Received: 9 January 2025 | Revised: 6 March 2025 | Accepted: 10 March 2025

DOI: 10.1111/dom.16347

ORIGINAL ARTICLE

WILEY

Low levels of soluble neuropilin-1 were associated with depression in adults with newly diagnosed type 2 diabetes

E. O. Melin PhD[1,2,3] | M. Thunander PhD[1,2,3] | P. Wanby PhD[4,5,6] | S. Holmberg PhD[3,4,7] | H. O. Thulesius PhD[4,8] | M. Landin-Olsson PhD[2,9] | M. Hillman PhD[1]

[1]Diabetes Research Laboratory, Biomedical Center, Lund University, Lund, Sweden

[2]Department of Clinical Sciences, Diabetology and Endocrinology, Lund University, Lund, Sweden

[3]Department of Research and Development, Region Kronoberg, Växjö, Sweden

[4]Department of Medicine and Optometry, Faculty of Health and Life Sciences, Linnaeus University, Kalmar, Sweden

[5]Department of Medical and Health Sciences, University of Linköping, Linköping, Sweden

[6]Department of Internal Medicine, Section of Endocrinology, Region Kalmar County, Sweden

[7]Division of Occupational and Environmental Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden

[8]Department of Clinical Sciences, Division of Family Medicine, Lund University, Malmö, Sweden

[9]Department of Endocrinology, Skane University Hospital, Lund, Sweden

Correspondence
E. O. Melin, Diabetes Research Laboratory, Biomedical Center, Lund University, Lund, Sweden.
Email: eva.o.melin@gmail.com

Funding information
The Research and Development fund of Region Kronoberg, Växjö, Sweden, Grant/Award Number: 932029; Research Council of South Eastern Sweden (FORSS), Grant/Award Numbers: FORSS-845251, FORSS-940428, FORSS-968754

Abstract

Aims: To explore the association between soluble neuropilin-1 (sNRP-1) and depression in patients with newly diagnosed type 2 diabetes (T2D).

Materials and Methods: Multicentre, cross-sectional study including adults with serologically confirmed newly diagnosed T2D. Included variables: sex, sNPR-1 (low sNRP-1 was defined as <226 ng/mL), psychometrically assessed depression and anxiety, antidepressants, BMI, haemoglobin A1c, C-peptide and pre-existing cardiovascular disease. Multiple regression analyses were performed with depression and low sNRP-1 as dependent variables.

Results: The study comprised 837 participants (18–94 years, younger patients <60 years 38%). Depressed patients ($n = 119$) compared to non-depressed ($n = 718$) had a higher prevalence of anxiety (64% vs. 14%), antidepressants (36% vs. 14%), low sNRP-1 (45% vs. 22%) (all $p < 0.001$); physical inactivity (42% vs. 29%, $p = 0.006$); smoking (20% vs. 12%, $p = 0.018$); and higher BMI ($p = 0.002$). Independently associated with depression ($n = 736$) were anxiety (adjusted odds ratio (AOR) 11.7, $p < 0.001$), low sNRP-1 (AOR 3.3, $p < 0.001$), BMI (per kg/m^2) (AOR 1.1, $p = 0.016$) and physical inactivity (AOR 1.8, $p = 0.018$).

In younger patients ($n = 288$), independently associated with low sNRP-1 were depression (AOR 3.3, $p < 0.001$), myocardial infarction (AOR 3.8, $p = 0.039$) and younger age (per year) (AOR 0.97, $p = 0.043$). In older patients ($n = 521$), independently associated with low sNRP-1 were depression (AOR 3.1, $p < 0.001$), and younger age (0.97, $p = 0.030$).

Conclusions: Low sNRP-1 (<226 ng/mL) was associated with depression in all patients with newly diagnosed T2D. In younger patients (<60 years), depression, pre-existing myocardial infarction and younger age were associated with low sNRP-1. In older patients, only depression and younger age were associated with low sNRP-1.

KEYWORDS
depression, diabetes mellitus type 2, inflammation, soluble neuropilin-1

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2025 The Author(s). *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

1 | INTRODUCTION

Depression is a well-established risk factor for the development of type 2 diabetes (T2D).[1–3] Persons with T2D are also at increased risk of developing depression due to cerebral microvascular complications,[4] inflammatory disturbances and reduced brain serotonin (5-hydroxytryptamine).[3] In a recent study from this cohort of patients with newly diagnosed T2D, the younger women with T2D had a higher prevalence of depression compared to young women in the Swedish general population.[5] The use of antidepressants was also higher in patients with newly diagnosed T2D than in the general Swedish population.[5] Several metabolic and immunological disturbances[5,6–14] as well as hormonal disturbances such as increased levels of cortisol secretion[13–16] have been demonstrated in people with depression. Both T2D and depression are risk factors for dementia[4,13] and Alzheimer's disease is often preceded by depression.[13] The comorbidity of depression and T2D is associated with an increased risk for cardiovascular disease and all-cause mortality.[4,17,18] Stress contributes to the development of depression,[15] T2D,[19] cardiovascular disease[20] and Alzheimer's disease.[21]

The neuropilin-1 (NRP-1) receptor is a multifunctional transmembrane glycoprotein that is critical for neuronal and cardiovascular development, and for the regulation of the immune system.[22–26] The NRP-1 receptor has the potential to be implicated in diabetes complications as it is expressed in the brain,[27–29] cardiovascular system,[25–27,29–31] kidney,[31] retina,[32] on pancreatic β-cell membranes[33] and in adipose tissue macrophages.[34]

NRP-1 serves as a receptor for several extracellular ligands such as vascular endothelial growth factor (VEGF), semaphorins and transforming growth factor beta (TGF-β).[24,29] Members of the VEGF family, which have neurogenic and angiogenic properties and regulate inflammation, are down-regulated by chronic stress and are up-regulated by antidepressants.[35–37] Down-regulation of the NRP-1 receptor is initiated by VEGF induction of the NRP-1 receptor cleavage by the two proteolytic enzymes ADAM 9 and 10, which are members of the disintegrin and metalloproteinase family.[38] After the NRP-1 receptor cleavage, soluble (s)NRP-1 circulates freely in blood and other body fluids.[38] Previous experimental research has shown that NRP-1 receptor expression in adipose tissue macrophages was protective against obesity and the metabolic syndrome,[34] and that ablation of the NRP-1 receptor in this type of cell led to reduced insulin sensitivity.[39] In people with human immunodeficiency virus (HIV), higher levels of the NRP-1 receptor were associated with coronary plaque, myocardial infarction and all-cause mortality.[25,26] In experimental studies, the NRP-1 receptor showed cardioprotective effects during myocardial ischaemia.[30] Increased levels of the NRP-1 receptor have been demonstrated in the brain tissue of patients with severe Alzheimer's disease,[28] while lower levels of sNRP-1 extracted from serum have been demonstrated in patients with Alzheimer's disease.[40]

As Alzheimer's disease is frequently preceded by or concurrent with depression,[13] and lower levels of serum sNRP-1 have been demonstrated in persons with Alzheimer's disease,[40] we hypothesized that lower levels of plasma sNRP-1 may be linked to depression in patients with newly diagnosed T2D. The aim was to explore associations between sNRP-1 and depression while adjusting for variables previously linked to depression in patients with newly diagnosed T2D.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

The study has a multicentre and cross-sectional design. Inclusion criteria were adults (≥ 18 years) with newly diagnosed serologically verified T2D, completion of the Swedish version of the Hospital Anxiety and Depression Scale (HADS) ($n = 1027$)[5] and performed biochemical analyses of sNRP-1 ($n = 837$ [81%]). Exclusion criterion was gestational diabetes.[5] The recruitment period lasted for 2 years, from 1 January 2016 to 31 December 2017 in Region Kronoberg, and from 1 March 2016 to 28 February 2017 in Region Kalmar in southeastern Sweden.[5] The participants were recruited from five hospitals and 54 primary care units in the two regions. At the time of the diagnoses or at the first follow-up, typically within 1–3 weeks, self-report instruments were distributed, blood samples were collected and anthropometrics were performed. Missing data are detailed in Tables 1 and 3. No data imputation was performed. A total of 837 patients were included in our second exploration of depression in patients with newly diagnosed T2D.

2.2 | Diagnosis and classification of diabetes

Serologically confirmed newly diagnosed T2D was defined as diabetes mellitus according to WHO and ADA criteria[5,41] without a previous history of a diabetes diagnosis or treatment, and with serological confirmation by negative islet antibody analyses (glutamic acid decarboxylase (GAD) antibodies <10 units/mL) and C-peptide levels ≥0.25 nmol/L.[5,42,43] C-peptide is a measure of endogenous insulin secretion.[43]

2.3 | Biochemical analyses

Plasma sNRP-1 (ng/mL) was analysed by commercial DuoSet enzyme-linked immune-sorbent assay (ELISA) (R&D systems®, Minneapolis, Minnesota, USA). sNRP-1 (dilution factor 1:500) was added to pre-coated 96-well microplates with sNRP-1 capturing antibodies and thereafter incubated for 2 h at room temperature. Horseradish peroxidase was added, resulting in a colour change with the intensity related to the concentration of sNRP-1. Data were analysed at 450 nm with 580 nm wavelength correction in a FLUOstar OPTIMA ELISA reader (BMG LABTECH®, Ortenberg, Germany). The protein concentration was determined via a 7-point standard curve with a 4-parameter fit. The intra-assay coefficient of variation was 2.0. SNRP-1 was used as a continuous variable, divided into quartiles and

dichotomized at the first quartile. Low levels of sNRP-1 were defined as <226 ng/mL.

C-peptide was analysed by using a commercial ELISA (Mercodia® [article nr 10-1136-01], Uppsala, Sweden), and GAD antibodies by using an ELISA from RSR® (Article nr Rs-GDE/96, RSR Ltd., Cardiff, UK).

Haemoglobin A1c (HbA1c) was analysed using Olympus automated clinical chemistry analysers with high specificity (Olympus AU®, Tokyo, Japan). The intra-coefficient of variation was <1.2%.

2.4 | Depression, anxiety and the use of antidepressants

Self-reported depression was defined as HADS – D (the depression subscale) ≥ 8 points, and anxiety as HADS – A (the anxiety subscale) ≥ 8 points.[5,7,10–12,44–47] Current use of antidepressants was recorded based on self-reports.[5]

2.5 | Cardiovascular disease

Diagnoses of myocardial infarction, heart failure, stroke/TIA and peripheral arterial insufficiency existing prior to the diagnosis of diabetes were registered.

2.6 | Age

Age was either used as a continuous variable, dichotomized into younger patients (<60 years) and older patients (≥60 years), or was divided into seven age groups.[5]

2.7 | Anthropometrics

Weight and length were measured by a nurse. Body mass index (BMI) kg/m^2 was calculated. Obesity was defined as BMI ≥ 30 kg/m^2.

2.8 | Smoking and physical activity

Smoking habits were dichotomized into current smokers (daily or occasionally) or non-smokers (never or previous (not within the last 6 months) smokers). Physical activity was defined as at least 30 min of regular moderate physical activity at least once a week, and physical inactivity was defined as less than 30 min once a week.[5]

2.9 | Statistical analysis

BMI, HbA1c, sNRP-1 and C-peptide were not normally distributed. The analyses were performed with Mann–Whitney *U* test. The results were presented as median (quartile [q]$_1$, q$_3$). Pearson's Chi-Squared test, Fisher's Exact Test (both two-tailed) and Linear-by-linear Association were performed for categorical data, which were presented as *n* (%). Crude odds ratios (CORs) were calculated for all included variables. Adjusted ORs (AORs) were calculated using multiple regression analysis (Backward: Wald) with depression or low sNRP-1 (<226 ng/mL) as dependent variables. Only variables with *p*-values ≤0.10 for the CORs were included in the multiple regression analyses. 95% confidence intervals (CI) were used. Linear regression analysis was performed between C-peptide and sNRP-1. $p < 0.05$ was considered statistically significant. SPSS® version 27 (IBM, Chicago, Il, USA) was used.

2.10 | Power calculation

To be able to demonstrate an association between low sNRP-1 and depression, and to reach a power of 0.8, with alpha 0.05 and beta 0.2, a minimum of 404 participants would be required. The power calculation was based on a prevalence of depression of 14% and on a prevalence of low sNRP-1 of 25%.

3 | RESULTS

In this cohort of 837 patients with newly diagnosed serologically verified T2D (women 39%; age 18–94 years), 119 (14%) patients were depressed. The prevalence of depression was higher in 327 women than in 510 men (18% vs. 12%, $p = 0.006$). Younger patients (<60 years, $n = 316$) compared to older patients (≥ 60 years, $n = 521$) had a higher prevalence of anxiety (31% vs. 15%, $p < 0.001$), smoking (19% vs. 10%, $p = 0.001$), depression (18% vs. 12%, $p = 0.008$) and physical inactivity (37% vs. 27%, $p = 0.005$); higher levels of HbA1c (mmol/mol) median (q$_1$, q$_3$) (54 (46, 84) vs. 49 (45, 57), $p < 0.001$) and of BMI (kg/m^2) (31.8 [28.5, 36.8], vs. 30.2 [27.1, 33.4], $p < 0.001$); and lower levels of C-peptide (nmol/L) (1.0 [0.7, 1.4] vs. 1.1 [0.8, 1.7], $p = 0.020$).

Median (q$_1$, q$_3$; range) sNRP-1 (ng/mL) was for all 837 patients 268 (226, 328; 66–901). The prevalence of low sNRP-1 (< 226 ng/mL) was 25% without any sex difference ($p = 0.23$). For the 119 depressed patients, the prevalence of low sNRP-1 did not differ between seven age groups ($p = 0.19$) in contrast to the 718 non-depressed patients, where the prevalence of low sNRP-1 was higher in the younger age groups and declined significantly within the older age groups ($p = 0.031$) (Figure 1). C-peptide ranged from 0.25 to 5.58 nmol/L.

Baseline characteristics and comparisons between depressed and non-depressed patients are presented in Table 1. The prevalence of depression differed significantly between the sNRP-1 quartiles for all 837 patients ($p < 0.001$), 316 younger patients ($p = 0.009$) and 521 older patients ($p < 0.001$). In all patients, the prevalence of depression was 13% in patients with the highest levels of sNRP-1 (corresponding to the fourth quartile) compared to 45% in patients

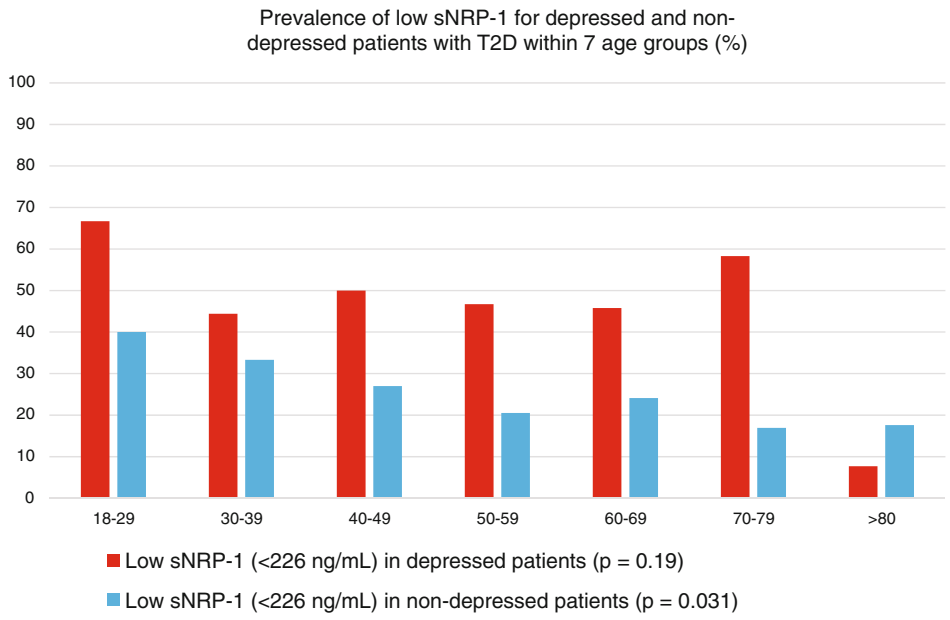

FIGURE 1 The prevalence of low sNRP-1 did not differ between the seven age groups for depressed patients with T2D. The prevalence of low sNRP-1 was highest within the younger age groups and declined with older age in non-depressed patients with T2D. A linear-by-linear association was used.

TABLE 1 Baseline characteristics of 837 patients with newly diagnosed T2D and comparisons between depressed and non-depressed patients.

		All	Depression (self-reported)								
		18–94 years	18–94 years ($n = 837$)			<60 years ($n = 316$)			≥60 years ($n = 521$)		
			Yes	No		Yes	No		Yes	No	
n		**837**	**119**	**718**	***p*[a]**	**58**	**258**	***p*[a]**	**61**	**460**	***p*[a]**
Age (years)		65 (55, 72)	61 (51, 72)	65 (56, 72)	0.027[b]	50 (41, 54)	53 (46, 57)	0.004[b]	72 (66, 78)	70 (66, 75)	0.08[b]
Sex	Women	327 (39)	60 (50)	267 (37)	0.006	34 (59)	74 (29)	<0.001	26 (43)	193 (42)	0.92
	Men	510 (61)	59 (50)	451 (63)		24 (41)	184 (71)		35 (57)	267 (58)	
Anxiety		175 (21)	76 (64)	99 (14)	<0.001	44 (76)	53 (20)	<0.001	32 (52)	47 (10)	<0.001
Antidepressants[c]		83 (18)	29 (36)	54 (14)	<0.001	20 (46)	20 (14)	<0.001	9 (24)	34 (14)	0.14[g]
sNRP-1 quartiles	4th	210 (25)	16 (13)	194 (27)	<0.001[d]	9 (16)	61 (24)	0.009[d]	7 (11)	133 (29)	<0.001[d]
	3rd	212 (25)	26 (22)	186 (26)		14 (24)	66 (26)		12 (20)	120 (26)	
	2nd	206 (25)	23 (19)	183 (25)		7 (12)	70 (27)		16 (28)	113 (25)	
	1st	209 (25)	54 (45)	155 (22)		28 (48)	61 (24)		26 (43)	94 (20)	
Low sNRP-1 (<226 ng/mL)		209 (25)	54 (45)	155 (22)	<0.001	28 (48)	61 (24)	<0.001	26 (43)	94 (20)	<0.001
HbA1c (mmol/mol)[e]		50 (45, 66)	50 (45, 64)	50 (45, 66)	0.99[b]	56 (48, 78)	53 (46, 85)	0.75[b]	49 (44, 55)	49 (45, 58)	0.24[b]
C-peptide (nmol/L)		1.1 (0.8, 1.6)	1.2 (0.9, 1.9)	1.0 (0.7, 1.6)	0.004	1.1 (0.8, 1.8)	1.0 (0.7, 1.4)	0.11	1.4 (1.0, 2.0)	1.1 (0.8, 1.6)	0.006
BMI (kg/m^2)[f]		31 (28, 34)	32 (28, 37)	31 (28, 34)	0.002[b]	36 (31, 39)	31 (28, 36)	<0.001[b]	30 (27, 34)	30 (27, 33)	0.69[b]
Obesity (BMI ≥30 kg/m^2)[f]		451 (54)	75 (66)	376 (54)	0.025	44 (82)	149 (61)	0.004	31 (52)	227 (51)	0.95
Physical inactivity[g]		240 (31)	45 (42)	195 (29)	0.006	27 (52)	82 (34)	0.013	18 (33)	113 (26)	0.28
Smoking[h]		109 (13)	23 (20)	86 (12)	0.018	15 (27)	42 (17)	0.055	8 (14)	44 (9)	0.36[i]
Stroke[j]		62 (8)	8 (7)	54 (8)	1.00[i]	3 (6)	5 (2)	0.16[i]	5 (9)	49 (11)	0.82[i]
MI[k]		93 (12)	13 (12)	80 (12)	0.97	3 (6)	8 (3)	0.43[i]	10 (18)	72 (16)	0.70[i]
Heart failure[l]		31 (4)	6 (6)	25 (4)	0.42[i]	1 (2)	2 (1)	0.48[i]	5 (11)	23 (6)	0.19[i]
PAI[m]		23 (3)	3 (3)	20 (3)	1.00[i]	0 (0)	2 (1)	1.00[i]	3 (7)	17 (5)	0.46[i]

Note: Data are presented as *n* (%), or as median (q_1, q_3). [a] Pearson Chi-Square unless otherwise indicated. [b] Mann–Whitney U Test. Missing values: [c]368/134/234. [d] Linear-by-Linear Association. Missing values: [e] 9/2/7; [f] 34/16/18; [g] 60/20/40; [h] 20/9/11. [i] Fisher's Exact Test. Missing values: [j] 54/25/29; [k]57/28/29; [l] 142/56/86; [m] 145/55/90. [j–m] Pre-existing.

Abbreviations: BMI, body mass index; HbA1c, haemoglobin A1c; MI, myocardial infarction; PAI, peripheral arterial insufficiency; sNRP-1, soluble neutropilin-1.

TABLE 2 Associations with depression presented for all, younger and older patients with newly diagnosed T2D.

		Depression (self-reported)							
		18–94 years				<60 years		≥60 years	
		COR (95% CI)	*p*	AOR (95% CI)	*p*[a]	AOR (95% CI)	*p*[b]	AOR (95% CI)	*p*[c]
Age (per year)		0.98 (0.96–0.99)	0.008	1.02 (1.00–1.04)	0.09	0.98 (0.94–1.02)	0.35	1.09 (1.04–1.14)	<0.001
Women		1.7 (1.2–2.5)	0.007	1.3 (0.8–2.1)	0.30	2.5 (1.1–5.5)	0.022	-	-
Anxiety		11.1 (7.2–17.0)	<0.001	11.7 (7.0–19.5)	<0.001	12.0 (5.3–27.0)	<0.001	11.9 (6.2–22.7)	<0.001
Antidepressants		3.4 (2.0–5.9)	<0.001	-	-	-	-	-	-
sNRP-1 quartiles	4th	0.24 (0.13–0.43)	<0.001	-	-	-	-	-	-
	3rd	0.40 (0.24–0.67)		-	-	-	-	-	-
	2nd	0.36 (0.21–0.62)		-	-	-	-	-	-
	1st	1		-	-	-	-	-	-
Low sNRP-1 (<226 ng/mL)		3.0 (2.0–4.5)	<0.001	3.3 (2.0–5.5)	<0.001	6.0 (2.6–13.8)	<0.001	2.8 (1.5–5.2)	0.001
BMI (per kg/m^2)		1.1 (1.0–1.1)	<0.001	1.1 (1.0–1.1)	0.016	1.1 (1.0–1.2)	0.021	-	-
Physical inactivity		1.8 (1.2–2.7)	0.006	1.8 (1.1–3.0)	0.018	2.4 (1.1–5.3)	0.031	-	-
Smoking		1.8 (1.1–3.1)	0.020	1.6 (0.8–3.0)	0.14	1.3 (0.5–3.2)	0.59	-	-

Note: [a–c] Multiple regression analysis (Backward Wald): $N =$ [a]736/[b]279/[c]457; Nagelkerke R Square [a]0.32/[b]0.46/[c]0.29.
Abbreviations: BMI, body mass index; sNRP-1, soluble neutropilin-1.

TABLE 3 Comparisons between patients with low and high levels of NRP-1 presented for all, for 316 younger and 521 older patients with newly diagnosed T2D.

		Low soluble neuropilin-1 (<226 ng/mL)								
		18–59 years ($n = 837$)			<60 years ($n = 316$)			≥60 years ($n = 521$)		
		Yes	No		Yes	No		Yes	No	
n		209	628	*p*[a]	89	227	*p*[a]	120	401	*p*[a]
Age (years)		63 (52, 70)	65 (56, 72)	0.009[b]	50 (43, 56)	53 (45, 57)	0.054[b]	69 (66, 74)	71 (66, 76)	0.11[b]
Sex	Women	89 (43)	238 (38)	0.23	35 (39)	73 (32)	0.23	54 (45)	165 (41)	0.45
	Men	120 (57)	390 (62)		54 (61)	154 (68)		66 (55)	236 (60)	
Depression		54 (26)	65 (10)	<0.001	28 (32)	30 (13)	<0.001	26 (22)	35 (9)	<0.001
Anxiety		61 (29)	114 (18)	0.001	33 (37)	64 (28)	0.12	28 (23)	50 (12)	0.003
Antidepressants[c]		28 (24)	55 (16)	0.041	15 (28)	25 (19)	0.19	30 (40)	13 (20)	0.18
HbA1c mmol/mol[d]		50 (46, 64)	50 (45, 66)	0.82[b]	53 (47, 82)	54 (46, 85)	0.93[b]	49 (45, 55)	49 (45, 58)	0.48[b]
C-peptide (nmol/L)		1.16 (0.80, 1.66)	1.05 (0.75, 1.57)	0.13	1.01 (0.72, 1.38)	1.02 (0.73, 1.43)	0.84	1.31 (0.88, 1.81)	1.09 (0.76, 1.65)	0.028
BMI (kg/m^2)[e]		31 (28, 34)	31 (28, 35)	0.72[b]	31 (28, 36)	33 (29, 37)	0.12[b]	31 (27, 33)	30 (27, 34)	0.71[b]
Physical inactivity[f]		54 (29)	186 (32)	0.43	28 (35)	81 (38)	0.69	26 (24)	10 (28)	0.37
Smoking[g]		35 (17)	74 (12)	0.069	21 (24)	36 (16)	0.11	14 (12)	38 (10)	0.50
Stroke[h]		17 (9)	45 (8)	0.60	4 (5)	4 (2)	0.22[i]	13 (12)	41 (11)	0.84
MI[j]		22 (11)	71 (12)	0.80	6 (8)	5 (2)	0.078[i]	16 (14)	66 (17)	0.42
Heart failure[k]		5 (3)	26 (5)	0.30[c]	1 (1)	1 (1)	1.00[i]	4 (4)	24 (7)	0.48[c]
PAI[l]		3 (2)	20 (4)	0.22[c]	0	2 (1)	1.00[i]	3 (3)	18 (5)	0.43[c]

Note: Data are presented as *n* (%), or as median (q_1, q_3). [a]Pearson Chi-Square unless otherwise indicated. [b]Mann–Whitney U Test. Missing values: [c] 368/134/234; [d] 9/2/7; [e] 34/16/18; [f] 60/20/40; [g] 20/9/11. [h] 54/25/29. [i] Fisher's Exact Test. Missing values: [j] 57/28/29; [k] 142/56/86; [l] 145/55/90. [h–l] Pre-existing.
Abbreviations: BMI, body mass index; HbA1c, haemoglobin A1c; MI, myocardial infarction; PAI, peripheral arterial insufficiency; sNRP-1, soluble neutropilin-1.

with low sNRP-1 (corresponding to the first quartile). Among the younger patients, comparisons between 58 depressed and 258 non-depressed patients showed that women had a higher prevalence of depression compared to men, and that the depressed patients had a higher prevalence of anxiety, use of antidepressants, low sNRP-1 and higher median BMI levels (all $p < 0.001$); were younger ($p = 0.004$); and had a higher prevalence of physical inactivity ($p = 0.013$). Among the older patients, 61 depressed patients compared to 460 non-depressed had a higher prevalence of anxiety and low sNRP-1 (both $p < 0.001$) and higher levels of C-peptide ($p = 0.028$).

Associations with depression are presented in Table 2. In all patients, the associations with depression were significantly lower for the 2nd, 3rd and 4th quartiles of sNRP-1 levels compared to the first quartile (COR 0.36, COR 0.40 and COR 0.24 respectively, $p < 0.001$). In patients aged 18–94 years ($n = 736$), anxiety (AOR 11.7, $p < 0.001$), low sNRP-1 (AOR 3.3, $p < 0.001$), BMI (per kg/m^2) (AOR 1.06, $p = 0.016$) and physical inactivity (AOR 1.8, $p = 0.018$) were independently associated with depression. The use of antidepressants was associated with depression in the whole cohort ($p < 0.001$) but was not included in the multiple logistic regression analyses. In the younger patients ($n = 279$), anxiety (AOR 12.0, $p < 0.001$), low sNRP-1 (AOR 6.0, $p < 0.001$), BMI (per kg/m^2) (AOR 1.08, $p = 0.021$), women (AOR 2.5, $p = 0.022$) and physical inactivity (AOR 2.4, $p = 0.031$) were independently associated with depression. In the older patients ($n = 457$), older age (per year) (AOR 1.09, $p < 0.001$), anxiety (AOR 11.9, $p < 0.001$) and low sNRP-1 (AOR 2.8, $p = 0.001$) were independently associated with depression. Variables with p-values >0.10 for the CORs were not included in the multiple regression analyses.

SNRP-1 (per ng/mL) was not associated with C-peptide (per nmol/L) (unstandardized B coefficient − 0.002, $p = 0.37$).

Comparisons between patients with low and high sNRP-1 are presented in Table 3. In the whole cohort, the patients with low sNRP-1 had a higher prevalence of depression ($p < 0.001$), anxiety ($p = 0.001$) and use of antidepressants ($p = 0.041$); and were younger ($p = 0.009$). In the younger patients, only the prevalence of depression was significantly higher in patients with low sNRP-1. In the older patients, the prevalence of depression ($p < 0.001$) and anxiety ($p = 0.003$), and the C-peptide levels were higher in patients with low sNRP-1 ($p = 0.028$).

Associations with low sNRP-1 are presented in Table 4. In patients aged 18–94 years ($n = 817$), depression (AOR 3.1, $p < 0.001$) and lower age (per year) (AOR 0.98, $p = 0.016$) were independently associated with low sNRP-1. In the younger patients ($n = 288$), depression (AOR 3.3, $p < 0.001$), myocardial infarction (AOR 3.8, $p = 0.039$) and lower age (per year) (AOR 0.97, $p = 0.043$) were independently associated with low sNRP-1. In the older patients ($n = 521$), depression (AOR 3.1, $p < 0.001$) and lower age (AOR 0.97, $p = 0.030$) were independently associated with low sNRP-1. Variables with p-values >0.10 for the CORs were not included in the multiple regression analyses.

4 | DISCUSSION

The main finding of this study of 837 adults with newly diagnosed T2D and maintained insulin production was that both younger and older patients with depression (self-reported) had a significantly higher prevalence of low sNRP-1 (<226 ng/mL) compared to those

TABLE 4 Associations with low levels of neuropilin-1 presented for all, younger and older patients with newly diagnosed T2D.

	Low soluble neuropilin-1 (<226 ng/mL)							
	18–94 years				<60 years		≥60 years	
	COR (95% CI)	p	AOR (95% CI)	p^a	AOR (95% CI)	p^b	AOR (95% CI)	p^c
Age	0.98 (0.97–0.99)	0.004	0.98 (0.97–1.00)	0.016	0.97 (0.94–1.00)	0.043	0.97 (0.94–1.00)	0.030
Women	1.2 (0.9–1.7)	0.23	-	-	-	-	-	-
Depression	3.0 (2.0–4.5)	<0.001	3.1 (2.0–4.7)	<0.001	3.3 (1.7–6.2)	<0.001	3.1 (1.8–5.5)	<0.001
Anxiety	1.9 (1.3–2.7)	0.001	1.2 (0.7–1.8)	0.52	-	-	1.4 (0.8–2.6)	0.24
Antidepressants	1.6 (0.8–3.4)	0.19	-	-	-	-	-	-
HbA1c (per mmol/mol)	1.00 (0.99–1.01)	0.80	-	-	-	-	-	-
C-peptide (nmol/L)	1.1 (0.9–1.4)	0.33	-	-		-	-	-
BMI (per kg/m^2)	1.0 (1.0–1.0)	0.65	-	-	-	-	-	-
HbA1c (per mmol/mol)	1.00 (0.99–1.01)	0.80	-	-	-	-	-	-
Physical inactivity	0.8 (0.6–1.2)	0.43	-	-	-	-	-	-
Smoking	1.5 (1.0–2.3)	0.071	1.2 (0.8–2.0)	0.34	-	-	-	-
Stroke [d]	1.2 (0.7–2.1)	0.60	-	-	-	-	-	-
MI [e]	0.9 (0.6–1.6)	0.80	-	-	3.8 (1.1–13.8)	0.039	-	-
Heart failure [f]	0.6 (0.2–1.5)	0.26	-	-	-	-	-	-
PAI [g]	0.4 (0.1–1.5)	0.18	-	-	-	-	-	-

Note: [a–c] Multiple regression analysis: Backward (Wald): N = [a]817/[b]288/[c]521; Nagelkerke R Square [a]0.063/[b]0.112/[c]0.052. [d–g] Pre-existing.
Abbreviations: BMI, body mass index; HbA1c, haemoglobin A1c; MI, myocardial infarction; PAI, peripheral arterial insufficiency; sNRP-1, soluble neutropilin-1.

without depression. In the younger patients (<60 years), low sNRP-1, anxiety, higher BMI, women and physical inactivity were independently associated with depression. In the older patients (≥60 years), low sNRP-1, anxiety and older age were independently associated with depression. In the younger patients, depression, pre-existing myocardial infarction and younger age were independently associated with low sNRP-1. In the older patients, only depression and younger age were independently associated with low sNRP-1. BMI, HbA1c, C-peptide, smoking, physical inactivity, anxiety and the use of antidepressants were not associated with low sNRP-1.

We hypothesized that low levels of sNRP-1 would be associated with depression and our hypothesis was confirmed. Our findings are new and as per our knowledge, a potential association between depression and sNRP-1 has not previously been explored. Depression may be both a risk factor for and a symptom of neurodegeneration due to dementia.[13] In people with Alzheimer's disease, increased levels of the NRP-1 receptor have been demonstrated in the brain tissue,[28] while lower levels of sNRP-1 have been demonstrated in serum.[40] We have not quantified the NRP-1 receptor, so we do not know whether low levels of sNRP-1 reflect high levels of the NRP-1 receptor in the brains of these patients. We also found an association between low sNRP-1 and pre-existing myocardial infarction in the younger patients. In previous clinical and experimental research, the NRP-1 receptor has been explored in relation to coronary plaque, myocardial ischaemia and infarction,[25,26,30,31] but we have not found any previous studies exploring the plasma levels of sNRP-1 in people with ischaemic cardiovascular disease. Depression, stress responses, T2D and cardiovascular disease share several pathophysiological mechanisms, such as disturbances of the hypothalamus–pituitary–adrenal (HPA) axis.[14–16,19,20,35,48] It has been demonstrated in previous research that VEGF is down-regulated by stress and up-regulated by antidepressants.[35,36] VEGF is essential for the induction of the proteolysis leading to the cleavage of the NRP-1 receptor and the secretion of sNRP-1.[38] This implies that low levels of sNRP-1 may be a consequence of stress. We found that younger age, independently of depression, was associated with a higher prevalence of low sNRP-1. According to the Swedish National Public Health Report (2012), younger people compared to older people experience higher levels of stress.[49] Both stress[19] and old age[41] contribute to the development of T2D, so the finding of an association between low sNRP-1 and younger age may be an important finding in patients with newly diagnosed T2D.

HbA1c was not associated with low sNRP-1, which is in line with results from a previous study of critically ill patients where sNRP-1 was not associated with HbA1c.[50] As low sNRP-1 was associated with depression but not with glycaemic control (HbA1c), BMI or C-peptide levels, our findings may not be restricted to T2D patients.

There were several strengths of our study. The number of participants was high and by far outreached the minimum necessary number of participants according to the power calculation. Precise ELISA techniques were used, and the assays showed low intra-assay coefficients of variation for sNRP-1. The self-report instrument used to explore depressive symptoms, HADS-D, has been widely used in research and has shown high validity for assessing depressive symptoms both at an individual and collective level.[5,7,10–12,16,44–47] The clinical diagnoses of T2D were serologically verified.[42] We controlled for relevant variables such as age,[18,51] sex,[45,51] obesity,[6] physical inactivity,[45,52] smoking,[45,53] HbA1c[7] and cardiovascular disease,[17,18,45] which all have been linked to depression. We also explored a potential association between C-peptide and sNRP-1, as the NRP-1 receptor has been linked to insulin sensitivity[34,39] and may be involved in β-cell failure.[33] We decided to present our results for both patients younger than 60 years and older as the likelihood of Alzheimer's disease is low in patients younger than 60 years. In western Europe, the prevalence of Alzheimer's disease is about 0.7% in people aged 60–64 years and increases by age.[54]

There are limitations to this study. We do not know if patients with Alzheimer's disease were included. However, people who could not complete HADS due to cognitive difficulties were not included, and the prevalence of low sNRP-1 was high also in the very young patients with depression, where the likelihood of Alzheimer's disease is very low. Self-reported depression was not verified by a clinical diagnosis, but there was a significant association between self-reported depression and the use of antidepressants.

We cannot determine any causality in this cross-sectional study. In further research, it would be of interest to systematically explore links between depression, stress, plasma VEGF, the NRP-1 receptor, sNRP-1, cortisol secretion, cardiovascular disease and Alzheimer's disease, both in people with and without T2D. Is perceived stress correlated to low sNRP-1 levels? In longitudinal studies it would be interesting to explore whether sNRP-1 can be used for evaluation of treatment efficacy. Will the levels of sNRP-1 increase if the symptoms of depression successfully decline? It would also be interesting to perform longitudinal studies exploring whether sNRP-1 could be used as a risk marker for the development of cardiovascular disease or Alzheimer's disease in general cohort studies.

Clinically, due to the strong links between depression and metabolic, immunological and hormonal disturbances,[5,6–14,16] dementia,[4,13] cardiovascular disease and all-cause mortality,[4,17,18] we find it of utmost importance to identify and treat depression in patients with newly diagnosed T2D. We suggest routinely using self-report instruments for the detection of depression at the time of the T2D diagnosis. There is research supporting that antidepressants may have neuroprotective effects, improve cognitive function in depressed elderly patients and reduce the risk of developing Alzheimer's disease.[13,55] Recent research has also shown antidepressant effects of GLP-1 receptor agonists,[56] which may also reduce weight and have protective effects against dementia and cardiovascular disease.[57,58]

In conclusion, low levels of sNRP-1 were clearly associated with depression in the whole cohort of adult patients with newly diagnosed T2D. In the younger patients, depression, pre-existing myocardial infarction and younger age were independently associated with low levels of sNRP-1.

AUTHOR CONTRIBUTIONS

EOM, MT, PW, SH, MLO, HT, MH, participated as investigators, planned and organized the study, contributed to data collection, and reviewed, edited and approved the final version of the manuscript. EOM performed the statistical analysis, drafted the manuscript, is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. MH takes full responsibility for the ELISA analyses.

ACKNOWLEDGEMENTS

We are grateful to all physicians and nurses in Region Kalmar and Region Kronoberg who have contributed by recruiting patients, performing interviews and anthropometrics. Additionally, we thank the participants for agreeing to take part in the study.

FUNDING INFORMATION

This research was supported by the Research Council of South Eastern Sweden (FORSS) Linköping, Sweden, grant numbers: FORSS-845251, FORSS-940428, FORSS-968754, and by The Research and Development fund of Region Kronoberg, Växjö, Sweden, grant number 932029. The funding sources were not involved in the collection, analysis or interpretation of the data, in the writing of the report or in the decision to submit the article for publication.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16347.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by the Regional Ethical Review Board of Linköping University, Linköping (Registration nos. 2015/350-31, date 2016-01-12, and 2017/354--32, date 2017-08-18). All participants provided written informed consent. The research was performed in accordance with the Declaration of Helsinki.

ORCID

E. O. Melin https://orcid.org/0000-0002-7835-2650

REFERENCES

1. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008; 31(12):2383-2390. doi:10.2337/dc08-0985
2. Deleskog A, Ljung R, Forsell Y, Nevriana A, Almas A, Möller J. Severity of depression, anxious distress and the risk of type 2 diabetes–a population-based cohort study in Sweden. *BMC Public Health*. 2019; 19(1):1-9. doi:10.1186/s12889-019-7322-z
3. Khawagi WY, Al-kuraishy HM, Hussein NR, et al. Depression and type 2 diabetes: a causal relationship and mechanistic pathway. *Diabetes Obes Metab*. 2024;26(8):3031-3044. doi:10.1111/dom.15630
4. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CD. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol*. 2020; 8(4):325-336. doi:10.1016/S2213-8587(19)30405-X
5. Melin EO, Wanby P, Neumark T, et al. Depression was associated with younger age, female sex, obesity, smoking, and physical inactivity, in 1027 patients with newly diagnosed type 2 diabetes: a Swedish multicentre cross-sectional study. *BMC Endocr Disord*. 2022;22(1):1-12. doi:10.1186/s12902-022-01184-3 273.
6. Fu X, Wang Y, Zhao F, et al. Shared biological mechanisms of depression and obesity: focus on adipokines and lipokines. *Aging*. 2023; 15(12):5917-5950. doi:10.18632/aging.204847
7. Melin EO, Thunander M, Svensson R, Landin-Olsson M, Thulesius HO. Depression, obesity and smoking were independently associated with inadequate glycemic control in patients with type 1 diabetes. *Eur J Endocrinol*. 2013;168:861-869. doi:10.1530/EJE-13-0137
8. Mac Giollabhui N, Ng TH, Ellman LM, Alloy LB. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. *Mol Psychiatry*. 2021; 26(7):3302-3314. doi:10.1038/s41380-020-00867-4
9. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: a meta-analysis. *J Affect Disord*. 2020;277:940-948. doi:10.1016/j.jad.2020.09.025
10. Melin EO, Dereke J, Thunander M, Hillman M. Depression in type 1 diabetes was associated with high levels of circulating galectin-3. *Endocr Connect*. 2018;7(6):819-828. doi:10.1530/EC-18-0108
11. Melin EO, Dereke J, Hillman M. Low levels of soluble TWEAK, indicating on-going inflammation, were associated with depression in type 1 diabetes: a cross-sectional study. *BMC Psychiatry*. 2020;20(1): 574. doi:10.1186/s12888-020-02977-3
12. Melin EO, Thulesius HO, Hillman M, Svensson R, Landin-Olsson M, Thunander M. Lower HDL-cholesterol, a known marker of cardiovascular risk, was associated with depression in type 1 diabetes: a cross sectional study. *Lipids Health Dis*. 2019;18(1):65. doi:10.1186/s12944-019-1009-4
13. Dafsari FS, Jessen F. Depression—an underrecognized target for prevention of dementia in Alzheimer's disease. *Transl Psychiatry*. 2020; 10(1):160. doi:10.1038/s41398-020-0839-1
14. de Menezes Galvão AC, Almeida RN, de Sousa Jr GM, et al. Pathophysiology of major depression by clinical stages. *Front Psychol*. 2021; 12:641779. doi:10.3389/fpsyg.2021.641779
15. Belleau EL, Treadway MT, Pizzagalli DA. The impact of stress and major depressive disorder on hippocampal and medial prefrontal cortex morphology. Revisiting neural circuitry depress. *Biopsych*. 2019; 85(6):443-453. doi:10.1016/j.biopsych.2018.09.031
16. Melin EO, Thunander M, Landin-Olsson M, Hillman M, Thulesius HO. Depression, smoking, physical inactivity and season independently associated with midnight salivary cortisol in type 1 diabetes. *BMC Endocr Disord*. 2014;14(1):75. doi:10.1186/1472-6823-14-75
17. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care*. 2005;28(6):1339-1345. doi:28/6/1339 [pii].
18. Shao A, Lin D, Wang L, Tu S, Lenahan C, Zhang J. Oxidative stress at the crossroads of aging, stroke and depression. *Aging Dis*. 2020;11(6): 1537-1566. doi:10.14336/AD.2020.0225
19. Kelly SJ, Ismail M. Stress and type 2 diabetes: a review of how stress contributes to the development of type 2 diabetes. *Annu Rev Public*

Health. 2015;36(1):441-462. doi:10.1146/annurev-publhealth-031914-122921
20. Popovic D, Bjelobrk M, Tesic M, et al. Defining the importance of stress reduction in managing cardiovascular disease-the role of exercise. *Prog Cardiovasc Dis*. 2022;70:84-93. doi:10.1016/j.pcad.2022.01.008
21. Justice NJ. The relationship between stress and Alzheimer's disease. *Neurobiol Stress*. 2018;8:127-133. doi:10.1016/j.ynstr.2018.04.002
22. Kitsukawa T, Shimono A, Kawakami A, Kondoh H, Fujisawa H. Overexpression of a membrane protein, neuropilin, in chimeric mice causes anomalies in the cardiovascular system, nervous system and limbs. *Development*. 1995;121(12):4309-4318. doi:10.1242/dev.121.12.4309
23. Kumanogoh A, Kikutani H. Immunological functions of the neuropilins and plexins as receptors for semaphorins. *Nat Rev Immunol*. 2013;13(11):802-814. doi:10.1038/nri3545
24. Chaudhary B, Khaled YS, Ammori BJ, Elkord E. Neuropilin 1: function and therapeutic potential in cancer. *Cancer Immunol Immunother*. 2014;63(2):81-99. doi:10.1007/s00262-013-1500-0
25. Kolossváry M, deFilippi C, Lu MT, et al. Proteomic signature of subclinical coronary artery disease in people with HIV: analysis of the REPRIEVE mechanistic substudy. *J Infect Dis*. 2022;226(10):1809-1822. doi:10.1093/infdis/jiac196
26. Schnittman SR, Kolossváry M, Beck-Engeser G, et al. Biological and clinical implications of the vascular endothelial growth factor Coreceptor Neuropilin-1 in human immunodeficiency virus. *Open Forum Infect Dis*. 2023;10(10):ofad467. doi:10.1093/ofid/ofad467
27. Bosseboeuf E, Raimondi C. Signalling, metabolic pathways and iron homeostasis in endothelial cells in health, atherosclerosis and Alzheimer's disease. *Cell*. 2020;9(9):2055. doi:10.3390/cells9092055
28. Lim KH, Yang S, Kim SH, Joo JY. Identifying new COVID-19 receptor neuropilin-1 in severe Alzheimer's disease patients group brain using genome-wide association study approach. *Front Genet*. 2021;12:741175. doi:10.3389/fgene.2021.741175
29. Saleki K, Alijanizadeh P, Azadmehr A. Is neuropilin-1 the neuroimmune initiator of multi-system hyperinflammation in COVID-19? *Biomed Pharmacother*. 2023;167:115558. doi:10.1016/j.biopha.2023.115558
30. Keller M, Mirakaj V, Koeppen M, Rosenberger P. Neuronal guidance proteins in cardiovascular inflammation. *Basic Res Cardiol*. 2021;116(1):6. doi:10.1007/s00395-021-00847-x
31. Broz M, Kolarič A, Jukič M, Bren U. Neuropilin (NRPs) related pathological conditions and their modulators. *Int J Mol Sci*. 2022;23(15):8402. doi:10.3390/biomedicines10040818
32. Cerani A, Tetreault N, Menard C, et al. Neuron-derived Semaphorin 3A is an early inducer of vascular permeability in diabetic retinopathy via Neuropilin-1. *Cell Metab*. 2013;18(4):505-518. doi:10.1016/j.cmet.2013.09.003
33. Kaneto H, Kimura T, Shimoda M, et al. Molecular mechanism of pancreatic β-cell failure in type 2 diabetes mellitus. *Biomedicine*. 2022;10(4):818. doi:10.3390/biomedicines10040818
34. Wilson AM, Shao Z, Grenier V, et al. Neuropilin-1 expression in adipose tissue macrophages protects against obesity and metabolic syndrome. *Sci Immunol*. 2018;3(21):eaan4626. doi:10.1126/sciimmunol.aan4626
35. Fournier NM, Duman RS. Role of vascular endothelial growth factor in adult hippocampal neurogenesis: implications for the pathophysiology and treatment of depression. *Behav Brain Res*. 2012;227(2):440-449. doi:10.1016/j.bbr.2011.04.022
36. Warner-Schmidt JL, Duman RS. VEGF as a potential target for therapeutic intervention in depression. *Neurosciences*. 2008;8(1):14-19. doi:10.1016/j.coph.2007.10.013
37. Zhou Y, Zhu X, Cui H, et al. The role of the VEGF family in coronary heart disease. *Front Cardiovasc Med*. 2021;8:738325. doi:10.3389/fcvm.2021.738325
38. Mehta V, Fields L, Evans IM, et al. VEGF (vascular endothelial growth factor) induces NRP1 (neuropilin-1) cleavage via ADAMs (a disintegrin and metalloproteinase) 9 and 10 to generate novel carboxy-terminal NRP1 fragments that regulate angiogenic signaling. *Arterioscler Thromb Vasc Biol*. 2018;38(8):1845-1858. doi:10.1161/ATVBAHA.118.311118
39. Dai X, Okon I, Liu Z, et al. Ablation of Neuropilin 1 in myeloid cells exacerbates high-fat diet–induced insulin resistance through Nlrp3 Inflammasome in vivo. *Diabetes*. 2017;66(9):2424-2435. doi:10.2337/db17-0132
40. Bogdan S, Puścion-Jakubik A, Klimiuk K, Socha K, Kochanowicz J, Gorodkiewicz E. The levels of leptin, cystatin C, Neuropilin-1 and tau protein in relation to dietary habits in patients with Alzheimer's disease. *J Clin Med*. 2023;12(21):6855. doi:10.3390/jcm12216855
41. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(1):S81-S90. doi:10.2337/dc14-S081
42. Thunander M, Petersson C, Jonzon K, et al. Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden. *Diabetes Res Clin Pract*. 2008;82(2):247-255. https://doi-org.ludwig.lub.lu.se/10.1016/j.diabres.2008.07.022
43. Jones A, Hattersley A. The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet Med*. 2013;30(7):803-817. doi:10.1111/dme.12159
44. Djukanovic I, Carlsson J, Årestedt K. Is the hospital anxiety and depression scale (HADS) a valid measure in a general population 65–80 years old? A psychometric evaluation study. *Health Qual Life Outcomes*. 2017;15(1):193. doi:10.1186/s12955-017-0759-9
45. Pogosova N, Kotseva K, De Bacquer D, et al. Psychosocial risk factors in relation to other cardiovascular risk factors in coronary heart disease: results from the EUROASPIRE IV survey. A registry from the European Society of Cardiology. *Eur. J Prev Cardiol*. 2017;24(13):1371-1380. doi:10.1177/2047487317711334
46. Rivenes AC, Harvey SB, Mykletun A. The relationship between abdominal fat, obesity, and common mental disorders: results from the HUNT study. *J Psychosom Res*. 2009;66(4):269-275. doi:10.1016/j.jpsychores.2008.07.012
47. Wu Y, Levis B, Sun Y, et al. Accuracy of the hospital anxiety and depression scale depression subscale (HADS-D) to screen for major depression: systematic review and individual participant data meta-analysis. *BMJ*. 2021;373:n972. doi:10.1136/bmj.n972
48. Chu B, Marwaha K, Sanvictores T, Awosika AO, Ayers D. Physiology, stress reaction. *StatPearls*. StatPearls Publishing; 2024.
49. Danielsson M, Heimerson I, Lundberg U, Perski A, Stefansson CG, Åkerstedt T. Psychosocial stress and health problems: health in Sweden: the National Public Health Report 2012. Chapter 6. *Scand J Public Health*. 2012;40(9 Suppl):121-134. doi:10.1177/1403494812459469
50. Hohlstein P, Schumacher E, Abu Jhaisha S, et al. Soluble Neuropilin-1 is elevated in sepsis and correlates with organ dysfunction and long-term mortality in critical illness. *Int J Mol Sci*. 2024;25(10):5438. doi:10.3390/ijms25105438
51. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Sex Differ Neurol Psychiatr Disord*. 2014;35(3):320-330. doi:10.1016/j.yfrne.2014.05.004
52. Achttien R, van Lieshout J, Wensing M, van der Sanden MN, Staal JB. Symptoms of depression are associated with physical inactivity but not modified by gender or the presence of a cardiovascular disease; a cross-sectional study. *BMC Cardiovasc Disord*. 2019;19(1):1-7. doi:10.1186/s12872-019-1065-8
53. Wu Z, Yue Q, Zhao Z, et al. A cross-sectional study of smoking and depression among US adults: NHANES (2005–2018). *Front Public Health*. 2023;11:1081706. doi:10.3389/fpubh.2023.1081706

54. Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement*. 2023;19(2):658-670. doi:10.1002/alz.12694
55. Ainsworth NJ, Marawi T, Maslej MM, et al. Cognitive outcomes after antidepressant pharmacotherapy for late-life depression: a systematic review and meta-analysis. *Am J Psychiatry*. 2024;181(3):234-245. doi:10.1176/appi.ajp.20230392
56. Chen X, Zhao P, Wang W, Guo L, Pan Q. The antidepressant effects of GLP-1 receptor agonists: a systematic review and meta-analysis. *Am J Geriatr Psychiatry*. 2024;32(1):117-127. doi:10.1016/j.jagp.2023.08.010
57. Nørgaard CH, Friedrich S, Hansen CT, et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. *Alzheimers Dement Transl Res Clin Interv*. 2022;8(1):e12268. doi:10.1002/trc2.12268
58. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. *Circulation*. 2022;146(24):1882-1894. doi:10.1161/CIRCULATIONAHA.122.059595

How to cite this article: Melin EO, Thunander M, Wanby P, et al. Low levels of soluble neuropilin-1 were associated with depression in adults with newly diagnosed type 2 diabetes. *Diabetes Obes Metab*. 2025;27(6):3299-3308. doi:10.1111/dom.16347