Association of Depressive Symptoms With Impaired Glucose Regulation, Screen-Detected, and Previously Known Type 2 Diabetes

Findings from the Finnish D2D Survey

PEKKA MÄNTYSELKÄ, MD, PHD[1,2]
KATARIINA KORNILOFF, MSC[3,4]
TIMO SAARISTO, MD[5,6]
HANNU KOPONEN, MD, PHD[7]
JOHAN ERIKSSON, MD, PHD[8,9,10,11]
HANNU PUOLIJOKI, MD, PHD[12]
MARKKU TIMONEN, MD, PHD[13]
JOUKO SUNDVALL, MSC[8]
HANNU KAUTIAINEN, MSC[14,15]
MAUNO VANHALA, MD, PHD[1,15]

OBJECTIVE — To study the association between impaired glucose regulation (IGR), screen-detected type 2 diabetes, and previously known diabetes and depressive symptoms.

RESEARCH DESIGN AND METHODS — Altogether, 2,712 participants from three hospital districts in Finland attended a health examination. Cutoff scores ≥10 and ≥16 in the 21-item Beck Depression Inventory (BDI-21) were used for depressive symptoms. The participants were defined as having known diabetes if they reported diabetes. An oral glucose tolerance test was used to detect normal glucose regulation (NGR), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and screen-detected diabetes. The participants were defined as having IGR if they had IFG or IGT.

RESULTS — Prevalence of depressive symptoms, defined as a BDI-21 cutoff score ≥10, was 14.4% for those with NGR, 13.7% for those with IGR, 14.8% for those with screen-detected diabetes, and 26.4% for those with previously known diabetes. The corresponding prevalences for a cutoff score ≥16 were 3.4, 3.4, 4.2, and 7.5%, respectively. Compared with NGR and adjusted for demographic, lifestyle, and biological factors, the odds ratios for IGR, screen-detected diabetes, and previously known diabetes were 0.91 (95% CI 0.69–1.20), 0.70 (0.45–1.08), and 1.35 (0.84–2.15), respectively, for a cutoff score ≥10. For a cutoff score ≥16, the corresponding odds ratios were 1.05 (0.62–1.76), 0.87 (0.40–1.90), and 1.56 (0.69–3.50), respectively.

CONCLUSIONS — Participants with diagnosed diabetes had a higher prevalence of depressive symptoms than participants with NGR, IGR, and previously unknown diabetes. When potential confounding factors were included in the analysis, previously known diabetes was not significantly associated with depressive symptoms.

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From the [1]School of Medicine, Unit of Primary Health Care, University of Eastern Finland, Kuopio, Finland; the [2]Unit of Family Practice, Kuopio University Hospital, Kuopio, Finland; the [3]Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland; the [4]Department of Physical and Rehabilitation Medicine, Central Finland Health Care District, Jyväskylä, Finland; the [5]Finnish Diabetes Association, Tampere, Finland; the [6]Pirkanmaa Hospital District, Pirkanmaa, Finland; the [7]Department of Psychiatry, University of Kuopio and Kuopio University Hospital, Kuopio, Finland; the [8]National Institute for Health and Welfare, Helsinki, Finland; the [9]Unit of General Practice, Helsinki University Hospital, Helsinki, Finland; the [10]Vasa Central Hospital, Vaasa, Finland; the [11]Folkhälsan Research Center, Helsinki, Finland; the [12]South Ostrobothnia Hospital District, Seinäjoki, Finland; the [13]Institute of Health Sciences, University of Oulu, Oulu, Finland; the [14]ORTON Orthopaedic Hospital, ORTON Foundation, Helsinki, Finland; and the [15]Unit of Family Practice, Central Hospital of Central Finland, Jyväskylä, Finland.

Corresponding author: Pekka Mäntyselkä, pekka.mantyselka@uef.fi.

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It is widely recognized that depression is more common among people with diabetes than in the general population (1). However, previous studies (2–10) that have assessed the relationship between depressive symptoms and impaired glucose tolerance (IGT) or diabetes have been inconsistent. A German study (4) that included 4,597 subjects and a Dutch study (2) that included 4,747 participants found no association between type 2 diabetes and depressive symptoms. In a general-practice setting study that included 2,849 male and 3,160 female subjects, depression was not more prevalent in people with screen-detected diabetes or impaired glucose regulation (IGR) than in people with normal glucose regulation (NGR) (5). Contrary to these studies, within the Hertfordshire Cohort Study (6) there was a relationship between depression scores and diagnosed and previously undiagnosed diabetes. A U.S. study (8) including 4,293 U.S. veterans indicated that men with undiagnosed type 2 diabetes had nearly double the odds of major depression compared with those with normal fasting glucose.

In 1992, it was stated about the relationship between depression and diabetes that "the etiology is unknown but is probably complex; and biological, genetic, and psychological factors remain as potential contributors. Several neuroendocrine and neurotransmitter abnormalities common to both depression and diabetes have been identified, adding to etiological speculations" (11). It has been suggested that stress-induced activation of the hypothalamic-pituitary-adrenal axis may result in the development of metabolic abnormalities and depression (12). In addition, possible neuroendocrine abnormalities associated with both diabetes and depressive symptoms may include abnormalities in vitamin B_{12} and sex hormone–binding globulin (SHBG) levels. Low vitamin B_{12} levels have been found to relate to type 2 diabetes (13) and depressive

symptoms (14–16). Low levels of SHBG may predict diabetes (17). SHBG binds circulating sex hormones, which have been suggested to be associated with depressive symptoms (18). In addition to these biological factors, the observed association between diabetes and depressive symptoms could be a reflection of the burden of diabetes and comorbidities.

In the present study, our aim was to analyze the prevalence of depressive symptoms in people with NGR, IGR (including impaired fasting glycemia and impaired glucose tolerance), screen-detected (previously unknown) diabetes, and previously known type 2 diabetes. Furthermore, our aim was to study the association between glucose tolerance and depressive symptoms, taking into account potential confounding demographic and biological factors as well as comorbidity.

RESEARCH DESIGN AND METHODS

The Finnish Type 2 Diabetes (FIN-D2D) Population Survey was conducted in the hospital districts of Pirkanmaa, southern Ostrobothnia, and central Finland between October and December 2007. A random sample of 4,500 people, aged 45–74 years, stratified according to sex, 10-year age-groups (45–54, 55–64, and 65–74 years), and geographical areas, was selected from the National Population Register in August 2007. The study participants were invited by mail to a health examination. A total of 2,868 subjects (64%) participated in the health examination. Information on glucose tolerance status was available from 2,712 participants. All the participants signed an informed consent form. Ethical permission for the study was granted by the ethics committee of the Hospital District of Helsinki and Uusimaa.

The participants attended a health examination conducted by a trained nurse in accordance with the multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) protocol (19). Fasting venous blood samples were drawn into a gel serum tube (Venosafe; Terumo Europe, Leuven, Belgium) that contained a clot activator for insulin, vitamin B_{12}, SHBG, tireotrophin-stimulating hormone (TSH), and high-sensitivity C-reactive protein (hs-CRP) and into a fluoride-citrate tube (Venosafe) for fasting plasma glucose (FPG). The serum and fluoride-citrate plasma were separated within 1 h by centrifuging at 2,200*g* for 11 min at room temperature. After which the serum and plasma were aliquoted into storage tubes (Nalgene; Thermo Fisher Scientific, Rochester, NY) and stored locally at a minimum of −20°C and then transported frozen to the National Institute for Health and Welfare, where all the samples were stored at −70 C° until analyzed. All the samples were analyzed in the same laboratory at the National Institute for Health and Welfare using an Architect ci8200 analyzer (Abbott Laboratories, Abbott Park, IL) for insulin, vitamin B_{12}, SHBG, hs-CRP, and FPG and an Axsym analyzer (Abbott) for TSH. The following methods were used: the chemiluminescent microparticle immuno method (Abbott) for measuring serum insulin, vitamin B_{12}, and SHBG; the microparticle enzyme immuno method (third generation; Abbott) for measuring serum TSH; the latex immunoturbidimetric method (Sentinel Diagnostics, Milan, Italy) for measuring serum hs-CRP; and the enzymatic hexokinase method for plasma glucose. To standardize its measurements, the laboratory has taken part in External Quality Assessment Schemes organized by Labquality (Helsinki, Finland). During the course of the study, the coefficient of variation of the different control levels ($n = 3$) between days (means ± SD) for insulin, vitamin B_{12}, SHBG, TSH, hs-CRP, and FPG measurements were 2.3 ± 0.5%, 6.7 ± 2.1%, 4.8 ± 0.2%, 5.0 ± 1.2%, 2.9 ± 0.8%, and 1.1 ± 0.1%, respectively. A 2-h 75-g standard oral glucose tolerance test (OGTT) was conducted. Height (in cm) and weight (in kg) were measured with light clothing and without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters.

We defined impaired glucose tolerance (IGT) (FPG level <7.0 mmol/l and a 2-h glucose value of 7.8–11.0 mmol/l) and impaired fasting glucose (IFG) (FPG 6.1–6.9 mmol/l and a 2-h glucose value <7.8 mmol/l). IFG and IGT were grouped together as IGR. Participants were defined as having screen-detected type 2 diabetes if they had not previously been diagnosed with diabetes and their FPG was ≥7.0 mmol/l or 2-h glucose ≥11.1 mmol/l at the health examination. Participants were defined as having previously known type 2 diabetes if they reported a history of diabetes. The participants were defined as having NGR if they had not been diagnosed with diabetes and if their FPG was <6.1 mmol/l and 2-h glucose <7.8 mmol/l. Accordingly, the glucose regulation categories were NGR, IGR, screen-detected diabetes, and previously known diabetes.

Depressive symptoms were assessed using the 21-item Beck Depression Inventory (BDI-21) (20). The items in the BDI-21 are summed into a total score (0–63), with higher scores indicating more severe depressive symptoms. The applied cutoff score for depressive symptoms was ≥10. In addition, we used a cutoff score of ≥16 to increase specificity for depression (21). Current use of antidepressive medication was asked in the questionnaire.

The participants reported their leisure-time physical activity (LTPA) into three categories: *1*) low: almost completely inactive (e.g., reading, watching television, or doing some minor physical activity); *2*) moderate: some physical activity more than 4 h a week (e.g., walking, cycling, light gardening, fishing, or hunting); and *3*) high: vigorous physical activity more than 3 h a week or regular exercise or competitive sports several times a week (e.g., running, jogging, skiing, swimming, ball games, or heavy gardening). Current smoking was assessed and dichotomized (no or yes). Education was assessed according to years of education. Marital status was asked, and marriage or common-law marriage were combined as cohabiting and single, divorced, or widowed were combined as living alone.

The participants were asked about chronic diseases and disorders diagnosed by a physician. Chronic pulmonary diseases included asthma and chronic obstructive pulmonary disease. Heart diseases included ischemic heart disease and chronic heart failure. Chronic musculoskeletal disorder included arthritis and other chronic joint disorders and chronic back disease. In addition, the presence of any cancer was asked.

The descriptive statistics are presented with means or medians and SDs or interquartile range (IQR) for continuous variables. Numbers and percentages are presented for categorical variables. The crude prevalence of depressive symptoms was calculated, and CIs for the percentages were obtained by exact (Clopper-Pearson) methods. The relationship between glucose tolerance status and depressive symptoms was estimated using multivariate logistic regression analysis. In addition to age, sex, physical activity, BMI, education, and marital status, we included hs-CRP, TSH, SHBH, vitamin B_{12}, and the comorbidity sum (including

Table 1—*Characteristics of the study population according to glucose regulation status*

	NGR	IGR	Screen-detected type 2 diabetes	Previously known type 2 diabetes
n	1,268	1,001	284	159
Female (%)	795 (63)	443 (44)	118 (42)	67 (42)
Age (years)	58 ± 8	60 ± 8	62 ± 8	64 ± 7
BMI (kg/m^2)	26.1 ± 4.2	27.9 ± 4.5	29.9 ± 4.9	31.8 ± 6.2
FPG (mmol/l)	5.7 ± 0.82	6.3 ± 0.38	7.3 ± 1.5	8.4 ± 2.1
Serum insulin (mU/l)	5.4 (4.1–7.2)	7.3 (5.4–10.1)	9.9 (6.9–14.2)	11.9 (7.2–16.9)
Hs-CRP (mg/l)	2.1 ± 4.3	3.1 ± 8.5	3.6 ± 7.7	3.4 ± 10.9
Serum vitamin B_{12} (pmol/l)	333 ± 123	329 ± 202	324 ± 116	266 ± 136
SHBG (nmol/l)	66.5 ± 31.6	56.3 ± 27.3	53.0 ± 27.3	48.0 ± 28.8
Serum TSH (mU/l)	3.26 ± 2.37	2.99 ± 1.67	3.10 ± 1.91	3.32 ± 2.77
LTPA				
Low	206 (16)	179 (18)	75 (26)	51 (32)
Moderate	737 (58)	597 (60)	172 (61)	90 (57)
High	325 (26)	225 (22)	37 (13)	18 (11)
Marriage or common-law marriage	966 (77)	783 (79)	203 (71)	119 (75)
Education in years	11 (9–15)	10 (8–13)	10 (8–12)	10 (8–12)
Current smoking	289 (23)	226 (23)	54 (19)	28 (18)
Antidepressive medication	64 (5)	53 (5)	23 (8)	11 (7)
Chronic pulmonary disease	95 (8)	70 (7)	30 (11)	29 (18)
Chronic heart disease	82 (6)	98 (10)	38 (13)	39 (25)
Chronic musculoskeletal disorder	371 (30)	306 (31)	96 (35)	64 (41)
Cancer	29 (2)	27 (3)	10 (4)	6 (4)

Data are means ± SD, median (IQR), *n*, or *n* (%).

chronic musculoskeletal, pulmonary and heart diseases, and cancer) in the multivariate analysis as potential factors interfering with the relationship between glucose tolerance status and depressive symptoms. Stata statistical software, release 11.0 (StataCorp, College Station, TX), was used for the analyses.

RESULTS — Of all the participants, 1,268 had NGR (47%), 1,001 had IGR (37%), 284 had screen-detected diabetes (10%), and 159 had previously known diabetes (6%). The descriptive characteristics of the study population according to these groups are presented in Table 1. The proportion of female subjects was highest in the NGR group. The people with screen-detected diabetes and previously known diabetes were older than those with NGR or IGR. In the people with previously known diabetes, BMI, hs-CRP, FPG, and fasting insulin were highest, but SHBG and vitamin B_{12} were lowest. A low level of LTPA and use of an antidepressant were most common among the people with diabetes. Smoking was least prevalent among the people with screen-detected and previously known diabetes. Compared with the people with NGR or IGR, the prevalence of chronic pulmonary disease was twofold and the prevalence of heart disease was fourfold among the people with previously known diabetes.

The median (IQR) BDI-21 scores were 4 (1–7), 3 (1–7), 4 (1–8), and 6 (3–10) for the people with NGR, IGR, screen-detected, and previously known diabetes, respectively. The crude prevalence of depressive symptoms with a cutoff score ≥10 was higher among the people with previously known diabetes (n = 42) (26.4% [95% CI 19.7–34.0]) than among the people with NGR (n = 183) (14.4% [12.5–16.5%]), IGR (n = 137) (13.7% [11.6–16.0]), and screen-detected diabetes (n = 42) (14.8% [10.9–19.5]) ($P < 0.001$, previously known diabetes vs. other groups). These prevalences were similar among the people with NGR, IGR, and screen-detected diabetes ($P = 0.84$). When a cutoff score of ≥16 was used, the corresponding prevalence was 3.4% for NGR (n = 43) (95% CI 2.5–5.4.5), 3.4% for IGR (n = 34) (95% CI 2.3–4.7), 4.2% for screen-detected diabetes (n = 12) (95% CI 2.2–7.3), and 7.5% for previously known diabetes (n = 12) (95% CI 4.0–12.8) ($P = 0.009$, previously known diabetes vs. other groups). These prevalences were similar among the people with NGR, IGR, and screen-detected diabetes ($P = 0.77$).

In the multivariate logistic regression analysis adjusted with sosiodemographic, lifestyle, and biological factors as well as comorbidity, with a cutoff score ≥10 for depressive symptoms, IGR, screen-detected diabetes, and previously known diabetes were not significantly associated with depressive symptoms when compared with NGR (Table 2). The findings were quite similar for both cutoff scores. However, when a BDI-21 cutoff score ≥16 was used, the odds ratio for diabetes was higher but the CIs were broader. LTPA, living alone, comorbidity, and depressive medication were associated with depressive symptoms for both cutoff scores, but female sex was associated with depressive symptoms only when a cutoff score ≥10 was used.

CONCLUSIONS — The present population-based study indicates that people with previously known type 2 diabetes have depressive symptoms more commonly than people with IGR or NGR or previously unknown (screen-detected) type 2 diabetes. However, when other potential confounding factors were included in the analysis, previously known diabetes was not significantly associated with depressive symptoms. Of these factors, female sex (not for a BDI-21 cutoff score ≥16), physical inactivity, living alone, comorbidities, and antidepressive medication were associated with depressive symptoms. Vitamin B_{12}, TSH, or SHBG were not associated with depressive symptoms, although vitamin B_{12} and SHBG levels were lower among the people with known diabetes. The crude prevalence of depressive symptoms among the participants with previously unknown diabetes was similar to that in the participants with normal or impaired glucose regulation.

Our results are in line with previous studies suggesting that depression is not more prevalent among people with screen-detected diabetes or IGR (2,4,22) and that there is no association between depressive symptoms and unrecognized glucose intolerance (3). Findings from the

Table 2—*Multivariate logistic regression analysis with depressive symptoms (BDI-21 ≥10 and BDI-21 ≥16) as an outcome*

	BDI-21 ≥10		BDI-21 ≥16	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Glucose regulation				
NGR	1.00 (Reference)		1.00 (Reference)	
IGR	0.91 (0.69–1.20)	0.50	1.05 (0.62–1.76)	0.86
Screen-detected type 2 diabetes	0.70 (0.45–1.08)	0.10	0.87 (0.40–1.90)	0.73
Previously known type 2 diabetes	1.35 (0.84–2.15)	0.22	1.56 (0.69–3.50)	0.28
Female	0.69 (0.53–0.89)	0.004	0.82 (0.51–1.33)	0.43
Age (years)		0.056*		0.077*
45–54	1. 00 (Reference)		1.00 (Reference)	
55–64	0.86 (0.63–1.19)		0.58 (0.33–1.02)	
65–74	1.37 (0.98–1.91)		0.56 (0.30–1.06)	
BMI	1.00 (0.98–1.03)	0.86	1.02 (0.98–1.07)	0.29
hs-CRP	1.00 (0.99–1.02)	0.61	0.99 (0.96–1.03)	0.68
Vitamin B_{12}	1.00 (1.00–1.00)	0.19	1.00 (1.00–1.00)	0.28
SHBG	1.00 (1.00–1.00)	0.82	1.00 (0.99–1.01)	0.98
LTPA		<0.001*		0.002*
Low	1.00 (Reference)		1.00 (Reference)	
Moderate	0.47 (0.35–0.62)		0.43 (0.27–0.69)	
High	0.29 (0.19–0.43)		0.28 (0.13–0.60)	
Marriage or common-law marriage	0.67 (0.51–0.87)	0.003	0.49 (0.31–0.78)	0.002
Education (per year)	0.97 (0.94–1.01)	0.14	0.98 (0.92–1.04)	0.50
Smoking	1.27 (0.95–1.69)	0.11	1.42 (0.86–2.33)	0.17
Comorbidity sum	1.71 (1.46–2.01)	< 0.001	1.59 (1.19–2.12)	0.002
Antidepressive medication	6.28 (4.33–9.12)	<0.001	9.57 (5.87–15.60)	<0.001

**P* value for linearity across the groups.

Whitehall II Study (7) indicated that people with low and very high glucose levels had elevated depression scores, but low depression scores were observed in both normal and prediabetic ranges of fasting glucose. A contradictory finding was published recently (8). That study suggested that a U-shaped association between fasting glucose and depression does not exist. Further, the study found that people fulfilling type 2 diabetes criteria were more depressed than healthy people, regardless of awareness of the disease. OGTT was not used in that study, and it included only men who were younger (mean age 39 years) than the participants in our study. In addition, that study population was exposed to long-lasting stressful circumstances in the Vietnam War, which may have had an influence on the occurrence of diabetes and depression.

Compared with low physical activity, moderate and especially high physical activity were inversely related to depressive symptoms. Previously, a systematic review (23) has reported an inverse association between physical activity and the likelihood of depressive symptoms. The association between smoking and depressive symptoms did not reach statistical significance, which is line with a previous population-based study (4). In that study, living alone was related to depressive symptoms, which was clearly indicated in the present study as well. These findings suggest that at least part of the increased level of depressive symptoms among the people with diabetes is explained by lifestyle factors and marital status. Antidepressive medication was strongly associated with depressive symptoms, especially when a higher BDI-21 cutoff score was used. Antidepressive medication can be regarded as an indicator of depressive people, but this finding may also reflect suboptimal treatment of depression.

The present study was based on a population-based sample, and fasting plasma glucose was included in categorizing the participants. As expected, screen-detected diabetes fasting plasma levels were elevated in people with IGR and more elevated in people with screen-detected diabetes. Fasting plasma glucose levels were highest among people with previously known diabetes, which indicates suboptimal hyperglycemic control. A meta-analytic review (24) has shown that depression is associated with hyperglycemia in patients with diabetes. A recent study (25) provided support for the view that high diabetes-related distress and clinical depression are related to disease management variables, but only diabetes-related distress is positively linked to A1C and inversely to physical activity. In addition to sociodemographic factors, smoking, physical activity, and comorbidities, we included several potential biological confounding variables in our analysis. In this analysis vitamin B_{12}, TSH, and SHBG did not play a role in the relationship between depressive symptoms and glucose regulation.

Recent population-based studies (2,4) have indicated that there was no clear association between diabetes and depressive symptoms. In line with those studies, the present study indicated that comorbidities were significantly associated with depressive symptoms. The data of the present study showed that people with diabetes very often have other somatic diseases. Having a somatic comorbidity seemed to be strongly associated with depressive symptoms. Therefore, the findings of the present study support the view that an increased prevalence of depressive symptoms among people with diabetes is related by their excessive disease burden. However, the current study cannot rule out the possibility that common underlying physiological factors play a role.

Depressive symptoms were defined on the basis of self-reported data. A diagnostic interview was not undertaken, which can be regarded as a limitation of our study. However, a BDI with a cutoff score of 10 points has been shown to be a feasible instrument for depression screening (20), and a cutoff score of 16 points has been shown to be feasible for detecting depression among outpatients with diabetes (21). The present study was based on cross-sectional data, and, therefore, we are not able to draw any conclusions about causality. Further, we are not able to exclude the possibility that duration of disease is related to the present findings. The strength of this study is the large representative population sample of middle-aged men and women. Contrary

to previous population-based studies (2,4,8), we used the standard diagnostic procedure with OGTT in defining diabetes and glucose regulation abnormalities.

We conclude that compared with people with NGR or IGR, people with diagnosed type 2 diabetes more commonly had depressive symptoms. People with previously unknown diabetes did not differ from people with NGR or IGR. The findings of the present study support the hypothesis that an increased level of depressive symptoms among people with type 2 diabetes is related to their excessive disease burden, physical activity, and marital status.

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P.M. researched data, contributed to discussion, and wrote the manuscript. K.K. researched data, contributed to discussion, and reviewed/edited the manuscript. T.S. contributed to discussion and wrote the manuscript. H.K. contributed to discussion and reviewed/edited the manuscript. J.E. contributed to discussion and reviewed/edited the manuscript. H.P. researched data, contributed to discussion, and reviewed/edited the manuscript. M.T. contributed to discussion and reviewed/edited the manuscript. J.S. contributed to discussion and reviewed/edited the manuscript. H.K. researched data, contributed to discussion, and reviewed/edited the manuscript. M.V. researched data, contributed to discussion, and reviewed/edited the manuscript. All authors contributed substantially to the conception and design or analysis and interpretation of data and the drafting of the article or critical revision for important intellectual content.

FIN-D2D, the implementation project of the National Program for the Prevention of Type 2 Diabetes, was conducted in five Finnish hospital districts covering a population of 1.5 million during the years 2003–2008 (Saaristo T, Peltonen M, Keinänen-Kiukaanniemi S, Vanhala M, Saltevo J, Niskanen L, Oksa H, Korpi-Hyövälti E, Tuomilehto J, the FIN-D2D Study Group. National type 2 diabetes prevention program in Finland: FIN-D2D. Int J Circumpolar Health 2007;66:101–112; Saaristo TE, Barengo NC, Korpi-Hyövälti E, Oksa H, Puolijoki H, Saltevo JT, Vanhala M, Sundvall J, Saarikoski L, Peltonen M, Tuomilehto J. High prevalence of obesity, central obesity and abnormal glucose tolerance in the middle-aged Finnish population. BMC Public Health 2008;8:423). The main objective was to build up a nationwide program for the prevention of type 2 diabetes. FIN-D2D was initiated by the Finnish Diabetes Association with five Finnish hospital districts in collaboration with the national National Institute for Health and Welfare and the Ministry of Social Affairs and Health in cooperation with the FIN-D2D Study Group. The specific aims were to improve screening of people at risk for diabetes and detection of undiagnosed diabetes. Furthermore, intensified interventions of high-risk individuals were developed and tested as part of normal clinical practice in primary health care.

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