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Association between symptoms of depression, diabetes complications and vascular risk factors in four European cohorts of individuals with type 1 diabetes – InterDiane Consortium

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Abstract

Aims: To investigate the association between depressive symptomatology and health markers in type 1 diabetes.

Methods: Four countries from the InterDiane Consortium had adopted the Finnish Diabetic Nephropathy Study protocol, including the Beck Depression Inventory (BDI). Associations between depression symptomatology, diabetes complications (diabetic nephropathy, proliferative retinopathy, major adverse cardiovascular events [MACE]) and vascular risk factors (metabolic syndrome, body mass index, glycaemic control) were investigated.

Results: In a sample of 1046 participants (Croatia *n*=99; Finland *n*=314; Latvia *n*=315; Lithuania *n*=318), 13.4% displayed symptoms of depression (BDI score ≥16) with no statistically significant difference in the prevalence of depression among the cohorts. The highest rates of diabetic nephropathy (37.1%) and proliferative retinopathy (36.3%) were observed in Lithuania. The rates of MACE and metabolic syndrome were highest in Finland. In joint analyses, individuals exhibiting depression symptomatology had higher HbA_{1c} (79 vs. 72 mmol/mol, $p<0.001$) and higher triglyceride concentration (1.67 vs. 1.28 mmol/l, $p<0.001$), than those without. In the multivariable model, BDI score was positively associated with the presence of diabetic nephropathy, proliferative retinopathy, MACE, and metabolic syndrome and its triglyceride component. Moreover, BDI score was positively associated with the number of metabolic syndrome components, triglyceride concentration, and HbA_{1c}.

Conclusions: Comorbid depression should be considered a relevant factor explaining metabolic problems and vascular outcomes. Causality cannot be inferred from this cross-sectional study.

Keywords: Depression; Diabetes complications; Metabolic syndrome; Type 1 diabetes

1. Introduction

Depression is a common feature in diabetes [1]. Comorbid depression negatively impacts the quality of life [2] and increases the medical symptom burden [3], diabetes symptom severity [4], and health-care costs [5]. Symptoms of depression, such as loss of interest in activities, loss of energy, and feelings of worthlessness, may compromise the appropriate self-management. Accordingly, comorbid depression has been associated with worse glycaemic control in type 1 diabetes [6,7]. However, results showing no association between depressive mood and glycaemia have also been reported [8,9].

Depressive mood may increase the risk for various diabetes-related long-term complications [10–12]. Most of the studies in this field have been conducted in individuals with type 2 diabetes, limiting the generalisability to people with type 1 diabetes. Importantly, type 1 and type 2 diabetes are distinct entities with different aetiologies, courses of disease, and management regimens. As pointed out in a recent review, there is a significant shortage of available data on the prevalence and characteristics of depression in individuals with type 1 diabetes [1]. In this study, we assessed the frequency of depressive symptomatology in four European cohorts of individuals with type 1 diabetes, and investigated the associations between symptoms of depression, diabetes complications, and vascular risk factors. Our hypothesis was that depressive symptomatology is associated with higher prevalence of diabetes complications and vascular risk factors.

2. Methods

The Finnish Diabetic Nephropathy (FinnDiane) Study was launched in 1997. The aim of the ongoing FinnDiane Study is to identify risk factors for diabetes complications in type 1 diabetes. Since 2010, 6 countries (Austria, Croatia, Estonia, Latvia, Lithuania, and Romania) have adopted the FinnDiane Study protocol, and together form the International Diabetic Nephropathy (InterDiane) Consortium. As the FinnDiane Study protocol is quite extensive, the participating InterDiane Study sites used their own consideration regarding which parts they wanted to include. Of the participating countries, data on

depression were collected in the Croatian, Finnish, Latvian, and Lithuanian sites. Study subjects were individuals with type 1 diabetes. Type 1 diabetes was defined as onset of diabetes prior to the age of 40 years and permanent insulin treatment initiated within a year of the diagnosis. The study protocols were approved by the ethics committees at each of the participating countries (Croatia: The Ethics Committee of Merkur University Hospital; Finland: The Ethics Committee of Helsinki and Uusimaa Hospital District; Latvia: The Latvian Central Ethics Committee; Lithuania; The Ethics Committee of Lithuanian University of Health Sciences in Kaunas. In Croatia, all patients with type 1 diabetes either attending at the outpatient clinic or hospitalized at the inpatient department were asked for their willingness to participate in the study. In Finland, the attending physicians recruited the study participants during regular patient visits related to the management of type 1 diabetes. In addition, a number of participants volunteered to the study after having heard about it via their friends, relatives, or social media. In Latvia, study subjects were recruited amongst patients with type 1 diabetes undergoing treatment at the Department of Endocrinology, Pauls Stradins University. Moreover, out-patients were recruited through endocrinologists and patient organisations. In Latvia, recruitment of the study participants was performed in agreement with the procedures of the Genome Database of the Latvian population. The study was performed in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. A written informed consent was obtained from all study participants prior to inclusion into the study.

Symptoms of depression were investigated with the Beck Depression Inventory I (BDI) [13]. This self-report questionnaire covers 21 symptom-attitude categories including mood, pessimism, sense of failure, lack of satisfaction, guilty feeling, sense of punishment, self-hate, self-accusations, self-punitive wishes, crying spells, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido. Each of these categories contain 4-6 statements of increasing symptom severity, and of these statements, participants selected the ones that best described their current situation. Each of the categories were scored from 0 to 3, giving a total score ranging between 0 and 63. Higher scores indicate more severe symptoms of depression. In the

current study, the BDI score was used as a continuous variable. Additionally, we divided participants into those with and without symptoms of depression, using a cut-off value of ≥16 [14].

At the study visit, height and weight were measured while wearing light clothing. Waist circumference was measured at the mid-point between the iliac crest and the lowest rib. Following a minimum of 10-minute rest, blood pressure was measured twice. Mean of the two measurements was calculated. Blood was drawn for central analyses of lipid and lipoprotein concentrations at each site. HbA_{1c} was measured locally using standardised assays. Smoking was self-reported, with current smoking referring to smoking at least one cigarette per day. Data on diabetes complications were collected from medical records. Major adverse cardiovascular events (MACE) were defined as acute myocardial infarction, coronary revascularisation procedure, stroke, non-traumatic amputation, or peripheral revascularisation procedure. Retinal laser treatment was used as indication of proliferative retinopathy in Finland and Latvia. In Lithuania, the diagnosis of proliferative retinopathy was based on the fundus examinations. In Croatia, proliferative retinopathy was diagnosed using two-field 45 degrees retinal images [15]. Albumin excretion rate (AER) was assessed in at least two out of three timed 24-h or overnight urine collections. Classifications into those with normal AER (AER <20 μg/min or <30 mg/24 h), microalbuminuria (AER ≥20 and <200 μg/min, or ≥30 and <300 mg/24 h), macroalbuminuria (AER ≥200 μg/min or ≥300 mg/24 h), and end-stage renal disease (dialysis or kidney transplant) were made. In Latvia, albumin-to-creatinine ratio >2.5 mg/mmol for men and >3.5 mg/mmol for women was used to define microalbuminuria. Diabetic nephropathy was defined either as macroalbuminuria, end-stage renal disease, or glomerular filtration rate below 60 ml/min/1.73m^2.

Metabolic syndrome was assessed according to Alberti et al. [16]. Accordingly, men and women with a waist circumference of ≥94 cm and ≥80 cm, respectively, fulfilled the waist criterion. Individuals with serum triglyceride concentration ≥1.70 mmol/l and HDL cholesterol concentration <1.00 mmol/l (men) and <1.30 mmol/l (women), or medication to manage dyslipidaemia fulfilled these respective criteria. For blood pressure criterion, blood pressure ≥130/85 mmHg or antihypertensive treatment was required. As all

participants had type 1 diabetes, they all fulfilled the elevated fasting blood glucose criterion. A metabolic syndrome score ranging between 1 and 5 was calculated for each participant. A score ≥3 was indicative of metabolic syndrome.

In the analyses, we included data from all participants with known depression status. Due to the long duration of the FinnDiane Study, we identified 1806 potential participants from Finland as compared to the cohort of 99 from Croatia, 315 from Latvia, and 318 from Lithuania. In order not to overpower the analyses with the data from Finland, we formed an age-, sex-, and diabetes duration matched sample from the Finnish cohort, with the Latvian cohort as a reference. Latvian cohort was selected because it most closely resembled the original Finnish cohort with respect to the symptoms of depression frequency (14.3% in Latvia and 12.8% in Finland).

2.1. Statistics

Descriptive data are presented as number (frequency) for categorical variables, and median (interquartile range) for continuous non-parametric variables. Differences among the four samples were investigated using Chi-squared test and Kruskal-Wallis test, respectively. Logistic regression was applied to study the associations between BDI score and the dichotomized health variables (diabetic nephropathy, retinopathy, MACE, metabolic syndrome, and the waist-, triglyceride-, HDL-cholesterol-, and blood pressure components as dependent variables). Generalised linear regression was used for investigating the associations between BDI score and the continuous health variables (metabolic syndrome score, waist circumference, triglyceride concentrations, HDL-cholesterol concentration, systolic blood pressure, diastolic blood pressure, BMI, HbA_{1c}, and the factor scores as dependent variables). In addition to the individual outcome variables, we also investigated whether BDI score was associated with the clusters of risk factors. In this process the continuous health variables were entered in a factor analysis (Maximal likelihood and Varimax rotation) to form factors of health variables with high inter-correlation. Eigenvalue >1.0 was used as a cut-off for identifying the factors. Variables with factor loadings |≥0.20| were included in each factor. Factors were intuitively named based on the variables included, with a particular stress on the variables with the

strongest loadings. Factor scores, for each emerging factor, were calculated for all participants. The factor scores were a sum of the scores for all items associated with a given factor, multiplied by the corresponding factor loading. Generalised linear regression was used to investigate the association between the factor scores and BDI scores. Analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA). A two-tailed *P* value <0.05 was considered statistically significant.

3. Results

Data were available from 99 participants from Croatia, 314 participants from Finland, 315 participants from Latvia, and 318 participants from Lithuania (Table 1). Age, diabetes duration, and smoking were comparable among the cohorts. Proportion of men was the highest in the Croatian sample. Highest median BMI, waist circumference, blood pressure, and HbA_{1c} concentration were observed in the Finnish cohort. The rates of diabetic nephropathy, proliferative retinopathy, and MACE were the lowest in the Croatian sample. The highest rates of diabetic nephropathy and proliferative retinopathy were observed in Lithuania, while the rates of the MACE were the highest in Finland. Altogether, 82.2% of the Finnish sample had metabolic syndrome, as opposed to 49.0% of the Croatian, 47.6% of the Lithuanian, and 42.5% of the Latvian samples. Also the waist-, triglyceride-, HDL-cholesterol-, and blood pressure components were most frequently fulfilled in the Finnish sample. The lowest rate of fulfilling the waist component was observed in the Latvian cohort, the lowest rates of fulfilling the triglyceride- and HDL-cholesterol components were observed in the Lithuanian sample, while the Croatian cohort had the lowest rate of fulfilling the blood pressure component.

Significant differences were observed in the BDI scores, with the lowest levels reported in the Croatian sample, and the highest in the Latvian and Lithuanian samples (Table 1). Frequencies of depressive symptomatology were, however, not significantly different between the cohorts. Samples combined, individuals with depressive symptomatology had higher metabolic syndrome score (3.0 [2.9–3.2] vs. 2.7

[2.6–2.8], p=0.004), triglyceride concentration (1.67 [1.53–1.82] mmol/l vs. 1.28 [1.22–1.34] mmol/l, p<0.001), and HbA_{1c} (79 [75–82] mmol/mol vs. 72 [70–73] mmol/mol, p<0.001), relative to those without.

In all the cohorts, the frequencies of diabetic nephropathy were higher in those with symptoms of depression (Table 2). However, in the Croatian sample this difference was not statistically significant. In the Finnish sample, compared to those without depressive symptomatology, the rate of proliferative retinopathy was higher in those with symptoms of depression. In the Lithuanian sample, the symptoms of depression were associated with higher rates of MACE and metabolic syndrome. Cohorts combined, individuals with symptoms of depression more frequently had diabetic nephropathy, proliferative retinopathy, MACE, and metabolic syndrome. Moreover, in the joint analysis, depressive symptomatology was associated with meeting the criteria for the waist-, triglyceride-, and blood pressure components.

In the Finnish and Latvian cohorts, adjusted for sex, age, and smoking, the BDI score positively associated with the presence of diabetic nephropathy (Table3). Higher BDI scores were related to proliferative retinopathy and MACE in the Finnish and Lithuanian cohorts, respectively. The metabolic syndrome was associated with BDI scores in Lithuania. In the Finnish, Latvian, and Lithuanian cohorts, fulfilling the triglyceride component was associated with higher BDI scores. Samples combined, higher BDI scores were associated with diabetic nephropathy, proliferative retinopathy, MACE, metabolic syndrome, and the triglyceride component of the metabolic syndrome.

The BDI score was positively associated with the metabolic syndrome score in the Finnish, Latvian, and Lithuanian samples (Table 4). In Croatia, the BDI score had a positive association with waist circumference and BMI, while in Finland and Latvia BDI score was associated with triglyceride concentration and HbA_{1c}. Cohorts combined, metabolic syndrome score, triglyceride concentration, and HbA_{1c} were all positively associated with the BDI score.

Three risk factor patterns were formed in the factor analysis, and were named as Obesity, Hypertension, and Dyslipidaemia (Supplementary Table 1). All cohorts together, individuals with depressive symptomatology had higher Dyslipidaemia factor scores relative to those without (0.09 [-0.37–0.79] vs. -

0.22 [-0.54–0.27], p<0.001). In the multivariable model, higher BDI scores were associated with higher factor scores of the Dyslipidaemia factor in Finland, Latvia, Lithuania, and in the joint analyses of the cohorts (Table 5).

4. Discussion

We observed a number of differences and a fair number of similarities in the depressive symptomatology and the associations between depressive symptoms and health variables in the four European cohorts of individuals with type 1 diabetes. First, the frequencies of symptoms of depression were comparable amongst the samples. Of importance, the country-specific and overall rates of depressive symptomatology were within the range of the observations made in other type 1 diabetes populations [1]. Second, in the whole sample, higher depression scores were positively associated with the presence of diabetic nephropathy, proliferative retinopathy, and MACE. However, potentially due to issues related to power, although having similar odds ratios, these associations did not reach statistical significance in all individual samples. Third, the BDI score was associated with the presence of the metabolic syndrome and the metabolic syndrome score in the whole sample, and the latter association was also seen in most of the individual cohorts. Of the components of the metabolic syndrome, instead, depression scores were most frequently associated with the triglycerides.

With respect to the associations between depression and the clinical variables, the Croatian sample seemed to differ from other cohorts the most. In particular, it exhibited no associations between depressive symptomatology and the metabolic syndrome or its triglyceride component, seen in other samples, but rather showed positive associations between the BDI score and waist circumference and BMI. Of interest, the Croatian sample was not only the smallest of the cohorts, but also had the highest frequency of men and, with many respect, featured clinical variables suggestive of an overall healthiest sample of the four. Instead, despite selecting an age-, sex-, and diabetes duration-matched sample from the FinnDiane Study population, the Finnish participants had, on average, the worst health profile. Notably,

in the Finnish sample, the rates of MACE, metabolic syndrome and all its components, and BMI, blood pressure, HbA_{1c}, and triglyceride concentration were the highest observed in the study. Why the Finnish cohort had the worse clinical profile of the four sites is not known. However, over the past 20 years the FinnDiane Study has become well established in Finland. It is therefore possible that individuals with emerging risk factors or complications more readily volunteer to this study, potentially in hope of receiving extra monitoring. In addition to the potential bias in the enrolment of the cohorts, a number of other factors may impact the clinical variables. Of interest, while the Finns were worst off with respect to most of the clinical variables, the cholesterol concentration was the lowest among the Finnish participants. This could suggest that high cholesterol levels are more aggressively treated in Finland as compared to the other countries. Additionally, genetics and lifestyle impact these health variables. For the current analyses, however, we did not have these data available. While genes may not be readily affected, special emphasis may need to be placed on the lifestyle, including healthy diet and increased physical activity, in order to improve the health of the Finnish individuals with type 1 diabetes. Indeed, although the consequences and reasons behind these striking health disparities are not known, our observation calls for further attention in order to reduce the potentially heightened long-term risks in the Finnish type 1 diabetes population.

In their early meta-analysis, de Groot et al investigated the associations between depression and complications in type 1 and type 2 diabetes [17]. The results revealed a consistent relationship between depression and diabetes complications. Of note, the observations were evident across the diabetes subtypes, suggesting common pathways between depression and complications. Since the publication of the meta-analysis, progression in the management of both depression [18] and diabetes [19] has taken place. Therefore, observations reflecting populations under more recent modes of disease management are warranted. Amongst the more recent studies is the one by Hirai et al., who investigated the association between symptoms of depression and diabetic retinopathy in 484 individuals with type 1 diabetes [20]. In their study, a higher frequency of depression was observed among those with more severe diabetic retinopathy and visual impairment. After controlling for confounders, however, these associations were no longer significant. In another study of 458 participants with type 1 diabetes, individuals reporting the

presence of at least one diabetes complication had a higher BDI score compared to those without complications [21]. Amongst the rare longitudinal studies is the one including 483 African-American individuals with type 1 diabetes, where high BDI scores at both baseline and follow-up were associated with progression of diabetic retinopathy over the 6 year follow-up [12].

Ever since the association between glycaemia and diabetes long-term complications was conclusively demonstrated in the Diabetes Control and Complications Trial [22], there has been increasing interest in the role of depression in determining glycaemia. In the current study, higher BDI scores were associated with worse glycaemic control, and higher HbA_{1c} was observed in those with depressive symptomatology. These results are in line with a study in 6172 individuals with type 1 diabetes, where mean HbA_{1c} was higher in those with symptoms of depression [23]. In the same study, participants with depressive symptomatology were more likely to miss insulin doses and exercise less often. Moreover, comorbid depression was reflected in more frequent episodes of diabetic ketoacidosis and severe hypoglycaemia. In another study, HbA_{1c} was not associated with depression score in individuals with type 1 diabetes [21]. Instead, those with history of depression exhibited higher HbA_{1c} relative to those without [21]. In another study in 313 newly diagnosed individuals with type 1 diabetes, symptoms of depression did not predict patients' membership in the identified trajectories of glycaemic control, nor were they associated with glycaemic control at any point during the 5-year assessment [8].

Our observations linking depressive symptomatology and dyslipidaemia, high triglyceride concentrations in particular, are in line with those by Katon et al., who reported high triglyceride concentrations in individuals with diabetes, evidence of heart disease, and symptoms of depression [24]. In another study of people with type 2 diabetes participating in an intensive lifestyle intervention, antidepressant medication use over the preceding year was associated with increased odds of low HDL-cholesterol concentration, high triglyceride concentration, high diastolic blood pressure, and obesity [25]. High BMI was also associated with symptoms of depression in another population of participants with either type 1 or type 2 diabetes [26]. In that study, however, depression status was not associated with blood pressure.

Metabolic syndrome, representing a cluster of vascular risk factors, has shown to be a frequent observation in type 1 diabetes [27]. In a sample of 1226 FinnDiane Study participants, we have previously shown an increase in the BDI score with increasing number of the components of the metabolic syndrome [28]. To our knowledge, the association between depression and metabolic syndrome has not been investigated in other populations of type 1 diabetes. In a group of elderly participants with type 2 diabetes, however, depression was significantly associated with an increased risk of metabolic syndrome and, comparable to the current observations, dyslipidaemia in particular [29]. Moreover, as seen in the current study, depression was not associated with either BMI or hypertension.

The precise mechanisms through which depression is linked to metabolic disturbances are not exhaustively known. It is likely, however, that both behavioural and physiological mechanisms have their roles to play in these processes. Depression is associated with non-adherence to healthy life-style and treatment regimen [30], and has therefore the potential to increase the prevalence of various risk factors. On the other hand, the emergence of complications may bring about depressive symptoms in the affected individuals [31]. The physiological manifestations of depression may also impact vascular risk factors. Of these, dysregulation of the hypothalamic-pituitary-adrenal axis, reduced brain serotonin activity and increased inflammation are noteworthy. The former may result in increased glucocorticoid secretion which, in excess, contributes to dyslipidaemia, hypertension, insulin resistance and visceral obesity [32]. The two latter manifestations, instead, are related both to metabolic syndrome and depression and could therefore mediate these two conditions [33–36].

This study is not without limitations. First, this study was cross-sectional in design and therefore does not reveal causalities between depressive mood and the health markers investigated. While depressive mood has shown to increase the risk of adverse health outcomes [10], the emergence of diabetes complications is also associated with increased risk of depression [1]. Second, to identify individuals with type 1 diabetes, we used the cut-off limit of 40 years of age at the diabetes diagnosis, and permanent use of insulin within a year from the diagnosis. While, using these criteria, we are quite confident to have included participants

with type 1 diabetes, there still remains a possibility that a few individuals with type 2 diabetes are also included. Third, due to a small number of individual cases and in order to limit the number of statistical test required, we used a composite variable of major adverse cardiovascular events to describe acute myocardial infarction, coronary revascularisation procedure, strike, non-traumatic amputation, and peripheral revascularisation procedure. However, it should be noted that these events are quite heterogeneous and might differ with respect to their relation to depressive symptoms. Fourth, instead of using diagnostic interviews, symptoms of depression were assessed using self-reported methods. Notably, the use of self-report methods may be subject to misreporting. Fifth, some selection bias may have occurred, as it is possible that individuals with severe depression or with more severe diabetes complications are under-represented. The likely consequence of such a selection bias is a dilution of the current observations. Sixth, with participants of European descendants, the current results may not be directly generalized to other populations with different ethnicities. While individual cohorts were relatively small and were thus restricted in their power to show significant results, for many observations we saw similar non-significant trends which were further strengthened when the cohorts were analysed together. As the majority of previous studies in this field have been conducted in people with type 2 diabetes, the current study adds to the pool of knowledge related to the depressive symptoms and their associations with health outcomes in type 1 diabetes. A major strength of the study was the inclusion of data from four countries with reasonably similar genetic backgrounds but differing in the latitudes (availability of sun light), dietary practices, culture, and health care systems.

In conclusion, in individuals with type 1 diabetes from four European cohorts, symptoms of depression were associated with diabetes complications, glycaemic control, metabolic syndrome, and the triglyceride component of the metabolic syndrome. Additionally, we observed a number of health differences in the four samples, with worst clinical profile observed in the Finnish sample. In the future, data collected in the framework of the InterDiane Consortium will be used to study the role of depression in the emergence and progression of diabetes complications.

Declaration of Competing Interests No competing financial interests exist.

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References

[1] Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord 2012;142 Suppl:S8-S21.

[2] Baumeister H, Hutter N, Bengel J, Harter M. Quality of life in medically ill persons with comorbid mental disorders: a systematic review and meta-analysis. Psychother Psychosom 2011;80:275-286.

[3] Ludman EJ, Katon W, Russo J, Von Korff M, Simon G, Ciechanowski P, et al. Depression and diabetes symptom burden. Gen Hosp Psychiatry 2004;26:430-436.

[4] Nguyen AL, Green J, Enguidanos S. The relationship between depressive symptoms, diabetes symptoms, and self-management among an urban, low-income Latino population. J Diabetes Complications 2015;29:1003-1008.

[5] Gilmer TP, O'Connor PJ, Rush WA, Crain AL, Whitebird RR, Hanson AM, et al. Predictors of health care costs in adults with diabetes. Diabetes Care 2005;28:59-64.

[6] Gilsanz P, Karter AJ, Beeri MS, Quesenberry CP,Jr, Whitmer RA. The Bidirectional Association Between Depression and Severe Hypoglycemic and Hyperglycemic Events in Type 1 Diabetes. Diabetes Care 2018;41:446-452.

[7] Ahola AJ, Harjutsalo V, Saraheimo M, Forsblom C, Groop PH, FinnDiane Study Group. Purchase of antidepressant agents by patients with type 1 diabetes is associated with increased mortality rates in women but not in men. Diabetologia 2012;55:73-79.

[8] Kampling H, Mittag O, Herpertz S, Baumeister H, Kulzer B, Petrak F. Can trajectories of glycemic control be predicted by depression, anxiety, or diabetes-related distress in a prospective cohort of adults with newly diagnosed type 1 diabetes? Results of a five-year follow-up from the German multicenter diabetes cohort study (GMDC-Study). Diabetes Res Clin Pract 2018;141:106-117.

[9] Hagger V, Hendrieckx C, Cameron F, Pouwer F, Skinner TC, Speight J. Diabetes distress is more strongly associated with HbA1c than depressive symptoms in adolescents with type 1 diabetes: Results from Diabetes MILES Youth-Australia. Pediatr Diabetes 2018;19:840-847.

[10] Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, et al. Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 2010;33:264-269.

[11] Williams LH, Rutter CM, Katon WJ, Reiber GE, Ciechanowski P, Heckbert SR, et al. Depression and incident diabetic foot ulcers: a prospective cohort study. Am J Med 2010;123:748-754.

[12] Roy MS, Roy A, Affouf M. Depression is a risk factor for poor glycemic control and retinopathy in African-Americans with type 1 diabetes. Psychosom Med 2007;69:537-542.

[13] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-571.

[14] 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.

[15] Aldington SJ, Kohner EM, Meuer S, Klein R, Sjolie AK. Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM Complications Study. Diabetologia 1995;38:437-444.

[16] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-1645.

[17] de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619-630.

[18] Ceskova E, Silhan P. Novel treatment options in depression and psychosis. Neuropsychiatr Dis Treat 2018;14:741-747.

[19] Prahalad P, Tanenbaum M, Hood K, Maahs DM. Diabetes technology: improving care, improving patient-reported outcomes and preventing complications in young people with Type 1 diabetes. Diabet Med 2018;35:419-429.

[20] Hirai FE, Tielsch JM, Klein BE, Klein R. Relationship between retinopathy severity, visual impairment and depression in persons with long-term type 1 diabetes. Ophthalmic Epidemiol 2012;19:196-203.

[21] Gendelman N, Snell-Bergeon JK, McFann K, Kinney G, Paul Wadwa R, Bishop F, et al. Prevalence and correlates of depression in individuals with and without type 1 diabetes. Diabetes Care 2009;32:575-579.

[22] Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.

[23] Trief PM, Xing D, Foster NC, Maahs DM, Kittelsrud JM, Olson BA, et al. Depression in adults in the T1D Exchange Clinic Registry. Diabetes Care 2014;37:1563-1572.

[24] Katon WJ, Lin EH, Russo J, Von Korff M, Ciechanowski P, Simon G, et al. Cardiac risk factors in patients with diabetes mellitus and major depression. J Gen Intern Med 2004;19:1192-1199.

[25] Rubin RR, Peyrot M, Gaussoin SA, Espeland MA, Williamson D, Faulconbridge LF, et al. Four-year analysis of cardiovascular disease risk factors, depression symptoms, and antidepressant medicine use in the Look AHEAD (Action for Health in Diabetes) clinical trial of weight loss in diabetes. Diabetes Care 2013;36:1088-1094.

[26] Kimbro LB, Steers WN, Mangione CM, Duru OK, Ettner SL. The Association of Depression and the Cardiovascular Risk Factors of Blood Pressure, HbA1c, and Body Mass Index among Patients with Diabetes: Results from the Translating Research into Action for Diabetes Study. Int J Endocrinol 2012:747460.

[27] Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, et al. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005;28:2019-2024.

[28] Ahola AJ, Thorn LM, Saraheimo M, Forsblom C, Groop PH, FinnDiane Study Group. Depression is associated with the metabolic syndrome among patients with type 1 diabetes. Ann Med 2010;42:495-501.

[29] Cardenas V, Mausbach BT, Sommerfeld D, Jimenez D, von Känel R, Ho JS, et al. Depression is Associated with Increased Risk for Metabolic Syndrome in Latinos with Type 2 Diabetes. Am J Geriatr Psychiatry 2017;25:646-653.

[30] Nefs G, Hendrieckx C, Reddy P, Browne JL, Bot M, Dixon J, et al. Comorbid elevated symptoms of anxiety and depression in adults with type 1 or type 2 diabetes: Results from the International Diabetes MILES Study. J Diabetes Complications 2019;33:523-529.

[31] Thomas AJ, Kalaria RN, O´Brien JT. Depression and vascular disease: what is the relationship? J Affect Disord 2004;79:81-95.

[32] Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annu Rev Public Health 2005;26:469-500.

[33] Muldoon MF, Mackey RH, Korytkowski MT. The metabolic syndrome is associated with reduced central serotonergic responsivity in healthy community volunteers. J Clin Endocrinol Metabol 2006;91:718-721.

[34] Heltzer H. Serotonergic dysfunction in depression. Br J Psychiatry 1989;155:25-31.

[35] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6; A meta-analysis. Psychosom Med 2009;71:171-186.

[36] Festa A, D`Agostino R, Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The insulin resistance atherosclerosis study (IRAS). Circulation 2000;102:42-47.

Table 1 Basic characteristics of the sample divided by participating country

	Croatia	Finland	Latvia	Lithuania		All
	N=99	N=314	N=315	N=318	*P*	N=1046
BDI score	4 (2–8)	5 (1–10)	7 (4–12)	7 (3–12)	<0.001	6 (2–12)
BDI score ≥16, %	6.1	13.4	14.3	14.8	0.149	13.4
Men, %	59.6	45.9	46.0	41.8	0.022	46.0
Age, years	38 (29–51)	35 (27–47)	35 (25–46)	34 (25–46)	0.070	35 (26–47)
Diabetes duration, years	18 (7–27)	17 (9–26)	15 (8–25)	17 (9–27)	0.194	17 (9–26)
Smoking, %	31.6	26.5	27.9	21.7	0.154	25.9
BMI, kg/m^2	24.1 (22.2–26.8)	26.1 (23.3–29.1)	24.2 (21.6–27.4)	24.6 (22.0–27.5)	<0.001	24.8 (22.2–27.8)
Waist circumference, cm	88 (80–95)	89 (81–98)	80 (73–89)	84 (76–93)	<0.001	85 (76–94)
Systolic BP, mmHg	120 (120–130)	137 (125–146)	125 (118–136)	128 (118–140)	<0.001	130 (120–141)
Diastolic BP, mmHg	80 (70–80)	83 (75–88)	80 (72–87)	80 (74–86)	0.018	80 (74–87)
HbA_{1c}, mmol/mol	55 (48–67)	76 (67–86)	70 (57–85)	67 (56–81)	<0.001	70 (58–84)
HbA_{1c}, %	7.2 (6.5–8.3)	9.1 (8.3–10.0)	8.6 (7.4–9.9)	8.3 (7.3–9.6)	<0.001	8.6 (7.5–9.8)
Total cholesterol, mmol/l	4.81 (4.23–5.56)	4.67 (4.14–5.31)	4.95 (4.10–5.61)	5.28 (4.56–6.18)	<0.001	4.95 (4.24–5.70)
HDL-cholesterol, mmol/l	1.66 (1.34–1.95)	1.40 (1.14–1.69)	1.85 (1.56–2.25)	1.49 (1.20–1.83)	<0.001	1.49 (1.21–1.80)
Triglyceride, mmol/l	1.02 (0.77–1.29)	1.24 (0.92–1.86)	1.07 (0.74–1.59)	1.03 (0.70–1.52)	<0.001	1.09 (0.77–1.60)
Diabetic nephropathy, %	4.0	19.2	10.8	37.1	<0.001	20.9
Proliferative retinopathy, %	23.2	25.6	27.6	36.3	0.008	29.2
MACE, %	4.0	10.5	6.3	7.6	0.103	7.8
Metabolic syndrome, %	49.0	82.2	42.5	47.6	<0.001	56.7
Waist component, %	44.9	65.6	32.4	47.2	<0.001	48.1
Triglyceride component, %	35.4	48.4	30.7	22.7	<0.001	34.3
HDL component, %	34.3	46.2	28.2	20.6	<0.001	32.2
BP component, %	53.5	80.9	61.1	61.9	<0.001	66.6

Continuous data are presented as medians (interquartile ranges), and categorical data are presented as frequencies. Differences amongst the four cohorts were investigated using Kruskal-Wallis test and Chi squared test, respectively. BDI, Beck Depression Inventory; BMI, body mass index; BP, blood pressure; MACE, major adverse cardiovascular events; Metabolic syndrome, fulfilling at least three of the components of the metabolic syndrome; Waist component, waist circumference in men ≥94 cm and ≥80 cm in women; Triglyceride component, serum triglyceride concentration ≥1.70 mmol/l or medication to manage dyslipidaemia; HDL component, serum HDL-cholesterol concentration <1.00 mmol/l in men and <1.30 mmol/l in women, or medication to manage dyslipidaemia; BP component, blood pressure ≥130/85 mmHg or antihypertensive treatment.

Table 2 Frequencies of metabolic syndrome and its components by the depressive symptomatology status divided by participating country

		Croatia	Finland	Latvia	Lithuania	All
	BDI score	N=99	N=314	N=315	N=318	N=1046
Diabetic nephropathy	<16	3 (3.2)	43 (16.2)**	21 (8.6)*	93 (34.3)*	160 (18.3)***
	≥16	1 (16.7)	16 (38.1)	10 (23.3)	25 (53.2)	52 (37.7)
Proliferative retinopathy	<16	20 (21.5)	62 (22.9)**	73 (27.0)	92 (34.1)	247 (27.3)***
	≥16	3 (50.0)	18 (42.9)	14 (31.1)	23 (48.9)	58 (41.4)
MACE	<16	3 (3.2)	26 (9.6)	16 (5.9)	14 (5.7)**	59 (6.7)**
	≥16	1 (16.7)	7 (16.7)	4 (8.9)	8 (18.6)	20 (14.7)
Metabolic syndrome	<16	42 (46.7)	219 (80.5)	109 (40.4)	118 (44.4)**	488 (54.3)***
	≥16	5 (83.3)	39 (92.9)	25 (55.6)	30 (66.7)	99 (71.7
Waist component	<16	35 (42.2)	174 (64.0)	85 (31.7)	122 (45.2)	416 (46.6)*
	≥16	5 (83.3)	32 (76.2)	16 (36.4)	27 (58.7)	80 (58.0)
Triglyceride component	<16	33 (35.5)	126 (46.3)	62 (27.8)	55 (21.0)	276 (32.5)**
	≥16	2 (33.3)	26 (61.9)	19 (46.3)	15 (32.6)	62 (45.9)
HDL component	<16	33 (35.5)	121 (44.5)	62 (27.7)	51 (19.6)	267 (31.4)
	≥16	1 (16.7)	24 (57.1)	13 (31.0)	12 (26.1)	50 (36.8)
Blood pressure component	<16	48 (51.6)	220 (80.9)	160 (59.5)	162 (60.2)	590 (65.3)*
	≥16	5 (83.3)	34 (81.0)	32 (71.1)	33 (71.7)	104 (74.8)

Data are presented as number (frequency). BDI, Beck Depression Inventory. Comparisons between individuals with (BDI score ≥16) and without (BDI score <16) symptoms of depression within each sample were done using Chi squared test. MACE, major adverse cardiovascular events. *p<0.05; **p<0.01; ***p<0.001.

Table 3 Associations between depression score and metabolic syndrome and its components, and diabetes complications divided by the participating country

	Croatia	Finland	Latvia	Lithuania	All
	N=99	N=314	N=315	N=318	N=1046
Diabetic nephropathy	1.11 (0.97–1.28)	1.09 (1.05–1.14)***	1.06 (1.02–1.11)*	1.02 (0.99–1.05)	1.05 (1.03–1.07)***
Proliferative retinopathy	1.04 (0.96–1.12)	1.07 (1.03–1.10)**	1.02 (0.98–1.06)	1.02 (0.99–1.05)	1.03 (1.01–1.05)**
MACE	1.11 (0.93–1.31)	1.05 (1.00–1.10)	1.04 (0.97–1.11)	1.07 (1.03–1.12)**	1.05 (1.02–1.08)***
Metabolic syndrome	1.00 (0.91–1.10)	1.06 (0.99–1.13)	1.03 (0.99–1.07)	1.04 (1.01–1.08)*	1.03 (1.01–1.05)*
Waist component	1.04 (0.96–1.13)	1.02 (0.98–1.05)	1.01 (0.97–1.04)	1.03 (0.99–1.07)	1.01 (0.99–1.04)
Triglyceride component	0.96 (0.88–1.05)	1.04 (1.01–1.07)*	1.04 (1.01–1.07)*	1.04 (1.01–1.08)*	1.03 (1.01–1.05)**
HDL component	0.94 (0.85–1.02)	1.02 (0.99–1.05)	1.03 (0.97–1.04)	1.03 (0.99–1.07)	1.01 (0.99–1.03)
Blood pressure component	1.03 (0.95–1.13)	1.02 (0.97–1.07)	1.03 (0.99–1.06)	1.01 (0.98–1.05)	1.02 (0.99–1.04)

Data are presented as Exp(B) (95% CI). Models are adjusted with sex, age, and smoking. The analyses with cohorts combined are additionally adjusted for the country. MACE, major adverse cardiovascular events Logistic regression analysis. *p<0.05; **p<0.01; ***p<0.001.

Table 4 Associations between depression score and metabolic syndrome score, the components of the metabolic syndrome, body mass index and HbA_{1c} divided by the participating country

	Croatia	Finland	Latvia	Lithuania	All
	N=99	N=314	N=315	N=318	N=1046
Metabolic syndrome score	-0.01 (-0.04–0.03)	0.02 (0.01–0.03)*	0.02 (0.01–0.03)*	0.02 (0.01–0.04)**	0.02 (0.01–0.03)**
Waist circumference	0.35 (0.04–0.67)*	0.09 (-0.10–0.29)	-0.01 (-0.18–0.16)	0.08 (-0.08–0.24)	0.06 (-0.04–0.16)
Triglyceride concentration	0.01 (-0.01–0.03)	0.04 (0.02–0.05)***	0.02 (0.01–0.04)***	0.01 (-0.01–0.02)	0.02 (0.01–0.03)***
HDL-cholesterol concentration	-0.01 (-0.02–0.01)	-0.01 (-0.01–0.01)	0.00 (-0.01–0.01)	0.00 (-0.01–0.00)	-0.01 (-0.01–0.01)
Systolic blood pressure	0.39 (-0.05–0.82)	-0.05 (-0.29–0.19)	0.12 (-0.09–0.32)	-0.04 (-0.28–0.20)	0.07 (-0.07–0.20)
Diastolic blood pressure	-0.09 (-0.38–0.19)	0.02 (-0.12–0.17)	0.12 (-0.03–0.27)	0.01 (-0.15–0.17)	0.07 (-0.01–0.16)
Body mass index	0.15 (0.03–0.28)*	-0.03 (-0.11–0.04)	-0.02 (-0.07–0.04)	0.03 (-0.03–0.09)	0.01 (-0.03–0.04)
HbA_{1c}	-0.02 (-0.52–0.49)	0.61 (0.38–0.83)***	0.45 (0.15–0.75)**	0.13 (0.15–0.41)	0.37 (0.21–0.52)***

Data are presented as B (95% CI). Models are adjusted with sex, age, and smoking. Additionally, the models with lipid variables are adjusted for the use of lipid-lowering medication, and the models with blood pressure variables are adjusted for the use of antihypertensive medication. The analyses with cohorts combined are additionally adjusted for the country. Generalised linear regression analysis. *p<0.05; **p<0.01; ***p<0.001.

Table 5 The associations between depression score and the factor-analysis derived risk factor pattern scores

	Croatia	Finland	Latvia	Lithuania	All
	N=99	N=314	N=315	N=318	N=1046
Obesity	0.023 (-0.001–0.047)	0.001 (-0.013–0.016)	-0.002 (-0.015–0.011)	0.007 (-0.005–0.019)	0.003 (-0.005–0.010)
Hypertension	0.021 (-0.006–0.049)	0.003 (-0.012–0.017)	0.009 (-0.004–0.022)	0.001 (-0.014–0.014)	0.003 (-0.005–0.011)
Dyslipidaemia	-0.005 (-0.022–0.013)	0.034 (0.023–0.046)***	0.021 (0.009–0.033)**	0.011 (0.001–0.022)*	0.020 (0.013–0.026)***

Data are presented as B (95% CI). Models are adjusted with sex, age, and smoking. The analyses with all cohorts are additionally adjusted for the country. Generalised linear regression analysis. *p<0.05; ***p<0.001.