Dear Editor,

Dementia is an incurable, irreversible progressive disorder, and a major cause of disability among older populations around the world; it is characterized by a gradual decline in cognitive abilities, and reductions in memory, thinking, behavior, and the ability to engage in daily activities [1]. The global prevalence of dementia is estimated to amount to 24 million and has been predicted to quadruple by the year 2050. Alzheimer’s disease (AD) is the most frequent cause of dementia, and mild cognitive impairment (MCI) is a major cause of disability among older populations around the world; it is characterized by a gradual decline in cognitive abilities, and reductions in memory, thinking, behavior, and the ability to engage in daily activities [1]. The global prevalence of dementia is estimated to amount to 24 million and has been predicted to quadruple by the year 2050. Alzheimer’s disease (AD) is the most frequent cause of dementia, and mild cognitive impairment (MCI) may represent a prodromal phase of AD, which places a considerable burden on society. Although acetylcholinesterase inhibitors (donepezil and rivastigmine) and the N-methyl-D-aspartate (NMDA)-type glutamate receptor antagonist (memantine) are widely used for the treatment of cognitive dysfunction, these drugs do not stop dementia from getting worse [1, 2]. Therefore, the identification of new therapeutic approaches and treatments to reduce the incidence of dementia patients is required.

Proton-pump inhibitors (PPIs), are commonly used for the treatment of several upper gastrointestinal disorders including gastroesophageal reflux disease (GERD) and peptic ulcer disease. Over the past decade, the use of PPIs in society is increasing, especially in the elderly, as they are generally regarded as safe medications with very few adverse effects. There is a well-recognized epidemiological link between PPIs and the increased risk of dementia [2, 3]. However, many studies have reported that PPIs are not associated with a greater risk of dementia or AD [4, 5]. But the evidence for this is limited. Although a number of clinical studies have assessed the association between PPIs and the outcome of dementia, this remains a matter for debate, and the uncertainty may be accounted for by the different outcome measures, study sizes, and populations used in the different studies.

A meta-analysis of 4 studies, involving 1,06,942 participants, conducted by Wijarnpreecha et al. [2] demonstrated an increased risk of dementia among PPIs users. This was the same conclusion as other large studies [3]. However, recently, Gray et al. [4] reported that PPI use is not associated with dementia risk, even for people with high cumulative exposure in a prospective population-based study. A prescription sequence symmetry analysis conducted by Park et al. [5] also indicated that the risk of PPIs being associated with dementia may be overestimated. This recent controversial report challenges whether or not PPIs are indeed associated with dementia.

It is therefore imperative to explore the attendant concerns. First of all, a specific statement of the differences between AD risk and dementia risk that come with PPI use should be conducted, although many studies have shown that the modulation of Aβ metabolism and serum vitamin B12 deficiency may directly influence the pathophysiology of AD or dementia. Secondly, experimental studies that assess PPIs in animal models of dementia should be conducted, preferably with a longer time window. Furthermore, fundamental cofounders such as age, sex, a history of stroke, smoking status, and the APOE gene, all of which are considered risk factors for dementia and AD, should be considered. It is necessary to examine higher-quality prospective evidence on the relationship between PPIs and dementia in different age groups.

In summary, certain recommendations should be considered for the evidence of in vivo or in vitro experiments using long-term potentiation protocols to slow the progress of dementia and AD. Further, pharmacoepidemiological and large prospective double-blind studies conducted with the use of standardized outcome measures at different levels are needed to identify the risk of dementia that comes with PPI use.

References

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