Dear editors and reviewers:

We would like to thank you for giving us constructive suggestions which have help us in depth to improve the quality of the paper. Here we submit the updated version of our manuscript, which has been revised according to the reviewers’ suggestions. We have marked all the changes in red in the revised manuscript.

The following is a point-to-point response to the two reviewers’ comments.

Response to Reviewer 1:

General comments:

Summary: Based on the research by Heyward also suggested that normal mice fed a HFD exhibit impaired hippocampus-dependent spatial memory and a corresponding alteration in the expression of Sirt1, which has been implicated in memory consolidation, the authors investigated the body weigh changes, the behavioral tests, the expression levels of Sirt1, Bcl-2, Bax and caspase-3 cleaved and found that HFD can increase body weight, aggravates POCD and possibly by down-regulating the expression levels of Sirt1 and Bcl-2 and up-regulating the
expression levels of Bax and caspase-3 cleaved, thereby increasing hippocampal neuron apoptosis.

Minor points:

1. How old were the mice in this research?

Thank you! The C57BL/6 male mice in this study were 13-14 M old (Page 4 line 5-6), as the C57BL/6 mice in the experiment by Zhang [1] were 12 M old.


2. How do you prove that apoptosis is not an accompanying phenomenon but a cause of cognitive impairment of the mice in your study?

Thank you! In our study, we found that the cognitive function was aggravated with the increase of apoptosis, as approved by the data of the HFS group compared with those of the ALS group. The levels of caspase-3 cleaved and Bax were significantly higher in the HFS group than those in the ALS group, and the cognitive impairment was more serious than that in the ALS group. Therefore, we conclude that apoptosis is a cause of the cognitive impairment of the mice in our study.

Response to Reviewer 2:

General comments:

This study is well written and has a new perspective to postoperative cognitive dysfunction. But I do some issue about the study.

1) In the background (50) you wrote 35% fat. is it the 35% of the calories?

Thank you! We’ve recognized that this description in the previous manuscript was not accurate. The sentence “In the typical American diet, the total intake per day is 35% fat” is now changed to “In the typical American diet, fat provides 35% caloric per day.” (Page 2 line 19).
2) In the background (56) you have to put some references for the "as well as for various forms of accelerated cognitive dysfunction"

Thank you! We have put some references for the "as well as for various forms of accelerated cognitive dysfunction [1, 2]"(Page 2 line 22).


3) In the materials and methods (12) the age of the rats is unclear.

Thank you! The C57BL/6 male mice in this study were 13-14 M old (Page 4 line 5-6), as the C57BL/6 mice in the experiment by Zhang [1] were 12 M old.


4) The approved number of ethics committee has to be written.

Thank you! The ethics committee of our hospital approved this study before the study began. However, the committee does not give any approved number for any laboratory animal study, they just issue the Certification for using the housing facilities of laboratory animal. So, we attached the Certification issued by the ethics committee, Zhongshan Hospital, Fudan University.
5) In the materials method section, the numbers of the groups (ALS, ALC, HFC, HFS) is not clear.

Thank you! The numbers of the groups (AL, HF) is 16, so there are 8 mice in each group (ALS, ALC, HFC, HFS). And we have added the numbers of the groups (ALS, ALC, HFC, HFS) in Page 4 line 16.

6) In the materials method section (animal model -4/23); the name of the anesthesia machine and monitoring equipment have to be written.

Thank you! We have added the name of the anesthesia machine and monitoring equipment in Page 5 line 2 and Page 5 line 11.

7) The arterial tension of the rats and the temperature also have to be monitored. Did you monitored or else, please clarify.

Thank you! We have not monitored the arterial tension of the mice in this study, because the experiment of Cesarovic [1] has proven that 1.5 minimum alveolar concentrations is suitable for mice. Both induction and recovery from anesthesia proceeded quickly within 1-2 min. During anesthesia, all reflex testing was negative, and no serious impairment of vital functions was found. As to the temperature, we used the electric blanket to maintain the temperature of the mice at about 37°C during the anesthesia. We added the item number of the electric blanket in Page 5 line 3-4.


8) In the materials method section (Morris water maze test-3-5) the name of the system and analyzed software have to be written.

Thank you! The names of the system and analyzed software were written in Page 6 line 14.
9) In the result section, -23, the explanation of the fig. 2c, is HFC group true or is it HFS groups. Thank you! We have revised the manuscript as suggested, and the sentence has been changed to “The times across the platform in the HFS group were lower than those in the ALC and HFC groups (P<0.05, C)” in Page 9 line 11-12.

10) In the discussion part, (56); "develop into Alzheimer's disease (19)". It can be more suitable to cite the author that present this study. In this review(19) there is no another knowledge about relationship and POCD. Thank you! We have changed and added the reference which has proven POCD may develop into Alzheimer's disease [1] in Page 11 line 3 and Page 18 line 16-17.


11) The other limitation of the study is one group (surgery group) had pain and the other had no surgery and pain. The analgesic drug might not be effective (only emla?) and after 48 hours pain might be persistent. Pain is one of the important factors of the POCD. Thank you! In this study, we established a POCD model, based on Hovens’ [1] model which was a very mature model. We have also considered the problem of postoperative pain, so we gave the treatment of postoperative pain. In addition, it is considered that postoperative pain occurs mainly in the early postoperatively. Therefore, we imitated the time of analgesia in clinical practice (48 h after surgery). On the other hand, the locomotor activity, daily food and water consumption showed no abnormalities after 48 h after surgery in the ALS group and the HFS group. It may show that the pain did not have adverse effects on the mice.
As the society aging, there is still no effective treatment for postoperative cognitive dysfunction. We did this research to observe the effects of high-fat diet and then to explore the preventive method.

Thank you very much for the valuable suggestions about our manuscript. We have carefully revised the manuscript, and hope that the corrections will meet with approval.

Yours sincerely,

ShengJin Ge

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