

Diabetes Care

Depression is associated with progression of diabetic nephropathy in type 1 diabetes

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Supplementary Table S1 List of antidepressant agents

ATC code	Antidepressants commonly used for treating painful neuropathy
N06AA02	
N06AA04	
N06AA06	
N06AA09	x
N06AA10	x
N06AA12	
N06AA21	
N06AA22	
N06AB03	
N06AB04	
N06AB05	
N06AB06	
N06AB08	
N06AB10	
N06AC01	
N06AC02	
N06AD02	
N06AG02	
N06AX03	
N06AX05	
N06AX11	
N06AX12	
N06AX16	x
N06AX17	
N06AX18	
N06AX21	x
N06AX22	
N06AX26	
N06CA01	x

Supplementary Table S2 Basis for defining depression based on antidepressant agent purchases

Medications	Considered “depressed”	N	% of purchases
N06 for depression	Yes	512	49.1
N06 for depression and N06 for neuropathy together with some other neuropathy medication	Yes	163	15.6
N06 for depression and N06 for neuropathy without other neuropathy medication	Yes	125	12.0
N06 for neuropathy with other neuropathy medication	No	131	12.6
N06 for neuropathy only	No	112	10.7

Supplementary Table S3 Basic characteristic of the sample divided by depression diagnosis

	Without depression diagnosis	With depression diagnosis	P
	N = 3219 (86.3%)	N = 511 (13.7%)	
Men, %	53.2	39.1	<0.001
Age, years	36.4 (28.0 – 46.4)	37.1 (29.5 – 44.6)	0.985
Diabetes duration, years	20.1 (11.3 – 29.9)	21.9 (14.1 – 31.0)	0.008
Age at diabetes onset, years	14.3 (9.3 – 23.2)	12.9 (8.6 – 19.7)	<0.001
Follow-up time, years	9.1 (5.4 – 14.1)	8.6 (5.0 – 14.1)	0.684
HbA _{1c} , mmol/mol	67 (57 – 77)	68 (61 – 79)	0.003
HbA _{1c} , %	8.3 (7.4 – 9.2)	8.4 (7.7 – 9.4)	0.003
Total cholesterol, mmol/l	4.8 (4.2 – 5.4)	4.9 (4.4 – 5.6)	0.023
HDL-cholesterol, mmol/l	1.30 (1.08 – 1.56)	1.34 (1.13 – 1.65)	0.004
Triglycerides, mmol/l	1.0 (0.8 – 1.4)	1.0 (0.8 – 1.5)	0.072
SBP, mmHg	131 (121 – 143)	129 (120 – 140)	0.002
DBP, mmHg	80 (72 – 86)	79 (73 – 85)	0.674
BMI, kg/m ²	24.8 (22.7 – 27.1)	25.0 (22.5 – 27.0)	0.876

Data are presented as percentages for frequencies or medians (interquartile ranges) for continuous, non-normally distributed data. Between-group comparisons were done with Chi-squared test and Mann-Whitney U-test, respectively. Depression diagnosis, depression-related hospitalizations as registered in the Finnish Care Register for Health Care either before or after the baseline visit; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Supplementary Table S4 Basic characteristic of the sample divided by antidepressant agent purchases

	Without purchases N = 2932 (78.6%)	With purchases N = 798 (21.4%)	P
Men, %	54.0	41.2	<0.001
Age, years	35.8 (27.6 – 45.7)	39.1 (30.6 – 47.1)	<0.001
Diabetes duration, years	19.7 (11.0 – 29.3)	23.1 (14.4 – 32.0)	<0.001
Age at diabetes onset, years	14.2 (9.2 – 22.8)	13.7 (9.0 – 21.8)	0.191
Follow-up time, years	8.0 (4.9 – 13.8)	11.8 (6.9 – 14.7)	<0.001
HbA _{1c} , mmol/mol	67 (57 – 77)	68 (60 – 78)	0.086
HbA _{1c} , %	8.3 (7.4 – 9.2)	8.4 (7.6 – 9.3)	0.086
Total cholesterol, mmol/l	4.8 (4.2 – 5.4)	4.9 (4.3 – 5.5)	0.056
HDL-cholesterol, mmol/l	1.30 (1.08 – 1.57)	1.32 (1.10 – 1.58)	0.551
Triglycerides, mmol/l	1.0 (0.8 – 1.4)	1.0 (0.8 – 1.5)	0.174
SBP, mmHg	131 (121 – 143)	131 (120 – 143)	0.999
DBP, mmHg	80 (72 – 86)	80 (73 – 85)	0.914
BMI, kg/m ²	24.7 (22.7 – 27.1)	25.0 (22.8 – 27.2)	0.153

Data are presented as percentages for frequencies or medians (interquartile ranges) for continuous, non-normally distributed data. Between-group comparisons were done with Chi-squared test and Mann-Whitney U-test, respectively. Antidepressant agent purchases, all purchases of N06A and N06CA coded medication as registered in the Drug Prescription Register of the Social Insurance Institute of Finland, excluding antidepressants commonly used for the treatment of painful neuropathy (i.e. N06AX21 Duloxetine, N06AA09 Amitriptyline, N06AA10 Nortriptyline, N06AX16 Venlafaxine, N06CA01 Amitriptyline and psycholeptics); SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Supplementary Table S5 Basic characteristic of the population divided by symptoms of depression

	Without symptoms of depression N = 1298 (87.2%)	With symptoms of depression N = 191 (12.8%)	P
Men, %	48.1	33.5	<0.001
Age, years	37.1 (28.8 – 46.8)	39.3 (30.5 – 48.9)	0.148
Diabetes duration, years	20.4 (11.3 – 30.6)	24.4 (16.1 – 33.2)	0.002
Age at diabetes onset, years	14.5 (9.5 – 23.5)	13.1 (8.9 – 19.5)	0.032
Follow-up time, years	12.9 (6.9 – 15.3)	13.3 (7.4 – 16.1)	0.209
HbA _{1c} , mmol/mol	65 (56 – 75)	68 (59 – 78)	0.037
HbA _{1c} , %	8.1 (7.3 – 9.0)	8.4 (7.5 – 9.3)	0.037
Total cholesterol, mmol/l	4.7 (4.2 – 5.3)	4.8 (4.4 – 5.5)	0.022
HDL-cholesterol, mmol/l	1.38 (1.14 – 1.63)	1.36 (1.18 – 1.65)	0.989
Triglycerides, mmol/l	0.9 (0.7 – 1.3)	1.0 (0.7 – 1.4)	0.220
SBP, mmHg	131 (120 – 143)	130 (120 – 142)	0.548
DBP, mmHg	79 (71 – 85)	80 (72 – 85)	0.257
BMI, kg/m ²	24.6 (22.7 – 26.9)	25.4 (23.3 – 27.9)	0.014

Data are presented as percentages for frequencies or medians (interquartile ranges) for continuous, non-normally distributed data. Between-group comparisons were done with Chi-squared test and Mann-Whitney U-test, respectively. Without symptoms of depression, Beck Depression Inventory score <16; With symptoms of depression, Beck Depression Inventory score ≥16; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Supplementary Table S6 Basic characteristics of the population by progression of diabetic nephropathy stratified by median age of the sample

	Age \leq 36.5 years			Age $>$ 36.5 years		
	Non-progressors n=1567 (84.0%)	Progressors n=298 (16.0%)	P	Non-progressors n=1475 (79.1%)	Progressors n=390 (20.9%)	P
Men, %	49.1	55.0	0.067	49.3	64.4	$<$ 0.001
Age, years	28.0 (23.1 – 32.3)	29.0 (23.2 – 32.9)	0.082	46.4 (41.2 – 52.4)	45.3 (41.1 – 50.9)	0.188
Diabetes duration, years	13.5 (7.3 – 19.7)	17.6 (11.6 – 23.2)	$<$ 0.001	28.9 (19.8 – 35.8)	30.7 (23.6 – 36.7)	0.002
Age at diabetes onset, years	12.6 (7.8 – 19.2)	9.8 (6.4 – 13.8)	$<$ 0.001	18.6 (11.4 – 27.5)	14.8 (10.0 – 23.4)	$<$ 0.001
Follow-up time, years	9.7 (5.6 – 14.5)	6.9 (3.3 – 11.8)	$<$ 0.001	9.8 (5.7 – 14.2)	7.8 (4.0 – 12.7)	$<$ 0.001
HbA _{1c} , mmol/mol	66 (55 – 77)	79 (67 – 93)	$<$ 0.001	65 (57 – 74)	74 (64 – 85)	0.001
HbA _{1c} , %	8.2 (7.2 – 9.2)	9.4 (8.3 – 10.7)	$<$ 0.001	8.1 (7.4 – 8.9)	8.9 (8.0 – 9.9)	$<$ 0.001
Total cholesterol, mmol/l	4.6 (4.1 – 5.2)	5.2 (4.5 – 5.9)	$<$ 0.001	4.9 (4.4 – 5.5)	5.2 (4.4 – 5.9)	$<$ 0.001
HDL-cholesterol, mmol/l	1.29 (1.09 – 1.54)	1.19 (0.98 – 1.43)	$<$ 0.001	1.38 (1.14 – 1.65)	1.21 (0.95 – 1.50)	$<$ 0.001
Triglycerides, mmol/l	1.0 (0.7 – 1.4)	1.4 (1.0 – 2.2)	$<$ 0.001	0.9 (0.7 – 1.3)	1.3 (0.9 – 2.1)	$<$ 0.001
SBP, mmHg	125 (118 – 136)	131 (121 – 142)	$<$ 0.001	134 (125 – 147)	145 (132 – 160)	$<$ 0.001
DBP, mmHg	79 (71 – 85)	82 (76 – 88)	$<$ 0.001	79 (72 – 85)	82 (76 – 89)	$<$ 0.001
BMI, kg/m ²	24.6 (22.5 – 26.7)	24.2 (22.0 – 26.6)	0.145	25.1 (23.0 – 27.3)	25.5 (23.1 – 28.4)	0.004

Data are presented as percentages for frequencies or medians (interquartile ranges) for continuous, non-normally distributed data. Between-group comparisons were done with Chi-squared test and Mann-Whitney U-test, respectively. Non-progressors, participants with no adverse change in the renal classification over the follow-up; Progressors, participants with any adverse change in the renal classification over the follow-up period (i.e. change from baseline normal AER to either microalbuminuria, macroalbuminuria, or ESRD; or from baseline microalbuminuria to either macroalbuminuria, or ESRD; or from baseline macroalbuminuria to ESRD); SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Supplementary Table S7 Depression in the sample divided by progression of diabetic nephropathy stratified by median age of the sample

	Age ≤36.5 years			Age >36.5 years		
	Non-progressors n=1567 (84.0%)	Progressors n=298 (16.0%)	P	Non-progressors n=1475 (79.1%)	Progressors n=390 (20.9%)	P
History of diagnosed depression, %	3.9	4.7	0.304	4.5	5.6	0.352
Diagnosed depression during follow-up, %	9.1	21.1	<0.001	10.7	17.4	<0.001
Any diagnosed depression, %	11.4	22.8	<0.001	12.9	18.7	0.005
History of antidepressant purchases, %	7.5	9.7	0.198	15.9	18.7	0.193
Antidepressant purchases during follow-up, %	19.8	24.5	0.072	27.9	34.1	0.020
Any antidepressant purchase, %	17.7	20.1	0.176	23.5	29.2	0.025
Number of any antidepressant purchases, %			0.765			0.063
0	82.3	79.9		76.5	70.8	
1-24	15.1	17.1		19.0	25.1	
25-49	21.9	2.3		3.3	3.1	
≥50	0.7	0.7		1.3	1.0	
BDI score ≥16, %	12.3	8.4	0.327	13.2	17.0	0.228

Data are presented as percentages. Between-group comparisons were done with Chi-squared test. Non-progressors, participants with no adverse change in the renal classification over the follow-up; Progressors, participants with any adverse change in the renal classification over the follow-up period (i.e. change from baseline normal AER to either microalbuminuria, macroalbuminuria, or ESRD; or from baseline microalbuminuria to either macroalbuminuria, or ESRD; or from baseline macroalbuminuria to ESRD); History of diagnosed depression, depression diagnosed prior to baseline; Diagnosed depression during follow-up, depression diagnosed after baseline; Any diagnosed depression, depression diagnosed before or after baseline; History of antidepressant purchases, antidepressant purchases prior to baseline; Antidepressant purchases during follow-up, antidepressant purchases after baseline; Any antidepressant purchase, antidepressant purchases before or after baseline; BDI score ≥16, symptoms of depression judged by the Beck Depression Inventory scores. BDI was completed by 711 of those aged ≤36.5 years and by 778 of those >36.5 years.

Supplementary Table S8 Multivariable associations between depression-related variables and progression of diabetic nephropathy in type 1 diabetes stratified by median age of the sample

	Age ≤36.5 years		Age >36.5 years	
	HR (95% CI)	P	HR (95% CI)	P
History of diagnosed depression, yes	1.153 (0.659 – 2.017)	0.617	1.775 (1.148 – 2.743)	0.010
Diagnosed depression during follow-up, yes	1.545 (1.148 – 2.078)	0.004	1.135 (0.865 – 1.489)	0.631
Any diagnosed depression, yes	1.508 (1.128 – 2.017)	0.006	1.151 (0.884 – 1.498)	0.297
History of antidepressant purchases, yes	1.288 (0.864 – 1.919)	0.214	1.275 (0.981 – 1.659)	0.069
Antidepressant purchases during follow-up, yes	0.879 (0.666 – 1.159)	0.360	0.835 (0.669 – 1.042)	0.110
Any antidepressant purchase, yes	0.823 (0.612 – 1.107)	0.199	0.851 (0.676 – 1.070)	0.168
Number of any antidepressant purchases	0.992 (0.979 – 1.004)	0.182	0.987 (0.976 – 0.997)	0.011
BDI score ≥16	2.255 (1.117 – 4.552)	0.023	0.848 (0.541 – 1.330)	0.473

Data are presented as hazard ratio (95% confidence interval). Cox regression. Models are adjusted for sex, diabetic nephropathy status at baseline, diabetes duration, age at diabetes onset, systolic blood pressure, HbA_{1c}, triglyceride concentration, and HDL-cholesterol concentration. History of diagnosed depression, depression diagnosed prior to baseline; Diagnosed depression during follow-up, depression diagnosed after baseline; Any diagnosed depression, depression diagnosed before or after baseline; History of antidepressant purchases, antidepressant purchases prior to baseline; Antidepressant purchases during follow-up, antidepressant purchases after baseline; Any antidepressant purchase, antidepressant purchases before or after baseline; BDI score ≥16, symptoms of depression judged by the Beck Depression Inventory scores.

Supplementary Table S9

The Finnish Diabetic Nephropathy Study Centers

Anjalankoski Health Center	S.Koivula, T.Uggeldahl
Central Finland Central Hospital, Jyväskylä	T.Forslund, A.Halonen, A.Koistinen, P.Koskiahho, M.Laukkanen, J.Saltevo, M.Tiihonen
Central Hospital of Åland Islands, Mariehamn	M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen
Central Hospital of Kymenlaakso, Kotka	R.Paldanius, M.Riihelä, L.Ryysy
Central Hospital of Länsi-Pohja, Kemi	H.Laukkanen, P.Nyländen, A.Sademies
Central Ostrobothnian Hospital District, Kokkola	S.Anderson, B.Asplund, U.Byskata, P.Liedes, M.Kuusela, T.Virkkala
City of Espoo Health Center:	
Espoonlahti	A.Nikkola, E.Ritola
Tapiola	M.Niska, H.Saarinen
Samaria	E.Oukko-Ruonen, T.Virtanen
Viherlaakso	A.Lyytinen
City of Helsinki Health Center:	
Puistola	H.Kari, T.Simonen
Suutarila	A.Kaprio, J.Kärkkäinen, B.Rantaeskola
Töölö	P.Kääriäinen, J.Haaga, A-L.Pietiläinen
City of Hyvinkää Health Center	S.Klemetti, T.Nyandoto, E.Rontu, S.Satuli-Autere
City of Vantaa Health Center:	
Korso	R.Toivonen, H.Virtanen
Länsimäki	R.Ahonen, M.Ivaska-Suomela, A.Jauhiainen
Martinlaakso	M.Laine, T.Pellonpää, R.Puranen
Myyrmäki	A.Airas, J.Laakso, K.Rautavaara
Rekola	M.Erola, E.Jatkola
Tikkurila	R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo
Heinola Health Center	P.Hentunen, J.Lagerstam
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology	M.Fedoroff, D.Gordin, O.Heikkilä, K.Hietala, J.Fagerudd, M.Korolainen, L.Kyllönen, J.Kytö, S.Lindh, K.Pettersson-Fernholm, M.Rosengård-Bärlund, A.Sandelin, L.Thorn, J.Tuomikangas, T.Vesisenaho, J.Wadén
Herttoniemi Hospital, Helsinki	V.Sipilä
Hospital of Lounais-Häme, Forssa	T.Kalliomäki, J.Koskelainen, R.Nikkanen, N.Savolainen, H.Sulonen, E.Valtonen
Hyvinkää Hospital	L. Norvio, A.Hämäläinen
Iisalmi Hospital	E.Toivanen
Jokilaakso Hospital, Jämsä	A.Parta, I.Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S.Aranko, S.Ervasti, R.Kauppinen-Mäkelin, A.Kuusisto, T.Leppälä, K.Nikkilä, L.Pekkonen
Jyväskylä Health Center, Kyllö	K.Nuorva, M.Tiihonen
Kainuu Central Hospital, Kajaani	S.Jokelainen, K.Kananen, M.Karjalainen, P.Kemppainen, A-M.Mankinen, A.Reponen, M.Sankari
Kerava Health Center	H.Stuckey, P.Suominen
Kirkkonummi Health Center	A.Lappalainen, M.Liimatainen, J.Santaholma
Kivelä Hospital, Helsinki	A.Aimolahti, E.Huovinen
Koskela Hospital, Helsinki	V.Iikka, M.Lehtimäki
Kotka Health Center	E.Pälikkö-Kontinen, A.Vanhanen
Kouvola Health Center	E.Koskinen, T.Siitonen
Kuopio University Hospital	E.Huttunen, R.Ikäheimo, P.Karhapää, P.Kekäläinen, M.Laakso, T.Lakka, E.Lampainen, L.Moilanen, S. Tanskanen, L.Niskanen, U.Tuovinen, I.Vauhkonen, E.Voutilainen
Kuusamo Health Center	T.Kääriäinen, E.Isopoussu
Kuusankoski Hospital	E.Kilki, I.Koskinen, L.Riihelä
Laakso Hospital, Helsinki	T.Meriläinen, P.Poukka, R.Savolainen, N.Uhlenius
Lahti City Hospital	A.Mäkelä, M.Tanner
Lapland Central Hospital, Rovaniemi	L.Hyvärinen, K.Lampela, S.Pöykkö, T.Rompasaari, S.Severinkangas, T.Tulokas
Lappeenranta Health Center	P. Erola, L.Härkönen, P.Linkola, T.Pekkanen, I.Pulli, E.Repo
Lohja Hospital	T.Granlund, K.Hietanen, M.Porrassalmi, M.Saari, T.Salonen, M.Tiikkainen,
Länsi-Uusimaa Hospital, Tammisaari	I.-M.Jousmaa, J.Rinne
Loimaa Health Center	A.Mäkelä, P.Eloranta
Malmi Hospital, Helsinki	H.Lanki, S.Moilanen, M.Tilly-Kiesi
Mikkeli Central Hospital	A.Gynther, R.Manninen, P.Nironen, M.Salminen, T.Vänttinen
Mänttä Regional Hospital	I.Pirttiniemi, A-M.Hänninen

North Karelian Hospital, Joensuu	U-M.Henttula, P.Kekäläinen, M.Pietarinen, A.Rissanen, M.Voutilainen
Nurmijärvi Health Center	A.Burgos, K.Urtamo
Oulaskangas Hospital, Oulainen	E.Jokelainen, P-L.Jylkkä, E.Kaarlela, J.Vuolaspuro
Oulu Health Center	L.Hiltunen, R.Häkkinen, S.Keinänen-Kiukaanniemi
Oulu University Hospital	R.Ikäheimo
Päijät-Häme Central Hospital	H.Haapamäki, A.Helanterä, S.Hämäläinen, V.Ilvesmäki, H.Miettinen
Palokka Health Center	P.Sopanen, L.Welling
Pieksämäki Hospital	V.Sevtsenko, M.Tamminen
Pietarsaari Hospital	M-L.Holmbäck, B.Isomaa, L.Sarelin
Pori City Hospital	P.Ahonen, P.Merisalo, E.Muurinen, K.Sävelä
Porvoo Hospital	M.Kallio, B.Rask, S.Rämö
Raahe Hospital	A.Holma, M.Honkala, A.Tuomivaara, R.Vainionpää
Rauma Hospital	K.Laine, K.Saarinen, T.Salminen
Riihimäki Hospital	P.Aalto, E.Immonen, L.Juurinen
Salo Hospital	A.Alanko, J.Lapinleimu, P.Rautio, M.Virtanen
Satakunta Central Hospital, Pori	M.Asola, M.Juhola, P.Kunelius, M.-L.Lahdenmäki, P.Pääkkönen, M.Rautavirta
Savonlinna Central Hospital	T.Pulli, P.Sallinen, M.Taskinen, E.Tolvanen, T.Tuominen, H.Valtonen, A.Vartia, S-L.Viitanen
Seinäjoki Central Hospital	O.Antila, E.Korpi-Hyövälti, T.Latvala, E.Leijala, T.Leikkari, M.Punkari, N.Rantamäki, H.Vähävuori
South Karelia Central Hospital, Lappeenranta	T.Ensala, E.Hussi, R.Härkönen, U.Nyholm, J.Toivanen
Tampere Health Center	A.Vaden, P.Alarotu, E.Kujansuu, H.Kirkkopelto-Jokinen, M.Helin, S.Gummerus, L.Calonius, T.Niskanen, T.Kaitala, T.Vatanen
Tampere University Hospital	P. Hannula, I.Ala-Houhala, R.Kannisto, T.Kuningas, P.Lampinen, M.Määttä, H.Oksala, T.Oksanen, A.Putila, H.Saha, K.Salonen, H.Tauriainen, S.Tulokas
Tiirismaa Health Center, Hollola	T.Kivelä, L.Petlin, L.Savolainen
Turku Health Center	A.Artukka, I.Hämäläinen, L.Lehtinen, E.Pyysalo, H.Virtamo, M.Viinikkala, M.Vähätalo
Turku University Central Hospital	K.Breitholz, R.Eskola, K.Metsärinne, U.Pietilä, P.Saarinen, R.Tuominen, S.Äyräpää
Vaajakoski Health Center	K.Mäkinen, P.Sopanen
Valkeakoski Regional Hospital	S.Ojanen, E.Valtonen, H.Ylönen, M.Rautiainen, T.Immonen
Vammala Regional Hospital	I.Isomäki, R.Kroneld, L.Mustaniemi, M.Tapiolinna-Mäkelä
Vasa Central Hospital	S.Bergkulla, U.Hautamäki, V-A.Myllyniemi, I.Rusk