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ESPS PEER-REVIEW REPORT

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ESPS manuscript NO: 18884
Title: Oily fish, Coffee and Walnuts: The role of specific dietary components in Non Alcoholic Fatty Liver Disease
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Overall, I loved reading this paper. Nonetheless, I feel that the paper deserves some comments for further improvement.

Section oily fish and fish oil

The authors should comment the recommended intake of omega-3 FAs for children.

The authors should comment the impact of omega-3 FA supplements to treat NAFLD in children. In that vein,they may wish to look up the recent review by Pacifico L et al. (Mini-Reviews in Medicinal Chemistry 2014;vol.14,791-804).

Reference #14: as suggested, the optimal dose of omega-3 PUFA is currently not known. Most trials have used ultrasound or liver enzymes as a semi-quantitative or non-specific measure of NAFLD severity. This should be emphasized.

Reference #16:almost 25% of subjects did not complete the trial!

Section Coffee

Reference #25.This study shows an inverse associations between coffee drinking and

most major causes of death, with the exception of cancer. Please include limitations of this study. Coffee consumption was assessed by self-report at a single time point and may not reflect long-term patterns of consumption. The distinction between persons who drank caffeinated coffee and those who drank decaffeinated coffee was subject to misclassification. The authors of reference #25 lacked data on how coffee was prepared (espresso, boiled, or filtered), and the constituents of coffee may differ according to the method of preparation.

In several case-control studies, coffee consumption has shown an inverse association with the incidence or diagnosis of liver cirrhosis, with significant trends in risk with dose and duration (Klatsky and Armstrong, 1992; Klatsky et al, 1993; Corrao et al, 1994, 2001; Gallus et al, 2002). Since liver cirrhosis is strongly related to the incidence of hepatocellular carcinoma (Adami et al,1992; La Vecchia et al, 1998, Kuper et al, 2000), the apparent protective effect of coffee consumption on hepatocellular carcinogenesis may be due to its inverse relation with liver cirrhosis.

Effect of coffee on the development of liver cancer. A large Finnish study, including over 60,000 individuals across a 19 year follow-up period, was able to show a dose-dependent decrease of the rate of HCC-development in the consumption of up to 6 cups of coffee per day (Hepatology 2008;48:129-136). Please mention it. A meta-analysis of the impact of coffee consumption on the risk of HCC-development was able to confirm this association (BMC Gastroenterol 2013;13:34).

Reference #27 is relevant. It shows a robust inverse relation of coffee drinking to risk of alcoholic cirrhosis, independent of several potential confounders. In contrast, there was no statistically significant relation of coffee drinking to risk of nonalcoholic cirrhosis. Cross-sectional data from reference #27 suggest that coffee is more specifically protective against severe chronic liver disease (ie, cirrhosis) when alcohol is the noxious agent.

Reference #29. The main strength of this analysis is that the study was based on prospective collection of exposure history (coffee or tea consumption) and clinical outcome (hospitalization or death due to chronic liver disease) in a large population-based sample (NHANES-I). Methodologically, however, this study was limited for a number of reasons. Firstly, a relatively large proportion of subjects were excluded from the analysis because of a lack of data on coffee or tea consumption; secondly, ascertainment of liver disease was based on hospital discharge records and death certificates, as opposed to verifiable clinical records; and thirdly, there was a lack of detail regarding the amount and type of beverage consumed. Weighing up these strengths and limitations, however, the reader becomes intrigued that coffee or tea consumption might, indeed, be good for the liver. Caution must be exercised, however, before physicians begin to advise patients with liver disease to consume more tea or coffee. Although these observational data show a consistent association between coffee

or tea consumption and chronic liver disease, it is premature to conclude a causal relationship between the two (i.e that these beverages reduce the risk of liver disease). Firstly, no known ingredients of coffee or tea have been linked with a protective effect in the pathogenesis of CLD. Caffeine might not be responsible, as caffeine-containing beverages other than coffee did not show any benefit in a study by Corrao *et al.* (reference #28). Despite the recent interest in the antioxidant and other potentially beneficial properties of catechins in tea, a protective
effect against chronic liver disease remains to be determined. (Cooper R *et al.* Medicinal benefits of green tea: part I. Review of noncancer health benefits. *J Altern Complement Med 2005;* **11:** 521–5283). Secondly, it is possible that the association revealed in this study might have been confounded with other dietary or behavioral factors that are indeed responsible for the reduced risk of CLD. For example, coffee or tea consumption was inversely associated with BMI. It could be that the consumption of these beverages is associated with healthier dietary practices, which might reduce the risk of the metabolic syndrome—itself associated with nonalcoholic fatty liver disease. Similarly, consumption of coffee or tea might be inversely correlated with heavy alcohol consumption. The lack of a consistent pattern between coffee or tea consumption and alcohol intake in the Ruhl and Everhart study might be attributable to the fact that all levels of alcohol consumption >2 drinks per day were lumped together; patients with alcoholic liver disease who consumed >2 alcoholic drinks per day could not be separately analyzed. Please consider and discuss these limitations when reviewing the effects of coffee or tea on NAFLD.

Effect of coffee on the progression of NAFLD. A meta-analytic review of the evidence for preventing development and progression of NAFLD by coffee consumption was able to substantiate the protective effect of coffee on NAFLD in the experimental as well as the clinical setting (Aliment Pharmacol Ther 2013;38:1038-1044). Please comment this review.

On the basis of available data, the effects of coffee on the etiology of liver disease are indeed multi-factorial, necessitating detailed mechanistic studies to understand its exact impact. Please take it into account.

The study by Birerdinc A et al (reference #37) : caffeine consumption was found to be an independent predictors of NAFLD, even after adjustment for race, gender and metabolic syndrome components.

As observed by Molloy et al. (reference #40), Bambha et al. also observed a beneficial effect of regular coffee consumption on liver fibrosis in NAFLD patients, however, only in patients with a low level of insulin resistance (Hepatology 2012;56:242A).

NUTS

Reference #67 shows that a low intake of nuts and seeds (OR, 3.66) was associated with a significantly higher risk for developing NAFLD.

Reference #68: Vitamin E was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes.

Reference #65 shows that significant inverse associations were also observed between nut consumption and deaths due to cancer, heart disease, and respiratory disease. This study supports.

The health benefits of nut consumption for many chronic diseases. As the study lacked data on how nuts were prepared (e.g., salted, spiced, roasted, or raw), the authors of reference #65 were unable to examine the influence of preparation method on mortality.

As outlined in reference #65, nutrients

in nuts, such as unsaturated fatty acids, high-quality protein, fiber, vitamins (e.g., folate, niacin,

and vitamin E), minerals (e.g., potassium, calcium, and magnesium), and phytochemicals (e.g., carotenoids, flavonoids, and phytosterols), may confer cardioprotective, anticarcinogenic, antiinflammatory, and antioxidant properties. Indeed, clinical trials have shown that nut consumption has beneficial effects on some intermediate markers of chronic diseases, such as high cholesterol levels, oxidation, endothelial dysfunction, hyperglycemia, and insulin resistance.

Reference #70 evaluated the effect of an almond-enriched (high monounsaturated fat, MUFA) or complex carbohydrate-enriched (high carbohydrate) formula-based low-calorie diet (LCD) on anthropometric, body composition and metabolic parameters in a weight reduction program. Ketone levels increased only in the almond-LCD group (+260 vs 0%, $P<0.02$).

Glucose, insulin, diastolic blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and LDL-C to HDL-C ratio decreased significantly to a similar extent in “both” dietary interventions. Homeostasis model analysis of insulin resistance (HOMAIR) decreased in “both” study groups over time.

RED WINE

Reference #93: this study was not placebo- controlled.

Reference #94: The main findings of this study are that red wine rich in polyphenols with or without alcohol (red wine and dealcoholized red wine interventions) but not gin, an alcoholic beverage devoid of polyphenols, improved glucose metabolism, as measured by HOMA-IR.

OLIVE OIL

Reference #118 found a dose-response effect, whereby the highest quartile of olive oil intake showed the greatest reduction in risk (reducing mortality risk by 44%). Please stress that the authors of reference #118 were able to analyze the effect of virgin and ordinary olive oil separately, although they did not observe any difference in their association with overall mortality.

Olive oil and decreased risk of certain cancers, in particular breast cancer (Curr Pharm

Des 2011;17:805–12).

Mediterranean diet and primary prevention of CVD: please mention and discuss the article by Ramón Estruch et al (NEJM April 4, 2013)