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

Running title: Antidepressants, Weight Gain and Diabetes

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Objective—To examine antidepressant medication use as a risk factor for type 2 diabetes and weight gain.

Research design and methods—A series of nested studies within a prospective cohort of 151,347 working-aged men and women including 9197 participants with continuing antidepressant medication, 224 with severe depression, and 851 with incident type 2 diabetes mellitus during a mean follow-up of 4.8 years, as indicated by national health and prescription registers (the Public Sector study, Finland 1995-2005).

Results—In the first analysis, the cases were individuals with incident type 2 diabetes compared with matched diabetes-free controls. Antidepressant use of >200 defined daily doses was associated with a doubling of diabetes risk in both participants with no indication of severe depression (odds ratio 1.93, 95% CI 1.48-2.51) and participants with severe depression (odds ratio 2.65 95% CI 1.31-5.39). In the further analyses, exposed group was antidepressant users and reference group non-users matched for depression-related characteristics. The 5-year absolute risk of diabetes was 1.1% for non-users, 1.7% for individuals treated with 200-399 defined daily doses a year, and 2.3% for those with >400 defined daily doses (p_trend<0.0001). An average self-reported weight gain, based on repeated surveys, was 1.4 kg (2.5%) among non-users and 2.5 kg (4.3%) among users of >200 defined daily doses (p_trend<0.0001). Separate analyses for tricyclic antidepressants and selective-serotonin-re-uptake inhibitors replicated these findings.

Conclusions—In these data, continuing use of antidepressant medication was associated with an increased relative risk of type 2 diabetes, although the elevation in absolute risk was modest.

Antidepressants are one of the most commonly prescribed drugs worldwide.(1, 2) Although their efficacy in the acute phase therapy of depression might be lower than initially thought,(3-6) there is substantial evidence that continuation of therapy reduces the risk of relapse in patients who initially respond to therapy.(7, 8) Long-term antidepressant therapy is routinely recommended for recurrent unipolar depression.(7, 8) Recent studies have raised the possibility that continuing antidepressant use might increase the risk of type 2 diabetes, as an unwanted side effect.(9-13) For several reasons, this hypothesis warrants further scrutiny. First, it is based on a small number of epidemiological studies with limited information on consumption of antidepressants (type, dose, duration). Second, owing to the absence of direct monitoring for diabetes risk and short follow-up periods (typically months), randomized controlled trials on antidepressants have, thus far, been unable to robustly examine the long-term antidepressant-diabetes association.(6, 14) Third, if antidepressant use does indeed influence the risk of diabetes, the mechanisms responsible, such as weight gain - a major risk factor for diabetes - need to be ascertained. Study members in the present epidemiologic cohort have been linked to complete national pharmacy records from which the daily dose of antidepressant medication, based on World Health Organization (WHO) definitions of average maintenance dose,(15) can be captured. In addition, participants' responses to surveys at study baseline and follow-up.
enable determining change in self-reported weight over time. Accordingly, the aim of this study is to examine whether exposure to antidepressant medication use is associated with type 2 diabetes risk in a large population of men and women (Aim 1) and whether there is a difference in weight gain among antidepressant users as compared with equally-depressed individuals who are not treated with antidepressants (Aim 2). As the benefits of antidepressant therapy may be substantial only for patients with severe depression,(3) we additionally examined the antidepressant-diabetes association separately in this group and among those with mild or moderate symptoms.

RESEARCH DESIGN AND METHODS
Participants—We performed 3 inter-related nested studies within an occupational cohort of 151,347 employees in Finland.(16) The eligible population of 151,347 participants was linked to national health and prescription 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.

Study 1 examined differences in antidepressant medication use between 851 incident type 2 diabetes cases and their 4234 individually matched diabetes-free controls with complete records of severe 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. 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. For a flow chart depicting sample selection, see eFigure1.

As the retrospective case-control design in Study 1 is unable to estimate absolute risk of diabetes associated with antidepressant use, we undertook Study 2. It is a prospective follow-up of all 9197 identified continuing antidepressant users (≥200 defined daily doses a year i.e. a treatment lasting over 6 months). 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 (eFigure2).

Study 3 is a prospective follow-up of 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 participating in the surveys and their 4133 matched controls (non-users)(eFigure3). We used propensity-based matching (a quasi-experimental "correction strategy") to select for each case 1-3 controls who had the same probability as the cases to receiving treatment with respect to depression status and other depression-related covariates, discarding unmatched individuals. Antidepressant users were matched for the same characters as those used in Studies 1 and 2 and additionally for diagnosed depression, ischaemic 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.

Measurements—Full details of the measurements and statistical analysis are provided in online appendix available at http://care.diabetesjournals.org. Briefly, antidepressant use for each year of the observation was derived from the nationwide Drug Prescription Register. The data contained 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, for specific drugs, see eTable4).

Severe depression was defined by psychiatric hospital admission (the National Hospital Discharge Register), record of long-term psychotherapy granted by the Social Insurance Institution (minimum 1 year) or record of work disability longer than 90 days (the Social Insurance Institution of Finland and the Finnish Centre for Pensions registers) for ICD-10 diagnostic codes F32-F34.

Participants were defined as incident type 2 diabetes mellitus 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. The Central Drug Register, maintained by the Social Insurance Institution, lists all such patients with physician-documented evidence of a fasting whole blood glucose >7.0 mmol/L (or fasting plasma glucose >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 >7.0 mmol/L is required. To exclude prevalent diabetes (i.e., 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 nationwide since 1994, according to the WHO ATC Classification.

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 clear differences in the associations of antidepressant use with diabetes or weight gain between men and women (p for all sex interactions>0.26), so the data were pooled and sex-adjusted. The cohort was racially homogeneous (white Europeans).

RESULTS
Relative Risk of Incident Type 2 Diabetes (Study 1)—Table 1 shows that antidepressant use was associated with increased risk of incident diabetes in both participants with no indication of severe depression (odds ratio 1.93, 95% CI 1.48-2.51, Comparison A in Table 1) and participants with severe depression (odds ratio 2.65 95% CI 1.31-5.39, Comparison C). In contrast, there was a weaker association between severe depression and incident diabetes both among non-users of antidepressants (odds ratio 1.20 95% CI 0.64-2.25, Comparison A) and antidepressant users (odds ratio 1.65 95% CI 1.09-2.48, Comparison B). This pattern of results was robust to adjustment for baseline chronic diseases, such as prevalent hypertension, coronary heart disease, stroke and cancer.

Analyses combining severely depressive and less severely depressive groups replicated these findings (figures not provided in table 1). Thus, participants with an exposure to >200 defined daily doses of antidepressants (n=490) had an odds ratio of 2.29 (95% CI 1.85-2.83) times higher for diabetes than those with antidepressant use less than 200 defined daily doses (n=4595). Severe depression (224 severe depression cases, 4861 non-cases) was also associated with an increased risk of type 2 diabetes (odds ratio 2.33, 95% CI 1.74-3.12). In a mutually adjusted model, the excess diabetes risk associated with antidepressant use was reduced only by 21.0% while the excess
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diabetes risk associated with severe depression attenuated by 68.4%.
In a sensitivity analysis, the depression-diabetes association was substantially attenuated after adjustment for antidepressant use irrespective of source of data for the diagnosis of depression: hospitalization records, work disability records, or records of long-term psychotherapy (online eTable2). Furthermore, tests for synergistic interaction (synergy index 1.94, 95% CI 0.82-4.55) and multiplicative interaction (p=0.41) were both negative suggesting that the excess risk of incident diabetes associated with antidepressant use and depression was not additive or multiplicative. In further sensitivity analyses, the association between antidepressant use and incident diabetes was seen irrespective of whether ≥200 defined daily doses (an exposure equivalent to over 6-month continuing antidepressant use during the 4-year period) or ≥400 defined daily doses (representing over 1-year continuing use) were used to define antidepressant medication use (eTable3) and for both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)(eTable4 and eTable5).

Absolute Risk of Diabetes (Study 2) — A prospective analysis with 9197 antidepressant users (≥200 defined daily doses within a year) and their 45,658 matched non-treated controls replicated the excess risk associated with long-term antidepressant use (eTable6). For 5 years, the absolute risk of incident diabetes was 1.8% for antidepressant users and 1.1% for matched non-users (calculated based on a mean follow-up 4.75 years, range 1 to 11 years). The corresponding absolute risk estimate for individuals treated with 200 to 399 defined daily doses a year (n=6878) was 1.7% and for those with ≥400 defined daily doses a year (n=2319) 2.3%. The relative risk estimates (hazard ratios) for incident diabetes associated with antidepressant use of 200 to 399 defined daily doses and ≥400 defined daily doses compared with no use were 1.53 (95% CI 1.25-1.87) and 2.00 (95% CI 1.51-2.66), respectively. A P-value of <0.0001 for a trend across antidepressant use categories supports a 'dose-response' association between antidepressant use and incident type 2 diabetes.
Figure 1 shows that there was separation of the survival curves between antidepressant users (≥200 defined daily doses within a year) and non-users across the entire follow-up period.

Weight Gain (Study 3) — Table 2 shows that antidepressant users (cases) were 0.9 kg heavier at baseline and 2.1 kg heavier at follow-up, an average of 3.7 years later (range 2-5 years), compared with equally-depressed controls with no record of antidepressant use (for baseline characteristics of cases and controls, see eTable7). Mean weight gain was 2.5 kg (4.3% in four years) in the antidepressant treatment cases but only 1.4 kg (2.5%) in controls with no such treatment. The 4-year proportional change in weight between the surveys was essentially the same for the cases across the major types of antidepressant medications: 4.6% for SSRI users and 4.7% for tricyclic antidepressant users.

For the incident users of any antidepressants, users of SSRIs, and users of tricyclic antidepressants, the proportional change in weight (with adjustment for weight before antidepressant treatment) was 4.5%, 4.7% and 7.5%, respectively, while among the non-users, these proportions ranged between 1.5%-2.4% (eTable8). When ≥400 defined daily doses was used to define long-term antidepressant use, mean weight gain was greater, 2.9 kg (4.9%) among the users and it was 1.4 kg (2.5%) among the non-users.

Due to the small numbers of incident diabetes cases between the baseline and follow-up surveys (N=32) among those who responded to both surveys, no meaningful analysis of the association
between antidepressant use and diabetes risk was possible.

CONCLUSIONS
Analyses of data drawn from a cohort of over 150,000 adults revealed a series of important results. First, antidepressant medication use, as indicated by completed prescriptions exceeding 200 defined daily doses, was associated with a doubling of the risk of developing type 2 diabetes, irrespective of a record of severe depression. The excess risk associated with antidepressants was observable for both SSRIs and tricyclic antidepressants. Second, in absolute terms, the 5-year risk of diabetes increased in a dose-response fashion depending on the level of exposure to antidepressant medication: 1.1% in non-users, 1.7% among those treated with 200-399 daily defined doses a year, and 2.3% among those using 400 doses or over. Third, supporting biological plausibility of this association, weight gain was more rapid among long-term antidepressant users than in non-users matched for depression-related characteristics.

Our findings add to the existing evidence from recent studies. In the randomized Diabetes Prevention Program of prediabetic individuals, use of antidepressants at baseline was associated with an increased risk of type 2 diabetes at follow-up whereas self-reported depressive symptoms at baseline were not predictive of subsequent diabetes risk. An analysis of medical records of depressive patients from the UK General Practice Research Database found that long-term use of antidepressants with high or moderate daily doses was associated with increased risk of diabetes, but treatment with lower daily doses was not. In the present study, the number of antidepressant users was 6 times higher than that in the two studies together, we targeted a non-clinical occupational cohort including also groups not covered by those studies, took in addition into account dose and duration of antidepressant use as well as baseline status of severe depression, and demonstrated a plausible mediating mechanism.

Other studies in the field have reported inconsistent findings. A Norwegian cross-sectional health survey, a study of spontaneous reports listed in the WHO Adverse Drug Reaction Database, and an analysis of data from one province in Canada all found support for an association between antidepressant use and diabetes. In a community sample of adults aged ≤55, treatment with antidepressants was not associated with an increased risk of diabetes, but the study lacked adequate statistical power as the number of antidepressant users who developed diabetes was only 4. Analyses using prescription data from the PHARMO database from the Netherlands did not find an increased risk of diabetes among antidepressant users. However, that study did not consider the duration nor the dose of antidepressant treatment. Our findings and other studies suggest that inclusion of short-term/low-dose treatments in the definition of antidepressant use is likely to dilute the association. In the present study, exposure to <200 defined daily doses of antidepressants was not associated with diabetes risk.

Weight gain, both in relative and absolute terms, was greater among antidepressant users than their controls matched for depression status using recorded and self-reported information on depression and related traits. A previous trajectory analysis of repeat body mass index measurements found on average of 0.03 units faster annual increase in BMI among individuals who later developed type 2 diabetes compared to those who remained disease free. This translates to approximately 0.1 kilograms excess weight gain per year for incident diabetes cases. Using that metrics, our findings suggest that antidepressant medication use is related to
approximately 0.3 kilograms excess yearly weight gain, a change clearly large enough to contribute to diabetes risk. Our findings are in agreement with previous studies that have confirmed that tricyclic antidepressants may induce weight gain and promote hyperglycemia(20, 21) and shown that SSRI use, despite being related to stable weight or even weight loss in the short term, is associated with an increased risk of weight gain in the longer term.(22)

In the weight gain study reported herein, we undertook a sensitivity analysis based on a subgroup of incident antidepressant medication users who started treatment between baseline and follow-up weight measurements excluding all prevalent antidepressant users. This exclusion affected little estimated significant weight gain associated with SSRIs but showed even a greater weight gain in relation to tricyclic antidepressant treatment. As weight gain is a recognized side effect of tricyclic antidepressants, the main analysis may include an under-representation of patients who did not tolerate antidepressant treatment well (the depletion of susceptibility bias), contributing to an underestimation of the weight gain associated with tricyclic treatment.

**Strengths and limitations**—Information on the daily dose of antidepressant medication, based on WHO definitions of average maintenance dose, is an advantage as it enabled determination of the level of exposure to these drugs. Use of records of completed antidepressant prescriptions is also a specific strength, because previous studies have typically relied on information on prescriptions irrespective of whether the patient actually uplifted them. Our data on antidepressants, being based on physician-prescribed medication that were then purchased by the user from a pharmacy, are likely to be more accurate, although we cannot ascertain the extent to which the purchased medication was actually taken. In this study, comprehensive records on medications, and diagnoses of depression and diabetes from national registers very unusually covered the entire cohort during the entire follow-up period. Thus, biases related to sample attrition were avoided.

Several limitations to this study are noteworthy. First, the assessment of type 2 diabetes and depression with records from national health registers does not capture non-diagnosed or non-treated diabetes or depression, introducing a source of misclassification. However, an association of antidepressant use and incident diabetes, similar to that found in the present study, has previously been confirmed in a study with glucose-based assessment of incident type 2 diabetes,(9) which will capture non-diagnosed and non-treated diabetes cases.

Second, we assessed weight change using self-reports. Although self-reported weights are correlated with objective weight measurements, there are errors in self-reports which are systematic instead of random, reflecting both roundings to the nearest point of heaping and a tendency to report weights closer to ideal weight. In the present study, the weight change calculated by deducting self-reported weight at follow-up from that at baseline may therefore have, if anything, underestimated large weight changes. The influence of antidepressant use on the accuracy of self-reporting is not known; such impacts could potentially introduce some bias to our results.

Third, other mechanisms beyond weight gain, such as hyperglycemic effects of noradrenergic activity of antidepressants, may have a role in the increased diabetes risk associated with antidepressants. Further research is therefore needed to examine the entire pathway from antidepressant use to subsequent physical and biochemical changes, including weight gain, and the onset of type 2 diabetes. Given that diabetogenic effects are
likely to vary depending on drug's chemical substance, antidepressant-specific analyses, beyond those of SSRIs and tricyclic medication, would be important and should cover, for example, the increasingly popular serotonin-norepinephrine reuptake inhibitors (SNRIs).

Fourth, the possibility of residual or unmeasured confounding cannot be excluded in epidemiological studies, such as ours. The fact that the association between antidepressant use and diabetes was similar in severely depressive patients and the remaining study members suggests that the observed association was not driven by confounding factors strongly related to depression. Similarly, the association of antidepressant use and weight gain was robust to matching for 16 depression-related characteristics, such as GHQ-12 caseness, a correlate of clinical depression.(23)

Fifth, observational data cannot prove causality. We therefore recommend confirmatory studies, such as post-intervention follow-ups for existing antidepressant trials for assessment of diabetes risk in randomized data.

Implications—Potential diabetes risk is currently not taken into consideration in clinical guidelines for treating depression.(8, 24) We observed a substantially increased relative and modestly increased absolute risk of type 2 diabetes associated with continuing antidepressant medication use. If this reflects a causal effect, then this risk should be incorporated into clinical decision making in recurrent depression because diabetes mellitus is a serious disease with potentially fatal complications.

Author Contributions: M.K. and J.V. formulated the initial hypothesis. M.K., M.H., G.D.B., J.R.G., A.G.T., J.P., M.V. and J.V. designed the study. J.P. analyzed the data. M.K. wrote the first draft. All the authors contributed to interpretation of the data and writing of the manuscript.

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REFERENCES


### Table 1—Severe depression and use of antidepressant medication during the 4 years preceding diabetes diagnosis among incident type 2 diabetes cases and individually matched controls*

<table>
<thead>
<tr>
<th>Severe depression</th>
<th>Antidepressant use†</th>
<th>No. of participants (no. of incident diabetes cases)</th>
<th>Odds ratio (95% CI) for incident diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparison A</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>4530 (696)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>331 (85)</td>
<td>1.93 (1.48 to 2.51)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>65 (12)</td>
<td>1.20 (0.64 to 2.25)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>159 (58)</td>
<td>3.17 (2.27 to 4.45)</td>
</tr>
</tbody>
</table>

**Additional adjustment for prevalent physical disease‡**

|                   |                     |                                               | Comparison A | Comparison B | Comparison C |
|                   |                     |                                               | 1 (reference) | 0.60 (0.45 to 0.79) | 0.95 (0.49 to 1.84) |
| No                | Yes                 | 331 (85)                                     | 1.68 (1.27 to 2.21) | 1 (reference) | 1.59 (0.79 to 3.22) |
| Yes               | No                  | 65 (12)                                      | 1.05 (0.55 to 2.04) | 0.63 (0.31 to 1.27) | 1 (reference) |
| Yes               | Yes                 | 159 (58)                                     | 2.76 (1.93 to 3.94) | 1.64 (1.06 to 2.54) | 2.61 (1.25 to 5.49) |

*Based on conditional logistic regression analysis.
†"Yes" refers to a minimum use of 200 defined daily doses of antidepressants and "No" to a use of 0-199 defined daily doses during 4 years.
‡Hypertension, coronary heart disease, cerebrovascular disease and cancer. Prevalence of cardiovascular diseases 4 years before the diabetes diagnosis was higher among diabetes cases than controls (hypertension 28.0% vs 9.3% p<0.0001; coronary heart disease 3.2% vs 1.4% p=0.0002). There was no difference in cerebrovascular disease (0.7% vs 0.8, p=0.88) or cancer prevalence (2.7% vs 2.4%, p=0.61) between the groups.
Table 2—Weight gain in antidepressant users and propensity score matched non-users

<table>
<thead>
<tr>
<th>Antidepressant users</th>
<th>Controls</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Any antidepressant</td>
<td>N=1404</td>
<td>N=4133</td>
</tr>
<tr>
<td>Weight at baseline, kg</td>
<td>70.5 (69.8-71.2)</td>
<td>69.6 (69.2-70.0)</td>
</tr>
<tr>
<td>Weight at follow-up§, kg</td>
<td>73.1 (72.4-73.8)</td>
<td>71.0 (70.6-71.4)</td>
</tr>
<tr>
<td>Weight change between baseline and follow-up§, kg</td>
<td>2.54 (2.28-2.80)</td>
<td>1.37 (1.22-1.52)</td>
</tr>
<tr>
<td>Relative change in weight#, %</td>
<td>4.25 (3.81-4.69)</td>
<td>2.48 (2.22-2.74)</td>
</tr>
<tr>
<td>SSRI</td>
<td>N=1210</td>
<td>N=3563</td>
</tr>
<tr>
<td>Weight at baseline, kg</td>
<td>70.6 (69.8-71.3)</td>
<td>69.4 (69.0-69.9)</td>
</tr>
<tr>
<td>Weight at follow-up§</td>
<td>73.4 (72.6-74.2)</td>
<td>70.8 (70.3-71.3)</td>
</tr>
<tr>
<td>Weight change between baseline and follow-up§, kg</td>
<td>2.79 (2.52-3.07)</td>
<td>1.38 (1.22-1.54)</td>
</tr>
<tr>
<td>Relative change in weight#, %</td>
<td>4.63 (4.17-5.09)</td>
<td>2.44 (2.16-2.71)</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>N=140</td>
<td>N=402</td>
</tr>
<tr>
<td>Weight at baseline, kg</td>
<td>72.6 (70.3-74.9)</td>
<td>70.1 (68.7-71.4)</td>
</tr>
<tr>
<td>Weight at follow-up§</td>
<td>75.3 (72.9-77.6)</td>
<td>71.4 (70.0-72.8)</td>
</tr>
<tr>
<td>Weight change between baseline and follow-up§, kg</td>
<td>2.70 (1.88-3.52)</td>
<td>1.29 (0.81-1.77)</td>
</tr>
<tr>
<td>Relative change in weight#, %</td>
<td>4.24 (2.91-5.57)</td>
<td>2.34 (1.56-3.12)</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>N=422</td>
<td>N=1237</td>
</tr>
<tr>
<td>Weight at baseline, kg</td>
<td>70.6 (69.3-71.9)</td>
<td>71.9 (71.1-72.6)</td>
</tr>
<tr>
<td>Weight at follow-up§</td>
<td>73.0 (71.6-74.3)</td>
<td>73.5 (72.7-74.3)</td>
</tr>
<tr>
<td>Weight change between baseline and follow-up§, kg</td>
<td>2.42 (1.93-2.91)</td>
<td>1.65 (1.36-1.94)</td>
</tr>
<tr>
<td>Relative change in weight#, %</td>
<td>4.15 (3.37-4.93)</td>
<td>2.69 (2.23-3.15)</td>
</tr>
</tbody>
</table>

*Matched for depression and 14 related factors. 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.

FIGURE LEGEND:
Figure 1—Cumulative hazard function for incident type 2 diabetes for participants with long-term antidepressant medication use (>200 defined daily doses a year) and their individually matched controls with no record of antidepressant use.
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No. at Risk

Users 9197 9169 7759 6532 5313 4243 3212 2392 1820 1311 819
Non-users 45658 45575 38696 32779 26847 21501 16357 12225 9295 6688 4220