Selective Serotonin Reuptake Inhibitors Decrease Pancreatic Insulin Secretion in Older Adults and Increase the Risk of Insulin Dependence in Type 2 Diabetes Patients

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ABSTRACT

Objective: Selective serotonin reuptake inhibitors (SSRIs) may decrease insulin secretion, but evidence from population studies is scarce. We investigated the association between SSRIs and markers for glucose-insulin homeostasis in a nondiabetic older population. Furthermore, we studied the association between SSRI use and insulin dependence in a diabetic population of older adults.

Methods: This study was embedded in the prospective population-based Rotterdam Study cohort (1991–2012). In nondiabetic participants, fasting glucose and insulin levels and the homeostasis model assessment for insulin sensitivity and secretion were compared between participants using SSRIs and participants using no antidepressant. In diabetic patients using oral glucose-lowering agents, the risk of insulin dependence, defined as the start of insulin treatment, was compared between participants using SSRIs and participants using no antidepressant.

Results: In nondiabetic participants, SSRI users (n = 87) had, compared with participants using no antidepressants (n = 5,505), a significantly ($P < .05$) lower level of insulin (8.8 mU/L and 9.9 mU/L, respectively), a lower degree of insulin resistance (2.2% and 2.4%, respectively), and less insulin secretion (89.1% and 100.4%, respectively), but a similar glucose level. Furthermore, > 90 days of consecutive use of SSRIs in diabetic patients was associated with a 2.17 times higher risk (95% confidence interval, 1.02–4.60) of starting insulin treatment than that of participants using no antidepressants.

Conclusions: Use of SSRIs was associated with lower insulin secretion in nondiabetic participants and an increased risk of insulin dependence in type 2 diabetics in older adults. However, additional studies are required to confirm our results.

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Depression has been associated with an increased risk of type 2 diabetes,[1–3] obesity,[4] and metabolic syndrome.[5] Independently of depression, use of antidepressants, specifically use of selective serotonin reuptake inhibitors (SSRIs), has also been associated with an increased risk of type 2 diabetes.[6–8] Interestingly, use of SSRIs was not associated with higher levels of glucose,[7] and it therefore remains unclear how SSRIs increase the risk of type 2 diabetes independently of glucose. For this reason, it has been hypothesized that the use of SSRIs has direct effects on the onset of type 2 diabetes.[7]

There is increasing evidence that serotonin is involved in the secretion of insulin. Mice deficient for tryptophan hydroxylase 1, an enzyme essential for peripheral serotonin production, had lower levels of serotonin in serum and a lower pancreatic insulin secretion.[9] Antagonizing the serotonin reuptake transporter on pancreatic β cells inhibits insulin secretion and activates apoptotic mechanisms in murine β-cell models.[10] Furthermore, the few studies conducted in humans showed that use of SSRIs results in lower insulin secretion.[11,12]

Based on these studies, it is biologically plausible that SSRIs decrease insulin secretion and that this might therefore be a mechanism underlying the previously observed association between SSRIs and increased risk of type 2 diabetes. Consequently, type 2 diabetes patients treated with SSRIs might also have a higher risk to develop insulin dependence, a condition associated with an increased risk of mortality.[13,14] In the present study, we aimed to investigate the association between SSRI use and glucose-insulin homeostasis in a nondiabetic older population. Furthermore, we aimed to study the association between the use of SSRIs and the risk of insulin dependence in a population of older adults with type 2 diabetes.

METHODS

Study Setting

We embedded the present study in the prospective population-based Rotterdam Study cohort, which was designed to investigate the incidence of, and risk factors for, several age-related diseases. A more detailed description of the design and rationale of the study has been published elsewhere.[15,16] In short, from 1990 to 1993, all inhabitants 55 years and older from a district (Ommoord) located in Rotterdam, the Netherlands, were asked to participate in the original cohort (denoted as RS-I). In total, 7,983 individuals agreed to participate (response rate 78%). An extension of the original cohort was initiated in 2000 (denoted as RS-II). Within this cohort, all inhabitants from Ommoord 55 years and older, and not already participating and invited in RS-I, were asked to participate in RS-II. In total, 3,011 individuals agreed to participate (response rate 67%). In 2006, a second extension (RS-III) was initiated. A total of 3,932 inhabitants from the same district agreed to participate

Clinical Points

- Selective serotonin reuptake inhibitors (SSRIs) may decrease pancreatic insulin secretion.
- In the Rotterdam Study cohort, use of SSRIs was associated with lower pancreatic insulin secretion in participants without diabetes mellitus and with higher risk of insulin dependence in participants with diabetes.

(response rate 65%). These inhabitants were not already participating in the other cohorts, were not invited before, and were 45 years or older. Follow-up examinations were conducted every 4–5 years after baseline examination. The Rotterdam Study has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. Written informed consent was obtained from all study participants.

Study Population and Designs

The research questions were addressed in 2 study populations. First, we conducted a cross-sectional analysis on the association between use of SSRIs and markers of glucose-insulin homeostasis. Fasting glucose and insulin levels were measured simultaneously during 1 visit round, namely during the third round of RS-I (1997–1999; N = 4,797) and the first round of RS-II (2000–2001; N = 3,011). No measurements were available for RS-III. Participants with diabetes at the date of examination were excluded. Diagnosis of diabetes was based on current treatment with oral glucose-lowering agents or insulin, a measured fasting glucose > 6.9 mmol/L at the date of examination, or a previous diagnosis of diabetes made by the general practitioner or medical specialist. Nondiabetic participants were excluded if they were nonfasting at the time of blood draw or had missing information on covariates.

Second, we conducted a follow-up study (1991–2012) in all persons with a history of diabetes at baseline and in persons with incident diabetes during follow-up who were using oral glucose-lowering drugs without insulin. These diabetics were followed until a first prescription for insulin, death, or end of the study period, whichever came first. These cases of insulin dependence were matched to all eligible diabetic participants in the 3 cohorts (in this analysis, RS-III was included) at the same calendar date (denoted hereafter as the index date). For every matched set, on the index date the exposure status to antidepressants in each case and its corresponding controls was assessed as described below.

Antidepressant Drug Exposure

From January 1, 1991, onward, more than 95% of the study participants had their drug prescriptions filled at one of the fully computerized regional pharmacies. Dispensing data included the Anatomic Therapeutic Chemical (ATC) code,[17] the dispensing date, the total number of drug units per prescription, the prescribed daily number of units, and the product name of the drug. The duration of a dispensing period was calculated by dividing the total number of filled tablets/capsules by the daily prescribed number. A participant was considered a current SSRI user (ATC code: N06AB) when the date of examination or the index date fell within an antidepressant dispensing episode. Participants were classified as a past SSRI user if they previously filled an SSRI drug prescription, but were not a current user at the date of examination or index date. For comparison to the effect of SSRIs, we also defined current and past use of tricyclic antidepressants (ATC code: N06AA) and other antidepressants (ATC code: N06AX). Participants who did not use any antidepressant drug during the study period were considered nonusers.

Study Outcomes

Fasting glucose (in mmol/L) was measured enzymatically using a hexokinase method (Boehringer Mannheim, Mannheim, Germany). Fasting insulin (in mU/L) was measured in serum on a Modular Analytics E170 analyzer using a Cobas Roche electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Both measurements were performed using the standard manufacturer's instructions. Peripheral insulin resistance was assessed using the homeostatic model assessment (HOMA-IR; [glucose (mmol/L) × insulin (mU/L)]/22.5). The homeostatic model assessment was also used to estimate pancreatic β cell function (HOMA-β; [20 × insulin (mU/L)]/[glucose – 3.5]).[18,19]

Insulin dependence was defined as the initiation of insulin treatment (ATC code: A10A) in type 2 diabetes patients already using oral glucose-lowering agents (ATC code: A10B) as add-on therapy or as therapy switch.

Covariates

The following covariates were considered as possible confounders in the analyses, in addition to age and sex: body mass index (BMI), the clinical diagnosis of depressive symptoms/depression, depressive symptoms score, number of concomitantly used oral glucose-lowering agents, and prevalent use of glucose-lowering agents (latter 2 only for the analysis of initiation of insulin treatment). For the analysis of insulin dependence, covariates were determined time-dependently (eg, the measurement closest to the index date was used for analyses). Length and height were measured by trained research nurses at the study center. BMI was calculated by dividing weight (in kg) by height (in meters) squared. The clinical diagnosis of depressive symptoms, syndromes, and disorders was defined based on reports from physicians and psychiatrists; this has been described in more detail elsewhere.[20] These data were available only for RS-I and RS-II, not for RS-III. In short, research nurses screened parts of the records of the general practitioner in which a possible case of depression/depressive symptoms is discussed. Two independent researchers reviewed all possible cases using records

from the general practitioner. These records included the observations made by the general practitioner, but also letters with diagnoses from medical specialists. When there was no consensus on a diagnosis, a psychiatrist was consulted and made the final decision. Because of a low number of cases with depressive syndromes and disorders at a particular moment during follow-up, we combined these with depressive symptoms into 1 variable. A Dutch version of the Center for Epidemiologic Studies Depression (CES-D) scale was used to screen for depressive symptoms in the total study population. The outcome of this questionnaire is a score ranging between 0 and 60. A higher score indicates more depressed feelings.[21,22] Prevalent use of oral glucose-lowering agents refers to the participants treated with oral glucose-lowering agents without insulin at the date of inclusion in the Rotterdam Study.

Table 1. Characteristics of the Study Population

	Nondiabetic Participants (n = 5,571)	Diabetic Participants (n = 1,677)
Age, mean (SD), y	69.1 (8.2)	72.3 (9.7)
Females, n (%)	3,212 (57.7)	944 (56.3)
BMI, kg/m^2, mean (SD)	26.7 (3.9)	29.1 (4.4)
Depression, n (%)	69 (1.2)	32 (1.9)
Glucose-lowering agents, n (%)		
Biguanides	NA	661 (39.4)
Sulfonamides, urea derivatives	NA	1,067 (63.6)
Prevalent use[a]	NA	508 (30.3)
Antidepressant use, n (%)		
TCAs	64 (1.1)	35 (2.1)
SSRIs	87 (1.6)	61 (3.6)
Others	15 (0.3)	13 (0.8)

[a]Participants treated with oral glucose-lowering agents without insulin at the date of inclusion in the Rotterdam Study.
Abbreviations: BMI = body mass index, NA = not applicable, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Statistical Analyses

For the population of nondiabetic participants, study characteristics were assessed at the date of examination. For the population of participants using oral glucose-lowering agents, study characteristics were assessed at baseline of the Rotterdam Study (for prevalent users) or at the date of the first oral glucose-lowering agent dispensing (for incident users).

The cross-sectional analyses on measures of glucose-insulin homeostasis were conducted with linear regression analyses. We compared the measures of glucose-insulin homeostasis between participants using SSRIs, participants using TCAs, and participants using no antidepressant. Users of other antidepressants were not studied as the number of users was too low (n = 15). Insulin levels and the homeostatic model assessment were not normally distributed and therefore log-transformed. Estimated means of these measures were back transformed on a normal scale as a geometric mean. We adjusted the analyses for age, sex, and BMI (model 1) and additionally for CES-D score (model 2) and the clinical diagnosis of depressive symptoms/depression (model 3). In a sensitivity analysis, we compared the measures of glucose-insulin homeostasis between users of SSRIs and TCAs. In addition, we studied the association between past use of antidepressants and the measures of glucose-insulin homeostasis. Together with statistical adjustment for depression, these 2 sensitivity analyses were conducted to reduce the possibility that our findings were observed because of confounding by indication.

The analyses on the risk of insulin dependence were conducted using conditional logistic regression models. Because the number of cases using other antidepressants was low, results are not presented for this drug class (n = 2). Analyses were adjusted for age, sex, BMI, prevalent use of glucose-lowering agents, and number of different concomitantly used oral glucose-lowering agents. We repeated the analyses on current use but added the first 90 days of consecutive treatment to the nonuse period. This was done as it is not expected that insulin dependence is an acute effect of SSRI use. Furthermore, we restricted the analyses to RS-I and RS-II, in which we had information available on depression, and statistically adjusted for the presence of depression. For the assessment of the association between past use of an antidepressant drug group, never use of that drug group was used as reference. In an additional analysis, we excluded prevalent users of oral glucose-lowering agents from the population of treated diabetic patients.

We used IBM SPSS Statistics (version 21.0, IBM Corp, Somers, New York) for all analyses. Two-sided *P* values less than .05 were considered statistically significant.

RESULTS

Characteristics of the Study Populations

A total of 5,571 nondiabetic participants were included in the cross-sectional analysis on measures of glucose-insulin homeostasis, and a total of 1,677 diabetic participants were included in the analysis on the risk of insulin dependence (Table 1). In short, both groups had a similar percentage of women and comprised older people (mean age approximately 70 years). Antidepressant use was approximately 2 times as frequent in the diabetic group as in the nondiabetic group.

Glucose-Insulin Homeostasis

The estimated means of the measures of glucose-insulin homeostasis for individuals not using antidepressants (n = 5,504), TCA users (n = 64), and SSRI users (n = 87) are presented in Table 2. Of the antidepressant classes, paroxetine (n = 65) and amitriptyline (n = 38) were most commonly prescribed.

After adjustment for age, sex, and BMI (model 1), the level of glucose was comparable between the group of nonusers and the groups of users of TCAs and SSRIs. However, the level of insulin was significantly lower in users of SSRIs than in participants not using antidepressants (8.8 and 9.9 mU/L, respectively; *P* = .03) and in users of TCAs (8.8 mU/L and 10.7 mU/L, respectively; *P* = .01). TCAs users

Table 2. Association Between Use of Antidepressants and Glucose-Insulin Homeostasis

	Nonuse (n = 5,505)	TCA Use (n = 64)		SSRI Use (n = 87)		SSRIs vs TCAs,
	Mean (95% CI)	Mean (95% CI)	*P* Value	Mean (95% CI)	*P* Value	*P* Value
Glucose (mmol/L)						
Model 1, basic model	5.6 (5.5–5.6)	5.6 (5.5–5.7)	.40	5.5 (5.4–5.6)	.76	.40
Model 2, CES-D score	5.6 (5.5–5.6)	5.6 (5.5–5.7)	.36	5.6 (5.4–5.7)	.99	.49
Model 3, clinical diagnosis	5.5 (5.5–5.6)	5.6 (5.5–5.7)	.37	5.5 (5.4–5.6)	.83	.41
Insulin (mU/L)						
Model 1, basic model	9.9 (9.8–10.1)	10.7 (9.6–12.1)	.20	8.8 (8.0–9.8)	.03	.01
Model 2, CES-D score	10.0 (9.9–10.1)	10.7 (9.5–12.0)	.28	8.6 (7.7–9.6)	.01	.01
Model 3, clinical diagnosis	10.3 (9.7–10.9)	11.1 (9.7–12.6)	.24	9.1 (8.1–10.1)	.02	.01
HOMA-IR (%)						
Model 1, basic model	2.4 (2.4–2.5)	2.7 (2.4–3.0)	.17	2.2 (1.9–2.4)	.04	.02
Model 2, CES-D score	2.5 (2.4–2.5)	2.6 (2.3–3.0)	.24	2.1 (1.9–2.4)	.01	.01
Model 3, clinical diagnosis	2.5 (2.4–2.7)	2.7 (2.4–3.1)	.21	2.2 (2.0–2.5)	.03	.01
HOMA-β (%)						
Model 1, basic model	100.4 (99.1–101.7)	105.5 (93.9–118.6)	.41	89.1 (80.3–98.8)	.02	.03
Model 2, CES-D score	100.8 (99.5–102.1)	104.5 (92.9–117.6)	.55	85.8 (77.1–95.5)	< .01	.01
Model 3, clinical diagnosis	104.5 (98.4–110.8)	109.1 (96.1–123.7)	.47	91.7 (82.0–102.4)	.02	.03

[a]Data presented as the estimated mean with 95% confidence interval. Analyses adjusted for age, sex, and body mass index (model 1) and additionally for CES-D score (model 2) and clinical diagnosis of depressive symptoms/depression (model 3).

Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale, CI = confidence interval, HOMA-β = homeostasis model assessment-estimated β cell function, HOMA-IR = homeostasis model assessment-estimated insulin resistance, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 3. Association Between Antidepressant and Start of Insulin in Diabetic Patients[a]

	Percentage[b]	No. of Cases	HR (95% CI)
Current use, unrestricted			
Nonuse of antidepressants	…	287	1.00 (reference)
TCAs	2.7	8	1.40 (0.67–2.96)
SSRIs	3.3	9	1.81 (0.89–3.71)
Current use, restricted to > 90 days treatment			
Nonuse of antidepressants	…	288	1.00 (reference)
TCAs	2.2	8	1.90 (0.89–4.06)
SSRIs	2.8	8	2.17 (1.02–4.60)
Past use of antidepressants			
Never used antidepressants	…	215	1.00 (reference)
TCAs	12.0	40	0.94 (0.65–1.38)
SSRIs	10.1	32	0.99 (0.65–1.51)

[a]Analyses adjusted for age, sex, prevalent use of glucose-lowering agents at start of the Rotterdam Study (yes/no), the number of concomitantly dispensed glucose-lowering agents, body mass index, and use of other antidepressants. Antidepressant drug groups were studied in a single statistical model.

[b]As we studied the associations with time-varying exposure analysis, controls could contribute more than once to the computations before they were censored or became a case. For this reason, exposure is reported as a percentage.

Abbreviations: CI = confidence interval, HR = hazard ratio, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

and participants not using antidepressants had a comparable level of insulin ($P = .20$). Users of SSRIs had a significantly lower HOMA-IR than participants not using antidepressants (2.2% and 2.4%, respectively; $P = .04$) and users of TCAs (2.2% and 2.7%, respectively; $P = .02$). Moreover, SSRI users had a significantly lower HOMA-β than participants not using antidepressants (89.1% and 100.4%, respectively; $P = .02$) and users of TCAs (89.1% and 106%, respectively; $P = .03$). No statistically significant difference in HOMA-IR and HOMA-β was observed between participants not using antidepressants and TCA users. Results did not materially differ when we additionally adjusted for CES-D score (model 2) and for the clinical diagnosis of depressive symptoms/depression (model 3).

We observed no statistically significant difference between never-users of antidepressants and past users of SSRIs or TCAs in these outcomes (results not shown).

Insulin Dependence

Of the 1,677 diabetic patients, 304 started insulin treatment during follow-up (Table 3). Compared with nonuse of antidepressants, current use of SSRIs was associated with a 1.81 (95% CI, 0.89–3.71) times higher risk of initiating insulin treatment, although this was not statistically significant. Current use of TCAs was associated with a 1.40 (95% CI, 0.67–2.96) times higher risk of initiating insulin treatment, which was also not statistically significant. When we defined current exposure of antidepressants after 90 days of consecutive treatment, current use of SSRIs was associated with a significantly 2.17 (95% CI, 1.02–4.60) times increased risk of starting insulin treatment. Past use of TCAs and SSRIs was not associated with an increased risk of initiating insulin treatment.

These results did not materially change after statistical adjustment for depression in the subcohorts for which we had data available on depression. Moreover, the point estimate did not materially change when prevalent users of glucose-lowering agents were excluded from the analyses (results not shown).

DISCUSSION

Our study yielded 2 findings. First, we observed that current use of SSRIs was associated with a lower level of insulin, lower pancreatic insulin secretion (assessed with HOMA-β), and lower peripheral insulin resistance (assessed with HOMA-IR) than were observed in participants not

using antidepressants in a population without history of type 2 diabetes mellitus. These results remained similar when adjusted for CES-D score and when compared to TCA users instead of nonusers of antidepressants. Second, we observed that in people with type 2 diabetes, current use of SSRIs for more than 90 consecutive days was associated with an approximately 2 times higher risk of starting insulin treatment than in nonusers of antidepressants.

This study is in agreement with the existing literature conducted in in vitro and mouse models. Serotonin inhibits the secretion of insulin from pancreatic β cells.[9] Pancreatic β cells express both the serotonin transporter and the vesicular monoamine transporter, channel proteins that are capable of transporting serotonin into the cells and that can be antagonized by SSRIs.[9,23,24] In line with this, SSRIs decrease insulin secretion in murine pancreatic β cells.[10] The few studies conducted in humans also observed a lower level of insulin in serum in users of SSRIs, similar to what we observed in our study.[11,12] SSRIs may also promote apoptosis of pancreatic β cells,[10] which suggests also a long-term effect of SSRI use. However, we did not observe an association between past use of SSRIs and the different study outcomes. Therefore, our study did not provide evidence of long-term effects on glucose-insulin homeostasis by SSRIs.

Although use of SSRIs has been associated with an increased risk of type 2 diabetes,[6–8] no difference in glucose levels has been observed between users of SSRIs and nonusers of antidepressants,[7] similar to results found in our study. This might indicate that the increased risk of type 2 diabetes in users of SSRIs is independent of fasting glucose levels. However, it remains unclear whether glucose disposal rate is also different between participants using SSRIs and participants using no antidepressants. Low insulin secretion, independently from peripheral insulin sensitivity, has also been associated with a higher risk of type 2 diabetes.[25,26] Therefore, the underlying mechanism of the association between SSRIs and type 2 diabetes might include a lower insulin secretion rather than a lower peripheral insulin sensitivity. To the contrary, we found that use of SSRIs was also associated with increased peripheral insulin sensitivity. One explanation for this finding might be that the higher peripheral insulin sensitivity is required to preserve glucose-insulin homeostasis. Possibly, in subsamples of individuals with higher fasting serum glucose levels, and thus a less preserved glucose-insulin homeostasis, effect sizes of use of SSRIs (eg, in fasting insulin level or peripheral insulin resistance) will be different. However, in the present study population with a limited number of antidepressant users, this could not be investigated.

To our knowledge, the association between use of SSRIs and insulin dependence has not been studied before. The higher risk of starting insulin treatment associated with use of SSRIs might be clinically relevant, as this condition is associated with a higher risk of mortality.[13,14] Thus, our data might suggest that progression of type 2 diabetes during the use of SSRIs is accelerated. Furthermore, the combination of a higher risk of depression in type 2 diabetes patients,[1,2] the higher frequency of antidepressant use in type 2 diabetes patients,[27] and the increasing prevalence of type 2 diabetes[28] make our findings relevant to an increasing population.

The present study has a number of strengths. First, the analyses on the start of insulin treatment were conducted using time-varying covariates and exposures. Using this method, the exposure to antidepressants during follow-up was analyzed more accurately than with conventional statistical models, as logistic regression models. Study participants of the Rotterdam Study cohort were not selected on health condition, which minimized selection bias. Second, exposure to antidepressants and glucose-lowering drugs (oral and insulin) was defined on the basis of prospectively collected automated pharmacy records, and insulin levels were measured blinded to antidepressant-use status which minimized the risk of information bias. And last, we adjusted for the presence of depression. Potential effects of depression on the study outcomes, as, for example, on immunology,[29] did not confound our findings. A drug effect was also supported by our observation that insulin secretion was lower in users of SSRIs than in users of TCAs. However, our study also had a few limitations. First, we had only few participants treated with SSRIs at the time of the blood examination (n = 87) and few individuals at the time that they developed insulin dependence (n = 8), which limits the possibilities of conducting additional sensitivity analyses (eg, duration effect, dose-response effect). Second, the analyses on the glycemic traits were done cross-sectionally, which made it impossible to infer causality. Theoretically, our observations could be the result of reverse causality. However, this was not expected, as that would mean that lower levels of insulin cause a higher rate of SSRI drug use. Furthermore, effect sizes were probably larger in case of confounding by contraindication because of obesity. Third, data on the diagnosis of depression/depressive symptoms were not available for RS-III at the time of the study, which resulted in a smaller study population to study insulin dependence. The proportion of missing data on depression was too large to impute using multiple imputations. Fourth, assessments of insulin resistance and insulin secretion by pancreatic β cells were based on homeostatic model assessment formulas, instead of a euglycemic clamp test. Because both formulas showed a high correlation with measures obtained by euglycemic clamp tests, interpretation of the study results is not substantially different.[18,19] Possible measurement errors by the formulas are most likely nondifferential between treated and untreated participants.

In conclusion, we found that SSRI use was associated with decreased secretion of insulin in pancreatic β cells and with an increased risk of insulin dependence in type 2 diabetes patients. Although biologically plausible, these findings should be investigated in more detail using independent and larger study populations to confirm our result.

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