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Exercise in type 2 diabetes mellitus: a meta-analysis of the effects of exercise on glycemic control, body composition and physical fitness.

by

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ABSTRACT

The purpose of the study was to systematically review and quantify the effect of exercise interventions on HbA1c and body mass in type 2 diabetes. A literature search was conducted to find all controlled clinical trials in type 2 diabetic adults comparing an exercise intervention (≥ 8weeks) to a non-exercise control. Weighted mean differences (WMD) and standardised mean differences (SMD) were used to calculate the size of the effect of exercise. Eleven aerobic training studies (average: 3.5 times/week for 18.6 weeks) and 2 resistance training studies (average: 10 exercises, 2.5 sets, 13 repetitions, 2.5 times/week for 15 weeks) met the inclusion criteria.

In the first set of analyses, the effects of exercise on HbA1c and body mass were studied. Aerobic training interventions produced a significant decrease in HbA1c compared to control (WMD = -0.74, p= 0.00003). Improvements in HbA1c with resistance training were similar in size (WMD = -0.64, p = 0.05). Although the exercise groups lost a mean of 2.5 kilograms, their post-intervention body mass was not statistically different from the control groups' (SMD = 0.10 standard deviations (SD), p= 0.76). In the second set of analyses, aerobic training produced a 11% increase in VO_2 max compared to control (SMD = 0.49 SD, p = 0.003). When only intense aerobic interventions are considered (≥ 75 % VO_2 max) the post-intervention VO_2 max was 30% higher than in the control group. Improvements in strength produced by resistance training were also significant (SMD = 1.00, p= 0.0001).

In summary, exercise training resulted in statistically and clinically significant improvements in HbA1c without change in body mass compared to control. On the other hand, there is little information available from controlled clinical trials on the effect of exercise on other elements of body composition and physical fitness in type 2 diabetes.

CHAPTER I

INTRODUCTION

1. Background

For many years, exercise has been considered to be one of the three cornerstones of diabetes therapy, along with diet and medication (Joslin, Root, & White, 1959). Regular physical activity is recommended in type 2 diabetes since it may have beneficial effects on physical and metabolic risk factors for the development of diabetic complications. The low-cost, non-pharmacological nature of physical activity further enhances its therapeutic appeal.

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycemia due to problems of insulin resistance, insulin secretion or a combination of both (Meltzer et al., 1998). Insulin resistance and compensatory hyperinsulinemia are linked to a cluster of metabolic and hematological abnormalities, therefore exposing people with type 2 diabetes at high risk of developing complications such as cardiovascular disease (DeFronzo & Ferrannini, 1991; National Diabetes Data Group & National Institutes of Health, 1995; Reaven, 1988). Obesity, especially excess visceral adipose tissue, is also common in this syndrome and likely plays a major role in its etiology (Després, 1993; Després, 1994b; Després, 1997). Cardiorespiratory fitness, as represented by maximal oxygen consumption (VO_2 max) is inversely associated with all-cause and cardiovascular disease mortality (Lee, Blair, & Jackson, 1999). People with type 2 diabetes, even in the absence of known complications, have reduced maximal oxygen consumption compared to age and activity matched controls (Regensteiner, Sippel, McFarling, Wolfel, & Hiatt, 1995). Mortality and diabetic complications such as

neuropathy, are associated with a lower VO_2 max (Estacio et al., 1998; Roy et al., 1989; Wei, Gibbons, Kampert, Nichaman, & Blair, 2000). A decreased exercise capacity may predict coronary artery disease in type 2 diabetes (Rubler, Gerber, Reitano, Chokshi, & Fisher, 1987).

Although there have been numerous small research studies on the effect of exercise in people with type 2 diabetes, often including detailed physiological and biochemical measures, their findings have varied. There have been no large studies with adequate statistical power to guide practitioners in recommending specific exercise plans for their diabetic patients. If indeed, exercise interventions in type 2 diabetes reduce hyperglycemia, increase insulin sensitivity (American Diabetes Association, 1997a; Després, 1997), improve body composition (National Institutes of Health, 1998), reduce blood pressure (Fagard & Tipton, 1994; Kelley & Tran, 1995) and increase physical fitness (Bouchard, Shephard, & Stephens, 1994), physical activity should be further emphasised as a major component of diabetic therapy. Many different types of exercise interventions exist. It remains unclear which exercise modality would be optimal for achieving different therapeutic goals in type 2 diabetes.

Nearly 50 review articles have been published on the topic of exercise and diabetes. Unfortunately, these reviews have typically used the traditional narrative approach. Synthesising research in this manner generally results in subjective, nonreplicable conclusions. The Quality of Reporting of Meta-analysis (QUORUM) statement defines meta-analysis as "a review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method".

Meta-analysis is especially useful in summarising prior research when the number of subjects per study and the number of studies are small, as is the case for exercise interventions in type 2 diabetes.

2. Objectives and hypothesis

The main objective of this study was to systematically review the effectiveness of different exercise interventions on glycemic control, body composition and physical fitness. Glycemic control was defined as the body's ability to maintain blood glucose at physiologically appropriate concentrations. Measurements of glycemic control included glycated hemoglobin (HbA1c), and fasting insulin levels. Changes in body composition were reflected in body mass (body weight or BMI), body anthropometrics, fat mass or lean body mass. The physical fitness variables of interest were maximal and submaximal exercise capacities, as well as resting heart rate and blood pressure.

It was hypothesised that exercise interventions are associated with improvements in the outcome measures although the time course and dose-response relationships between amount, intensity and frequency of exercise and clinical effects may well be quite different for the different outcomes. We expected that all exercise interventions would be associated with improvements in glycemic control. Furthermore, we expected that aerobic training would increase maximal and submaximal aerobic exercise capacity and reduce body mass through a reduction in fat mass. On the other hand, resistance training was expected to increase lean body mass and strength. Modest improvements in resting blood pressure and heart rate should also be evident with exercise training

This thesis has been written in article format and is comprised of 2 journal articles. Both articles are based on a systematic review and meta-analysis of all controlled

clinical trials (randomised and non-randomised) on the effects of exercise interventions in type 2 diabetes, and are presented in chapter III. The first article is entitled: *A meta-analysis of the effects of exercise on glycemic control and body mass in type 2 diabetes mellitus.* This article presents important information for practitioners on 2 clinically significant variables that are routinely measure in patients with type 2 diabetes: glycemic control and body mass. The second article: *A systematic review of the effect of exercise on health-related physical fitness in type 2 diabetes mellitus*. Both the articles will be submitted to the peer reviewed journals. This article presents information on the effect of exercise on variables typically of interest for exercise physiologist such as maximal and submaximal exercise capacities as well as a more detailed evaluation of changes in body composition.

Before presenting these articles, brief reviews will be presented in chapter II on 1) the importance of the selected outcome measures for the prevention of diabetic complications; 2) the biological mechanism by which exercise has been proposed to affects diabetic risk factors and that have guided our hypotheses; and 3) details on the meta-analysis procedures and technique which can not be included in the articles because of page limitations. After the presentation of the articles, a general discussion of the two journal articles and overall conclusions and recommendations will be presented in chapter IV. This thesis also includes a number of appendixes. In Appendix A a summary of studies measuring the energy cost of resistance training sessions are presented. Appendix B describes the quality assessment tools. Appendix C includes all the tables and figures resulting from the analysis of the results, many of which are not presented in the articles because of page limitations.

CHAPTER II

REVIEW OF LITERATURE

1. Type 2 diabetes

1.a. Description of diabetes mellitus. Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycemia (elevated blood glucose concentration) due to problems of insulin action, insulin secretion or a combination of both (Meltzer et al., 1998). Type 2 diabetes is the most common form of diabetes mellitus, accounting for over 90% of all diabetes cases in North America (Health Canada, Laboratory Center for Disease Control, & Diabetes Division, 1999; National Diabetes Data Group & National Institutes of Health, 1995). Type 2 diabetes is a complex disease in which environmental and genetic factors play major roles in the development (Gudat, Berger, & Lefèbvre, 1994; Gurwitz et al., 1994). This disease has also been called non-insulin-dependent diabetes mellitus (NIDDM), but this terminology is slowly being eliminated because of the confusion it caused by being based on the treatment rather than the pathogenesis of the disease.

In the United States, type 2 diabetes affects approximately 3.1% of the population and 10.2% of people over 65 (National Diabetes Data Group & National Institutes of Health, 1995). In Canada, these numbers are almost identical, with 3.2% of the population and 10.4% of those over 65 being diagnosed with diabetes (Health Canada et al., 1999). It is estimated that almost half of the cases may be undiagnosed (Bonen, 1995). For reasons that are not yet fully understood, some cells (i.e., muscle cells) of people with type 2 diabetes are resistant to the effect of insulin. Consequently this disease is characterised by hyperglycemia. In order to lower glucose levels, the pancreatic β-cells

in turn secret more insulin, resulting in hyperinsulinemia. As the disease progresses, the relative insulin deficiency may eventually evolve to an absolute secretory deficiency as β-cells become exhausted.

Type 2 diabetes is not to be confused with Type 1 diabetes, which occurs when the pancreas is unable to produce insulin because of the destruction of the β-cells. Type 1 diabetes is usually an auto-immune disease although in some cases the etiology is unknown (Meltzer et al., 1998). Type 1 diabetes patients depend on exogenous sources of insulin. This disease usually develops in childhood or adolescence but may appear at any age. Type 2 diabetes usually develops after the age of 40 and has a strong positive association with obesity.

1.b. Type 2 diabetes complications. Because of poor control of glucose levels, type 2 diabetic patients are at a higher risk of developing other diseases and/or health complications. The United Kingdom Prospective Diabetes Study (UKPDS) is a large trial with 3896 participants with type 2 diabetes allocated to intensified glucose lowering treatment or conventional treatment. Patients receiving intensive treatment had HbA1c only 0.9% lower than the conventional treatment (7.0% vs 7.9%, $p < 0.001$) but had significant reduction in diabetes related clinical end points (40.9 vs 46 events per 1000 patients, $p = 0.029$) (U.K. Prospective Diabetes Study Group, 1999) The organs and tissues that are damaged by chronic hyperglycemia include those in which glucose uptake is dependent on glucose concentration and independent of the effect of insulin. These include the eyes, kidneys, nerves, blood vessels and pancreatic β-cells (Yki-Yarvinen, 1998). On the other hand, tissues for which glucose uptake is independent of glucose concentration (i.e.,

brain), or dependant on glucose and insulin concentrations (i.e., muscles and adipose tissue) are not damaged by chronic hyperglycemia.

Diabetic kidney disease is the leading cause of end stage renal disease in the Western world (National Institutes of Health & Diseases, 1995). More than 40% of people with diabetes have elevated urinary albumin excretion (Nelson, Knowler, Pettitt, & Bennett, 1995), which is a widely accepted and appropriate surrogate marker for diabetic kidney disease. Hyperglycemia interferes with filtration mechanisms, but it is not entirely clear how. The risk of diabetic kidney disease increases exponentially at higher glucose levels (Krolewski, Laffel, Krolewski, Quinn, & Warram, 1995). Hyperglycemia not only generates increased oxygen free radicals but also hampers antioxidative mechanisms by glycating scavenging enzymes. Oxidative stress is also likely to play a role in the pathogenesis of diabetic nephropathy (Ha & Kim, 1995).

Sixty to seventy percent of patients with diabetes have some form of neuropathy, but in many cases there are no symptoms (Eastman, 1995). The two main categories of neuropathy are peripheral neuropathy (mostly affecting the feet and hands) and autonomic neuropathy (affecting the internal organs). Symptoms of neuropathy include numbness and sometimes pain in the hands, feet, or legs. Neuropathy is also a risk factor for foot ulcers and amputations (National Institutes of Health, 1995). Nerve damage caused by diabetes can lead to problems with internal organs such as the digestive tract, heart, and sexual organs (National Institutes of Health, 1995). The Diabetes Control and Complications Trial (DCCT), a 10-year multicentre randomised controlled clinical trial that involved 1,441 volunteers with type 1 diabetes, suggests that keeping blood sugar levels as close to the normal range as possible slows the onset and progression of nerve

disease caused by diabetes (DCCT Research Group, 1993). It is not known exactly how hyperglycemia affects neuropathy. High blood glucose causes chemical changes in nerves; these changes impair the nerves' ability to transmit signals. Furthermore, high blood glucose damages blood vessels that carry oxygen and nutrients to the nerves (National Institutes of Health, 1995). Neuropathy is also associated with a lower fitness level, as represented by maximal oxygen consumption (VO_2 max) (Estacio et al., 1998; Roy et al., 1989).

Diabetic retinopathy disease is the leading cause of blindness in American adults (Klein & Klein, 1995). It is caused by changes in the blood vessels of the retina. In some people with diabetic retinopathy, retinal blood vessels may swell and leak fluid. In other people, abnormal new blood vessels grow on the surface of the retina. These changes may result in vision loss or blindness. Nearly half of all people with diabetes will develop some degree of diabetic retinopathy during their lifetime. The DCCT demonstrated that intensive diabetes therapy (lowering of blood glucose) delays the onset and slows the progression of retinopathy, nephropathy, and neuropathy in patients with type 1 diabetes (DCCT Research Group, 1993).

1.c. Type 2 diabetes and cardiovascular disease. The incidence of diabetic complications such as nephropathy, neuropathy and retinopathy could be even higher, but because of cardiovascular disease diabetic patients often do not live long enough for these complications to develop. People with type 2 diabetes have cardiovascular mortality and morbidity rates that are 2 to 4 fold higher than in age and sex matched groups from non-diabetics population (Meltzer et al., 1998; Yki-Yarvinen, 1998). The risk of coronary

artery disease and stroke is also increased 2 fold in men and 3 to 4 fold in women with diabetes (Meltzer et al., 1998).

People with type 2 diabetes are at a greater risk for the development of cardiovascular disease not only because of the associated hyperglycemia and hyperinsulinemia but because they often also have dislipidemia, high blood pressure and abnormalities of the coagulation system. These abnormalities tend to cluster and are often referred to as the metabolic syndrome (Grundy, 1998). The metabolic syndrome is related to the development of cardiovascular disease in diabetic and non-diabetic populations (DeFronzo & Ferrannini, 1991; Després, 1997; Eriksson, Taimela, & Koivisto, 1997; Grundy, 1998, Reaven, 1988 #893; Reaven & Laws, 1994; Zimmet, McCarty, & de Courten, 1997). Obesity, especially excess visceral adipose tissue is common in the metabolic syndrome and likely plays a major role in its etiology (Després, 1993; Després, 1994b; Després, 1998). All components of the metabolic syndrome are more common and on average more severe in type 2 diabetic individuals than in the background population (Cowie & Harris, 1995).

Cardiorespiratory fitness, as represented by maximal oxygen consumption (VO_2 max) is inversely associated with all-cause and cardiovascular disease mortality (Lee et al., 1999). People with type 2 diabetes, even in the absence of known complications, have reduced maximal oxygen consumption's compared to age and activity matched controls (Regensteiner et al., 1995). A decreased exercise capacity may predict mortality and coronary artery disease in type 2 diabetes (Rubler et al., 1987; Wei et al., 2000).

1.d. Summary. Hyperglycemia is a major risk factor for future diabetic complications such as: nephropathy, neuropathy, retinopathy and macrovascular disease.

It is therefore a variable of major clinical importance. Insulin resistance and obesity (especially visceral obesity) are major risk factors for the future development of cardiovascular disease in diabetic and non-diabetic individuals. Low levels of aerobic fitness are also associated with cardiovascular disease. Therefore, reducing these risk factors are major goals of diabetic therapy.

The following section will briefly review the cross-sectional, longitudinal and experimental evidence supporting the biological mechanism by which exercise may have a beneficial impact on these risk factors. Particular attention will be placed on the exercise characteristics (type, intensity, frequency and duration) that are related to these improvements.

2. Mechanism by which exercise affects diabetic risk factors

2.a. Mechanism by which exercise affects glycemic control. Before describing how exercise may affect this variable, it is important to describe how glycemic control is measured. Glycated hemoglobin (HbA1c) is considered the gold standard measure for glycemic control since it reflects the average blood glucose concentration over the last two to three months (Goldstein, Little, Wiedmeyer, England, & McKenzie, 1986). However, glycated hemoglobin is not used for the clinical diagnosis of diabetes. Fasting plasma glucose and/or the Oral Glucose Tolerance Test (OGTT) 2-hour plasma glucose concentration have been and are currently recommended for the diagnosis of diabetes (American Diabetes Association, 1997b; National Diabetes Data Group, 1979; WHO, 1980) and are often reported in scientific articles as an indication of short-term glycemic control. Fasting insulin and the insulin response to an OGTT are often used as an

indication of insulin resistance. The "homeostasis model Assessment" (HOMA) is a model that estimates insulin resistance and β-cell function from fasting plasma insulin and glucose concentrations (Matthews et al., 1985). The gold standard for measuring insulin resistance is the euglycemic hyperinsulinemic clamp whereas the gold standard for the quantification of β-cell sensitivity to glucose is the hyperglycemic clamp technique (DeFronzo, Tobin, & Andres, 1979).

When describing the mechanisms by which exercise affects these factors, it is important to distinguish between the long-term (chronic) and short-term (acute) effects. Even if studies on the long-term effect of exercise on HbA1c in type 2 diabetes have led to conflicting results, a single exercise bout has repetitively been shown to improve glucose tolerance and insulin sensitivity in diabetic and non diabetic populations (Bonen, Ball-Burnett, & Russel, 1998; Braun, Zimmermann, & Kretchmer, 1995; Gudat et al., 1994; Wallberg-Henriksson, Rincon, & Zierath, 1998). These improvements are short lived, lasting from 24-72 hours (Gudat et al., 1994; King et al., 1995) and are explained by an increase in the number and activity of glucose transporters and glycogen synthase activity in order to replenish muscle and liver glycogen (American Diabetes Association, 1997a; Devlin, 1992; Holloszy, Schultz, Kusnierkiewicz, Hagberg, & Ehsani, 1986). Since the effects of aerobic exercise disappear shortly after the last exercise bout, the long-term benefits of aerobic exercise on HbA1c are sometimes interpreted as being the cumulative effect of the individual exercise bouts repetitively lowering blood glucose concentrations (Wallberg-Henriksson et al., 1998).

Exercise may have further long-term benefits on glycemic control when its potential influence on fat loss is considered (Wallberg-Henriksson et al., 1998). Exercise

interventions that produce fat losses should produce improvements in glycemic control or insulin sensitivity, especially if the fat loss is from visceral deposits. Even if fat loss is not present, reductions in HbA1c may be observed as a result of the cumulative acute effects of the individual exercise bouts. Because of the short duration of the acute effect of exercise, if fasting glucose, fasting insulin or OGTT are performed more than 48 hours after the last exercise bout, the beneficial effects of regular exercise may be underestimated. Finally, since HbA1c provides an estimate of the average blood glucose values over the last 2-3 months, exercise interventions that are shorter than this will not be of sufficient duration to exert their full effect on HbA1c.

The intensity of an exercise bout may also be an important parameter to study. People may be more likely to adhere to low intensity home based exercise programs (Hillsdon & Thorogood, 1996), therefore it would be important to know if low intensity exercises are as beneficial as high intensity ones. A cross-sectional study by Mayer-Davis et al. (Mayer-Davis et al., 1998) provided information on how the intensity and amount of physical activity are associated with insulin sensitivity in a type 2 diabetic population. The correlation coefficient between the estimated energy expenditure from exercise and insulin sensitivity was 0.14 ($P<0.001$). Both vigorous and non vigorous levels of estimated energy expenditure were positively and independently associated with insulin sensitivity after adjustment for confounding variables ($P<0.01$). This is supported by experimental evidence in a study by Bonen et al. (Bonen et al., 1998) wherein two different exercise intensities matched for energy expenditure were associated with similar improvements in plasma glucose and insulin responses to an OGTT. Similar acute improvements in insulin sensitivity were found after low and high intensity exercise

bouts matched for energy expenditure in women with type 2 diabetes (Braun et al., 1995).

A negative energy balance is positively associated with weight loss. Furthermore, high intensity exercises do not seem necessary for the acute improvements in glucose tolerance and insulin sensitivity. Therefore the volume of exercise or weekly energy expenditure may be the strongest predictor of improvements in glycemic control and insulin resistance.

The type of exercises performed may also have an influence on glycemic control and insulin sensitivity. Exercises such as cycling, walking, running, swimming and skiing have generally been grouped together under the term: aerobic (or endurance) exercises. No published studies have compared the benefits of different types of aerobic exercise on metabolic control. There have been few studies on the effects of exercises designed to increase muscle strength and size such as resistance training in type 2 diabetes. It remains unclear how the benefits of resistance training compare to aerobic training. Interestingly, while the effects of aerobic exercise on insulin sensitivity dissipates within a few days after exercise cessation (Gudat et al., 1994), one study in 60-75 year old men showed that a program of resistance training could lead to an increased insulin sensitivity at least one week after the last bout of exercise (Zachwieja, Toffolo, Cobelli, Bier, & Yarasheski, 1996). Increasing muscle mass has a theoretical appeal since muscle is the major site of glucose disposal, increasing muscle mass could increase glucose storage area and reduce the amount of insulin required to maintain a normal glucose tolerance (Ivy, 1997). Furthermore, the main determinant of resting energy expenditure is lean body mass (Poehlman, 1989), this may be important since resting metabolic rate is the principal component of the total daily energy expenditure.

It is unclear whether any specific type of aerobic exercise would be more beneficial than another when matched for intensity, energy expenditure and frequency of the workouts. Even if the energy expenditure associated with resistance exercises is not very high (see appendix A), this type of training may promote improvements of insulin resistance and glycemic control through other mechanisms.

2.b. Mechanism by which exercise affects body composition. In the United stated an estimated 97 million adults are estimated to be overweight or obese (National Institutes of Health, 1998). Overweight is defined as a body mass index (BMI) of 25-29.9 24% $kg/m^{2,}$, whereas obesity is defined as a BMI equal or above 30 kg/m^2. The last results from the National Health and Nutrition Examination Survey (NHANES) suggest that 63% of men and 55% of women over the age of 20 had a BMI equal or above 25 kg/m^2 (Must et al., 1999). In Canada, these values are similar (Health Canada, 1997). Body weight and BMI are very practical measures. Although an elevated BMI is a very crude indication of higher body fat accumulation, it is a risk factor for the development of the metabolic syndrome and type 2 diabetes (Després, 1997). An even stronger risk factor is when body fat accumulates in the abdominal area, more specifically known as visceral obesity (Bouchard et al., 1994; Després, 1993; Després, 1997). Visceral obesity is strongly related to insulin resistance (low insulin-mediated glucose uptake), and to elements of the metabolic syndrome including: dislipidemia, elevated blood pressure and hyperglycemia (Bjorntorp, 1995; Després, 1997). Visceral obesity can be precisely assessed by modern imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI), although these techniques are often impractical and expensive. Waist circumference, sagital abdominal diameter or the waist-to-hip ratio

(WHR) are used as practical indicators of abdominal obesity. Figure 1 represents the relative risk of developing type 2 diabetes over a 13.5 year follow-up according to the classification of BMI and WHR into tertiles (Ohlson et al., 1985). An elevated BMI (3rd tertile) is associated with 2.9 relative risk of developing diabetes, an elevated WHR (3rd tertile) is associated with 0.5 relative risk of developing diabetes, but when both BMI and WHR are in the 3rd tertile the relative risk is increased to 15.2.

The importance of obesity in the development of type 2 diabetes and of elements of the metabolic syndrome makes weight reduction one of the main objectives in the control and prevention of diabetes and of diabetic complications. Diet and exercise are the primary methods used to achieve fat loss. A significant amount of research has been conducted on the effects of exercise on weight loss. The *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* (National Institutes of Health, 1998) summarises the results of different clinical trials with the following recommendations: "Physical activity is recommended as part of a weight loss therapy and weight maintenance program because it: (a) modestly contributes to weight loss in overweight and obese adults (Evidence category A), (b) may decrease abdominal fat (Evidence category B), (c) increases cardiorespiratory fitness (Evidence category A), and (d) may help with maintenance of weight loss (Evidence category C).". The term "evidence category A" indicates that a rich body of data from randomised controlled trials (RCTs) support the findings, whereas "evidence category B" indicates that limited body of RCTs support the findings and "evidence category C" indicates that evidence is from outcomes of uncontrolled, non randomised trials (National Institutes of Health, 1998).

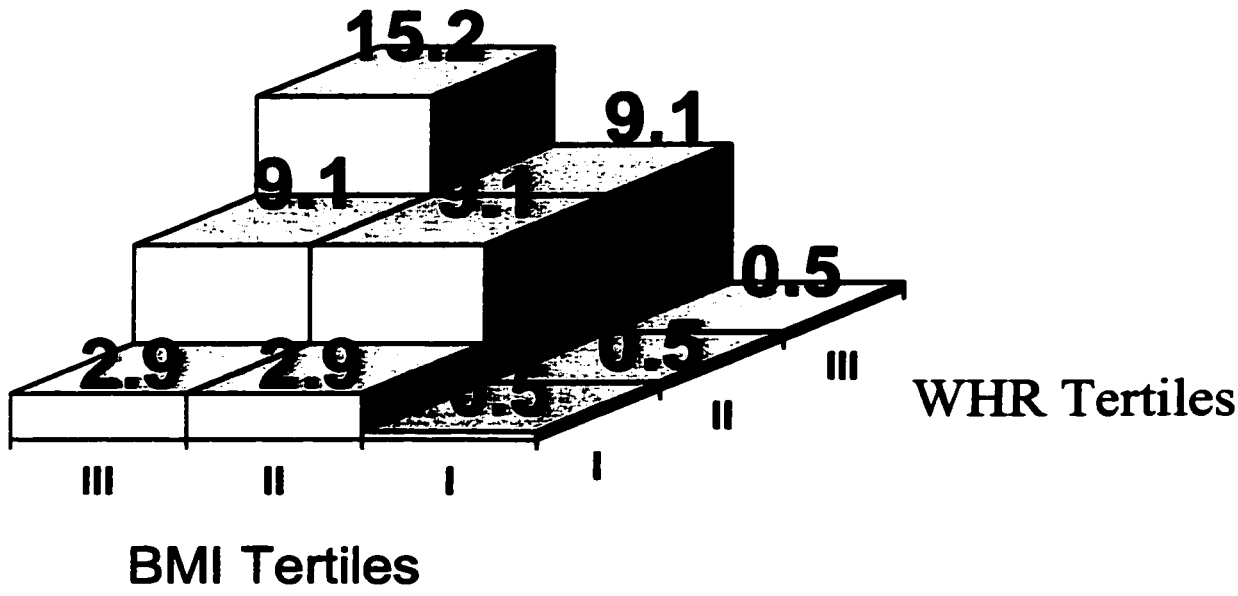

Figure 1: Probability of developing type 2 diabetes in men of the Göteborg prospective study classified into tertiles of BMI and WHR, reproduced from (Ohlson et al., 1985).

Exercise may influence the reduction in body fat by contributing to a negative energy balance. The size of this negative balance is proportional to the energy cost of exercise if the energy intake is kept constant (Bouchard et al., 1994). Exercise may influence energy expenditure acutely and chronically. Acute increases in energy expenditure corresponds to the energy cost of the exercise session itself. Therefore, exercise sessions that use larger muscle masses for longer periods of time at higher intensities will help promote a larger energy deficit. Whereas chronic increases in energy expenditure are due to an increase in resting metabolic rate, often due to increases in lean body mass which is the major determinant of resting metabolic rate (Poehlman, 1989). With diet induced weight loss, there is usually an accompanied loss in lean body mass, resulting in a decrease in resting metabolic rate (Ballor & Poehlman, 1995). A decreased resting metabolic rate may make further weight loss even more difficult. In a recent study, aerobic exercise alone did not increase lean body mass or resting metabolic rate while resistance or concurrent resistance and aerobic training did (Dolezal & Potteiger, 1998).

Exercise training can result in a loss of adipose tissue. Furthermore, the adipose tissue loss resulting from exercise is often preferentially of visceral rather than subcutaneous fat (Després, 1994a). Recent reviews highlights the importance of energy expenditure associated with exercise as the main contributor to exercise induced weight loss (Bouchard et al., 1994; Després, 1997; Després & Lamarche, 1994). Traditionally, aerobic exercises have been recommended for the loss of body fat whereas resistance training has been recommended for increasing muscle mass.

2.c. Effect of exercise on other components of health-related fitness. Many definitions of physical fitness exist. As a general concept, fitness can be interpreted as the matching of an individual to his or her physical environment (Bouchard & Shephard, 1994). The World Health Organisation defines fitness as " the ability to perform muscular work satisfactorily" (Organization, 1968). Therefore physical fitness is often measure by various maximal and submaximal exercise test.

Over the last decades, the definition of fitness has evolved. In 1992, the Second International Consensus Symposium on Physical Activity, Fitness, and Health was held in Toronto, Canada. The proceedings from this conference differentiated between performance-related fitness and health-related fitness (Bouchard & Shephard, 1994) (p.80): "Performance related fitness refers to those components of fitness that are necessary for optimal work or sport performance".... "It (health related fitness) has been defined as a state characterised by (a) an ability to perform daily activities with vigor and (b) demonstration of traits and capacities that are associated with a low risk of premature development of hypokinetic diseases and conditions". Health related fitness include 5 components: morphological, muscular, motor, cardiorespiratory and metabolic fitness. These components are further described in table 1.

The concepts of metabolic and morphological fitness have been described in previous sections. We now direct our attention to other potentially important components of health-related fitness in type 2 diabetes: muscular and cardiorespiratory fitness.

Table 1: The components of health related fitness as described by Bouchard and Shephard (Bouchard & Shephard, 1994) (P.81)

Fitness components
Morphological component
Body mass for height
Body Composition
Subcutaneous fat distribution
Abdominal visceral fat
Bone density
Flexibility
Muscular component
Power
Strength
Endurance
Motor component
Agility
Balance
Co-ordination
Speed of movement
Cardiorespiratory component
Submaximal exercise capacity
Maximal aerobic power (VO_2 max)
Heart functions
Lung functions
Blood pressure
Metabolic component
Glycemic control
Insulin sensitivity
Lipid and lipoprotein metabolism
Substrate oxidation characteristics

Although not traditionally considered a risk factor for diabetic complications, exercise capacities may be important variables to consider in type 2 diabetes. The cardiorespiratory component has often been seen as the most important component of physical fitness. People with type 2 diabetes often have a lower maximal oxygen uptake (VO_2 max) during exercise than people in the general population (Schneider, Khachadurian, Amorosa, Clemow, & Ruderman, 1992). It is unclear if this is a consequence of the diabetic state, genetic predisposition, or lower physical activity levels.

Many studies have demonstrated an inverse relationship between VO_2 max and all cause mortality or cardiovascular mortality (Blair et al., 1996; Blair et al., 1995; Lee et al., 1999). However, this type of study cannot establish a cause and effect relationship between VO_2 max and cardiovascular mortality. On a population based scale, VO_2 max and physical activity participation are well correlated but some authors believe that it is the energy expenditure associated with physical activity and not the increase VO_2 max that causes the reduction in cardiovascular disease risk (Després, 1997; Després & Lamarche, 1994).

Even if increased submaximal and maximal exercise capacities may not directly reduce the risk of cardiovascular mortality, they may have beneficial effects on quality of life. Aerobic exercise has been associated with improved quality of life in type 2 diabetes (Kaplan, Hartwell, Wilson, & Wallace, 1987). Exercise interventions designed to increase strength have also been shown to increase quality of life in cardiac rehabilitation populations (Beniamini, Rubenstein, Zaichkowsky, & Crim, 1997). With increased strength, increased levels of physical activity have been seen in older participants (American College of Sports Medicine, 1998a). Poor maximal and submaximal physical

work capacities may make every day activities more demanding or impossible, thereby lowering patients' quality of life and reducing the probability of patients participating in potentially beneficial physical activity.

Exercise may help promote many beneficial adaptations. These physiological adaptations may make every day activities seem relatively easier and help promote more independence in the elderly. The typical training adaptations associated with aerobic and resistance training are described in table 2 and 3.

The physiological changes described in tables 2 and 3 are typical adaptations found in a normal healthy population. Little information is available on many of these parameters in type 2 diabetes and results have not been consistent. People with type 2 diabetes are often very inactive and therefore an increase in any type of physical activity may have benefits usually not seen in a more active group. For example, it would not be surprising for a walking program to cause an increase in leg strength in a very inactive population, this is usually not the case in more active segments of the population.

When designing exercise interventions to improve maximal and submaximal exercise capacities, it is important to keep four fundamental physiological principles in mind: a) overload, b) specificity, c) reversibility and d) individuality.

The application of an appropriate stressor is sometimes called "overloading" the system (Brooks, Fahey, & White, 1995). An exercise load can be quantified in terms of intensity, duration, frequency and type. Not all exercises produce increases in exercise capacities. The stimulus must be of strong enough intensity and of appropriate frequency in order to be effective (i.e. jogging once a week typically does not produce a significant change in maximal oxygen uptake after 3 months of training).

Table 2

Changes in Cardiovascular and Pulmonary Function as a result of aerobic type training

Variables	Resting	Submaximal exercise	Maximal exercise
Oxygen consumption	No change	No change	Increase
Heart rate	Decrease	Decrease	No change
Stroke Volume	Increase	Increase	Increase
Cardiac Output	No Change	No change	No change
Muscle blood flow	Reduce	No change	Increase
Pulmonary capillary blood volume	Increase	Increase	Increase
Recovery rate	Not applicable	Increase	Increase
Oxygen extraction	No change	No change	Increase

Note. Table 2 was partially reproduced from (Brooks et al., 1995; Mitchell & Raven, 1994)

Table 3.

Comparison of physiological adaptations to resistance training and aerobic training.

Variable	Following resistance training	Following aerobic training
Muscle strength	Increases	No change
Muscle endurance	Increases for high power output	Increases for low power output
VO_2 max	No change or slight increase	Increase
Anaerobic power	Increase	No change
Muscle fibre size	Increase	No change or small increase
Capillary density	No change or slight decrease	Increase
Mitochondrial density	Decrease	Increase
Stored glycogen	Increase	Increase
Fat-free mass	Increase	No change
Percent body fat	Decrease	Decrease

Note. Table 3 was partially reproduced from (Baechle, 1994).

Another important principle is specificity. The closer the training routine is to the requirement of the test, the better the outcome on the test will be (Canadian Society for Exercise Physiology, 1993). For example: a participant whose training program consists of exercise on a stair climber will show greater improvements in the heart rate response to a step test than a participant whose exercise program consist of swimming.

The training response is not permanent, it is reversed by inactivity. This is the principle of reversibility, once a desired level of training is obtained a regular maintenance exercise program must sustain it. Therefore the results of maximal and submaximal exercise testing are dependent on the timing of the test and the presence of maintenance programs.

Finally, it is important to remember that individuals differ widely in their response to a training program. This principle of individuality is strongly influenced by the individual's previous training level because of the overload principle that was previously described. The contribution of genetic factors may also influence exercise capacities. Aerobic fitness depends on many phenotypes associated with cardiac, respiratory, vascular and muscular functions. Heredity has been shown explains less than 10% of the variance in submaximal aerobic capacity and less than 25% of maximal aerobic capacity (Bouchard & Pérusse, 1994).

As described in table 1, other elements of cardiorespiratory fitness also include blood pressure and heart function. Hypertension is considered as both a risk factor for cardiovascular disease and a disease in itself. Primary or essential hypertension represents above 90% of all diagnosed cases. With prolonged hypertension there is an increased workload on the heart, which may result in heart failure. Hypertension is also a risk factor

for the development of kidney disease in people with diabetes. Furthermore, since hypertension accelerates atherosclerotic changes in larger arteries, hypertensive patients often die as a result of the progression of atherosclerosis to a thrombus and the occlusion of coronary or cerebral blood vessels (Bouchard et al., 1994). The chronic elevation in blood pressure is thought to begin with an elevated cardiac output. This leads to vasoconstriction of the blood vessels in order to decrease the blood flow that was beyond the needs of the organs. Over time, structural changes occur in the walls of the chronically vasoconstricted vessels, hypertension causes small arteries and arterioles to show medial hypertrophy and intima fibrous thickening. The walls of the heart also thicken (known as concentric hypertrophy) leading to a reduced chamber size. Increase cardiac output may have different causes such as the increase in sympathetic stimulation and primary retention of electrolytes and water by the kidneys.

Genetic predisposition is one of the primary risk factors for the development of hypertension. In recent years, the "insulin theory" of hypertension has been proposed to explain the link between increased body mass and hypertension (Fagard & Tipton, 1994). This is especially important in type 2 diabetes patients who often have elevated blood insulin concentrations in response to hyperglycemia (Yki-Yarvinen, 1998). Higher insulin concentration may increase sympathetic nervous system activity as well as sodium retention in the kidneys (Fagard & Tipton, 1994).

Aerobic exercise training has generally been shown to lower blood pressure in non-diabetic population (Fagard, 1993; Halbert et al., 1997; Kelley & Tran, 1995; Suskin & McKelvie, 1996). In meta-analyses of randomised trials, regular aerobic exercise lowered blood pressure (systolic/diastolic) by 4.5/3.8 mmHg in normotensives (Kelley &

Tran, 1995) and 7/6 mmHg in hypertensives (Arroll & Beaglehole, 1992; Kelley & McClellan, 1994). A recent meta-analysis of studies using resistance exercise found an overall mean decrease of 4.5/3.8 (Kelley, 1997). Since this effect is comparable to that of aerobic exercise in normotensive men, and hypertensive men were excluded or rare in the resistance exercise studies, it is reasonable to believe that the effects of the two modalities of exercise on blood pressure are similar in magnitude.

As was the case for glycemic control, exercise may have acute and chronic effects on hypertension. It is well demonstrated that resting blood pressure is reduced immediately following an exercise bout in normotensive and hypertensive participants. This effect may persist for hours (Fagard & Tipton, 1994). An inverse relationship has been reported between blood pressure and physical activity levels (Fagard & Tipton, 1994). There seems to be no consensus on an optimal type, duration, frequency or intensity for exercise intervention to reduce hypertension. Although some have slightly larger reductions in blood pressure when workouts were more frequent and at low to moderate intensities, while others have noticed that the improvements were related to improvements in exercise capacity (Fagard & Tipton, 1994). As mentioned, high levels of body fat and insulin resistance are positively related to hypertension, therefore exercise-induced improvements in hypertension may also be due to the reduction in body fat or insulin resistance.

Cross-sectional studies have often established an inverse relationship between physical activity levels and resting heart rate. Over months or years of aerobic training there is a gradual increase in left ventricular mass and chamber size. This is known as eccentric hypertrophy and may be beneficial (unlike the concentric hypertrophy seen with

hypertension). Although cardiac output at rest remains similar, heart rate is reduce because of the larger stroke volume.

2.d. Summary. The general consensus is that aerobic exercise may have positive effects on different elements of the metabolic syndrome, such as: glycemic control, insulin resistance, obesity and blood pressure. One of the main mechanisms for the improvements may be through weight loss. Exercise training may also be associated with other improvements in health-related fitness such as an increase in muscle mass and exercise capacities. Although cross-sectional, longitudinal and experimental studies suggest exercise training may be beneficial in type 2 diabetes, these benefits have not been consistently observed in controlled clinical trials (randomised and non randomised). A systematic review of all controlled clinical trials in which an exercise intervention was used in type 2 diabetes may be helpful in explaining these discrepancies.

3. The Meta-analytic procedure

3.a. A brief history of meta-analysis. A review of literature is a part of all types of research. Sometimes, a literature review stands alone as a research paper when it involves the evaluation and integration of published literature. Good research synthesis should result in several conclusions and propose interest for future research. Review articles are typically prone to biases and are often not reproducible. It is often not known how thorough the literature search was, on what basis studies were included or excluded from the review or how authors arrive at particular conclusions. Valid research should have a systematic approach to problem solving.

In recent years, systematic literature reviews are becoming much more popular. One of the most notable early attempts to systematically review literature was in the social sciences with an article by Glass in 1976 (Glass, 1976). In 1982, he later came out with a book proposing a technique called meta-analysis.

Systematic reviews and meta-analysis have become very popular in the medical field as well. Health care providers and decision-makers in the health field are often overwhelmed with information but now have a powerful tool among their information resources to help guide their decisions. Systematic reviews have quickly gained acceptance in the medical field over the last decades. This is in great part due to organisations such as the Cochrane Collaboration, an international organisation that aims to help people make well informed decisions about health by preparing, maintaining and ensuring the accessibility of systematic reviews of the benefits and risks of healthcare interventions. The Cochrane Collaboration was named in honour of Archie Cochrane who wrote: "It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials." (Cochrane, 1979). The Cochrane Collaboration provides reviewers with the support and expert knowledge needed to conduct systematic reviews. Apart from providing instruction manuals for conducting systematic reviews (Cochrane Collaboration, 1997), this organisation also supplies software to perform the meta-analysis and an electronic library which includes a registry of clinical trials. The software provided by the Cochrane Collaboration is called Review Manager (RevMan) and will be used within the present review.

3.b. Obtaining the data. One of the most important steps in the meta-analysis process is in the initial stages. In order to have the least amount of bias, it is important to obtain all the information available on the specific research question that was developed *a priori*. A good research question includes the population, the intervention, the outcomes and the study design of interest. Comprehensive literature searches must then be undertaken to find all studies that may address the specific question. Other possible sources included computerized bibliographic, databases, abstracts, review articles, conference proceedings, dissertation books, journal hand-searching, personal communications, etc... It is often suggested that two independent reviewers determine whether or not an article should be included in the meta-analysis in order to minimise bias. Although still controversial, including all languages and unpublished trials in the search strategy may help minimise biases (Cook et al., 1993; Egger et al., 1997). This brings us to the important point of the quality of the included trials. Expert opinion and quantitative data suggest that lower quality trials often overestimate the effect of an intervention (Jadad et al., 1996; Schultz, Chalmers, Hayes, & Altman, 1995). That is why meta-analyses are typically performed on high quality randomised-controlled trials. Many different scales and checklist have been developed to estimate the quality of clinical trials. We have chosen to use the validated 5 point scale developed by Jadad et al. (Jadad et al., 1996) (even if it is not validated for exercise intervention trials) and the allocation concealment variable described by Schultz et al. (Schultz et al., 1995). More details of the quality assessment tools we have used are given in appendix B.

The next step in the meta-analytic process is extracting the data. It is important for the data extraction procedure to be explicit, unbiased and reproducible. This step is often

done independently by two reviewers in order to minimise transcription errors. In many cases the desired information is not available in the article and every attempt should be made to contact the investigators of the original studies for the missing information.

3.b. Data analysis and Review Manager (RevMan) software. RevMan 4.0.4 was the software used to analyse the data, since the outcomes of our analysis are continuous data (as opposed to discrete) the following discussion of the techniques used by RevMan will pertain to continuous data.

In RevMan, the size of the effect of an intervention on variable is measured with weighted mean difference (WMD) or standardised mean difference (SMD). Weighted mean difference may be used when the mean, standard deviation and sample size in each group are known. The weight given to each study (e.g. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale. The difference between two means divided by an estimate of the within-group standard deviation. Studies may report an outcome on different scales. For example, in an adult population (where body height remains stable) changes in body mass may be presented as changes in body mass index (BMI) in some studies and as changes in body weight (kg) in others. By expressing the effects as a standardised (divided by the standard deviation) value the results can be combined since they no longer have units. This is know as standardised mean difference.

The fixed effects model is a statistical model in which only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval). This model assumes that the variable is analysed in people from the population of

interest. Variation between the estimates of effect from study to study (heterogeneity) does not effect the confidence interval in a fixed effect model. On the other hand, significant heterogeneity can make it difficult to interpret the pooled estimates.

RevMan software provides an estimation of heterogeneity using the Chi-square test, more details on how to interpret this test are provided when describing how to interpret the figures. There are different ways to deal with heterogeneity: 1) it may be the data should not be pooled at all, 2) ideally the heterogeneity of the results may be explain by a pre-specified subgroup or regression analysis, 3) use a random effects model.

Using a random effects model assumes that the size of the effect really varies across studies and is not normally distributed. There are therefore 2 sources of variation; within studies (between patients) and between studies (heterogeneity). When using the random effects model in RevMan, the software will take both components of the variation into account and revise the weight assigned to each study. If there is significant heterogeneity among the results of the included studies, random effects models will give wider confidence intervals than fixed effect models.

The results obtained in RevMan are presented by MetaView software. For a selected outcome, the figure will display an estimate (the square), 95% confidence interval (the line) and the weight allocated to each trial (the size of the square), see appendix C for an example. If the 95% confidence interval line crosses the solid vertical line, then the effect is not significant ($p > 0.05$). The same principle applies to the diamond, which represents the combined estimates and 95% confidence interval. Heterogeneity is indicated in the bottom left hand corner of the figure produced by Meta-View; a Chi-Square result which is larger than the degrees of freedom (df) is an

indication of heterogeneity. All the data in terms of mean, standard deviation (SD) and number of participants per study (n), is also indicated.

3.d. Limitations associated with the meta-analysis technique. As might be anticipated with the introduction of any relatively new approach such as meta-analysis, this approach is not free from criticism. Meta-analysis have been accused of over-simplifying the results by focussing on overall effects and downplaying the mediating or interaction effects. Better meta-analysis will therefore build potential mediating effects into their design a priori rather than ignore them. Mediating characteristics must non-the less be identified. Meta-analysis have typically been criticised of "mixing apples with oranges" when pooling studies which have different procedures, methodological quality, populations and outcome measures. Well-conducted meta-analyses appropriately codes the differences between the studies in order to empirically test for differences. It is importance to justify if studies are appropriate for statistical pooling or not. Published literature is often biased in favour of significant findings, this is known as publication bias and may artificially increase the size of the effect of the intervention.

Never the less, meta-analysis remain an efficient way to summarise large literatures and often permit reaching stronger conclusions. The meta-analysis techniques may provide excellent guidance for future research and permits addressing the problem from many different point of views. The ability to generalise the results of a meta-analysis is dependent on the external validity of the included studies. We are aware that most of the studies within the present meta-analysis may limit their inclusion criteria to relatively "healthy" individuals with diabetes. Therefore the results may not be generalisable to all diabetic patients.

CHAPTER III

PRESENTATION OF THE JOURNAL ARTICLES

Two journal articles are presented in this chapter, *A meta-analysis of the effects of exercise on glycemic control and body mass in type 2 diabetes mellitus* and *A systematic review of the effect of exercise on physical fitness in type 2 diabetes mellitus*. Both articles are based on a systematic review of the literature on the effects of exercise in type 2 diabetes mellitus and both have been prepared for publication in academic journals.

Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials.

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Abstract

Context. Exercise is widely perceived to be beneficial for glycemic control and weight loss in type 2 diabetes. However, clinical trials on the effects of exercise in type 2 diabetes have had small sample sizes and conflicting results.

Objective. To systematically review and quantify the effect of exercise on HbA1c and body mass in type 2 diabetes.

Data Source. Computerized databases (MEDLINE, EMBASE, Health Star, Sports Discuss, Dissertation Abstracts, Cochrane Library) were searched up to July 2000.

Study Selection. Randomized controlled trials and non-randomized controlled clinical trials where exercise interventions were prescribed (≥8 wk) to adults with type 2 diabetes.

Data Extraction. Two reviewers independently extracted baseline and post-intervention data (sample size (n), mean ($\bar{x}$), standard deviation (SD) from the intervention and control group. The characteristics of the exercise intervention and the methodological quality of the trials were also extracted.

Data Synthesis. Eleven aerobic training studies (average: 3.5 times/week for 18.6 weeks) and 2 resistance training studies (average: 10 exercises, 2.5 sets, 13 repetitions, 2.5 times/week for 15 weeks) met the inclusion criteria. Exercise interventions produced a significant decrease in HbA1c compared to control (weighted mean difference = -0.74%, p= 0.00003). Although the exercise groups lost a mean of 2.5 kilograms, their post-intervention body mass was not statistically different from the control groups' (standardized mean difference = 0.10 standard deviations (SD), p= 0.76).

Conclusion. Exercise training resulted in statistically and clinically significant improvements in HbA1c without greater change in body mass compared to control.

INTRODUCTION

For many years, exercise along with diet and medication has been considered to be one of the three cornerstones of diabetes therapy [1]. Regular physical activity is recommended in type 2 diabetes since it may have beneficial effects on metabolic and hemodynamic risk factors for the development of diabetic complications [2]. The low-cost, non-pharmacological nature of physical activity further enhances its therapeutic appeal.

Two of the major goals of diabetes therapy are to reduce hyperglycemia and body fat. Chronic hyperglycemia is associated with significant long-term complications, particularly damage to various organs such as the kidneys, eyes, nerves, heart and blood vessels [3]. Obesity, especially abdominal obesity, is associated with insulin resistance, hyperglycemia, abnormal blood lipid profiles and hypertension [4, 5]. These abnormalities tend to cluster and are often referred to as the "metabolic syndrome" [6]. Elements of the metabolic syndrome are strong risk factors for cardiovascular disease [7, 8].

Many different types of exercise interventions exist. Aerobic training refers to forms of exercise such as walking, cycling or jogging, which demand repetitive movements of large muscle groups. Resistance training refers to forms of exercise that use muscular strength to move a weight or work against a resistive load. Examples include exercise with free weights and or weight machines.

Although there have been numerous small research studies on exercise in type 2 diabetic participants their findings have varied. There have been no large studies with adequate statistical power to guide practitioners in recommending adequate exercise plans for their diabetic patients. Exercise interventions reduced HbA1c in some studies [9,

[10] but not in others [11, 12]. Meta-analysis may be especially useful in summarizing prior research when the number of subjects per study is small and the results are somewhat conflicting, as is the case for exercise interventions in type 2 diabetes [13].

Nearly 50 review articles or position statements have been published on the topic of exercise and diabetes, reflecting the immense interest in this topic [14]. However, only one of these [15] was a meta-analysis. Brown et al. [15] systematically reviewed the effects of different weight loss strategies in type 2 diabetes. Among the 89 studies included, only 9 were aerobic exercise intervention studies and just 6 of these had control groups. Exercise produced a statistically significant 1.5 kg decrease in bodyweight and approximately 0.8% reduction in HbA1c. The present meta-analysis includes 6 new trials that have been published since 1994, and has less potential for bias since all included studies had a non-exercising diabetic control group.

The main objective of this study was to systematically review the effect of exercise interventions on glycemic control as represented by HbA1c and body mass as represented by body weight (Kg) or body mass index (BMI = kg/m^2).

METHODS

Study Selection

Computer based searches (MEDLINE, EMBASE, Sport Discuss, Health Star, Dissertation Abstracts and the Cochrane Controlled Trials Register) were performed up to and including July 2000. The reference lists of major textbooks, review articles and of all included articles identified by the search were hand searched to find other potentially eligible studies. Potential missing articles and unpublished literature were sought from contact with experts in the field. Studies were not excluded due to their language of publication.

The computer-based search is described in figure 1, it included common text words and Medical Subject Headings (MeSH) related to exercise and type 2 diabetes. The findings limited to human subjects and were combined with a validated and highly sensitive search filter for randomized controlled trials (RCTs) and controlled clinical trials (CCTs) [16].

Only RCTs and CCTs that prescribed an exercise intervention in adult type 2 diabetic participants were included. Acceptable diagnostic criteria for type 2 diabetes include those described by the National Diabetes Data Group [17], the World Health Organization [18] or the American Diabetes Association [19]. If studies reported data for which it was impossible to discriminate between participants with type 2 diabetes and those with IGT, we attempted to contact authors for the individual patient data for those with diabetes.

All studies included in the present meta-analysis were limited to exercise interventions lasting at least 8 weeks in duration since our main outcome of interest,

HbA1c, reflects average blood glucose concentration from the previous 8-12 weeks. An exercise intervention was defined as a predetermined program of physical activity, described in terms of type, frequency, intensity and duration. Studies in which the intervention consists of recommending increasing physical activity were not included within the analyses since it would be impossible to quantify the exercise intervention and to be sure of compliance. In order to be included, exercise interventions compliance had to be assessed by to be supervision or by exercise diaries. Studies that included drug co-interventions were excluded from the analysis.

Two reviewers (N.B. and E.H.) independently assessed the titles and abstracts of the articles for inclusion. All potentially eligible articles were obtained and further assessed, any disagreements on inclusion were resolved by discussion with a third party (R.S.).

Data Extraction

The same two reviewers then independently extracted all relevant baseline and post-intervention data (sample size (n), mean (x), standard deviation (SD)) from both the intervention and control group. For trials with more than 2 groups data were analyzed comparing groups in which only difference between groups was the exercise intervention. For example, if a study had a 2 x 2 factorial design and assigned participants to 4 groups (1-exercise alone, 2-non-exercise, non-diet control, 3-exercise and diet, 4-diet alone) we analyzed the data as 2 comparisons: 1- exercise alone vs. control, 2- exercise and diet vs. diet alone. Data were entered in Review Manager (RevMan 4.1), statistical software from the Cochrane Collaboration that permits double data entry in the system for accuracy.

The primary author of potentially eligible studies was contacted when necessary to resolve ambiguities in reported methodologies or results, and to seek additional pertinent information that may have been gathered but not described in the published manuscript. In some cases (i.e. [20-22]) post-intervention standard deviations (SD) were not available. In these cases we imputed the baseline standard deviation. This was assumed to be valid since baseline and post-intervention standard deviation were found to be similar within other trials. Where necessary, means and measures of dispersion were approximated from figures in the manuscripts using an image scanner (Compaq Keyboard Scanner RT6l5CTW) and a computer to count the number of pixels with a resolution of 200 dpi.

Particular attention was place on extracting the characteristics of the exercise intervention, including its type, frequency, duration, intensity and energy cost. Most studies did not provide estimates of energy expenditure; therefore the compendium of physical activity was used to estimate the energy expenditure in the other studies [23].

The methodological quality of each included trial was assessed by the 2 reviewers using a validated 5-point scale as described by Jadad [24]. This instrument assigned scores for reported randomization, blinding and withdrawals. In addition to this quality scoring, we recorded separately whether allocation concealment was adequate, as described by Schultz [25]. Disagreements in quality assessment were resolved by discussion with a third reviewer (R.S.).

Statistical Analysis

Statistical analysis was performed using Review Manager (RevMan 4.1) and SPSS software. In each study the size of the effect of the intervention was calculated by the

difference of the means between the exercise and control groups at the end of the intervention. Each mean difference was weighted according to the inverse of its variance, this is known as the weighted mean difference (WMD). When the same outcome was measured by two different scales (i.e. body weight and BMI), the mean difference was standardized by dividing it by the within-group standard deviation; this is known as the standardized mean difference (SMD). The weighted mean differences or standardized mean differences in each study were pooled with a fixed effects model [26]. The chi-square test of homogeneity was performed. If the test was significant (heterogeneity) the studies were examined for outliers. If the heterogeneity was secondary to an outlier, the analysis was repeated without it.

Subgroup and sensitivity analyses were also performed and in some cases explained the heterogeneity of the results. Where the amount of data permitted, subgroup analyses were conducted to compare aerobic vs. resistance exercise intervention. Sensitivity analyses was performed to examine the robustness of the results according to the quality of the included trials. Meta-regression [26] was used to determine whether the post-intervention weighted mean differences in HbA1c were associated with changes in body mass or energy expenditure (expressed as MET hours; one MET is equivalent to an oxygen uptake of 3.5 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$). This was done with a linear regression model with studies assigned weights according to their sample sizes. The Funnel Plot technique, as described by Cooper [27], was used in order to detect any publication bias.

RESULTS

Participants, Study Design and Exercise Interventions

The computer searches revealed 2093 potential articles. After application of the filter for controlled clinical trials, the number of potential studies was reduced to 1193. Eventually, 13 trials were deemed appropriate for inclusion, but because of duplicate publications of trials 20 articles met inclusion criteria. One of the publications trials (in abstract form) was found through hand searching of reference list (Ronnemaa [28]), while the others were found from the computer search. Further details are presented in table 1.

A total of 512 participants were included in the 13 trials. The mean age of participants in studies for which this information was available was 55.0 years, and the average duration of diabetes was 6.0 years. In most trials participants were simply assigned to an exercise group or a control group, although 4 studies presented data for 2 comparisons (see table 2), therefore 17 comparisons were included.

Of the 13 trials, 9 were RCTs and 4 were CCTs (see table 2). None of the trials was double blinded or had adequate allocation concealment. Nine trials had adequately described dropouts [9, 10, 22, 29-34], there were no dropouts in two of the studies [21, 35], while two studies did not describe dropouts [36, 37]. The average quality score on the scale described by Jadad [24] was 1.54 out of possible 5 points. The quality assessment criterion, which permitted the greatest discrimination between studies, was judged to be randomization since the studies obtained similar scores on other methodological quality characteristics. The compliance to the exercise interventions was relatively high. Two studies [10, 32] simply indicated that compliance was good while in 8 studies [9, 22, 29, 31,

[33, 34, 36, 37] the mean participation rate was above 76% and 3 studies did not describe compliance [21, 30, 35].

All data used for the analysis were available in the published articles except for those of Dunstan [22, 30, 38] where additional details were found in the PhD. thesis he provided us. Abstracts and unpublished literature other than Dunstan's thesis were not the source of any information that was available in journal articles.

The exercise interventions in each study are described in table 2. The exercise interventions typically prescribed 3 workouts per week, each lasting for 53 minutes on average (including 10 minutes of warm-up and cool-down). The exercise interventions lasted a mean of 23 weeks. The intensity of the aerobic exercise was moderate and typically consisted of walking or cycling. Two studies used resistance exercise training as an intervention.

The results are presented for two types of comparisons. The exercise vs. non-exercise control comparison included studies in which there were no diet co-intervention or in which the same diet co-intervention was given to both the exercise and control groups. The second set of comparisons was between combined exercise and diet interventions vs. a control group.

Effect of Exercise on Glycemic Control

HbA1c was measured in 10 studies. For the 10 comparisons between exercise and non-exercise control groups there were no significant differences at baseline (weighted mean difference = 0.06%, $p = 0.8$). As shown in figure 2, when the post-intervention results are pooled, HbA1c was significantly reduced in the exercise group compared to control

(weighted mean difference = -0.74%, p = 0.00003). Figure 2 also illustrates the effects of exercise and diet interventions compared to control. When diet and exercise were combined, the effect on HbA1c was almost identical to the effect of exercise alone (weighted mean difference = –0.76%, p =0.008).

A sensitivity analysis identified no significant differences between the results from RCTs and CCTs, the weighted mean difference for the 5 RCTs post-intervention was -0.72% (p = 0.001), whereas the weighted mean difference for the CCTs was –0.78 (p = 0.009). Further subgroup analysis comparing aerobic or resistance training to the control condition revealed no significant difference between the two, aerobic training weighted mean difference = -0.78%, p = 0.0002; resistance training weighted mean difference = -0.64%, p = 0.05.

Fasting insulin concentration was measured before and after the intervention period in 5 exercise vs. control studies. The difference in post-intervention fasting insulin values failed to reach statistical significance (weighted mean difference = -2.46, p =0.09).

Effect of Exercise on Body Mass

In all but 1 of the 12 trials the details on the changes in body mass were given in Kilograms (Raz et al. [33] only provided changes in BMI values). Body weight (kg) and BMI were pooled using the standardized mean difference (SMD) method. No significant difference was found when exercise and control groups were compared for all studies post-intervention (standardized mean difference = 0.1, p = 0.4), see figure 3. Similar results were obtained when RCTs, CCTs, aerobic training and resistance training studies were considered separately. Although there were no significant post-intervention

differences between exercise and control groups, it would seem that both groups lost weight. In the 13 exercise vs. non-exercise control comparisons that measured body weight, the exercise group lost 2.5 kg (from 82.7 kg to 80.2 kg), while the non-exercise control group lost 1.8 kg (from 80.1 kg to 78.3 kg).

A greater trend for weight loss was found when exercise and diet interventions were compared to control (see figure 3), but this did not reach statistical significance (standardized mean difference = -0.2, p = 0.2).

Abdominal obesity was represented by changes in WHR or waist circumference. This information was available in 4 studies. No significant differences were observable when exercise was compared to a non-exercise control (standardized mean difference = -0.38 p = 0.12) or when exercise and diet interventions were compared to control (standardised mean difference = 0.26, p= 0.3). Only one study in our meta-analysis [9] directly measured abdominal obesity by magnetic resonance imaging (MRI). Their aerobic training program (55 minutes, 3 times/week, 10 weeks) resulted in a significant reduction in both abdominal subcutaneous adipose tissue (227.3 to186.7 cm^2, $p < 0.05$) and visceral adipose tissue (156.1 to 80.4 cm2, $p < 0.05$) while no significant reductions were found in the control group. Interestingly, in the same study, waist circumference and waist-to-hip ratio did not significantly change, from 98.4 cm to 97.4 cm and from 0.97 to 0.94 respectively.

Meta-regression Analyses

Further analyses were performed to determine the degree to which changes in body weight predicted changes in HbA1c. There were no significant association between post-

intervention weighted mean difference for body weight and those for HbA1c ($r = -.146$, $p = 0.344$). On the other hand, there was a strong association between the change in body weight and HbA1c from baseline to post-intervention within the control group ($r = .78$, $p = 0.001$), the exercise group ($r = .69$, $p = 0.005$) and for the exercise and control group combined ($r = .787$, $p < 0.001$). The regression slopes between body weight changes and HbA1c changes for the exercise and control groups were parallel and co-linear.

Evaluation of Potential Bias

Figure 4 illustrates a funnel plot of weighed mean differences in HbA1c post-intervention plotted against the sample size of the study. Significant publication bias was not likely, as the plot did not show any asymmetry towards large trials and beneficial results.

Furthermore, although the quality scores of the included studies was relatively low according to criteria described by Jadad et al. and Schultz et al. [24, 25], a sensitivity analysis failed to detect any differences between results of RCTs and CCTs. Other traditional characteristics of methodological quality such as blinding, allocation concealment and withdrawals were very constant among studies and therefore were not used in sensitivity analyses.

COMMENT

The general findings of the present meta-analysis were that post-intervention HbA1c values were significantly reduced in the exercise group compared to control while body mass was not. The post-intervention HbA1c values were 0.74% lower in the exercise groups when compared to non-exercise control groups. A reduction in HbA1c of this magnitude is clinically significant. The United Kingdom Prospective Diabetes Study (UKPDS) was a large trial with 3896 participants with type 2 diabetes allocated to intensified glucose lowering treatment or conventional treatment. Patients receiving intensive treatment had HbA1c only 0.9% lower than the conventional treatment (7.0% vs 7.9%, $p < 0.001$) but had significant reduction in diabetes related clinical end points (40.9 vs 46 events per 1000 patients, $p = 0.029$) [39]. An even greater reduction in cardiovascular complications might be anticipated with exercise since, unlike some of the oral medications in the UKPDS, exercise is associated with other cardio-protective benefits [4, 38, 40-43] in both diabetic and normal populations and does not cause weight gain. The importance of good glycemic control is supported in a recent meta-regression study, which demonstrated an exponential relationship between glucose concentration and the incidence of cardiovascular events [44].

Insulin resistance and compensatory hyperinsulinemia are risk factors for the development of the metabolic syndrome and cardiovascular disease [7, 45, 46]. In our analysis, the small sample size (exercise n = 82, control n =82) and the inter-individual variability in fasting insulin gave us little power to detect significant changes in this value (weighted mean difference = -2.46, $p = 0.12$).

The previous meta-analysis by Brown [15] reported a 1.54 kg reduction in body mass with exercise training. In the present analysis we found a 2.5 kg reduction in the exercise group and a 1.8 kg reduction in the control group, with no significant post-intervention body mass differences between the exercise and control groups. Brown's analysis considered differences between pre-test and post-test body mass values, without comparing to a control group even when they existed, this method increases the potential for biased conclusions and overestimates the benefits of exercise on the reduction of body mass. In many exercise studies, dietary advice is given in both the exercise and control group for ethical reasons, therefore weight loss may not be a direct result of exercise. Furthermore, participants may become more health-conscious simply by becoming involved in the study. Combining diet and exercise interventions may be preferable for producing weight loss

We believe that the short mean duration (22.7 weeks) of the exercise interventions and their relatively low mean associated energy expenditure (12 MET hours/ week) explains the lack of statistically significant reductions in body mass. In contrast, a NIH meta-analysis [47] of 13 clinical trails concluded that exercise produces significant weight loss. In the NIH analysis, six of the trials lasted 1 year (range: 16 weeks to 1 year) [47].

A reduction in other daily physical activities or an increase in calorie intake may have counterbalanced the increased energy expenditure from exercise. Alternatively, people assigned to the control group may have become more careful about their diets. Another explanation for the non-significant effect of exercise compared to control on body mass found in our meta-analysis is that in relatively inactive people, increasing

levels of physical activity may be associated with an increase in lean body mass [48, 49]. If these changes were present, they may have masked a reduction in body fat. More direct measures of body composition may be necessary to measure changes in body fat associated with exercise training. In the one study in diabetic subjects with MRI analysis of body composition measures [9] significant increases in muscle mass and decreases in subcutaneous and visceral abdominal fat mass were seen while no significant change in waist circumference or waist-to-hip ratio were observable. Abdominal obesity has been suggested to play a major role in type 2 diabetes and other elements of the metabolic syndrome [50-52]. The results from Mourier et al. [9] and by other authors [53] lead us to question the sensitivity of changes in waist circumference or waist-to-hip ratio as surrogates of visceral fat distribution in studies with small sample sizes. Very few other studies presented details on body composition changes [30, 32].

Reduction in body weight through diet or exercise improves glycemic control. The results of this meta-analysis suggest that although weight loss is beneficial, it is not necessary in order to achieve improvements in glycemic control through exercise.

There is little research on resistance training in diabetes. There are several relevant resistance training studies that were excluded from the present analysis because of the absence of an appropriate control group [54] or because they were performed in non-diabetic participants [55-63]. With age, there is a progressive decline in lean body mass but regular resistance training may slow or reverse this trend [64]. In type 2 diabetes, increasing muscle mass has a theoretical appeal since muscle is the major site of glucose disposal. Increasing muscle mass could therefore decrease insulin resistance and improve

glycemic control [65]. In the present meta-analysis, the post-intervention weighted mean difference for HbA1c in the resistance training vs. non-exercise control was slightly lower than in aerobic training (0.64% and 0.78% respectively). Further well-designed studies on the effects of resistance training are needed in order to better understand the impact of this type of training in type 2 diabetes and how it compares to the more traditional aerobic training. Particular emphases should be placed on the role the reduction of fat mass and the increase lean body mass

Adherence rates to the exercise programs were high in most studies included in the present meta-analysis (mean > 76%). Participants included in exercise studies are volunteers who may have stronger motivation to exercise than is the average person with type 2 diabetes. Exercise studies often have inclusion and exclusion criteria that limit participants to people with relatively well-controlled type 2 diabetes. Furthermore, almost all the studies included in the present meta-analysis include an exercise specialist within the intervention team and these specialized professionals may have enhanced adherence. Adherence rates may strongly affect the size of the anticipated changes.

In conclusion, exercise reduces HbA1c by approximately 0.74%, an amount that would be expected to reduce the risk of microvascular and macrovacular diabetes complications significantly. The studies reviewed in this meta-analysis did not find significantly greater weight loss in the exercising participants compared to control. Therefore exercise should be viewed as beneficial on its own, not merely as an avenue to weight loss. Future research should include longer interventions with better quantification of body composition changes. In the interim, our analysis has strengthened the evidence for exercise as a cornerstone of diabetes therapy.

References:

1. Joslin EP, Root EF, White P. The Treatment of Diabetes Mellitus. . Philadelphia: Lea & Febiger; 1959.

2. American Diabetes Association. Diabetes mellitus and exercise. *Diabetes Care.* 1997;20:1908-12.

3. Yki-Yarvinen H. Toxicity of Hyperglycaemia in Type 2 Diabetes. *Diabetes and Metabolism Reviews.* 1998;14:S45-S50.

4. Després JP. Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. *Exercise and Sport Science Reviews.* 1997;25:271-300.

5. Bouchard C, Shephard RJ, Stephens TE. Physical activity fitness, and health: international proceedings and consensus statement. In: Bouchard C, Shephard RJ, Stephens T, eds: Champaign, Ill, Human Kinetics Publishers; 1994:1055.

6. Grundy SM. Multifactorial causation of obesity: Implications for prevention. *American Journal of Clinical Nutrition.* 1998;67(suppl):567S-572S.

7. Reaven GM, Laws A. Insulin resistance, compensatory hyperinsulinaemia, and coronary heart disease. *Diabetologia.* 1994;37:948-52.

8. Lamarche B, Tchernof A, Mauriege P, et al. Fasting insulin and apolipoprotein B levels and low-density lipoprotein particle size as risk factors for ischemic heart disease. *JAMA.* 1998;279:1955-61.

9. Mourier A, Gautier JF, De Kerviler E, et al. Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in

NIDDM. Effects of branched-chain amino acid supplements. *Diabetes Care.* 1997;20:385-91.

10. Ronnemaa T, Mattila K, Lehtonen A, Kallio V. A controlled randomized study on the effect of long-term physical exercise on the metabolic control in type 2 diabetic patients. *Acta Medica Scandinavia.* 1986;220:219-24.

11. Lehmann R, Kaplan V, Bingisser R, Bloch KE, Spinas GA. Impact of physical activity on cardiovascular risk factors in IDDM. *Diabetes Care.* 1997;20:1603-11.

12. Ligtenberg PC, Hoekstra JB, Bol E, Zonderland ML, Erkelens DW. Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. *Clin Sci (Colch).* 1997;93:127-35.

13. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie R, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUORUM statement. *Lancet.* 1999;354:1896-900.

14. Gudat U, Berger M, Lefèbvre PJ. Physical Activity, Fitness, and Non-Insulin-Dependent (Type 2) Diabetes Mellitus. : In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers; 1994:669-683.

15. Brown SA, Upchurch S, Anding R, Winter M, Ramirez G. Promoting weight loss in type II diabetes. *Diabetes Care.* 1996;19:613-24.

16. Dickersin K, Larson K. Establishing and maintaining and international register for RCT's. *The Cochrane Collaboration Handbook*; 1995.

17. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28:1039-1057.

18. World Health Organization. WHO expert committee on diabetes mellitus. *World Health Organization Tecnical Report Series*. 1980;646:1-80.

19. American Diabetes Association. Report on the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 1997;20:1183-1197.

20. Verity LS, Ismail AH. Effects of exercise on cardiovascular disease risk in women with NIDDM. *Diabetes Research & Clinical Practice*. 1989;6:27-35.

21. Fujii S, Okuno Y, Okada K, et al. Effects of physical training on glucose tolerance and insulin response in diabetics. *Osaka City Medical Journal*. 1982;28:1-8.

22. Dunstan DW, Mori TA, Puddey IB, et al. The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. *Diabetes Care*. 1997;20:913-21.

23. Ainsworth BE, Haksell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Medicine & Science in Sports & Exercise. 1993;25:71-80.

24. Jadad A, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*. 1996;17: 1-12.

25. Schultz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with treatment effects in controlled trials. *Journal of the American Medical Association*. 1995;273:408-412.

26. Mulrow CD, Oxman AD. Analysing and presentng results. . *Cochrane Collaboration Handbook. Section 8.* Oxford: The Cochrane Collaboration; 1997.

27. Cooper H, Hedges LV. The handbook of research synthesis. . NewYork: Russell Safe Foundation; 1994.

28. Ronnemaa T, Mattila K, Lehtonen A, Kallio V. Factors related to improved metabolic control in type 2 (non-insulin-dependent) diabetic patients during long-term physical exercise: a controlled randomized study. Abstract.

29. Agurs-Collins TD, Kumanyika SK, Ten Have TR, Adams-Campbell LL. A randomized controlled trial of weight reduction and exercise for diabetes management in older African-American subjects. *Diabetes Care*. 1997;20:1503-11.

30. Dunstan DW, Puddey IB, Beilin LJ, Burke V, Morton AR, Stanton KG. Effects of a short-term circuit weight training program on glycaemic control in NIDDM. *Diabetes Research and Clinical Practice*. 1998;40:53-61.

31. Kaplan RM, Hartwell SL, Wilson DK, Wallace JP. Effects of diet and exercise interventions on control and quality of life in non-insulin-dependent diabetes mellitus. *Journal of General Internal Medicine*. 1987;2:220-8.

32. Lehmann R, Vokac A, Niedermann K, Agosti K, Spinas GA. Loss of abdominal fat and improvement of the cardiovascular risk profile by regular moderate exercise training in patients with NIDDM. *Diabetologia*. 1995;38:1313-9.

33. Raz I, Hauser E, Bursztyn M. Moderate exercise improves glucose metabolism in uncontrolled elderly patients with non-insulin-dependent diabetes mellitus. *Isr J Med Sci*. 1994;30:766-70.

34. Skarfors ET, Wegener TA, Lithell H, Selinus I. Physical training as treatment for Type 2 (non-insulin-dependent) diabetes in elderly men - A feasibility study over 2 years. *Diabetologia*. 1987;30:930-933.

35. Honkola A, Forsen T, Eriksson J. Resistance training improves the metabolic profile in individuals with type 2 diabetes. *Acta Diabetol.* 1997;34:245-8.

36. Wing RR, H. EL, M. P-B, A. K, P. NM, W. G. Exercise in a behavioural weight control programme for obese patients with Type 2 (non-insulin-dependent) diabetes. *Diabetologia.* 1988;31:902-9.

37. Vanninen E, Uusitupa M, Siitonen O, Laitinen J, Lansimies E. Habitual physical activity, aerobic capacity and metabolic control in patients with newly -diagnosed Type 2 (non-insulin-dependent) diabetes mellitus: effect of 1-year diet and exercise intervention. *Diabetologia.* 1992;35:340-346.

38. Dunstan DW, Mori TA, Puddey IB, et al. A randomised, controlled study of the effects of aerobic exercise and dietary fish on coagulation and fibrinolytic factors in type 2 diabetics. *Thrombosis & Haemostasis.* 1999;81:367-72.

39. U.K. Prospective Diabetes Study Group. Intensive blood glucose control reduced type 2 diabetes mellitus-related end points. *Evidence Based Medicine.* 1999;4.

40. Després JP, Lamarche B. Low-intensity endurance exercise training, plasma lipoproteins and the risk of coronary heart disease. *Journal of Internal Medicine.* 1994;236:7-22.

41. Kelley G, McClellan P. Antihypertensive effects of aerobic exercise. A brief meta-analytic review of randomized controlled trials. *American Journal of Hypertension.* 1994;7:115-9.

42. Halbert JA, Silagy CA, Finucane P, Withers RT, Hamdorf PA, Andrews GR. The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer. *J Hum Hypertens.* 1997;11:641-9.

43. Ponjee GA, Janssen GM, van Wersch JW. Prolonged endurance exercise and blood coagulation: a 9 month prospective study. *Blood Coagul Fibrinolysis*. 1993;4:21-5.

44. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. *Diabetes Care*. 1999;22:233-240.

45. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173-94.

46. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595-607.

47. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report. ; 1998.

48. Brooks GA, Fahey TD, White TP. Exercise Physiology: Human Bioenergetics and Its Applications. . 2nd ed. Montain View (cal): Mayfield Publishing Company; 1995.

49. Foss ML, Keteyian SJ. Fox's Physiological Basis for Exercise Physiology. . 6 ed. U.S.A.: WBC McGraw-Hill; 1998.

50. Després JP. Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition*. 1993;9:452-9.

51. Després JP, Lemieux S, Lamarche B, et al. The insulin resistance-dyslipidemic syndrome: contribution of visceral obesity and therapeutic implications. *International Journal of Obesity*. 1995;19:S76-86.

52. Lemieux S, Despres JP. Metabolic complications of visceral obesity: contribution to the aetiology of type 2 diabetes and implications for prevention and treatment. *Diabete Metab*. 1994;20:375-93.

53. Van der Koy K, Leenen R, Seidell JC, Deurenberg P, Droop A, Bakker CJG. Waist-to-hip ratio is a poor predictor of changes in visceral fat. *American Journal of Clinical Nutrition*. 1993;57:327-333.

54. Eriksson J, Taimela S, Eriksson K, Parviainen S, Peltonen J, Kujala U. Resistance training in the treatment of non-insulin-dependent diabetes mellitus. *International Journal of Sports Medicine*. 1997;18:242-6.

55. Fluckey JD, Hickey MS, Brambrink JK, Hart KK, Alexander K, Craig BW. Effects of resistance exercise on glucose tolerance in normal and glucose-intolerant subjects. *Journal of Applied Physiology*. 1994;77:1087-92.

56. Miller JP, Pratley RE, Goldberg AP, et al. Strength training increases insulin action in healthy 50- to 65-yr-old men. *Journal of Applied Physiology*. 1994;77:1122-7.

57. Ryan AS, Pratley RE, Goldberg AP, Elahi D. Resistive training increases insulin action in postmenopausal women. *J Gerontol A Biol Sci Med Sci*. 1996;51:M199-205.

58. Eriksson J, Tuominen J, Valle T, et al. Aerobic endurance exercise or circuit-type resistance training for individuals with impaired glucose tolerance? *Horm Metab Res*. 1998;30:37-41.

59. Craig BW, Everhart J, Brown R. The influence of high-resistance training on glucose tolerance in young and elderly subjects. *Mech Ageing Dev*. 1989;49:147-57.

60. Fujitani J, Higaki Y, Kagawa T, et al. Intravenous glucose tolerance test-derived glucose effectiveness in strength-trained humans. *Metabolism*. 1998;47:874-7.

61. Wallace MB, Mills BD, Browning CL. Effects of cross-training on markers of insulin resistance/hyperinsulinemia. *Medicine and Science in Sports and Exercise.* 1997;29:1170-1175.

62. Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. Medicine & Science in Sports & Exercise. 1984;16:539-43.

63. Zachwieja JJ, Toffolo G, Cobelli C, Bier DM, Yarasheski KE. Resistance exercise and growth hormone administration in older men: effects on insulin sensitivity and secretion during a stable-label intravenous glucose tolerance test. *Metabolism.* 1996;45:254-60.

64. American College of Sports Medicine. Exercise and physical activity for older adults. *Medicine and Science in Sports and Exercise.* 1998;30:992-1008.

65. Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. *Sports Medicine.* 1997;24: 321-36.

66. Blonk MC, Jacobs MA, Biesheuvel EH, Weeda-Mannak WL, Heine RJ. Influences on weight loss in type 2 diabetic patients: little long-term benefit from group behaviour therapy and exercise training. *Diabet Med.* 1994;11:449-57.

67. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH. Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes.* 1984;33:311-318.

68. Smutok MA, Reece C, Kokkinos PF, et al. Effects of exercise training modality on glucose tolerance in men with abnormal glucose regulation. *International Journal Sports Medicine*. 1994;15:283-9.

69. Burleson MA, Jr., O. Bryant H, Stone MH, Collins MA, Triplett-McBride T. Effect of weight training exercise and treadmill exercise on post- exercise oxygen consumption. Medicine & Science in Sports & Exercise. 1998;30:518-22.

Table 1. The number of studies at each step in of the literature search and reasons for exclusion.

Stage In trial flow	Number of Studies
Potentially relevant publications identified by computer search	2093
Publications identified after filter for RCT and CCT	1193
Studies excluded	1151
Reasons: review articles, animal study, not type 2 diabetes	
Control group, acute effect if exercise only, or no control group	
Trials retrieved for more detailed evaluation	72
Trials excluded	49
Reasons: no supervision or exercise diaries, exercise intervention < 8 weeks, no control group or control group without type 2 diabetes, drug/medication co-intervention	
Potentially appropriate publications to be included in mete-analysis	23
Publications included in meta-analysis	20
Publications meeting inclusion criteria excluded from meta-analysis	3
Reasons: exercise intervention was 3 months on/ 3 month off [66], could not distinguish results between IGT and type 2 diabetes[67, 68]	
Trials with usable information (7 duplication of publications)	13
HbA1c	10
Fasting insulin	6
Body weight or BMI	12
Waist circumference or Waist-to-hip ratio	4

Table 2: description of exercise interventions.

Study	Treatment	N	Control	N	Design	Session/wk	Weeks	Intensity	Type	Minutes	MET hr/wk
Aerobic training (exercise vs. non exercise control)											
Dunstan A	Exercise + Fish + Diet	14	Fish + Diet *1	12	RCT	3	8	50-65% VO2 max	C	40	8.75
Dunstan B	Exercise + Diet	11	Diet*2	12		3	8	50-65% VO2 max	C	40	8.75
Fujii	Exercise + Diet	10	Diet*3	15	CCT	5	26	Approx. 40% VO2 max	J	30	10
Kaplan A	Exercise	18	Control*4	15	RCT	3	10	60-70 max HR	W	80	12.5
Kaplan B	Exercise + Diet	16	Diet*5	16		3	10	60-70 max HR	W	80	12.5
Lehmann	Exercise + Diet	16	Diet*6	13	CCT	3	13	50-70% max effort	W,C,J,R,ST	90	16.88
Mourier	Exercise	10	Control*7	11	RCT	3	10	75% VO2peak + Intervals	C	55	11.6
Raz	Exercise	19	Control*8	19	RCT	3	12	65% VO2max	C,T,R,S	55	12.5
Ronnemaa	Exercise	13	Control*8	12	RCT	6	17.5	70% VO2max	W,J,Sk	45	24.75
Skarfors	Exercise	6	Control*9	8	CCT	3	104	75% VO2 max	J,C,CAL	45	13.5
Wing A	Exercise + Diet	10	Diet*10	12	RCT	3	10	3miles/ session	W	60	9.9
Wing B	Exercise + Diet	13	Diet*10	15		3	10	3miles/ session	W	60	9.9
Resistance training (exercise vs. non exercise control)											
Dunstan 2	Exercise	11	Control*8	10	RCT	3	8	3 sets, 10-15 reps, 10 ex	circuit	60	11.44
Honkola	Exercise	18	Control*8	21	CCT	2	22	2 sets, 12-15 reps, 8-10 ex	circuit	45	8.25

Aerobic training (exercise + diet vs. control)											
Agurs-Collins	Exercise + Diet	31	Control*8	27	RCT	3	13	Low-impact aerobic activity	T, C, R, A	30	5.75
Vanninen A	Exercise (men)	21	Control *11	24	RCT	3.5	52	HR 110-140 (age= 53)	W,J,C,S,Sk	45	13.13
Vanninen B	Exercise (women)	16	Control *11	17		3.5	52	HR 110-140 (age= 53)	W,J,C,S,Sk	45	13.13
TOTAL	**13 Trials**	**253**		**259**	**9**						
AVERAGE					**RCTs**	**3.3**	**22.7**			**53**	**12**

Note: W= walking, C = cycling, S = swimming, Sk = skiing, J = jogging, Cal= callisthenics, R = rowing, R-T = resistance training, A = aerobics (low impact), R = rope skipping, ST = stair climbing. Burleson [69] estimated that resistance training corresponded to 40% of VO_2 max. BCAA = Branched-chain amino acids

*1 note: Diet= <30% of total calories from fat.... <100 mmol/day sodium. Fish= 1 fish meal/day

*2 note: Diet= <30% of total calories from fat.... <100 mmol/day sodium.

*3 note: Diet = mild caloric restriction: 30-35 kcal/ kilogram of ideal body weight

*4 note: groups received information on exchange diet of 1200 kcal/day

*5 note: groups received information on exchange diet of 1200 kcal/day and behavior modification

*6 note: Diet = 50% of calories from Carbohydrates, 35% from fat and 15% from protein

*7 note: control did easy exercise for 20 min. 1/week. 1/2 of each group took BCAA supplements

*8 note: no co-intervention

*9 note: all groups received dietetic info by dietician >2 months before intervention

*10 note: Diet = diet and behavioral strategies (goal: -1kg/week),

*11 note: all participants had basic education on physical activity and diet before group allocation

Figure 1. Computer search strategy for all controlled clinical exercise trials in type 2 diabetes. The search for physical activity and diabetes was developed with experts in the field of exercise and diabetes as well as with an experienced librarian. The filter for controlled clinical trials was developed by Dickersin et al. [16].

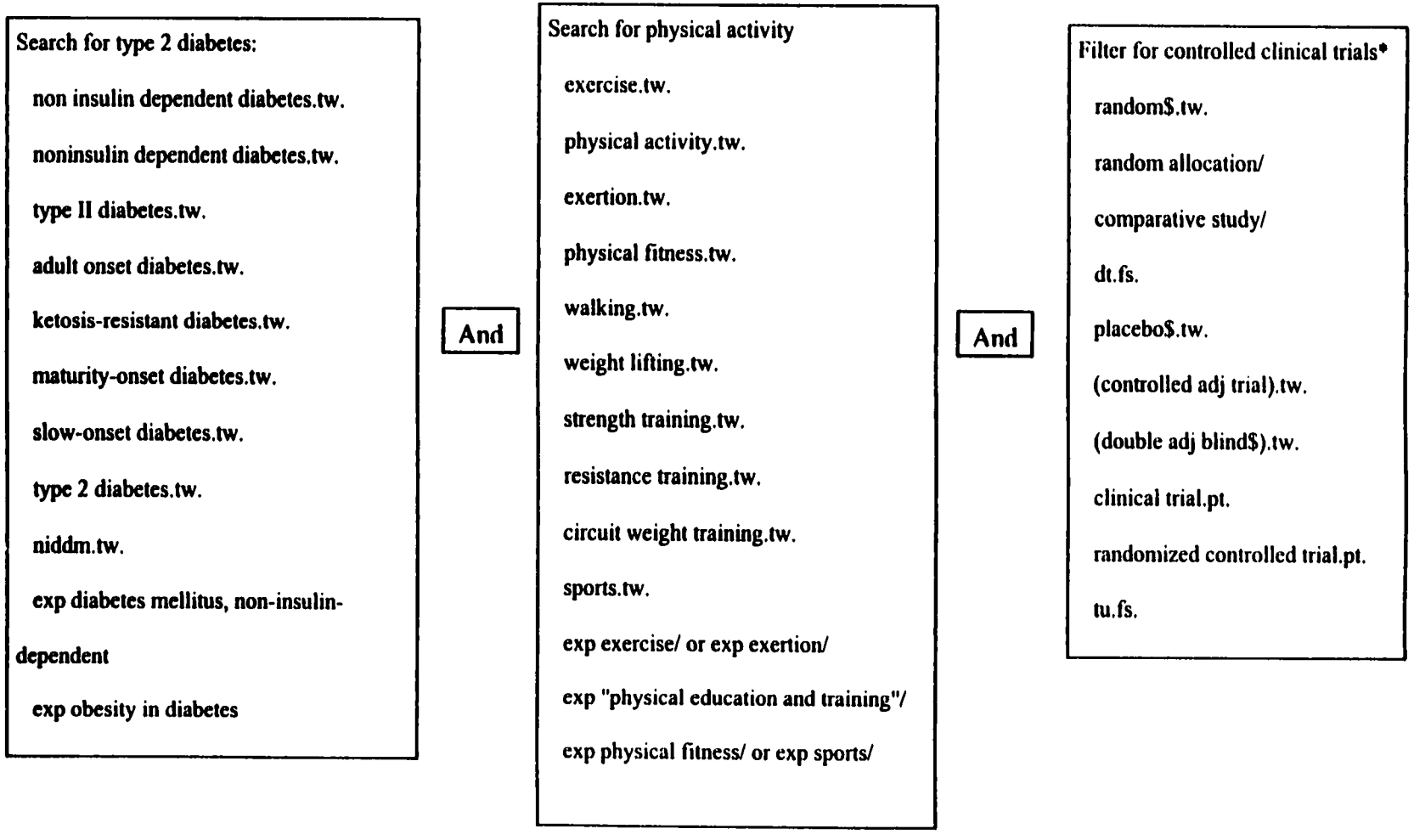


Figure 2: Differences in HbA1c from baseline to post-intervention.

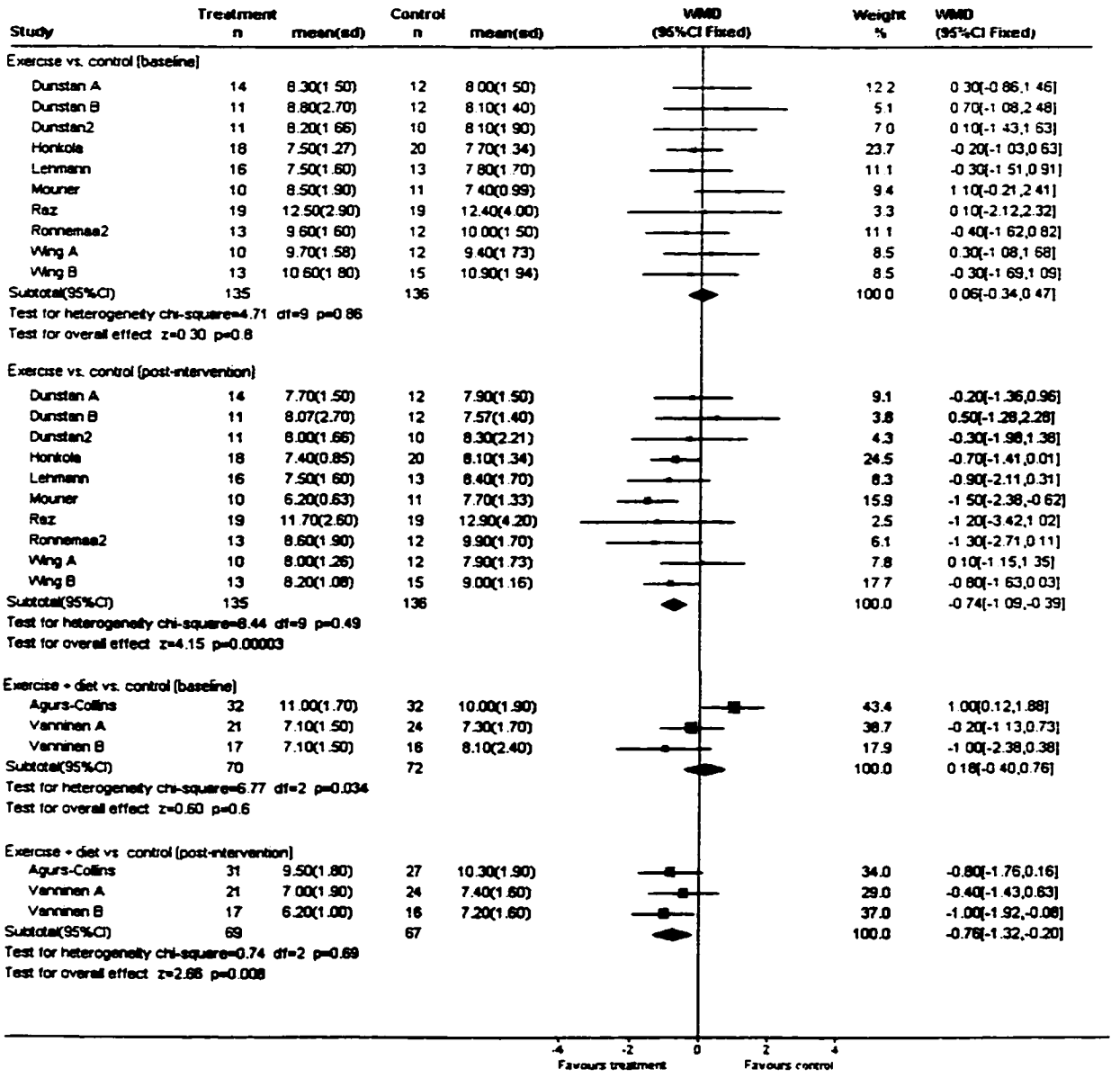


Figure 3: Differences in body mass from baseline to post-intervention.

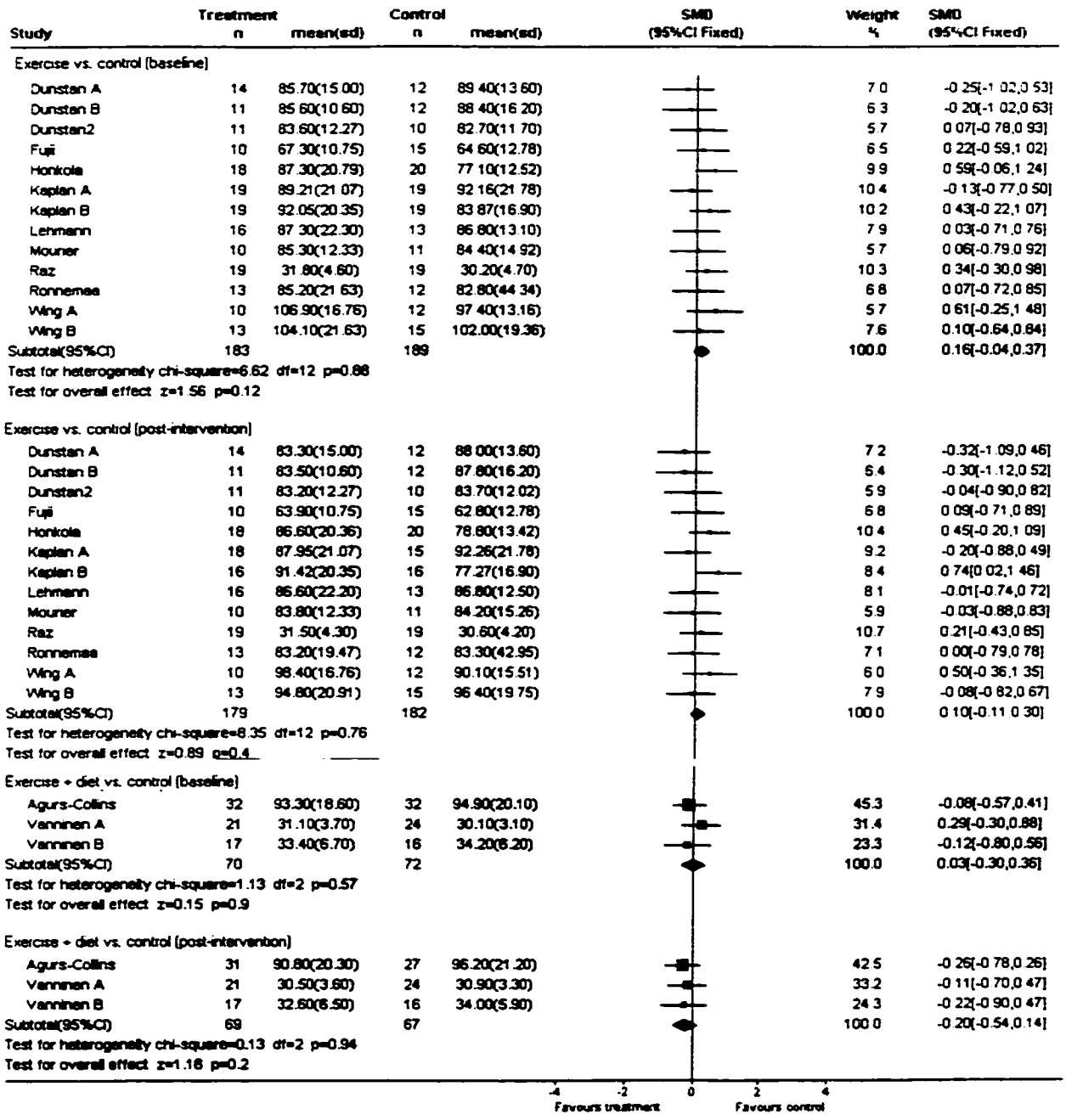
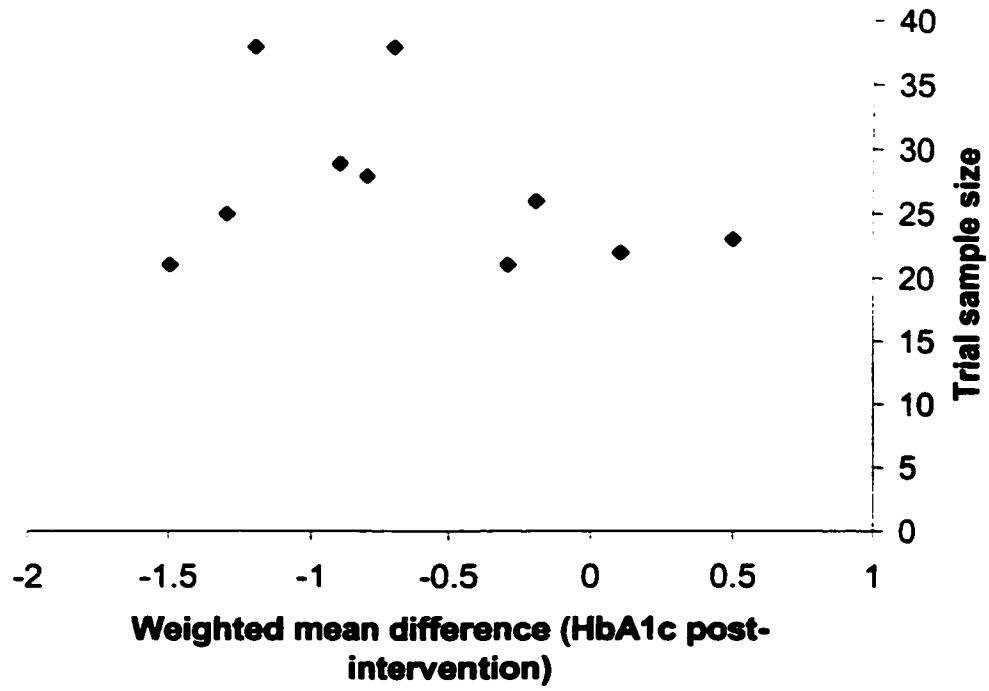


Figure 4: Funnel plot for determination of publication bias



A systematic review of the effect of exercise on health related physical fitness in type 2 diabetes mellitus

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Running Head: Exercise in type 2 diabetes

Abstract

Aims: To systematically review the effectiveness of different exercise interventions on improving physical fitness in type 2 diabetes mellitus.

Methods: A literature search (MEDLINE, EMBASE, Health Star, Sports Discuss, Dissertation Abstracts, Cochrane Library) was conducted to find all controlled clinical trials in type 2 diabetic adults comparing an exercise intervention to a non-exercise control. Two reviewers independently extracted data from all trials meeting the inclusion criteria. Weighted mean differences and standardised mean were used to calculate the size of the effect of exercise.

Results: Eleven aerobic training studies (average: 3.5 times/week for 18.6 weeks) and 2 resistance training studies (average: 10 exercises, 2.5 sets, 13 repetitions, 2.5 times/week for 15 weeks) met the inclusion criteria. Aerobic training interventions produced a 11% increase in VO2 max compared to control (standardised mean difference = 0.51, p = 0.049). When only intense aerobic interventions are considered (≥ 75 % VO2 max) the post-intervention VO2 max was 30% higher than in the control group. There was a significant improvement in strength following resistance training compared to baseline values (standardised mean difference = 1.00, p= 0.0001).

Conclusion/interpretation: Results suggests that exercise should be recommended because of its statistically and clinically significant effects on some aspects of the cardiorespiratory and muscular components of health-related physical fitness. Clinical trials often fail to measure or report important aspects of health related-fitness.

1. Introduction

For many years, exercise along with diet and medication has been considered to be one of the three cornerstones of diabetes therapy [1]. One of the most recognised effects of regular physical activity is the associated improvement in physical fitness. Cardiorespiratory fitness, as represented by maximal oxygen consumption (VO_2 max), has traditionally been seen as the most important component of health-related fitness. In non-diabetic participants, cardiorespiratory fitness is inversely associated with all-cause and cardiovascular disease mortality [2]. People with type 2 diabetes, even in the absence of known complications, have reduced maximal oxygen consumption's compared to age and activity matched controls [3]. Diabetic complications, such as neuropathy, are associated with a lower VO_2 max [4, 5]. A decreased exercise capacity may predict mortality and coronary artery disease in type 2 diabetes [6, 7].

Many definitions of physical fitness exist. As a general concept, fitness can be interpreted as the matching of an individual to his or her physical environment [8]. The World Health Organisation defines fitness as "the ability to perform muscular work satisfactorily" [9]. Bouchard and Shephard differentiate between performance-related fitness and health-related fitness [8] (p.80): "Performance related fitness refers to those components of fitness that are necessary for optimal work or sport performance.... It (health-related fitness) has been defined as a state characterised by (a) an ability to perform daily activities with vigour and (b) demonstration of traits and capacities that are associated with a low risk of premature development of hypokinetic diseases and conditions". Health related fitness includes 5 components: morphological, muscular,

motor, cardiorespiratory and metabolic fitness. These components are further described in table 1.

Although there have been numerous small research studies on exercise in people with type 2 diabetes, it is still unclear how exercise intervention influences many aspects of health-related fitness in type 2 diabetes. The literature pertaining to exercise in diabetes is generally concerned with the acute and chronic metabolic effects of exercise. The focus is typically on changes in metabolic fitness and elements such as glycemic control or lipid profiles, rather than on the impact on other elements of health related fitness, such as maximal and submaximal exercise capacities and body composition.

In a previous article [10], we systematically review the effects of exercise on two variables of major clinical importance: (a) HbA1c, reflecting average blood glucose values over the last 2-3 months, and (b) body mass, as represented by body weight or BMI. These variables have strong epidemiological evidence supporting their importance [2, 11] and are commonly used by physicians because of the practical aspects. Unfortunately, these variables provide only part of the information to exercise physiologists who are also very concerned with the other aspects of health-related fitness. The effects of exercise on all aspects of health-related fitness should be well understood in order to help develop optimal exercise interventions in type 2 diabetes.

The main objective of this study was to systematically review the effectiveness of different exercise interventions on the different components of health-related fitness, including body composition, muscular fitness and cardiorespiratory fitness. We hypothesised that, even if participants with type 2 diabetes have low initial levels of

fitness, the general exercise adaptations found in the normal population should be reproducible in type 2 diabetes.

Nearly 50 review articles or position statements have been published on the topic of exercise and diabetes, reflecting the immense interest in this topic [12]. Almost all of these reviews have used the traditional narrative approach. Synthesising research in this manner can result in subjective, nonreplicable conclusions. Meta-analysis is "a review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method" [13]. Meta-analysis may be especially useful in summarising prior research when the number of subjects per study is small and the results are somewhat conflicting, as is the case for exercise interventions in type 2 diabetes.

2. Method

Criteria for considering studies for this review. The search strategy was developed to identify all relevant controlled trials (randomised and non-randomised) that include an exercise intervention in adult type 2 diabetic participants. Acceptable diagnostic criteria for type 2 diabetes include those described by the National Diabetes Data Group [14], the World Health Organization [15] or the American Diabetes Association [16]. Studies performed on nondiabetic participants with impaired glucose tolerance (IGT) were not included in the analysis. If studies reported data for which it was impossible to discriminate between participants with type 2 diabetes and those with IGT, we attempted to contact authors for the individual patient data.

All studies included in the meta-analysis included an exercise intervention lasting at least 8 weeks in duration. An exercise intervention was defined as a predetermined supervised program of physical activity, described within the corresponding manuscript. Studies in which the intervention consist of recommending increasing physical activity were not included within the analyses since it would be impossible to quantify the exercise intervention and to be sure of compliance. In order to be included, studies in which qualified personnel did not directly supervise exercise sessions were required to assess compliance using exercise diaries.

Search strategy for identification of studies. The search consisted of computer based searches (MEDLINE, EMBASE, Sport Discuss, Health Star, Dissertation Abstracts and the Cochrane Controlled Trials Register) up to and including March 2000. The reference lists of major textbooks, review articles and of all included articles identified by the

search were hand searched to find other potentially eligible studies. Potential missing articles and unpublished literature were sought from contact with experts in the field.

The computer-based search included common text words and Medical Subject Headings (MeSH) related to exercise and type 2 diabetes. The terms were then connected through Boolean operators and the results were limited to those reporting only on human subjects. No articles were excluded because of their language of publication. The findings were combined with a validated search filter for controlled clinical trials. The filter used is a validated and highly sensitive search strategy [17]. See figure 1 for the complete computer search strategy. Two reviewers (N.B. and E.H.) independently assessed the titles and abstracts of these studies for inclusion. All potential articles were obtained and further assessed, any disagreements on inclusion were resolved by discussion with a third party (R.S.).

Data extraction. The two primary reviewers then independently extracted the relevant data from all identified articles. Data were entered in Review Manager (RevMan 4.0.4.), statistical software from the Cochrane Collaboration which permits double data entry in the system for accuracy. The primary author of potentially eligible studies was contacted when necessary to resolve ambiguities in their reported methodologies or results, and to seek additional pertinent information that may have been gathered but not described in the published manuscript. In some cases (i.e. [18-20]) post-intervention standard deviations (SD) were not available. We therefore imputed the baseline standard deviation. This was assumed to be valid since baseline and post-intervention standard deviation were found to

be similar within other trials. Where necessary means and measures of dispersion were approximated from figures in the manuscripts.

The methodological quality of each included trial was assessed by the 2 reviewers using a validated 5-point scale as described by Jadad [21]. This instrument assigned scores for reported randomization, blinding and withdrawals. "Double-blinding" is inherently difficult (if not impossible in exercise studies). A study was regarded as double blind if the word "double blind" is used. An appropriate method of double blinding was present when the person doing the assessment or the study participant could identify the intervention being assessed. In addition to this quality scoring, we recorded separately whether allocation concealment was adequate, as described by Schultz [22]. Allocation concealment was adequate if it was deemed that adequate measures to conceal allocation were taken (i.e. central randomization, serial numbered, sealed envelopes or other descriptions that contained elements convincing of concealment). Disagreements in quality assessment were resolved by discussion with a third reviewer (R.S.)

Statistical analysis. Statistical analysis was performed using the Review Manager (RevMan 4.0.4) and SPSS software. In each study the effect of the intervention was calculated by the difference of the means between the exercise and control groups. Each mean difference was weighted according to the inverse of its variance, this is known as the weighted mean difference (WMD). When the same outcome was measured by two different scales (i.e. body weight and BMI), the mean difference was standardised by dividing it by the within group standard deviation; this is known as the standardised mean difference (SMD). The weighed mean difference or standardised mean difference in each

study were initially pooled with a fixed effects model [23]. When heterogeneity was present, the studies were examined for outliers. If the heterogeneity was secondary to an outlier, the analysis was repeated without it.

Subgroup and sensitivity analysis were also performed and in some cases explained the heterogeneity of the results. Where the amount of data permitted, subgroup analyses were conducted according to aerobic vs. resistance exercise intervention. A sensitivity analysis was performed to examine the robustness of the results according to the quality of the included trials, duration of the intervention or the participant characteristics. If heterogeneity was still present we used a random effects model [23]. The Funnel Plot technique, as described by Cooper [24] was used in order to detect any publication bias.

3. Results

Literature search findings. The computer searches revealed 2093 potential articles. After application of the filter for controlled clinical trials, the number of potential studies was reduced to 1193. Eventually, 13 trials were deemed appropriate for inclusion, but because of duplicate publications of trials 20 articles met inclusion criteria. One of the publications trials (in abstract form) was found through hand searching of reference list (Ronnemaa [25]), while the others were found from the computer search. Further details are presented in table 2.

Description of studies A total of 512 participants were included in the 13 trials. The mean age of participants in studies for which this information was available was 55.0 years, and the average duration of diabetes was 6.0 years. In most trials participants were simply assigned to an exercise group or a control group, although 4 studies presented data for 2 comparisons (see table 3), therefore 17 comparisons were included.

Of the 13 trials, 9 were RCTs and 4 were CCTs (see table 3). None of the trials was double blinded or had adequate allocation concealment. Nine trials had adequately described dropouts [20, 26-33], there were no dropouts in two of the studies [19, 34], while two studies did not describe dropouts [35, 36]. The average quality score on the scale described by Jadad [21] was 1.54 out of possible 5 points. The quality assessment criterion, which permitted the greatest discrimination between studies, was judged to be randomization since the studies obtained similar scores on other methodological quality characteristics. The compliance to the exercise interventions was relatively high. Two studies [29, 32] simply indicated that compliance was good while in 8 studies [20, 26, 28,

[30, 31, 33, 35, 36] the mean participation rate was above 76% and 3 studies did not describe compliance [19, 27, 34].

All data used for the analysis were available in the published articles except for those of Dunstan [20, 27, 37] where additional details were found in the PhD. thesis he provided us. Abstracts and unpublished literature other than Dunstan's thesis were not the source of any information that was not available in journal articles.

The exercise interventions in each study are described in table 3. The exercise interventions typically prescribed 3 workouts per week, each lasting for 53 minutes on average (including 10 minutes of warm-up and cool-down). The exercise interventions lasted a mean of 23 weeks. The intensity of the aerobic exercise was moderate and typically consisted of walking or cycling. Two studies used resistance exercise training as an intervention.

The results are presented for two types of comparisons. The exercise vs. non-exercise control comparison included studies in which there were no diet co-intervention or in which the same diet co-intervention was given to both the exercise and control groups. The second set of comparisons was between combined exercise and diet interventions vs. a control group.

Effects of exercise on the morphological component of health-related fitness. Only 2 studies, 1 aerobic training [30] and 1 resistance training [27] presented data on the sum of skinfolds; neither exercise modality had a significant effect on sum of skinfolds. Two aerobic training studies measured changes in percent body fat, they used skinfolds [30],

and hydrostatic weighing [18]. Aerobic training did not significantly improve body fat; at baseline the exercise group had 3.16% less fat while after the intervention they had 3.2 % less fat then the control group. Of the aerobic training studies, only one reported changes in lean body mass. There was no significant effect of aerobic exercise on lean body mass. No resistance training studies presented data on percent fat or lean body mass.

Mourier et al. [30] also presented detailed information on Magnetic Resonance Imaging (MRI) at the level of the mid-thigh and of the umbilicus. Both subcutaneous and visceral abdominal tissue were significantly reduced with exercise whereas mid-thigh muscle mass was significantly increased, see table 4 for details.

Effects of exercise on muscular and motor component of health-related fitness. Although Mourier et al. [30], have shown an increase muscle mass with aerobic exercise in type 2 diabetes (morphological), there have been no controlled clinical trials that have attempted to measure changes in muscular or motor components of health-related fitness associated with aerobic exercise.

The resistance training studies have attempted to quantify muscular strength and endurance gains associated with the exercise protocols. Dunstan et al.[27] performed 1 repetition maximum (RM) strength testing before and after the intervention. Improvements in strength ranged from 24 % in the circuit weight training group. Honkola et al. [34] measured muscular endurance by multiplying the load by the amount of repetitions performed. The 2 resistance training articles only reported changes in strength for the exercise group. Therefore the weighted mean differences were calculated for pre vs. post-intervention changes. Resistance training resulted in a significant increase in

muscular strength (standardised mean difference = 0.81 SD, p = 0.00001, random effects model), see figure 2. The thesis presenting more detailed information for the Dunstan study described no significant changes in strength in the control group, except for the leg curl for which strength was reduced. In the study by Honkola et al. [34] muscular endurance was significantly improved by 220% from baseline to post intervention (standardised mean difference = 1.24 SD, p = 0.02 random effects model) (see figure 2).

Controlled clinical trials reporting information on changes in the motor component of health-related fitness were not available.

Cardiorespiratory component of health-related fitness. Five studies presented data on cardiorespiratory fitness in the form of maximal oxygen consumption (VO_2 max) values before and after the interventions. At baseline, the average VO_2 max for 187 of these participants was 23.42 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. The change in VO_2 max favored the exercise vs. the control group (standardised mean difference = 0.51 SD, p = 0.049), see figure 3. This corresponds to about a 11% increase in VO_2 max. The calculation was done with a random effects model since the Chi-square test revealed heterogeneity. Heterogeneity was mostly explained by the intensity of the exercise bouts as demonstrated by a subgroup analysis comparing trials with exercise interventions with an intensity above 70% VO_2 max to those equal or below to 70 % VO_2 max. The two trials who had an intensity of above 70% VO_2 max (Mourier et al. [30] and Skarfors et al. [33]) improved VO_2 max by about 30.0 % compared to control (standardised mean difference = 1.59 SD, p = 0.0001). The 3 trials with lower intensities had a much smaller effect of 6.8% increase in VO_2 max (standardised mean difference = 0.23 SD, p =0.15). Maximal work capacity

demonstrated a tend for improvement (standardised mean difference = 3.95 SD, p = 0.18, random effects model) but was only measured in 2 small studies [30, 31].

Submaximal aerobic exercise capacity can be defined as the tolerance to low-intensity power output for prolonged periods of time. None of the controlled clinical trails directly measured this capacity, although Vanninen [36], measured oxygen consumption at the anaerobic threshold (VO_2 AT), VO_2 at anaerobic threshold was not significantly increased with exercise.

Heart rate and blood pressure, both at rest and during exercise, are also considered components of cardiorespiratory fitness. None of the studies in the present meta-analysis present data on the heart rate or blood pressure responses to exercise. Exercise significantly reduced resting heart rate when compared to control (weighted mean difference = -3.01 beats/min, p = 0.004), see figure 4. Systolic and diastolic blood pressure were not significantly affected by exercise training, see figure 5.

Effects of exercise on the metabolic component of health-related fitness. The effects of exercise on the metabolic aspects of health-related fitness are often the primary concern for clinicians and have been systematically reviewed in a previous article of this meta-analysis [10].

4. Discussion

As described in a previous article [10], exercise did not produce a significant change in body mass (body weight or BMI) or in waist-to-hip circumference ratio. In the present analysis we hoped to get a better understanding of the body composition changes associated with exercise, both in terms of fat mass or lean body mass and in terms of their distribution. Very few studies reported detailed body composition measures and therefore there was very little statistical power to detect changes.

Changes in skinfold thickness and lean body mass were not significant in both resistance and aerobic training intervention studies. Aerobic exercise was not expected to significantly increase lean body mass muscle although small increases have previously been shown in the active musculature when high volume or intensities are performed or when participants initial activity levels are low [38]. Only 2 small aerobic training studies presented information on changes in body fat. Since the results were very heterogeneous there was a lack in statistical power to detect changes. Muscle mass is the primary site of insulin resistance in type 2 diabetes. It is also the major site of glucose disposal in response to an oral glucose load. With ageing there is a sharp decline in muscle mass, mostly due to a marked decline in type 2 muscle fibres [39]. The reduction in lean body mass strongly contributes to the reduction of resting metabolic rate associated with ageing. Resistance training typically increases muscle mass when performed regularly, even in older adults [40-42]. It is unfortunate that non of the resistance training studies in the present analysis measured lean body mass. This was probably due to the short duration of the studies ad therefore unlikelihood of increases in muscle mass, which become evident after longer periods of training. Choosing an appropriate measure of

body composition is also critical in resistance training studies, it has previously been demonstrated many body-composition techniques were not sensitive to the changes in fat-free mass identified by hydrostatic weighing.

The measures of body composition used within these few studies should be more sensitive to changes in fat mass and lean body mass than the measurement of body weight, it is possible that the sensitivity of the instruments used was still weak None of the studies used a gold standard technique for the measurement of body composition such as hydrostatic weighing. Mourier et al. [30] used a sensitive technique for the measurement of body fat distribution (MRI). It is somewhat surprising that in the study by Mourier et al. [30], subcutaneous abdominal tissue and visceral adipose tissue were significantly reduced by 18% and 48% respectively, while no significant changes could be detected by waist circumference, waist-to-hip ratio or body mass. The exercise program followed in this study was representative of the average exercise programs used within the meta-analysis; aerobic training 55 minutes per workout, 3 workouts per week over a 10 period. Exercise may preferentially reduce abdominal obesity, this may be especially important since abdominal obesity is a very strong predictor of cardiovascular disease [43].

The American College of Sports Medicine Position Stand on Exercise and physical activity for older adults [39] reports that changes of 1-4% body fat is expected with exercise training in older adults even if body weight is maintained. The methodological quality and the variability of the controlled clinical trials in type 2 diabetes do not provided strong evidence in favour or against the role of exercise as a weight loss therapy in type 2 diabetes. There is no evidence suggesting that the effect of

exercise on morphological fitness may be different in type 2 diabetes than in the general population.

There is no evidence from controlled clinical trials suggesting the benefits of exercise on motor control in type 2 diabetes. The exercise programs often prescribed warm-up and cool-down periods witch included light callisthenics and stretching exercises. It remains unclear how the warm-up/cool-down or the core exercises during a session influenced motor control.

The aerobic training studies in the present analysis did not measure changes in muscle strength endurance or power. Although increases in muscular strength are not typically associated with aerobic training, they are likely to occur in participants who initially had very low levels of physical activity. The resistance training studies measured changes in strength or endurance. The studies by Dunstan et al. [27] used 1 repetition maximum testing, whereas the data presented by Honkola et al. [34] is the product of the number of repetitions multiplied by the load. It is therefore unclear if the results in Honkola's study represented many repetitions at a light load or a few repetitions of a heavy load. Nevertheless it would seem that increases in muscular strength and endurance are not impaired in type 2 diabetes.

Both motor control and muscular strength are important for quality of life and for the prevention of falls with ageing. Few studies report the effects of exercise on quality of life in type 2 diabetes. A studies by Kaplan et al. [28] demonstrated a changes in quality of life over 18 months following a 10 week intervention period, this combined diet and exercise intervention improved quality of life, when compared to diet alone, independently of changes in body weight. In a study by Ligtenberg et al.[44], which did not

meet the inclusion criteria, feelings of well-being are positively affected by the training program when the participation to the training activities is continued.

Cardiorespiratory fitness is often considered the most important components of health-related fitness [8]. It has support from many cross-sectional and longitudinal studies showing an inverse relationship between cardiorespiratory fitness, as represented by VO_2 max, and all cause mortality and morbidity [2, 7]. In a recent study [6], both low cardiorespiratory fitness and physical inactivity were predictors of mortality in men with type 2 diabetes. The post-intervention VO_2 max favored the exercise intervention group, standardised mean difference of 0.51, this represents approximately 3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$. This may be clinically significant, especiallyl in a population who has very low initial levels of cardiorespiratory fitness, such as people with type 2 diabetes. As previously described, the average VO_2 max at baseline for participants in the present meta-analysis is approximately 23 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ and increased by 11% with aerobic training when compared to control. Intensity is considered to be the most important variable for improving VO_2 max [45]. Therefore, as expected, improvements in maximal oxygen uptake were even larger (30%) when intense aerobic interventions were considered. Our findings are very similar to the ACSM position stand on exercise and physical activity in older adults, which suggest improvements of 10-30% [39].

The lower VO_2 max associated with type 2 diabetes has been investigated in several experimental studies. It has been hypothesised that the lower VO_2 max may be a consequence of a reduced rate of circulatory adjustments to an increase workload (i.e. cardiac output) [3, 5], or poor diffusion and utilisation of oxygen at the level of skeletal

muscle [46]. There is also a general decrease of 5-15% VO_2 max per decade, which is a consequence of a decrease in cardiac output and maximal ateriovenous O_2 difference [39]. It is encouraging that despite initially low VO_2 max, our findings suggest that people with type 2 diabetes show similar improvements in VO_2 max as does the general population following aerobic training. Some experimental studies even suggest larger improvements in VO_2 max and VO_2 kinetics in people with type 2 diabetes than in overweight (otherwise healthy) participants [47], probably due to their initial low levels.

It is unfortunate that very little information is available on the submaximal improvements associated with exercise training, as most daily activities do not elicit require maximal exercise responses. In the general population, endurance training often causes a reduction in heart rate at submaximal intensities as well as a reduced feeling of breathlessness and/or muscle fatigue [45]. Increased feelings of vigour may provide greater independence, as for example: people who would like to spend more time shopping or doing housework without feeling exhausted. The study by Vanninen et al. [36] found no changes in VO_2 at the anaerobic threshold with exercise training. Previous studies suggest that the anaerobic threshold occurs at lower absolute VO_2 in people with type 2 diabetes than in non-diabetic control patience [3]. Consequently, there may be greater limitations on exercise performance in type 2 diabetes.

In the present meta-analysis resting heart rate was reduced as a result of aerobic exercise training, possibly indicating an increase efficiency of the heart muscle. When heart rate is reduced, a larger stroke volume maintains cardiac output. Less peripheral vascular resistance or greater contractility of the heart may promote larger stroke

volumes. Contrarily to the findings of previous meta-analysis in normal and hypertensive people [48, 49], we did not find a significant reduction in both systolic and diastolic blood pressure. According to the insulin theory of hypertension [48], one would expect a reduction in blood pressure associated with a reduction in hyperinsulinemia. As described in our first meta-analysis, hyperinsulinemia was significantly reduced with exercise training in type 2 diabetes [10]. A possible reason for our results is that the participants initially had normal blood pressure. In the meta-analysis by Fagard et al. [48] blood pressure was only reduced by 3.2/3.1 mmHg in people with normal blood pressure, whereas we found a non significant change of -2.04/0.99 mmHg. The difference between the 2 meta-analyses may be explained by the small number of studies presenting data on changes in blood pressure in the type 2 diabetes studies.

It is also important to consider the population in which the studies were conducted before generalising the results of this meta-analysis. Participants included in exercise studies are volunteers who may have stronger motivation to exercise than the average person with type 2 diabetes. Adherence rates may strongly affect the size of the anticipated changes. Furthermore, exercise studies often have inclusion and exclusion criteria that limit participants to people with relatively well controlled type 2 diabetes with the absence of major complications. It is very important for the exercise specialist to work within the entire diabetes care team and to follow pre-established guidelines for safe exercise participation in type 2 diabetes [50, 51].

The quality score of the included trials is relatively poor (average score of 1.64 out of 5 on the scale described by Jadad et al.[21]). The relatively low-quality of the

included trials is to be expected in exercise interventions where some elements such as blinding are very difficult to implement. Nevertheless, results of the present meta-analysis should be interpreted with caution; studies in other fields suggest that poor quality studies may overestimate the size of the effect in a favourable direction [22], although this may not be the case with exercise interventions. As previously described [10], sensitivity analysis comparing randomised studies vs. non-randomised studies failed to detect any differences and significant publication bias was not detected, as a funnel plot did not show any asymmetry towards large trials and beneficial results.

Conclusions. The present meta-analysis was conducted in order to estimate the effects of exercise on components of health related fitness which are particularly important to the exercise specialist working with type 2 diabetes. The evidence brought forward by this meta-analysis is relatively week because of the surprisingly low number of controlled clinical trials presenting detailed information on various aspects of health-related physical fitness. This is especially true for the number of studies that precisely measure changes in body composition. Nevertheless, it seems reasonable to conclude that, in type 2 diabetes, maximal strength and aerobic capacity, although initially low, may be improved through exercise training to a similar extent as in the general population.

We therefore make the following recommendations. Exercise specialists working with type 2 diabetes should recommend complete exercise programs (aerobic and resistance training) for improvements in body composition but should not expect large reductions in body fat. Careful consideration should be taken while choosing the

instrument to assess exercise induced weight loss. Research on exercise in type 2 diabetes should include also more precise evaluation of changes in morphological fitness

There is no evidence suggesting exercise may have different effects of the muscular and motor components of health-related fitness in type 2 diabetes than in the normal population. If safe, resistance exercise should be prescribed for people with type 2 diabetes in order to help improve and/or maintain the muscular component of fitness, this may help increase quality of life and prevention of falls. Studies in exercise in diabetes are typically concerned with relatively short-term outcomes. More research is needed on longer-term aspects, such as quality of life, and how they are mediated improvements in components of health-related fitness (especially the motor and muscular component).

Although cardiorespiratory fitness may be lower in people with type 2 diabetes, evidence suggest that improvements occur to a similar extend as would be expected in the general population. Higher intensity aerobic training should be used if greater improvements in VO_2 max are desired. It is important to consider the importance of submaximal exercise capacities when prescribing and designing exercise interventions.

Cardiorespiratory fitness (especially VO_2 max) has traditionally been recognised as the most important component of health related fitness. It is unclear as to how much of this is due to the association between VO_2 max and physical activity participation. Research has demonstrated that people with type 2 diabetes are unlikely to participate in physical activity of sufficient intensity to produce optimal increases in VO_2 max. A better understanding of the importance of increasing VO_2 max as opposed to simply increasing physical activity is needed so that exercise specialists may appropriately emphasise specific exercise interventions.

References:

1. Joslin EP, Root EF, White P. The Treatment of Diabetes Mellitus. . Philadelphia: Lea & Febiger; 1959.

2. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *American Journal of Clinical Nutrition*. 1999;69:373-80.

3. Regensteiner JG, Sippel J, McFarling ET, Wolfel EE, Hiatt WR. Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise [corrected and republished article originally printed in Med Sci Sports Exerc 1995 May;27(5):661-7]. Medicine & Science in Sports & Exercise. 1995;27:875-81.

4. Estacio RO, Regensteiner JG, Wolfel EE, Jeffers B, Dickenson M, Schrier RW. The association between diabetic complications and exercise capacity in NIDDM patients. *Diabetes Care*. 1998;21:291-5.

5. Roy TM, Peterson HR, Snider HL, et al. Autonomic influences on cardiovascular performance in diabetic subjects. *The American Journal of Medicine*. 1989;87:382-388.

6. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Annals of Internal Medicine*. 2000;132:605-611.

7. Rubler S, Gerber D, Reitano J, Chokshi V, Fisher VJ. Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. *American Journal of Cardiology*. 1987;59:1310-1313.

8. Bouchard C, Shephard RJ. Physical activity fitness and health: The model and key concepts. : In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and

health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers; 1994:669-683.

9. World Health Organization. Meeting of investigators on exercise test in relation to cardiovascular function. *WHO technical report.* 1968;388.

10. Boulé NG, Haddad E, Kenny GP, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: A meta-analysis of controlled clinical trials. Unpublished.

11. U.K. Prospective Diabetes Study Group. Intensive blood glucose control reduced type 2 diabetes mellitus-related end points. *Evidence Based Medicine.* 1999;4.

12. Gudat U, Berger M, Lefèbvre PJ. Physical Activity, Fitness, and Non-Insulin-Dependent (Type 2) Diabetes Mellitus. : In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers; 1994:669-683.

13. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie R, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUORUM statement. *Lancet.* 1999;354:1896-900.

14. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 1979;28:1039-1057.

15. WHO. WHO expert committee on diabetes mellitus. *World Health Organization Tecnical Report Series.* 1980;646:1-80.

16. American Diabetes Association. Report on the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 1997;20:1183-1197.

17. Dickersin K, Larson K. Establishing and maintaining and international register for RCT's. . *The Cochrane Collaboration Handbook*; 1995.

18. Verity LS, Ismail AH. Effects of exercise on cardiovascular disease risk in women with NIDDM. *Diabetes Research & Clinical Practice*. 1989;6:27-35.

19. Fujii S, Okuno Y, Okada K, et al. Effects of physical training on glucose tolerance and insulin response in diabetics. *Osaka City Medical Journal*. 1982;28:1-8.

20. Dunstan DW, Mori TA, Puddey IB, et al. The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. *Diabetes Care*. 1997;20:913-21.

21. Jadad A, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials*. 1996;17:1-12.

22. Schultz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with treatment effects in controlled trials. *Journal of the American Medical Association*. 1995;273:408-412.

23. Mulrow CD, Oxman AD. Analysing and presentng results. . *Cochrane Collaboration Handbook. Section 8*. Oxford: The Cochrane Collaboration; 1997.

24. Cooper H, Hedges LV. The handbook of research synthesis. . NewYork: Russell Safe Foundation; 1994.

25. Ronnemaa T, Mattila K, Lehtonen A, Kallio V. Factors related to improved metabolic control in type 2 (non-insulin-dependent) diabetic patients during long-term physical exercise: a controlled randomized study. Abstract.

26. Agurs-Collins TD, Kumanyika SK, Ten Have TR, Adams-Campbell LL. A randomized controlled trial of weight reduction and exercise for diabetes management in older African-American subjects [see comments]. *Diabetes Care*. 1997;20:1503-11.

27. Dunstan DW, Puddey IB, Beilin LJ, Burke V, Morton AR, Stanton KG. Effects of a short-term circuit weight training program on glycaemic control in NIDDM. *Diabetes Res Clin Pract*. 1998;40:53-61.

28. Kaplan RM, Hartwell SL, Wilson DK, Wallace JP. Effects of diet and exercise interventions on control and quality of life in non-insulin-dependent diabetes mellitus. *J Gen Intern Med*. 1987;2:220-8.

29. Lehmann R, Vokac A, Niedermann K, Agosti K, Spinas GA. Loss of abdominal fat and improvement of the cardiovascular risk profile by regular moderate exercise training in patients with NIDDM. *Diabetologia*. 1995;38:1313-9.

30. Mourier A, Gautier JF, De Kerviler E, et al. Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM. Effects of branched-chain amino acid supplements. *Diabetes Care*. 1997;20:385-91.

31. Raz I, Hauser E, Bursztyn M. Moderate exercise improves glucose metabolism in uncontrolled elderly patients with non-insulin-dependent diabetes mellitus. *Isr J Med Sci*. 1994;30:766-70.

32. Ronnemaa T, Mattila K, Lehtonen A, Kallio V. A controlled randomized study on the effect of long-term physical exercise on the metabolic control in type 2 diabetic patients. *Acta Medica Scandinavia*. 1986;220:219-24.

33. Skarfors ET, Wegener TA, Lithell H, Selinus I. Physical training as treatment for Type 2 (non-insulin-dependent) diabetes in elderly men - A feasibility study over 2 years. *Diabetologia*. 1987;30:930-933.

34. Honkola A, Forsen T, Eriksson J. Resistance training improves the metabolic profile in individuals with type 2 diabetes. *Acta Diabetol*. 1997;34:245-8.

35. Wing RR, H. EL, M. P-B, A. K, P. NM, W. G. Exercise in a behavioural weight control programme for obese patients with Type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1988;31:902-9.

36. Vanninen E, Uusitupa M, Siitonen O, Laitinen J, Lansimies E. Habitual physical activity, aerobic capacity and metabolic control in patients with newly -diagnosed Type 2 (non-insulin-dependent) diabetes mellitus: effect of 1-year diet and exercise intervention. *Diabetologia*. 1992;35:340-346.

37. Dunstan DW, Mori TA, Puddey IB, et al. A randomised, controlled study of the effects of aerobic exercise and dietary fish on coagulation and fibrinolytic factors in type 2 diabetics. *Thrombosis & Haemostasis*. 1999;81:367-72.

38. Foss ML, Keteyian SJ. Fox's Physiological Basis for Exercise Physiology. . 6 ed. U.S.A.: WBC McGraw-Hill; 1998.

39. American College of Sports Medicine. Exercise and physical activity for older adults. *Medicine and Science in Sports and Exercise*. 1998;30:992-1008.

40. Ballor DL, Harvey-Berino JR, Ades PA, Cryan J, Calles-Escandon J. Contrasting effects of resistance and aerobic training on body composition and metabolism after diet-induced weight loss. *Metabolism*. 1996;45:179-83.

41. Dolezal BA, Potteiger JA. Concurrent resistance and endurance training influence basal metabolic rate in nondieting individuals. *J Applied Physiology*. 1998;85:695-700.

42. Nelson ME, Fiatarone MA, Layne JE, et al. Analysis of body-composition techniques and models for detecting change in soft tissue with strength training. *American Journal Clinical Nutrition*. 1996;63:678-86.

43. Després J-P. Physical activity and adipose tissue. : In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers; 1994:358-368.

44. Ligtenberg PC, Hoekstra JB, Bol E, Zonderland ML, Erkelens DW. Influence of a physical training program on psychological well-being in elderly type 2 diabetes patients. *Diabetes Care*. 1998;21:2196-2197.

45. Brooks GA, Fahey TD, White TP. Exercise Physiology: Human Bioenergetics and Its Applications. . 2nd ed. Mountain View (cal): Mayfield Publishing Company; 1995.

46. Regensteiner JG, Bauer TA, Reusch JE, et al. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. *Journal of Applied Physiology*. 1998;85:310-7.

47. Brandenburg SL, Reuch JEB, Bauer TA, Jeffers BW, Hiatt WR, Regensteiner JG. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. *Diabetes Care*. 1999;22:1640-1646.

48. Fagard RH, Tipton CM. Physical Activity, Fitness, and Hypertension. : In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health:

international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers; 1994:633-655.

49. Kelley G, McClellan P. Antihypertensive effects of aerobic exercise. A brief meta-analytic review of randomized controlled trials. *American Journal of Hypertension*. 1994;7:115-9.

50. Association AD. The health professional's guide to diabetes and exercise. In: Ruderman N, Devlin JT, eds. *Clinical Education Series*. U. S. A.: American Diabetes Association; 1995.

51. Soukup JT, Maynard TS, Kovaleski JE. Resistance training guidelines for individuals with diabetes mellitus. *Diabetes Educator*. 1994;20:129-37.

52. Blonk MC, Jacobs MA, Biesheuvel EH, Weeda-Mannak WL, Heine RJ. Influences on weight loss in type 2 diabetic patients: little long-term benefit from group behaviour therapy and exercise training. *Diabet Med*. 1994;11:449-57.

53. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH. Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes*. 1984;33:311-318.

54. Smutok MA, Reece C, Kokkinos PF, et al. Effects of exercise training modality on glucose tolerance in men with abnormal glucose regulation. *International Journal Sports Medicine*. 1994;15:283-9.

55. Burleson MA, Jr., O. Bryant H, Stone MH, Collins MA, Triplett-McBride T. Effect of weight training exercise and treadmill exercise on post- exercise oxygen consumption. Medicine & Science in Sports & Exercise. 1998;30:518-22.

Table 1: The components of health related fitness as described by Bouchard and Shephard [8] (P.81)

Fitness components	Number of RCTs or CCTs measuring the outcome
Morphological component	
Body mass for height	12
Body Composition	2
Subcutaneous fat distribution	1
Abdominal visceral fat	4
Bone density	0
Flexibility	0
Muscular component	
Power	0
Strength	1
Endurance	1
Motor component	
Agility	0
Balance	0
Coordination	0
Speed of movement	0
Cardiorespiratory component	
Submaximal exercise capacity	1
Maximal aerobic power (VO_2 max)	5
Heart functions	0
Lung functions	0
Blood pressure	5
Metabolic component	
Glycemic control	10 (HbA1c)
Insulin sensitivity	6 (fasting insulin)
Lipid and lipoprotein metabolism	8
Substrate oxidation characteristics	0

Table 2. The number of studies at each step in of the literature search and reasons for exclusion.

Stage In trial flow	Number of Studies
Potentially relevant publications identified by computer search	2093
Publications identified after filter for RCT and CCT	1193
Studies excluded	1151
Reasons: review articles, animal study, not type 2 diabetes	
Control group, acute effect if exercise only, or no control group	
Trials retrieved for more detailed evaluation	72
Trials excluded	49
Reasons: no supervision or exercise diaries, exercise intervention < 8 weeks, no control group or control group without type 2 diabetes, drug/medication co-intervention	
Potentially appropriate publications to be included in mete-analysis	23
Publications included in meta-analysis	20
Publications meeting inclusion criteria excluded from meta-analysis	3
Reasons:exercise intervention was 3 months on/ 3 month off [52], could not distinguish results between IGT and type 2 diabetes[53, 54]	
Waist circumference or Waist-to-hip ratio	4

Table 2: description of exercise interventions.

Study	Treatment	N	Control	N	Design	Session/wk	Weeks	Intensity	Type	Minutes	MET hr/wk
Aerobic training (exercise vs. non exercise control)											
Dunstan A	Exercise + Fish + Diet	14	Fish + Diet *1	12	RCT	3	8	50-65% VO2 max	C	40	8.75
Dunstan B	Exercise + Diet	11	Diet*2	12		3	8	50-65% VO2 max	C	40	8.75
Fujii	Exercise + Diet	10	Diet*3	15	CCT	5	26	Approx. 40% VO2 max	J	30	10
Kaplan A	Exercise	18	Control*4	15	RCT	3	10	60-70 max HR	W	80	12.5
Kaplan B	Exercise + Diet	16	Diet*5	16		3	10	60-70 max HR	W	80	12.5
Lehmann	Exercise + Diet	16	Diet*6	13	CCT	3	13	50-70% max effort	W,C,J,R,ST	90	16.88
Mourier	Exercise	10	Control*7	11	RCT	3	10	75% VO2peak + Intervals	C	55	11.6
Raz	Exercise	19	Control*8	19	RCT	3	12	65% VO2max	C,T,R,S	55	12.5
Ronnemaa	Exercise	13	Control*8	12	RCT	6	17.5	70% VO2max	W,J,Sk	45	24.75
Skarfors	Exercise	6	Control*9	8	CCT	3	104	75% VO2 max	J,C,CAL	45	13.5
Wing A	Exercise + Diet	10	Diet*10	12	RCT	3	10	3miles/ session	W	60	9.9
Wing B	Exercise + Diet	13	Diet*10	15		3	10	3miles/ session	W	60	9.9
Resistance training (exercise vs. non exercise control)											
Dunstan 2	Exercise	11	Control*8	10	RCT	3	8	3 sets, 10-15 reps, 10 ex	circuit	60	11.44
Honkola	Exercise	18	Control*8	21	CCT	2	22	2 sets, 12-15 reps, 8-10 ex	circuit	45	8.25

Aerobic training (exercise + diet vs. control)											
Agurs-Collins	Exercise + Diet	31	Control*8	27	RCT	3	13	Low-impact aerobic activity	T, C, R, A	30	5.75
Vanninen A	Exercise (men)	21	Control *11	24	RCT	3.5	52	HR 110-140 (age= 53)	W,J,C,S,Sk	45	13.13
Vanninen B	Exercise (women)	16	Control *11	17		3.5	52	HR 110-140 (age= 53)	W,J,C,S,Sk	45	13.13
TOTAL	**13 Trials**	**253**		**259**	**9**						
AVERAGE					**RCTs**	**3.3**	**22.7**			**53**	**12**

Note: W= walking, C = cycling, S = swimming, Sk = skiing, J = jogging, Cal= callisthenics, R = rowing, R-T = resistance training, A = aerobics (low impact), R = rope skipping, ST = stair climbing. Burleson [69] estimated that resistance training corresponded to 40% of VO_2 max. BCAA = Branched-chain amino acids

*1 note: Diet= <30% of total calories from fat.... <100 mmol/day sodium. Fish= 1 fish meal/day

*2 note: Diet= <30% of total calories from fat.... <100 mmol/day sodium.

*3 note: Diet = mild caloric restriction: 30-35 kcal/ kilogram of ideal body weight

*4 note: groups received information on exchange diet of 1200 kcal/day

*5 note: groups received information on exchange diet of 1200 kcal/day and behavior modification

*6 note: Diet = 50% of calories from Carbohydrates, 35% from fat and 15% from protein

*7 note: control did easy exercise for 20 min. 1/week. 1/2 of each group took BCAA supplements

*8 note: no co-intervention

*9 note: all groups received dietetic info by dietician >2 months before intervention

*10 note: Diet = diet and behavioural strategies (goal: -1kg/week),

*11 note: all participants had basic education on physical activity and diet before group allocation

Figure 1. Computer search strategy for all controlled clinical exercise trials in type 2 diabetes. The search for physical activity and diabetes was developed with experts in the field of exercise and diabetes as well as with an experienced librarian. The filter for controlled clinical trials was developed by Dickersin et al. [16].

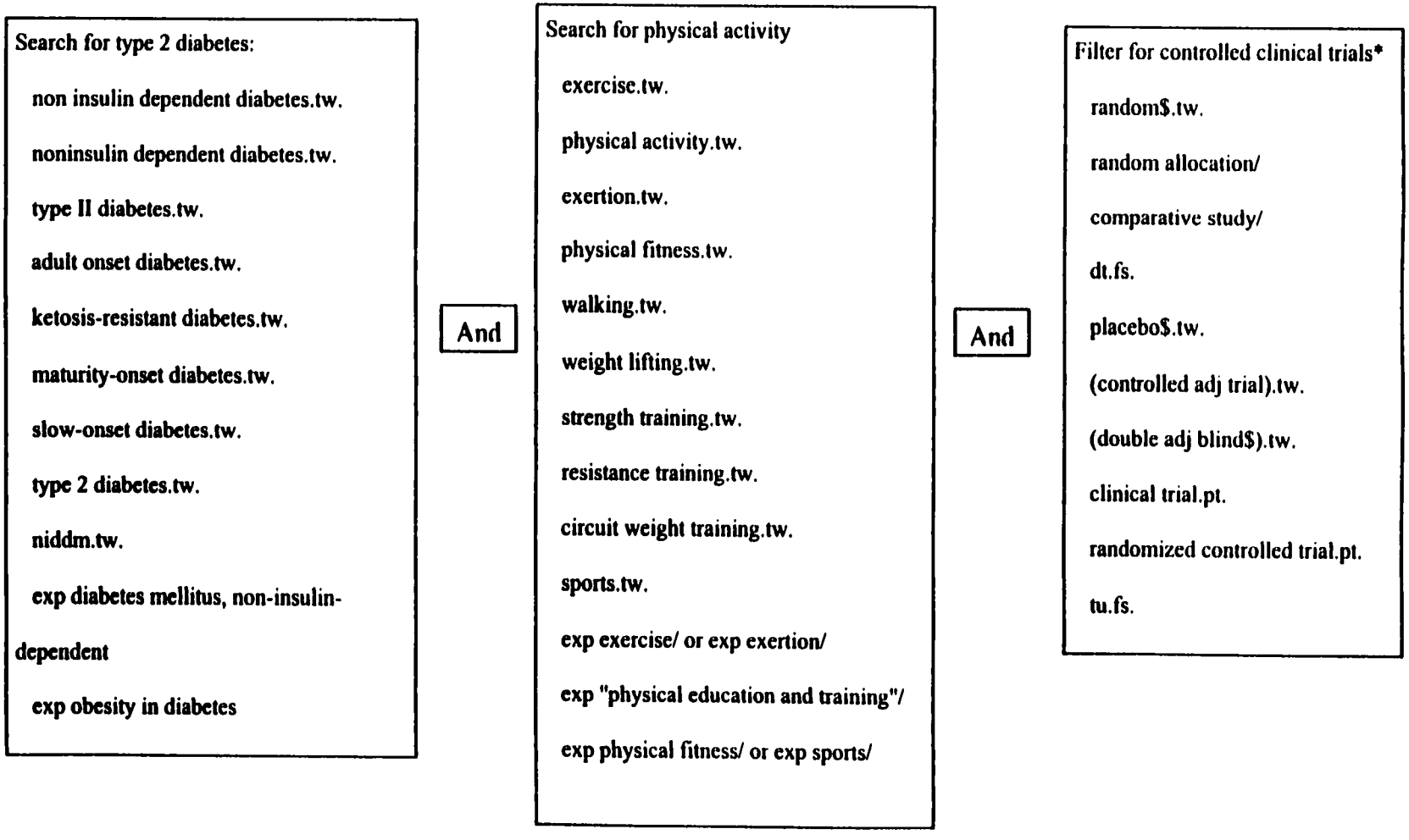
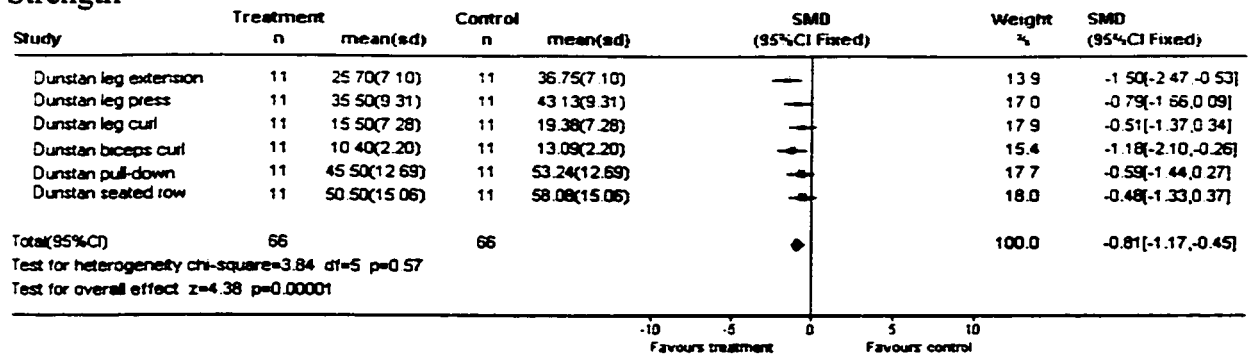


Figure 2: Changes is strength and changes in muscular endurance from baseline to post-intervention.

Strength



Endurance

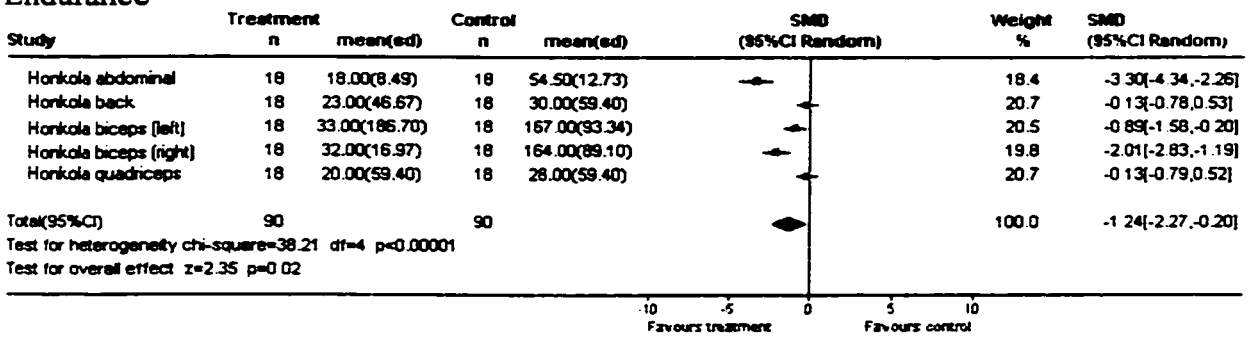


Figure 3: Differences in VO_2 max for exercise vs non-exercise control at baseline and post-intervention.

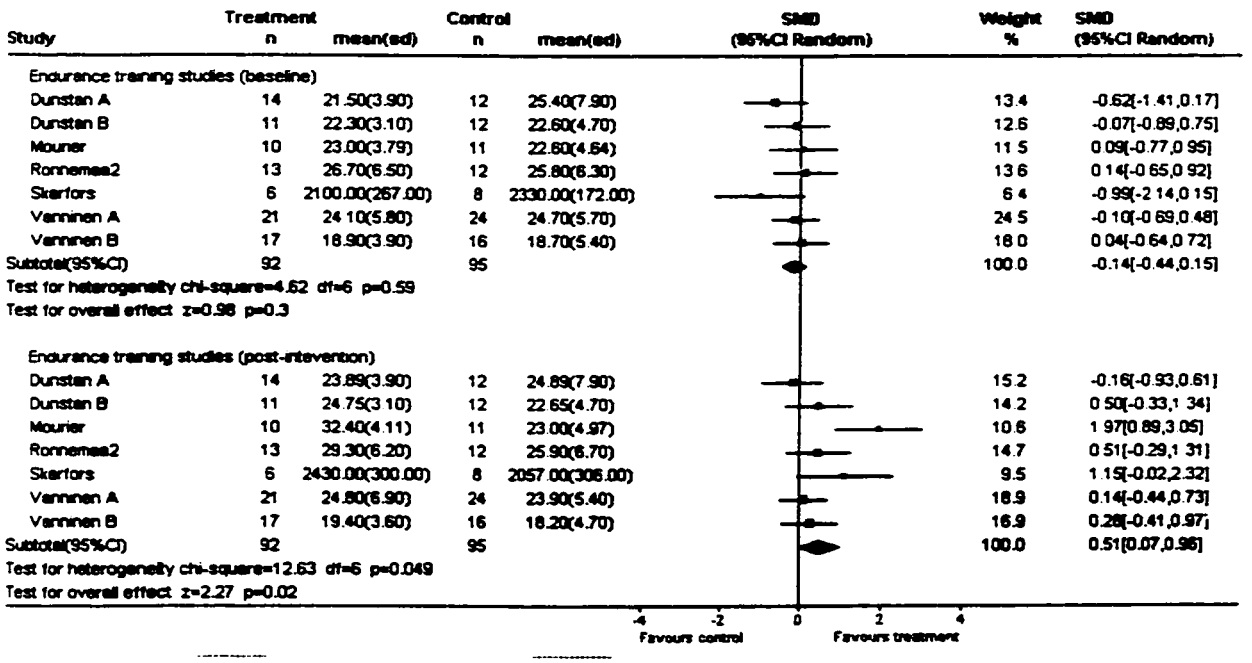


Figure 4: Differences in resting heart rate for exercise vs non-exercise control at baseline and post-intervention.

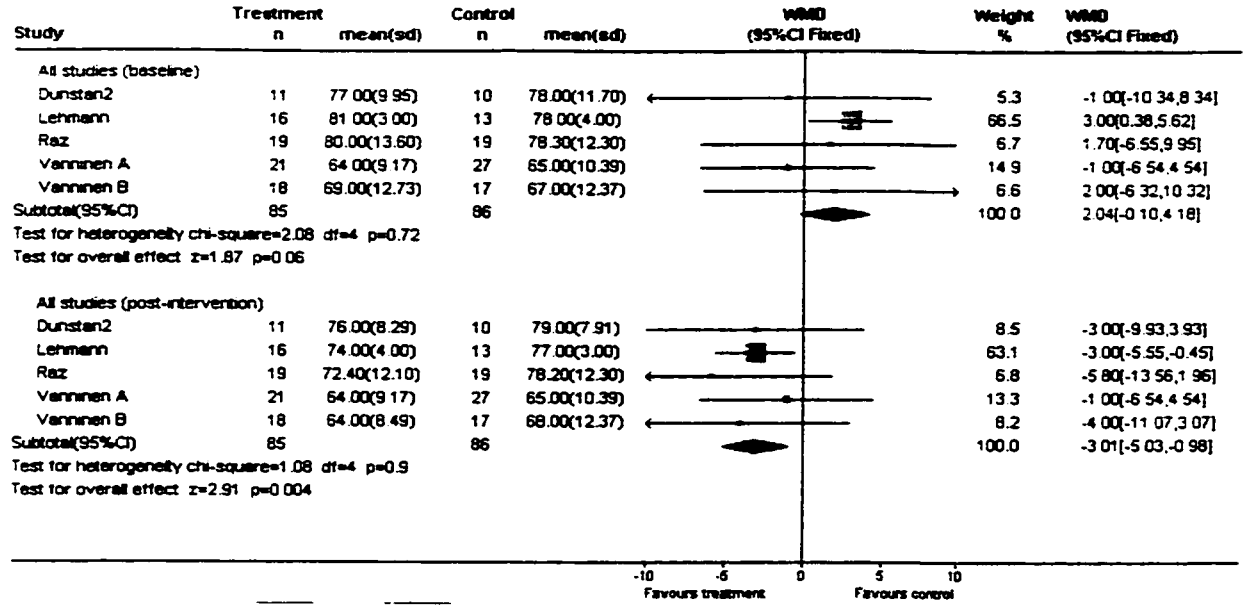
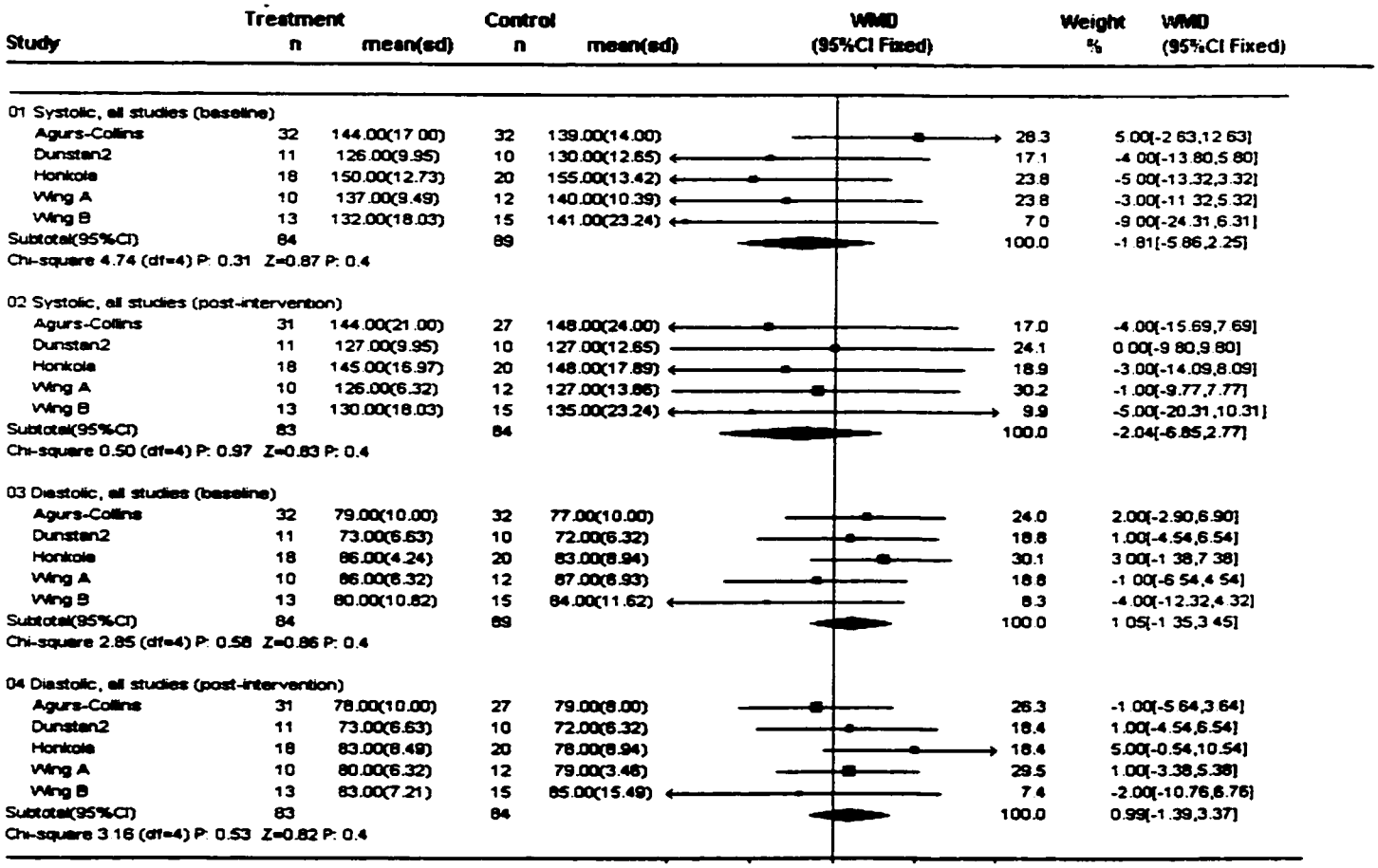


Figure 5: Differences in systolic and diastolic blood pressure for exercise vs non-exercise control at baseline and post-intervention.



CHAPTER IV

GENERAL DISCUSSION

Both these articles independently provided important knowledge for the advancement of practice and research in the field of exercise in type 2 diabetes mellitus. The first article, *A meta-analysis of the effects of exercise on glycemic control and body mass in type 2 diabetes mellitus,* provides relatively strong evidence supporting the role of exercise interventions on improving metabolic control. More specifically exercise interventions produced statistically significant improvements in HbA1c and in fasting insulin when compared to control. The size of the improvements in HbA1c (weighted mean difference = 0.74% for studies of more than 8 weeks duration) is clinically significant, as previous studies have shown that reductions of this magnitude are associated with a reduction in clinical end points (40.9 vs 46 events per 1000 patients) (U.K. Prospective Diabetes Study Group, 1999).

The second article presented in this thesis, *A systematic review of the effect of exercise on physical fitness in type 2 diabetes mellitus,* demonstrates how other elements of health-related fitness may be improved through exercise training. Most importantly, although people with type may have low cardiorespiratory fitness, as represented by VO_2 max, this component of fitness was shown to improve to a similar degree as in people without type 2 diabetes (from 10-30%) (American College of Sports Medicine, 1998b). A recent study demonstrates a strong association between cardiorespiratory fitness and mortality in type 2 diabetes (Wei et al., 2000). Although there is some evidence that

resistance training increases muscular strength in type 2 diabetes, there is very little information on other potential effects of exercise on maximal or submaximal exercise capacities in type 2 diabetes.

Even after combining the results from the two articles it is still unclear how to interpret the lack in improvement in body mass or body composition associated with exercise training in type 2 diabetes. Although reductions in body mass were expected with exercise training, it is not completely surprising that no significant changes were observed. We discuss in the first articles that body mass may not be a reliable indication of changes in fat mass following exercise interventions. Unfortunately in the second article reductions in waist-to-hip ratio and percent body fat did not reach statistical significance. This non-significant trend towards improvement is probably do to the small sample size as very few studies included these easy and important measures. This lack of change in body composition may also be explained by the short duration of the included trials (mean = 20.39 weeks). Significant fat loss, such as those found in National Institutes of Health guidelines (National Institutes of Health, 1998), may be due to longer exercise interventions.

Valuable information can be gained from these articles for both the practitioner and exercise specialist working with people with type 2 diabetes. First of all, the concept of metabolic fitness has only recently been introduced as a part of health related fitness for exercise specialist (Bouchard & Shephard, 1994). Exercise specialists should remember that exercise need not improve maximal and submaximal exercise capacities in order to be beneficial. Improvements in the metabolic component of health-related fitness, such as improvements in HbA1c and in insulin sensitivity have strong health

implications in type 2 diabetes. The exercise specialists should be able to work within the diabetes care team and have appropriate feedback on the changes in metabolic control of their diabetic participants.

On the other hand, physicians who treat people with diabetes often do not have the time or the resources to measure other components of health related fitness or to prescribe appropriate exercise interventions. Exercise specialist should further be incorporated within the diabetes care team.

The present meta-analysis strongly contributes to the growing evidence supporting exercise interventions in type 2 diabetes. The challenge of getting people with type 2 diabetes to exercise regularly still remains. Only then will exercise interventions have the opportunity to have their full impact as one of the three cornerstones of diabetic therapy.

REFERENCES

American College of Sports Medicine. (1998a). American College of Sports Medicine Position Stand. Exercise and physical activity for older adults. Med Sci Sports Exerc, 30(6), 992-1008.

American College of Sports Medicine. (1998b). Exercise and physical activity for older adults. Medicine and Science in Sports and Exercise, 30(6), 992-1008.

American Diabetes Association. (1997a). Diabetes mellitus and exercise. Diabetes Care, 20(12), 1908-12.

American Diabetes Association. (1997b). Report on the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care, 20, 1183-1197.

Arroll, B., & Beaglehole, R. (1992). Does physical activity lower blood pressure: a critical review of the clinical trials. Journal of Clinical Epidemiology, 45(5), 439-47.

Baechle, T. R. (1994). Essentials of strength training and conditioning. Champlain, Il: Human Kinetics.

Ballor, D. L., & Poehlman, E. T. (1995). A meta-analysis of the effects of exercise and/or dietary restriction on resting metabolic rate. European Journal Applied Physiology, 71(6), 535-42.

Beniamini, Y., Rubenstein, J. J., Zaichkowsky, L. D., & Crim, M. C. (1997). Effects of high-intensity strength training on quality-of-life parameters in cardiac rehabilitation patients. American Journal of Cardiology, 80(7), 841-6.

Bjorntorp, P. (1995). Insulin resistance: The consequence of a neuroendocrine disturbance. International Journal of Obesity, 19(suppl 4), S6-S10.

Blair, S. N., Kampert, J. B., Kohl, H. W., 3rd, Barlow, C. E., Macera, C. A., Paffenbarger, R. S., Jr., & Gibbons, L. W. (1996). Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. Journal of the American Medical Association, 276(3), 205-10.

Blair, S. N., Kohl, H. W., 3rd, Barlow, C. E., Paffenbarger, R. S., Jr., Gibbons, L. W., & Macera, C. A. (1995). Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men . Journal of the American Medical Association, 273(14), 1093-8.

Bonen, A. (1995). Benefits of exercise for type II diabetics: convergence of epidemiologic, physiologic, and molecular evidence. Can Journal of Applied Physiology, 20(3), 261-79.

Bonen, A., Ball-Burnett, M., & Russel, C. (1998). Glucose tolerance is improved after low- and high-intensity exercise in middle-age men and women. Canadian Journal of Applied Physiology, 23(6), 583-93.

Bouchard, C., & Pérusse, L. (1994). Heredity, Activity Level, Fitness and Health: In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers.

Bouchard, C., & Shephard, R. J. (1994). Physical activity fitness and health: The model and key concepts: In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity

fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers.

Bouchard, C., Shephard, R. J., & Stephens, T. E. (1994). Physical activity fitness, and health: international proceedings and consensus statement: Champaign, Ill, Human Kinetics Publishers.

Braun, B., Zimmermann, M. B., & Kretchmer, N. (1995). Effects of exercise intensity on insulin sensitivity in women with non- insulin-dependent diabetes mellitus. Journal Applied Physiology, 78(1), 300-6.

Brooks, G. A., Fahey, T. D., & White, T. P. (1995). Exercise Physiology: Human Bioenergetics and Its Applications. (2nd ed.). Mountain View (cal): Mayfield Publishing Company.

Canadian Society for Exercise Physiology. (1993). Certified Fitness Appraiser. Resource Manual. Gloucester, ON: Canadian Society for Exercise Physiology.

Cochrane, A. (1979). 1931-1971: a critical review, with particular reference to the medical profession. London: Office of Health Economics.

Collaboration, T. C. (1997). The Cochrane Collaboration Handbook.

Cook, D. J., Guyatt, G. H., Ryan, G., Clifton, J., Buckingham, L., Mcllroy, W., & Oxman, A. D. (1993). Should Unpublished data be included in Meta-analyses. Journal of the American Medical Association, 269, 2749-2753.

Cowie, C. C., & Harris, M. I. (1995). Physical and metabolic characteristics of persons with diabetes. In M. I. Harris (Ed.), Diabetes in America, 2nd ed. (pp. 117-164). Washington, DC: U.S. Government Printing Office.

DCCT Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med, 329(14), 977-86.

DeFronzo, R. A., & Ferrannini, E. (1991). Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care, 14(3), 173-94.

DeFronzo, R. A., Tobin, J. D., & Andres, R. (1979). Glucose clamp technique: a method for quantifying insulin secretion and resistance. American Journal of Physiology, 6(3), E214-E223.

Després, J.-P. (1994a). Physical activity and adipose tissue: In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers.

Després, J. P. (1993). Abdominal obesity as important component of insulin-resistance syndrome. Nutrition, 9(5), 452-9.

Després, J. P. (1994b). Dyslipidaemia and obesity. Baillieres Clin Endocrinol Metab, 8(3), 629-60.

Després, J. P. (1997). Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. Exercise and Sport Science Reviews, 25, 271-300.

Després, J. P. (1998). The insulin resistance-dyslipidemic syndrome of visceral obesity: effect on patients' risk. Obesity Research, 6(Suppl 1), 8S-17S.

Després, J. P., & Lamarche, B. (1994). Low-intensity endurance exercise training, plasma lipoproteins and the risk of coronary heart disease. Journal of Internal Medicine, 236(1), 7-22.

Devlin, J. T. (1992). Effects of exercise on insulin sensitivity in humans. Diabetes Care, 15(11), 1690-3.

Dolezal, B. A., & Potteiger, J. A. (1998). Concurrent resistance and endurance training influence basal metabolic rate in nondieting individuals. Journal of Applied Physiology, 85(2), 695-700.

Eastman, R. C. (1995). Neuropathy in Diabetes, In: National Institutes of Health, Diabetes in America (Vol. Publication No. 95-1468, pp. 339-348).

Egger, M., Zellweger-Zähner, T., Schneider, M., Junker, C., Lengeler, C., & Antes, G. (1997). Language bias in randomised controlled trials published in English and German. Lancet, 350, 326-29.

Estacio, R. O., Regensteiner, J. G., Wolfel, E. E., Jeffers, B., Dickenson, M., & Schrier, R. W. (1998). The association between diabetic complications and exercise capacity in NIDDM patients. Diabetes Care, 21(2), 291-5.

Fagard, R. H., & Tipton, C. M. (1994). Physical Activity, Fitness, and Hypertension: In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers.

Glass, G. V. (1976). Primary, seconday and meta-analysis of research. Educational Researcher, 5(10), 3-8.

Goldstein, D. E., Little, R. R., Wiedmeyer, H. M., England, J. D., & McKenzie, E. M. (1986). Glycated hemoglobin: methodologies and clinical applications. [Review] [70 refs]. Clinical Chemistry, 32(10 Suppl).

Grundy, S. M. (1998). Multifactorial causation of obesity: Implications for prevention. American Journal of Clinical Nutrition, 67(suppl), 567S-572S.

Gudat, U., Berger, M., & Lefèbvre, P. J. (1994). Physical Activity, Fitness, and Non-Insulin-Dependent (Type 2) Diabetes Mellitus: In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers.

Gurwitz, J. H., Field, T. S., Glynn, R. J., Manson, J. E., Avorn, J., Taylor, J. O., & Hennekens, C. H. (1994). Risk factors for non-insulin-dependent diabetes mellitus requiring treatment in the elderly. Journal of the American Geriatrics Society, 42(12), 1235-40.

Ha, H., & Kim, K. H. (1995). Role of oxidative stress in the development of diabetic nephropathy. Kidney International, 48(Suppl. 51), S18-S21.

Health Canada. (1997). Canadians and healthy eating: How are we doing? : Minister of Supply and Services Canada.

Health Canada, Laboratory Center for Disease Control, & Diabetes Division, B. o. C.-R. D. a. D. (1999). Diabetes in Canada: National Statistics and Opportunities for Improved Surveillance, Prevention, and Control.

Hillsdon, M., & Thorogood, M. (1996). A systematic review of physical activity promotion strategies. British Journal of Sports Medicine, 30(2), 84-9.

Holloszy, J. O., Schultz, J., Kusnierkiewicz, J., Hagberg, J. M., & Ehsani, A. A. (1986). Effects of exercise on glucose tolerance and insulin resistance. Brief review and some preliminary results. Acta Medica Scandinavia Suppl, 711, 55-65.

Ivy, J. L. (1997). Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. Sports Medicine, 24(5), 321-36.

Jadad, A., Moore, A., Carroll, D., Jenkinson, C., Reynolds, D. J. M., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials, 17, 1-12.

Joslin, E. P., Root, E. F., & White, P. (1959). The Treatment of Diabetes Mellitus. Philadelphia: Lea & Febiger.

Kaplan, R. M., Hartwell, S. L., Wilson, D. K., & Wallace, J. P. (1987). Effects of diet and exercise interventions on control and quality of life in non-insulin-dependent diabetes mellitus. Journal of General Internal Medicine, 2(4), 220-8.

Kelley, G. (1997). Dynamic resistance exercise and resting blood pressure in adults: a meta-analysis. Journal Applied Physiology, 82(5), 1559-65.

Kelley, G., & McClellan, P. (1994). Antihypertensive effects of aerobic exercise. A brief meta-analytic review of randomized controlled trials. American Journal of Hypertension, 7(2), 115-9.

Kelley, G., & Tran, Z. V. (1995). Aerobic exercise and normotensive adults: a meta-analysis. Medicine & Science in Sports & Exercise, 27(10), 1371-7.

King, D. S., Baldus, P. J., Sharp, R. L., Kesl, L. D., Feltmeyer, T. L., & Riddle, M. S. (1995). Time course for exercise-induced alterations in insulin action and glucose tolerance in middle-aged people. Journal Applied Physiology, 78(1), 17-22.

Klein, R., & Klein, B. E. K. (1995). Vision Disorders in Diabetes, In: National Institutes of Health, Diabetes in America (Vol. Publication No. 95-1468, pp. 293-338).

Krolewski, A. S., Laffel, L. M., Krolewski, M., Quinn, M., & Warram, J. H. (1995). Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. New England Journal Medicine, 332(19), 1251-5.

Lee, C. D., Blair, S. N., & Jackson, A. S. (1999). Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. American Journal of Clinical Nutrition, 69, 373-80.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 28(7), 412-9.

Mayer-Davis, E. J., D. Agostino R, J., Karter, A. J., Haffner, S. M., Rewers, M. J., Saad, M., & Bergman, R. N. (1998). Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. Journal of the American Medical Association 279(9), 669-74.

Meltzer, S., Leiter, L., Daneman, D., Gerstein, H. C., Lau, D., Ludwig, S., Yale, J.-F., Zinman, B., & Lillie, D. (1998). 1998 clinical practice guidelines for the management of diabetes in Canada. Canadian Medical Association Journal, Journal de L'Association Médicale Canadienne, 8 Suppl, S1-S29.

Mitchell, J. H., & Raven, P. B. (1994). Cardiovascular Adaptation to Physical Activity: In Bouchard, C. Shephard, R. J. Stephens, T. Physical activity fitness, and health: international proceedings and consensus statement. Champaign, Ill, Human Kinetics Publishers.

Must, A., Spadano, J., Coakley, E. H., Field, A. E., Colditz, G., & Dietz, W. H. (1999). The disease burden associated with overweight and obesity. Journal of the American Medical Association, 282(16), 1523-1529.

National Diabetes Data Group. (1979). Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes, 28, 1039-1057.

National Diabetes Data Group, & National Institutes of Health, N. I. o. D. a. D. a. K. D. (1995). Diabetes In America. (2nd ed.). (Vol. NIH Publication No. 95-1468).

National Institutes of Health. (1995). Diabetic Neuropathy, the Nerve Damage of Diabetes. , Publication No. 95-3185.

National Institutes of Health. (1998). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report.

National Institutes of Health, & Diseases, N. I. o. D. a. D. a. K. (1995). Kidney Disease of Diabetes. (Vol. Publication No. 97-3925).

Nelson, R. G., Knowler, W. C., Pettitt, D. J., & Bennett, P. H. (1995). Kidney Diseases in Diabetes, In: National Institutes of Health, Diabetes in America (Vol. Publication No. 95-1468, pp. 349-400).

Ohlson, L. O., Larsson, B., Svärdsudd, K., Welin, L., Eriksson, H., Wilhelmsen, L., Björntrop, P., & Tibblin, G. (1985). The influence of body fat distribution on the

incidence of diabetes mellitus- 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes, 34, 1055-1058.

Poehlman, E. T. (1989). A review: exercise and its influence on resting energy metabolism in man. Medicine and Science in Sports and Exercise, 21, 515-525.

Reaven, G. M. (1988). Banting lecture 1988. Role of insulin resistance in human disease. Diabetes, 37(12), 1595-607.

Regensteiner, J. G., Sippel, J., McFarling, E. T., Wolfel, E. E., & Hiatt, W. R. (1995). Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise [corrected and republished article originally printed in Med Sci Sports Exerc 1995 May;27(5):661-7]. Medicine and Science in Sports and Exercise, 27(6), 875-81.

Roy, T. M., Peterson, H. R., Snider, H. L., Cyrus, J., Broadstone, V. L., Fell, R. D., Rothchild, A. H., Salmols, E., & Pfeifer, M. (1989). Autonomic influences on cardiovascular performance in diabetic subjects. The American Journal of Medicine, 87, 382-388.

Rubler, S., Gerber, D., Reitano, J., Chokshi, V., & Fisher, V. J. (1987). Predictive value of clinical and exercise variables for detection of coronary artery disease in men with diabetes mellitus. American Journal of Cardiology, 59, 1310-1313.

Schneider, S. H., Khachadurian, A. K., Amorosa, L. F., Clemow, L., & Ruderman, N. B. (1992). Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care, 15(11), 1800-10.

Schultz, K. F., Chalmers, I., Hayes, R. J., & Altman, D. G. (1995). Empirical evidence of bias: Dimensions of methodological quality associated with treatment effects in controlled trials. Journal of the American Medical Association, 273(5), 408-412.

U.K. Prospective Diabetes Study Group. (1999). Intensive blood glucose control reduced type 2 diabetes mellitus-related end points. Evidence Based Medicine, 4(10).

Wallberg-Henriksson, H., Rincon, J., & Zierath, J. R. (1998). Exercise in the management of non-insulin-dependent diabetes mellitus. Sports Medicine, 25(1), 25-35.

Wei, M., Gibbons, L. W., Kampert, J. B., Nichaman, M. Z., & Blair, S. N. (2000). Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Annals of Internal Medicine, 132(605-611), 605-611.

World Health Organization. (1968). Meeting of investigators on exercise test in relation to cardiovascular function. WHO technical report., 388.

World Health Organization. (1980). WHO expert committee on diabetes mellitus. World Health Organization Tecnical Report Series, 646, 1-80.

Yki-Yarvinen, H. (1998). Toxicity of Hyperglycaemia in Type 2 Diabetes. Diabetes and Metabolism Reviews, 14, S45-S50.

Zachwieja, J. J., Toffolo, G., Cobelli, C., Bier, D. M., & Yarasheski, K. E. (1996). Resistance exercise and growth hormone administration in older men: effects on insulin sensitivity and secretion during a stable-label intravenous glucose tolerance test. Metabolism, 45(2), 254-60.

APPENDIX A

Summary of energy expenditure in resistance training

Study	*Type*	*METs*	*N*	*Sex*
Reilly, 1983	CWT	6.1	13	M
Wilmore, 1978	CWT	6.15	40	M+F
DeGroot, 1998	CWT	2.3	9	M
Hempel, 1985	CWT	5.4	18	M=F
Burleson, 1998	CWT	5.5	15	M
Van Ettan, 1997	Weight Lifting	5.2	26	M
Melby, 1993	Weight Lifting	5.9	13	M
Hickson, 1984	Weight Lifting	5.2	4	M
Ballor, 1988	Weight Lifting	3.3	5	F
Ballor, 1987	Hydraulic	7.6	13	M
Katch, 1985	Hydraulic	7	20	M
AVERAGE		**5.4 METs**		

Note: CWT = circuit weight training, M = male, F = female

Details of Studies

1. Circuit weight training (CWT) studies:

In a study by (Reilly et al., 1983), 13 males with some weight training experience (age average 37), performed circuit weight training.

- Mean Body weigh (kg): 81.5
- Intensity: 3 sets of 10 to 20 reps (10 exercises)
- rest interval: no rest, 10 minute workout
- Reported energy expenditure: 1.75 LO_2/min

Estimated METs : ≈ 6.1

In a study by (Wilmore et al., 1978), 20 males (age 17-36) and 20 females (age 17-26), with weight training experience, performed circuit weight training.

- Mean Body weigh (kg): 77.5 for men and 61 for women
- Intensity: 3 sets of 15-18 reps, 10 exercises at 40% 1RM
- rest interval: 30sec of work: 15 sec rest,
- Reported energy expenditure: men: 9 kcal/min and women: 6.1 kcal/min

Estimated METs : ≈ 6.6 for men 5.7 for women

In a study by (DeGroot, Quinn, Kertzer, Vroman, & Olney, 1998), 9 males from a cardiac rehabilitation population, age 56 to 72, performed circuit weight training.

- Mean Body weigh (kg): 86.74
- Intensity: 3 sets 40 or 60 %1RM
- rest interval: 30 or 60 sec rest between sets
- Reported energy expenditure: 2.98-3.81 kcal/min

- **Estimated METs : ≈ 2.3**

In a study by (Hempel & Wells, 1985), 10 males and 8 females, very active but no mention of weight training experience (age average 27), performed the Nautilus Express Circuit.

- Mean Body weigh (kg): 66.9
- Intensity: 14 Nautilus exercises 7 sec/rep, 1 set of 8-12 reps
  interval: no rest
- Reported energy expenditure: 19.2 mlO_2/kg/min
- **Estimated METs : ≈ 5.4**

In a study by (Burleson, O. Bryant, Stone, Collins, & Triplett-McBride, 1998), 15 males with 6-months of weight training experience, age 20 to 26, performed circuit weight training.

- Mean Body weigh (kg): 82
- Intensity: 2 sets of 8 exercise, 8-12 reps at 60% 1RM
- rest interval:
- Reported energy expenditure: 7.9 kcal/min
- **Estimated METs : ≈ 5.5** (corresponds to 44% of treadmill VO_2 max)

2. Weight lifting studies (non CWT)

In a study by (Van Etten, 1997), 26 males healthy but sedentary, average age 33, performed resistance training.

- Mean Body weigh (kg): 78.8
- Intensity: 3 set of 10 exercises, 15 reps/set
- rest interval: 1:1 work:rest ratio
- Reported energy expenditure: 7.2 kcal/min
- **Estimated METs : ≈ 5.2** (corresponds to 44% of treadmill VO_2 max)

In a study by (Melby, Scholl, Edwards, & Bullough, 1993), 13 males with weight training experience (age 20 to 40), performed resistance training.

- Mean Body weigh (kg): 78
- Intensity: 6 sets of 10 exercises at 70% of 1RM (8-12 reps),
- rest interval: sets started every 3 minutes. Total 90 minutes
- Reported energy expenditure: 7-9 kcal/min
- **Estimated METs : ≈ 5.86**

In a study by (Hickson, Wilmore, Buono, & Constable, 1984), 4 males with weight training experience (age 19 to 26), performed resistance training.

- Mean Body weigh (kg): 82
- Intensity: 3 sets of 6-9 reps at 75-80% 1Rm, 5 exercise
  (universal)
- rest interval: 30sec work:1min rest
- Reported energy expenditure: 6.7- 8.2 kcal/min
- **Estimated METs : ≈ 5.2**

In a study by (Ballor, Katch, Becque, & Marks, 1988), 5 obese females (32.9), performed resistance training.

- Mean Body weigh (kg): ≈75
- Intensity: 10-12 reps, for 3 sets of 8 exercises
- rest interval:
- Reported energy expenditure: 36.30 LO_2/ 42 minutes

Estimated METs : ≈ 3.3

3. Hydraulic resistance training studies

In a study by (Ballor, Becque, & Katch, 1987), 13 males "highly fit" (age average 24), performed hydraulic resistance training.

- Mean Body weigh (kg): 84.6
- Intensity: 7 Hydraulic exercises at different speeds
- rest interval: 30:30 seconds work:rest ratio
- Reported energy expenditure: 26.7 ml O_2/kg

Estimated METs : ≈ 7.63

In a study by (Katch, Freedson, & Jones, 1985), 20 males with no previous weight lifting experience (age average 24), performed hydraulic resistance training.

- Mean Body weigh (kg): 73.3
- Intensity: 3 Hydraulic exercises at different speeds,
- rest interval: 20sec work: 20sec rest ratio
- Reported energy expenditure: 9 kcal/min
- **Estimated METs : ≈ 7**

***** all conversions from kcal/min to METs were done assuming that RQ= 1.**

***** Most of these studies do not measure energy expenditure during recovery. Energy expenditure during recovery of resistance training may be much higher than during the recovery from aerobic exercise [Burleson, 1998].**

References:

Ballor, D. L., Becque, M. D., & Katch, V. L. (1987). Metabolic responses during hydraulic resistance exercise. Medicine & Science in Sports & Exercise, 19(4), 363-7.

Ballor, D. L., Katch, V. L., Becque, M. D., & Marks, C. R. (1988). Resistance weight training during caloric restriction enhances lean body weight maintenance. American Journal of Clinical Nutrition, 47, 19-25.

Burleson, M. A., Jr., O. Bryant, H., Stone, M. H., Collins, M. A., & Triplett-McBride, T. (1998). Effect of weight training exercise and treadmill exercise on post-exercise oxygen consumption. Med Sci Sports Exerc, 30(4), 518-22.

DeGroot, D. W., Quinn, T. J., Kertzer, R., Vroman, N. B., & Olney, W. B. (1998). Circuit weight training in cardiac patients: determining optimal workloads for safety and energy expenditure [In Process Citation]. J Cardiopulm Rehabil, 18(2), 145-52.

Hempel, L. S., & Wells, C. L. (1985). Cardiorespiratory Cost of the Nautilus Express Circuit. The Physician and Sports Medicine, 13(4), 82-86,91-97.

Hickson, J. F., Wilmore, J. H., Buono, M. J., & Constable, S. H. (1984). Energy cost of weight training exercise. National Strength & Conditioning Association journal, 6(5), 22-23.

Katch, F. I., Freedson, P. S., & Jones, C. A. (1985). Evaluation of acute cardiorespiratory responses to hydraulic resistance exercise. Medicine & Science in Sports & Exercise, 17(1), 168-73.

Melby, C., Scholl, C., Edwards, G., & Bullough, R. (1993). Effect of acute resistance exercise on postexercise energy expenditure and resting metabolic rate. J Appl Physiol, 75(4), 1847-53.

Reilly, T., De Looze, M. P., M., T. H., A., C. D., P., J. M., & J., S. A. (1983). Energy cost and mechanical efficiency of circuit weight-training
Relationships between energy expenditure and positive and negative mechanical work in repetitive lifting and lowering. Journal of human movement studies, 9(1), 39-45.

Van Etten, L. M. L. A., Westerterp, F. T. J., Boon, B. J. B., & Saris, W. H. M. (1997). Effect of 18-wk weight-training program on energy expenditure and physical activity. Journal of Applied physiology, 82(1), 298-304.

Wilmore, J. H., Parr, R. B., Ward, P., Vodak, P. A., Barstow, T. J., Pipes, T. V., Grimditch, G., & Leslie, P. (1978). Energy cost of circuit weight training. Medicine & Science in Sports, 10(2), 75-8.

APPENDIX B:

Quality assessment scales

1. Scale for assessing Randomization, Blinding, and Withdrawals (Jadad et al., 1996)

Trial Characteristics	Yes	No	Bonus
Was the study described as randomised? This includes words such as random, randomly, and randomization			
Was the study described as double blind?			
Was there a description of withdrawals and dropouts?			**N/A**

Total score = _____

Scoring the items:

Give a score of 1 point for each "yes" and a score of 0 points for each "no". There are no in between marks.

Give 1 additional point if:

For question 1, the method of randomization was described and was appropriate (random number table, computer-generated schedule, coin toss).
And/or
For question 2, the method of double blinding was described and was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if:

For question 1, the method of randomization was described and was inappropriate (alternating allocation, date of birth, chart number, etc.).
And/or
For question 2, the method of double blinding was described and was inappropriate (comparison of injectables and oral preparations without a "double dummy").

Guidelines for assessment

Randomization
A method to generate sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

Double-blinding
A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessment nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebo, identical placebo or dummies is mentioned.

Withdrawals and drop-outs
Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement of withdrawals, this item must be given no points.

2. Criteria for assessing Allocation Concealment (Schultz et al., 1995)

A) Adequately concealed trials
If it was deemed that adequate measures to conceal allocation were taken (i.e. central randomization, number or coded bottles or containers, drugs prepared by pharmacy, serial numbered, sealed envelopes or other descriptions that contained elements convincing of concealment)

B) Inadequately concealed trials
Trials in which concealment was inadequate (such as alternation or reference to case number or to date of birth).

C) Unclearly concealed trials
Trials in which the author did not report allocation concealment approach at al or reported an approach that did not fit into one of the categories just named.

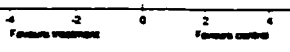
APPENDIX C

Tables and figures of results for all analyses performed.

The following pages represent all the figures analyzed with RevMan and MetaView software. Many of the figures have not been included in the articles because of space limitations; this is often the case for subgroup analysis or less clinically important findings

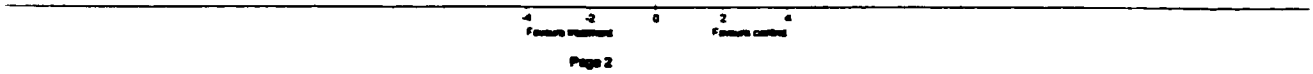
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 01 HbA1c

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Dunstan A	14	8.30(1.50)	12	8.00(1.50)		12.2	0.30[-0.88,1.48]
Dunstan B	11	8.80(2.70)	12	8.10(1.40)		5.1	0.70[-1.08,2.48]
Dunstan2	11	8.20(1.68)	10	8.10(1.80)		7.0	0.10[-1.43,1.63]
Honkola	18	7.50(1.27)	20	7.70(1.34)		23.7	-0.20[-1.03,0.63]
Lehmann	16	7.50(1.60)	13	7.80(1.70)		11.1	-0.30[-1.51,0.91]
Mourier	10	8.50(1.90)	11	7.40(0.99)		9.4	1.10[-0.21,2.41]
Raz	19	12.50(2.90)	19	12.40(4.00)		3.3	0.10[-2.12,2.32]
Ronnemaa2	13	9.60(1.60)	12	10.00(1.50)		11.1	-0.40[-1.62,0.82]
Wing A	10	9.70(1.58)	12	9.40(1.73)		8.5	0.30[-1.08,1.68]
Wing B	13	10.60(1.80)	15	10.90(1.94)		8.5	-0.30[-1.69,1.09]
Subtotal(95%CI)	135		136			100.0	0.05[-0.34,0.47]
Test for heterogeneity chi-square=4.71 df=9 p=0.86							
Test for overall effect z=0.30 p=0.8							
02 All studies (post-intervention)							
Dunstan A	14	7.70(1.50)	12	7.90(1.50)		9.1	-0.20[-1.36,0.96]
Dunstan B	11	8.07(2.70)	12	7.57(1.40)		3.8	0.50[-1.28,2.28]
Dunstan2	11	8.00(1.68)	10	8.30(2.21)		4.3	-0.30[-1.98,1.38]
Honkola	18	7.40(0.85)	20	8.10(1.34)		24.5	-0.70[-1.41,0.01]
Lehmann	16	7.50(1.60)	13	8.40(1.70)		8.3	-0.90[-2.11,0.31]
Mourier	10	6.20(0.63)	11	7.70(1.33)		15.9	-1.50[-2.38,-0.62]
Raz	19	11.70(2.60)	19	12.90(4.20)		2.5	-1.20[-3.42,1.02]
Ronnemaa2	13	8.60(1.90)	12	9.90(1.70)		6.1	-1.30[-2.71,0.11]
Wing A	10	8.00(1.26)	12	7.90(1.73)		7.8	0.10[-1.15,1.35]
Wing B	13	8.20(1.08)	15	9.00(1.16)		17.7	-0.80[-1.63,0.03]
Subtotal(95%CI)	135		136			100.0	-0.74[-1.08,-0.39]
Test for heterogeneity chi-square=8.44 df=9 p=0.49							
Test for overall effect z=4.15 p=0.00003							
03 RCT's (baseline)							
Dunstan A	14	8.30(1.50)	12	8.00(1.50)		19.7	0.30[-0.88,1.48]
Dunstan B	11	8.80(2.70)	12	8.10(1.40)		8.3	0.70[-1.08,2.48]
Dunstan2	11	8.20(1.68)	10	8.10(1.80)		11.2	0.10[-1.43,1.63]
Mourier	10	8.50(1.90)	11	7.40(0.99)		15.3	1.10[-0.21,2.41]
Ronnemaa2	13	9.60(1.60)	12	10.00(1.50)		17.9	-0.40[-1.62,0.82]
Wing A	10	9.70(1.58)	12	9.40(1.73)		13.8	0.30[-1.08,1.68]
Wing B	13	10.60(1.80)	15	10.90(1.94)		13.7	-0.30[-1.69,1.09]
Subtotal(95%CI)	82		84			100.0	0.23[-0.29,0.74]
Test for heterogeneity chi-square=3.59 df=6 p=0.73							
Test for overall effect z=0.86 p=0.4							
04 RCT's (post -intervention)							
Dunstan A	14	7.70(1.50)	12	7.90(1.50)		14.1	-0.20[-1.36,0.96]
Dunstan B	11	8.07(2.70)	12	7.57(1.40)		5.9	0.50[-1.28,2.28]
Dunstan2	11	8.00(1.68)	10	8.30(2.21)		6.8	-0.30[-1.98,1.38]
Mourier	10	6.20(0.63)	11	7.70(1.33)		24.5	-1.50[-2.38,-0.62]
Ronnemaa2	13	8.60(1.90)	12	9.90(1.70)		9.5	-1.30[-2.71,0.11]
Wing A	10	8.00(1.26)	12	7.90(1.73)		12.0	0.10[-1.15,1.35]
Wing B	13	8.20(1.08)	15	9.00(1.16)		27.4	-0.80[-1.63,0.03]
Subtotal(95%CI)	82		84			100.0	-0.72[-1.15,-0.28]
Test for heterogeneity chi-square=6.18 df=6 p=0.23							
Test for overall effect z=3.23 p=0.001							
05 Endurance training studies (baseline)							
Dunstan A	14	8.30(1.50)	12	8.00(1.50)		17.6	0.30[-0.88,1.48]
Dunstan B	11	8.80(2.70)	12	8.10(1.40)		7.4	0.70[-1.08,2.48]
Lehmann	16	7.50(1.60)	13	7.80(1.70)		16.0	-0.30[-1.51,0.91]
Mourier	10	8.50(1.90)	11	7.40(0.99)		13.8	1.10[-0.21,2.41]
Raz	19	12.50(2.90)	19	12.40(4.00)		4.8	0.10[-2.12,2.32]
Ronnemaa2	13	9.60(1.60)	12	10.00(1.50)		16.0	-0.40[-1.62,0.82]
Wing A	10	9.70(1.58)	12	9.40(1.73)		12.3	0.30[-1.08,1.68]
Wing B	13	10.60(1.80)	15	10.90(1.94)		12.3	-0.30[-1.69,1.09]
Subtotal(95%CI)	108		108			100.0	0.15[-0.34,0.63]
Test for heterogeneity chi-square=4.20 df=7 p=0.76							
Test for overall effect z=0.60 p=0.6							



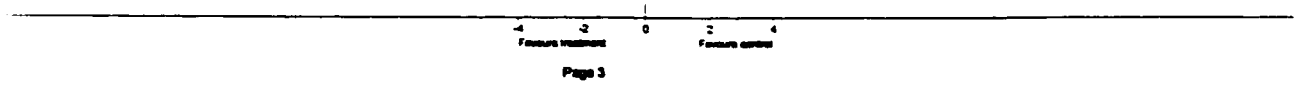
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 01 HbA1c

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
06 Endurance training studies (post-intervention)							
Dunstan A	14	7.70(1.50)	12	7.90(1.50)		12.8	-0.20[-1.36,0.96]
Dunstan B	11	8.07(2.70)	12	7.57(1.40)		5.4	0.50[-1.28,2.28]
Lehmann	16	7.50(1.80)	13	8.40(1.70)		11.7	-0.90[-2.11,0.31]
Mourier	10	6.20(0.63)	11	7.70(1.33)		22.2	-1.50[-2.38,-0.62]
Raz	19	11.70(2.60)	19	12.90(4.20)		3.5	-1.20[-3.42,1.02]
Ronnemaa2	13	8.60(1.90)	12	9.90(1.70)		8.6	-1.30[-2.71,0.11]
Wing A	10	8.00(1.26)	12	7.90(1.73)		10.9	0.10[-1.15,1.35]
Wing B	13	8.20(1.06)	15	9.00(1.16)		24.9	-0.80[-1.63,0.03]
Subtotal(95%CI)	135		136			100.0	0.06[-0.34,0.47]
Test for heterogeneity chi-square=4.71 df=9 p=0.86							
Test for overall effect z=0.30 p=0.8							
07 Resistance training studies (baseline)							
Dunstan2	11	8.20(1.66)	10	8.10(1.60)		22.7	0.10[-1.43,1.63]
Honkola	18	7.50(1.27)	20	7.70(1.34)		77.3	-0.20[-1.03,0.63]
Subtotal(95%CI)	135		136			100.0	-0.74[-1.08,-0.39]
Test for heterogeneity chi-square=0.44 df=9 p=0.49							
Test for overall effect z=4.15 p=0.00003							
08 Resistance training studies (post-intervention)							
Dunstan2	11	8.00(1.66)	10	8.30(2.21)		15.0	-0.30[-1.98,1.38]
Honkola	18	7.40(0.65)	20	8.10(1.34)		85.0	-0.70[-1.41,0.01]
Subtotal(95%CI)	82		84			100.0	0.23[-0.29,0.74]
Test for heterogeneity chi-square=3.59 df=6 p=0.73							
Test for overall effect z=0.86 p=0.4							
13 non RCT's (baseline)							
Honkola	18	7.50(1.27)	20	7.70(1.34)		62.2	-0.20[-1.03,0.63]
Lehmann	16	7.50(1.80)	13	7.80(1.70)		29.2	-0.30[-1.51,0.91]
Raz	19	12.50(2.80)	19	12.40(4.00)		8.7	0.10[-2.12,2.32]
Subtotal(95%CI)	82		84			100.0	-0.72[-1.15,-0.28]
Test for heterogeneity chi-square=6.18 df=6 p=0.23							
Test for overall effect z=3.23 p=0.001							
14 non RCT's (post-intervention)							
Honkola	18	7.40(0.65)	20	8.10(1.34)		69.4	-0.70[-1.41,0.01]
Lehmann	16	7.50(1.80)	13	8.40(1.70)		23.6	-0.90[-2.11,0.31]
Raz	19	11.70(2.60)	19	12.90(4.20)		7.0	-1.20[-3.42,1.02]
Subtotal(95%CI)	108		108			100.0	0.15[-0.34,0.63]
Test for heterogeneity chi-square=4.20 df=7 p=0.76							
Test for overall effect z=0.60 p=0.6							



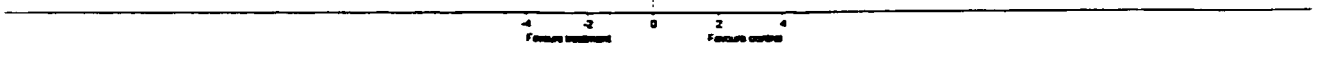
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 02 Fasting glucose

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Dunstan A	14	10.00(3.50)	12	8.90(2.60)		8.0	1.10[-1.25,3.45]
Dunstan B	11	9.60(3.30)	12	8.80(2.10)		8.5	0.80[-1.48,3.08]
Dunstan2	11	9.60(2.98)	10	9.90(3.78)		5.1	-0.30[-3.24,2.64]
Lehmann	16	9.00(3.20)	13	9.80(1.80)		12.9	-0.80[-2.85,1.05]
Mourier	10	9.20(1.28)	11	8.40(1.99)		22.1	0.80[-0.61,2.21]
Raz	19	11.40(2.30)	19	11.80(4.60)		8.2	-0.40[-2.71,1.91]
Ronnemaa2	13	11.80(3.40)	12	11.40(1.70)		10.2	0.40[-1.68,2.48]
Stanfors	6	11.00(4.40)	8	8.50(3.40)		2.5	2.50[-1.74,6.74]
Wing A	10	10.20(2.53)	12	9.90(2.77)		9.0	0.30[-1.92,2.52]
Wing B	13	11.60(2.16)	15	12.60(2.71)		13.5	-1.00[-2.81,0.81]
Subtotal(95%CI)	123		124			100.0	0.17[-0.49,0.84]
Test for heterogeneity chi-square=5.88 df=9 p=0.75							
Test for overall effect z=0.52 p=0.6							
02 All studies (post-intervention)							
Dunstan A	14	9.42(3.50)	12	8.05(2.60)		8.3	1.37[-0.98,3.72]
Dunstan B	11	9.16(3.30)	12	9.27(2.10)		8.8	-0.11[-2.39,2.17]
Dunstan2	11	9.40(2.65)	10	9.80(4.11)		5.1	-0.40[-3.39,2.58]
Lehmann	16	8.50(3.20)	13	9.30(2.52)		10.6	-0.80[-2.88,1.28]
Mourier	10	9.50(1.58)	11	8.60(1.88)		23.9	0.90[-0.49,2.29]
Raz	19	10.20(3.30)	19	12.30(4.40)		7.5	-2.10[-4.57,0.37]
Ronnemaa2	13	10.50(4.40)	12	11.20(2.20)		6.3	-0.70[-3.40,2.00]
Stanfors	6	9.60(3.40)	8	6.80(1.80)		5.1	2.80[-0.19,5.79]
Wing A	10	7.80(2.53)	12	7.80(3.12)		8.2	-0.20[-2.58,2.16]
Wing B	13	8.40(1.80)	15	9.20(2.71)		16.2	-0.80[-2.48,0.88]
Subtotal(95%CI)	123		124			100.0	0.01[-0.67,0.68]
Test for heterogeneity chi-square=10.85 df=9 p=0.29							
Test for overall effect z=0.03 p=1							
03 RCT's (baseline)							
Dunstan A	14	10.00(3.50)	12	8.90(2.60)		9.4	1.10[-1.25,3.45]
Dunstan B	11	9.60(3.30)	12	8.80(2.10)		10.0	0.80[-1.48,3.08]
Dunstan2	11	9.60(2.98)	10	9.90(3.78)		6.0	-0.30[-3.24,2.64]
Mourier	10	9.20(1.28)	11	8.40(1.99)		26.2	0.80[-0.61,2.21]
Raz	19	11.40(2.30)	19	11.80(4.60)		9.7	-0.40[-2.71,1.91]
Ronnemaa2	13	11.80(3.40)	12	11.40(1.70)		12.0	0.40[-1.68,2.48]
Wing A	10	10.20(2.53)	12	9.90(2.77)		10.6	0.30[-1.92,2.52]
Wing B	13	11.60(2.16)	15	12.60(2.71)		16.0	-1.00[-2.81,0.81]
Subtotal(95%CI)	101		103			100.0	0.26[-0.47,0.98]
Test for heterogeneity chi-square=3.61 df=7 p=0.82							
Test for overall effect z=0.69 p=0.5							
04 RCT's (post-intervention)							
Dunstan A	14	9.42(3.50)	12	8.05(2.60)		9.8	1.37[-0.98,3.72]
Dunstan B	11	9.16(3.30)	12	9.27(2.10)		10.4	-0.11[-2.39,2.17]
Dunstan2	11	9.40(2.65)	10	9.80(4.11)		6.1	-0.40[-3.39,2.58]
Mourier	10	9.50(1.58)	11	8.60(1.88)		28.3	0.90[-0.49,2.29]
Raz	19	10.20(3.30)	19	12.30(4.40)		8.9	-2.10[-4.57,0.37]
Ronnemaa2	13	10.50(4.40)	12	11.20(2.20)		7.5	-0.70[-3.40,2.00]
Wing A	10	7.80(2.53)	12	7.80(3.12)		9.8	-0.20[-2.58,2.16]
Wing B	13	8.40(1.80)	15	9.20(2.71)		19.2	-0.80[-2.48,0.88]
Subtotal(95%CI)	101		103			100.0	-0.09[-0.80,0.88]
Test for heterogeneity chi-square=6.90 df=7 p=0.44							
Test for overall effect z=0.15 p=0.9							
05 Endurance training studies (baseline)							
Dunstan A	14	10.00(3.50)	12	8.90(2.60)		8.4	1.10[-1.25,3.45]
Dunstan B	11	9.60(3.30)	12	8.80(2.10)		8.9	0.80[-1.48,3.08]
Lehmann	16	9.00(3.20)	13	9.80(1.80)		13.6	-0.80[-2.85,1.05]
Mourier	10	9.20(1.28)	11	8.40(1.99)		23.3	0.80[-0.61,2.21]
Raz	19	11.40(2.30)	19	11.80(4.60)		8.7	-0.40[-2.71,1.91]
Ronnemaa2	13	11.80(3.40)	12	11.40(1.70)		10.7	0.40[-1.68,2.48]
Stanfors	6	11.00(4.40)	8	8.50(3.40)		2.6	2.50[-1.74,6.74]
Wing A	10	10.20(2.53)	12	9.90(2.77)		9.5	0.30[-1.92,2.52]
Wing B	13	11.60(2.16)	15	12.60(2.71)		14.3	-1.00[-2.81,0.81]
Subtotal(95%CI)	112		114			100.0	0.20[-0.48,0.88]
Test for heterogeneity chi-square=5.78 df=8 p=0.67							
Test for overall effect z=0.58 p=0.6							



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 02 Fasting glucose

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (96%CI Fixed)	Weight %	WMD (96%CI Fixed)
06 Endurance training studies (post-intervention)							
Dunstan A	14	9.42(3.50)	12	8.05(2.80)		8.8	1.37[-0.98,3.72]
Dunstan B	11	9.16(3.30)	12	9.27(2.10)		9.3	-0.11[-2.39,2.17]
Lehmann	16	8.50(3.20)	13	9.30(2.52)		11.2	-0.80[-2.88,1.28]
Mourier	10	9.50(1.58)	11	8.60(1.68)		25.2	0.90[-0.49,2.29]
Raz	19	10.20(3.30)	19	12.30(4.40)		7.9	-2.10[-4.57,0.37]
Ronnemaa2	13	10.50(4.40)	12	11.20(2.20)		6.7	-0.70[-3.40,2.00]
Skarfors	6	9.60(3.40)	8	6.80(1.80)		5.4	2.80[-0.19,5.79]
Wing A	10	7.60(2.53)	12	7.80(3.12)		8.7	-0.20[-2.56,2.16]
Wing B	13	8.40(1.80)	15	9.20(2.71)		17.0	-0.80[-2.48,0.88]
Subtotal(95%CI)	123		124			100.0	0.17[-0.49,0.84]
Test for heterogeneity chi-square=5.88 df=9 p=0.75							
Test for overall effect z=0.52 p=0.6							
07 Resistance training studies (baseline)							
Dunstan2	11	9.60(2.98)	10	9.90(3.79)		100.0	-0.30[-3.24,2.64]
Subtotal(95%CI)	123		124			100.0	0.01[-0.67,0.69]
Test for heterogeneity chi-square=10.85 df=9 p=0.29							
Test for overall effect z=0.03 p=1							
08 Resistance training studies (post-intervention)							
Dunstan2	11	9.40(2.65)	10	9.80(4.11)		100.0	-0.40[-3.39,2.58]
Subtotal(95%CI)	101		103			100.0	0.25[-0.47,0.98]
Test for heterogeneity chi-square=3.81 df=7 p=0.82							
Test for overall effect z=0.69 p=0.5							

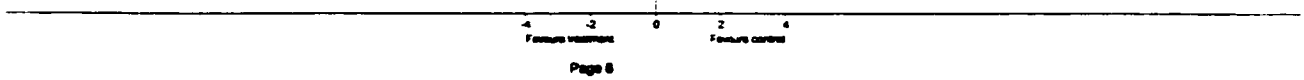


Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 03 Fasting insulin

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Dunstan A	14	13.05(5.62)	12	13.03(7.87)		31.3	0.02[-5.32,5.36]
Dunstan B	11	14.92(16.20)	12	16.72(8.87)		7.6	-1.80[-12.61,9.01]
Dunstan2	11	10.72(7.02)	10	13.77(5.53)		30.8	-3.05[-8.43,2.33]
Lehmann	16	24.97(38.60)	13	18.10(11.84)		2.5	6.87[-12.18,25.92]
Skarfors	6	17.10(11.10)	8	17.40(11.00)		6.5	-0.30[-12.00,11.40]
Wing A	10	25.17(8.96)	12	24.17(8.08)		17.2	1.00[-6.19,8.19]
Wing B	13	40.00(19.83)	15	29.17(19.36)		4.2	10.83[-3.74,25.40]
Subtotal(95%CI)	81		82			100.0	-0.29[-3.28,2.69]
Test for heterogeneity chi-square=4.00 df=6 p=0.68							
Test for overall effect z=0.19 p=0.8							
02 All studies (post-intervention)							
Dunstan A	14	11.38(5.62)	12	12.03(7.87)		28.0	-0.65[-5.99,4.69]
Dunstan B	11	13.58(16.20)	12	17.88(8.87)		6.8	-4.30[-15.11,6.51]
Dunstan2	11	10.52(6.99)	10	15.63(8.64)		23.6	-5.11[-10.93,0.71]
Lehmann	16	20.30(19.60)	13	27.50(19.47)		3.9	-7.20[-21.49,7.09]
Skarfors	6	19.40(8.00)	8	17.40(9.40)		9.6	2.00[-7.13,11.13]
Wing A	10	12.67(5.27)	12	15.50(8.08)		25.3	-2.83[-8.45,2.79]
Wing B	13	30.50(18.63)	15	29.33(27.11)		2.7	1.17[-15.88,18.22]
Subtotal(95%CI)	81		82			100.0	-2.46[-5.28,0.37]
Test for heterogeneity chi-square=2.88 df=6 p=0.82							
Test for overall effect z=1.70 p=0.09							

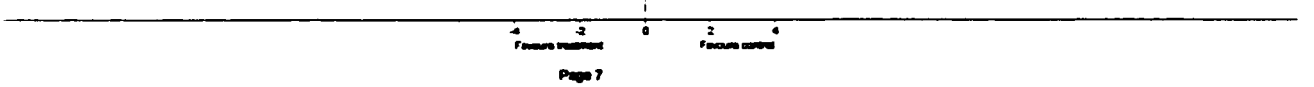
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 04 Body mass (Kg or BMI)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	SMD (95%CI Fixed)	Weight %	SMD (95%CI Fixed)
01 All studies (baseline)							
Dunstan A	14	85.70(15.00)	12	89.40(13.80)		7.0	-0.25[-1.02,0.53]
Dunstan B	11	85.60(10.60)	12	88.40(16.20)		6.3	-0.20[-1.02,0.63]
Dunstan2	11	83.60(12.27)	10	82.70(11.70)		5.7	0.07[-0.78,0.93]
Fujii	10	67.30(10.75)	15	64.60(12.78)		6.5	0.22[-0.59,1.02]
Honkola	18	67.30(20.79)	20	77.10(12.52)		9.9	0.59[-0.06,1.24]
Kaplan A	19	89.21(21.07)	19	92.16(21.78)		10.4	-0.13[-0.77,0.50]
Kaplan B	19	92.05(20.35)	19	83.87(16.90)		10.2	0.43[-0.22,1.07]
Lehmann	16	87.30(22.30)	13	86.80(13.10)		7.9	0.03[-0.71,0.76]
Mourier	10	85.30(12.33)	11	84.40(14.92)		5.7	0.06[-0.79,0.92]
Raz	19	31.80(4.60)	19	30.20(4.70)		10.3	0.34[-0.30,0.98]
Ronnemaa	13	85.20(21.63)	12	82.80(44.34)		6.6	0.07[-0.72,0.85]
Wing A	10	106.90(16.76)	12	97.40(13.16)		5.7	0.61[-0.25,1.46]
Wing B	13	104.10(21.63)	15	102.00(19.36)		7.6	0.10[-0.64,0.84]
Subtotal(95%CI)	183		189			100.0	0.16[-0.04,0.37]
Test for heterogeneity chi-square=6.62 df=12 p=0.88							
Test for overall effect z=1.56 p=0.12							
02 All studies (post-intervention)							
Dunstan A	14	83.30(15.00)	12	88.00(13.80)		7.2	-0.32[-1.09,0.46]
Dunstan B	11	83.50(10.60)	12	87.80(16.20)		6.4	-0.30[-1.12,0.52]
Dunstan2	11	83.20(12.27)	10	83.70(12.02)		5.9	-0.04[-0.90,0.82]
Fujii	10	63.90(10.75)	15	62.80(12.78)		6.8	0.09[-0.71,0.89]
Honkola	18	86.60(20.38)	20	78.80(13.42)		10.4	0.45[-0.20,1.09]
Kaplan A	18	87.95(21.07)	15	92.28(21.78)		9.2	-0.20[-0.88,0.48]
Kaplan B	16	91.42(20.35)	16	77.27(16.90)		8.4	0.74[0.02,1.46]
Lehmann	16	86.60(22.20)	13	86.80(12.50)		8.1	-0.01[-0.74,0.72]
Mourier	10	83.80(12.33)	11	84.20(15.28)		5.9	-0.03[-0.88,0.83]
Raz	19	31.50(4.30)	19	30.60(4.20)		10.7	0.21[-0.43,0.85]
Ronnemaa	13	83.20(19.47)	12	83.30(42.95)		7.1	0.00[-0.78,0.78]
Wing A	10	98.40(16.76)	12	90.10(15.51)		6.0	0.50[-0.36,1.35]
Wing B	13	94.60(20.91)	15	98.40(19.75)		7.9	-0.08[-0.82,0.67]
Subtotal(95%CI)	179		182			100.0	0.10[-0.11,0.30]
Test for heterogeneity chi-square=8.35 df=12 p=0.76							
Test for overall effect z=0.89 p=0.4							
03 RCT's (baseline)							
Dunstan A	14	85.70(15.00)	12	89.40(13.80)		8.8	-0.25[-1.02,0.53]
Dunstan B	11	85.60(10.60)	12	88.40(16.20)		7.7	-0.20[-1.02,0.63]
Dunstan2	11	83.60(12.27)	10	82.70(11.70)		7.1	0.07[-0.78,0.93]
Kaplan A	19	89.21(21.07)	19	92.16(21.78)		12.8	-0.13[-0.77,0.50]
Kaplan B	19	92.05(20.35)	19	83.87(16.90)		12.5	0.43[-0.22,1.07]
Lipkenberg A	30	30.80(4.00)	28	31.20(3.30)		19.5	-0.11[-0.62,0.41]
Mourier	10	85.30(12.33)	11	84.40(14.82)		7.1	0.06[-0.79,0.92]
Ronnemaa	13	85.20(21.63)	12	82.80(44.34)		8.4	0.07[-0.72,0.85]
Wing A	10	106.90(16.76)	12	97.40(13.16)		7.0	0.61[-0.25,1.46]
Wing B	13	104.10(21.63)	15	102.00(19.36)		8.4	0.10[-0.64,0.84]
Subtotal(95%CI)	150		150			100.0	0.05[-0.18,0.27]
Test for heterogeneity chi-square=4.58 df=9 p=0.87							
Test for overall effect z=0.40 p=0.7							
04 RCT's (post-intervention)							
Dunstan A	14	83.30(15.00)	12	88.00(13.80)		11.3	-0.32[-1.09,0.46]
Dunstan B	11	83.50(10.60)	12	87.80(16.20)		10.0	-0.30[-1.12,0.52]
Dunstan2	11	83.20(12.27)	10	83.70(12.02)		9.3	-0.04[-0.90,0.82]
Kaplan A	18	87.95(21.07)	15	92.28(21.78)		14.4	-0.20[-0.88,0.48]
Kaplan B	16	91.42(20.35)	16	77.27(16.90)		13.1	0.74[0.02,1.46]
Mourier	10	83.80(12.33)	11	84.20(15.28)		9.3	-0.03[-0.88,0.83]
Ronnemaa	13	83.20(19.47)	12	83.30(42.95)		11.0	0.00[-0.78,0.78]
Wing A	10	98.40(16.76)	12	90.10(15.51)		9.3	0.50[-0.36,1.35]
Wing B	13	94.60(20.91)	15	98.40(19.75)		12.3	-0.08[-0.82,0.67]
Subtotal(95%CI)	116		115			100.0	0.03[-0.23,0.29]
Test for heterogeneity chi-square=6.79 df=9 p=0.66							
Test for overall effect z=0.25 p=0.8							
05 Endurance training studies (baseline)							
Dunstan A	14	85.70(15.00)	12	89.40(13.80)		8.4	-0.25[-1.02,0.53]
Dunstan B	11	85.60(10.60)	12	88.40(16.20)		7.5	-0.20[-1.02,0.63]



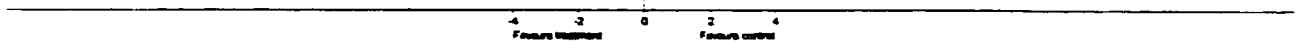
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 04 Body mass (Kg or BMI)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	SMD (95%CI Fixed)	Weight %	SMD (95%CI Fixed)
05 Endurance training studies (baseline)							
Fujii	10	67.30(3.40)	15	64.60(3.30)		7.2	0.78[-0.05,1.62]
Kaplan A	19	88.21(21.07)	19	92.16(21.78)		12.4	-0.13[-0.77,0.50]
Kaplan B	19	92.05(20.35)	19	83.87(16.80)		12.1	0.43[-0.22,1.07]
Lehmann	16	87.30(22.30)	13	86.80(13.10)		9.4	0.03[-0.71,0.76]
Mourier	10	85.30(12.33)	11	84.40(14.92)		6.8	0.06[-0.79,0.92]
Raz	19	31.80(4.60)	19	30.20(4.70)		12.2	0.34[-0.30,0.98]
Ronnemaa	13	85.20(21.63)	12	82.50(44.34)		8.2	0.07[-0.72,0.85]
Wing A	10	106.90(16.76)	12	97.40(13.16)		6.7	0.61[-0.25,1.48]
Wing B	13	104.10(21.63)	15	102.00(19.36)		9.1	0.10[-0.64,0.84]
Subtotal(95%CI)	163		189			100.0	0.16[-0.04,0.37]
Test for heterogeneity chi-square=6.62 df=12 p=0.88							
Test for overall effect z=1.56 p=0.12							
06 Endurance training studies (post-intervention)							
Dunstan A	14	83.30(15.00)	12	88.00(13.60)		8.6	-0.32[-1.09,0.46]
Dunstan B	11	83.50(10.60)	12	87.80(16.20)		7.7	-0.30[-1.12,0.52]
Fuja	10	63.90(10.75)	15	62.80(12.78)		8.1	0.09[-0.71,0.89]
Kaplan A	18	87.95(21.07)	15	92.28(21.78)		11.0	-0.20[-0.88,0.49]
Kaplan B	16	91.42(20.35)	16	77.27(16.80)		10.0	0.74[0.02,1.46]
Lehmann	16	86.60(22.20)	13	86.50(12.50)		9.7	-0.01[-0.74,0.72]
Mourier	10	83.80(12.33)	11	84.20(15.28)		7.1	-0.03[-0.88,0.83]
Raz	19	31.50(4.30)	19	30.60(4.20)		12.8	0.21[-0.43,0.85]
Ronnemaa	13	83.20(19.47)	12	83.30(42.95)		8.4	0.00[-0.78,0.78]
Wing A	10	98.40(16.76)	12	90.10(15.51)		7.1	0.50[-0.38,1.35]
Wing B	13	94.80(20.91)	15	98.40(19.75)		9.4	-0.09[-0.82,0.67]
Subtotal(95%CI)	179		182			100.0	0.10[-0.11,0.30]
Test for heterogeneity chi-square=8.35 df=12 p=0.76							
Test for overall effect z=0.89 p=0.4							
07 Resistance training studies (baseline)							
Dunstan2	11	83.60(12.27)	10	82.70(11.70)		36.7	0.07[-0.78,0.93]
Honkola	18	87.30(20.79)	20	77.10(12.52)		63.3	0.58[-0.08,1.24]
Subtotal(95%CI)	150		150			100.0	0.35[-0.18,0.27]
Test for heterogeneity chi-square=4.58 df=9 p=0.87							
Test for overall effect z=0.40 p=0.7							
08 Resistance training studies (post-intervention)							
Dunstan2	11	83.20(12.27)	10	83.70(12.02)		36.2	-0.04[-0.90,0.82]
Honkola	18	88.60(20.39)	20	78.80(13.42)		63.8	0.45[-0.20,1.08]
Subtotal(95%CI)	116		115			100.0	0.03[-0.23,0.29]
Test for heterogeneity chi-square=6.79 df=6 p=0.58							
Test for overall effect z=0.25 p=0.8							



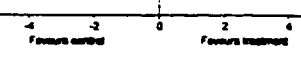
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 05 Abdominal obesity (WHR or waist circumference)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	SMD (96%CI Fixed)	Weight %	SMD (96%CI Fixed)
01 All studies (baseline)							
Dunstan2	11	0.98(0.03)	10	1.03(0.32)		29.6	-0.22[-1.08,0.64]
Lehmann	16	0.96(0.11)	13	0.98(0.12)		40.6	-0.17[-0.90,0.56]
Mourier	10	0.97(0.08)	11	0.97(0.07)		29.8	0.00[-0.86,0.86]
Subtotal(95%CI)	37		34			100.0	-0.13[-0.60,0.33]
Test for heterogeneity chi-square=0.14 df=2 p=0.93							
Test for overall effect z=0.56 p=0.6							
02 All studies (post-intervention)							
Dunstan2	11	0.98(0.03)	10	1.03(0.32)		30.2	-0.22[-1.08,0.64]
Lehmann	16	0.92(0.10)	13	0.98(0.11)		39.8	-0.56[-1.31,0.19]
Mourier	10	0.94(0.06)	11	0.96(0.07)		30.0	-0.29[-1.16,0.57]
Subtotal(95%CI)	37		34			100.0	-0.38[-0.85,0.10]
Test for heterogeneity chi-square=0.39 df=2 p=0.82							
Test for overall effect z=1.56 p=0.12							



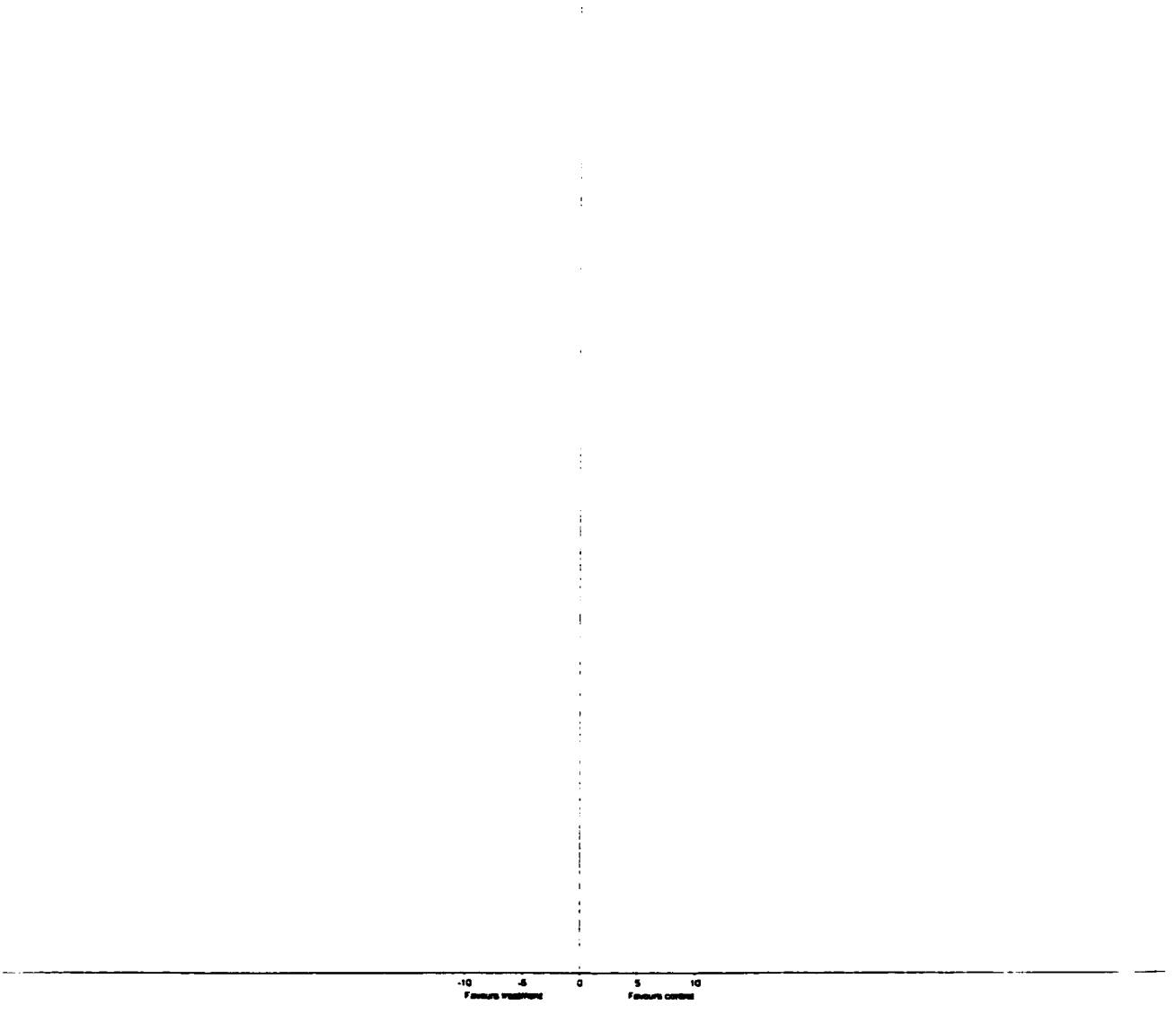
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 06 VO2 max

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	SMD (95%CI Random)	Weight %	SMD (95%CI Random)
01 Endurance training studies (baseline)							
Dunstan A	14	21.50(3.90)	12	25.40(7.80)		13.4	-0.62[-1.41,0.17]
Dunstan B	11	22.30(3.10)	12	22.60(4.70)		12.6	-0.07[-0.89,0.75]
Mourier	10	23.00(3.79)	11	22.60(4.64)		11.5	0.09[-0.77,0.95]
Ronnemaa2	13	26.70(6.50)	12	25.80(6.30)		13.6	0.14[-0.65,0.92]
Skarfors	6	2100.00(287.00)	8	2330.00(172.00)		6.4	-0.99[-2.14,0.15]
Vanninen A	21	24.10(5.80)	24	24.70(5.70)		24.5	-0.10[-0.69,0.48]
Vanninen B	17	18.90(3.90)	16	18.70(5.40)		18.0	0.04[-0.64,0.72]
Subtotal(95%CI)	92		95			100.0	-0.14[-0.44,0.15]
Test for heterogeneity chi-square=4.62 df=6 p=0.59							
Test for overall effect z=0.98 p=0.3							
02 Endurance training studies (post-intervention)							
Dunstan A	14	23.89(3.90)	12	24.89(7.90)		15.2	-0.16[-0.93,0.61]
Dunstan B	11	24.75(3.10)	12	22.65(4.70)		14.2	0.50[-0.33,1.34]
Mourier	10	32.40(4.11)	11	23.00(4.97)		10.6	1.97[0.89,3.05]
Ronnemaa2	13	29.30(6.20)	12	25.90(6.70)		14.7	0.51[-0.29,1.31]
Skarfors	6	2430.00(300.00)	8	2057.00(308.00)		9.5	1.15[-0.02,2.32]
Vanninen A	21	24.80(6.90)	24	23.90(5.40)		18.9	0.14[-0.44,0.73]
Vanninen B	17	19.40(3.60)	16	18.20(4.70)		16.9	0.28[-0.41,0.97]
Subtotal(95%CI)	92		95			100.0	0.51[0.07,0.96]
Test for heterogeneity chi-square=12.63 df=6 p=0.049							
Test for overall effect z=2.27 p=0.02							
03 Endurance training studies (>70% VO2 max)(baseline)							
Mourier	10	23.00(3.79)	11	22.60(4.64)		56.4	0.09[-0.77,0.95]
Skarfors	6	2100.00(287.00)	8	2330.00(172.00)		43.6	-0.99[-2.14,0.15]
Subtotal(95%CI)	16		19			100.0	-0.36[-1.44,0.67]
Test for heterogeneity chi-square=2.21 df=1 p=0.14							
Test for overall effect z=0.71 p=0.5							
04 Endurance training studies (> 70% VO2 max) (post-intervention)							
Mourier	10	32.40(4.11)	11	23.00(4.97)		53.9	1.97[0.89,3.05]
Skarfors	6	2430.00(300.00)	8	2057.00(308.00)		46.1	1.15[-0.02,2.32]
Subtotal(95%CI)	16		19			100.0	1.59[0.79,2.39]
Test for heterogeneity chi-square=1.01 df=1 p=0.31							
Test for overall effect z=3.90 p=0.00010							
05 Endurance training studies (< or = 70% VO2 max)(baseline)							
Dunstan A	14	21.50(3.90)	12	25.40(7.80)		16.3	-0.62[-1.41,0.17]
Dunstan B	11	22.30(3.10)	12	22.60(4.70)		15.3	-0.07[-0.89,0.75]
Ronnemaa2	13	26.70(6.50)	12	25.80(6.30)		16.6	0.14[-0.65,0.92]
Vanninen A	21	24.10(5.80)	24	24.70(5.70)		29.8	-0.10[-0.69,0.48]
Vanninen B	17	18.90(3.90)	16	18.70(5.40)		22.0	0.04[-0.64,0.72]
Subtotal(95%CI)	76		76			100.0	-0.11[-0.43,0.21]
Test for heterogeneity chi-square=2.16 df=4 p=0.7							
Test for overall effect z=0.68 p=0.5							
06 Endurance training studies (< or = 70% VO2 max) (post-intervention)							
Dunstan A	14	23.89(3.90)	12	24.89(7.90)		17.3	-0.16[-0.93,0.61]
Dunstan B	11	24.75(3.10)	12	22.65(4.70)		14.8	0.50[-0.33,1.34]
Ronnemaa2	13	29.30(6.20)	12	25.90(6.70)		16.1	0.51[-0.29,1.31]
Vanninen A	21	24.80(6.90)	24	23.90(5.40)		29.8	0.14[-0.44,0.73]
Vanninen B	17	19.40(3.60)	16	18.20(4.70)		21.9	0.28[-0.41,0.97]
Subtotal(95%CI)	76		76			100.0	0.23[-0.08,0.55]
Test for heterogeneity chi-square=1.97 df=4 p=0.74							
Test for overall effect z=1.43 p=0.15							



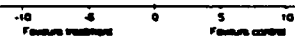
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 08 Resting Heart Rate

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Dunstan2	11	77.00(9.85)	10	78.00(11.70)		5.3	-1.00[-10.34,8.34]
Lehmann	16	81.00(3.00)	13	78.00(4.00)		66.5	3.00[0.38,5.62]
Raz	19	80.00(13.60)	19	78.30(12.30)		6.7	1.70[-6.55,9.95]
Vanninen A	21	64.00(9.17)	27	65.00(10.39)		14.9	-1.00[-6.54,4.54]
Vanninen B	18	69.00(12.73)	17	67.00(12.37)		6.6	2.00[-6.32,10.32]
Subtotal(95%CI)	85		86			100.0	2.04[-0.10,4.18]
Test for heterogeneity chi-square=2.06 df=4 p=0.72							
Test for overall effect z=1.87 p=0.06							
02 All studies (post-intervention)							
Dunstan2	11	76.00(8.29)	10	79.00(7.91)		8.5	-3.00[-9.93,3.93]
Lehmann	16	74.00(4.00)	13	77.00(3.00)		63.1	-3.00[-5.55,-0.45]
Raz	19	72.40(12.10)	19	78.20(12.30)		6.8	-5.80[-13.56,1.96]
Vanninen A	21	64.00(9.17)	27	65.00(10.39)		13.3	-1.00[-6.54,4.54]
Vanninen B	18	64.00(8.49)	17	68.00(12.37)		8.2	-4.00[-11.07,3.07]
Subtotal(95%CI)	85		86			100.0	-3.01[-5.03,-0.98]
Test for heterogeneity chi-square=1.08 df=4 p=0.9							
Test for overall effect z=2.91 p=0.004							



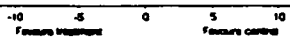
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 09 skinfolds

Study	Treatment n	mean(sd)	Control n	mean(sd)	SMD (95%CI Random)	Weight %	SMD (95%CI Random)
01 Endurance training studies (baseline)							
Mourier	10	46.30(3.30)	11	57.20(4.10)		100.0	-2.80[-4.07,-1.53]
Subtotal(95%CI)	10		11			100.0	-2.80[-4.07,-1.53]
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=4.31 p=0.00002							
02 Endurance training studies (post-intervention)							
Mourier	10	45.90(4.20)	11	55.00(3.20)		100.0	-2.36[-3.52,-1.19]
Subtotal(95%CI)	10		11			100.0	-2.36[-3.52,-1.19]
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=3.98 p=0.00007							
03 Resistance training studies (baseline)							
Dunstan2	11	155.40(62.35)	10	186.50(55.97)		100.0	-0.50[-1.38,0.37]
Subtotal(95%CI)	11		10			100.0	-0.50[-1.38,0.37]
Test for heterogeneity chi-square=0.00 df=0 p=1							
Test for overall effect z=1.13 p=0.3							
04 Resistance training studies (post-intervention)							
Dunstan2	11	158.80(58.37)	10	190.80(51.55)		100.0	-0.56[-1.43,0.32]
Subtotal(95%CI)	11		10			100.0	-0.56[-1.43,0.32]
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=1.24 p=0.2							



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 10 Percent fat

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
01 Endurance training studies (baseline)							
Lehmann	16	35.30(7.20)	13	33.40(7.50)		45.2	1.90[-3.48,7.28]
Mourier	10	24.40(3.47)	11	29.50(4.31)		54.8	-5.10[-8.43,-1.77]
Subtotal(95%CI)	26		24			100.0	-1.93[-8.78,4.86]
Test for heterogeneity chi-square=4.68 df=1 p=0.03							
Test for overall effect z=0.56 p=0.6							
02 Endurance training studies (post-intervention)							
Lehmann	16	33.00(8.00)	13	32.90(7.30)		37.3	0.10[-5.48,5.68]
Mourier	10	23.80(3.16)	11	28.20(4.64)		62.7	-4.40[-7.77,-1.03]
Subtotal(95%CI)	26		24			100.0	-2.72[-6.99,1.54]
Test for heterogeneity chi-square=1.83 df=1 p=0.18							
Test for overall effect z=1.25 p=0.2							
03 Resistance training studies (baseline)							
Subtotal(95%CI)	0		0			0.0	Not Estimable
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.0 p=1							
04 Resistance training studies (post-intervention)							
Subtotal(95%CI)	0		0			0.0	Not Estimable
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.0 p=1							



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 11 Lean body mass

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 Endurance training studies (baseline)							
Lehmann	16	55.50(11.50)	13	54.60(7.70)		100.0	0.90[-6.12,7.92]
Subtotal(95%CI)	16		13			100.0	0.90[-6.12,7.92]
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.25 p=0.8							
02 Endurance training studies (post-intervention)							
Lehmann	16	56.60(10.40)	13	55.10(7.90)		100.0	1.50[-5.16,8.16]
Subtotal(95%CI)	16		13			100.0	1.50[-5.16,8.16]
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.44 p=0.7							
03 Resistance training studies (baseline)							
Subtotal(95%CI)	0		0			0.0	Not Estimable
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.0 p=1							
04 Resistance training studies (post-intervention)							
Subtotal(95%CI)	0		0			0.0	Not Estimable
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.0 p=1							

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 12 maximal work capacity

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	SMD (98%CI Random)	Weight %	SMD (98%CI Random)
01 all studies (baseline)							
Mourier	10	161.00(6.00)	11	139.00(8.00)		46.5	2.97[1.65,4.28]
Raz	19	86.70(22.60)	19	69.20(22.10)		53.5	0.77[0.11,1.43]
Subtotal(95%CI)	29		30			100.0	1.79[-0.36,3.94]
Test for heterogeneity chi-square=8.59 df=1 p=0.0034							
Test for overall effect z=1.63 p=0.10							
02 all studies (post-intervention)							
Mourier	10	220.00(13.00)	11	139.00(9.00)		47.8	7.02[4.51,9.53]
Raz	19	99.70(24.60)	19	71.20(24.50)		52.2	1.14[0.45,1.83]
Subtotal(95%CI)	29		30			100.0	3.95[-1.61,9.71]
Test for heterogeneity chi-square=19.67 df=1 p<0.00001							
Test for overall effect z=1.34 p=0.18							

-10 -5 0 5 10
Favours treatment Favours control

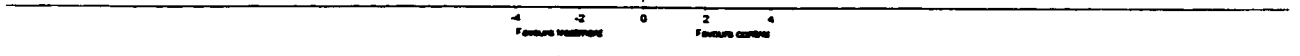
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 13 VO2 at anaerobic threshold

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 all studies (baseline)							
Vanninen A	21	14.50(3.40)	24	14.40(2.80)		53.8	0.10[-1.76,1.96]
Vanninen B	17	12.70(2.50)	16	12.80(3.30)		46.2	-0.10[-2.11,1.91]
Subtotal(95%CI)	38		40			100.0	0.01[-1.36,1.37]
Test for heterogeneity chi-square=0.02 df=1 p=0.89							
Test for overall effect z=0.01 p=1							
02 all studies (post-intervention)							
Vanninen A	21	15.10(4.10)	24	15.00(3.20)		40.3	0.10[-2.07,2.27]
Vanninen B	17	12.80(2.40)	16	12.60(2.80)		59.7	0.20[-1.58,1.98]
Subtotal(95%CI)	38		40			100.0	0.16[-1.22,1.54]
Test for heterogeneity chi-square=0.00 df=1 p=0.94							
Test for overall effect z=0.23 p=0.8							

-10 -5 0 5 10
Favours treatment Favours control

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 01 Exercise vs Non-exercise control
Outcome: 14 Blood pressure

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 Systolic, all studies (baseline)							
Agurs-Collins	32	144.00(17.00)	32	139.00(14.00)		22.6	5.00[-2.63,12.63]
Dunstan A	14	133.00(17.40)	12	131.00(15.30)		8.3	2.00[-10.57,14.57]
Dunstan B	11	124.00(11.90)	12	114.00(13.80)		11.8	10.00[-0.55,20.55]
Dunstan2	11	126.00(9.95)	10	130.00(12.65)		13.7	-4.00[-13.80,5.80]
Honkola	18	150.00(12.73)	20	155.00(13.42)		19.0	-5.00[-13.32,3.32]
Wing A	10	137.00(9.49)	12	140.00(10.39)		19.0	-3.00[-11.32,5.32]
Wing B	13	132.00(18.03)	15	141.00(23.24)		5.6	-9.00[-24.31,6.31]
Subtotal(95%CI)	109		113			100.0	-0.10[-3.72,3.53]
Test for heterogeneity chi-square=9.05 df=6 p=0.17							
Test for overall effect z=0.05 p=1							
02 Systolic, all studies (post-intervention)							
Agurs-Collins	31	144.00(21.00)	27	148.00(24.00)		17.0	-4.00[-15.69,7.69]
Dunstan2	11	127.00(9.95)	10	127.00(12.65)		24.1	0.00[-9.80,9.80]
Honkola	18	145.00(16.97)	20	148.00(17.89)		18.9	-3.00[-14.09,8.09]
Wing A	10	126.00(6.32)	12	127.00(13.86)		30.2	-1.00[-9.77,7.77]
Wing B	13	130.00(18.03)	15	135.00(23.24)		9.9	-5.00[-20.31,10.31]
Subtotal(95%CI)	83		84			100.0	-2.04[-6.85,2.77]
Test for heterogeneity chi-square=0.50 df=4 p=0.97							
Test for overall effect z=0.83 p=0.4							
03 Diastolic, all studies (baseline)							
Agurs-Collins	32	79.00(10.00)	32	77.00(10.00)		19.2	2.00[-2.90,6.90]
Dunstan A	14	74.00(10.50)	12	74.00(7.10)		9.9	0.00[-6.81,6.81]
Dunstan B	11	72.00(6.40)	12	68.00(9.80)		10.2	4.00[-2.71,10.71]
Dunstan2	11	73.00(6.63)	10	72.00(8.32)		15.0	1.00[-4.54,6.54]
Honkola	18	86.00(4.24)	20	83.00(8.94)		24.0	3.00[-1.38,7.38]
Wing A	10	86.00(6.32)	12	87.00(6.93)		15.0	-1.00[-6.54,4.54]
Wing B	13	80.00(10.82)	15	84.00(11.62)		6.7	-4.00[-12.32,4.32]
Subtotal(95%CI)	109		113			100.0	1.25[-0.90,3.38]
Test for heterogeneity chi-square=3.65 df=6 p=0.72							
Test for overall effect z=1.14 p=0.3							
04 Diastolic, all studies (post-intervention)							
Agurs-Collins	31	78.00(10.00)	27	79.00(8.00)		26.3	-1.00[-5.64,3.64]
Dunstan2	11	73.00(6.63)	10	72.00(8.32)		18.4	1.00[-4.54,6.54]
Honkola	18	83.00(8.49)	20	78.00(8.94)		18.4	5.00[-0.54,10.54]
Wing A	10	80.00(6.32)	12	79.00(3.48)		29.5	1.00[-3.38,5.38]
Wing B	13	83.00(7.21)	15	85.00(15.48)		7.4	-2.00[-10.76,6.76]
Subtotal(95%CI)	83		84			100.0	0.98[-1.39,3.37]
Test for heterogeneity chi-square=3.16 df=4 p=0.53							
Test for overall effect z=0.82 p=0.4							



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 02 Others
Outcome: 01 age

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	32	62.40(5.80)	32	61.00(5.70)		13.1	1.40[-1.44,4.24]
Dunstan A	14	52.60(7.20)	12	54.10(8.20)		3.0	-1.50[-7.48,4.48]
Dunstan B	11	52.30(8.30)	12	53.00(7.00)		2.7	-0.70[-7.00,5.60]
Dunstan2	11	50.30(6.63)	10	51.10(6.98)		3.1	-0.80[-6.63,5.03]
Fuji	10	38.20(4.70)	15	40.30(7.20)		4.9	-2.10[-6.77,2.57]
Honkote	18	62.00(8.49)	20	67.00(8.94)		3.4	-5.00[-10.54,0.54]
Kaplan A	19	53.81(8.04)	19	54.50(8.83)		3.7	-0.69[-6.06,4.68]
Kaplan B	19	56.96(8.95)	19	54.87(12.32)		2.3	2.09[-4.76,8.94]
Mourier	10	45.00(6.32)	11	46.00(9.95)		2.1	-1.00[-8.07,6.07]
Raz	19	56.70(6.20)	19	56.50(6.70)		6.3	0.20[-3.90,4.30]
Skarfors	8	59.00(1.40)	8	59.30(1.60)		48.8	-0.30[-1.77,1.17]
Wing A	10	56.20(7.50)	12	52.50(8.90)		2.3	3.70[-3.15,10.55]
Wing B	15	56.10(6.40)	15	55.10(7.20)		4.5	1.00[-3.88,5.88]
Total(95%CI)	196		204			100.0	-0.18[-1.21,0.84]

Test for heterogeneity chi-square=7.02 df=12 p=0.86
Test for overall effect z=0.35 p=0.7

-10 -5 0 5 10
Favours treatment Favours control

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 02 Others
Outcome: 03 duration of diabetes (baseline)

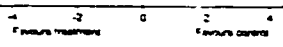
Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Dunstan A	14	6.80(5.10)	12	3.70(3.00)		11.6	3.10[-0.07,6.27]
Dunstan B	11	3.80(3.20)	12	4.40(4.10)		13.0	-0.60[-3.59,2.39]
Dunstan2	11	5.30(4.64)	10	5.10(3.79)		8.9	0.20[-3.41,3.81]
Honkola	18	8.00(8.49)	20	8.00(8.94)		3.8	0.00[-5.54,5.54]
Lqtenberg A	30	6.60(4.60)	28	9.40(7.30)		11.6	-2.80[-5.97,0.37]
Lqtenberg B	30	6.60(4.60)	28	9.40(7.30)		11.6	-2.80[-5.97,0.37]
Lqtenberg C	30	6.60(4.60)	28	9.40(7.30)		11.6	-2.80[-5.97,0.37]
Skarnes	8	2.90(2.80)	8	2.30(3.10)		13.9	0.60[-2.29,3.49]
Wing A	10	4.30(3.50)	12	4.80(6.30)		7.2	-0.50[-4.53,3.53]
Wing B	15	7.00(5.30)	15	7.00(6.10)		6.9	0.00[-4.09,4.09]
Total(95%CI)	177		173			100.0	-0.63[-1.73,0.45]

Test for heterogeneity chi-square=11.79 df=9 p=0.23
Test for overall effect z=1.14 p=0.3

-10 -5 0 5 10
Favours treatment Favours control

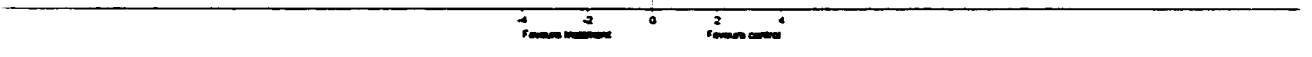
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 03 Exercise + Diet vs Non-exercise control
Outcome: 01 HbA1c

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Agurs-Collins	32	11.00(1.70)	32	10.00(1.90)		43.4	1.00[-0.12,1.88]
Vanninen A	21	7.10(1.50)	24	7.30(1.70)		38.7	-0.20[-1.13,0.73]
Vanninen B	17	7.10(1.50)	16	8.10(2.40)		17.9	-1.00[-2.38,0.38]
Subtotal(95%CI)	70		72			100.0	0.18[-0.40,0.76]
Test for heterogeneity chi-square=6.77 df=2 p=0.034							
Test for overall effect: z=0.60 p=0.6							
02 All studies (post-intervention)							
Agurs-Collins	31	9.50(1.80)	27	10.30(1.90)		34.0	-0.80[-1.76,0.16]
Vanninen A	21	7.00(1.90)	24	7.40(1.60)		29.0	-0.40[-1.43,0.63]
Vanninen B	17	6.20(1.00)	16	7.20(1.60)		37.0	-1.00[-1.92,-0.08]
Subtotal(95%CI)	69		67			100.0	-0.76[-1.32,-0.20]
Test for heterogeneity chi-square=0.74 df=2 p=0.69							
Test for overall effect: z=2.66 p=0.008							



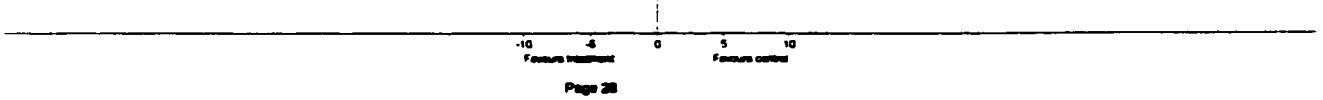
Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 03 Exercise + Diet vs Non-exercise control
Outcome: 02 Fasting glucose

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Vanninen A	21	6.60(2.10)	24	6.30(1.20)		79.6	0.30[-0.72,1.32]
Vanninen B	17	6.70(2.20)	16	8.50(3.50)		20.4	-1.80[-3.81,0.21]
Subtotal(95%CI)	38		40			100.0	-0.13[-1.04,0.78]
Test for heterogeneity chi-square=3.34 df=1 p=0.068							
Test for overall effect z=0.28 p=0.8							
02 All studies (post-intervention)							
Vanninen A	21	6.70(2.10)	24	5.70(1.40)		63.6	1.00[-0.06,2.06]
Vanninen B	17	7.30(2.20)	16	7.20(1.90)		36.4	0.10[-1.30,1.50]
Subtotal(95%CI)	38		40			100.0	0.67[-0.17,1.52]
Test for heterogeneity chi-square=1.01 df=1 p=0.31							
Test for overall effect z=1.56 p=0.12							



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 03 Exercise + Diet vs Non-exercise control
Outcome: 03 Fasting Insulin

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
01 All studies (baseline)							
Vanninen A	21	27.83(12.67)	24	31.17(29.70)		34.2	-3.34[-16.40,9.72]
Vanninen B	17	28.17(11.50)	16	29.17(15.67)		65.8	-1.00[-10.43,8.43]
Subtotal(95%CI)	38		40			100.0	-1.80[-9.44,5.84]
Test for heterogeneity chi-square=0.08 df=1 p=0.78							
Test for overall effect z=0.46 p=0.6							
02 All studies (post-intervention)							
Vanninen A	21	21.67(16.00)	24	23.17(16.50)		39.5	-1.50[-11.01,8.01]
Vanninen B	17	21.67(8.50)	16	25.67(13.33)		60.5	-4.00[-11.68,3.68]
Subtotal(95%CI)	38		40			100.0	-3.01[-8.99,2.96]
Test for heterogeneity chi-square=0.16 df=1 p=0.69							
Test for overall effect z=0.99 p=0.3							

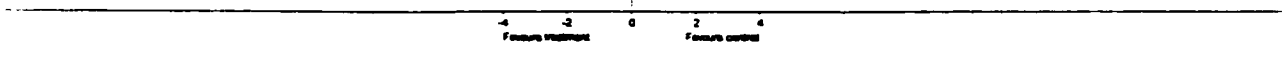


Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 03 Exercise + Diet vs Non-exercise control
Outcome: 04 Body mass (Kg or BMI)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	SMD (95%CI Fixed)	Weight %	SMD (95%CI Fixed)
01 All studies (baseline)							
Agurs-Collins	32	93.30(18.60)	32	94.90(20.10)		45.3	-0.08[-0.57,0.41]
Vanninen A	21	31.10(3.70)	24	30.10(3.10)		31.4	0.29[-0.30,0.88]
Vanninen B	17	33.40(6.70)	16	34.20(6.20)		23.3	-0.12[-0.80,0.56]
Subtotal(95%CI)	70		72			100.0	0.03[-0.30,0.36]
Test for heterogeneity chi-square=1.13 df=2 p=0.57							
Test for overall effect z=0.15 p=0.9							
02 All studies (post-intervention)							
Agurs-Collins	31	90.60(20.30)	27	96.20(21.20)		42.5	-0.26[-0.78,0.26]
Vanninen A	21	30.50(3.60)	24	30.90(3.30)		33.2	-0.11[-0.70,0.47]
Vanninen B	17	32.60(6.50)	16	34.00(5.90)		24.3	-0.22[-0.90,0.47]
Subtotal(95%CI)	69		67			100.0	-0.20[-0.54,0.14]
Test for heterogeneity chi-square=0.13 df=2 p=0.94							
Test for overall effect z=1.16 p=0.2							

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 03 Exercise + Diet vs Non-exercise control
Outcome: 05 Abdominal obesity (WHR or waist circumference)

Study	Treatment n	mean(sd)	Control n	mean(sd)	SMD (95%CI Fixed)	Weight %	SMD (95%CI Fixed)
01 All studies (baseline)							
Ajuru-Collins	32	0.94(0.08)	32	0.92(0.08)		100.0	0.28[-0.21,0.77]
Subtotal(95%CI)	32		32			100.0	0.28[-0.21,0.77]
Test for heterogeneity chi-square=0.00 df=0 p=1							
Test for overall effect z=1.11 p=0.3							
02 All studies (post-intervention)							
Ajuru-Collins	29	0.94(0.09)	27	0.92(0.08)		100.0	0.26[-0.27,0.78]
Subtotal(95%CI)	29		27			100.0	0.26[-0.27,0.78]
Test for heterogeneity chi-square=0.0 df=0							
Test for overall effect z=0.95 p=0.3							



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 10 Total Cholesterol (mmol/L)
Outcome: 01 baseline

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	32	6.47(1.02)	32	6.16(1.28)		5.9	0.31[-0.25,0.87]
Honkola	18	6.00(1.27)	20	6.10(1.34)		2.7	-0.10[-0.93,0.73]
Kaplan2a	16	5.09(1.18)	16	5.38(1.63)		1.9	-0.29[-1.28,0.70]
Kaplan2b	18	5.22(0.90)	15	4.86(1.19)		3.5	0.36[-0.37,1.09]
* Lehmann	16	5.60(0.80)	13	0.00(0.00)		0.0	Not Estimable
Raz	19	5.70(1.00)	19	6.00(1.10)		4.2	-0.30[-0.97,0.37]
Ronnemaa	13	6.74(0.97)	12	6.20(1.28)		2.3	0.54[-0.36,1.44]
Skarfors	6	6.09(0.88)	8	5.96(0.86)		2.2	0.13[-0.79,1.05]
Vanninen A	21	6.30(1.20)	24	6.10(1.00)		4.4	0.20[-0.45,0.85]
Vanninen B	17	6.00(1.20)	16	6.50(0.80)		3.9	-0.50[-1.19,0.19]
Wing A	10	5.51(0.42)	12	5.80(0.23)		22.0	-0.29[-0.58,0.00]
Wing B	13	4.86(0.31)	15	4.78(0.21)		47.0	0.08[-0.12,0.28]
Total(95%CI)	199		202			100.0	-0.01[-0.15,0.13]

Test for heterogeneity chi-square=11.51 df=10 p=0.32
Test for overall effect z=0.16 p=0.9

-10 -5 0 5 10
Favours treatment Favours control

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 10 Total Cholesterol (mmol/L)
Outcome: 02 post treatment

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	32	5.87(0.93)	32	5.98(1.01)		5.1	-0.11[-0.58,0.37]
Honkola	18	5.30(1.27)	20	5.90(1.34)		1.7	-0.60[-1.43,0.23]
Kaplan2a	16	5.17(1.03)	16	4.98(1.42)		1.6	0.18[-0.68,1.04]
Kaplan2b	18	5.33(1.08)	15	4.89(0.94)		2.4	0.44[-0.25,1.13]
x Lehmann	16	5.60(0.80)	13	0.00(0.00)		0.0	Not Estimable
Raz	19	5.60(1.00)	19	6.00(1.00)		2.8	-0.40[-1.04,0.24]
Ronnemaa	13	6.37(0.90)	12	6.10(1.00)		2.1	0.27[-0.48,1.02]
Skarfors	6	5.81(0.79)	8	5.96(0.92)		1.4	-0.15[-1.05,0.75]
Vanninen A	21	6.00(1.00)	24	6.20(1.00)		3.4	-0.20[-0.79,0.39]
Vanninen B	17	6.00(1.00)	16	6.70(0.70)		3.4	-0.70[-1.29,-0.11]
Wing A	10	5.33(0.31)	12	5.12(0.18)		24.3	0.21[-0.01,0.43]
Wing B	13	4.21(0.23)	15	4.44(0.16)		51.9	-0.23[-0.38,-0.08]
Total(95%CI)	199		202			100.0	-0.11[-0.22,0.00]

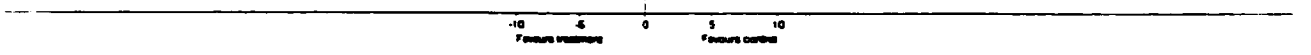
Test for heterogeneity chi-square=20.81 df=10 p=0.022
Test for overall effect z=1.98 p=0.05

-10 -5 0 5 10
Favours treatment Favours control

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 11 HDL (mmol/L)
Outcome: 01 baseline (mmol/L)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (96%CI Fixed)	Weight %	WMD (96%CI Fixed)
Agurs-Collins	31	1.27(0.28)	28	1.36(0.39)		12.0	-0.09[-0.27,0.09]
Honkola	18	1.28(0.42)	20	1.14(0.31)		6.6	0.14[-0.10,0.38]
Kapten2a	16	1.14(0.41)	16	1.11(0.28)		6.5	0.03[-0.21,0.27]
Kapten2b	18	1.14(0.31)	15	1.19(0.28)		9.1	-0.05[-0.25,0.15]
x Lehmann	16	1.15(0.04)	13	0.00(0.00)		0.0	Not Estimable
Raz	19	1.10(0.30)	19	1.10(0.30)		10.2	0.00[-0.19,0.19]
Ronnemaa	13	1.22(0.36)	12	1.22(0.31)		5.4	0.00[-0.26,0.26]
Skarfors	6	1.04(0.33)	8	0.93(0.35)		2.9	0.11[-0.25,0.47]
Vanninen A	21	1.00(0.28)	24	1.10(0.24)		15.7	-0.10[-0.25,0.05]
Vanninen B	17	1.13(0.18)	16	1.25(0.36)		9.6	-0.12[-0.32,0.08]
Wing A	10	0.95(0.25)	12	0.99(0.21)		9.7	-0.04[-0.24,0.16]
Wing B	13	1.01(0.25)	15	0.98(0.21)		12.4	0.02[-0.15,0.19]
Total(95%CI)	198		198			100.0	-0.03[-0.09,0.03]

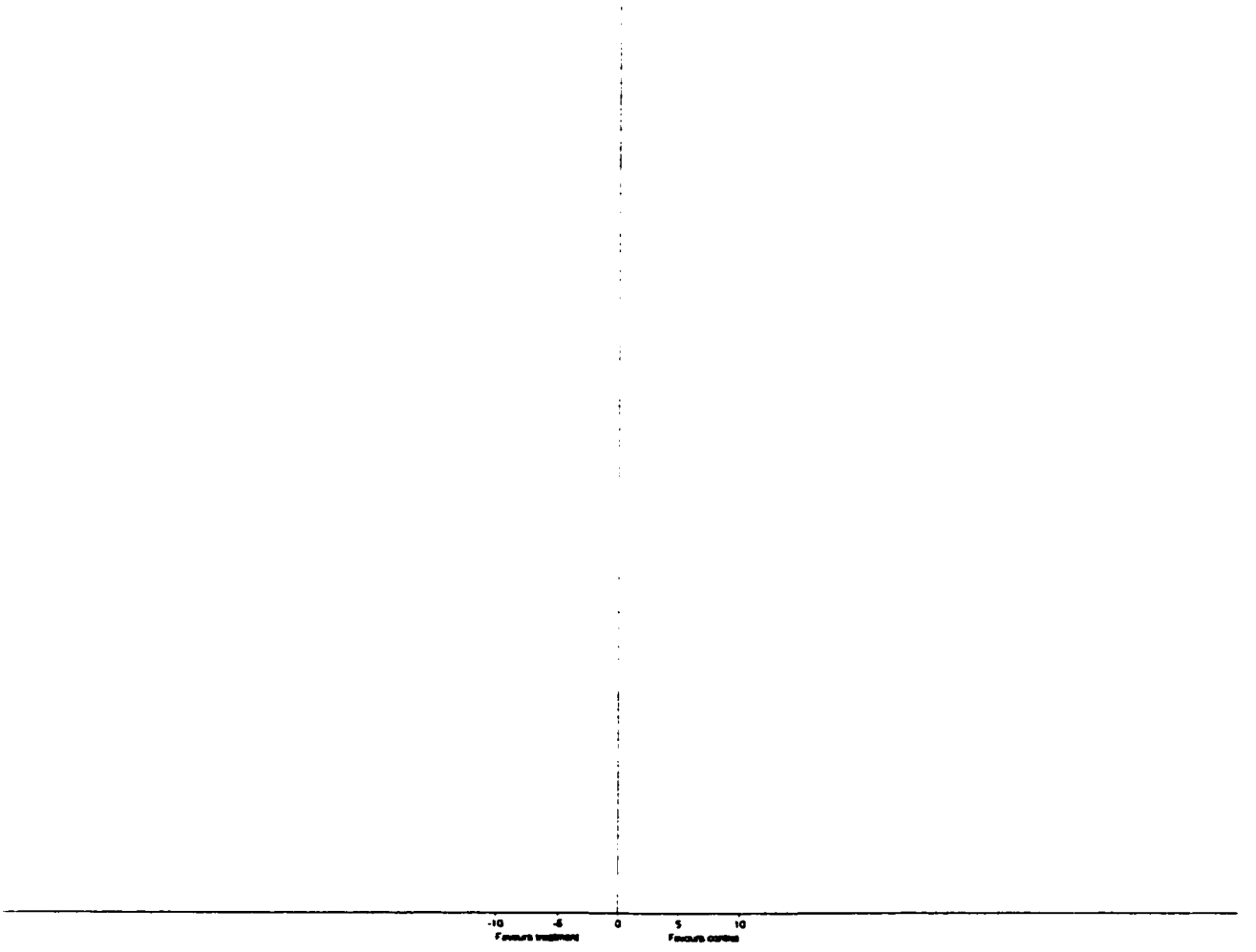
Test for heterogeneity chi-square=5.38 df=10 p=0.86
Test for overall effect z=0.95 p=0.3



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 11 HDL (mmol/L)
Outcome: 02 post treatment (mmol/L)

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	31	1.19(0.21)	28	1.32(0.33)		14.4	-0.13[-0.28,0.02]
Honkola	18	1.30(0.38)	20	1.21(0.31)		6.3	0.08[-0.13,0.31]
Kaptan2a	16	1.16(0.21)	16	1.24(0.27)		11.0	-0.08[-0.25,0.09]
Kaptan2b	18	1.16(0.35)	15	1.09(0.37)		5.1	0.07[-0.18,0.32]
x Lehmann	16	1.42(0.44)	13	0.00(0.00)		0.0	Not Estimable
Raz	19	1.10(0.30)	19	1.10(0.30)		8.5	0.00[-0.19,0.19]
Ronnemaa	13	1.29(0.36)	12	1.26(0.31)		4.5	0.03[-0.23,0.29]
Skarfors	6	1.07(0.37)	8	0.93(0.27)		2.5	0.14[-0.21,0.49]
Vanninen A	21	1.11(0.28)	24	1.15(0.27)		11.9	-0.04[-0.20,0.12]
Vanninen B	17	1.25(0.22)	16	1.29(0.29)		9.9	-0.04[-0.22,0.14]
Wing A	10	0.90(0.22)	12	0.98(0.21)		9.5	-0.08[-0.26,0.10]
Wing B	13	0.94(0.18)	15	0.98(0.19)		16.5	-0.02[-0.16,0.12]
Total(95%CI)	198		196			100.0	-0.03[-0.09,0.02]

Test for heterogeneity chi-square=5.40 df=10 p=0.86
Test for overall effect z=1.16 p=0.2



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 14 LDL (mmol/L)
Outcome: 01 baseline (mmol/L)

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	31	4.45(0.98)	31	4.03(1.24)		20.6	0.42[-0.13,0.97]
Honkola	18	3.90(0.93)	20	3.94(0.94)		17.7	-0.04[-0.64,0.56]
Kaplan2a	16	3.36(1.20)	16	3.54(1.34)		8.1	-0.18[-1.08,0.70]
Kaplan2b	18	3.24(0.90)	15	3.10(0.91)		16.3	0.14[-0.48,0.76]
Lehmann	16	3.12(0.92)	13	3.51(0.87)		14.7	-0.38[-1.04,0.28]
Ronnemaa	13	4.62(0.83)	12	4.19(1.07)		11.0	0.43[-0.33,1.19]
Skarfors	6	4.11(0.76)	8	4.21(0.61)		11.5	-0.10[-0.84,0.64]
Total(95%CI)	118		115			100.0	0.07[-0.18,0.32]

Test for heterogeneity chi-square=5.01 df=6 p=0.54
Test for overall effect z=0.52 p=0.6

-10 -5 0 5 10
Favours treatment Favours control

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 14 LDL (mmol/L)
Outcome: 02 post treatment (mmol/L)

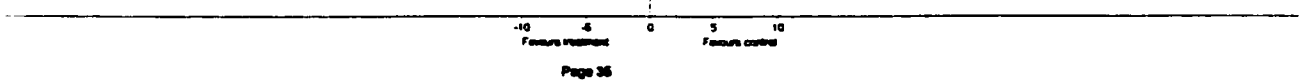
Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	31	4.04(0.85)	24	3.88(0.72)		32.8	0.16[-0.28,0.58]
Honkola	18	3.35(0.89)	20	3.79(1.07)		14.5	-0.44[-1.08,0.18]
Kaplan2a	16	3.94(1.20)	16	3.21(1.33)		7.3	0.73[-0.15,1.61]
Kaplan2b	18	3.41(0.90)	15	3.36(0.91)		14.7	0.05[-0.57,0.67]
Lehmann	16	2.98(0.98)	13	3.19(1.05)		10.3	-0.21[-0.95,0.53]
Ronnemaa	13	4.29(0.87)	12	4.11(0.90)		11.7	0.18[-0.51,0.87]
Skarfors	6	4.09(0.75)	8	4.21(0.79)		8.6	-0.12[-0.93,0.69]
Total(95%CI)	118		108			100.0	0.04[-0.20,0.28]

Test for heterogeneity chi-square=5.71 df=6 p=0.46
Test for overall effect z=0.32 p=0.8

Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 16 Triglyceride (mmol/L)
Outcome: 01 baseline (mmol/L)

Study	Treatment n	mean(sd)	Control n	mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	32	1.62(0.84)	32	1.87(1.70)		12.1	-0.25[-0.92,0.42]
Honkola	18	1.91(1.08)	20	2.60(2.15)		4.8	-0.69[-1.75,0.37]
Kaplan2a	16	2.28(1.51)	16	2.20(1.01)		6.9	0.08[-0.83,0.95]
Kaplan2b	18	1.85(0.73)	15	2.10(1.22)		11.0	-0.25[-0.95,0.45]
x Lehmann	16	2.81(1.48)	13	0.00(0.00)		0.0	Not Estimable
Raz	19	2.00(0.70)	19	2.10(0.60)		31.8	-0.10[-0.51,0.31]
Ronnemaa	13	2.16(1.30)	12	1.91(0.80)		7.8	0.25[-0.58,1.09]
Skarfors	6	2.82(0.78)	8	2.72(1.10)		5.6	0.10[-0.89,1.09]
Vanninen A	21	2.90(1.70)	24	2.30(1.40)		6.5	0.60[-0.32,1.52]
Vanninen B	17	2.10(1.00)	16	2.30(1.50)		7.1	-0.20[-1.08,0.68]
Wing A	10	2.10(0.54)	12	2.93(2.36)		2.9	-0.83[-2.21,0.55]
Wing B	13	2.51(2.13)	15	1.82(0.97)		3.5	0.69[-0.57,1.95]
Total(95%CI)	199		202			100.0	-0.07[-0.30,0.16]

Test for heterogeneity chi-square=7.32 df=10 p=0.7
Test for overall effect z=0.58 p=0.6



Review: Exercise for type 2 diabetes mellitus (JAMA, 13 studies)
Comparison: 16 Triglyceride (mmol/L)
Outcome: 02 post treatment (mmol/L)

Study	Treatment n	Treatment mean(sd)	Control n	Control mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Agurs-Collins	31	1.38(0.68)	28	1.88(2.12)		5.5	-0.50[-1.35,0.35]
Honkola	18	1.53(0.93)	20	2.23(1.97)		4.3	-0.70[-1.66,0.26]
Kaplan2a	16	2.37(2.55)	16	1.81(1.48)		1.9	0.56[-0.89,2.01]
Kaplan2b	18	1.76(0.68)	15	2.02(1.14)		9.3	-0.26[-0.91,0.39]
x Lehmann	16	2.24(1.08)	13	0.00(0.00)		0.0	Not Estimable
Raz	19	2.00(0.70)	19	2.10(0.80)		23.0	-0.10[-0.51,0.31]
Ronnemaa	13	1.91(0.97)	12	1.75(0.62)		9.9	0.16[-0.47,0.79]
Skarfors	6	2.87(1.36)	8	2.72(1.34)		1.9	0.15[-1.28,1.58]
Vanninen A	21	2.90(1.70)	24	2.30(1.40)		4.7	0.60[-0.32,1.52]
Vanninen B	17	2.10(1.00)	16	2.30(1.40)		5.7	-0.20[-1.03,0.63]
Wing A	10	1.90(0.57)	12	1.94(1.11)		7.6	-0.04[-0.76,0.68]
Wing B	13	0.69(0.19)	15	1.64(0.74)		26.2	-0.95[-1.34,-0.56]
Total(95%CI)	198		198			100.0	-0.31[-0.51,-0.11]

Test for heterogeneity chi-square=20.54 df=10 p=0.025
Test for overall effect z=3.06 p=0.002