Reviewer’s report

Title: The emerging role of dietary fructose in obesity and cognitive decline

Version: 1 Date: 6 June 2013

Reviewer: Natalie Parletta

Reviewer’s report:

This is an interesting and important review, and mostly well written although there a number of major and minor changes need to be made as outlined in chronological order below, and the conclusion needs to be revised to accurately reflect the findings of the review.

Background: Typo line 6 ‘incidence o childhood obesity’

Inaccurate description of Alzheimer’s disease on page 4 ‘Similarly, the incidence of Alzheimer’s Disease, characterised by an age-related decline in memory and cognitive functioning…’ – AD is not characterised by an age-related decline in memory and cognition but rather a progressive and debilitating decline beyond that which is normally experienced with aging.

Page 6 – what is meant by ‘above normal weight circumference’ in the sentence ‘Obesity … and poor cognitive performance were associated with above normal weight circumference, and poor cognitive performance was negatively associated with overweight’? Do the authors mean waist circumference? In fact the whole sentence does not make sense.

Page 6 please be more specific about the direction of the associations in the studies summarised at the end of the paragraph regarding associations between obesity and cognitive function in the elderly.

Page 6-7 did the study in middle aged adults also control for education levels and socio-economic status, both of which may be associated with obesity and cognitive performance?

What did the studies reported with children control for?

Page 8 first paragraph – ‘Moreover, when obesity was measured in late life’ – do the authors mean obesity that developed in late life? The statement that ‘this can be seen as evidence that obesity does in fact cause cognitive decline’ is unsubstantiated by the observational evidence and the argument that verbal ability remains stable until very old age. At most you could suggest that it may support the suggestion that obesity is associated with cognitive decline.

Page 8, next paragraph – summary of the Whitehall study does not make sense, particularly the first outcome reported, that those who were ‘obese at late midlife had lower MMSE, memory and executive function scores …’ and then later (on the last line of the page) that ‘this association was weaker in late life. It appears that the association between obesity and cognition starts early and takes many years to develop’. Do the authors mean in the first instance that people who were
obese at early or mid-life had lower MMSE scores at late midlife?

Page 10 – under ‘Fructose’ first sentence needs to be restructured (put a semi-colon or full-stop/new sentence after ‘equal amounts’).

Page 10 – there is also HFCS with 90% fructose (HFCS-90).

Page 10 typo on last line ‘accounting which accounts for..’

Page 11 – would reword ‘HFCS, like sucrose, did not pose a significant health risk’ to ‘HFCS, like sucrose, was not perceived to pose…’

The study methodology by Agrawal on page 13 could be described more clearly – they had four groups; either with dietary omega-3 or omega-3 deficient diet, and each of those were given fructose or no fructose. Also when summarising the findings it should be highlighted that it showed metabolic syndrome in the brain (which was ameliorated by omega-3s) – which is the primary focus of this review. Regarding the last sentence, note that a few RCTs have been conducted with omega-3s to investigate their influence on cognitive aging in healthy adults (and have not found anything – omega-3s seem to be most helpful for people in very early stages of dementia/mild cognitive impairment). I would remove this sentence altogether or at least cite a review paper on omega-3s in cognitive aging.

Page 13, next paragraph states that ‘only a few studies have investigated the association of fructose intake with cognitive function in humans’ and yet only one study is outlined. What are the others and what did they find?

Page 15: the heading ‘Obesity and cognitive function: underlying mechanisms’, particularly in light of the preceding section, does not fully capture the role of sugar (e.g. sugar-sweetened beverages mentioned in the second paragraph; MetS and fructose discussed later).

Page 17: it is not accurate that DHA is the principle omega-3 in brain and heart – it is the principle omega-3 (PUFA) in brain and has benefits for brain and heart. There are many effects that DHA has been shown to have on brain function – this reads like it is only ‘due to its effects on neuronal membrane activity, which modulates cell signalling’

I note that there is a section on omega-3s, page 18 – this could be more comprehensive as there are other studies in aging that have been done, both epidemiological studies and clinical trials.

The conclusion does not accurately reflect the findings of the review – particularly indications that fructose and sucrose may mediate the influence of obesity on cognitive function. Also doesn’t seem appropriate to add in the reference on adolescents with MetS [135] here – that should be in the review.

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.