Time Spent Sitting as an Independent Risk Factor for Cardiovascular Disease

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Abstract

Sedentary behavior is highly prevalent despite growing evidence of adverse effects on the cardiovascular and metabolic system that are independent of the level of recreational physical activity. We present results for the association between sitting time and cardiovascular disease (CVD) from selected cohort and cross-sectional studies published in or after the year 2010 according to the domains where sitting time is accumulated during the day. These include TV viewing, occupational sitting, sitting during transportation as well as overall sitting. The outcomes considered in this review are total CVD, coronary heart disease and stroke as well as CVD risk factors, namely hypertension, hypercholesterolemia and type 2 diabetes and their associated biomarkers. Finally, several current issues with regards to studying the effects of sitting time on CVD are discussed, including how sedentary behavior is assessed, isotemporal substitution modelling, examination of joint associations for sitting and physical activity, and benefits of breaks in sitting time. Overall, the scientific evidence supports public health recommendations that encourage adults to limit their sedentary time in order to improve their cardiovascular health.

Key words. Sedentary behavior, TV watching, coronary heart disease, stroke, diabetes

INTRODUCTION

A preponderance of scientific evidence has shown that physical activity lowers risk of all-cause mortality as well as diseases such as coronary heart disease, diabetes, stroke and some forms of cancer[1,2]. Despite the clear evidence, only one in five adults met the 2008 Physical Activity Guidelines for Americans in 2015[3]. Physical inactivity is defined as not meeting the physical activity guidelines of 150 minutes per week of moderate-to vigorous-intensity physical activity. Physical inactivity is considered the fourth leading cause of death and it is estimated that 6% of coronary heart disease, 7% of type 2 diabetes, 10% of breast cancer, and 10% of colon cancer are attributed to physical inactivity[4,5].

In addition to the many adults who do not meet the physical activity guidelines, there are adults who do meet the guidelines but are otherwise sedentary[6]. Sedentary behavior is a distinct concept from physical inactivity and is defined as "any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents [of task] (METs), while in a sitting, reclining or lying posture"[7]. This definition from the Sedentary Behavior Research Network takes into account both energy expenditure and posture. Sedentary comes from the Latin word 'sedere' and means 'to sit'. Sedentary activities include activities such as watching TV, listening to music, reading and writing, knitting and sewing, playing video or computer games, and riding in a car[8].

Measurement of Sedentary Behavior

General assessment techniques for sedentary behaviors and sedentary time include self-report questionnaires, accelerometers, and direct observation[9]. The latter is rarely used in population studies due to high cost, but can serve as the criterion measure to validate other instruments[10]. Historically, self-report questionnaires were used in large, epidemiological studies while accelerometers were used mainly in smaller randomized controlled trials. Although large

studies still commonly assess sedentary time with questionnaires, due to declining costs, accelerometers have been used in population-based cross-sectional studies like the National Health and Nutrition Examination Survey (NHANES) and the Health Survey for England[11]. More recently, longitudinal studies such as the Women's Health Study, the Women's Health Initiative, and the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study in the U.S. and the UK Biobank Study have begun to collect objective activity data as well[11-14].

There are benefits and limitations to both accelerometer assessment of sedentary behavior as well as self-report. Accelerometers are advantageous because they provide an objective assessment of total sedentary time, but domain-specific information is lacking. Self-report questionnaires often include information on domain, but do not provide adequate measures of breaks in sitting time or estimates of light-intensity activity. Furthermore, there may be a great deal of measurement error for sedentary behavior when assessed by self-report. In a study by Clark et al., self-reported TV viewing time was modestly correlated with accelerometer-assessed total sitting time (Spearman ρ=0.22, 95% CI: 0.20–0.25)[16]. This correlation based on the NHANES data from the 2003-2004 and 2005-2006 cycles was similar for men and women as well as three race groups (non-Hispanic white, non-Hispanic black and Mexican American). Given the strength of the correlation being only fair, this finding emphasizes the importance of including all domains of sitting to fully capture sedentary behaviors.

In a review of reliability and validation studies, self-report measures tended to be more reliable for TV viewing and computer use, compared to other sedentary behaviors such as reading, sitting while socializing, and listening to music, as these activities occur more consistently and for longer time blocks[17]. Additionally, questionnaires that asked participants to recall time spent sitting in a typical day were found to have higher validity compared to 7-day or

12-month recall. Finally, Clark et al.[17] and Bauman et al.[18] mention that sedentary behaviors tend to be under-reported potentially due to social desirability bias. Based on NHANES and Swedish data, accelerometer-assessed sitting time was up to 20% higher compared to self-reported sitting time[18]. Bauman and colleagues, however, note that most accelerometers cannot differentiate between standing and sitting when there is no movement which potentially explains part of the discrepancy. One possible remedy is adding an assessment of posture to the accelerometer counts that will improve classification of sedentary behavior. The activPAL (PAL Technologies, Glasgow, Scotland) has been rated as the most accurate accelerometer for measurements of sedentary time[19]. The activPAL is a small device that is typically worn on the thigh that can better distinguish between sitting/lying and upright activities due to an inclinometer. In a small validation study, Kozey-Keadle et al.[19] compared accuracy and precision of the activPAL and the ActiGraph GT3X triaxial accelerometer to direct observation of 20 overweight and inactive office workers. They found a very high correlation between the activPAL and direct observation for sitting time (r=0.94) while the Actigraph was only moderately correlated with the criterion measure (r=0.39). More recently, a study by Clark et al. compared the relative validity of the sitting questionnaire used in the AusDiab studies with the activPAL[20]. They found that self-reported overall sitting time was moderately correlated with activPAL-assessed sitting time in a sample of 700 Australian adults (r=0.46, 95% CI: 0.40-0.52). However, the authors also point out that even though correlations were lower for the context-specific sitting time that self-reported measures work well to rank participants according to their sitting time but not to accurately estimate sitting time.

Given all of these issues, it has been recommended that population studies assess sedentary time using a combination of a self-report instrument, to obtain domain-specific

information, and accelerometers, to measure total sedentary time and patterns of sitting time throughout the day[21].

Physiological Mechanisms Linking Sedentary Time and Cardiovascular Disease

Extended sitting time and low levels of physical activity have independent physiological effects[22]. Hamilton and colleagues[23,24] suggest that the lack of muscle contractility, evident in sitting, induces biological consequences. Unfortunately, these results have not been replicated in humans since the work was conducted 13 years prior. In more recent studies, prolonged sitting has been associated with increased total cholesterol, triglycerides and waist circumference as well as decreased glucose uptake[25,26]. Additionally, previous research has shown that repeated bouts of prolonged sitting result in low shear rates leading to endothelial dysfunction, which has been linked to vascular mortality[27].

METHODS

In this review article, we focused on sedentary behaviors in the adult general population. Similar to a previous review by Owen et al.[6], our results are presented according to different settings where sitting typically occurs: TV watching, occupational and transportation as well as total overall sitting. Outcomes included in this review are cardiovascular disease (CVD) as well as stroke, coronary heart disease (CHD) and heart failure separately. Additionally, we examined intermediate endpoints that are known risk factors for CVD: diabetes, hypertension and hypercholesterolemia. To identify articles, we searched PubMed and Google Scholar for studies containing keywords related to the exposures and outcomes described above. Additionally, we reviewed reference sections of the identified papers and other recent reviews. We included studies that were published in or after the year 2010 and adjusted for physical activity in their

statistical analysis. Preference for inclusion was given to meta-analyses and articles based on prospective cohort studies followed by cross-sectional studies.

TV WATCHING

Trends

TV watching is the most common leisure time sedentary activity. According to the American Time Use Survey 2014, of the 5.1 hours of leisure and sports time in an average day, 2 hours and 49 minutes were spent watching TV, compared to 19 minutes for reading and only 18 minutes for sports, exercise and recreational activities[28]. Time spent watching TV was even higher among adults 75 years and older, who spent 4.5 hours per day watching TV[29]. Over the past 15 years, TV viewing has increased slightly from 2.58 hours/day in 2003 to 2.8 hours/day in 2015[30]. TV watching is not only problematic due to its sedentary nature, but also due to its association with increased caloric intake, for example through energy-dense snacks[31-34]. In early studies, TV watching was used as an indicator of overall sedentary behavior[35].

Associations between T.V. Watching and Cardiovascular Risk Factors

The harmful association between TV watching and diabetes is well established. In two large U.S. prospective cohort studies, Hu and colleagues found a detrimental association between TV watching and the risk of type 2 diabetes in 68,497 women[36] and 37,918 men[37]. In multivariable-adjusted models, the risk ratio for diabetes comparing the highest quintile of TV watching (more than 40 hours/week) to the lowest quintile (0-1 hour/week) was 1.77 (95% CI: 1.24–2.52) in women[36] and 2.87 (95% CI: 1.46–5.65) in men[37]. Additionally, two meta-analyses[38,39] have reported positive associations between TV watching and type 2 diabetes with risk ratios ranging from 1.16 to 1.37 per 2 hours of TV viewing per day[38] and 1.22 to 4.0 comparing the highest to the lowest categories[39]. The pooled risk ratios for type 2 diabetes in the

two meta-analyses were 1.20 per 2 hours of TV viewing (95% CI: 1.14–1.27)[38] and 2.12 (95% CI: 1.61–2.78) comparing the highest TV viewing category to the lowest[39]. While Grontved and Hu[38] included four prospective studies, published between 2001 and 2010, with a total of 175,938 individuals, Wilmot et al.[39] also incorporated findings from five cross-sectional studies in addition to the five prospective cohort studies, published between 2003 and 2012. Interestingly, in the Wilmot et al. meta-analysis, the pooled association based on the prospective studies was attenuated compared to the pooled risk ratio of the cross-sectional studies (pooled RR=1.93, 95% CI: 1.40–2.84, for prospective studies, pooled RR=2.36, 95% CI: 1.30–4.09, for cross-sectional studies). More recently, the increased risk for type 2 diabetes due to TV watching has been observed in other populations. Among women with a history of gestational diabetes in the Nurses' Health Study II, Bao and colleagues found a 77% (95% CI: 28%–145%) higher risk for type 2 diabetes in women who viewed TV more than 20 hours/week compared to less than 5 hours/week[40]. In the prospective EPIC-Potsdam study, Ford et al. estimated a 73% (95% CI: 24%–141%) higher risk for type 2 diabetes comparing 4 or more hours of TV viewing to less than one hour among middle-aged German men and women[41].

Unlike the strong evidence for the association between TV watching and diabetes based on several prospective cohort studies, support for an association between TV viewing and hypertension is limited to cross-sectional studies. In a cross-sectional study among 5,527 adults aged 16 to 99 years in the Scottish Health Survey, those reporting 3 or more hours/day of TV viewing or screen time were at a 27% higher risk of developing hypertension compared to individuals reporting less than 3 hours/day (OR=1.27 , 95% CI: 1.13–1.42)[42]. In a cross-sectional study of 7,445 British men and women born in 1958, Pinto Pereira and colleagues[25] reported an odds ratio of 1.11 (95% CI: 1.01–1.23) for hypertension per category increase in TV viewing in

women only. It should be noted that this association was fully attenuated after adjustment for diet and BMI, suggesting that BMI may be a confounder or mediator of the association between TV watching and hypertension.

Additionally, three studies (2 cross-sectional[25,43] and one cohort study[44]) have reported on associations between TV viewing time and cardiovascular biomarkers. In a cross-sectional analysis among 4,864 adults in the Australian AusDiab cohort, Thorp and colleagues found higher systolic blood pressure (β=0.92, 95% CI: 0.36–1.45) and diastolic blood pressure (β=0.59, 95% CI: 0.28–0.89) and lower HDL cholesterol (β = -0.01, 95% CI: -0.02 – -0.001) per hour of daily TV viewing in women only[43]. Fasting blood glucose was slightly higher with each additional hour of TV watching in both men (β=0.01, 95% CI: 0.001–0.01) and women (β=0.004, 95% CI: 0.001–0.01). In a prospective analysis within the same cohort, an increase of 10 hours/week of TV watching over a five year period was associated with higher DBP, but not SBP, in women only (β=0.47, 95% CI: 0.02–0.92, men: β=0.37, 95% CI: -0.11–0.86)[44]. There was no association between change in TV viewing and other CVD biomarkers over the 5-year period. Finally, using data from a cohort of 7,660 individuals born in 1958, Pinto Pereira et al.[25] examined cross-sectional associations between categories of TV viewing time ('0–1 hour/day', '1–2 hours/day', '2–3 hours/day' and '≥3 hours/day') and several biomarkers. Per TV viewing time category increase, they found that systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol and LDL cholesterol were higher and HDL cholesterol was lower in women. However, these associations were fully mediated (SBP) or attenuated (DBP, total, LDL, HDL cholesterol) after adjustment for diet and BMI. Similarly, in men, SBP and DBP were higher and HDL cholesterol was lower per TV viewing category increase, but fully mediated (SBP, DBP) or attenuated (HDL cholesterol) after adjustment for diet and BMI.

Associations between T.V. Watching and Cardiovascular Disease

A meta-analysis of four prospective cohort studies that were all published in 2010 or 2011 found an increased risk of fatal and nonfatal CVD per 2 hours of daily TV watching with a linear dose-response relationship (RR=1.15, 95% CI: 1.06–1.23)[38]. The absolute risk difference per 2 hours/day of TV watching was estimated to be 38 cases of fatal CVD per 100,000 individuals per year. Overall, these four studies included 34,253 individuals with 1,052 incident cases of fatal or nonfatal CVD. Stamatakis et al.[45] examined the associations between screen time, including TV watching, and confirmed CVD events among Scottish Health Survey 2003 respondents, which included adults aged ≥ 35 years, with follow-up until 2007. They found a strong positive relationship between screen time and CVD events (fatal and nonfatal combined) with a HR of 2.25 (95% CI: 1.30–3.89) for 4 or more hours/day of screen time compared to less than 2 hours/day. Interestingly, in a small subsample the authors did a mediation analysis and found that C-reactive protein, BMI and HDL cholesterol were mediators of the screen time-CVD association, explaining approximately 25% of the association collectively.

Wijndaele and colleagues reported that TV watching was associated with a higher risk for total CVD, CHD and nonfatal CVD in a prospective cohort study of 12,608 middle aged British adults in EPIC-Norfolk study[46]. For each hour of daily TV watching, the adjusted hazard ratios were 1.06 (95% CI: 1.03–1.08) for total CVD, 1.06 (95% CI: 1.03–1.09) for nonfatal CVD and 1.08 (95% CI: 1.03–1.13) for CHD. Additionally, effect modification by age and metabolic risk was reported for total CVD and non-fatal CVD, but not for CHD. Among older participants and those with higher metabolic risk score (standardized summary score of waist circumference, triglycerides, HDL cholesterol, SBP, DBP and HbA_{1c}) the associations between TV watching

and CVD were weaker compared to younger participants and those with a lower metabolic risk score.

The findings have been inconsistent for the association between TV watching and cardiovascular mortality. One study using NHANES data from the 1999-2000 and 2001-2002 cycles with updated mortality status until 2006 found no significant associations between TV watching and computer use time and mortality from diseases of the circulatory system (HR=1.14, 95% CI: 0.51–2.54, comparing ≥5 hours/day screen time to <1 hour/day)[47]. Similarly, in a longitudinal study of 7,744 healthy U.S. men aged 20-89 years at baseline, time spent watching TV was not associated with CVD mortality[48]. However, the null association in this study may be explained by the fact that TV watching was assessed only at baseline and follow-up time was 21 years. These findings are in contrast to those from Matthews et al.[49] and Wijndaele et al.[50], both in older adults. Matthews et al.[49] reported a strong positive association between TV viewing and CVD mortality in 240,819 US adults aged 50-71 years with HR of 1.85 (95% CI: 1.56–2.20) comparing 7 or more hours/day of TV viewing to less than one hour/day in the prospective NIH-AARP Diet and Health Study. Joint effects with PA showed that prolonged TV viewing time was associated with higher risk for cardiovascular mortality for both physically active and inactive individuals. TV viewing for more than 7 hours/day but meeting or exceeding the PA guidelines was associated with a 2- to 2.5-fold increased risk for CVD mortality. Still, the risk for CVD mortality was much higher in individuals that were inactive and were watching TV for more than 7 hours/day (HR=3.5 for <1 hour/week of MVPA and HR=4.2 for never/rarely MVPA, both $p<0.05$, compared to <1 hour/day of TV viewing and >7 hours/week of MVPA). In the EPIC Norfolk study among British adults aged 45 to 79 years at baseline, each additional hour of TV viewing time per day was associated with an 8% (HR=1.08, 95% CI: 1.01–1.16)

higher risk of CVD mortality[50]. Likewise, in a prospective study of 8,800 Australian adults in the AusDiab cohort, Dunstan et al. found a borderline significant association for CVD mortality for the highest TV watching category (≥4 hours/day) compared to lowest (<2 hours/day) (HR=1.80, 95% CI: 1.00–3.25)[51].

OCCUPATIONAL SEDENTARY TIME

Trends

In the last few decades, the number of low activity occupations has greatly increased while the number of high activity and physically demanding occupations has declined[34,52]. Jobs in agriculture and manufacturing are disappearing while service-providing jobs, which primarily require light or sedentary activity, are increasing[53]. Between the 1960s and 2008, the percentage of sedentary jobs in the US private sector increased from 15% to 25%, while the percentage of moderate-intensity physical activity jobs decreased from 48% to 20%.[53]. Individuals in sedentary occupations may accumulate large amounts of prolonged sitting time during the workday. For example, a small accelerometer-based study among Australian office workers revealed that 82% of work hours were spent sedentary[54]. Furthermore, 41% of sedentary time occurred in bouts longer than 30 minutes[54].

Associations between Occupational Sitting Time and Cardiovascular Risk Factors

Evidence supporting a significant association between occupational sitting time and cardiovascular risk factors is limited. In a recent cross-sectional study, Garcia et al.[55] examined the association between sedentary work, defined as being seated at work most of the time and walking only short distances, and cardiovascular risk factors among 47,477 Brazilian workers. Compared to non-sedentary work, they found that sedentary work was associated with a 20% higher risk of hypertension, a 41% higher risk of hypercholesterolemia, and a 25% higher risk of

type 2 diabetes in men. In women, sedentary work was associated with a 16% higher risk of hypercholesterolemia only. These findings are in contrast to a recent Dutch prospective cohort study by Picavet et al.[56] that did not find significant associations between occupational sitting and cardiovascular risk factors among 1,509 middle-aged men and women. Occupational sitting was assessed four times (every 5 years) between 1993 and 2012 using the following categories: mainly sedentary, mainly standing, manual, involves high physical loads. This information was used to divide participants into two groups --stable sitter or stable non-sitter-- at work over 15 years. Stable sitting was defined as having a sedentary job for at least three out of the four assessments. Similarly, stable non-sitters were defined as being in a non-sedentary occupation 3-4 times during the assessments. Additionally, they used a more detailed questionnaire in the last data assessment asking for the hours of sitting at work in a typical week. Compared to stable non-sitters, stable sitters did not have a higher risk of hypertension or hypercholesterolemia (longitudinal: HR_{HT}=1.08, 95% CI: 0.84–1.39, HR_{HC}=0.80, 95% CI: 0.60–1.07, comparing stable sitters to non-sitters at work). Furthermore, hours of occupational sitting time was also not associated with either risk factor (HR_{HT}=0.97, 95% CI: 0.73–1.29, HR_{HC}=0.92, 95% CI: 0.66–1.28, comparing >20 hours/week to less than 4 hours/week). The authors suggest their null findings could be due to the healthy worker effect or the beneficial effects of breaks in sitting time counteracting the harmful effects of occupational sedentary behavior on health.

In a cross-sectional study that assessed the separate and joint associations between leisure sitting time and occupational sitting time with cardiovascular biomarkers, Saidj et al.[57] found detrimental associations of prolonged occupational sitting for HDL cholesterol (p=0.0042). Examination of the joint associations indicated that, compared to low leisure / low occupational sitting time, high leisure / high occupational sitting was most harmful, followed by high leisure /

low occupational sitting and low leisure / high occupational sitting (p-values: HDL cholesterol <0.001, LDL cholesterol p=0.0074, plasma glucose and total cholesterol not significant). Similarly, in the previously mentioned study by Pinto Pereira et al. among British adults, sitting at work was associated with lower HDL cholesterol in men only[25]. Compared to the associations for TV watching in the same study, occupational sitting was found to have weaker and fewer significant associations with cardiovascular biomarkers.

Associations between Occupational Sitting Time and Cardiovascular Disease

For the most part, studies examining occupational sitting time and hard CVD outcomes have found no significant associations. In a recent prospective cohort study among almost 12,000 Danish workers, sedentary work (defined as more than 25 hours/week of sitting time at work) was not significantly associated with ischemic heart disease compared to non-sedentary work (HR=0.95, 95% CI: 0.78–1.16)[58]. Additionally, Chau and colleagues did not find significant associations between occupational sitting and cardiometabolic mortality in the large HUNT3 Norwegian cohort consisting of 50,817 adults aged 20 years and older (p for trend across 4 categories of occupational sitting time=0.185)[59]. Similarly, in a pooled analysis of seven English and Scottish cohorts, Stamatakis et al. found that sitting at work was not associated with higher risk for CVD mortality[60]. In this study, Stamatakis and colleagues recorded 177 CVD-related deaths among 11,168 men and women over a mean follow-up time of almost 13 years. Comparing individuals in standing/walking occupations to those in sitting occupations, the HR for CVD mortality was 1.53 (95% CI: 0.72–3.24) in women and 0.98 (95% CI: 0.66–1.45) in men.

In a prospective cohort study of 58,208 healthy Finnish men and women, Wang and colleagues[61] found an increased risk of heart failure for individuals in mainly sitting, office

occupations. Compared to mainly sitting at work, moderate and high levels of occupational physical activity were associated with a 15% (HR=0.85, 95% CI: 0.77–0.93) and 13% (HR=0.87, 95% CI: 0.80–0.94) lower risk for heart failure, respectively (p trend<0.001). Additionally, when the joint associations for occupational, commuting and leisure time physical activity were examined, moderate to high occupational PA alone (i.e., no active commuting and low level of leisure PA) compared to mainly sitting at work was beneficial to lower the risk for heart failure in men (HR=0.78 with p-value<0.05), but not women. The combination of moderate to high occupational PA with either active commuting or moderate to high leisure-time PA or both reduced the risk for heart failure for men and women even further. The hazard ratios for moderate to high levels in all three types of PA, compared to low levels, were 0.69 for men and 0.66 for women (both p-values<0.05).

TRANSPORTATION SEDENTARY TIME

Trends

Sitting time during transportation is highly connected with the topics of active commuting, the built-environment, and community safety[5,6,62]. According to the 2009 US National Household Transportation Survey (NHTS), individuals used their personal car for daily transport 83% of the time, compared to 1.9% for public transportation, 10.4% for walking, and 4.2% for other[63]. The average time spent in a vehicle was 56 minutes on a typical day, a decrease compared to 62 minutes/day in 2001[63]. Residents in large urban areas report higher amounts of active commuting, walking 14.2% of the time and using public transportation 4.1% of the time, and less car use (77.3%). Compared to those commuting by car, individuals who commute by foot or public transportation are estimated to walk 19.8 and 5.0 more minutes per day,

respectively[64]. Thus, utilizing other forms of transportation instead of an automobile may lower overall sedentary time.

Associations between Transportation Sitting Time and Cardiovascular Risk Factors

The evidence between transportation sitting time and cardiovascular risk factors is currently limited to cross-sectional studies. In cross-sectional analyses of the 2007-2008 and 2009-2010 cycles of NHANES, Furie and Desai[65] found significantly lower odds of hypertension (OR=0.69, 95% CI: 0.58–0.83) and diabetes (OR=0.69, 95% CI: 0.54–0.88) among individuals with high levels of active transportation (walking and biking, ≥150 minutes/week) compared to no active transportation (0 minutes/week). Interestingly, in stratified analyses, these associations were stronger in individuals that did not meet the physical activity guidelines but not significant in individuals that met the guidelines. A recent cross-sectional analysis of data from 2,800 participants in the 2011-2012 Australian Diabetes, Obesity and Lifestyle Study found that self-reported time spent in cars of more than 1 hour/day, compared to 15 minutes/day or less, was associated with higher fasting blood glucose levels (β=0.013, 95% CI: 0.000–0.026)[66]. There were no significant associations between time spent in cars and other cardiovascular biomarkers (HDL cholesterol and systolic and diastolic blood pressure) in the same study.

Similarly, in a cross-sectional analysis of data from a large group of mainly younger Brazilian workers, Garcia et al.[55] found that sitting during the commute to work was detrimentally associated with some CVD risk factors. Specifically, in women, car or motorcycle use increased the odds of diabetes by more than 40% compared to walking or cycling (OR=1.48, 95% CI: 1.01–2.17) while the use of buses increased the odds of hypercholesterolemia and hypertension by more than 20% ($OR_{HC.}$=1.27, 95% CI: 1.09–1.50, OR_{HT}=1.24, 95% CI: 1.08–

1.42). In men, use of a car or motorcycle led to an increase in odds for hypercholesterolemia by 15% (95% CI: 1.02–1.29) while the other associations were not significant.

Associations between Transportation Sitting Time and Cardiovascular Disease

Recent evidence on the association between transportation-related sedentary behavior and CVD is sparse. In the Aerobics Center Longitudinal Study which included 7,744 men aged 20-89 years, Warren et al.[48] found that more time spent riding in a car was positively associated with CVD mortality. Men that reported 10 or more hours/week riding in a car had a 50% greater risk of CVD mortality compared to men who reported less than 4 hours/week (HR=1.50, 95% CI: 1.08–2.09). Subgroup analyses for effect modification revealed that this association was stronger among inactive (p for trend=0.02), overweight/obese individuals (p for trend=0.004) and younger (under 60 years old, p for trend=0.0009) individuals and not significant in physically active, normal weight and older men. Similarly, in a large prospective Finnish cohort of healthy men and women, active commuting was inversely associated with the risk for heart failure. Compared to 0 minutes/day of active commuting, the HR for 1–29 minutes/day and ≥30 minutes/day were 0.88 (95% CI: 0.81–0.96) and 0.88 (95% CI: 0.80–0.96), respectively[61]. However, these results were no longer significant once adjusted for other types of physical activity.

TOTAL SEDENTARY TIME

Trends

Matthews and colleagues were among the first groups to objectively quantify the total time spent in sedentary behaviors. Using the accelerometer data collected during the NHANES 2003-2004 cycle[67], they found that, on average, individuals spent more than half of their waking hours (7.7 hours/day) sedentary. Additionally, they reported that older adolescents and

individuals over 60 years of age were most sedentary. Differences by race were also reported with Mexican-Americans being less sedentary compared to white and African-American adults. Of the 24 hours of a day, adults spend on average 7.7 hours sedentary, 8.3 hours sleeping, 7.8 hours with light activities and only 0.2 hours in moderate to vigorous activities[67,68].

Associations between Total Sitting Time and Cardiovascular Risk Factors

There is growing evidence from cross-sectional studies that higher daily sitting time is associated with CVD risk factors and cardiovascular biomarkers. In their study among younger industry workers in Brazil, Garcia et al.[55] found that a sedentary lifestyle was associated with higher risk of hypertension and hypercholesterolemia in men but not in women (men: OR_{HT}=1.25, 95% CI: 1.13–1.39, and OR_{HC}=1.44, 95% CI: 1.29–1.60; women: OR_{HT}=0.87, 95% CI: 0.75–1.02, and OR_{HC}=0.97, 95% CI: 0.83–1.13). Sedentary lifestyle was defined as the combination of TV viewing for more than 2 hours/day, reporting a sedentary commute to work, and also being sedentary at work. This finding is consistent with results from the 45 and Up study among 63,048 middle-aged males in Australia. In this cross-sectional analysis, sitting 8 or more hours/day was associated with an increased risk (OR=1.06, 95% CI: 1.00–1.12) of high blood pressure compared to sitting less than 4 hours/day[69].

Recent evidence regarding the association between overall sitting time and type 2 diabetes is more consistent for men compared to women. In the cross-sectional study mentioned above by Garcia et al.[55], individuals reporting the combination of TV viewing of 2 or more hours/day, transportation by car/motorcycle, and predominantly sitting at work were found to have an increased risk of type 2 diabetes in men only (OR=1.26, 95% CI: 1.02–1.56) compared to individuals reporting a non-sedentary lifestyle. Similarly, in a cross-sectional analysis of more

than 60,000 middle-aged males in Australia, sitting 8 or more hours/day was associated with a 21% higher risk of diabetes (95% CI: 1.09–1.33) compared to less than 4 hours/day of sitting[69].

With regards to cardiovascular biomarkers, current evidence is strongest for an association between total sitting time and HDL cholesterol. Two cross-sectional studies in NHANES, one utilizing accelerometers[70] and the other self-report[71], found that higher sitting time was associated with lower HDL cholesterol. Furthermore, Healy and colleagues[70] found that the association between accelerometer-assessed sedentary time and HDL cholesterol was modified by race/ethnicity (p for interaction=0.004). Higher sitting time in non-Hispanic whites was found to be significantly associated with lower HDL cholesterol (p for trend=0.008), but no association was found for either Mexican-Americans or non-Hispanic blacks (p for trend=0.40 and 0.31, respectively). In a cross-sectional study of 661 Japanese adults, Honda et al.[72] found that both accelerometer-assessed total sitting time and self-reported sitting time were inversely associated with HDL cholesterol (β for each hour of accelerometer-assessed sitting = -1.312, 95% CI: -2.086 – -0.537; β for each hour of self-reported sitting = -0.434, 95% CI: -0.767 – -0.102). In the same study, self-reported daily sitting time was also positively associated with blood glucose levels (β=0.004, 95% CI: 0.001–0.007). Similarly, Qi et al. also objectively assessed sitting time, using the Actical accelerometer, in 12,083 Hispanic and Latino participants in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL).[73] After adjusting for PA, sedentary time was detrimentally associated with several cardiometabolic biomarkers such as HDL cholesterol (p=0.04), triglycerides, 2-hour glucose and fasting insulin (all p<0.001). These associations (with the exception of that for triglycerides) remained significant even in participants that were meeting the 2008 PA guidelines.

Cross-sectional studies by Chau et al.[74] and Thorp et al.[43] provide evidence that total sitting time is associated with systolic and diastolic blood pressure. Chau and colleagues examined this association in the Norwegian HUNT study which includes 40,000 adults that are 20 years of age and older. They found that individuals that reported 10 or more hours of daily sitting had a 0.98 mmHg higher diastolic blood pressure (95% CI: 0.62–1.35) and 0.74 mmHg higher systolic blood pressure (95% CI: 0.18–1.29) compared to participants that sat less than 4 hours/day. Similarly, among women in the AusDiab study, each hour of daily sitting was associated with higher systolic (β=0.39 mmHg, 95 % CI: 0.13–0.64) and diastolic (β=0.25 mmHg, 95 % CI: 0.11–0.39) blood pressure. In contrast, among men in the same study, the association of sitting time and diastolic blood pressure was not significant, while higher total sitting time was associated with lower systolic blood pressure (β=-0.29 mmHg, 95% CI: -0.56 – -0.03). The authors suggest that this unexpected finding might be due to hemodynamic responses to sitting in highly sedentary men.

Associations between Total Sitting Time and Cardiovascular Disease

The evidence for the association between overall daily sitting time and CHD has been inconsistent. In a large Danish cohort study among more than 70,000 men and women, the risk for MI was 38% higher in participants that reported 10 or more hours of daily sitting compared to less than 6 hours (HR=1.38, 95% CI: 1.01–1.88)[75]. However, in the same study, total CHD, which additionally included angina pectoris, certain current complications following acute MI, other acute CHD and chronic CHD, was not associated with sitting time (HR=1.07, 95% CI: 0.91–1.27). Similarly, in the cross-sectional 45 and Up Study among middle-aged men in Australia, there was no association between sitting time and heart disease (OR=0.99, 95% CI: 0.90–1.08, for ≥8 hours/day of sitting compared to <4 hours/day)[69].

Prolonged sitting time was associated with incident CVD among individuals in the prospective FINRISK study[76]. In this study among 4,516 Finnish adults aged 25 to 74 years, sedentary time was assessed at baseline in 2002 by self-report and follow-up time for incident fatal and nonfatal CVD was on average 8.6 years. Each hour of daily sitting time was associated with a 6% increase in incident fatal and non-fatal CVD (95% CI: 1%–11%)[76]. In contrast, Herber-Gast et al.[77] did not find significant associations between total self-reported sitting time and nonfatal and fatal CVD incidence in a prospective cohort of 6,154 women from the Australian Longitudinal Study on Women's Health (HR=0.97, 95% CI: 0.92–1.03). One possible explanation for this null finding was the lower average sitting times compared to other cohorts (5.4 hours/day of average sitting time overall, and 8.4 hours/day of sitting in highest quartile).

Several studies have recently used the Women's Health Initiative Observational Study (WHI-OS) to examine the association between overall sitting time and various disease endpoints. Chomistek et al.[78] found that total sitting time was associated with higher risk for CHD, stroke and total CVD. Sitting for 10 or more hours per day, compared to 5 or less hours/day, was associated with hazard ratios of 1.18 (95% CI: 1.05–1.32) for CHD, 1.21 (95% CI: 1.07–1.37) for stroke and 1.18 (95% CI: 1.09–1.29) for total CVD. Additionally, subgroup analyses revealed significant effect modification by age and BMI (p for interaction=0.026 and 0.044, respectively). Sitting time was associated with higher risk for CVD in overweight/obese (BMI $\geq$ 25) and older women (aged 70 years and older), but not associated in normal weight and younger women ($HR_{BMI\geq25}$=1.26, 95% CI: 1.13–1.40, and $HR_{age\geq70}$=1.22, 95% CI: 1.09–1.36, comparing $\geq$10 hours/day of total sitting to $\leq$5 hours/day). In a different study in the WHI-OS, total sitting time was associated with higher CHD mortality (HR=1.27, 95% CI=1.04–1.55) but not with CVD mortality (HR=1.13, 95% CI=0.99–1.29)[79]. Finally, in the most recent study in the WHI-OS,

there was not a significant association between sitting time at baseline or change in sitting time during follow-up and CVD mortality[80].

Two other large prospective cohort studies also examined the association between total sitting time and cardiovascular mortality. In a study among more than 240,000 participants aged 50 to 71 years in the NIH-AARP Diet and Health Study, sitting for 9 or more hours/day was associated with 16% higher risk for CVD mortality (95% CI: 1.02–1.30) compared to sitting for less than 3 hours/day[49]. Likewise, in the Cancer Prevention Study II Nutrition Cohort that included more than 120,000 men and women aged 50 to 74 years, self-reported sitting time of more than 6 hours/day was associated with a RR of 1.33 (95% CI: 1.17–1.52) for women and 1.18 (95% CI: 1.08–1.30) for men, compared to less than 3 hours/day of sitting time[81].

DISCUSSION

In recent years, the topic of sedentary behavior and CVD has received increased attention from the research community. Several reviews[9,35,82-86] and meta-analyses[38,83,87] on this topic have been published in the last seven years. At the same time, time spent in sedentary behaviors has remained high after increases since the middle of the last century despite the evidence that sedentary time is associated with increased risk of several diseases, such as CHD, diabetes, metabolic syndrome and obesity, and mortality independent of physical activity[9,22,31,35,82,88].

The purpose of the current review was to summarize the most recent evidence with regards to sitting time and CVD. We presented findings by the domains in which sedentary behaviors occurs: TV viewing, occupational, transportation and overall sitting. We considered outcomes such as total CVD, stroke, CHD and heart failure, as well as CVD risk factors including diabetes, hypertension, hypercholesterolemia and associated biomarkers. Based on this review, the most consistent associations were between TV watching and risk of type 2 diabetes

as well as fatal and nonfatal CVD. In addition, there was evidence to support associations between transportation-related sedentary time and cardiovascular risk factors as well as CVD and associations between total sitting time and risk of diabetes and CVD mortality. Less consistent associations were found between occupational sitting, cardiovascular risk factors, and CVD.

Throughout this manuscript we presented results from multivariate models that adjusted for physical activity. Commonly included covariates are age, gender, race, education, smoking history, alcohol consumption, and diet. Even though investigators attempted to adjust for these confounders, there is the possibility of residual confounding due to measurement error or imperfect adjustment, in particular for socio-economic status and diet. Additionally, unmeasured confounding by other covariates because they were not measured or the data is not available remains a limitation as well. For example, mental health/depression is potentially an unmeasured confounder in most studies as it is related both to sitting and cardiovascular outcomes. On a similar note, caution should to be used when interpreting results from cross-sectional studies due to the potential for reverse causation as individuals that are obese or have type 2 diabetes or other cardiovascular risk factors may sit more due to their comorbidities. To minimize the potential for reverse causation in studies of sedentary behavior and cardiovascular outcomes, prospective studies should be conducted whenever possible and include additional analyses excluding outcomes occurring in the first years of follow-up.

As pointed out in the Introduction, assessment of sedentary behavior remains difficult as objective and self-report measures both have disadvantages. Gibbs and colleagues[89] recently recommended the expanded use of objective measures in longitudinal studies along with standardizing methods when accelerometers are used, in particular with regards to cut points. The usual threshold to distinguish between sedentary and light activity behaviors is 100

accelerometer counts per minute (cpm) for uniaxial data, but depending on the performed activity the use of this cut point can lead to misclassification of these behaviors. For example, in a small validation study, time spend standing still was incorrectly classified as sedentary and riding in a car was misclassified as light activity when using the 100 cpm threshold[90]. Therefore, it was recommended that adding an assessment of posture to the accelerometer counts will improve the correct classification of sedentary behavior.

Another important issue to consider is the interdependence of time spent in activities of different intensity levels because the number of hours in a day are fixed. Recently, isotemporal substitution modeling has been used, where total time is kept fixed and one examines how increasing time spent in one activity (e.g. light-intensity physical activity) while reducing time spent in another activity (e.g. sedentary time) is associated with an outcome of interest[91]. For example, in a subsample of 698 adults from the 2011/12 wave of the AusDiab3 Study, Healy and colleagues used the isotemporal modeling approach and found that replacing 2 hours/day of sitting with standing and stepping was associated with improved levels of cardiometabolic biomarkers, lower BMI and lower waist circumference[92]. Similarly, in the Nurses' Health Study, Mekary and colleagues found that substituting TV watching with slow walking, brisk walking or jogging/running was associated with lower body weight[91]. Thus, using the isotemporal substitution approach can highlight the benefits of replacing sedentary time with more active behaviors, which is important for public health recommendations.

In addition to total sitting time, breaks in sitting time have also been shown to be associated with certain cardiovascular and metabolic risk factors. In a cross-sectional analysis among 168 participants of the AusDiab study, Healy and colleagues found that breaks in sitting were beneficially associated with waist circumference, BMI, triglycerides and 2-h plasma

glucose, independent of total sedentary time[93]. On top of epidemiologic studies, several randomized trials, some in crossover design, have examined the effect of breaks in sitting time on glucose metabolism in adults at risk for or already diagnosed with type 2 diabetes. In these trials, when sitting was interrupted by light- or moderate intensity walking or resistance activities, postprandial glucose and insulin levels were lower, compared to uninterrupted sitting[94-96]. Although more studies are needed, it appears that breaking up prolonged periods of sedentary behavior with short bouts of activity may counteract some of the ill effects of high amounts of sitting time. Objective assessment is preferred over self-report questionnaires to measure breaks in sitting and bouts of sitting accurately.

In this review, we have only included studies that adjusted for levels of physical activity. In addition to adjustment, some studies have also examined effect modification by physical activity as well as joint associations for the combination of physical activity and sitting time. In a stratified analysis of data on 7,744 men in the Aerobics Center Longitudinal Study, Warren et al. found the association between time spent riding in a car and CVD mortality was significant only among inactive men (p for trend=0.02) but not among active men (p for trend=0.13, p for interaction=0.11)[48]. Likewise, in a meta-analysis of 9 prospective cohort studies, Ekelund et al. found that high levels of moderate- to vigorous-intensity physical activity seemed to remove the increased cardiovascular mortality risk associated with high amounts of sitting time[97]. For individuals in the most active quartile (>35.5 MET-hours/week), high amounts of daily sitting time were not associated with an increased risk for cardiovascular mortality (HR=1.07; 95% CI: 0.96–1.20, comparing >8 hours/day of sitting with <4 hours/day). Results for the association between TV viewing and cardiovascular mortality were similar. In their study on joint associations between sitting and physical activity in the WHI observational study, Chomistek et

al. found there was no association between sitting time and CVD among women in the highest category of physical activity (>20 MET-hours/week)[78]. However, among women that reported lower levels of physical activity (either 1.8-8.3 MET-hours/week or 8.4-20 MET-hours/week) those who reported sitting more than 10 hours/day were still at an increased risk for CVD, although it is important to note that the interaction was not statistically significant.

In the studies described above, when the joint association of sedentary time and physical activity on risk of CVD was examined, individuals reporting high amounts of sitting and low amounts of physical activity consistently had the highest risk of CVD. In the meta-analysis by Ekelund et al., individuals who reported more than 8 hours/day of sitting and less than 2.5 MET-hours/week of physical activity had a cardiovascular mortality risk that was 74% higher than those who were most active (>35.5 MET-hours/week) and least sedentary (<4 hours/day) (HR=1.74, 95% CI: 1.60-1.90). In the Chomistek et al. study, women that reported 1.8 MET-hours/week or less of physical activity and 10 hours/day or more of sitting had a significantly higher rate of total CVD (HR=1.63, 95% CI: 1.39–1.90) compared to women with more than 20 MET-hours/week and 5 hours or less of daily sitting[78]. Petersen et al. reported similar trends in a cross-sectional study among 15,235 Danish adults. Study participants that reported 10 or more hours of daily sitting time and were inactive in leisure time had much higher odds (OR=3.29, 95% CI: 2.60–4.15) for metabolic syndrome compared to adults that reported leisure-time MVPA and less than 6 hours/day of sitting[98]. Thus, public health recommendations should encourage individuals to both meet the physical activity guidelines and avoid accumulating high amounts of sedentary time throughout the day.

Future directions of research should include conducting more prospective, longitudinal studies that assess sedentary time with an accelerometer. Accelerometers provide the best

information on total accumulated sitting time throughout the day as well as time spent in activities of other intensities, which are likely correlated with sitting time. For example, using accelerometry, Healy et al.[99] found that sedentary time and light-intensity activities were strongly negatively correlated (Pearson's r=-0.96) while moderate-to-vigorous-intensity PA (MVPA) was only weakly correlated with sedentary time (Pearson's r=-0.27), in a subsample of participants in the AusDiab study. Thus, in order to best examine the detrimental associations sedentary time may have with disease outcomes, accounting for time spent in other types of activity via isotemporal substitution modeling seems critical. Noteworthy here are findings from Maher and colleagues[100]. In a series of cross-sectional models using the NHANES data from 2003/04 and 2005/2006, Maher et al. showed that the associations between sitting and several cardiometabolic biomarkers were significant when adjusting for MVPA, but that these associations disappeared when adjusting for total PA instead of MVPA. This underlines the importance of carefully addressing confounding throughout the whole spectrum of PA which includes light physical activity and also moderate-to-vigorous PA.

In addition to more prospective, longitudinal studies of objectively measured sedentary time, future efforts should also be more specific to the domains where sedentary behaviors occur. Many adults of working age are employed in office occupations and spend the majority of their day sedentary. More observational but also intervention studies at the workplace are needed to better understand the long-term effects of these high amounts of accumulated sitting time and to learn about successful strategies to break up these long blocks of sitting time. Generally, interventions that aim to reduce sitting time have been shown effective in children and adolescents[101], but more evidence is needed in the adult population[6]. Prince and colleagues[83] found interventions that focus primarily on reducing sedentary behavior showed larger

reductions in sitting time, compared to interventions with a focus on physical activity or combined physical activity and sedentary behavior components. Owen et al.[6] describe possible strategies of behavior change for sedentary time in the home environment and at the workplace. These can include standing desks or even treadmill desks at the workplace, and infrastructure (such as showers) to increase active transportation. At home, individuals can be encouraged to stand during TV commercials or while making phone calls, and to iron while they are watching TV. Additionally, innovations in community infrastructure and the built environment can and should be used to study their effectiveness on reducing sitting time and, ideally, improving cardiovascular health.

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