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# Study on lifestyle-intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results

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**Abstract**

The study on lifestyle-intervention and impaired glucose tolerance Maastricht (SLIM) is a 3 years randomised clinical trial designed to evaluate the effect of a combined diet and physical activity intervention program on glucose tolerance in a Dutch population at increased risk for developing type 2 diabetes. Here the design of the lifestyle-intervention study is described and results are presented from the preliminary population screening, conducted between March 1999 and June 2000. In total, 2820 subjects with an increased risk of having disturbances in glucose homeostasis (i.e. age $>40$ years and BMI $>25$ kg/m$^2$ or a family history of diabetes) underwent a first oral glucose tolerance test (OGTT). Abnormal glucose homeostasis was detected in 826 subjects (30.4%): 226 type 2 diabetes (type 2DM, 8.3%), 215 impaired fasting glucose (IFG, 7.9%) and 385 impaired glucose tolerance (IGT, 14.2%). Both increasing age and BMI were strongly related to the prevalence of IGT and diabetes. After a second OGTT, 114 subjects with glucose intolerance and in otherwise good health were eligible for participation in the intervention study (SLIM). The high prevalence of disturbances in glucose homeostasis observed in the preliminary screening underscore the importance of early (lifestyle) interventions in those at risk for developing diabetes. SLIM will address this topic in the Dutch population.
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*Keywords:* Lifestyle intervention; Prevalence; Impaired glucose tolerance; Type 2 diabetes; Population screening

## 1. Introduction

Type 2 diabetes mellitus is rapidly becoming one of the main health issues in the 21st century. Prevalence has increased explosively in the last two

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decades, and global estimates indicate a further rise from a current 150 million people with diabetes, to 300 million in 2025 [1,2]. Impaired glucose tolerance (IGT) is the obligatory transition state preceding type 2 diabetes. Prevalence of IGT varies widely between populations, from as low as 2.0% in rural populations to more than 20% in high-risk populations [3]. The cumulative incidence of type 2 diabetes in subjects with IGT ranged from 3.6 to 8.7% per year in six prospective studies [4], and is strongly related to the fasting and the 2-h plasma glucose concentrations at the time of IGT recognition [4,5]. The most important modifiable risk factor for progression from IGT to diabetes is obesity. Body mass index (BMI) at the time of IGT recognition is a strong predictor of progression, independently of fasting and 2-h blood glucose concentrations [4]. Dietary factors, especially a high fat intake, are also related to the risk of conversion from IGT to diabetes [6].

Several recent studies have reported the feasibility and efficacy of interventions to prevent or delay the progression to type 2 diabetes in subjects with IGT [7–13]. Acarbose, [13], as well as metformin [12], have been shown to reduce the incidence of diabetes in a population with IGT. Other studies have focused on the potential of lifestyle changes to reduce the progression rate from IGT to type 2 diabetes. The Finnish diabetes prevention study (DPS) [11] and the US diabetes prevention program (DPP) [12] reported that weight-loss, changes in dietary intake, and increased physical activity resulted in a 58% reduction in the incidence of diabetes after a mean follow-up of only 3 years. Moreover, lifestyle-intervention was much more effective in reducing the incidence of diabetes than pharmacological intervention (i.e. metformin) [12]. It is important to confirm these observations in different populations, with a different dietary and physical activity background, and a different attitude towards changing lifestyle-habits.

The study on lifestyle-intervention and impaired glucose tolerance Maastricht (SLIM) is a 3 years randomised clinical trial designed to evaluate the effect of a combined diet and physical activity intervention program on glucose tolerance in a Dutch population at increased risk for developing type 2 diabetes. Furthermore, we will consider changes in anthropometric measurements, aerobic capacity and cardiovascular risk factors. Additional measurements will be performed in subgroups of the study population in a search for underlying mechanisms.

The objective of this report is to describe the design of the lifestyle-intervention study and to evaluate the results of the preliminary population screening, from which the subjects were recruited for the intervention study. Data are presented about the prevalence of disturbances in glucose homeostasis in a middle-aged Dutch population.

## 2. Study design and methods

SLIM is designed to study whether a diet/physical activity intervention program can improve glucose tolerance in subjects with a high risk for developing type 2 diabetes mellitus. The total duration of the study is 3 years. The medical ethical review committee of Maastricht University approved the study protocol, and all subjects gave their written informed consent before the start of the study.

### 2.1. Recruitment of subjects

The recruitment period started in March 1999 and was completed at the end of May 2000.

#### 2.1.1. Preliminary screening

Subjects with an increased risk for glucose intolerance, i.e. those of age $>40$ years and a family history of diabetes or a BMI $>25$ kg/m$^2$, were selected from a large existing cohort, monitoring health and disease in the general population [14], and invited to undergo a standard oral glucose tolerance test (OGTT) (glucose load 75 g) [15]. Blood glucose was measured in capillary blood using the Glucometer Elite (Bayer, Zurich, Schweiz). Furthermore, body weight was measured, without wearing shoes and jackets. Subjects with known diabetes, or those with fasting glucose values $>8.5$ mmol/l did not participate in the OGTT.

#### 2.1.2. Second OGTT

Those subjects with a 2-h blood glucose concentration $>7.8$ mmol/l at the preliminary screening and which were otherwise in good health (i.e. no history of cardiovascular disease, or any (chronic) disease or medication use that makes participation in a lifestyle intervention program impossible) were invited for a second OGTT. During this second OGTT, glucose tolerance was measured in venous plasma. Furthermore a medical history was taken, a physical examination was performed and several additional measurements were performed (see Section 2.3, below).

#### 2.1.3. Final recruitment

For definitive inclusion in the lifestyle-intervention study, mean 2-h glucose concentration of both OGTTs had to be between 7.8 and 12.5 mmol/l, together with a fasting glucose concentration of less than 7.8 mmol/l. Other inclusion and exclusion criteria for participation in the intervention study are indicated in Table 1. To follow changes in glucose tolerance over time, data obtained by the second (venous) OGTT were used as baseline values.

After final recruitment, subjects were randomised to two study groups, the lifestyle intervention group or the control group. Randomisation was carried out with stratification for sex and mean 2 h-plasma glucose concentration.

Table 1
Inclusion and exclusion criteria for the lifestyle-intervention study (SLIM)

| | |
|---|---|
| Inclusion criteria | Mean 2-h blood glucose $\geq 7.8$ and $\leq 12.5$ mmol/l |
| | Mean fasting blood glucose $\leq 7.8$ mmol/l |
| | Caucasian |
| | Age 40–70 years |
| Exclusion criteria | Known diabetes mellitus |
| | Mean 2-h blood glucose $>12.5$ mmol/lMean fasting blood glucose $>7.8$ mmol/l |
| | Any chronic illness that makes 5-years survival improbable, or that interferes with glucose tolerance, or that makes participation in a lifestyle-intervention impossible |
| | Medication known to interfere with glucose tolerance |
| | Participation in a regular vigorous exercise and/or diet program |

Based on the preliminary results after 1 year of the Finnish DPS [16], we calculated that 50–60 subjects per group would be sufficient to detect a 1.0 mmol/l difference in the 2-h glucose concentration between groups.

### 2.2. Lifestyle-intervention program

The intervention program consists of a dietary and physical activity part.

#### 2.2.1. Dietary intervention

Dietary recommendations are based on the Dutch guidelines for a healthy diet (Dutch Nutrition Council, 1992, see Table 2). Participants are encouraged to stop smoking and, if necessary, to reduce alcohol intake. Dietary advice is given at regular intervals by a skilled dietician on an individual basis after consideration of a 3 days food record (see Table 2). A body weight loss of 5–7% is the objective. If subjects do not loose weight on this regimen during the first year, mild energy restriction is prescribed during the second year. No very-low calorie diet or dietary products are used to encourage weight loss.

#### 2.2.2. Exercise intervention

Subjects are encouraged to increase their level of physical activity to at least 30 min of moderate physical activity a day for at least 5 days a week [17]. Individual advice is given on how to increase daily physical activity (walking, cycling, swimming), and goals are set. Furthermore, subjects are encouraged to participate in an exercise program, especially designed for this study, including components of aerobic exercise training and components of resistance training [18]. Subjects have free access to these training sessions, and are stimulated to participate for at least 1 h a week. Participation in the exercise sessions is recorded.

#### 2.2.3. Control group

Subjects in the control group are given, oral and written information, about the beneficial effects of a healthy diet, weight loss and increased physical activity, whereas no individual advice or programs are provided. No additional appointments are

Table 2
Details of the dietary intervention

*Dietary guidelines*

| | |
|---|---|
| Carbohydrates: | ±55% energy |
| | Maximum 15–25% energy mono- and disaccharides |
| Fat: | 30–35% energy |
| | ≤10% energy saturated fatty acids |
| | <33 mg/MJ cholesterol, maximal 300 mg a day |
| Proteins: | 10–15% energy |
| | ±0.8 g/kg bodyweight |
| Fiber: | >3 g/MJ a day |

| Visit | Time | Visit and topic |
|---|---|---|
| 1 | 0 | Baseline visit |
| 2 | 4–6 weeks | Discussion baseline food-record |
| 3 | 3 months | 'Fat' |
| 4 | 6 months | 'Carbohydrates' |
| 5 | 9 months | Group-session: 'label-reading' and 'novel foods' |
| 6 | 12 months | 1-year meeting |
| 7 | 15 months | 'Artificial sweeteners' |
| 8 | 18 months | 'Special occasions, e.g. a party' |
| 9 | 21 months | Group session: 'a dietary game' |
| 10 | 24 months | 2-year meeting |
| 11 | 27 months | 'Vegetarian food' |
| 12 | 30 months | 'Vitamins and minerals' |
| 13 | 33 months | Group-session: 'lifestyle and diabetes' |
| 14 | 36 months | 3-year meeting |

scheduled, apart from the annual visits for follow-up measurements.

### 2.3. Measurements

At the start of the study, and every year thereafter several measurements are performed, in both the intervention and control group.

#### 2.3.1. Laboratory assessments

A standard OGTT is performed every year, according to the guidelines described by the WHO [15]. Venous blood samples are immediately centrifuged and plasma is frozen at −80 °C until analysis. Plasma glucose and FFA concentrations are measured using a standard enzymatic techniques (Glucose HK 125, ABX diagnostics, Montpellier, France; FFA-C test kit, Wako Chemicals, Neuss, Germany, respectively). Plasma insulin concentration is measured with an ELISA assay (Mercodia, Uppsala, Sweden) which shows no cross-reactivity with pro-insulin. Glycated haemoglobin ($HbA_{1c}$) is determined with the HPLC technique (reference value for our laboratory 4.4–6.2%). Insulin sensitivity is estimated with the HOMA-index and insulin secretion with the insulinogenic index 30′ (Insulin30–Insulin0)/(glucose 30–glucose0) [19]. Blood lipids are measured with standard enzymatic techniques in fasting serum samples (triglycerides: Sigma, St. Louis, USA; cholesterol: cholesterol 100, ABX diagnostics; HDL: HDL-C Roche, Indianapolis, USA).

LDL cholesterol is calculated according to the formula of Friedewald [20].

*2.3.2. Anthropometry*

Body weight is measured on an electronical scale. BMI is calculated as the ratio of weight and height squared (kg/m$^2$). Skinfold measurements are performed to calculate fat mass, fat free mass and body fat percentage [21]. Waist circumference (waist) is measured at the level midway between the lowest rib and the iliacal crest. Hip circumference is measured as the maximum circumference over the buttocks. Sagittal and transverse abdominal diameter are measured with the subject in a recumbent position, at the level of the iliacal crest using a sliding beam calliper.

*2.3.3. Maximal aerobic capacity*

To evaluate changes in aerobic fitness, an incremental exhaustive exercise test is performed on an electronically braked bicycle ergometer (Lode Excalibur, Groningen, Netherlands). The test starts at a workload of 0.75 W/kg FFM for 3 min, followed by 3 min at 1.5 W/kg FFM. Subsequently, workload is increased every 3 min by 0.5 W/kg FFM until exhaustion. $O_2$ consumption and $CO_2$ production are measured with an Oxycon-Beta (Mijnhardt, Breda, Netherlands) to define maximal peak $VO_2$.

*2.3.4. Other measurements*

At every (annual) visit a physical examination is performed, including recording a 12-lead resting ECG. Blood pressure is measured twice on the right arm with a standard sphygmomanometer, after at least 10 min of rest. Subjects taking any blood pressure-lowering medication are asked not to take these on the morning of the measurements. A 3 days food record (2 weekdays and 1 weekend day) is kept at the start of the study and every year thereafter. Food records are checked by a dietician and intake of nutrients is calculated with a computer program according to the Dutch food table.

*2.3.5. Outcome*

Primary outcome measure is the change in glucose tolerance (i.e. 2-h plasma glucose), one of the most important risk factors for progression to diabetes [4]. Secondary outcome measures are changes in fasting plasma glucose concentration, plasma insulin concentration, insulin resistance, $HbA_{1c}$, and changes in body weight, body composition and $VO_2$max. Furthermore changes in cardiovascular risk factors are assessed (blood pressure and blood lipid profile).

*2.4. Statistical analysis*

Data from the intervention study are analysed according to the intention-to-treat principle. Differences between groups (over time) are analysed by unpaired $t$-tests or ANOVA (repeated measures). The level of significance is set at 0.05.

Results of the preliminary screening were analysed with ANOVA (differences between categories) and $\chi^2$-testing (frequency distribution of disturbances in glucose homeostasis).

## 3. Results

In total 6108 subjects were invited to participate in the preliminary screening. Of those, 2820 subjects were willing to participate in this first OGTT. Non-response was observed in 3288 cases (53.8%). Mean age of the non-responders was $55.7 \pm 0.1$ years, which was significantly lower than the responders ($n = 2820$; age $56.8 \pm 0.1$; $P$-value $< 0.001$). No difference was seen in gender between responders and non-responders (50.6 male vs. 50.9% male, respectively, $P =$ ns). After considering the selection criteria, 379 men and women were invited for the second OGTT, of whom 177 were willing to participate. Finally, 114 subjects, 64 men and 50 women, were included in the lifestyle intervention study (SLIM).

From the 2820 subjects participating in the screening OGTT, 105 were excluded from the analysis: 48 because of recently diagnosed diabetes; 57 because of non-Caucasian ethnicity, non-fasting state, or incomplete data. Results from the remaining 2715 subjects are depicted in Table 3. WHO criteria of 1999 for capillary plasma were applied, as the glucometer Elite measures glucose levels equivalent to capillary plasma [15]. Abnor-

Table 3
Results of the screening OGTT

| | | NGT | IFG | IGT | Type 2 DM | *P*-value |
|---|---|---|---|---|---|---|
| Number | % (*n*) | 69.9 (1889) | 7.9 (215) | 14.2 (385) | 8.3 (226) | |
| Sex | (% Male) | 47.5 | 61.2 | 49.1 | 67.8 | $<0.0001$ |
| Age | (Year) | 55.9±0.2 | 58.8±0.4 | 57.1±0.5 | 59.8±0.4 | $<0.0001$ |
| BMI | (kg/m$^2$) | 28.0±0.1 | 29.7±0.3 | 29.5±0.2 | 30.6±0.3 | $<0.0001$ |
| FBG | (mmol/l) | 5.2±0.1 | 6.3±0.1 | 5.8±0.1 | 7.4±0.1 | $<0.0001$ |
| 2 h BG | (mmol/l) | 6.5±0.1 | 6.8±0.1 | 10.1±0.1 | 13.0±0.2[a] | $<0.0001$ |

Data are mean±S.E.M.; $n=2715$. FBG, fasting blood glucose; 2 h BG, 2-h blood glucose; comparison of frequencies was done by $\chi^2$-test.
[a] Subjects with fasting glucose $>8.5$ mmol/l did not undergo an OGTT ($n=28$).

mal glucose homeostasis was detected in 826 subjects (30.4%): 226 subjects with type 2 Diabetes (type 2DM, 8.3%), 215 with impaired fasting glucose (IFG, 7.9%) and 385 with impaired glucose tolerance (IGT, 14.2%). Of the latter group, almost two-thirds ($n=244$) had normal fasting glucose (NFG/IGT) and one-third ($n=141$) impaired fasting glucose (IFG/IGT). The prevalence of type 2 DM and IFG was higher among men than women. A strong upward trend for age and BMI was seen from NGT to type 2 DM, with IGT and IFG in between (Table 3).

In Table 4 the prevalence of NGT, IFG, IGT and type 2 DM is given for age and BMI groups, for men and women separately. In both men and women, prevalence of disturbed glucose homeostasis increased with age, except for IFG which reached the highest prevalence in the age group of 55–59 years. In the population of 65 years and older, only 55.5% of the men and 63.5% of the

Table 4
Prevalence of type 2 diabetes, IGT, IFG and NGT in the screening population

| | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | DM (%) | IGT (%) | IFG (%) | NGT (%) | *n* | DM (%) | IGT (%) | IFG (%) | NGT (%) |
| *Age (years)* | | | | | | | | | | |
| $<50$ | 289 | 6.6 | 8.0 | 6.2 | 79.2 | 254 | 0.8 | 9.1 | 2.4 | 87.8 |
| 50–54 | 256 | 7.8 | 10.2 | 13.7 | 68.4 | 252 | 2.4 | 13.9 | 6.7 | 77.0 |
| 55–59 | 289 | 11.1 | 14.5 | 12.5 | 61.9 | 281 | 6.8 | 14.6 | 7.8 | 70.8 |
| 60–64 | 301 | 14.0 | 16.3 | 9.0 | 60.8 | 322 | 8.6 | 15.8 | 6.8 | 70.5 |
| $\geq 65$ | 238 | 16.8 | 20.6 | 7.1 | 55.5 | 233 | 10.3 | 19.7 | 6.4 | 63.5 |
| *BMI (kg/m$^2$)* | | | | | | | | | | |
| $<27$ | 477 | 6.7 | 10.5 | 6.1 | 76.7 | 515 | 3.1 | 10.1 | 4.1 | 82.7 |
| 27–30 | 484 | 8.9 | 10.5 | 9.7 | 70.9 | 415 | 4.1 | 15.7 | 5.5 | 74.7 |
| $\geq 30$ | 412 | 18.9 | 21.4 | 13.8 | 45.9 | 412 | 9.7 | 19.2 | 9.2 | 61.9 |
| Total | 1373 | 11.1 | 13.8 | 9.7 | 65.4 | 1342 | 5.4** | 14.6 | 6.1** | 73.8** |

**, $P<0.001$ between sexes ($\chi^2$-test).

women had normal glucose homeostasis. In men and women with a BMI above 30 kg/m$^2$, diabetes was three times more prevalent and IFG and IGT were two times more prevalent, compared with those with a BMI below 27 kg/m$^2$. The prevalence of newly diagnosed diabetes was almost two times higher in men than in women in each BMI and age group. Likewise, IFG was 1.5 times more frequent in men than in women, especially in the age groups below 55 years. Additionally, more women were normoglycaemic than men ($P < 0.001$).

## 4. Discussion

### 4.1. Lifestyle-intervention

The justification of lifestyle-intervention studies is that they may prevent or postpone the onset of type 2 diabetes and related complications. Both the Finnish DPS and the US DPP reported that changing dietary and physical activity habits reduce the incidence of diabetes by about 58% [11,12]. Confirmation of these results in different populations is important. SLIM will consider this in a middle-aged Dutch population at increased risk for diabetes. The Dutch population has a low prevalence of obesity [22], and Dutch subjects are known for their relatively high level of physical activity. In 1997 slightly more than one-half of the population was, on average, moderately active for more than half an hour per day [23], compared with about one-third of US adults [24]. As obesity and physical activity are important factors associated with diabetes, it is important to know whether lifestyle changes result in a comparable risk reduction in the Dutch population as in the Finnish and American population.

Dietary and physical activity intervention strategies are combined, as earlier reports indicated that the combination is most effective [25,26]. The intervention strategy in this randomised study is based on general public health recommendations for nutritional intake and physical activity. A regimen, based on general recommendations, is much more suitable to prevent diabetes, as it is less time consuming and much better tolerated than very intensive intervention programmes. Furthermore, we will perform additional measurements in small subgroups of the intervention and control population ($n = 10$ per group) using stable isotopes, indirect calorimetry and muscle biopsies. Since type 2 diabetes and IGT are characterised by disturbances in skeletal muscle fatty acid uptake and oxidation [27–29], the question will be addressed whether changes in glucose tolerance are accompanied by changes in skeletal muscle fatty acid metabolism. These additional measurements could identify some of the mechanisms underlying the development of insulin resistance and type 2 diabetes mellitus.

### 4.2. Methodological considerations

Participation rate was relatively low in the present study, approximately 50%. As subjects were selected from an ongoing monitoring project for health and disease, some 'research-fatigue' could not be excluded, and this could have led to some selection bias. Classification of the subjects was based on a single OGTT (with the glucometer Elite), and was not confirmed by repeated testing as recommended. Some misclassification might have occurred because of the known high intra-individual variability in glucose levels. However, a previous Dutch study showed that the prevalence of IGT and diabetes was not different between the first and the second test [30]. Only when the diagnosis was based on meeting classification criteria at both OGTT's, did the prevalence decrease. Finally, we tested the consistency in classification between measurements made with the glucometer Elite and measurements made with a standard enzymatic technique in venous plasma. Consistency in classification according to the WHO criteria was good (69%, kappa 0.55, $P$-value $< 0.001$; $n = 245$; [31]).

### 4.3. Preliminary screening

The results of the preliminary screening confirm the high-risk profile of the population under study. Three out of every ten subjects had disturbed glucose homeostasis, which is quite comparable with the results reported in the STOP-NIDDM trial, which also screened in a high-risk population

[32]. The prevalence of IGT and newly diagnosed diabetes in the screening population was higher than reported in the Dutch Hoorn Study over the period 1989–1992 (10.3% for IGT and 4.8% for newly diagnosed diabetes [33]). This may reflect the world-wide increasing prevalence of disturbances in glucose homeostasis [1], and parallels the increasing prevalence of obesity reported in the Dutch population [22]. However, in the Hoorn study the old WHO-criteria (1985) were used. Since the fasting glucose level for the diagnosis of diabetes has now been reduced, this could partly explain the higher prevalence of diabetes in our study, but not the higher prevalence of IGT.

In line with other populations, the present study confirmed that IGT is considerably more prevalent than IFG, and that overlap between the two categories is limited [3]. This limited overlap points towards the difference in metabolic background: IGT is primarily associated with insulin resistance while IFG is associated with a more pronounced defect in insulin secretion and endogenous glucose output [34].

A strong positive relation was observed between increasing age and prevalence of IGT and diabetes. For IFG, the highest prevalence was seen in middle-aged subjects (aged 55–59 years). This is a consistent finding in European populations, particularly among men [3]. The prevalence of disturbances in glucose homeostasis was almost 2-fold higher in the group with a BMI $> 30$ kg/m$^2$ compared with those with a BMI $< 30$ kg/m$^2$. This underscores earlier reports, showing dramatic increases in the relative risk of diabetes in the highest BMI groups, compared with the lowest BMI group [35].

Type 2 diabetes is generally more prevalent in women compared with men [1]. In contrast, we observed a prevalence of diabetes being two times higher in males than in females, in all BMI and age groups. In the Finnmark study [36], BMI was reported to be a dominant risk factor for both sexes. In women, however, the relationship was confounded by other factors such as blood pressure, height, HDL, glucose, smoking and physical activity. Furthermore, in addition to over-all adiposity, body fat distribution is an important risk factor for diabetes [35]. Thus, differences in other risk factors, beside age and BMI, can underlie the observed higher prevalence of diabetes in men in the present study.

### 4.4. Conclusion

The high prevalence of disturbances in glucose homeostasis observed in the preliminary screening underscores the importance of early interventions in those at risk for developing diabetes. Changes in dietary habits and physical activity have shown to reduce the incidence of diabetes. Additional studies are required to confirm these results in different populations with a different dietary and physical activity background. SLIM will address this question in the Dutch population.

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