Physical activity and risk of chronic diseases

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

Background document to:

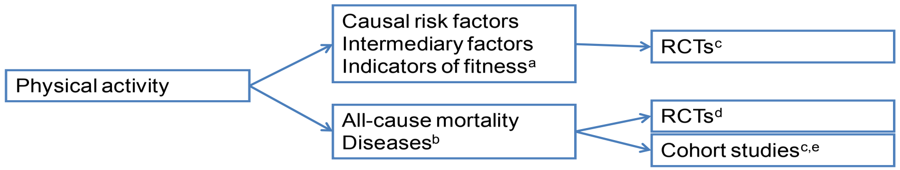
Dutch physical activity guidelines 2017

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

Health Council of the Netherlands

contents

methodology in brief



a. The committee evaluated the effect of physical activity on the following causal risk factors: systolic blood pressure, LDL cholesterol, body weight (adults) and body mass index (children), and insulin sensitivity; the intermediary factors: blood glucose, fat mass, abdominal fat, waist circumference, fat-free mass, bone density, cognitive decline, depressive symptoms, and ADHD symptoms; indicators of fitness: cardiorespiratory fitness, functional performance, and muscle strength; and musculoskeletal injuries.
b. The committee evaluated the association of physical activity with all-cause mortality and the following diseases: coronary heart disease, stroke, heart failure, breast cancer, colorectal cancer, lung cancer, chronic obstructive pulmonary disease, type 2 diabetes mellitus, disability, fractures, osteoarthritis, dementia and cognitive decline, and depression.
c. The committee primarily studied pooled analyses, meta-analyses, and systematic reviews.
d. RCTs (Randomised Controlled Trials) on the effect on disease outcomes are scarce. In view of the importance of these studies for conclusions on causality, these RCTs are described irrespective of the availability of meta-analyses or systematic reviews.
e. The term cohort studies is used for all types of prospective observational research.

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 physical activity has on intermediary factors and diseases, 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 used conclusions taken from the American evidence report[3] to examine topics which were not covered by the Australian reports. These resulting conclusions were supplemented with more recent meta-analyses and systematic reviews of RCTs and prospective cohort studies. In addition, cohort studies with objectively measured sedentary behaviour were described separately. For this purpose, literature was searched in PubMed (from 2008 or 2012[a] to 1 October 2016). Publications were searched using the MeSH-terms: *motor activity, exercise, leisure activity, physical activity, physical inactivity, energy expenditure, vigorous activity resistance training, strength training, locomotor activity* and a number of non-indexed terms: *physical exercise, aerobic exercise, weight-bearing, walking, running, tai chi, fitness, moderate vigorous physical activity, circuit training.*
These terms were combined with the respective outcome measures (e.g. diabetes mellitus, type 2). 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'.

[a] 2012 if the Australian evidence reports could be used as a starting point and 2008 if the American evidence report had to be used.

02 randomised controlled trials of physical activity

Below, the committee describes the effect of physical activity on the risk of developing type 2 diabetes mellitus; cardiometabolic risk factors: systolic blood pressure, LDL cholesterol, and insulin sensitivity; cardiorespiratory fitness; body weight and body mass index; body composition: fat mass, abdominal fat, waist circumference, and fat-free mass; muscle strength (children and adolescents, and older adults); functional performance in terms of gait speed, the time-up-and-go test, and short physical performance battery (older adults); bone health: fractures (older adults) and bone density (children and adolescents); musculoskeletal injuries; cognitive decline (older adults); and depressive symptoms.
The committee did not find any RCTs on the effect of physical activity on the incidence of cardiovascular diseases, breast, colorectal or lung cancer, chronic obstructive lung disease, disability, fractures, osteoarthritis, dementia (as distinct from cognitive decline), depression (as distinct from depressive symptoms), or on the incidence of ADHD symptoms in children.

2.1 Diabetes

Conclusion: 150 minutes of physical activity per week lowers the risk of diabetes in subjects with impaired glucose tolerance.
Level of evidence: Weak.

Explanation
Research into the prevention of diabetes by performing physical activity mainly pertains to individuals with 'prediabetes', that is impaired fasting glucose levels or impaired glucose tolerance which does not meet the threshold for diabetes, or those at a very high risk of developing diabetes as evaluated on the basis of screening instruments. According to the Australian guidelines,[2] there is strong evidence for the effectiveness of physical activity in reducing diabetes incidence in such populations from several large-scale randomised trials conducted in the USA, Finland, China and India, and smaller ones in Japan and Sweden. However, in the vast majority of cases, the interventions were lifestyle-change interventions which included other components besides physical activity, in particular dietary elements. As far as physical activity is concerned, the target was mostly 150 minutes of physical activity per week. Only one study, the Chinese Da Qing study,[4] carried out in subjects with impaired glucose tolerance, included a group in which the intervention consisted of exercise only (Table 1). Next to the control group, there were also groups with a dietary intervention only, or a combination of exercise and diet. The exercise group were taught and encouraged to increase their leisure-time exercise by at least one unit per day and by two units per day if possible for those < 50 years with no evidence of cardiovascular disease or arthritis. Units were defined in terms of intensity and duration: one unit was equal to 30 minutes of mild activity, 20 minutes of moderate activity, 10 minutes of strenuous activity, or 5 minutes of very strenuous activity.

Table 1. RCTs into the effect of physical activity on the risk of developing diabetes in subjects with impaired glucose tolerance

	Number of participants	Study duration (months); design	Intervention (intensity, frequency, duration)	Control	Number of cases interven-tion vs. control	RR of diabetes (p-value)
RCTs						
Da Qinq 1997[4]	577 prediabetics	73; RCT	1-2 units/d of 30' mild; 20' moderate; 10' strenuous; or 5' very strenuous exercise	Diet or general health education	8.3 vs. 15.7 per 100,000 person years	0.54 (P<0.0005)

Compared to the control group, the relative risk of developing diabetes was 0.54 in the exercise group, 0.58 in the exercise plus diet group and 0.69 in the diet group.[4] In a few other studies,[5,6] the independent effects of physical activity could be estimated. From these analyses, the Australian evidence report concluded that changes in physical activity alone (150 minutes per week) had an independent effect on the risk of developing diabetes.[2]

Overall, the number of RCTs designed to test the effectiveness of physical activity in the prevention of diabetes is very limited. Only 1 systematic review, stemming from 2007, was identified in which 3 RCTs and 1 non-randomised CT included incidence of diabetes as an outcome.[7] A recent meta-analysis by Gong et al.,[8] which included 9 RCTs conducted in individuals with impaired glucose tolerance, only used insulin sensitivity as an endpoint, and therefore is outside the scope of this summary.

Because no new RCTs have been published since 2011, the committee has based its conclusion on the description in the Australian evidence report.[2] In conclusion, 150 minutes per week of physical activity lowers the risk of developing diabetes in subjects with impaired glucose tolerance. As there is only one RCT in which an independent effect of physical activity was studied, while a few subgroup analyses in other RCTs showed effects in the same direction, the level of evidence is weak.

2.2 Cardiometabolic risk factors

The Australian evidence report on adults does not describe any effects of physical activity on cardiometabolic risk factors, as it focused predominantly on prospective cohort studies with disease outcomes.[2]

The Australian evidence report on children does not describe the evidence for blood pressure, LDL cholesterol, blood glucose, and insulin sensitivity separately, but combines data on various cardiometabolic health indicators. In the report it is concluded that the accumulation of evidence from 23 studies that report significant changes in cardiometabolic risk show that, in order for benefits to be obtained, physical activity should be of the endurance type, practised at moderate-to-vigorous intensity, occur on a minimum of three days per week and last a minimum of 40-70 minutes duration on each occasion. Consistent with previous reviews, there was no evidence that has considered the impact of the dose of physical activity in terms of frequency, duration, or intensity, or age and sex effects when considering cardiometabolic risk. The report does not provide a conclusion on the effect of weight-bearing exercises on cardiometabolic risk.[1] Because the Australian report does not provide a detailed description of the effects of physical activity on specific cardiometabolic risk factors, the committee describes below the conclusions of the American evidence report[3] and reviews publications released since 2008 (the year of publication of the American evidence report), or, if no conclusion is available, earlier publications too. The committee did not find any meta-analyses or systematic reviews of RCTs on the effect of physical activity on blood glucose levels. The effect on body weight and body mass index is reported in Chapter 2.4.

2.2.1 Systolic blood pressure

The American evidence report[3] concludes that both endurance and progressive resistance training[a] yield important reductions in systolic blood pressure in adult humans, although the evidence for endurance training is more convincing. Traditional endurance training programmes of 40 minutes of moderate to high-intensity exercise training 3 to 5 times per week and involving more than 800 MET-minutes of endurance training per week appear to have reproducible effects on blood pressure reduction.

[a] A method of increasing the strength of a muscle by gradually increasing the resistance against which the muscle works, such as by using graduated weights.

Since 2008, 11 meta-analyses and two systematic reviews of the effect of physical activity on systolic blood pressure in adults[9-20] have been published and one meta-analysis and three systematic reviews in children.[21-24] The findings in Cornelissen et al.,[11] Murtagh et al.,[13] Batacan et al.,[17] Ramos et al.[18] and Inder et al.[19] in adults, and Cesa et al.,[21] Dobbins et al.,[24] Kelley et al.[22] and Janssen et al.[23] in children and adolescents are described below (Table 2). The committee excluded references,10,15 and 16, as these meta-analyses were updated by Cornelissen in 2013;[11] Carlson et al.[20] as it summarised 10 RCTs that were also summarised by Inder et al.[19] in combination with one other RCT; Cornelissen et al.[9] as it focused on differences between day and night time blood pressure; Huang et al.[25] as it summarised RCTs published up to 2001; Kelley and Kelley[14] as they summarised meta-analyses which had been published before 2008; and Pattyn et al.[12] as they studied patients with metabolic syndrome and combined CTs and RCTs.
Twelve studies were summarised by both Cornelissen et al. and Murtagh et al.[11,13] In the studies summarised by Cornelissen et al. the control groups were described as sedentary and by Murtagh et al. as no-exercise. The meta-analyses did not include a description of whether the intervention also resulted in a change in total physical activity in the intervention and/or control group.

Endurance training and systolic blood pressure in adults

Summary of evidence for the effect of endurance training on systolic blood pressure

Aspect	Explanation
Selected studies	2 meta-analyses of 59[11] and 16 RCTs[13]
Heterogeneity	Yes, in one meta-analysis, explained by differences in baseline blood pressure and training intensity
Strength of the effect/association	-3.5 (-4.6 to -2.3) mmHg overall for moderate and high intensity physical activity of at least 30 minutes per session -0.8 (-2.2 to +0.7) mmHg in normotensives -2.1 (-3.3 to -0.8) mmHg in prehypertensives -8.3 (-10.7 to -6) mmHg in hypertensives
Study population	Normo, pre- and hypertensive adults

Conclusion 1: Moderate- to high-intensity endurance training (2 to 7 times per week, 20 to 60 minutes per session, for 1 to 12 months) versus no exercise, lowers systolic blood pressure by about 3 mmHg in adults, especially in people with (pre-) hypertension.
Level of evidence: Strong.

Conclusion 2: An effect of light-intensity endurance and flexibility training on systolic blood pressure in healthy adults is unlikely.

Explanation

Cornelissen et al.[11] summarised the effect of endurance training on blood pressure in adults (Table 2) and found that this type of exercise reduced blood pressure. There was moderate heterogeneity in the analysis of endurance training. There was no forest plot available for visual inspection. In sensitivity analyses Cornelissen et al.[11] found the largest effects in persons with hypertension in comparison to prehypertensives and normotensives. Exercise frequency did not affect blood pressure lowering, whereas session duration of 30 to 45 minutes tended to show larger reductions in blood pressure (not significant). The analysis of the effect of session duration was limited by the small number of subjects in the group with a session duration of less than 30 minutes (N=9). A weekly exercise time of less than 210 minutes was associated with a larger blood pressure lowering. The authors explained this finding by the fact that programmes of more than 120 minutes are usually performed at lower intensity, whereas blood pressure lowering was only found at moderate- and high-intensity endurance training, but not at light-intensity endurance training.

Murtagh et al.[13] focused specifically on the effect of walking in comparison to no exercise on blood pressure. The duration ranged from 20 to 60 minutes walking per session on two to seven days per week for 1 to 12 months; most studies included a moderate-intensity walking group. Murtagh et al.[13] found a similar blood pressure lowering as Cornelissen et al.,[11] without significant heterogeneity. They found no effect of intervention duration (months) and did not look into the effect of session duration.[11,13]

In two other systematic reviews, the effect of light-intensity physical activity and high-intensity interval training were summarised narratively. Batacan et al.[17] systematically reviewed the effect of light-intensity endurance and flexibility training on blood pressure. Three of nine studies reported significant decreases in systolic blood pressure. These were confined to physically inactive populations with a medical condition. The authors found no effect of light-intensity endurance and flexibility training on systolic blood pressure in healthy adults, which is in line with the findings by Cornelissen et al.[11] described above.

Ramos et al.[18] systematically reviewed the effect of high-intensity interval training on blood pressure in comparison to moderate-intensity continuous training.[a] The two types of training were isocaloric in six of the seven RCTs. Out of seven RCTs incorporating 182 participants,[b] two reported that high-intensity interval training decreased systolic blood pressure in comparison to moderate-intensity continuous training, whereas the other five found no significant difference in effect. As four of the seven studies were carried out by the same research group, results of this meta-analysis should be interpreted with caution.

Thus, the findings above are in concordance with the conclusions in the American evidence report,[3] which states that traditional endurance training programmes of 40 minutes of moderate- to high-intensity exercise training 3 to 5 times per week and involving more than 800 MET-minutes of endurance training per week appear to have reproducible effects on blood pressure reduction. The meta-analyses described above provide evidence that moderate to high-intensity physical activity at a wider range of session frequencies and durations lowers systolic blood pressure.

In conclusion, moderate- to high-intensity endurance training, such as brisk walking (2 to 7 times per week, 20 to 60 minutes per session, for 1 to 12 months) versus no exercise lowers systolic blood pressure by about 3 mmHg in adults, especially in people with (pre-) hypertension. The level of evidence for this effect is strong. An effect of light-intensity endurance and flexibility training on systolic blood pressure in healthy adults is unlikely.

Dynamic resistance training and systolic blood pressure in adults

Summary of evidence for the effect of dynamic resistance training on systolic blood pressure in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 13 RCTs[11]
Heterogeneity	No
Strength of the effect/association	-1.8 (-3.7 to -0.01) mmHg
Study population	Normo, pre- and hypertensive adults

Conclusion 3: Dynamic resistance training versus no training lowers systolic blood pressure in adults.
Level of evidence: Weak.

Explanation

Cornelissen et al.[11] summarised the effect of dynamic resistance training[c] on blood pressure in adults (Table 2). They found that dynamic resistance training reduced blood pressure. However, the upper limit of the

[a] Any training without rest intervals.
[b] Postmenopausal women, patients with cardiovascular diseases, obesity, hypertension, and metabolic syndrome.
[c] Involves concentric and/or eccentric contractions of muscles while both the length and the tension of the muscles change.

confidence interval for the effect estimate of dynamic resistance training was close to zero, despite the large number of studies. There was little heterogeneity. The findings are in concordance with the conclusion in the American evidence report[3] which describes progressive resistance training yielding important reductions in systolic blood pressure in adult humans, although the evidence for endurance training is more convincing. In conclusion, dynamic resistance training versus no training lowers systolic blood pressure in adults. As the upper limit of the confidence interval is close to zero despite the large number of studies, the level of evidence is weak.

Isometric resistance training and systolic blood pressure in adults

Summary of evidence for the effect of isometric resistance training on systolic blood pressure in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 11 RCTs[19]
Heterogeneity	Yes in size of effect, partly explained
Strength of the effect/association	-5.2 (-6.0 to -4.3) mmHg
Study population	Normo, pre- and hypertensive adults

Conclusion 4: Isometric resistance training (10-40% maximum voluntary contraction 3 to 5 days per week, 4 x 2 minutes isometric contractions per session, for 1 to 2.5 months) versus no training lowers systolic blood pressure in adults.
Level of evidence: Strong.

Explanation
Inder et al.[19, a] summarised the effect of isometric resistance training[b] on blood pressure in adults (Table 2) and found that isometric resistance training reduced blood pressure by 5 mmHg. There was considerable heterogeneity in the size of the effect. Subgroup analyses partly explained the heterogeneity: they showed that the effect was larger when training programmes lasted more than 8 weeks, were unilateral instead of bilateral, and were performed with arms instead of lower limbs.
In conclusion, isometric resistance training (10-40% maximum voluntary contraction 3 to 5 days per week, 4 x 2 minutes isometric contractions per session, for 1 to 2.5 months) versus no training lowers systolic blood pressure in adults. In view of the heterogeneity in the size of the effect, the committee did not quantify it. In view of the consistent findings on the direction of the effect, the level of evidence is strong.

[a] As the four RCTs on isometric resistance training in the meta-analysis by Cornelissen et al.[11] were also described in the meta-analysis by Inder et al.,[19] the committee has based its conclusions on the latter.
[b] Involves sustained contraction against an immovable load or resistance with no or minimal change in length of the involved muscle group.

Combination of endurance and dynamic resistance training and systolic blood pressure in adults

Summary of evidence for the effect of the combination of endurance and dynamic resistance training on systolic blood pressure in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 4 RCTs[11]
Heterogeneity	No
Strength of the effect/association	-1.4 (-4.2 to + 1.5) mmHg
Study population	Normo, pre- and hypertensive adults

Conclusion 5: There is too little research to draw a conclusion on the effect of the combination of endurance and dynamic resistance training versus no training on systolic blood pressure in adults.

Explanation

Cornelissen et al.[11] also summarised the effect of the combination of endurance and dynamic resistance training on blood pressure in adults (Table 2). They found no significant effect. However, the number of studies was relatively small (N=4).

In conclusion, there is too little research to draw a conclusion on the effect of the combination of endurance and dynamic resistance training versus no training on systolic blood pressure.

Physical activity and systolic blood pressure in children and adolescents

Summary of evidence for the effect of physical activity on systolic blood pressure in children and adolescents

Aspect	Explanation
Selected studies	3 meta-analyses of 3,[21] 6[26] and 12[22] RCTs
Heterogeneity	Yes, in both the direction and size of the effect, in one meta-analysis unexplained
Strength of the effect/association	Varies from -1.3 (-2.4 to -0.02) mmHg to +0,1 (-0.1 to +0.3) mmHg
Study population	Normotensive children and adolescents 6 - 20 years

Conclusion 6: An effect of moderate- to high-intensity physical activity (2 to 5 times per week, 45 to 245 mins per session for 2 months to 4 years) on systolic blood pressure in school children and adolescents is unlikely.

Explanation

There are three meta-analyses[21,22,26] and two systematic reviews[23,24] into the effect of physical activity on systolic blood pressure in school children. As Dobbins et al. focused on the effect of school-based public health interventions, and not exclusively on physical activity, it has not been included in this review.[24]

Cesa et al.[21] showed that long-term (at least 9 months) physical activity of at least 150 minutes per week improved blood pressure in 6-12 year old children in comparison to less intensive or no physical activity (Table 2). The number of studies was limited (N=3) and the interventions consisted of additional classroom sessions, additional physical education lessons or additional sport exercise. The upper level of the confidence interval was close to zero. There was no indication of heterogeneity, which could partly be explained by the small number of studies (N=3).

Guerra et al.[26] summarised two of the three RCTs in the meta-analysis by Cesa et al.[21] in combination with four other RCTs on school-based interventions. The interventions ranged from circuits, dance and games to recreational athletics and endurance training. In one of the four RCTs the difference in the weekly amount of physical activity between intervention and control group was 120 minutes, whereas the other three did not provide information on the difference. Guerra et al. found no indications of an effect of school-based exercise programmes on systolic blood pressure (+0.1 mmHg; -0.1 to +0.3 mmHg). There was considerable heterogeneity, which was not explained by study quality. The authors did not provide a forest plot and ascribed the heterogeneity to large variations in the nature and objective of study protocols, age ranges and follow-up times between studies. Although RCTs with nutritional interventions were excluded, three RCTs combined the intervention with health education and in one RCT family support was included. From the text, it is unclear whether the control group also received these co-interventions. If not, a larger effect is to be expected.[26]

Kelley et al.[22] summarised the effect of exercise in 12 RCTs in children and adolescents under 21 years. The interventions ranged from organised games, gymnastics and other exercises to fitness, endurance and/or resistance training. They found that short-term training (2 to 9 months) did not have a significant effect on blood pressure (-1; -2 to 0 mmHg) compared to the control. The control treatment consisted of standard physical education, no intervention, or was not specified. The authors did not provide a heterogeneity estimate. Visual inspection of the forest plot indicated that there was both heterogeneity in the size and the direction of the effect estimate. However, subgroup analyses only found an effect on body mass index. There was no difference in the effect of endurance versus resistance training.

Janssen et al.[23] narratively summarised nine clinical trials in children and adolescents between 5-17 years. However, only four of the trials were randomised, and two of the RCTs comprised five or six participants respectively. Each of the four RCTs found a non-significant blood pressure lowering effect of exercise (endurance or resistance).

In conclusion, Cesa et al.[21] found a small blood-pressure-lowering effect of at least 150 minutes of physical activity per week based on 3 RCTs, which was not confirmed by Guerra et al.[26] or Kelley et al.,[22] who summarised larger numbers of RCTs. In the meta-analyses by Guerra et al.[26] and Kelley et al.[22] there was considerable heterogeneity, which was not or only partially explained. As all effect estimates were close to zero, the committee concludes that an effect of moderate- to high-intensity physical activity (two to five times per week and 45 to 245 mins per session for 2 months to four years) on systolic blood pressure in school children and adolescents is unlikely.

Table 2. RCTs into the effect of physical activity, endurance training, and resistance training on blood pressure

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in blood pressure (mmHg) compared to control (95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis						
Cornelissen 2013[11]	59[b]; 3,839 adults	1-12	Dynamic endurance at 35-95% VO_2max on 2-7 days/wk, 20-60'/ session	Sedentary	-3.5 (-4.6 to -2.3)	48
	29[b] in normotensives				-0.8 (-2.2 to +0.7)	
	50[b] in prehypertensives				-2.1 (-3.3 to -0.8)	
	26[b] in hypertensives				-8.3 (-10.7 to -6)	
	13[b]; 391	1.5-12	Dynamic resistance 30-100% of 1-RM[c], 2-3 times/wk	Sedentary	-1.8 (-3.7 to -0.01)	4
	4[b]; 172 adults	2-6	Combination of dynamic endurance and dynamic resistance	Sedentary	-1.4 (-4.2 to + 1.5)	24
Murtagh 2015[13]	16; 816 adults	1- 12	Walking, predominantly at moderate intensity; 2-7 days/wk; 20-60'/session	No exercise sedentary	-3.6 (-5.1 to -1.9)	39
Inder 2016[19]	11; 278 adults	1-2.5	Isometric resistance 10-40% maximum voluntary contraction; 3-5 days/wk; 4 x 2' isometric contractions/ session	No exercise; sedentary	-5.2 (-6.0 to -4.3)	71
Kelley 2003[22]	12; 1,266 children and adolescents < 21 years	2-9	Physical activity	Standard physical education, no intervention, or control	-1 (-2 to 0)	n.r.[d]
Guerra 2013[26]	6; 1,549 children and adolescents 6-16 years	0.5[e]-48	Endurance and/or resistance training moderate-intensity; 2-5 times/wk; 45-245'/session	Sedentary behaviour	+0.1 (-0.1 to +0.3)	70
Cesa 2014[21]	3; 1,037 children 6-12 years	9 - 24	Physical activity of at least 150'/wk moderate- to high-intensity	Less intensive or standard physical education classes	-1.3 (-2.4 to -0.02)	0

[a] Confidence interval.
[b] Number of study groups.
[c] 1-repetition maximum. The maximum amount of force that can be generated in one maximum contraction.
[d] Not reported.
[e] Data of 6-month follow-up study.

2.2.2 LDL cholesterol

The American evidence report concludes that some inconsistent evidence suggests that LDL-cholesterol levels may respond favourably to exercise training under some conditions, i.e. when it is at a volume threshold of 600 to 800 MET-min per week.[3,27]

Endurance training and LDL-cholesterol levels in adults

Summary of evidence for the effect of endurance training on LDL-cholesterol levels in adults

Aspect	Explanation
Selected studies	4 meta-analyses of 6,[28] 14[13] and 21[29] RCTs or 59 comparisons[30]
Heterogeneity	No
Strength of the effect/association	Ranged from -0.05 (-0.17 to +0.07) to +0.01 (-0.35 to +0.36) mmol/l
Study population	Adults 50+; sedentary but otherwise healthy adults

Conclusion 1: An effect of moderate-intensity endurance training (2 to 5 times per week, 15 to 90 minutes per session, for at least 2 months) versus control, on LDL-cholesterol levels in healthy adults is unlikely.

Explanation

The committee found five meta-analyses[13,28-31,a] on the effect of endurance training on LDL-cholesterol levels in adults (Table 3). The meta-analysis by Tran et al.[31] was excluded because it also comprised studies with a (non-randomised) before-and-after design. Lin et al.[30] had 1 RCT which overlapped with Hespanhol et al.,[28] 6 with Kelley et al.,[29] and 8 with Murtagh et al.[13] The overlap between Kelley et al.[29] and Murtagh et al.[13] was 2 RCTs, whereas the two did not show any overlap with Hespanhol et al.[28]

Lin et al. summarised the effect of predominantly endurance training on LDL-cholesterol levels in adults. They found no significant effect (-0.10 mmol/l); the upper level of the confidence interval was +0.01 mmol/l. There was no information on heterogeneity or a forest plot. In subgroup analyses, there was no effect of exercise intensity (moderate vs. vigorous), age, sex, lifestyle, obesity or intervention duration on the outcome. However, endurance training reduced LDL cholesterol by -0.30 (-0.51 to -0.08) mmol/l in patients with type 2 diabetes, hypertension, hyperlipidemia, and/or metabolic syndrome in comparison to the control group, whereas there was no significant change in healthy subjects (-0.08; -0.20 to +0.04 mmol/l).[30]

Kelley et al.[29] summarised the effect of endurance training in adults aged 50 years and older. In the overall analysis they found that exercise at a predominantly moderate intensity lowered LDL cholesterol by 0.10 mmol/l in adults aged 50 and over. However, after adjustment for publication bias, the effect was smaller and no longer significant. The study quality ranged from 1 to 4 (median 2) on a five point scale, with higher numbers representing greater study quality. The authors did not provide information on heterogeneity.

a The meta-analysis by Kuhle et al.[32] of four RCTs in older adults has not been included as three RCTs combined endurance training with resistance training.

Meta-analyses on the effects of walking[13] and/or running[28] at moderate intensity in sedentary but otherwise healthy adults confirmed the findings of Kelley et al.[29] Murtagh et al.[13] emphasized that most RCTs did not provide sufficient information to make firm judgements about bias.

In a narrative review Batacan et al.[17] systematically described the effect of light-intensity endurance and flexibility training on LDL cholesterol. None of the six studies found an effect on LDL cholesterol. However, Batacan et al. did not provide any numbers or a quantitative estimate, which hampers the interpretation of this finding.[17]

The five meta-analyses did not include an account of whether the intervention also resulted in a change in total physical activity in the intervention and/or control group.

Recent evidence does not confirm a potential benefit of physical activity on LDL-cholesterol levels in healthy adults as described in the American evidence report, although there might be a beneficial effect in specific patient groups.[3]

In conclusion, an effect of moderate-intensity endurance training (2 to 5 times per week, 15 to 90 minutes per session, for at least 2 months) vs. a no exercise control group on LDL cholesterol in healthy adults is unlikely.

Progressive resistance training and LDL-cholesterol levels in adults

Summary of evidence for the effect of progressive resistance training on LDL-cholesterol levels in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 23 RCTs[33]
Heterogeneity	Yes, in both the direction and size of the effect, unexplained
Strength of the effect/association	-0.15 (-0.28 to -0.02) mmol/l
Study population	Normo- and hyperlipidemic adults, obese, diabetics, history of CVD

Conclusion 2: The evidence for an effect of progressive resistance training versus control, on LDL-cholesterol levels in adults is ambiguous.

Explanation

The committee found one meta-analysis into the effects of progressive resistance training on LDL cholesterol (Table 3).[33] Kelley et al. found that progressive resistance training lowered LDL cholesterol by 0.15 mmol/l. Decreases were larger in studies conducted in the US, with higher intensity training programmes and greater compliance. However, heterogeneity was considerable (85%) and pertained both to the direction and the size of the effect estimate. Additional sensitivity analyses did not explain the heterogeneity, according to the authors.

In conclusion, evidence for the effect of progressive resistance training versus control on LDL-cholesterol levels is ambiguous, in view of considerable heterogeneity in the direction and size of the effect estimate.

Physical activity and LDL-cholesterol levels in children and adolescents

Summary of evidence for the effect of physical activity on LDL-cholesterol levels in children and adolescents

Aspect	Explanation
Selected studies	1 meta-analysis of 8 RCTs[34] and a systematic review of 6 RCTs[23]
Heterogeneity	Yes, in both the direction and size of the effect, unexplained
Strength of the effect/association	+0.03 (-0.11 to +0.17) mmol/l
Study population	Children aged 5-19 years

Conclusion 3: An effect of physical activity on LDL-cholesterol levels in children and adolescents is unlikely.

Explanation

The committee found a meta-analysis[34] and a systematic review[23] on the effect of physical activity on LDL-cholesterol levels in children. Kelley and Kelley[34] did not find any indications of an effect of endurance training on levels of LDL cholesterol in children aged 5 to 19 years (Table 3). Visual inspection of the forest plot suggested heterogeneity in both the size and the direction of the effect. The authors indicated that compliance, defined as the percentage of exercise sessions attended, ranged from 80 to 100%.

Janssen and LeBlanc[23] narratively reviewed the effect of endurance

Table 3. RCTs into the effect of physical activity, endurance training, and resistance training on LDL-cholesterol levels

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in LDL cholesterol (mmol/l) compared to control (95%-C.I.[a])	Hetero-geneity (I^2 %)
Meta-analysis						
Kelley 2005[29]	21; 814 adults 50+	2-12	Endurance training at 60-88% MHR[b] or 40-80% VO_2max or 54-80% MHRR[c], 2-5 d/wk, 17-90' per session	Control	-0.03 (-0,12 to +0.05)[d]	n.r.[e]
Kelley 2009[33]	23; adults (number n.r.)	2-20	Progressive resistance training 50-87% of 1-RM[f], 2-3 d/wk, 24-60'/session	Control	-0.15 (-0.28 to -0.02)	85
Hespanhol Junior 2015[28]	6; 535 adults	5 (average)	Running 60-90% MHR, 3,7 d/wk, 2,3 h/wk (average)	Physically inactive	Men: -0.01 (-0.12 to +0.10) Women: +0.01 (-0.35 to +0.36)	0 0
Lin 2015[30]	59; 3,026 adults	n.r.	Mostly endurance exercise	Control	-0.10 (-0.21 to +0.01)	n.r.
Murtagh 2015[13]	14; 664 adults	1- 12	Walking, 56-86% MHR[b], 3-7 d/wk, 20-60'/session	No exercise control	-0.05 (-0.17 to +0.07)	0
Kelley 2007[34]	8 ; children 5-19 years (number n.r.)	≥ 1	Endurance training	Control	+0.03 (-0.11 to +0.17)	n.r.

[a] Confidence interval.
[b] Maximal heart rate.
[c] Heart rate reserve.
[d] After adjustment for bias.
[e] Not reported.
[f] 1-repetition maximum.

training (4 RCTs), resistance training (1 RCT) and a combination (1 RCT) on LDL cholesterol in children aged 5-17 years. For the most part, these studies were limited to children with high cholesterol or obesity. The effect on LDL cholesterol varied from -0.37 to +0.64 mmol/l across RCTs. The authors emphasized that some of the studies were likely to be underpowered.

The two publications did not provide information on whether the intervention resulted in changes in total physical activity in the intervention and/or control group.

In conclusion, an effect of physical activity on LDL-cholesterol levels in children is unlikely.

2.2.3 Insulin sensitivity

The American evidence report[3] states that RCTs show that physical activity improves insulin sensitivity in obese youth. In addition, acute bouts of physical activity improve insulin sensitivity and increase glucose uptake by skeletal muscle for up to 12 hours, and chronic exercise training results in prolonged improvements in insulin sensitivity. Although body composition has been strongly associated with insulin sensitivity, exercise-induced changes in insulin sensitivity can occur from physical activity, independent of changes in weight or body composition.

The committee found three meta-analyses[30,35,36] and two systematic reviews[17,18] on the effect of physical activity on insulin sensitivity[*] in adults and one meta-analysis[37] and two systematic reviews in children (Table 4).[23,38]

Lin et al.[30] summarised the effect of physical activity on homeostatic model assessment (HOMA) insulin sensitivity. The physical activity ranged from endurance training to resistance training or a combination of both, but was endurance training in most studies.

Mann et al.[36] summarised the effect of endurance training (16 RCTs), resistance training (10 RCTs) and both combined (8 RCTs) on insulin sensitivity in healthy individuals and type 2 diabetics. In the RCTs insulin sensitivity was measured as fasting blood or plasma glucose, glycated hemoglobin (HbA1c), homeostatic model assessment (HOMA), insulin-mediated glucose disposal, oral glucose tolerance test, or 2-hour glucose load test. Because of the different outcome measures, the authors first calculated Cohen's d for each study and then summarised the effect estimates. The overlap between the two meta-analyses is two RCTs.

Jelleyman et al.[35] compared the effect of high-intensity interval training with a control group and with moderate-intensity continuous exercise in healthy adults.

The meta-analyses did not include a description of whether the intervention also resulted in a change in total physical activity in the intervention and/or control group.

* The term insulin sensitivity also covers insulin resistance.

Endurance training and insulin sensitivity in adults

Summary of evidence for the effect of endurance training on insulin sensitivity in adults

Aspect	Explanation
Selected studies	2 meta-analyses of 14 RCTs[30] and of 14 comparisons[30]
Heterogeneity	Yes, in the size of the effect, unexplained.
Strength of the effect/association	Cohen's d: +1.07 (+0.7 to +1.44) and +0.3 (+0.11 to +0.49) (beneficial)
Study population	Healthy and type 2 diabetics

Conclusion 1: Moderate and high-intensity endurance training (3 to 6 times per week, 24 to 90 minutes per session or high-intensity interval training for 0.5 to 6 months) versus control improves insulin sensitivity.
Level of evidence: Strong.

Explanation

In the meta-analysis of Lin et al.[30] interventions ranged from endurance training to resistance training or a combination of both, with endurance training occurring the most frequently (Table 4). The authors found that this improved insulin sensitivity significantly. There was considerable heterogeneity, but no forest plot was provided. In subgroup analyses, the authors found a somewhat stronger improvement for vigorous-intensity exercise (+0.47; +0.12 to +087) than moderate-intensity exercise (+0.30; -0.06 to +0.66), but this was not significant.

Mann et al.[36] concluded that endurance training improved insulin sensitivity at a variety of exercise intensities. Visual inspection of the scatter plot suggests heterogeneity in the size of the effect, as all effect estimates were larger than zero. The heterogeneity was not examined further, but is possibly related to the wide range of exercise programmes and outcome measures. The authors stated that studies in healthy and/or sedentary individuals showed significant improvements in insulin sensitivity by interval training (high-intensity exercise separated by rest intervals) as well as continuous endurance training.

A systematic review comparing high-intensity interval training with moderate-intensity continuous training in obese individuals and patients with type 2 diabetes or metabolic syndrome showed no consistent effects: one RCT found no change in insulin sensitivity on either training protocol, one RCT found a similar decrease between protocols and one a decrease of greater magnitude on the high-intensity interval training protocol.[18]

Another systematic review concluded that light-intensity activity had no effect on glucose in healthy adults who were either physically active or inactive. One of 16 studies reported a significant decrease in glucose. However, the fact that the effects were not summarised quantitatively, limits the interpretation of this finding.[17]

The findings are in line with the conclusion in the American evidence report described above.[3]

In conclusion, moderate- and high-intensity endurance training (3 to 6 times per week, 24 to 90 minutes per session or high-intensity interval training for 0.5 to 6 months) versus control improves insulin sensitivity.

Because of the unexplained heterogeneity in the size of the effect, the effect cannot be quantified. In view of the consistent findings in the direction of the effect, the level of evidence is strong.

Resistance training and insulin sensitivity in adults

Summary of evidence for the effect of resistance training on insulin sensitivity in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 10 RCTs[36]
Heterogeneity	Yes, in the size of the effect, unexplained.
Strength of the effect/association	Cohen's d: +0.84 (+0.26 to +1.42) (beneficial)
Study population	Healthy and type 2 diabetics

Conclusion 2: Resistance training (50% of 1-RM or more, 2 to 3 times per week for 2 to 6 months) versus control improves insulin sensitivity.
Level of evidence: Strong.

Explanation

Mann et al.[36] found that resistance training at, or above, 50% of 1-repetition maximum[a] improved insulin sensitivity (Table 4). In one study resistance training at 40-45% 1-repetition maximum was studied. This study did not find any effect on insulin sensitivity at a low level of intensity, but did find effects at higher intensity levels.

[a] 1-repetition maximum is the maximum amount of force that can be generated in one maximum contraction.

Visual inspection of the scatter plot suggests heterogeneity in the size of the effect of resistance training; all effect estimates were larger than zero. The heterogeneity was not examined further. The findings are in line with the conclusion in the American evidence report.[3]
In conclusion, resistance training of 50% 1-repetition maximum or more, two to three times per week improves insulin sensitivity. Because of the unexplained heterogeneity in the size of the effect, the effect cannot be quantified. In view of the consistent findings in the direction of the effect, the level of evidence is strong.

Endurance training and resistance training combined and insulin sensitivity in adults

Summary of evidence for the effect of endurance training and resistance training combined on insulin sensitivity in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 8 RCTs[36]
Heterogeneity	Yes in the size of the effect, unexplained.
Strength of the effect/association	Cohen's d: +0.86 (+0.42 to +1.30) (beneficial)
Study population	Healthy and type 2 diabetics

Conclusion 3: The combination of moderate- or high-intensity endurance training (3 to 6 times per week, 24 to 90 minutes per session or high-intensity interval training) and resistance training (50% 1-RM or more, 2 to 3 times per week, for 3-12 months) versus the control group improves insulin sensitivity.
Level of evidence: Strong.

Explanation

Mann et al.[36] concluded that the combination of endurance training and resistance training improved insulin sensitivity in both healthy subjects and type 2 diabetics (Table 4). Three studies comparing three types of exercise regimens found a larger improvement in the group that combined endurance and resistance training than those in the endurance training and the resistance training group. However the combined group received the full endurance training and resistance training programmes, thus increasing the total volume of exercise. The studies differed in the ways exercise sessions were structured; for instance, in some cases endurance training and resistance training were combined in one session, whereas in others they were given in different sessions; a similar problem is evident in relation to the order of the different exercises when combined.

Visual inspection of the scatter plot suggests heterogeneity in the size of the effect of resistance training and the combination; all effect estimates were larger than zero. The heterogeneity was not examined further.

The findings are in line with the conclusion in the American evidence report.[3]

In conclusion, the combination of moderate or high-intensity endurance training (3 to 6 times per week, 24 to 90 minutes per session or high-intensity interval training) and resistance training (50% 1-RM or more, 2 to 3 times per week for 3-12 months) versus control, improves insulin sensitivity. Because of unexplained heterogeneity in the size of the effect, the effect cannot be quantified. In view of the consistent findings in the direction of the effect, the level of evidence is strong.

High-intensity interval training and insulin sensitivity in healthy adults

Summary of evidence for the effect of high-intensity interval training on insulin sensitivity in healthy adults

Aspect	Explanation
Selected studies	1 meta-analysis of 5 RCTs and 6 RCTs[36]
Heterogeneity	Yes, in size and direction of effect, unexplained.
Strength of the effect/association	Healthy adults +0.44 (-0.34 to +1.22) (beneficial) in comparison to control +0.40 (-0.08 to +0.88) (beneficial) in comparison to moderate-intensity continuous training Adults at increased risk of cardiovascular disease +0.49 (+0.12 to +0.87) in comparison to control +0.35 (+0.02 to +0.68) in comparison to moderate-intensity continuous training
Study population	Healthy adults, adults at increased risk of cardiovascular disease

Conclusion 4: The evidence for an effect of high-intensity interval training on insulin sensitivity in healthy adults in comparison to a control treatment is ambiguous.

Conclusion 5: There is too little research to draw a conclusion on the effect of high-intensity interval training on insulin sensitivity in healthy adults in comparison to moderate-intensity continuous training.

Conclusion 6: High-intensity interval training improves insulin sensitivity in comparison to moderate-intensity continuous training

in adults at increased risk of, or with, cardiovascular diseases. Level of evidence: Weak.

Explanation

Jelleyman et al.[35] summarised five RCTs on the effect of high-intensity training (HIIT) on insulin sensitivity in comparison to a control and six RCTs in comparison to moderate-intensity continuous training[a] in healthy adults (Table 4). They found no significant differences in effects on insulin sensitivity. There was considerable heterogeneity, both in the size and the direction of the effect in the two analyses.

In analyses which also included subjects with obesity, metabolic syndrome, type 2 diabetes or cardiovascular diseases (N > 350), however, differences were observed that reached significance (+0.49; +0.12 to +0.87 HIIT versus control and +0.35; +0.02 to +0.68 HIIT versus continuous training).

However, the total volume of exercise was only similar between the high-intensity interval training group and the moderate-intensity continuous training group in a proportion of the RCTs. For this reason, the findings of this meta-analysis need to be treated with caution.

In sensitivity analyses of 29 controlled and uncontrolled studies in healthy subjects and patients, heterogeneity was explained to some extent by the method used for assessing insulin sensitivity and the time between the final exercise session and post-test blood sample. There was, however, no clear explanation for the heterogeneity observed in the subgroup analyses.

In conclusion, in view of the unexplained heterogeneity, the evidence for an effect of high-intensity interval training on insulin sensitivity in healthy adults is ambiguous in comparison to a control treatment.

In the comparison between high-intensity interval training and moderate-intensity continuous training, there was heterogeneity in the size of the effect, which means that there is little certainty about the size of the effect. As the estimate is non-significant and far from zero and the number of subjects was small (N=126), the committee concludes that there is too little research to draw a conclusion on the effect of high-intensity interval training in comparison to moderate-intensity continuous training on insulin sensitivity in healthy adults.

In adults at increased risk of, or with, cardiovascular diseases, high-intensity interval training improves insulin sensitivity in comparison to continuous training. As the total volume of exercise was only similar in the high-intensity interval training group and the moderate-intensity continuous training group in a proportion of the RCTs, the level of evidence is weak.

[a] Continous training involves activity without rest intervals.

Endurance training and resistance training combined and insulin sensitivity in children and adolescents

Summary of evidence for the effect of endurance training and resistance training combined on insulin sensitivity in children and adolescents

Aspect	Explanation
Selected studies	1 meta-analysis of 12 RCTs[37]
Heterogeneity	Yes, in the size of the effect, unexplained.
Strength of the effect/association	Hedges' g: +0.86 (+0.42 to +1.30) (beneficial)
Study population	Healthy, normal weight, overweight and obese children 9-18 years

Conclusion 7: The combination of endurance training and resistance training (2 to 4 times per week, 40 to 90 minutes per session, for 2 to 6 months) versus control, improves insulin sensitivity in children and adolescents.
Level of evidence: Strong.

Explanation
Fedewa et al.[37] summarised 12 RCTs on the effect of physical activity on insulin sensitivity in children (2 RCTs) and adolescents (10 RCTs) (Table 4). The 12 RCTs include the two that were narratively summarised by Janssen and LeBlanc[23] and two of the three that were narratively summarised by Guinhouya et al.[38] The committee, therefore, discusses the findings by Fedewa et al.[37] here.
Insulin sensitivity was calculated in each RCT from fasting levels of insulin and glucose by using the homeostasis model assessment (HOMA) technique. Physical activity improved insulin sensitivity by 0.31 (Hedges' g). There was considerable heterogeneity. In sensitivity analyses three outliers were removed from the analysis, resulting in a larger effect estimate of 0.38 (0.19-0.57). The authors found no differences in effect on insulin sensitivity between endurance and resistance training protocols or between short-term and long-term interventions. The findings are in line with the conclusion in the American evidence report.[3]
In conclusion, the combination of endurance training and resistance training (2 to 4 times per week, 40 to 90 minutes per session for 2 to 6 months) versus control, improves insulin sensitivity in children and adolescents. Because of unexplained heterogeneity in the size of the effect, the committee did not quantify the effect. In view of the consistent findings in the direction of the effect, the level of evidence is strong.

2.3 Cardiorespiratory fitness

2.3.1 Cardiorespiratory fitness in children

Conclusion: A combination of moderate- and vigorous-intensity physical activity improves cardiorespiratory fitness in children and adolescents.
Level of evidence: Strong.

Table 4. RCTs into the effect of endurance training and resistance training on insulin sensitivity

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in insulin sensitivity compared to control (95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis						
Mann 2014[36]	16; n.r.[b] adults	0.5-6	Endurance training at 50-75 VO_2max; 3-6 times/wk; 24'-90'/session or high-intensity interval training	Control	+1.07 (+0.7 to +1.44)[c]	n.r.
	10; n.r.	2-6	Resistance training 45-85% 1-RM,[d] 2-3 times/wk		+0.84 (+0.26 to +1.42)[c]	n.r.
	8; n.r.	3-12	Combination		+0.86 (+0.42 to +1.30)[c]	n.r.
Fedewa 2015[37]	12; 762 children and adolescents 6-19 years	2-6 and in 1 RCT 12	Endurance training, resistance training or combination; 40-90' /session; 2-4 times/wk	Control	+0.31 (+0.06 to +0.56)[e]	58
Lin 2015[30]	14[f]; 1,945 adults	n.r.	Mostly endurance training	Control	+0.3 (+0.11 to +0.49)	78
Jelleyman 2015[35]	5; 116 adults	n.r.	High-intensity interval training	Control	+0.44[g] (-0.34 to +1.22)	75
	6; 126	n.r.	High-intensity interval training	Continuous training	Healthy: +0.40[g] (-0.08 to +0.88)	43

[a] Confidence interval.
[b] Not reported.
[c] Standardised estimate: Cohen's d.
[d] 1-repetition maximum.
[e] Hedges' g.
[f] Number of eligible independent comparisons.
[g] Standardised mean difference. Values reported for insulin resistance were changed into insulin sensitivity.

Explanation

The Australian evidence report on children[1] described 40 studies on the impact of physical activity on cardiorespiratory fitness, 25 of which were RCTs. In general, a combination of moderate- and vigorous-intensity physical activity was necessary to bring about gains in cardiorespiratory fitness. Two studies that only included moderate-intensity physical activity did not show any benefits. Further, studies that utilised a vigorous-intensity of physical activity showed a greater improvement in cardiorespiratory fitness than those that did not. A variety of physical activities were included in studies that showed benefits for cardiorespiratory fitness. Most studies utilised endurance activities, however, sports training and active games, as well as resistance and plyometric activities also showed benefits.

The committee did not find any more recent meta-analyses or systematic reviews on the effect of physical activity on cardiorespiratory fitness in children. The committee therefore bases its conclusions on the Australian evidence report. In conclusion, a combination of moderate and vigorous-intensity exercise improves cardiorespiratory fitness in children and adolescents. In view of the consistent findings, the level of evidence is strong.

2.3.2 Cardiorespiratory fitness in adults

The Australian evidence report in adults[2] did not describe effects of physical activity on cardiorespiratory fitness (VO_2max). The American evidence report[3] stated that cardiorespiratory fitness is a sensitive and useful measure of changes in response to physical activity. It demonstrated a dose-response relationship with overall exercise volume and also with each of the various components of exercise volume (intensity, frequency, duration).

The committee found three meta-analyses[13,28,30] on the effect of endurance training on cardiorespiratory fitness in adults, one meta-analysis[35] and one systematic review[18] on the effect of high-intensity interval training and one systematic review[17] on the effect of light-intensity activity. Six of the 12 RCTs that were included in the meta-analysis by Murtagh et al.,[13] were also included by Lin et al.[30] There was no overlap between the meta-analyses by Murtagh et al.[13] and Hespanhol Junior et al.[28], whereas there were three studies in which there was an overlap between the latter meta-analysis and the one by Lin et al.[30]

Endurance training and cardiorespiratory fitness in adults

Summary of evidence for the effect of endurance training on cardiorespiratory fitness in adults

Aspect	Explanation
Selected studies	3 meta-analyses of 18,[28] 18[13] and 85 RCTs[30]
Heterogeneity	Yes, in two of the three meta-analyses, unexplained
Strength of the effect/association	Men: 4.6 (4.0 to 5.2) and 5.4 (4.3 to 6.5) ml/kg/min Women: 3.0 (1.7 to 4.2) and 3.2 (2.6 to 3.8) ml/kg/min
Study population	Physically inactive but healthy at baseline.

Conclusion: Endurance training improves cardiorespiratory fitness in a dose-response way for exercise volume.
Level of evidence: Strong.

Explanation

Lin et al.[30] showed that exercise, which was endurance in most of the studies, improved cardiorespiratory fitness (VO_2max) by 5.4 ml/kg/min in men and 3.2 ml/kg/min in women. Heterogeneity was however considerable (Table 5). There were no forest plots available for visual inspection. In subgroup analyses the effect was larger in participants under 50 than those aged 50 or more (5.6 vs. 3.3 ml/kg/min). There was no significant difference between moderate- and vigorous-intensity exercise. Heterogeneity remained considerable in these analyses.
Hespanhol et al.[28] showed that running at moderate intensity improved cardiorespiratory fitness by 4.6 ml/kg/min in men and by 3.0 ml/kg/min in women. The effect tended to be larger in the three studies which lasted up

to 12 months or more (7.1; 5.0-9.1 ml/kg/min) than in the four which lasted up to 6 months (4.1; 3.0-5.1 ml/kg/min) or in the 14 studies[a] which lasted up to 3 months (3.8; 3.1-4.6 ml/kg/min). Heterogeneity was low in these analyses.

Murtagh et al.[13] found that walking improved cardiorespiratory fitness by 3.0 ml/kg/min. Heterogeneity was considerable and was not explored further in subgroup analyses. The authors, for instance, did not distinguish between men and women. There were no forest plots available for visual inspection.

Batacan et al.[17] concluded that the evidence for an effect of light physical activity on cardiorespiratory fitness was inconclusive in physically inactive or healthy adults. They found significant improvements in cardiorespiratory fitness in three out of eight studies.

In comparison to the US report[3] the new meta-analyses only provide an average effect of endurance training on cardiorespiratory fitness. Effects were larger in men than in women. However, they do not shed more light on dose-response relationships. Therefore the committee has based its conclusion on the American evidence report.[3]

In conclusion, endurance training improves cardiorespiratory fitness in adults in a dose-response way for exercise volume. The level of evidence is strong.

[a] As some studies were included in the estimate up to three months, six months and/or 12 months, the total number adds up to 21 instead of 18.

High-intensity interval training and cardiorespiratrory fitness in adults

Summary of evidence for the effect of high-intensity interval training on cardiorespiratory fitness in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 42 RCTs[35] and 1 systematic review of 6 RCTs[18]
Heterogeneity	Yes, not explained
Strength of the effect/association	HIIT vs. control: 0.28 (0.12 to 0.44) ml/kg/min HIIT vs. moderate-intensity continuous: 0.16 (0.07-0.25) ml/kg/min
Study population	Healthy adults and adults at risk of, or with, cardiovascular disease.

Conclusion: High-intensity interval training improves cardiorespiratory fitness in comparison to moderate-intensity continuous training.
Level of evidence: Weak.

Explanation

Jelleyman et al.[35] compared high-intensity training with control treatment or continuous training (Table 5). The authors found that high-intensity training improved cardiorespiratory fitness by 0.28 ml/kg/min (weighted mean difference) compared to a control and by 0.16 ml/kg/min compared to continuous training. Heterogeneity was considerable, and not explained by subgroup analyses comparing healthy subjects with overweight and obese subjects, patients with chronic disease or patients with metabolic syndrome or type 2 diabetes. The total volume of exercise was only similar in the high-intensity interval training group and the moderate-intensity continuous training group in a proportion of the RCTs. For this

Table 5. RCTs into the effect of endurance training on cardiorespiratory fitness

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in VO_2max compared to control (95%-C.I.[a]) (ml/kg/min)	Heterogeneity (I^2, %)
Meta-analysis						
Hespanhol Junior 2015[28]	18; 870 men and 217 women	5 (average)	Running 60-90% MHR,[b] 3.7 d/wk, 2.3 h/wk (average)	Physically inactive	Men: 4.6 (3.9 to 5.2) Women: 3.0 (1.7 to 4.2)	4 0
Lin 2015[30]	37[c] in men 48[c] in women; 4,792 in total	0.5-2.0	Mostly endurance training	Control	Men: 5.4 (4.3 to 6.5) Women: 3.2 (2.6 to 3.8)	90 89
	64[c]		Moderate		3.2 (2.6 to 4.1)	n.r.[d]
	68[c]		Vigorous		3.3 (2.6 to 3.8)	n.r.
Murtagh 2015[13]	18; 894 adults	2-6	Walking, predominantly at moderate intensity; 2-7 d/wk; 20-60'/session	No exercise sedentary	3.0 (2.5 to 3.6)	71
Jelleyman 2015[35]	42; n.r.	n.r.	High-intensity interval training	Control	0.28[e] (0.12 to 0.44)	92
		n.r.	High-intensity interval training	Continuous training	0.16[e] (0.07 to 0.25)	76

[a] Confidence interval.
[b] Maximum heart rate.
[c] Number of eligible, independent comparisons.
[d] Not reported.
[e] Weighted mean difference.

reason, the findings of this meta-analysis need to be treated with caution. In their systematic review, Ramos et al.[18] described five studies in different clinical patients, in which cardiorespiratory fitness (as a secondary outcome measure) improved to a greater extent following 3 months of high-intensity interval training compared to (isocaloric[f]) moderate-intensity continuous training. Two other RCTs did not find any significant difference. In one of the two, however, the two training programmes were not isocaloric, and in the other, the training only lasted two weeks. Thus, findings point in the same direction as in the meta-analysis by Jelleyman et al.[35]

In comparison with the US report,[3] the meta-analysis[35] and systematic review[18] provide evidence that high-intensity interval training improves cardiorespiratory fitness in comparison to moderate-intensity continuous training. The new studies do not provide insight as to whether there is a relationship between the duration of exercise bouts and fitness responses when total volume is held constant, especially for high-intensity exercise. In conclusion, high-intensity interval training improves cardiorespiratory fitness in comparison to moderate-intensity continuous training for 3 months. The committee could not quantify the effect because of limitations in the meta-analysis. Because the interventions in the studies in the meta-analysis were not necessarily isocaloric and cardiorespiratory fitness was

[f] Total energy expenditure is similar between the two types of training.

a secondary outcome measure in the systematic review, the level of evidence is weak.

Minimum required duration of exercise bouts required to improve cardiorespiratory fitness

Conclusion: There is too little research to draw a conclusion on the minimum duration of exercise bouts required to improve cardiorespiratory fitness.

Explanation

In the American evidence report[3] it is stated that, from a few well-designed studies, it appears that both single long bouts and multiple shorter bouts of endurance training elicit significant improvements in cardiorespiratory fitness. The evidence is relatively strong that comparable fitness effects can be achieved with different fractionisation of the volume, given that the daily volume of the exposure is the same. The committee did not find any meta-analyses or systematic reviews of what the minimum required duration of the exercise bouts should be. It therefore concludes that there is insufficient evidence to draw a conclusion on the minimum duration of exercise bouts required for improving cardiovascular fitness.

2.4 Body weight and body mass index

Below, the committee discusses the effect of physical activity on body weight (in adults) and body mass index (in children) as reported in meta-analyses of RCTs that were not specifically designed to bring about weight loss. Most of the studies on body weight and body composition have been carried out in overweight and obese subjects. For BMI and body weight, meta-analyses that did, and did not, specifically select studies with overweight and obese subjects are described separately.

One of the outcome measures in the Australian evidence report on adults[2] was primary prevention of weight gain. The report summarises RCTs, prospective cohort and cross-sectional studies. The overall conclusion is that the very limited available evidence indicates that at least 60 minutes per day of moderate intensity activity, or the equivalent volume of more vigorous activity, is the dose required for the primary prevention of weight gain. For those who are already overweight or obese, it is unlikely that this level of physical activity will prevent further weight gain without concurrent dietary change. The US evidence report[3] describes that available data on weight stability are sourced from short-term clinical trials. Based on these trials, a dose of physical activity in the range of 13 to 26 MET-hours per week resulted in a modest 1% to 3% weight loss, consistent with weight stability over time. The magnitude of weight loss resulting from studies of resistance exercise is typically less than 1 kilogram. However, this result may be affected by the relatively short duration of these studies and gains in fat-free mass that accompany such interventions.

2.4.1 Body weight in adults

Endurance training and body weight in adults

Summary of evidence for the effect of endurance training on body weight in adults

Aspect	Explanation
Selected studies	4 meta-analyses of 3 to 25 RCTs[13, 28, 39, 40]
Heterogeneity	Yes, in one meta-analysis, partly explained by sex
Strength of the effect/association	Ranged from -0.9 (-2.6 to +0.8) to -3.3 (-4.1 to -2.5) kg
Study population	Sedentary but otherwise apparently healthy adults

Conclusion 1: Moderate- to high-intensity endurance training (3 to 5 times per week, 30 to 60 minutes per session, for one year) versus no exercise or flexibility training reduces body weight by about 1 kilogram in adults.
Level of evidence: Strong.

Explanation

There are four meta-analyses[13,28,39,40] and one systematic review[17] on the effect of endurance training on body weight or body weight gain in adults (Table 6).

Murtagh et al.[13] and Gao et al.[39] summarised the effect of walking in adults and postmenopausal women respectively; three RCTs overlap between the two meta-analyses. They both showed that walking at moderate- to high-intensity lowers body weight by 1 kilogram in one year in comparison to no exercise. In the meta-analysis by Murtagh et al.[13] there was considerable heterogeneity. There was no forest plot available for visual inspection. Subgroup analyses showed that heterogeneity was partly explained by sex: the effect was larger in studies carried out in women only (-1.9; -2.5 to -1.3), than in studies which also included some men (-0.7; -1.0 to -0.3), but heterogeneity remained considerable in the women-only studies. In both meta-analyses there was evidence of publication bias. In the meta-analysis by Gao et al.[39] heterogeneity was low.

Weber Buchholz et al.[40] summarised three RCTs in women, showing that moderate- to high-intensity endurance training reduced body weight by 0.5 kilograms within 0.5 to 1.5 years in comparison to no intervention or flexibility training. The authors did not provide information on heterogeneity.

Hespanhol et al.[28] summarised the effect of running on body weight. The authors found a non-significant effect (-1 kg) after 3 and 6 months of running and a 3 kilogram lowering after 1 to 1.25 years of running in comparison to inactivity. Heterogeneity was low.

In a systematic review Batacan et al.[17] found no indications for an effect of light-intensity physical activity on body weight in 4 RCTs carried out in healthy adults.

None of the meta-analyses included a description of whether the intervention also resulted in a change in total physical activity in the intervention and/or control group.

The findings above are roughly in line with the conclusions in the Australian evidence report that the very limited available evidence indicates that at least 60 minutes per day of moderate intensity endurance training, or the equivalent volume of more vigorous exercise, is the dose required for the primary prevention of weight gain.[2] The findings are also in line with the US evidence report[3] that a dose of physical activity in the range of 13 to 26 MET-hours per week resulted in a modest 1% to 3% weight loss, consistent with weight stability over time.
In conclusion, moderate- to high-intensity endurance training (3 to 5 times per week, 30 to 60 minutes per session for one year) versus no exercise or flexibility training reduces body weight by about 1 kilogram in adults. In view of the consistent findings between meta-analyses, the level of evidence is strong.

Endurance and combination of endurance with resistance training and body weight in overweight and obese adults

Summary of evidence for the effect of endurance and the combination of endurance with resistance training on body weight in overweight and obese adults

Aspect	Explanation
Selected studies	2 meta-analyses of 3 RCTs (endurance vs. inactive)[41] and of 13 RCTs (endurance vs. resistance) and 4 RCTs (endurance & resistance vs.resistance)[42]
Heterogeneity	Yes, in both size and direction for endurance vs.resistance
Strength of the effect/association	Endurance vs. inactive: -1.6 (-1.64 to -1.56) kg Endurance vs. resistance: -1.2 (-2.2 to -0.1) kg Endurance & resistance vs. resistance: -2.0 (-2.9 to -1.1) kg
Study population	Overweight and obese adults

Conclusion 1: Endurance training lowers body weight in comparison to inactivity in overweight and obese adults.
Level of evidence: Strong.

Conclusion 2: Endurance training lowers body weight in comparison to resistance training in overweight and obese adults.
Level of evidence: Weak.

Conclusion 3: The combination of endurance and resistance training versus resistance training alone lowers body weight in overweight and obese adults.
Level of evidence: Weak.

Explanation
There are three meta-analyses summarising studies solely carried out in overweight or obese people (Table 6).[14,41,42] The meta-analysis by Kelley et al.[14] is excluded as the authors summarised findings from previous meta-analyses that had been published before 2008. Thorogood et al.[41] compared endurance training with physical inactivity, whereas Schwingshackl et al.[42] compared the effect of endurance training, resistance training and the combination of endurance and resistance training. Therefore, the committee describes both meta-analyses. Thorogood et al.[41] summarised 3 RCTs in which endurance training lowered body weight by about 1.5 kg within six months in overweight and

obese subjects. The authors did not provide a heterogeneity estimate. In each of the three studies body weight was consistently lowered. However the number of subjects was small. The authors narratively described 5 studies of shorter duration, showing mean differences ranging from -2.5 to +0.6 kg. There were too few studies of longer duration (12 months, N=2) in the meta-analysis to draw a conclusion.

Schwingshackl et al.[42] showed that both endurance training and the combination of endurance and resistance training lowered body weight by 1 to 2 kg in comparison to resistance training alone. There was heterogeneity (I^2=34%) in the analysis of endurance training versus resistance training that related to the direction and size of the effect. In addition, publication bias could not completely be excluded in this comparison.

There was no significant difference in body weight change between endurance training and the combination of endurance and resistance training. A similar effect was found on fat mass (endurance versus resistance -1.1 (-1.8 to -0.4) kg; combination versus resistance -1.9 (-2.7 to -1.0) kg), whereas resistance training and the combination of endurance and resistance training increased fat-free mass by about 1 kg in comparison to endurance training (+1.3 (+0.7 to +1.8) kg and +0.9 (+0.3 to +1.4) kg respectively) . Heterogeneity was low in these analyses.

A limitation of this meta-analysis, however, was that the exercise volume was not isocaloric between the interventions of some of the included studies.[42]

The findings above are roughly in line with the conclusions in the Australian evidence report that the very limited available evidence indicates that at least 60 minutes per day of moderate intensity endurance training, or the equivalent volume of more vigorous exercise, is the dose required for the primary prevention of weight gain.[2] The findings are also in line with the US evidence report[3] that a dose of physical activity in the range of 13 to 26 MET-hours per week resulted in a modest 1% to 3% weight loss, consistent with weight stability over time.

In conclusion, endurance training lowers body weight in comparison to inactivity in overweight and obese adults. Although the number of studies in the meta-analysis is small, the conclusion is consistent with the conclusion in the American evidence report,[3] which was based on four RCTs in overweight and obese adults. Therefore, the level of evidence is strong.

Both Australian and American evidence reports[2,3] did not compare the effect of endurance training and resistance training. The committee therefore bases its conclusions on the meta-analysis by Schwingshackl et al.[42]

Endurance training also lowers body weight in comparison to resistance training in overweight and obese adults. In view of potential publication bias and the fact that not all the included studies matched exercise interventions for volume, the level of evidence is weak.

The combination of endurance and resistance training lowers body weight in comparison to resistance training in overweight and obese adults. In view of the small number of studies and the fact that not all the included studies matched exercise interventions for volume, the level of evidence is weak.

Table 6. RCTs into the effect of endurance training and resistance training on body weight in adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in body weight compared to control (95%-C.I.[a]) (kg)	Heterogeneity (I^2 %)
Meta-analysis						
Weber Buchholz 2013[40]	3; 290 women	6-18	Physical activity moderate- to high-intensity; 3-6 times/wk; 30-60'/session	No intervention or flexibility	-0.5 (-0.7 to -0.2)[b]	n.r.[c]
Murtagh 2015[13]	25; 1,138 adults	2-12	Walking at 56-86% MHR[d]; 2-7 times/wk; 28-65'/session	No exercise control	-1.4 (-1.7 to -1.0)	66
Hespanhol 2015[28]	15; 463 adults	3	Running 60-90% MHR, 3.7 d/wk, 2.3 h/wk (average)	Physically inactive	-0.9 (-2.5 to +0.7)[b]	0
	4; 181 adults	6			-0.9 (-3.5 to +1.8)[b]	0
	5; 335 adults	12-16			-3.3 (-4.0 to -2.5)[b]	0
Gao 2016[39]	8; 853 postmenopausal women	3-8	Walking moderate- to high-intensity; 3-5 times/wk; 20-60'/session	No exercise control	-1.1 (-1.8 to -0.4)	20
Thorogood 2011[41]	3; 723 overweight and obese adults	6	Endurance training 140-180'/wk, 70% VO_2max or 40-85 MHR	Inactive (personal attention or none)	-1.6 (-1.64 to -1.56)	n.r.
Schwingshackl 2013[42]	14; 560 overweight and obese adults	n.r.	Endurance training	Resistance training	-1.2 (-2.2 to -0.1)	34
	3; 173 overweight and obese adults		Endurance and resistance training	Resistance training	-2.0 (-2.9 to -1.1)	19
	4; 184 overweight and obese adults		Endurance training	Combined training	-0.3 (-1.0 to +0.3)	0

[a] Confidence interval.
[b] Weighted mean difference in BMI or body weight.
[c] Not reported.
[d] Maximum heart rate.

2.4.2 Body mass index in children and adolescents

The Australian evidence report on children states that there was high-level evidence for an effect of physical activity on adiposity and unhealthy weight gain, with 36 RCTs, 16 CTs, 8 longitudinal analyses and 1 quasi-experimental study. About half of the studies (N=32) found that physical activity had a significant impact on adiposity and weight gain, in terms of BMI, BMI z-score, waist circumference, and skin fold measurements. In the RCTs, physical activity included endurance activities, sport-based games, plyometric[a] training, and resistance training. In the report, it is emphasized that more research investigating dose-response relationships with regard to frequency, intensity and duration is required.[1]

[a] Explosive powerful training exercises that are aimed at activating the quick response and elastic properties of the major muscles in the body.

Physical activity and BMI in children and adolescents

Summary of evidence for the effect of physical activity on BMI in children and adolescents

Aspect	Explanation
Selected studies	3 meta-analyses of 5,[43] 9[21] and 11 RCTs[26]
Heterogeneity	Yes, in size and direction of the effect in two of the three meta-analyses, unexplained
Strength of the effect/association	Ranges from -0.13 (-0.29 to +0.04) to -0.02 (-0.13 to +0.17) kg/m^2
Study population	Children and adolescents

Conclusion 1: An effect of moderate- to high-intensity physical activity for at least 150' per week on BMI in children and adolescents is unlikely.

Explanation

Five meta-analyses[21,26,43-45] studied the effect of physical activity on body mass index in school children (Table 7). Most RCTs were carried out in primary school children, although in two meta-analyses one or two studies in secondary school children were summarised.[26,45] Because only two of the 18 studies that Harris et al.[44] summarised concerned a physical activity intervention carried out in a (cluster) RCT, this meta-analysis is excluded. The overlap between the other four meta-analyses ranges from one to four RCTs.[21,26,43,45]

Three of the four meta-analyses provide indications that an effect of physical activity on body mass index is unlikely. The level of heterogeneity was only low in the meta-analysis by Cesa et al.[21] This could be explained by the stringent selection criteria used by Cesa et al.: school children aged 6 to 12 years; any physical activity programme lasting longer than 6 months, with at least 150 minutes per week in comparison to a less intensive or no intervention.

In the other three meta-analyses there was considerable heterogeneity.[26,43,45] Guerrra et al.[26] ascribe this heterogeneity to the large variations in the nature and objective of study protocols, age ranges and follow-up times between studies. Although RCTs with nutritional interventions were excluded, three RCTs had co-interventions with health education and family support was included in one RCT. From the text, it is, however, unclear whether the control group also received these co-interventions.[26]

In the meta-analysis by Mei et al.[43] the analysis of the effect of physical activity was already a subgroup analysis. The authors did not explore heterogeneity further within this subgroup. Visual inspection of the forest plots in the two meta-analyses indicates that the heterogeneity is associated with both the size and direction of the effect.

In the meta-analysis of Lavelle et al.[45] 10 studies were summarised on the effect of physical activity on body mass index. The authors showed a reduction in BMI of -0.1 kg/m^2 in comparison to standard physical education. One of the 10 studies had a linear design. Visual inspection of the scatter plot suggests considerable heterogeneity in size and direction of the effect. As the analysis was already a subgroup analysis, heterogeneity was not further explored by the authors. This limits the interpretation of this meta-analysis.

Of the meta-analyses, the committee weighs the one by Cesa et al.[21] more strongly than the others in view of its more stringent selection criteria and the low heterogeneity.

The findings do not confirm the conclusions in the Australian evidence report,[1] namely, that there was high-level evidence for an effect of physical activity on adiposity and unhealthy weight gain in children and adolescents. One explanation may be that the Australian evidence report also based its conclusions on studies with other designs and studies carried out in children who are overweight or obese (see below), whereas the meta-analyses focused on physical activity in school children.

In conclusion, an effect of moderate- to high-intensity physical activity for at least 150' per week on BMI in children and adolescents is unlikely.

High-intensity interval training and BMI in adolescents

Summary of evidence for the effect of high-intensity interval training on BMI in adolescents

Aspect	Explanation
Selected studies	1 meta-analysis of 8 RCTs[46]
Heterogeneity	No
Strength of the effect/association	-0.6 (-0.9 to -0.4) kg/m^2
Study population	Adolescents

Conclusion 2: High-intensity interval training (for 2 to 6 months) versus usual behaviour or light- to moderate-intensity training, reduces the gain in BMI in adolescents.
Level of evidence: Weak.

Explanation

Costigan et al.[46] summarised 8 RCTs on the effect of high-intensity interval training on the gain in body mass index in adolescents (Table 7). The authors showed that this type of training lowers the body mass index by 0.6 kg in 2 to 6 months in comparison to control or moderate-intensity training. The level of heterogeneity was low. However, it is unclear from the text whether the volume of exercise in the high-intensity interval training is similar to that of the moderate-intensity training.

The Australian and US evidence reports did not discuss the effect of high-intensity interval training on gain in body mass index.[2,3]

In conclusion, high-intensity interval training (for 2 to 6 months) versus usual behaviour or light- to moderate-intensity training reduces the gain in BMI in adolescents. As it is unclear whether the exercise volume of the high-intensity interval training was similar to that of the moderate-intensity training, the level of evidence is weak.

Endurance training and BMI in overweight and obese children and adolescents

Summary of evidence for the effect of endurance training on BMI in overweight and obese children and adolescents

Aspect	Explanation
Selected studies	2 meta-analyses of 10 (BMI z-score)[47], 8 (BMI)[47] and 6 RCTs (BMI)[48]
Heterogeneity	Yes, in the size of the effect in one of the two meta-analyses
Strength of the effect/association	BMI z-score: -0.06 (-0.09 to -0.03) BMI: ranged from -0.47 (-0.86 to -0.08) to -0.36 (-0.65 to -0.08) kg/m^2
Study population	Overweight and obese children and adolescents

Conclusion 3: Moderate- to high-intensity endurance training (2 to 7 times per week, 6 to 90 minutes per session, for 6 months) versus control, lowers gain in BMI in overweight and obese children and adolescents by about 0.4 kg/m^2.
Level of evidence: Strong.

Explanation

There are three meta-analyses exclusively focusing on the effect of physical activity on BMI in overweight and obese children (Table 7).[47-49] Kelley et al.[47] used BMI z-scores as outcome measure, which is a preferred measure, particularly for children, for combining the results from several studies. As one of the other meta-analyses[49] was carried out by the same authors and covered the same studies, it was excluded. There was no overlap in studies between the meta-analyses by Kelley et al.[47] and Stoner et al.[48] Therefore both are discussed below. Both meta-analyses summarised studies on predominantly endurance training.

Kelley et al.[47] showed that endurance exercise reduced the BMI z-score by about 3% in overweight and obese children and adolescents in comparison to the control group. The reduction in BMI was about -0.5 kg/m^2 in comparison to the control. There was considerable heterogeneity in the size of both effects which was not explored further by the authors.

Stoner et al.[48] found that endurance exercise reduced BMI by about -0.4 kg/m^2 in overweight and obese children and adolescents. Heterogeneity was low. The authors, however, used a fixed-effects model, which results in a smaller confidence interval than a random-effects model.

The findings are in accordance with the conclusions in the Australian evidence report[1] that there was high-level evidence for an effect of endurance training on adiposity and unhealthy weight gain in children and and adolescents.

In conclusion, moderate- to high-intensity endurance training (2 to 7 times per week, 6 to 90 minutes per session, for 6 months) versus control, lowers gain in BMI in overweight and obese children and adolescents by about 0.4 kg/m^2. In view of the consistent findings between meta-analyses, the level of evidence is strong.

Table 7. RCTs into the effect of physical activity and endurance training on body mass index in children and adolescents

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in BMI compared to control (95%-C.I.[a]) (kg/m²)	Heterogeneity (I^2%)
Meta-analysis						
Lavelle 2011[45]	10; n.r. children and adolescents <5 to 18 years	1-15	Physical activity	Standard physical education	-0.13 (-0.22 to -0.04)	n.r.
Guerra 2013[26]	11; 4,273 children and adolescents 6-16 years	0.5[b]-48	Endurance and/or resistance training moderate-intensity; 2-5 times/wk; 45-245'/session;	Sedentary behaviour	+0.02 (-0.13 to +0.17)	77
Cesa 2014[21]	9; 10,355 children 6-12 years	6-36	Physical activity of at least 150'/wk moderate- to high-intensity	Less intensive or standard physical education classes	-0.03 (-0.16 to +0.13)	0
Costigan 2015[46]	8; 870 adolescents 11-18 years	2-6	High-intensity interval training	Usual behaviour or low-to-moderate intensity training	-0.6 (-0.9 to -0.4)	0
Mei 2016[43]	5; primary school children	12- >24	Endurance training at low/moderate/high-intensity; 1-10 times/wk; 10-90'/session	Control	-0.13 (-0.29 to +0.04)	90
Kelley 2014[47]	10; 835 overweight and obese children and adolescents 9-16 years 8; 562 overweight and obese children and adolescents 9-16 years	2-6	Endurance training at moderate/high-intensity; 2-7 times/wk; 6-75'/session; resistance training (1 study) or combination (1 study) Idem	Control Idem	-0.06 (-0.09 to -0.03)[c] -0.47 (-0.86 to -0.08)	60 71
Stoner 2016[48]	6; 196 overweight and obese children and adolescents 10-19 years	1.5-9	Endurance training (and resistance training in one study) 2-4 times/wk; 40-90'/session	Usual care (and tai chi in one study)	-0.36 (-0.65 to -0.08)	0

[a] Confidence interval.
[b] Data of 6-month follow-up.
[c] BMI z-score.

2.5 Fat mass, abdominal fat and waist circumference

Below the committee discusses the effect of physical activity on fat mass, abdominal fat and waist circumference, as reported in meta-analyses of RCTs that were not specifically designed to bring about weight loss. Most of the studies on body composition have been carried out in overweight and obese subjects. Meta-analyses on visceral fat and waist circumference were, for instance, exclusively available for studies in (on average) overweight and obese subjects.

The Australian evidence report did not discuss changes in body composition.[2] The US evidence report[3] concluded that ample evidence exists for a positive dose-response relationship between the volume of endurance and/or resistance training, the training duration, and the amount

of total and regional fat loss. The studies that the report summarised examined the effect of endurance training rather than resistance training, however. Moreover, the evidence suggests that regional fat loss is greater with greater amounts of exercise-induced total weight loss and among those with the highest levels of adiposity. In the absence of coincident caloric restriction, endurance training in the range of 13 to 26 MET-hours per week resulted in decreases in total and abdominal adiposity that are consistent with improved metabolic function. However, when more training is done (e.g., 42 MET-hours per week), decreases in abdominal fat approached 3 to 4 times the level seen with this range of training.
As described in the chapter on body weight and body mass index in children and adolescents, the Australian evidence report on children states that there was high-level evidence for an effect of physical activity on adiposity and unhealthy weight gain from 61 studies with various study designs. About half of the studies (32) found a significant impact of physical activity on adiposity and weight gain, in terms of BMI, BMI z-score, waist circumference, and skin fold measurements.[1]

2.5.1 Fat mass in adults

Summary of evidence for the effect of endurance training on fat mass in adults

Aspect	Explanation
Selected studies	3 meta-analyses of 3,[39] 3-7[28] and 14 RCTs[13]
Heterogeneity	Yes in one meta-analysis, unexplained
Strength of the effect/association	Varies from -1.2 (-1.7 to -0.7) to -2.7 (-5.0 to -0.2)%
Study population	Sedentary but otherwise apparently healthy adults

Conclusion 1: Moderate- to high-intensity endurance training (3 to 5 times per week, 30 to 60 minutes per session, for one year) versus no exercise, reduces fat mass by 2% in adults.
Level of evidence: Strong.

Explanation
There are three meta-analyses[13,28,39] and three systematic reviews[17,18,50] on the effect of physical activity on fat mass in adults (since 2012, Table 8). Murtagh et al.[13] summarised 14 RCTs on walking, two of which were also summarised by Gao et al.[39] in combination with one other RCT. As Gao et al.[39] used more stringent selection criteria, such as the inclusion of at least 25 participants (peri- or postmenopausal women) and a drop-out rate of less than 35%, the committee describes the findings of both meta-analyses. Murtagh et al.[13] found that moderate- to high-intensity walking reduced fat mass by 1% within one year and Gao et al.[39] found a reduction of 2% within half a year. The latter authors used a fixed-effects model, which results in a smaller confidence interval than a random-effects model. In the meta-analysis completed by Murtagh et al.,[13] there was considerable heterogeneity, which was not investigated further by the authors. A forest plot was not available for visual inspection.
Hespanhol et al.[28] found similar effects of running on the percentage of body fat. The decrease in fat mass increased with the duration of the intervention: from 1% after three months to 3% after 1 to 1.5 years. Heterogeneity was low.

Table 8. RCTs into the effect of endurance training on fat mass in adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in % fat mass compared to control (95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis						
Murtagh 2015[13]	14; 654 adults	2-12	Walking at 56-86% MHR;[b] 2-7 times/wk; 28-65'/session	No exercise control	-1.2 (-1.7 to -0.7)	68
Gao 2016[39]	3; 444 postmenopausal women	4-6	Walking moderate- to high-intensity; 3-5 times/wk; 45-60'/session	No exercise control	-2.3 (-3.2 to -1.5)	0
Hespanhol 2015[28]	7; 264 adults	3	Running 60-90% MHR, 3.7 d/wk, 2.3 hrs/wk (average)	Physically inactive	-1.3 (-1.9 to -0.6)	0
	4; 278 adults	6			-1.9 (-2.7 to -0.9)	0
	3; 115 adults	12-16			-2.7 (-5.0 to -0.2)	24

[a] Confidence interval.
[b] Maximal heart rate.

None of the meta-analyses included a description of whether the intervention also resulted in a change in total physical activity in the intervention and/or control group.

The three systematic reviews focused on the effect of light-,[17] moderate- and high-intensity exercise[18] on fat mass in healthy adults and the effect of physical activity in frail older adults.[50] In a systematic review of two RCTs, Batacan et al.[17] found no indications for an effect of light-intensity physical activity on fat mass in physically inactive adults. In another systematic review of two RCTs, Ramos et al.[18] found no indications for a difference in fat mass lowering between high-intensity interval training and moderate-intensity continuous training. A systematic review[50] summarising two RCTs in frail older adults found no indications for an effect of physical exercise interventions on fat mass.

Thus, the results of the three meta-analyses taken together suggest that moderate- to high-intensity endurance training decreases fat mass by 2% (conservative estimate) after one year.[13,28,39] This is in line with the conclusions in the US evidence report[3] that there is ample evidence for a dose-response relationship between the volume of endurance training and the amount of total fat loss.

In conclusion, moderate- to high-intensity endurance training (3 to 5 times per week, 30 to 60 minutes per session, for one year) versus no exercise reduces fat mass by 2% in adults. In view of the consistent findings, the level of evidence is strong.

2.5.2 Fat mass in children and adolescents

The committee found four meta-analyses on the effect of physical activity on fat mass in children: two on predominantly endurance training,[47,48] one on bone-strengthening exercise,[51,a] and one on high-intensity interval training.[46]

Endurance training and fat mass in children and adolescents

Summary of evidence for the effect of endurance training on fat mass in overweight and obese children and adolescents

Aspect	Explanation
Selected studies	2 meta-analyses of 6[48] and 9 RCTs[47]
Heterogeneity	Yes, in one meta-analysis
Strength of the effect	-1.0 (-1.4 to -0.5)% -1.2 (-2.5 to +0.5)%
Study population	Overweight and obese children and adolescents

Conclusion 1: Moderate- to vigorous-intensity endurance training lowers fat mass in overweight and obese children and adolescents. Level of evidence: Strong.

Explanation

The overlap between the meta-analyses by Kelley et al.[47] and Stoner et al.[48] could not be assessed exactly, as Kelley et al.[47] did not provide information on the individual studies included in the analysis on fat mass (Table 9). As only one of the five studies in the meta-analysis of Stoner et al.[48] was described in the table with characteristics of the studies in the meta-analysis by Kelley et al.,[47] the overlap is one at most. In the studies, endurance training was studied predominantly.

Kelly et al.[47] showed that moderate- to high-intensity endurance training[b] lowered fat mass by 1% in overweight and obese children and adolescents. The RCTs included at least 20 participants. Heterogeneity was, however, considerable and not investigated by the authors. There was no forest plot available for visual examination.

Stoner et al.[48] found a similar effect (-1.2%) that was not significant. Five of the trials were of endurance training and one was a combination of endurance and resistance training. Four out of six RCTs comprised less than 15 participants. The authors used a fixed-effect model for analysis. Fixed-effects models, however, result in smaller confidence intervals than random-effects models. Heterogeneity was low.

The findings of the two meta-analyses are in accordance with the conclusions in the Australian evidence report[1] that there was high-level evidence for an effect of endurance training on adiposity and unhealthy weight gain children and adolescents.

In conclusion, moderate- to high-intensity endurance exercise lowers fat mass in overweight and obese children and adolescents. As the heterogeneity was considerable in one meta-analysis[47] the conclusion is not quantified. In view of the consistent findings in the direction of the effect in the other meta-analysis[48] and the conclusions in the Australian evidence report[1], the level of evidence is strong.

[a] Consists of resistance training and activities as jumping, climbing stairs, walking, running and dancing.

[b] In one trial resistance training was studied and in another the combination of endurance with resistance training.

Bone-strengthening exercise and fat mass in children and adolescents

Summary of evidence for the effect of bone-strengthening exercise on fat mass in children and adolescents

Aspect	Explanation
Selected studies	1 meta-analysis of 5 RCTs and 3 other trials[51]
Heterogeneity	Yes, both in size and direction of effect, partly explained
Strength of the effect/association	-0.25 (-0.40 to -0.08) (weighted mean difference)
Study population	Children and adolescents

Conclusion 2: Bone-strengthening exercises, whether done in combination with moderate- to high-intensity endurance training or not, reduce the gain in fat mass in children and adolescents.
Level of evidence: Weak.

Explanation

There is one meta-analysis on the effect of bone-strengthening exercise on gain in fat mass (Table 9). Nogueira et al.[51] summarised five RCTs in combination with three other trials and found that bone-strengthening exercise mitigated gain in fat mass. The level of heterogeneity was moderate. Visual inspection of the forest plot indicates that heterogeneity was both related to the size and the direction of the effect. Results were similar when the analysis was restricted to the six studies with a low to moderate risk of bias (-0.27; -0.43 to -0.12). The trials that combined jumping activities with some other moderate- to high-intensity endurance training resulted in the greatest changes in fat mass (results not shown). The Australian and American evidence report did not specifically discuss the effects of bone strengthening exercise on fat mass.[1,3]

In conclusion, bone-strengthening exercise, whether done in combination with moderate- to high-intensity endurance training or not, reduce the gain in fat mass in children and adolescents. As the analysis is based on both RCTs and other studies and the heterogeneity was partly explained, the level of evidence is weak.

High-intensity interval training and fat mass in adolescents

Summary of evidence for the effect of high-intensity interval training on fat mass in adolescents

Aspect	Explanation
Selected studies	1 meta-analysis of 6 RCTs[46]
Heterogeneity	Yes, in both size and direction of effect, partly explained by study duration
Strength of the effect/ association	< 2 months: +1.2; 1.6 to +4.1% 2-6 months: -2.1; -3.3 to -0.8%
Study population	Adolescents

Conclusion 3: High-intensity interval training versus usual behaviour or light- to moderate-intensity training lowers the gain in fat mass in adolescents.
Level of evidence: Weak.

Explanation

Costigan et al.[46] summarised 6 RCTs on the effect of high-intensity interval training on fat mass in adolescents of normal weight, who were overweight or who were obese (Table 9). The authors show that this type of training lowers fat mass by 1.6% in comparison to the control or moderate-intensity training in 2 to 6 months. The level of heterogeneity was high and pertained to both the size and the direction of the effect. Study duration was a significant moderator of training effects, with larger effects in four studies lasting at least two months (-2.1; -3.3 to -0.8%) compared to two studies lasting 7 weeks (+1.2; -1.6 to +4.1%). Heterogeneity estimates were not reported for these subgroup analyses. As the confidence interval for the RCTs lasting at least two months is relatively narrow, heterogeneity is likely to be limited.

However, it is unclear from the text whether the volume of exercise is similar between the high-intensity interval training and moderate-intensity training. The Australian and American evidence reports do not specifically discuss the effects of high-intensity interval training on fat mass.[1,3]

In conclusion, high-intensity interval training versus usual behaviour or light- to moderate-intensity training lowers the gain in fat mass in adolescents. As it is unclear whether the exercise volume was similar between the high-intensity interval training and the moderate-intensity training, the level of evidence is weak.

Table 9. RCTs into the effect of endurance training and resistance training on fat mass in children and adolescents

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change in fat mass compared to control (95%-C.I.[a]) (%)	Heterogeneity (I^2 %)
Meta-analysis						
Nogueira 2014[51]	5 RCTs and 3 other trials; 749 children and adolescents 5-14 years	7-20	Primarily high-impact, weight bearing exercise; some multiple exercise modes	Usual physical education classes or stretching	-0.25 (-0.40 to -0.08)[b]	33
Costigan 2015[46]	6; 786 adolescents 11-18 years 2; n.r.[c] 4; n.r.	1.75-6 <2 2-6	High-intensity interval training	Usual behaviour or low-to-moderate intensity training	-1.6 (-2.8 to -0.4)[d] +1.2 (-1.6 to +4.1)[d] -2.1 (-3.3 to -0.8)[d]	63 n.r. n.r.
Kelley 2014[47]	9; 759 overweight and obese children 9-16 years	n.r.	Endurance exercise at moderate/high-intensity; 2-7 times/wk; 6-75'/session; resistance training or combination	Control	-1.0 (-1.4 to -0.5)[d]	52
Stoner 2016[48]	6; 196 overweight and obese children and adolescents 10-19 years	1.5-9	Endurance exercise (and resistance training in one study) 2-4 times/wk; 40-90'/session	Usual care (and tai chi in one study)	-1.2 (-2.5 to +0.5)[b]	0

[a] Confidence interval.
[b] Standardised mean difference.
[c] Not reported.
[d] % fat mass.

2.5.3 Abdominal fat in adults

Summary of evidence for the effect of endurance training on abdominal fat in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 50 RCTs and CTs[52]
Heterogeneity	Yes in the size of the effect, partly explained by sex
Strength of the effect/association	-0.47 (-0.56 to -0.39) (Hedges' g)
Study population	Overweight and obese adults

Conclusion: Endurance training (40 to >75% VO_2max, 1 to 7 sessions per week, 15 to 90 minutes, for 1 to 15 months) reduces abdominal fat in overweight and obese adults; effects are larger at larger volumes of training.
Level of evidence: Strong.

Explanation

The committee found three meta-analyses on the effect of exercise on abdominal fat (Table 10).[52-54] Vissers et al.[53] summarised 9 controlled studies, all of which were summarised with 41 others by Verheggen et al.[52] and 6 of which were summarised with 27 others by Ismail et al. The overlap between the meta-analyses of Verheggen et al.[52] and Ismail et al.[54] was 12 studies. Because all the controlled studies in the meta-analysis by Vissers et al.[53] were summarised in the meta-analysis by Verheggen et al.,[52] the committee excludes the meta-analysis by Vissers et al.[53]

Ismail et al.[54] investigated the effect of endurance and resistance training on abdominal fat. However, in part of the studies the exercise intervention was combined with a dietary intervention. Therefore, the committee also excludes this meta-analysis.[54]

Verheggen et al.[52] summarised the effect of endurance training on abdominal fat as quantified by radiographic imaging in overweight and obese adults. The authors showed that endurance training reduced abdominal fat by -0.47 (Hedges' g). There was considerable heterogeneity, which was partly explained by sex: men experienced a larger reduction in abdominal fat than women. The authors did not report whether energy intake was controlled for in the studies. In additional analyses, in the absence of weight loss, endurance training was associated with a 6% reduction in abdominal fat. There was no forest plot available for assessing whether heterogeneity was only present in the size or also in the direction of the effect. As in the excluded meta-analyses of Vissers et al.[53] and Ismail et al.[54] heterogeneity was predominantly present in the size of the effect, the committee considers it likely that this is also the case in the meta-analysis by Verheggen et al.[52] There was no evidence of publication bias.

The findings of Verheggen et al.[52] are in line with the conclusions in the US evidence report[3] that endurance training reduces abdominal fat. Verheggen et al.,[52] however, did not look into the effect of exercise volume on abdominal fat reduction, whereas the US report[3] indicated that the level of fat reduction increased with increasing volume of endurance training.

In conclusion endurance training (40 to >75% VO_2max, 1 to 7 sessions per week, 15 to 90 minutes, for 1 to 15 months) reduces abdominal fat in overweight and obese adults, with larger effects at larger volumes of training.

As the findings in the meta-analysis of Verheggen et al.[52] are in line with the conclusions in the US evidence report,[3] the level of evidence is strong.

Table 10. RCTs into the effect endurance training on abdominal fat in overweight and obese adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a])	Hetero-geneity (I^2 %)
Meta-analysis						
Verheggen 2016[52]	50; 2,404 adults overweight or obese	1-15	Endurance training at 40->75% VO_2max or 40-80% MHR,[b] 1-7 sessions/wk; 15 to 90 minutes per session	Control	-0.47 (-0.56 to -0.39)[c]	68

[a] Confidence interval.
[b] Maximal heart rate.
[c] Hedges' g.

2.5.4 Waist circumference in adults

Summary of evidence for the effect of endurance training and the combination of endurance with resistance training on waist circumference in adults

Aspect	Explanation
Selected studies	2 meta-analyses of 6[32] and 11[13] RCTs
Heterogeneity	Yes in size of effect in one meta-analysis
Strength of the effect/association	-3.09 (-4.14 to -2.04) cm -1.51 (-2.34 to -0.68) cm
Study population	Overweight and obese adults, adults aged 60+ years, apparently healthy and sedentary adults

Conclusion 1: Moderate- and high-intensity endurance training reduces waist circumference.

Level of evidence: Strong.

Conclusion 2: There is too little research to draw a conclusion on the effect of the combination of moderate- and high-intensity endurance training with resistance training on waist circumference.

Explanation
The committee found three meta-analyses into the effect of physical activity on waist circumference (Table 11).[13,32,41] There was no overlap in studies between the meta-analyses.
However, as Thorogood et al.[41] summarised two RCTs with a duration of six months and two RCTs with a duration of 12 months separately, the number of studies was too small to be used for meta-analysis. Therefore, the committee excludes this publication.
Kuhle et al.[32] studied the effect of moderate- to high-intensity endurance training alone (N=3) or in combination with resistance training (N=3) on waist circumference in six RCTs in overweight and obese adults aged 60+. The authors found that training lowered waist circumference by 3 cm. Heterogeneity in the size of the effect was considerable and not further explored, because of the small number of studies.
Murtagh et al.[13] showed that moderate-intensity walking reduced waist circumference by 1.5 cm in comparison to the sedentary control. Hetero-geneity was moderate, and there was an indication of publication bias.

Table 11. RCTs into the effect of endurance training and resistance training on waist circumference in adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a]) (cm)	Heterogeneity (I^2 %)
Meta-analysis						
Kuhle 2014[32]	6; 384 overweight and obese adults 60+ years	3-9	Endurance training at 60-90% VO_2max and/or resistance training on 2 to 3 days/wk	Control	-3.09 (-4.14 to -2.04)	>50
Murtagh 2015[13]	11; 574 adults	2-6	Walking, predominantly at moderate intensity; 2-7 days/wk; 20-60'/session	No intervention, sedentary	-1.51 (-2.34 to -0.68)	38

[a] Confidence interval.
[b] Maximal heart rate.
[c] Not reported.

The findings in the two meta-analyses[13,32] confirm the conclusions in the US evidence report[3] that endurance training reduces abdominal fat.[32] In conclusion, moderate- or high-intensity endurance training reduces waist circumference. As effect sizes differ between meta-analyses, there is considerable heterogenity in one of the effect sizes, and there is a suggestion of publication bias in the other, the committee, therefore, has not quantified the effect.[13,32] In view of the consistent findings between the meta-analyses and US evidence report,[3] the level of evidence is strong. In view of the small number of studies in the meta-analysis by Kuhle et al.[32] on the combination of endurance training and resistance training and the absence of subgroup analyses by training type, the committee concludes that there is too little research to draw a conclusion on the effect of the combination of endurance and resistance training on waist circumference.

2.6 Fat-free mass

Below the committee discusses the effect of physical activity on fat-free mass in older adults. In the Australian evidence report, fat-free mass was not specifically discussed.[2] In the American evidence report,[3] it is stated that resistance training increases fat-free mass and thus reduces the percentage of body fat, but not body weight or (absolute) body fat.

Summary of evidence for the effect of resistance training on fat-free mass in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 18 RCTs and 31 CTs[55]
Heterogeneity	Yes, in size of effect, partly explained
Strength of the effect/association	+1.1 (+0.9 to +1.2) kg
Study population	Adults 50+

Conclusion: Resistance training (50 to 80%1-RM, 2 to 3 times per week, 7 to 39 sets of 2 to 20 repetitions, for 2.5 to 12 months) versus control, increases fat-free mass in adults aged 50 years and over. Level of evidence: Strong.

Explanation

The committee found two recent meta-analyses,[33,55] one[33] of which was described in combination with three other meta-analyses from before 2008[56-58] in the meta-analysis by Peterson et al.[55] Therefore, the committee chooses to describe the latter meta-analysis (Table 12).[55] In addition, the committee found a systematic review of studies in frail older adults.[50]

Table 12. RCTs into the effect of resistance training on fat-free mass in (older) adults

	Number of studies and number of participans	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a]) (kg)	Hetero-geneity (I^2 %)
Meta-analysis						
Peterson 2011[55]	18 RCTs and 31 CTs; 1,328 adults 50+ years	2.5 to 12	50-80%1-RM,[b] 2 to 3 times/wk; 7-39 sets, 2-20 repetitions	Control	+1.1 (+0.9 to +1.2)	84

[a] Confidence interval.
[b] 1-repetition maximum.

Peterson et al.[55] summarised 18 RCTs and 31 CTs in adults aged 50 and over and showed that resistance training increased fat-free mass by about 1 kilogram. There was considerable heterogeneity in the size of the effect. Heterogeneity was partly explained by volume and age: higher volume interventions resulted in larger increases in fat-free mass, whereas with increasing age the gain became less.

In a systematic review, De Labra et al.[50] described two RCTs in frail older adults, one showing an increase in fat-free mass (measured by DEXA) following a combined endurance and resistance training programme, and another showing no significant effect on body composition. In view of the small number of studies, the findings of this systematic review are not conclusive.

Findings in the meta-analyses by Peterson[55] correspond with the conclusion in the American evidence report that resistance training increases fat-free mass.[3]

In conclusion, resistance training (50 to 80%1-RM, 2 to 3 times per week, 7 to 39 sets of 2 to 20 repetitions, for 2.5 to 12 months) versus control increases fat-free mass in adults aged 50 and over. Effects appear stronger in studies with a higher volume of exercise and subjects of a lower age. Because of the heterogeneity in the size of the effect, the committee does not quantify the effect. In view of the consistent findings in the direction of the effect, the level of evidence is strong.

2.7 Muscle strength

Resistance training and muscle strength in older adults

Summary of evidence for the effect of physical activity on muscle strength in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 25 RCTs[59] and one systematic review of 5 RCTs[50]
Heterogeneity	Yes, partly explained
Strength of the effect/association	+1.57 (+1.20 to 1.94) (mean weighted standardised mean difference)
Study population	Healthy older adults, frail older adults

Conclusion: Resistance training versus control improves muscle strength in older adults, with larger effects at increasing intensities. Level of evidence: Strong.

Explanation

The Australian evidence report on adults[2] did not describe the effects of physical activity on muscle strength. The American evidence report[3] stated that in older adults, investigators have used a relatively long duration (4 to 12 months) resistance training alone or in combination with endurance training, endurance/balance, or endurance/resistance/balance/coordination/flexibility regimens to successfully increase strength in an effort to counteract the late-life decline in physical functioning. High-intensity and/or high-velocity resistance training may be particularly effective in enhancing muscle strength. Also resistance training of shorter duration (2-3 months) resulted in improved muscle strength.

The committee found five meta-analyses[59-63] on the effect of resistance training on muscle strength in older adults (Table 13) and one systematic review[50] on the effect in frail older adults. Borde et al.[59] carried out the most recent and comprehensive meta-analysis, focusing on RCTs only, and based on a comparison between an intervention group and a physically inactive control group. The authors also examined how specific training variables as volume, intensity and rest affected muscle strength. Therefore, the committee has based its conclusions on the meta-analysis by Borde et al.[59]

Borde et al.[59] studied both upper and lower extremity muscle strength. If more than one outcome was available, the authors chose the outcome with the highest functional relevance for mobility in old age. In other words, lower extremity muscle strength tests were preferred over upper extremity muscle strength tests; isokinetic or dynamic muscle strength tests were preferred over isometric tests; and multi-joint tests were chosen rather than single-joint strength tests. The authors found that resistance training improved muscle strength by 1.57 (weighted mean standardised mean difference; hereinafter SMD) in healthy older adults. Effects were similar for upper and lower extremities. There was considerable heterogeneity. Dose-response analyses showed that training period, intensity and time under tension modified the effect of resistance training on muscle strength. It seemed that a training period of about 1 year, a training frequency of two sessions per week, a training volume of two to three sets per exercise, seven to nine repetitions per set, a training intensity from 70-79% of the 1-repetition maximum, a total time under tension of 6 seconds, a rest of 60 seconds between sets and 4.0 seconds between repetitions had greater effects on improving maximum voluntary strength in adults. However, these findings are rather preliminary: training periods of 6 to 9 weeks were, for instance, only slightly less effective than 1 year; the range in training frequencies was narrow (2 to 3 sessions per week); high-intensity training produced the largest effects on muscle strength, followed by moderate-intensity training, low-intensity training and inactivity.; the estimation of the optimal number of sets per exercise was limited by the paucity of data; the number of repetitions was strongly correlated with training intensity; results concerning total time under tension and required rest time were limited by the small number of studies and lack of studies into the effect of contraction duration on muscle strength.

Borde et al.[59] also summarised six studies that directly compared resistance training protocols of different intensities. This analysis showed that high-intensity resistance training had the largest effects on muscle strength in comparison to moderate- (high vs. moderate SMD=0.60) or low-intensity (high versus low SMD=0.88) training regimens. Also, moderate-intensity resistance training produced a larger effect than low-intensity resistance training (SMD=0.93). Moderate- and low-intensity resistance training had favourable effects on muscle strength compared with a passive control (SMD=1.75 and 1.02 respectively). Thus the effect increased with increasing intensity.

De Labra et al.[50] described seven trials in frail older adults which measured knee extension strength. Five of the seven showed a significant improvement in knee extension strength following various forms of resistance training, whereas two showed no significant effect. Exercise intensity varied from 30-40 to 70% of 1-repetition maximum. Thus, also in frail older adults, resistance training can be effective in improving muscle strength, although the optimal programme remains unclear.

Compared to the evidence described in the US-report,[3] the meta-analysis by Borde et al.[59] provides additional information on the characteristics of training programmes potentially required for a large improvement in muscle strength.

In conclusion, resistance training versus control improves muscle strength in older adults, with larger effects at increasing intensities. As there was considerable heterogeneity in the size of the effect, the committee did not quantify the conclusion. In view of the consistency in the direction of the effect, the level of evidence is strong.

Resistance training and muscle strength in children and adolescents

Summary of evidence for the effect of resistance training on muscle strength in children and adolescents

Aspect	Explanation
Selected studies	2 meta-analyses of 16[64] and 42 RCTs[65]
Heterogeneity	Yes, in one meta-analysis, partly explained by characteristics of the resistance training programme
Strength of the effect/association	Children and adolescents: +1.12 (+0.90 to +1.34) (standardised effect size) Young athletes: +1.09 (+0.65 to +1.53) (weighted mean of standardised effect size)
Study population	Untrained children and adolescents and young athletes

Conclusion: Resistance training versus control improves muscle strength in young people.
Level of evidence: Strong.

Explanation

The Australian evidence report[1] on children described 15 RCTs, 8 non-randomised CTs, 2 quasi-experimental studies and one longitudinal study on the effect of physical activity on muscle strength. Of the studies that reported increases in muscular strength, the majority used a resistance training programme, including activities of both a moderate and vigorous intensity, and both intensities were sufficient to increase muscle strength. Conclusions regarding a dose-response relationship for frequency, duration and intensity were inconclusive; however, evidence pointed to a beneficial effect for both moderate- and vigorous-intensity resistance training performed at least weekly. In order to achieve gains in muscular health, activities of a vigorous intensity were typically undertaken on 2 to 3 days per week, while moderate-intensity activities were required on 3-5 days per week.

The committee found two meta-analyses and a systematic review on the effect of resistance training on muscle strength in children (Table 13).[64-66] As Granacher et al.[66] based the conclusions on muscle strength in their systematic review on the meta-analysis by Lesinski et al.,[64] the former is not reviewed further.

Behringer et al.[65] described the effect of resistance training in children and adolescents in 69 comparisons in 42 studies: 19% of the comparison groups consisted of novices, 1% had experience with resistance training, and in 80% of the comparison groups training status was not reported; 10% of the comparisons groups consisted of athletes. The authors showed that resistance training improved muscle strength in comparison to control. There was moderate heterogeneity in the size of the effect. Sensitivity analyses showed that the effect was larger in post- and intrapubertal (1.91 +/- 0.41) than prepubertal children (0.81 +/- 0.18). The effect increased with duration of the intervention and the number of performed sessions. The number of performed sets or mean intensity had no effect. The lack of effect of the mean intensity might be explained by

Table 13. RCTs into the effect of resistance training on muscle strength

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a]) (units)	Heterogeneity (I^2%)
Meta-analysis						
Behringer 2010[65]	42; 1,728 children and adolescents 8-18 years	1-14	On average 41' per session; 3 sessions/wk; 2-3 sets of 8-15 repetitions at 60-80% 1-RM[b] on 6-8 exercises	Control	+1.12[c] (+0.90 to +1.34)	37
Lesinski 2016[64]	16; 278 youth athletes 6-18 years	1-18	1-3 sessions/wk; 1-8 sets per exercise of 4-15 repetitions at 35-88% 1-RM, and 20-220 seconds rest between sets	Active control	+1.09[d] (+0.65 to +1.53)	81
Borde 2015[59]	25; 819 older adults 60-90 years	1.5-12	Resistance training	Control	+1.57[d] (+1.20 to 1.94)	80

[a] Confidence interval.
[b] 1-repetition maximum.
[c] Standardised effect size.
[d] Weighted mean standardised mean difference.

the fact that in most studies the intensity ranged from 60-80% of 1-repetition maximum. As lower intensities are less likely to induce changes in muscle strength, they are studied less by the researchers. Effects were larger for training with free weights (1.31 +/- 0.28) than with machines (0.93 +/- 0.13).

Lesinski et al.[64] described the effect in young athletes aged 6-18 years. The training programmes consisted of training with machines, free weights, a combination thereof, functional resistance training, complex training[a] or plyometric training. They showed a beneficial effect of resistance training on muscle strength (weighted mean of standardised mean difference versus control group, SMD, +1.09). There was considerable heterogeneity in the effect size. Subgroup analyses revealed that the effect of conventional resistance training (i.e. not plyometric training) was larger in studies lasting more than 23 weeks (SMD +3.40) than those of shorter duration (SMD not reported). High-intensity conventional resistance training (80-90% 1-RM) resulted in more pronounced improvements (SMD +2.52) compared with lower training intensities (in the range of 30-79% of 1-repetition maximum, SMD not reported). Five sets per training resulted in larger improvements (SMD +2.76) in muscle strength compared with fewer sets (SMD not reported). Six to eight repetitions per set produced the largest effect (SMD +2.42) on muscle strength. Three to four minutes of rest between sets resulted in larger improvements (SMD 2.09) compared with shorter durations of rest (SMD not reported). There was no significant difference in effect of training frequency (1, 2 or 3 times per week). For plyometric training, subgroup analyses showed no significant effect on muscle strength of training frequency.

The effect of resistance training was larger when free weights were used (SMD +2.97) than machines (SMD +0.36), or a combination (SMD +1.16). Functional training and plyometric training also led to smaller increases in strength than resistance training using free weights (SMD +0.62 and 0.39 respectively). In contrast to Behringer et al.,[65] Lesinki et al.[64] did not find any differences in effects on strength between prepubertal and postpubertal children. However, most studies did not report the biological maturity status of participants, which limits the interpretation of these findings.

However, a major limitation of both meta-analyses is that they cannot provide insights into the interactions between reported training parameters (e.g. training frequency, number of sets, intensity), as the analyses were based on a variety of studies using different combinations of training parameters magnitudes.

The meta-analyses by Behringer et al.[65] and Lesinksi et al.[64] largely confirmed the conclusions in the Australian evidence report.[2,64] The overall effects in the meta-analyses are of moderate size.[64]

In conclusion, resistance training improves muscle strength in young people. In view of the consistency in findings with the Australian report, the level of evidence is strong.

[a] Complex training integrates resistance training, plyometrics, and sometimes sport-specific movement.

2.8 Functional performance

In the Australian evidence report, functional parameters, such as gait speed, timed up-and-go test, and short physical performance battery were not described. The American evidence report described a meta-analysis of 62 RCTs that found that progressive resistance training had a modest effect on certain functional parameters, such as gait speed.[3,67]

2.8.1 Gait speed

The committee found five recent meta-analyses[68-72] on the effect of physical activity on gait speed (Table 14). Two of the meta-analyses[68,69] are based on one or all of three previous meta-analyses[70-72], respectively. Therefore, the committee describes the findings of the two first-mentioned.[68,69]

Van Abbema et al.[68] summarised the effect of various forms of exercise on preferred gait speed[a] in 25 RCTs in adults aged 65 and over. They excluded studies solely using a treadmill gait speed, a gait speed test with a load, a turn, or with a course longer than 30 m, as these tests measure other skills besides gait speed. The number of RCTs per type of exercise varied from 3 to 5.

Hortobagyi et al.[69] summarised RCTs and non-randomised CTs on preferred and fast gait speed in healthy older adults. In contrast to Van Abbema et al.,[68] they included various types of gait speed tests. In subgroup analyses, Hortobagyi et al.[69] made a distinction between preferred and fast gait speed and tests involving a short (<30 m) or long distance.

Progressive resistance training and gait speed in older adults

Summary of evidence for the effect of resistance training on gait speed in older adults

Aspect	Explanation
Selected studies	2 meta-analyses of 5 RCTs[68] and 23 CTs and RCTs[69]
Heterogeneity	Yes, in the size of the effect in one of the two meta-analyses, unexplained
Strength of the effect/association	+0.13 (+0.09 to +0.16) m/s
Study population	Healthy and frail older adults

Conclusion: Progressive resistance training (75 to 80% 1-RM, 2 to 3 times per week, 45 to 60 minutes per session, for 2.5 to 6 months) versus habitual activities or attention control activities, improves gait speed in older and frail older adults by 0.13 m/s.
Level of evidence: Strong.

Explanation

Van Abbema et al.[68] showed that progressive resistance training for 2.5 to 6 months improved gait speed by 0.13 m/s (Table 14). Heterogeneity was low. Hortobagyi et al.[69] also showed an improvement in gait speed of 0.11 m/s by resistance training based on 23 CTs and RCTs. Heterogeneity was considerable with respect to the size of the effect. In subgroup analyses, the effect was rather similar between fast and preferred gait speed. It is unclear to what extent this subgroup analysis explains the heterogeneity. The authors did not carry out an analysis of RCTs only.

The findings in the two meta-analyses are in line with conclusions in the

[a] Preferred gait speed is defined as a person's usual or comfortable, self-selected pace and fast gait speed as a person's "as fast as safely possible", self-selected pace.

American evidence report.[3]
In view of the unexplained heterogeneity in the analysis by Horotbagyi et al. and the fact that the two meta-analyses show similar effect estimates, the committee has based its conclusions on the meta-analysis by Van Abbema.[68] In conclusion, progressive resistance training (75 to 80% 1-RM, 2 to 3 times per week, 45 to 60 minutes per session, for 2.5 to 6 months) versus habitual activities or attention control activities improves gait speed in older and frail older adults by 0.13 m/s.

Progressive resistance training and balance training combined and gait speed in older adults

Summary of evidence for the effect of a combination of progressive resistance training and balance training on gait speed in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 4 RCTs[68]
Heterogeneity	Yes, in the size and direction of the effect, unexplained
Strength of the effect/association	+0.02 (-0.05 to +0.10) m/s
Study population	Healthy and frail older adults

Conclusion: There is too little research to draw a conclusion on the effect of progressive resistance training in combination with balance training on gait speed in older and frail older adults.

Explanation

Van Abbema et al.[68] also summarised four RCTs into the effect of progressive resistance training in combination with balance training (Table 14). They found no significant effect of the combination with balance training. There was considerable heterogeneity in size and direction of the effect, which was not further explained and the number of studies was small (N=4).
In conclusion, there is too little research to draw a conclusion on the effect of progressive resistance training in combination with balance training on gait speed in older and frail older adults.

Progressive resistance training, balance and endurance training combined and gait speed in older adults

Summary of evidence for the effect of progressive resistance training, balance and endurance training combined on gait speed in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 5 RCTs[68]
Heterogeneity	No
Strength of the effect/association	+0.05 (0.00 to +0.09) m/s
Study population	Healthy and frail older adults

Conclusion: Progressive resistance training in combination with balance and endurance training improves gait speed in older and frail older adults.
Level of evidence: Weak.

Explanation

Van Abbema et al.[68] summarised 5 RCTs into the combination of progressive resistance training with balance and endurance training (Table

14). This combination improved gait speed by 0.05 m/s, with the lower limit of the confidence interval being zero. Heterogeneity was low.
In conclusion, progressive resistance training in combination with balance and endurance training improves gait speed in older and frail older adults. As the lower limit of the confidence interval was zero and the number of studies is small, the level of evidence is weak.

Physical activity interventions with a rhythmic component and gait speed in older adults

Summary of evidence for the effect of physical activity interventions with a rhythmic component on gait speed in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 3 RCTs[68]
Heterogeneity	No
Strength of the effect/association	+0.07 (+0.03 to +0.10) m/s
Study population	Healthy and frail older adults

Conclusion: Physical activity interventions with a rhythmic component improve gait speed in healthy and frail older adults. Level of evidence: Weak.

Explanation

Van Abbema et al.[68] found a significant effect of physical activity interventions with a rhythmic component lasting two to six months on gait speed (Table 14). Heterogeneity was low. However, this might also be explained by the small number of RCTs on which the meta-analysis is based.
Therefore the committee concludes that physical activity interventions with a rhythmic component improve gait speed in healthy and frail older adults. As the number of studies is small, the level of evidence is weak.

Stretching and gait speed in older adults

Summary of evidence for the effect of stretching on gait speed in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 3 RCTs[68]
Heterogeneity	No
Strength of the effect/association	+0.06 (-0.01 to +0.13) m/s
Study population	Healthy and frail older adults

Conclusion: There is too little research to draw a conclusion on the effect of stretching on gait speed in healthy and frail older adults.

Explanation

Van Abbema et al.[68] found no significant effect of stretching on gait speed (Table 14). Heterogeneity was low. However, this might also be explained by the small number of RCTs that the meta-analysis is based on.
As the effect is not close to zero, the committee concludes that there is too little research to draw a conclusion on the effect of stretching on gait speed in healthy and frail older adults.

Table 14. RCTs into the effect of physical activity, resistance, balance and coordination training, and stretching on gait speed in older adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a]) (m/s)	Heterogeneity (I^2 %)
Meta-analysis						
Van Abbema 2015[68]	5; 239 older adults ≥ 65 years	2.5-6	Progressive resistance training 75-80% 1-RM[b]; 2-3 times/wk; 45-60'	Normal activities or attention control activities	+0.13 (+0.09 to +0.16)	0
	4; 426 older adults ≥ 65 years	3-6	Progressive resistance and balance training	Idem	+0.02 (-0.05 to +0.10)	67
	5; 502 older adults ≥ 65 years	4-6	Progressive resistance, balance and endurance training	Idem	+0.05 (0.00 to +0.09)	15
	3; 228 older adults ≥ 65 years	2-6	Interventions with a rhythmic component	Idem	+0.07 (+0.03 to +0.10)	0
	3; 252 older adults ≥ 65 years	2-11	Stretching interventions	Idem	+0.06 (-0.01 to +0.13)	51
Hortobagyi 2015[69]	23; 613 older adults ≥ 65 years	3.5 on average	Resistance training at 50-80 1-RM	Normal activities, stretching and light physical activity or educational information	+0.11 +/- 0.15[c]	84 9
	8; 198 older adults ≥ 65 years	3 on average	Coordination training; intensity not defined; 31 sessions on average	Normal activities or educational information	+0.09 +/- 0.06[c]	0
	18; 486 older adults ≥ 65 years	4.5 on average	Multimodal training at moderate to high intensity; 41 sessions on average	Normal activities or educational information	+0.09 +/- 0.16[c]	85

[a] Confidence interval.
[b] 1 repetition maximum.
[c] +/- SD.

Coordination training and gait speed in older adults

Summary of evidence for the effect of coordination training on gait speed in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 8 RCTs and CTs[69]
Heterogeneity	Yes, in the direction of the effect, unexplained
Strength of the effect/association	+0.09 +/- 0.06 m/s
Study population	Healthy older adults

Conclusion: Coordination training improves gait speed in healthy older adults.
Level of evidence: Weak.

Explanation

Hortobagyi et al. summarised 8 CTs and RCTs on the effect of coordination training on gait speed (Table 14).The authors showed an improvement of 0.09 m/s. Heterogeneity was considerable and mostly present in the direction of the effect. The effect was larger for fast gait speed (+0.17 m/s) than for preferred gait speed (+0.07 m/s). It is, however, unclear to what extent this subgroup analysis explained heterogeneity. The authors did not carry out an analysis of RCTs only.

The committee concludes that coordination training improves gait speed in healthy older adults. As there was heterogeneity in the direction of the effect and there was no analysis of RCTs only, the level of evidence is weak.

2.8.2 Timed up-and-go test

Summary of evidence for the effect of endurance and resistance training on timed up-and-go test in older adults

Aspect	Explanation
Selected studies	2 meta-analyses of 3[70] and 4[71] RCTs and 1 systematic review of 5 RCTs[50]
Heterogeneity	Yes, in the size of the effect, unexplained
Strength of the effect/association	-0.11 (-2.98 to +2.75) seconds -2.47 (-5.08 to +0.14) seconds
Study population	Frail older adults

Conclusion: There is too little research to draw a conclusion on the effect of endurance and resistance training on timed up-and-go test in frail, older adults.

Explanation

There are two meta-analyses and one systematic review on the effect of physical activity on the timed up-and-go test in frail older adults (Table 15).[50,70,71] There is no overlap in RCTs between the meta-analyses, but there are two RCTs in the systematic review that are described in either the one or the other meta-analysis.[50,71]

Giné-Garra et al.[71] summarised four RCTs in independent-living, frail, older adults. The timed up-and-go test improved in the physical activity group by 2.5 seconds; however, this was not significant. Physical activity interventions consisted of strength, balance and/or endurance training. There was considerable heterogeneity which was mostly present in the size of the effect and was not explored further by the authors.

Table 15. RCTs into the effect of endurance and resistance training on the timed up-and-go test in older adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a]) (s)	Hetero-geneity (I^2 %)
Meta-analysis						
Chou 2012[70]	3 RCTs; 400 older adults 78-86 years	2-3	Ambulatory strength, functional and/or balance training	Usual care; flexibility exercise; home visit	-0.11 (-2.98 to +2.75)	96
Giné-Garriga 2014[71]	4 RCTs; 190 frail older adults (age not reported)	2.5-3	Lower body strength, functional balance and/or endurance 2-3 times/wk; 45-60'/session	Usual care; and/ or advice not to change habits; advice on physical activity and diet	-2.47 (-5.08 to +0.14)	72

[a] Confidence interval.
[b] 1 repetition maximum.
[c] +/- SD

Chou et al.[70] did not find any significant effect of physical activity in the form of ambulatory strength, functional and/or balance training on the timed up-and-go test in frail older adults. There was considerable heterogeneity which pertained to both the size and the direction of the

effect: one small study with 35 participants found a significant deterioration of 10 seconds, whereas the other two respectively showed an improvement of 3 seconds or no effect (+0.4 seconds).
In their systematic review of five RCTs in frail older adults, De Labra et al.[50] describe four RCTs which showed a significant improvement (including the two RCTs from the meta-analyses) and no significant effect in one.
Taken together, the studies indicate that there is a protective effect of physical activity on the timed up-and-go test. However, as the number of RCTs per meta-analysis was small and none of the overall effect estimates were significant, the committee concludes that there is too little research to draw a conclusion on the effect of endurance and resistance training on the timed up-and-go test in frail, older adults.

2.8.3 Short physical performance battery test (SPPB)

Summary of evidence for the effect of the combination of endurance and resistance training on the score on the SPPB in older adults

Aspect	Explanation
Selected studies	1 meta-analysis of 4 RCTs[71]
Heterogeneity	Yes, in the size of the effect, unexplained
Strength of the effect/association	+1.87 (+1.17 to +2.57) units
Study population	Frail older adults

Conclusion: The combination of endurance training and resistance training versus usual care or a social programme improves the score on the SPPB test in frail older adults.
Level of evidence: Weak.

Explanation
There is one meta-analysis[71] on the effect of physical activity (resistance, balance and endurance) on the score on the SPPB test in community-dwelling, frail, older adults (Table 16). Giné-Garriga et al.[71] summarised four RCTs, two small and two large, showing that physical activity improves SPPB-test scores in frail older adults. There was considerable heterogeneity in the size of the effect, which was not further explored.

Table 16. RCTs into the effect of the combination of endurance and resistance training on theSPPB-test scores in older adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a]) (units)	Hetero-geneity (I^2 %)
Meta-analysis						
Giné-Garriga 2014[71]	4 RCTs; 530 frail older adults (age not reported)	2-12	Resistance, balance and endurance 2-5 times/wk; 26-90'/session	Social programme; usual care; and/or advice not to change habits	+1.87 (+1.17 to +2.57)	47

[a] Confidence interval.

In conclusion, the combination of endurance training and resistance training versus usual care or a social programme improves the score on the SPPB test in frail older adults. As there was considerable heterogeneity in the size of the effect, the effect could not be quantified. As the number of studies is relatively small (N=4) and consisted of two large and two small studies, the level of evidence is weak.

2.9 Bone health

For bone health, the committee looked into the effects of physical activity on fracture risk in older adults and on bone density in children.

2.9.1 Older adults: fracture

Summary of evidence for the effect of the combination of endurance training with resistance training on the incidence of fractures in adults

Aspect	Explanation
Selected studies	1 meta-analysis of 9 RCTs and 1 CT[73]
Heterogeneity	No
Strength of the effect/association	RR=0.49 (0.31-0.76)
Study population	(Early) postmenopausal women and older men, 45+ years

Conclusion: The combination of endurance training and resistance training, especially focusing on fall prevention and bone strength (gait, balance, functional, and resistance training; 30% to 90% 1-RM or brisk walking to 85% HRmax or endurance 1 to 7 times per week, 20 to 90 minutes, for 4 to 120 months) versus no exercise, reduces the risk of fractures in older adults.
Level of evidence: Strong.

Explanation

In the Australian evidence report only RCTs on the effect of physical activity on bone mineral density and cohort studies on fracture risk were summarised. There is no description of the evidence for an effect of physical activity on fracture risk from RCTs.[2] The US report states that there are no large RCTs to determine whether physical activity reduces the risk of fractures and mentions only one small RCT.[3]

There are two meta-analyses[73,74] and one multi-centre RCT[75] of the effect of exercise on the incidence of fractures in older adults (Table 17). Kemmler et al.[73] summarised nine RCTs and one non-randomised CT and El-Khoury et al.[74] summarised 6 RCTs, four of which were also summarised by Kemmler et al.[73] Kemmler et al.[73] showed that exercise predominantly focusing on bone strength and fall reduction reduces the risk of fractures by 51%. Heterogeneity was low. There was, however, some suggestion of publication bias. One explanation for the publication bias is that risk of fractures was a secondary endpoint in most studies, which might make it more likely that studies with positive effects were reported.

El-Khoury et al.[74] summarised the effect of fall prevention exercise programmes on fall-related fractures in community-dwelling older adults. The authors found a 61% reduced risk of fall-related fractures. Heterogeneity was low. However, there was some indication that studies were more likely to report injurious falls when there tended to be a positive effect on them. The authors do not provide information about whether this was also the case for fall-related fractures. However, as the injuries in ‘injurious’ falls consist for a large part of fall-related fractures, the committee considers this likely.

In addition to the meta-analyses, there is a recent multicentre RCT, the LIFE-study, that showed that a moderate physical activity intervention, not specifically designed to reduce the risk of fractures, reduced risk of fractures by 13% (not significant).[75]

In conclusion, the combination of endurance training and resistance training, especially focusing on fall prevention and bone strength (gait, balance, functional, and resistance training; 30% to 90% 1-RM or brisk walking to 85% HRmax or endurance 1 to 7 times per week, 20 to 90 minutes, for 4 to 120 months) versus no exercise reduces the risk of fractures in older adults. Because there are indications of publication bias, the effect was not quantified. The level of evidence is strong, as, although there were weak indications for publication bias, the reduction in relative risk was considerable and the findings were consistent.

Table 17. RCTs into the effect of the combination of endurance training with resistance training on the risk of fractures in older adults

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Number of cases	RR of fracture (95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis							
Kemmler 2013[73]	10; 1,424 adults ≥ 45 years	6-120	Focus on bone strength, fall reduction, physical functioning, back pain; 30% to 90% 1-RM[b] or brisk walking to 85% HRmax[c]; 1-7 times/wk; 20-60’	No intervention, no exercise, usual care, social interaction, wellness programme or exercise for upper limbs	109	0.49 (0.31-0.76)	17
El Khoury 2013[74]	6; 913 adults > 60 years	4-12	Gait, balance and functional training; either or not in combination with flexibility; modified Tai Chi exercises; strengthening; physical activity; endurance; 3-7 times/wk; 20-90’ per session	No intervention, no exercise, usual care, social interaction, wellness programme, group discussions, seminars, or exercises not designed to improve fitness or balance	n.r.[d]	0.39 (0.22– 0.66)	0
LIFE-study 2015[75]	1; 1,635 older adults 70-89 years	31; multicentre-RCT	Endurance (150’ /wk; 30’ per session), resistance (10’ per session), flexibility (3-5’ per session) and balance training (10’ per session); moderate intensity; 5-6 times/pw; 150 min/wk	Health education programme	142 n.r. in men n.r. in women	0.87 (0.63-1.19)[e] Men: 0.47 (0.25-0.86) Women: 1.12 (0.77-1.64)	n.a.[f]

[a] Confidence interval.
[b] Not reported.
[c] 1 repetition maximum.
[d] Maximal heart rate.
[e] Fall-related fractures.
[f] Not applicable.

2.9.2 Children: bone mineral density

Summary of evidence for the effect of weight-bearing exercise on bone mineral density in children

Aspect	Explanation
Selected studies	1 meta-analysis of 27 randomised and non-randomised CTs on bone mineral content and 10 RCTs on areal bone mineral density[76]
Heterogeneity	No
Strength of the effect/ association	Bone mineral content: +0.17 (+0.05 to +0.29) (Hedges' g) Areal bone mineral density: +0.17 ± 0.09 (Hedges' g)
Study population	6-16 year old children and adolescents

Conclusion: Weight-bearing exercise (1 to 5 times per week, 10 to 60 minutes per session, for 2.5 to 48 months) versus control, improves bone mineral content and areal bone mineral density, especially in prepubertal children. The effect is small (Hedges' g = 0.17).
Level of evidence: Strong.

Explanation
In the Australian evidence report,[1] 13 studies (7 RCTs and 6 CTs) were summarised on the impact of physical activity on skeletal health (bone mineral content or density). Ten of these studies reported significant benefits, while three did not. Benefits were found for a wide range of physical activities, including sport participation, physical education, endurance and resistance exercises. However, the most consistent results were found for high-impact activities such as jumping. Each of the studies that used high-impact activity were conducted on a minimum of three days per week. Some evidence was present, with moderate-impact physical activity conducted on three days per week found not to improve skeletal health, while higher-impact activities did. In the report it was concluded that further research is needed that explicitly examines a dose-response relationship between physical activity and skeletal health for the frequency, intensity and time of physical activity.[1]
The committee found four meta-analyses[51,76-78] on the effect of weight-bearing exercise,[a] such as jump-training or resistance-training programmes on bone mineral content and density in children and adolescents (Table 18). Two of the three meta-analyses suffered from methodological limitations, as effect sizes were not adjusted for changes in the control group.[77,78] The seven studies described in the meta-analysis by Nogueira et al.,[51] were also summarised in a meta-analysis by Behringer et al.[76] in combination with 20 other studies. Therefore, the committee has based its conclusions on the latter meta-analysis.[76]
Behringer et al.[76] summarised 27 randomised and non-randomised studies, showing that weight-bearing exercise improved bone mineral content by 0.17 and areal bone mineral density[b] by 0.26. Heterogeneity was low. However, funnel plots suggest the possibility of publication bias for both outcome measures which means that the effect is possibly overestimated.
There was no significant difference in effect size between randomised and

[a] Exercise during which the body works against the force of gravity and the feet and legs carry a person's weight.
[b] Areal bone mineral density is the bone mineral content, measured by dual-energy x-ray absorptiometry (DEXA), divided by the bone area in square centimetres.

non-randomised trials for bone mineral content (0.18 ± 0.01 versus 0.15 ± 0.01), whereas the effect on areal bone mineral density tended to be smaller in 10 randomised trials in comparison to 4 non-randomised (0.17 ± 0.09 versus 0.55 ± 0.35; n.s.). Effects on bone mineral content were larger in prepubertal than in pubertal or postpubertal children (0.28 ± 0.01 versus 0.02 ± 0.00); there was a similar trend in areal bone mineral density (0.33 ± 0.19 versus 0.16 ± 0.10). The effect of resistance training type (body weight, resistance training machines or a combination) did not differ significantly.

The findings of the meta-analysis confirm the conclusions in the Australian evidence report that most consistent effects were found for high-impact exercise (such as jumping), but also underline the importance of other weight-bearing exercises such as resistance training.

In conclusion, weight-bearing exercise (1 to 5 times per week, 10 to 60 minutes per session, for 2.5 to 48 months) versus a control improves bone mineral content and areal bone mineral density, especially in prepubertal children. The effect is small (Hedges' g = 0.17). In view of the consistent effects, the level of evidence is strong.

2.10 Musculoskeletal injuries

The Australian evidence report on children[1] concluded that there is too little research to reach a conclusion on the relationship between physical activity and negative health outcomes including injury and fracture.

The Australian evidence report on adults[2] based its description of negative health effects of physical activity primarily on the US evidence report.[3] As literature on physical activity in relation to injuries is rather scarce, the evidence from RCTs, cohort studies and a not peer-reviewed systematic review were described collectively.

Physical activity promotion and the risk of musculoskeletal injuries

Conclusion: An increase in physical activity is unlikely to increase the risk of severe injury, and a small proportion of individuals who increase their physical activity can be expected to experience minor injuries.

Level of evidence: Weak.

Explanation

In the US report[3] it is stated that the risk of activity-related injury is greater in people who are more active. As active people are less likely to be injured in other contexts (e.g. at work), the overall risk of injury is not greater in active than in inactive people. The conclusion is based on two population-based studies conducted by the same research group. One reported that people who ran or participated in sports activities were 50% more likely to report an injury (sports-related or not) than people who reported walking or were sedentary.[79] The other reported no significant differences in overall injury rates (activity-related or not) between inactive people, active people, and people who met the current recommendations for physical activity.[80]

Table 18. RCTs into the effect of weight-bearing exercise on bone mineral density in children

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis						
Behringer 2014[76]	25 randomised and non-randomised CTs; 2,686 children and adolescents 4-16 years	2.5-48	Weight bearing exercise intensity not reported; 1-5 sessions/wk; 10-60'	Control, not specified	Bone mineral content +0.17 (+0.05 to +0.29)[b]	16
	14 randomised and non-CTs	2.5-48	See above	See above	Areal bone mineral density: +0.25 (+0.03 to +0.46)[b]	21
	10 RCTs				0.17[b] ± 0.09	n.r.[c]
	4 non-randomised CTs				0.55[b] ± 0.35	n.r.

[a] Confidence interval.
[b] Hedges' g.
[c] Not reported.

In a more recent publication Morrow et al.[81] showed that, in a cohort of 909 women, meeting versus not meeting the American physical activity guidelines was associated with increased risk of musculoskeletal injuries for up to three years of follow up (HR=1.39; 1.05-1.85), but was not significantly associated with musculoskeletal injuries unrelated to physical activity (HR=0.99; 0.75-1.29) or with musculoskeletal injuries overall (HR=1.15; 0.95-1.39). According to the US evidence report,[3] injury rates at the level of activity commonly recommended (150 minutes per week of moderate intensity, or about 500 MET-minutes per week of activity) have been uncommonly documented but appear to be low.

The committee found a systematic review of the Canadian BC Injury Research and Prevention Unit,[82] which was, although not peer-reviewed, of good quality, in which 55 intervention studies were summarised that studied the effect of physical activity promotion on the risk of injuries. In most studies, authors did not provide information that clearly indicated how injuries were defined and whether they were evaluated during exercise only, or also during other forms of physical activity. 82% of the studies had an RCT design. The majority of physical activity promotion programmes incorporated more than one type of exercise, including endurance or resistance training, stretching or flexibility training, and balance training. Almost two-thirds of the reports did not clearly indicate how participants were asked to report injuries related to physical activity. In the other studies, injuries were assessed with a questionnaire, recorded in diaries or logs, measured through the use of a trial-related monitoring system for adverse events, or self-reported without an explanation as to how they occurred.

The Canadian report[82] states that in only one of the 11 studies that included children and/or adolescents were any injuries reported that occurred during the prescribed exercise sessions. In one of the few studies in which injury was a primary outcome, Collard et al.[83] reported injury rates of 0.33 per 1,000 hours of physical activity for a sub-sample of the intervention group who engaged in high levels of physical activity. In the other nine studies, the authors reported that no injuries occurred or were reported during the physical activity promotion as part of the intervention.

The Canadian report[82] states that in 7 of 9 studies in adults under the age of 65 years, one or more participants were reported to have experienced injuries. In one of the few studies in which injury was a primary outcome, Janney and Jakicic[84] reported that 13% of participants reported lower body musculoskeletal injures that could be attributed to any form of physical activity over an 18-month period. In the study three groups of overweight and obese participants were encouraged to walk for 150, 200, and 300 minutes per week, and the control group was given printed materials related to exercise, but no specific prescription. No significant differences were observed between four intervention groups in the frequency of injury.

The Canadian report[82] states that in 5 of 12 studies that included adults of the age of 65 years or over, one or more participants were reported to have experienced injuries.[82] In one of the few studies in which injury was a primary outcome, Campbell et al.[85] stated that the number of subjects reporting a musculoskeletal injury did not differ between the moderate-to-vigorous endurance training and the usual lifestyle control group (27% vs. 28%). The most common causes of injury were sports and other forms of physical activity (55% intervention group and 30% control group, not significant).

The committee agrees with the conclusion in the Canadian report[82] that an increase in physical activity is unlikely to increase the risk of severe injury, and only a small proportion of individuals who increase their physical activity can be expected to experience minor injuries. In view of the limited number of studies in which the risk of injuries was studied systematically, the level of evidence is weak.

Characteristics of physical activity and the risk of injury

Conclusion: The risk of injury is higher for collision or contact sports than for limited- or non-contact activities.
Level of evidence: Strong.

Conclusion: There is too little research to draw a conclusion on the effect of specific training characteristics in terms of frequency, duration or intensity of the activity on the risk of injuries during training.

Explanation

The Australian and US reports[2,3] state that the risk of injury during activity largely reflects the frequency and force of contact with others (e.g. in team sports), the ground, or objects (e.g. a hockey stick). Activities with less frequent and less forceful contacts have lower rates of injury (a cohort

study reported 0.3 and 1.2 injuries per 1,000 hours of golf and walking respectively) than collision and contact sports (7.0 and 9.1 per 1,000 hours of volleyball and basketball respectively). The American evidence report based its conclusion on five surveys of the general population. According to the two evidence reports, both the overall amount of activity, and the rate of change in this amount, are determinants of injury.[2,3] In other words, the same amount of new activity is more likely to cause injury in inactive than in active people. Gradual augmentation of activity levels is, therefore, associated with fewer injuries in inactive populations. Although there is little research, it is thought that increasing the frequency, duration or intensity of activity can be associated with injury, but that the overall volume is also important. In general, injury rates from walking are thought to be lower than from running, but few studies have adjusted for the total amount of activity, and runners generally do more in terms of volume than walkers. Two recent systematic reviews focusing on the association between training characteristics and injury risk confirm the finding that there is little conclusive evidence.[86,87] Oostergaard-Nielsen et al.[86] concluded that it was not possible to identify which training characteristics[a] were related to running-related injuries in novice, recreational, and elite athletes. Drew et al.[87] found that training load was associated with an increased risk of injuries in 15 studies and with a decreased risk in 10 studies.
In conclusion, the risk of injury is higher for collision or contact sports than for limited- or non-contact activities. In view of the consistent evidence, the level of evidence is strong. There is too little research to draw a conclusion on the effect of specific training characteristics in terms of frequency, duration or intensity of the activity on the risk of injuries during training.

2.11 Cognitive decline

Summary of evidence for the effect of physical activity on cognitive function

Aspect	Explanatory notes
Selected studies	3 meta-analyses of 8, 12 and 12 RCTs[88, 89, 90]
Heterogeneity	Not reported
Strength of the effect/association	Overall cognition and memory: no effect;[88] Working memory g is +0.123 (+0.021 to +0.225); Memory g is +0.128 (+0.015 to +0.241);[89] No effect on memory.[90]
Study populations	18 yrs and above;[89] 55 yrs and above.[88, 90] Subjects without cognitive impairment

Conclusion: The evidence for an effect of physical activity on cognitive function in older adults without cognitive impairments is ambiguous.

Explanation

The Australian evidence report does not cover dementia, Alzheimer or mild cognitive impairment as an outcome.[2] The American evidence report describes a meta-analysis of 18 RCTs showing that endurance training improved performance on all cognitive tasks.[3,91]
We identified no RCTs with the incidence of dementia as an outcome, neither in the general population nor in individuals with mild cognitive impairment. We found five meta-analyses on the effect of physical

[a] In terms of volume, distance or mileage, time or duration, frequency, intensity, speed or pace.

activity on cognitive function that have been published since 2008 (Table 19).[88-90,92,93]

In the meta-analysis by Zhu et al.,[88] the effect on cognition was studied in combined cognitive and physical activity interventions compared to cognitive intervention alone in healthy older adults. The authors combined 6 randomised controlled trials with 3 non-randomised trials. Interventions consisted mostly of combinations of flexibility, resistance, endurance, coordination, and balance exercises. They found no indications for a difference in effect on overall cognition or memory. There were no indications for heterogeneity. Zhu et al.[88] did not describe whether the intervention resulted in a change in total physical activity either in the intervention or in the control group.

Four other meta-analyses[89,90,92,93] on the effect of physical activity on cognition have been published since 2008. As Smith et al.[89] and Young et al.[90] also summarised the results of previous meta-analyses, the committee describes the results of these two meta-analyses.

In 2010, Smith et al.[89] performed a systematic review and meta-analysis of RCTs in adults of 18 years and above without cognitive impairment, covering the period 1966 to 2009. In most studies, participants were older adults. They included interventions with a duration of at least 1 month, incorporating endurance training components and reporting on a range of neurocognitive functions. In total, they included 29 studies in the meta-

Table 19. Meta-analyses of the effect of physical activity and endurance training on cognitive function

	Number of studies and number of participants	Study duration (month)	Intervention (intensity, frequency, duration)	Control	Memory (effect size and 95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis						
Smith et al., 2010[89]	12; Number of participants not reported separately; overall 2,049 participants included 18-94 years[b]	At least 1 month	Endurance training components	Non-endurance training	Working memory +0.123 (+0.021 to +0.225);[c] Memory +0.128 (+0.015 to +0.241)[c]	n.r.[d]
Young 2015[90]	12; 754 individuals without cognitive impairment > 55 years	2-6	Endurance training of any intensity, duration or frequency aimed at improving cardiorespiratory fitness	No treatment, resistance or balance exercise, or programme-me of social activities	No effects were found on verbal memory, visual memory, working memory, or delayed memory functions	Varied
Zhu 2016[88]	9; N n.r. adults > 50 years 8; N n.r. adults > 50 years	1.5-20	Combined physical activity and cognitive intervention	Cognitive intervention	Overall cognition: +0.06 (-0.12 to +0.25)[e] Memory -0.02 (-0.22 to +0.18)[e]	0 0

[a] Confidence interval.
[b] Participants were in the majority of studies ≥ 60 years.
[c] Hedges' g.
[d] Not reported.
[e] Standardised mean difference.

analysis. They presented effect sizes separately for attention and processing speed, executive function, and memory and working memory. As far as working memory is concerned, they calculated effect sizes, reported as Hedges' g and 95% CI, based on 12 RCTs. The effect sizes for memory were based on the same studies (minus 2) plus 6 additional studies. The overall effect sizes are represented in the Table 19. Their conclusion (with regard to memory) was that endurance training is associated with modest improvements in memory, with the effects on working memory being less consistent. Smith et al.[89] did not describe whether the intervention in the included RCTs resulted in a change in total physical activity in the studied groups (intervention or control). In their discussion they also reviewed previous meta-analyses published in 2008 or before,[91-96] explaining why the stronger effects found in some of these studies might be due to methodological limitations.

A recent review by the Cochrane collaboration[90] reached a different conclusion. They included 12 trials, nine of which were also included in the meta-analysis by Smith et al.[89] Together, the trials included 754 participants without cognitive impairment. Trials lasted from 8 to 26 weeks and compared endurance training of any intensity, duration or frequency, aimed at improving cardiovascular fitness, with either no intervention, or resistance or balance exercises, or a programme of social activities. For inclusion in the meta-analysis, it was a requirement that objective measures of cardiovascular fitness had been reported. As far as quality was concerned, they judged that the risk of bias was moderate to high for all the trials. As endpoints 11 cognitive domains were used, tested with neuropsychological tests or a test battery. Within the category memory, verbal memory, visual memory, working memory, and (delayed) memory function were distinguished. The authors concluded that the meta-analysis showed no evidence of benefit in any cognitive domain, also not when exercise was found to have improved cardiorespiratory fitness. They also commented on possible explanations for the discrepancy with results from previous meta-analyses (mentioned above).

Because the conclusions in the three meta-analyses are equivocal, the evidence for an effect of physical activity on cognitive function in cognitively-healthy older adults is ambiguous.

2.12 Depressive symptoms

Endurance and/or resistance training and depressive symptoms in adults

Summary of evidence for the effect of endurance and/or resistance training on depressive symptoms in adults

Aspect	Explanation
Selected studies	2 meta-analyses of 14 RCTs[97] and 40 RCTs[98]
Heterogeneity	Yes, in size of effect
Strength of the effect/association	-0.36 (-0.64 to +0.08)
Study population	Older adults who do not have disorders of orientation and who are capable of independent living

Conclusion: Moderate- to vigorous-intensity endurance and/or resistance training lowers depressive symptoms in adults.
Level of evidence: Strong.

Explanation

In the Australian evidence report,[2] it was concluded that the evidence provides strong support that physical activity is associated with psychosocial health benefits in otherwise healthy adults. The research demonstrates small to moderate effects with significant heterogeneity, indicating wide individual variation in psychosocial benefit. The evidence is strongest for a protective effect against depression. This conclusion was based on the American evidence report[3] and four more recent meta-analyses, three of which summarised intervention studies.

According to the Australian review,[2] there was insufficient evidence to make recommendations on the specific dose of physical activity, although some general trends were observed. In almost all studies, some activity was better than none. The type of physical activity, or an improvement in fitness, did not appear important. There was some evidence of beneficial effects from low-intensity activity and low-dose of activity, e.g. 1-3 sessions per week, 1-2 hours per week, increases of 1 hour per week, etc. for depressive symptoms. The evidence report did not specifically focus on older adults. The committee found one more recent meta-analysis[97,a] on effects of exercise on depressive symptoms in older adults who did not have disorders of orientation and who were capable of independent living (Table 20). The authors found no significant effect of physical activity on depressive symptoms, which was measured by the Geriatric Depression Scale in most RCTs. There was considerable heterogeneity mostly in the size of the effect. Subgroup analyses showed a significant reduction after three months, which was no longer significant after six or twelve months. In each subgroup analyses, heterogeneity remained considerable. There were also indications of mild publication bias.

The findings by Park et al.[97] point in the same direction as the findings from four other systematic reviews and/or meta-analyses that had previously been described by the Australian evidence report,[2] but appear less convincing due to the considerable heterogeneity in the size of the effect and indications of mild publication bias. Therefore, the committee also bases its conclusion on the meta-analysis by Rethorst et al.,[98] which was the only meta-analysis of the three in the Australian evidence report exclusively focusing on RCTs.[98-101]

Rethorst et al.[98] summarised 40 RCTs in non-clinical subjects. Studies compared moderate- to vigorous-intensity endurance and/or resistance training with no treatment or waiting list control. The authors showed a moderate overall protective effect. There was considerable heterogeneity

[a] The meta-analysis completed by Conn et al. in 2010[99] is included in the Australian evidence report.[2]

in the size of the effect. However, as subgroup analyses were only carried out for the combination of RCTs in clinical and non-clinical populations, it is not certain to what extent heterogeneity was explained by age, sex, exercise type and training characteristics.
In conclusion, moderate- to vigorous-intensity endurance and/or resistance training lowers the risk of depressive symptoms. In view of the considerable heterogeneity in the effect size of the two meta-analyses,[97,98] the committee does not quantify the association. In view of the consistency in the direction of the effect, the level of evidence is strong.

Endurance training and depressive symptoms in children and adolescents

Summary of evidence for the effect of endurance training on depressive symptoms in children and adolescents

Aspect	Explanation
Selected studies	1 meta-analysis of 5 RCTs[102]
Heterogeneity	Yes, in the size of the effect, unexplained
Strength of the effect/association	-0.34 (-0.56 to -0.12)
Study population	Children and adolescents 9-18 years, from the general population (1 RCT) or individuals at risk of depressive symptoms (4 RCTs)

Conclusion: Moderate- to high-intensity endurance training (2 to 3 sessions per week, 20 to 90 minutes per session, for 3 to 7 months) versus usual care or light physical activity, lowers depressive symptoms in children and adolescents at risk of depressive symptoms.
Level of evidence: Strong.

Explanation
In the Australian evidence report on children,[1] several mental health indicators such as quality of life, depression, self-esteem, physical perceptions, anger and emotional problems and perceived stress were collectively described. The report concludes that the accumulation of evidence suggests that, for mental health benefits, a minimum of moderate to vigorous-intensity physical activity is needed on at least three days per week for 60 minutes each day. One RCT in children with a BMI > 85 percentile is described in detail, showing that 20 minutes of moderate to vigorous-intensity physical activity for 13 weeks improved depressive symptoms in comparison to no moderate to vigorous-intensity physical activity, and that 40 minutes provided benefits beyond those reported for 20 minutes.[103] The report concludes with the remark that more experimental evidence is needed on the impact of varying intensities of physical activity on mental health.[1]
There is one meta-analysis on the effect of physical activity interventions on depressive symptoms in children and adolescents, summarising five RCTs (Table 20).[102] Brown et al.[102] summarise the studies in other systematic reviews[104-106] and also include the RCT[103] referred to in the Australian evidence report.[1] They showed that physical activity improved depressive symptoms in children and adolescents in comparison to a control. In four of the five RCTs children were at risk of depressive symptoms (e.g. obese, labelled criminally institutionalised). Endurance training was the most common activity and a variety of assessment tools

Table 20. RCTs into the effect of endurance and/or strength training on depressive symptoms

	Number of studies and number of participants	Study duration (months)	Intervention (intensity, frequency, duration)	Control	Change compared to control (95%-C.I.[a])	Heterogeneity (I^2 %)
Meta-analysis						
Park 2014[97]	14; 1,875 older adults 65+ years	1-24	Walking, resistance training, balance training, qigong, tai chi, dance 1-3 times/wk; 30-60'/ session	No exercise: no treatment/ placebo, routine nursing care, counselling or health education	-0.36[b] (-0.64 to +0.08)	93
	10	> 3			-0.34[b] (-0.65 to -0.02)	74
	9	> 6			-0.42[b] (-1.12 to +0.28)	95
	5	> 12			-0.29[b] (-0.82 to +0.24)	96
Rethorst 2009[98]	40; 2,408	Acute-12	Moderate to vigorous endurance and/or resistance training	Waiting list or no treatment	-0.59[c] (-0.67 to -0.50)	84
Brown 2013[102]	5; 425 children and adolescents 9-18 years at risk of depressive symptoms	3-7	Endurance training, physical fitness programme, vigorous exercise, yoga-based physical activity; moderate or high intensity; 2-3 sessions/wk; 20-90'/session	Usual physical education; light physical activity; flexibility	-0.34[c] (-0.56 to -0.12)	66

[a] Confidence interval.
[b] Standardised mean difference.
[c] Hedges' g.

was used to measure depressive symptoms.

There was considerable heterogeneity in the size of the effect: all five RCTs showed an improvement, which was significant in two. As the analysis of the RCTs was already a subgroup analysis, heterogeneity within this group of studies was not further explored.[102] The findings are in line with the conclusion in the Australian evidence report.

In conclusion, moderate- to high-intensity endurance training (2 to 3 sessions per week, 20 to 90 minutes per session, for 3 to 7 months) versus usual care or light physical activity improves depressive symptoms in children and adolescents at risk of depressive symptoms. Because of unexplained heterogeneity in the size of the effect, the effect cannot be quantified. The level of evidence is strong.

2.13 Conclusion

There is strong evidence for the beneficial effects of moderate- to vigorous-intensity endurance training on systolic blood pressure, insulin sensitivity, cardiorespiratory fitness, body weight, fat mass, abdominal fat, and waist circumference in adults. Resistance training has beneficial effects on systolic blood pressure and insulin resistance. The combination of the two training types also improves insulin sensitivity. Both types of training at moderate to vigorous intensity lower depressive symptoms.

In older adults, resistance training improves fat-free mass, muscle strength, and gait speed. The combination of endurance and resistance training reduces the risk of fractures.

There is strong evidence that moderate- to vigorous-intensity endurance training improves cardiorespiratory fitness in children and adolescents, reduces gain in BMI and fat mass in overweight and obese children and adolescents, and lowers the risk of depressive symptoms in children and adolescents at risk of these symptoms. Resistance training improves muscle strength and weight-bearing exercise improves bone mineral content and density in young people. The combination of endurance training and resistance training improves insulin sensitivity in children and adolescents.

The risk of injury is higher for collision or contact sports than for limited- or non-contact activities.

There is weak evidence for the beneficial effects of physical activity on the risk of diabetes and dynamic resistance training on systolic blood pressure in adults. There is also weak evidence for the beneficial effect of various other types of exercise: high-intensity interval (versus continuous) training improves insulin sensitivity in adults at increased risk of cardiovascular disease, and improves cardiorespiratory fitness in adults, and endurance versus resistance training lowers body weight in overweight and obese adults.

In older adults, progressive resistance training in combination with other forms of training, physical activity interventions with a rhythmic component, and coordination training improve gait speed, and the combination of endurance with resistance training improves the score on the short physical performance battery.

In adolescents, high-intensity interval training reduces gain in BMI and fat mass, and, in both children and adolescents, bone-strengthening exercise reduces gain in fat mass. There is also weak evidence that an increase in physical activity is unlikely to increase the risk of severe injury, and a small proportion of individuals can be expected to experience minor injuries.

It is unlikely that light-intensity exercise and flexibility training affect systolic blood pressure in healthy adults, or that moderate-intensity endurance training affects LDL cholesterol in healthy adults.

In school children and adolescents it is unlikely that moderate- to high-intensity physical activity affects systolic blood pressure or BMI or that physical activity affects LDL cholesterol.

In adults, the evidence for an effect of progressive resistance training on LDL cholesterol and of high-intensity interval training (versus control) on insulin sensitivity is ambiguous.

In addition, the evidence for an effect of physical activity on cognitive function in older adults without cognitive impairments is ambiguous.

There is too little research to draw a conclusion on the effect of high-intensity interval (versus continuous) training on insulin sensitivity in healthy adults, on the minimum required duration of exercise bouts for improving cardiorespiratory fitness, and on the effect of the combination of endurance training with resistance training on systolic blood pressure and waist circumference.

For frail, older adults, there is too little research to draw a conclusion on the effect of progressive resistance training in combination with balance training or the effect of stretching on gait speed and on the effect of physical activity on the timed up-and-go test.

Finally there is too little research to draw a conclusion on the effect of specific training characteristics in terms of frequency, duration, or intensity of the activity on the risk of injuries during training.

03 cohort studies physical activity

In this chapter, the association between physical activity and the risk of all-cause mortality; cardiovascular diseases: coronary heart disease, stroke, and heart failure; breast cancer, colorectal cancer, and lung cancer; diabetes; disability; fractures; osteoarthritis; dementia and cognitive decline; and depressive symptoms is described. The committee did not find any meta-analyses of cohort studies on physical activity and risk of developing chronic obstructive pulmonary disease. This topic was also not reviewed in the Australian and American evidence reports.[2, 3] The committee found three cohort studies on the association between objectively-measured physical activity and the risk of all-cause mortality; it did not identify these types of study for the remaining outcome measures.

3.1 All-cause mortality

Summary of evidence for the association between physical activity and all-cause mortality

Aspect	Explanation
Selected studies	1 analysis of 6 cohorts,[107] 1 multi-centre cohort study,[108] and 1 meta-analysis of 9 cohorts[109]
Heterogeneity	Yes, between pooled centres in one pooled analysis, unexplained; not reported in the other; yes in meta-analysis
Strength of the association	Leisure-time physical activity RR= 0.80 (0.78-0.82) at >0 to <450 MET-min/wk vs. none RR=0.69 (0.67-0.70) at 450 to <900 MET-min/wk vs. none RR=0.63 (0.62-0.65) at 900 to <1,350 MET-min/wk vs. none RR=0.61 (0.59-0.62) at 1,350 to <2,400 MET-min/wk vs. none RR=0.61 (0.58-0.64) at 2,400 to <4,500 MET-min/wk vs. none RR=0.69 (0.59-0.78) at ≥4,500 MET-min/wk vs. none
Study population	Europe, North America, Australia

Conclusion: Leisure-time physical activity is associated with a lower risk of all-cause mortality in comparison to no leisure-time physical activity: >0 to <450 versus 0 MET-min per week of leisure-time physical activity is associated with a 20% lower risk and 450 to <900 MET-min per week with a 31% lower risk, and increasing amounts of leisure-time physical activity are associated with progressively decreasing risk to almost 40% at 900 to <4,500 MET-min per week. Level of evidence: Strong.

Explanation

The Australian evidence report[2] describes the findings in the American evidence report[3] and more recent meta-analyses. In the American evidence report[3] it was concluded that moderate physical activity was associated with a 30% lower risk of death during on average 11-12 years follow-up compared to no or low physical activity. More recent meta-analyses described in the Australian report confirm this finding, some suggesting that the reduction in relative risk is larger in women than in men. Another meta-analysis which is described in the Australian report showed a larger risk reduction for leisure-time physical activity (35%) and activities of daily living (36%) than for occupational physical activity (17%). The committee has found two pooled analyses, one multi-cohort study and two meta-analyses on physical activity and mortality (Table 21).[107-111] One of the pooled analyses[107] was an update of the other one.[110] Therefore the latter was excluded. Arem et al.[107] pooled data from six studies in the

National Cancer Institute Cohort Consortium. In comparison to no leisure-time physical activity, performing less than 450 MET-min/wk[a] was associated with a 20% decrease in the risk of all-cause mortality. In stratified analyses risk was 25 to 30% lower at higher levels of physical activity. There was no evidence of harm at levels of ≥4,500 MET-min/wk. There was considerable heterogeneity between cohorts for all physical activity categories. Cohort-specific risk estimates and excluding cohorts from analysis one at a time showed results consistent with the main findings, although heterogeneity remained moderate to considerable. According to the authors, the heterogeneity might partly be explained by differences in questionnaires between cohorts, variations in baseline age, relative physical fitness, and length of follow-up. Stratified analyses showed that the upper threshold of benefit was consistent in men and women, different age groups, various lifestyle factors, and individuals with, and without, CVD and cancer.

When comparing intensity activity levels, levels of moderate-intensity activity up to 450 MET-min per week and 450-900 MET-min/wk were associated with a lower risk (20% and 27% risk reduction respectively) that was not further reduced at higher levels of intensity. For vigorous-intensity activity, any level was associated with an approximate 20% lower mortality risk.[107]

Hupin et al.[109] summarised the association between moderate-to-vigorous physical activity and risk of mortality in nine cohort studies carried out in people aged 60 and above and found similar risk reductions as Arem et al.[107] A low dose of moderate-to-vigorous physical activity was associated with a 22% reduction in mortality risk in comparison to none, a moderate dose was associated with a 28% risk reduction, and a high dose with a 35% risk reduction. There was moderate heterogeneity, which related to the size of the association and not to the direction. The authors did not report subgroup analyses. Results of one study (the Cardiovascular Health Study) were included in the meta-analysis after both five and 13 years follow-up. As results were not different from those in other studies, the committee considers this of minor concern.[109]

Kelly et al.[111] summarised data on the association of walking (14 studies) and cycling (7 studies) with mortality in a meta-analysis. Cycling to work was the most common domain assessed. They found that both walking and cycling 675 MET-min/wk were associated with a 10% lower risk of all-cause mortality. The risk estimates are for the same energy expenditure, but as cycling is more intense, this would be achieved in a shorter time. Dose-response analyses suggest decreasing rates of benefit at higher exposures: for walking 9% at 675 MET-min/wk, 12% at 1,320 MET-min/wk, and 20% at 3,000 MET-min/wk. For cycling 7% at 660 MET-min/wk, 24% at 1,920 MET-min/wk, and 30% at 3,900 MET-min/wk. Thus the greatest impact is seen in the first 120 minutes per week for walking and the first 100 minutes per week for cycling. There was considerable heterogeneity in the estimate for walking. As all but one risk estimate of the individual

[a] The authors report exposure in MET-h/wk. This was multiplied by 60 to obtain MET-min/wk.

studies was below 1, heterogeneity appeared to be predominantly related to the effect size. One study had a much greater risk reduction at 675 MET-min/wk than the other studies. Exclusion of this study did not change the overall estimate for walking.

Ekelund et al.[108] combined data from 23 centres of the EPIC study in 10 countries. They compared the association between physical activity (leisure time, occupational and household) and all-cause mortality within strata of BMI. Within these strata moderate activity was associated with a 20-30% lower risk of all-cause mortality. In normal weight and overweight individuals, higher levels of physical activity were associated with further reductions in risk, which were most pronounced in the normal-weight group. In contrast, in obese individuals, no further reduction in risk was observed with increasing levels of physical activity beyond that for the moderately active group. Similar to overall activity, higher levels of leisure-time physical activity were associated with lower risks of all-cause mortality. However, occupational activity was not associated with mortality in working individuals: risk estimates were similar for standing, manual work, and heavy manual work in comparison to sitting.

The pooled analysis,[107] the meta-analysis in people over 60[109] and the EPIC study[108] show similar risk estimates as previous meta-analyses described in the Australian evidence report (30% risk reduction),[2] whereas risk estimates in the meta-analysis on walking and cycling were smaller.[111] As Arem et al.[107] comprised the largest number of subjects, used individual data, and quantified the amount of physical activity, the committee has based its conclusions on their pooled analysis.

In addition to these pooled and meta-analyses, the committee has found three cohort studies with objectively-measured physical activity or energy expenditure. In the past few years several articles on this topic based on data from NHANES have been published.[112-115] The committee describes the analysis by Fishman et al.,[115] as it comprises the largest number of subjects and the longest follow-up. In the NHANES study, a moderate to high amount of light physical activity and a moderate to high amount of moderate to vigorous physical activity were independently associated with a lower risk of all-cause mortality.[115] In a German cohort an inverse association between walking duration and the risk of all-cause mortality during four years of follow-up was found.[116] Manini et al.[117] showed that a high energy expenditure measured by the doubly labelled water technique was associated with a 69% lower risk of all-cause mortality. The risk reductions were larger than in the pooled analyses.

In conclusion, leisure-time physical activity is associated with a lower risk of all-cause mortality: >0 to 450 versus 0 MET-min/wk of leisure-time physical activity is associated with a 20% lower risk in comparison to none and 450 to 900 MET-min/wk with a 31% lower risk, and increasing amounts of leisure-time physical activity are associated with a progressively decreasing risk to almost 40% at 900 to 4,500 MET-min/wk. There was no evidence of harm at higher amounts. As the associations were very similar in the two pooled analyses and meta-analysis in people over 60, the level of evidence is strong.

Table 21. Cohort studies into the association between physical activity and all-cause mortality

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I^2 (%)
Pooled analysis								
Arem 2015[107]	Leisure-time physical activity vs. none:	6	14	661,137	116,686			
	>0 to <450 MET-min/wk					0.80	0.78-0.82	n.r.[b]
	450 to <900 MET-min/wk					0.69	0.67-0.70	n.r.
	900 to <1,350 MET-min/wk					0.63	0.62-0.65	n.r.
	1,350 to <2,400 MET-min/wk					0.61	0.59-0.62	n.r.
	2,400 to <4,500 MET-min/wk					0.61	0.58-0.64	n.r.
	≥4,500 MET-min/wk					0.69	0.59-0.78	n.r.
Multi-centre cohort study								
Ekelund 2015[108]	Moderately inactive vs. Inactive	27	12	334,161	21,438	0.76	0.72-0.81	n.r.
	Moderately active vs. Inactive					0.71	0.67-0.76	n.r.
	Active vs. Inactive					0.65	0.60-0.70	n.r.
	Per one level difference in activity level					0.87	0.85-0.89	n.r.
Meta-analysis								
Kelly 2014[111]	Walking 675 MET-min/wk	14	n.r.	280,000	n.r.	0.89	0.83-0.96	82
	Cycling 675 MET-min/wk	7	n.r.	187,000	n.r.	0.90	0.87-0.94	20
Hupin 2015[109]	1-499 MET-min/wk vs. 0 MET-min/wk	9	10	122,417	18,122	0.78	0.71-0.87	33
	500-999 MET-min/wk			60+ years		0.72	0.65-0.80	44
	≥1,000 MET-min/wk					0.65	0.61-0.70	20
Cohort study with objectively-measured physical activity								
Manini 2006[117]	T3 vs.T1 energy expenditure[e]	1	6	302 70-82 years	55	0.31	0.14-0.69	n.a.[d]
Activity and Function in the Elderly in Ulm 2016[116]	Q2 vs.Q1 walking duration[f]	1	4	1,271	110	0.58	0.33-1.02	n.a.
	Q3 vs. Q1 walking duration			65+ years		0.30	0.14-0.66	n.a.
	Q4 vs. Q1 walking duration					0.47	0.23-0.99	n.a.
NHANES 2016[115]	T2 vs. T1 total physical activity	1	6.5	3,029	387	0.39	0.22-0.70	n.a.
	T3 vs. T1 total physical activity			50-79 years		0.30	0.14-0.62	n.a.
	T2 vs. T1 moderate and vigorous physical activity					0.49	0.30-0.80	n.a.
	T3 vs. T1 moderate and vigorous physical activity					0.22	0.10-0.48	n.a.
	T2 vs. T1 light activity					0.37	0.20-0.69	n.a.
	T3 vs. T1 light activity					0.47	0.25-0.86	n.a.

[a] Confidence interval.
[b] Not reported.
[c] Risk estimates for the BMI stratum 18.5 to 24.9 kg/m^2.
[d] Not applicable.
[e] T: tertile.
[f] Q: quartile.

3.2 Cardiovascular disease

The evidence report for the Australian guidelines[2] summarises the evidence for all cardiovascular diseases, including coronary heart disease, peripheral vascular disease, stroke and other cardiovascular diseases. It concludes that there is strong evidence to support dose-response relationships between physical activity and a range of cardiovascular outcomes. In addition, some studies show benefits at levels below 150 minutes per week of moderate intensity physical activity, and almost all show progressively declining risk with increasing amount of activity.
Associations for physical activity were described for persons categorised into low, moderate or high physical activity, showing that moderate physical activity is associated with a 20% lower risk of cardiovascular disease in comparison to low physical activity and higher amounts or more intense physical activity with a 30% lower risk. This conclusion is largely based on the 2008 evidence report underpinning the development of the US physical activity guidelines.[3] This report, however, includes both cohort and case-control studies. In the Australian report this is considered acceptable because, although recall bias is substantial in case-control studies, it is not generally thought to demonstrate differential measurement error.[2]
In the text below, the committee evaluates new scientific developments with respect to the association between physical activity and coronary heart disease, stroke and heart failure.

3.2.1 Coronary heart disease

Summary of evidence for the association between physical activity and the risk of coronary heart disease

Aspect	Explanation
Selected studies	1 meta-analysis of 33 cohorts[118]
Heterogeneity	No
Strength of the association	Leisure-time physical activity in comparison to none: RR=0.86 (0.76-0.97) for 75 min/wk moderate intensity RR=0.91 (0.79-1.04) for 150 min/wk moderate intensity in men RR= 0.80 (0.69-0.92) for 150 min/wk moderate intensity in women RR=0.82 (0.74-0.91) for 300 min/wk moderate intensity in men RR= 0.72 (0.74-0.91) for 300 min/wk moderate intensity in women
Study population	Europe, North America, Asia

Conclusion: Moderate-intensity versus no leisure-time physical activity is associated with a lower risk of coronary heart disease: 75 minutes of moderate-intensity leisure-time physical activity per week versus none is associated with a 14% lower risk, 150 minutes with an 18% lower risk and increasing amounts of moderate-intensity leisure-time physical activity are associated with a progressively decreasing risk to 20% at 300 minutes per week.
Level of evidence: Strong

Explanation
Two meta-analyses of cohort studies into the association between physical activity and the risk of coronary heart disease have been published since

Table 22. Cohort studies into the association between physical activity and the risk of coronary heart disease

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I^2 (%)
Meta-anaysis								
Sattelmair 2011[118]	Highest vs. lowest category of total physical activity	33	2-25	635,887	n.r.[b]	0.74	0.62-0.90	0
	Highest vs. lowest category of leisure-time physical activity				n.r.	0.74	0.69-0.76	28
	Amount of leisure-time physical activity at moderate intensity in comparison to none:	5 in men 5 in women	n.r.	n.r.				
	75 min/wk moderate intensity			Men & Women		0.86	0.76-0.97	n.r.
	150 min/wk moderate intensity			Men		0.91	0.79-1.04	n.r.
				Women		0.80	0.69-0.92	n.r.
	300 min/wk moderate intensity			Men		0.82	0.74-0.91	n.r.
				Women		0.72	0.63-0.83	n.r.
	750 min/wk moderate intensity			Men		0.81	n.r.	n.r.
				Women		0.52	0.40-0.67	n.r.
Kyu 2016[119]	600-3,999 MET-min/wk	43	n.r.	16,583,824[c]		0.84	0.79-0.88	n.r.
	4,000-7,9999 MET-min/wk					0.77	0.69-0.83	n.r.
	≥ 8,000 MET-min/wk					0.75	0.70-0.80	n.r.

[a] Confidence interval.
[b] Not reported.
[c] Person years.

the Australian evidence report (Table 22).[2,118,119][a] Sattelmaier et al.[118] summarised 33 cohort studies and showed that high total physical activity[b] is associated with a 26% lower risk of coronary heart disease in comparison to low physical activity. The risk reductions for the various physical activity types varied from 6% to 51%. High occupational physical activity was, for instance, associated with a 16% lower risk of coronary heart disease in comparison to low occupational physical activity (RR=0.84; 95% CI 0.79-0.90). This analysis was based on four studies. A previous meta-analysis described in the Australian evidence report was based on two studies with at least 1,000 participants and a follow-up time of at least 5 years. This meta-analysis found an about 10% lower risk of moderate occupational physical activity in comparison to low occupational physical activity in men and an about 20% lower risk in women. High occupational physical activity was associated with similar risk reductions as moderate.[120]

Sattelmair et al.[118] carried out a dose-response meta-analysis to quantify the specific amounts of moderate-intensity leisure-time physical activity required to lower risk of coronary heart disease. The authors found that

[a] The meta-analysis by Li et al. was included in the Australian evidence report.[2,120]
[b] In terms of leisure-time physical activity, walking time, walking pace, occupational physical activity, transport physical activity, total physical activity and nonspecific physical activity.

people reporting leisure-time physically activity at about 75 minutes per week at moderate intensity had a 14% lower risk of coronary heart disease (95% CI -0.24 to -0.03) in comparison to persons reporting none. People reporting 150 minutes at moderate-intensity per week had also a 14% lower risk of coronary heart disease (95% CI -0.23 to -0.04) and people engaging in the equivalent of 300 minutes at moderate intensity per week had a 20% lower risk (95% CI -0.26 to -0.12). The risk was further reduced to up to 750 minutes per week of moderate intensity physical activity (RR=0.75). The association was stronger for women than for men.

The risk estimates in the recent meta-analysis appear rather similar to those in the overall conclusions on cardiovascular disease in the Australian evidence report.[2]

Kyu et al.[119] summarised 43 cohort studies and quantified the dose-response relation between total physical activity across all domains and the risk of coronary heart disease. The authors mapped domain-specific physical activity to total activity. In a continuous analysis 600 MET-min per week was associated with a 9% lower risk of coronary heart disease in comparison to no physical activity. An increase from 600 to 3,600 MET-min per week reduced the risk by an additional 15%. The same amount of additional activity yielded much smaller returns at higher levels of activity. In categorical dose-response analyses a similar pattern was observed: in comparison to less than 600 MET-min per week, 600 to 3,999 MET-min per week were associated with a 16% and 4,000 to 7,999 MET-min per week with a 23% lower risk of coronary heart disease. The pattern of the dose-response relationship is similar to the conclusions in the Australian evidence report. However, the amount of physical activity required for the prevention of coronary heart disease is higher than previously reported, possibly because of dilution effects of inaccurately reported occupational and domestic activities and over-estimation of their MET-values, and because values based on all physical activity below 600 MET-minutes per week were used as reference categories.[121] Because of the uncertainties in the assessment of the exposure in the meta-analysis by Kyu et al., the committee has based its conclusions on the meta-analysis by Sattelmair et al.[118,119]

In conclusion, moderate-intensity versus no leisure-time physical activity is associated with a lower risk of coronary heart disease: 75 minutes of moderate-intensity leisure-time physical activity per week versus none is associated with a 14% lower risk, 150 minutes with an 18% lower risk and increasing amounts of moderate-intensity leisure-time physical activity are associated with progressively decreasing risk to 20% at 300 minutes per week. The level of evidence for this association is strong.

3.2.2 Stroke

Summary of evidence for the association between physical activity and the risk of stroke

Aspect	Explanation
Selected studies	1 meta-analysis of 7 cohorts (men) and 6 cohorts (women)[120]
Heterogeneity	No
Strength of the association	RR=0.73 (0.62-0.85) for moderate vs. low intensity in men RR=0.71 (0.60-0.84) for high vs. low intensity in men RR=0.89 (0.79-1.00) for moderate vs. low intensity in women RR=0.78 (0.66-0.92) for high vs. low intensity in women
Study population	Europe, North America

Conclusion: Moderate- versus low-intensity leisure-time physical activity is associated with a 27% lower risk of stroke in men and an 11% lower risk in women; high- versus low-intensity leisure-time physical activity is associated with a 29% lower risk of stroke in men and a 22% lower risk in women.
Level of evidence: Strong.

Explanation
The committee found one recent meta-analysis that was published since the publication of the Australian report (Table 23).[2,119]
Kyu et al.[119] summarised 27 cohort studies and quantified the dose-response relationship between total physical activity across all domains and the risk of ischemic stroke. The authors mapped domain-specific physical activity to total activity. In a continuous analysis, 600 MET-min per week was associated with a 9% lower risk of ischemic stroke in comparison to no physical activity. An increase from 600 to 3,600 MET-min per week reduced the risk by an additional 13%. The same amount of additional activity yielded much smaller returns at higher levels of activity. In categorical dose-response analyses a similar pattern was observed: in comparison to less than 600 MET-min/wk, 600 to 3,999 MET-min/wk were associated with a 16% and 4,000 to 7,999 MET-min/wk with a 19% lower risk of ischemic stroke. The pattern of the dose-response relationship is similar to the conclusions in the Australian evidence report. However, the amount of physical activity required for prevention of coronary heart disease is higher than previously reported, possibly because of dilution effects of inaccurately reported occupational and domestic activities and over-estimation of their MET-values, and because values based on all physical activity below 600 MET-min/wk were used as reference categories.[121] Because of the uncertainties in the assessment of the exposure in the meta-analysis by Kyu et al. and the fact that the analysis focused on ischemic stroke, the committee has based its conclusions on a recent meta-analysis described in the Australian evidence report.[2,119,120]
In the meta-analysis by Li et al.[120] inclusion criteria were peer-reviewed English papers with original data, studies with at least 1,000 participants and a follow-up time of at least 5 years, and information on major confounders. The authors conclude that moderate-intensity leisure-time physical activity is associated with a 27% lower risk of stroke in men and 11% lower risk in women in comparison to low-intensity leisure-time

Table 23. Cohort studies into the association between physical activity and the risk of stroke

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.	Heterogeneity I² (%)
Meta-analysis								
Li 2012[120]	Moderate vs. low-intensity leisure-time physical activity	7	8-32	Men, n.r.[b]	n.r.	0.73	0.62-0.85	n.r.
		6	8-32	Women, n.r.	n.r.	0.89	0.79-1.00	n.r.
	High vs. low-intensity leisure-time physical activity	7	8-32	Men, n.r.	n.r.	0.71	0.60-0.84	n.r.
		6	8-32	Women, n.r.	n.r.	0.78	0.66-0.92	n.r.
Kyu 2016[119]	600-3,999 MET-min/wk	26	n.r.	13,670,573	n.r.	0.84[d]	0.77-0.91	n.r.
	4,000-7,9999 MET-min/wk					0.81	0.69-0.93	n.r.
	≥ 8,000 MET-min/wk					0.74	0.65-0.81	n.r.

[a] Confidence interval.
[b] Not reported.
[c] Person years.
[d] Ischemic stroke.

physical activity and high-intensity leisure-time physical activity with a 29% lower risk in men and a 22% lower risk in women. There were no indications for heterogeneity based on the visual inspection of forest plots.

The meta-analysis describes only one cohort study on the association between occupational physical activity and the risk of stroke. This number is too small for a conclusion.

The committee has not found any cohort studies on the association between objectively-measured physical activity and risk of stroke.

In conclusion, moderate- versus low-intensity leisure-time physical activity is associated with a 27% lower risk of stroke in men and an 11% lower risk in women; high- versus low-intensity leisure-time physical activity is associated with a 29% lower risk of stroke in men and a 22% lower risk in women.

3.2.3 Heart failure

Summary of evidence for the association between physical activity and the risk of heart failure

Aspect	Explanation
Selected studies	1 meta-analysis of 12 cohorts[122]
Heterogeneity	No
Strength of the association	500 MET-min/wk RR=0.90 (0.87-0.92) 1,000 MET-min/wk RR=0.81 (0.77-0.86) 2,000 MET-min/wk RR=0.65 (0.58-0.73)
Study population	Europe, North America

Conclusion: Leisure-time physical activity is associated with a lower risk of heart failure: 500 versus 0 MET-min per week is associated with a 10% lower risk, 1,000 versus 0 MET-min per week with a 19% lower risk and 2,000 versus 0 MET-min per week with a 35% lower risk.
Level of evidence: Strong.

Explanation

The committee has found two meta-analyses on the association between physical activity and the risk of heart failure (Table 24).[122,123] The ten[a] studies summarised by Echouffo-Tcheugui et al.[123] were summarised by Pandey et al.[122] in combination with two other studies. In addition, Pandey et al.[122] describe a dose-response relationship, whereas Echouffo-Tcheugui et al.[123] compare a high with a low level of physical activity and fitness. Therefore, the committee has based its conclusions on the meta-analysis by Pandey et al.[122]

Pandey et al.[122] selected prospective cohort studies on physical activity and risk of heart failure in participants > 18 years that had been published between January 1995 and September 2014. The time restriction was applied to reflect likely changes in physical activity categorisation by investigators after publication of the 1995 American physical activity guidelines. When studies reported risk estimates for various types of physical activity, Pandey et al.[122] used estimates for leisure-time physical activity. They found that risk of heart failure decreased gradually from the lowest category of total physical activity to the highest, with subjects in the highest total physical activity category having a 30% lower risk of heart failure in comparison to subjects in the lowest category. Heterogeneity was low to moderate. Moderate heterogeneity was present in the effect size: risk estimates were below 1 for each comparison in the individual studies. There was no significant change in magnitude or direction of the effect in additional sensitivity analyses for the comparison between the highest and the lowest level of physical activity.

In a dose-response analysis Pandey et al. showed a continuous inverse association between the amount of leisure-time physical activity expressed in MET-minutes per week and the risk of heart failure. Participants who had leisure-time physical activity levels at 500 versus 0 MET-min per week had a 10% lower risk of heart failure compared with those with no leisure-time physical activity, levels at 1,000 versus 0

[a] Wang et al.[124] in the meta-analysis by Pandey et al.[122] describe the same study as Hu et al.[125] in the meta-analysis by Echouffo-Tcheugui et al.[123].

Table 24. Cohort studies into the association between physical activity and the risk of heart failure

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I² (%)
Meta-analysis								
Pandey 2015[122]	Amount of total physical activity:	12	5-30	370,460	20,203			
	Light vs. Lowest	4		20,564		0.85	0.79-0.92	3
	Moderate vs. Lowest	10		131,014		0.78	0.75-0.82	20
	Highest vs. lowest	12		117,733		0.70	0.67-0.73	36
	Dose response leisure-time compared to no leisure-time physical activity:	8						
	500 MET-min/wk					0.90	0.87-0.92	n.r.[b]
	1,000 MET-min/wk					0.81	0.77-0.86	n.r.
	2,000 MET-min/wk					0.65	0.58-0.73	n.r.

[a] Confidence interval.
[b] Not reported.

MET-min per week a 19% lower risk and at 2,000 versus 0 MET-min per week a 35% lower risk.[122]

The risk estimates are rather similar to those in the overall conclusions on cardiovascular disease in the Australian evidence-report.[2]

The committee has not found any cohort studies on the association between objectively-measured physical activity and risk of heart failure.

The committee concludes that leisure-time physical activity is associated with a lower risk of heart failure: 500 MET-min per week is associated with a 10% lower risk, 1,000 MET-min per week with a 19% lower risk and 2,000 MET-min per week with a 35% lower risk. In view of the consistency of the findings, the level of evidence is strong.

3.3 Type 2 diabetes mellitus

The Australian report[2] describes a systematic review of Warburton et al.[126] of 20 primary prevention cohort studies which showed, without exception, that there was a substantial and consistent association between (increasing) physical activity and reduced risk of type 2 diabetes. This relationship was robust; it existed irrespective of the physical activity measure used, and there was a consistent dose-response relationship. The median magnitude of the risk reduction was around 42% across all studies.[126] However, this is likely to be an overestimation, as the data supporting this estimate stemmed from studies of both physical activity and physical fitness. The Australian report also describes the findings in the American evidence report that there was evidence of increased risk reduction with increasing total volume of activity, with benefits starting at fairly low levels of activity and increasing up to a level of about one hour of walking a day (i.e. 300 minutes/week of moderate intensity activity, or 1,000 MET-min/week).[3]

The committee found one multicentre cohort study[127] and four meta-analyses[119,128-130] into the association between physical activity and risk of diabetes (Table 25). As the multicentre cohort study was included in one of the meta-analyses,[128] it is not described separately. As the 8 cohort studies summarised in the meta-analysis by Huai et al.[130] were also summarised by Aune et al.[128] in combination with 47 other cohort studies, the meta-analysis by Huai[130] was excluded.

Each of the three remaining meta-analyses had a different purpose and methodology. Aune et al.[128] studied various characteristics of physical activity, Cloostermans et al.[129] carried out a harmonized meta-analysis by reanalysing the raw data from published and unpublished cohort studies following a standardised protocol with, for instance, standard adjustment for a set of potential confounders and Kyu et al.[119] mapped domain-specific activity to total physical activity. The overlap between the meta-analysis of Cloostermans et al. and the others was difficult to assess, due to the re-analysis of published and unpublished data.[119,128,129] There is an overlap in six cohort studies between the meta-analyses of Aune et al. and Kyu et al.[119,128]

Total physical activity and diabetes

Summary of evidence for the association between total physical activity and the risk of type 2 diabetes mellitus

Aspect	Explanation
Selected studies	2 meta-analyses of 9 and 14 cohort studies[128, 129]
Heterogeneity	No
Strength of the association	High vs. low: RR=0.65 (0.59-0.71) and RR=0.81 (0.71-0.91)
Study population	Europe, North America, New Zealand, Asia

Conclusion: A high versus low level of physical activity is associated with a 19% lower risk of diabetes.
Level of evidence: Strong.

Explanation

Each of the three meta-analyses looked into the association between total physical activity and risk of diabetes (Table 25). Total physical activity was defined as the sum of leisure-time and transport physical activity by Cloostermans et al.,[129] as the sum of leisure-time, transport and occupational physical activity by Aune et al.,[128] and as the sum of leisure-time, transport, occupational and household physical activity by Kyu et al., for which the authors mapped domain-specific physical activity to total activity.[119]

The relative risk varied from 0.81[129] to 0.65[128] when comparing a high with a low level of physical activity. Heterogeneity was low in each meta-analysis. Cloostermans et al.[129] carried out a harmonised meta-analysis in which risk estimates from each study were adjusted for a standard set of confounders. A high level of physical activity was associated with a 19% lower risk of diabetes.

In the meta-analysis by Aune et al.,[128] separate analyses were carried out comparing a high with a low level of physical activity for three categories: vigorous, moderate and light physical activity, all showing relative risks between 0.61 and 0.68. In each of the three analyses, there was considerable heterogeneity in the size of the effect, which makes the size of the risk estimate less certain.

In an analysis with physical activity as a continuous variable Kyu et al.[119] showed that 600 MET-min per week was associated with a 2% lower risk of diabetes in comparison to no physical activity. An increase from 600 to 3,600 MET-min per week reduced the risk by an additional 19%. The same amount of additional activity yielded much smaller returns at higher levels of activity. In dose-response analyses with physical activity as a categorical variable a similar pattern was observed: in comparison to less than 600 MET-min per week, 600 to 3,999 MET-min per week was associated with a 15% and 4,000 to 7,999 MET-min per week with a 25% lower risk of diabetes. The pattern of the dose-response relation is similar to the conclusions in the Australian evidence report. However, the amount of physical activity required for prevention of diabetes is higher than previously reported, possibly because of dilution effects of inaccurately reported occupational and domestic activities and over-estimation of their

MET-values, and because values based on all physical activity below 600 MET-min per week were used as reference categories.[121] Because of the uncertainties in the assessment of the exposure in the meta-analysis by Kyu et al., the committee has based its conclusions on the estimates in the other two meta-analyses.[128,129]

As in the meta-analysis of Cloostermans et al.[129] all risk estimates were adjusted for potential confounders, whereas in the meta-analysis by Aune et al.[128] this was not the case, the committee has based its conclusion on the meta-analysis by Cloostermans (19% lower risk).[129] This estimate is about half that of the study referred to in the Australian report. As explained in the introduction, the latter might have been an overestimation as physical activity was combined with physical fitness.[2,126]

In conclusion, a high versus low level of total physical activity is associated with a 19% lower risk of diabetes. In view of the consistency in findings, the level of evidence is strong.

Table 25. Cohort studies into the association between physical activity and the risk of type 2 diabetes mellitus

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95/% C.I.[a]	Heterogeneity I² (%)
Meta-analysis								
Aune 2014[128]	High vs. low total physical activity	14	n.r.[b]	104,908	18,276	0.65	0.59-0.71	18
	High vs. low leisure-time physical activity	55	5-12	1820,188	151,677	0.74	0.70-0.79	84
	Per 1,200 MET-min leisure-time physical activity	5	n.r.	318.049	8.025	0.85	0.81-0.89	0
	High vs. low vigorous activity	8	n.r.	272,599	17,062	0.61	0.51-0.74	73
	High vs. low moderate activity	5	n.r.	184,067	14,790	0.68	0.52-0.90	93
	High vs. low light activity	3[c]	n.r.	107,269	3,856	0.66	0.47-0.94	47
	High vs. low walking	7	n.r.	326,779	11,032	0.85	0.79-0.91	0
	High vs. low resistance training	3	n.r.	131,318	5,769	0.72	0.57-0.91	0
	High vs. low occupational physical activity	3	n.r.	91,139	9,246	0.85	0.79-0.92	0
Clooostermans 2015[129]	High vs. low total physical activity	7	9	117,878	11,237	0.81[d]	0.71-0.91	0
	High vs. medium total physical activity	9	9			0.92[d]	0.88-0.96	0
Kyu 2016[119]	600-3,999 MET-min/wk	55	n.r.	14,051,132[a]	n.r.	0.86	0.81-0.90	n.r.
	4,000-7,9999 MET-min/wk					0.75	0.70-0.79	n.r.
	≥ 8,000 MET-min/wk					0.72	0.67-0.76	n.r.

[a] Confidence interval.
[b] Not reported.
[c] In combination with one RCT.
[d] In the original publication high physical activity acted as the reference group. In order to make the figures comparable with other publications, the inverse of the relative risks and confidence intervals was reported in this table (1/RR).
[e] Person years.

Leisure-time physical activity and diabetes

Summary of evidence for the association between leisure-time physical activity and the risk of type 2 diabetes mellitus

Aspect	Explanation
Selected studies	1 meta-analysis of 55 (high-low) and 5 (per 1,200 MET-min/wk) cohort studies[128]
Heterogeneity	Yes in high vs. low analysis
Strength of the association	High vs. low RR= 0.74 (0.70-0.79) Per 1,200 MET-min RR=0.85 (0.81-0.89), but indications of non-linear association
Study population	Europe, North America, New Zealand, Asia

Conclusion: A high versus low level of leisure-time physical activity is associated with a lower risk of diabetes. The reduction in risk is more pronounced at low levels of physical activity than at high levels.
Level of evidence: Strong.

Explanation

The committee found one meta-analysis focusing on the association between leisure-time physical activity and risk of diabetes (Table 25).[128] Aune et al.[128] showed that a high level of leisure-time physical activity was associated with a 24% lower risk. Heterogeneity in the size of the effect was considerable. In subgroup analyses this was explained by geographic location, number of cases and adjustment for age, with a weaker association in Asian studies, in studies with a large number of cases, and in studies with adjustment for age.

In a dose-response analyses of 5 cohort studies, each 1,200 MET-min increase in leisure-time physical activity was associated with a 15% lower risk. Heterogeneity was low. There was evidence of a non-linear association between MET-min per week of leisure-time physical activity and diabetes, with a slightly more pronounced reduction at low levels of activity than at high levels.[128]

In additional analyses the association of walking and occupational physical activity with risk of diabetes were also studied. A high level of walking and a high level of occupational physical activity were associated with a 15% lower risk of diabetes, which is 10 percentage points smaller than the overall estimate of leisure-time physical activity. A high level of resistance training was associated with a 28% lower risk. Heterogeneity in the three analyses was low. However, this might be explained in part by the small number of studies (N=3 each) on occupational physical activity and resistance training.

In conclusion, a high versus low level of leisure-time physical activity is associated with a lower risk of diabetes. The reduction in risk is more pronounced at low levels of physical activity than high levels. In view of the large heterogeneity in the effect size of the high-low comparison and the indications of a non-linear association in the dose-response analyses, the committee did not quantify the association. In view of the consistent findings in the direction of the association, the level of evidence is strong.

3.4 Breast cancer

Summary of evidence for the association between physical activity and the risk of breast cancer

Aspect	Explanation
Selected studies	1 pooled analysis of 10 cohort studies[131] and 2 meta-analyses of 31 cohort studies[132] and 33 cohort studies[133]
Heterogeneity	No
Strength of the association	RR=0.90 (0.87-0.93) high vs. low leisure-time physical activity at moderate or vigorous intensity RR=0.88 (0.84-0.91) high vs. low leisure-time physical activity RR=0.87 (0.83-0.92) high vs. low total physical activity RR=0.97 (0.95-0.98) per 600 MET-min leisure-time physical activity
Study population	Europe, North America, Asia

Conclusion 1: A high versus low level of total physical activity is associated with a 13% lower risk of breast cancer. The reduction in risk is more pronounced at low levels of physical activity than at high levels.
Level of evidence: Strong.

Conclusion 2: A high versus low level of leisure-time physical activity is associated with a 10 to 12% lower risk of breast cancer. The reduction in risk is more pronounced at low levels of physical activity than high levels.
Level of evidence: Strong.

Explanation

In the Australian evidence report,[2] it is stated that physical activity was associated with a 20% to 25% lower risk of breast cancer in comparison to physical inactivity. The estimates were based on meta-analyses in which cohort studies and case-control studies had been combined. There was some evidence of a dose-response relationship, with most studies suggesting that one hour of activity per day confers a greater risk reduction than 30 minutes per day, and that the significant risk reduction occurs in the range of 4-7 hours per week of moderate-vigorous physical activity. The role of lower intensity activity was not yet clear. There was some evidence that physical activity might be more protective in postmenopausal women.

Reviews by the World Cancer Research Fund on physical activity and breast cancer date from before 2012 and are, therefore, not included in this review.[134,135]

The committee found one pooled analysis[131] and four meta-analyses[119,132,133,136] on the association between physical activity and breast cancer (Table 26). Because the 7 cohort studies in the meta-analysis of Goncalves et al.[136] were described in combination with 24 other cohort studies in the meta-analysis by Wu et al.,[132] the committee excluded the meta-analysis by Goncalves et al.[136] The overlap in cohort studies between Wu et al.[132] and Kyu et al.[119] amounted to 28. The overlap in cohort studies of Liu et al.[133] was 18 with Wu et al.[132] and 23 with Kyu et al.[119]

Moore et al.[131] pooled data from 12 cohort studies and showed that the 90th percentile of moderate- and vigorous-intensity leisure-time physical

Table 26. Cohort studies into the association between physical activity and the risk of breast cancer

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I^2 (%)
Pooled analysis								
Moore 2016[131]	High vs. low moderate-and high intensity leisure-time physical activity	10	n.r.[b]	n.r.	35,178	0.90	0.87-0.93	n.s.[c]
Meta-analysis								
Wu 2013[132]	High vs. low total physical activity	31	n.r.	n.r.	63,786	0.87	0.83-0.92	30
	High vs. low moderate activity	16	n.r.	n.r.	21,148	0.95	0.90-0.99	27
	High vs. low vigorous activity	21	n.r.	n.r.	31,048	0.85	0.80-0.90	33
	Per 1,500 MET-min/wk non-occupational physical activity	3	n.r.	n.r.	12,175	0.98	0.97-0.99	n.r.
	Per 600 MET-min/wk leisure-time physical activity	7	n.r.	n.r.	19,882	0.97	0.95-0.98	n.r.
	Per 2 hrs/wk moderate and vigorous leisure-time physical activity	8	n.r.	n.r.	13,877	0.95	0.93-0.97	n.r.
Kyu 2016[119]	600-3,999 MET-min/wk	35	n.r.	50,949.108[d]	n.r.	0.97	0.93-0.99	n.r.
	4,000-7,9999 MET-min/wk					0.94	0.90-0.98	n.r.
	≥ 8,000 MET-min/wk					0.86	0.82-0.90	n.r.
Liu 2016[133]	High vs. low leisure-time physical activity	33	n.r.	n.r.	n.r.	0.88	0.84-0.91	19
	600 MET-min vs. 0	19	n.r.	n.r.	n.r.	0.96	0.94-0.99	n.r.
	1,200 MET-min vs. 0					0.95	0.93-0.98	n.r.
	2,400 MET-min vs. 0					0.93	0.90-0.96	n.r.
	3,600 MET-min vs. 0					0.90	0.86-0.95	n.r.
	4,800 MET-min vs. 0					0.88	0.81-0.95	n.r.

[a] Confidence interval.
[b] Not reported.
[c] Not significant.
[d] Person years.

activity was associated with a 10% lower risk of breast cancer than the 10th percentile. A test on heterogeneity was not significant. The association was similar across categories of BMI and smoking behaviour.

Wu et al.[132] found that a high level of total physical activity was associated with a 13% lower risk of breast cancer in comparison to a low level. The authors did not describe how total physical activity was defined. There was moderate heterogeneity in the size of the risk estimate. Subgroup analyses showed similar risk reductions for occupational, non-occupational, leisure-time, and household physical activity and walking (results not shown here). The risk reduction tended to be larger for a high versus low level of vigorous activity (RR=0.85; 0.80-0.90) than for a high versus a low level of activity at moderate intensity (RR=0.95; 0.90-0.99), in premenopausal

(RR=0.77; 0.69-0.87) in comparison to postmenopausal women (RR=0.87; 0.77-0.92), and in women with an BMI under 25 kg/m^2 (RR=0.72; 0.65-0.81) than above (RR=0.93; 0.83-1.05).

In a dose-response analysis, there was a linear association between non-occupational, leisure-time physical activity and moderate and vigorous leisure-time physical activity and risk of breast cancer. The relative risk was 0.97 per 600 MET-min of leisure-time physical activity per week.[132]

Liu et al.[133] also looked into the association between leisure-time physical activity and risk of breast cancer. They showed a 12% lower risk comparing a high with a low level of leisure-time physical activity. In a dose-response analysis, risk became smaller as levels of physical activity increased, with the risk reduction attenuating at higher levels, although the test for non-linearity was not significant.[132]

Kyu et al.[119] quantified the dose-response relationship between total physical activity across all domains and the risk of breast cancer. The authors mapped domain-specific physical activity to total activity. They showed in an analysis with total physical activity as a continuous variable that 600 MET-min per week was not associated with risk of breast cancer in comparison to no physical activity. An increase from 600 to 3,600 MET-min per week reduced the risk by 4%. The same amount of additional activity yielded much smaller returns at higher levels of activity. In categorical dose-response analyses a similar pattern was observed: in comparison to less than 600 MET-min per week, 600 to 3,999 MET-min per week were associated with a 3% and 4,000 to 7,999 MET-min per week with a 6% lower risk of breast cancer, and 8,000 MET-min or more with a 14% lower risk. The amount of physical activity required for prevention of breast cancer emerging from this study is higher than previously reported, possibly because of dilution effects of inaccurately reported occupational and domestic activities and over-estimation of their MET-values, and because physical activity below 600 MET-minutes per week was used as reference category in all analyses.[121] Because of the uncertainties in the assessment of the exposure in the meta-analysis by Kyu et al.,[119] the committee has based its conclusions on the pooled analysis by Moore et al.[131] and the meta-analyses by Wu et al.[132] and Liu et al.[133]

The new findings are largely in line with previous conclusions in the Australian report, showing an attenuation of the risk reduction at higher levels. However, the size of the risk reduction was smaller in the pooled analysis[131] and more recent meta-analyses.[132,133] One explanation is that the recent risk estimates were exclusively based on cohort studies, whereas previous estimates were based on the combination of cohort studies with case-control studies. Case-control studies generally find stronger associations with cancer risk than cohort studies.[135] The finding that physical activity was more protective in postmenopausal women was not replicated, in fact, the reverse was found by Wu et al.[2,132] The committee did not find any new evidence for differences between a half and one hour of exercise per day, as reported in the Australian evidence report.[2] A new finding was that there was a larger reduction in relative risk for high intensity physical activity than for moderate intensity physical activity.[132]

In conclusion, a high versus low level of total physical activity is associated with a 13% lower risk of breast cancer. The reduction in risk is more pronounced at low levels of physical activity than high levels. Associations were similar over various domains of physical activity, whereas associations were stronger for high-intensity physical activity, in premenopausal women and in women with a BMI< 25 kg/m^2. A high versus low level of leisure-time physical activity is associated with a 10 to 12% lower risk of breast cancer. The reduction in risk is more pronounced at low levels of physical activity than at high levels. In view of the consistent findings, the level of evidence is strong for both findings.

3.5 Colorectal cancer

Summary of evidence for the association between physical activity and the risk of colorectal cancer

Aspect	Explanation
Selected studies	1 pooled analysis of 12 cohort studies[131] and meta-analyses of 19[137] and 31 cohort studies[133]
Heterogeneity	No
Strength of the association	Colon cancer: RR=0.84 (0.77-0.91); RR=0.81 (0.75-0.88) Rectal cancer: RR=0.98 (0.88-1.08); RR=1.07 (0.93-1.24)
Study population	Europe, North America, Asia

Conclusion 1: A high versus low level of leisure-time physical activity is associated with a 16% lower risk of colon cancer.
Level of evidence: Strong.

Conclusion 2: An association between total and leisure-time physical activity and the risk of rectal cancer is unlikely.

Explanation

In the Australian evidence report,[2] it is stated that physical activity was associated with a 20% lower risk of colon cancer in the most active in comparison to the least active group (based on data from the American evidence report[3]). A, at the time, more recent review showed smaller changes in risk of 20% in men and 14% in women. The association was independent of obesity, diet or family history. The lower threshold for benefit ranged from 1,200-1,800 MET-min per week, which equates to about 60 minutes of daily moderate-to-vigorous physical activity. The findings for rectal cancer were equivocal, with more than half of the studies showing no association.[2] As the reviews by the World Cancer Research Foundation of the association between physical activity and risk of colon and rectal cancer date from before 2012, they are not reviewed here.[135,138]
The committee found one pooled analysis[131] and four meta-analyses[119,133,137,139] on the association between physical activity and colorectal/colon cancer (Table 27). As all but one of the studies in the meta-analysis by Boyle et al.[139] were also included by Robsahm et al.,[137] the committee excluded the meta-analysis by Boyle et al.[139] There were 13 cohort studies summarised both by Kyu et al.[119] and Robsahm et al.[137] The overlap between Liu et al.[133] and Kyu et al.[119] was 10 cohort studies and between Liu et al.[133] and Robsahm et al.[137] 11 cohort studies.

Moore et al.[131] pooled data from 12 cohort studies and showed that the 90th percentile of moderate- and vigorous-intensity leisure-time physical activity was associated with a 16% lower risk of colon cancer than the 10th percentile, after correction for potential confounding factors. The association was similar across categories of BMI and smoking behaviour.

Robsahm et al.[137] defined total physical activity in the order of lifetime, leisure-time, or occupational activity, if a study reported risk estimates for one, two or three of these domains. They showed that high total physical activity was associated with a respectively 24 and 23% lower risk of proximal and distal colon cancer, whereas there was no significant association with rectal cancer. Heterogeneity was low. There was some evidence for publication bias for the association of physical activity with rectal cancer. In subgroup analyses risk estimates were weaker for occupational physical activity than for lifetime or leisure-time physical activity. In these subgroup analyses risk reductions for rectal cancer were significant. As the number of studies in the subgroup analyses was relatively small (ranging from 4 to 9 cohort studies) and adjustment for potential confounders was limited in part of the studies, the committee has weighted these findings less heavily.

Liu et al.[133] found that a high level leisure-time physical activity was associated with a 16% lower risk of colorectal cancer and a 19% lower risk of colon cancer, whereas it was not significantly associated with risk of rectal cancer (RR=1.07; 0.93-1.24). There was a non-linear dose-response relationship, with risk lowering attenuating from 1,200 MET-min per week onwards. However, the adjustment for potential confounding factors was limited in part of the studies.

Kyu et al.[119] quantified the dose-response relationship between total physical activity across all domains and the risk of colon cancer. The authors mapped domain-specific physical activity to total activity. They showed in a continuous analysis that 600 MET-min per week was associated with a 2% lower risk of colon cancer in comparison to no physical activity. An increase from 600 to 3,600 MET-min per week reduced the risk by an additional 15%. The same amount of additional activity yielded much smaller returns at higher levels of activity. In categorical dose-response analyses a similar pattern was observed: in comparison to less than 600 MET-min per week, 600 to 3,999 MET-min per week were associated with a 10% and 4,000 to 7,999 MET-min per week with a 17% lower risk of colon cancer, and 8,000 MET-min or more with a 21% lower risk. The amount of physical activity required for prevention of colon cancer in this study is higher than previously reported, possibly because of the dilution effects of inaccurately reported occupational and domestic activities and over-estimation of their MET-values, and because physical activity below 600 MET-minutes per week was used as a reference category in all analyses.[121]

Because of the uncertainties in the assessment of the exposure in the meta-analysis by Kyu et al.,[119] and the incomplete adjustment for potential confounding factors in the meta-analyses by Liu et al.[133] and Robsahm et al.,[137] the committee has based its conclusions for colon cancer on the

Table 27. Cohort studies into the association between physical activity and the risk of colorectal cancer

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I² (%)
Pooled analysis								
Moore 2016[131]	High vs. low moderate- and high-intensity leisure-time physical activity	12	n.r.[b]	n.r.	14,160	0.84[c]	0.77-0.91	n.s.[d]
Meta-analysis								
Robsahm 2013[137]	High vs. low total physical activity	19	n.r.	n.r.	Proximal colon	0.76	0.70-0.83	6
		19	n.r.	n.r.	Distal colon	0.77	0.71-0.83	0
		16	n.r.	n.r.	Rectum	0.98	0.88-1.08	16
Kyu 2016[119]	600-3,999 MET-min/wk	19	n.r.	53,929,648[e]	n.r.	0.90[c]	0.85-0.95	n.r.
	4,000-7,9999 MET-min/wk					0.83[c]	0.77-0.89	n.r.
	≥ 8,000 MET-min/w					0.79[c]	0.73-0.85	n.r.
Liu 2016[133]	High vs. low leisure-time physical activity	31	n.r.	n.r.	n.r. Colorectal	0.84	0.77-0.93	48
		15	n.r.	n.r.	Colon	0.81[c]	0.75-0.88	4
		9			Rectum	1.07	0.93-1.24	0
	600 MET-min vs. 0	10			n.r.	0.92	0.85-1.00	n.r.
	1,200 MET-min vs. 0					0.85	0.79-0.92	n.r.
	2,400 MET-min vs. 0					0.86	0.80-0.94	n.r.

[a] Confidence interval.
[b] Not reported.
[c] Colon cancer.
[d] Not significant.
[e] Person years.

pooled analysis by Moore et al.[131] Results of the meta-analyses by Robsahm et al.[137] and by Liu et al.[133] were used for the conclusion on rectal cancer.

In recent meta-analyses a less strong or similar association between physical activity and colon cancer was found in comparison to the Australian evidence report.[2] Previous indications for a lower threshold for benefit ranged from 1,200-1,800 MET-min per week were not confirmed: Liu et al. showed a benefit of up to 1,200 MET-min of leisure-time physical activity, beyond which risk lowering attenuated.[133] The Australian evidence report's[2] inconclusive findings on rectal cancer have progressed into the conclusion that there are no indications of an association.

In conclusion, a high versus low level of leisure-time physical activity is associated with a 16% lower risk of colon cancer. In view of the consistent findings, the level of evidence is strong. An association between total and leisure-time physical activity and risk of rectal cancer is unlikely.

3.6 Lung cancer

Summary of evidence for the association between physical activity and the risk of lung cancer

Aspect	Explanation
Selected studies	1 pooled analysis of 12 cohort studies[131] and 1 meta-analysis of 19 cohort studies[140]
Heterogeneity	Yes, in the size of the effect in the meta-analysis for former smokers, unexplained.
Strength of the association	Smokers: RR=0.80 (0.70-0.90) Former smokers: RR=0.68 (0.51-0.90) Non-smokers: RR=1.05 (0.78-1.40)
Study population	Europe, North America, Asia

Conclusion 1: A high versus low level of total physical activity is associated with a 20% lower risk of lung cancer in current smokers. Level of evidence: Strong.

Conclusion 2: A high versus low level of total physical activity is associated with a lower risk of lung cancer in former smokers. Level of evidence: Weak.

Conclusion 3: There is too little research to draw a conclusion on the association between total physical activity and risk of lung cancer in non-smokers.

Explanation

In the Australian evidence report,[2] it was stated that physical activity was associated with a 20-24% lower risk of lung cancer in the most active in comparison to the least active group in 15 cohort and 6 case-controls studies (based on data from the American evidence report[3]). The associations remained after stratification by smoking status. As the WCRF-report dates from before 2012, it has not been included in this review.[135]

The committee found one pooled analysis[131] and five meta-analyses on the association between physical activity and the risk of lung cancer (Table 28).[133,140-144] The meta-analysis by Liu et al.[133] and Brenner et al.[144] were excluded as it did not make a distinction between current, former and non-smokers. As Schmid et al.[140] also included the cohort studies that had been summarised in the meta-analyses by Zhong et al.,[143] Sun et al.,[142] and Buffart et al.,[141,a] the committee describes the meta-analysis by Schmid et al.[140] below.

As smoking is an important risk factor for lung cancer, the committee describes the associations between physical activity and lung cancer separately for current smokers, former smokers and non-smokers.

Moore et al.[131] showed in a pooled analysis of 12 cohorts that leisure-time physical activity at a moderate or vigorous level was associated with a 26% lower risk of lung cancer. Smoking status modified this association: the association was present in current smokers and former smokers, whereas physical activity was not associated with lung cancer in non-smokers.[b]

[a] For one cohort Buffart et al.[141] used more recent follow-up data from the Harvard Alumni Health Study[145, 146] than Schmid et al.[140]

[b] Based on a figure in the publication, the authors did not report any quantitative data.[131]

Table 28. Cohort studies into the association between physical activity and the risk of lung cancer

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I^2 (%)
Pooled analysis								
Moore 2016[131]	High vs. low leisure-time physical activity	12	n.r.[b]	n.r.	19,133	0.74[c]	0.71-0.77	n.s.[c]
Meta-analysis								
Schmid 2016[140]	High vs. low physical activity	6	n.r.	1,095,950	11,351 current smokers	0.80	0.70-0.90	41
		3	n.r.	538,436	7,752 former smokers	0.68	0.51-0.90	50
		3	n.r.	538,436	7,752 non-smokers	1.05	0.78-1.40	9

[a] Confidence interval.
[b] Not reported.
[c] Not significant.

Schmid et al.[140] summarised the association for total physical activity. When risk estimates in different domains were presented, they prioritised total physical activity. If studies did not provide this information, the authors used non-occupational or leisure-time physical activity. Total physical activity was associated with a 20% lower risk of lung cancer in current smokers and a 32% lower risk in former smokers, whereas there was no significant association in non-smokers. The associations were not modified by the degree of adjustment for smoking. However, there was respectively moderate and considerable heterogeneity in the effect size for current smokers and former smokers. The number of studies for the analyses on former smokers and non-smokers was small (N=3). Subgroup analyses did not explain the heterogeneity.

In comparison to the Australian report, new evidence shows a differential association between physical activity for current and former smokers and non-smokers. However, as the absolute risk of lung cancer is very small in non-smokers, this might be an explanation for the absence of an association in this group.[2]

In conclusion, a high versus low level of total physical activity is associated with a 20% lower risk of lung cancer in current smokers. In view of the consistent findings, the level of evidence is strong. A high versus low level of total physical activity is also associated with a lower risk of lung cancer in former smokers. In view of the small number of cohorts (N=3), the level of evidence is weak. As the association is not significant in non-smokers and based on a small number of cohorts (N=3), the committee concludes that there is too little research to draw a conclusion on the association between total physical activity and the risk of lung cancer in non-smokers.

3.7 Disability

Summary of evidence for the association between physical activity and the risk of disability

Aspect	Explanation
Selected studies	1 meta-analysis of 9 cohorts[147]
Heterogeneity	Yes, in size of effect, unexplained
Strength of the association	Disability: RR=0.51 (0.38-0.68)
Study population	Europe, North America, Asia

Conclusion 1: A medium to high versus low level of physical activity is associated with a lower risk of disability in older adults.
Level of evidence: Strong.

Explanation

In the Australian evidence report[2] risk of disability was not addressed as it focused on adults up to the age of 65 years. In the US evidence report[3] it was concluded that strong, consistent observational evidence indicated that mid-life and older adults who participate in regular physical activity had reduced risk of moderate or severe functional limitations and role limitations. Active mid-life and older individuals – both men and women – had an approximately 30% lower risk of developing moderate or severe functional limitations or role limitations compared with inactive individuals. The observational evidence of benefit was strong for endurance training, but limited for other types of activity (muscle-strengthening, balance, and flexibility activities). In the four studies with repeated measures of physical activity during follow-up, adults who reported regular physical activity at all measurement occasions were at lowest risk of functional limitations, and two studies that assessed change in physical activity over time reported that change from lower levels of activity to higher levels of activity over time was associated with reduced risk of limitations.

The committee found one meta-analysis[147] and one systematic review[148] on physical activity and risk of disability (Table 29). Tak et al.[147] summarised nine cohort studies on the association between physical activity and disability in activities of daily living and four on disability progression. Physical activity was categorised into low: 914-2110 kcal/day, moderate: 2110-2534 kcal/day, and high: 2534-6360 kcal/day. They showed that a high or medium compared to a low level of physical activity was associated with a 49% lower risk of disability. There was considerable heterogeneity in the size of the effect. Subgroup analyses for age, follow-up period, and number of potential confounders adjusted for, did not significantly alter the association.

Table 29. Cohort studies into the association between physical activity and the risk of disability

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Hetero-geneity I^2 (%)
Meta-analysis								
Tak 2013[147]	Medium-high vs. low	9	3-10	~17,000 older adults 50+ years[c]	Disability (N n.r.[b])	0.51	0.38-0.68	77

[a] Confidence interval.
[b] Not reported.
[c] Most cohort studies included participants aged 70 to 80 years at baseline, with only one study reporting on 50 years.

In their systematic review, Lafortune et al.[148] described 7 cohort studies, one of which was included in the meta-analysis by Tak et al.[147] Of the seven studies, five reported a beneficial association between mid-life physical activity and physical mobility, physical functioning or reduction in disability. One study reported no significant association with disability and one found no significant association between inactivity in leisure time and risk of disability. Thus the findings by Lafortune et al.[148] are largely in line with those by Tak et al.[147]

In comparison to the US-report[3], risk estimates for disability in activities of daily living in the meta-analysis by Tak et al.[147] were stronger. One explanation may be that, in the US-report, a wider variety of measures were included, i.e. not only measures of functional limitations but also measures of mobility, ADL (Activities of Daily Living), instrumental ADL, measures of overall ("global") functional and role limitations, and occupational status.

In conclusion, a medium to high versus low level of physical activity is associated with a lower risk of disability in older adults. In view of the considerable heterogeneity in the size of the effect, the committee did not quantify the conclusion. In view of the consistent findings on the direction of the effect, the level of evidence is strong.

3.8 Fracture

In the Australian evidence report it is stated that there is consistent evidence from prospective and retrospective longitudinal epidemiological studies that physical activity reduces fracture-related risks in people with osteoporosis, especially fractures of the proximal femur (hip). Overall, there was a 2.5 fold increase in the risk of hip fracture in the least active group, compared with the most active groups. There is mixed evidence regarding vertebral fracture risk, and some evidence of risk reduction for any fracture.[2] These conclusions were based on the American evidence report, which summarised not only prospective cohort studies, but also retrospective cohort studies, case-control and cross-sectional comparisons.[3]

The committee found two meta-analyses on the association between physical activity and the risk of fractures in predominantly older adults (Table 30).[149,150] Qu et al.[149] summarised 22 cohort studies on the risk of any fractures, and the subtypes hip (13 cohort studies), wrist (2 cohort studies) and vertebral fractures (4 cohort studies). Rong et al.[150] described nine cohort studies on hip fractures, five of which were also summarised by Qu et al.[149], and 3 cohort studies on wrist fractures, one of which was also summarised by Qu et al.[149]

Qu et al.[149] compared a high with a low level of physical activity, whereas Rong et al.[150] carried out a dose-response analysis per 3 units increase in physical activity. For this purpose, Rong et al.[150] selected studies with at least three quantitative categories of physical activity. It is, however, unclear how these units were defined.

Physical activity and the risk of fractures in older adults

Summary of evidence for the association between physical activity and the risk of fractures

Aspect	Explanation
Selected studies	1 meta-analysis of 22 studies[149]
Heterogeneity	Yes, in the size of the effect, partly explained
Strength of the association	RR=0.71 (0.63-0.80)
Study population	Europe, North America

Conclusion: A high versus low level of physical activity is associated with a lower risk of fractures in older adults.
Level of evidence: Strong.

Explanation

Qu et al.[149] showed that a high level of physical activity was associated with a 29% lower risk of fractures (Table 30). Heterogeneity was considerable and mostly pertained to the size of the effect. According to subgroup analyses, heterogeneity seemed to be associated with geographical region, with relative risks in European studies of 0.81 and in other regions below 0.65, and duration of the follow-up, with larger risk reductions with longer follow-up. Exclusion of any one study from the analysis did not substantially affect the risk estimate (RRs ranged from 0.67 to 0.73).

The meta-analysis by Qu al[149] provides additional evidence for an association between physical activity and risk of fractures, the level of evidence being previously described in the Australian evidence report as "some evidence".[2]

In conclusion, a high versus low level of physical activity is associated with a lower risk of fractures in older adults. As heterogeneity was limited to the size of the effect and only partly explained, the committee did not quantify the association. In view of the consistent findings on the direction of the association, the level of evidence is strong.

Physical activity and the risk of hip fractures

Summary of evidence for the association between physical activity and the risk of hip fractures

Aspect	Explanation
Selected studies	2 meta-analyses of 9 and 13 studies[149,150]
Heterogeneity	Yes, partly explained
Strength of the association	RR=0.93 (0.91-0.96) per 3 units increase in physical activity RR=0.61 (0.54-0.69) for high vs. low physical activity
Study population	Europe, North America, New Zealand, Asia

Conclusion: A high versus low level of physical activity is associated with a lower risk of hip fractures in older adults.
Level of evidence: Strong.

Explanation

Qu et al.[149] and Rong et al.[150] both showed an association between high physical activity and a reduced risk of hip fractures (Table 30). Heterogeneity was considerable in both analyses, which was not further investigated by Qu et al.[149] and there was also no forest plot available for visual inspection. In the meta-analysis of Rong et al.[150] heterogeneity pertained to the size of the effect, as all risk estimates were below 1. Exclusion of two studies from the meta-analysis of Rong et al.[150] reduced heterogeneity without essentially affecting the risk estimate (RR=0.94; 0.93-0.96).

The findings correspond with the conclusions in the Australian evidence report.[2]

In conclusion, a high versus low level of physical activity is associated with a lower risk of hip fractures in older adults. As heterogeneity is limited to the size of the effect and partly explained, the committee did not quantify the association. In view of the consistent findings on the direction of the association, the level of evidence is strong.

Physical activity and the risk of wrist and vertebral fractures

Summary of evidence for the association between physical activity and the risk of wrist and vertebral fractures

Aspect	Explanation
Selected studies	2 meta-analyses of 2 and 3 studies (wrist)[149,150] and 1 meta-analysis of 4 studies (vertebral)[149]
Heterogeneity	Yes for wrist, partly explained No for vertebral
Strength of the association	Wrist: RR=1.00 (0.98-1.03) per 3 units increase in physical activity RR=0.72 (0.49-0.96) for high vs. low physical activity Vertebral: RR=0.87 (0.72-1.03) for high vs. low physical activity
Study population	Europe, North America, New Zealand, Asia

Conclusion: There is too little research to draw a conclusion on the association between physical activity and the risk of wrist or vertebral fractures in older adults.

Explanation

The Australian report did not include wrist fractures as a separate category.[2] Qu et al.[149] found a decreased risk of wrist fractures, whereas Rong et al.[150] did not find any indication for an association (Table 30). The number of studies on wrist fractures was small in both analyses, which limits the interpretation of this finding.

The Australian report stated that there was mixed evidence for the risk of vertebral fractures.[2] Qu et al.[149] showed a non-significant association between physical activity and a reduced risk of vertebral fractures. Because of the small number of studies, the conclusion in the Australian evidence report still holds.

In conclusion, there is too little research to draw a conclusion on the association between physical activity and the risk of wrist or vertebral fractures in older adults.

3.9 Osteoarthritis

Conclusion: The evidence for an association between physical activity and risk of osteoarthritis is ambiguous.

Table 30. Cohort studies into the association between physical activity and the risk of fractures

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I^2 (%)
Meta-analysis								
Qu 2014[149]	High vs. low physical activity	22	4-30	1,235,768 adults 20-93 years[c]	14,843 any fractures	0.71	0.63-0.80	74
		13			8,874 hip fractures	0.61	0.54-0.69	50
		2			690 wrist fractures	0.72	0.49-0.96	45
		4			927 vertebral fractures	0.87	0.72-1.03	0
Rong 2016[150]	Per 3 units increase in physical activity	9	7-28	1,345,946 women 40-70 years	hip fractures	0.93	0.91-0.96	85
		3			wrist fractures	1.00	0.98-1.03	81

[a] Confidence interval.
[b] Not reported.
[c] Most studies included participants aged 50 years or over at baseline.

Explanation

In the Australian evidence report[2] it is stated that there is some evidence, from case-control studies, some cross sectional studies, and a few cohort studies, that physical activity has a protective role in reducing the incidence of osteoarthritis.

The committee found three recent systematic reviews[151-153] and one descriptive review[154] into the association between physical activity and risk of osteoarthritis. The reason for including the latter review is that it included additional cohort studies. In three of the four meta-analyses, studies were included if osteoarthritis was self-reported or assessed by radiography or magnetic resonance imaging.[151,153,154] Hart et al.[152] only included studies on radiographic osteoarthritis. Of the cohort studies summarised by Blagojevic et al.[151] seven were also summarised by Hart et al.,[152] six by Lefèvre-Colau et al.[154] and one by Richmond et al.[153] The overlap between Hart et al.[152] and Lefèvre-Colau et al.[154] also amounts to six cohort studies, whereas there is no overlap in cohort studies between the two reviews and the one by Richmond et al.[153]

Blagojevic et al.[151] stated that higher quality studies, which tended to be cohort studies, generally suggested an increased risk of knee osteoarthritis in those who exercise more regularly or intensely. The authors however based their conclusion on results from both cohort and case-control studies.

Hart et al. 2008[152] concluded on the basis of 10 cohort studies that the evidence for an association of physical activity with radiographic osteoarthritis was ambiguous.

Lefèvre-Colau et al.[154] found no indications that low, moderate or high levels of physical activity were associated with risk of knee or hip osteoarthritis.

Richmond et al.[153] showed that increased physical activity was associated with an increased risk of osteoarthritis.

The more recent reviews[151,152,154] do not confirm the findings in the Australian evidence report[2] and may even indicate that a high level of exercise is associated with an increased risk of osteoarthritis. Taking the evidence together, the committee concludes that the evidence for an association of physical activity with risk of osteoarthritis is ambiguous.

3.10 Dementia and cognitive decline

Summary of evidence for the association between physical activity and the risk of dementia and cognitive decline

Aspect	Explanation
Selected studies	2 meta-analyses of 9[155] and 26 cohorts[156]
Heterogeneity	Yes in the size of the effect in the meta-analysis on cognitive decline and dementia, partly explained
Strength of the association	Cognitive decline RR=0.65 (0.55-0.76) Dementia RR=0.86 (0.76-0.97) Alzheimer's disease RR=0.61 (.52-0.73)
Study population	Europe, North America, Asia

Conclusion 1: A high versus low level of physical activity is associated with a lower risk of cognitive decline and dementia in older adults.
Level of evidence: Strong.

Conclusion 2: A high versus low level of physical activity is associated with a 35% lower risk of Alzheimer's disease in older adults.
Level of evidence: Strong.

Explanation

As the Australian evidence report[2] focused on adults up to the age of 65 years, risk of dementia and cognitive decline were not discussed. In the US evidence report,[3] it was concluded that physical activity delayed the incidence of dementia and the onset of the cognitive decline associated with ageing. The relative risk of dementia and Alzheimers's disease was 0.63 (0.50 to 0.80) comparing a high with a low level of physical activity. The committee found two meta-analyses (Table 31).[155,156] Blondell et al.[156] summarised 21 cohort studies on physical activity and cognitive decline and 26 on dementia (including Alzheimer's disease), whereas Beckett et al.[155] summarised nine cohort studies on Alzheimers's disease, eight of which were also summarised by Blondell et al.[156] Neither meta-analysis provided a definition of physical activity.

Blondell et al.[156] stated that cognitive decline was mostly assessed with the mini-mental state examination (MMSE) test or the modified MMSE. Dementia was primarily assessed with the use of a version of the Diagnostic and Statistical Manual of Mental Disorders. The authors used a quality effects model for estimating the effect, which, in contrast to the random-effects model, does not take into account observed between-trial heterogeneity, but measures methodological heterogeneity between studies. In the meta-analysis a high versus low level of physical activity was associated with a 35% lower risk of cognitive decline and a 14% lower risk of dementia. Heterogeneity was considerable in both analyses. Visual inspection of the scatter plot showed that it was mostly confined to

Table 31. Cohort studies into the association between physical activity and the risk of cognitive decline and dementia

	Exposure	Number of cohorts	Follow up time (years)	N	N cases	RR	95% C.I.[a]	Heterogeneity I^2 (%)
Meta-analysis								
Blondell 2014[156]	High vs. low	17 21	1-21 1-26	n.r.[b] ≥ 40 years	Cognitive decline (N n.r.) Dementia (N n.r.)	0.65 0.86	0.55-0.76 0.76-0.97	52 66
Beckett 2015[155]	High vs. low	9	4-7	20,326 ≥ 65 years	1,358 Alzheimer's disease	0.61	0.52-0.73	0
Cohort study with objectively measured physical activity								
Middelton 2011[157]	T3 vs. T1 energy expenditure[d]	1	2 or 5	197 mean age 75 years	Incident cognitive impairment (> 1.0 SD (9 points) decline in Modified Mini-Mental State Examination score)	0.09	0.01-0.79	n.a.[c]

[a] Confidence interval.
[b] Not reported.
[c] Not applicable.
[d] T: Tertile.

the size of the effect. Subgroup analyses showed that studies of high quality and with a greater number of adjustments provided more conservative findings for cognitive decline, but not for dementia (RR for cognitive decline were 0.73 and 0.68 respectively in these subgroup analyses and for dementia 0.87 and 0.86). It was, however, unclear to what extent these subgroup analyses explained heterogeneity. There was some suggestion of publication bias in the findings for dementia.

Beckett et al.[155] only included studies that diagnosed Alzheimer according to standardised clinical criteria. The authors found that physical activity was associated with a 39% lower risk of Alzheimer's disease. Heterogeneity was low. The authors, however, employed a fixed-effects model, which leads to a smaller confidence interval than a random effects model.

In addition to the meta-analyses, the committee found one cohort study with objectively-measured energy expenditure, which was also included in the meta-analysis by Blondell.[156] Middleton et al.[157] showed that a high energy expenditure measured by the doubly labelled water technique was associated with a lower risk of incident cognitive impairment. The risk reduction was larger than in the meta-analyses.

The risk estimate for dementia of Blondell et al.[156] is less strong, whereas the risk estimate for Alzheimer's disease of Becket et al.[155] is of a similar magnitude as the combined risk estimate for dementia and Alzheimer's disease in the US-report. The US-report stated at the time that the risk estimate for Alzheimer's disease was stronger than for other dementias, including vascular dementia.[3]

In conclusion, a high versus low level of physical activity is associated with a lower risk of cognitive decline and dementia. In view of considerable heterogeneity in the size of the effect, the committee did not quantify the associations. In view of the consistent findings on the direction of the effect, the level of evidence is strong. A high versus low level of physical activity is associated with a 35% lower risk of Alzheimer's disease. In view of the consistent findings, the level of evidence is strong.

3.11 Depressive symptoms

Summary of evidence for the association between physical activity and the risk of depressive symptoms

Aspect	Explanation
Selected studies	1 meta-analysis of 28 cohort studies[3] and one systematic review of 30 cohort studies[158]
Heterogeneity	No
Strength of the association	RR=0.82 (78-0.86) high vs. low physical activity
Study population	Europe, North America, Asia

Conclusion 1: A high versus low level of physical activity is associated with an 18% lower risk of depressive symptoms in children, adolescents and adults.
Level of evidence: Strong.

Conclusion 2: Moving from inactivity to activity or maintaining activity in comparison to becoming inactive are associated with a lower risk of depressive symptoms in adults.
Level of evidence: Strong.

Explanation

In the Australian evidence report,[2] the results of the American evidence report[3] are described. Results from 28 prospective cohort studies demonstrated that the average odds of developing depressive symptoms were approximately 15-25% lower among active than inactive people, after adjustment for potential confounders (OR=0.82, 95%CI 0.78-0.86). Protective effects were not limited to studies with self-rated symptoms, but were also present in studies that used a clinical diagnosis. The Australians concluded that the evidence from the American report in combination with more recent evidence provide strong support that physical activity is associated with a lower risk of depressive symptoms. Effects are likely to be greater among those who are inactive, and those with lower levels of psychosocial functioning. On the basis of this review, there was insufficient evidence to make recommendations on the specific dose of physical activity required, although a general trend was observed that for almost all studies, "some" activity was better than "none".

The committee found two recent systematic reviews, one across the lifespan and the other focusing on children and adolescents.[106,158] Two of the four cohort studies in the meta-analysis by Bursnall et al.[106] on children and adolescents were also included in the meta-analysis by Mammen et al.[158] Mammen et al.[158] described 30 cohort studies comprising people aged from 11 to 100 years. Neither systematic review provided a definition of physical activity, however. Mammen et al.[158] reported that, relative to those using subjective physical activity measures of endurance training, only one used objectively measured physical activity. The majority of studies in this meta-analysis assessed depressive symptoms or depression through well-validated measures, such as the Center for Epidemiologic Studies Depression Scale; several other studies used the DSM-VI. Six studies measured depression more directly, via physician diagnosis, hospital discharge register, or use of antidepressants. Twenty-five of the 30 cohort studies found a significant inverse association between physical activity and risk of depressive symptoms. The majority of the 25 cohort studies were of modest (n=6) or high quality (n=17), whereas three of the five studies that did not find a significant association were of modest quality, one was of low and one was of high quality.[158] In three out of four cohort studies in children and adolescents in the meta-analysis of Bursnall et al.,[106] physical activity was associated with a lower risk of depressive symptoms.

Mammen et al.[158] stated that, given the heterogeneity in physical activity measurement, a clear dose-response relationship was not readily apparent. There were nevertheless suggestions that any level of physical activity, including low levels, was associated with a lower risk of depressive symptoms.

Eleven studies in the systematic review of Mammen et al.[158] also studied the association between change in physical activity levels over time and risk of depressive symptoms. Two of the studies found no significant association. Four studies showed that reducing physical activity was associated with a greater risk of depressive symptoms in comparison to remaining active or increasing activity levels. Conversely, three studies showed that subjects who increased physical activity over time were at reduced risk of depressive symptoms, and two studies showed that subjects maintaining physical activity levels were at a lower risk relative to those who were inactive throughout.

As the two recent systematic reviews[106,158] did not provide a risk estimate, the committee looked into the meta-analysis of the US-report (OR=0.82, 95%CI 0.78-0.86). Heterogeneity estimates were not available, but visual inspection of the forest plot suggested no considerable heterogeneity.[3]

In conclusion, a high versus low level of physical activity is associated with an 18% lower risk of depressive symptoms in children, adolescents and adults. Moving from inactivity to activity or maintaining activity in comparison to becoming inactive is associated with a lower risk in adults. In view of the consistent findings, the level of evidence is strong.

3.12 Conclusion

There is strong evidence that a moderate to high level of physical activity, mostly in the form of leisure-time physical activity is associated with a lower risk of all-cause mortality, coronary heart disease, stroke, heart failure, diabetes, breast cancer, colon cancer, and lung cancer (in current smokers). The reduction in risk is more pronounced at low levels of physical activity than high levels. Moving from inactivity to activity or maintaining activity in comparison to becoming inactive are associated with a lower risk of depressive symptoms in adults.

In older adults, there is strong evidence for an association between a moderate to high level of physical activity and a lower risk of disability, and between a high level of physical activity and a lower risk of total fractures and hip fractures, cognitive decline, dementia, and Alzheimer's disease. A high versus a low level of physical activity is associated with a lower risk of depressive symptoms across all age groups.

There is weak evidence for an association between total physical activity and risk of lung cancer in former smokers.

An association between total and leisure-time physical activity and the risk of rectal cancer is unlikely.

The evidence for an association between physical activity and risk of osteoarthritis is ambiguous.

There is too little research to draw a conclusion on the association between total physical activity and risk of lung cancer in non-smokers and between physical activity and the risk of wrist or vertebral fractures.

04 conclusions

The committee has based the Dutch physical activity guidelines 2017 on effects and associations for which there is a strong level of evidence. The following were found.

4.1 All age groups

4.1.1 *Effects* with a strong level of evidence:

Physical activity

Muscoskeletal injuries

- The risk of injury is higher for collision or contact sports than for limited- or non-contact activities.

Mental symptoms

- A high versus low level of physical activity is associated with an 18% lower risk of depressive symptoms in children, adolescents and adults.

4.2 Adults

4.2.1 *Effects* with a strong level of evidence:

Endurance training

Cardiometabolic outcomes

- Moderate- to vigorous-intensity endurance training (2 to 7 times per week, 20 to 60 minutes per session, for 1 to 12 months) versus no exercise, lowers systolic blood pressure by about 3 mmHg in adults, especially in people with (pre-) hypertension.
- Moderate and vigorous-intensity endurance training (3 to 6 times per week, 24 to 90 minutes per session, or high-intensity interval training for 0.5 to 6 months) versus control, improves insulin sensitivity.
- Endurance training improves cardiorespiratory fitness in a dose-response way for exercise volume.
- Moderate-to vigorous-intensity endurance training (3 to 5 times per week, 30 to 60 minutes per session, for one year) versus no exercise or flexibility training, reduces body weight by about 1 kilogram in adults.
- Endurance training lowers body weight in comparison to inactivity in overweight and obese adults.

- Moderate- to vigorous-intensity endurance training (3 to 5 times per week, 30 to 60 minutes per session, for one year) versus no exercise, reduces fat mass by 2% in adults.
- Endurance training (40 to >75% VO_2max, 1 to 7 times per week, 15 to 90 minutes per session, for 1 to 15 months) reduces abdominal fat in overweight and obese adults; effects are larger at larger volumes of training.
- Moderate- and vigorous-intensity endurance training reduces waist circumference.

Mental symptoms
- Moderate- to vigorous-intensity endurance and/or resistance training lowers depressive symptoms in adults.

Resistance training and weight-bearing exercise

Cardiometabolic outcomes
- Isometric resistance training (10-40% maximum voluntary contraction, 3 to 5 days per week, 4 x 2 minutes isometric contractions per session, for 1 to 2.5 months) versus no training, lowers systolic blood pressure in adults.
- Resistance training (50% of 1-RM or more, 2 to 3 times per week, for 2 to 6 months) versus control, improves insulin sensitivity.

Combination of endurance and resistance training

Cardiometabolic outcomes
- The combination of moderate- or vigorous-intensity endurance training (3 to 6 times per week 24 to 90 minutes per session or high-intensity interval training) and resistance training (50% 1-RM or more 2 to 3 times per week for 3-12 months) versus the control group, improves insulin sensitivity.

4.2.2 *Associations* with a strong level of evidence:

Physical activity

All-cause mortality
- Leisure-time physical activity is associated with a lower risk of all-cause mortality in comparison to no leisure-time physical activity: >0 to <450 versus 0 MET-min per week of leisure-time physical activity is associated with a 20% lower risk and 450 to <900 MET-min per week with a 31% lower risk, and increasing amounts of leisure-time physical activity are associated with a progressively decreasing risk to almost 40% at 900 to <4,500 MET-min per week.

Cardiometabolic diseases

- Moderate-intensity versus no leisure-time physical activity is associated with a lower risk of coronary heart disease: 75 minutes of moderate-intensity leisure-time physical activity per week, versus none, is associated with a 14% lower risk, 150 minutes with an 18% lower risk and increasing amounts of moderate-intensity leisure-time physical activity are associated with a progressively decreasing risk to 20% lower at 300 minutes per week.
- Moderate- versus low-intensity leisure-time physical activity is associated with a 27% lower risk of stroke in men and an 11% lower risk in women, high- versus low-intensity leisure-time physical activity is associated with a 29% lower risk of stroke in men and a 22% lower risk in women.
- Leisure-time physical activity is associated with a lower risk of heart failure: 500 versus 0 MET-min per week is associated with a 10% lower risk, 1,000 versus 0 MET-min per week with a 19% lower risk and 2,000 versus 0 MET-min per week with a 35% lower risk.
- A high versus low level of physical activity is associated with a 19% lower risk of diabetes.
- A high versus low level of leisure-time physical activity is associated with a lower risk of diabetes. The reduction in risk is more pronounced at low levels of physical activity than at high levels.

Cancer

- A high versus low level of total physical activity is associated with a 13% lower risk of breast cancer. The reduction in risk is more pronounced at low levels of physical activity than at high levels.
- A high versus low level of leisure-time physical activity is associated with a 10 to 12% lower risk of breast cancer. The reduction in risk is more pronounced at low levels of physical activity than at high levels.
- A high versus low level of leisure-time physical activity is associated with a 16% lower risk of colon cancer.
- A high versus low level of total physical activity is associated with a 20% lower risk of lung cancer in current smokers.

Mental symptoms

- Moving from inactivity to activity or maintaining activity in comparison to becoming inactive are associated with a lower risk of depressive symptoms in adults.

4.3 Older adults

4.3.1 *Effects* with a strong level of evidence:

Resistance training and weight-bearing exercise

Fat-free mass, muscle strength functional outcomes

- Resistance training (50 to 80%1-RM, 2 to 3 times per week, 7 to 39 sets of 2 to 20 repetitions, for 2.5 to 12 months) versus control, increases fat-free mass in adults aged 50 years and over.
- Resistance training versus control improves muscle strength in older adults, with larger effects at increasing intensity.
- Progressive resistance training (75 to 80% 1-RM, 2 to 3 times per week, 45 to 60 minutes per session, for 2.5 to 6 months) versus habitual activities or attention control activities, improves gait speed in older and frail older adults by 0.13 m/s.

Combination of endurance training and resistance training

Fractures

- The combination of endurance training and resistance training, especially focusing on fall prevention and bone strength (gait, balance, functional, and resistance training; 30% to 90% 1-RM, or brisk walking to 85% HRmax, or endurance, 1 to 7 times per week, 20 to 90 minutes, for 4 to 120 months) versus no exercise, reduces the risk of fractures in older adults.

4.3.2 *Associations* with a strong level of evidence:

Physical activity

Fractures and disability

- A medium to high versus low level of physical activity is associated with a lower risk of disability.
- A high versus low level of physical activity is associated with a lower risk of fractures.
- A high versus low level of physical activity is associated with a lower risk of hip fractures.

Mental disorders

- A high versus low level of physical activity is associated with a lower risk of cognitive decline and dementia.
- A high versus low level of physical activity is associated with a 35% lower risk of Alzheimer's disease.

4.4 Children and adolescents

4.4.1 *Effects* with a strong level of evidence

Endurance training

Cardiometabolic outcomes

- Moderate- to vigorous-intensity endurance training (2 to 7 times per week, 6 to 90 minutes per session, for 6 months) versus control, lowers gain in BMI in overweight and obese children and adolescents by about 0.4 kg/m^2.
- Moderate- to vigorous-intensity endurance training lowers fat mass in overweight and obese children and adolescents.
- A combination of moderate- and vigorous-intensity physical activity improves cardiorespiratory fitness in children and adolescents.

Mental symptoms

- Moderate- to vigorous-intensity endurance training (2 to 3 sessions per week, 20 to 90 minutes per session, for 3 to 7 months) versus usual care or light physical activity, lowers depressive symptoms in children and adolescents at risk of depressive symptoms.

Resistance training and weight-bearing exercise

Bone mineral density

- Resistance training versus control improves muscle strength in young people.
- Weight-bearing exercise (1 to 5 times per week, 10 to 60 minutes per session, for 2.5 to 48 months) versus control, improves bone mineral content and areal bone mineral density, especially in prepubertal children. The effect is small (Hedges' g = 0.17).

Combination of endurance training and resistance training

Cardiometabolic outcomes

- The combination of endurance training and resistance training (2 to 4 times per week, 40 to 90 minutes per session, for 2 to 6 months), versus control, improves insulin sensitivity in children and adolescents.

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