A 3-year lifestyle intervention in primary health care

Effects on physical activity, cardiovascular risk factors, quality of life and cost-effectiveness

Margareta Eriksson
“If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would found the safest way to health.”

Hippocrates, 460-370 f Kr
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ABSTRACT

Background: A sedentary lifestyle diminishes quality of life (QOL) and contributes to increasing prevalence of obesity, diabetes and cardiovascular diseases (CVD), and thus increases the economic burden on health care and society. Expensive and tightly controlled lifestyle interventions reduce cardiovascular risk and onset of diabetes. Transferring these findings to the primary care setting is of clinical importance. The primary aim of this thesis was to apply a lifestyle intervention program in the primary care setting among individuals with moderate-to-high risk for CVD, and evaluate the effects on physical activity, cardiovascular risk factor levels and QOL. A secondary aim was to investigate the cost-effectiveness.

Methods: A randomized controlled trial with one intervention group (n=75) and one control group (n=76) with follow-up at 3, 12, 24 and 36 months was used. Patients with the diagnosis obesity, hypertension, dyslipidemia, type 2 diabetes or any combination thereof (mean age 54 yr, 57% female) were recruited from a primary health centre in northern Sweden. The three-month intervention period consisted of group-based supervised exercise sessions and diet counselling, followed by regular, but sparse, group meetings with a behavioural approach during three years. Clinical measurements included anthropometrics, aerobic fitness, blood pressure and metabolic traits. Questionnaires on self-reported physical activity, stages of change for physical activity, and QOL were used. In a cost-utility analysis the costs, gained quality-adjusted life years (QALY), and savings in health care were considered. Probability of cost-effectiveness was described using Net Monetary Benefit Method.

Results: Overall, the lifestyle intervention generated beneficial improvements in anthropometrics, blood pressure, aerobic fitness and activity level, and QOL, compared to the control group which only received one information meeting. At 36 months, intention-to-treat analyses showed that lifestyle modification reduced waist circumference (−2.2 cm), waist-hip ratio (−0.02), systolic blood pressure (−5.1 mmHg), and diastolic blood pressure (−1.6 mmHg) and significantly improved aerobic fitness (5%). BMI, lipid or glucose values did not differ between groups. Progression to active stages of change for physical activity and increases in time spent exercising and total physical activity were reported. Both physical and mental dimensions of QOL were improved during the study period, but after 3 years differences persisted mainly in physical dimensions. Cost per gained QALY was low, 1668-4813 USD (savings not counted). Visits to family physicians significantly decreased and there was a net saving of 47 USD per participant. Probabilities of cost-effectiveness were 89-100% when 50 000 USD was used as threshold of willingness to pay for a gained QALY.
Conclusions: A group-based lifestyle intervention program in a primary health care setting favourably influences cardiovascular risk-factor profiles, increases physical activity level, and improves several dimensions of QOL in high-risk individuals, at least up to 3 years. The intervention method was highly cost-effective in relation to standard care. The results emphasize the advantage of an intervention that combines supervised exercise with regular follow-ups for reaching long term effects. The study high-lights the feasibility of lifestyle interventions in the primary care setting and the importance of health care professionals supporting change in lifestyle.

Key words: Lifestyle intervention, primary health care, randomized controlled trials, cardiovascular risk factors, physical activity, exercise, quality of life, quality-adjusted life years, cost-effectiveness

Registration: ClinicalTrials.gov Identifier: NCT00486941

Det övergripande syftet med denna avhandling var att undersöka om en livsstilsintervention i primärvården riktat till personer med måttligt till hög risk för hjärt-kärlsjukdom kan påverka riskfaktorer, fysisk aktivitetsnivå och hälsorelaterad livskvalitet. Syftet var också att utvärdera om intervention var kostnadseffektiv.

Avhandlingen är baserad på en randomiserad kontrollerad studie med en interventionsgrupp (n=75) och en kontrollgrupp (n=76) som följdes upp efter 3, 12, 24 och 36 månader. Patienter med en eller flera av diagnoserna fetma, diabetes, blodfettssrubbing och högt blodtryck (medelålder 54 år, 57 % kvinnor) rekryterades från en vårdecentral i norra Sverige. Intervenien bestod av handled gruppträning och kosträdgivning i grupp under 3 månader, följt av regelbundna men successivt utglesade beteendeinriktade uppföljningsträffar under tre år. De kliniska mätningarna inkluderade kroppsmätningar, syreupptagningsförmåga, blodtryck och metabola prover. Fysisk aktivitetsnivå, motivation och livskvalitet undersöktes med hjälp av frågeformulär. En hälsoekonomisk analys gjordes utifrån beräkning av vunna kvalitetsjusterade levnadsår (QALY) och besparingar av sjukvårdskostnader. Net Monetary Benefit Method användes för att undersöka kostnadseffektiviteten.

Sammantaget resulterade livsstilsinterventionen i förbättringar av kroppsmätt, blodtryck, fysisk kapacitet och aktivitetsnivå samt livskvalitet, till skillnad från kontrollgruppen vilken endast erbjöds en informationsträff. Efter 36 månader visade intention-to treat analyser att livsstilsförändring signifikant reducerade midjemåttet (-2.2 cm), midjehöftkvoten (-0.002), sistoliskt blodtryck (-5.1 mmHg) och diastoliskt blodtryck (-1.6 mmHg) samt förbättrade syreupptagningsförmågan med 5 procent. Det fanns ingen skillnad mellan grupperna gällande BMI, blodfetter och blodsockervärden. Ökad motivation för fysisk aktivitet och ökad tid för träning och total fysisk aktivitet rapporterades. Under studieperioden förbättrades både de mentala och fysiska dimensionerna av hälsorelaterad livskvalitet men efter 3 år kvarstod i huvudsak enbart skillnaden mellan grupperna i de fysiska dimensionerna. Kostnaden per vunnen QALY var låg, 1668-4813 USD (besparingar inte inräknade). Besöken hos distriktsläkarna
minskade signifikant och nettobesparingen per patient uppgick till 47 USD. Kostnadseffektiviteten beräknades till 89-100% då 50 000 USD användes som tröskelvärde för kostnaden för en vunnen QALY.

Sammanfattningsvis uppvisade en gruppbaserad livsstilsintervention i primärvården gynnsamma effekter åtminstone upp till 3 år på riskfaktorer för hjärt-kärlsjukdomar, fysisk aktivitetsnivå och på flera dimensioner av livskvalitet i en hög-risk population. Interventionen var i hög grad kostnadseffektiv i jämförelse med sedvanlig vård. Resultaten indikerar en fördel med en intervention som kombinerar handledd träning och regelbunden uppföljning över lång tid för att uppnå långtidseffekter. Studien visar att det är möjligt att genomföra livsstilsintervention i primärvård och att det är viktigt att sjukvårdspersonal stöttar livsstilsförändringar.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CHD</td>
<td>Coronary heart diseases</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular diseases</td>
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<tr>
<td>DPP</td>
<td>Diabetes Prevention Program</td>
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<td>FDPS</td>
<td>Finnish Diabetes Prevention Study</td>
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<tr>
<td>GEE</td>
<td>Generalized estimating equations</td>
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<tr>
<td>GLUT4</td>
<td>Glucose transporter isoform 4 protein</td>
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<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
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<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<td>HRQOL</td>
<td>Health related quality of life</td>
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<td>IGT</td>
<td>Impaired glucose tolerance</td>
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<td>ITT</td>
<td>Intention-to-treat</td>
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<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
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<td>LPA</td>
<td>Leisure time physical activity</td>
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<td>MET</td>
<td>Metabolic equivalent turnover</td>
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<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PA</td>
<td>Physical activity</td>
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<td>PAP</td>
<td>Physical activity on prescription</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RPE</td>
<td>Ratings of perceived exertion</td>
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<td>RS</td>
<td>Rating scale</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SF-36</td>
<td>Short Form 36 item health survey</td>
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<td>TPA</td>
<td>Total physical activity</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>VO2max</td>
<td>Maximal oxygen uptake</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life years</td>
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This Thesis is based on the following papers, which will be referred to by their Roman numerals I-III:


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A sedentary lifestyle, unhealthy diet, smoking and excessive alcohol consumption are the leading causes of morbidity and mortality worldwide, and impose a burden on health care and society (1-3). The impact of lifestyle factors on the development of chronic diseases emphasises effective lifestyle modification strategies in health care. Physical inactivity, poor dietary habits, obesity and smoking are considered the main underlying causes of the established cardiovascular risk factors as hypertension, dyslipidaemia and diabetes mellitus (1-2, 4).

In the INTERHEART case-control study conducted in 52 countries and including about 30,000 study subjects, nine modifiable cardiovascular risk factors were identified accounting for 90% of the risk of a myocardial infarction; abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, poor diet, alcohol, physical inactivity and psychosocial factors. In contrast, regular moderate or strenuous physical activity, avoidance of smoking and a diet including a daily consumption of fruit and vegetables were protective (5). Other prospective studies have shown that more than 70% of total cardiovascular events, 80% of coronary heart events (CHD) and 90% of new cases of diabetes are attributable to lifestyle factors (6-7).

A decrease in the classical risk factors smoking, cholesterol and blood pressure explains most of the decline in the incidence and mortality of cardiovascular disease in western societies during the last decades (8). On the other hand, the prevalence of obesity and abdominal obesity (9-10) have increased in the population, and metabolic disturbance are more common (11-12). The positive effects of the decline in smoking may be counteracted by the negative effects of obesity (13). The primary health care has broad access to the population and is therefore an important setting for disease prevention and lifestyle modification among people at risk for chronic diseases.

There are compelling evidence that interventions designed to increase physical activity can moderately increase physical activity, at least in the short-term but the evidence on long-term effectiveness is very limited (14). There are many different approaches used to promote a healthy lifestyle; brief advice, counselling, written prescription, monitoring, behaviour interventions, and more extensive lifestyle interventions, but no gold standard exists (14-15). Conclusions regarding the effectiveness of different methods are limited and there is not enough evidence to claim any approach superior to another. Nevertheless, interventions which provide professional guidance about starting an exercise program and then offer ongoing support may be more effective in promoting physical activity (14).
Evidence from extensive and tightly controlled randomized lifestyle interventions trials demonstrate the efficacy on cardiovascular and diabetes risk reduction in populations at risk for diabetes, by increase in physical activity, change in dietary habits, and weight reduction (16-17). Transferring these findings to the primary care setting is of importance if such knowledge is to be of clinical utility. There are few attempts made to apply these methods in ordinary primary health care, and little is known about the long-term effects and cost-effectiveness of such interventions. However, interventions that beneficially impact on cardiovascular risk factor levels in high risk individuals are likely to improve individuals’ well-being, may be more cost-effective than population wide lifestyle modification strategies (18). An important question is to which extent such intervention is cost-effective.

The overall all aim of this thesis was to apply such lifestyle intervention into the primary care setting and to investigate the effects on cardiovascular risk factors, physical activity level and quality of life (QOL) in a population at high risk for cardiovascular diseases (CVD). Using data from the study we also performed a cost-utility analysis and assessed cost-effectiveness. This thesis is based on results from the RCT. In the introduction evidence from the literature on the effect of physical activity on cardiovascular risk factors and quality of life are presented.

Cardiovascular diseases

Cardiovascular diseases (CVD) are still the leading cause of death in western countries (5), although the incidence and mortality of CVD have markedly declined during the last decades (8). The two major CVD subgroups are coronary heart diseases (CHD) and stroke. CVD are caused by atherosclerosis and atherothrombosis and affects the heart and the brain by narrowing the blood vessels that supply blood and oxygen. Atherosclerosis is a complex process involving, dyslipidaemia, oxidative stress, endothelial dysfunction, and perturbations in the inflammatory and coagulator systems (4). Atherothrombosis occurs by a rupture of atherosclerotic plaque and involves inflammatory components and altered fibrinolysis. Atherothrombosis in the coronary and cerebral arteries causes myocardial infarction and ischaemisk stroke (4).

The decrease in CVD events are mainly explained by reduction of established CVD risk factors cholesterol, blood pressure and smoking (8), and by improved coronary care and secondary prevention (19). Other established risk factors are diabetes and obesity. These established risk factors are modifiable and strongly influenced by lifestyle factors as physical inactivity and dietary habits (1, 5-6).

A systematic review of dietary studies has shown evidence for a strong protective effect by a Mediterranean diet (20). This diet includes high
intake of vegetables, nuts, fruit, fish, whole grain, fibre and high intake of monounsaturated fat in proportion to saturated fat. Harmful factors included intake of trans-fatty acids and food with a high glycaemic index or load (20). Regular physical activity counteracts the atherosclerosis process by favourable influencing several biological mechanisms. Regular physical activity contributes to weight regulation, increases aerobic fitness, reduces blood pressure, and improves blood lipid profile and glucose homeostasis. Physical activity also beneficially influences inflammation, fibrinolysis and endothelial function. Thus physical activity modifies CVD risk factors and contributes to CVD risk reduction (4, 21-22).

Additionally, socioeconomic factors such as low income and low education level as well as the psychosocial factors depression, anxiety and lack of social support, strongly influence the modifiable cardiovascular risk factors thereby increasing the risk of CVD (23-26). In addition, those factors are also shown to have negative impact on health-related quality of life (27).

**Health-related quality of life**

Good health is important for both individual and society (3). Quality of life (QOL) refers to the individual’s experience of illness and health status such as pain, fatigue and disability. QOL also incorporates broader aspects of health status e.g. physical, emotional and social well-being (28). Measures of QOL are used for monitoring health in different populations, as patient-reported outcomes in clinical trials, and can also be used in routine care (27-29). When using QOL as an outcome measure, the individual’s subjective perspective of well-being is incorporated, and therefore QOL is an important complement to conventional medical outcomes (28). Different generic and disease specific instruments are used to measure QOL (30). Commonly used instruments are the generic questionnaires EuroQol (31) and 36-Item Short Form Health Survey (SF-36) (32). These instruments assess health in different dimensions. Both instruments cover physical, global and mental aspects of health. Weighted QOL scores or utility scores can be computed.

**Epidemiological findings on quality of life**

Cross-sectional studies have demonstrated that chronic diseases such as CVD and diabetes (27, 33-34) negatively affects QOL, and also the prevalence of obesity and other cardiovascular risk factors as hypertension and dyslipidemia (33, 35-36). People with obesity report more problems regarding mobility and pain (35), and in diabetic patients the presence of coronary heart diseases deteriorates QOL (34). In
contrast, prospective studies have shown that regular physical activity positively affects well-being and is associated with higher self-reported QOL compared to being sedentary (37-40). Individuals being moderate physically active at least 30 min per day had better QOL than those not meeting that goal, and those practicing more intense activities had additional higher QOL (41). Clinical trials have also shown that physical activity reduces anxiety (42) and improve the ability to endure psychosocial stress (43-44).

Physical activity

Physical activity definitions

Physical activity is defined as “any bodily movement produced by the contraction of skeletal muscle that results in energy expenditure” while exercise is defined as “a subset of physical activity that is planned, structured and repetitive and has as final or an intermediate objective, the improvement or maintenance of physical fitness” (45). Different terms describe physical activity level and are used somewhat inconsistent in literature. Physical activity, exercise or leisure time physical activity are often used as synonyms. Other terms used are occupational and commuting activity where occupational activity refers to activities performed during work and commuting activities describes different modes of transportation to work.

Due to the definition, physical activity includes all every day physical activity such as household activities indoors- and outdoors, commuting actives, occupational activities and leisure time activities as well as planned exercise. Physical activity less than needed to maintain health is denominated physical inactivity (46-47). When physical activity level was assessed in the present thesis the term total physical activity was used for all physical activities performed, leisure time activities refers to activities in daily life and recreational activities, and exercise concern planned exercise.

Physical fitness

Fitness can be expressed in different ways but often refers to cardiorespiratory capacity, i.e. the ability of the oxygen transport system to deliver blood and the ability of cells to take up and utilize oxygen in energy production during sustained physical activity (48-49). Cardiorespiratory fitness (CRF) is expressed as maximum oxygen uptake (VO₂max); litre oxygen uptake per minute (l/min) or millilitre oxygen uptake per kilogram body weight per minute (ml/kg/min). In the literature fitness, aerobic fitness/capacity or cardiorespiratory fitness/capacity is often used interchangeably. CRF declines with age and
the decline accelerate after 45 years of age but physical activity delay the decline (50). In the present thesis the term aerobic fitness is used for estimated maximum oxygen uptake.

The health-related fitness concept is broader and can be expressed in five major components; a morphological, a muscular, a cardiorespiratory, metabolic, and a motor skill component. These components include for example body composition, fat distribution, abdominal fat, blood pressure, glucose tolerance, insulin sensitivity, and lipid and lipoprotein metabolism, besides the cardiorespiratory and muscular components. Fitness refers to the health state that defines premature development of diseases and morbidity (51-52). This concept proposes a complex relationship between environmental conditions as lifestyle behaviours, physical activity level, heredity, fitness and health. Genetic contributions to fitness are important but physical fitness is mainly determined by physical activity level. An increase in physical activity results in an increase in physical fitness, although the amount of adaption in fitness to a standard exercise dose varies among individuals and is under genetic control (52-54). Recent findings have shown that increased risk of obesity owing to genetic susceptibility can be blunted through physical activity (55).

**Aerobic exercise**

$\text{VO}_{2\text{max}}$ is limited by the ability of the cardiorespiratory system to transport oxygen ($\text{O}_2$) to the muscles. Regular participation in aerobic exercises improves the function of the cardiovascular system and skeletal muscles by increases in cardiac output, stroke volume, $\text{O}_2$ transport capacity, and amelioration in mitochondrial function, leading to an increase in endurance performance. Aerobic exercises are referred to as repeatedly performed dynamic movements involving large muscle groups, resulting in increased heart rate and energy expenditure (48, 56-57). In the present study aerobic exercises, Nordic walking, aqua aerobics and cycling on ergometer bicycles were performed.

**Resistance exercise**

Resistance exercise aims to increase muscular strength and endurance. Muscular strength reflects the amount of force a muscle can generate or can be expressed as the amount of external force that a muscle can exert, while muscular endurance relates to the ability to sustain repeated muscle actions. The type of resistance exercise is determined by the resistance, the number of repetitions and number of sets performed for each muscle group (45, 56). In this study circuit-resistance training was used, mostly aimed to increase muscular endurance and functional capacity.
**Dose of physical activity**

The dose of physical activity refers to the total amount of energy expended during a certain period, for example during a day or during a week. The amount of energy required for an activity is often measured in kilocalories (kcal) (45). Physical activity-associated energy expenditure is the most important source of variation in energy expenditure among individuals, and accounts for 20-30% of total energy expenditure (58). All types of physical activities contribute to increase total energy expenditure.

Dose-response refers to the relationship between increasing physical activity level and proportional changes in a defined health measure, i.e. decrease in risk factor levels or diseases and increase in quality of life (56). Epidemiological data have shown decreased all-cause mortality and reduced risk for CVD among subjects who expend >1000 kcal per week in physical activities, but already an energy expenditure as low as 500-700 kcal has beneficial impact on health, “Less is good, more is better” (59).

When defining the dose there is an important relationship between frequencies, duration and intensity of the activity. The frequency is described as the number of activity sessions per day, week or month, and duration refers to the length in time (minutes, hours) of the activity sessions. Intensity is often described by the effort associated with the specific activity, categorized into different levels; low/light, moderate, or high/vigorous/strenuous (45). Moderate intensity reflects a moderate level of effort relative to an individual’s fitness. Moderate intensity produces noticeable increases in heart rate and breathing while vigorous intensity activity produces large increases in heart rate and breathing (60).

Intensity reflects the rate of energy expenditure during an activity session and can be described in absolute or relative terms (51, 56). Absolute intensity refers to the energy used referenced to body mass and is often expressed as metabolic equivalents (METs), where 1 MET is the energy (oxygen) used by the body at rest (56, 61-62). Relative intensity refers to the percent of aerobic power utilized and can be described as percent of maximal oxygen uptake or percent of heart rate. Moderate intensive activity such as brisk walking is performed at an absolute intensity of 3-6 MET equivalent to a relative intensity of 40-60% of VO₂max or 55-70% of maximal heart rate, while vigorous intensity activities are performed at an relative intensity of >60% of VO₂max or 65-90 of maximal heart rate equivalent to a absolute intensity > 6 MET (51, 56).

One problem when using absolute intensity categories is that an activity at an absolute intensity expressed in a given MET unit, for example 4 MET, can be considered low for a young and trained person but vigorous for an old or untrained person, expressed in relative terms (63). Another method to determinate intensity is the Borg Rating of Perceived Exertion (RPE)
scale, which was used in the current study (64). RPE rating during exercise is linearly related to exercise intensity, oxygen consumption and heart rate. Thus the RPE scale is appropriate to monitor perceived exertion during exercise, and also to regulate exercise intensity. It should be noted is that the energy expenditure, i.e. oxygen consumption, during exercise at same level perceived effort, differs between a high fit person and a low fit person so that the high fit person is able to perform exercise at a higher relative intensity level.

Measurement of physical activity and fitness

Physical activity is not easily measured as an individual’s physical activity level is a very complex behaviour and includes all type of activities. There are a numerous of methods used to measure physical activity and fitness, and the selection of approach depends on the purpose and extension of the study, and economic resources. Each method has advantages and disadvantages. Physical activity can be measured in terms of behaviour or energy expenditure (58, 65).

Energy expenditure can be measured by direct methods as the doubly-labelled water, and calorimetry, i.e. measurement of heat production, or indirect by measuring oxygen consumption and/or carbon dioxide production. These methods are used as criterion methods for validation of other methods (58). A maximal exercise test performed on a treadmill or a bicycle is the gold standard for measurement of maximal oxygen uptake, VO₂peak, the maximal VO₂ achieved during a maximal test. But VO₂ peak is often not a true VO₂max, as not many individuals reach their true VO₂ max. High level of motivation is required by the individual for a maximal test, and musculoskeletal impairment or fatigue are limiting factors.

Sub maximal exercise test are predictive tests that estimates VO₂max by extrapolating the relationship between heart rate at a given workload and oxygen uptake, to an age-predicted maximal heart rate. Common used test are the 2 km walk test and sub maximal tests on treadmill or bicycle ergometer. The sub maximal bicycle test is objective, valid and reliable. It can easily be performed in clinical practice and do not require additional monitoring equipment or laboratory staff and is feasible for most individuals (66-68).

Different activity monitors as accelerometers, pedometers or heart rate monitors are used as objective physical activity measures. Pedometers measure acceleration in the vertical plane, while accelerometers are able to measure movements in more than one plane. Thus, pedometers are useful when measuring activities as walking or running but not when measuring cycling, swimming or resistance or upper body training (58, 65).
Self-reported physical activity questionnaires are widely used. Other subjective methods are diaries and activity logs. Physical activity questionnaires are easy to use and cheap, but have limitations in validity and reliability. Some international physical activity questionnaires have been validated showing that questionnaires might be valid to classify a population into physical activity categories as low, moderate or highly active, but not appropriate to quantify energy expenditure. Disadvantages with questionnaires are difficulties to cover all types of activities, and the risk that respondent either over- or underestimates physical activity level. Questionnaires also often fail to assess the amount of sedentary time, i.e. time spent sitting or lying (58, 65). In the present study physical activity level was assessed by questionnaires, aerobic fitness was estimated by a sub maximal test on a bicycle ergometer (68), and measures of other health-related fitness components were measurements of anthropometrics, blood pressure and metabolic traits.

**Physical activity and cardiovascular risk**

**Epidemiological evidence on physical activity**

*Physical activity and CVD*

During the last decades epidemiological studies have demonstrated overwhelming evidence for the positive association between regular physical activity and health. Fifty years ago Morris *et al* (69) showed the association between occupational physical activity and incidence in CHD, by reporting higher incidence rates of CHD in bus drivers than in bus conductors who had higher level of occupational physical activity. In the 1970s Paffenbarger *et al* showed that physical activity during leisure time protected against CHD in a dose-response manner (70), which has been confirmed by several others. Recently, a large Finnish study including more than 40 000 participants demonstrated a reduced 10-year risk of CDH events among people with moderate to high levels of occupational or leisure time activity, and daily walking or cycling to and from work (71). Similar results were observed in a Swedish nested case-control study in Northern Sweden reporting a reduced risk of myocardial infarction with higher leisure time physical activity, and furthermore an association between car commuting and increased risk for myocardial infarction (72).

The impact of high energy expenditure was demonstrated in a cross-sectional study investigating the association between energy expenditure and CVD risk factors in different populations in Tanzania (73). Despite an intake of a potentially atherogenic high fat/low carbohydrate diet, the Masai people had lower blood pressure and body mass index (BMI) than the rural and urban population, and they revealed a favourable lipid
profile. The results were explained by their higher energy expenditure, corresponding to 2565 kcal/d over basal metabolism.

A study among men has shown that the average intensity was associated with reduced risk of CHD independent of the numbers of MET-hours spent in physical activity (74). Higher exercise intensity was associated with additional risk reduction. Activities such as running, rowing and weight lifting were each associated with reduced risk and walking pace was strongly related to reduced risk independent of walking MET-hours. Walking at least 30 minutes per day was associated with an 18% risk reduction, while running an hour or more per week reduced the risk by 42%. Weight training 30 minutes or more per week reduced the risk 23% and rowing for one hour or more per week was associated with 23% reduced risk. The authors concluded; “Increasing total volume of activity, increasing intensity of aerobic exercise from low to moderate and from moderate to high, and adding weight training to the exercise program are among the most effective strategies to reduce the risk of CDH in men” (74).

Similar findings have been shown for women (75). Women who either walked briskly or exercised vigorously at least 2.5 hours per week reduce their risk of CVD approximately 30%. Performing both walking and vigorous activities further reduced the risk. Both walking pace and furthermore time spent sitting was of importance. Women who spent 12-15 hours per day sitting had 1.38 relative risk of CVD, and if 16 hours or more per day were spent sitting the relative risk was 1.68.

**Physical activity, fitness and mortality**

Several prospective studies have shown an inverse relationship between the dose of physical activity and all cause of mortality (59). Physical activity yielding an energy expenditure of about 1000 kcal per week is associated with a 20-30% reduction in all-cause of mortality in both men and women, and further risk reductions are observed at higher expenditure. In earlier studier Paffenbarger has shown that energy expenditure of at least 2000 kcal per week and participating in vigorous activities reduced mortality risk by approximately 40%, and was associated with increase in life expectancy of 1 to 2 years at the age of 80 (70). Similar dose-response findings were demonstrated in a Danish study where physically active people had a lower mortality rate compared to inactive. Participating in sports activities or bicycling to work yielded further benefits even after adjustments for other leisure time activities (76).

Both physical activity level and high cardiorespiratory fitness (CRF) are shown to be associated with a reduced risk of CVD morbidity and mortality and all-cause of mortality (53). Low CRF has the same impact as
Introduction

diabetes and other CVD risk factors (77). Some studies indicate that low CRF is the most important predictor for premature death (66). In contrast, high fitness seems to be protective even in the presence of other risks factors as obesity, smoking (78-79), hypertension (80) and diabetes (81).

People with diabetes have a markedly higher risk of myocardial infarction and stroke and mortality than people free from diabetes (81-83). Also in people with diabetes, participating in regular physical activity markedly decreases the risk (84-86), even at all levels of weight, blood pressure and total cholesterol and among smoking and non smoking individuals (85). Maximum risk reduction of both CVD and mortality in diabetic subjects was observed at an energy expenditure 12-21.7 MET-hours/week, corresponding to 3-5 hours of brisk walking or 2 to 3 hours of jogging. To achieve a walking pace causing increase in breathing and heart rate was considered important (84, 86).

The interaction between physical fitness and aggregation of risk factors is shown by Lee et al who recently observed that men who had normal waist, were physically fit, and did not smoke had 59% lower risk of CHD events, 77% lower risk of CVD mortality, and 69% lower risk of all-cause of mortality compared with those who not did fulfil these criteria. Men with those risk factors had a shorter life expectancy by 14.2 years compared with slim, non smoking and physically active men (87). The authors stated that 31% of CHD might have been avoided if these low-risk criteria were fulfilled. If additionally blood pressure and lipid levels were at target levels 51% events might have been avoided.

When expressing CRF in MET categories the minimum CRF level associated with lower CHD event rate for men and women is approximately 9 and 7 METs (at 40 years old), 8 and 6 METs (at 50 years old), and 7 and 5 METs (at 60 years old). In terms of walking speed this means that a 50 year old man must be capable of continuous walking at a speed of 6.4 km/h and a woman at a speed of 4.8 km/h for prevention of CVD and CVD mortality (88).

Sedentary lifestyle, sitting time and CVD

One recent Canadian (89) and Australian (90) study demonstrated a dose-response association between sitting time and CVD mortality and all-cause mortality independent of leisure time physical activity. The Australian study showed that relative to those watching television less than 2 h /day, there was a 46% increased risk of all-cause mortality and an 80% increased risk of CVD mortality in those watching more than 4 hours of television per day. These findings were independent not only of leisure time activity but also of smoking, blood pressure, cholesterol, waist-circumference as well as diet (90). In the Canadian study the
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The highest risk of mortality were in obese individuals spending most of their time sitting, but even within the group of physically active individuals there was a strong association between higher sitting time and mortality risk (89). These results indicate the importance of reducing sitting time in addition to promoting physical activity (89-90).

Sedentary lifestyle, fitness, metabolic syndrome and CVD

Several cross-sectional and prospective studies have shown that physical inactivity and low fitness is associated with the metabolic syndrome (MS) (91-93) and may be major determinants of this metabolic disturbance (92). Men with VO₂max <29.1 ml/kg/min were almost seven times more likely to have MS than men with VO₂max ≥35.5 ml/kg/min (92). Also a decrease in muscle strength is associated with the MS (94). Unhealthy diet, obesity and genetic factors all contribute to the development of the MS which is characterized by abdominal obesity and varying degrees of glucose intolerance, insulin resistance, hypertension and dyslipidaemia; high levels of triglycerides and of small atherogenic low-density lipoprotein cholesterol, and low levels of high-density lipoprotein cholesterol. The MS may over years progress to diabetes, and together with the high prevalence of CVD risk factors increases the risk of cardiovascular disease and mortality (22, 96-97).

Body mass index (BMI) and waist circumference (WC) are measures that independently define obesity, but abdominal obesity is considered a stronger CVD risk factor than obesity classified by BMI (98). Increase in WC in all the BMI categories (normal weight < 24.9, overweight ≥25-29.9, obesity ≥30) is associated with increase in visceral fat (99) leading to insulin resistance and high level of triglycerides (100-101). In men WC >94 cm are considered as abdominal obesity, and in women WC >80 cm. People with high WC in all BMI categories are more likely to have hypertension, dyslipidaemia, metabolic syndrome and diabetes (99).

Physical activity, inactivity, obesity and risk of diabetes

Associations between sedentary behaviours, especially TV watching, with elevated risk of obesity and type 2 diabetes in both men and women, have been observed in large prospective studies (102-103). This association was independent of diet habits and exercise. Obesity was one of the most important risk factor for type 2 diabetes. Other factors contributing were smoking and poor diet; high intake of total energy, total and saturated fat, refined grain products, snacks, sweets and processed meat, and low intake of fish, vegetables, fruit and whole grains (103-104). Those with BMI >35 were approximately 20 times more likely to develop diabetes compared to those with BMI <24.9 (105).
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These studies also show that even light to moderate physical activity reduced the risk of diabetes. The inverse association observed between walking and risk reduction was similar to that to vigorous activities (103), although higher walking pace was independently associated with risk reduction. The authors estimated that 43% of new cases of diabetes could be prevented by brisk walking at least 30 min per day and TV watching less than 10 h per week. A recent review of prospective studies confirm that 30 min/d of moderate or high-level physical activity, healthy diet and avoiding excessive weight gain are effective to prevent type 2 diabetes in all populations, and most studies show a 30-50% in risk reduction. This review also shows somewhat stronger associations between risk of diabetes and fitness than between physical activity and diabetes. Low fitness substantially increased the risk of diabetes (106).

The prevalence of diabetes increases with age (107), although even in older adults combined lifestyle factors prevents onset of diabetes (6). As many as 9 of 10 new cases of diabetes might be prevented if older people stay physically active, keep a healthy diet, do not smoke, avoid obesity and abdominal obesity, and excessive alcohol use (6).

Effects of physical activity and evidence from RCT

Lifestyle factors as regular physical activity, minimizing sedentary time, weight reduction, healthy diet and avoidance of smoking contributes to CVD risk reduction (Figure 1). Regular physical activity beneficially influences risk factors for diabetes and CVD by modifying several biological mechanisms (4, 21-22, 52). Physical adaptations to exercise occur both as an acute response to a single session of exercise, and as adaption and response over time to stress of repeated activity (57).
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**Figure 1.** Lifestyle factors influence on CVD risk factors, diabetes and atherosclerotic diseases. Genetics factors, age, and gender modify the health effects of physical activity. Socioeconomic and psychosocial factors affect behaviour.

**Blood pressure**

Different mechanisms contribute to the reduction of blood pressure by physical activity; reduced sympathetic activity and lower level of noradrenalin, even during workload and stress, attenuated vasoconstriction and peripheral resistance, improved insulin sensitivity, vascular adaptations (108) and improved endothelial function by increasing nitric oxide (NO) bioavailability (109).

One single exercise session reduces blood pressure and the reduction may persist up to 16-22 hours, due to the duration and type of exercise. Both aerobic and circuit resistance exercise reduce blood pressure which most pronounced in individuals with hypertension and after aerobic exercise. Among people with stage I hypertension decreases of 10-20 mmHg systolic and 7-9 mmHg diastolic blood pressure have been reported (57, 108). Meta-analyses of randomized controlled trials (RCT) show a mean reduction in systolic and diastolic blood pressure about 3.8-6/2.6-5 mmHg after periods of exercise (110-111). The addition of weight loss enhances blood pressure reduction (112-113).
Body composition and weight

Physical activity increases energy expenditure and high-intensity exercise also increases resting metabolic rate (RMR) for several hours afterwards, thus contributing to weight regulation (114). Physical activity yielding an energy expenditure equivalent to 20 km walking per week have been shown to prevent weight gain and accumulation of visceral fat (115-116). Several RCT have shown weight loss and reduction of both abdominal fat and total fat mass after exercise intervention (115-119), and many report a dose response between energy expenditure and weight loss (115-117, 119). High intensity exercise seems to interact with training volume and may be effective for inducing changes in body composition by reduction of abdominal subcutaneous fat and abdominal visceral fat (120). Notably, some exercise intervention studies show reduction in abdominal obesity even in the absence of weight loss (121).

A systematic review of 43 exercise studies in overweight subjects with at least 3-month follow-up, demonstrated small weight losses across studies, which increased if, combined with caloric restriction, mean -1.0 kg. Increasing activity intensity increased the weight loss, mean -1.5 kg (122). A systematic review of nine lifestyle interventions studies for weight loss and weight control for overweight or obese people with prediabetes, showed decreased BMI and weight reduction of 2.6-2.8 kg after 1-2 years, compared to usual care (123). To achieve greater and sustained weight loss high energy expenditure is needed. Women, who reported an energy expenditure approximately 1835 kcal week equivalent with physical activity 275 min per week and restricted caloric intake to 1200-1500 kcal, reduced 10% of body weight after 24 months of intervention (124).

Some weight loss interventions report favourable effects on other CVD risk factors as blood pressure, blood lipids, insulin sensitivity, fasting plasma glucose and insulin (119, 122, 125). There are also reports on reduction of inflammatory markers (126) and improved fibrinolysis (127).

Metabolic effects

Blood lipids and exercise

Regular physical activity enhances lipid metabolism and improves blood lipid profile, likely due to higher energy expenditure. Endurance athletes have higher levels of HDL cholesterol and lower levels of triglycerides (57, 114). The effects on LDL cholesterol are somewhat more unclear, possibly regular physical activity might increase the LDL particle size, thereby making LDL less atherogenic (128-129).

Exercise training increases the ability of muscle tissue to take up and oxidize non-esterified fatty acids by an altered enzyme activity, mainly by
increase in lipoprotein lipase. Thus an increased triglyceride catabolism results in a decrease in circulating triglycerides and an increased synthesis of HDL. Decrease in triglycerides occurs about 18-24 hours after an exercise session and persist for up to 72 hours and the effects on HDL occurs parallel (57, 114). It is unclear if long-term effects on lipid profile solely are results of repeated single bouts of exercise. Key factors for the effects on the lipid profile are the individual’s physical fitness, preexercise lipid levels and the duration and intensity of the exercise session (57, 114).

In a meta-analysis of 25 RCTs the minimal weekly exercise volume to increase HDL level was estimated to be 120 min of exercise per week equivalent with energy expenditure of 900 kcal per week (88). There was also a dose-response between higher dose of physical activity and higher levels of HDL, and duration was the most important factor.

Glucose metabolism and exercise

Physical activity improves glucose tolerance and insulin sensitivity acutely and over time (57, 114, 130-131), and reduces hyperinsulinaemia (132-133). One single exercise session can improve glucose control in people with type 2 diabetes. Muscle contraction increases glucose uptake in the skeletal muscles via an insulin-independent mechanism and improve the ability to resynthesize glycogen by increase in glycogen synthase activity. Increased muscle glucose uptake is related to changes in insulin signalling as increased expression, activity and translocation of GLUT4 glucose transporters to the cell surface. The effect on insulin sensitivity persists about 12-48 hours but repeated exercise yield long-term effects.

The increase in GLUT4 in trained individuals contributes to an increase in the responsiveness of muscle glucose uptake to insulin (57, 114, 130). Exercise also increases capillary and mitochondrial density in the skeletal muscles and improve mitochondrial oxidative capacity (134). Reduction of non-esterified fatty acids and muscle triglycerides may contribute to the acute improvement in insulin sensitivity, and exercise may beneficially alter muscle fibre type which contributes to the long-term effects of physical activity (57).

Exercise and HbA1c

In two meta-analyses of aerobic and resistance exercise RCTs for type 2 diabetes it was shown a reduction in HbA1c compared to control but no weight reduction. Some studies show reduction in fat mass but increase in muscle mass (135-136). In a study comparing resistance training, aerobics training and combined training each training group improved HbA1c, but more in the combined aerobic and resistance training group (137). Also high-intensity resistance exercise among older people with type 2 diabetes improved HbA1c (138-139). In a meta-analysis of weight loss
interventions for adults with type 2 diabetes, with follow-up between 1 to 5 years, the mean weight loss was -1.7 kg compared to controls (123). Interventions used were exercise, caloric restriction and behavioural approaches, alone or in combination. Those receiving more intense physical activity interventions lost -3.9 kg. Changes in HbA1 generally corresponded to changes in weight.

Exercise and glucose tolerance

Several RCTs have been successful to prevent type 2 diabetes in individuals with impaired glucose tolerance. In two meta-analyses of eight lifestyle interventions using exercise and diet ≥ 6 months diet and exercise was effective to both reduce 2-h plasma glucose and to prevent diabetes. The incidence of diabetes was reduced by approximately 50% (140-141). The interventions also had favourable effects on weight, BMI, waist, waist-to-hip ratio and reduced blood pressure; -4/-2 mm Hg but had only modest effect on lipids (140). Several lifestyle interventions have shown favourable long-term effects (16-17, 142-151) (Table 1).

Recently lifestyle intervention turned out to be effective to prevent diabetes also in older populations, with a mean age of 67.5 years. The combination of resistance and aerobic exercise was shown to be the most optimal strategy to improve both insulin sensitivity and the functional limitations in abdominally obese older individuals (152).

Quality of life and physical activity

In a meta-analysis of 66 reports including both randomized and not randomized studies assessing QOL as outcome from physical activity interventions, the mean QOL effect size was 0.11 in favour to the treatment group (29). The treatment group’s mean pre-post test comparison effect size was 0.27. The intervention methods varied from brief motivational sessions to extended supervised programs, and diverse measures were used to assess QOL and physical activity. Studies that used supervised centre-based exercise reported larger QOL improvements than studies that used only educational or motivational methods (29).

In a meta-analysis of 36 studies in people age 54 or older the weighted mean-change effect size was 0.24. Aerobic exercise was the most beneficial activity and moderate intensity activities were most beneficial intensity (153). Reports on long-term effect on lifestyle programs for increased QOL are rare, somewhat inconsistent and seldom carried out in primary health care (154-160) (Table 2).
<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up and outcome</th>
<th>Lifestyle intervention 4 years</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindström et al 2003</td>
<td>Mean follow-up on physical activity and CVD risk factors after 3.2 years</td>
<td>Control group: Brief advice and exercise counselling</td>
<td>Increase in moderate-to-vigorous physical activity and decrease in the proportion of sedentary individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention group: Intensive individualized instruction on weight reduction, food intake and increasing physical activity Voluntary group meetings and supervised resistance exercise</td>
<td>Weight reduction 2.6 kg</td>
</tr>
<tr>
<td>Tuomiletho et al 2001</td>
<td>Mean follow-up on diabetes incidence after 3.2 years</td>
<td>Frequency: 7 sessions in the first year; then 3-monthly; total=15 contacts</td>
<td>BMI reduction 1.0 kg/m²</td>
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<td>Goals: Weight loss &gt;5%; Diet; total fat &lt;30% and saturated fat &lt;10% of energy; fibre &gt;15g/1000 kcal; Exercise &gt; 30 min/day Facilitator: Nutritionist</td>
<td>Waist reduction 2.1 cm</td>
</tr>
<tr>
<td>Lindström et al 2006</td>
<td>Follow-up on diabetes incidence after 4 years and after 7 years (3 yr post intervention)</td>
<td></td>
<td>Decreases in triglycerides and HBA1c</td>
</tr>
<tr>
<td></td>
<td>Follow-up on exercise effect after 4 years</td>
<td></td>
<td>Relative risk reduction of diabetes 58%</td>
</tr>
<tr>
<td>Laaksonen et al 2007</td>
<td></td>
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<td>None of the participants who achieved 4-5 goals developed diabetes</td>
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<td>Relative risk reduction of diabetes 43%</td>
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<td>Relative risk reduction of diabetes 36%</td>
</tr>
<tr>
<td>Lindström et al 2008</td>
<td></td>
<td></td>
<td>Moderate-to vigorous activity ≥2.5 h/week reduced risk of diabetes by 50% compared to &lt;1h week independent of dietary factors and BMI</td>
</tr>
<tr>
<td></td>
<td>Following on determinants of the effectiveness of the lifestyle intervention</td>
<td></td>
<td>Those who increased &quot;moderate-to vigorous” walking and strenuous activities most decreased the risk by 63-65%</td>
</tr>
<tr>
<td></td>
<td>Follow-up on cardiovascular morbidity after 10 years</td>
<td></td>
<td>Lifestyle intervention was most effective among those with high baseline FINDRISC score or age ≥61</td>
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<td>Cardiovascular morbidity did not differ between groups or from a population cohort, but total mortality was lower than in the general population for both groups</td>
</tr>
<tr>
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<td></td>
<td>The groups did not differ in drug treatment for elevated lipids or blood pressure</td>
</tr>
</tbody>
</table>

To be continued....
### Table 1. Long-term lifestyle interventions to prevent type 2 diabetes among individuals with impaired glucose tolerance

**The Diabetes Prevention Program, DPP**

**Study design:** Randomized Controlled Trial, 27 centres; three study arms  
**Study population:** n=3234, mean age 51 years, 68% female, BMI 34

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up and outcome</th>
<th>Lifestyle intervention 3 years</th>
<th>Results</th>
</tr>
</thead>
</table>
| Knowler et al, 2002 (16) | Mean follow-up on physical activity, CVD risk factors and diabetes incidence 2.8 years | Control group: Placebo pills and written standard information on diet and exercise and annual 20-30 individual sessions  
Metformin group: 1700 mg/day, standard information on diet and exercise and annual 20-30 min individual sessions  
Intervention group: Intensive individualized instruction in diet, exercise and behaviour modification  
Frequency: 16 individual sessions in the first 24 weeks, then monthly both individual and in groups; total=40 contacts  
Goals: Weight loss >7%; Diet: low-caloric diet, total fat <25 E%; Exercise > 150 min/week  
Facilitator: Case managers | Increase in physical activity in the lifestyle group  
Weight reduction 4.1 kg with lifestyle  
Weight reduction 2.0 kg with metformin  
Decreases in fasting glucose and HBA1c in intervention groups  
Relative risk reduction diabetes 56% in lifestyle group  
Relative risk reduction 31% in metformin  
Weight loss, determined by change in diet (reduced % fat), and exercise are the primary factor resulting in reduced incidence of diabetes. For every kg of weight loss the risk reduction was 18%. Increased physical activity supported sustained weight loss and independently reduced diabetes risk among those who did not lose weight. Those who did not achieve weight goal but achieved physical activity goals reduced the risk of diabetes by 44%.  
Weight reduction ca 2 kg in lifestyle and metformin group  
Relative risk reduction diabetes 34% lifestyle group (0-10 years)  
Relative risk reduction 18% metformin (0-10 years)  
No difference between groups the period 5.7-10 years  
The lifestyle effect was greatest in participants aged 60-85 at randomization  
The median delay of diabetes was 4 years in the lifestyle group and 2 years in the metformin group  
Averaged over all follow-up, systolic and diastolic blood pressure and triglycerides were lower in the lifestyle group, but not significant at 10 years time point  
To be continued... |
| Hamman et al, 2006 (143) | Follow-up on contribution of weight, diet and exercise after 3.2 years | Increase in physical activity in the lifestyle group  
Weight reduction 4.1 kg with lifestyle  
Weight reduction 2.0 kg with metformin  
Decreases in fasting glucose and HBA1c in intervention groups  
Relative risk reduction diabetes 56% in lifestyle group  
Relative risk reduction 31% in metformin  | To be continued... |
| Knowler et al, 2009 (144) | Follow-up on weight loss and diabetes incidence after 10 years (n=2786) | Increase in physical activity in the lifestyle group  
Weight reduction 4.1 kg with lifestyle  
Weight reduction 2.0 kg with metformin  
Decreases in fasting glucose and HBA1c in intervention groups  
Relative risk reduction diabetes 56% in lifestyle group  
Relative risk reduction 31% in metformin  | To be continued... |
<table>
<thead>
<tr>
<th>Author</th>
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<th>Lifestyle intervention 4 years</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al 1997</td>
<td>Mean follow-up on diabetes risk reduction after 6 years</td>
<td>Control group: No intervention&lt;br&gt;Diet group: Goals for BMI ≤25: Diet 25-30 kcal/kg body weight, 55-65% carbohydrate, 10-15% protein, 20-25% fat, increase intake of vegetables and reduce intake of sugar; Goals for BMI ≥25: weight loss 0.5-1.0 kg/month&lt;br&gt;Exercise: Counselling, increase in daily physical activities&lt;br&gt;Frequency: One individual counselling; than group counselling weekly for 1 month; monthly for 3 months; then 3-monthly, total 30 contacts&lt;br&gt;Facilitator: Physician and team</td>
<td>Relative risk reduction diabetes vs usual care group:&lt;br&gt;Diet alone: 31%&lt;br&gt;Exercise alone: 46%&lt;br&gt;Diet and exercise: 42%&lt;br&gt;The combined lifestyle groups had 43% lower incidence of diabetes compared to the control.&lt;br&gt;No difference between groups in rate of first CVD event or in all-cause mortality</td>
</tr>
<tr>
<td>Lio et al 2008</td>
<td>Mean-follow-up on diabetes incidence and CVD mortality and all-cause mortality after 20 years</td>
<td>Control group: standard care (IGT)&lt;br&gt;Control group: standard care (normal GT)&lt;br&gt;Intervention group; Exercise 6 month / diet 6 month (IGT)&lt;br&gt;Intervention group: Diet 6 month / exercise 6 month (DM)&lt;br&gt;Individual counselling followed by voluntary group sessions and supervised exercise, one subgroup sustained supervised exercise 12 months&lt;br&gt;Facilitator: physician, nurse, dietician, physiotherapist</td>
<td>Improved aerobic fitness in intervention groups by 14-14%, decrease in the control group: 5-9%&lt;br&gt;Weight reduction in intervention group: 2.0-2.5 kg, increase in the control control: 0.2-2.0 kg.&lt;br&gt;Reduction of total cholesterol, triglycerides and serum insulin in interventions group&lt;br&gt;Glucose tolerance was normalized &gt;50% in the IGT group.&lt;br&gt;More than 50% of diabetes patients were in remission</td>
</tr>
</tbody>
</table>
Table 2. Randomized Controlled Exercise and Lifestyle trials with measurement on Quality of life (QOL)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Follow-up and outcome</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Martin et al 2009</td>
<td>430 American sedentary hypertensive women, mean age 57.4 years, BMI 31.8</td>
<td>Follow-up after 6 months on QOL (SF-36) of three different dose of exercise</td>
<td>Four study arms: Control group: non exercise group Exercise group: Supervised exercise sessions 3-4 / week on bicycle ergometers and treadmill at an intensity of 50% of VO2peak, energy expenditure 4 kcal/kg, 8 kcal/kg or 12 kcal/kg corresponding to 50%, 100% and 150% of current public health recommendations</td>
<td>Exercise improved physical and mental dimensions of QOL in a dose-dependent fashion independent on weight change. Even exercise 50% of the recommendations (approximately 74 min/week) improved four of eight SF-36 subscales</td>
</tr>
<tr>
<td>Grandes et al 2009</td>
<td>4317 Spanish sedentary men and women, 66.6% females, mean age 51.1 year</td>
<td>Follow-up after 6 months on physical activity, estimated maximal oxygen uptake and QOL (SF-36)</td>
<td>Two study arms: Control group: standard care Intervention group: Physical advice by a physician at first visit Subgroup: 30% of participants received a physical activity prescription at a second visit</td>
<td>Increase in physical activity 18 min/week compared to the control Physical activity prescription increased physical activity more, 31.5 min/week No effect on estimated maximal oxygen uptake or QOL</td>
</tr>
<tr>
<td>Lawton et al 2008</td>
<td>1089 sedentary women in New Zealand mean age 59.1 years, Recruited from 17 primary care practices</td>
<td>Follow-up after 24 months on physical activity and QOL (SF-36), weight, waist, blood pressure, blood lipids, HbA1c, glucose and insulin</td>
<td>Two study arms: Control group: Standard care Intervention group: Physical activity prescription by a nurse, telephone support at five occasions during 9 months and visit with the primary care nurse at 6 months.</td>
<td>Increase in physical activity, 39% in the intervention group compared to 33% in the control achieved physical activity goal 150 min/week. Increase in SF-36 Physical functioning and Mental health but decrease in Role physical No increase in clinical or laboratory outcomes</td>
</tr>
<tr>
<td>Ackerman et al 2009</td>
<td>DPP study population 3206 68% female mean age 51 years, BMI 34</td>
<td>Follow-up after 12 months on QOL (SF-6D), SF-36 physical (PCS) and mental summary scores (MCS)</td>
<td>Control group: Placebo pills and written standard information on diet and exercise and annual 20-30 min individual sessions Metformin group: 1700 mg/day, standard information on diet and exercise and annual 20-30 min individual sessions Intervention group: Intensive individualized instruction in diet, exercise and behaviour modification Frequency: 16 individual sessions in the first 24 weeks, then monthly both individual and in groups; total=40 contacts Goals: Weight loss &gt;7%; Diet: low-caloric diet, total fat &lt;25 E% Exercise &gt; 150 min/week Facilitator: Case managers</td>
<td>Lifestyle intervention increased QOL; PCS but decrease in MCS, no change in SF-6D Changes in QOL were associated with change in weight and more strongly in PCS-36 scores</td>
</tr>
<tr>
<td>Herman et al 2003</td>
<td>DPP study population 3234, 68% female mean age 51 years, BMI 34</td>
<td>Follow-up after 3 years on QALY gained by changes in QOL (Self-Administrated Quality of Well-Being Index, QWB-SA)</td>
<td>Control group: Placebo pills and written standard information on diet and exercise and annual 20-30 min individual sessions Metformin group: 1700 mg/day, standard information on diet and exercise and annual 20-30 min individual sessions Intervention group: Intensive individualized instruction in diet, exercise and behaviour modification Frequency: 16 individual sessions in the first 24 weeks, then monthly both individual and in groups; total=40 contacts Goals: Weight loss &gt;7%; Diet: low-caloric diet, total fat &lt;25 E% Exercise &gt; 150 min/week Facilitator: Case managers</td>
<td>Lifestyle intervention resulted in 0.072 gained QALY compared to control and 0.050 compared to the metformin group</td>
</tr>
<tr>
<td>Authors</td>
<td>Population</td>
<td>Follow-up and outcome</td>
<td>Intervention</td>
<td>Results</td>
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<tr>
<td>Kinmonth et al</td>
<td>365 British sedentary adults aged 30-50 with a</td>
<td>Follow-up after 12 months on physical activity, fitness, anthropometrics, blood pressure, blood lipids, HbA1c and blood glucose QOL (SF-36)</td>
<td>Three study arms:</td>
<td>Both groups increased physical activity equivalent to 20 min brisk walk/day but no differences between groups</td>
</tr>
<tr>
<td>2008 (157)</td>
<td>familiar risk of diabetes</td>
<td></td>
<td>Control group: Brief leaflet advice on physical activity</td>
<td>No improvements in fitness</td>
</tr>
<tr>
<td></td>
<td>Recruited from diabetes or family history registers</td>
<td></td>
<td>Intervention group: Behaviour-change program delivered by facilitators in participants home during 1 year and brief advice leaflet. Four 1 hour visits and two telephone calls during 5 months, then monthly telephone calls for 7 months</td>
<td>No improvements in anthropometrics, clinical or laboratory measures</td>
</tr>
<tr>
<td></td>
<td>at 20 general practice clinics</td>
<td></td>
<td>Intervention group: Behaviour-change program delivered by telephone and brief advice leaflet. Four 45 min telephone calls 15 min telephone calls during 5 months, then monthly postal contact for 7 months</td>
<td>Improvement in 6 of eight SF-36 subscales</td>
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<tr>
<td>Williamson et al</td>
<td>5145 American adults with obesity, mean BMI 36.0 and</td>
<td>Follow-up after 12 months on QOL (SF-36; PCS, MCS) Weight and fitness</td>
<td>Two study arms:</td>
<td>Lifestyle intervention improved QOL; PCS but not MCS</td>
</tr>
<tr>
<td>2009 (160)</td>
<td>type 2 diabetes Mean age 58.7 female 59.5% Recruited</td>
<td></td>
<td>Lifestyle program: Goal: reduce weight at least 7% and physical activity at least 175 min/week</td>
<td>Improved fitness and weight reduction in the lifestyle group compared to the education program.</td>
</tr>
<tr>
<td></td>
<td>by 16 outpatient research centres</td>
<td></td>
<td>One individual and 3 group sessions per month during 6 months, then one individual and two group sessions per months to follow-up. Self-monitoring of energy intake and physical activity. Weight measure at each meeting. Diabetes support and education; Three educational group sessions per year focusing on diet, physical activity and support</td>
<td>Improvement in PCS was only partly mediated by weight loss. Other factors as social support, improved metabolic variables or functional abilities accounted for improvements in QOL.</td>
</tr>
</tbody>
</table>
Physical activity recommendations

The impact of type, amount and intensity of physical activity on biological mechanism and quality of life has been fully realized only during the last decade, leading to an update in 2007 of the physical activity recommendation from the American College of Sports and Medicine and the Centre for Disease Control and Prevention (161). The current recommendation for healthy adults 18-65 years includes both moderate- and vigorous intensity activities, and also muscular strength and endurance activities.

- “To promote and maintain health all healthy adults need 30 min of moderate-intensity aerobic (endurance) physical activity for a minimum on five days each week or vigorous-intensity aerobic physical activity for a minimum of 20 min on three day each week.

- Combinations of moderate and vigorous-intensity activities can be performed to meet this recommendation. Moderate-intensity aerobic activity can be accumulated towards the 30-min minimum by performing bouts each lasting 10 or more minutes.

- In addition every adult should perform activities that maintain or increase muscular strength and endurance a minimum of two days a week.

- Because of the dose-response relation between physical activity and health, persons who wish to further improve their personal fitness, reduce their risk for chronic diseases and disabilities or prevent unhealthy weight gain may benefit by exceeding the minimum recommended amounts of physical activity”.

The updated recommendation for older adults ≥65 years and adults aged 50-64 years with clinically significant chronic medical conditions, low fitness level and/or functional limitations are similar but also includes flexibility and balance training (60);

- “The recommended intensity of aerobic activity takes into account the older adult’s aerobic fitness. Activities that maintain or increase flexibility are recommended. Balance exercises are recommended for older adults at risk of falls. Older adult should have an activity plan for achieving recommended physical activity that integrates preventive and therapeutic recommendations. The promotion of physical activity in older adults should emphasize moderate-intensity aerobic activity, muscle-strengthening activity, reducing sedentary behaviour, and risk management”.

For people with impaired glucose tolerance and type 2 diabetes, the American Diabetes Association (ADA) has published physical activity
recommendations. The recommendation includes both aerobic exercise and resistance exercise (162);

- “To improve glycemic control, assist with weight maintenance, and reduce risk of CVD, we recommend at least 150 min/week of moderate-intensity aerobic physical activity (40-60% of VO\textsubscript{2max} or 50-70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (>60% of VO\textsubscript{2max} or >70% of maximal heart rate). The physical activity should be distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity.

- In absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance exercise three times a week, targeting all major muscle groups, progressing to three sets of 8-10 repetitions at a weight that cannot be lifted more than 8-10 times."

- Performing ≥4h/week of moderate to vigorous aerobic and/or resistance exercise physical activity is associated with greater CVD risk reduction compared with lower volumes of activity.

- For long-term maintenance of major weight loss, larger volumes of exercise (7h/week of moderate or vigorous aerobic physical activity) may be helpful.

**Promoting physical activity and lifestyle changes**

Compelling evidence suggest that exercise therapy in many cases is just as effective as medical treatment and promotion and prescription of physical activity and exercise should be a tool in health care (2, 49, 108, 161, 163-167). Interventions to increase physical activity among individuals with risk factors for diseases or with chronic illness are intended to prevent or slow down disease progression, to reduce disease complications and to improve QOL (2, 163, 165). People with chronic disease should have specific program developed by health care professionals and initially supervised exercise sessions (162-164, 167). For people with type 2 diabetes, the American Diabetes Association recommends initially supervised resistance exercises by a qualified exercise specialist to ensure maximize health benefits and correct performance, and to minimize the risk of injury (162).

But no gold standard exists for interventions aiming to increase physical activity level and supporting lifestyle changes among people at risk for chronic diseases. There are many different approaches used to increase physical activity; from brief advice to counselling, written prescription, monitoring, behaviour intervention, and more extensive interventions (14-15). Behaviour approaches help individuals to develop skills that allow
them to achieve a healthier behaviour, focusing on how to change. One frequently used model in lifestyle interventions is the Transtheoretical Model of Behaviour Change (168). The model postulates that individuals engaged in changing behaviour move through five stages of change: precontemplation, contemplation, preparation, action and maintenance. Interventions based on cognitive theories are often use together with other intervention and therefore it is difficult to test the utility of any specific theoretic model (15).

A systematic review of diverse physical activity interventions reported a moderate increase in self-reported physical activity and a moderate increase also in cardiorespiratory fitness, at least in the short-term. Evidence on long-term effects was limited. Due to the heterogeneity of methods, measurements and outcomes, no conclusions on the effectiveness of different methods to promote physical activity could be drawn. Nevertheless, more sustained interventions which provide initial guidance and ongoing support may be more effective (14).

A systematic review from the Swedish Council on Technology Assessment in Health Care (SBU) in 2007 evaluated the effectiveness of different methods to promote physical activity. Only RCTs with at least 6 months of follow-up were included (169). Advice and counselling in clinical practice increased physical activity for at least six months. Further benefits occurred after repeated counselling, and supplemented by written prescriptions, diaries, information brochures and pedometers. Also supervised exercise and behaviour interventions increased physical activity. Interventions that included several lifestyle factors as diet, physical activity and stress management further improved physical activity level (169).

“Physical activity on prescription” (PAP) synonymous to “Exercise on prescription” (EoP) mainly refers to a health care professional’s written advice to a patient to be physically active. The content of EoP may differ in different countries and may include written advice, additional counselling, and telephone follow-up or supervised exercise. Comparisons of interventions are therefore often not feasible (170). A review of EoP in general practice, showed a moderate effect on physical activity in approximately 10% of patients and slightly increased VO2max compared to controls (170). The authors underscored that comparisons of the interventions were complicated by different definitions and methods to measure physical activity, and also varying types of control group.

In a small study with 52 participants, low EoP including counselling only, and high EoP including supervised exercise, were compared. Both groups increased their physical activity and fitness after 10 months of follow-up, but the groups did not differ (171). Recently a Swedish RCT has shown improvements in physical activity level and reduction in weight 6 months after a PAP intervention (172). Another Swedish study carried out in the
primary care setting using PAR intervention and involving 6300 participants, but no control group, reported approximately half of the patients being more physical active after 12 months, and the proportion of inactive patients had decreased (173).

Exercise-referral schemes are another term used for physical activity promotion (174). Exercise-referral can involve an individual program, monitoring, or supervised exercise, mainly in public leisure facilities. A review including 18 studies of exercise-referrals showed small increase in physical activity level but no improvement in clinical measures. The lack of risk reduction was due to low participation and adherence. A review of epidemiological studies and RCTs found that use of pedometers can increase physical activity, decrease BMI and blood pressure in the short run but long-term effects are lacking. Some of the studies also included counselling (175). Another review evaluating methods promoting walking demonstrated an overall increase in average walking time in short-term. Very few studies reported long-term changes or changes in clinical variables (176).

Results from counselling interventions are somewhat inconsistent. Sustained counselling with a behavioural approach increased physical activity and fitness in sedentary women but not in men (177). Counselling with specified recommendations on dose and intensity of physical activity was effective to increase physical activity and fitness in both men and women, in contrast to standard advice (178). In a systematic review lifestyle counselling interventions in primary care to patients at risk for CVD appeared to be of marginal benefit in low-risk subjects compared to standard care (179). There were small improvements in blood pressure in the range of 2 mmHg, and patients of higher risk benefit more. The authors suggested that more sustained lifestyle counselling delivered by health educators with a background in nutrition and exercise might be more effective.

**Health economic analyses**

Health-economic analyses are important in health care decision-making, and can be used as tools for prioritizing the use of scarce resources. Cost-effectiveness analyses assess if a treatment or an intervention is good value for money from the societal perspective. The general approach is to compare the consequences of health care programs with their costs and with a competing method (30). A health care perspective includes only direct medical costs for the health care sector. A societal perspective includes both direct costs and indirect cost, *i.e.* costs for lost production, as time costs for patients receiving care and cost for transports, sick-leave and similar. The preventive value of improvements in health states can also be included in health economic analyses by modelling the predicted effects of the intervention, or the analysis can have a treatment
perspective. The modelling predicts reduction in, e.g., coronary heart events based on risk factor reductions (30).

Different health economic methods are used depending on the research question, study design and the outcome measure. In cost-effectiveness analysis (CEA) the outcome is for example, cost per life year gained, cost per life saved, cost for disease averted or cost per case found. It can also be a clinical measure as costs for a certain amount of blood pressure reduction (30).

A broader form of the CEA is the cost-utility analysis (CUA)(30). The CUA incorporates also the quality of life aspect and a valuation of health states, and the outcome is based on changes in quality of life (QOL). Thus the quality of life years gained can be assessed, not only the number of years. The consequences of an intervention are adjusted by health state preference scores or QOL-weights. The most common outcome measure in the CUA is quality-adjusted life years (QALY). The QALY concept incorporates both the qualitative aspect of health (QOL-weight) and the quantitative aspect, time. A year in perfect health is considered as equal to 1.0 QALY. Calculating QALYs can show change in health status in a population during a certain period, for example after an intervention or during life time. The cost-effectiveness of the intervention can be measured as cost per gained QALY. Using cost per gained QALY as an outcome it is possible to compare results across studies i.e. different interventions and different diagnoses or health problems (30).

The broadest form of analysis is the cost-benefit analysis (CBA)(30). In the CBA the consequences of an intervention is valued in monetary terms. Thus it is possible to decide if the consequences of an intervention justify the costs. A commonly used method to calculate the net benefit of an intervention is by assuming a threshold value of the decision-makers willingness-to-pay for a QALY or a life-year (30). There is no official level of willingness to pay, but in the USA 50 000 and 100 000 USD are often used, and also used as thresholds in this study. In Great Britain 32 000-50 000 USD are applied as acceptable values, and in Sweden 37 500 USD has been a threshold for decision makers in subsidizing pharmaceutical treatments. According to The Swedish National Board of Health and Welfare, costs per QALY gained in SEK are regarded as: low<100 000, moderate 100 000-500 000, high 500 000-1 000 000 and very high >1 000 000.

Costs of inactivity

In Sweden, the direct health care cost of physical inactivity have been calculated to 750 million SEK, and costs for losses in production due to illness to 5.3 billion SEK per year (180). Another report calculated the direct health care cost for overweight and obesity related diseases to 3 billion SEK per year (181). In international studies the costs for obesity
related diseases are estimated to at least 2% of total health care costs, which corresponds to 3 billion SEK in Sweden (182). Promotion of physical activity and a healthy lifestyle may be cost-effective using different methods and in different settings, but cost-effectiveness analyses of lifestyle interventions are rare.

Cost-effectiveness of lifestyle interventions

There is a lack of evidence for effectiveness of specific methods. A systematic review found no reports concerning cost-effectiveness of physical activity promotion in primary care used as a treatment method alongside standard care (183).

The cost-effectiveness of the Diabetes Prevention Program has been assessed. With a 3-year time horizon and a societal perspective, the cost per gained QALY was 51 600 USD in the lifestyle group and 99 200 in the metformin group. Both interventions were seen as cost-effective from both a health care system and a societal perspective and affordable in routine care, especially if implemented in a group format (184). When the time horizon was lifetime and the perspective health care, the cost per gained QALY was estimated to 1100 USD for the lifestyle group and 31 300 for metformin treatment. With a societal perspective the corresponding costs per gained QALY were 8800 USD respectively 29 900 USD. In these analyses also the preventive effects were considered by a modelling procedure (156).

Other studies using preventive modelling have shown lifestyle interventions to be cost-effective. Dietary advice was shown more cost-effective than exercise advice, but both methods were cost-effective in the model compared to no intervention (185). Another study assessed the consequences of implementing a program similar to the DPP in a Swedish setting. The result showed a predicted cost of 2363 Euro per gained QALY, when the health care perspective was used. The authors concluded that lifestyle intervention among high-risk individuals would be cost saving for healthcare and highly cost-effective also from a societal perspective (18).

One study modelled the costs and health outcomes of six different physical activity interventions; pedometers, mass-media community based programs, internet-based program, programs encouraging active transport, GP prescriptions, and GP referrals to exercise specialist (186). Use of pedometers and mass-media based community programs were the most cost-effective interventions, and GP-referral to exercise specialist the less cost-effective method. But all six interventions were found to be cost-effective for the health sector although the authors pointed to an uncertainty about the long-term effects due to the quality of studies on intervention effectiveness.
Rationale of the thesis

Obesity and metabolic disturbances are common in the population (10-12). It is also found that patients in the primary care in Sweden have even higher prevalence of obesity than the general population (10). In northern Sweden, overweight and obesity have increased in both men and women, during the last decades, and since 1990 also the prevalence of abdominal obesity (9). Some risk factor patterns shows a positive trend, less people smoke and the cholesterol level and blood pressure have decreased, similar as in other parts of Sweden and western societies (187). The prevalence of diabetes has remained unchanged, but the prevalence of undiagnosed diabetes is as high as diagnosed type 2 diabetes (82). Since abdominal obesity is linked with increased risk of the metabolic syndrome, diabetes, hypertension and CVD (4, 21, 77, 97) this increase is predicted to cause negative effects on the health status in the population and may counteract the positive effects of the decline in smoking (13).

Several individuals are not physical active enough to reach the physical activity recommendations. In men, a decrease in physical activity and an increase in sedentary working conditions have been observed, while physical activity among women has been relatively unchanged in the Northern Sweden MONICA Study. Approximately 20% of both sexes were sedentary defined by reported physical activity less than two hours per week (188). Between 1986 and 1999 the intake of saturated fat decreased and low-glycaemic carbohydrates increased (189). It is speculated that the increase in abdominal obesity the last decade reflects difficulty in maintaining healthy lifestyle changes (9).

To prevent the development of chronic diseases effective methods for risk reduction are needed. Lifestyle modification should be an alternative or a complement to conventional medical treatment (161, 163, 165, 167). Healthcare providers in primary care meet a large amount of the population each year, and the local health centre is thus an important setting for health promotion. Brief advice and counselling are the traditionally used methods in healthcare to promote lifestyle changes. The last decade also written prescription of physical activity has been more commonly used (170, 172-173).

The health care staff at Swedish health care centres includes not only physicians and nurses, but also several other professions, which make team work possible. Including also physiotherapists and dieticians in the lifestyle team, as experts in exercise and diet, and with knowledge in behaviour modification, makes it possible to offer more extensive interventions as complement to other methods.

There is not enough evidence to claim that any approach to promoting lifestyle changes is superior to another. But it is acknowledged that more sustained interventions providing initial guidance and support, and
delivered by exercise and nutrition specialists are more effective, at least to high risk individuals (14, 179). Large multicenter studies have demonstrated the efficacy of more extensive lifestyle modification on diabetes and cardiovascular risk reduction (16-17). But there have been few attempts to apply these methods in the ordinary primary health care, or “real life” setting. Interventions targeted to individuals with high risk of CVD are supposedly more cost-effective than a low risk strategy. But evidence on long-term effectiveness and cost-effectiveness of such interventions is very limited (18, 149).

Therefore we conducted a 3-year lifestyle intervention program in the primary care setting in a small town in Norrbotten, northern Sweden, targeted to middle-aged individuals at high risk for cardiovascular disease.
AIMS OF THE THESIS

The overall aim of this thesis was to apply a 3-year lifestyle intervention program in an ordinary primary care setting among individuals at moderate to high risk of cardiovascular diseases, and evaluate the short (one year) and long-term effects (up to three years) on physical activity, cardiovascular risk-factor levels and health related quality of life. A secondary aim was to investigate the cost-effectiveness of the intervention.

Specific aims

- To evaluate the effects of the lifestyle intervention on aerobic fitness, total physical activity level, and time spent in exercise after one year, and after three years. *Paper I & II.*

- To evaluate the effects of the lifestyle intervention on anthropometrics after one year, and after three years. *Paper I & II.*

- To evaluate the effects of the lifestyle intervention on blood-pressure and metabolic traits after one year, and after three years. *Paper I & II.*

- To evaluate the effects of the lifestyle intervention on health related quality of life during the 3-year study period. *Paper III.*

- To evaluate cost-effectiveness of the intervention. *Paper III.*
METHODS

Study design

This thesis is based on a prospective randomized controlled trial with one intervention group (n=75) and one control group (n=76). Participants assigned to the intervention arm of the study received standard care and a program of lifestyle modification including structured exercise training sessions and diet counselling, followed by regular group meetings. Those assigned to the control arm received standard care alone. Individuals were follow-up at 3, 12, 24 and 36 months. This thesis is based on the same study sample (n=151), paper I, II & III.

![Time axis of the study.](image)

Participants and settings

The study was carried out in a primary care setting in the northern of part Sweden. All study participants were, at the time of data collection living in the town of Boden in Norrbotten County. Participants, aged 18-65 years were recruited from the catchment area of the Björknäs health care centre. Inclusion criteria were a clinical documented diagnosis of obesity, diabetes type 2, dyslipidaemia and hypertension or any combination thereof. Individuals with a diagnosis of coronary heart disease, stroke, transient ischemic attack, severe hypertension (>SBP180 or DPB>105 mmHg), dementia or severe psychiatric morbidity were excluded.
Methods

Participants were identified by from computerized case records and enrolled in the study by the medical supervisor of the health care centre. Of a total of 9741 inhabitants, 340 meet the inclusion criteria and were invited by letter. Of those, 177 (52%) agreed to participate but 18 withdrew before randomization and a further eight meet the study's exclusion criteria (Figure 2).

Randomization

A total of 151 participants were enrolled, participated in the baseline examinations, and were randomly allocated using a computer-generated random numbers sequence to the intervention group (n=75) or the control group (n=76). An independent statistician generated the allocation sequence and randomization numbers were kept in sealed, opaque envelopes. The allocation was concealed until after the baseline examinations were completed and participants were assigned to their groups by the research physiotherapist. Four individuals allocated to the lifestyle modification program did not start the intervention, and two subjects allocated to the control group had incomplete baseline data and were excluded. Finally, the numbers of participants included in the study were 71 in the intervention group and 74 in the control group.

Registration

The study was registered for clinical trials in the ClinicalTrials.gov: Identifier; NCT004486941. The study was reported as recommended in the CONSORT statement (190).

Ethical approval

All participants received written and verbal information regarding the study. The individuals were informed that the participation was voluntary, they could withdraw at any time without stating a reason, and they were promised confidentiality. All participants who agreed to participate gave written informed consent. The study protocol was approved by the Research Ethics Committee at the Medical Faculty of Umeå University (§10/03, dnr 02-512).
Methods

340 eligible subjects aged 18-65 with the diagnosis hypertension, type 2 diabetes, dyslipidemia or obesity were invited

Baseline examination
Randomisation
n = 151

52% gave their written consent
n = 177

Withdraw before randomisation
n = 18
11 due to workload
5 due to other diseases
1 stroke
1 did not show up

Withdraw before
intervention start
Due to other diseases
n = 4
excluded in analysis

Withdraw where
intervention, n = 4
3 due to workload
1 moved the area

Withdraw before 12-month examination
n = 7
1 moved from the area
1 due to fracture and myocardial infarction
1 due to other disease
2 due to pain
2 did not show up

Withdraw before 24-month examination
n = 2
2 did not want to participate any more

Met exclusion criteria
n = 8

Withdraw, no complete baseline test
n = 2
excluded in analysis

Withdraw before 3-month examination
n = 5
1 due to other disease
3 wanted to participate in the intervention group
1 away on a journey

Withdraw before 12-month examination
n = 6
1 moved from the area
2 drop out
3 did not show up

Baseline examination
Randomisation
n = 151

Intervention group
n = 71

Control group
n = 74

Information meeting
n = 57

3-month examination
n = 67

Start of intervention
n = 71
divided into six groups with 10-13 participants in each

3-month examination
n = 69

6 follow-up meetings
once a month

12-month examination
n = 60

4 follow-up meetings
quarterly

12-month examination
n = 63

36-month examination
n = 58

2 follow-up meetings
semi-annually

24-month examination
n = 63

24-month examination
n = 63

36-month examination
n = 62

340 eligible subjects aged 18-65 with the diagnosis hypertension, type 2 diabetes, dyslipidemia or obesity were invited

Baseline examination
Randomisation
n = 151

52% gave their written consent
n = 177

Withdraw before randomisation
n = 18
11 due to workload
5 due to other diseases
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intervention, n = 4
3 due to workload
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Withdraw before 12-month examination
n = 7
1 moved from the area
1 due to fracture and myocardial infarction
1 due to other disease
2 due to pain
2 did not show up

Withdraw before 24-month examination
n = 2
2 did not want to participate any more

Met exclusion criteria
n = 8

Withdraw, no complete baseline test
n = 2
excluded in analysis

Withdraw before 3-month examination
n = 5
1 due to other disease
3 wanted to participate in the intervention group
1 away on a journey

Withdraw before 12-month examination
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Baseline examination
Randomisation
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quarterly

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n = 63

36-month examination
n = 58

2 follow-up meetings
semi-annually

24-month examination
n = 63

24-month examination
n = 63

36-month examination
n = 62

Figure 3. Participants flow Diagram
Methods

Procedure

Recruitment and follow-up examinations

Participants were recruited in January 2003 and underwent baseline examinations in February 2003. Follow-up examinations were conducted 3, 12, 24 and 36 months after the baseline examination. The participants visited the health care centre at two occasions at baseline and at each follow-up time point to undergo clinical examinations. The examinations comprised interviews, questionnaires, clinical and laboratory measurements. The two different examinations procedures were often within the same week or within two or three weeks. The 3-year follow-up was completed in March 2006.

Figure 4. Scheme for examinations

Data collection

Clinical examination

Interview (Paper I and II)

Interviews were conducted by the same research physiotherapist (ME) at each time point. At baseline focus was on the participant’s history of previous diseases and current medication usage. Changes in pharmacological treatment and disease status were followed yearly.

Anthropometrics (Paper I and II)

The participants were weighted in light indoor clothing without shoes to the nearest 0.1 kg using an electronic balance (Seca model). Height was measured without shoes using a fixed scale on the wall. Body mass index (BMI) was calculated as weight in kilo / height in meters squared. Waist circumference was measured from the point midway between the inferior margin of the last rib and the iliac crest. Hip circumference was measured
Methods

at the widest point between hips and buttocks. Waist-to-hip ratio was calculated as waist circumference / hip circumference.

**Blood pressure (Paper I and II)**

Blood pressure (BP) was measured by a standard auscultatory method with appropriate-sized cuff and determined to the nearest 2 mmHg. BP was measured twice from the right arm in the supine position after 10 min rest. The average of these two measures was used. A trained research physiotherapist (ME) undertook the anthropometric and blood pressure measurements to minimize observer bias.

**Aerobic fitness (Paper I and II)**

Maximal oxygen uptake (VO$_2$max) l/min, ml/kg per min, was estimated as described by Åstrand (68) from each participant’s individual heart response to a given submaximal workload (i.e. 50-150 W depending on the participants weight and self-reported physical activity) using a bicycle ergometer (Monark 818 E and Monark 828, Varberg, Sweden) and recorded at steady-state with a heart rate of ≥120 beats/min. Participants on beta-blockers were excluded from analyses. Two trained physiotherapists performed the exercise tests.

**Laboratory measurements**

**Blood lipids and blood glucose (Paper I and II)**

Blood samples were drawn after an overnight fast. At 2 and 3-year follow-up all non-diabetic participants underwent a two-hour oral glucose tolerance test (OGTT), using 75 g glucose dissolved in 300 ml water (protocol by the WHO). Blood sampling and OGTT were performed by the laboratory nurse at the health care centre. Total cholesterol and triglycerides were analysed by enzymatic colorimetry (slide method, Viros 5.1. Ortho-Clinical diagnostics, Raritan, New Jersey). High-density lipoprotein cholesterol (HDL) was analysed by enzymatic (dextran sulfate procedure) colorimetry (Hitachi 917, Roche Diagnostics Scandinavia AB, Bromma, Sweden). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Serum glucose was analysed by enzymatic (glucose oxidase) colorimetry (Vitros 5.1, Ortho-Clinical diagnostics, Raritan, New Jersey). Glycosylated haemoglobin (Hb) A1c was analysed by High Performance Liquid Chromatography, Ion Exchange Chromatography, Photometry (VARIANT™II, BIORAD laboratories, Hercules California). All biochemical analyses were performed at clinical chemistry laboratory at Sunderby Hospital, Luleå, Sweden.
Behaviour assessments (*Paper I and II*)

Physical activity (PA) and tobacco habits were assessed by a modified self-administrated questionnaire, previously used in the national project “Physical activity on prescription” by the Swedish Institute of Public Health (191). The questions concerning tobacco habits comprised; no smoking, previous or current smoking.

**Physical activity**

The questionnaire included four different questions intending to characterise an individual’s levels of leisure time activity (LPTA), structured exercise, and total physical activity (TPA). LTPA includes activities such as housekeeping, gardening, walking and biking to work, and exercise includes structured activities such as aerobics, jogging, swimming, and ball games during a normal week. Four activity levels were determined for LTPA and exercise (Table 3).

<table>
<thead>
<tr>
<th>Exercise during a normal week</th>
<th>LTPA during a normal week</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. None</td>
<td>1. None</td>
</tr>
<tr>
<td>2. &lt;30 min/d</td>
<td>2.&lt;30 min/d</td>
</tr>
<tr>
<td>3. 30-60 min/d</td>
<td>3. 30-60 min/ d</td>
</tr>
<tr>
<td>4. &gt;60 min/d</td>
<td>4.&gt;60 min/d</td>
</tr>
</tbody>
</table>

Two questions on TPA were included that were intended to estimate all forms of physical activity in daily life and exercise undertaken during the past 12 months. A constructed TPA index with four activity levels was used (Table 4).

<table>
<thead>
<tr>
<th>Physical activity level in daily life over the last 12 months</th>
<th>Exercise over the last 12 months, beyond physical activity in daily life</th>
<th>Index of total physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. None</td>
<td>1. Hardly anything</td>
<td>1. Sedentary</td>
</tr>
<tr>
<td>2. A few times a week</td>
<td>2. Hardly anything, but walked some times</td>
<td>2. Minimally active</td>
</tr>
<tr>
<td>3. Several times a week</td>
<td>3. Light activity at least once a week</td>
<td>3. Moderately active</td>
</tr>
<tr>
<td>4. Every day</td>
<td>4. Moderate activity at least once a week</td>
<td>4. Regularly active</td>
</tr>
<tr>
<td></td>
<td>5. Vigorous activity on regular basis</td>
<td></td>
</tr>
</tbody>
</table>

No validation studies have been performed for this questionnaire, but the TPA question has been used by Swedish regional health authorities to assess public health within the community. The questionnaire was chosen...
since there were no validated PA questions to use at the time for the start of the study.

**Stage of change for Physical activity**

Motivational readiness for increasing physical activity level was assessed by Stage of change for Physical Activity. It is a validated questionnaire consisting of six items designed to identify in which motivational stage the individuals are for a behavioural change. The different items are pre contemplation, contemplation, preparation, action, maintenance or relapse (192).

**Diet**

Changes in dietary habits was followed by questionnaires from the Northern MONICA project but are not analyzed in the present thesis.

**Health-related quality of life (Paper III)**

Quality of life was measured by the validated self-administrated generic questionnaires; (1) EuroQol (EQ) (31, 193) and (2) 36-item Short Form Health Survey (SF-36) (32) and (3) SF-6D derived from SF-36 (194).

EQ includes EQ-5D self-classifier, EQ-VAS (visual analogue scale) and EQ-SDQ (standard set of socio-demographic questions). EQ-5D consists of a 5-item descriptive system that measures five dimensions of health status: mobility, self care, usual activities, pain/discomfort and anxiety/depression. Each dimension is measured on a 3-point scale where a lower score corresponds to a better health state (no problem, some problem and extreme problem). A total of 243 health states are defined by combining one level from each of the dimensions. A weighted utility index can be computed for each of these states based on the values from a general population using a time-trade-off (TTO) technique. The British algorithm (195) was used since there are no Swedish TTO weights for EQ-5D. EQ-5D index is scored on a scale from -0.59 to 1.00, with 1.00 indicating full health and 0 representing death, negative scores are seen worse than death. EQ-VAS is a rating scale and records the respondent’s current subjective perception of his/her overall health status on a 20-cm VAS graduated between 0 (indicating worst imaginable health) and 100 (indicating best imaginable health). EQ-VAS can be transformed into a 0 to 1 scale, by dividing the actual score by 100 (196).

The Swedish version of the SF-36, which is proven valid, reliable and includes standardized norms, was used (32). The SF-36 consists of 36 items grouped into eight domains; physical functioning (PF), limitation in physical role functioning (RP), bodily pain (BP), general health (GH),
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vitality (VT), social functioning (SF), limitation in emotional role functioning (RE), and mental health (MH). Each domain generates a subscale score. All subscale scores are transformed to a score from 0 (worst imaginable health) to 100 (best imaginable health). It is regarded that PF, RF, BP and GH covers primarily physical aspects of health while VT, SF, RE and MH are seen as measuring mental aspect, although GH and VT measures more general aspects of health. Physical component summary score (PCS) and Mental component summary score (MCS) were calculated according to the manual guide (32).

The SF-6D is a utility score derived from responses to 11 questions in the SF-36 questionnaire, and consists of six dimensions of health (PF, RP, BP, MH, VT, and RE). Of 18,000 defined health status, selection of 249 has been evaluated by a general population using a standard gambling technique (194). From that work, a more predictive non-parametric model, producing a separate parameter for each of the 18,000 health status levels, has been developed and was used in this study (197). Full health is scored as 1 and lowest score is 0.2031 (197).

The three main QOL scores (QOL weights) (i.e. EQ-index, EQ-VAS/100 and SF-6D) can also be used in cost-utility analyses when calculating gained quality adjusted life years (QALYs) (30). In this study QOL weights were used to assess QOL and also used in the health economic calculation in this study.

Lifestyle intervention program

The lifestyle intervention program was broadly based from the Finnish Diabetes Prevention Study (FDPS) (17) and the American Diabetes Prevention Program (DPP) (16) but was adapted to limited resources in a primary care setting. Lifestyle modification included supervised exercise sessions, diet counselling and regular follow-up meetings. The first three months of the intervention included three sessions per week of supervised progressive exercise training and diet counselling on a total of five occasions. The active intervention period was followed by regular group meetings (Figure 1, figure 2). Staff from the health care centre including a physiotherapist, a dietician and a physician was responsible for the intervention. The team also consisted of two more physiotherapists, two physiotherapy assistants and a laboratory nurse.

Exercise training

The exercise sessions was delivered by the physiotherapists and physiotherapist assistants at the health care centre. Exercise training consisted of aerobic exercises such as Nordic walking (brisk walking with poles), interval training on a bicycle ergometer, circuit-type resistance training, and aqua-aerobic (Table 5). Exercise training was performed in
Methods

small groups (n=10-13) with each group comprising participants of similar ages and fitness. All groups were offered one session of each activity every week. The exercise sessions lasted 40-45 min during the first month and increased to 60 min during the second and third month. The duration of the bicycle ergometry exercise was increased from 20 to 30 min after one month. The resistance training consisted of 12 different movements per circuit: two sets of 10-15 repetitions were performed at each station. The load was individualized and increased over time as the participants strength improved. All sessions included a warm-up period and a cool-down period with stretching. The aim of the exercise training was to increase cardiorespiratory fitness and to improve functional capacity, endurance, and strength of the large muscle groups of the arms, torso and legs. To regulate optimal exercise intensity, the Borg scale of perceived exertion was used (64). A moderate intensity (60-80% of maximal heart rate) corresponding to 13-15 on the Borg scale was recommended for all activities.

Diet counselling

The dietary advice was given in small groups (n=10-13), at five occasions during the 3-months active intervention. Each meeting lasted for 20-min and a trained dietician was responsible for the diet counselling. The participants received both written and verbal information. No individual counselling was provided. The diet advice was in accordance with the Nordic nutrition recommendations (198). The participants were encouraged to increase their intake of fish, fruits, vegetables, fibre-rich products and complex carbohydrates. Participants were also advised to restrict total caloric intake by reducing consumption of sugar and saturated fat and to use low-fat milk products, soft margarines and vegetable oils rich in monosaturated fatty acids (Table 5).

Follow-up meetings

After the active intervention period, participants from each training group were invited to attend regular but sparse follow-up meetings, on six occasions during the first year (from September to February), on four occasions during the second year, and on two occasions during the third year (Figure 1, figure 2). The objectives of the follow-up meetings were to (1) improve knowledge about the relationship between lifestyle and health, (2) to encourage participants to favourably modify their lifestyles, and (3) to provide social support and to facilitate adherence to the intervention. Discussions at the meetings focused on physical activity, diet, coping with stress and the effect of tobacco on health. Participants were encouraged to maintain at least 30 min/day of physical activity and they were encouraged to fill in activity logs during study phase.
They also received information about community-based physical activities and a study visit at local gym was provided for each group. The stage-of-change model of behavioural change was used as a theoretical basis for these meetings (168). After the active intervention period, most participants were in the active stages and the technique used therefore was standardized for all participants. Focus was on self-regulatory strategies such as goal setting, action planning and relapse avoidance. Participants were encouraged to established individual goals for weight reduction and to develop a personal activity plan. They were asked to reflect upon benefits, barriers and costs of adherence to a healthier lifestyle. Emphasis was placed on identifying situations that inhibit healthy behaviours such as holidays or heavy workloads and strategies to handle these situations to avoid relapses were discussed. The progress of each participant was discussed at the meetings during follow-up, and at the final stage of the trial, the importance of maintaining healthy habits was reinforced.

Physiotherapists supervised most of these group meetings, and a dietician provided further diet counselling on three occasions, once a year during the follow-up period. The medically responsible physician took part in one meeting at the beginning of the study and in the end of the study to answer participant’s questions about the health aspects of the intervention and to reinforce the message being delivered by the physiotherapists and the dietician. Each year, participants were given a written summary of their clinical and laboratory tests. Participants in the intervention group continued with their routine care, delivered for example by their family practitioner or specialist throughout the study.

Standard care control group

Participants in the control arm of the study received standard care at the health care centre. They were also given information about healthy behaviours, including exercise and diet, at one single group meeting following the baseline examination. The dietary advice was given verbally and in written form, and the advice concerning physical activity was given verbally. This information was delivered by the physician, a physiotherapist and a dietician. Also participants in the control group were encouraged to fill in activity logs during study phase, and were given a written summary of their clinical and laboratory tests.

Blinding

Neither the participants nor the family practitioners or the physiotherapists who delivered the intervention and were responsible for the clinical examinations were blinded to the allocation of treatment.
### Table 5. Summary of physical activity and diet recommendations provided to participants randomized to the control and intervention groups

<table>
<thead>
<tr>
<th></th>
<th>Control group (standard recommendations)</th>
<th>Intervention group (extended recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical activity</strong></td>
<td>- Aim to accumulate at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week</td>
<td>- Aim to accumulate at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week</td>
</tr>
<tr>
<td>Swedish Institute of Public Health</td>
<td>- Additional health benefits can be achieved by extending the time spent in moderate-intensity activities, or by increasing the intensity of activities</td>
<td>- Additional health benefits can be achieved by extending the time spent in moderate-intensity activities, or by increasing the intensity of activities</td>
</tr>
<tr>
<td></td>
<td>- Aim to undertake 20-30 minutes of moderate to vigorous intensity of aerobic activities lasting 20-30 minutes, three times each week (e.g. bicycle ergometry exercise, Nordic walking, aqua-aerobics)</td>
<td>- Aim to undertake muscle-strengthening activities, lasting 20-30 minutes, at least twice each week (e.g. circuit-type resistance exercise, aqua-aerobics)</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>Energy percent, E%, - Carbohydrates, 55% (50-60) sugar &lt;10% - Protein, 15% (10-20) - Fat, 30% (25-35) saturated fat and trans fat, 10% monounsaturated fat, 10-15% polyunsaturated fat, 5 (-10) General advice: - Increase intake of fish, fruits, vegetables, fibre rich products and complex carbohydrates - Reduce consumption of sugar and saturated fat - Use low-fat milk products, soft margarines and vegetable oils rich in monosaturated fatty acids. - Restrict total caloric intake. - Regular meal distribution.</td>
<td>Energy percent, E%, - Carbohydrates, 55% (50-60) sugar &lt;10% - Protein, 15% (10-20) - Fat, 30% (25-35) saturated fat and trans fat, 10% monounsaturated fat, 10-15% polyunsaturated fat, 5 (-10) General advice - Increase intake of fish, fruits and vegetables, fibre rich products and complex carbohydrates. - Reduce consumption of sugar and saturated fat. - Use low-fat milk products, soft margarines and vegetable oils rich in monosaturated fatty acids. - Restrict total caloric intake. - Regular meal distribution. Information about meal content and function of: - Fat, carbohydrates, protein, vitamins, minerals and antioxidants. - Energy balance and energy expenditure. - Alcohol.</td>
</tr>
</tbody>
</table>
Methods

Health economic analysis method

Cost-utility analysis (Paper III)

Gained QALY and costs per gained QALY

The analysis in this study was a cost-utility analysis with a societal perspective, using gained QALY and costs per gained QALY as the measurement effect. Gained QALYs was calculated based on changes in QOL weights (i.e. EQ VAS, EQ-5D and SF-6D) between the intervention and the control group at follow-up time points: 3, 12, 24 and 36 months. Cost-effectiveness ratios were based on the changes in QALYs and net costs for the intervention group and the control group. In the analysis, cost for stakeholder of intervention, patients cost, treatment effect, and savings in health care use were considered. All changes in costs and effects were assumed to change linearly between measurements times and were discounted 3% per year. A summary of the cost-utility analysis are shown in (Table 6).

Table 6. Measurement methods for variables in the health economic analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variable</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>Program costs for</td>
<td>Accounts of primary health care providers. Costs were calculated based on estimated time consumption, and estimated fractions of costs for</td>
</tr>
<tr>
<td></td>
<td>the stakeholders</td>
<td>care center rent, equipment, and overheads.</td>
</tr>
<tr>
<td></td>
<td>Participants’ expenses</td>
<td>Physical activity, at least 30 minutes a day, was assumed to cost 400 USD/yr, representing a yearly fee at exercise centres in Sweden, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>physical activity less than 30 minutes a day was assumed to cost 67 USD/yr. Empirical data were not available.</td>
</tr>
<tr>
<td>Treatment effect</td>
<td>QOL</td>
<td>EQ-5D in combination with preference scores from a British population (31,193,195)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EQ Rating Scale (31,196).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SF-6D in combination with preference scores from a British population (194,197)</td>
</tr>
<tr>
<td>Savings</td>
<td>Health care costs</td>
<td>Health care records regarding the last 6 months’ health care use before baseline and the 3 yr use after start of the intervention. Number of visits to family physicians and nurses in primary health care, and visits and admissions in hospital care were counted. Standard production prices negotiated for trade of health care between county councils were used.</td>
</tr>
</tbody>
</table>

Costs

Health care costs included costs for personnel based on time consumption, costs for health care rent, equipment and overhead costs. A summary of personnel recourses used and health care rent for the lifestyle
Methods

intervention are given in table 7. Participants costs were based on imposed costs for spending more time exercising, but the cost for participants exercise time or change in production were not included. All costs were transformed from Swedish currency to USD using the exchange rate 1 USD=7.5 SEK. Costs were recalculated to the price level of 2009 using the Swedish consumer price index. Research costs and costs relating to the development of the method were not included.

<table>
<thead>
<tr>
<th>Time consumption</th>
<th>Health care providers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (n=71)</td>
<td>Control group (n=74) / 6 groups (n=12)</td>
<td>Intervention control care rent</td>
</tr>
<tr>
<td>First year</td>
<td>Hours</td>
<td>Hours</td>
<td>Hours</td>
</tr>
<tr>
<td>Supervised exercise:</td>
<td>(20 h preparation)</td>
<td>6*3 * 12+20 =236</td>
<td>72 gym</td>
</tr>
<tr>
<td>Physiotherapists</td>
<td></td>
<td>0</td>
<td>72 pool</td>
</tr>
<tr>
<td>Group meetings/ counseling</td>
<td>(1 h preparation each meeting)</td>
<td>(1 h preparation each meeting)</td>
<td>2</td>
</tr>
<tr>
<td>Dietician</td>
<td>6°*0.75+5 =27.5</td>
<td>2*1+1 =3</td>
<td>22.5</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>6°6 + 6 =42</td>
<td>2*1+1 =3</td>
<td>36</td>
</tr>
<tr>
<td>Family physicians</td>
<td>6°0.5+1 =4</td>
<td>2*1+1 =3</td>
<td></td>
</tr>
<tr>
<td>Second year</td>
<td>Hours</td>
<td>Hours</td>
<td>Hours</td>
</tr>
<tr>
<td>Group meetings/ counseling</td>
<td>(1 h preparation each meeting)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dietician</td>
<td>6°*1+1 =7</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>6°3*3=21</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Family physicians</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Third year</td>
<td>Hours</td>
<td>Hours</td>
<td>Hours</td>
</tr>
<tr>
<td>Group meetings/ counseling</td>
<td>(1 h preparation each meeting)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dietician</td>
<td>6°*1+1 =7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>6°2+2=14</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Family physicians</td>
<td>6°0.5+1 =4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total physician</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total dietician</td>
<td>41.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total physiotherapist</td>
<td>293</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total health care rent</td>
<td>94.5</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Health care use

Health care utilisation data were extracted from electronic patient records from all health care centres and hospitals in the county, and were followed from six months before start of the intervention to three year after that the intervention had started. Number of visits to family physicians and nurses in primary health care, number of visits to specialists and nurses at hospital, and number and duration of admissions were counted. The investigation was done by a blinded researcher. Visits to physiotherapists during the study period were not included in analyses since data on visits to physiotherapists in the private health care sector was not available, neither were visits to dieticians included (199).
Net Monetary Benefit Method

The uncertainty from the trial was handled with the Net Monetary Benefit method (NMB). This method is based on replacing health effects (QALY) with the amount of money decision makers are willing to pay for a gained QALY. When both effects and resource use are expressed in monetary units, it is possible to calculate a confidence interval (CI) for cost-effectiveness and the probability that an intervention is cost-effective in relation to a competing intervention.

Probability ($P$) of cost effectiveness can be expressed as follows:

Where $C$ are mean treatment costs, $S$ are savings in health care cost compared with baseline, $Q$ are effects in QALY gained, and 1 and 0 denote intervention group and control group, respectively.

$$P \left( \frac{(C_1 - S_1) - (C_0 - S_0)}{Q_1 - Q_0} \right) < 50,000 \text{ USD} \quad P \left( \frac{(C_1 - S_1 - (Q_1 \times 50,000)) - (C_0 - S_0 - (Q_0 \times 50,000))}{Q_1 - Q_0} \right)$$

Or expressed in net monetary benefit (NMB)

$$P \left( \text{NMB}_1 > \text{NMB}_0 \right)$$

This is the probability of cost-effectiveness, or the probability that NMB$_1$ is preferable as compared with NMB$_0$ given a certain level of willingness to pay for a QALY (50 000 USD in this example).

A scatter plot of 5000 bootstrapped incremental cost-effectiveness ratios was created, by repeatedly drawing a random sample with replacement using parameters estimated from the RCT. Individual values were used for savings in health care costs and gained QALY, and mean values were used for costs in intervention and control group. This produces estimates of the probability that the intervention was cost-effective using several thresholds of willingness to pay for a QALY. Results are presented in a cost-effectiveness acceptability curve (200). Further, mean NMB and confidence interval of NMB were estimated for these different thresholds values.

Statistical analyses

Statistics

SPSS for Windows version 10.0 (Paper I) and version 14-15.0 (paper II - III) (Chicago, IL, USA) and SAS for Windows (V9.1), Carey NC) (Paper II) were used for statistical analyses. A $p$-value less than 0.05 was considered significant in all analyses. In Paper I all analyses were performed per-protocol (patients who completed the 1-year follow-up). Changes within-groups between baseline and follow-up were analysed using a two-tailed
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unpaired t-test, and differences between groups were analysed using an independent two sample t-test (continuous variables) and Pearson’s Chi squared test (categorical variables). Non-parametric statistics, Wilcoxon Signed Ranks Test and Mann-Whitney U-Test, were used for ordinal data such as questionnaires.

In Paper II and III all analyses were done on an Intention-to treat basis (ITT), if data were missing last observation was carried forward (LOCF). In Paper II, intervention overall main effects on continuous variables were analysed using general linear model repeated measures of variance, adjusted for baseline values (ANCOVA), and when needed also for medication use. Mixed-model analyses were used to calculate the adjusted effects of the intervention at each follow-up point for continuous variables and to investigate the overall effect of the intervention. For ordinal data the non-parametric Mann-Whitney U-Test was used for analyses between groups at each follow-up point, and mixed-models were used to assess the overall effect. For other categorical variables the Pearson Chi-Square test and repeated measures were used.

In paper III, general linear model repeated analysis of variance (ANOVA) was used to estimate mean changes in continuous variables over time, overall main effects, testing also for effects of time and interaction. An independent two sample t-test, with Bonferroni correction when needed, was used for comparison at singular time point. All outcome variables were also analysed per-protocol, using only available data and also adjusted for sex and age. Effect size as standardized response mean was calculated according to Cohen (201); mean change between groups divided by the total SD of the change.

Ordinal outcome variables Stage of Change for physical activity, measured repeatedly over time, were dichotomized and analysed using logistic Generalized Estimation Equations (GEE). These results are only presented only in the cover story of the thesis.

The sample size calculation was based on weight change and performed in Paper I and II.
RESULTS

Characteristics of the study population

Participants flow and drop outs (Paper I & I & III)

The total study population consisted of 145 participants, 71 in the lifestyle intervention group and 74 in the standard care control group. Attrition was greatest during the first year, and the 3-year follow up was completed by 120 participants (83%) (Figure 2). Those lost to follow-up did not differ between the groups; 12 women and 5 men in the intervention group compared to 5 women and 9 men in the control group. Characteristics among the participants who withdrew during the study did not differ from those who completed the trial. Neither were there any differences in demographic characteristics or CVD risk profile between the individuals who denied participating or those that participated.

Mean age in the study group was 54.4 years and 57% were female. Most of the participants had upper secondary school education (57%), 53% were employed and 36% were retired. Overweight (BMI 25-29.9) or obesity (BMI ≥30) was present in 86.8%, and abdominal obesity was common in both sex (median value men 106.5 cm women 95.5 cm). Most participants had one or more additional CVD risk factor, 66% had a diagnosis of hypertension, 22% a diagnosis of diabetes and 22 % had dyslipidaemia (Table 6). Although, compared to population data from Norrbotten County in the 2004 MONICA population survey (187), the study population had lower levels of total cholesterol and fasting blood glucose (Table 7). An inactive lifestyle was common; 54% reported being sedentary or minimally active, and 84.2% reported none or less than 30 min of exercise per day (Table 6) (Paper I&II).

Not all characteristics were equally distributed between the intervention and control groups. The intervention group tended to be less physical active and to have larger waist. Smoking, diabetes and treatment with lipid-lowering drugs were more frequent in the intervention group, while hypertensive medication was more common in the control group (Table 8, table 9). The intervention group reported lower mean scores in all QOL subscales at baseline (Table 10), and a larger proportion reported problems in the EQ dimension anxiety/depression.
### Results

**Table 8.** Patient characteristics at baseline in the Swedish Björknäs study

<table>
<thead>
<tr>
<th>Variable</th>
<th>All participants (n=145)</th>
<th>Intervention group (n=71)</th>
<th>Control group (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>54.4</td>
<td>55.7 (6.6)</td>
<td>53.1 (8.2)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (42.8)</td>
<td>35 (49)</td>
<td>27 (36.5)</td>
</tr>
<tr>
<td>Female</td>
<td>83 (57.2)</td>
<td>36 (51)</td>
<td>47 (63.5)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary grade</td>
<td>28 (19.3)</td>
<td>14 (20)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Upper secondary school</td>
<td>82 (56.6)</td>
<td>41 (58)</td>
<td>41 (55)</td>
</tr>
<tr>
<td>University college education</td>
<td>35 (24.1)</td>
<td>16 (22)</td>
<td>19 (26)</td>
</tr>
<tr>
<td><strong>Main occupation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working employed/self-employed</td>
<td>77 (53.1)</td>
<td>38 (53)</td>
<td>39 (53)</td>
</tr>
<tr>
<td>Retired</td>
<td>52 (35.9)</td>
<td>26 (37)</td>
<td>26 (35)</td>
</tr>
<tr>
<td>Unemployed/other</td>
<td>16 (11)</td>
<td>7 (10)</td>
<td>9 (12)</td>
</tr>
<tr>
<td><strong>Smoking habits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>30 (20.7)</td>
<td>17 (24)</td>
<td>13 (18)</td>
</tr>
<tr>
<td><strong>Overweight or obesity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction with BMI ≥ 25</td>
<td>125 (86.8)</td>
<td>64 (90)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Fraction with BMI ≥ 30</td>
<td>62 (42.8)</td>
<td>32 (45)</td>
<td>30 (41)</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>40 (27.6)</td>
<td>23 (32)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Hypertension medication</td>
<td>95 (65.5)</td>
<td>45 (63)</td>
<td>50 (68)</td>
</tr>
<tr>
<td>Dyslipidaemia medication</td>
<td>32 (22.1)</td>
<td>24 (34)</td>
<td>8 (11)</td>
</tr>
<tr>
<td><strong>Total physical activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>17 (11.7)</td>
<td>14 (20)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Minimally active</td>
<td>62 (42.8)</td>
<td>27 (38)</td>
<td>35 (47)</td>
</tr>
<tr>
<td>Moderately active</td>
<td>47 (32.4)</td>
<td>22 (31)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>Very active</td>
<td>19 (13.1)</td>
<td>8 (12)</td>
<td>11 (15)</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>80 (55.2)</td>
<td>43 (61)</td>
<td>37 (50)</td>
</tr>
<tr>
<td>&lt;30 min/d</td>
<td>42 (29)</td>
<td>20 (28)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>30-60 min/d</td>
<td>21 (14.5)</td>
<td>8 (11)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>&gt;60 min/d</td>
<td>2 (1.4)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Leisure-time Activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (27)</td>
<td>14 (20)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>&lt;30 min/d</td>
<td>48 (66)</td>
<td>23 (32)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>30-60 min/d</td>
<td>59 (82)</td>
<td>30 (43)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>&gt;60 min /d</td>
<td>19 (26)</td>
<td>4 (6)</td>
<td>15 (20)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) other variables are given as number and percent (%).
### Table 9. Participants characteristics at baseline and population data from northern Sweden

<table>
<thead>
<tr>
<th>Study group (mean age 54)</th>
<th>MONICA 2004 45-64 years</th>
<th>Study group Sub groups by sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group n=71</td>
<td>Control group n=74</td>
</tr>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>87.4 (16.5)</td>
<td>84.3 (20)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>30.2 (5.2)</td>
<td>29.4 (5.1)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>104.1 (13.2)</td>
<td>100.2 (15.9)</td>
</tr>
<tr>
<td>Hip, circumference, cm</td>
<td>108.6 (10.2)</td>
<td>107.4 (8.6)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.96 (0.08)</td>
<td>0.93 (0.09)</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mmHg</td>
<td>145.6 (15.5)</td>
<td>144.7 (17.6)</td>
</tr>
<tr>
<td>Diastolic, mmHg</td>
<td>88.2 (7.1)</td>
<td>88.6 (8.4)</td>
</tr>
<tr>
<td><strong>Exercise test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal oxygen uptake l/min</td>
<td>2.1 (0.6)</td>
<td>2.2 (0.5)</td>
</tr>
<tr>
<td>Maximal oxygen uptake ml/kg</td>
<td>25.4 (6.4)</td>
<td>25.8 (6.0)</td>
</tr>
<tr>
<td><strong>Laboratory measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol, mmol/l</td>
<td>5.49 (1.05)</td>
<td>5.43 (0.91)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.39 (0.32)</td>
<td>1.46 (0.40)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.17 (0.91)</td>
<td>3.12 (0.82)</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>2.08 (1.24)</td>
<td>1.90 (1.15)</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/l</td>
<td>5.24 (0.50)</td>
<td>5.20 (0.50)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.30 (1.35)</td>
<td>6.62 (2.05)</td>
</tr>
</tbody>
</table>

Data are given as means and (SD).
Results

Table 10. Quality of life score at baseline in the Swedish Björknäs study.

<table>
<thead>
<tr>
<th>Quality of life score</th>
<th>All participants (n=145)</th>
<th>Intervention group (n=71)</th>
<th>Control group (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D</td>
<td>0.81 (0.21)</td>
<td>0.78 (0.24)</td>
<td>0.83 (0.16)</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>0.66 (0.18)</td>
<td>0.63 (0.20)</td>
<td>0.70 (0.15)</td>
</tr>
<tr>
<td>SF-6D</td>
<td>0.70 (0.10)</td>
<td>0.68 (0.10)</td>
<td>0.71 (0.10)</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>82.6 (17.1)</td>
<td>80.2 (17.6)</td>
<td>84.9 (16.5)</td>
</tr>
<tr>
<td>Role Limitation Physical</td>
<td>78.1 (34.2)</td>
<td>74.6 (36.7)</td>
<td>81.4 (31.5)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>67.4 (26.3)</td>
<td>64.0 (27.7)</td>
<td>70.5 (25.8)</td>
</tr>
<tr>
<td>General Health</td>
<td>66.6 (19.8)</td>
<td>64.8 (19.4)</td>
<td>68.4 (20.0)</td>
</tr>
<tr>
<td>Vitality</td>
<td>65.7 (21.4)</td>
<td>62.9 (22.8)</td>
<td>68.4 (19.7)</td>
</tr>
<tr>
<td>Social Function</td>
<td>89.3 (18.5)</td>
<td>87.0 (21.3)</td>
<td>91.6 (15.1)</td>
</tr>
<tr>
<td>Role Limitation Emotional</td>
<td>88.5 (26.5)</td>
<td>84.5 (29.2)</td>
<td>92.1 (23.1)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>83.8 (14.6)</td>
<td>81.3 (16.7)</td>
<td>86.2 (11.8)</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>45.8 (9.9)</td>
<td>44.8 (10.1)</td>
<td>46.7 (9.7)</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>52.1 (8.4)</td>
<td>50.8 (9.7)</td>
<td>53.4 (6.7)</td>
</tr>
</tbody>
</table>

Data are given as mean (SD)

In the whole study group EQ-VAS score and the physical dimensions of SF-36 were lower than the Swedish population (27, 32). However the EQ-5D score and the mental dimensions of SF-36 were similar to the Swedish population (Figure 5, figure 6). A larger proportion reported problems in the EQ dimension pain/discomfort and a smaller proportion reported anxiety/depression than the Stockholm population (27) (Figure 7) (Paper III).

Figure 5. SF-36 scores at baseline in the total study population and Swedish norm means. Data are means and SD.
Results

Figure 6. EuroQol scores in the total study population at baseline and in the Stockholm population. Data are means.

Figure 7. EQ-5D in the total study population at baseline and in the Stockholm population. Data are percent.

The mean baseline score for QOL scales across subgroups confirmed expected QOL differences among groups. All QOL scores were lower in females, unemployed, and among those with lower education, in obese and sedentary individuals, compared to males, employed, people with college or university education, people with normal weight and more physically active individuals (Table 11).
Results

### Table 11. Baseline Quality of life scores by Subgroup

<table>
<thead>
<tr>
<th>Baseline Category</th>
<th>No (n)</th>
<th>EQ-5D Score</th>
<th>EQ VAS Score</th>
<th>SF-6D Score</th>
<th>SF-36 Physical Component Summary</th>
<th>SF-36 Mental Component Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤44</td>
<td>15</td>
<td>0.81 (0.22)</td>
<td>0.53 (0.22)</td>
<td>0.70 (0.11)</td>
<td>46.6 (10.8)</td>
<td>49.5 (7.9)</td>
</tr>
<tr>
<td>45-54</td>
<td>55</td>
<td>0.82 (0.20)</td>
<td>0.68 (0.17)</td>
<td>0.71 (0.10)</td>
<td>47.8 (8.1)</td>
<td>51.1 (9.3)</td>
</tr>
<tr>
<td>≥55</td>
<td>75</td>
<td>0.80 (0.21)</td>
<td>0.68 (0.17)</td>
<td>0.69 (0.10)</td>
<td>44.1 (10.8)</td>
<td>53.3 (7.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62</td>
<td>0.83 (0.20)</td>
<td>0.68 (0.16)</td>
<td>0.70 (0.11)</td>
<td>46.2 (10.6)</td>
<td>53.1 (6.7)</td>
</tr>
<tr>
<td>Female</td>
<td>83</td>
<td>0.79 (0.21)</td>
<td>0.65 (0.19)</td>
<td>0.69 (0.10)</td>
<td>46.5 (9.4)</td>
<td>51.3 (8.4)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary grade</td>
<td>28</td>
<td>0.79 (0.21)</td>
<td>0.65 (0.16)</td>
<td>0.68 (0.09)</td>
<td>44.1 (10.2)</td>
<td>53.5 (7.9)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>82</td>
<td>0.79 (0.22)</td>
<td>0.65 (0.19)</td>
<td>0.70 (0.10)</td>
<td>46.2 (9.4)</td>
<td>50.6 (9.2)</td>
</tr>
<tr>
<td>University</td>
<td>35</td>
<td>0.86 (0.17)</td>
<td>0.71 (0.17)</td>
<td>0.71 (0.10)</td>
<td>46.1 (10.9)</td>
<td>54.4 (5.9)</td>
</tr>
<tr>
<td>Main occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed/ self-employed</td>
<td>77</td>
<td>0.85 (0.18)</td>
<td>0.67 (0.17)</td>
<td>0.71 (0.09)</td>
<td>48.6 (8.1)</td>
<td>51.8 (7.8)</td>
</tr>
<tr>
<td>Retired</td>
<td>52</td>
<td>0.77 (0.22)</td>
<td>0.68 (0.16)</td>
<td>0.68 (0.10)</td>
<td>43.0 (10.5)</td>
<td>53.3 (8.9)</td>
</tr>
<tr>
<td>Unemployed/ other</td>
<td>16</td>
<td>0.73 (0.26)</td>
<td>0.57 (0.26)</td>
<td>0.65 (0.12)</td>
<td>41.5 (12.2)</td>
<td>49.5 (9.5)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smokers</td>
<td>115</td>
<td>0.82 (0.19)</td>
<td>0.69 (0.17)</td>
<td>0.71 (0.10)</td>
<td>46.8 (9.4)</td>
<td>53.6 (6.8)</td>
</tr>
<tr>
<td>(Former)</td>
<td>(53)</td>
<td>0.83 (0.19)</td>
<td>0.70 (0.16)</td>
<td>0.70 (0.11)</td>
<td>47.0 (9.9)</td>
<td>53.4 (6.1)</td>
</tr>
<tr>
<td>Current</td>
<td>30</td>
<td>0.75 (0.26)</td>
<td>0.56 (0.19)</td>
<td>0.65 (0.10)</td>
<td>42.1 (11.0)</td>
<td>46.0 (11.1)</td>
</tr>
<tr>
<td>BMI range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ≤24.9</td>
<td>19</td>
<td>0.84 (0.12)</td>
<td>0.71 (0.14)</td>
<td>0.71 (0.08)</td>
<td>46.7 (9.2)</td>
<td>51.5 (7.9)</td>
</tr>
<tr>
<td>Overweight</td>
<td>64</td>
<td>0.84 (0.20)</td>
<td>0.71 (0.15)</td>
<td>0.71 (0.10)</td>
<td>47.8 (9.1)</td>
<td>53.9 (6.7)</td>
</tr>
<tr>
<td>Obesity ≥30</td>
<td>62</td>
<td>0.77 (0.23)</td>
<td>0.60 (0.20)</td>
<td>0.67 (0.11)</td>
<td>43.4 (10.6)</td>
<td>50.4 (9.8)</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>40</td>
<td>0.77 (0.23)</td>
<td>0.63 (0.19)</td>
<td>0.67 (0.11)</td>
<td>43.3 (11.6)</td>
<td>52.7 (8.1)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary/ Minimally</td>
<td>79</td>
<td>0.80 (0.22)</td>
<td>0.63 (0.18)</td>
<td>0.67 (0.10)</td>
<td>44.4 (10.6)</td>
<td>50.9 (8.9)</td>
</tr>
<tr>
<td>Very active</td>
<td>66</td>
<td>0.82 (0.19)</td>
<td>0.70 (0.18)</td>
<td>0.72 (0.10)</td>
<td>47.4 (8.9)</td>
<td>53.4 (7.6)</td>
</tr>
</tbody>
</table>

Data are unadjusted means and (SD).

### Compliance

Attendance at the supervised exercise sessions during the 3-month active period varied among participants. Mean attendance was 70% of the sessions, but differed between 15% and 100%. No adverse events occurred during the specific exercise sessions. Sixty-four percent took part in 3-5 diet-counselling sessions but 36% participated on only one or two occasions. Low attendance was mainly due to the participant’s employment. During the first year of follow-up mean attendance at the group meetings was 70%, during the second year 63% and during the third year 66%. In the control group 77% attended the information meeting offered after the randomization.
Effects on clinical measurements (Paper I & II)

All analyses at the 3-year follow-up were performed on ITT basis, if data were missing last observation was put forward. Mixed model analyses, using only available data, were used as ancillary analyses in paper II, and for exploratory reasons also per protocol analyses were performed. All analyses generated results in accordance, therefore the per-protocol results were not published in paper II and III.

**Anthropometrics**

The intervention beneficially influenced anthropometrics by reducing waist and waist-to-hip ratio, and prevented weight gain. (Paper I & II). Improvements were seen in both groups during study phase, although generally greater in the lifestyle group. Reductions in waist circumference and waist-to-hip ratio were shown in the intervention group after the 3-month active intervention period. The differences between groups were significant at all follow-up time points and persisted over time. After 3 years ITT analysis showed an -2.2 cm decrease in waist (Table 12, figure 7). Significant reductions in weight between groups were seen during the first year but did not persist at the 3-year follow-up. Per protocol analyses somewhat strengthens the results.

**Table 12. Anthropometrics after 3 years**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (n=71)</th>
<th>Control group (n=74)</th>
<th>p-value ANCOVA</th>
<th>p-value Mixed model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist, cm</td>
<td>100.7 (99.7; 101.7)</td>
<td>102.9 (101.9; 103.9)</td>
<td>0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>107.0 (106.3; 107.7)</td>
<td>107.4 (106.7; 108.0)</td>
<td>0.18</td>
<td>0.36</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.94 (0.93; 0.95)</td>
<td>0.96 (0.95; 0.96)</td>
<td>0.000</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.0 (84.0; 86.0)</td>
<td>85.6 (84.6; 86.6)</td>
<td>0.15</td>
<td>0.19</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.5 (29.2; 29.9)</td>
<td>29.8 (29.4; 30.1)</td>
<td>0.16</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Per protocol analyses n=120**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (n=58)</th>
<th>Control group (n=62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist, cm</td>
<td>99.0 (97.8; 100.3)</td>
<td>101.9 (100.7; 103.1)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>105.9 (105.1; 106.7)</td>
<td>106.3 (105.6; 107.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.93 (0.93; 0.94)</td>
<td>0.96 (0.95; 0.96)</td>
<td>0.000</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83.1 (81.9; 84.3)</td>
<td>83.7 (82.6; 84.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.8 (28.5; 29.3)</td>
<td>29.1 (28.7; 29.5)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Data are estimated marginal means (95% CI) derived from general linear model with repeated measures.
Results

Figure 7. Changes in anthropometrics during study phase. Data are estimated marginal means (95% CI) derived from repeated measures ANCOVA.
The proportion of participants classified as normal weight (i.e. BMI 20-29.9 kg/m²) increased during the study period, although this change did not differ statistically between groups (Table 13).

**Table 13. Normal weight, overweight and obesity at baseline and at 3 years**

<table>
<thead>
<tr>
<th>BMI groups</th>
<th>Intention-to treat analyses n=145</th>
<th>Pre protocol analyses n=120</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group n (%)</td>
<td>Control group n (%)</td>
</tr>
<tr>
<td>Baseline</td>
<td>n=71</td>
<td>n=74</td>
</tr>
<tr>
<td>≤24.9</td>
<td>7 (10)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>32 (45)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>≥30</td>
<td>32 (45)</td>
<td>30 (41)</td>
</tr>
<tr>
<td>3 years</td>
<td>n=71</td>
<td>n=74</td>
</tr>
<tr>
<td>≤24.9</td>
<td>12 (17)</td>
<td>15 (20)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>27 (38)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>≥30</td>
<td>32 (45)</td>
<td>30 (41)</td>
</tr>
</tbody>
</table>

Data are given as number (percent).

Unadjusted mean changes in anthropometrics between groups are presented in Table 14.

**Table 14. Changes in anthropometrics between groups and in sub groups from baseline to 3 years**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Differences between groups</th>
<th>p-value</th>
<th>Differences between groups</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist, cm</td>
<td>-2.4 (-3.8; -0.99)</td>
<td>0.002</td>
<td>-3.1 (-4.8; -1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>-0.4 (-1.3; 0.5)</td>
<td>0.41</td>
<td>-0.5 (-1.6; 0.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>-0.02 (-0.03; -0.01)</td>
<td>&lt;0.0001</td>
<td>-0.02 (-0.04; -0.12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>-0.7 (-2.1; 0.7)</td>
<td>0.35</td>
<td>-0.7 (-2.4; 0.95)</td>
<td>0.40</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>-0.2 (-0.7; 0.3)</td>
<td>0.41</td>
<td>-0.2 (-0.8; 0.4)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Data are unadjusted mean changes (95% CI) derived from independent two sample t-test and descriptive analyses.

**Blood pressure**

The intervention decreased blood pressure levels (Paper I & II). Reductions in blood pressure were greater in the intervention group and the differences between groups were significant over time (Table 13, figure 8). At three years follow-up the groups differed in systolic blood (-5.1 mmHg) pressure and in diastolic blood pressure (-1.6 mmHg), in the ITT analyses. Analyses were adjusted for medication load, but the results were in accordance also when no adjustments for treatment were done. During follow-up, the use of blood-pressure lowering drugs increased in both groups; but did not differ between groups (Paper II).
Results

Table 15. Blood pressure at 3 years in the Swedish Björknäs study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group</th>
<th>Control group</th>
<th>p-value ANCOVA</th>
<th>p-value Mixed model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>141.7 (139.0; 144.4)</td>
<td>146.8 (144.2; 149.5)</td>
<td>0.030</td>
<td>0.0062</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>83.4 (81.7; 85.2)</td>
<td>85.0 (83.4; 86.7)</td>
<td>0.005</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Per protocol analyses n=120

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group</th>
<th>Control group</th>
<th>p-value ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>141.4 (138.3; 144.6)</td>
<td>147.4 (141.5; 145)</td>
<td>0.014</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>83.0 (80.9; 85.0)</td>
<td>84.8 (82.8; 86.7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data are estimated marginal means (95%CI), adjusted for medication load, derived from general linear model repeated measures ANCOVA.

![Figure 8](image1.png)

Figure 8. Systolic and diastolic blood pressure during study phase. Data are estimated marginal means (95% CI) derived from repeated measures ANCOVA.
Aerobic fitness

The intervention prevented decrease in aerobic fitness (Figure 9). Estimated oxygen uptake initially improved in both groups, greater in the intervention group (0.3 l/min, 4.0 ml/kg/min), but showed a slightly decline towards baseline values during the 3-year study period. Compared to baseline, the intervention group slightly increased their aerobic fitness (5%) while a decrease was seen in the control group (-5%). At 3-year, ITT analyses showed significant differences between groups in estimated oxygen uptake in absolute terms (2.2 l/min) in the intervention group, (2.1 l/min) in the control group, although not when expressed relative to body mass (26 ml/kg/min v.s 25 ml/kg/min) (Paper I & II). Per protocol showed the similar results.

Figure 9. Maximal oxygen uptake during study phase. Data are estimated marginal means derived from repeated measures ANCOVA. Numbers analyzed n=92. Subjects on beta-blockers excluded from analyses.
Results

Effects on laboratory measurements (Paper I & II)

There were no significant improvements observed in metabolic traits during the intervention period (Paper I & II).

*Blood lipids variables*

No significant differences in blood lipids were shown between groups over the study period (Table 14). The medication load of lipid lowering drugs was higher in the intervention group than in the control group at all time points, including baseline (Paper II).

*Blood glucose and glucose tolerance*

In participants without known diabetes no differences in fasting-blood glucose were shown during follow-up (Table 14). However, one new clinical diagnosis of diabetes occurred in the control group and none were observed in the intervention group. The prevalence of impaired glucose tolerance tended to be higher in the control group (34%), than in the lifestyle group (24%) at three years. In participants with known diabetes, no differences were observed in HbA1c levels or medication usages during follow-up (Table 16).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (n=71)</th>
<th>Control group (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>5.34 (5.17; 5.55)</td>
<td>5.37 (5.21; 5.53)</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>1.37 (1.32; 1.42)</td>
<td>1.35 (1.31; 1.47)</td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>3.15 (2.30; 3.30)</td>
<td>3.21 (3.06; 3.35)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2.01 (1.83; 2.20)</td>
<td>1.71 (1.53; 1.89)</td>
</tr>
<tr>
<td>Fasting-blood glucose</td>
<td>5.43 (5.30; 5.55)</td>
<td>5.52 (5.41; 5.64)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.54 (6.25; 6.83)</td>
<td>6.78 (6.45; 7.12)</td>
</tr>
</tbody>
</table>

Data are estimated marginal means adjusted for medication load, derived from general linear model repeated measures ANCOVA.

Effects on behavioural assessments (Paper I &II)

*Smoking habits*

The intervention reduced smoking. In the intervention group seven participants (41% of the smokers) quit smoking and one quit snuffing during the study period, compared to in the control group where only one individual quit smoking.
**Results**

**Physical activity**

The lifestyle intervention increased physical activity level (Paper I and II) and the motivation for being more physical active. Individuals in the lifestyle group reported increase in total physical activity, leisure time activity and exercise during follow-up. Over time, the increase in total physical and exercise were significant between groups in the overall mixed model and repeated measures analyses. At baseline 20 % of the intervention group reported being sedentary, whereas only 3% were sedentary at 3-year follow-up. In the lifestyle group the proportions of those reporting being moderate to very active had increased from 42% to 59%. Correspondingly, in the lifestyle group the proportion reporting exercising at least 30 min/day or more increased from 11% to 28%. Contrasting, in the control group total physical activity slightly decreased from 49% to 43%, and the proportion reporting exercising at least 30 min/day were unchanged, 19%. At 3-year about 70% of both groups reported LTPA at least 30 min/day and the difference at baseline did not persisted (Figure 10, figure 11).

![Figure 10. Changes in total physical activity level. Data are given in percent.](image-url)
Figure 11. Changes in exercise and leisure time activity. Data are given in percent.
Results

Figure 12 shows the proportions in action or maintenance stage for physically active during follow-up. These two stages represent being physically active for at least the last six months or longer. Intervention participants were significantly more likely to progress through to the active stages. After 3 months 86% in the intervention group were in action or maintenance phase, and after three years 51% reminded in these advanced stages. The corresponding proportions in the control group were 50% and 37% respectively (ITT analyses). The result after 3 years was the same when per protocol analyses were performed but after the 3-month intervention period 93% were in active stages.

![Proportion in Action and Maintenance stage](image)

*Figure 12. Stage of Change for physical activity*

Effects on Quality of life (Paper III)

**Main QOL scores**

Lifestyle modification improved quality of life. EQ VAS differed significantly between the groups at all time points and over the whole the 3-year study period, and improvements were greater in the intervention group. SF-6D improved in the intervention group and the difference was significant between groups over time. However, EQ-5D score did not change significantly during follow-up (Table 17).

There were no significant changes in the different EQ-5D dimensions during follow-up, although the significant overall difference between groups in the dimension anxiety/depression did not persisted at 3-year (Figure 13).
Results

Figure 13. The proportions reporting problems in the EQ-5D dimension Anxiety/depression. Data are percent.

Table 17. Mean changes in main Quality of Life Scores from baseline to 3 years in the Swedish Björknäs study (Δ intervention group – control group)

<table>
<thead>
<tr>
<th>Quality of Life Score</th>
<th>Study phase</th>
<th>Mean difference (95% Confidence Interval)</th>
<th>p-value T-test</th>
<th>p-values Repeated measures Between subjects</th>
<th>Time *group effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D</td>
<td>0-3 m</td>
<td>0.02 (-0.04; 0.08)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.02 (-0.03; 0.07)</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.03 (-0.02; 0.09)</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.03 (-0.02; 0.07)</td>
<td>0.28</td>
<td>0.24</td>
<td>0.939</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>0-3 m</td>
<td>0.08 (0.03; 0.13)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.08 (0.02; 0.13)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.06 (0.002; 0.11)</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.09 (0.03; 0.15)</td>
<td>0.002</td>
<td>0.002</td>
<td>0.504</td>
</tr>
<tr>
<td>SF-6D</td>
<td>0-3 m</td>
<td>0.03 (0.01; 0.05)</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.02 (-0.01; 0.42)</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.02 (-0.01; 0.05)</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.04 (0.02; 0.07)</td>
<td>0.002</td>
<td>0.010</td>
<td>0.197</td>
</tr>
</tbody>
</table>

Data are estimated marginal means (95% CI) derived from general linear model with repeated measures ANOVA. Bonferroni correction when significant time *group effect.

SF-36 scores

Significant differences over the 3-year period were seen in SF-36 sub scores physical functioning and bodily pain. No significant main time effect were seen for most QOL variables, but significant time interaction effect were seen in bodily pain, vitality and social functioning. The groups were changing in different directions over time; increase in the intervention group and decrease in the control group. After the 3-month active intervention period, there were improvements in several dimensions in the intervention group, and significant differences between the groups in physical functioning, vitality, social functioning and mental health.
At two years the group differed in general health and bodily pain and at the 3-year follow-up time point the differences persisted in physical functioning and bodily pain. Physical component summary score improved in the intervention group over time and the groups differed significantly, but no differences were seen in the mental component score (Table 18).

### Table 18. Mean changes and in SF-36 scores from baseline to 3 years in the Swedish Björknäs study (∆ intervention group – control group)

<table>
<thead>
<tr>
<th>Quality of Life Score</th>
<th>Study phase</th>
<th>Mean difference (95% Confidence Interval)</th>
<th>p-value (T-test)</th>
<th>p-values Repeated measures Between subjects</th>
<th>Time *group effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td>0-3 m</td>
<td>4.7 (1.2; 8.1)</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>0-12 m</td>
<td>3.5 (-0.04; 7.1)</td>
<td>0.052</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>1.3 (-3.3; 5.9)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>5.3 (1.2; 9.4)</td>
<td>0.012</td>
<td>0.017</td>
<td>0.256</td>
</tr>
<tr>
<td>Role Limitation</td>
<td>0-3 m</td>
<td>-3.4 (-12.5; 5.3)</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>0-24 m</td>
<td>2.4 (-9.1; 14)</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>-0.1 (-12; 11)</td>
<td>0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>0-3 m</td>
<td>11 (-16; 23)</td>
<td>0.09</td>
<td>0.58</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>1.4 (-4.6; 7.5)</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>6.6 (0.08; 12)</td>
<td>0.108</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>6.6 (-0.5; 14)</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>0-3 m</td>
<td>12 (4.8; 20)</td>
<td>0.004</td>
<td>0.012</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>2.9 (-1.2; 6.9)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>6.0 (1.3; 11)</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>3.5 (-1.2; 8.2)</td>
<td>0.08</td>
<td>0.012</td>
<td>0.113</td>
</tr>
<tr>
<td>Vitality</td>
<td>0-3 m</td>
<td>8.1 (3.0; 13)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.8 (-5.0; 6.5)</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.1 (-3.5; 3.5)</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>3.9 (-1.8; 9.5)</td>
<td>0.18</td>
<td>0.13</td>
<td>0.025</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>0-3 m</td>
<td>7.2 (2.6; 12)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>2.3 (-3.5; 8.2)</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>-3.6 (-9.4; 2.2)</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>4.0 (-1.6; 9.6)</td>
<td>0.11</td>
<td>0.16</td>
<td>0.021</td>
</tr>
<tr>
<td>Role Limitation</td>
<td>0-3 m</td>
<td>2.1 (-7.4; 12)</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>0-12 m</td>
<td>2.8 (-7.2; 13)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>3.4 (-7.4; 14)</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>1.5 (-1.0; 13)</td>
<td>0.80</td>
<td>0.58</td>
<td>0.979</td>
</tr>
<tr>
<td>Mental</td>
<td>0-3 m</td>
<td>4.3 (0.3; 8.3)</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>0-12 m</td>
<td>-0.3 (-4.6; 4.0)</td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>2.0 (-2.3; 6.3)</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>2.4 (-2.0; 6.8)</td>
<td>0.28</td>
<td>0.23</td>
<td>0.168</td>
</tr>
<tr>
<td>Physical Component</td>
<td>0-3 m</td>
<td>0.6 (-1.5; 2.6)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>0-12 m</td>
<td>1.7 (-0.6; 4.1)</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>1.3 (-1.2; 3.7)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>3.8 (1.4; 6.3)</td>
<td>0.012</td>
<td>0.041</td>
<td>0.059</td>
</tr>
<tr>
<td>Mental</td>
<td>0-3 m</td>
<td>2.8 (0.3; 5.3)</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td>0-12 m</td>
<td>0.1 (-2.5; 2.7)</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>0-24 m</td>
<td>0.6 (-2.3; 3.4)</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.4 (-2.4; 3.2)</td>
<td>0.78</td>
<td>0.37</td>
<td>0.147</td>
</tr>
</tbody>
</table>

Data are estimated marginal means (95% CI) derived from general linear model with repeated measures ANOVA. Bonferroni correction when significant time * group effect.
Results

Calculations of effect size at 3 months showed that the effect was moderate on EQ VAS, vitality and social functioning. It was small-to-moderate on SF-6D, physical functioning, mental health and mental component summary. The effect size at 3-year indicated moderate effect on EQ VAS, SF-6D, bodily pain and physical component summary, and small-to-moderate effect on physical functioning (Figure 14).

![Effect size according to Cohens criteria: trivial<0.2, small 0.2-0.5, moderate 0.5-0.8, large >0.8.](image)

Effects on cost-effectiveness (Paper III)

*Gained quality adjusted life years, (QALY)*

The intervention was highly cost-effective compared to standard care. After the 3-year study period, the intervention group had increased their QOL scores 0.026-0.090 more than the control group in the three used main QOL scorers (EQ-5D, EQ-VAS, SF-6D). The increase for the intervention group was greater at all time points in all three QOL scores, and was significant in 6 of 12 cases (Table 17). Based on the data on changed QOL, gained QALY per participant in the intervention group compared to the control group during the three years was 0.075 ($p=0.24$) using the EQ-5D, 0.202 ($<0.01$) using the EQ VAS, and 0.070 ($p=0.03$) using the SF-6D (Table 22).

*Costs*

Costs were 337 USD (2527 SEK) higher for the intervention group than for the control group (Table 19). Health care financed 197 USD (1480
Results

SEK) of these costs, and 140 USD (1047 SEK) were participant costs due to higher level of exercise. Cost for laboratory measurements, such as blood lipids, HbA1c and OGTT, were 185 USD (1385 SEK) per patient and year, and were the same for both groups.

| Table 19. Costs for the Intervention group and the control group |
|------------------------|------------------------|------------------------|
| Type of costs                | Intervention group | Control group | Intervention vs. control |
| First year, 11 group meetings with, physiotherapist and dietician. Family physician participated once. | 35.7 | 0 | 35.7 |
| Second year, 4 group meetings with physiotherapist and dietician. | 12.4 | 0 | 12.4 |
| Third year, 2 group meetings with, physiotherapist and dietician. Family physician participated once. | 12.8 | 0 | 12.8 |
| First year, 1 group meeting with family physician, physiotherapist and dietician. | 0 | 5.5 | -5.5 |
| Counseled group exercise 3 times a week during 12 weeks | 103.1 | 0 | 103.1 |
| Equipment | 6.0 | 1.9 | 4.1 |
| Proportion of costs for health care centre rent | 15.1 | 0 | 15.1 |
| Overhead costs 11 % | 20.4 | 0.8 | 19.6 |
| Sum of costs for primary health care | 205.5 | 8.2 | 197.3 |
| Participants’ costs for increased physical activity | 206.4 | 66.8 | 139.6 |
| Sum of costs per participant | 411.9 | 75.0 | 336.9 |

All costs are in USD, and discounted 3 % per yr.

Savings

The lifestyle intervention reduced health care use (Table 20). In the intervention group the mean numbers of visits to the family physician decreased by 0.28 per half year as compared to baseline, and increased by 0.10 in the control group, which differed significantly between groups. For other health care use there were no significant changes between the groups. Savings in family physician visits was 492 USD (3689 SEK) for the 3-year period, and savings for all health care use was 384 USD (2882 SEK) (Table 21).
Results

Table 20. Change in health care use in the Swedish Björknäs study.

<table>
<thead>
<tr>
<th>Health care</th>
<th>Intervention</th>
<th>Control</th>
<th>Changes</th>
<th>Intervention vs. control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base-line</td>
<td>Follow</td>
<td>Changes</td>
<td>Base-line</td>
<td></td>
</tr>
<tr>
<td></td>
<td>up</td>
<td>up</td>
<td></td>
<td>up</td>
<td></td>
</tr>
<tr>
<td>Family physician visits</td>
<td>1.20</td>
<td>0.91</td>
<td>-0.28</td>
<td>1.08</td>
<td>1.18</td>
</tr>
<tr>
<td>Nurse visits</td>
<td>1.06</td>
<td>1.12</td>
<td>+0.07</td>
<td>0.87</td>
<td>0.94</td>
</tr>
<tr>
<td>Hospital specialist visits</td>
<td>0.39</td>
<td>0.45</td>
<td>+0.05</td>
<td>0.42</td>
<td>0.44</td>
</tr>
<tr>
<td>Hospital nurse visits</td>
<td>0.07</td>
<td>0.14</td>
<td>+0.07</td>
<td>0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>All health care use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
</tbody>
</table>

Data are healthcare use 6 mo before baseline and during the three yr after start. Numbers of visits are presented as a mean for 6 months.

Table 21. Savings in health care costs in the Swedish Björknäs study.

<table>
<thead>
<tr>
<th>Health care</th>
<th>Price per unit</th>
<th>Savings during 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family physician visits</td>
<td>221.6</td>
<td>-491.9</td>
</tr>
<tr>
<td>Nurse visits</td>
<td>88.5</td>
<td>-2.7</td>
</tr>
<tr>
<td>Hospital specialist visits</td>
<td>376.8</td>
<td>77.9</td>
</tr>
<tr>
<td>Hospital nurse visits</td>
<td>150.4</td>
<td>32.4</td>
</tr>
<tr>
<td>All health care use</td>
<td></td>
<td>-384.3</td>
</tr>
</tbody>
</table>

Prices are negotiated and represent production costs. For hospital visits, costs for visits to the internal medicine clinic were used. All savings are in USD and were discounted 3 % per yr.

Cost-effectiveness

There were net savings with 47 USD (355 SEK) per participant in the intervention compared to the control group. Gross cost (savings not counted) per gained QALY were 1668 -4813 USD (12 510-36 100 SEK) using the three different QOL scales (Table 20).

Using 50 000 USD as threshold of willingness to pay for a QALY, net monetary benefits for the intervention were significant higher than for the control using the EQ VAS and the SF-6D, but not using the EQ-5D (Table 22). When stakeholders are willing to pay 50.000 USD for a QALY the probability of cost-effectiveness is 98.5% using the SF-6D, 88.6% using the EQ-5D and 99.9% using the EQ VAS (Figure 15). When using Swedish currency and 100 000 SEK as threshold value for willingness to pay for a QALY, the probability of cost-effectiveness is 99% using the SF-6D, 96% using the EQ-5D and 100% using the EQ VAS.
Results

Table 22. Cost-effectiveness of the intervention.

<table>
<thead>
<tr>
<th></th>
<th>EQ-5D</th>
<th>EQ Rating SCALE</th>
<th>SF-6D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gained QALY</td>
<td>0.075</td>
<td>0.202</td>
<td>0.070</td>
</tr>
<tr>
<td>Program costs</td>
<td>197.3</td>
<td>197.3</td>
<td>197.3</td>
</tr>
<tr>
<td>Participants’ out-of-pocket expenses</td>
<td>139.6</td>
<td>139.6</td>
<td>139.6</td>
</tr>
<tr>
<td>Sum of costs (gross costs)</td>
<td>336.9</td>
<td>336.9</td>
<td>336.9</td>
</tr>
<tr>
<td>Savings in health care costs</td>
<td>-384.3</td>
<td>-384.3</td>
<td>-384.3</td>
</tr>
<tr>
<td>Net savings</td>
<td>-47.4</td>
<td>-47.4</td>
<td>-47.4</td>
</tr>
<tr>
<td>Gross costs per gained QALY</td>
<td>4492.0</td>
<td>1667.8</td>
<td>4812.9</td>
</tr>
<tr>
<td>NMB (95 % confidence interval), 1 QALY = 50 000 USD</td>
<td>4,170 (4,298–8,006)</td>
<td>3,908 (384–7,685)</td>
<td></td>
</tr>
<tr>
<td>NMB (95 % confidence interval), 1 QALY = 100 000 USD</td>
<td>8,292 (5,039–21,953)</td>
<td>7,769 (931–14,929)</td>
<td></td>
</tr>
</tbody>
</table>

Costs per gained QALY, probability of cost-effectiveness and net monetary benefit. All results are for intervention vs. control. All costs are in USD, and discounted 3 % per yr. NMB = Net Monetary Benefit.

Figure 15. Probability of cost-effectiveness using EQ-5D, EQ-VAS and SF-6D presented in a cost-effectiveness acceptability curve with 0, 10 000, 30 000, 50.000 and 1 000 000 USD as value of a QALY.
DISCUSSION

This thesis investigated the effectiveness of a lifestyle intervention on cardiovascular risk factors, physical activity and quality of life among middle-aged individuals at moderate to high-risk for cardiovascular diseases. The study was carried out in a conventional primary care setting during three years. The cost-effectiveness of the intervention was assessed by a cost-utility analysis and based on gained quality adjusted life years and nets cost for the intervention compared to the control. Overall the intervention generated beneficial improvements in anthropometrics, blood pressure, aerobics fitness and activity level, and quality of life, compared to the control group. Cost per gained QALY was low and the probability of cost-effectiveness was high.

Methodological considerations

Study design

We conducted a randomized controlled trial (RCT) with a 3-year follow-up. The design and the long follow-up time strengthen our findings. A randomized control trial, in which the study participants are randomly assigned either to a control group or an intervention group, is the gold standard to establish causality between an intervention and a health outcome. Random allocation to intervention or control group protects against bias, maximizing internal validity, although it does not guarantee that the groups are equivalent at baseline (190).

The context of the trial and characteristics of participants affects the generalizability, or the external validity (202). Large extensively resourced multi-centre lifestyle trials have been successful in diabetes and CVD risk reduction (16-17), but if such interventions are effective in a “real life” setting has been unknown. There is a gap between research and practice, and lack of data on how to achieve translation of effective interventions into clinical settings, moving from efficacy to effectiveness (203). This study aimed to transfer the findings from tightly controlled trials in highly selected settings to a “real-life” setting. The study was conducted at a conventional primary health care centre with limited recourses. Our results address the effectiveness of interventions outside of a tightly controlled and well-founded setting, and therefore strengthen the generalizability to other populations in the primary care setting.

External and internal validity

This study was carried out in a small town in a rural area in northern Sweden. Middle-aged men and women were included in the study
population, most participants had secondary school education but the cohort also included individuals with academic education or elementary education. Thus the study population is representative for patients with similar cardiovascular risk in the primary care setting in Sweden. The study population also is rather similar in demographic, cultural and ethnic characteristics to the cohort in the Finnish DPS, although more heterogeneous and not so highly selected.

In contrast to other studies (204), the recruitment rate was high in this study, which also strengthens the generalizability of the results. Approximately half of the participants eligible were randomized to treatment, compared to only 16% in a similar lifestyle intervention in the same northern region of Sweden (204). In that study participants were recruited by advertisement, while in the present study participants were invited by health care providers from their own health care centre. Thus, our strategy of recruiting through the established health care infrastructure might have been fundamental to the effectiveness of our intervention.

Most of the participants had several risk factors for CVD, and already had an established contact with the health care. These factors might have contributed to their motivation to participate in the intervention program. We assessed the participant’s motivational stages and readiness to change to a more physically active lifestyle. At baseline most of the participants were in pre action stages for being more physically active, which might indicate they would benefit for an intervention (168).

On the other hand when inviting participants, there is a risk of selection bias as the study participants who agreed to participate may reflect individuals with greater interest in lifestyle changes. Thus our study population may not have been truly representative of the population at high risk for CVD. However, those who denied participating did not differ from those who took part with respect to demographic characteristics and risk profile. Attrition rate was rather low, 83% completed the 3-year follow-up and there were no differences between those who dropped-out and those who full-filled the study.

It is agreed that primary analysis of randomized trials should be based on the initial treatment assignment and include data for all that were initially included and ranomized (190, 202), but there are different methods to handle missing data which might bias the results (202, 205). In this study all analyses on 3-year data were performed as an intention-to-treat basis. If data were missing we used the recommended method last observation moved forward (205-206). In general, imputation of missing data underestimate the magnitude of treatment effect and is seen as a conservative approach (202, 205-206).

For explanatory reasons we also performed per-protocol analysis, and also an ancillary modelling analysis, with a mixed-effects model, using all
available data, which provide results in accordance which strengthens our findings. Despite randomly assignment, not all characteristics were equally distributed in the intervention respective control group. To adjust for baseline differences we used analysis of covariance and mean changes calculations (207). Repeated measures analyses were used to correct for several follow-up time points. For quality of life data we also calculated effect size.

One consequences of performing a clinical intervention study in a “real life” setting is some limitations of internal validity. With sparse resources it is not possible to tightly control the intervention as in large and well financed studies. Thus, a limitation in this study is the lack of blinding. As in other lifestyle intervention trials, neither the participants nor the study staff were blinded, not being possible, but the lack of blinded assessors in this study diminishes intern validity somewhat but only outcomes that are observer dependent.

On the other hand, the control group may have benefit from a “mini-intervention” by receiving information about lifestyle and health, activity logs, and yearly follow-ups. This mini-intervention included more than conventional standard care and may have diluted differences between groups. The assessor who evaluated the health care use during the study period was blinded, which strengthens intern validity of the health economic evaluation.

A strength of this study is the use of different methods to evaluate improvements in health related to lifestyle changes. We assessed changes in physical activity by self-reported questionnaires, and also by objective measurements of changes in physical fitness by clinical and laboratory tests. To minimize observer bias the same physiotherapist (ME) performed the anthropometric and blood pressure measurements, and two other physiotherapists performed the exercise stress test. All clinical and laboratory measurements were done by standardized measurements procedures. We used a submaximal test on bicycle ergometer to estimate changes in aerobic fitness (68). The method error is high (±15%) when comparing different individuals to each other due to individual variation in maximal heart rate. Thus some individuals will be over or underestimated. In the original test Åstrand reported a correlation of r=0.78 between estimated and measured VO2max. Other authors have reported correlations within the range r=0.69-0.95, varying by age and gender. However, the method error is low in repeated measures of the same individuals (67-68), which was the objective in this study. The Åstrand test is also feasible to perform at most health care centres.

Another limitation is that the physical activity questionnaire used in this study was not validated. It was chosen as there were no validated questionnaire available at the start of the investigation, and being used in other studies (191). In general self-reported physical activity
questionnaires have limitations in validity and reliability, but are in found be valid to classify a population into physical activity categories (58, 65).

Motivational readiness to increase physical activity level was assessed by validated questions (192). We recorded changes in dietary habits at follow-ups, but these analyses are not incorporated in this thesis which limits interpretation of the results. Therefore, conclusions of the effectiveness of the intervention are based on the interventions as whole, a “black box”, and not contributable to any singular component of the intervention.

We measured participant’s experience of quality of life (QOL), as a complement to clinical parameters, which strengthen this study. QOL outcomes are very useful to incorporate in randomized trials providing information about the effectiveness of an intervention. QOL reflects the individual’s subjective perceived health status, and measurement of QOL can be seen as a quality marker of an intervention (28, 194). In evidence-based medicine patient-related outcomes such as QOL are central for deciding on the effectiveness of an intervention, lying closer to what matters to the patient than biochemical and anthropometrical measurements, being surrogate outcomes.

There is no gold standard for measurements of QOL and valuation of health states. In this study we used the EuroQol (31, 193), the SF-36 (32) and the SF-6D (194), valid and reliable instruments, and used in populations similar to our study cohort (33, 154, 157, 160). The instruments are generic, but are based on different health state descriptions and three different standard techniques for valuation of health, and therefore produce somewhat different utility scores, which in turn affect the QALY calculation. Thus different aspects of QOL were considered, which strengthens the health economic evaluation. Another strength with the health economic evaluation is that it is completely based on data from the trial and no assumption were needed, except for expenses for physical activity.

**Main findings**

This thesis shows the feasibility of applying a 3-year lifestyle intervention, using the core features from extensive lifestyle trials, to the “real life” primary care setting. The intervention was carried out using available personnel resources at the health care centre and was delivered mainly by physiotherapists and dieticians. The study demonstrates the effectiveness of group-based supervised exercise and dietary counselling, and sustained support, among middle-aged individuals at high risk for cardiovascular diseases. It favourably impacted several risk factors for CVD and improved quality of life by an increase in exercise and total physical activity level. Lifestyle modification reduced waist circumference, waist-
Discussion

Quality of life (QOL) improved. During the study period the participants in the intervention group reduced visits to the family physicians compared to the control group. The health economic evaluation showed that the intervention was highly cost-effective compared to standard care.

Effects on clinical and laboratory measurements and behaviour assessment

**Anthropometrics**

After 3 years the lifestyle intervention significantly decreased waist circumference and waist-to-hip-ratio, thus reducing abdominal obesity. No significant reductions in weight or BMI were shown. On the other hand, the intervention prevented weight gain, which contrasts with the trend in the general population of northern Sweden (9). Reductions in weight occurred during the first year but did not persist at the 3-year follow-up, while reduction in waist was significant at all time points. Similar findings were reported by the Women's Healthy Lifestyle Project. The 5-year behavioural lifestyle intervention among middle-aged women increased physical activity, decreased waist and prevented weight gain (208). In the present study, the reduction in waist was 2.2 cm at the 3-year follow-up, which was similar to the waist reduction shown in the Finnish Diabetes Prevention Study (FDPS) at 3-year, although the FDPS also showed weight reduction (148).

The reduction in waist is of clinical importance as each unit of waist circumference (cm) is associated with 5% clustered risk for other conventional risk factors (209-210). Reduction in waist is associated with improved insulin sensitivity even in absence of weight loss, although greater weight loss also decreases insulin secretion (91). Other studies have shown similar results (211). Eklund *et al* demonstrated that increases in physical activity in middle-aged men and women over a 5-year period were associated with improvements in insulin sensitivity, glucose tolerance and clustered metabolic risk, independent of decrease in adiposity or aerobic fitness (212). Reduction in waist but not in weight is consistent with findings from other exercise studies (121, 213). Among sedentary overweight or obese women, aerobic exercise during 6-months significantly reduced waist 2-3 cm independent of weight reduction (214).
Discussion

*Glucose homeostasis*

No improvements in fasting blood-glucose or glycosylated haemoglobin were shown in our study. The lack of impact of on glucose metabolism may partly be explained by the modest weight reduction. But it is also notable that the subgroup of diabetes patients in this study already at baseline was well regulated in HbA1c, and that the small study sample may yield insufficient power to detect changes. Among patients with diabetes, it is shown that exercise even without weight reduction moderately improves HbA1c (135).

Several lifestyle interventions have successfully demonstrated improvement in glucose tolerance (141) among people with impaired glucose tolerance. In the DPP and the FDPS weight reduction was of importance for decrease in risk of diabetes, but exercise alone also had an independent effect (143, 145). We did not performed oral glucose tolerance test (OGTT) at baseline, only at the 2-and 3-year examination. Therefore no conclusion can be drawn how the intervention affected glucose tolerance although, the prevalence of impaired glucose tolerance and diabetes diagnosed by OGTT tended to be lower in the intervention group than in the control at 3-year follow-up.

*Blood lipids*

Lifestyle intervention did not provided any discernable impact on blood lipids and the groups did not differ during follow-up. However, lipid-lowering treatment was common and baseline values were close to target levels, which may have masked any subtle changes in lipid levels resulting from the intervention. Notably, at baseline the value for total cholesterol was lower in the study population than in the general population in northern Sweden. In both groups there was an increase in lipid lowering treatment during the study period, which may reflect newer treatment recommendations that emphasise reaching specific target levels. Treatment with lipid-lowering drugs was more frequent in the intervention group at baseline and at all time points.

Improvements in blood lipids after physical activity are mainly reported as reduction in triglycerides and increase in HDL. People with higher values of total cholesterol and BMI < 28 kg/m² at start show larger increases in HDL (215). But reports on blood lipids after lifestyle interventions are somewhat inconsistent and several trials do not report any improvements (123, 140), while other do (142, 148, 216-218).
**Blood pressure**

Significant moderate reductions of blood pressure were demonstrated during follow-up. At 3-year the lifestyle intervention had decreased systolic blood pressure by -5.1 mm Hg and diastolic blood pressure by -1.6 mm Hg. These findings are of clinical importance as such reductions in blood pressure reduce the risk of stroke approximately 20%, and the risk of ischemic heart disease 15% (219). These results are in accordance with results from many exercise RCTs (110-111) and lifestyle interventions (16, 142, 218, 220). In both groups blood pressure treatment slightly increased during follow-up, but did not differ between groups. Similar to the increase in lipid treatment, this increase probably reflects emphasis on specific target levels in accordance with current treatment recommendations. It is also possible that it may reflect a higher belief in medical treatment than in lifestyle modification among the physicians.

**Aerobic fitness**

The lifestyle intervention prevented decrease in aerobic fitness. Compared to baseline the intervention group slightly increased aerobic fitness by 5% while a reduction by 5% was observed in the control group. Even small improvements are of clinical importance as each unit (ml/kg/min) are associated with 5% decrease in the clustered risk of other conventional CVD risk factors (209-210). There are also associations between maintenance and increase in fitness and lesser physician visits or overnight hospital stays (221). We observed a significant improvement in estimated oxygen uptake (VO2max) during the first three months of the trial. At 3 years the improvements in VO2max differed significantly only when expressed as in absolute term, indicating some improvement in cardiac function (48), but not when expressed relative to body mass. This difference is likely to reflect the fact that when VO2max is expressed relative to weight, changes in VO2max are influenced by changes in body mass. The group differed in weight at the first part of the study but not significantly after 3 years.

Not many studies reports on long-term effects on VO2max. Among sedentary overweight or obese women supervised exercise at different intensity during 6 months, resulted in a dose-response increase in VO2max between 4-8 % (213). Intense behaviour counselling during 24 months improved VO2max approximately 5% among sedentary women, but was not effective among men (177). Counselling including specified recommendations of intensity and frequencies of physical activity resulted in increase in VO2max 5% after 24 months among sedentary of both sexes, in contrast to standard physical activity advice (178). One lifestyle intervention trial has reported increase in VO2max 10-14% after 6 years (142).
Physical activity and smoking habits

The improvements in aerobic fitness supposedly reflect an effect of increased physical activity reported among participants in the intervention group. They reported significantly more exercise participation and higher level of total physical activity compared to the control group at 3-year follow-up. A slight increase in leisure time activity was reported. In accordance participants also increased their motivation for physical activity, and more than half reported being in active stages at 3-year.

Self-reported measurement of physical activity is subjective and includes several sources of error. However, all the questions showed increase in different physical activities, which also was confirmed by difference between groups in aerobic fitness. Together these findings strongly indicate that the study population had beneficially increased their physical activity level. The intervention group also reported reduction of sedentary time. Both these findings are of importance as high level of sitting time independent of regular physical activity are a risk factor for diabetes (103, 222) and CVD (89-90).

Another important CVD risk reduction that occurred was that more than half of the smokers in the intervention group quit smoking, although the intervention was not designed to especially promote smoking cessation. This could be explained by the broad focus on healthy living at the follow-up meetings whereas also tobacco habits and the effects of tobacco on health were discussed.

Effects on quality of life

A strong graded dose-response effect of exercise on QOL was recently shown in a RCT (159), but other reports on QOL from physical activity interventions are somewhat inconsistent (37, 155, 157-158, 184). In this study the lifestyle intervention beneficially influenced quality of life (QOL). EQ-VAS and SF-6D significantly improved during follow-up, although the increase in EQ-5D did not reach significance at 3-year. This discrepancy in findings may be explained by the different valuation and sensitivity. EQ-VAS reflects the current state of health, i.e. the respondents’ personal valuation of their health status, while EQ-5D and SF-6D reflect how a general population values the health status described by the patient; therefore, EQ-VAS might be more suitable for detecting effects of an intervention than EQ-5D. The EQ-5D score in this study was similar to the Stockholm population at baseline, and therefore probably not sensitive enough to show significant differences or changes.

Similar to other lifestyle interventions studies (154, 160) this lifestyle intervention improved physical but not mental dimensions of SF-36. A positive effect on mental scales was seen in our 3-months data which may
reflect a positive group effect, while the lack of impact on the mental aspects at 3 year may be due to the loss of exercise group support.

Increased enjoyment with group exercise has recently been shown in a Swedish one-year study in primary care (223). Notably also that the study population at baseline was already similar to, or better than the Swedish normal population. That might have diminished the possibility to show persistent improvements. Changes ≥ 3-5 scale points in SF-36 scale scores are seen as clinically important (224). Such improvements were seen also in some dimensions that did not reach statistically significance, which may indicate insufficient power to detect changes. In this study the power calculation were based primarily on weight change, not change in QOL. To put the size of the changes into perspective we also calculated effect size, showing small and moderate effects on QOL in several dimensions.

Effects on cost-effectiveness

This study showed that lifestyle intervention in primary health care, used alongside standard care, among a population at high-risk for cardiovascular diseases was highly cost-effective. Cost per gained QALY, 1668-4813 USD (12 510-36 100 SEK), savings not counted, was low. The intervention also reduced health care used by significantly decreasing visits to family physicians, as compared to the control group. When also savings in health care were considered, there were net savings.

The probability of cost-effectiveness for the intervention group compared to the control group was high and was significant using EQ VAS and SF-6D, but not when EQ-5D was use. When 50 000 USD was used as threshold value for willingness to pay for a QALY, the probability of cost-effectiveness was 100% using EQ VAS, 99% using SF-6D, and 89% using EQ-5D. There is no official level for acceptable value of a QALY but in the US 50 000 and 100 000 are often used. The cost-effectiveness of the intervention was good in relation to what western countries are willing to pay for a QALY.

In the DPP, the lifestyle intervention showed a treatment effect of 0.072 QALY gained and the cost per gained QALY was 51 600 USD. That intervention was based mainly on individual meetings and costs were about ten times higher than in the present study, but still the intervention was found to be cost-effective (184). The DPP study group assumed that if the intervention might be implemented in routine care, and group based, the cost per gained QALY would be 27 100 USD. In the present study the treatment effect was similar to the treatment effect in the DPP.

The main reason for cost-effectiveness was the sustainable increase in QOL and exercise level. An important aspect in the performance of the intervention was probably the long-time contact with the participants. Another important aspect was that the group activities generated low cost
Discussion

per participant. We did not include participants time cost for exercise which we did not consider important in the long run. On the other hand we assumed a rather high cost for exercise expenses representing a yearly fee at an exercise centre; most physically active individuals choose cheaper alternatives. The actual analysis had only a treatment perspective but there were also preventive effects against CVD, as the intervention beneficially influenced several risk factors, thus the effects are likely underestimated.

Clinical implications and future perspective

Findings from the Björknäs study provide novel and strong support that promotion of physical activity and a healthy lifestyle in primary care are effective in cardiovascular risk reduction and also improve quality of life. We demonstrate the feasibility to deliver more extensive interventions in clinical practice when available personnel resources as physiotherapists and dieticians are involved. Furthermore, a more extensive intervention results in not only short-time improvements, but also improvements persisting over three years.

Our focus was individuals with moderate to high risk for CVD that already had an ongoing contact with the primary health care. The health economic analysis showed that lifestyle intervention targeted to this group was highly cost-effective compared to standard care, demonstrating the successfulness of this strategy. Therefore such programs may be a wise use of recourses in the primary health care, others to follow.

Sustained support seems to be of importance for the maintenance of new behaviours. Several lifestyle studies have shown short-term impact but long-term adherence problems (225-226). In studies demonstrating long-term effects on CVD risk factors and physical activity level the participants were provided sustained support during several years, both on individual level and through group activities (142, 144, 147, 177). We offered regular but sparse support during a 3-year period, but only on the group level, although participants in both groups underwent yearly individual follow-up examinations.

Supervised exercise studies provides beneficial short-term effects on clinical parameters as blood pressure, aerobic fitness and weight, (159, 213-214), but adherence and long-term effects has been questioned. Notably, contrary to earlier findings it was recently shown that high-intensity, interval type of exercise may lead to greater health benefits than moderate continuous for various populations, including patients with CVD, and would not lead to reduced exercise adherence (227-228). Supervised group activities also beneficially affect enjoyment of exercise which may strengthen adherence (223). It has been suggested that engaging the patient in self-adjusted physical activity may be more
beneficial than supervised exercise in the long run. But there are evidence that adherence do not differ between lifestyle activities and exercise (227). In the Björknäs study we used both strategies, but did not provide any individual counselling. It is possible that adding also individual counselling would have improved the results, but to a higher cost.

Therefore, after the study period, when this lifestyle intervention was integrated in the clinical practice at the health care centre, we somewhat modified the concept. We included also a social welfare officer in the team to further support the behaviour approach. The patients now participate in supervised circuit-resistance training combined with interval training on ergometer bicycles, and water aerobics, each activity once a week, and receive instructions to perform Nordic walking or brisk walks on their own. They are offered group meetings with the physiotherapist, the dietician and the social welfare officer during six months period. After the active exercise period they are also offered individual counselling by the physiotherapist and receive a prescription of suitable continued physical activity, and individual follow-up after 3, 6, and 12 months.

We still have much to learn about exactly who will benefit from what type of intervention, predictors of a successful intervention. The exercise prescription should be based primarily on the health-related fitness and safety goals of the individual (163, 165, 227). To decide which approach that is suitable for each individual we also need to consider age, sex, risk profile, motivation, self-efficacy, psychosocial factors and social support (227). Those factors are of greater importance for physical activity adherence than is the choice of lifestyle activity or exercise, or prescription of different frequency, intensity or duration of the activity. This also gives the opportunity to use a wide range of methods and prescriptions adaptable for different individuals (227).

Healthcare can promote physical activity by initializing changes, but also provide sustained support, but we know little about long-term effects and cost-effectiveness of different methods. Further studies of different methods with long-term follow-up, including incident cardiovascular disease and diabetes as well as mortality, are needed. Research should also focus on measurements of QOL and costs to find out what the best use of money. We lack knowledge on how to reach disadvantaged groups, and little is known about effectiveness of lifestyle promotion among cultural and ethnical minority groups. We also need qualitative studies to better understand determinants of physical activity and physical activity adherence.

It is important to systematically target those individuals at risk who would benefit most from an intervention. Opportunistic screening, or case-finding, is one method shown to be effective (216). Opportunistic screening of cardiovascular risk factors by self-reported questionnaire followed by lifestyle intervention target to high-risk individuals reduced
blood-pressure and improved lipid profile. The intervention was most successful among younger individuals with longer education (229). Measurement of VO$_2$max as important predictor of metabolic and CVD risk, may provide an efficient means to target individuals who may benefit from more intensive intervention (22). This is easily done at most health care centres but involves physiotherapists or trained nurses. An important challenge for health care is to reach the most inactive groups and the socio-economic groups with high prevalence of risk-factors and diseases to successfully improve public health, and interventions to be cost-effective (18, 149).

To translate effective clinic-based physical activity interventions into practice, there is evidence that brief counselling by physicians should be supported by other health care professionals, health educators and/or community actions (203). Standard advice and generic prescriptions are insufficient for maintenance. The 5As of behaviour change are found to be related to effective clinical interventions, and may be of importance to consider when integrating new methods to promote lifestyle change:

- **Assessing** physical activity status, ability and readiness to change.

- **Advice** on possible changes relative to personalized benefits. Advice on amount, intensity and type of physical activity.

- **Ask and agree** collaboratively set physically activity goals based on patients interest and confidence to perform the behaviour. Make a plan of action and identify barriers to the plan.

- **Assist**; identify strategies to overcome personal barriers to behaviour change. Identify potential community opportunities for physical activity and social support.

- **Arrange** for follow-up assessment, feedback and support. (203).
CONCLUSIONS

A more extensive group-based lifestyle intervention program during three years is feasible to implement within existing primary health care infrastructure.

A group-based exercise and diet lifestyle intervention in the primary care setting targeted to a population at moderate to high risk for cardiovascular disease can be delivered mainly by physiotherapists and dieticians.

Group-based supervised aerobic exercise and resistance training, and group-based dietary counselling during three months, are effective in cardiovascular risk reduction, increases physical activity levels, and improves quality of life among a high risk population.

A 3-months group-based lifestyle intervention followed by regular but sparse group-meetings with a behavioural approach during three years, improves CVD risk factors as blood pressure, abdominal obesity and smoking habits at least up to three years, among a population at moderate to high risk of cardiovascular disease.

A 3-months group-based lifestyle intervention followed by regular, but sparse, group-meetings with a behavioural approach during three years, increases exercise and total physical activity level and aerobic fitness, among a population at moderate to high risk of cardiovascular disease.

A 3-months group-based lifestyle intervention followed by regular but sparse group-meetings with a behavioural approach during three years improves quality of life and reduces visits to family physicians, among a population at moderate to high risk of cardiovascular disease.

A 3-year group-based lifestyle intervention in the primary care setting among individuals at moderate to high risk for cardiovascular disease is highly cost-effective compared to standard care.
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A randomized trial of lifestyle intervention in primary healthcare for the modification of cardiovascular risk factors
The Björknaäs study

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Abstract
Aims: To evaluate the effects of a lifestyle intervention programme in primary healthcare, targeted to patients with moderate to high risk of cardiovascular disease in terms of cardiovascular risk factors, physical activity, and quality of life. Method: Randomized controlled trial with one-year follow-up, carried out in a primary healthcare centre in Northern Sweden. A total of 151 middle-aged men and women, with hypertension, dyslipidemia, type 2 diabetes, or obesity were enrolled. The subjects were randomized to either the intervention (n=75) or the control group (n=76). A total of 123 subjects completed the one-year follow-up. Interventions: Exercise: supervised endurance and circuit training in groups three times a week for three months. Diet: five group sessions of diet counselling with a dietitian. Follow-up meetings with a physiotherapist were conducted monthly thereafter. Primary outcomes were changes in anthropometry, maximal oxygen uptake, health-related quality of life, and self-reported physical activity. The secondary outcomes were changes in blood pressure and metabolic variables. Results: After one year the intervention group significantly increased maximal oxygen uptake, physical activity, and quality of life and significantly decreased body weight, waist and hip circumference, body mass index, waist–hip ratio, systolic and diastolic blood pressure, triglycerides, and glycosylated haemoglobin. There were significant differences between groups, mean changes (and their 95% confidence intervals, CI) in waist circumference -2.19 cm (-2.80 to -0.90; p<0.001), in waist–hip ratio -0.01 (-0.02 to -0.004; p<0.01) and in diastolic blood pressure -2.3 mmHg (-4.04 to -0.51; p<0.05). Conclusion: A prevention programme in primary healthcare with a focus on physical activity and diet counselling followed by structured follow-up meetings can favourably influence several risk factors for cardiovascular diseases and quality of life in high-risk subjects for at least one year.

Key Words: Cardiovascular risk factors, exercise, lifestyle changes, physical activity, prevention, primary healthcare

Introduction
A sedentary lifestyle and low cardiorespiratory fitness increases the risk of cardiovascular disease (CVD) with the same impact as the presence of risk factors such as smoking, high blood pressure, or high levels of cholesterol [1–3]. Sedentary behaviour also elevates the risk of obesity and diabetes [4]. The prevention of CVD is a public health concern and several guidelines have put increasing emphasis on primary prevention [5–6]. Primary prevention intends both to prevent and modify risk factors and to prevent the development of chronic diseases [7]. Several intervention trials have demonstrated the feasibility and efficacy of lifestyle-intervention programmes in high-risk populations [8–13]. Recent Finnish [14] and American [15] lifestyle intervention trials have shown decreases in the incidence of diabetes by 58% in subjects with impaired glucose tolerance.

In primary health care centres in Sweden [16] and Finland [17], multi-professional diet and exercise interventions trials in cardiovascular high-risk groups have resulted in favourable effects on several cardiovascular risk factors. The Swedish study compared the effects of a six-month diet, exercise, or diet and...
exercise intervention [16]. In the Finnish study the effects of an individual tailored multi-factorial intervention programme were compared with standard care [17]. The study subjects in these studies were recruited from ongoing screening programmes.

At many healthcare centres systematic preventive strategies are still not integrated into the ordinary healthcare system. There is a paucity of intervention studies carried out in primary healthcare, using only the limited resources that are available at the healthcare centres. Our purpose was to evaluate the feasibility and the effects on cardiovascular risk factors, physical activity, and quality of life of a lifestyle intervention programme consisting of supervised endurance and circuit training, diet counselling, and regular follow-up meetings for high-risk patients in primary care.

Material and methods

Study design

We conducted a randomized controlled parallel group clinical trial with one intervention group and one control group with a one-year follow-up.

Study subjects

Subjects were selected from the catchment population of the Bjo¨rkna¨s primary healthcare centre in Boden, Sweden. Inclusion criteria were a diagnosis of hypertension, dyslipidemia, type 2 diabetes, obesity, or any combination thereof in patients aged 18–65 years. Subjects with a diagnosis of coronary heart disease, stroke, TIA, blood pressure \( \geq 180/105 \) mmHg, dementia, or severe psychiatric disease were excluded. Potential participants were identified from computerized case records since the healthcare centre has no specific screening programme. Of a total of 9,742 inhabitants, 340 subjects met the inclusion criteria and received an invitation by letter. 52% gave written consent to participate (Figure 1). A total of 151 subjects were included, participated in the baseline investigation, and were randomly allocated by computer-generated random numbers to the intervention group (\( n=75 \)) or the control group (\( n=76 \)). Randomization numbers were kept in sealed, opaque envelopes, which were opened at the healthcare centre after the baseline investigation. The study was approved by the ethics committee of Umeå University, Sweden.

Procedure

The subjects visited the health centre on three occasions, at baseline and at the 3-month and 12-month follow-ups to undergo examinations and blood sampling. Data from the three-month follow-up are not shown.

Clinical examination. A history of previous diseases and current medication was taken. The subjects were weighed in light indoor clothing without shoes to the nearest 0.1 kg using an electronic balance (Seca model). Height was measured without shoes to the nearest 0.1 cm using a scale fixed to the wall. BMI was calculated from the measured weight and height as kg/m\(^2\). Circumference of the waist was measured from the point midway between the inferior margin of the last rib and the crest of ileum, above the umbilicus, in a relaxed standing position. Circumference of the hip was measured at the widest point between hips and buttocks. Both circumferences were measured with a tape measure to the nearest 0.5 cm. Waist-to-hip ratio was calculated as waist circumference/hip circumference.

Blood pressure (BP) measurements were performed by a standard auscultatory method with appropriate-sized cuff and were recorded to the nearest 2 mmHg. BP was measured twice from the right arm after 10 min of rest in supine position. The average of these values was used. Maximal oxygen uptake (\( \text{VO}_2\text{max} \), l/min, ml/kg) was estimated as described by Åstrand [18]. Monark 818 E and Monark E 828 ergometer bicycles were used. The same physiotherapist performed the interviews, anthropometric and blood pressure measurements to avoid the influence of different observers. Two other physiotherapists performed the ergometer tests.

Laboratory measurements. Total cholesterol and triglycerides were analysed on a Vitros multi-analyser. High-density lipoprotein (HDL) cholesterol was analysed on a Hitachi 917. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedwald equation. Fasting blood glucose was analysed in subjects without known diabetes. Glycosylated haemoglobin (HbA1c) and urine micro-albumin were analysed in participants with diabetes. Blood samples were drawn after overnight fasting and were performed by the laboratory nurse at the primary healthcare centre. Analyses were performed at the Clinical Chemistry Laboratory at Sunderveld Hospital.

Questionnaires. Physical activity and smoking habits were assessed by a modified self-administered questionnaire, which was used earlier in the national project “Physical activity on recipe” by the Institute of Public Health. Health-related quality
340 eligible subjects aged 18-65 with the diagnosis hypertension, type 2 diabetes, dyslipidemia or obesity were invited

52% gave their written consent, n = 177

Met exclusion criteria, n = 8

Baseline examination
Randomisation
n = 151

Withdraw before randomisation, n = 18
11 due to workload
5 due to other diseases
1 stroke
1 did not show up

Intervention group
n = 75

Withdraw before intervention start due to other diseases, n = 4

Start of intervention
n = 71
divided into six groups with 10-13 participants in each.

6 follow-up meetings, once a month

Withdraw during intervention, n = 4
3 due to workload
1 moved from the area

Withdraw before 12-month examination
n = 7
1 moved from the area
1 due to myocardial infarction
1 other disease
2 due to pain
2 did not show up

Control group
n = 76

Information meeting
n = 57

Withdraw before 3-month examination
n = 7
1 due to other disease
3 wanted to participate in the intervention group
1 away on a journey
2 drop out

Withdraw before 12-month examination
n = 6
1 moved from the area
2 drop out
3 did not show up

12-month examination
n = 60

12-month examination
n = 63

Figure 1. Participants’ flow.
of life was assessed by using the EuroQol instrument which consists of EQ-VAS (self-rating scale on a thermometer) and EQ-5D (5-digit health state classification) [19]. The EQ-5D describes health status according to five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [19].

**Intervention**

A physiotherapist, a dietitian, and a physician were responsible for the intervention. The team also included two more physiotherapists, a laboratory nurse, and two physiotherapy assistants. The intervention consisted of supervised exercise, diet counselling, and follow-up meetings.

The intervention group (n=75) was divided into six groups with 10–13 participants in each, considering age and fitness. During the first three months, each group had three weekly sessions of supervised progressive exercise training. The exercise consisted of endurance training such as stick-walking or brisk walking, interval training on ergometer bicycles in combination with circuit-type resistance training, and water aerobics, and was led by physiotherapists. The endurance training aimed to increase aerobic capacity and cardiorespiratory fitness, and the resistance training aimed to improve the functional capacity and strength of the large muscle groups of the upper and lower body and trunk. The resistance training consisted of 12 different movements per circuit: two sets of 10–15 repetitions were performed at each station. The load was individual for each subject and was increased over time as strength improved. Time on bicycles was increased from 20 min to 30 min after one month. The exercise sessions lasted for 40–45 min during the first month and were increased to 60 min during the second and third months. All programmes included about 10 min warming up and a cool-down period with stretching. To attain optimal intensity the Borg scale of perceived exertion was used [20]. A moderate intensity at 60–80% of max heart rate corresponding to 13–15 on the Borg scale was recommended in all activities.

During the three-month intervention period each group had five 20-min long meetings with a dietitian. The participants received both written and verbal information. The dietary advice was given verbally and in written form, and advice concerning physical activity was given verbally. A physician, a physiotherapist and a dietician took part at the meeting. The meetings at the end of the study period focused on current physical activity and diet, and maintenance of a physically active lifestyle and new diet habits. Emphasis was placed on identifying situations that might affect behaviour such as holidays or heavy workload. Strategies to handle these high-risk situations were discussed. A physiotherapist led the follow-up meetings and a dietitian and a physician took part in one meeting each. Each participant met his/her ordinary medical professionals/physician in accordance with previous agreements.

**Control group**

The control subjects received the usual care and treatment at the primary healthcare centre and were invited to one single meeting where they were informed about the relationship between lifestyle and health. The dietary advice was given verbally and in written form, and advice concerning physical activity was given verbally. A physician, a physiotherapist and a dietician took part at the meeting.

**Statistical analyses**

With the inclusion of 120 subjects, the study had 90% chance of finding a clinically relevant difference in weight development of 3 kg with a two-sided p-value of less than 0.05. This calculation is based on longitudinal data from the Northern Sweden MONICA-study [23]. Parametric statistical methods were used for quantitative, continuous variables; a two-tailed paired t-test was used for analysis of within-groups changes at 12 months compared with baseline, and an unpaired t-test for analysis between the groups. Mean changes and their 95% confidence intervals were calculated. For ordinal data such as questionnaires non-parametric methods were used: a Wilcoxon signed-ranks test was used to detect within-groups changes from baseline to 12 months and a Mann-Whitney U test was used for analysis between groups. The analyses were done using SPSS.
A total of 123 subjects completed the one-year follow-up, 60 from the intervention group and 63 from the control group. The drop out rate was 18%. For cause of withdrawal see Figure 1. The baseline data are given in Tables I and II. The control group rated total quality of life (EQ-VAS score) as significantly higher (p=0.023), and the dimension anxiety/depression on EQ-5D significantly lower (p=0.034) than the intervention group. No differences between groups were observed concerning the other dimensions.

Statistically significant improvements in most anthropometric and clinical variables were noted in both groups after three months (data not shown). After one year, improvements persisted as statistically significant only in the intervention group (Tables III and IV). In the intervention group, the mean decrease in weight was 1.5 kg and in waist circumference 2.0 cm. Also significant reductions of both systolic and diastolic blood pressure and a significant increase of maximal oxygen uptake (systolic $\Delta -4.7$ mmHg, diastolic $\Delta -3.8$ mmHg, $V_{O2}c$=0.14 l/min) were noted (Table III). Statistically significant differences between groups after one year were reached for waist circumference ($-1.9$ cm),

The baseline data are given in Tables I and II. The Bjo¨rkna¨s Study
The present study provides evidence that primary prevention through lifestyle intervention in primary healthcare has favourable effects on several cardiovascular risk factors in moderate- to high-risk patients, and the improvements can persist for up to one year. No significant differences between groups were noted at baseline in the intervention group after one year (see Table III). Between groups there was no significant difference in the intervention group but after one year there were no significant differences between the groups on any of the five dimensions of EQ-5D.

Changes in tobacco habits are given in Table IV. Most subjects in both the intervention and control groups were receiving pharmacological treatment for hypertension, dyslipidemia, or diabetes during the one-year follow up. Only small changes in pharmacological treatment were seen in both groups (data not shown).

**Discussion**

The present study provides evidence that primary prevention through lifestyle intervention in primary healthcare has favourable effects on several cardiovascular risk factors in moderate- to high-risk patients, and the improvements can persist for up to one year. No significant differences between groups were noted at baseline in the intervention group but after one year there were no significant differences between the groups on any of the five dimensions of EQ-5D.
to one year. The ordinary multi-professional primary care team carried out this intervention and we thereby showed the feasibility of such an intervention programme.

Despite a strict randomization process there was a general tendency towards higher levels of some cardiovascular risk factors in the intervention group. The groups differed significantly for waist–hip ratio and lipid-lowering medication. This may lead to a regression towards the mean in within-group analysis, but should not influence the analysis between groups.

Our result regarding decrease in waist circumference is in concordance with favourable results from other diet and exercise intervention trials \[8,12,16,24\]. Decreases in waist circumference but not total body weight indicate changes in body composition with increase in muscle mass and decrease in fat mass, and improved metabolism \[11,12,25\]. Reduced waist circumference is positively correlated with changes in both fasting triglycerides and HDL cholesterol \[12,24\].

In the present study there were no significant differences between groups in metabolic variables.

In the intervention group there was a significant decrease in triglycerides but a significant increase in LDL cholesterol. The decrease in triglycerides may be due to a higher level of exercise capacity, since there are dose-response relationships between the level of physical activity, triglycerides, and HDL cholesterol \[12,25\]. The increased level in LDL may be explained by differences in dietary composition but the lack of information on dietary intake limits interpretation. Similar results with a decrease in triglycerides but no changes in levels of cholesterols after exercise intervention were found in a German study \[26\].

An elevated level of triglycerides is also associated with insulin insensitivity \[12,25\]. In the intervention group HbA1c was significantly decreased after one year, but the number of diabetes patients was small. Several exercise intervention trials have demonstrated favourable effects on glycaemic control, especially after intervention with resistance exercise

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**Table IV. Presence of overweight and obesity, level of self-reported exercise, level of total physical activity, tobacco habits, at baseline and at one year in the 123 subjects with high cardiovascular risk who completed the one-year follow-up in the Bjoerknas study: Data are given as number and percentages.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group n=60</th>
<th>Control group n=63</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>One year</td>
</tr>
<tr>
<td>Tobacco</td>
<td>46 (76.7)</td>
<td>49 (81.7)</td>
</tr>
<tr>
<td>Smokers</td>
<td>14 (23.3)</td>
<td>11 (18.3)</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>93 (88.3)</td>
<td>92 (86.6)</td>
</tr>
<tr>
<td>Smokers</td>
<td>7 (11.7)</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Presence of overweight and obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight, BMI&lt;24.9</td>
<td>6 (10.0)</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>Overweight, BMI 25.0 – 29.9</td>
<td>29 (48.3)</td>
<td>30 (50.0)</td>
</tr>
<tr>
<td>Obesity, BMI&gt;30.0</td>
<td>25 (41.7)</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>Total physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>12 (20.0)</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Not so active</td>
<td>24 (40.0)</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Fairly active</td>
<td>16 (26.7)</td>
<td>27 (45.0)</td>
</tr>
<tr>
<td>Regularly active</td>
<td>8 (13.3)</td>
<td>12 (20.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (3.3)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>57 (81.7)</td>
<td>15 (25.0)</td>
</tr>
<tr>
<td>Less than 30 min/day</td>
<td>17 (28.2)</td>
<td>24 (40.0)</td>
</tr>
<tr>
<td>30–60 min/day</td>
<td>6 (10.0)</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>More than 60 min/day</td>
<td>2 (3.2)</td>
<td>3 (4.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

Significance within groups on Wilcoxon signed-ranks test; $\gamma <0.01$, $\gamma <0.001$. Mann–Whitney unpaired test for significance between groups.
A submaximal test on an ergometer bicycle was used to estimate maximal oxygen uptake (VO$_2$). The method is established and changes between measurements can be estimated [18]. In the present study there was a significant increase in maximal oxygen uptake and in rating of total physical activity and exercise level in the intervention group at one year. Together, these results strengthen the assumption that the subjects in the intervention group had improved their cardiorespiratory fitness. Improvement in cardiorespiratory fitness is an important factor reducing the risk in cardiovascular events [1].

The differences between groups in maximal oxygen uptake, exercise, and total physical activity were statistically significant after three months (data not shown) but did not reach statistical significance after one year. The lack of between-group differences after one year may be explained by variation in compliance among subjects in the intervention group. During the first three months, exercise sessions were supervised and attendance was high. In the following nine months participants had to exercise on their own. This result could also reflect some difficulties in these subjects finding suitable exercise activities out in the community.

Increase in physical activity after lifestyle intervention may also affect quality of life favourably [29]. In the present study the intervention group significantly increased its rating of health-related quality of life and significantly decreased its rating on the dimension anxiety/depression after one year.

Some limitations of our study should be addressed. We had no quantitative method available for measurement of physical activity and the level of physical activity was assessed only by self-reported questionnaires. This is not optimal as there is a risk of either over- or underestimating exercise, thereby introducing some bias in estimation of the dose–response relationship. However, self-reported questionnaires have been used in several other prospective and intervention trials [16,27,24].

The control group received information on the associations between lifestyle and health on one occasion. This minor intervention may have diluted the results and decreased the differences between the groups, since the control-group subjects may have benefited from this advice. The study subjects, who were recruited by letter and agreed to participate, may reflect subjects with a greater interest in lifestyle changes. Thus our study groups may not have been truly representative of the population at risk. The strength of this study is the methodological design. The participants were randomized to intervention or control group, and the number of subjects was large enough to give statistical power to detect biologically important changes. Data were analysed conservatively according to the principle “intention to treat”, irrespective of degree of participation in the supervised exercise, or compliance with the recommended diet and exercise. One weakness of this study was that some subjects dropped out, but the dropout rate did not differ between the groups.

Several studies have shown the importance of regular follow-up meetings and behaviour change strategies for achieving long-term effects and maintenance [24,28]. Usual care and standard advice are insufficient to change diet and exercise habits and modify cardiovascular risk factors [30]. The primary care team plays an important part in primary prevention of CVD [17].

In this study we used a unique combination of methods: structured exercise, diet counselling, and regular follow-ups with a behavioural approach. Despite the short intervention period, our one-year results are important and encouraging. The follow-up meetings were probably significant for maintaining new behaviour and to avoid relapses although the results also indicate some variation in compliance among the study subjects.

We conclude that lifestyle intervention in primary healthcare consisting of aerobic exercise and circuit resistance training, in combination with diet counselling and regular follow-up, has favourable effects on several cardiovascular risk factors in patients with a moderate to high risk of CVD. The level of physical activity increases and health-related quality of life improves. Such intervention can be implemented in the primary healthcare system.

References


A 3-Year Randomized Trial of Lifestyle Intervention for Cardiovascular Risk Reduction in the Primary Care Setting: The Swedish Björknäs Study

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Abstract

Background: Successfully transferring the findings of expensive and tightly controlled programmes of intensive lifestyle modification to the primary care setting is necessary if such knowledge is to be of clinical utility. The objective of this study was to test whether intensive lifestyle modification, shown previously in tightly-controlled clinical trials to be efficacious for diabetes risk-reduction among high-risk individuals, can reduce cardiovascular risk factor levels in the primary care setting.

Methodology / Principal Findings: The Swedish Björknäs study was a randomized controlled trial conducted from 2003 to 2006 with follow-up on cardiovascular risk factors at 3, 12, 24 and 36 months. A total of 151 middle-aged men and women at moderate- to high-risk of cardiovascular disease from northern Sweden were randomly assigned to either an intensive lifestyle intervention (n = 75) or control (n = 76) group. The intervention was based broadly on the protocol of the Diabetes Prevention Program. The three-month intervention period was administered in the primary care setting and consisted of supervised exercise sessions and diet counselling, followed by regular group meetings during three years. The control group was given general advice about diet and exercise and received standard clinical care. Outcomes were changes in anthropometrics, aerobic fitness, self-reported physical activity, blood pressure, and metabolic traits. At 36 months post-randomisation, intensive lifestyle modification reduced waist circumference (−2.2 cm: p = 0.001), waist-hip ratio (−0.02: p = 0.001), systolic blood pressure (−4.9 mmHg; p = 0.036), and diastolic blood pressure (−1.6 mmHg; p = 0.005), and improved aerobic fitness (5%; p = 0.038). Changes in lipid or glucose values did not differ statistically between groups. At 36 months, self-reported time spent exercising and total physical activity had increased more in the intervention group than in the control group (p<0.001).

Conclusion / Significance: A program of intensive lifestyle modification undertaken in the primary health care setting can favourably influence cardiovascular risk factor profiles in high-risk individuals.

Trial Registration: ClinicalTrials.gov NCT00486941

Introduction

Evidence from epidemiological and experimental studies overwhelmingly illustrates the beneficial impact of healthy lifestyle behaviours on cardiovascular risk [1–2]. Lifestyle factors such as physical inactivity, diets rich in saturated fats and sugar, and central obesity contribute to the development of type 2 diabetes and cardiovascular disease (CVD) [1–5]. People who maintain physically active lifestyles have lower levels of most atherosclerotic and metabolic risk factors [1–5], spend more years free from type 2 diabetes [1], and live longer [1–2]. A low level of cardiometabolic fitness, which is influenced by physical activity levels, is a powerful, independent risk factor for premature mortality [1–2].

Physical activity is also associated with a reduced risk of CVD and with reduced rates of cardiovascular and total mortality in people with type 2 diabetes [1]. A variety of different intervention methods have been used to increase physical activity levels. These include paradigms involving individual- or group-level interventions. The methods to promote physical activity have involved activity feedback using pedometers, activity counseling, and exercise prescription [4–6], or more extensive lifestyle programs such as those implemented in the Finnish Diabetes Prevention Study (DPS) [7] and the Diabetes Prevention Program (DPP) [8]. These more extensive lifestyle intervention programs have been shown to induce around 5–7% weight loss and consequently achieve clinically relevant reductions in cardiovascular risk factor levels [9–10] and delay the onset of type 2 diabetes [7,11–12] and CVD [1–5]. Exercise interventions can reduce central obesity in a...
dose-dependent manner independently of changes in nutrient or caloric intake [13-14], thus improving CVD risk profiles [14-15]. In people with type 2 diabetes, both structured exercise training [16-19] and physical activity counseling [20-21] result in weight loss and improved metabolic homeostasis. Although weight loss certainly mediates many of the beneficial effects of exercise on type 2 diabetes risk reduction, exercise may also prevent or delay the onset of type 2 diabetes through independent mechanisms [22] involving insulin signaling, glucose and lipid oxidation, and reduced hepatic glucose production.

Although a number of randomized controlled trials have successfully demonstrated the efficacy of intensive lifestyle intervention for cardiovascular [23-25] and type 2 diabetes [11-12] risk reduction, to our knowledge only a few attempts to apply the protocols used in these studies for lifestyle modification in the primary health-care setting have been documented [26-27], none of which were randomized or involved long-term follow-up.

We recently reported the provisional results (at 12 months follow-up) of a randomized controlled trial, where individuals at moderate- to high-risk of cardiovascular disease were randomly assigned to receive either intensive lifestyle modification or standard care [20]. In that study, which was run from a primary health-care centre in northern Sweden, we were able to demonstrate that lifestyle modification improves cardiovascular risk factor levels. The intervention was group-based, focusing on aerobic and resistance training, improvements in dietary habits, motivation, and maintenance of behavioral changes, and was carried out without additional resources at a primary-care centre.

In this report from the same clinical trial, we describe the overall trial results from baseline through three years follow-up.

Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

The Swedish Björkääh Study was a randomized controlled clinical trial. Participants assigned to the control arm of the study received standard care and those assigned to the intervention arm received a program of lifestyle modification including structured exercise training sessions and diet counselling. Individuals were followed-up at 3, 12, 24 and 36 months (Figure 1.)

Participants

The study population was selected from the catchment area of the Swedish Björkääh primary health care center in the town of Boden in northern Sweden. Participants were enrolled in the study by the medical supervisor of the health care at the center. All individuals aged 18-85 years with a clinically documented diagnosis of hypertension, dyslipidemia, type 2 diabetes, obesity or any combinations thereof were identified from computerized case records. Individuals with a diagnosis of coronary heart disease, stroke, transient ischemic attack, severe hypertension (SBP>180 or DBP>105 mmHg), dementia or severe psychiatric morbidity were excluded. The remaining 948 eligible individuals were invited by letter to participate in the trial (Figure 1). Of those, 177 individuals agreed to participate (52% of those eligible). 18 withdrew before randomisation, and a further eight met the study’s exclusion criteria.

Randomization

A total of 151 enrolled participants were randomly allocated using a computer-generated random numbers sequence to the intervention group (n = 75) or the control group (n = 76). An independent statistician generated the allocation sequence and randomisation numbers were kept in sealed, opaque envelopes. The allocation was concealed until after the baseline examinations were completed and participants were assigned to their groups by the research physiotherapist. After excluding four subjects who were allocated to the lifestyle intervention but did not start the intervention period, and excluding two subjects with incomplete baseline data allocated to control group, the numbers of participants were 71 and 74 in the intervention and control groups, respectively.

Ethics

All participants provided written informed consent to participate and the study protocol was approved by institutional review board of Umeå University, Sweden.

Clinical examination

At each examination, measurements of weight, height, circumferences of the waist and hips, blood pressure by a standard auscultatory method, and an estimate of maximal oxygen uptake (VO2max) were obtained. Body mass index (BMI: weight in kg / height in meters squared) and waist-to-hip ratio were calculated. VO2max was estimated as described by Astrand [29] from each participant’s individual heart rate response to a given submaximal workload (i.e. 50-130 W, depending on the participant’s weight and self-reported physical activity) using a bicycle ergometer (Monark, Varberg, Sweden) and recorded at steady-state with a heart rate of ±10 beats/min. In the original test Astrand reported a correlation of r = 0.78 between estimated and measured VO2max [29]. Other authors have reported correlations within the range r = 0.69-0.95, varying by age and gender. The method has also proven reliable when repeated measures are available within the same individual [10].

A history and physical exam was undertaken at baseline focusing on cardiovascular disease and current medication usage. Changes in pharmacological treatment were followed yearly. A trained research physiotherapist (MI) performed all interviews and undertook the anthropometric and blood pressure measurements to minimize observer bias. Two other trained physiotherapists performed the exercise stress tests. The physiotherapists were not blinded to allocation of treatment at the follow-up examinations.

Laboratory measurements

The methods for blood collection, storage and analysis have been described in detail previously [29]. In brief, total cholesterol and triglycerides were analysed by enzymatic colorimetry (slide method, Vitros 5.1 Ortho-Clinical diagnostics, Raritan, New Jersey). High-density lipoprotein cholesterol (HDL-C) was analysed by enzymatic (dextran sulphate procedure) colorimetry (Hitachi 917, Roche Diagnostics Scandinavia AB, Bromma, Sweden). Low-density lipoprotein cholesterol (LDL) cholesterol was calculated using the Friedewald equation. Serum glucose was analysed by enzymatic (glucose oxidase) colorimetry (Vitros 5.1, Ortho-Clinical Diagnostics, Raritan, New Jersey). Glycoylated haemoglobin (HbA1c) was analysed by High Performance Liquid Chromatography. Ion exchange Chromatography. Photometry (VARIANT™ H1, BIORAD laboratories, Hercules, California). All biochemical analyses were performed at the clinical chemistry laboratory at Sunderby Hospital, Luleå, Sweden. All non-diabetic participants underwent a 75 g oral glucose tolerance test, using the protocol recommended by the WHO, at two and three years post-randomisation.

Behaviour assessments

Physical activity and tobacco habits were assessed using a self-administered questionnaire, previously used in the national project...
The questionnaire has also been used by a number of Swedish regional health authorities to assess public health within the community. However, no validation studies have been performed for this questionnaire. The questionnaire is intended to characterize a participant’s levels of leisure-time activity (LTPA), structured exercise, and total physical activity (TPA). LTPA includes activities such as housekeeping, gardening, walking or biking to work, and ‘exercise’ includes structured activities such as aerobics, jogging, swimming, and ball games carried out during a normal week. Four activity levels were determined for LTPA and exercise: none’, ‘<30 min/d’, ‘30–60 min/d’, and ‘≥60 min/d’.

Figure 1. Participants flow diagram.

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min/d’ and ‘>60 min/d’. Nine questions on TPA were included that were intended to estimate all forms of physical activity undertaken during the past 12 months. A TPA index with four activity levels was constructed: ‘sedentary’, ‘minimally active’, ‘moderately active’, and ‘very active’. Participants in both groups were also requested to complete physical activity logs.

Interventions

The lifestyle intervention consisted of supervised exercise training and diet counselling, followed by regular group meetings. The first three months of the intervention included three sessions per week of supervised progressive exercise training and diet counselling on a total of five occasions. The exercise training sessions consisted of aerobic exercises such as Nordic walking (brisk walking with poles), interval training on a bicycle ergometer, circuit-type resistance exercise, and aqua-aerobics. These activities were led by physiotherapists and physiotherapy assistants at the primary care center. The physiotherapists were responsible for both the clinical examinations and delivering the exercise interventions. Exercise training was performed in small groups (n = 10–13) with each group comprising participants of similar ages and fitness levels. All groups were offered one session of each activity every week. The exercise training sessions lasted 40–45 min during the first month and increased to 60 min during the second and the third months. The duration of the bicycle ergometry exercise was increased from 20 min to 30 min after one month. The resistance training consisted of 12 different movements per circuit: two sets of 10–15 repetitions were performed at each station. The load was individualized and increased over time as the participant’s strength improved. All programmes included a warm-up and a cool-down period with stretching. The aim of the exercise sessions was to increase cardiorespiratory fitness and to improve functional capacity and strength of the large muscle groups of the arms, torso, and legs. To approximate optimal exercise intensity, the Borg scale of perceived exertion was used [32]. A moderate intensity (60–80% of maximal heart rate) corresponding to 13–15 on the Borg scale was recommended for all activities.

A trained dietician was responsible for the diet counselling. The dietary advice was given in small groups but no individual counselling was provided. The participants received both written and verbal dietary information. The counselling was in accordance with the Nordic nutrition recommendations [33]. Briefly the participants were encouraged to increase their intake of fish, fruits, vegetables fiber-rich products and complex carbohydrates. Participants were also advised to restrict total caloric intake by reducing consumption of sugar and saturated fat and to use low-fat milk products, soft margarines and vegetable oils rich in monounsaturated fatty acids (See table 1).

After the active intervention period, participants from each training group were invited to attend regular follow-up meetings on four occasions during the first year (from September to February), on four occasions during the second year and on two occasions during the third year (Figure 1). The objectives of the follow-up meetings were (i) to improve the participant’s knowledge about the relationships between lifestyle and health, (ii) to encourage participants to favourably modify their lifestyles, and (iii) to provide social support and to facilitate adherence to the intervention. The stages-of-change model of behavioural change was used as theoretical basis for the intervention [34]. The techniques used were standardized for all participants. After the active intervention period most individuals were in the ‘preparation’ or ‘action’ phases. Participants were asked to investigate benefits, barriers, and costs of adherence to a healthier lifestyle and were encouraged to establish individual goals for weight reduction and to develop a personal physical activity plan. They were encouraged to maintain at least 30 min/day of physical activity. Participants also received information about community-based physical activity and a study visit at a local gym was provided for each training group.

At the group meetings discussions focused on physical activity, diet, coping with stress, and the effects of tobacco on health. The progress of each participant was discussed at the meetings during the follow-up period. Emphasis was placed on identifying situations that inhibit healthy behaviours such as holidays or heavy workloads and strategies to handle these situations were discussed. During the final stage of the trial, the importance of maintaining healthy habits and on avoiding relapses was reinforced.

Physiotherapists supervised most of the in-person meetings, and a dietician provided further diet counselling on three occasions, once each year during the follow-up period. The medically responsible physician took part in one meeting at the beginning of the study and one at the end of the study to answer participants’ questions about the health aspects of the intervention and to reinforce the messages being delivered by the physiotherapists and the dietician.

Participants in the standard care control group were given verbal and written information about healthy behaviours, including exercise and diet. This information was delivered by the physician, a physiotherapist and a dietician at a group meeting following the baseline examination (Figure 1).

Blinding

Neither the participants nor the family practitioners or physiotherapists who delivered the intervention were blinded to the allocation of treatment. Each year, participants in both groups were given a written summary of their laboratory and clinical test results. Participants in both groups continued with their routine care, delivered for example by their family practitioner or specialist, throughout the study, and no special instructions were given regarding other preventive measures.

Objectives

Our objective was to test the hypothesis that a lifestyle intervention program in the primary health care setting facilitates long-term (up to 3 yrs) clinically relevant improvements in cardiovascular and metabolic risk profiles in people who, at baseline, were at high risk of cardiovascular disease.

Outcomes

Outcome measures were changes in anthropometry (BMI, weight, waist, waist-to-hip ratio), VO2 max, self-reported physical activity, blood pressure, triglycerides, cholesterol (total, HDL, and LDL), fasting blood glucose, glucose tolerance, and HbA1c.

Sample size

In the DPP, weight loss at 1 and 3.4 years within the lifestyle intervention group averaged 6.8 kg and 4.1 kg, respectively [33]. For sample size calculations, we assumed 20% of participants from our study would withdraw before completion, and that our intervention would yield approximately half the weight loss at three years post-randomization than observed in the DPP (e.g. 2.1 kg, SD = ±1 kg). We also assumed that because the control group was receiving standard health advice and was not blinded to treatment allocation, those in that group would lose up to 1 kg (SD ±1 kg) in weight during the trial. We selected a two-sided p-value of .05.
of 0.001 to account for multiple statistical comparisons. With these parameters, our study was powered at 99% to detect the predicted difference in weight change between groups at 3 years follow-up. Power was calculated using STATA v9.2 SE (StataCorp, TX, USA).

### Statistical methods

SPSS for Windows (v13.0; Chicago, IL) and SAS for Windows (v9.1, Cary, NC) were used for all statistical analyses. Data were analysed on an intention-to-treat (ITT) basis, regardless of adherence to the intervention and included all randomly allocated persons, with the exception of the six individuals excluded for the reasons given above (Figure 1). If data were missing, the last observation was carried forward.

Generalized linear models with repeated measures analysis of variance and univariate tests of variance were used to investigate changes in the dependent variables (as continuous traits) over time at each of the follow-up time points, adjusted for baseline values. To determine the independent effects of the intervention on blood pressures, lipids, or HbA1c, these variables were adjusted for “medication load”. To this end, a variable was computed from the number of specific drugs prescribed to treat the respective trait by assigning values of 1 for low doses and 2 for high doses and subsequently summing these values.

### Ancillary analyses

Mixed-model analyses were used to calculate the adjusted effects of the intervention at each of the follow-up points for continuous trait outcomes and to investigate the overall effect of the intervention. The mixed-model included all available follow-up data. To account for multiple observations within individual, models were fitted using an unstructured covariance matrix. The choice of matrix was determined by comparing Akaike’s Information Criterion for different structures and selecting the matrix that best fitted the data. This method allows for trait correlations between different examinations within the same individual. The results of these models indicate whether changes in the values of a trait from baseline to follow-up differ significantly

### Table 1. Summary of physical activity and diet recommendations provided to participants randomized to the control and intervention groups.

<table>
<thead>
<tr>
<th></th>
<th>Control group (standard recommendations)</th>
<th>Intervention group (extended recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical activity</strong></td>
<td>Aim to accumulate at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week.</td>
<td>Aim to accumulate at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week.</td>
</tr>
<tr>
<td>Swedish Institute of Public Health</td>
<td>Additional health benefits can be achieved by extending the time spent in moderate-intensity activities, or by increasing the intensity of active tasks.</td>
<td>Additional health benefits can be achieved by extending the time spent in moderate-intensity activities, or by increasing the intensity of active tasks.</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>Energy percent, E%,</td>
<td>Energy percent, E%,</td>
</tr>
<tr>
<td>National food administration</td>
<td>Carbohydrates, 55% (50–60)</td>
<td>Carbohydrates, 55% (50–60)</td>
</tr>
<tr>
<td>- Protein, 15% (10–20)</td>
<td>Protein, 15% (10–20)</td>
<td></td>
</tr>
<tr>
<td>(SUI)</td>
<td>Fat, 30% (25–35)</td>
<td>Fat, 30% (25–35)</td>
</tr>
<tr>
<td>saturated fat and trans fat, 10%</td>
<td>saturated fat and trans fat, 10%</td>
<td></td>
</tr>
<tr>
<td>monounsaturated fat, 10–15%</td>
<td>monounsaturated fat, 10–15%</td>
<td></td>
</tr>
<tr>
<td>polyunsaturated fat, 5 (%)</td>
<td>polyunsaturated fat, 5 (%)</td>
<td></td>
</tr>
<tr>
<td><strong>General advice</strong></td>
<td>- Increase intake of fish, fruits, vegetables, fibre rich products and complex carbohydrates.</td>
<td>- Increase intake of fish, fruits and vegetables, fibre rich products and complex carbohydrates.</td>
</tr>
<tr>
<td>- Reduce consumption of sugar and saturated fat.</td>
<td>- Reduce consumption of sugar and saturated fat.</td>
<td></td>
</tr>
<tr>
<td>- Use low-fat milk products, soft margarines and vegetable oils rich in monounsaturated fatty acids.</td>
<td>- Use low-fat milk products, soft margarines and vegetable oils rich in monounsaturated fatty acids.</td>
<td></td>
</tr>
<tr>
<td>- Restrict total caloric intake.</td>
<td>- Restrict total caloric intake.</td>
<td></td>
</tr>
<tr>
<td>- Regular meal distribution.</td>
<td>- Regular meal distribution.</td>
<td></td>
</tr>
<tr>
<td><strong>Information about meal content and function of:</strong></td>
<td>- Fat, carbohydrates, protein, vitamins, minerals and antioxidants.</td>
<td></td>
</tr>
<tr>
<td>- Alcohol.</td>
<td>- Alcohol.</td>
<td></td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0005195.e001
between the intervention and the control groups. In addition to the
data, the mixed-model estimates components of variance (random effects) representing the relationship between different observations for the same individual. For continuous or rank-
ordered data, the parameters of these variables were estimated by a maximum-likelihood procedure. For ordinal data such as those obtained from questionnaires, the non-parametric Mann-Whitney U-test was used for analysis between groups at each follow-up time
point, and mixed-models were used to assess the overall effects of
the intervention. For other discrete variables, the Pearson Chi-
Square test and repeated measures analysis were used. A p-value
<0.05 was considered statistically significant.

Results

Recruitment

Participants were recruited in January 2003 and underwent baseline examinations in February 2003. Follow-up examinations were conducted 3, 12, 24 and 36 months after the baseline examination. The study was completed in March 2006.

Participants flow

From the original 151 volunteers, a total of 120 completed the 3-year follow-up examination (80%); n = 58/75 in the intervention group and n = 62/75 in the control group. Attrition was greatest during the first year of the study, attributed mainly to ill health, heavy workloads, or relocation to another geographic region during follow-up (Figure 1).

Subject characteristics

There were no differences in demographic characteristics or CVD risk profiles between study participants and the 163 subjects who declined to participate. Mean age in the study group was 54.4 years vs. 53.8 years in the group of non-participants. Gender distribution and the prevalence of risk factors were similar. In the study group 43% were male, 66% had a diagnosis of hypertension, 28% had a diagnosis of type 2 diabetes, and 23% had dyslipidemia. The corresponding proportions among those who did not participate were male 50%, hypertension 69%, type 2 diabetes 32%, and dyslipidemia 14%. Of all eligible subjects about half had at least one CVD risk factor and a third had two or
more CVD risk factors besides being overweight or obese. Only 60 of the 340 individuals had “overweight” or “obesity” recorded as clinical diagnoses in their case records, which were an underes-
timate of the true prevalence of these conditions (see Table 2).

In the intervention group 12 women and 5 men withdrew, compared with 5 women and 9 men in the control group. Mean age at recruitment among individuals who withdrew was 53.2 years, which was not statistically different from those who completed the trial (mean age 55.2 years). In both groups the individuals who withdrew were obese or overweight, with one or

Compliance

Seventy percent of the intervention group attended the supervised exercise sessions during the three-month intervention period, but varied from 15% to 100% across sessions. Sixty-four percent took part in 3-5 diet-counselling sessions but 36%
participated on only one or two occasions. Low attendance was mainly due to employment commitments. During the first year of

the trial mean attendance at the follow-up meetings was 70%,

Numbers analysed

Although participants were randomly assigned to the study arms, not all characteristics were distributed equally between the control and intervention groups. As shown in Table 2 and Table 3, at baseline participants in the intervention group tended to have larger waists, undertook less LTPA and were more frequently treated with lipid lowering drugs than those in the control group.

Outcomes and estimation

At baseline, the proportions of normal weight, overweight and

Baseline data

All data analyses were performed on an ITT basis. Accordingly, if data were missing, the last observation was carried forward. Analyses included 71 participants from the intervention group and 74 participants from the control group, except in analyses of fasting blood glucose, HbA1c and VO2max (Table 2). Fasting blood glucose concentrations were analysed only in participants without known diabetes and HbA1c was analysed in participants with diagnosed diabetes. Participants on beta-blockers were excluded from analyses where VO2max was the outcome, as the heart rate response to exercise (a necessary component of the VO2max prediction equation) is blunted with this type of medication.
Table 2. Baseline Characteristics of randomised participants in the Swedish Björknaäs Study*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention group (n = 71)</th>
<th>Control group (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr, mean (SD)</strong></td>
<td>55.7 (6.6)</td>
<td>53.1 (8.2)</td>
</tr>
<tr>
<td><strong>Sex, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (49)</td>
<td>27 (36.5)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (51)</td>
<td>47 (63.5)</td>
</tr>
<tr>
<td><strong>Non-smokers, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54 (76)</td>
<td>61 (82)</td>
</tr>
<tr>
<td><strong>Ex-smokers, No. (%)</strong></td>
<td>24 (34)</td>
<td>29 (39)</td>
</tr>
<tr>
<td><strong>Anthropometrics, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>87.4 (16.5)</td>
<td>84.3 (20.0)</td>
</tr>
<tr>
<td>Body Mass Index, Kg/m² †</td>
<td>30.2 (5.2)</td>
<td>29.4 (5.1)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>104.1 (13.2)</td>
<td>100.2 (15.9)</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>108.6 (15.2)</td>
<td>107.4 (8.6)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.96 (0.06)</td>
<td>0.85 (0.06)</td>
</tr>
<tr>
<td><strong>Presence of overweight or obesity, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index 25–29.9</td>
<td>32 (45)</td>
<td>32 (45)</td>
</tr>
<tr>
<td>Body Mass Index ≥30</td>
<td>32 (45)</td>
<td>30 (41)</td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mmHg</td>
<td>146 (15.5)</td>
<td>145 (17.6)</td>
</tr>
<tr>
<td>Diastolic, mmHg</td>
<td>86 (7.1)</td>
<td>87 (8.4)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol, mmol/L</td>
<td>5.49 (1.05)</td>
<td>5.43 (0.91)</td>
</tr>
<tr>
<td>High Density Lipoprotein Cholesterol, mmol/L</td>
<td>1.39 (0.32)</td>
<td>1.46 (0.40)</td>
</tr>
<tr>
<td>Low Density Lipoprotein Cholesterol, mmol/L</td>
<td>3.17 (0.91)</td>
<td>3.12 (0.82)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.08 (1.24)</td>
<td>1.90 (1.15)</td>
</tr>
<tr>
<td>Fasting Blood Glucose, mmol/L</td>
<td>5.24 (0.50)</td>
<td>5.20 (0.50)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.30 (1.31)</td>
<td>6.32 (2.05)</td>
</tr>
<tr>
<td><strong>Type 2 diabetes, No. (%)</strong></td>
<td>23 (32)</td>
<td>17 (23)</td>
</tr>
<tr>
<td><strong>Exercise text variables, mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal Oxygen uptake, VO₂, L/min ‡</td>
<td>2.1 (0.6)</td>
<td>2.2 (0.5)</td>
</tr>
<tr>
<td>Maximal Oxygen uptake, mL/kg per minute ‡</td>
<td>25.4 (6.4)</td>
<td>25.8 (6.2)</td>
</tr>
<tr>
<td><strong>Total physical activity, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>14 (20)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Minimally active</td>
<td>27 (38)</td>
<td>35 (47)</td>
</tr>
<tr>
<td>Moderately active</td>
<td>22 (31)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>Very active</td>
<td>8 (11)</td>
<td>11 (15)</td>
</tr>
<tr>
<td><strong>Exercise, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>43 (61)</td>
<td>37 (50)</td>
</tr>
<tr>
<td>&lt;30 min/d</td>
<td>20 (28)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>30–60 min/d</td>
<td>8 (11)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>&gt;60 min/d</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Leisure-time activity, No. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (20)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>&lt;30 min/d</td>
<td>23 (32)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>30–60 min/d</td>
<td>30 (43)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>&gt;60 min/d</td>
<td>4 (6)</td>
<td>15 (20)</td>
</tr>
</tbody>
</table>

*Age and anthropometric, clinical and metabolic data are given as mean (SD); for other variables data are given as the number of observations (%).
† Calculated as weight in kilograms divided by the square of height in meters.
‡ n = 49/57.
§ n = 22/17 only in known diabetics.
¶ n = 50/42.
doi:10.1371/journal.pone.0005195.t002
three years (mean 141.7 mmHg; 95% CI 139.0–144.4 mmHg vs. mean 146.8 mmHg; 95% CI 144.2–149.4 mmHg). Diastolic blood pressure was significantly lower in the intervention group at all time points except at three years (Figure 3). During follow-up, the use of blood pressure lowering drugs increased in both groups; this increase did not differ between groups (Table 3).

No significant differences in lipid variables were observed between groups during follow-up (Figure 4). The medication load of lipid lowering drugs was higher in the intervention group than in the control group at all time points (Table 3).

In participants with known diabetes, no differences between groups were observed in HbA1c levels or medication usage during follow-up and no differences between groups were observed in fasting-blood glucose levels in participants without known diabetes (Figure 4). However, one new clinical diagnosis of diabetes occurred in the control group and none was observed in the intervention group. An OGTT was carried out at the examinations after 2 and 3 years. The prevalence of impaired glucose tolerance and diabetes diagnosed by OGTT tended to be lower in the intervention group (24%) than in the control group (34%), although these proportions were not statistically different (Table 5).

After an initial improvement in estimated maximal oxygen uptake in both groups, which was greatest in the intervention group (VO2max 0.3 l/min; p = 0.006, 4.0 ml/kg/min; p < 0.001), a gradual decline toward baseline values was observed during follow-up (Figure 5). In the ITT analysis, the improvement by study end in estimated maximal oxygen uptake was greater in the intervention group (VO2max 2.2 l/min; 95% CI 2.11–2.29) than in the control group (VO2max 2.1 l/min; 95% CI 2.00–2.19) when expressed in absolute terms (p = 0.038), although not when expressed relative to body mass (VO2max 26.0 ml/kg/min; 95% CI 25.0–26.9 vs 25.0 ml/kg/min; 95% CI 24.0–26.1) (p = 0.061). In the mixed model analysis, the differences in VO2max reflected those observed in the ITT analyses (VO2max l/min: p = 0.049; VO2max ml/kg/min: p = 0.12).

The improvements in VO2max may reflect an effect of increased physical activity levels in participants in the intervention group; those individuals reported more exercise participation (p < 0.0001) and greater TPA (p < 0.0001) compared with participants in the control group by the end of the trial. At baseline 20% of the lifestyle intervention group was sedentary, whereas only 7% was sedentary at the 3-year examination. At three years about 70% of both groups reported LTPA of at least 30 min/d, but in the intervention group the proportions of those reporting being moderately or very physical active had increased from 42% to 59%, respectively. This contrasted the control group, where

### Table 3. Changes in medication treatment and cigarette smoking from baseline to 3 years follow-up in the Swedish Björknaés study*.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention group (n = 73)</th>
<th>Control group (n = 74)</th>
<th>P-Value</th>
<th>P-value 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current cigarette smoking. No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17 (24)</td>
<td>13 (18)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>16 (23)</td>
<td>13 (18)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>14 (20)</td>
<td>13 (18)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>12 (17)</td>
<td>13 (18)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>10 (14)</td>
<td>12 (16)</td>
<td>0.72</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension, medication load 0–7, M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.42 (1.86)</td>
<td>1.92 (2.52)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>1.64 (1.81)</td>
<td>1.49 (1.51)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>1.58 (1.77)</td>
<td>1.62 (1.61)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>1.75 (1.80)</td>
<td>1.82 (1.63)</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>1.90 (1.88)</td>
<td>1.88 (1.69)</td>
<td>0.63</td>
<td>0.65</td>
</tr>
<tr>
<td>Dyslipidemia, medication load 0–2, M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.39 (0.60)</td>
<td>0.15 (0.46)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>0.39 (0.60)</td>
<td>0.18 (0.48)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>0.46 (0.61)</td>
<td>0.20 (0.52)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>0.51 (0.65)</td>
<td>0.23 (0.54)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>0.55 (0.60)</td>
<td>0.28 (0.63)</td>
<td>0.000</td>
<td>0.41</td>
</tr>
<tr>
<td>Diabetes mellitus and Impaired glucose tolerance at Oral glucose tolerance test, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>9 (24)</td>
<td>15 (31)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>9 (24)</td>
<td>16 (33)</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as the number of observations (%) or mean (SD).

1 Last observation carried forward for individuals who withdrew. Number of participants at 3 months: IG = 66, CG = 69; n at 1 year IG = 60, CG = 63; n at 3 year IG = 58, CG = 62.

2 P-value for difference between groups generated using the Pearson Chi-Square test.

3 P-value generated using a general linear model with repeated measures.

4 IG/CG n = 37/49.

5 IG/CG n = 37/48.

6 NIG/CG n = 37/46.

7 doi:10.1371/journal.pone.0005195.t003
Discussion

Adverse advents

No adverse events (i.e., fractures, sprains, or serious cardiovascular events associated with exercise) were reported by participants during the study.

Discussion

We present here the full results from the Swedish Bjo¨rkna¨s Study, a three-year randomised controlled trial of intensive lifestyle modification for cardiovascular risk reduction in patients at moderate- to high-risk of cardiovascular disease. The study protocol was adapted from the DPP, but was delivered with limited resources at a primary health care center in the northern Swedish town of Boden. The lifestyle intervention favourably impacted physical activity and aerobic fitness, waist circumference, waist-to-hip ratio, blood pressure, and smoking cessation. No effect of the intervention was observed on glycaemia or lipidemia.

Being obese or having diabetes diminishes quality of life [35–36] and imposes considerable economic burdens on health care systems [35]. Thus, interventions that beneficially impact cardiovascular risk-factor levels in high-risk individuals are likely to improve individual well-being, may be more cost-effective than population-wide lifestyle modification strategies [57], and safer and less expensive than drug therapy [30]. Several large-scale intervention studies during the past decade have illustrated the efficacy of lifestyle intervention for diabetes risk reduction. In the DPP [8] and the Finnish DPS [7], the reduction in diabetes risk attributable to lifestyle modification was 35% in both studies using ITT analyses. The DPP authors predicted that in individuals with similar characteristics to the DPP volunteers, seven would need to participate in a similar lifestyle intervention program to prevent one case of diabetes during a 3-year follow-up period [8]. In the DPP, the level of diabetes risk reduction in people who met the goals for weight loss, physical activity and diet modification was 89% [39]. Other reports from the DPP have highlighted the beneficial impact of lifestyle modification on other cardiovascular risk factors including glucose homeostasis, insulin sensitivity, lipid levels, inflammation, coagulation, and obesity [40]. These observations illustrate the remarkable potential of lifestyle change for diabetes and cardiovascular risk reduction.

Notwithstanding the considerable health benefits conferred by the DPP lifestyle intervention, the protocol was costly and, as delivered in the DPP, beyond the scope of many primary health care agencies (for further details, see: www.bsc.gwu.edu/dpp/lifestyle/dpp-part.html). The within-trial costs of the DPP lifestyle intervention totalled $24400 (USD) per case of diabetes prevented or delayed [41]. By the conclusion of the initial intervention period, the running costs of the DPP had totalled $174.3 million (USD) (http://www.nlm.nih.gov/databases/alerts/diabetes01.html). An important and hitherto largely unanswered question is whether the DPP protocol of lifestyle intervention is effective outside a tightly controlled and well-funded setting of an extemely supported multi-centre randomised clinical trial. Although a small number of studies have attempted to address this question [42–43], all were non-randomised and none was carried out in the primary care setting with long-term follow-up.

Interpretation

In an earlier publication from the Swedish Bjo¨rkna¨s Study we reported the interim (one year) results of the trial [20]. We presented crude between-group comparisons showing favourable effects on waist circumference, waist-to-hip ratio and diastolic blood pressure. In the present report, we show that through reductions in central obesity, physical activity and smoking cessation, the lifestyle intervention also favourably impacted blood pressure levels. However, we did not observe improvements in glycemic control or weight reduction, which contrasts the results from the DPP and Finnish DPS. The lack of impact on glucose homeostasis in the present study may be explained by the relatively modest level of weight loss observed here and the close biologic relationship between weight and glucose concentrations. We observed a significant improvement in VO2max during the first three months of the trial. At 3 years the improvement in VO2max persisted only when expressed in absolute terms but not when expressed per unit body mass. This difference is likely to reflect the fact that when VO2max is expressed relative to weight, the VO2max per kg of body mass was significantly lower in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.04) (Table 3).

Adverse advents

Correspondingly, in the intervention group the proportion of individuals who quit smoking in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.001). The results from the mixed-model analyses were consistent with the ITT analyses for both exercise (p = 0.001) and TPA (p = 0.0009).

The proportion of individuals who quit smoking in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.0009) (Table 3).

The proportion of individuals who quit smoking in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.0009) (Table 3).

Data are adjusted means (95% confidence intervals) for each time point derived from generalised linear models with mean differences adjusted for baseline value and randomly assigned treatment. The proportion reporting exercising at least 30 min/d or more increased from 11% to 28% (Figure 5). The results from the mixed-model analyses were consistent with the ITT analyses for both exercise (p = 0.001) and TPA (p = 0.0009).

The proportion of individuals who quit smoking in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.0009) (Table 3).

Conversely, in the intervention group the proportion of individuals who quit smoking in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.0009) (Table 3).

Conversely, in the intervention group the proportion of individuals who quit smoking in the intervention group (41%) was significantly greater than in the control group (8%) (p = 0.0009) (Table 3).
The Swedish Björknäs Study

A

Repeted measures p value = 0.005

Diastolic blood pressure (mmHg)

0 3 6 9 12 15 18 21 24 27 30 33 36

Time since randomization (months)

Control group

Intervention group

B

Repeted measures p value = 0.005

Systolic blood pressure (mmHg)

0 3 6 9 12 15 18 21 24 27 30 33 36

Time since randomization (months)

Control group

Intervention group

C

Repeted measures p value = 0.036

Maximal oxygen uptake [L O2/min]

0 3 6 9 12 15 18 21 24 27 30 33 36

Time since randomization (months)

Control group

Intervention group

D

Repeted measures p value = 0.061

Maximal oxygen uptake [L O2/min]

0 3 6 9 12 15 18 21 24 27 30 33 36

Time since randomization (months)

Control group

Intervention group
in at-risk adults, even when applied in the conventional primary care setting, without additional resources. However, it is worth highlighting that although our cohort is likely similar in demographic characteristics to the cohorts enrolled in the Finnish DPS, which yielded comparable results to the DPP, the population in the northern part of Sweden is culturally and ethnically different from the cohorts enrolled into the DPP. It is also important to highlight that participants in the present study were invited by health care providers from their own health care centres to participate in this study, which may have facilitated recruitment rates. For example, more than half of those eligible to participate in our study were eventually randomised to treatment. By contrast, in a recent report from the same region of Sweden in which advertisements were used to recruit participants for a similar lifestyle intervention program, only 16% of eligible individuals agreed to participate [46]. Thus, our strategy of recruiting through the established health care infrastructure may be fundamental to the success of our project and others that may follow.

It is also important to bear in mind that, as in all other lifestyle intervention trials, neither the participants nor the study staffs in this study were blinded to the allocation of treatment. Thus it is possible that placebo effects explain some of the beneficial changes
in health associated with the lifestyle intervention. On the other hand, providing participants in the standard care arm of the trial with information about lifestyle and health, activity logs, and regular follow-up exams may have diluted differences between groups.

We present data analysed on an ITT basis, which is a highly conservative method for assessing the impact of an intervention. We also used mixed-models incorporating all available data without imputation of missing data points. Both methods yielded similar results, highlighting the robustness of our findings.

At baseline we asked the participants “if the beneficial effects of physical activity and drug treatment were the same, which method would you prefer?” and “if both physical activity on prescription and drug treatment were free of charge, which would you prefer?” The vast majority of our participants responded that they would prefer the physical activity option and none opted for drug therapy. This preference for physical activity as a form of treatment may reflect the cultural emphasis on healthy living in the north of Sweden. However, in both groups there was an increased use of lipid and blood pressure lowering medication during the study, which may reflect current treatment recommendations that emphasise reaching specific target levels.

Although this intervention was not designed to specifically promote smoking cessation, tobacco habits and the effects of tobacco on health were discussed at the follow-up meetings. That broad focus on healthy living may explain why more smokers quit in the lifestyle than in the control group. In combination with the reductions in waist circumference and systolic blood pressure observed in this trial and increased exercise and overall physical activity levels, the reductions in tobacco usage are likely to yield continuing improvements in the health of our participants.

Our study addresses the important objective of translating the findings from extensively resourced trials, which focused on highly selected populations and study settings, to a real-life setting where resources are limited and the population is more heterogeneous. However, an inherent limitation of studies that seek to do this is that they suffer from lower internal validity. In this respect, the Bjo¨rkna¨s study was not blinded and the intervention was less tightly controlled and less well resourced than several previous studies. In this study as in the DPP, only half of all eligible subjects were randomized to treatment [47]. However, those who declined to participate did not differ from those who took part with respect to all key characteristics. Because attrition rates were modest and we used ITT analyses, our findings may be less prone to bias than some other studies. Nonetheless, as indicated by the wide confidence intervals for several traits, our study was underpowered to detect small improvements in the clinical traits examined. Thus, some of our findings may be prone to type 2 error.

Figure 5. (A–C) Changes in physical activity level. Proportion of participants reporting the level of each variable, total physical activity, leisure time physical activity and exercise and ordered as follows: TPA, sedentary; minimally active, moderately active and very active. LTPA and exercise; ‘none’ = 0, ‘<30 min/day’ = 1, ‘30–60 min/day’ = 2, and ‘≥60 min/day’ = 3. P values from general linear model repeated measures analysis. doi:10.1371/journal.pone.0005195.g005
Overall evidence

In summary, a lifestyle intervention program applied in the primary care setting beneficially impacts cardiovascular risk factors combining diet and exercise prescription. This finding provides some of the first empirical evidence that affordable programs of lifestyle intervention, which can be widely prescribed, effectively reduce risk factors for cardiovascular disease in initially high-risk individuals. Our study also shows that such interventions can be integrated within existing health care infrastructures, at least in the Swedish setting. Studies such as ours support the emphasis of the use of drug therapies in favour of safer, more holistic, and more effective treatments combining diet and exercise prescription.

Supporting Information

Checklist S1 CONSORT Checklist

Found at: doi:10.1371/journal.pone.0001519.s001

Protocol S1 Trial Protocol

Found at: doi:10.1371/journal.pone.0001519.s002

Author Contributions

Conceived and designed the experiments: ME. Performed the experiments: ME. Analyzed the data: ME. Contributed reagents/materials/analysis tools: ME. Wrote the paper: ME. PMF ME.

References

Quality of life and cost-effectiveness of a three year trial of lifestyle intervention in primary health care

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ABSTRACT
Background: Lifestyle interventions reduce cardiovascular risk and diabetes but reports on long term effects on quality of life (QOL) and health care utilization are rare. The aim was to investigate the impact of a primary health care based lifestyle intervention program on QOL and cost-effectiveness over 3 years.

Methods: 151 men and women, age 18-65 yr, at moderate-to-high risk for cardiovascular disease, were randomly assigned to either lifestyle intervention with standard care or standard care alone. Intervention consisted of supervised exercise sessions and diet counseling for 3 months, followed by regular group meetings during 3 years. Change in QOL was measured with EuroQol (EQ-5D, EQ VAS), the 36-item Short Form Health Survey (SF-36), and the SF-6D. The health economic evaluation was performed from a societal view and a treatment perspective. In a cost-utility analysis the costs, gained quality-adjusted life years (QALY) and savings in health care were considered. Cost-effectiveness was also described using the Net Monetary Benefit Method.

Results: Significant differences between groups over the 3-yr period were shown in EQ VAS, SF-6D and SF-36 physical component summary but not in EQ-5D or SF-36 mental component summary. There was a net saving of 47 USD per participant. Costs per gained QALY, savings not counted, were 1,668 – 4,813 USD. Probabilities of cost-effectiveness were 89 – 100 %, when 50 000 USD was used as stakeholder’s threshold of willingness to pay for a gained QALY.

Conclusion: Lifestyle intervention in primary care improves QOL and is highly cost-effective in relation to standard care.

Trial registration: ClinicalTrials.gov identifier: NCT00486941

People who are sedentary have a higher relative risk of mortality than the physically active and unfit people have a higher risk than fit people 1-3. Most people in developed countries do not reach recommended level of physical activity (PA) 4 thereby contributing to public health problems 5. Extensive and intensive lifestyle intervention programs delay the onset of diabetes and reduce cardiovascular risk by increasing PA, reducing overweight and changes in dietary habits 6.

Health-related quality of life (QOL) is a patient-centered outcome and incorporates the patient’s perspective of physical, mental and social well-being. Individuals with obesity, diabetes and other cardiovascular risk factors such as hypertension and hyperlipidemia report diminished well-being and QOL 7, 8, while being active is associated with a higher QOL 9, 10.

For a comprehensive assessment of an intervention program it is essential to incorporate the individual’s broader perspective of well-being - not only the conventional medical outcomes11. One recent RCT showed a dose-response effect of PA on both physical and mental aspects of QOL12. Otherwise, reports on the long term effect of programs for increased PA on QOL are rare, inconsistent and very seldom carried out in primary health care13-18.
Despite the evidence that health care can promote PA, and that it is an effective treatment method, its promotion is rarely used as standard care.

An important factor in the selection of interventions in health care should be the cost-effectiveness as compared with competing methods. A systematic review found no report concerning cost-effectiveness of PA promotion in primary health care used as a treatment method alongside standard care 19.

We recently reported a 3-yr follow-up on an RCT with lifestyle intervention carried out in a primary health care setting 20. It involved a population at moderate-to-high risk for cardiovascular disease and favorably reduced several risk factors. Our hypothesis was that the program improved QOL and was cost-effective.

METHODS

STUDY DESIGN

A complete description of the Björknäs study has been published 20. In brief, the study was a 3-yr RCT with a control group, which received standard care and an intervention group, which also received a lifestyle-modification program. All individuals were followed-up at 3, 12, 24 and 36 months (Figure 1).

PARTICIPANTS, RANDOMIZATION AND BLINDING

The study population was recruited from a primary care center in northern Sweden. Individuals aged 18-65 yr with hypertension, dyslipidemia, type 2-diabetes, obesity or any combination thereof was identified. Individuals with a diagnosis of coronary heart disease, stroke, severe hypertension, and severe psychiatric morbidity were excluded. The 340 eligible subjects were invited by letter, and 177 (52%) agreed to participate. Of those, 18 withdrew before randomization and a further eight met the study’s exclusion criteria. A total of 151 enrolled participants were randomly allocated to the intervention group (n=75) or the control group (n=76), using a computer-generated random numbers sequence. The allocation was concealed until after the baseline examinations were completed. There was no blinding.
340 eligible subjects aged 18-65 with the diagnosis hypertension, type 2 diabetes, dyslipidemia or obesity were invited.

Met exclusion criteria
n = 8

Baseline examination
Randomisation
n = 151

52% gave their written consent
n = 177

Intervention group
n = 71

Control group
n = 74

Information meeting
n = 57

Start of intervention
n = 71
divided into six groups
with 10-13 participants in each

3-month examination
n = 67

6 follow-up meetings
once a month

12-month examination
n = 60

4 follow-up meetings quarterly

24-month examination
n = 58

2 follow-up meetings semi-annually

36-month examination
n = 58

Withdrew before randomisation
n = 18
11 due to workload
5 due to other diseases
1 stroke
1 did not show up

Withdrawn before intervention start
Due to other diseases
n = 4
excluded in analysis

Withdrawn during intervention,
n = 4
3 due to workload
1 moved the area

Withdrawn before 12-month examination
n = 7
1 moved from the area
1 due to fracture and myocardial infarction
2 due to other disease
2 did not show up

Withdrawn before 24-month examination
n = 2
2 did not want to participate any more

Withdrawn before 3-month examination
n = 5
1 due to other disease
3 wanted to participate in the intervention group
1 away on a journey

Withdrawn before 12-month examination
n = 6
1 moved from the area
2 drop out
3 did not show up

Withdrawn before 36-month examination
n = 1
1 moved from the area

Withdrew no complete baseline test
n = 2
excluded in analysis

Baseline examination
Randomisation
n = 151

52% gave their written consent
n = 177

Intervention group
n = 71

Control group
n = 74

Information meeting
n = 57

Start of intervention
n = 71
divided into six groups
with 10-13 participants in each

3-month examination
n = 67

6 follow-up meetings
once a month

12-month examination
n = 60

4 follow-up meetings quarterly

24-month examination
n = 58

2 follow-up meetings semi-annually

36-month examination
n = 58

Withdrew before randomisation
n = 18
11 due to workload
5 due to other diseases
1 stroke
1 did not show up

Withdrawn before intervention start
Due to other diseases
n = 4
excluded in analysis

Withdrawn during intervention,
n = 4
3 due to workload
1 moved the area

Withdrawn before 12-month examination
n = 7
1 moved from the area
1 due to fracture and myocardial infarction
2 due to other disease
2 did not show up

Withdrawn before 24-month examination
n = 2
2 did not want to participate any more

Withdrawn before 3-month examination
n = 5
1 due to other disease
3 wanted to participate in the intervention group
1 away on a journey

Withdrawn before 12-month examination
n = 6
1 moved from the area
2 drop out
3 did not show up

Withdrawn before 36-month examination
n = 1
1 moved from the area

Withdrew no complete baseline test
n = 2
excluded in analysis

340 eligible subjects aged 18-65 with the diagnosis hypertension, type 2 diabetes, dyslipidemia or obesity were invited.

Figure 1. Participants flow Diagram
INTERVENTION
The intervention consisted of supervised progressive exercise training three times a week and diet counseling on five occasions during the first three months, followed by regular group meetings. All activities were performed in small groups (n=10-13). The exercise sessions were led by physiotherapists and consisted of Nordic walking, aqua-aerobics, and interval training on a bicycle ergometer combined with circuit-type resistance training. Each training group was offered one session of each activity every week. The diet counseling was in accordance with the Nordic nutrition recommendations and was given both verbal and written by a trained dietician.

After the 3-mo active intervention period, participants were invited to attend group meetings on six occasions during the first year, on four occasions during the second year and on two occasions during the third year. Participants were encouraged to maintain at least 30 min/day of PA. Focus was on self-regulatory strategies such as goal-setting, action planning and relapse avoidance. Participants were asked to reflect upon benefits, barriers, and costs of adherence to a healthier lifestyle.

The control group was given both verbal and written information about exercise and diet at one group meeting. Both groups were requested to complete activity logs and continued with their routine care.

OUTCOMES
Primary outcomes were change in QOL measured as EQ-5D, EQ VAS and SF-6D based on the self-administrated generic questionnaires EuroQol (EQ) and Short-Form-Health Survey (SF-36), gained quality adjusted life years (QALY) and change in resource use.

EQ includes the EQ-5D self-classifier, a descriptive system that measures five dimensions of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. We computed a single score based on the value tariff from a British population. EQ VAS records the respondent’s perception of overall health status on a 20-cm line graduated between 0 (indicating worst imaginable health) and 100 (indicating best imaginable health). We transformed EQ-VAS to a 0-1 scale by dividing the actual score by 100.

SF-36 consists of 36 items grouped into eight domains: physical functioning, limitations in physical role functioning, bodily pain, general health, vitality, social functioning, limitations in emotional role functioning, and mental health. Each domain is scored from 0 (worst imaginable health) to 100 (best imaginable health) obtained from the patient’s raw scales. Changes ≥ 3-5 scale points may be clinically relevant. The SF-36 physical component summary score and mental component summary score were calculated using the Swedish manual. SF-6D is a utility score derived from responses to 11 questions in the SF-36 questionnaire and consists of six dimensions of health.

Health economic analysis method
The analysis in this study was a cost-utility analysis with a societal perspective. Cost-effectiveness ratios were based on gained quality adjusted life years (QALY) and net costs for the intervention group as compared with the control group. In the analysis, costs for stakeholder of intervention, patients’ costs, treatment effect, and savings in health care use were considered but not the cost for the participants’ exercise time or changes in production.
Table 1. Measurement methods for variables in the health economic analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variable</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>Program costs for the stakeholders</td>
<td>Accounts of primary health care providers. Costs were calculated based on estimated time consumption, and estimated fractions of costs for care center rent, equipment, and overheads.</td>
</tr>
<tr>
<td></td>
<td>Participants' expenses</td>
<td>Physical activity, at least 30 minutes a day, was assumed to cost 400 USD/yr, representing a yearly fee at exercise centers in Sweden, and physical activity less than 30 minutes a day was assumed to cost 67 USD/yr. Empirical data were not available. Methods used for measuring time for exercise were not validated, but frequently used by the Swedish National Institute for Public Health.</td>
</tr>
<tr>
<td>Treatment</td>
<td>QOL</td>
<td>EQ-5D in combination with preference scores from a British population 35, 36. EQ VAS 35. SF-6D in combination with preference scores from a British population 25, 26.</td>
</tr>
<tr>
<td>Savings</td>
<td>Health care costs</td>
<td>Health care records regarding the last 6 months’ health care use before baseline and the 3 yr use after start of the intervention. Number of visits to family physicians and nurses in primary health care, and visits and admissions in hospital care were counted. Standard production prices negotiated for trade of health care between county councils were used. Gained QALY is calculated from the difference in QOL between intervention and control groups at the follow-up times. Differences were assumed to develop linearly between follow-up times. For instance, if QOL had increased 0.04 more at 3 mo and 0.08 more at 1 yr in the intervention group than in the control group, the mean change the first three mo would be 0.02 (0.00+0.04/2) and the following 9 mo 0.06 (0.04+0.08/2). Gained QALY for this yr would be 0.05 ((0.02x3/12)+(0.06x9/12)). A scatter plot of 5 000 bootstrapped incremental cost-effectiveness ratios was created, by repeatedly drawing a random sample with replacement using parameters estimated from the RCT. Individual values were used for savings in health care costs and gained QALY, and mean values were used for costs in intervention and control groups. This produced estimates of the probability that the intervention was cost-effective using several thresholds of willingness to pay for a QALY. Results are presented in a cost-effectiveness acceptability curve 28. Further, mean NMB and confidence intervals of NMB were estimated for these different threshold values.</td>
</tr>
</tbody>
</table>

Health care utilization data were extracted from electronic patient records from all health care centers and hospitals in the county, and were followed from 6 mos before start of the intervention to 3 yr after that the intervention was started.

Measurements made at baseline and at the follow-ups that were used in the calculation are given in Table 1. All costs were transformed from Swedish currency to USD using the exchange rate 1 USD = 7.5 Skr. Costs were recalculated to the price level of 2009 using the Swedish consumer price index. Research costs and costs relating to the development of the method were not included. All changes in effect and costs were discounted 3% per yr.

The uncertainty from the underlying trial is handled with the Net Monetary Benefit method 27. The method is based on replacing health effects (QALY) with that amount of money decision makers are willing to pay for a gained QALY. When both effects and resource use are expressed in monetary units, it is possible to calculate a confidence interval for cost-effectiveness and the probability that an intervention is cost-effective in relation to a competing intervention.
STATISTICAL ANALYSES
Differences between groups in changes in outcome variables over 3 yr were analyzed on an Intention-to-treat (ITT) basis. If data were missing the last observation was carried forward. General linear model repeated measures of variance was used to investigate mean changes in QOL over time, overall main effects, testing also for effects of time and interaction time*group. For exploratory reasons all outcomes were also analyzed per-protocol using only available data and also adjusted for age and sex. These results did not differ substantially from the unadjusted ITT analysis which therefore is presented. T-tests, with Bonferroni correction when needed, were used for comparison at singular time points.

We calculated a statistical index of responsiveness, effect size, as standardized response mean according to Cohen 29. A change in effect size of 0.2-0.5 should be regarded as “small”, 0.5-0.8 as “moderate” and > 0.8 as “large”.

RESULTS
A total of 151 individuals were randomized with greatest attrition during the first year. Those lost to follow-up did not differ between the groups, 17 intervention and 14 control subjects. Six subjects were excluded: four did not start the intervention and two from the control group had incomplete baseline data (Figure 1). Finally, 71 intervention and 74 control subjects were included and the 3-yr follow-up was completed by 120 participants (83%).

OUTCOMES AND ESTIMATIONS
The mean age of the study population was 54.4 years and 57% were female (Table 2). Overweight or obesity was present in 86.8% and most had one or more additional risk factor. An inactive lifestyle was common; 54.5% being sedentary or minimally active and 84.2% reported none or less than 30 min of exercise per day. Smoking, diabetes and treatment with lipid-lowering drugs were more common in the intervention group, while hypertensive medication was less common. The intervention groups tended to be less physically active and reported lower mean scores in all QOL questions at baseline.

EQ-5D score and the mental dimensions of SF-36 were similar to the Swedish population 23, 30 while the EQ VAS and the physical dimensions of the SF-36 were lower (Figure 2 A-B). Problems in the dimension pain/discomfort were more common and anxiety/depression less common than in the Stockholm population 30 (Figure 2 C).

Quality of life
EQ-5D did not change significantly during the 3-yr period (Table 3). However, the EQ VAS differed significantly between the groups over the 3-yr period (p=0.002) with greater improvement in the intervention group. The improvement in the SF-6D mean score was higher in the intervention group than in the control group (p=0.010).

Mean changes in scores and summaries in the SF-36 dimensions are shown in Table 3. Over three years an improved physical functioning (p=0.017) and less bodily pain (p=0.012) was found in the intervention group. The physical component summary improved to a higher degree in the intervention group (p=0.041) but not the mental component summary or its subscales.
Table 2. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>All participants (n=145)</th>
<th>Intervention group (n=71)</th>
<th>Control group (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.4</td>
<td>55.7 (6.6)</td>
<td>53.1 (8.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (42.8)</td>
<td>35 (49)</td>
<td>27 (36.5)</td>
</tr>
<tr>
<td>Female</td>
<td>83 (57.2)</td>
<td>36 (51)</td>
<td>47 (63.5)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary grade</td>
<td>28 (19.3)</td>
<td>14 (20)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Upper secondary school</td>
<td>62 (46.6)</td>
<td>41 (58)</td>
<td>41 (55)</td>
</tr>
<tr>
<td>University college education</td>
<td>35 (24.1)</td>
<td>16 (22)</td>
<td>19 (26)</td>
</tr>
<tr>
<td><strong>Main occupation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working employed/self-employed</td>
<td>77 (53.1)</td>
<td>38 (53)</td>
<td>39 (53)</td>
</tr>
<tr>
<td>Retired</td>
<td>52 (35.9)</td>
<td>20 (27)</td>
<td>26 (35)</td>
</tr>
<tr>
<td>Unemployed/other</td>
<td>16 (11)</td>
<td>7 (10)</td>
<td>9 (12)</td>
</tr>
<tr>
<td><strong>Smoking habits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>30 (20.7)</td>
<td>17 (24)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Presence of overweight or obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction with BMI ≥ 25</td>
<td>125 (86.8)</td>
<td>64 (90)</td>
<td>62 (84)</td>
</tr>
<tr>
<td>Fraction with BMI ≥ 30</td>
<td>62 (42.8)</td>
<td>32 (45)</td>
<td>30 (41)</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>40 (27.6)</td>
<td>23 (32)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Hypertension medication</td>
<td>95 (65.5)</td>
<td>45 (63)</td>
<td>50 (68)</td>
</tr>
<tr>
<td>Dyslipidemia medication</td>
<td>32 (22.1)</td>
<td>24 (34)</td>
<td>8 (11)</td>
</tr>
<tr>
<td><strong>Total physical activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>17 (11.7)</td>
<td>14 (20)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Minimally active</td>
<td>62 (42.8)</td>
<td>27 (38)</td>
<td>35 (47)</td>
</tr>
<tr>
<td>Moderately active</td>
<td>47 (32.4)</td>
<td>22 (31)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>Very active</td>
<td>19 (13.1)</td>
<td>8 (12)</td>
<td>11 (15)</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>80 (55.2)</td>
<td>43 (61)</td>
<td>37 (50)</td>
</tr>
<tr>
<td>&lt;30 min/d</td>
<td>42 (29)</td>
<td>20 (28)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>30-60 min/d</td>
<td>21 (14.5)</td>
<td>8 (11)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>≥60 min/d</td>
<td>2 (1.4)</td>
<td>0 (0)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Quality of life score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-SD</td>
<td>0.81 (0.21)</td>
<td>0.76 (0.24)</td>
<td>0.83 (0.16)</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>0.66 (0.18)</td>
<td>0.63 (0.20)</td>
<td>0.70 (0.15)</td>
</tr>
<tr>
<td>SF-6D</td>
<td>0.70 (0.10)</td>
<td>0.68 (0.10)</td>
<td>0.71 (0.10)</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>82.6 (17.1)</td>
<td>80.2 (17.6)</td>
<td>84.9 (16.5)</td>
</tr>
<tr>
<td>Role Limitation Physical</td>
<td>76.1 (34.2)</td>
<td>74.6 (36.7)</td>
<td>81.4 (31.5)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>67.4 (28.8)</td>
<td>64.0 (27.7)</td>
<td>70.5 (25.8)</td>
</tr>
<tr>
<td>General Health</td>
<td>66.6 (19.8)</td>
<td>64.8 (19.4)</td>
<td>68.4 (20.0)</td>
</tr>
<tr>
<td>Vitality</td>
<td>65.7 (21.4)</td>
<td>62.9 (22.8)</td>
<td>68.4 (19.7)</td>
</tr>
<tr>
<td>Social Function</td>
<td>89.3 (18.5)</td>
<td>87.0 (21.3)</td>
<td>91.6 (15.1)</td>
</tr>
<tr>
<td>Role Limitation Emotional</td>
<td>88.5 (26.5)</td>
<td>84.5 (29.2)</td>
<td>92.1 (23.1)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>83.8 (14.6)</td>
<td>81.3 (16.7)</td>
<td>86.2 (11.8)</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>45.8 (9.9)</td>
<td>44.8 (10.1)</td>
<td>46.7 (9.7)</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>52.1 (8.4)</td>
<td>50.8 (9.7)</td>
<td>53.4 (8.2)</td>
</tr>
</tbody>
</table>

Age, SF-36 and EuroQol data are given as mean (SD); other variables are given as number and (percent)
Figure 2. Baseline QOL in the Björknäs Study Group and Swedish Norm Data. Data are means and SDs (A-B) and the proportion (percent) reporting problem in the EQ dimensions (C).
Table 3. Mean changes in Quality of Life Scores from baseline to 3 years in the Swedish Björknäs study *(Δ intervention group – control group). Effect size according to Cohen’s criteria: trivial <0.20, small 0.2-0.5, moderate 0.5-0.8, large >0.8

<table>
<thead>
<tr>
<th>Quality of Life Score</th>
<th>Study phase</th>
<th>Mean difference (95% Confidence Interval)</th>
<th>p-value T-test</th>
<th>p-values Repeated measures</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Between subjects</td>
<td>Time*group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>0-3 m</td>
<td>0.02 (-0.04; 0.08)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.02 (-0.03; 0.07)</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.03 (-0.02; 0.09)</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.03 (-0.02; 0.07)</td>
<td>0.28</td>
<td>0.24 0.939</td>
<td></td>
</tr>
<tr>
<td>EQ VAS</td>
<td>0-3 m</td>
<td>0.06 (0.03; 0.13)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.06 (0.02; 0.13)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.06 (0.02;0.11)</td>
<td>0.043</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.09 (0.03; 0.15)</td>
<td>0.002</td>
<td>0.002 0.504</td>
<td></td>
</tr>
<tr>
<td>SF-6D</td>
<td>0-3 m</td>
<td>0.03 (-0.01; 0.05)</td>
<td>0.17</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>0-12 m</td>
<td>0.02 (-0.01; 0.04)</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>0.02 (-0.01; 0.05)</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>0.04 (0.02; 0.07)</td>
<td>0.002</td>
<td>0.010 0.197</td>
<td>0.51</td>
</tr>
<tr>
<td>SF-36</td>
<td>0-3 m</td>
<td>4.7 (1.2; 8.1)</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>0-12 m</td>
<td>3.5 (-0.4; 7.1)</td>
<td>0.052</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functioning</td>
<td>0-24 m</td>
<td>1.3 (3.3; 5.9)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-36 m</td>
<td>5.3 (1.2; 9.4)</td>
<td>0.012</td>
<td>0.017 0.256</td>
<td>0.41</td>
</tr>
<tr>
<td>Limitation</td>
<td>0-3 m</td>
<td>1.4 (-0.4; 3.2)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>0-12 m</td>
<td>2.3 (0.4; 4.3)</td>
<td>0.19</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>0-3 m</td>
<td>1.4 (-0.1; 3.0)</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>0-3 m</td>
<td>2.9 (-1.2; 6.9)</td>
<td>0.16</td>
<td></td>
<td></td>
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<tr>
<td>Health</td>
<td>0-12 m</td>
<td>0.8 (-3.6; 5.3)</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>6.0 (-1.3; 11)</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>0-3 m</td>
<td>3.5 (-1.2; 8.2)</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functioning</td>
<td>0-12 m</td>
<td>1.3 (0.1; 2.5)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-24 m</td>
<td>5.0 (0.0; 10.0)</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role</td>
<td>0-3 m</td>
<td>1.3 (-0.1; 3.7)</td>
<td>0.58</td>
<td></td>
<td>0.13 0.025</td>
</tr>
<tr>
<td>Limitation</td>
<td>0-12 m</td>
<td>1.3 (-0.1; 3.7)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>0-3 m</td>
<td>1.3 (0.3; 2.3)</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>0-3 m</td>
<td>1.4 (0.4; 2.5)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>0-3 m</td>
<td>1.4 (-1.2; 4.0)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>0-12 m</td>
<td>1.3 (-0.0; 3.6)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental</td>
<td>0-3 m</td>
<td>1.3 (0.3; 2.3)</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>0-12 m</td>
<td>0.6 (-1.5; 2.6)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td>0-3 m</td>
<td>2.8 (0.3; 5.3)</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>0-12 m</td>
<td>1.7 (0.6; 2.8)</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td>0-24 m</td>
<td>1.3 (-2.7; 1.7)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental</td>
<td>0-3 m</td>
<td>1.3 (-2.7; 1.7)</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Component</td>
<td>0-12 m</td>
<td>1.1 (0.5; 2.7)</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>0-24 m</td>
<td>0.6 (-2.3; 3.4)</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Data are given as estimated marginal means (95% confidence interval) derived from general linear model with repeated measures. P-values for group differences at each time point were assessed by independent sample t-test using Bonferroni correction when significant time*group interaction effect.
There were no significant main time effects or time*group interaction for most QOL variables. But in the SF-36 bodily pain groups were changing in different directions over time, increasing in the intervention group and decreasing in the control group (Table 3). Also vitality and social functioning showed a significant interaction over time - the intervention group improving and the control group decreasing slightly. Main time effect was only significant for social functioning (p=0.005).

Calculations of effect size at 3 yr showed moderate effects on EQ VAS, SF-6D, bodily pain and physical component summary and small-to-moderate effects on physical functioning (Table 3).

Costs
Costs were 337 USD higher for the intervention group than for the control group. 197 USD of those costs were financed by health care, and the remaining 140 USD were costs imposed on the participants due to increased PA (Table 4). Costs for medical testing, such as serum lipids, glucose and HbA1c, were 185 USD per patient and yr for both intervention and control groups.

Gained QALY
Gained QALY per participant in the intervention group compared to the control group during the three yr was 0.075 (p=0.24) using the EQ-5D, 0.202 (p<0.01) using the EQ VAS, and 0.070 (p=0.03) using the SF-6D (discounted 3 % per yr).

Savings
The mean number of visits to the family physician in the intervention group decreased by 0.28 per half yr as compared with baseline, and increased by 0.097 in the control group (p=0.04). For other health care use there were no significant changes between the groups. Savings in family physician visits was 493 USD for the three-yr period, and savings for all health care use was 384 USD (p=0.44) (Table 4).

Cost-effectiveness
There were net savings with 47 USD per participant in the intervention group compared to the control group. Gross costs per gained QALY were 1,668 – 4,813 USD using the three different QOL-scales (Table 5). Using 50 000 USD as threshold of willingness to pay for a QALY, net monetary benefits for the intervention were significant higher than for the control using the EQ VAS and the SF-6D, but not using the EQ-5D. The probability of cost-effectiveness when stakeholders are willing to pay 50,000 USD for a QALY is 98.5 % using the SF-6D, 88.6 % using the EQ-5D and 99.9 % using the EQ VAS (Figure 3).
Table 4. Costs per participant, and changes in healthcare use 6 mo before baseline and during the three yr after start.

<table>
<thead>
<tr>
<th>TYPE OF COSTS AND SAVINGS</th>
<th>INTERVENTION GROUP</th>
<th>CONTROL GROUP</th>
<th>INTERVENTION VS. CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year, 11 group meetings with physiotherapist and dietician. Family physician participated once.</td>
<td>36</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Second year, 4 group meetings with physiotherapist and dietician.</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Third year, 2 group meetings with family physician, physiotherapist and dietician.</td>
<td>13</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>First year, 1 group meeting with family physician, physiotherapist and dietician.</td>
<td>0</td>
<td>5</td>
<td>-5</td>
</tr>
<tr>
<td>Counseled group exercise 3 times a week during 12 weeks</td>
<td>103</td>
<td>0</td>
<td>103</td>
</tr>
<tr>
<td>Equipment</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Proportion of costs for health care center rent</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Overhead costs 11 %</td>
<td>20</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Sum of costs for primary health care</td>
<td>205</td>
<td>8</td>
<td>197</td>
</tr>
<tr>
<td>Participants’ costs for increased physical activity</td>
<td>207</td>
<td>67</td>
<td>140</td>
</tr>
<tr>
<td>Sum of costs</td>
<td>412</td>
<td>75</td>
<td>337</td>
</tr>
<tr>
<td>Family physician visits</td>
<td>-369</td>
<td>125</td>
<td>(-24 - 960)</td>
</tr>
<tr>
<td>Nurse visits</td>
<td>35</td>
<td>37</td>
<td>-2</td>
</tr>
<tr>
<td>Hospital specialist visits</td>
<td>113</td>
<td>35</td>
<td>78</td>
</tr>
<tr>
<td>Hospital nurse visits</td>
<td>60</td>
<td>27</td>
<td>-600 – 756</td>
</tr>
<tr>
<td>Sum of savings</td>
<td>-160</td>
<td>224</td>
<td>(-1355 – 586)</td>
</tr>
<tr>
<td>Net costs</td>
<td>252</td>
<td>299</td>
<td>-47</td>
</tr>
<tr>
<td>(95 % confidence intervals are presented within brackets. All costs and savings are in USD and were discounted 3 % per yr.)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Costs per gained QALY, probability of cost-effectiveness and net monetary benefit, intervention vs. control. All costs are in USD, and discounted 3 % per yr. NMB = Net Monetary Benefit.

<table>
<thead>
<tr>
<th></th>
<th>EQ-5D</th>
<th>EQ RATING SCALE</th>
<th>SF-6D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gained QALY</td>
<td>0.075</td>
<td>0.202</td>
<td>0.070</td>
</tr>
<tr>
<td>Program costs</td>
<td>197.3</td>
<td>197.3</td>
<td>197.3</td>
</tr>
<tr>
<td>Participants’ out-of-pocket expenses</td>
<td>139.6</td>
<td>139.6</td>
<td>139.6</td>
</tr>
<tr>
<td>Sum of costs (gross costs)</td>
<td>336.9</td>
<td>336.9</td>
<td>336.9</td>
</tr>
<tr>
<td>Savings in health care costs</td>
<td>-384.3</td>
<td>-384.3</td>
<td>-384.3</td>
</tr>
<tr>
<td>Net savings</td>
<td>-47.4</td>
<td>-47.4</td>
<td>-47.4</td>
</tr>
<tr>
<td>Gross costs per gained QALY</td>
<td>4492.6</td>
<td>1667.8</td>
<td>4812.9</td>
</tr>
<tr>
<td>NMB (95 % confidence interval), 1 QALY = 50 000 USD</td>
<td>4.176</td>
<td>11,865</td>
<td>3,968</td>
</tr>
<tr>
<td></td>
<td>(-2,586–11,049)</td>
<td>(4,438–19,793)</td>
<td>(384–7,685)</td>
</tr>
<tr>
<td>NMB (95 % confidence interval), 1 QALY = 100 000 USD</td>
<td>8.292</td>
<td>23,082</td>
<td>7,789</td>
</tr>
<tr>
<td></td>
<td>(-5,039–21,953)</td>
<td>(8,844–39,349)</td>
<td>(931–14,929)</td>
</tr>
</tbody>
</table>

All costs are in USD, and discounted 3 % per yr. NMB = Net Monetary Benefit.
DISCUSSION

The Björknäs Study demonstrates for the first time that a lifestyle intervention over three years, targeted to a population at moderate-to-high-risk for CVD, carried out in “real life” primary healthcare, improves quality of life and is highly cost-effective. The intervention used the core features of the American Diabetes Prevention Program\textsuperscript{13} and the Finnish Diabetes Prevention Study\textsuperscript{31} but was delivered at a conventional primary care setting in northern Sweden, without additional resources. These results should be viewed in the context of the previously reported favorable impact on PA, fitness, waist circumference, waist-to-hip ratio, blood pressure and smoking cessation over the 3-yr period\textsuperscript{20}. We have not been able to find any previous reports on the effect on QOL or cost-effectiveness of group-based lifestyle interventions in primary health care, focusing on physical activity with a follow-up over many years.

Physical activity and quality of life

People with obesity and other cardiovascular risk factors have lower QOL\textsuperscript{7, 8} and obese patients have more problems regarding mobility and pain\textsuperscript{7} in concordance with our comparison with the Swedish population. Women with higher levels of exercise reports higher QOL\textsuperscript{15}. The causality between higher level of PA and improved QOL was recently confirmed in an RCT with sedentary postmenopausal women which demonstrated a strong and graded effect of three different doses of supervised exercise on QOL during six months\textsuperscript{12}. Even a small increase in exercise was associated with improvements in some SF-36 dimensions. The magnitude of improvements in QOL was similar to our study with better physical and mental health after the initial supervised exercise period. We noted that the mental improvement waned over a longer period, in accordance with other lifestyle interventions\textsuperscript{17, 18}

The effects of PA on QOL in clinical trials are inconsistent, the methods to promote it differ\textsuperscript{13-16}, some studies include only women\textsuperscript{12} or have short follow-up. “Physical activity on prescription” involves a health professional’s written advice to a patient to be more physically active. Some
randomized trials in primary care, using PA on prescription, but not supervised exercise sessions, report no effect on QOL or fitness at a 6-mo follow-up 14, or some improvements in QOL after 2 yr 16.

The ProActive study targeted a sedentary population at risk of diabetes and investigated effects of a theory-based behavioral intervention 15. The program taught behavior change and was delivered regularly during 1 year by health professionals by telephone or in participants' homes. The intervention was not more effective than written advice to promote PA or improve fitness but improved some SF-36 scales.

Physical activity and cost-effectiveness
Costs per gained QALY were low (1,668 – 4,813 USD). When also savings in health care were considered, there were 47 USD in net savings. The probability for cost-effectiveness using 50,000 USD per QALY as threshold for cost-effectiveness was between 88.8 and 99.9%. Net monetary benefits for the intervention were significantly higher than for the control using the EQ VAS and SF-6D, but not when EQ-5D was used. There is no official level of willingness to pay for a gained QALY in the USA, but 50,000 and 100,000 USD are often used. Nor in Great Britain is there an official level, but NICE applies 32,000-50,000 USD as acceptable values, and in Sweden a threshold of 37,500 USD has been guiding decisions about subsidized medicine. Thus, cost-effectiveness of the intervention was good in relation to what western countries are willing to pay for a QALY, and the probability for cost-effectiveness was very high in this study. Most important for low cost-effectiveness ratio are patients increase in QOL. Higher QOL may also have had impact on less number of family physician visits, which enhanced good cost-effectiveness.

The main reasons for cost-effectiveness were the sustainable increases in exercise level and QOL as compared with the control group. An important aspect in the performance of the intervention method was probably the long-time contact with the participants. Another important aspect was that the group activities generated rather low costs per participant.

Strengths and weaknesses
The Björknäs study was carried out in an ordinary primary care setting, typical of Northern and Western European health care systems, with limited resources. The intervention went on for the whole 3-yr period, albeit with tapering of intensity, and attrition was rather low. More than half of those eligible were randomized, in contrast to most major intervention studies 33, which strengthens internal and external validity. The study population and the drop-outs did not differ, nor did the group who declined to participate 20. All data were analyzed conservatively on an ITT basis.

Clinically relevant effect sizes were noted for many, but not all, outcomes and the use of two valid and reliable QOL instruments provided similar results. The study was initially powered for anthropometric measurements, not for QOL, and may thus be too small to detect significant improvements in less responsive scales.

A strength with the health economic analysis is that it is completely based on data from the trial, and only the three-year follow up time is considered in the analysis. Hence, no assumptions are needed, except for expenses for PA. The assumed costs represent a common yearly fee at exercise centres in Sweden. If the fee is doubled from 140 to 280 USD), the costs per gained QALY were still very low: 456 – 1,317 USD, instead of 47 USD in net savings. The main uncertainty is from the underlying trial. This uncertainty is managed according to recommendation from Drummond 27 when patient level data
is used. The Net Monetary Benefit concept is an improvement in dealing with uncertainty as compared with using sensitive analysis, especially when insignificant changes between groups are used in the calculation of cost-effectiveness ratios.

The costs for the participants’ exercise time were not considered in this analysis. It is a topic concerning loss of enjoyment when exercising. For some individuals, PA may represent a loss of enjoyment, but those who frequently perform PA do not seem to lose enjoyment when spending time on exercise. Neither were savings in production considered. In a situation with full employment such savings may be important, but with significant unemployment, the savings will be restricted to costs to replace a sick worker with a new one, and of restricted magnitude.

The actual program and The Diabetes Prevention Program (DPP) are two of few interventions lasting for three yr. DPP was an intense lifestyle program and showed a treatment effect as compared with placebo of 0.072 QALY in three yr, very similar to the Björknäs Study. That program was very costly (2,780 USD for program holder year 2000) with mostly individual meetings. Costs were more than 10 times higher than for the actual project, which mainly used group meetings, but despite the high costs, the DPP was cost-effective.

Most important for cost-effectiveness is the effect in QALY, but there is no golden standard in method to estimate QALY. We have used tariffs based on all three standard techniques (Time-Trade Off, Standard Gamble and Rating Scale), and the valuation of QOL is made by both patients and a general population. We think the result is more convincing when acceptable cost-effective ratios are achieved with different methods.

Probably the cost-effectiveness is even better. Gains in QOL may remain after the 3 yr period. The actual analysis had only a treatment perspective, but there were also preventive effects against cardiovascular diseases and type 2 diabetes. Several lifestyle interventions have shown good cost-effectiveness from only a preventive perspective for similar patient groups. Further, the results are likely to be an underestimate, since the control group received more promotion of healthy lifestyle than is generally common in primary health care.

Thus, high-intensity and long-lasting interventions can produce sustainable improvements in QOL and can obviously be cost-effective. Such programs may be a wise use of resources in primary health care for patients with diseases where inactivity strongly contributes.

Author Contributions: Dr Mats Eliasson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Margareta Eriksson and Mats Eliasson. Acquisition of data: Margareta Eriksson, Jonas Österlind. Analysis and interpretation of data: Margareta Eriksson, Eva-Britt Malmgren-Olsson, Lars Hagberg, Lars Lindholm, Jonas Österlind, Mats Eliasson. Drafting of the manuscript: Margareta Eriksson, Eva-Britt Malmgren-Olsson, Lars Hagberg, Mats Eliasson. Critical revision of the manuscript for important intellectual content: Margareta Eriksson, Eva-Britt Malmgren-Olsson, Lars Hagberg, Lars Lindholm and Mats Eliasson. Statistical analysis: Margareta Eriksson, Lars Hagberg. Obtained funding: Margareta Eriksson, Eva-Britt Malmgren-Olsson and Mats Eliasson. Administrative, technical, or material support: Margareta Eriksson and Mats Eliasson. Study supervision: Mats Eliasson, Eva-Britt Malmgren-Olsson.

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