

Sedentary behaviour and risk of chronic diseases

No. 2017/08C, The Hague, August 22, 2017

Background document to:

Dutch physical activity guidelines 2017

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Health Council of the Netherlands

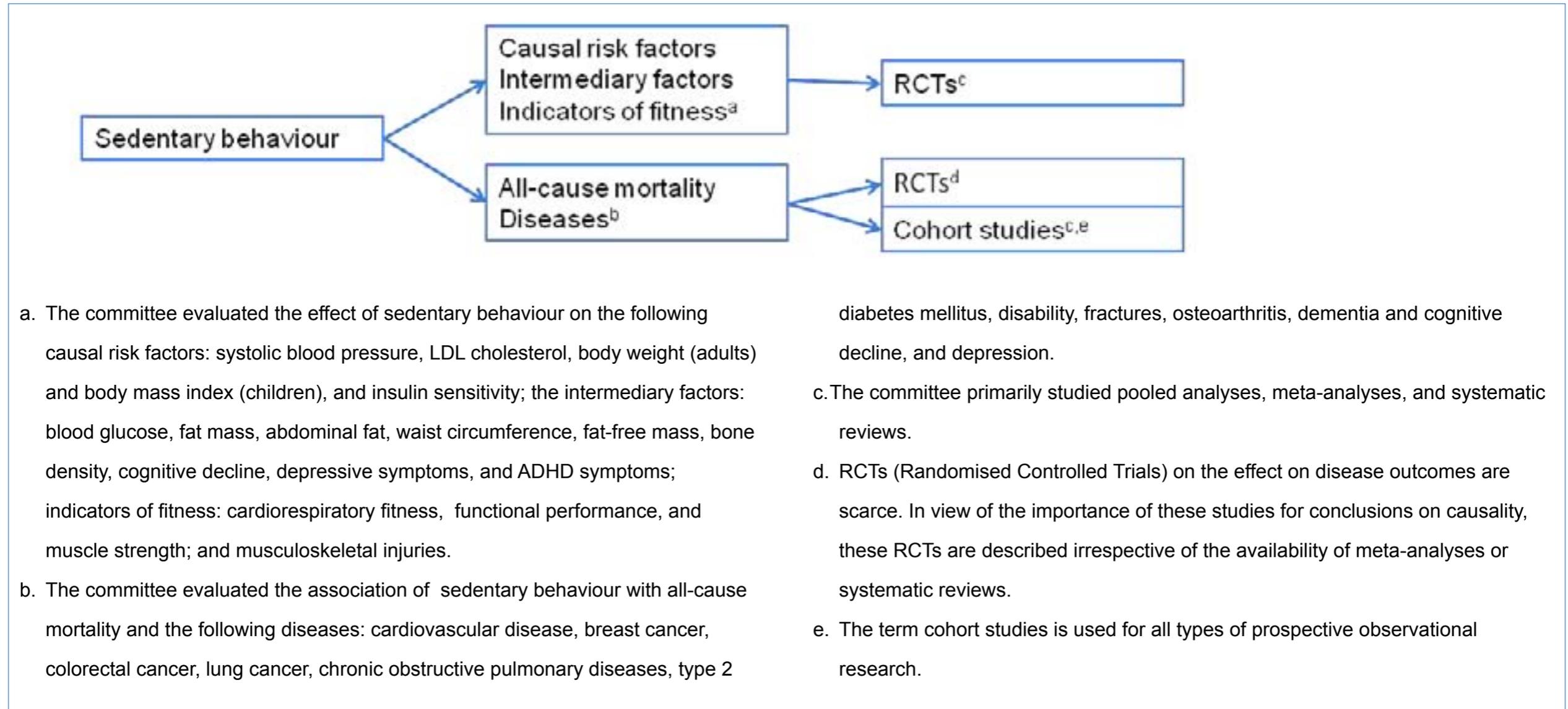


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methodology in brief



Conclusions in the background document are based on the amount of research, indications of heterogeneity, strength of the association, study participants' characteristics, and specific considerations which are described in the explanation. The options for conclusions are: strong or weak level of evidence, an effect or association is unlikely, the level of evidence is ambiguous, or there is too little research to draw a conclusion.

The background document 'Methodology for the evaluation of the evidence' provides an extensive description and explanation of the methodology.



01 introduction

In this background document the Dutch physical activity guidelines 2017 committee describes the evidence it has collated on the effect that sedentary behaviour has on intermediary factors and its association with the risk of mortality and chronic disease.

Search strategy

Conclusions drawn in the Australian evidence reports for adults and children^{1,2} were used as a starting point for the literature search. These covered publications up to 2012. The committee supplemented the Australian conclusions with more recent meta-analyses and systematic reviews of RCTs and of cohort studies. In addition, cohort studies with objectively measured sedentary behaviour were described separately. For this purpose, literature was searched in PubMed (from 1996 to 1 October 2016) with the following strategy:

“Sedentary Lifestyle”[Mesh] OR “Computers, Handheld”[Mesh] OR “Video Games”[Mesh] OR “Television”[Mesh] OR “sedentary”[tiab] OR “sitting time”[tiab] OR “prolonged sitting”[tiab] OR “computer time”[tiab] OR “computer use”[tiab] OR “screen time”[tiab] OR “screen-time”[tiab] OR “screen based media”[tiab] OR gaming[tiab] OR “personal computer”[tiab] OR “low energy expenditure”[tiab]

Several restrictions were applied: ‘Meta-Analysis’ and ‘Systematic Reviews’ within the filter ‘Articles type’, ‘Humans’ within the filter ‘Species’, and ‘English’ within the filter ‘Languages’.

02 randomised controlled trials of sedentary behaviour

Below, the committee describes the effect of (reducing) sedentary behaviour on body mass index (BMI). The committee did not find systematic reviews or meta-analyses of randomised controlled trials (RCTs) of the effect on systolic blood pressure, LDL cholesterol, body weight (adults), insulin sensitivity, blood glucose, fat mass, abdominal fat, waist circumference, fat-free mass, bone density, cognitive decline, depressive symptoms, ADHD symptoms, cardiorespiratory fitness, functional performance, muscle strength, and musculoskeletal injuries. In addition, the committee did not find any systematic reviews or meta-analyses of RCTs on the effect of sedentary behaviour on the incidence of cardiovascular diseases; breast, colorectal or lung cancer; chronic obstructive lung diseases; type 2 diabetes mellitus, disability, fractures, osteoarthritis, dementia (as distinct from cognitive decline), depression (as distinct from depressive symptoms).



2.1 Body Mass Index

Summary of evidence for the effect of reducing sedentary behaviour on BMI in children and adolescents

Aspect	Explanatory notes
Selected studies	1 meta-analysis of 5 RCTs ³
Heterogeneity	No
Strength of the effect	Hedges' g -0.15 (-0.35 to +0.05)
Study populations	Children and adolescents

Conclusion: An effect of reducing sedentary behaviour on BMI in children and adolescents is unlikely.

Explanation

The Australian evidence report on children¹ does not describe any RCTs conducted with children or adolescents on the effect of reducing sedentary behaviour on BMI, but does describe eight observational studies which provided evidence that more than 2 hours screen-time per day was associated with increased BMI.

Based on three systematic reviews of cross-sectional, case-control and/or cohort studies, the Australian evidence report in adults² concluded that the evidence for an association between sedentary behaviour and weight gain was mixed.

The committee found two meta-analyses that studied the effect of interventions aimed at reducing sedentary behaviour on BMI in children and adolescents (Table 1).^{3,4} The committee did not find any meta-analyses or systematic reviews of adults. Meta-analyses of studies that

combined sedentary behaviour interventions with other lifestyle interventions were excluded, such as those of Wahi et al.,⁵ Hebden et al.,⁶ Kamath et al.⁷ and Tremblay et al.⁸

Liao et al.³ made a distinction between interventions which focused solely on reducing sedentary behaviour, on reducing sedentary behaviour in combination with increasing physical activity, and on the combination of reducing sedentary behaviour and increasing physical activity with dietary advice, whereas Van Grieken et al.⁴ combined studies focused solely on reducing sedentary behaviour with those reducing sedentary behaviour and increasing physical activity, without conducting separate analyses.

Therefore, the committee excludes the meta-analysis of Van Grieken et al.⁴ Liao et al.³ showed that interventions focusing on reducing sedentary behaviour had no significant effect on BMI compared to no treatment or verbal advice on reducing sedentary behaviour (Hedges' g -0.15). There were no indications of heterogeneity. In an analysis in which reducing sedentary behaviour was combined with increasing physical activity there was also no significant effect found (Hedges' g -0.09). However, there was moderate heterogeneity and the lower level of the confidence interval for the combined intervention was close to zero.

As the effect estimate is close to zero and heterogeneity is low, the committee concludes that an effect of reducing sedentary behaviour on BMI in children and adolescents is unlikely.



Table 1. Meta-analyses of the effect of reducing sedentary behaviour on BMI in children and adolescents

	Number of studies and number of participants	Study duration (month)	Intervention (intensity, frequency, duration)	Control	BMI (effect size and 95%-C.I. ^a)	Heterogeneity (I ² %)
<i>Meta-analysis</i>						
Liao 2015 ³	5; 389 children and adolescents 2.5-12 years	1.5-24 2-48	Home-based or home- and school-based intervention Among others: TV-time budget, education, suggestions for alternative behaviours	No treatment or (in 1 RCT) verbal advice on general strategies to reduce TV-watching time	-0.15 (-0.35 to +0.05) ^b	0
	10; 2,805 children and adolescents 4-14 years		Reducing sedentary behaviour and increasing physical activity	No treatment	-0.09 (-0.20 to +0.02) ^b	41

^a Confidence interval.^b Hedges' g.

2.2 Conclusion

An effect of reducing sedentary behaviour on BMI in children and adolescents is unlikely.

03 cohort studies of sedentary behaviour

In this chapter the association between sedentary behaviour and risk of all-cause mortality, cardiovascular disease,^a type 2 diabetes mellitus, breast cancer, colorectal cancer, lung cancer, and depression is described. The committee did not find any meta-analyses of cohort studies on sedentary behaviour and risk of chronic obstructive pulmonary

^a There were no meta-analyses on the separate associations between sedentary behaviour and coronary heart disease, stroke, and heart failure.

diseases, disability, fractures, osteoarthritis, and dementia.

3.1 All-cause mortality

Summary of evidence for the association between sedentary behaviour and all-cause mortality

Aspect	Explanation
Selected studies	1 harmonised analysis of 13 cohorts (sitting) and 6 cohorts (TV-watching time) ⁹ and 3 meta-analyses of 6 ¹⁰ , 10 ¹¹ and 14 cohorts ¹²
Heterogeneity	Yes, in the size of the effect in (non-harmonised) meta-analyses. No, in the stratified analyses in the harmonised meta-analysis.
Strength of the association	RRs for >8 vs. <4 hrs sitting/day ≤150 MET-min/wk: RR=1.27 (1.22-1.32) 960 MET-min/wk: RR=1.12 (1.07-1.17) 1,800 MET-min/wk: RR=1.10 (1.04-1.16) 2,130 MET-min/wk: RR=1.04 (0.98-1.10) RRs for ≥5 vs. <1 hr TV-watching time/day ≤150 MET-min/wk: RR=1.44 (1.34-1.56) 960 MET-min/wk: RR=1.29 (1.19-1.39) 1,800 MET-min/wk: RR=1.41 (1.28-1.56) 2,130 MET-min/wk: RR=1.15 (1.05-1.27)
Study population	Europe, North America, Australia



Conclusion: A high versus low level of sedentary behaviour is associated with an increased risk of all-cause mortality, except for those in the most active quartile (2,130 MET-min per week). Sitting more than 8 hours versus less than 4 hours per day is associated with a 27% increased risk of all-cause mortality at a physical activity level of less than 150 MET-min per week, a 12% increased risk at 960 MET-min per week and a 10% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week.

Level of evidence: Strong.

Conclusion: 3 to 4 hours versus less than 1 hour TV-watching time per day is associated with an 8 to 17% increased risk of all-cause mortality, except for those in the most active quartile (2,130 MET-min per week). In the most active quartile, TV-watching time of 5 hours or more per day was associated with a 15% increased risk of all-cause mortality, whereas it ranged from 29 to 44% in the other three quartiles of physical activity (≤ 150 , 960 and 1,800 MET-min per week).

Level of evidence: Strong.

Explanation

On the basis of three systematic reviews, the Australian evidence report² concludes that most of the prospective studies found an association between occupational or leisure-time sitting and all-cause mortality.

Therefore the level of evidence was considered strong or convincing. The committee found one harmonised meta-analysis⁹ and five meta-analyses on sedentary behaviour and all-cause mortality (Table 2).¹⁰⁻¹⁴ As the three RCTs in the meta-analysis by Grontved et al.¹³ were also summarised by Biswas et al.¹² and Sun et al.,¹¹ the committee excluded the meta-analysis by Grontved et al.¹³ Chau et al.¹⁰ and Wilmot et al.¹⁴ each included a cohort study that was not included by Biswas et al.,¹² whereas Sun et al.¹¹ summarised three cohort studies that were not included by Biswas et al.¹² The overlap between the meta-analyses of Chau et al.,¹⁰ Wilmot et al.,¹⁴ and Sun et al.¹¹ ranged from two to four cohort studies.

Ekelund et al.⁹ carried out a harmonised meta-analysis of 16 cohort studies on sitting and 6 cohort studies on TV-watching time. Sedentary behaviour was analysed as sitting time. In the analyses the authors stratified the association between sitting time and risk of all-cause mortality by level of physical activity and showed that, at a physical activity level of less than 150 MET-min per week, more than 8 hours of sitting per day versus less than 4 was associated with a 27% increased risk of all-cause mortality and a level of 960 MET-min/week on average with a 12% increased risk. At these physical activity levels there was evidence for a dose-response association. At higher levels of physical activity, the association became weaker (at 1,800 MET-min/week: 10% increased risk and >2,130 MET-min per week: 4% (not significant) and there was no longer evidence for a dose-response relationship. Those in the most



active quartile, but who also reported the most sitting time had a significantly lower risk of all-cause mortality (HR=1.04; 0.99-1.10) than did the least active group who also sat the least (HR=1.27; 1.22-1.30). To exclude possible bias from any single study, each study was excluded one at a time. Results were essentially unchanged. For TV-watching time, the results were similar, except that high physical activity attenuated, but did not eliminate the risk increase: watching TV for 3 hrs or more per day was associated with increased mortality risk, except in the most active group, where mortality was significantly increased only in people who watched five hours per day or more (HR=1.16; 1.05-1.28). Heterogeneity was low to moderate in the stratified analyses.

In line with the findings above, the four (non-harmonised) meta-analyses showed that a high level of sedentary behaviour was associated with an increased risk of total mortality.^{10,11,13,14} However, heterogeneity in the size of the effect was considerable in each of these meta-analyses.

Biswas et al.¹² defined sedentary behaviour as a distinct class of waking behaviours characterised by little physical movement and low energy-expenditure (≤ 1 MET) which included sitting, TV-watching, and adopting a reclined posture. In the overall analysis, in which the association was adjusted for physical activity, the authors showed that a high level of sedentary behaviour was associated with a 22% increased risk of all-cause mortality. There was considerable heterogeneity in the size of the effect. In sensitivity analyses the exclusion of any individual study did not change the findings substantially. The authors showed that the

association between sedentary behaviour and risk of all-cause mortality was modified by the amount of physical activity. Sedentary time was associated with a 30% lower relative risk of all-cause mortality at a high level of physical activity compared with a low level (RR=1.16 versus 1.46). There was evidence of publication bias.

In the other meta-analyses, associations were not stratified by level of physical activity.

Chau et al.¹⁰ carried out a dose-response analysis between total daily sitting time and risk of all-cause mortality, adjusted for physical activity. The authors found a non-linear dose-response relationship between total daily sitting time and risk of all-cause mortality. With physical activity adjustment, the dose-response relationship showed RR of 1.00, 1.02 and 1.05 for every 1-hour increase in sitting time in intervals between 0-3, >3-7, and >7 hours per day. Only the last relative risk estimate was significant. There was considerable heterogeneity which was only investigated in a linear analysis. In these sensitivity analyses the exclusion of any individual study did not change the findings substantially. There was some suggestion of publication bias, with larger cohort studies reporting smaller associations.

Sun et al.¹¹ focused on TV-watching time, as total screen time (watching TV or video or using a computer) predominantly stemmed from TV-watching. Eight of the ten studies adjusted for physical activity. Results hardly changed when the two studies that did not adjust for physical activity were excluded. Other subgroup analyses showed that adjustment



for diet quality index partly explained the considerable heterogeneity in the analysis. However, the number of studies adjusting for diet quality was small (N=3). In a dose-response analysis, the association was J-shaped: up to 3 hours TV-watching time, there were no indications for an association, at a daily rate of 4 hours TV-watching time there was an increased risk of 1.12 (1.00-1.25), followed by a continuously increasing risk with ascending exposure level. There were no indications for publication bias.

Wilmot et al.¹⁴ found that high level of sedentary behaviour was associated with a 49% higher risk of all-cause mortality. In their meta-analysis, the studies included reported sedentary time as either self-reported sitting time or TV- or screen-based entertainment or both. In three of the included

cohort studies risk estimates had not been adjusted for physical activity. The authors also did not perform any subgroup analyses to explain the considerable heterogeneity, nor did they assess publication bias as the number of studies was too small. Therefore, the committee has not included the findings of this meta-analysis in their conclusion.

In addition to these meta-analyses, the committee found two cohort studies with objectively-measured sedentary behaviour and physical activity. In the past few years several articles on this topic, based on data from NHANES, have been published.^{15,16} The committee describes the analysis by Koster et al.,¹⁵ as it comprised the largest number of cases. The study was also included in the meta-analyses described above. In the NHANES study the association between sedentary time and all-cause

Table 2. Cohort studies into the association between sedentary behaviour and all-cause mortality

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I ² (%)
<i>Meta-analysis</i>								
Wilmot 2012 ¹⁴	High vs. low	8	4-12	497,211	77,748	1.49	1.14-2.03	High
Chau 2013 ¹⁰	Per hour increase in sitting	6	3-9	595,086	53,760	1.03	0.98-1.08	85
	Linear							
	Non-linear							
	0-3 hrs sitting							
	>3-7 hrs sitting							
	>7 hrs sitting							
Biswas 2015 ¹²	High vs. low sedentary time	14	2-14	828,580	15,455	1.22	1.08-1.38	96
	High physical activity ($\geq 1,185$ MET-min/wk or ≥ 300 min/wk)	6	4-14	606,992	8,318	1.16	0.84-1.59	90
	≥ 1 hr/day sitting time to ≥ 11 hrs/day sitting time vs. less	6	4-14	606,992	8,318	1.46	1.22-1.75	90
	Low physical activity (0-2,004 MET-min/wk): ≥ 1 hrs/day sitting time to ≥ 11 hrs/day sitting vs. less							



	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I ² (%)
Sun 2015 ¹¹	High vs. low TV-watching	10	n.r. ^b	647,475	61,494	1.33	1.20-1.47	67
Ekelund 2016 ⁹	≤ 150 MET-min/wk	13	2-18	1,005,791	84,609			
	6-8 vs. <4 hrs sitting/day	6	6-14	465,450	43,740	1.09	1.05-1.14	^c
	>8 vs. <4 hrs sitting/day					1.27	1.22-1.32	^c
	960 MET-min/wk							
	6-8 vs. <4 hrs sitting/day					1.06	1.02-1.10	^c
	>8 vs. <4 hrs sitting/day					1.12	1.07-1.17	^c
	1,800 MET-min/wk							
	6-8 vs. <4 hrs sitting/day					1.03	0.98-1.08	^c
	>8 vs. <4 hrs sitting/day					1.10	1.04-1.16	^c
	2,130 MET-min/wk							
	6-8 vs. <4 hrs sitting/day					1.01	0.97-1.06	^c
	>8 vs. <4 hrs sitting/day					1.04	0.98-1.10	^c
	≤ 150 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.10	1.02-1.18	^c
	≥5 vs. <1 hr TV-watching time/day					1.44	1.34-1.56	^c
	960 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.08	1.01-1.15	^c
	≥5 vs. <1 hr TV-watching time/day					1.29	1.19-1.39	^c
	1,800 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.17	1.07-1.27	^c
	≥5 vs. <1 hr TV-watching time/day					1.41	1.28-1.56	^c
	2,130 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.01	0.93-1.10	^c
	≥5 vs. <1 hr TV-watching time/day					1.15	1.05-1.27	^c
<i>Cohort study with objectively-measured sedentary behaviour</i>								
NHANES 2012 ¹⁵	7.4-9.2 vs. <7.4 hrs/day	1	3	1,906	145	1.16	0.48-2.83	n.a. ^d
	9.2-10.4 vs. <7.4 hrs/day			50+		2.94	1.42-6.08	
	>10.4 vs. <7.4 hrs/day					3.22	1.39-7.44	
	18 vs. 15 hrs/day					0.59	0.28-1.22	
	20 vs. 15 hrs/day					1.52	0.81-2.83	

^a Confidence interval.

^b Not reported.

^c Heterogeneity ranged from 5% to 42% in the stratified analyses.

^d Not applicable.



mortality – after adjustment for moderate to vigorous physical activity – was stronger than estimated in the meta-analyses analysis. In the other cohort study,¹⁷ the authors included sleeping in the assessment of sedentary behaviour, hereby introducing bias into the exposure measure. Therefore, the committee has not examined the results further. Thus, there are too few studies with objectively-measured sedentary behaviour and physical activity to draw a conclusion on the association with mortality. The harmonised meta-analysis⁹ and the meta-analyses by Biswas et al.,¹² Chau et al.¹⁰ and Sun et al.¹¹ confirmed the conclusion in the Australian evidence report and provided more insight in the shape of the association and the role of physical activity. As heterogeneity was low to moderate in the stratified analyses in the harmonised meta-analysis, the committee has based its conclusion on its findings.⁹

In conclusion, a high versus low level of sedentary behaviour is associated with an increased risk of all-cause mortality, except for those in the most active quartile. Sitting more than 8 hours versus less than 4 hours per day is associated with a 27% increased risk of all-cause mortality at a physical activity level of less than 150 MET-min per week, a 12% increased risk at 960 MET-min per week and a 10% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week. 3 to 4 hours versus less than 1 hour TV-watching time per day is associated with an 8 to 17% increased risk of all-cause mortality, except for those in the most active quartile (2,130 MET-min per week). In the most active quartile, TV-watching time of 5

hours or more per day was associated with a 15% increased risk of all-cause mortality, whereas it ranged from 29 to 44% in the other three quartiles of physical activity (≤ 150 , 960 and 1,800 MET-min per week). In view of the consistent findings, the level of evidence is strong for both associations.

3.2 Cardiovascular disease

On the basis of three systematic reviews, the Australian evidence report² concludes that there was insufficient evidence to support any relationship between sedentary behaviour and cardiovascular disease. Below, the committee reviews the evidence for cardiovascular disease and cardiovascular mortality.

Cardiovascular disease

Summary of evidence for the association between sedentary behaviour and cardiovascular disease

Aspect	Explanation
Selected studies	2 meta-analyses of 4 ¹³ and 3 ¹² cohorts
Heterogeneity	Yes, in the size of the effect
Strength of the association	Cardiovascular disease: RR=1.15 (1.06-1.23) per 2 hour TV-watching RR=1.14 (1.00-1.30) high vs. low
Study population	Europe, North America, Australia

Conclusion: A high versus low sedentary time is associated with an increased risk of cardiovascular disease.

Level of evidence: Weak.



Explanation

The committee found three meta-analyses on the association between sedentary behaviour and risk of cardiovascular disease, each summarising three or four cohort studies (Table 3).¹²⁻¹⁴ The overlap between the meta-analyses ranged from 1 to 2 cohort studies.

Biswas et al.¹² defined sedentary behaviour as a distinct class of waking behaviours characterised by little physical movement and low energy-expenditure (≤ 1 MET) which included sitting, TV-watching, and adopting a reclined posture. The authors found that sedentary behaviour was associated with a 14% increased risk of cardiovascular disease (including diabetes) independent of physical activity. There was considerable heterogeneity in the size of the effect which did not change substantially when excluding any individual study. In view of the small number of studies, the authors did not assess publication bias.

Grontved et al.¹³ studied the association of TV-watching with fatal and/or non-fatal cardiovascular disease. Three of the four summarised cohort studies adjusted for physical activity. The authors found that TV-watching was associated with a 15% increased risk of cardiovascular disease/mortality for every 2 hours of TV-watching. A linear dose-response association was found. Heterogeneity was low, which could also be explained by the small number of studies. There was no evidence of publication bias. Because cardiovascular disease and cardiovascular

mortality were combined in this study, the committee weighs the results of this meta-analysis less heavily.

Wilmot et al.¹⁴ included in their meta-analysis three cohort studies reporting sedentary time as either self-reported sitting time or TV-watching/screen-based entertainment or both. Each of the studies had a short follow-up of 3 to 4 years. Sedentary behaviour was associated with a 47% greater risk of cardiovascular disease. Heterogeneity was considerable, and not further investigated by the authors. Only one of the cohort studies adjusted for physical activity in the form of energy expenditure, whereas adjustments in the other two were limited to respectively age and sex or age, sex, marital status, and education. The authors did not assess publication bias as the number of studies was too small. In view of the short follow-up time and the limited adjustment for potential confounding factors, the committee weighs the findings less heavily when drawing its conclusion.

Thus, the meta-analysis of Biswas et al.,¹² in particular, provides new evidence for an association between sedentary behaviour and risk of cardiovascular disease in comparison to the Australian report.²

In conclusion, a high level of sedentary time is associated with an increased risk of cardiovascular disease. In view of the small number of studies, the level of evidence is weak.



Cardiovascular mortality

Summary of evidence for the association between sedentary behaviour and cardiovascular mortality

Aspect	Explanation
Selected studies	1 harmonised analysis of 9 cohorts (sitting) and 4 cohorts (TV-watching time) ⁹ and 1 meta-analysis of 7 cohorts ¹²
Heterogeneity	No
Strength of the association	Cardiovascular mortality: RR >8 vs. <4 hrs sitting/day and ≤150 MET-min/wk ≤150 MET-min/wk: RR=1.74 (1.60-1.90) 960 MET-min/wk: RR=1.37(1.25-1.50) 1,800 MET-min/wk: RR=1.16 (1.04-1.28) 2,130 MET-min/wk: RR=1.07 (0.96-1.20) RRs for ≥5 vs. <1 hr TV-watching time/day ≤150 MET-min/wk: RR=2.26 (1.93-2.66) 960 MET-min/wk: RR=1.71 (1.46-2.01) 1,800 MET-min/wk: RR=1.48 (1.24-1.78) 2,130 MET-min/wk: RR=1.19 (0.99-1.24)
Study population	Europe, North America, Australia

Conclusion 1: A high versus low level of sedentary behaviour is associated with an increased risk of cardiovascular mortality, except for those in the most active quartile (2,130 MET-min per week).

Compared to the combination of less than 4 hours sitting and at least 2,130 MET-min/week of physical activity, more than 8 hours per day is associated with a 74% increased risk at a physical activity level of less than 150 MET-min per week, a 37% increased risk at 960 MET-min per week and a 16% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week.

Level of evidence: Strong.

Conclusion 2: A high versus low level of TV-watching time is associated with an increased risk of cardiovascular mortality, except for those in the most active quartile.

Level of evidence: Weak.

Explanation

The committee found one harmonised meta-analysis⁹ and two meta-analyses of the association between sedentary behaviour and risk of cardiovascular death (Table 3).^{12,14}

Ekelund et al.⁹ carried out a harmonised meta-analysis of 9 cohort studies. Sedentary behaviour was analysed as sitting time. In the analyses the authors used a different approach than for total mortality: for cardiovascular mortality the reference group consisted of subjects who sat less than 4 hours per day and had a physical activity level of more than 2,130 MET-min per week. Thus associations were not analysed by each level of physical activity, as was the case for total mortality.

The authors showed that, compared to less than 4 hours sitting and at least 2,130 MET-min/week of physical activity, more than 8 hours per day is associated with a 74% increased risk at a physical activity level of less than 150 MET-min per week, a 37% increased risk at 960 MET-min per week and a 16% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week. Those in the most active quartile, but who also reported the most sitting time had a lower risk of cardiovascular mortality (HR=1,07; 0.96-1.20) than did the



least active group who also sat the least (HR=1.34; 1.24-1.43). Using TV-watching time instead of sitting did not materially change the results, although the estimates were less precise, possibly because of the smaller sample sizes. Heterogeneity was low to moderate in the stratified analyses.

The other two meta-analyses also summarised the association between sedentary behaviour and risk of cardiovascular mortality.^{12,14} Six of the studies overlapped between the two meta-analyses.

Biswas et al.¹² found a 15% larger risk of cardiovascular mortality comparing a high with a low sedentary time. In all seven included studies, the association was adjusted for physical activity. Heterogeneity was moderate. The association did not change significantly with the exclusion of each individual study. There were too few studies to analyse the association separately by level of physical activity. There was no evidence of publication bias.

Wilmot et al.¹⁴ found a 90% higher risk for a high versus a low level of sedentary behaviour. Four of the eight cohort studies did not adjust for potential confounding and one for age only, which may explain the large estimate as compared to the findings by Biswas et al.¹² Visual inspection of the forest plot suggested considerable heterogeneity in the size of the effect. In view of the limitations of the meta-analysis by Wilmot et al.,¹⁴ the committee did not consider the findings when drawing its conclusion.

Thus, the harmonised meta-analysis by Ekelund et al.⁹ and the meta-analysis by Biswas et al.¹² provide new evidence for an association between sedentary behaviour and risk of cardiovascular mortality and the interaction with physical activity as compared to the Australian report.² As the meta-analysis by Ekelund et al.⁹ based its conclusion on harmonised data and on a larger numbers of studies and cases than the meta-analysis by Biswas et al.,¹² the committee has based its conclusion on the harmonised meta-analysis findings.⁹

In conclusion, a high versus low level of sedentary behaviour is associated with an increased risk of cardiovascular mortality, except for those in the most active quartile. Compared to the combination of less than 4 hours sitting and at least 2,130 MET-min/week of physical activity, more than 8 hours per day is associated with a 74% increased risk at a physical activity level of less than 150 MET-min per week, a 37% increased risk at 960 MET-min per week and a 16% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week. In view of the consistent findings, the level of evidence is strong.

A high versus low level of TV-watching time is associated with an increased risk of cardiovascular mortality, except for those in the most active quartile. In view of the small number of studies (N=4) and wide confidence intervals around the estimates, the level of evidence is weak.



Table 3. Cohort studies into the association between sedentary behaviour and cardiovascular disease and cardiovascular mortality

	Exposure	Number of cohorts	Follow up time (years)	N	N	RR	95% C.I.	Heterogeneity I ² (%)
<i>Meta-analysis cardiovascular disease</i>								
Wilmot 2012 ¹⁴	High vs. low	3	3-4	80,221	2,005	2.47	1.44-4.24	55
Grontved 2014 ¹³	Per 2 hrs TV-watching per day	4	4-21	34,253	1,052	1.15	1.06-1.23	0
Biswas 2015 ¹²	High vs. low	3	4-12	31,054	3,175	1.14	1.00-1.30	82
<i>Meta-analysis cardiovascular mortality</i>								
Wilmot 2012 ¹⁴	High vs. low	8	4-21	421,921	13,023	1.90	1.36-2.66	High
Biswas 2015 ¹²	High vs. low	7	4-14	532,920	7,356	1.15	1.07-1.24	38
Ekelund 2016 ⁹	≤150 MET-min/wk	9	5-18	849,108	24,481			
	6-8 vs. <4 hrs sitting/day					1.56	1.44-1.69	^b
	>8 vs. <4 hrs sitting/day					1.74	1.60-1.90	^b
	960 MET-min/wk							
	6-8 vs. <4 hrs sitting/day					1.23	1.13-1.34	^b
	>8 vs. <4 hrs sitting/day					1.37	1.25-1.50	^b
	1,800 MET-min/wk							
	6-8 vs. <4 hrs sitting/day					1.04	0.95-1.14	^b
	>8 vs. <4 hrs sitting/day					1.16	1.04-1.28	^b
	2,130 MET-min/wk							
	6-8 vs. <4 hrs sitting/day					0.99	0.91-1.09	^b
	>8 vs. <4 hrs sitting/day					1.07	0.96-1.20	^b
	≤150 MET-min/wk	4	6-14	449,300	13,331			
	3-4 vs. <1 hr TV-watching time/day					1.68	1.44-1.95	^b
	≥5 vs. <1 hr TV-watching time/day					2.26	1.93-2.66	^b
	960 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.36	1.18-1.58	^b
	≥5 vs. <1 hr TV-watching time/day					1.71	1.46-2.01	^b
	1,800 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.23	1.05-1.44	^b
	≥5 vs. <1 hr TV-watching time/day					1.48	1.24-1.78	^b
	2,130 MET-min/wk							
	3-4 vs. <1 hr TV-watching time/day					1.08	0.92-1.26	^b
	≥5 vs. <1 hr TV-watching time/day					1.19	0.99-1.24	^b

^a Confidence interval.

^b Heterogeneity ranged from 5% to 42% in the stratified analyses.



3.3 Type 2 diabetes mellitus

Summary of evidence for the association between sedentary behaviour and diabetes

Aspect	Explanation
Selected studies	2 meta-analyses of 4 ¹³ and 5 ¹⁴ cohort studies
Heterogeneity	Yes, in the size of the effect
Strength of the association	RR=1.93 (1.40-2.82) high vs. low level of TV-watching time RR=1.20 (1.14-1.27) per 2 hours of TV-watching per day
Study population	Europe, North America

Conclusion: A high versus low level of TV-watching time is associated with an increased risk of diabetes.

Level of evidence: Weak.

Explanation

On the basis of three systematic reviews, the Australian evidence report² concludes that there was moderate evidence for an association between sedentary behaviour and the risk of diabetes.

The committee found three meta-analyses¹²⁻¹⁴ of the association between sedentary behaviour and the risk of diabetes (Table 4). In each of the

meta-analyses sedentary behaviour was defined as TV-watching time. There were no meta-analyses available on the association between sedentary behaviour and risk of diabetes. As Biswas et al.¹² combined four cohort studies with one case-control study and because Grontved et al.¹³ and Wilmot et al.¹⁴ summarised the same four cohort studies, the committee excluded the meta-analysis by Biswas et al.¹² Of the four cohort studies that were included in each of the meta-analyses, two (Women's Health Study and Health Professionals Follow-up Study) had been carried out by the same research group.

Wilmot et al.¹⁴ combined the four cohort studies with one other cohort study which, unlike the other four, did not adjust for physical activity. Therefore, the committee weighs the findings of Wilmot et al.¹⁴ less heavily. The authors found that high versus low level of TV-watching time per day was associated with a 93% higher risk of diabetes. The authors did not provide any heterogeneity estimate. Visual inspection of the forest plot suggests considerable heterogeneity in the size of the effect. In view of the small number of studies, publication bias could not be investigated.

Table 4. Cohort studies into the association between sedentary behaviour and diabetes

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I ² (%)
<i>Meta-analysis</i>								
Wilmot 2012 ¹⁴	High (>4 to 6 hrs TV-watching/day) vs. low (<1-2 hrs/day or <1 hr/wk)	5	3-10	177,904	6,675	1.93	1.40-2.82	High
Grontved 2014 ¹³	Per 2 hrs of TV-watching time per day	4	6-10	175,938	6,428	1.20	1.14-1.27	50

^a Confidence interval.



Grontved et al.¹³ summarised four cohort studies, showing that every additional 2 hours of TV-watching per day was associated with a 20% increased risk of diabetes after adjustment for physical activity. The dose-response association was linear. There was considerable heterogeneity in the size of the effect. Adjusting for dietary variables slightly attenuated the risk estimate (RR=1.18; 1.12-1.25). When studies with an additional adjustment for BMI or other obesity measure were pooled, the summary estimate was attenuated to 1.13 (1.08-1.18) per 2 hours TV-watching time. Omitting one study at a time showed that none of the studies substantially influenced the risk estimates.

In comparison to the findings of the recent meta-analyses^{12,14} the conclusions in the Australian evidence report² still apply.

In conclusion, a high versus low level of TV-watching time is associated with an increased risk of diabetes. As the number of independent cohort studies was limited, the level of evidence is weak.

3.4 Breast cancer

Summary of evidence for the association between sedentary behaviour and breast cancer

Aspect	Explanation
Selected studies	3 meta-analyses of 3, ¹⁸ 4 ¹⁹ and 7 ²⁰ cohort studies
Heterogeneity	No
Strength of the association	RR=1.09 (1.04-1.15)
Study population	Europe, North America, Australia, Asia

Conclusion: A high versus low level of sedentary behaviour is

associated with an increased risk of breast cancer.

Level of evidence: Weak.

Explanation

On the basis of three systematic reviews, the Australian evidence report² concludes that there was insufficient evidence to support any relationship between sedentary behaviour and cancers.

The committee found three meta-analyses (Table 5).¹⁸⁻²⁰ A fourth meta-analysis, by Ekelund et al.,⁹ summarised the association between sedentary behaviour and the combined risk of breast, colon and rectal cancer. As the authors did not provide separate risk estimates, the meta-analysis was not included in the literature review of these cancers. Shen et al.¹⁸ summarised three cohort studies, two of which were summarised with two other cohort studies by Schmid et al.¹⁹ and with five other by Zhou et al.²⁰ Therefore, the meta-analysis by Shen et al. was excluded.¹⁸ Both Zhou et al.²⁰ and Schmid et al.¹⁹ combined cohort studies with case-control studies in a main analysis. In subgroup analyses, cohort studies were analysed separately. In each of the three meta-analyses, studies were included that reported TV-watching time, recreational, occupational, and/or total sitting time.

Zhou et al.²⁰ showed, in a meta-analysis of seven cohort studies, that a high level of sedentary behaviour was associated with a 9% increased risk of breast cancer. Heterogeneity was low. However, only one of the seven cohort studies adjusted for physical activity.



Table 5. Cohort studies into the association between sedentary behaviour and breast cancer

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I ² (%)
<i>Meta-analysis</i>								
Schmid 2014 ¹⁹	High vs. low: 6-8 vs. <2 hrs/day or ≥4 vs. <1.2 hrs/day occupational sitting; ≥9 vs. <3 hrs/day total sitting; ≥6 vs. <3 hrs/day recreational sitting.	4	n.r. ^b	306,240	9,019	1.06	0.92-1.22	n.r.
Shen 2014 ¹⁸	High vs. low: ≥4 vs. <1.2 hrs/day or ≥9 vs. <1.2 hrs/day or ≥12 vs. <5.5 hrs/day	3	7-9	172,818	4,699	1.17	1.03-1.33	13
Zhou 2015 ²⁰	High vs. low: ≥9 vs. <3 hrs/day or ≥5 vs. <1 hr/day TV-watching; ≥6 vs. <3 hrs/day or ≥4 <1.2 hrs/day or 6-8 vs. <2 hrs/day sitting; heavy vs. sedentary occupational work	7	n.r.	2,580,046	63,354	1.09	1.04-1.15	2

^a Confidence interval.

^b Not reported.

Shen et al.¹⁸ showed, on the basis of three cohort studies (one large and two small studies), two of which adjusted for physical activity, that a high level of sedentary behaviour was associated with a 17% increased risk of breast cancer. The relative risk was lower in the larger study (RR=1.09) than in the two small studies (RR=1.23 and 1.41).

Schmid et al.¹⁹ found no significant association (RR=1.06) on the basis of four studies, two of which adjusted for physical activity. The authors did not report a heterogeneity estimate. The forest plot showed that relative risks in the studies ranged from 0.83 to 1.23, none of them being significant.

Compared to the Australian evidence report, the recent meta-analyses provide new insights. As the meta-analysis by Zhou et al.²⁰ is considerably

larger than the other two, the committee based its conclusions on the meta-analysis by Zhou et al.¹⁸⁻²⁰

In conclusion, high versus low level of sedentary behaviour is associated with an increased risk of breast cancer. As adjustment for physical activity was limited, the level of evidence is weak.

3.5 Colorectal cancer

On the basis of three systematic reviews the Australian evidence report² concludes that there was insufficient evidence to support any relationship between sedentary behaviour and cancers.



Colon cancer

Summary of evidence for the association between sedentary behaviour and colon cancer

Aspect	Explanation
Selected studies	2 meta-analyses of 5 ¹⁹ and 12 ²¹ cohort studies
Heterogeneity	Yes, in the size of the effect
Strength of the association	RR=1.27 (1.18-1.36) RR=1.23 (1.08-1.40)
Study population	Europe, North America, Asia

Conclusion: A high versus low level of sedentary behaviour is associated with an increased risk of colon cancer.

Level of evidence: Weak.

Explanation

The committee found three meta-analyses into the association of sedentary behaviour and risk of colorectal cancer (Table 6). Because the two cohort studies summarised by Shen et al.¹⁸ were summarised in combination with three other cohort studies by Schmid et al.¹⁹ and in combination with 10 other by Cong et al.,²¹ the committee excluded the meta-analysis by Shen et al.¹⁸ A fourth meta-analysis, by Ekelund et al.,⁹ summarised the association between sedentary behaviour and the combined risk of breast, colon and rectal cancer. As the authors did not provide separate risk estimates, the meta-analysis was not included in the literature review of these cancers.

Cong et al.²¹ showed that a high level of sedentary behaviour was

associated with a 27% larger risk of colon cancer. In the studies, sedentary behaviour ranged from occupational behaviour (heavy versus light work or standing versus sitting work) and recreational sitting time to TV or video watching time. However, only four of the twelve cohort studies adjusted for physical activity. The pooled risk estimate (RR=1.30; 1.16-1.46) in these four studies was close to the combined risk estimate. There was considerable heterogeneity in the size of the effect. Exclusion of any single study did not materially change the results. There was a weak indication of publication bias based on the visual inspection of the funnel plot of case-control studies and cohort studies combined.

Schmid et al.¹⁹ found that a high level of sedentary behaviour was associated with a 23% increased risk of colon cancer. However, only one of the five included studies adjusted for physical activity. Visual inspection of the funnel plot suggests considerable heterogeneity in the size of the effect. There was a weak indication of publication bias when case-control studies and cohort studies were analysed in combination.

Compared to the Australian evidence report², recent meta-analyses provide new insights into the association between sedentary behaviour and risk of colon cancer.^{19,21}

In conclusion, a high versus low level of sedentary behaviour is associated with an increased risk of colon cancer. In view of the limited adjustment for physical activity and the indications of publication bias, the level of evidence is weak.



Rectal cancer

Summary of evidence for the association between sedentary behaviour and rectal cancer

Aspect	Explanation
Selected studies	1 meta-analysis of 10 ²¹ cohort studies ²¹
Heterogeneity	No
Strength of the association	RR=1.06 (1.01-1.12)
Study population	Europe, North America

Conclusion: A high versus low level of sedentary behaviour is associated with an increased risk of rectal cancer.

Level of evidence: Weak.

Explanation

The committee found one meta-analysis into the association between sedentary behaviour and risk of rectal cancer (Table 6).²¹ Another meta-analysis, by Ekelund et al.,⁹ summarized the association between sedentary behaviour and the combined risk of breast, colon and rectal

cancer. As the authors did not provide separate risk estimates, the meta-analysis was not included in the literature review of these cancers. Based on 10 cohort studies, two of which adjusted for physical activity, Cong et al.²¹ showed that sedentary behaviour was associated with a 5% increased risk of rectal cancer. Sedentary behaviour ranged in the studies from occupational behaviour (heavy vs. light or standing vs. sitting) and recreational sitting time to TV- or video-watching time. Heterogeneity was low and there was no evidence of publication bias. The lower limit of the confidence interval was close to 1.

As compared to the Australian evidence report², recent meta-analyses provide new insights into the association between sedentary behaviour and risk of rectal cancer.²¹

In conclusion a high versus low level of sedentary behaviour is associated with an increased risk of rectal cancer. As the confidence interval is close to 1, despite the large number of cases and the limited adjustment for physical activity, the level of evidence is weak.

Table 6. Cohort studies into the association between sedentary behaviour and colorectal cancer

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I ² (%)
<i>Meta-analysis colon cancer</i>								
Cong 2014 ²¹	High vs .low	12	n.r. ^b	4300,659	25,645	1.27	1.18-1.36	50
Schmid 2014 ¹⁹	High: >6 (to 8) vs. <2 hrs/day or ≥50% vs. ≤20% or medium/high vs. low occupational sitting; total sitting time ≥9 vs. <3 hrs/day	5	n.r.	1799,818	10,295	1.23	1.08-1.40	n.r.
<i>Meta-analysis rectal cancer</i>								
Cong 2014 ²¹	High vs. low	10	n.r. ^b	3757,461	12,388	1.06	1.01-1.12	20

^a Confidence interval.

^b Not reported.



Table 7. Cohort studies into the association between sedentary behaviour and lung cancer

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I ² (%)
<i>Meta-analysis</i>								
Shen 2014 ¹⁸	≥4 vs. <2 hrs/day or ≥5 vs. <3 hrs/day TV-watching time	2 ^b	11 and 16	212,673	1.321	1.20	1.12-1.28	7

^a Confidence interval.

^b Three strata.

3.6 Lung cancer

Summary of evidence for the association between sedentary behaviour and lung cancer

Aspect	Explanation
Selected studies	1 meta-analysis of 2 cohort studies (3 strata) ¹⁸
Heterogeneity	No
Strength of the association	RR=1.06 (1.01-1.12)
Study population	North America, Asia

Conclusion: There is too little research to draw a conclusion on the association between sedentary behaviour and risk of lung cancer.

Explanation

On the basis of three systematic reviews the Australian evidence report² concludes that there was insufficient evidence to support any relationship between sedentary behaviour and cancers.

The committee found one meta-analysis^a of two cohort studies (three

^a The meta-analysis of Schmid et al.¹⁹ combined the three cohort studies with one case-control study and was, therefore, not included.

strata) from the US and Japan (Table 7).¹⁸ The authors found that sedentary behaviour in the form of TV-watching time was associated with an increased risk of lung cancer. One of the two cohort studies adjusted for physical activity.

Compared to the Australian evidence report², the recent meta-analysis provides indications that TV-watching time is associated with lung cancer, however the number of studies is small (N=2).

The committee concludes that there is too little research to draw a conclusion on the association between sedentary behaviour and risk of lung cancer.

3.7 Depressive symptoms

Summary of evidence for the association between sedentary behaviour and depressive symptoms

Aspect	Explanation
Selected studies	1 meta-analysis 9 cohort studies ²²
Heterogeneity	Yes
Strength of the association	RR=1.14 (1.06-1.21)
Study population	Europe, North America, Australia, Asia



Conclusion: A high versus low level of sedentary behaviour is associated with an increased risk of depressive symptoms.

Level of evidence: Weak.

Explanation

On the basis of one systematic review, the Australian evidence report² concludes that there was limited evidence to support a relationship between sedentary behaviour and risk of depression. The evidence was limited by methodological weaknesses.

The committee found one meta-analysis of 9 cohort studies (Table 8).²² The authors did not define sedentary behaviour, although subgroup analyses were carried out for TV-watching time and computer or internet use. The meta-analysis showed that a high level of sedentary behaviour was associated with increased risk of depressive symptoms. Three of the studies used physician's diagnosis (or beginning regular use of antidepressant medication) and the other six used scales or questionnaires to assess the presence of depression or depressive symptoms. In an overall analysis, in which the cohort studies were

combined with case-control studies, there was considerable heterogeneity in the size of the effect ($I^2=51\%$). Visual inspection of the forest plot suggests that both case-control and cohort studies contributed to the heterogeneity. However, the analysis in cohort studies was a subgroup analysis and heterogeneity was not specifically reported or explored within this subgroup.

Four of the nine studies adjusted for physical activity. In the subgroup analysis in which case-control and cohort studies that adjusted for physical activity were compared to those that did not, relative risks were smaller in the former (RR=1.12; 1.06-1.18) than in the latter (RR=1.34; 1.22-1.48). There was no evidence of publication bias for case-control and cohort studies combined.

Compared to the Australian report², the findings in the meta-analysis support the association between sedentary behaviour and depressive symptoms.²²

In conclusion, a high versus low level of sedentary behaviour is associated with an increased risk of depressive symptoms. As more than half of the studies did not adjust for physical activity, the level of evidence is weak.

Table 8. Cohort studies into the association between sedentary behaviour and depressive symptoms

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I. ^a	Heterogeneity I^2 (%)
<i>Meta-analysis</i>								
Zhai 2015 ²²	High vs. low	9	n.r.	n.r.	n.r.	1.14	1.06-1.21	n.r. ^b

^a Confidence interval.

^b Not reported.



3.8 Conclusion

A high versus low level of sedentary behaviour is associated with an increased risk of all-cause mortality and cardiovascular mortality, except for those in the most active quartile (2,310 MET-min per week). A high versus low level of TV-watching time is associated with an increased risk of mortality, which is smaller at high than at low levels of physical activity. The level of evidence is strong for these associations.

A high versus low level of TV-watching time is associated with an increased risk of cardiovascular mortality, except for those in the most active quartile. A high versus low level of TV-watching time is associated with an increased risk of diabetes. A high versus a low level of sedentary time is associated with an increased risk of cardiovascular disease, breast cancer, colon cancer, rectal cancer, and depressive symptoms. The level of evidence for these associations is weak.

There is too little research to draw a conclusion on the association between sedentary behaviour and risk of lung cancer.

04 conclusions with a strong level of evidence

The committee has based these Dutch physical activity guidelines 2017

on effects and associations for which there is a strong level of evidence. The following associations with a strong level of evidence were found in adults:

- A high versus low level of sedentary behaviour is associated with an increased risk of all-cause mortality, except for those in the most active quartile (2,130 MET-min per week). Sitting more than 8 hours versus less than 4 hours per day is associated with a 27% increased risk of all-cause mortality at a physical activity level of less than 150 MET-min per week, a 12% increased risk at 960 MET-min per week and a 10% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week.
- 3 to 4 hours versus less than 1 hour TV-watching time per day is associated with an 8 to 17% increased risk of all-cause mortality, except for those in the most active quartile (2,130 MET-min per week). In the most active quartile, TV-watching time of 5 hours or more per day was associated with a 15% increased risk of all-cause mortality, whereas it ranged from 29 to 44% in the other three quartiles of physical activity (≤ 150 , 960 and 1,800 MET-min per week).
- A high versus low level of sedentary behaviour is associated with an increased risk of cardiovascular mortality, except for those in the most active quartile (2,130 MET-min per week). Compared to the combination of less than 4 hours sitting and at least 2,130 MET-min per week of physical activity, more than 8 hours per day is associated with a 74% increased risk at a physical activity level of less than 150



MET-min per week, a 37% increased risk at 960 MET-min per week and a 16% increased risk at 1,800 MET-min per week, whereas there is no significant association at 2,130 MET-min per week.

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