviewers. Pooled hazard ratios (HRs) were calculated using a fixed-effects model. The quality assessment and meta-analysis procedures were completed in 2018.

Evidence synthesis: Nine studies with 448,285 participants were included. A higher total daily sitting time was associated with a significantly increased risk of cardiovascular disease (HR=1.29, 95% CI=1.27, 1.30, $p<0.001$) and diabetes (HR=1.13, 95% CI=1.04, 1.22, $p<0.001$) incidence when not adjusted for physical activity. The increased risk for diabetes was unaffected when adjusting for physical activity (HR=1.11, 95% CI=1.01, 1.19, $p<0.001$). For cardiovascular disease, the increased risk was attenuated but remained significant (HR=1.14, 95% CI=1.04, 1.23, $p<0.001$).

Conclusions: Higher levels of total daily sitting time are associated with an increased risk of cardiovascular disease and diabetes, independent of physical activity. Reductions in total daily sitting may be recommended in public health guidelines.

Am J Prev Med 2019;57(3):408–416.

CONTEXT

At the population level, sedentary behaviors occupy most of adults' waking hours. Based on accelerometry, adults may spend 50%–60% of their day engaged in sedentary behaviors with an average daily sedentary time of 8.4 hours.[1] Sedentary behavior includes a range of activities that involve sitting or lying down with minimal energy expenditure of ≤1.5 METs during waking time.[2] Such activities include watching TV, sitting in a car, and office work. Sedentary behavior is distinct from physical inactivity, which refers to insufficient levels of moderate-to-vigorous physical activity. A number of systematic reviews and meta-analyses have explored the association of sedentary behavior with cardiovascular disease (CVD) and Type 2 diabetes. One meta-analysis reported that TV viewing was associated with an increased risk of CVD and Type 2 diabetes.[3] However, TV viewing time is a poor indicator of total

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0749-3797/$36.00
https://doi.org/10.1016/j.amepre.2019.04.015

sedentary time and thus may misclassify the true effect of this exposure on CVD and diabetes risk.[4] Another meta-analysis reported that individuals who engaged in the highest amount of sedentary time had an increased risk of diabetes (112%) and cardiovascular events (147%) compared with those who engaged in the lowest amount of sedentary time.[4] However, the meta-analysis conducted by Wilmot et al.[4] included both cross-sectional and prospective studies that varied considerably with regard to sedentary behavior exposure (e.g., TV viewing, leisure-time sedentary behavior, and total sitting), which were combined in the same analysis. Therefore, it was not possible to make conclusions regarding the prospective associations of total daily sitting time with CVD and diabetes, which could be important for public health guidelines.

The World Health Organization physical activity guidelines recommend that adults accumulate ≥150 minutes per week of moderate-intensity physical activity or ≥75 minutes per week of vigorous-intensity physical activity.[5] However, there is no recommendation with respect to sitting time, and it remains unclear if increasing physical activity alone is sufficient for health or whether reductions in daily sitting are also required. Ekelund and colleagues[6] reported in a meta-analysis of more than 1 million adults that engaging in high levels (60–75 minutes per day) of moderate-intensity physical activity attenuated the increased mortality risk associated with high total daily sitting time. However, this level of daily physical activity may not be achievable for large amounts of the population and guidelines may need to recommend both increases in physical activity and reductions in sitting time. The meta-analysis by Wilmot et al.[4] demonstrated that the increased risk of CVD and diabetes with high amounts of sedentary behavior (including measures of TV viewing, leisure-time sedentary behavior, and total daily sitting) remained, although somewhat attenuated, after adjustment for physical activity.[4] Two other meta-analyses showed that higher total daily sitting[7] and higher sedentary time (including studies with total daily sitting and TV viewing as the exposure)[8] were associated with increased incidence of CVD and Type 2 diabetes. However, they did not report whether adjustment for physical activity affected these associations. Thus, whether physical activity attenuates any potential associations of higher amounts of total daily sitting time with CVD and diabetes has not been evaluated and is required to inform public health guidelines. The aim of this study is to quantitatively synthesize prospective evidence relating total daily sitting time to incident CVD and diabetes with and without adjustment for physical activity.

EVIDENCE ACQUISITION

This review was conducted following the PRISMA guidelines[9] and the protocol was registered with PROSPERO: International Prospective Register of Systematic Review Protocols (registration number CRD42017054222). Ethical approval for the protocol was obtained from the Institute for Sport and Physical Activity Research Ethics Committee at the University of Bedfordshire (2018ISPAR004).

Study Selection

A systematic search was conducted to identify relevant studies within the following databases: PubMed, Web of Science, BASE, MEDLINE, Academic Search Elite, and ScienceDirect. The search terms used were as follows: *(sitting time OR sedentary behavior OR sedentary behaviour OR sedentary lifestyle) AND (cardiometabolic disease OR cardiovascular disease OR diabetes OR heart disease OR stroke OR myocardial infarction OR angina OR heart failure OR heart attack OR coronary disease) AND (risk OR Cox OR hazard OR survival analysis OR odds)*. Titles and abstracts were independently reviewed by RBC and DPB and the full text was obtained for articles that were potentially eligible for inclusion and reviewed by the same authors. The reference lists of included articles and the authors' personal collections were then checked to identify any additional articles for potential inclusion and were screened using the process described above.

Eligibility Criteria

Studies published in English between January 1, 1989, and February 15, 2019, were included if they met the following criteria:

1. included male and female adults aged ≥18 years, healthy, and disease free at baseline;
2. were observational prospective/follow-up studies that included a measure of total daily sitting time as an exposure variable, collected subjectively by self-report or objectively by inclinometers;
3. reported associations of different levels of total daily sitting time with objectively determined or self-reported CVD or diabetes incidence; and
4. had an outcome of CVD or diabetes.

Data Extraction and Synthesis

Data were independently extracted from identified articles by 2 reviewers (DPB and SMS), which were compared for consistency. The reviewers settled any discrepancies through discussion. The extracted data included the following: author(s); study design; sample size; mean follow-up duration; CVD or diabetes outcome; number of outcome cases; total sitting time measure; hazard ratio (HR), RR, or OR estimates with 95% CIs; and confounding variables adjusted for in the analysis. The measurement of total daily sitting time varied between studies with respect to grouping participants into different sitting categories using either quantile splits or arbitrarily determined groups that were not consistent across studies. Therefore, the CVD and diabetes outcomes associated with the highest amount of total daily sitting were compared with the lowest amount of total daily sitting time for the purpose of this review to overcome these discrepancies in reporting.[4]

Corresponding authors were contacted by e-mail to clarify or retrieve missing data, and the responses were incorporated into the analysis.

Study Appraisal

The methodologic quality of the selected articles was independently assessed by DPB and SMS. Disagreements were resolved with scores from a third reviewer (RBC). A checklist developed from Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and STROBE was used to assess the methodologic quality of the studies.[10,11] The total score available was 9 points: 1 point for a prospective study design; 1 point for reported reliability and 1 point for reported validity if sitting time was self-reported; 2 points if sitting time was objectively measured; 1 point if 2 or more confounders were controlled for in the analysis; 1 point if the analysis controlled for physical activity; 1 point if an objective measure of the health outcome was used; and 1 point for an adequate description of the population. A score of ≥7 was considered high quality, 4–6 moderate quality, and ≤3 poor quality.

Analysis

The HR or RR and 95% CIs comparing the highest level of total daily sitting with the lowest level were extracted from each study. RRs were considered equal to HRs in this study. Data were extracted from the most adjusted model without physical activity adjustment and the least adjusted model with adjustment for physical activity.[12] Where sitting time was reported in hours per week, the result was divided by 7 to provide sitting time in hours per day. If a study did not present HR or RR, the RR was calculated from the raw data.

Heterogeneity was calculated using the I^2 statistic and interpreted based on Higgins and colleagues,[13] where 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. Four fixed-effects meta-analyses were performed following Cochrane guidelines[14]: 1 for CVD outcomes without adjustment for physical activity; 1 for CVD outcomes with adjustment for physical activity; 1 for diabetes outcomes without adjustment for physical activity; and 1 for diabetes outcomes with adjustment for physical activity. Natural logarithm HRs were pooled across studies and weighted based on the inverse of variance for each study. Fixed effects models were used, as there was no evidence of high heterogeneity across studies. Data were reported as mean effect HR (95% CI) and statistical significance accepted as $p<0.05$.

EVIDENCE SYNTHESIS

Article Selection

The PRISMA flow diagram of the article selection process is shown in Figure 1. The literature search resulted in 4,304 articles, which were reduced to 2,690 after removing duplicates. Titles and abstracts were then screened and 2,670 were excluded because they did not meet the eligibility criteria for this review. This resulted in retrieval of 20 articles for full-text screening. Of these 20 articles, 11 were excluded as they did not satisfy the inclusion criteria, resulting in a total of 9 articles being included for analysis.

Study Characteristics

The characteristics and main outcomes for each study can be seen in Appendix Table 1 (available online). Data from 224,414 participants were included in the CVD meta-analysis with 4,575 incidences during follow-up, and 223,871 participants were included for diabetes with 11,472 incidences during follow-up. Five studies had diabetes as an outcome,[15–19] 3 studies had CVD as an outcome,[20–23] and 1 study reported outcomes separately for myocardial infarction and coronary heart disease.[24] Thus, data for 10 outcomes (CVD, n=5; diabetes, n=5) from these 9 studies were included in the meta-analysis. The cohorts were from a range of countries including Norway, Denmark, Finland, U.S., Australia, and Britain. The mean age of the samples in these studies ranged from 44 to 64 years. Six studies included male and female participants in their sample,[15,17–21,24] and 3 studies included only female participants.[16,22,23] The mean follow-up period ranged from 2.7 to 13.0 years. All studies used a single-item self-report measure of total daily sitting time (Appendix Table 2, available online) and divided sitting time into categories for analysis. The cut points for these categories were not consistent across studies with the threshold for being in the highest sitting group ranging from ≥7.1 hours to ≥16 hours per day and the threshold for being in the lowest sitting group ranging from <4 hours to <8 hours per day. One study did not report the threshold for being in the highest and lowest daily sitting categories and instead reported the mean total daily sitting for these categories, which were 8.4±1.8 hours per day versus 2.7±0.8 hours per day, respectively. Physical activity was self-reported in all studies using a range of different questions and categorization approaches (Appendix Table 2, available online) to measure leisure-time physical activity, MET minutes or MET hours per week, or moderate-to-vigorous physical activity. All studies, other than Borodulin et al.,[21] reported data for risk associations of total daily sitting time with CVD and diabetes with and without adjustment for physical activity.

Study Quality

The overall quality of the studies included in this review was moderate to high (Table 1). All included studies reported a prospective association.[20] All studies used a self-report measure of sitting time. Four studies reported the validity and reliability of the self-report tool used,[16,17,21,24] 1 study reported the validity only,[19] and 4 studies did not report the validity or reliability of the tool used.[15,18,22,23] The quality of the studies varied from 4/9 to 7/9.

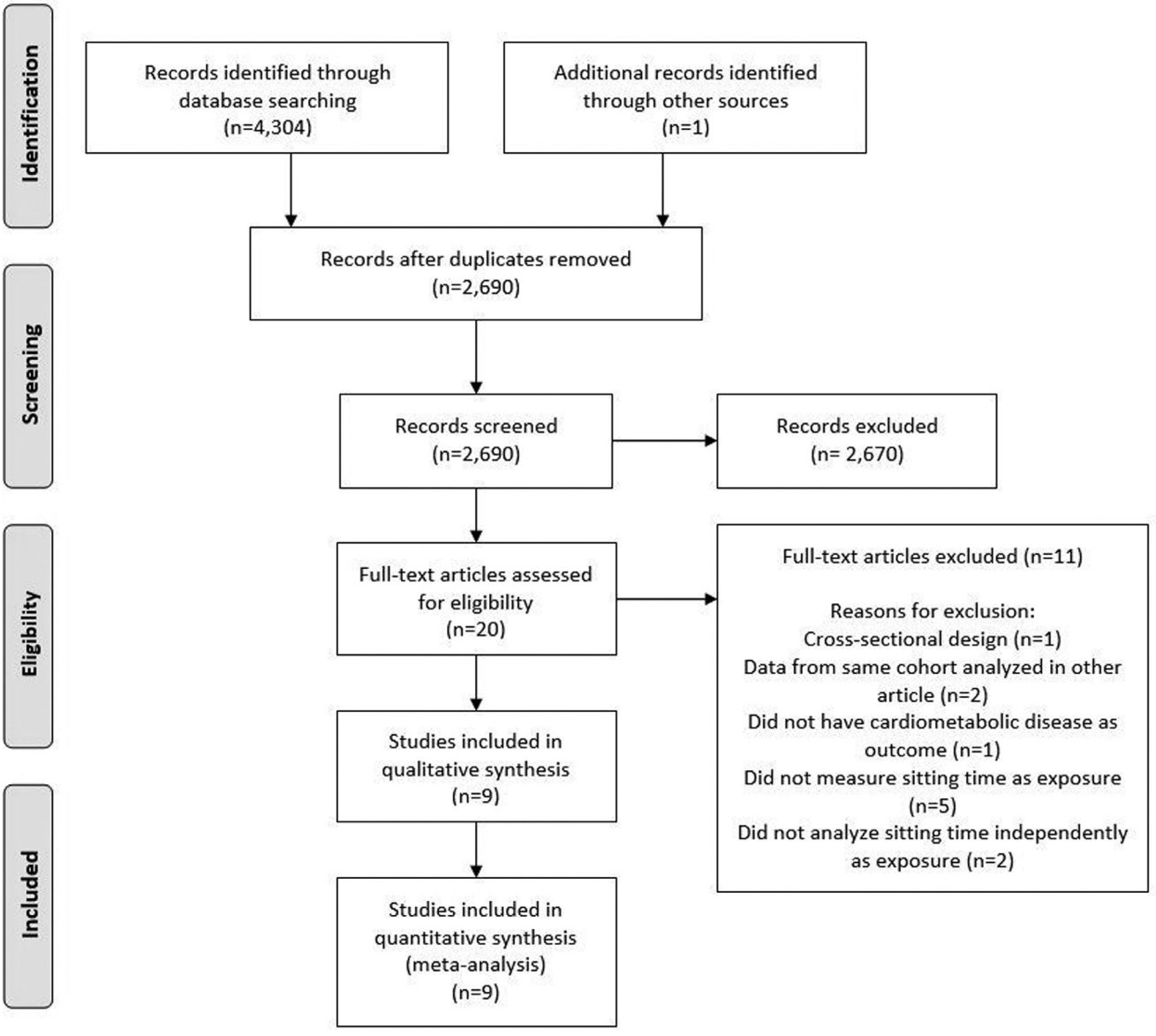

Figure 1. PRISMA flow chart of study selection.

Associations of Total Daily Sitting Time With Cardiovascular Disease and Diabetes Incidence

Higher total daily sitting time was associated with a significantly increased risk of CVD when physical activity was not adjusted for (HR=1.29, 95% CI=1.27, 1.30, $p<0.001$); this risk was attenuated but remained significant with adjustment for physical activity (HR=1.14, 95% CI=1.04, 1.23, $p<0.001$). There was a significantly increased risk of diabetes associated with higher total daily sitting time without adjustment for physical activity (HR=1.13, 95% CI=1.04, 1.22, $p<0.001$) and this association was not attenuated with adjustment for physical activity (HR=1.11, 95% CI=1.01, 1.19, $p<0.001$). The forest plot of the hazards for higher amounts of total daily sitting can be seen in Figure 2 (without adjustment for physical activity) and Figure 3 (adjusted for physical activity).

Publication Bias and Heterogeneity

Publication bias was not assessed for either CVD or diabetes, as there was a small number of published studies for each of these outcomes. However, visual inspection of the forest plot (Figures 2 and 3) would suggest that publication bias was likely not present for CVD or diabetes because there was no consistent pattern in studies with regard to the size of effect reported for smaller or larger sample sizes. Heterogeneity was low for CVD outcomes with and without adjustment for physical activity (I^2=4%, p=0.37,

Table 1. Study Quality Appraisal Criteria and Scores for Each Study

Criterion	Asvold et al.[15]	Bjork Petersen et al.[24]	Borodulin et al.[21]	Chomistek et al.[22]	Herber-Gast et al.[23]	Manini et al.[16]	Nguyen et al.[18]	Petersen et al.[17]	Stamatakis et al.[19]	Studies meeting criteria, *n*
1. Does the study report a prospective association?	1	1	1	1	1	1	1	1	1	9/9
2. If sitting time was self-reported, was reliability and validity reported?[a]	0	2	2	0	0	2	0	2	1	9/18
3. Was an objective measure of sitting used?	0	0	0	0	0	0	0	0	0	0/18
4. Were 2 or more confounders controlled for in the analysis?	1	1	1	1	1	1	1	1	1	9/9
5. Did the analysis control for physical activity?	1	1	1	1	1	1	1	1	1	9/9
6. Was an objective measure of the health outcome used?	0	1	1	1	1	0	0	1	1	6/9
7. Was there an adequate description of the study population including age, sex, and country of residence?	1	1	1	1	1	0	1	1	1	8/9
Score	4	7	7	5	5	5	4	7	6	

Note: 0=no, 1=yes. Two points are available for criterions 2 and 3 and the total score is thus out of 18.
[a]For criterion 2, 1 point was assigned for reporting reliability and 1 point was assigned for reporting validity.

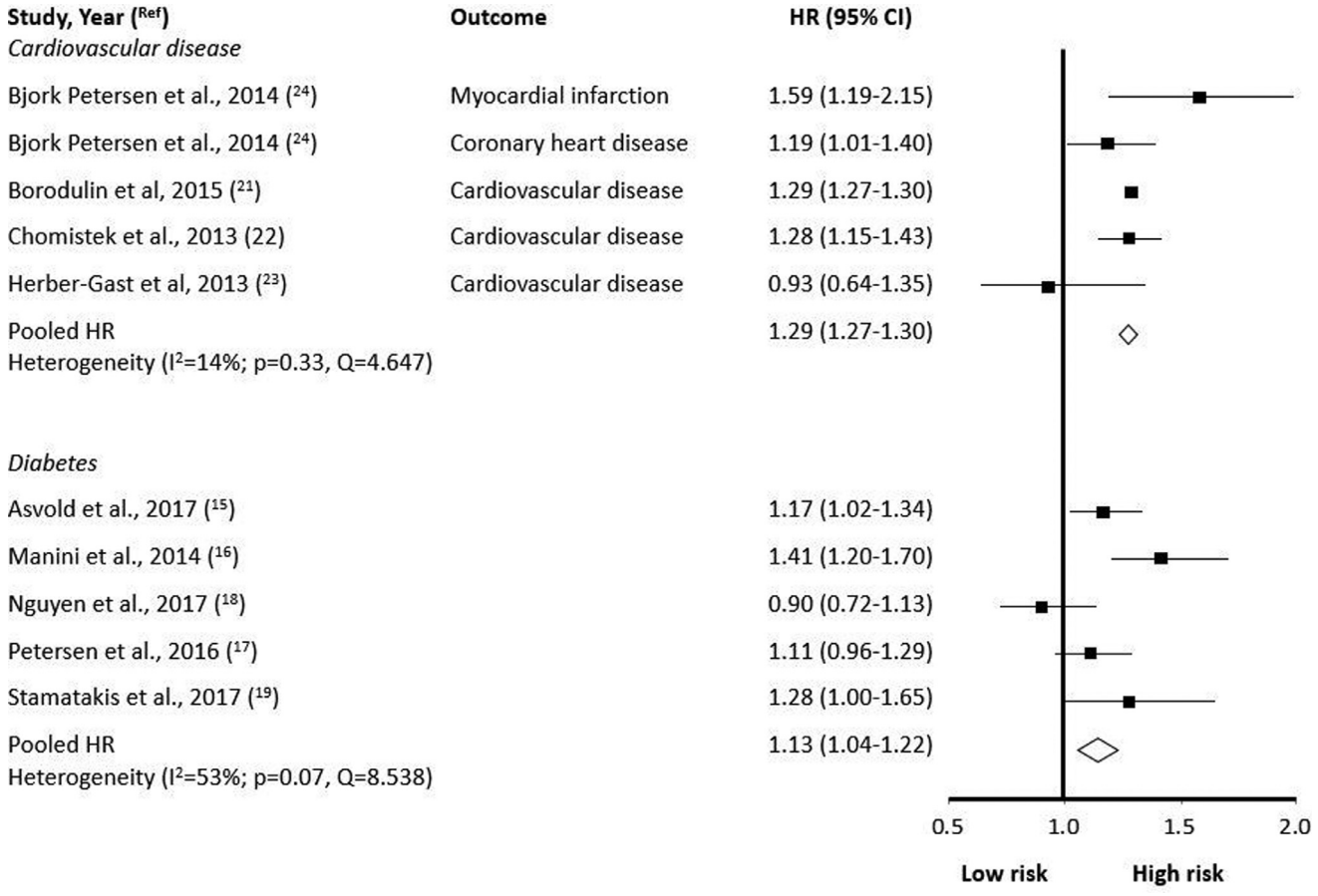

Figure 2. The association between higher total daily sitting time and health outcomes without adjustment for physical activity. HR, hazard ratio.

Q=3.122 and I^2=14%, p=0.33, Q=4.647, respectively) and moderate for diabetes outcomes both with and without adjustment for physical activity (I^2=38%, p=0.16, Q=6.503 and I^2=53%, p=0.07, Q=8.538, respectively).

DISCUSSION

This meta-analysis of prospective studies, incorporating 448,285 participants, demonstrates an increased risk for the incidence of CVD and diabetes in individuals who engage in higher levels of total daily sitting time. The increased risk of diabetes was not attenuated after adjustment for physical activity, whereas the increased risk of CVD was attenuated, but remained significant, after adjustment for physical activity. This suggests that the risk of CVD and diabetes outcomes associated with higher levels of sitting time are independent of physical activity levels.

The findings of the present study agree with previous meta-analyses demonstrating an increased risk of CVD and diabetes in individuals who engage in higher levels of sedentary time.[4,8] However, pooled HRs for incident diabetes associated with the higher levels of sedentary time were greater in magnitude than the present study: HR=1.91[8] and 2.47 (without adjustment for physical activity).[4] For CVD incidence, Wilmot and colleagues[4] reported a greater effect than the present study (HR=2.47), although in the study by Biswas et al.,[8] the effect was similar (HR=1.14). The disparity in effects could be due to the type of sedentary behavior exposures that were included (e.g., TV viewing, leisure-time sedentary behavior, and total daily sitting time). For instance, in a previous meta-analysis, the association of high daily sitting with all-cause mortality was attenuated with high physical activity levels, whereas the association with TV viewing time was not.[6] The domain of sitting may thus affect the associations with observed health outcomes, meaning it is not appropriate to combine different sitting time exposures in the same analysis. The findings of this study address these limitations by including only total daily sitting time as the sedentary behavior exposure.

The increased risk of CVD and diabetes associated with higher amounts of total daily sitting in the present

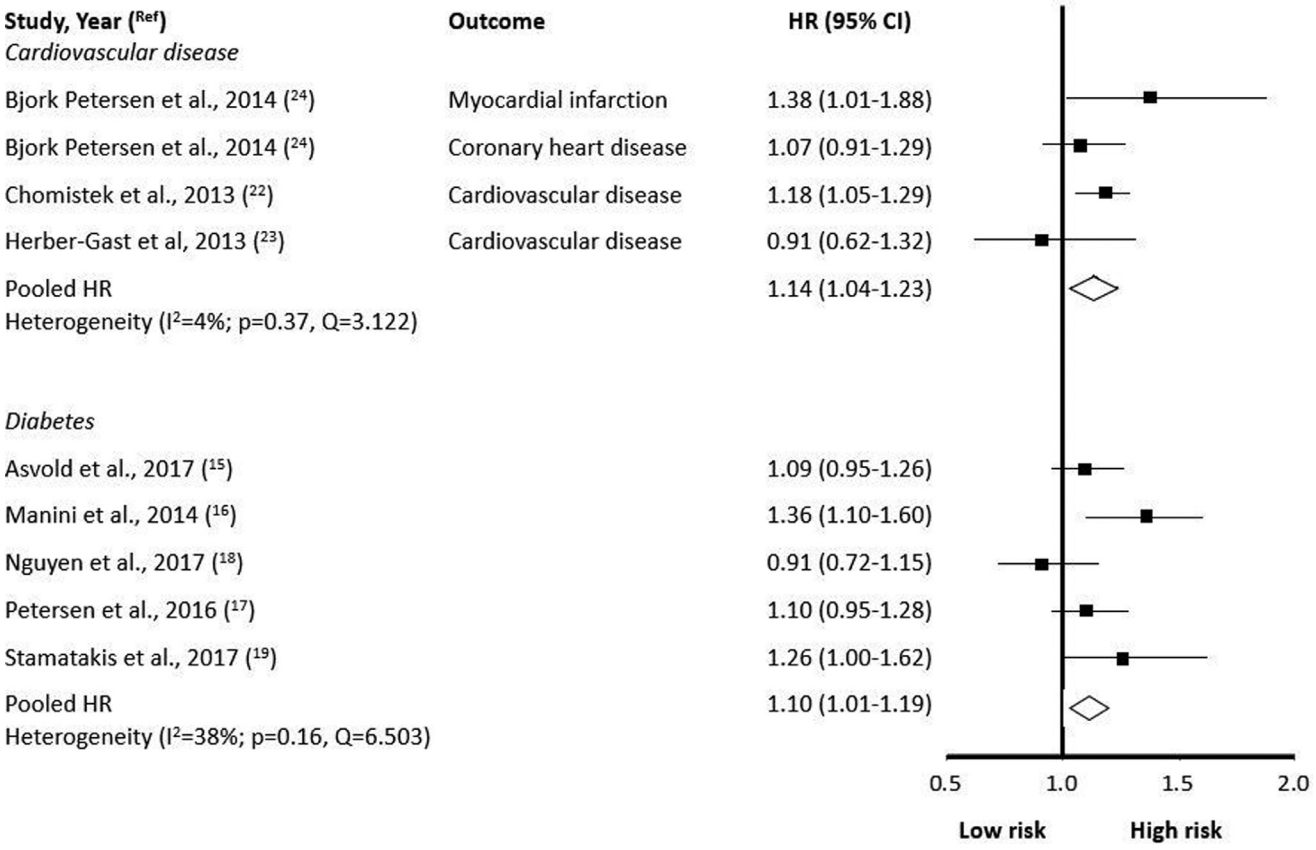

Figure 3. The association between higher total daily sitting time and health outcomes with adjustment for physical activity. HR, hazard ratio.

study remained after adjustment for physical activity. This has also been documented in a previous meta-analysis comparing the highest with the lowest group of sedentary time (including a mix of sedentary behavior exposures) for these health outcomes.[4] Two other meta-analyses showed that incident CVD and Type 2 diabetes risk were positively associated with significantly higher levels of sedentary time when adjusting for physical activity.[7,8] However, these studies did not present data for models without physical activity adjustment; thus, whether physical activity attenuated this risk was unknown.[7,8] Ekelund et al.[6] reported in their meta-analysis that the mortality risk associated with high amounts of total daily sitting was attenuated in individuals who engaged in high amounts (60–75 minutes per day) of moderate-intensity physical activity. It was not feasible to use an approach similar to that of Ekelund and colleagues[6] in the present study, as the included articles did not report on associations of sitting time with CVD and diabetes for separate physical activity categories. Future research should address this gap to inform CVD and diabetes prevention guidelines.

The independent associations of total daily sitting time with CVD and diabetes may be explained by several potential biological mechanisms. A number of experimental studies have shown that prolonged sitting results in higher levels of lipids, glucose, and insulin,[25–27] and that regularly interrupting sitting or substituting sitting with light-, moderate-, or high-intensity physical activity attenuates these responses.[28–33] Prolonged sitting is theorized to negatively affect carbohydrate metabolism through changes in muscle glucose transporter protein content and activity.[27] Interrupting sitting with regular short bouts of physical activity upregulates glucose uptake pathways[34] and alters gene expression that modulates lipid and glucose metabolism.[35] In animal models, prolonged periods of muscular inactivity lead to decreased lipoprotein lipase activity (essential in the regulation of lipid levels) through cellular pathways uniquely different to exercise responses,[36] although this requires confirmation in humans. Prolonged sitting can also cause vascular dysfunction through changes in blood flow and shear stress within blood vessels, thus promoting inflammation and atherosclerosis.[37] However, it is not clear whether these suggested mechanisms

can be applied to the current findings, as the analysis was unable to examine the pattern of sitting time.

Limitations

The major strength of this study is the meta-analysis for associations of total daily sitting time with CVD and diabetes outcomes with and without adjustment for physical activity. Inclusion of large population-based prospective cohort studies is also a strength. However, the included studies were limited to the use of self-report questionnaires to measure exposure. This is problematic, as self-report measures underestimate total daily sitting time,[38] which may lead to underestimations of health outcome risks associated with sitting time. Furthermore, only 4 studies reported the reliability and validity of the questions used.[16,17,21,24] How questions are phrased, the time period they consider, and whether assessed by a single question or multiple domains can all affect the validity of total daily sitting measures.[39] Thus, there is a need for studies to employ objective measures of sitting time to address these limitations. Furthermore, the cut points used to categorize high and low levels of daily sitting varied across studies. Although this may affect the associations reported in the individual studies and in this meta-analysis, there was low heterogeneity across studies for all subgroup analyses, suggesting that this may not have affected this study's findings. Moreover, physical activity was self-reported in all studies and the physical activity outcomes (e.g., leisure-time physical activity, moderate-to-vigorous physical activity, and MET hours per week) were not consistent across studies. This could have affected the observed associations of sitting time with CVD and diabetes when adjusting for physical activity. Measuring total daily sitting and physical activity using devices would help to overcome some of these limitations in future research. There is also a need for further research to examine the joint associations of total daily sitting and physical activity with CVD and diabetes incidence to better determine if higher levels of physical activity attenuate the negative cardiometabolic health outcomes associated with higher total daily sitting. Other limitations include the small number of prospective studies reporting on the association of total daily sitting with CVD and diabetes incidence and the use of only studies published in English.

CONCLUSIONS

This study suggests that higher levels of total daily sitting time are associated with an increased risk of CVD and diabetes, even after adjustment for physical activity. The findings support a focus on reducing total daily sitting time in public health guidelines and the need for experimental studies investigating the effectiveness of reducing daily sitting on cardiometabolic health.

ACKNOWLEDGMENTS

No sources of funding supported this study.

DPB and SMS conceived the study and designed the experiments. DPB, DJH, RBC, and SMS performed the experiments and wrote the paper.

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 https://doi.org/10.1016/j.amepre.2019.04.015.

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