Sitting time and risk of cardiovascular disease and diabetes: A systematic review and meta-analysis

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Abstract

Context: Whether physical activity attenuates the association of total daily sitting time with cardiovascular disease (CVD) and diabetes incidence is unclear. This systematic review and meta-analysis examined the association of total daily sitting time with CVD 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 1st January 1989 and 15th February 2019 examining the association of total daily sitting time with CVD or diabetes outcomes. Data extraction and study quality assessments were conducted by two independent reviewers. Pooled Hazard Ratios (HRs) were calculated using a fixed-effects model. The quality assessment and meta-analytic procedures were completed in 2018. **Evidence Synthesis:** Nine studies with 448,285 participants were included. Higher total daily sitting time was associated with a significantly increased risk of CVD (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 physical activity was not adjusted for. 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 CVD, 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 CVD and diabetes, independent of physical activity. Reductions in total daily sitting may thus be recommended in public health guidelines.

Context

At population level, sedentary behaviours occupy the majority of adults' waking hours. Based on accelerometry, adults may spend 50-60% of their day engaged in sedentary behaviours with an average daily sedentary time of 8.4 h.[1] Sedentary behaviour includes a range of activities that involve sitting or lying down with minimal energy expenditure of ≤1.5 metabolic equivalents (METs) during waking time.[2] Such activities include watching TV, sitting in a car, and office work. Sedentary behaviour is distinct from physical inactivity, which refers to insufficient levels of moderate-to-vigorous physical activity (MVPA). There have been a number of systematic reviews and meta-analyses that have explored the association of sedentary behaviour 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 sedentary time and may thus 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 considerable with regards to sedentary behaviour exposure (e.g. TV viewing, leisure-time sedentary behaviour and total sitting), which were combined in the same analysis. It was thus 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 min/week of moderate-intensity physical activity or ≥75 min/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, et al.[6] reported in a meta-analysis of more than 1 million adults that engaging in high levels (60-75 min/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 thus 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 behaviour (including measures of TV viewing, leisure-time sedentary behaviour and total daily sitting) remained, although was 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 was to quantitatively synthesise 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 (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: ("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 reviewed independently by R. B. Champion and D. P. Bailey 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 1st January 1989 and 15th February 2019 were included if they met the following criteria: (i) males and females aged 18 and over, healthy and disease free at baseline; (ii) observational prospective/follow-up studies that included a measure of total daily sitting time as an exposure variable collected subjectively via self-report or objectively via inclinometers; (iii) reported associations of different levels of total daily sitting time with objectively determined or self-reported CVD and/or diabetes incidence; and (iv) had an outcome of CVD or diabetes.

Data extraction and synthesis

Data was extracted from identified articles independently by two reviewers (D. P. Bailey and S. M. Sayegh), which was compared for consistency. The reviewers settled any discrepancies via discussion. The data extracted 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, 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. The CVD and diabetes outcomes associated with the highest amount of total daily sitting were thus 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 email to clarify or retrieve missing data and responses were incorporated into the analysis.

Study appraisal

The methodological quality of the selected articles was independently assessed by D. P. Bailey and S. M. Sayegh. Disagreements were resolved with scores from a third reviewer (R. B. Champion). A checklist developed from MOOSE (meta-analysis of observational studies in epidemiology) and STROBE (strengthening the reporting of observational studies in epidemiology) was used to assess the methodological 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 two 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 were extracted from each study. Risk ratios were considered to be 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 h/week, this was divided by seven to provide sitting time in h/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, et al.[13] where 25%, 50% and 75% represent low, moderate and high heterogeneity, respectively. Four fixed-effects meta-analyses were performed following Cochrane guidelines[14]: one for CVD outcomes without adjustment for physical activity, one for CVD outcomes with adjustment for physical activity, one for diabetes outcomes without adjustment for physical activity, and one 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 are 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 4304 articles, which was reduced to 2690 after removing duplicates. Titles and abstracts were then screened and 2670 were excluded on the basis that 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 nine articles being included for analysis.

Study characteristics

The characteristics and main outcomes for each study can be seen in Supplementary Table 1. 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] three studies had CVD as an outcome,[20-23] and one study reported outcomes separately for myocardial infarction and coronary heart disease.[24] Data for 10 outcomes (CVD n=5; diabetes n=5) from these nine studies was thus included in the meta-analysis. The cohorts included were from a range of countries including Norway, Denmark, Finland, USA, Australia, and Britain. The mean age of the samples in these studies ranged from 44 to 64 years. Six studies included males and females in their sample[15,17-21,24] and three studies included females only.[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 (see Supplementary Table 2) 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 h to ≥16 h/day and the threshold for being in the lowest sitting group ranging from <4 h to <8 h/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 this categories, which were

198 8.4±1.8 h vs. 2.7±0.8 h/day, respectively. Physical activity was self-reported in all studies
199 using a range of different questions and categorisation approaches (see Supplementary Table
200 2) to measure leisure-time physical activity, MET-min or MET-h per week or MVPA. All
201 studies other than Borodulin, et al.[21] reported data for risk associations of total daily sitting
202 time with CVD and diabetes with and without adjustment for physical activity.
203
204 *Study quality*
205 The overall quality of the studies included in this review was moderate to high (see Table 1).
206 All included studies reported a prospective association[20]. All studies used a self-report
207 measure of sitting time. Four studies reported the validity and reliability of the self-report tool
208 used,[16,17,21,24] one study reported the validity only,[19] and four studies did not report the
209 validity or reliability of the tool used.[15,18,22,23] The quality of the studies varied from 4/9 to
210 7/9.
211
212 *Associations of total daily sitting time with cardiovascular disease and diabetes incidence*
213 Higher total daily sitting time was associated with a significantly increased risk of CVD when
214 physical activity was not adjusted for (HR 1.29; 95% CI 1.27, 1.30, p=<0.001); this risk was
215 attenuated but remained significant with adjustment for physical activity (HR 1.14; 1.04,
216 1.23, p=<0.001). There was a significantly increased risk of diabetes associated with higher
217 total daily sitting time without adjustment for physical activity (HR 1.13; 1.04, 1.22,
218 p=<0.001) and this association was not attenuated with adjustment for physical activity (HR
219 1.11; 1.01, 1.19, p=<0.001). The forest plot of the hazards for higher amounts of total daily
220 sitting can be seen in Figure 2 (without adjustment for physical activity) and Figure 3
221 (adjusted for physical activity).
222

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 as there was no consistent pattern in studies with regards 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, 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).

Conclusions

This meta-analysis of prospective studies incorporating 448,285 participants demonstrates an increased risk for 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 are in agreement with previous meta-analyses demonstrating 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, et al.[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 behaviour exposures included e.g. TV viewing, leisure-time sedentary behaviour and/or total daily sitting time. For instance, 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 in a previous meta-analysis[6]. The domain of sitting may thus affect the associations with health outcomes observed meaning it is not appropriate to combine different sitting time exposures in the same analysis. The findings of this current study address these limitations by including only total daily sitting time as the sedentary behaviour exposure.

The increased risk of CVD and diabetes associated with higher amounts of total daily sitting in the present study remained after adjustment for physical activity. This has also been documented in a previous meta-analysis comparing the highest to lowest group of sedentary time (including a mix of sedentary behaviour exposures) for these health outcomes.[4] Two other meta-analyses showed that incident CVD and Type 2 diabetes risk was significantly positively associated with 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 were attenuated in individuals who engaged in high amounts (60-75 min/day) of moderate-intensity physical activity. It was not feasible to use an approach similar to Ekelund, et al.[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 thus 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 a number of 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 theorised to negatively affect carbohydrate metabolism via changes in muscle glucose transporter (GLUT) 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 leads to decreased lipoprotein lipase activity (essential in the regulation of lipid levels) via cellular pathways uniquely different to exercise responses[36], although this requires confirmation in humans. Prolonged sitting can also cause vascular dysfunction via 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.

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 studies included 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 four 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 via a single question or

multiple domains can all affect 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 categorise 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 sub-group 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, MVPA, MET-h 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 may attenuate the negative cardiometabolic health outcomes associated with higher total daily sitting. Other limitations included 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.

In conclusion, 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 supports the need for experimental studies investigating the effectiveness of reducing daily sitting on cardiometabolic health.

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325 Sayegh performed the experiments and wrote the paper. No financial disclosures were
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References

1. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. *European heart journal.* 2011;32(5):590-597.
2. Tremblay MS, Aubert S, Barnes JD, et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. *Int. J. Behav. Nutr. Phys. Act.* 2017;14(1):75.
3. Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA.* 2011;305(23):2448-2455.
4. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia.* 2012;55(11):2895-2905.
5. World Health Organization. Global strategy of diet, physical activity and health. http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf (Accessed on 19 February 2019). 2010.
6. 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.
7. Patterson R, McNamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur. J. Epidemiol.* 2018.
8. 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.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.

10. 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.

11. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J. Clin. Epidemiol.* 2008;61(4):344-349.

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control. Clin. Trials.* 1986;7(3):177-188.

13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.

14. Deeks J, ., Higgins J, Altman D. Analysing data and undertaking meta-analyses. . In: *Cochrane handbook for systematic reviews of interventions.* Cochrane book series.; 2008.

15. Asvold BO, Midthjell K, Krokstad S, Rangul V, Bauman A. Prolonged sitting may increase diabetes risk in physically inactive individuals: an 11 year follow-up of the HUNT Study, Norway. *Diabetologia.* 2017;60(5):830-835.

16. Manini TM, Lamonte MJ, Seguin RA, et al. Modifying effect of obesity on the association between sitting and incident diabetes in post-menopausal women. *Obesity (Silver Spring).* 2014;22(4):1133-1141.

17. Petersen CB, Bauman A, Tolstrup JS. Total sitting time and the risk of incident diabetes in Danish adults (the DANHES cohort) over 5 years: a prospective study. *Br. J. Sports Med.* 2016.

18. Nguyen B, Bauman A, Ding D. Incident Type 2 Diabetes in a Large Australian Cohort Study: Does Physical Activity or Sitting Time Alter the Risk Associated With Body Mass Index? *J Phys Act Health.* 2017;14(1):13-19.

19. Stamatakis E, Pulsford RM, Brunner EJ, et al. Sitting behaviour is not associated with incident diabetes over 13 years: the Whitehall II cohort study. *Br. J. Sports Med.* 2017;51(10):818-823.

20. Jefferis BJ, Parsons TJ, Sartini C, et al. Does total volume of physical activity matter more than pattern for onset of CVD? A prospective cohort study of older British men. *Int. J. Cardiol.* 2019;278:267-272.

21. Borodulin K, Karki A, Laatikainen T, Peltonen M, Luoto R. Daily Sedentary Time and Risk of Cardiovascular Disease: The National FINRISK 2002 Study. *J Phys Act Health.* 2015;12(7):904-908.

22. Chomistek AK, Manson JE, Stefanick ML, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. *J. Am. Coll. Cardiol.* 2013;61(23):2346-2354.

23. Herber-Gast GC, Jackson CA, Mishra GD, Brown WJ. Self-reported sitting time is not associated with incidence of cardiovascular disease in a population-based cohort of mid-aged women. *Int. J. Behav. Nutr. Phys. Act.* 2013;10:55.

24. Bjork Petersen C, Bauman A, Gronbaek M, Wulff Helge J, Thygesen LC, Tolstrup JS. Total sitting time and risk of myocardial infarction, coronary heart disease and all-cause mortality in a prospective cohort of Danish adults. *Int. J. Behav. Nutr. Phys. Act.* 2014;11:13.

25. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. *Metabolism.* 2011;60(7):941-949.

26. Lyden K, Keadle SK, Staudenmayer J, Braun B, Freedson PS. Discrete features of sedentary behavior impact cardiometabolic risk factors. *Med. Sci. Sports Exerc.* 2015;47(5):1079-1086.

27. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. *Appl. Physiol. Nutr. Metab.* 2010;35(6):725-740.

28. Duvivier BMFM, Schaper NC, Koster A, et al. Benefits of Substituting Sitting with Standing and Walking in Free-Living Conditions for Cardiometabolic Risk Markers, Cognition and Mood in Overweight Adults. *Front. Physiol.* 2017;8(353).

29. 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.

30. Maylor BD, Zakrzewski-Fruer JK, Orton CJ, Bailey DP. Beneficial postprandial lipaemic effects of interrupting sedentary time with high-intensity physical activity versus a continuous moderate-intensity physical activity bout: A randomised crossover trial. *J. Sci. Med. Sport.* 2018:Online first.

31. 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.

32. Henson J, Davies MJ, Bodicoat DH, et al. Breaking Up Prolonged Sitting With Standing or Walking Attenuates the Postprandial Metabolic Response in Postmenopausal Women: A Randomized Acute Study. *Diabetes Care.* 2016;39(1):130-138.

33. Miyashita M, Edamoto K, Kidokoro T, et al. Interrupting Sitting Time with Regular Walks Attenuates Postprandial Triglycerides. *Int. J. Sports Med.* 2016;37(2):97-103.

34. Bergouignan A, Latouche C, Heywood S, et al. Frequent interruptions of sedentary time modulates contraction- and insulin-stimulated glucose uptake pathways in muscle: Ancillary analysis from randomized clinical trials. *Sci. Rep.* 2016;6:32044.

35. Latouche C, Jowett JB, Carey AL, et al. Effects of breaking up prolonged sitting on skeletal muscle gene expression. *J Appl Physiol (1985).* 2013;114(4):453-460.

36. 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.

37. Carter S, Hartman Y, Holder S, Thijssen DH, Hopkins ND. Sedentary Behavior and Cardiovascular Disease Risk: Mediating Mechanisms. *Exerc. Sport Sci. Rev.* 2017;45(2):80-86.

38. Chastin SF, Culhane B, Dall PM. Comparison of self-reported measure of sitting time (IPAQ) with objective measurement (activPAL). *Physiol. Meas.* 2014;35(11):2319-2328.

39. Healy GN, Clark BK, Winkler EAH, Gardiner PA, Brown WJ, Matthews CE. Measurement of Adults' Sedentary Time in Population-Based Studies. *Am. J. Prev. Med.* 2011;41(2):216-227.

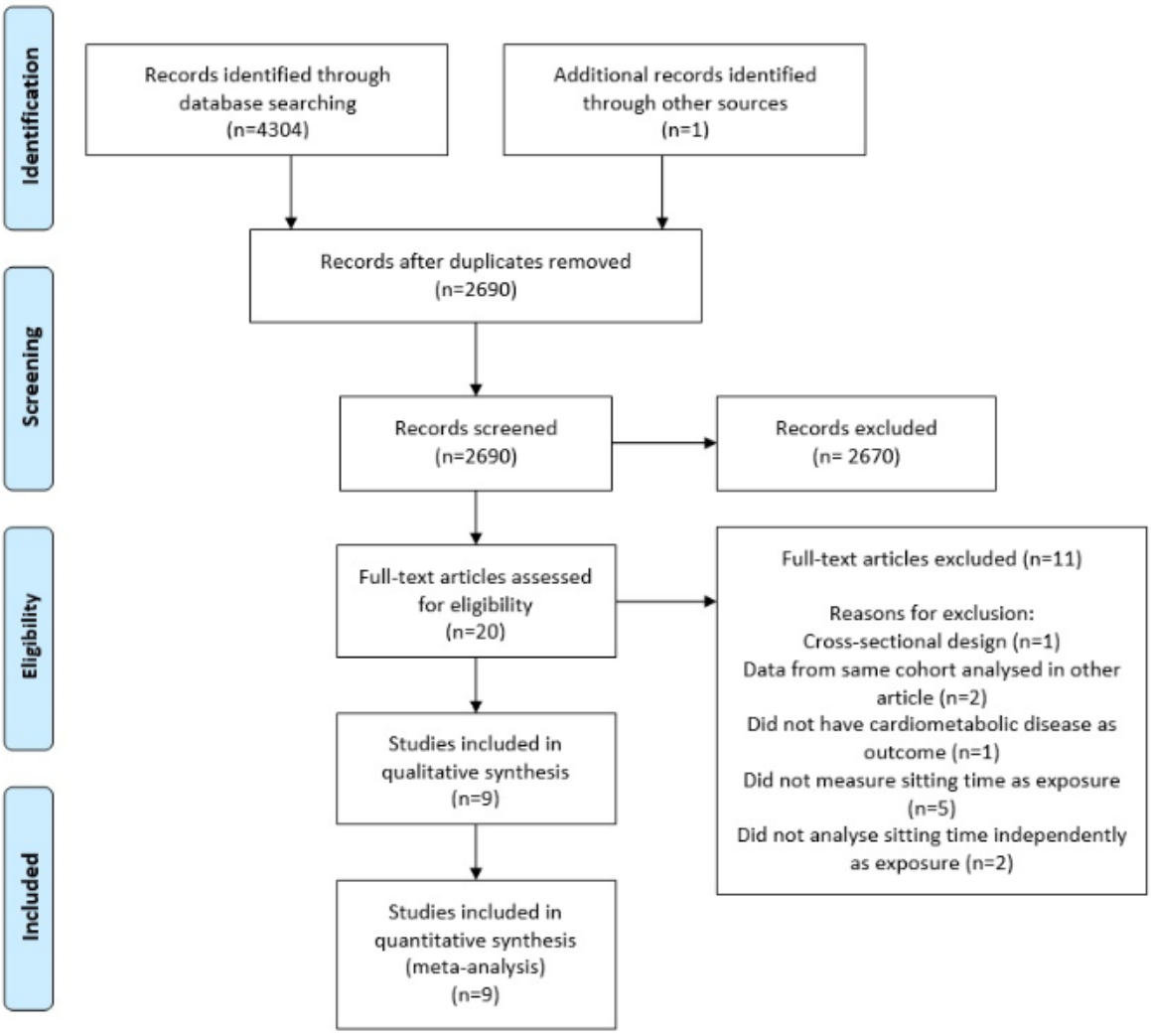

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow chart of study selection.

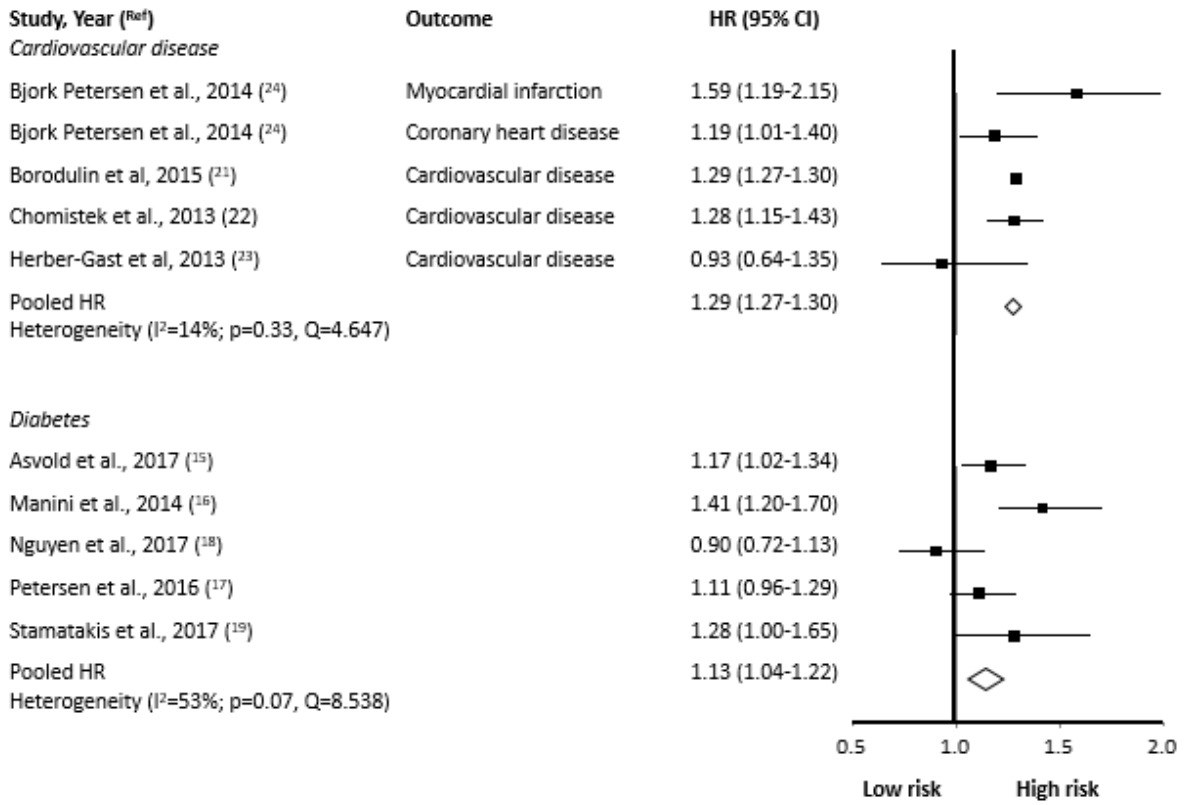

Figure 2 The association between higher total daily sitting time and health outcomes without adjustment for physical activity.

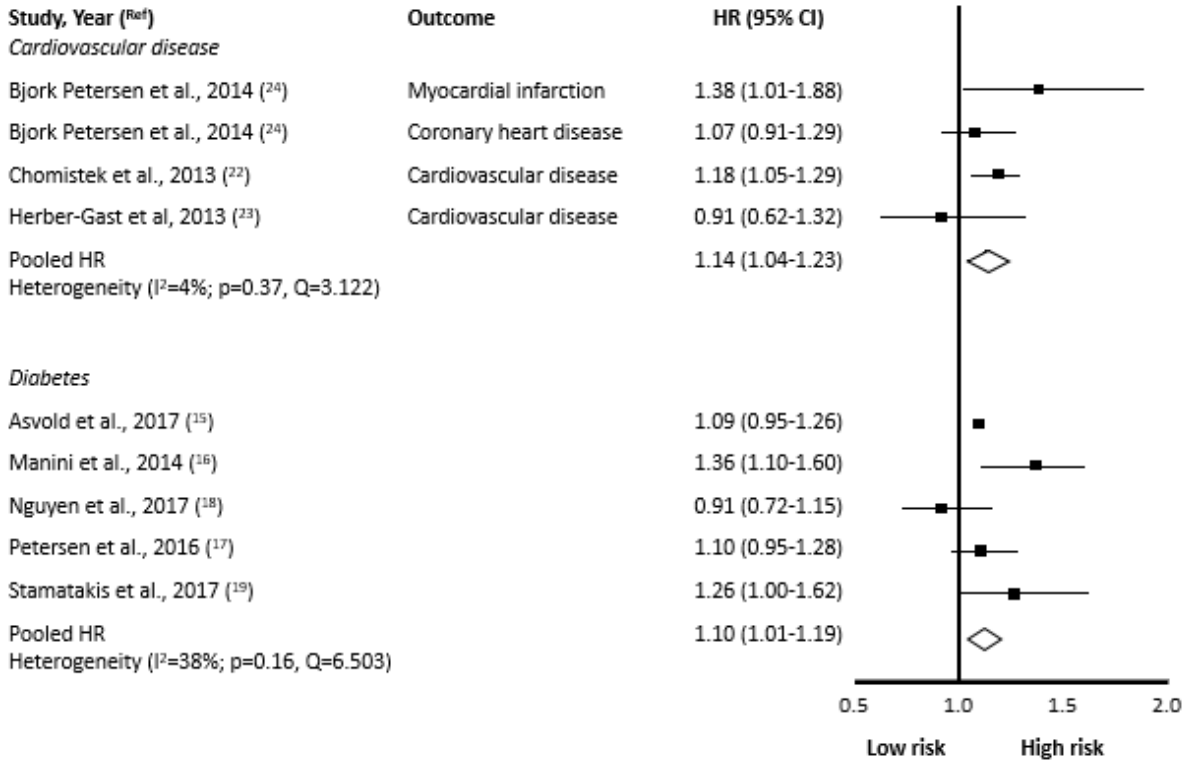

Figure 3 The association between higher total daily sitting time and health outcomes with adjustment for physical activity.

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]	N of studies meeting criteria
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?	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 two 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	

0=no, 1=yes. For item 2, 1 point was assigned for reporting reliability and 1 point assigned for reporting validity.