Author’s response to reviews

Title: Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison

Authors:

Eva.O. Melin (eva.melin@kronoberg.se)
Maria Thunander (maria.thunander@kronoberg.se)
Mona Landin-Olsson (mona.landin-olsson@med.lu.se)
Magnus Hillman (magnus.hillman@med.lu.se)
Hans Thulesius (hans.thulesius@kronoberg.se)

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Author’s response to reviews:

To BMC Psychiatry

Dear editor Professor Anna Clark,

We thank you for the valuable advice given by reviews and editor, and for the opportunity to revise the following manuscript:

Depression differed by midnight cortisol secretion, alexithymia and anxiety between diabetes types: a cross sectional comparison by authors Eva. O. Melin, Maria Thunander, PhD, Mona Landin-Olsson, Magnus Hillman, Hans O. Thulesius, (BPSY-D-16-00694R1).

We will now give point by point answers to the suggested revisions. We will also inform that we have included three new references and excluded two references. The three included are ref. nr 15, 25 and 36.

Eva Melin

Corresponding author
Answers to Editor Comments:

1. Figure: Please ensure that your figure is cited in the text of your manuscript.

Answer: We now write:

The enrolment process, inclusion and exclusion criteria are illustrated in Fig.1. Exclusion criteria were systemic corticosteroid treatment; pregnancy; severe somatic comorbidities (cancer, hepatic failure); severe diabetes complications (end-stage renal disease, stroke with cognitive deficiency); severe mental disorders (psychotic disorder, bipolar disorder, severe personality disorder, severe substance abuse, mental retardation); visual impairment to such a degree that reading the questionnaires was impossible; or inadequate knowledge of Swedish. (Methods section, line 135-142, page 7-8).

2. Email addresses: Please include the contact email addresses of all authors on the title page of your revised manuscript.

Answer: We have included the contact email addresses for all authors on the title page.

Emily Baron (Reviewer 3): however the discussion is still a little thin, both in terms of findings' interpretation and implications. My major concern is that authors explain how different types of depression may have to be addressed differently in practice, but don't explain how this may differ among diabetes patients, or how detection/treatment may have to be tailored for this specific population.

Answer: We have rewritten several parts of the discussion; some of them will be described later. We have written: As increased cortisol secretion is causative in the development of cognitive and cardiovascular complications, it is of utmost importance to treat depression in T1D due to the demonstrated increase in cortisol secretion [17-19]. (Discussion; lines 284-286, p 14).

When meeting an inactive, obese patient with diabetes, inadequate glycemic control, who seems to be walled off, we suggest that the patient could be tested with a self-report instrument for depression, such as the Hospital Anxiety and Depression Scale (HADS [4,24,28,29], and a self-report instrument for alexithymia, Toronto Alexithymia Scale-20 items (TAS-20) [29–32]. (Discussion section, lines 295-300, page 14).

Third, interventions targeting increased emotional awareness in weight reduction programs for patients with obesity and alexithymia, with or without depression, might be beneficial for both diabetes types, as we have recently showed that alexithymia was associated with obesity in T1D patients [25]. (Discussion, lines 301-305, p 14-15).
Due to well-known link between impaired glycemic control and depression [7], we suggest that a self-report instrument for the detection of depression should be used routinely for all patients with diabetes and impaired glycemic control. (Discussion; lines 314-316, p15).

Introduction:

- I see that authors have made an effort to describe different clinical features in more detail, but it is still unclear in places how these relate to depression, and more specifically, how these relate to melancholia and atypical depression. Eg. p5 line 96-100 and p5 line 103-107

Answer: We describe the clinical differences and differences in the CRH system and between melancholia and atypical depression and we write:

Melancholia and atypical depression are two subtypes of depression with marked differences in clinical expression [1] and in the corticotropin releasing hormone (CRH) system [2], where the changes in the CRH system are responsible for several of the clinical features [2]. In melancholia, there is an activation of the CRH system including the hypothalamic-pituitary-adrenal (HPA) axis with increased cortisol secretion, the locus coeruleus, and the sympathetic nervous system [2]. Depression in melancholia is accompanied by anxiety, a readiness to negatively charged memories, and is characterized by hyper-arousal, insomnia, loss of appetite, and weight loss. In atypical depression, there is CRH deficiency with a down-regulation of the HPA axis with decreased cortisol secretion, and a decreased sympathetic activity [2]. Atypical depression is generally not accompanied by anxiety, but is associated with a sense of emptiness, and persons with atypical depression seem to be “walled off”. The clinical picture is characterized by hypo-arousal, inactivity, hypersomnia, hyperphagia, and weight gain [2]. (Introduction section, lines 69-82, p 5).

In order to further explain why cortisol secretion in depression is important to study in patients with diabetes we have added: As increased cortisol secretion is causative in the development of certain diabetes complications such as cognitive decline and ischemic heart disease [17–19], it is of interest to study cortisol secretion in depressed T1D and T2D patients. (Introduction section, lines 100-102, page 6).

In order to bind together depression, cortisol secretion and cardiovascular complications, we have included the word cardiovascular in the following sentence: Depression in diabetes is deleterious as it is associated with impaired glycemic control [6,7], increased prevalence of diabetes complications, cardiovascular and all-cause mortality [8–10]. (Introduction, 85-87, p 5).

We have added information regarding alexithymia and introduced a new reference. We write: Alexithymia, a personality trait characterized by deficits in emotional awareness and expressiveness [22], has previously been linked to depression [23,24], obesity in T1D patients
[25], and to increased cardiovascular mortality [26]. We therefore consider that alexithymia might be of interest to study in the context of depression, diabetes, obesity and diabetes complications. We also hypothesize that alexithymia might be responsible for the “walled off” impression seen in patients with atypical depression. Alexithymia in depressed patients might have clinical implications. The reduced capacity of communicating feelings for persons with alexithymia, might lead to an increased risk to suffer from a depressive disorder that will not be diagnosed and thus not treated. (Introduction, 108-116, p 6-7).

- P5 line 108: perhaps worth explaining "Given the different aetiology of T2D and T1D, the aim was to compare the clinical features of the patients with T2D and T1D in terms of self-reported depression…etc."

Answer: we have followed your advice. (Introduction section, lines 117-119, page 7).

Methods

- P7 line 134: please specify which aspects you are referring to

Answer: We write: The T1D patients that delivered MSC samples were compared to the T1D patients of the same age that did not deliver MSC samples. (Methods, lines 145-146, p 8).

The 148 T1D patients that delivered MSC were compared to the 70 T1D patients (age 32-59 years) that did not deliver MSC samples. They did not differ by diabetes duration, gender, HbA1c, clinical psychiatric diagnoses, self-reported depression, self-reported anxiety, alexithymia, antidepressant use, obesity, smoking, physical inactivity; cardiovascular complications, foot complications, or diabetes retinopathy (P-values were between 0.21 and > 0.99). (Methods, lines 207-212, p 10-11).

- Authors added 'data collection' as a subtitle in methods - perhaps best to use the term 'measures' and then separate this subsection into 3 sections and describe each measure under relevant section: 1) measures collected as part of the register and medical records; self-reported measures; 3) samples

Answer: We have introduced “Measures” as heading and 3 subheadings:

1) Data collected from the Swedish National Diabetes Register (S-NDR) and from medical records (Methods section, line 153-154, page 8).
2) Self-report measures (Methods section, line 176, page 9)

3) Saliva samples, blood samples and anthropometrics (Methods section, line 188, p 10).

- The authors added the section 'clinical psychiatric diagnoses' after the first round of reviews. Given that the authors now specify that they refer to self-reported measures when they discuss 'depression' or 'anxiety', I would suggest providing the classification numbers for melancholia and atypical depression when they first refer to them in the introduction. As for the clinical psychiatric diagnoses, the authors should be very clear that these were diagnoses made before recruitment, and collected as part of the medical records.

Answer: We write as follows: Clinical psychiatric diagnoses were made prior to recruitment, and were collected from the medical records. No clinical differentiation was performed between melancholia and atypical depression by their physicians. The DSM-IV/ICD-10 depression classification codes were for a single episode 296.2/F32, for recurrent episodes 296.3/F33, and for unspecified depression 311/F32.9 [1]. Clinical psychiatric diagnoses were dichotomized as having or not having a clinical psychiatric diagnosis. (Methods section, lines 158-163, pages 8-9).

However, we disagree that the classification codes should be given in the introduction as no clinical differentiation was performed between melancholia and atypical depression by their physicians, and the depression codes for single episode, recurrent episodes or unspecified depression are not of particular interest for this study. In the methods section we have described which patients that were excluded (patients with psychotic disorder, bipolar disorder, severe personality disorder, severe substance abuse, mental retardation) (Methods section, lines 139-140, p 8).

- P 7 line 151: The reason for collecting information relating to diabetes complications should be mentioned here (rather than in discussion p12 line 262-263)

Answer: We write: Diabetes complications could potentially induce depression and were therefore included in the analyses. (Methods section, line 164-165, page 9).

As increased cortisol secretion is causative in the development of certain diabetes complications such as cognitive decline and ischemic heart disease [17–19], it is of interest to study cortisol secretion in depressed T1D and T2D patients. Even a mild increase in cortisol secretion in a non-diabetic population without clinical signs of overt hypercortisolism, is associated with an increased risk of cardiovascular events and mortality [20]. (Introduction, lines 100-105, p 6)
- P 8 line 163-170 - I would take out the explanation of associations between the screening tools and antidepressants use etc. - this can be (and is) mentioned in the discussion, to help justify the use of screening tools rather than diagnoses. Plus, the evidence is not that convincing.

Answer: We have followed your advice and we have excluded the proposed section. Instead the prevalence of antidepressant use and of clinical psychiatric diagnoses are presented for patients with and without self-reported depression for T2D patients in Table 2 and for T1D patients in Table 3. We have also in the two tables included COR for the association between clinical psychiatric diagnoses and self-reported depression for both diabetes types.

- How long before/after the self-report measures were the samples taken (MSC and HbA1c)?

Answer: The patients were asked to complete the self-report instruments before leaving the outpatient clinic the day for recruitment (Methods section, line 177-178, page 9).

MSC samples returned within one week after recruitment were included in the study. (Methods section, line 191-192, page 10).

Blood samples were collected the day for recruitment (Methods section, line 213, page 11).

- P 9 line 198: please explain what HbA1c is for the lay reader

Answer: HbA1c reflects the average glucose concentration during 8-12 weeks prior to testing, and high levels indicate impaired glycemic control [6]. (Methods, lines 213-215, P 11).

- P 10 line (statistical analyses): explain analyses were conducted separately for both types of diabetes

Answer: We have followed your advice: Multiple logistic regression analysis (Backward: Wald) were conducted separately for the two diabetes types. (Methods, lines 226-227, p 11)

Results:
- P 10 line 218-223: I think it's worth including the proportion of each sample who has a psychiatric diagnosis in table 1
We have followed your advice. (Table 1). We have also included information of clinical psychiatric diagnoses in Table 2-3. We have in order to clarify the difference between clinical psychiatric diagnoses and self-reported depression and anxiety, included the definitions in all 3 tables.

- The authors refer several times to 'non-significant differences' - in instances when this refers to marginal p values, then rather say 'marginal difference' (e.g. p11, line 232 and 235); if there is no significant difference (p>0.1 for example), then don't say there is a difference at all - it's really misleading (e.g. p 12 line 268)

Answer: We have excluded both sentences.

- The sections on p11 line 238-240, and line 246-248 should both go after the section describing baseline characteristics between T2D and T1D, and before you compare depressed vs non-depressed patients in both populations

Answer: We have moved both sections and they are presented at Results section, lines 248-250, 253-255 page 12.

- Page 11 line 241: to differentiate this section from the previous section (line 229-237), perhaps specify you are referring to adjusted associations.

Answer: We have changed Tables 2-3: prevalence, medians and the results of the logistic regression analyses are presented for T2D in table 2 and for T1D in table 3. I think the way it is presented now in the text it will not be difficult to understand when we refer to prevalence and when we refer to associations, as we present all the adjusted odds ratios (AOR) for all the significant values. We write: Differences between depressed and non-depressed T2D patients are presented in Table 2. (Insert Table 2). The depressed T2D patients compared to the non-depressed had higher prevalence of alexithymia (67% versus 11%, P = 0.018). In the depressed T2D patients the obesity prevalence was 83%. Self-reported depression was associated with alexithymia (AOR 15.0) in 23 T2D patients (Table 2). (Results, lines 256-260, p 13).

Differences between depressed and non-depressed T1D patients are presented in Table 3. (Insert Table 3). The depressed T1D patients compared to the non-depressed had higher prevalence of alexithymia (47% versus 8%, P = < 0.001), anxiety (76% versus 30%, P = < 0.001), high MSC (≥ 9.3 nmol/L) (53% versus 18%, P = 0.003). The obesity prevalence was in the depressed T1D patients 6%. Self-reported depression was associated with anxiety (AOR 11.0), foot
complications (AOR 8.5), high HbA1C (AOR 6.4), and high MSC (≥9.3 nmol/L) (AOR 4.8) in 141 T1D patients, (Table 3). (Results, lines 261-267, p 13).

- Authors explain in their feedback that they want to keep table 2 to be able to report prevalence etc. I understand that, but my suggestion was to drop the actual unadjusted non-parametric analysis from table 2. I suggest authors include the prevalence rates included in table 2, into table 3. This way only unadjusted and adjusted regression models are provided as statistics. Also, it seems a bit odd that some variables are included in table 3, but not in table 2. The analysis in the statistical analysis section of the methods would have to be adjusted accordingly.

Answer: There was not enough space to include the prevalence rates in table 3 together with the logistic regression analyses. We therefore presented the prevalence rates and the results from the logistic regression analyses for T2D in table 2, och for T1D in table 3. We also added the prevalence rates for the variables that previously not were included in Table 2. According to your suggestion, we also dropped the non-parametric analyses in table 2, except for age and diabetes duration. We also had to change the text in the result section accordingly, see above. (Results, lines 256-267, p 13).

- Why isn't BMI included in Table 3? Also in table 3, define acronym AOR in footnote, even if explain this in the text.

Answer: We have corrected the mistake and BMI is included and we now write obesity (BMI ≥30 kg/m2) in both Table 2 and 3. We define AOR as adjusted odds ratio in footnotes in Tables 2-3.

Discussion

- Section p12 line 253-255 - explain here whether these findings support or refute the hypotheses you outlined in the introduction.

Answer: We write: The clinical presentation of depression in the T1D and T2D patients differed by associated anxiety, alexithymia, obesity, and midnight salivary cortisol secretion. Depression in the T2D patients was associated with alexithymia, but not with anxiety or with high midnight cortisol secretion (≥ 9.3 nmol/L). The obesity prevalence was very high in the depressed T2D patients. In the T1D patients, depression was associated with anxiety, high midnight cortisol secretion, impaired glycemic control (HbA1c > 70 mmol/mol (> 8.6%)) and with foot
complications. The obesity prevalence in the depressed T1D patients was low. (Discussion, lines 272-279, p13).

We also write in the conclusion section: The clinical presentation of depression in T1D and T2D patients differed by associated anxiety, alexithymia, obesity, and midnight salivary cortisol secretion. The hypothesis that depressed patients with T2D mainly suffer from features linked to atypical depression was in this study supported by the very high prevalence of obesity, the association with alexithymia, the lack of associated anxiety, and lack of increment of midnight cortisol secretion in the depressed T2D patients. The hypothesis that depressed T1D patients mainly suffer from features linked with melancholic depression was supported by the presence of associated anxiety, increased midnight cortisol secretion, and the low prevalence of obesity in the depressed T1D patients. We have not found any previous study where different subtypes of depression were explored in T1D and T2D. Awareness of the presence of the two different depression sub types, melancholia and atypical depression, can have implications both for the ability to identify depression in patients with diabetes and for the treatment of depression. (Conclusion, lines 370-382, p 17-18).

- The section on strengths and limitations should come after the interpretations of the findings, at the end of the discussion, before the conclusion.

Answer: We have moved the strengths and limitations according to your suggestions and performed some changes: Strengths of our study are that the population was well defined. Users of systemic corticosteroid treatment, pregnant women, persons with severe somatic or psychiatric disorders, or with severe substance abuse, were excluded. We have previously shown that MSC increases by age [21]. By excluding younger T1D patients (< 32 years), we made sure the two populations were matched by age, so that age wouldn't bias the association between MSC and depression. We explored whether patients that delivered MSC samples differed from those that did not, and we did not find any difference for any variable included in the study. We included diabetes complications in the analyses as the presence of complications could induce depression. We explored whether there were seasonal variations of MSC secretion in the T2D patients, as previously shown in T1D patients [21], which was not the case. (Discussion, lines 341-351, p 16).

The main limitation of our study was the small number of patients with T2D. It will be necessary to explore whether our findings of the very strong association between depression and alexithymia, and the absence of associations between anxiety, high MSC and depression in T2D can be confirmed in a larger population. To explore seasonal variation of MSC in a larger population of T2D patients would be interesting. A larger study of depression, alexithymia, anxiety, seasonal variation and MSC in persons with T2D is therefore planned in primary care settings [27]. (Discussion, lines 352-358, P 17).
- Similarly, the section on prevalence of depression p13 line 276-278 should come right after you report the prevalence in your study (p12 line 252); bear in mind that if the study you compare your results with did not use a screening tool, but rather used a diagnostic assessment, your results are not comparable.

Answer: In the first part of the discussion we just present the major findings, so we prefer not to discuss the depression prevalence here as you suggest.

According to your advice we have however changed how we discuss the depression prevalence. “The prevalence of depression were in accordance with previous research for both diabetes types, but we did not find any significant difference between the two diabetes types [3,4,5]. The depression prevalence would most probably have been higher for both diabetes types if we had not excluded persons with severe substance abuse, bipolar disorder, depression with psychotic features, and severe somatic comorbidities. The depression prevalence reported in previous research depends on which method that was used for the diagnosis [3,4,5]. Our results would probably have differed if we had performed a diagnostic interview. (Discussion, lines 306-313, p 15)

- The section p13 line 280-252 should come right after p12 line 253-256

Answer: Unfortunately, here we do not know if you mean the lines 280-282 or 250-252. Anyway we have performed several changes in the discussion section.

- When you report the use of screening tools as a limitation, the evidence you report as a rationale for the use of screening tools is quite weak - mere associations is not enough. You need to provide evidence of validation studies that have assessed the psychometric properties of the tools used in your study

Answer: We report the results from a validation study of HADS: Another limitation is that depression and anxiety were self-reported and not confirmed by a diagnostic interview. HADS has however recently been validated and showed good reliability and discriminant validity [28]. The conclusion of the validation was that HADS is a useful instrument for detecting anxiety and depression symptoms, both at an individual and a collective level [28]. (Discussion, lines 358-362, p 17).

In this study, the T1D patients with self-reported depression had a higher prevalence of clinical psychiatric diagnoses and antidepressant use than patients without self-reported depression,
which indicates that the scale is relevant for detecting depressive symptoms. (Discussion, lines 363-366, p 17)

- In the strength section of your discussion, p 12 line 258-260, you explain that the population was well defined. However, it was very restrictive, so your findings may actually not be representative of people with T2D and T1D in Sweden… this is worth mentioning.

Answer: We write: The depression prevalence would most probably have been higher if we had not excluded persons with severe substance abuse, bipolar disorder, depression with psychotic features, and severe somatic comorbidities. (discussion, lines 308-310, p 15).

- You also explain that both groups had the same average age, but that's because you explicitly excluded participants from the T1D who were less than 32 years old… so did you mean that you made sure the two populations matched by age so that age wouldn't bias the association between MSC and depression? If so, then state this.

Answer: We write: We have previously shown that MSC increases by age [21]. By excluding younger T1D patients (< 32 years), we made sure the two populations were matched by age, so that age wouldn't bias the association between MSC and depression. (discussion, 343-346, p 16)

- P 13 line 252-283: Authors state "We have not found any study where melancholia and atypical depression were compared between diabetes types." Rather state this earlier in the discussion, where you highlight the different association of depression among patients with different diabetes types, to emphasise the original findings of your research

Answer: We state this earlier: The findings of our research support our hypothesis that depressed T2D patients mainly suffer from features of atypical depression, and depressed T1D patients mainly suffer from features of melancholic depression. We have not found any previous study where features of melancholia and atypical depression were compared between the two diabetes types. (Discussion, lines 280-284, p 14).

We also have added in the conclusion: We have not found any previous study where different subtypes of depression were explored in T1D and T2D. (Discussion, 378-379, p 18).

- P14 line 300-309: authors explain how different subtypes of depression may be treated - but don't specify for which types of patients (T2D or T1D) this may be useful for. It seems you
discuss issues about subtypes of depression, but don't refer to how these may apply for patients with different types of diabetes

Answer: As increased cortisol secretion is causative in the development of cognitive and cardiovascular complications, it is of utmost importance to treat depression in T1D due to the demonstrated increase in cortisol secretion [17-19]. (Discussion, lines 284-286, p 14).

The low emotional awareness and the reduced capacity of communicating feelings, features of alexithymia [22], might have clinical implications. First, there is a risk that depression in persons with alexithymia will remain undiagnosed as alexithymic persons have difficulties recognizing and communicating their own feelings, thus also their depressive state. When meeting an inactive, obese patient with diabetes, inadequate glycemic control, who seems to be walled off, we suggest that the patient could be tested with a self-report instrument for depression, such as the Hospital Anxiety and Depression Scale (HADS [4,24,28,29], and a self-report instrument for alexithymia, Toronto Alexithymia Scale-20 items (TAS-20) [29–32]. Second, alexithymic depressed persons might benefit from different types of psychotherapy than non-alexithymic depressed persons. Third, interventions targeting increased emotional awareness in weight reduction programs for patients with diabetes, obesity, alexithymia and/or depression, might be beneficial for both diabetes types, as we have recently showed that alexithymia was associated with obesity in T1D patients [25]. (discussion, lines 291-305, p 14-15).

However we also include that we cannot be certain that cortisol secretion and glycemic control will improve in treated depressed patients and we write: There are several subjects for future research. Will cortisol secretion decrease in T1D patients recovered from depression? (Discussion, lines 324-325, p 15).?

-I also feel that authors should report on the clinical differences found between the two types of diabetes patients, other than depression - were any differences or lack of differences found expected? Were any findings surprising etc?

Answer: We explored whether there were seasonal variations of MSC secretion in the T2D patients, as in the T1D patients [21], which was not the case. (discussion, lines 349-351, 16).

To explore seasonal variation of MSC in a larger population of T2D patients would be of interest. (discussion, 355-356, 17).

-P14: line 311-314: state if the two types of diabetes indeed presented with what seemed like different types of depression, and state which (melancholia or atypical depression, or only partial presentation etc.). Nowhere in your paper do you actually say whether your hypothesis was supported or not.
Conclusions

The clinical presentation of depression in T1D and T2D patients differed by associated anxiety, alexithymia, obesity, and midnight salivary cortisol secretion. The hypothesis that depressed patients with T2D mainly suffer from features linked to atypical depression was in this study supported by the very high prevalence of obesity, the association with alexithymia, the lack of associated anxiety, and lack of increment of midnight cortisol secretion in the depressed T2D patients. The hypothesis that depressed T1D patients mainly suffer from features linked with melancholic depression was supported by the presence of associated anxiety, increased midnight cortisol secretion, and the low prevalence of obesity in the depressed T1D patients. (Conclusion, lines 369-378, pp 17-18).

Third, all the features that might differ between melancholia and atypical depression were not explored, for example patterns of sleeping disturbances [2]. (Discussion, lines 366-368, p 17)

- P14 line 313 "The obesity prevalence was high in depressed T2D patients and low in depressed T1D patients" you repeat this several times in your article - please explain what this means and the implications this has in your discussion section
Answer: we have rewritten almost the whole discussion section. New is for example: Compared to the obesity prevalence in the general Swedish population, the obesity prevalence was lower for the depressed T1D patients, and more than 7 times higher for the depressed T2D patients, and more than 4 times higher for the non-depressed T2D patients [15]. The high obesity prevalence in the T2D patients is deleterious as obesity significantly contributes to cardiovascular disease [36]. (Discussion, 317-321, p 15).

Grammar and typos:

Abstract:

- P 2, line 26-28: I appreciate that you've modified the aim, which is now a lot clearer, but perhaps rephrase to "The aim was to compare the clinical presentation of T1D and T2D patients in relation to self-reported depression, self-reported anxiety, alexithymia …etc."

Answer: The aim was to compare the clinical presentation of T1D and T2D patients in relation to self-reported depression, self-reported anxiety, alexithymia, obesity, and midnight salivary cortisol (MSC). (Abstract: P 2, line 30-32).

- P2 line 47: This sentence is not grammatically correct; rephrase to "…was 80% for T2D depressed patients and 6% for T1D depressed patients"

Answer: We have changed according to your suggestions. (Abstract, P2 line 51-52).

Introduction:

- P6 line 115-116: Rather "Being able to differentiate between melancholia and atypical depression can (not might!) have clinical implications…"

Answer: We have performed the change according to your suggestion. (Introduction, p. 6 line 125-126).

Method:

- P 9 line 195-196: this sentence is not grammatically correct. You could rewrite this is this way "The number of T2D and T1D patients recruited were 9 & 60 in spring, 5 and 34 in summer, and 10 & 54 in autumn/early winter, respectively. (Method, P 9 line 195-196)
Answer: We have performed the changes according to your suggestions. (Methods, P 10, line 204-206)

Results:
- p10 line 217: TID (with a capital i), rather than T1D
Answer: We have corrected and wrote T1D.

Discussion:
- p 12 line 253-255: rather begin the sentence with 'In T1D patients', rather than say this at the end
Answer: We have changed the word order according to your suggestion. (discussion, line 276, p 13).

- p 12 line 271: start a new paragraph with "Another limitation is that depression and anxiety…"
Answer: We have followed your suggestion. (discussion, line 359, p 17)

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Declarations

- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
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- Authors' Information

Answer: We have included all these sections in the manuscript according to your instructions.