Association of depressive symptoms with impaired glucose regulation, screen-detected, and previously known type 2 diabetes – findings from the Finnish D2D survey

Running head: Depressive symptoms and glucose regulation

Pekka Mäntyselkä, MD, PhD1,2, Katarina Korniloff, MSc3,4, Timo Saaristo, MD5,6, Hannu Koponen, professor7, Johan Eriksson, professor8,9,10,11, Hannu Puolijoki, MD, PhD12, Markku Timonen, professor13, Jouko Sundvall, MSc8, Hannu Kautiainen, MSc14,15, Mauno Vanhala, professor1,15

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

Corresponding author
Pekka Mäntyselkä
e-mail: pekka.mantyselka@uef.fi

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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 2712 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 glycemia (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 NGR, 13.7% for IGR, 14.8% for screen-detected diabetes, and 26.4% for previously known diabetes. The corresponding prevalences for a cutoff score ≥ 16 were 3.4%, 3.4%, 4.2%, and 7.5%. 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).

Conclusions - Participants with diagnosed diabetes had depressive symptoms more commonly than participants with NGR, IGR, and previously unknown diabetes. When potential confounding factors were included in analysis, previously known diabetes was not significantly associated with depressive symptoms.

It is widely recognized that depression is more common among people with diabetes than in the general population (1). However, previous studies assessing the relationship between depressive symptoms and impaired glucose tolerance or diabetes have been inconsistent (2-10). A German study (4) including 4597 and a Dutch study (2) including 4747 participants found no association between type 2 diabetes and depressive symptoms. In a general practice setting study including 2849 males and 3160 females, depression was not more prevalent in people with screen-detected diabetes or impaired glucose regulation (IGR) than in people with normal glucose regulation (5). Contrary to these studies, within the Hertfordshire Cohort Study there was a relationship between depression scores and diagnosed and previously undiagnosed diabetes (6). A US study including 4293 US veterans indicated that men with undiagnosed type 2 diabetes had nearly double the odds of major depression compared with those with normal fasting glucose (8).

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 development of metabolic abnormalities and depression (12). In addition, possible neuroendocrine abnormalities associated with both diabetes
and depressive symptoms may include abnormalities in vitamin B₁₂ and sex-hormone-binding globulin (SHBG) levels. Low vitamin B₁₂ 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 co-morbidities.

In the present study our aim was to analyze the prevalence of depressive symptoms in people with normal glucose regulation (NGR), impaired glucose regulation (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 carried out in the hospital districts of Pirkanmaa, Southern Ostrobothnia, and Central Finland between October and December 2007. A random sample of 4500 people aged 45-74 years, stratified according to gender, 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 2868 persons (64%) participated in the health examination. Information on glucose tolerance status was available from 2712 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 carried out by a trained nurse according to the multinational monitoring of trends and determinants in cardiovascular disease (MONICA) protocol (19). Fasting venous blood samples were drawn into a gel serum tube (Venisafe, Terumo Europe, Leuven, Belgium) containing a clot activator for insulin, vitamin B₁₂, sex-hormone-binding globulin (SHBG), tyroethropin-stimulating hormone (TSH), and high-sensitivity c-reactive protein (hs-CRP) and into a fluoride-citrate tube (Venisafe) for fasting plasma glucose (FPG). The serum and fluoride-citrate plasma were separated within one hour by centrifuging at 2200 g for 11 min at room temperature. After that the serum and plasma were aliquoted into storage tubes (Nalgene, Thermo Fisher Scientific, Rochester, NY, USA) 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, USA) for insulin, vitamin B₁₂, 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 B₁₂, and SHBG; the microparticle enzyme immuno method (3rd generation, Abbott) for measuring serum TSH; the latex immunoturbidimetric method (Sentinel Diagnostics, Milan, Italy) for measuring serum hsCRP; 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 (mean ± SD) for insulin, vitamin B₁₂, SHBG, TSH, hs-CRP, and FBG 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 two-hour 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 kg/m².

We defined impaired glucose tolerance (IGT, FPG level < 7.0 mmol/l and a two-hour glucose value of 7.8-11.0 mmol/l) and impaired fasting glycemia (IFG, FPG 6.1-6.9 mmol/l and a two-hour glucose value < 7.8 mmol/l). IFG and IGT were grouped together as impaired glucose regulation (IGR). The participants were defined as having screen-detected type 2 diabetes if they had not previously been diagnosed with diabetes and their FPG ≥ 7.0 mmol/l or 2-h glucose ≥ 11.1 mmol/l at the health examination. The 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 < 6.1 mmol/l and a 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 ≥ 16 in order 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, 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, 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 standard deviation (SD) 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 B₁₂, and the comorbidity sum (including chronic musculoskeletal, pulmonary and heart diseases, and cancer) in the multivariate analysis as potential factors interfering with the relationship between
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glucose tolerance status and depressive symptoms. Stata statistical software, release 11.0 (StataCorp, College Station, Texas), was used for the analyses.

RESULTS
Out of all the participants, 1268 had NGR (47%), 1001 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 females 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, hsCRP, FPG, and fasting insulin were highest, but SHBG and vitamin B₁₂ 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. 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 versus other groups). These prevalences were similar among the people with NGR, IGR, and screen-detected diabetes (P = 0.84). When a cutoff score ≥ 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 versus 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 socioeconomic, 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 bigger but the confidence intervals were broader. LTPA, living alone, comorbidity, and depressive medication were associated with depressive symptoms for both cutoff scores, but female gender was associated with them only when a cutoff score ≥ 10 was used.

CONCLUSIONS
The present population-based study indicates that people with previously known type 2 diabetes mellitus have depressive symptoms more commonly than people with impaired or normal glucose regulation 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 gender (not for a BDI-21 cutoff score ≥ 16), physical inactivity, living alone, comorbidities, and antidepressive medication were associated with depressive symptoms. Vitamin B₁₂, TSH, or SHBG were not associated with depressive symptoms, although vitamin B₁₂...
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 Whitehall II study 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 (7). 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 has reported an inverse association between physical activity and the likelihood of depressive symptoms (23). The association between smoking and depressive symptoms did not reach statistical significance, which is in 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 has shown that depression is associated with hyperglycemia in patients with diabetes (24). A recent study 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 (25).

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 have indicated that there was no clear association between diabetes and depressive symptoms (2, 4). 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 ten 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 normal or impaired glucose regulation, people with diagnosed type 2 diabetes more commonly had depressive symptoms. People with previously unknown diabetes did not differ from people with normal or impaired glucose regulation. 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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REFERENCES
1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069-1078.
2. Knol MJ, Heerdink ER, Egberts AC, Geerlings MI, Gorter KJ, Numans ME, Grobbee DE, Klungel OH, Burger H. Depressive symptoms in subjects with diagnosed and undiagnosed type 2 diabetes. Psychosom Med 2007;69:300-5.
3. Rhee MK, Musselman D, Ziemer DC, Vaccarino V, Kolm P, Weintraub WS, Caudle JM, Varughese RM, Irving JM, Phillips LS. Unrecognized glucose intolerance is not associated with depression. Screening for Impaired Glucose Tolerance study 3 (SIGT 3). Diabet Med 2008 ;25:1361-1365.
4. Icks A, Kruse J, Dragano N, Broecker-Preuss M, Slomiany U, Mann K, Jöckel KH, Erbel R, Giani G, Moebus S; Heinz Nixdorf Recall Study Investigator Group. Are symptoms of depression more common in diabetes? Results from the Heinz Nixdorf Recall study. Diabet Med 2008;25:1330-1336.
5. Aujla N, Abrams KR, Davies MJ, Taub N, Skinner TC, Khunti K. The prevalence of depression in white-European and South-asian people with impaired glucose regulation and screen-detected type 2 diabetes mellitus. PLoS One 2009;4:e7755.
6. Holt RI, Phillips DI, Jameson KA, Cooper C, Dennison EM, Peveler RC. The relationship between depression and diabetes mellitus: findings from the Hertfordshire Cohort Study. Hertfordshire Cohort Study Group. Diabet Med 2009;26:641-648.
7. Kivimaki M, Tabak AG, Batty GD, Singh-Manoux A, Jokela M, Akbaraly TN, Witte DR, Brunner EJ, Marmot MG, Lawlor DA. Hyperglycemia, type 2 diabetes, and depressive symptoms: the British Whitehall II study. Diabetes Care 2009;32:1867-1869.
8. Gale CR, Kivimaki M, Lawlor DA, Carroll D, Phillips AC, Batty GD Fasting glucose, diagnosis of type 2 diabetes, and depression: the Vietnam experience study. Biol Psychiatry 2010;67:189-192.
9. Knol MJ, Twos JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837-845.
10. Hildrum B, Mykletun A, Midthjell K, Ismail K, Dahl AA. No association of depression and anxiety with the metabolic syndrome: the Norwegian HUNT study. Acta Psychiatr Scand 2009;120: 14-22.
11. Lustman PJ, Griffith LS, Gavard JA, Clouse RE. Depression in adults with diabetes. Diabetes Care 1992;15:1631-1639.
12. Björntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2001;2:73-86.
13. Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Topolski R. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study. J Am Board Fam Med 2009;22:528-534.
14. Sánchez-Villegas A, Doreste J, Schlatter J, Pla J, Bes-Rastrollo M, Martínez-González MA. Association between folate, vitamin B(6) and vitamin B(12) intake and depression in the SUN cohort study. J Hum Nutr Diet 2009;22:122-133.
15. Ng TP, Feng L, Niti M, Kua EH, Yap KB. Folate, vitamin B12, homocysteine, and depressive symptoms in a population sample of older Chinese adults. J Am Geriatr Soc. 2009;57:871-876.
16. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Predictive value of folate, vitamin B12 and homocysteine levels in late-life depression. Br J Psychiatry 2008;192:268-274.
17. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, Buring JE, Gaziano JM, Liu S. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. N Engl J Med 2009;361:1152-163.
18. Ryan J, Burger HG, Szoeke C, Lehert P, Ancelin ML, Henderson VW, Dennerstein L. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women. Menopause. 2009;16:509-517.
19. WHO MONICA Project. MONICA Manual. URL: http://www.ktl.fi/publications/monica/manual/index.htm
20. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol Rev 1988;8:77-100.
21. Lustman PJ, Clouse RE, Griffith LS, Carney RM, Freedland KE. Screening for depression in diabetes using the Beck Depression Inventory. Psychosom Med 1997;59:24-31.
22. Paile-Hyvärinen M, Räikkönen K, Forsén T, Kajantie E, Ylihärsilä H, Salonen MK, Osmond C, Eriksson JG. Depression and its association with diabetes, cardiovascular disease, and birth weight. Ann Med 2007;39:634-640.
23. Teychenne M, Ball K, Salmon J. Physical activity and likelihood of depression in adults: a review. Prev Med 2008;46:397-411.
24. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934-42.
25. Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. Diabetes Care 2010;33:1034-6.
Table 1. Characteristics of the study population according to glucose regulation status.

|                          | Normal glucose regulation | Impaired glucose regulation | Screen-detected type 2 diabetes | Previously known type 2 diabetes |
|--------------------------|---------------------------|-----------------------------|---------------------------------|---------------------------------|
| **n**                    | 1268                      | 1001                        | 284                             | 159                             |
| Female, (%)              | 795 (63)                  | 443 (44)                    | 118 (42)                        | 67 (42)                         |
| Age (years), mean (SD)   | 58 (8)                    | 60 (8)                      | 62 (8)                          | 64 (7)                          |
| BMI (kg/m$^2$), mean (SD)| 26.1 (4.2)                | 27.9 (4.5)                  | 29.9 (4.9)                      | 31.8 (6.2)                      |
| Fasting plasma glucose (mmol/l), mean (SD) | 5.7 (0.82) | 6.3 (0.38) | 7.3 (1.5) | 8.4 (2.1) |
| Serum insulin, (mU/l), median (IQR) | 5.4 (4.1, 7.2) | 7.3 (5.4, 10.1) | 9.9 (6.9, 14.2) | 11.9 (7.2, 16.9) |
| High-sensitivity c-reactive protein, (mg/l), mean (SD) | 2.1 (4.3) | 3.1 (8.5) | 3.6 (7.7) | 3.4 (10.9) |
| Serum vitamin B$_{12}$ (pmol/l), mean (SD) | 333 (123) | 329 (202) | 324 (116) | 266 (136) |
| Serum sex-hormone-binding globulin (nmol/l), mean (SD) | 66.5 (31.6) | 56.3 (27.3) | 53.0 (27.3) | 48.0 (28.8) |
| Serum thyroid-stimulating hormone (mU/l), mean (SD) | 3.26 (2.37) | 2.99 (1.67) | 3.10 (1.91) | 3.32 (2.77) |
| Leisure-time physical activity, n (%)                          |                        |                             |                                 |                                 |
| 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, n (%) | 966 (77) | 783 (79) | 203 (71) | 119 (75) |
| Education in years, median (IQR) | 11 (9, 15) | 10 (8, 13) | 10 (8, 12) | 10 (8, 12) |
| Current smoking, n (%)   | 289 (23)                  | 226 (23)                    | 54 (19)                         | 28 (18)                         |
| Antidepressive medication, n (%) | 64 (5)      | 53 (5)                      | 23 (8)                          | 11 (7)                          |
| Chronic pulmonary disease, n (%) | 95 (8)      | 70 (7)                      | 30 (11)                         | 29 (18)                         |
| Chronic heart disease, n (%) | 82 (6)      | 98 (10)                     | 38 (13)                         | 39 (25)                         |
| Chronic musculoskeletal disorder, n (%) | 371 (30) | 306 (31) | 96 (35) | 64 (41) |
| Cancer, n (%)            | 29 (2)                   | 27 (3)                      | 10 (4)                          | 6 (4)                           |
## Table 2. Multivariate logistic regression analysis with depressive symptoms (21-item Beck Depression Inventory score ≥ 10, and 21-item Beck Depression Inventory score ≥ 16) as an outcome.

| Glucose regulation                                      | Beck Depression Inventory score ≥ 10 | Beck Depression Inventory score ≥ 16 |
|---------------------------------------------------------|------------------------------------|-------------------------------------|
|                                                         | Odds Ratio (95% CI) | P value | Odds Ratio (95% CI) | P value |
| Normal glucose regulation                               | 1.00 (Reference) | | 1.00 (Reference) | |
| Impaired glucose regulation                             | 0.91 (0.69-1.20) | 0.50 | 1.05 (0.62-1.76) | 0.86 |
| Screen-detected type 2 diabetes mellitus                | 0.70 (0.45-1.08) | 0.10 | 0.87 (0.40-1.90) | 0.73 |
| Previously known type 2 diabetes mellitus               | 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 |
| High-sensitivity C-reactive protein                      | 1.00 (0.99-1.02) | 0.61 | 0.99 (0.96-1.03) | 0.68 |
| Vitamin B12                                             | 1.00 (1.00-1.00) | 0.19 | 1.00 (1.00-1.00) | 0.28 |
| Sex-hormone-binding globulin                            | 1.00 (1.00-1.00) | 0.82 | 1.00 (0.99-1.01) | 0.98 |
| Leisure-time physical activity                          |                       | < 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