The manuscript by Tong et al. describes effects of high fat diet and nitrosamines in promoting type 2 diabetes mellitus (T2DM) and neurodegeneration, specifically on Alzheimer’s disease (AD) related neuropathological changes. This subject is of great significance since both T2DM and AD are linked to insulin resistance. In my opinion, there are several major issues that need to be addressed before accepting the manuscript for publication.

It is particularly intriguing why the authors selected to study the effects of HFD and nitrosamines on cerebella, considering that this region is preserved in AD. It would be more logical to have selected hippocampal and cortical regions. This is a very important issue to see how relevant are the effects of the treatments in areas that are affected in the disease. In my opinion the study should include relevant brain areas for AD.

The diets used are described as HFD (60% calories) and LFD (5% calories). This description is very poor and more details should be required that include cholesterol levels, fatty acid composition, etc. This is relevant for the interpretation of the results and the comparison between studies.

Although list of references is considerably large, there are no references of studies showing the effects of HFD on neurodegeneration. The authors should discuss their own findings with those published in the literature.

Other methodological aspects are also poorly described, some of them important for the interpretation of the results:

- A full statistical description of the results is necessary. As example, in table 1 the authors assess that the highest insulin and glucose levels were seen in HFD+NDEA treated rats. Were those values significant against the group on only HFD? Is it a significant synergic or additive effect between HFD and NDEA? A correct comparison between groups is lacking in several figures of the manuscript. The results should be discussed accordingly to multiple comparisons.

- Several ELISAs are used in order to measure effects on the levels of proteins involved in AD. Some important information is missing about the antibodies used in those ELISAs. For example: which Tau isoforms recognize the total and the P-tau Abs? Is the P-GSK3 ab against the active (Tyr2169) or the inactive form (Ser9) of GSK-3? Moreover, I which cells are the found changes occurring?
Neurons or glial cells? Immunohistochemical studies in AD relevant brain areas should be included.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests