ONLINE APPENDIX: SUPPLEMENTAL DATA

Antidepressant Medication Use, Weight Gain and Risk of Type 2 Diabetes Mellitus: A population-based Study

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Detailed Description of Methods

Sample Selection

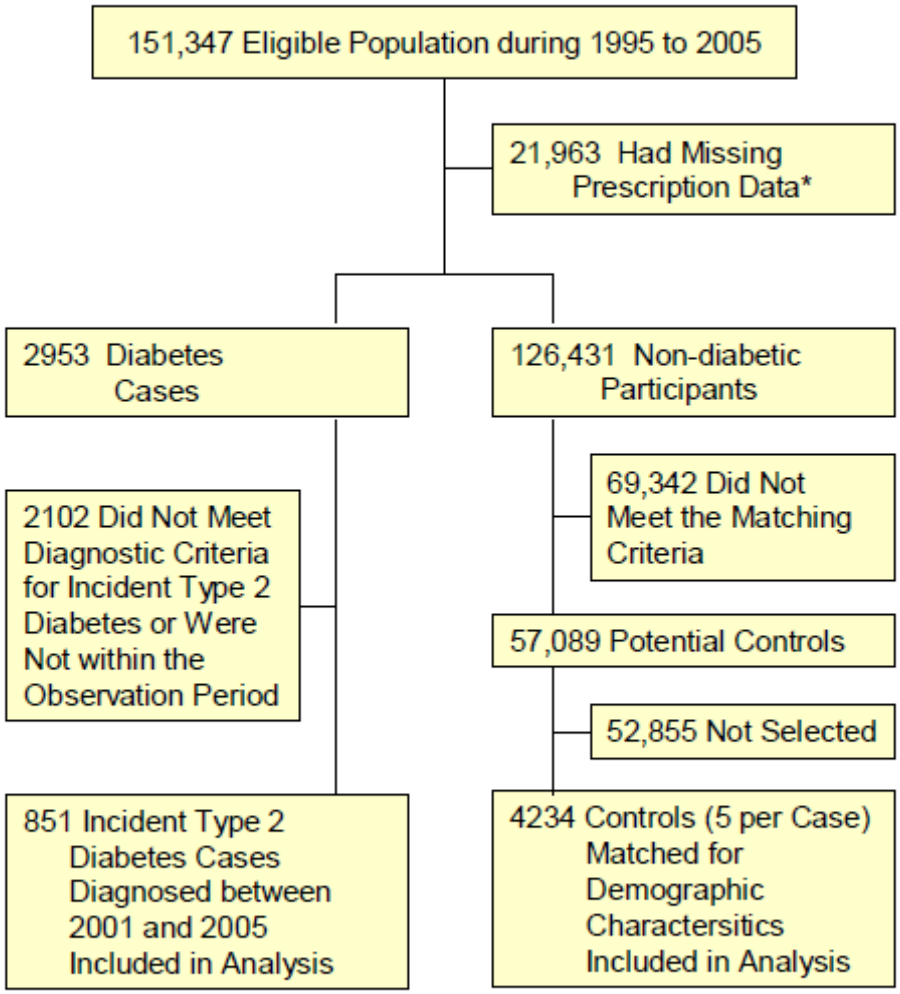
Data for the 3 sets of analyses presented in this study were drawn from the Finnish Public Sector study which includes the entire public sector personnel of 10 towns (municipalities) and 21 hospitals in the areas where these towns are located.(16) The eligible population of 151,347 participants comprised workers with an employment contract between 1995 and 2005 and a record linkage to national health registers through unique personal identification codes assigned to all citizens in Finland. For all participants in the eligible population, the linkage to registers was 100% complete and there was no sample attrition during the follow-up. This study was approved by the ethics committee of the Finnish Institute of Occupational Health.

Study 1: This case-control study examined diagnosed depression and antidepressant medication use as risk factors for incident diabetes among 851 cases who developed type 2 diabetes and their 4234 individually matched diabetes-free controls. The randomly selected controls were drawn in a 5:1 ratio for each diabetes case, matching individually for age group, sex, socioeconomic position, type of employment contract, type of employer and geographic area. A flow chart depicting sample selection is given in eFigure1. All cases and controls had complete records of clinically significant diagnosed depression and prescribed antidepressant use over a fixed period of 4 years before the diagnosis of type 2 diabetes between Jan 1, 2001 and Dec 31, 2005.

Study 2. As the retrospective case-control design in Study 1 is unable to estimate absolute risk of diabetes associated with antidepressant use and is not based on a maximum number of antidepressant users in the cohort, we undertook a prospective follow-up of all 9197 identified long-term antidepressant users ($\geq$200 defined daily doses i.e. a treatment lasting over 6 months) to examine their risk of incident type 2 diabetes. For comparison, we selected non-user controls (N=45,658) using the same record-based matching method as in Study 1. A minimum follow-up for incident diabetes was set at 12 months (for detailed sample selection procedure, see eFigure2).

Study 3: This prospective follow-up of weight change associated with antidepressant use assessed self-reported weight change between baseline survey in 2000-2002 and follow-up survey in 2004-2005 for all identified 1404 cases of antidepressant users at baseline and their 4133 propensity-score matched controls (non-users). The flow chart for sample selection is presented in eFigure3. We used propensity-based matching (a quasi-experimental "correction strategy") to select for each case 1-3 controls who had the same probability than the cases to receiving treatment with respect to depression status and other depression-related covariates, discarding unmatched individuals.(25) Antidepressant users were matched for the same characters as those used in the diabetes study and additionally for diagnosed depression, ishaemic heart disease, stroke, cancer, use of pain killers, hypnotics or anxiolytics, self-rated psychological distress, sleeping problems, and anxiety, to the closest control whose propensity score differed by less than 0.01.

eFigure1. Case-Control Selection Flow for Study 1



*These are employees of one town where the medication costs were paid by the employer during employment

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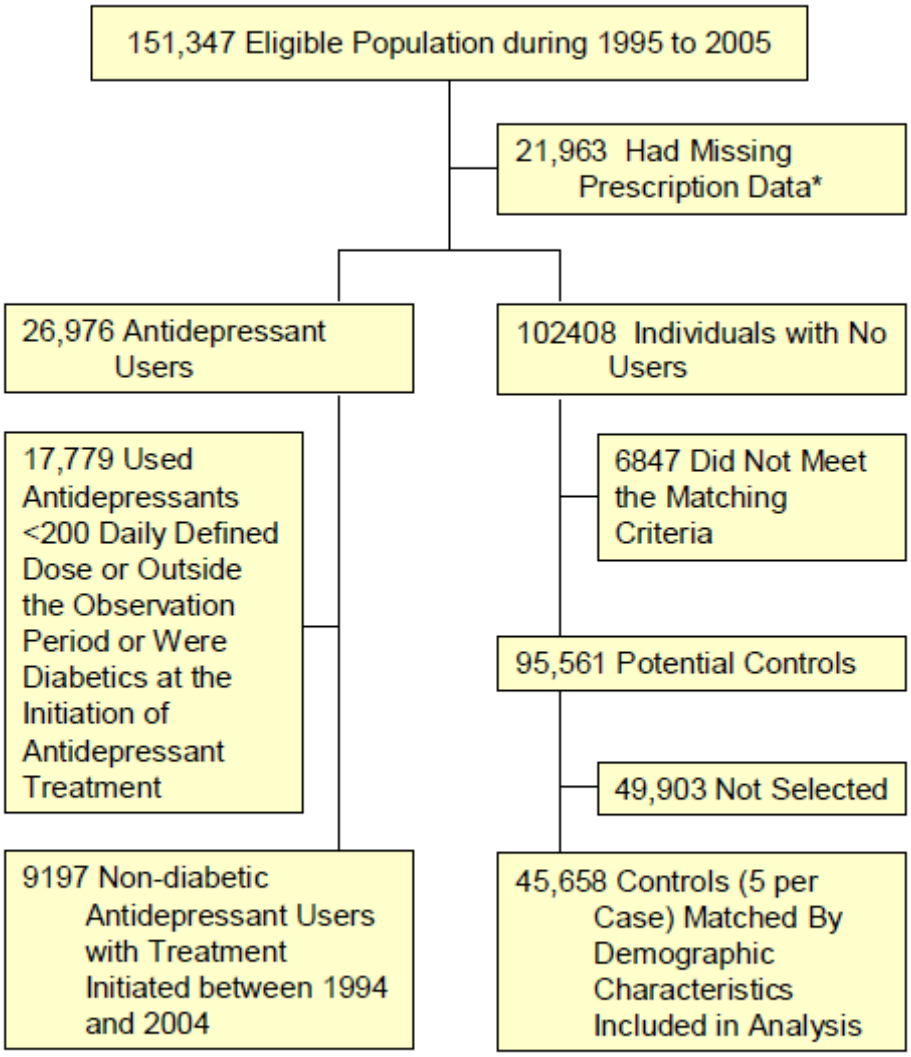
eFigure2. Case-Control Selection Flow for Study 2



*These are employees of one town where the medication costs were paid by the employer during employment

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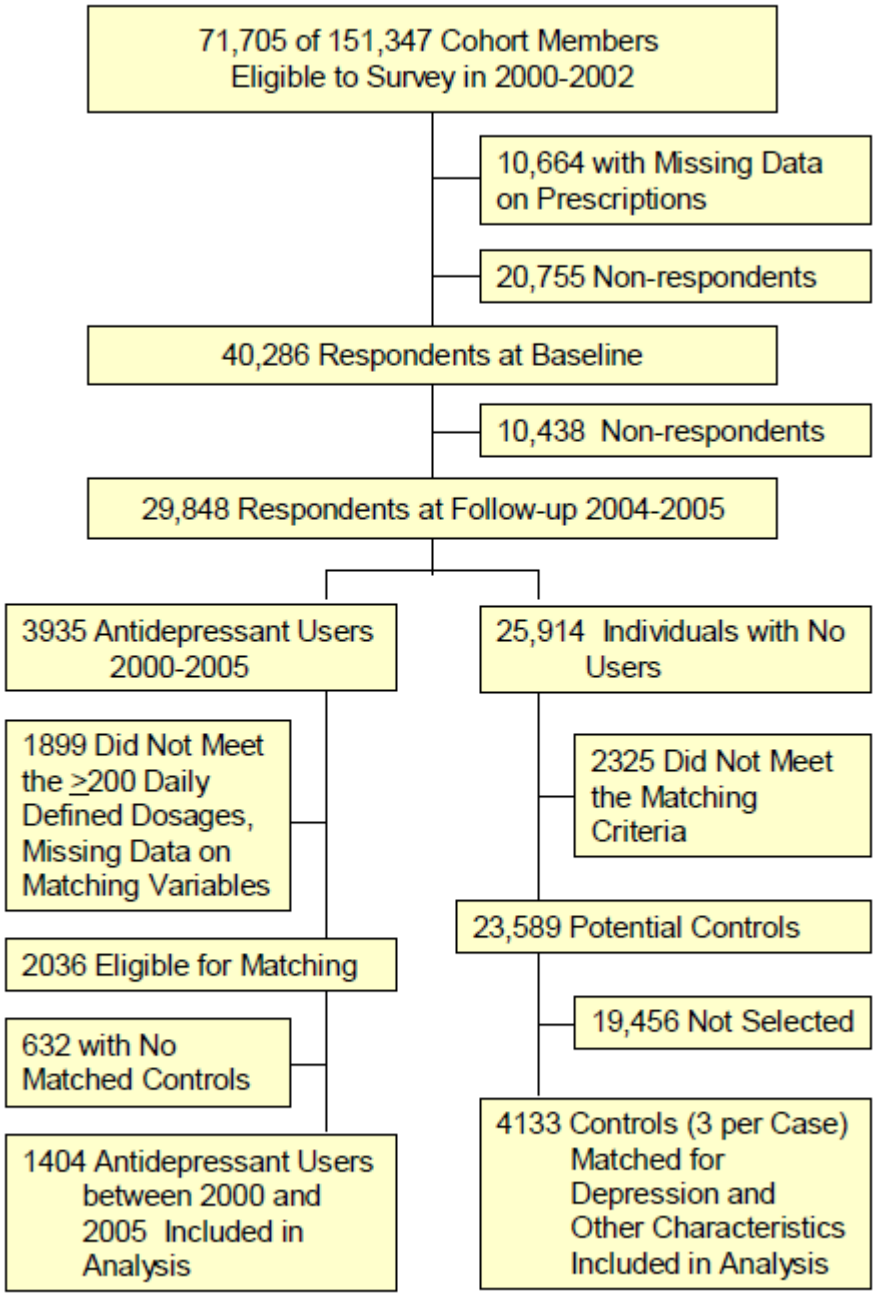
eFigure3. Case-Control Selection Flow for Study 3



*These are employees of one town where the medication costs were paid by the employer during employment

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Measurements - Study 1

Study 1, the two exposure variables are diagnosed depression and antidepressant use and the outcome is incident type 2 diabetes mellitus. We used the participants' personal identification numbers for all data linkages

Severe depression: We used 3 data sources to assess severe depression. First, we identified participants admitted to hospital due to depression by extracted data on psychiatric episodes with WHO International Classification of Diseases and Health-related Problems 10th Revision (ICD-10) diagnoses from the National Hospital Discharge Register. This register provides a virtually complete follow-up for hospitalizations and related ICD-diagnoses for all participants who are treated in a hospital in Finland. Second, we derived registered data on psychotherapy granted by the Social Insurance Institution, including the main diagnosis and the years psychotherapy was granted. A requirement for granting is the identified need for rehabilitation, the suitability for psychotherapy and the expected gain from psychotherapy explicitly affirmed in a statement by a treating psychiatrist, after a minimum of six months follow-up and treatment. Third, we retrieved information on depression-related sickness absence spells longer than 90 days (diagnoses not available for shorter absences) and temporary and permanent disability pensions, both with ICD10 diagnoses, from the Social Insurance Institution of Finland and the Finnish Centre for Pensions registers. All permanent residents aged 16–67 were entitled to daily allowances due to sickness absence and all gainfully employed people were insured in a pension scheme, so these data were complete for all participants. Diagnoses were available for 97% of all the days that comprised sickness absence periods obtained from the registers. Depression was denotated by ICD-10 diagnostic codes F32-F34 in any of these 3 data sources.

Exposure to antidepressant medication use. Antidepressant use for each year of the observation was derived from the nationwide Drug Prescription Register. We used the same period for the cases and controls to avoid confounding due to secular trends in antidepressant use. In Finland, prescriptions for antidepressant medications are filed by the National Social Insurance Scheme at the Social Insurance Institution and the available data contain information on the day of purchase; dose, stated as the international standard defined daily dose; and medication classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification.(15) We determined the consumption of antidepressants on the basis of defined daily doses for the purchases of all antidepressants (ATC code N06A) and the following classes: tricyclic antidepressants (ATC code N06AA), selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB) and other antidepressants (ATC codes N06AF, N06AG, N06AX).

Type 2 diabetes mellitus: Since 1965, drug treatment for diabetes has been free of charge in Finland for individuals with verified diabetes. The Central Drug Register, maintained by the Social Insurance Institution, lists all such patients with physician-documented evidence of a fasting whole blood glucose $\geq$7.0 mmol/L (or fasting plasma glucose $\geq$8.0 mmol/L) and symptoms of diabetes, such as polyuria, polydipsia, and glucosuria. If symptoms are not present, evidence of a second elevated blood glucose level of $\geq$7.0 mmol/L is required. In this study, participants were defined as incident type 2 diabetes cases the first time they were listed in the Central Drug Register as eligible for diabetes treatment due to type 2 diabetes mellitus (code E11, ICD-10) between Jan 1, 2001 and Dec 31, 2005. There were no missing diagnoses for the eligible participants. To exclude prevalent diabetes (i.e., diabetes diagnosed before Jan 31, 2001), we additionally linked the data to the Finnish Hospital Discharge Register that lists all discharged hospital patients with information on dates of admission and discharge since 1987 and to the Drug Prescription Register (Social Insurance Institution) that includes all prescriptions for insulin medications, drugs to lower blood glucose, and other drugs for diabetes in Finland

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nationwide since 1994, according to the WHO ATC Classification. We excluded individuals who were recorded as having diabetes (code E10 or E11, ICD-10) in the Central Drug Register or the Hospital Discharge Register or had prescriptions of insulin or its analogues, blood glucose lowering drugs, or other drugs for diabetes during any of the years of observation in the Central Drug Register, Hospital Discharge Register and Drug Prescription Register. From the potential control group, we excluded all participants with any of these indicators of diabetes up to Dec 31, 2005.

Matching variables: Cases were matched for age group (25-45, 46-52, 53-64), sex, socioeconomic position (upper non-manual, lower non-manual, manual), type of employment contract (permanent vs. temporary), type of employer (hospital vs. municipality) and geographic area (Southern, Middle, Northern Finland, based on the location of the workplace), all obtained from employers' registers. Age at diagnosis was calculated from the dates of diagnosis and birth, using register data.

Additional covariates: We assessed the status of coronary heart disease (ICD-10 codes I20–I25), cerebrovascular disease (I60-I69), hypertension (I10-I15) and cancer (C00-C97) at each year of observation. Information on these diseases was obtained from the Finnish Hospital Discharge Register, the Central Drug Register and the Finnish Cancer Register

Measurements - Study 2

In this study, information on antidepressant use, incident type 2 diabetes and matching variables was derived as in Study 1.

Measurements - Study 3

In Study 3, antidepressant use is the exposure variable and self-reported weight change the outcome. Antidepressant use in between the years of baseline and follow-up surveys, inclusive of the survey years was defined and assessed as in the Diabetes study. Self-reported weight change was measured by deducting self-reported weight (kg) at follow-up from that at baseline. We employed a wide range of matching variables to identify two groups which are as similar as possible in terms of depression except for antidepressant use. In addition to those variables in the Diabetes study, controls were matched for diagnosed depression (meeting the case definition in the Diabetes study or a positive response to a question of ever been diagnosed by a physician as having depression), psychological distress (the 12-item General Health Questionnaire score >4),(26) sleep problems (mean score in the Jenkins scale),(27) anxiety (mean score in the Spielberger Trait Anxiety scale),(28) diagnosed ishaemic heart disease, stroke or cancer (as in the Diabetes study), recorded use of pain killers (ATC code M01 or N02 with defined daily doses $\geq$ 100), hypnotics (ATC N05C) or anxiolytics (ATC N05B) at baseline or during the 3 preceding years (the Central Drug Register).

Statistical Analysis

All statistical analyses were carried out using the SAS 9.2 programme package (SAS Institute Inc., Cary, NC, USA). Statistical significance was inferred at a 2-tailed $P<0.05$. There were no differences in any of the 5 record-based matching characteristics between the cases and controls in the first two studies (online tables S1 and S6) or in the 15 record- and survey-based matching characteristics in the third study (online table S7).

Study 1: We used conditional logistic regression analysis to explore the associations of depression (diagnosis of depression recorded in any health register during the 4-year

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observation period) and exposure to antidepressant use (filled prescriptions >=200 defined daily doses during the 4-year observation period) with incident type 2 diabetes. We fitted a mutually adjusted model to examine whether these exposures independently predicted diabetes and calculated change in odds ratio between unadjusted and mutually adjusted models using the formula: Odds Ratio unadjusted - Odds Ratio adjusted/(Odds Ratio unadjusted - 1) x 100%. We calculated the synergy index(29, 30) to explore the synergistic (biological) interaction between depression and antidepressant use on diabetes risk, using the algorithm provided by Andersson and colleagues.(31) The synergy index is equal to the calculation of [OR(AB)-1]/[(OR(Ab)-1)+(OR(aB)-1)], where A and B denote the presence of the two risk factors and a and b are designated as the absence of the risk factors, respectively. A synergy index of 1.0 implies perfect additivity and >1 indicates a synergistic interaction. To test multiplicative interaction, we tested the significance of an interaction term "severe depression x antidepressant use" in a model including the main effects. We also examined the association of depression-antidepressant use combinations with incident type 2 diabetes by dividing participants into four groups: (1) no severe depression and no antidepressant use; (2) no severe depression but exposure to antidepressant use; (3) severe depression but no antidepressant use; and (4) severe depression and antidepressant use. We ran a series of sensitivity analyses with alternative depression and antidepressant use definitions, as well as adjusting for additional covariates to examine the robustness of observed associations.

Study 2: Participants were followed up until diagnosis of type 2 diabetes, death or the end of the follow-up period December 31 2005 whichever came first. We calculated absolute risk of incident diabetes per 5 years separately for individuals on antidepressant treatment at baseline or those with no antidepressant use. We used Cox proportional hazards models to compute hazard ratios with accompanying 95% confidence intervals for the association between antidepressant use and incident diabetes. The proportional hazards assumption was examined by entering interaction term exposure x follow-up time (p=0.36), although no appreciable violations were noted.

Study 3: Propensity-based matching is used to select control patients who are similar to patients receiving treatment with respect to propensity score and other covariates, discarding unmatched individuals, thereby matching on many confounders simultaneously.(32, 33) Although matched analyses may analyze a non-representative sample of patients receiving treatment, they may provide a more valid estimate of treatment effect than multivariable adjusted epidemiologic studies because they compare patients with similar observed characteristics, all of whom are potential candidates for the treatment. Cases using antidepressants were matched to 13 controls whose propensity score differed by less than 0.01. Of all 2036 antidepressant users, 632 were excluded as there were no controls available with the same propensity score. We computed the propensity score by using logistic regression with the dependent variable being purchases of antidepressant prescriptions ($\geq$200 vs. 0 defined daily doses), and the independent variables (covariates) being the 15 individual and area variables. Maxed-rescaled R^2 was 0.329 and the region of common support ranged from 0.01 to 0.95. To ensure that the matching was successful, we tested differences in matching variables between the cases and controls using multilevel ANOVA or logistic or multinomial regression analysis where appropriate. We used the difference in self-reported weight between baseline and follow-up as the outcome variable to examine absolute differences in weight gain between antidepressant users and controls. For analyses of relative 4year change in weight, we constructed an outcome variable using the formula: weight change (kg)/ baseline weight (kg) /length of follow-up (years) x 4. Multilevel analyses of variance were used to compare weight change between the participants who did or did not receive antidepressant treatment, using the

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matched group as the random variable. Sensitivity analyses repeated these analyses with different thresholds in defined daily doses to define antidepressant use and with different types of antidepressants. Finally, we repeated the analyses with incident antidepressant treatment (new users, who had no antidepressant purchases within 3 years preceding the baseline survey), adding baseline body mass index into the propensity score matching variables (cut-off points 22.5, 25, 27.5, 30 kg/m^2). We used Proc Glimmix SAS version 9.2 in the propensity score matching analyses.

Supplemental Tables for Study 1

eTable1. Sample Characteristics at Entry to Study 1

	Diabetes cases	Controls
N	851	4234
Male sex - %	34.3	34.1
Age group - %		
20-42 yr	33.3	33.3
43-48 yr	32.3	32.4
49-64 yr	34.4	34.3
Socioeconomic position - %		
Upper non-manual	18.7	18.6
Lower non-manual	42.2	42.3
Manual	39.1	39.1
Temporary contract - %	33.5	33.4
Geographic area - %		
Southern Finland	63.9	64.2
Middle Finland	16.8	16.6
Northern Finland	19.3	19.3

*There were no missing data in any of the variables. Slight differences in matching variables between cases and controls are because 1.2% of the cases had less than 5 individually controls available in the data.

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eTable2. Association of diagnosed depression (BY SOURCE OF INFORMATION) with subsequent diagnosis of type 2 diabetes.

Depression category	Number of participants (number of incident diabetes cases)	Odds ratio (95% CI) for type 2 diabetes	
		Unadjusted	Adjusted for antidepressant use
Work disability			
No	4883 (788)	1 (reference)	1 (reference)
Yes	202 (63)	2.30 (1.69 to 3.13)	1.39 (0.98 to 1.97)
Hospitalization			
No	5044 (840)	1 (reference)	1 (reference)
Yes	41 (11)	1.85 (0.92 to 3.70)	0.90 (0.43 to 1.85)
Psychotherapy			
No	5071 (846)	1 (reference)	1 (reference)
Yes	14 (5)	2.46 (0.81 to 7.52)	1.39 (0.44 to 4.40)

eTable3. Association of prevalent severe depression and use of antidepressant medication (ASSESSED WITH MULTIPLE DOSE CATEGORIES) with subsequent diagnosis of type 2 diabetes before and after mutual adjustment.

Predictor	No. of participants (no. of incident diabetes cases)	Odds ratio (95% CI) for type 2 diabetes	
		Univariate model	Mutually adjusted*
Severe depression			
No	4861 (781)	1 (reference)	1 (reference)
Yes	224 (70)	2.33 (1.74 to 3.12)	1.42 (1.01 to 1.99)
Antidepressant use			
0	4218 (635)	1 (reference)	1 (reference)
1-199	377 (73)	1.37 (1.04 to 1.80)	1.32 (1.00 to 1.74)
200-399	140 (39)	2.17 (1.49 to 3.18)	2.00 (1.36 to 2.96)
≥400	350 (104)	2.43 (1.90 to 3.11)	2.13 (1.61 to 2.82)

*Diagnosed depression and antidepressant use entered in the same model.

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eTable4. Number of antidepressant use by WHO Anatomical Therapeutic Chemical classification category.

Antidepressants by type and defined daily dose	Number (% of all users)	
	Monotherapy	Combined with other antidepressant medication
Broad category	Total N = 628	Total N = 239
SSRI (ATC N06AB)		
1-199	177 (28.2)	63 (26.4)
200+	226 (36.0)	144 (60.3)
Tricyclic antidepressants (ATC N06AA)		
1-199	71 (11.3)	79 (33.1)
200+	25 (4.0)	35 (14.6)
Other (ATC N06AF, N06AG, N06AX)*		
1-199	85 (13.5)	121 (50.6)
200+	44 (7.0)	75 (31.4)
Detailed category (substance name)	Total N = 555	Total N = 312
N06AB03 (Fluoxetine)	103 (18.6)	118 (37.8)
N06AB04 (Citalopram)	163 (29.4)	142 (45.5)
N06AB05 (Paroxetine)	28 (5.1)	43 (13.8)
N06AB06 (Sertraline)	34 (6.1)	71 (22.8)
N06AB08 (Fluvoxamine)	8 (1.4)	15 (4.8)
N06AB10 (Escitalopram)	10 (1.8)	13 (4.2)
N06AA04 (Clomipramine)	7 (1.3)	7 (2.2)
N06AA06 (Trimipramine)	3 (0.5)	15 (4.8)
N06AA09 (Amitriptyline)	56 (10.1)	63 (20.2)
N06AA10 (Nortriptyline)	4 (0.7)	5 (1.6)
N06AA12 (Doxepin)	23 (4.1)	37 (11.9)
N06AA22 (Venlafaxine)†	0 (0)	4 (1.3)
N06AG02 (Moclobemide)	11 (2.0)	24 (7.7)
N06AX03 (Mianserin)	11 (2.0)	46 (14.7)
N06AX05 (Trazodone)	0 (0)	7 (2.2)
N06AX11 (Mirtazapine)	69 (12.4)	111 (35.6)
N06AX16 (Venlafaxine) †	24 (4.3)	69 (22.1)
N06AX17 (Milnacipran)	0 (0)	5 (1.6)
N06AX18 (Reboxetine)	1 (0.2)	15 (4.8)

Abbreviations: ATC, the WHO Anatomical Therapeutic Chemical classification; SSRI, Selective-serotonin reuptake inhibitor.

*N06AF: Monoamine oxidase inhibitors, non-selective; N06AG: Monoamine oxidase A inhibitors; N06AX: Other antidepressants.

†The ATC code for venlafaxine changed from N06AA22 to N06AX16 in 1999.

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eTable5. Association of use of SPECIFIC antidepressant medications with subsequent diagnosis of type 2 diabetes.

Use of antidepressants by type and defined daily dose	No. of participants (no. of incident diabetes cases)	Odds ratio (95% CI) for type 2 diabetes	
		Unadjusted	Adjusted for diagnosed depression
SSRI (ATC N06AB)			
0	4475 (688)	1 (reference)	1 (reference)
1-199	240 (53)	1.57 (1.14 to 2.15)	1.46 (1.05 to 2.01)
200+	370 (110)	2.35 (1.85 to 2.98)	2.02 (1.14 to 2.20)
Tricyclic antidepressants (ATC N06AA)			
0	4875 (795)	1 (reference)	1 (reference)
1-199	150 (31)	1.35 (0.90 to 2.01)	1.14 (0.76 to 1.72)
200+	60 (25)	3.71 (2.20 to 6.25)	3.09 (1.81 to 5.28)
Other (ATC N06AF, N06AG, N06AX)*			
0	4760 (781)	1 (reference)	1 (reference)
1-199	206 (40)	1.23 (0.86 to 1.75)	1.02 (0.70 to 1.47)
200+	119 (30)	1.72 (1.13 to 2.61)	1.12 (0.71 to 1.78)

Abbreviations: ATC, the WHO Anatomical Therapeutic Chemical classification; SSRI, Selective-serotonin reuptake inhibitor.
*N06AF: Monoamine oxidase inhibitors, non-selective; N06AG: Monoamine oxidase A inhibitors; N06AX: Other antidepressants, including mianserin, trazodone, mirtazapine, venlafaxine, milnacipran, reboxetine.

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Supplemental Table for Study 2

eTable6. Sample Characteristics at Entry to Study 2.

	Antidepressant users*	Controls
N	9 197	45 658
Male sex - %	18.4	18.3
Age group - %		
17-34 yr	34.0	34.1
35-43 yr	31.0	31.0
44-63 yr	35.0	34.9
Socioeconomic position - %		
Upper non-manual	28.0	28.0
Lower non-manual	50.0	50.1
Manual	22.1	21.9
Temporary contract - %	46.7	46.7
Geographic area - %		
Southern Finland	68.7	68.9
Middle Finland	14.3	14.2
Northern Finland	17.0	16.9

*A minimum of 200 defined daily doses.

There were no missing data in any of the variables. Slight differences in matching variables between cases and controls are because 1.3% of the cases had less than 5 individually controls available in the data.

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Supplemental Tables for Study 3

eTable7. Distribution of Covariates Used in Propensity Score Matching in Study 3.

	Antidepressant cases (N = 1404)	Controls (N = 4133)	P-value
Propensity score - mean (range)	0.180 (0.01-0.95)	0.172 (0.01-0.95)	
Male sex - %	11.2	12.4	0.20
Mean (SD) age - yr	45.8 (8.3)	45.8 (8.9)	0.77
Socioeconomic position - %			0.85
Upper non-manual	28.0	28.1	
Lower non-manual	57.8	58.0	
Manual	14.2	13.9	
Temporary contract - %	14.5	15.2	0.49
Geographic area - %			0.61
Southern Finland	58.8	58.1	
Middle Finland	23.5	23.7	
Northern Finland	17.7	18.3	
Employed by hospitals - %	41.1	41.2	0.97
GHQ caseness - %	39.0	39.4	0.73
Jenkins scale mean (SD)	2.92 (1.23)	2.94 (1.24)	0.45
Trait anxiety, mean (SD)	2.15 (0.59)	2.17 (0.60)	0.14
Depression* - %	34.3	32.3	0.34
IHD or stroke* - %	0.9	1.5	0.08
Cancer* - %	2.1	1.7	0.40
Pain killers*, - %	20.2	20.5	0.76
Hypnotics*, - %	14.3	13.4	0.47
Anxiolytics*, - %	14.5	13.9	0.65

Cases purchased prescribed antidepressants ≥200 vs. 0 defined daily doses.

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eTable8. Weight gain in INCIDENT antidepressant cases and propensity score matched controls.*

	Antidepressant users (N=910) Mean (95% CI)	Controls (N=2686) Mean (95% CI)	P-value†
Any antidepressant	N=910	N=2686	
Weight change between baseline and follow-up‡	2.78 (2.45-3.10)	1.33 (1.14-1.52)	<0.0001
Relative change in weight#, %	4.46 (3.94-4.98)	2.25 (1.94-2.55)	<0.0001
SSRI	N=758	N=2241	
Weight change between baseline and follow-up‡	2.95 (2.59-3.31)	1.37 (1.15-1.58)	<0.0001
Relative change in weight#, %	4.68 (4.10-5.27)	2.36 (2.02-2.71)	<0.0001
Tricyclic antidepressants	N=27	N=79	
Weight change between baseline and follow-up‡	4.74 (2.87-6.62)	0.80 (-0.36-1.97)	0.0007
Relative change in weight#, %	7.87 (4.94-10.79)	1.47 (-0.38-3.24)	0.0004
Other	N=192	N=571	
Weight change between baseline and follow-up‡	2.73 (2.00-3.46)	1.64 (1.22-2.06)	0.01
Relative change in weight#, %	4.55 (3.33-5.76)	2.62 (1.92-3.33)	0.002

*Matched for depression and 15 related factors (INCLUDING BASELINE BMI). Antidepressant use refers to a minimum use of 200 defined daily doses of antidepressants during 4 years.

†Multilevel analysis of variance.

‡Mean (SD) follow-up 3.7 (0.9) years.

#Calculated for 4 years.

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