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Prevention of the metabolic syndrome in IGT subjects in a lifestyle intervention: Results from the SLIM study

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Abstract *Background and aims:* The Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM), a randomized controlled trial, directed at diet and physical activity in impaired glucose tolerant subjects was effective to improve glucose tolerance and prevent type 2 diabetes. The aim of this study was to determine the effects of the SLIM lifestyle intervention on the incidence and prevalence of the metabolic syndrome (MetS) during the active intervention and four years thereafter.

Methods and results: MetS was diagnosed according to the NCEP ATP III criteria. At baseline, 66.4% of all participants ($n = 146$, age 57 ± 7 years, BMI 29.7 ± 3.6, 51.3% female) fulfilled the criteria for MetS. No significant difference in MetS prevalence was observed between the intervention (63.9%) and control group (68.9%). At the end of active intervention (average duration 4.2 ± 2.0 years), prevalence of MetS was significantly lower in the intervention group (52.6%, $n = 57$) compared to the control group (74.6%, $n = 59$) ($p = 0.014$).

Furthermore, in participants without MetS at baseline, cumulative incidence of MetS was 18.2% in the intervention group at the end of active intervention, compared to 73.7% in the control group (Log-rank test, $p = 0.011$). Four years after stopping active intervention, the reduced incidence of MetS was maintained (Log-rank test, $p = 0.002$).

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Conclusion: In conclusion, a combined diet-and-exercise intervention to improve glucose tolerance, not only prevented type 2 diabetes, but also reduced the prevalence of MetS and prevented MetS development, showing the long-term impact of lifestyle intervention on cardiovascular risk reduction.

Clinical trial registration number: NCT 00381186 (www.clincialtrials.gov).

Introduction

The prevalence of metabolic syndrome (MetS) is rapidly rising worldwide. MetS is a clustering of several metabolic and cardiovascular risk factors, including abdominal obesity, elevated fasting glucose, blood pressure, triglycerides, and low HDL-cholesterol [1]. MetS increases the risk of both cardiovascular disease and type 2 diabetes (T2D) [2—5].

Two large lifestyle intervention studies, the Finnish Diabetes Prevention Study (DPS) and the US Diabetes Prevention Program (DPP), designed to prevent type 2 diabetes in impaired glucose tolerant (IGT) subjects through changes in diet and physical activity, revealed a 58% risk reduction in the development of type 2 diabetes [6,7], and a reduced prevalence of MetS in the intervention group [8,9]. Weight loss seems a major determinant of improvements in glucose tolerance and the reduction of MetS prevalence [10—12], whereas physical activity and dietary composition may contribute independently [13].

In the Netherlands, a lifestyle intervention designed to study the impact of diet and physical activity on glucose tolerance in impaired glucose tolerant subjects has been performed: the Study of Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM). This study has also shown a 58% reduction in diabetes risk after 3 year and a 47% reduction at the end of intervention [14], despite a relatively moderate weight reduction. The purpose of the present study was to investigate the effect of the SLIM study on the prevalence and prevention of metabolic syndrome, both during the active intervention and 4 years thereafter.

Methods

Study design and population

The SLIM study is a randomized controlled intervention trial conducted at the University of Maastricht, the Netherlands. It was designed to study the effect of a combined dietary and physical activity intervention on glucose tolerance in IGT subjects [15,16]. Subject recruitment and design have been extensively described previously [14,15,17]. Participants were recruited in two phases (1999 and 2001). Originally, study duration was 3 years, but this was extended with 1—3 years (depending on recruitment) in 2002. At the completion of the study in 2006, intervention duration was 3—6 years (on average 4.2 years). Four years later, a follow-up measurement was performed. For inclusion at baseline, mean 2 h glucose concentration of 2 screening oral glucose tolerance tests (OGTT) had to be between 7.8 and 12.5 mmol/L with the first OGTT showing a concentration of 7.8 mmol/L or more. Known diabetes and chronic illness were main exclusion criteria (see Mensink et al. [15] for more detailed eligibility criteria). In total, 147 participants were included and randomized to the intervention and control groups, with stratification for sex and mean 2 h plasma glucose concentration. The Medical Ethical Review Committee of Maastricht University approved the study protocol and all participants gave their written informed consent before the start of the study.

Lifestyle intervention

The intervention program consisted of a dietary and physical activity part, as described previously [15]. Briefly, dietary recommendations were based on the Dutch guidelines for a healthy diet (Dutch Nutrition Council), and consisted of: carbohydrate intake of at least 55% of total energy intake, a reduction in fat intake of to 30—35% of total energy intake, and increased intake of dietary fiber (>3 g/MJ/day) [15]. A skilled dietician, trained in motivational interviewing, gave personal dietary advice during a 1-h session every 3 months, after consideration of a 3-day food record. At each visit, one topic was discussed in detail and goals were set for the next three months, as described in detail elsewhere [15]. Additionally, participants received individual advice on how to increase physical activity to at least 30 min a day for at least 5 days a week with the type of activity (i.e. walking, swimming) depending on personal preferences [15]. Participation in a free supervised, aerobic- and resistance-training program for at least once a week was encouraged.

Control subjects received general information about beneficial effects of a healthy diet and increased physical activity, whereas no individual advice was provided.

Annual measurements

In the control and intervention group, anthropometry, glucose tolerance, blood profile and blood pressure and aerobic fitness were determined annually during the intervention and at the follow-up. Body weight was measured with an electronic scale to the nearest 0.1 kg. Height and waist circumference were measured to the nearest 0.5 cm, with the subject in standing position. Waist was measured using an anthropometric measuring tape, midway between the lowest rib and the crest. Blood pressure was measured twice with an Omron 705CP (Omron Healthcare GmbH, Hamburg, Germany) in sitting position. An incremental exhaustive exercise test was performed on an electronically braked bicycle ergometer to determine maximal peak oxygen consumption (VO_2max). Changes in glucose tolerance were studied using an OGTT. Blood samples were drawn after

overnight fast and again 30 min, 1 and 2 h after an oral glucose load (75 g glucose). Plasma glucose, HDL-cholesterol and triglycerides were measured with standard enzymatic techniques, automated on a Cobas Fara centrifugal analyzer. LDL-cholesterol was estimated using the Friedewald equation [18].

MetS diagnosis

Patients were evaluated for the presence of MetS, according to the modified Third Report of the US National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 'NCEP ATP III criteria' (Table 2). These criteria are defined as the presence of three or more of the following criteria: large waist circumference; elevated blood pressure, triglycerides, and fasting plasma glucose; and decreased levels of HDL-cholesterol [1].

Statistical analysis

Groups were compared for prevalence of MetS (criteria) using chi-square statistics and average clinical parameters were compared using Student's *t*-test. Wilcoxon's non-parametric test was used to compare the prevalence of metabolic syndrome and its components within the groups at different timepoints compared to baseline. Cumulative incidence of the metabolic syndrome in the intervention and control groups was compared using the Log-rank test. Multivariate Cox regression analysis was performed to study MetS development in the intervention and control groups for all participants without MetS at baseline. Endpoint was the first diagnosis of MetS or the last measurement, when no MetS developed. Analysis was adjusted for gender and age. Changes over time between groups were assessed using ANOVA for repeated measures. Participants were followed from study entry until withdrawal, death, emigration, or the end of follow-up period. The level of significance was set at 5% (two-tailed). Statistical Package for the Social Sciences (SPSS) version 16.0 for Macintosh was used to create a database and perform the statistical analyses.

Results

Clinical characteristics of participants

At baseline, data for MetS diagnosis were available in 146 of the 147 participants. Apart from age, baseline characteristics were comparable between the intervention and control groups. Despite randomization, age was higher in the control (58.2 $\pm$ 7.2 years) compared to the intervention group (55.1 $\pm$ 6.5 years) ($p = 0.008$). As previously reported [19], after the first intervention year, there was a more pronounced decrease in body weight, BMI, 2 h glucose and 2 h free fatty acids (FFA) in the intervention group as compared to the control group, whilst there was a more pronounced increase in maximal aerobic capacity in the intervention group (Table 1). At the end of the intervention (average duration 4.2 $\pm$ 2.0 years), the changes in body weight, 2 h FFA, blood pressure and aerobic capacity were significantly different between the groups. At follow-up (average 4.5 $\pm$ 0.5 years after end of active intervention), apart from the change in aerobic capacity, these differences could no longer be detected. Glucose, lipid and blood pressure lowering medication use increased over time in both groups, without significant differences between the groups. All participants using lipid-lowering medication were treated with statins. At the end of the intervention, most participants treated with anti-hypertensive drugs used beta-blockers (57%), angiotensin-2-blockers (34%), thiazide-diuretics (26%), ACE inhibitors (23%) and calcium blockers (13%). Percentages of participants on the different types of anti-hypertensives were relatively constant over time, and no differences between intervention and control groups were observed (data not shown).

MetS prevalence

Overall, 66.4% of the participants fulfilled the criteria for MetS according to the NCEP ATP III criteria. The prevalence of MetS did not differ at baseline between the intervention and control groups (Table 2). High blood pressure and large waist circumference were most commonly present in our IGT population at baseline, with percentages of 90.3 and 76.7 respectively, whereas 57.9% fulfilled the criteria for low HDL-cholesterol, 40.4% for high fasting glucose and 30.3% for hypertriglyceridemia. No differences between the intervention and control groups at baseline were observed for the individual MetS components, except for high blood pressure, which was more often present in control subjects (Table 2). No age or gender differences were detected for overall MetS prevalence (men 68.0% and women 64.8%).

As indicated in Table 2, no significant difference in MetS prevalence was detected at year 1. Interestingly, at the end of the intervention, significantly fewer participants in the intervention group (52.6%) had MetS compared to the control group (74.6%) ($p = 0.014$, Table 2). Because participants in the control group were significantly older than in the intervention group, differences in MetS prevalence were age adjusted. No effect of age on MetS incidence was detected (data not shown).

Resolution and prevention of MetS

At the start of the SLIM intervention participants with ($n = 97$) and without ($n = 49$) MetS joined the lifestyle intervention. The effect of the intervention may differ for people with or without MetS at baseline. Indeed, in participants who already had MetS at baseline, no difference between the intervention and control groups in prevalence of MetS over time was observed. At the end of the intervention, MetS was resolved in 25.0% in the control group and 25.7% in the intervention group.

Interestingly, in participants who did not have MetS at baseline, in the intervention group only 18.2% had MetS (4 of 22) at the end of active intervention, compared to 73.7% in the control group (14 of 19). Cumulative incidence of MetS over the intervention period was significantly lower in this group without MetS at baseline in intervention subjects as compared to control subjects (Fig. 1, Log-rank test:

Table 1 Development of characteristics of the SLIM population during the lifestyle intervention.

Parameter		Baseline				Year1					End of intervention (year 3–6)					Follow-up (4.5 years after intervention)				
		Control		Intervention		Control		Intervention		*p*-value[a]	Control		Intervention		*p*-value[a]	Control		Intervention		*p*-value[a]
		Mean	St.dev.	Mean	St.dev.	Mean	St.dev.	Mean	St.dev.	Time* Group	Mean	St.dev.	Mean	St.dev.	Time* Group	Mean	St.dev.	Mean	St.dev.	Time* Group
N		74		72		67		63			59		57			28		32		
Sex	male/female	37/37		34/38		36/31		35/28			32/27		31/26			14/14		16/16		
Age	(years)	58.2	7.2	55.1	6.5	59.3	7.1	56.1	6.7		63.1	7.2	59.4	6.8		67.7	7.5	65.9	5.8	
Weight	(kg)	84.3	12.2	86.2	12.8	84.2	11.4	84.1	13.1	0.005	84.5	12.5	85.8	13.3	0.046	85.1	10.8	86.7	13.4	0.364
BMI	(kg/m^2)	29.8	3.7	29.5	3.5	29.6	3.5	28.6	3.5	0.006	29.7	3.8	29.1	3.5	0.050	30.2	3.7	28.9	3.7	0.388
Waist	(cm)	103.7	9.7	102.9	10.2	101.9	9.6	99.9	11.2	0.117	103.6	8.5	101.4	11.0	0.123	103.5	8.3	103.0	10.5	0.864
Fasting glucose	(mmol/L)	5.9	0.7	6.1	0.9	5.9	0.6	6.0	0.9	0.112	6.4	0.8	6.2	0.9	0.088	6.2	0.7	6.2	1.1	0.755
2h glucose	(mmol/L)	8.8	2.1	8.9	2.1	8.7	2.2	8.2	2.0	0.009	9.7	2.6	9.0	2.5	0.073	10.0	2.7	9.4	2.9	0.735
HbA1c	(%)	6.0	0.5	5.9	0.5	5.7	0.4	5.7	0.4	0.359	6.2	0.7	6.1	0.4	0.595	5.9	0.4	6.0	0.5	0.833
BP diastolic	(mmHg)	88.9	8.0	89.0	9.2	88.4	8.0	87.7	7.3	0.292	85.4	8.8	82.6	6.1	0.020	78.8	9.5	78.0	12.2	0.291
BP systolic	(mmHg)	144.9	14.5	141.6	17.0	140.4	16.0	138.3	14.7	0.828	139.7	14.8	134.4	13.1	0.625	132.8	16.1	131.0	23.2	0.975
Triglycerides	(mmol/L)	1.43	0.78	1.53	1.19	1.59	1.17	1.53	1.42	0.275	1.49	1.05	1.35	0.81	0.355	1.35	0.67	1.28	0.54	0.563
HDL	(mmol/L)	1.12	0.28	1.14	0.31	1.10	0.30	1.14	0.30	0.847	1.19	0.28	1.27	0.36	0.673	1.39	0.35	1.36	0.31	0.880
Estimated LDL[b]	(mmol/L)	3.52	0.75	3.33	0.95	3.56	0.84	3.30	0.89	0.460	3.59	0.89	3.43	0.78	0.709	3.80	0.98	4.39	1.03	0.005
Total cholesterol	(mmol/L)	5.28	0.85	5.17	0.83	5.39	0.84	5.14	0.82	0.282	5.46	0.94	5.32	0.79	0.666	5.57	1.45	6.36	1.12	0.003
Fasting FFA	(μmol/L)	557	178	599	211	485	136	473	152	0.103	445	132	442	132	0.254	523	166	497	174	0.965
2h FFA	(μmol/L)	103	40	115	72	87	33	81	38	0.015	92	38	85	64	0.010	79	34	79	49	0.659
VO_2max	(L/min)	2.06	0.57	2.18	0.59	2.14	0.60	2.38	0.63	0.036	2.02	0.63	2.34	0.61	0.003	1.99	0.58	2.11	0.51	0.012
Glucose-lowering medication	% (yes/total)	0.0% (0/74)		0.0% (0/72)		0.0% (0/67)		0.0% (0/63)			8.5% (5/59)		7.3% (4/55)			17.9% (5/28)		9.1% (3/33)		
Anti-hypertensive medication	% (yes/total)	23.0% (17/74)		30.6% (22/72)		25.4% (17/67)		33.3% (21/63)			35.1% (20/57)		50.0% (28/56)			53.6% (15/28)		56.3% (18/32)		
Lipid-lowering medication	% (yes/total)	8.1% (6/74)		8.3% (6/72)		11.9 (8/67)		6.3% (4/63)			19.3% (11/57)		17.9% (10/56)			53.6% (15/28)		34.4% (11/32)		

[a] Repeated measures ANOVA.
[b] LDL-cholesteol levels were estimated using the Friedewald equation, deducting both HDL-cholesterol and triglycerides from total cholesterol.

Table 2 Intervention group specific prevalence of metabolic syndrome according to NCEP ATP III criteria during the SLIM lifestyle intervention.

Criterion	Baseline			Year 1			End of intervention			Follow-up		
	Control	Intervention	*p*-value χ^2-test	Control	Intervention	*p*-value χ^2-test	Control	Intervention	*p*-value χ^2-test	Control	Intervention	*p*-value χ^2-test
N	74	72		67	63		59	57		28	32	
Metabolic syndrome $\geq$ 3 criteria	68.9%	63.9%	0.520	61.2%	54.0%	0.405	74.6%	52.6%	0.014	77.8%	64.5%	0.268
1. Fasting glucose: $\geq$6.1 mmol/L or on glucose-lowering medication	39.2%	41.7%	0.760	25.4%*	38.1%	0.119	55.9%*	43.9%	0.194	60.7%*	40.6%	0.121
2. Blood pressure $\geq$ 130/85 mmHg or on anti-hypertensive medication	97.3%	83.3%	0.005	83.6%**	83.9%	0.874	84.7%*	78.9%	0.417	85.2%	87.5%	0.796
3. Triglyceride $\geq$ 1.70 mmol/L or on lipid-lowering medication	27.0%	33.8%	0.375	32.8%	32.3%	0.944	47.5%*	35.1%	0.176	68.0%**	50.0%	0.178
4. HDL-cholesterol $<$ 1.03 mmol/L for men, $<$1.29 mmol/L for women	62.2%	53.5%	0.292	65.7%	50.0%	0.071	54.2%	47.4%	0.459	66.7%	50.0%*	0.203
5. Waist circumference $\geq$ 102 cm for men, $\geq$88 cm for women	77.0%	76.4%	0.972	77.6%	61.9%**	0.051	86.4%*	75.4%	0.131	85.7%	75.0%	0.301

* = $p < 0.05$, Wilcoxon's nonparametric test compared to baseline.
** = $p < 0.01$, Wilcoxon's nonparametric test compared to baseline.

$p = 0.003$). In a Cox proportional hazards analysis, the intervention yielded a reduction of 72.5% in incidence of metabolic syndrome compared to the control group ($p = 0.011$, hazard ratio (HR) 0.375, 95% CI, 0.176–0.800). Adjustment for age and gender resulted in an HR of 0.297, 95% CI 0.133–0.660 ($p = 0.003$). Moreover, all intervention participants who developed MetS had the minimum of 3 positive MetS criteria, whereas the average was 3.9 $\pm$ 0.9 positive criteria in the control group (unpaired *t*-test, $p = 0.003$) at the end of active intervention.

Interestingly, although the MetS prevalence was not significantly different between the intervention group and the control group at the follow-up, all control participants without MetS at baseline had developed MetS during the intervention or follow-up, whereas 45.5% of the intervention subjects remained free of MetS at all times, showing a preventive effect of the SLIM lifestyle intervention in the long term (Fig. 1, Log-rank test, $p = 0.002$).

Dropouts

As reported previously, during active intervention, no significant differences in number of dropouts between the intervention ($n = 16$) and control groups ($n = 16$) were present. At baseline, adherent subjects had lower 2 h glucose levels, a lower BMI and higher VO_2 max and were higher educated [14].

Sixty participants attended the follow-up measurements 4.5 $\pm$ 0.5 years after the last measurement in the active intervention. Main reasons for dropout at the follow-up measurement were medical (22%), no time or motivation (each 17%), and age (11%). One participant died (cause of death unknown). Non-fatal cardiovascular events took place during the follow-up period (i.e. atrial fibrillation and heart infarction), 4 in the control and 5 in the intervention group. The follow-up participants were 53–79 years old (mean age 66.8 $\pm$ 6.6 years), a comparable number of participants from the intervention ($n = 32$) and control group ($n = 28$) were measured and half of the participants

Figure 1 MetS free survival in subjects without MetS at baseline. MetS was determined in subjects without MetS at baseline, during active intervention (year 3–6) and at the follow-up measurement. Percentage MetS free survival in the intervention (closed circles) and control group (open circles).

were female. In line with results at the end of active intervention, adherent subjects at follow-up had lower baseline 2 h glucose values (8.42 ± 1.82 mmol/L versus 9.17 ± 2.19 mmol/L in dropouts, $p = 0.032$) and were higher educated (Chi-square test, $p = 0.012$) compared to dropouts. MetS prevalence at baseline did not differ between adherent subjects and dropouts, neither at the end of active intervention (Chi-square test, $p = 0.447$) nor at follow-up (Chi-square test, $p = 0.759$). No differences in baseline MetS prevalence in the intervention or control group were observed between adherent subjects and dropouts.

Discussion

Our data show that the combined diet-and-exercise SLIM intervention program not only prevented type 2 diabetes (47% reduction) [14], but also reduced MetS prevalence at the end of active intervention and prevented development of new MetS cases in the intervention group. This preventive effect on MetS incidence was sustained in intervention participants until 4.5 years after stopping the active intervention.

Our data are consistent with results from the DPP lifestyle intervention, which showed prevention of new MetS cases three years after start of the intervention [8]. The preventive effect of the SLIM intervention on MetS incidence was present at the end of active intervention, but not yet detected after one year, whereas changes in weight, glucose tolerance and aerobic fitness were largest in the first year of intervention. Reduction of cardiovascular risk factors as clustered in the MetS through lifestyle intervention may only become apparent after several years.

Although new cases of MetS were prevented in the SLIM intervention group, resolution of existing MetS was not different in the intervention and control groups. In contrast to our findings, existing MetS was resolved in the intervention group in the DPS [9] and DPP [8]. In both studies, the lower prevalence of MetS in the intervention group was strongly related to a reduction in waist circumference, which is likely to correspond to the pronounced weight loss achieved. In the SLIM lifestyle intervention waist circumference (−2.9 ± 4.6 cm) and weight (−2.4 ± 3.6 kg) reduction in the intervention group in the first year was limited compared to the DPS (−4.2 ± 5.1 kg) [7] and DPP (−5.6 kg) [6]. This may explain the difference in active resolution of MetS in participants who already had the syndrome at baseline. In line, several studies demonstrated that weight loss was associated with a decrease in the number of MetS components [20,21].

Average MetS prevalence in IGT participants of the SLIM study was 66.4% at baseline. In the DPS, 74% of IGT subjects had MetS at baseline, whereas the DPP reported 53%. The lower MetS prevalence in the DPP could be due to the younger age of participants. In the DPS, the fasting glucose criterion for MetS was considered positive at 5.6 mmol/L, in contrast to 6.1 mmol/L as used in this study and the DPP. The American Diabetes Association recently redefined prediabetes as fasting plasma glucose greater than 5.6 mmol/L [22]. Lowering the cut-off to 5.6 mmol/L would result in a MetS prevalence of 76.7% in the SLIM population, which is comparable to the prevalence in the DPS.

A limitation of our study is the relatively high number of dropouts during active intervention and during follow-up. These dropout rates were higher than reported in the DPS [7,23], which had a similar set-up as the SLIM study. Nevertheless, our dropout rate during intervention was similar to other studies, like the DREAM trial [24]. Explanations for the different dropout rates in the SLIM and DPS intervention may be the recruitment of participants. Because SLIM participants were recruited from the general population, and not via advertisements as in the DPS [25], they may have had less internal motivation to participate in the study. In addition, because weight loss was limited in the SLIM study, participants may have been less satisfied with the results of intervention.

During active intervention and follow-up, the highest dropout occurred in participants with the worst metabolic profile. As also previously reported these subjects also had a low socio-economic status [14]. This is in line with other data in literature suggesting that participants at higher risk are more likely to dropout [26,27]. This selective dropout stresses the difficulty to reach and sustain changes in this vulnerable group and the need for programs tailored towards these vulnerable groups to achieve and maintain positive lifestyle changes.

In conclusion, a combined diet-and-exercise lifestyle intervention to improve glucose tolerance, not only prevented type 2 diabetes, but also reduced the prevalence of MetS in the intervention group, and thereby could contribute to cardiovascular risk reduction.

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