Reviewer 02459030:

This study indicated that statin use was associated with cognitive impairment, particularly affecting memory, in these middle-aged adults with childhood-onset T1D. Logistic and linear regression models tested the association between three-level degree of statin use (covariate of interest) and cognitive impairment or cognitive domain z-scores (outcomes). The statistical methods were used properly. Importantly, the authors take into account of confounding data, including age, education, CAD,LDL-c and apo E4 allele status. There is one question needed to be answered. We have known that statin could decreased TCH and LDL, and delayed the development of atherosclerosis in brain vessels. Thus, why does statin lead to cognitive impairment? Please discussed the possible potential mechanisms.

The manuscript's presentation of possible mechanisms for the link between statins and cognitive impairment have been enhanced in both the introduction (pages 5-6):

"…Age at initial statin exposure is an important consideration because the brain's white matter continues to undergo myelination well into the 4th decade of life.[14, 15] If statins do compromise myelin integrity, then statin use may differentially impact the brain depending on the age at which statin use begins. Additionally, long-term statin use may also reduce the number of glial progenitor cells available for future recruitment as these patients age.[16] Thus, exposure to statins prior to age 40 years, in combination with the metabolic dysregulation that accompanies T1D, may noticeably disrupt brain myelination or myelin integrity, whereas little to no discernable disruption of brain myelin/myelination occurs when delaying exposure to statins until after age 50, and/or in the absence of T1D."

and discussion (pages 13-14):

"…lipophilic statins may accumulate in the brain more readily and/or rapidly than hydrophilic statins.[37] With evidence from animal studies that statins can exert negative impacts on both myelin [38-40] and neuronal health,[2, 3]…

… Third, most prior studies were conducted in populations with much shorter exposure to statins than our participants have experienced. This is important because statins appear to promote glial progenitor cells to differentiate into oligodendrocytes, accompanied by a loss of uncommitted glial progenitor cells.[44] Thus, initiation of long-term statin use by middle-age, as recommended for T1D patients, may reduce the pool of progenitor cells for future recruitment, making these patients less resilient to cerebral insults from normal aging or T1D-related vascular damage. This, in turn, may contribute to an increased risk for cognitive impairment in this vulnerable patient population."

Reviewer 00646289:

This paper aims to test the correlation between statin use and cognitive impairment in adults with childhood-onset Type 1 Diabetes (T1D), as a group of patients with chronic exposure to metabolic dysregulation. It is a valuable study, and the results are well analyzed. It should be

published for utilization of both clinicians and basic researchers. Although statin has already been correlated to cognitive impairment to some extent in different disorders, there is only one study reported on the situation in T1D patients, which is referred and discussed in the paper by the authors. It is a significant issue, considering that FDA has recently expanded advice on statin risks. The points that need to be considered are;

-The Introduction section will be improved if the authors add statements giving brief information on why and when statins are prescribed in T1D patients.

We have revised the introduction to include a brief statement about recommendations for statin use in people with diabetes (page 5):

> "Second, to minimize cardiovascular events, the American Diabetes Association recommends moderate to high intensity statin treatment for diabetic patients at any age who also have atherosclerotic cardiovascular disease, or its risk factors (e.g., hypertension, dyslipidemia, overweight/obese), and for all diabetic patients aged 40 years and older, regardless of cardiovascular risk.[11]…"

- Do the authors have information on the exact ages of patients when statin use has started?

Unfortunately, no, we do not have the ages at which each participant began using a statin.

- Authors state that patients used mostly lipophilic statins. Do they have the information regarding the intensity of the statin treatments that these patients received (high/moderate/mild)? Such a correlation would be informative.

Unfortunately, only medication name/type, but not dose/intensity, was collected.

- Introductory sentences should be added to the Discussion section that summarizes the study before going on to the discussion of the results.

We have revised the opening sentences of the Discussion section to summarize the study (page 11):

> "This study analyzed correlations between statin use and cognitive impairment in a sub-group of participants with T1D from the on-going, observational Pittsburgh Epidemiology of Diabetes Complications Study. These now middle-aged adults were diagnosed with T1D prior to age 18 years, and have reported medication use biennially since the parent study baseline in 1986. Among the 108 participants with a cognitive assessment in 2010-2013, …"

- The manuscript should be over-read for minor mistakes in language, such as: Page 11, Line 8 from the bottom: "with an higher prevalence" should be "with a higher prevalence" Page 16, Line 5 from top: "adult ages 60 years and older.." should be "adults of ages 60 years and older.." Page 16, Line 7 from top: the statement "although at least one examined participants with 10+ years of statin use.." may be better as; "although at least one examined participant was on statins for 10+ years.."

The manuscript has been re-read and we have corrected any grammar or spelling errors.

Reviewer 02446617:

The author's provides compelling evidence of correlation between statin use and cognitive impairment in patients with T1D. Robust statistical analysis has been utilized in order to rule out any confounding data that is limited by sample size. The author's analysis takes into account cardiovascular risks, gender differences and ApoE4 allele status, which is involved in both cardiovascular and Alzheimer's disease. The study also addresses the issue as to why their conclusion is different from the previous studies conducted including comparing and contrasting the reason for disparity between findings. Effect of stain was discussed well on the adverse effect it has on myelination however, compelling evidence also exist on statin effect on angiogenesis and vascular genesis. This becomes important in development of the brain as statin in a concentration dependent manner can either aid or disrupt angiogenesis. Shedding light on this in the discussion will strengthen the argument. Lastly the study in cooperates several major parameters affecting the patient's life that can affect the outcome of the results. However, the socio-economic impact such as employment and average household income has not been clearly addressed this study. If the data is readily available the author's should speculate the socio-economic impact on the outcome.

We provide education as a measure of socio-economic status. We chose education rather than other measures because we have previously shown that education, but not income or type of employment, was related to coronary artery disease and end stage renal disease (see Secrest et al., Associations between socioeconomic status and major complications in type 1 diabetes: The Pittsburgh Epidemiology of Diabetes Complication (EDC) Study. *Ann Epidemiol*. 2011;21(5):374-381). As shown in Table 2, education did not differ by statin use group (p=0.52) and this is reported in our results section.

Strengths: 1) Robust statistical analysis. 2) Takes into account major parameters such as BMI and cardiovascular risk effecting T1D. 3) Follows the patient from childhood to adulthood and provides a good time line for the correlation of statin use and cognitive impairment. Weakness: 1) If possible please indicate when the patients started taking statin and the dosage given to each patient. This can aid is the deciphering the onset of cognitive impairment.

Unfortunately, we do not have the age at which each participant began using statins, nor do we have dosage information.

2) Please discuss the effect of statin on angiogenesis in a developing brain.

We now include a sentence about the effect of statins on angiogenesis on a developing brain in our discussion section (page 14):

"…In addition, statins appear to promote cerebral angiogenesis at therapeutic doses, although angiostatic effects occur at higher concentrations.[45] "

Reviewer 01002592:

The present version of this report must be amended in some parts. It needs at first to be more attractive for readers being rather difficult to follow in the present version. Major points:

-data presentation is a key point and in this article they are rather confusing and without accompanying graphs easy to understand. The Tables are plenty of numbers: albeit they are needed, focused graphs must help readers;

> We have added a figure to display statin use over time. While we understand the visual appeal of figures over tables, our results are somewhat impractical for graphical display. Displaying results in tables allows readers to fully appreciate the robustness of the associations we found between statin use and cognitive impairment in this type 1 diabetes population.

-the whole article needs to be better written either in English (an extensive editing is necessary) and in its content because the presentation lacks of consequentiality and must be less dispersive;

> We apologize for any difficulties associated with reading the manuscript. We have re-read the article and made minor edits to improve flow; we feel it is well-written, in a manner that is easy to follow and that presents an important issue with public health consequences.

-type 1 diabetes and the related problems are not presented and discussed at the beginning of the discussion whose first sentences are unsound. Discussion cannot start as in this paper. I suggest to look at the main syndrome that is type 1 diabetes and start on two or three main research questions such as the role of islet beta cell apoptosis (see J Cell Physiol. 2005 204:124-30 regarding the apoptosis of beta cells and the role of NF-KappaB transcription factor and IL-18 in K. Bendtzen studies Eur J Immunol. 2003 33:2278-86 and some two or three other articles in 2015/6 of other authors). Then you must start with the relationship between statins and brain injuries.

> We respectfully decline to present information about the main syndrome that is type 1 diabetes, its etiology including beta cell apoptosis, or related problems, in this manuscript. While we understand that non-clinicians also read the journal, we expect the readers to have some understanding of diabetes; it is not within the scope of this article to provide a detailed background of type 1 diabetes, especially considering such information is readily available from a multitude of sources.

At the end, the Conclusions must be also shown in a figure containing the main results of the study, attracting the reader on that has been found and demonstrated: a figure and not Table or only words.

> As we responded to your earlier comment regarding figures vs tables, the results of this study are better presented in tabular formation.

Please revise completely the references either deleting the redundant ones and checking them because they are written in a casual manner: no one seems to be the same of the other. Moreover you reported the dog while the volume and pages are present. In some cases only the dog is present, etc. Please check all carefully.

> The references have been carefully checked for duplicates and to ensure consistent style throughout.