



Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: <http://www.elsevier.com/locate/pcd>PCDE
primary care diabetes Europe

Original research

Long-term outcomes of lifestyle intervention to prevent type 2 diabetes in people at high risk in primary health care



Reeta Rintamäki^{a,*}, Nina Rautio^{b,c}, Markku Peltonen^d, Jari Jokelainen^{c,e},
Sirkka Keinänen-Kiukaanniemi^{b,c,f}, Heikki Oksa^g, Timo Saaristo^g, Hannu Puolijoki^h,
Juha Saltevoⁱ, Jaakko Tuomilehto^{d,j,k}, Matti Uusitupa^l, Leena Moilanen^a

^a Department of Endocrinology and Clinical Nutrition, Kuopio University Hospital, Kuopio, Finland

^b Centre for Life Course Health Research, University of Oulu, Oulu, Finland

^c Unit of Primary Health Care, Oulu University Hospital, Oulu, Finland

^d Public Health Prevention Unit, Finnish Institute for Health and Welfare, Helsinki, Finland

^e Infrastructure for Populations Studies, University of Oulu, Oulu, Finland

^f Healthcare and Social Services of Selänne, Pyhäjärvi, Finland

^g Tampere University Hospital, Tampere, Finland

^h Southern Ostrobothnia Central Hospital, Seinäjoki, Finland

ⁱ Central Finland Central Hospital, Jyväskylä, Finland

^j Department of Public Health, University of Helsinki, Helsinki, Finland

^k Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

^l Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

ARTICLE INFO

Article history:

Received 10 November 2020

Received in revised form 23 February 2021

Accepted 12 March 2021

Available online 23 March 2021

Keywords:

Type 2 diabetes

Prevention

Primary care

Follow-up

Cardiovascular events

Mortality

ABSTRACT

Aims: The Finnish National Diabetes Prevention Program (FIN-D2D) was the first large-scale diabetes prevention program in a primary health care setting in the world. The risk reduction of type 2 diabetes was 69% after one-year intervention in high-risk individuals who were able to lose 5% of their weight. We investigated long-term effects of one-year weight change on the incidence of type 2 diabetes, cardiovascular events, and all-cause mortality.

Methods: A total of 10,149 high-risk individuals for type 2 diabetes were identified in primary health care centers and they were offered lifestyle intervention to prevent diabetes. Of these individuals who participated in the baseline screening, 8353 had an oral glucose tolerance test (OGTT). Complete follow-up data during one-year intervention were available for 2730 individuals and those were included in the follow-up analysis. The long-term outcome events were collected from national health registers after the median follow-up of 7.4 years.

Results: Among individuals who lost weight 2.5–4.9% and 5% or more during the first year, the hazard ratio for the incidence of drug-treated diabetes was 0.63 (95% CI 0.49–0.81, $p = 0.0001$), and 0.71 (95% CI 0.56–0.90, $p = 0.004$), respectively, compared with those with stable weight. There were no significant differences in cardiovascular events or all-cause mortality among study participants according to one-year weight changes.

Conclusions: High-risk individuals for type 2 diabetes who achieved a moderate weight loss by one-year lifestyle counseling in primary health care had a long-term reduction in the incidence of drug-treated type 2 diabetes. The observed moderate weight loss was not associated with a reduction in cardiovascular events.

© 2021 The Authors. Published by Elsevier Ltd on behalf of Primary Care Diabetes Europe. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author at: Kuopio University Hospital, Department of Endocrinology and Clinical Nutrition, PO Box 100, FI 70029 KYS, Kuopio, Finland.

E-mail address: reeta.rintamaki@kuh.fi (R. Rintamäki).

1. Introduction

Type 2 diabetes is a chronic disease associated with many comorbidities and premature mortality. Cardiovascular disease is a major cause of mortality in people with type 2 diabetes [1]. According to a meta-analysis, cardiovascular disease and all-cause

mortality risk is much higher in people with type 2 diabetes compared with non-diabetic people [2]. Prevention of type 2 diabetes and its complications is essential in order to reduce the global burden of type 2 diabetes.

Randomized controlled trials (RCT's) have shown that lifestyle intervention comprising healthy diet, physical activity, and weight control in high-risk individuals is efficient for the prevention of type 2 diabetes and management of cardiovascular risk factors [3–6]. Among people with impaired glucose tolerance (IGT), the reduction in risk of diabetes was 58% during the lifestyle intervention trial lasting for approximately three years in both the Finnish Diabetes Prevention Study (DPS) [3] and the US Diabetes Prevention Program (DPP) [4].

There is the paucity of evidence that also the incidence of cardiovascular disease may be reduced by such lifestyle interventions; the diabetes prevention RCT's have not been designed to test such a hypothesis. Nevertheless, the recent long-term follow-up of the Da Qing diabetes prevention trial in Chinese people with IGT has indicated that in long-term also cardiovascular mortality may be reduced by lifestyle intervention among people who participated in a diet and/or physical activity intervention [7].

Furthermore, benefits of type 2 diabetes prevention by lifestyle intervention in RCTs have been shown to sustain at least 10–20 years; the long-term diabetes risk reduction in RCTs where the intervention lasted for 3–6 years has varied between 27–43% [7–12], while the absolute risk reduction remained unchanged or even increased further between randomisation groups in the DPS follow-up [8]. In the DPS, no difference between the initial intervention and control groups was found in cardiovascular morbidity or all-cause mortality after ten years follow-up, but compared with a population-based observational cohort of people with IGT cardiovascular mortality in both groups in the DPS was significantly lower [13]. The recent sub-study based on the DPS data suggests a lower incidence of early retinopathy in the former intervention group [14]. On the other hand, at the 15-year follow-up of the DPP observational study, there were no overall differences in aggregate microvascular outcomes between the original lifestyle intervention and placebo groups [11]. The Chinese Da Qing study showed the benefits of lifestyle interventions on diabetes prevention, retinopathy incidence, and cardiovascular and all-cause mortality during the 23-year follow-up, and the difference between the intervention and control groups started to appear after 10 years from baseline [15]. Recently reported 30-year results of the Chinese Da Qing study strengthen these earlier findings [7]. A systematic review and meta-analysis of 20 RCT's which addressed the progression from pre-diabetes to overt type 2 diabetes found that lifestyle interventions effectively decreased the incidence of type 2 diabetes, but did not reduce all-cause mortality or cardiovascular and microvascular disease [16].

Longer-term effectiveness of lifestyle interventions for diabetes prevention in the primary care settings is still unclear, because there are limited numbers of studies with long follow-up time. Lifestyle intervention in primary care in Poland showed that modest weight reduction decreased diabetes risk and reduction in cardiovascular risk factors were maintained at the three-year follow-up [17]. Similar findings were found in a three-year follow-up study in Finland [18]. A prospective cohort study in Spain with a four-year follow-up showed that intensive lifestyle intervention in primary care reduced diabetes incidence by 37% among high-risk individuals identified by the Finnish diabetes risk score (FINDRISC) [19].

The Finnish National Diabetes Prevention Programme (FIN-D2D) was the first large-scale diabetes prevention program in a primary health care setting in the world. After a one-year follow-up, the incidence of diabetes decreased and there were favourable changes in cardiovascular disease risk factors in the high-risk

cohort identified by the FINDRISC [20]. The risk reduction of type 2 diabetes was directly related to the magnitude of weight change; it was 69% of the individuals who were able to lose at least 5% of their initial weight [20]. In this report, we explored long-term effects of weight loss achieved during one-year lifestyle intervention on the incidence of drug-treated type 2 diabetes, cardiovascular events, and all-cause mortality in the FIN-D2D high-risk cohort.

2. Methods

2.1. Study design

This study is a 7.4-year follow-up of the FIN-D2D high-risk cohort. The original study was conducted in five hospital districts during years 2003–2008, and has been described in more detail elsewhere [20]. In the high-risk strategy of the FIN-D2D programme, individuals at risk for type 2 diabetes were screened mostly through primary health care centres, but also pharmacies and public events and were invited to join the FIN-D2D programme [20]. Screening was conducted using the FINDRISC [21]. Persons scoring ≥ 15 points in the FINDRISC were invited to receive lifestyle counselling. The rationale for the choice of the FINDRISC threshold has been described in our earlier publications [22,23]. In addition, eligible persons were those with a history of impaired fasting glucose (IFG), IGT, ischemic cardiovascular disease or gestational diabetes. After identification of high-risk persons for type 2 diabetes, they were invited to visit voluntarily in one of the over 400 primary health care units or occupational health care clinics located in the FIN-D2D program area. In these clinics, health check-ups with a short interview and measurements of anthropometric characteristics, blood pressure and brief counselling for healthier lifestyle were conducted by local nurses, who had received training regarding lifestyle prevention of type 2 diabetes. Study participants were also referred to laboratory tests including a 2-h OGTT and the measurement of fasting blood lipids.

Participants were offered either individual or group-based lifestyle counselling. The topics of the individual counselling and group sessions were weight reduction, a healthy diet and physical activity based on the person's individual needs. Due to the local resources and other circumstances in the large number of clinics that took care of the intervention there was no uniform protocol for the frequency and intensity of the intervention.

During the visits to the clinics, the participants were asked to fill in a questionnaire about lifestyle and intervention activities. Baseline visits were conducted during 2004–2007 and the one-year follow-up visits during 2005–2008 (9–18 months after baseline). Individuals, who had a follow-up visit before ($n = 172$) or after ($n = 1470$) one-year follow-up were excluded from analyses. In total, 10,149 high-risk individuals (3379 men and 6770 women) aged 18–87 years participated in baseline visit and 3880 persons in the one-year follow-up visit and they also had OGTT data from both visits (Fig. 1). Altogether 1150 individuals were excluded from the present analysis because they had screen-detected diabetes at baseline or one-year follow up since they did not have data on weight change prior to the onset of diabetes, or other necessary data were missing. Complete follow-up data during one-year intervention were available for 2730 individuals and they were included in the present follow-up analysis (Fig. 1).

During the health examination, weight and height were measured and body mass index (BMI) was calculated. In the present analyses change in weight at the one-year follow-up visit was categorized into four classes, lost 5% or more, lost 2.5–4.9%, stable weight (<2.5%) and gained (>2.5%) [20]. Data on socio-demographic factors, health status and regular medication were collected by a self-report questionnaire.

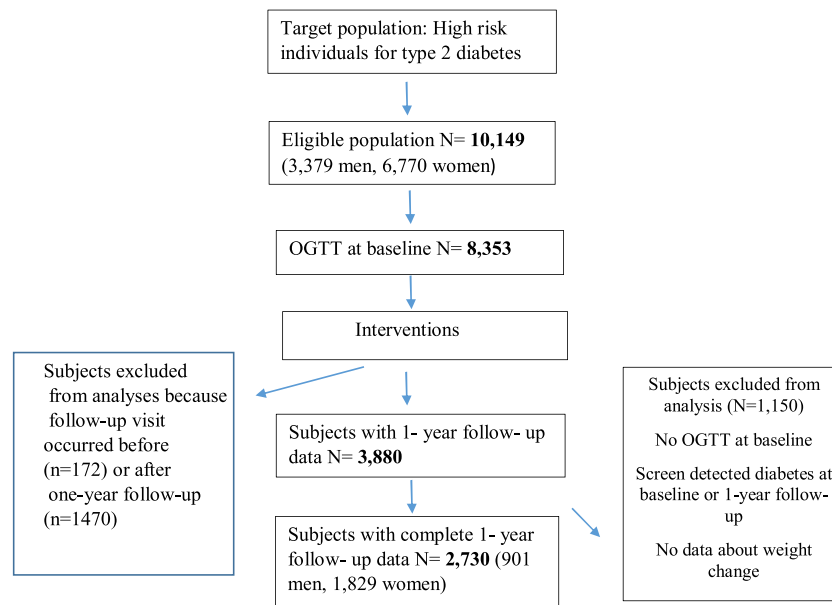


Fig. 1. The number of people in the FIN-D2D high-risk cohort identified during 2004 to 2008 and the participants with the one-year and seven-year follow-up data.

2.2. Incidence of drug-treated diabetes, cardiovascular events and all-cause mortality

Data on the incidence of drug-treated diabetes, cardiovascular events, and all-cause mortality were collected from three nationwide health registers using computerized data linkage with the national personal identification number until study close of 31st of December 2012 with the median follow-up time of 7.4 years.

The incidence of drug-treated diabetes was identified by the record data linkage to the National Prescription Register (ATC class A10, drugs for diabetes) and Register for Drug Cost Reimbursement (class 103, diabetes). Register data do not distinguish the type of diabetes. The incidence of cardiovascular events was examined through a data linkage with the National Hospital Discharge Register, which covers discharges of in-patient admissions to any hospital in Finland. Data on deaths were obtained from the National Death Register that provided the underlying cause of death based on official death certificates. The diagnoses were coded according to the International Classification of Diseases [24]. Cardiovascular events included the ICD-10 codes I20–I25, I61, I63, which stand for acute coronary events, coronary heart disease and stroke.

2.3. Research ethics

The data were collected according to the guidelines of the Declaration of Helsinki and international ethical standards. The ethical steering committee within the National Institute for Health and Welfare gave approval for the FIN-D2D-follow-up study and for data linkage to nationwide health registers.

2.4. Statistical analysis

Cox proportional hazards models, expressed as hazard ratios (HRs) and 95% confidence intervals (CI's) were used to examine effects of weight change on the incidence of drug-treated type 2 diabetes, cardiovascular events, and mortality after adjustment for age, sex, BMI, fasting glucose, 2-h glucose, drug treatment for drug hypertension and treatment for lipids at baseline. Analyses were conducted separately for men and women when calculating the incidence of drug-treated type 2 diabetes and when weight change was categorized into two classes: lost weight and stable

or gained weight. People who initiated treatment with glucose-lowering drugs before the one-year follow-up visit were excluded from the analyses since their weight change prior to the diagnosis of diabetes could not be obtained. Statistical analyses were done with the statistics package STATA, version 15 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Baseline characteristics according to the weight change

Baseline characteristics of the high-risk individuals for drug-treated type 2 diabetes according to weight change during the one-year lifestyle intervention are presented in Table 1 and Supplemental Tables 1 and 2. The majority of participants were obese, and the mean BMI was over 30 kg/m². The mean FINDRISC score was 17 points in all study groups.

The participants who gained weight were younger and their BMI and 2-h glucose level were slightly lower than those of the participants who had stable weight or lost weight, and their prevalence of IGT was lower (Table 1).

3.2. Incidence of drug-treated diabetes according to weight change

Among the 2730 individuals who participated in the one-year lifestyle intervention, 594 had started glucose-lowering drug treatment during the follow-up. The overall incidence of diabetes per 1000 person-years was 33.2 (CI 30.6–36.0) and the annual conversion rate was 0.8%.

In individuals who lost weight 2.5–4.9% and 5% or more during the one-year intervention, the incidence of drug-treated diabetes was reduced by 37% (HR = 0.63, CI 0.49–0.81, $p = 0.0001$) and 29% (HR = 0.71, CI 0.56–0.90, $p = 0.004$), respectively, compared with the people with stable weight when adjusted for age, sex, BMI, fasting glucose, 2-h glucose, drug treatment for hypertension and drug treatment for lipids at baseline (Fig. 2 and Table 2). In individuals who gained weight 2.5% or more, the incidence of drug-treated diabetes tended to be higher than in those with stable weight (HR = 1.22, CI 0.99–1.51, $p = 0.059$).

Table 1
Baseline characteristics of the participants by one-year weight change during the intervention (mean and SD; or percentage and p value).

	N	Weight loss ≥5%	N	Weight loss 2.5–4.9%	N	Stable weight	N	Gained weight	p
Age (years)	481	54.0 (10.7)	459	55.8 (9.8)	1257	55.5 (10.2)	533	52.4 (10.6)	<0.001
Sex: men (%)	481	30.8	459	30.5	1275	35.7	533	29.6	0.013
FINDRISC score	404	17.2 (3.0)	382	17.2 (3.1)	1068	17.1(3.2)	447	16.9 (3.2)	0.249
BMI (kg/m ²)	481	32.6 (5.6)	458	31.5 (4.9)	1257	31.2 (5.0)	532	30.6 (5.2)	<0.001
Education low (%) ^a	450	72.2	435	73.8	1209	70.6	501	70.1	0.546
Smoking (%)	451	16.0	434	11.5	1210	13.6	499	17.3	0.036
Fasting glucose (mmol/l)	481	5.8 (0.6)	459	5.7 (0.6)	1257	5.8 (0.6)	533	5.7 (0.6)	<0.001
2-h glucose (mmol/l)	481	7.2 (1.9)	459	7.0 (1.8)	1257	7.0 (1.8)	533	6.7 (1.8)	<0.001
NGT (%)	481	43.7	459	51.9	1257	48.6	533	58.5	<0.001
IFG (%)	481	21.8	459	21.1	1257	23.2	533	16.7	0.020
IGT (%)	481	34.5	459	27.0	1257	28.2	533	24.8	0.006
Total cholesterol (mmol/l)	453	5.2 (0.9)	433	5.2 (1.0)	1208	5.2 (1.0)	507	5.1 (1.0)	0.186
LDL cholesterol (mmol/l)	440	3.1 (0.9)	426	3.1 (0.9)	1186	3.1 (0.9)	501	3.0 (0.8)	0.098
HDL cholesterol (mmol/l)	448	1.4 (0.4)	431	1.4 (0.4)	1203	1.4 (0.4)	507	1.4 (0.4)	0.230
Triglycerides (mmol/l)	448	1.6 (0.9)	430	1.6 (1.1)	1200	1.6 (0.9)	507	1.5 (1.0)	0.426
Systolic blood pressure (mmHg)	477	140 (17.0)	457	141 (17.0)	1251	139 (17.5)	528	138 (17.5)	0.033
Diastolic blood pressure (mmHg)	477	86 (9.0)	457	86 (9.3)	1251	86 (9.5)	528	86 (9.5)	0.461
Drug treatment for elevated blood pressure (%)	481	46.6	459	54.0	1257	51.2	533	52.0	0.129
Drug treatment for dyslipidemia (%)	481	21.4	459	26.6	1257	24.7	533	24.2	0.310

BMI = Body Mass Index, NGT = normal glucose tolerant, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, LDL = low-density lipoprotein, HDL = high-density lipoprotein.

^a Education was categorized into two classes: low (primary, basic or middle school, vocational school or corresponding, upper secondary school) and high (college, polytechnic, and academic degree).

Table 2
Diabetes incidence, cardiovascular events and total mortality during follow-up by weight changes.

Weight changes	Weight loss ≥5%	Weight loss 2.5–4.9%	Stable weight	Gained weight
Diabetes incidence				
Number of drug treated type 2 diabetes	89	74	296	135
Rate per 1000 person-years (95% CI)	27.6 (22.4–33.9)	23.7 (18.9–29.8)	36.5 (32.6–40.9)	39.5 (33.3–46.7)
Hazard ratio (95% CI) ^a	0.71 (0.56–0.90)	0.63 (0.49–0.81)	1.00	1.22 (0.99–1.51)
p-value	0.004	0.0001	(ref)	0.059
Cardiovascular events				
Number of CVD events	19	26	76	22
Rate per 1000 person-years (95% CI)	5.6 (3.6–8.8)	8.0 (5.5–11.8)	8.6 (6.9–10.8)	5.8 (3.8–8.8)
Hazard ratio (95% CI) ^a	0.75 (0.45–1.24)	1.01 (0.65–1.56)	1.00	0.85 (0.53–1.37)
p-value	0.261	0.963	(ref)	0.504
Total mortality				
Number of deaths	9	10	24	10
Rate per 1000 person-years (95% CI)	2.6 (1.3–5.0)	3.0 (1.6–5.6)	2.6 (1.8–3.9)	2.6 (1.4–4.8)
Hazard ratio (95% CI) ^a	1.11 (0.51–2.41)	1.22 (0.58–2.56)	1.00	1.26 (0.59–2.69)
p-value	0.790	0.603	(ref)	0.547

^a Adjusted for age, sex, BMI, fasting glucose, 2-h glucose, drug treatment for hypertension and drug treatment for lipids at baseline.

In men, the incidence of drug-treated diabetes was 41% lower in those who lost weight 2.5–4.9% than in those with stable weight (HR = 0.59, CI 0.39–0.89, $p = 0.012$) when adjusted for age and BMI at baseline. In men who lost weight 5% or more, the difference compared with those with stable weight was numerically reduced, but not statistically significant (HR = 0.72, CI 0.50–1.04, $p = 0.080$). In women, the incidence of drug-treated diabetes was 34% lower (HR = 0.66, CI 0.48–0.92, $p = 0.013$) in those who lost weight 2.5–4.9% compared with those with stable weight when adjusted for age and BMI at baseline, and 31% (HR = 0.69, CI 0.51–0.95, $p = 0.021$) lower in those who lost weight 5% or more. Both in men and women who gained weight, the incidence of diabetes tended to increase.

In men who lost weight compared with men with stable or increased weight the incidence of drug-treated diabetes was 38% lower when adjusted for age and BMI at baseline (HR = 0.62, CI 0.4–0.83, $p = 0.001$). In women who lost weight compared with women with stable or increased weight the incidence of drug-treated diabetes was 36% lower when adjusted for age and BMI at baseline (HR = 0.64, CI 0.51–0.81, $p < 0.001$).

3.3. Incidence of cardiovascular events and all-cause mortality according to weight change

Overall, 143 cardiovascular events were ascertained in the study cohort during the follow-up (Table 2). There were no statistically significant differences in incidence of cardiovascular events among the weight change groups after adjustment for age, sex, BMI, fasting glucose, 2-h glucose, drug treatment for hypertension and drug treatment for lipids at baseline (Supplemental Fig. 1 and Table 2).

There were 53 individuals who deceased during the follow-up (Table 2). There were no statistically significant differences in all-cause mortality among the weight change groups.

4. Discussion

This extended median 7.4-year follow-up of the subsample of the FIN-D2D cohort of people at high risk of type 2 diabetes showed that a moderate weight reduction ($\geq 2.5\%$) one year after the lifestyle intervention had sustained long-term benefits and was translated to a significant 29–37% reduction in the incidence of

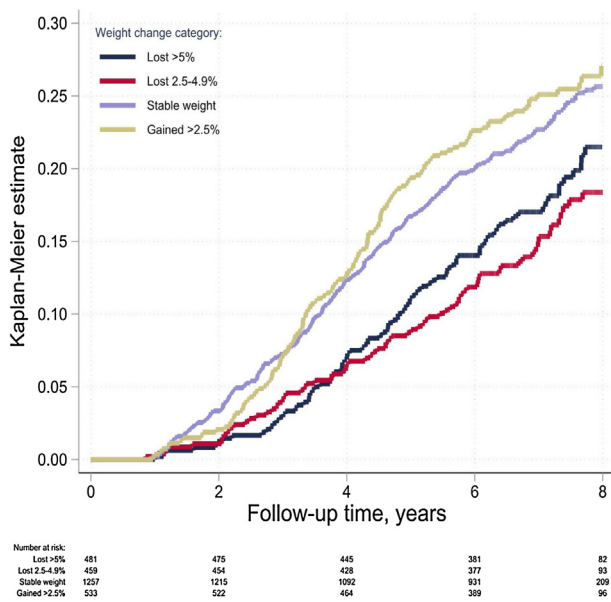


Fig. 2. The cumulative incidence (%) of drug-treated type 2 diabetes during the seven-year follow-up in individuals at high-risk of type 2 diabetes according to the weight change in one-year intervention.

drug-treated diabetes. The observed moderate weight loss was not associated with a reduction in cardiovascular events or all-cause mortality in a post-hoc analysis, but the number of the events was small resulting in low statistical power. A limited number of implementation studies exist that have evaluated effects of lifestyle interventions for diabetes prevention in primary care settings with a long follow-up time [17–19]. Findings from previous short-term studies were similar to our results [25], but the follow-up time was at least three years longer in our study.

The challenge has been how the available evidence from successful RCT’s proving the efficacy of lifestyle intervention on type 2 diabetes prevention could be translated to the current health care practice. A systematic review and meta-analysis of 22 real-world implementation studies showed that the prevention of type 2 diabetes can be effective in the real-world settings during a 12-month follow-up [25]. Seven studies included in this meta-analysis were done in primary care settings and the rest in community or outpatients settings [25]. Johnson et al. reported that in 19 translational studies based on the DPP and DPS methodology, but with modifications to increase feasibility, weight loss was achieved in a range of settings, but no consistent changes associated with interventions were found in blood glucose or waist circumference [26]. The strong association between overweight and obesity and increased diabetes incidence is well established. Obesity is associated with more than ten-fold increase in the incidence of type 2 diabetes compared with people with normal weight [27], and the risk steeply increases with increasing level of BMI or waist circumference [28]. In most clinical trials, weight reduction has been the key point of a lifestyle intervention for the prevention of type 2 diabetes [4]. Recently, the 2-year results of DiRECT trial showed that 70% of patients with type 2 diabetes who took part in the primary care-based weight management programme and lost more than 15 kg were in remission after two years [29].

Thus, the target of lifestyle interventions to prevent type 2 diabetes should be focused on weight reduction, although other aspects of unhealthy lifestyle should also be addressed. Previous diabetes prevention trials, such as the DPS and DPP, showed that the maximum weight reduction was achieved after one year, and thereafter some regain of weight gradually occurred. Still, the lifestyle intervention group kept lower body weight in long-term compared

with the control group [3,4]. Thus, a one-year weight change is a valid indicator of the success of lifestyle intervention for diabetes prevention, especially in participants who are obese or overweight at baseline.

In our study, only 17.5% of participants had lost at least 5% of their body weight during the one-year follow-up [20]. In the Spanish study from the Diabetes in Europe–Prevention Using Lifestyle, Physical Activity and Nutritional Intervention (DE-PLAN) project in primary care, 24% of participants in the intensive group reduced the weight by at least 3%, and in the Polish study 27% of participants achieved a BMI reduction of >5% after one-year follow-up [17,19]. In the Norwegian study only 8.7% of participants had evidence of >5% weight loss during follow-up [30]. In a meta-analysis of 22 real-world implementation studies the average weight loss was 2.6 % at the one-year follow-up [25]. Longer duration and intensity of session attendance resulted in a higher weight loss.

Prior research on translational diabetes prevention programs shows that the intervention programs were most effective when they included a minimum of four to six months of weekly sessions followed by periodic maintenance sessions for at least one year [31]. Our study intervention was done in a clinical setting in primary care without extra facilities or manpower, which explains the low number of intervention visits [20]. Participants had on average 2.9 intervention visits during the one-year intervention and only 29% of them had three or more visits [20], and those with a higher number of intervention visits succeeded to lose more weight than others. The relatively small number of intervention visits may explain the smaller weight loss of participants in this study compared with the above-mentioned other studies. The recent report from the DE-PLAN study cohort identified by the FINDRISC in Norway also showed that a very low intensity lifestyle intervention did not result in significant benefits regarding the prevention of type 2 diabetes [30].

Selection bias is a possible limitation of our study, because only 69% of individuals who had an OGTT at baseline had any follow-up data and many people did not participate in the intervention program. These participants with follow-up data were probably more motivated to do lifestyle changes, which might affect the result of this study, but the extent of this bias remains unclear. However, the weight change groups did not differ in their baseline sex and FINDRISC-score. The incidence of diabetes was comparable in this cohort (33/1000 person-years) compared with a meta-analysis where the incidence of diabetes was 36 (95% CI 15.1–83.0)/1000 person-years in people with raised HbA1C [32]. It is of note that the incidence varies according to the criteria used to diagnose diabetes.

Data on drug-treated diabetes to ascertain the incident cases of diabetes were obtained from the register data (the National Prescription Register and the Register for Drug Cost Reimbursement). Although the coverage of these registers is virtually complete, only the people who received drug treatment for diabetes were identified. Many people with asymptomatic new-onset diabetes can only be detected by assessing glycemia by laboratory tests, and some such cases have been missed. Since our cohort was known to have a high risk of diabetes by the local health personnel, it is possible that they had been monitored by glycaemia re-testing, but we do not have information about it. However, it is unlikely that the one-year weight change would have caused bias in the detection of diabetes during the seven-year follow-up. The type of diabetes was not defined by the register data, but this limitation is a minor issue since the majority of cases in this age group would have type 2 diabetes.

In the FIN-2D2 programme, the participants in the high-risk cohort were at a very high risk to develop diabetes. Obviously, measures to prevent diabetes even earlier are needed. The main inclusion criteria for the high-risk cohort in the FIN-D2D program was FINDRISC score ≥ 15 . [20] The ideal cut-point for the FINDRISC

score based on sensitivity and specificity would have been 11 or 12 [20] that was also proposed by the Norwegian study [30]. The reason for choosing a FINDRISC score of ≥ 15 for inclusion criteria was that a lower score threshold would have identified too many high-risk persons and resources in primary care would not have been able to organize lifestyle intervention and follow-up for so many people. Even the cut-point of the FINDRISC score of ≥ 15 seemed to produce too many individuals for many primary care centres to cope with. Over the past ten years, mobile and digital services have developed rapidly which makes it possible to increase flow also in health care and diabetes prevention programs can be implemented in much larger groups of high-risk persons.

Our study showed benefits of lifestyle intervention on diabetes prevention, but there were no effects on cardiovascular events or total mortality. These findings are similar to those obtained in most previous follow-up studies [11,13]. None of the diabetes prevention studies have been designed for preventing cardiovascular events or all-cause mortality, and all studies have been clearly underpowered for this, but some post-hoc analyses of previous trials have been published. The Chinese study showed benefits of lifestyle interventions on cardiovascular and all-cause mortality to appear only after 10 years follow-up [7,9,15]. In the Look AHEAD study, intensive lifestyle intervention did not reduce cardiovascular morbidity and mortality in persons with type 2 diabetes who were overweight or obese during median of 9.6-year follow-up [33]. In the post-hoc analysis of the Look AHEAD study with a follow-up of 10.2 years, when the intensive lifestyle intervention and control groups were combined, the risk of cardiovascular events or mortality was reduced by 21% in the trial participants who were able to lose at least 10% of their weight at one year compared with the participants whose weight remained stable or who gained weight [34]. However, it may also be that people at high risk of type 2 diabetes through their lifestyle will have also a higher risk for cardiovascular events due to other risk factors such as hypertension and dyslipidaemia, and they may have changed their lifestyle for this reason as well, not only due to the risk of diabetes.

5. Conclusions

This study shows that individuals at high-risk for type 2 diabetes who achieved a moderate weight loss during a one-year program of lifestyle counselling in primary health care had a long-term benefit in terms of reduced incidence of new-onset drug-treated type 2 diabetes. The observed moderate weight loss was not associated with a reduction in cardiovascular events.

Contributors

MU, JT, SKK designed the FIN-D2D study, TS coordinated the study implementation. LM conceived the present study. LM, MP, RR, NR, SKK, JS, HO HP, JT, MU designed and implemented the study. MP, RR and JJ analysed the data. RR wrote the first draft of the report. All authors reviewed the draft and contributed to the revision of the report. RR, MP, JJ had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Conflict of interest

None declare.

Funding

RR is supported by Finnish Government Research Funding.

The FIN-D2D programme was supported by financing from hospital districts of Pirkanmaa, Southern Ostrobothnia, North Ostrobothnia, Central Finland and Northern Savo, the Finnish National Public Health Institute, the Finnish Diabetes Association, the Ministry of Social Affairs and Health in Finland, Finland's Slottery Machine Association, the Academy of Finland (grant no. 129293) and Commission of the European Communities, Directorate C-Public Health (grant agreement no. 2004310) in cooperation with the FIN-D2D Study Group, and the Steering Committee: Huttunen J, Kesäniemi A, Kiuru S, Niskanen L, Oksa H, Pihlajamäki J, Puolakka J, Puska P, Saaristo T, Vanhala M, and Uusitupa M.

The funding organizations (except for the hospital districts) had no role in the design and conduct of the study; the collection management, analysis and interpretation of data, or the writing of the manuscript for publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.pcd.2021.03.002>.

References

- [1] M. Tancredi, A. Rosengren, A. Svensson, et al., Excess mortality among persons with type 2 diabetes, *N. Engl. J. Med.* 373 (2015) 1720–1732.
- [2] C. Nwaneri, H. Cooper, D. Bowen-Jones, Mortality in type 2 diabetes mellitus: magnitude of evidence from a systematic review and meta-analysis, *Br. J. Diabetes Vasc. Dis.* 13 (2013) 192–207.
- [3] J. Tuomilehto, J. Lindström, J.G. Eriksson, Finnish Diabetes Prevention Study Group, et al., Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance, *N. Engl. J. Med.* 344 (2001) 1343–1350.
- [4] Diabetes Prevention Program Research Group, Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, *N. Engl. J. Med.* 346 (2002) 393–403.
- [5] X.R. Pan, G.W. Li, Y.H. Hu, et al., Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study, *Diabetes Care* 20 (1997) 537–544.
- [6] A. Ramachandran, C. Snehalatha, S. Mary, Indian Diabetes Prevention Programme (IDPP), et al., The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1), *Diabetologia* 49 (2006) 289–297.
- [7] Q. Gong, P. Zhang, J. Wang, et al., Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study, *Lancet Diabetes Endocrinol.* 7 (2019) 452–461.
- [8] J. Lindström, P. Ilanne-Parikka, M. Peltonen, Finnish Diabetes Prevention Study Group, et al., Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish diabetes prevention study, *Lancet* 368 (2006) 1673–1679.
- [9] G. Li, P. Zhang, J. Wang, et al., The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing diabetes prevention study: a 20-year follow-up study, *Lancet* 371 (2008) 1783–1789.
- [10] Diabetes Prevention Program Research Group, 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study, *Lancet* 374 (2009) 1677–1686.
- [11] Diabetes Prevention Program Research Group, Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the diabetes prevention program outcomes study, *Lancet Diabetes Endocrinol.* 3 (2015) 866–875.
- [12] G. Kerrison, R.B. Gillis, S.I. Jiwani, et al., The effectiveness of lifestyle adaptation for the prevention of prediabetes in adults: a systematic review, *J. Diabetes Res.* (2017) 8493145.
- [13] M. Uusitupa, M. Peltonen, J. Lindström, Finnish Diabetes Prevention Study Group, et al., Ten-year mortality and cardiovascular morbidity in the Finnish diabetes prevention study—secondary analysis of the randomized trial, *PLoS One* 4 (2009) e5656.
- [14] A. Aro, A. Kauppinen, N. Kivinen, et al., Life style intervention improves retinopathy status—the Finnish diabetes prevention-study, *Nutrients* 23 (2019) 1.
- [15] G. Li, P. Zhang, J. Wang, et al., Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing diabetes prevention study: a 23-year follow-up study, *Lancet Diabetes Endocrinol.* 2 (2014) 474–480.

- [16] E.S. Schellenberg, D.M. Dryden, B. Vandermeer, et al., Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis, *Ann. Intern. Med.* 159 (2013) 543–551.
- [17] A. Gilis-Januszewska, J. Lindström, J. Tuomilehto, et al., Sustained diabetes risk reduction after real life and primary health care setting implementation of the diabetes in Europe prevention using lifestyle, physical activity and nutritional intervention (DE-PLAN) project, *BMC Public Health* 17 (2017) 198.
- [18] P. Absetz, B. Oldenburg, N. Hankonen, et al., Type 2 diabetes prevention in the real world: three-year results of the GOAL lifestyle implementation trial, *Diabetes Care* 32 (2009) 1418–1420.
- [19] B. Costa, F. Barrio, J.J. Cabré, DE-PLAN-CAT Research Group, et al., Delaying progression to type 2 diabetes among high-risk Spanish individuals is feasible in real-life primary healthcare settings using intensive lifestyle intervention, *Diabetologia* 55 (2012) 1319–1328.
- [20] T. Saaristo, L. Moilanen, E. Korpi-Hyövälti, et al., Lifestyle intervention for prevention of type 2 diabetes in primary health care: one-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D), *Diabetes Care* 10 (2010) 2146–2151.
- [21] J. Lindström, A. Louheranta, M. Mannelin, Finnish Diabetes Prevention Study Group, et al., The Finnish diabetes prevention study (DPS): lifestyle intervention and 3-year results on diet and physical activity, *Diabetes Care* 26 (2003) 3230–3236.
- [22] T. Saaristo, M. Peltonen, J. Lindström, L. Saarikoski, J. Sundvall, J. Eriksson, et al., Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome, *Diabetes Vasc. Dis. Res.* 2 (2005) 67–72.
- [23] T. Saaristo, M. Peltonen, S. Keinänen-Kiukaanniemi, FIN-D2D Study Group, et al., National type 2 diabetes prevention programme in Finland: FIN-D2D, *Int. J. Circumpolar Health* 66 (2007) 101–112.
- [24] World Health Organisation, Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus, Geneva, 1999.
- [25] A.J. Dunkley, D.H. Bodicoat, C.J. Greaves, et al., Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis, *Diabetes Care* 37 (2014) 922–933.
- [26] M. Johnson, R. Jones, C. Freeman, et al., Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence, *Diabet. Med.* 30 (2013) 3–15.
- [27] D.P. Guh, W. Zhang, N. Bansback, et al., The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis, *BMC Public Health* 9 (2009) 88.
- [28] F.B. Hu, J.E. Manson, M.J. Stampfer, et al., Diet, lifestyle, and the risk of type 2 diabetes mellitus in women, *N. Engl. J. Med.* 345 (2001) 790–797.
- [29] M.E. Lean, W.S. Leslie, A.C. Barnes, et al., Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial, *Lancet Diabetes Endocrinol.* 7 (2019) 344–355.
- [30] A. Jølle, B.O. Åsvold, J. Holmen, et al., Basic lifestyle advice to individuals at high risk of type 2 diabetes: a 2-year population-based diabetes prevention study. The DE-PLAN intervention in the HUNT Study, Norway, *BMJ Open Diabetes Res. Care* 9 (2018) 6.
- [31] E.M. Venditti, M.K. Kramer, Necessary components for lifestyle modification interventions to reduce diabetes risk, *Curr. Diab. Rep.* 12 (2012) 138–146.
- [32] D.H. Morris, K. Khunti, F. Achana, et al., Progression rates from HbA1c 6.0–6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis, *Diabetologia* 56 (2013) 1489–1493.
- [33] Look AHEAD Research Group, Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes, *N. Engl. J. Med.* 369 (2013) 145–154.
- [34] Look AHEAD Research Group, Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the look AHEAD randomised clinical trial, *Lancet Diabetes Endocrinol.* 4 (2016) 913–921.