Impact of positive family history and genetic risk variants on the incidence of diabetes – the Finnish Diabetes Prevention Study

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Objective- We aimed to investigate the influence of positive family history of diabetes (FH) and 19 known genetic risk loci on the effectiveness of lifestyle changes, and their predictive value on the incidence of type 2 diabetes in the Finnish Diabetes Prevention Study (DPS).

Research Design and Methods- A total of 522 subjects with impaired glucose tolerance (IGT) were randomized into the control (*n*=257) and intervention (*n*=265) group. The mean follow-up was 6.2 years (median 7 years), and the lifestyle intervention, aimed at weight reduction, healthy diet and increased physical activity, lasted for 4 years (range 1-6 years). An oral glucose-tolerance test and assessment of basic clinical variables was performed annually.

Results- The effect of intervention on the incidence of diabetes was almost similar in subjects with FH+ than in FH- during the entire follow-up. In the Cox model including FH, genetic risk SNPs and randomization group, and adjusted for the effects of age, sex, BMI and study center, only lifestyle intervention had significant effect (HR 0.55, 95 % CI 0.41–0.75, p<0.001) on the incidence of diabetes. Further analyses showed that besides the baseline glucose and insulin values, 1-year changes in 2-h glucose and 2-h insulin achieved by lifestyle intervention had significant effect on the incidence of diabetes.

Conclusions- These results emphasize the effectiveness of lifestyle intervention in reducing the risk of diabetes in high risk individuals independent of genetic or familial risk of type 2 diabetes.

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Both genetic and environmental factors play major roles in the development of type 2 diabetes mellitus. In recent years, the research aiming to explore the genetic basis of type 2 diabetes has progressed very significantly. Currently, over 30 genetic variants have been identified in large multi-center studies with sufficient power to be associated with an increased risk of type 2 diabetes (1, 2, 3). Typically, each variant has only a very limited effect on the risk, i.e. the risk may increase by 10 to 15 % per copy of each risk allele except for *TCF7L2,* which is so far the most convincing type 2 diabetes risk gene, increasing the risk 1.4-fold (2). Interestingly, the known risk variants explain only ~10% of the genetic basis of type 2 diabetes (2). Based on findings in a limited number of longitudinal studies, the risk variants have only a small effect on the ability to predict the development of type 2 diabetes (4, 5, 6). In two lifestyle-based diabetes prevention trials in persons with impaired glucose tolerance (IGT), the Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (DPS), it has been possible to examine the interaction between the genetic and lifestyle factors regarding the future risk of diabetes. In these studies, lifestyle changes modified the risk of diabetes depending on the genetic variation (2, 7, 8). Specifically, the increased risk of type 2 diabetes was completely abolished by lifestyles in both DPP and DPS among the

persons with the risk allele for *TCF7L2* (9, 10). It is commonly believed that type 2 diabetes is highly heritable (11), and a positive family history (FH+) predicts the development of the type 2 diabetes even after adjustment for common risk factors for type 2 diabetes (4, 5, 6, 12, 13, 14). Interestingly, in the DPP the known genetic risk variants did not associate with an increased risk of diabetes, and only one potential genotype-intervention interaction for *CDKN2A/B* was reported (15). However, the responses to lifestyle according to family history of diabetes were not documented.

The aim of the present study was to investigate whether a positive FH of diabetes or genetic variants of type 2 diabetes could modulate the effect of lifestyle changes achieved in the Finnish DPS (16, 17) on the incidence of type 2 diabetes. Furthermore, we aimed to assess the ability of FH and genetic risk variants, in addition to lifestyle changes and basic clinical variables, to predict the incidence of type 2 diabetes in individuals at high risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

The DPS is a clinical trial with five participating centers (Helsinki, Kuopio, Turku, Tampere, and Oulu) in Finland (ClinicalTrials.gov NCT00518167). Details of the DPS study design, methods, and procedures have been published previously (16, 17, 18, 19). Briefly, study participants were recruited mainly by screening of high-risk groups who voluntarily responded to local advertisements. The inclusion criteria were 1) age 40 to 64 years at screening, 2) body mass index (BMI) >25 kg/m^2 at screening, and 3) the mean value of two 75-g oral glucose tolerance tests (OGTT) in the IGT range based on WHO 1985 criteria. Exclusion criteria included recent (within 6 months) cardiovascular disease (CVD) event. The randomization of participants started in 1993 and continued until 1998.

A total of 522 overweight men and women were randomly allocated to one of the two treatment modalities, the intensive diet-exercise counseling group (*n*=265, the proportion of women 66%) or the control group (*n*=257, the proportion of women 69%). The participants randomized to intensive lifestyle intervention were given individualized counseling by the study nutritionists to achieve the lifestyle goals. They were also advised to increase their level of physical activity, and voluntary physical activity sessions were offered. The lifestyle goals were 1) weight reduction of ≥5%, 2) <30% of the daily energy intake from fat, 3) <10% of the daily energy intake from saturated fat, 4) fiber intake ≥15 grams per 1000 kcal, and 5) moderately intense physical activity ≥30 minutes per day. The control participants were given general health behavior information at randomization. The median length of the active intervention period was 4 years (range 1–6 year).

All participants had an annual OGTT, a medical history, and a physical examination with measurements of height (without shoes), weight (in light indoor clothes), waist circumference (midway between the lowest rib and iliac crest) and systolic and diastolic blood pressure. Serum total cholesterol, HDL-cholesterol and triglycerides were determined from fasting samples using an enzymatic assay method.

The diagnosis of diabetes was based on the repeated OGTT (16, 17). Family history of diabetes was based on a questionnaire applied in the DPS. If one of the first degree relatives (father, mother, sister, brother) had diabetes, family history was regarded as positive (FH+). These data are based on the follow-up of 4 years when active intervention was finished and on the three years of follow-up after active intervention with a total follow-up

of an average of 6.4 years (median 7 years). Altogether 75 persons (28 %) in the intervention group and 110 persons (43 %) in the control group developed diabetes during the entire follow-up. During the entire study period, the incidence of diabetes was substantially lower in the intervention as compared to control group (HR 0.57; 95% CI 0.43–0.76, p<0.001) (18). No significant difference was found in mortality rates between the groups (19).

Genotyping. Nineteen type 2 diabetes-susceptibility SNPs *(PPARG* rs1801282, *KCNJ11* rs5219, *TCF7L2* rs7903146, *SLC30A8* rs13266634, *HHEX* rs1111875, *CDKN2B* rs10811661, *IGF2BP2* rs4402960, *CDKAL1* rs7754840, *FTO* rs9939609, *HNF1B* rs757210, *WFS1* rs10010131, *JAZF1* rs864745*, CDC123* rs12779790, *TSPAN8* rs7961581, *THADA* rs7578597, *ADAMTS9* rs4607103, *NOTCH2* rs10923931, *KCNQ1* rs2283228, *MTNR1B* rs10830963) were genotyped using the TaqMan Allelic Discrimination Assay (Applied Biosystems). The genotyping call rate was 99.2–100%. Genotype distributions of all SNPs were in Hardy-Weinberg equilibrium (p>0.05).

Calculations. Genetic risk score for type 2 diabetes (GRS) was calculated as a sum of type 2 diabetes-risk alleles in 19 confirmed type 2 diabetes-susceptibility SNPs. Furthermore, GRS_{SECR} based on 8 SNPs influencing insulin secretion (at loci *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2B*, *IGF2BP2*, *CDKAL1*, *MTNR1B*) (20) was calculated.

Statistical analysis. Baseline differences in characteristics of the groups with and without FH of diabetes were tested with t-test for continuous variables and with Fisher's exact test or χ^2-test for dichotomous variables. Changes during follow-up (Δ values between the value at 1 year of follow-up and the baseline value) in body weight, glucose and other variables were analyzed with the general linear model, adjusting for age, sex, study center, BMI and fasting glucose at baseline. Interaction between FH and the randomization group was tested for each model, modeled as fixed factor. Variables with non-normal distribution were log-transformed prior to analyses. Kaplan-Meier method was used to estimate the incidence of diabetes in the two groups. The difference in incidence between the groups was tested with the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio for the development of diabetes between the groups. Hazard ratios for continuous traits are expressed as unit change per 1 standard deviation. If not stated otherwise, the models were adjusted for age, sex, BMI at baseline, fasting glucose at baseline, and study center. No multicolinearity problems were found for any model. Interaction between FH (or GRS) and randomization group was modeled as a covariate in Cox regression. All comparisons of the endpoints were based on the intention-to-treat principle. The results for continuous variables are given as means ± SD. P-value <0.05 was considered statistically significant. Analyses were done with the statistics package Stata version 10.1 and SPSS 14.0.

RESULTS

Baseline characteristics and 1-year changes in clinical variables by family history. No significant difference in the prevalence of FH of diabetes was observed between the intervention and control groups (66% vs. 61%). Table 1 shows baseline characteristics of the DPS participants according to the family history of diabetes. Besides the one year difference in age (p=0.012), the two groups (FH+ vs. FH-) did not differ significantly from each other. Furthermore, persons with FH+ and FH- were similar regarding their diet at baseline, but the total

leisure time physical activity was greater in persons with FH-.

The 1-year changes in the main clinical and metabolic characteristics according to FH and randomization group (intervention vs. control group) are shown in Supplementary Table 1 in the online appendix available at http://care.diabetesjournals.org. As shown previously, weight reduction was greater and glycemic control improved more in the intervention group than in the control group (17, 18). In the intervention group, persons with FH+ achieved significantly greater reduction in 2-h plasma glucose than did persons with FH-. However, no significant interactions between FH and control/intervention group were found in the changes in body weight, fasting plasma glucose, 2-h plasma glucose, HOMA-IR, HOMA-IS or energy intake. In addition, no major differences were found in the distribution of macronutrients or physical activity between FH+ and FH- group after 1-year of intervention (data not shown).

Incidence of type 2 diabetes by family history. Incidence of type 2 diabetes in the intervention and control group by FH of diabetes is shown in Figure 1 (data in Supplementary Table 2). Interestingly, during the original randomized trial period of 4 years on average, the incidence of diabetes seemed to be lower in the intervention group than in control group in persons with FH+ (p=0.0002), but not in those with FH- (p=0.61). After adjustment for age, gender, baseline BMI, fasting glucose, and study center, the HR for diabetes in the intervention group compared with the control group was 0.42 (95% CI: 0.26–0.70; p=0.0008) in persons with FH+, whereas it was 0.61 (95% CI: 0.33–1.12; p=0.11) in persons with FH-. During the entire follow-up, in the adjusted model, the effect of intervention was, however, significant in both FH+ (p=0.002) and FH- group (p=0.006), and there was no significant interaction between the family history and randomization group, (p=0.19 for the follow-up during intervention, p=0.97 for the entire follow-up).

Effect of gene variants and genetic risk score (GRS) on the incidence of type 2 diabetes. We did not find any significant effects of the 19 risk variants on the incidence of type 2 diabetes (data not shown). Similarly, combined type 2 diabetes risk alleles of 19 SNPs (presented as GRS) did not have significant effect on the incidence of diabetes during the entire follow-up period (p=0.784 in the adjusted model). GRS based on 8 SNPs influencing insulin secretion (20) (GRS_{SECR}) did not have significant effect (p=0.459), either. The persons with FH+ and FH- did not differ in the GRS (17.5±2.7 vs. 17.6±2.8, *p*=0.726). No statistical evidence for an interaction between GRS (or GRS_{SECR}) and randomization group on the incidence of type 2 diabetes was found (p=0.656 or 0.340 for the interaction).

Predictors of the incidence of type 2 diabetes. In the Cox regression analysis including GRS (19 SNPs), FH and randomization group, adjusted for age, BMI, sex and center, only the intervention group had a significant effect on the incidence of diabetes (Table 2A). A further Cox regression analysis including age, sex, BMI, fasting and 2-h glucose and fasting and 2-h insulin at baseline, GRS (as a continuous variable), FH, randomization group, and study center in the model was performed to determine the predictors of the incidence of type 2 diabetes during the entire follow-up period (Table 2B). It showed that fasting and 2-h plasma glucose, fasting insulin and the randomization group predicted significantly the development of diabetes. Fasting glucose was the strongest predictor ($p=2.2 \times 10^{-10}$). This could be explained by the inclusion criteria of the study, comprising only subjects with IGT. However, when the 1-year changes of

metabolic variables were added in the model baseline fasting and 2-h glucose, baseline fasting insulin and the changes in 2-h glucose and insulin predicted the incidence of diabetes (Table 2C). Neither FH nor GRS were significant predictors of the development of type 2 diabetes, and the effect of the intervention became non-significant (HR 0.74, p=0.106) due to the fact that the effect of lifestyles surely was mediated through glucose and insulin metabolism.

CONCLUSIONS

In the present study we wanted to investigate whether the positive family history *per se*, or the genetic risk variants and GRS based on 19 known type 2 diabetes-risk SNPs, modulated the effects of lifestyle intervention in the DPS participants. Family history did not affect the result of lifestyle intervention during the entire follow-up. We did not observe any aggregation of known genetic risk variants in persons with FH+ nor did genetic risk variants modify the incidence of diabetes. Based on different analyses, besides the intervention, fasting and 2-h plasma glucose and fasting insulin at baseline, and the 1-year changes of 2-h plasma glucose and 2-hour insulin were the main determinants of the development of diabetes during the follow-up, independent of the effects of genetic risk variants and FH.

Although the participants with FH+ seemed to have a lower incidence of diabetes than those with FH- during the first 4 years of follow-up when the active intervention was carried out, this early difference disappeared during the entire follow-up. The seemingly better early response could be explained by the fact that individuals with FH+ may be more aware of the risk of diabetes than others (21) and thus more motivated, as suggested also by their greater decrease in total caloric intake during the first year of intervention (p=0.012). Also, the mean 1-year change in the 2-h plasma glucose values was greater among the participants with FH+ in the lifestyle intervention group. It should be noticed that at baseline no differences were found in any clinical or biochemical measurements, which could explain the present findings of the differences during the intervention phase in the incidence of diabetes between individuals with FH+ and FH-.

The known genetic risk variants were not associated with the family history of diabetes. However, this may not be an unexpected finding because it is known that risk loci confer only 10% of the risk of type 2 diabetes (2, 22). Furthermore, all participants in the DPS had screened IGT based on two OGTT and over 60 % had a positive family history, which also might indicate an aggregation of genetic risk variants. In general population a positive family history varies from 25 to 40% depending on selection of populations in different studies (4, 12, 13, 14). It could be argued that a small sample size could explain why no significant association between genetic risk variants and family history or the type 2 diabetes risk was found. However, this may not be a case, because in regression analyses not even a trend to an association with the diabetes risk was found. It is of note that the total number of diabetes cases was 185 during the entire follow-up. This figure is almost comparable to 255 cases in the Framingham Offspring Study (5) including 2377 participants and with 28 years of follow-up. In that study the adjusted C-statistic was 0.595 without the genotype score and 0.615 with the score (p=0.11). In a larger study on Swedish and Finnish cohorts including altogether 18 831 individuals (4), of whom 2201 developed diabetes during a median follow-up of 23.5 years, the addition of specific genetic information to clinical factors slightly improved the prediction of future diabetes, from 0.74 to 0.75 (the area under the receiver-operating characteristic curve), however, the p-value was significant (p=1.0 x

10^{-4}). These results are in line with the Health Professionals Follow-up Study and Nurses' Health Study (6) applying case-control study design, where genetic risk score based on 10 polymorphisms in 9 loci increased the predictive value from 0.78 to 0.79 ($p<0.001$). In the latter study, however, glucose values were not included into the analyses (6). Interestingly, in both the DPP and DPS, where gene-lifestyle interactions have been examined, lifestyle changes abolished the increased risk of type 2 diabetes in the carriers of the risk allele at *TCF7L2* locus (9, 10). No other studies have used a similar approach. Thus, lifestyle intervention *per se*, at least in part, seems to abolish the genetic risk associations observed in observational cross-sectional and longitudinal studies.

The main predictors of the incidence of type 2 diabetes in our study were the lifestyle intervention, fasting and 2-h glucose, fasting insulin at baseline, and 1-year change in 2-h glucose and 2-h insulin. The finding that the 1-year changes in the 2-h glucose and insulin levels were powerful predictors of diabetes, whereas the 1-year change in fasting glucose level, which reflects insulin secretion mainly, did not contribute to the success rate of prevention, suggests a significant role of an improvement of insulin sensitivity along with weight reduction. Indeed, in a sub-study of DPS, there was a marked improvement of insulin sensitivity based on IVGTT along with weight loss, but only small changes were found in insulin secretion (23). Overall, these results show that an elevation of fasting glucose with poor insulin secretion capacity, and the degree of insulin resistance and obesity remain the main predictive factors among known risk factors for type 2 diabetes. We cannot exclude the possibility that the known genetic risk variants could have been operative in earlier phase of development of diabetes, but along with this line also the changes in lifestyle might be more effective in earlier phases of this disease.

Since insulin secretion and insulin sensitivity are not independent of each other, both mechanisms could be operative when searching biological explanations for the markedly lowered risk of diabetes in the prevention trials like the DPS. It has been hypothesized that lifestyle intervention may have beneficial effects on insulin secretion avoiding the exhaustion of beta-cells and thus delaying the progression of disturbed insulin secretion capacity. Because the decrease in the 2-h glucose and insulin had a marked impact on the risk reduction of diabetes we believe that an improvement in insulin sensitivity and perhaps concomitant recovery of beta-cell sensitivity to glucose (24) could mainly explain the observed beneficial effects of changing lifestyles on the diabetes risk.

To conclude, conventional risk factors and lifestyle changes known to decrease the risk of diabetes are the most important predictors of type 2 diabetes in persons with IGT, and lifestyle changes overcome the impact of the known genetic and familial risk. This information is important both for health professionals and persons at increased risk for type 2 diabetes. Our results in conjunction with some former population based studies and the DPP genetic studies indicate that genetic risk testing at this point may not offer much additional information applicable to prevention strategies of type 2 diabetes to that obtained from patients' family history and the well known clinical risk markers.

Author contributions. MU and JT are the principal investigators of the DPS. MU and AS wrote the manuscript, AS and MP analyzed the data, JT, JL, MU, S-KK, SA, P I-P and JGE participated in the data collection and interpretation of the results, ML was responsible for genetic analyses and contributed to the interpretation of the results.

All authors have seen the final version of the manuscript and have commented on it before the acceptance of the manuscript.

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Table 1. Baseline characteristics, diet, and physical activity of the DPS participants by family history of type 2 diabetes.

	Family history +	**Family history -**	**p-value**
N, men/women	327, 95/231	195, 76/119	
Age, years	55 (7)	56 (7)	**0.012**
Men, BMI kg/m2	30.1 (3.8)	29.6(3.3)	0.365
Women, BMI kg/m2	32.1(5.0)	31.4(4.3)	0.185
Fasting glucose, mmol/l	6.1(0.7)	6.2(0.8)	0.737
2-h glucose, mmol/l	8.9(1.4)	8.9(1.6)	0.897
Fasting insulin, mU/l	15(7)	14(8)	0.381
2-h insulin, mU/l	96 (60)	94 (73)	0.282
HOMA-IR	4.2 (2.3)	4.0 (2.3)	0.250
HOMA-B	120 (67)	115 (67)	0.217
Drug treatment for hypertension, %	28.8	30.4	0.692
CVD at baseline	7.9	8.6	0.866
Energy intake, kcal/d	1788 (529)	1705 (511)	0.079
Fat, E %	36.6 (6.6)	36.4 (6.6)	0.724
Saturated fats, E %	16.6 (4.2)	16.5 (4.2)	0.784
Carbohydrates, E %	43.5 (6.9)	43.2 (7.4)	0.664
Protein, E %	17.5 (3.5)	17.8 (3.3)	0.364
Dietary fibre, g/1000kcal	11.6 (3.7)	11.9 (4.4)	0.305
Total LTPA, h/wk	6.6 (5.6)	8.1 (6.5)	**0.007**
Moderate-vigorous LTPA, h/wk	2.6 (3.0)	2.9 (3.2)	0.279

Means (SD) are shown for continuous variables. CVD, History of cardiovascular disease. LTPA, Leisure time physical activity

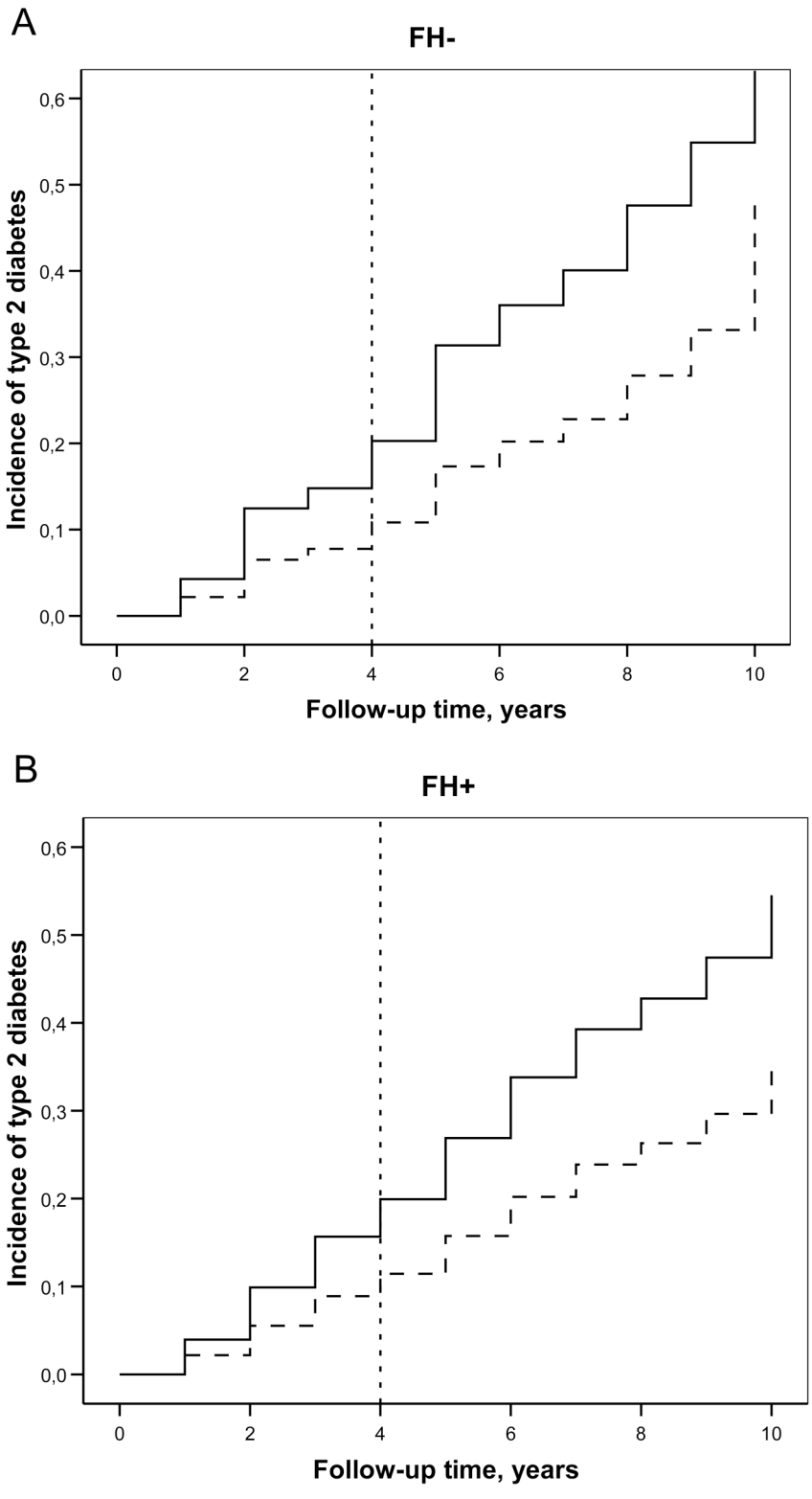
Table 2. Effect of family history of diabetes, genetic risk score, intervention, and clinical variables on the incidence of type 2 diabetes. A, B, C represent alternative models: A – effects of family history, genetic risk score, and intervention without clinical variables, B - including clinical variables at baseline, C – including 1-year changes in these variables (Cox regression, all models are adjusted for age, gender, baseline BMI, and study center).

A	**HR**	**95% CI**	**p value**
Family history of T2DM	0.78	(0.57; 1.06)	0.118
Genetic risk score (19 SNPs)	1.04	(0.90; 1.20)	0.617
Intervention vs. control group	0.55	(0.41; 0.75)	**1.2E-04**
B			
Family history of T2DM	0.80	(0.57; 1.11)	0.180
Genetic risk score (19 SNPs)	1.02	(0.87; 1.18)	0.840
Intervention vs. control group	0.52	(0.38; 0.72)	**5.9E-05**
Fasting glucose (baseline)	1.69	(1.44; 1.99)	**2.2E-10**
2-h glucose (baseline)	1.35	(1.14; 1.60)	**0.0005**
Fasting insulin (baseline)	1.25	(1.03; 1.53)	**0.025**
2-h insulin (baseline)	0.81	(0.63; 1.02)	0.076
BMI (baseline)	1.17	(0.98; 1.39)	0.077
C			
Family history of T2DM	0.92	(0.65; 1.29)	0.609
Genetic risk score (19 SNPs)	1.02	(0.88; 1.18)	0.797
Intervention vs. control group	0.74	(0.52; 1.06)	0.106
Fasting glucose (baseline)	1.93	(1.57; 2.38)	**3.5E-10**
Δ Fasting glucose (1-year change)	1.15	(0.96; 1.38)	0.129
2-h glucose (baseline)	1.69	(1.39; 2.05)	**9.1E-08**
Δ 2-h glucose (1-year change)	1.62	(1.32; 1.98)	**3.4E-06**
Fasting insulin (baseline)	1.35	(1.06; 1.73)	**0.015**
Δ Fasting insulin (1-year change)	1.18	(0.97; 1.44)	0.103
2-h insulin (baseline)	1.05	(0.79; 1.39)	0.755
Δ 2-h insulin (1-year change)	1.36	(1.05; 1.75)	**0.018**
BMI (baseline)	1.18	(0.99; 1.40)	0.061
Δ BMI (1-year change)	1.19	(0.98; 1.44)	0.084

For dichotomous variables, hazard ratios are shown for the intervention group, positive family history of type 2 diabetes, and males. For continuous variables, hazard ratios are expressed as unit change per 1 standard deviation.

Figure 1. Incidence of type 2 diabetes during the intervention period of 4 years (A) (end indicated by a vertical line) and during the entire follow-up period (B) by family history and randomization group (intervention vs. control) in the DPS. Solid line is for the control group.
During the intervention follow-up of 4 years on average, intervention had significant effect on the incidence of type 2 diabetes in FH+ (p=0.0002, p*=0.0008) but not in FH- group (p=0.61, p*=0.11). During the entire follow-up, intervention had an effect in both FH+ (p=0.0004, p*=0.002) and FH- group (p=0.13, p*=0.006). p is from Kaplan-Meier analysis, p* after adjustment for age, sex, baseline BMI, baseline fasting glucose, and study center in Cox regression model.

Figure


A
FH-
Incidence of type 2 diabetes
0,0
0,1
0,2
0,3
0,4
0,5
0,6
0
2
4
6
8
10
Follow-up time, years
B
FH+
Incidence of type 2 diabetes
0,0
0,1
0,2
0,3
0,4
0,5
0,6
0
2
4
6
8
10
Follow-up time, years