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ORIGINAL ARTICLE

General effect on high-risk persons when general practitioners are trained in intensive treatment of type 2 diabetes

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Abstract

Objective. Within the frame of a randomized clinical trial to examine whether training of general practitioners (the intervention group) in intensive lifestyle modification and pharmacological treatment of patients with type 2 diabetes has a spillover effect on individuals with impaired fasting glycaemia (IFG) or impaired glucose tolerance (IGT). *Design.* A high-risk screening study for type 2 diabetes with an intervention programme, where general practices were randomized to provide standard treatment versus intensive lifestyle modification and pharmacological treatment to newly diagnosed diabetic patients. *Setting.* General practices in Denmark. *Subjects.* Of 1821 individuals identified with IFG or IGT, results from oral glucose tolerance tests after one and three years were available in 1510 individuals. *Main outcome measures*. Progression rates from IFG and IGT to diabetes and effect of intervention were estimated in a regression model using interval censoring. *Results.* A total of 442 persons developed diabetes. There was no significant overall effect of intervention on progression rates. For risk factors, no difference in rate of change was found between randomization groups, but a difference was found between general practices within the same randomization groups. *Conclusion.* General practitioners identify a high number of incident diabetes cases in individuals with IFG or IGT found by high-risk screening. Intervention at the general practitioner's level in intensive treatment type 2 diabetes does not have a significant spillover effect reducing the risk of diabetes from pre-diabetic conditions. This could indicate that intervention strategies should be specifically targeted at individuals with IFG or IGT, either by training general practitioners or directly at the individual level.

Key Words: *Clustering, family practice, general practice, impaired fasting glucose, impaired glucose tolerance, intervention studies, risk management, type 2 diabetes*

Lifestyle intervention in individuals with impaired glucose tolerance (IGT) reduces the risk of developing diabetes by up to 58% in clinical trials [1–5]. The incidence of diabetes was high in individuals with impaired fasting glucose (IFG) and IGT identified by high-risk screening in general practice [6]. Development of prevention strategies concerning these individuals seems necessary. A real-world implementation trial showed little effect on weight and blood pressure by intervention delivered by public health nurses as part of their existing work schedule [7]. In Denmark, preventive health screening in general practice improved cardiovascular risk profiles [8] and increased life expectancy [9]. It is therefore conceivable that risk of diabetes could be reduced by intervention in general practice.

In the ADDITION study, GPs were trained in management of type 2 diabetes [10]. As the GPs were trained in lifestyle modification there may be a generalized effect on other lifestyle-related conditions, especially IGT (and maybe IFG). If so, this may reduce the risk of diabetes, suggesting a way for less resource-demanding, generalized prevention strategies in high-risk individuals.

We sought to examine whether progression rates from IFG and IGT to diabetes were reduced in general practices trained in intensive management of type 2 diabetes.

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In a trial screening for and intervention on screen-detected cases of diabetes, individuals with impaired fasting glucose and impaired glucose tolerance were followed up to study whether training of general practitioners (GPs) also had a general effect on high-risk individuals.

- Training GPs in optimal management of diabetes did not affect progression rates from impaired fasting glucose and impaired glucose tolerance to diabetes.
- Changes in risk-factor levels in persons with impaired fasting glucose and impaired glucose tolerance were similar for GPs giving standard care and for those trained in risk assessment in screen-detected diabetic patients.
- Differences in change in risk factors were seen between general practices within the same randomization groups and a modest, non-significant effect was seen of education in motivational interviewing.

Material and methods

Study design

The ADDITION study is a high-risk screening study for type 2 diabetes with an intervention programme [10]. The Danish screening programme and the follow-up of IFG and IGT have been evaluated [6,11].

General practices in the counties of Copenhagen, Aarhus, Ringkoebing, Ribe, and Southern Jutland were invited to participate (Figure 1). The general practices were randomized into two groups stratified by practice and community size. Both groups were educated in the screening technique. One group gave standard treatment based on the latest updates of national guidelines for type 2 diabetes and prevention of cardiovascular disease [12,13]. The other group received training in treatment of patients with newly diagnosed diabetes. This consisted of lifestyle advice (diet, physical activity, and smoking), aspirin and drug treatment of blood glucose, blood pressure, and lipids according to strict targets. The training included a full-day course at the entry of the study, half-yearly "after-work" meetings, written patient reports and practice visits by experts in diabetes. The intervention group was further sub-randomized where half the practices received a course in motivational interviewing. Individuals with IFG or IGT were not targeted by the intervention programme. For these individuals, standard treatment of cardiovascular risk factors and annual glucose measurement was recommended.

The reference population of the standard and intervention group was 69 603 and 68 673 persons, respectively, of whom 62 595 and 64 103 were invited for screening. The age and sex profile were similar.

The study adhered to the Helsinki Declaration II and was approved by the scientific ethics committee of Aarhus. All participants gave written informed consent.

Study population

This study includes persons identified from 2001 to December 2005. Persons aged 40–69 years attending the participating practices received a risk questionnaire [6]. Based on self-referral, persons with high scores were tested by a stepwise approach (random blood glucose and HbA1c, fasting blood glucose (FBG), and oral glucose tolerance test (OGTT)). At screening, anthropometric measurements, blood samples, and questionnaire data were collected.

From 2002 to December 2006, invitations for follow-up on glucose were given after one and three years. At the three-year visit anthropometric measurements, blood samples, and a questionnaire on lifestyle changes were collected (extended follow-up). Individuals entering the ADDITION study in 2004–2005 were invited at study end in 2006 for this extended follow-up. Persons with severe concurrent illnesses, alcohol abuse, or who moved to GPs not participating in the study were not invited (Figure 2). Individuals identified with diabetes before planned follow-up were classified as incident cases of diabetes from the date of diagnosis but were not re-invited.

Based on FBG and two-hour blood glucose (2hBG) 1821 individuals were identified with IFG or IGT. Glucose measurements at follow-up were available in 1510 individuals, of whom 1002 attended the extended follow-up. In the analyses on extended follow-up data, the number of persons per general practice had a similar balanced distribution as for the 1510 individuals (see Figure 1). Seven practices dropped out of the study after screening. Two did not want to do OGTT at follow-up visits. One GP gave up the OGTT as he had no assistant employee.

Definitions and measurements

Glucose tolerance was classified by the WHO (1999) definition on FBG and 2hBG [14]. Incident diabetes was defined as *one* diabetic value of FBG or 2hBG.

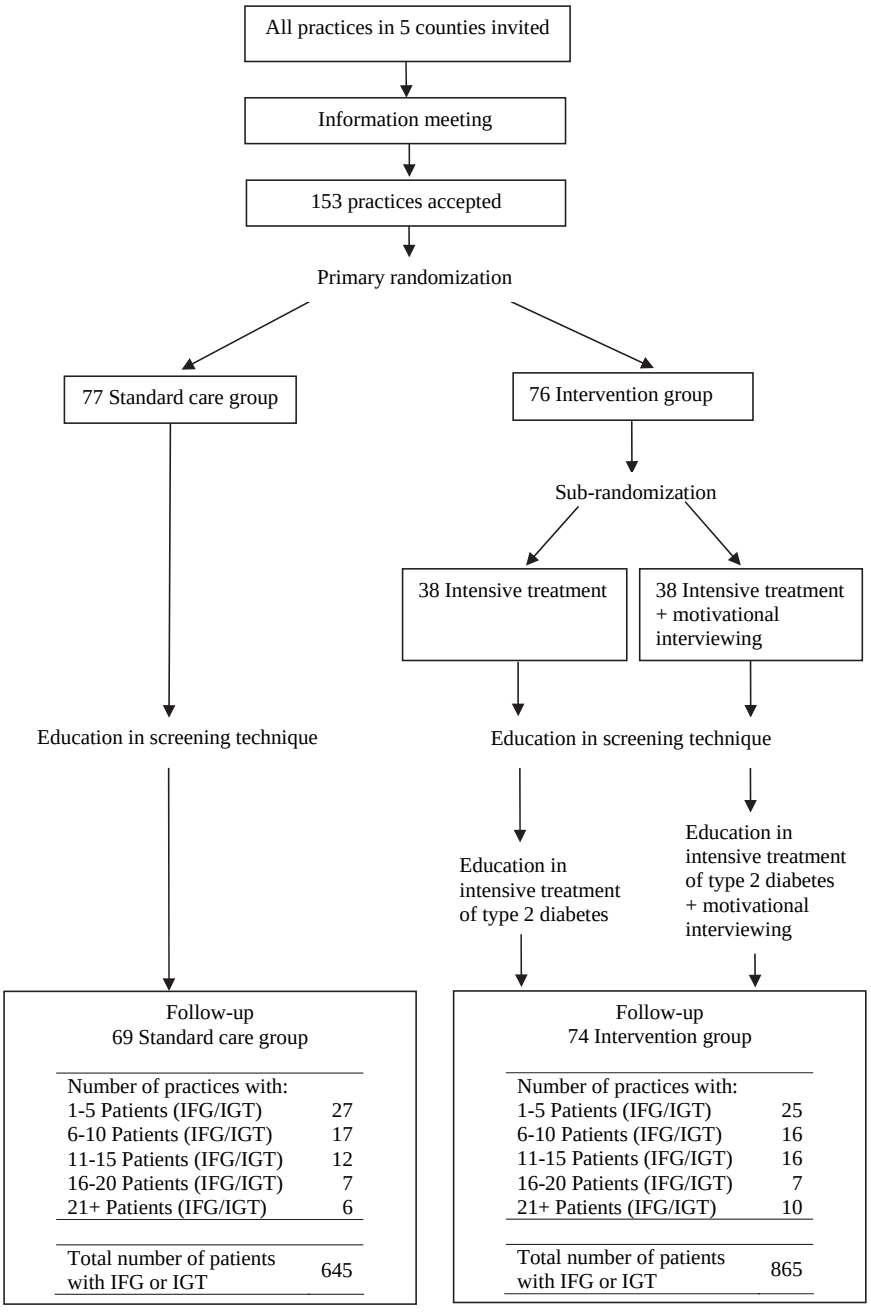

Figure 1. The ADDITION study design at the general practice level.
Note: Number of practice refers to the population with IFG or IGT. Eight practices in the standard group and two in the intervention group dropped out of the study between screening and follow-up visits.

Capillary whole blood was analysed using glucose dehydrogenase reaction (HemoCue AB, Ängelholm, Sweden). Two capillary blood samples were taken and the average result was used [15]. Fasting venous blood samples were mailed to the central laboratory (University Hospital of Aarhus). S-cholesterol, s-HDL, and s-triglyceride were measured enzymatically (Hitachi 971 system, Roche Diagnostics GmbH, Germany). S-LDL was calculated using Friedewald's formula.

Statistical analyses

Continuous variables were compared with a two-sided *t*-test between groups at screening, and proportions with a chi-squared test. Progression rates and effect of intervention rate ratios (RRs) of progression to diabetes were estimated in a regression model using interval censoring [16,17], which is implemented in the EPI package in R. Risk-time referred to in the results is based on: person-years (py) = (last known non-diabetes date − screening

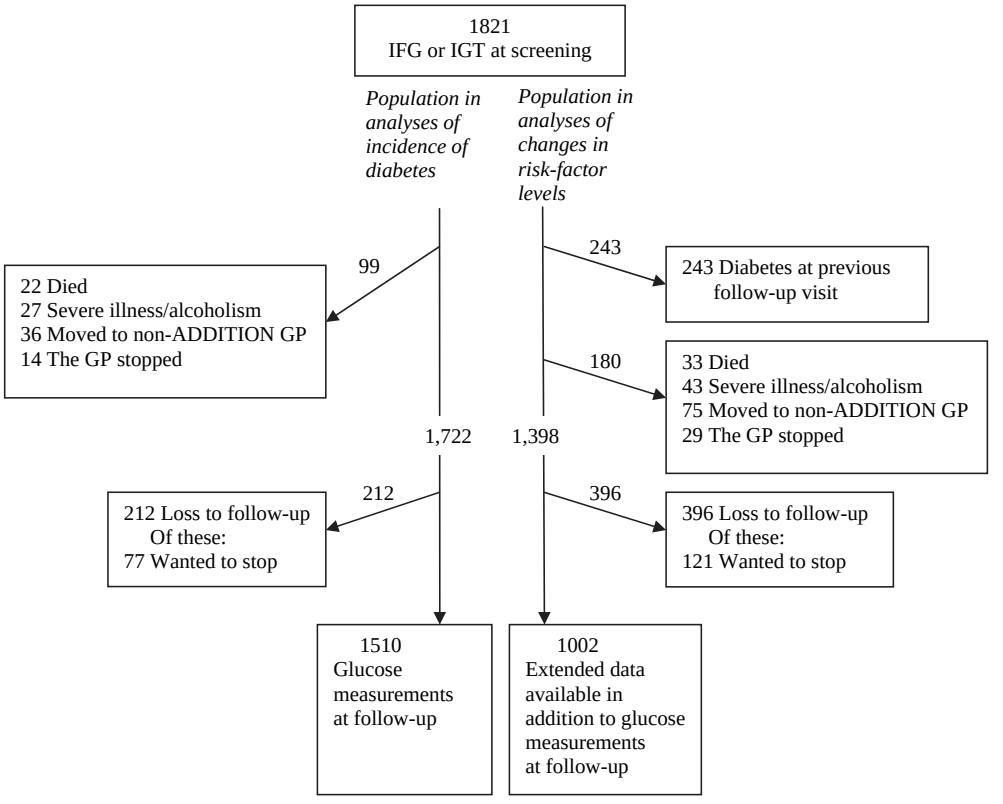

Figure 2. Attendance at the follow-up visits of individuals with IFG or IGT in the ADDITION study, Denmark.
Note: Fasting and two-hour blood glucose were measured at all follow-up visits. The three-year visit (or at study end for those more recently screened) was extended to include anthropometric measurements, blood samples, and a questionnaire with focus on changes in lifestyle since screening. The GP stopped: individuals attending GPs who after randomization stopped participation in the ADDITION study or were unable to do OGTT.

date) + ((conversion date − last known non-diabetes date)/2). Intra-individual changes in continuous variables between screening and last follow-up were summarized with mean (95% CI). Effect of intervention on changes in risk factors was assessed in a mixed model controlling for the baseline value of the variable and with random effect of general practice as well as a random slope per general practice. From these models, we report the difference between randomization groups with regard to:

- rate of change per time between examinations;
- mean change after one year.

To illustrate the random between-practice variation we report the median difference in change between two persons from the *same* randomization group [18]. Proportions in terms of reported changes were compared with a chi-square-test. A p-value of <0.05 was considered significant.

Results

At screening, 56% of the individuals with IFG or IGT were identified by the intervention group versus 44% by the standard group ($p<0.0001$). No systematic tendency in baseline characteristics between individuals in the standard and intervention groups was seen (Table I). In the standard and intervention group, respectively, 34.6% and 38.3% stated that they took blood pressure lowering medication and 10% stated they took cholesterol lowering medication (not shown).

Follow-up rate was 88% (1510/1722) with regard to glucose measuring and 72% (1002/1398) at the extended follow-up visit (see Figure 2). It was similar in the intervention and in the standard group: 89% (95% CI 87–91) versus 87% (85–90). Of the attendees at follow-up, 25% (95% CI 23–28) were daily smokers and 80% (77–82) stated low physical activity at screening, compared with 37% (32–43), $p<0.001$, and 89% (85–92), $p<0.001$, respectively, for non-attendees. No significant difference in screening values of age, sex, BMI, systolic blood pressure, and cholesterol was seen between attendees and non-attendees. Non-attendees did not differ between randomization groups.

There were 442 diabetes cases during 3.5 years. Estimated progression rates to diabetes in the standard and intervention group, respectively, were

Table I. Progression rates and baseline characteristics of individuals with IFG or IGT in the standard and intervention groups.

	IFG			IGT		
	Standard	Intervention	p[1]	Standard	Intervention	p[1]
n	248	359		397	506	
Person-years; median (interquartile range)	2.3 (81.4–2.9)	2.6 (1.1–3.0)	0.401	2.1 (0.6–2.9)	2.1 (0.8–2.9)	0.927
Progression rate, %/py (95% CI)	12.6 (9.4–15.7)	11.4 (8.9–13.8)		18.0 (14.7–21.2)	16.3 (13.6–19.0)	
Age, years; mean ± SD	59.8 ± 6.7	60.0 ± 6.1	0.654	61.2 ± 6.7	61.3 ± 6.6	0.846
BMI, kg/m^2; mean ± SD	29.1 ± 4.8	29.1 ± 4.6	0.932	29.8 ± 5.1	29.5 ± 5.0	0.402
Systolic BP, mmHg; mean ± SD	141 ± 19	139 ± 18	0.188	142 ± 18.1	142 ± 18.5	0.806
Total cholesterol, mmol/l; mean ± SD	5.7 ± 1.0	5.7 ± 1.0	0.940	5.9 ± 1.1	5.8 ± 1.1	0.540
HDL, mmol/l; mean ± SD	1.6 ± 0.4	1.6 ± 0.4	0.240	1.5 ± 0.5	1.5 ± 0.4	0.556
LDL, mmol/l; mean ± SD	3.4 ± 0.8	3.5 ± 0.9	0.868	3.6 ± 1.0	3.6 ± 0.9	0.821
Triglyceride, mmol/l; mean (CV)[2]	1.2 (0.5)	1.2 (0.5)	0.568	1.5 (0.5)	1.4 (0.5)	0.072
Women; % (n)	43.2 (107)	42.6 (153)	0.897	59.7 (237)	52.8 (267)	0.037
Known hypertension; % (n)	48.9 (115)	40.7 (138)	0.051	53.3 (204)	52.7 (251)	0.727
Low physical activity; % (n)	74.0 (176)	77.4 (267)	0.340	80.7 (314)	83.0 (405)	0.385
Daily smoker; % (n)	27.4 (68)	26.3 (93)	0.754	20.6 (80)	27.5 (137)	0.016

Notes: [1]Student's *t*-test (continuous variables) or chi-squared test (proportions) between standard and intervention groups. [2]Geometric mean (coefficient of variation). Numbers may differ because of missing data in known hypertension (5.7%), low physical activity (3.3%) and daily smoker (1.4%).

15.8 and 14.1 cases/100 person-years, with no significant effect of intervention (RR = 0.89 (95% CI 0.78–1.02), p = 0.089). A tendency of effect was seen when analysing the two intervention subgroups separately: Motivation + intensive treatment: RR = 0.83 (0.68–1.00), p = 0.055 and intensive treatment alone: RR = 0.95 (0.80–1.14), p = 0.610. Stratified by glucose tolerance, the effect of intervention was: IFG: RR = 0.90 (0.73–1.12), p = 0.359 and IGT: RR = 0.90 (0.77–1.07), p = 0.240 (see Table I).

In both randomisation groups, mean change in systolic blood pressure was notable (Table II). Changes in weight and lipid levels were small. Beneficial changes in risk factors were more pronounced in individuals with IGT than with IFG (not shown). No difference in rate of change in risk factors between randomization groups was found. The median difference in change in risk factors between two randomly selected persons from different general practices in the same randomization group was larger than the intervention effect in several of the risk factors tested. Separate analyses on the two sub-randomization groups and analyses in IFG and IGT separately showed no differences between randomization groups (not shown).

Table II. Change in risk-factor level in individuals with IFG or IGT: Absolute intra-individual change in the standard and intervention groups, difference in rate of change per observation time, and difference in change after one year.

Changes in risk factors	Standard care group mean (95% CI)	Intervention group mean (95% CI)	Difference in rate of change per observation time, between randomization groups[1]	Difference in change after one year, between randomization groups[1] (fixed effect)	Between practice variation in change after one year (difference in change between practices)[2] (random effect)
n	445	557			
Weight, kg	−0.35 (−0.79, 0.08)	−0.50 (−0.93, −0.06)	0.47 (−0.99, 1.94)	−0.50 (−1.88, 0.87)	1.21
Waist, cm	0.29 (−0.37, 0.96)	0.75 (0.11, 1.39)	0.17 (−1.99, 2.33)	−0.08 (−1.96, 1.80)	2.07
Systolic BP, mmHg	−4.4 (−6.2, −2.6)	−2.7 (−4.1, −1.3)	−0.8 (−5.4, 3.7)	1.8 (−3.1, 6.7)	2.31
Total Cholesterol, mmol/l	−0.19 (−0.29, −0.10)	−0.16 (−0.25, −0.08)	−0.08 (−0.36, 0.20)	0.06 (−0.25, 0.38)	0.17
HDL, mmol/l	0.05 (0.02, 0.07)	0.05 (0.02, 0.07)	0.03 (−0.04, 0.11)	−0.02 (−0.09, 0.05)	0.03
LDL, mmol/l)	−0.22 (−0.30, −0.14)	−0.22 (−0.30, −0.14)	−0.09 (−0.32, 0.15)	0.04 (−0.22, 0.31)	0.06
Triglyceride, mmol/l	−0.04 (−0.11, 0.02)	0.03 (−0.03, 0.10)	−0.04 (−0.22, 0.15)	0.07 (−0.11, 0.25)	0.02

Notes: Differences were analysed in a mixed model controlling for the initial value of the measurement, and with random effect of general practices as well as a random slope per general practice. [1]Mean (95% CI), [2]median (95% CI).

Table III summarizes self-reported changes since screening. Based on those who responded, no significant difference was seen. There was a tendency for more individuals in the intervention group to be influenced by their GPs to change lifestyle.

Discussion

The intervention group identified more individuals with IFG and IGT than the standard group of GPs. This indicates that the intervention group may have been more active in the study, though attendance at follow-up was similar and progression rates from IFG and IGT to diabetes were high in both groups. Individuals in the intervention group had a non-significant rate reduction of 11%. This tendency was more prominent in the sub-group trained in motivational interviewing. Analyses of rate of change in risk-factor levels showed a considerable difference between general practices in the same randomization group. Taking this into account, we found no difference in rate of change in risk-factor levels or habits from screening to follow-up between individuals in the standard and intervention groups. This was also the case in separate analyses of the two intervention sub-groups. Furthermore, improvements in risk factors were more pronounced in individuals with IGT than with IFG, but no effect of intervention was seen in separate analyses for IFG and IGT.

Table III. Proportions of persons who reported change in habits from screening to follow-up in the standard and intervention groups for individuals with IFG or IGT.

	Standard	Intervention	p[1]
New BP medication; % (n)	18.1 (70)	18.9 (88)	0.980
New cholesterol medication; % (n)	13.5 (51)	16.0 (76)	0.300
My GP influenced me; % (n)	22.7 (101)	27.8 (155)	0.063
More leisure activity; % (n)	28.0 (116)	26.2 (138)	0.556
Less smoking; % (n)	8.9 (32)	10.9 (51)	0.331
Less quantity of food; % (n)	30.3 (128)	28.4 (153)	0.522
More vegetables; % (n)	44.8 (191)	44.3 (242)	0.873
More fruit; % (n)	42.2 (179)	41.2 (225)	0.752
Less sugar; % (n)	51.7 (219)	51.5 (276)	0.961
Less fat; % (n)	60.0 (255)	60.7 (329)	0.825
Less meat; % (n)	18.3 (78)	17.5 (96)	0.762
More fish; % (n)	27.9 (116)	30.9 (167)	0.315
Less alcohol; % (n)	17.7 (74)	18.8 (98)	0.673

Notes: [1]Chi-squared test between standard and intervention groups. Numbers may differ because of missing data: new BP medication (16.4%), new cholesterol medication (15.0%), more leisure time activity (6%), less smoking (17%), less quantity of food (4%), more vegetables (3%), more fruit (3%), less sugar (4%), less fat (3%), less meat (3%), more fish (5%), less alcohol (6%).

Pre-screening randomization is a strength of this study. Consequently, the reference populations of the two randomization groups were similar in size, age, and sex distribution. They covered a broad geographic region within Denmark. All participating GPs volunteered and were thus more motivated than an average GP. GPs in the intervention group received education and training after randomization and differed from those in the standard group in treatment goals and intensity, and education level in terms of diabetes. The scale of the intervention would be practically applicable in everyday clinical work.

Few general practices dropped out of the follow-up study. The follow-up rates of individuals with IFG and IGT were comparable to those in other follow-up studies [19–21]. Hence, follow-up on high-risk individuals is feasible in general practice. For conditions not disease-labelled higher attendance rate may be unrealistic. Attendees had a healthier lifestyle than non-attendees, which may underestimate the progression rates but presumably equally in both randomization groups. Attendees and non-attendees did not differ concerning other major risk factors tested.

As all participating GPs volunteered to be part of a randomized trial, generalizability to GPs in general is not justified. Those not volunteering may be less motivated or have fewer resources in their clinic. Since the general effect of intervention in the participating practices was weak and non-significant, this effect would presumably not be more beneficial in the general population of general practices, though. Another limitation was that the GPs were acquiring study logistics at the same time as performing screening and being trained in intensive treatment. A spillover effect on other individuals than those at target may be unrealistic at the beginning of the study. Nevertheless, we found no effect in post-hoc analyses excluding the first year (not shown). Hence, these limitations do not qualitatively affect the results.

Decreases in risk-factor levels and beneficial changes in dietary pattern did not differ between randomization groups. This may be explained by a dilution effect. Influenced by contemporary trends in society, the standard group of GPs and individuals may have changed behaviour as well. Individuals may also be influenced by knowledge of their abnormal glucose metabolism. A decrease in systolic blood pressure of clinical significance with regard to cardiovascular disease was seen, indicating that GPs in both groups were active in prevention of cardiovascular disease. Nevertheless, few stated much improvement in healthy lifestyle (physical activity, smoking, or total quantity of food eaten; not shown).

Weight reduction was not near the target in previous prevention trials (5% weight reduction) [1,2,4]. Mean decreases in cholesterol were insufficient according to guidelines [12], although 60% declared a reduced intake of fat and about 15% having added cholesterol-lowering medications. Therefore, a possible general influence with regard to prevention of diabetes seems to be small.

Due to different pathophysiological mechanisms between IFG and IGT interventions may not reduce risk of diabetes in IFG as in IGT [22]. We conducted separate analyses stratified by glucose tolerance status yet no spillover effect of intervention was detectable.

We cannot distinguish between behavioural changes in GPs and acceptance by individuals of being at risk and change of lifestyle – a dilemma dealt with by others [23]. Motivational interviewing is appreciated by motivated GPs and changes their professional behaviour towards patients with diabetes [24]. On the other hand, GPs express concerns about making healthy persons ill and about their compliance [25], which may be part of the overall lack of spillover effect seen in this study on high-risk individuals not targeted in the education programme. Spillover effect on treatment of one patient group to another by the same GP has rarely been studied. A Canadian study found no effect of continuing medical education on conditions not covered by the education programme [26].

From a public health point of view, it is important to know how broad an impact education of GPs has. In this study, training GPs in handling one disease did not imply general effects on closely related conditions. Prevention of progression from IGT to diabetes is possible in high-risk individuals, but how to implement an intervention strategy in the real world remains to be evaluated. It seems as if any intervention has to target high-risk individuals directly, either at the GP or the individual level.

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