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Antidepressant Use Before and After the Diagnosis of Type 2 Diabetes:

A Longitudinal Modeling Study

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ABSTRACT

Objective-To examine antidepressant use before and after the diagnosis of diabetes.

Research Design and Methods-Longitudinal analysis of diabetic and non-diabetic groups selected from a prospective cohort study of 151,618 men and women in Finland (the Finnish Public Sector Study, 1995-2005). We analyzed the use of antidepressants in those 493 individuals who developed type 2 diabetes and their 2450 matched non-diabetic controls for each year during a period covering 4 years before and 4 years after the diagnosis. For comparison, we undertook a corresponding analysis on 748 individuals who developed cancer and their 3730 matched controls.

Results-In multilevel longitudinal models, odds ratio for antidepressant use in those who develop diabetes was 2.00 (95% CI 1.57-2.55) times greater compared to that in non-diabetics. The relative difference in antidepressant use between these groups was similar before and after the diabetes diagnosis except for a temporary peak in antidepressant use at the year of the diagnosis (OR=2.66, 95% CI 1.94-3.65). Antidepressant use in incident cancer cases, being similar in cases and cancer-free subjects before the diagnosis, substantially increased after the cancer diagnosis, demonstrating that our analysis was sensitive in detecting changes in antidepressant trajectories when they existed.

Conclusions-Awareness of the diagnosis of type 2 diabetes may temporarily increase risk of depressive symptoms. Further research is needed to determine whether more prevalent use of antidepressants noted before the diagnosis of diabetes relates to excess diabetes risk associated with depression, a common causal pathway for depression and diabetes or the side-effects of antidepressant use.

[Words 248]

INTRODUCTION

Diabetes is a chronic disease with substantial public health importance,[1, 2] but its psychological effects are not well understood. Although several (but not all) studies have reported an association between type 2 diabetes and depressive disorders,[3-10] few studies have examined the stage of disease when the onset of depression is most likely. The diagnosis of diabetes in itself may be a life event that increases risk of depressive symptoms, arising from the awareness of having a pernicious chronic condition.[7] However, it is equally possible that psychological impacts are not apparent until patients reach advanced disease state because at diagnosis type 2 diabetes is usually mild in symptoms.[4]

The suggestion that depressive symptoms among non-diabetic individuals also increase the risk of diabetes complicates the isolated examination of the effect of diabetes on depression, as this association may be bidirectional and thus affected by simultaneous causation and reverse causation.[7] To date, the evidence on the status of depressive symptoms as a risk factor for type 2 diabetes is mixed as both positive and null findings have been reported.[7, 11] It is therefore important to assess depression both before and after the diagnosis of diabetes in a single methodological setup to ensure the adequate estimation of the effect sizes in both directions, accounting for causation and reverse causation. To our knowledge, no such study exists.

We employ multiple repeated measurements of antidepressant use, both before and after the diagnosis of type 2 diabetes, to examine whether awareness of diabetes diagnosis is associated with elevations in depression risk and whether individuals who develop type 2 diabetes are more likely to be depressed already before the diagnosis than their non-diabetic counterparts. For comparison, we examine antidepressant use among individuals who developed cancer, a serious disease which is known to increase risk of depression.[12]

RESEARCH DESIGN AND METHODS

Sample Selection

Data were drawn from the Finnish Public Sector study[13] which includes the entire public sector personnel of 10 towns (municipalities) and 21 hospitals in the areas where these towns are located (see online-Figures S1 and S2). The eligible population comprised 151,347 employees with an employment contract between 1995 and 2005 and a record linkage to national health registers through unique personal identification codes which are assigned to all citizens in Finland. For all the participants in the eligible population, the linkage to registers was 100% complete and there was no sample attrition during the follow-up.

We report data from two independent cohorts: 493 participants who developed type 2 diabetes (hereafter referred to as the 'diabetes study') and 748 individuals who developed cancer (the 'cancer study'). All cases in both studies had complete data on prescribed antidepressant use and other register measures over a fixed period of 4 years before, and 4 years after, the diagnosis of type 2 diabetes/cancer, because we limited the study to those incident cases who received the diagnosis of diabetes or cancer between Jan 1, 1999 and Dec 31, 2001 and were alive a minimum of 4 years after the diagnosis. This ensured an observation period of 4 years before and after the diagnosis without any sample attrition.

We randomly selected controls in a 5:1 ratio for each diabetes case and each cancer case, matching individually 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 (7 areas based on the location of the workplace), as these characteristics could be related to differences in the likelihood of achieving diagnosis or treatment. The diabetes study included 2450 matched diabetes-free controls and the cancer study 3730 matched cancer-free controls.

Assessment of Antidepressant Use

We determined antidepressant use, the primary outcome, for each year of the observation period from 4 year before to 4 years after the diabetes and cancer diagnoses using the nationwide Drug Prescription Register. We used the same period for the incident diabetes/cancer cases and their disease-free 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 daily defined dose; and medication classified according to the WHO Anatomical Therapeutic Chemical (ATC) classification. For each year of observation, we defined antidepressant use as the purchase of antidepressants (ATC code N06A) of at least 30 daily defined doses. In addition, we conducted a sensitivity analysis limiting the outcome to selective-serotonin reuptake inhibitor (SSRI, ATC code N06AB) as the outcome as these drugs have lower risk of cardiotoxicity than tricyclic antidepressants[14] and therefore may be more likely to be selectively prescribed in individuals with diabetes.

Case Definition for Incident Type 2 Diabetes and Cancer

Since 1965, drug treatment for diabetes has been free of charge in Finland. The Central Drug Register, maintained by the Social Insurance Institution, lists all such individuals with physician-documented evidence of a fasting plasma glucose $\geq$7.0 mmol/L, or a non-fasting plasma glucose $\geq$11.1 mmol/L and symptoms of diabetes, such as polyuria, polydipsia, and glucosuria. If the symptoms are not present, then evidence of repeatedly measured elevated glucose levels is required. In this study, participants were defined as incident type 2 diabetes cases if they were first time diagnosed in the Central Drug Register as eligible for diabetes treatment between Jan 1, 1999 and Dec 31, 2001.

To exclude type 1 diabetes cases, we additionally linked the data to the Finnish Hospital Discharge Register listing all discharged hospital patients with information on dates of admission and discharge 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. We excluded individuals who were recorded as having type 1 diabetes (code E10, ICD-10) in the Central Drug Register or the Hospital Discharge Register. For these registers, type 1 diabetes is always diagnosed by a diabetes specialist. For sensitivity analyses, we additionally excluded from the cases those who were prescribed insulin or its analogous (ATC code A10A, the Drug Prescription Register) and were diagnosed at age 35 or below. Type 1 diabetes cases were also not allowed to be selected as controls. From the potential control group, we excluded all individuals with 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.

Cancer cases were identified via the nationwide Finnish Cancer Register which records all cancer patients with any type of cancer. In Finland, all physicians, all hospitals and other institutions are legally bound to send notifications of all malignant cancers, carcinoid tumors, carcinoma in situ lesions and tumors with borderline malignancy to the Register. In this study, an individual was defined as a cancer case if he/she was diagnosed for the first time with cancer between January 1, 1999 and December 31, 2001.

Other Variables

Age, 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 (7 areas based on the location of the workplace) were obtained from employers' registers. We also obtained data on several additional variables. Age at diagnosis was calculated from the dates of diagnosis and birth, using register data. We assessed the status of coronary heart disease at each year of observation, as this condition is known to be associated with both depression and diabetes. Information on coronary heart disease was obtained from the Finnish Hospital Discharge Register and Central Drug Register, ICD-10 codes I20–I25.

Statistical Analysis

We analyzed the diabetes study and the cancer study separately. The observation period started at the date of diagnosis (year 0) for those who developed type 2 diabetes or had cancer (i.e., cases) and at a matched year for the controls. Participants were then traced backwards and forwards from year 0 to assess antidepressant use for a period covering 4 years before and 4 years after the diagnosis (i.e., years -4 to +4).

We applied a repeated-measures logistic regression analysis using the generalized estimating equations (GEE) method to estimate trajectories of antidepressant use before and after the diagnosis. Data were structured so that the repeated measurements were nested within participants (i.e., the same individuals contributed more than one observations to the dataset) and the non-independence of the within person observations was taken into account in estimating the standard errors. Differences in trajectories between incident cases and controls were modeled in multiple steps. We created 3 time variables to describe temporal changes: observation time (a continuous variable ranging from -4 to +4), time at diagnosis (a dummy variable, 1=at year 0 and 0=all other times) and period (a dummy variable, 0=years -4 to 0 and 1=years +1 to +4, to separate periods before and after the diagnosis). We adjusted all models for age, sex, and calendar year of diagnosis. We determined the final model with a

backward elimination procedure by first fitting a model with interactions between case status and time variables in addition to their main effects and then removing step-by-step the non-significant interaction terms and main effects. Non-significant main effects were retained when interactions were significant.

We conducted all analyses using STATA statistical software, version 10.1 for Windows. Statistical significance was inferred at a 2-tailed $P<0.05$.

RESULTS

Table 1 shows the characteristics of participants at baseline, i.e., four years before the diagnosis in cases. In the studies of type 2 diabetes and cancer, there were no differences in baseline characteristics between the incident cases and disease-free participants ($p>0.11$), including job type and geographical area that are not shown in the tables ($p>0.95$ in the diabetes study and $p>0.93$ in the cancer study). Comparison of the two studies shows that participants in the diabetes study were 2.4 (95% CI 2.2 to 2.7) years older, more likely to be male (odds ratio 2.80, 95% 2.64 to 2.97) and from manual occupation (odds ratio 2.25, 95% 2.15 to 2.38) compared to participants from the cancer study. These differences were expected given that male sex and low socioeconomic position tend to be stronger risk factors for type 2 diabetes than cancer in working populations.

Antidepressant Use Before and After Diagnosis of Diabetes

Crude odds ratios for antidepressant use for incident diabetes cases versus non-diabetic controls at each year of observation were 2.19 (year -4), 1.95, 1.90, 2.33, 2.66 (Year 0, diagnosis), 1.93, 1.73, 1.87 and 1.97 (Year 4). The 95% confidence intervals for the lowest odds ratio, 1.73, were 1.26 to 2.38 and for the highest odds ratio (year of diagnosis) 1.94 to 3.65 (complete results available upon request from the first author).

Figure 1 shows the final model to describe trajectory of antidepressant use among incident diabetes cases and non-diabetic controls (for model parameters, see online-table S1). There was an overall upward trend in the use of antidepressants across the 9-year observation period in diabetes cases and non-diabetic participants (time $p<0.0001$), reflecting the nationwide increase in prescription for these drugs.[15] Across the entire observation period, the odds ratio of antidepressant use was 2.00 (95% CI 1.57 to 2.55) times higher for the incident diabetes cases than the controls ($p<0.0001$). There were no differences in the slopes between the groups or in slopes before and after the diagnosis ($p=0.32$), but the temporary increase in antidepressant use during the year of diagnosis among the incident diabetes cases reached statistical significance ($p=0.01$).

In four sensitivity analyses we repeated the main analysis first, after excluding all incident cases who were on insulin treatment and those aged 35 or less at the time of diagnosis; second, excluding subjects with prevalent CHD; third, including additionally socioeconomic position, job contract and geographical area in the model; and fourth, using SSRIs as the outcome. These sensitivity analyses largely replicated the findings in the main analysis (online-tables S2 and S3).

Antidepressant Use Before and After Diagnosis of Cancer

Figure 2 presents the final model to describe trajectories in antidepressant use before and after the diagnosis of cancer (for model parameters, see online-table S1). The slope in antidepressant use did not differ between cases and controls before year 0 ($p=0.21$); antidepressant use during the year of diagnosis was slightly higher among incident cancer cases compared to controls ($p=0.03$). There was a substantial increase in antidepressant use in cases after the diagnosis (12.2% one year after the diagnosis compared to 6.3% in one year before the diagnosis, caseness x period $p=0.004$). The odds of antidepressant use were 1.92

(95% CI 1.49 to 2.48) times higher in incident cancer cases one year after the diagnosis than the controls. Antidepressant use declined somewhat in the second year following the diagnosis of cancer (p for caseness x time x period=0.01), but remained higher in incident cancer cases compared cancer-free participants for the whole 4 year period after diagnosis.

CONCLUSIONS

Serial measurements show that antidepressant use among men and women who develop type 2 diabetes was approximately 2 times greater compared to that in non-diabetics. Except for a temporary change in risk at the year of diagnosis, the relative difference in antidepressant use between these groups was similar during the 4 years before and 4 years after the diagnosis of diabetes. By contrast, there was no difference in antidepressant use before diagnosis of cancer between the incident cases and cancer-free participants, but the use of antidepressants sharply increased after diagnosis and remained higher in cases throughout the 4 years post diagnosis.

Our findings provide support for the hypothesis that awareness of the diagnosis of type 2 diabetes may temporarily increase risk of depressive symptoms.[7] However, as the antidepressant use was similarly elevated both before and after the diagnosis among diabetes cases, it seems likely that awareness of the diagnosis has no lasting effect on depression risk. These findings do not support the concern that overlap of symptoms between type 2 diabetes and depression (e.g. fatigue) would make it less likely for depression to be appropriately recognized in diabetic patients.[16, 17] The parallel trends in the use of antidepressant treatment between diabetic and non-diabetic subjects suggest that the recognition of depression may be equally appropriate in these groups before and after the diagnosis of type 2 diabetes.

Having a contact with a physician because of type 2 diabetes might make detection of unrecognized depression more likely and cause elevation in antidepressant use at diagnosis without actual increase in depression rates. However, elevated prescriptions rates would have

remained after diagnosis if increased recognition of untreated depression explained the finding. This was not the case and therefore we believe the temporary elevation in antidepressant use may represent true temporary increase in depression risk as a result of the diagnosis. Credibility of our observations is strengthened by the findings related to cancer as they demonstrate that our analysis was sensitive to detecting long-term changes in depression trajectories when they existed.

There are several possible explanations for more prevalent use of antidepressants already *before* the diagnosis of diabetes:

First, bidirectional effect is a possibility as depression, as indicated by antidepressant use, could increase the risk of type 2 diabetes. The totality of existing evidence provides some support for such a reverse association.[7, 11] Furthermore, the effect of depression on diabetes risk is plausible because depression is associated with several behavioral and metabolic factors that can increase risk of diabetes and insulin resistance, including obesity-promoting health behaviors, such as physical inactivity and hypercaloric diets,[18-23] and activation of the neuroendocrine[24-27] and inflammatory responses.[28, 29]

Second, it is also conceivable that the bidirectional association between depression and diabetes we observe in adult life is a consequence of early factors such as low birth weight and childhood adversity, which have an impact throughout life and predispose to both depression[30] and obesity/type 2 diabetes.[31, 32] Further research is needed to test this hypothesis empirically.

Third, there is some, although not completely consistent, evidence that specific antidepressant drugs may increase the risk of diabetes.[33-36] In the Diabetes Prevention Program (DPP) for individuals at high risk for developing type 2 diabetes, a strong association between antidepressant use and subsequent diabetes onset was not accounted for by measured confounders or mediators.[33] Tricyclic antidepressants may induce weight gain[37]

and, in diabetic patients, promote hyperglycemia.[38] By contrast SSRIs and related agents may, at least in short-term, be related to reduced weight gain and improved insulin sensitivity.[39,40,41] However, in our investigation those treated with SSRIs had increased risk of incident diabetes and in the DPP study the association between antidepressant use and diabetes risk was not accounted for by weight changes.[33]

Finally, we cannot exclude the possibility that diabetes was only more likely diagnosed (ie undiagnosed diabetes picked up) in depressed individuals on antidepressant treatment than other groups because they were regularly seeing a doctor. However, this interpretation is not consistent with recent studies suggesting that both treated and untreated depression are related to elevated risk of diabetes.[36, 42]

Strenghts and limitations

Nine repeated measurements of anti-depression drug use, encompassing the period both before and after diagnosis, enabled a better characterization of the association between diabetes diagnosis and antidepressant use than was possible in previous studies with fewer measurement points.[33] Comprehensive records from national registers made it possible to avoid issues related to sample attrition. As we selected matched controls for socioeconomic position and other key confounding factors, major confounding due to social stratification of type 2 diabetes or treatment of this disease is unlikely.[43] This design is more efficient for reducing confounding than simply adjusting analyses for these factors in the total cohort, the most widely used method in this field of research. Obviously, no observational study can exclude the possibility of residual confounding.

We included in the study only participants alive 4 years after diagnosis. This means that patients with most aggressive cancers leading to death within the first 4 years were excluded. As these patients are particularly likely to experience depression, our findings may

provide an underestimate of post-cancer antidepressant use. For diabetic patients, in turn, with only 4 years of follow-up we probably did not capture all the potentially detrimental psychological impacts which may become most apparent when patients have reached an advanced state of diabetes and experience the burden of dealing with its complications. It is therefore possible that our findings on post-diabetes antidepressant use are a conservative estimate.

Misclassification between type 1 and type 2 diabetes is an important potential source of error in epidemiological studies on type 2 diabetes. Our sensitivity analyses, excluding all diabetes cases on insulin treatment and at age 35 or younger, strongly suggest that our findings are not due to falsely coded type 1 diabetes patients. In this study, 25% of the incident diabetics were on insulin therapy 4 years after the diagnosis. It is likely that most of these cases were true type 2 diabetes patients, as the projected need for insulin therapy for patients with type 2 diabetes is over 20% in this time window.[44]

The Finnish nationwide registries validly identified individuals pharmacologically treated for type 2 diabetes and depression, but did not capture undiagnosed disease or conditions treated without medication. Furthermore, in addition to depression, antidepressants are used in the treatment of other disorders, such as chronic pain and sleeping disorders, and they are sometimes prescribed for smoking cessations. When interpreting the present data, it is important to recognize that antidepressants treatment is not exactly the same as a diagnosis of depression, although patients with such disorders are likely to represent a vast majority of those taking antidepressants.

Finally, we could not address some potentially important issues, such as the precise timing of diabetes onset (rather than when it was recognised), the severity of depression, and the status of other clinical conditions, because all these would have required a clinical examination. With repeated clinical examinations, however, the present study design with 9

repeated assessments around the diagnosis would be very costly (the current study is based on 151,618 individuals followed up for 11 years) and therefore future studies should seek solutions to overcome these limitations.

Implications

Depression is known to be associated with poor glycemic control and negative clinical outcomes.[45, 46] We found that individuals recently diagnosed with type 2 diabetes had an excess use of antidepressants similar in size to that among 4-year cancer survivors immediately post-diagnosis. Thus, diabetes diagnosis may be a marker of significantly elevated depression prevalence, in particular at the time of the diagnosis, and therefore our findings support the recommendation of the American Diabetes Association to screen diabetic patients for depression.[47]

The finding that elevated antidepressant use exists already before diabetes is diagnosed warrants further research. As these agents are routinely offered to patients with moderate and severe depression,[14] it would be important to determine whether antidepressants have side-effects that increase diabetes risk and, if this were the case, make appropriate modifications to treatment of patients. It is also possible that depression rather than antidepressant use is a risk factor for diabetes or that the two share common risk factors. This would indicate that research is needed to assess potential benefits of diabetes prevention interventions targeted especially to patients treated for depression.

[3541 words]

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FIGURE LEGENDS

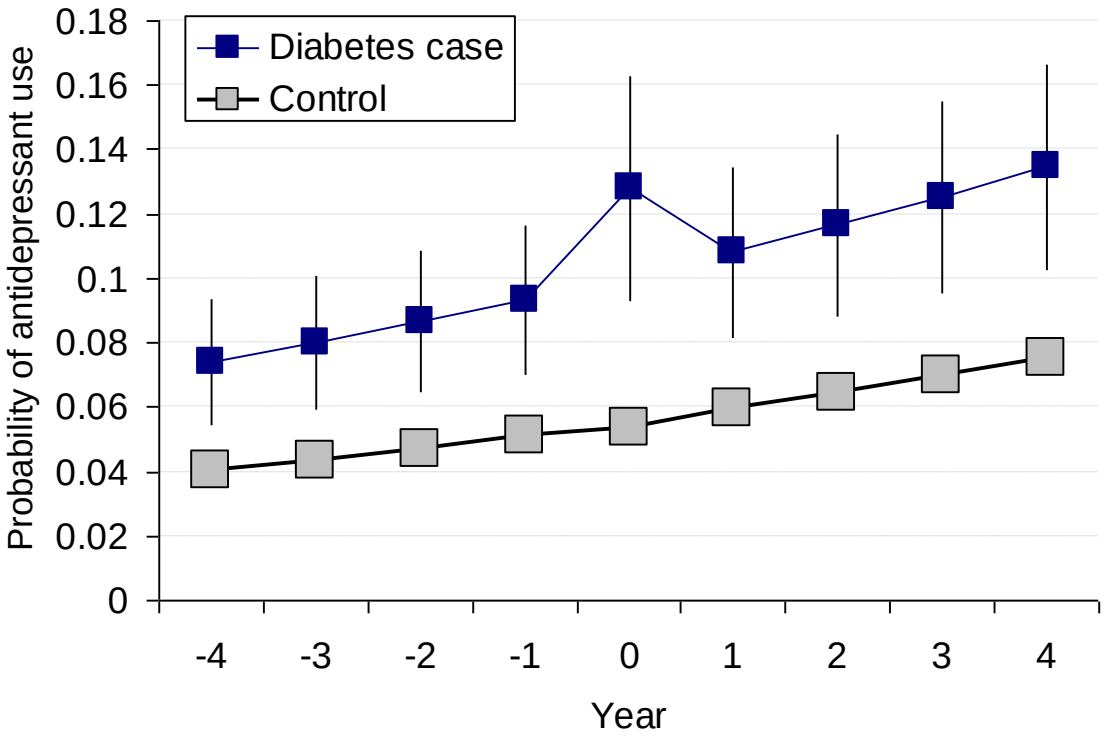
Figure 1. Probability (95% Confidence Interval) of Antidepressant Use Before and After Diagnosis of Type 2 Diabetes.

Figure 2. Probability (95% Confidence Interval) of Antidepressant Use Before and After Diagnosis of Cancer

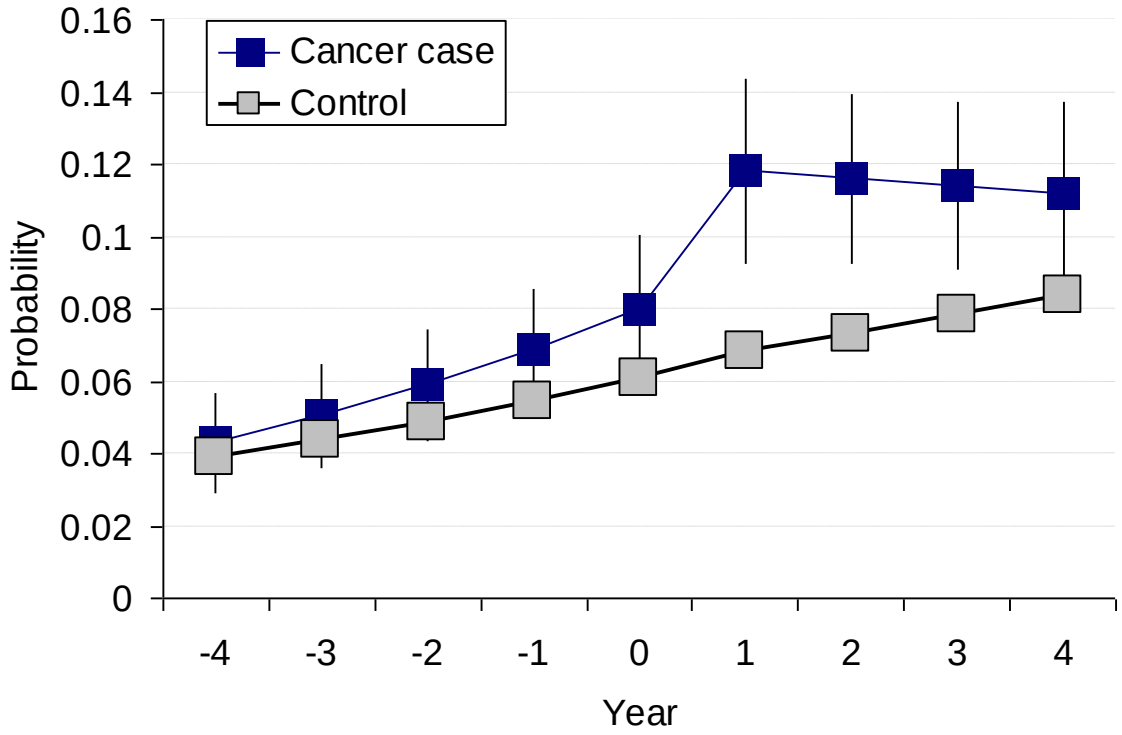
Table 1. Baseline Characteristics of Study Participants

	Diabetes study (n = 2943)*			Cancer study (n = 4478)*		
	Incident cases	Controls	P-value	Incident cases	Controls	P-value
N	493	2450		748	3730	
Male sex - %	42.0	41.8	0.95	18.7	18.5	0.83
Age group - %			0.11			0.39
26-44 yr	18.9	23.8		31.2	34.3	
45-54 yr	48.1	45.7		42.4	41.8	
45-64 yr	30.6	28.7		24.1	21.9	
65-70 yr	2.4	1.8		2.1	2.0	
Mean (SD) age - yr	50.9 (7.4)	50.0 (8.1)		47.9 (9.6)	47.7 (8.9)	
Socioeconomic position - %			0.95			1.00
Upper non-manual	19.1	19.2		33.2	33.2	
Lower non-manual	39.2	39.2		43.6	43.7	
Manual	41.8	41.6		23.3	23.2	
Prevalent coronary heart disease - %	3.3	2.4	0.28	2.1	1.5	0.17

*There were no missing data in any of the variables.



Antidepressant Use in Diabetes Cases, N									
Yes	36	40	44	53	64	57	57	60	63
No	457	453	449	440	429	436	436	433	430
Antidepressant Use in Controls, N									
Yes	85	106	120	120	130	155	172	169	170
No	2365	2344	2330	2320	2320	2295	2278	2281	2280



Antidepressant Use in Cancer Cases, N									
Yes	33	38	45	47	63	91	85	82	87
No	715	710	703	701	685	657	663	666	661
Antidepressant Use in Controls, N									
Yes	142	166	188	196	228	251	278	292	311
No	3588	3564	3542	3534	3502	3479	3452	3438	3438

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Conflict of Interest Statement

We declare that we have no conflict of interest.

Dear Prof. Fonseca, Editor

Re: DC09-2359 / "Antidepressant Use Before and After the Diagnosis of Type 2 Diabetes: A Longitudinal Modeling Study"

Thank you for your and the referees' comments on this manuscript and for the invitation to resubmit. We are of course delighted to do so in order to aim for publication in Diabetes Care.

We feel that the editorial committee and the referees made some very valid points and we have therefore revised the manuscript accordingly.

Our point-by-point response to the referee's comments can be found below. We would like to thank you for your consideration and look forward to hearing from you.

Sincerely,

Mika Kivimaki, on behalf of al the authors

EDITORS LETTER

Dear Prof. Kivimäki:

Thank you for submitting your manuscript as titled above. It has been examined by reviewers and by the Editorial Committee; copies of the reviewers comments are included with this letter. We are willing to reconsider this manuscript, contingent upon satisfactory revision as outlined in the reviewers' critiques. In particular, the Committee wishes you to address possible explanations for the results. They are very interesting, but epidemiological results of this kind are often subject to major problems concerning the influence of third or fourth unaccounted for influences, and the clear lack of causative pathways. One way out of these problems is to address a broader literature that might help explain the findings and can lead to the next stage of studies. Also, please address in more detail the fact that use of antidepressants can no longer clearly be used as an indicator of major depressive disorder--issues of other clinical problems, lack of control over severity of disorder and whether or not there really is a clinical disorder present. These are major confounders that need to be addressed.

OUR RESPONSE 1: Thank you for this positive feedback. Firstly, we have undertaken a careful literature review and summarise the findings of 18 new studies in the revised manuscript. In the Introduction section, following the first paragraph which introduces alternative ways in which diabetes may influence depression risk, we have added the following:

"...The suggestion that depressive symptoms among non-diabetic individuals also increase the risk of diabetes complicates the isolated examination of the effect of diabetes on depression, as this association may be bidirectional and thus affected by simultaneous causation and reverse causation. To date, the evidence on the status of depressive symptoms as a risk factor for type 2 diabetes is mixed as both positive and null findings have been reported.7, 11 It is therefore important to assess depression both before and after the diagnosis of diabetes in a single methodological setup to ensure the adequate estimation of the effect sizes in both directions, accounting for causation and reverse causation. To our knowledge, no such study exists." P. 3.

We further elaborate upon this issue in the revised Discussion:
"...First, bidirectional effect is a possibility as depression, as indicated by antidepressant use, could increase the risk of type 2 diabetes. The totality of existing evidence provides some support for such a reverse association.7, 11 Furthermore, the effect of depression on

diabetes risk is plausible because depression is associated with several behavioral and metabolic factors that can increase risk of diabetes and insulin resistance, including obesity-promoting health behaviors, such as physical inactivity and hypercaloric diets,18-23 and activation of the neuroendocrine24-27 and inflammatory responses.28, 29

Second, it is also conceivable that the bidirectional association between depression and diabetes we observe in adult life is a consequence of early factors such as low birth weight and childhood adversity, which have an impact throughout life and predispose to both depression30 and obesity/type 2 diabetes.31,32 Further research is needed to test this hypothesis empirically." P. 11.

In the Discussion section, we now clearly note that antidepressant treatment is not exactly the same as a diagnosis of depression:

"...The Finnish nationwide registries validly identified individuals pharmacologically treated for type 2 diabetes and depression, but did not capture undiagnosed disease or conditions treated without medication. Furthermore, in addition to depression, antidepressants are used in the treatment of other disorders, such as chronic pain and sleeping disorders, and they are sometimes prescribed for smoking cessations. When interpreting the present data, it is important to recognize that antidepressants treatment is not exactly the same as a diagnosis of depression, although patients with such disorders are likely to represent a vast majority of those taking antidepressants." P. 13.

In the revised manuscript, we also discuss confounding and reverse causation as follows:

"...we cannot exclude the possibility that diabetes was only more likely diagnosed (ie undiagnosed diabetes picked up) in depressed individuals on antidepressant treatment than other groups because they were regularly seeing a doctor. However, this interpretation is not consistent with recent studies suggesting that both treated and untreated depression are related to elevated risk of diabetes.35, 41" P. 13.

"...As we selected matched controls for socioeconomic position and other key confounding factors, major confounding due to social stratification of type 2 diabetes or treatment of this disease is unlikely.40 This design is more efficient for reducing confounding than simply adjusting analyses for these factors in the total cohort, the most widely used method in this field of research. Obviously, no observational study can exclude the possibility of residual confounding." P. 12.

We also clarify other limitations raised by the Editor:

"... Finally, we could not address some potentially important issues, such as when diabetes actually developed (rather than was recognised), the severity of depression, and the status of other clinical conditions, because all these would have required a clinical examination. With repeated clinical examinations, however, the present study design with 9 repeated assessments around the diagnosis would be very costly (the current study is based on 151,618 individuals followed up for 11 years) and therefore future studies should seek solutions to overcome these limitations." P. 13

EDITORIAL Comments:

Sometimes a paper is allowed to be evaluated even though it did not initiallly meet formatting guidelines. However, a revised paper should conform to word count, text format, reference limits, abstract format, table and figure specifications. Current Instructions to Authors are available at http://care.diabetesjournals.org/misc/ifora.shtml.

If you have not already done so, all signed manuscript submission forms must be faxed to the Editorial Office prior to submission of the revision (1-317-859-3592).

OUR RESPONSE 2: The signed manuscript submission forms have been faxed to the Editorial Office.
****

Revised papers that do not meet guidelines, or have not had all signed submission forms faxed to the Editorial Office, will automatically be unsubmitted.
Please address all formatting errors:
None

OUR RESPONSE 3: We are pleased that there were no formatting errors.
****

REVIEWER(s)' Comments to Author:

Reviewer: 1
Comments to the Author
This manuscript reports a "matched cohort" study of antidepressant use in three groups: a control group, a group destined to develop diabetes (incident cases of type 2 diabetes mellitus T2DM), and a group destined to develop cancer (incident cases of cancer). The research design and analysis are impeccable.

OUR RESPONSE 4: Thank you for this positive feedback.
****
An axiom of epidemiology is that one can always quibble about the selection of the control group, but it is difficult to find any fault with the study. The details regarding the specifics of the matching process are a bit sketchy, but the results are credible. Comparison statistics of the three groups are reported.

OUR RESPONSE 5: In the revised manuscript, further details on the matching process have been given:

"... We randomly selected controls in a 5:1 ratio for each diabetes case and each cancer case, matching individually 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 (7 areas based on the location of the workplace), as these characteristics could be related to differences in the likelihood of achieving diagnosis or treatment. The diabetes study included 2450 matched diabetes-free controls and the cancer study 3730 matched cancer-free controls." P. 4.
****
There is a selection bias (or survivor bias) operating in that the cancer cases had to live for four years after diagnosis to be included in the study. This bias eliminates aggressive types of cancer, but is not a major shortcoming as those persons would likely be more severely depressed.

OUR RESPONSE 6: We think this is an important point and therefore have added this to the revised discussion:

"... We included in the study only participants alive 4 years after diagnosis. This means that patients with most aggressive cancers leading to death within the first 4 years were excluded. As these patients are particularly likely to experience depression, our findings may provide an underestimate of post-cancer antidepressant use. For diabetic patients, in turn, with only 4 years of follow-up we probably did not capture all the potentially detrimental psychological impacts which may become most apparent when patients have reached an advanced state of diabetes and experience the burden of dealing with its complications. It is therefore possible that our findings on post-diabetes antidepressant use are a conservative estimate." P. 12
****

The authors consider a number of permutations of the data, e.g., definitions of antidepressants, and report appropriately.

The authors apparently assume that antidepressant use equals a diagnosis of depression. This is probably reasonable, but use of antidepressants for a variety of other diagnoses has evolved, such as for insomnia or smoking cessation or for obsessive-compulsive disorder. Verification of depression from another source would have been nice, but certainly is not essential.

OUR RESPONSE 7: Thank you. We have dealt with this same point made above by the Editor (please see Our Response #1 and p. 13 in the revised manuscript).
****

The authors draw the inference that depressed persons are at risk for diabetes mellitus type 2. Perhaps I missed it, but the authors fail to speculate that the antidepressant use may in fact cause diabetes, as has been found for atypical antipsychotic medications. This study certainly does not cover all appropriate criteria to infer causation, but there is a hypothesis exigent that may merit further investigation.

OUR RESPONSE 8: This as a very important point. Thus, we carried out a literature research on this issue and added the following discussion:

"... there is some, although not completely consistent, evidence that specific antidepressant drugs may increase the risk of diabetes.32-34 In the Diabetes Prevention Program (DPP) for individuals at high risk for developing type 2 diabetes, a strong association between antidepressant use and subsequent diabetes onset was not accounted for by measured confounders or mediators.32 Tricyclic antidepressants may induce weight gain35 and, in diabetic patients, promote hyperglycemia.36 By contrast SSRIs and related agents may, at least in short-term, be related to reduced weight gain and improved insulin sensitivity.37,38, 39 However, in our investigation those treated with SSRIs had increased risk of incident diabetes and in the DPP study the association between antidepressant use and diabetes risk was not accounted for by weight changes.32" P. 11-12.

"...The finding that elevated antidepressant use exists already before diabetes is diagnosed warrants further research. As these agents are routinely offered to patients with moderate and severe depression,14 it would be important to determine whether antidepressants have side-effects that increase diabetes risk and, if this were the case, make appropriate modifications to the treatment of patients. It is also possible that depression rather than antidepressant use is a risk factor for diabetes or that the two share common risk factors. This would indicate that research is needed to assess potential benefits of diabetes prevention interventions targeted especially to patients treated for depression." P. 14.

In addition, we have noted this possibility in the Abstract:

"These findings provide support for the hypothesis that awareness of the diagnosis of type 2 diabetes may temporarily increase risk of depressive symptoms. Further research is needed to determine whether more prevalent use of antidepressants noted before the diagnosis of diabetes relates to excess diabetes risk associated with depression, a common causal pathway for depression and diabetes or the side-effects of antidepressant use." P. 2.
****

The use of the specific statistical analysis in STATA is sophisticated and appropriate; I am more familiar with the PROC GENMOD in SAS, but consider the procedures comparable.

OUR RESPONSE 9: The Reviewer is correct. In addition to STATA, we have run trajectory analyses with SAS (e.g., Westerlund et al. Lancet 2009;374:1889-96) and SPSS (e.g., Tabak et al. Lancet 2009;373:2215-21) and found the procedures compatible.
****

The use of cancer as a comparison condition is appropriate and well-done.
OUR RESPONSE 10: Thank you for this positive feedback.
****

The possibilities of misclassification of exposure or condition are dealt with in the manuscript. Confounding of the association noted between the exposure and development of the condition is possible, but I find it difficult to identify or postulate a potential confounding variable.

The discussion and conclusions support the manuscript. There are rare grammatical errors.

OUR RESPONSE 11: Thank you. We have checked the manuscript for grammatical errors.
****

In sum, this is a very nice paper on excellent research. Other than entertaining the possibility that antidepressants might be more than a marker for depression, but actually might be associated with the onset of the disease of T2DM might merit exploration, there is little to merit criticism.

OUR RESPONSE 12: Thank you. As noted in our earlier response, we have considered the possibility that antidepressants might be more than simply a marker for depression in the revised manuscript. Please, see our response #1 above (and p. 13 in the revised manuscript).
****

Reviewer: 2
Comments to the Author
This is a crisp clearly written study with excellent and clearly described methods addressing a critically important question: the inter-relationship of diabetes and depression. The analyses and results are well-described. However, the contribution of the paper would be enhanced with a more extensive review of prior literature on the association of diabetes and depression and with a more thorough discussion of possible reasons for the somewhat surprising findings that antidepressant use is higher among adults who develop diabetes even 4 years before diagnosis. Is there any prior research (including biological research) that can help shed light on reasons for this? More exploration of this in the Discussion would be fascinating and increase the paper's contribution.

OUR RESPONSE 13: Thank you for the positive feedback. We have now provided a more extensive review of the literature examining the association of diabetes with depression (19 new references added), including a discussion of possible reasons for the finding that antidepressant use is higher among adults who develop diabetes. As indicated in previous our responses, the following text has been added:

"There are several possible explanations for more prevalent use of antidepressants already before the diagnosis of diabetes:

First, bidirectional effect is a possibility as depression, as indicated by antidepressant use, could increase the risk of type 2 diabetes. The totality of existing evidence provides some support for such a reverse association.7, 11 Furthermore, the effect of depression on diabetes risk is plausible because depression is associated with several behavioral and metabolic factors that can increase risk of diabetes and insulin resistance, including obesity-promoting health behaviors, such as physical inactivity and hypercaloric diets,18-23 and activation of the neuroendocrine24-27 and inflammatory responses.28, 29

Second, it is also conceivable that the bidirectional association between depression and diabetes we observe in adult life is a consequence of early factors such as low birth weight and childhood adversity, which have an impact throughout life and predispose to both depression30 and obesity/type 2 diabetes.31,32 Further research is needed to test this hypothesis empirically.

Third, there is some, although not completely consistent, evidence that specific antidepressant drugs may increase the risk of diabetes.32-34 In the Diabetes Prevention Program (DPP) for individuals at high risk for developing type 2 diabetes, a strong association between antidepressant use and subsequent diabetes onset was not accounted for by measured confounders or mediators.32 Tricyclic antidepressants may induce weight gain35 and, in diabetic patients, promote hyperglycemia.36 By contrast SSRIs and related agents may, at least in short-term, be related to reduced weight gain and improved insulin sensitivity.37,38, 39 However, in our investigation those treated with SSRIs had increased

risk of incident diabetes and in the DPP study the association between antidepressant use and diabetes risk was not accounted for by weight changes.32

Finally, we cannot exclude the possibility that diabetes was only more likely diagnosed (ie undiagnosed diabetes picked up) in depressed individuals on antidepressant treatment than other groups because they were regularly seeing a doctor. However, this interpretation is not consistent with recent studies suggesting that both treated and untreated depression are related to elevated risk of diabetes.35, 41" Pp. 11-12.

****

Similarly, more discussion of the possible clinical implications of these findings would be useful beyond noting that there is only a slight increase in odds of antidepressant use in the year of diagnosis.

OUR RESPONSE 14: The following implications for this study are provided in the revised manuscript:

"Depression is known to be associated with poor glycemic control and negative clinical outcomes.42, 43 We found that individuals recently diagnosed with type 2 diabetes had an excess use of antidepressants similar in size to that among 4-year cancer survivors immediately post-diagnosis. Thus, diabetes diagnosis may be a marker of significantly elevated depression prevalence, in particular at the time of the diagnosis, and therefore our findings support the recommendation of the American Diabetes Association to screen diabetic patients for depression.44

The finding that elevated antidepressant use exists already before diabetes is diagnosed warrants further research. As these agents are routinely offered to patients with moderate and severe depression,14 it would be important to determine whether antidepressants have side-effects that increase diabetes risk and, if this were the case, make appropriate modifications to treatment of patients. It is also possible that depression rather than antidepressant use is a risk factor for diabetes or that the two share common risk factors. This would indicate that research is needed to assess potential benefits of diabetes prevention interventions targeted especially to patients treated for depression." P. 14.

****

Specific:

Abstract: Please include years of study and geographic location in the abstract.

OUR RESPONSE 15: Done.

page 3: The authors note that an a priori hypothesis was that individuals who develop type 2 diabetes are more likely to be depressive already before the diagnosis. They provide no basis for this hypothesis. Please provide supporting evidence/prior research that led to this hypothesis in the Introduction.

OUR RESPONSE 16. Done. We have added the following justification:

"... The suggestion that depressive symptoms among non-diabetic individuals also increase the risk of diabetes complicates the isolated examination of the effect of diabetes on depression, as this association may be bidirectional and thus affected by simultaneous causation and reverse causation. To date, the evidence on the status of depressive symptoms as a risk factor for type 2 diabetes is mixed as both positive and null findings have been reported.7, 11 It is therefore important to assess depression both before and after the diagnosis of diabetes in a single methodological setup to ensure the adequate estimation of the effect sizes in both directions, accounting for causation and reverse causation. To our knowledge, no such study exists." P. 3.

In the Discussion section the findings regarding the hypothesis are discussed. Please, see our next response

****

Discussion: Again, please flesh this out more than current sparce discussion.

OUR RESPONSE 17: We have added the following sections to the Discussion:

"... Our findings provide support for the hypothesis that awareness of the diagnosis of type 2 diabetes may temporarily increase risk of depressive symptoms.7 However, as the antidepressant use was similarly elevated both before and after the diagnosis among diabetes cases, it seems likely that awareness of the diagnosis has no lasting effect on depression risk. These findings do not support the concern that overlap of symptoms between type 2 diabetes and depression (e.g. fatigue) would make it less likely for depression to be appropriately recognized in diabetic patients.16, 17 The parallel trends in the use of antidepressant treatment between diabetic and non-diabetic subjects suggest that the recognition of depression may be equally appropriate in these groups before and after the diagnosis of type 2 diabetes.

Having a contact with a physician because of type 2 diabetes might make detection of unrecognized depression more likely and cause elevation in antidepressant use at diagnosis without actual increase in depression rates. However, elevated prescriptions rates would have remained after diagnosis if increased recognition of untreated depression explained the finding. This was not the case and therefore we believe the temporary elevation in antidepressant use may represent true temporary increase in depression risk as a result of the diagnosis. Credibility of our observations is strengthened by the findings related to cancer as they demonstrate that our analysis was sensitive to detecting long-term changes in depression trajectories when they existed." Pp. 10-11.

At the end of the Discussion, we have extended discussion regarding the clinical implications
****

Limitations: Please discuss more possible limitations from relying on antidepressant use as an indicator of depression.

OUR RESPONSE 18: Done. Please see our response #1 to the Editor and p. 13 in the revised manuscript.
