enhancing the growth of altered cholangiocytes and leading to increased CCa susceptibility [8,9].

These case reports suggest a need for prospective follow-up of patients with *MDR3* mutations, in order to identify the CCa risk. It would probably also be interesting to look for an *MDR3* mutation in young patients with CCa, especially if there exists a familial history of CCa or biliary disease.

Conflict of interest

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The optimal dose of omega-3 supplementation for non-alcoholic fatty liver disease

To the Editor:
Non-alcoholic fatty liver disease (NAFLD) is a burgeoning health problem that affects one-third of adults and an increasing number of children in developed countries [1]. It was previously reported that various therapeutic regimens can be adopted for NAFLD [2], including weight loss agents, bariatric surgery, insulin-sensitizing agents, lipid-lowering agents, antioxidants, and other novel compounds. However, there is no consensus on its treatment. Both lifestyle therapy and pharmacotherapy have limitations due to poor compliance and side effects. Therefore, new therapeutic approaches to managing NAFLD are urgently needed.

We read with interest the study by Parker *et al.* [3]. This is the first meta-analysis to investigate the effect of omega-3 polyunsaturated fatty acid (PUFA) on liver fat in humans. The authors found that omega-3 PUFA could decrease liver fat and that benefits were seen with a consumption of >0.83 g/day. The results are instructive for the therapeutic regimen of NAFLD; however, we have some concerns over the optimal dose mentioned in the article.

Given the complications of NAFLD, especially cardiovascular disease (CVD), the optimal dose of omega-3 PUFA should be much higher than 0.83 g/day. Targher *et al.* revealed a strong association between NAFLD and CVD risk by reviewing accumulating clinical evidence [4]. Previous evidence suggests that CVD dictates the outcome in patients with NAFLD more frequently and to a greater extent than does the progression of liver disease, and CVD is the most important cause of death in NAFLD patients [5]. On the other hand, many investigators have demonstrated that omega-3 PUFA could prevent CVD [6]. In a large-scale intervention trial of secondary prevention after myocardial infarction, GISSI-Prevenzione investigators identified a substantial reduction in all-cause and cardiovascular mortality with 1 g per day of n-3 PUFA supplementation [7]. In addition, McKenney *et al.* recommend n-3 PUFA supplementation at a dose of 2–4 g per day to patients with high triglyceride concentrations [8]. At present, Saravanan *et al.* found that omega-3 PUFA could act as beneficial pleiotropic agents to prevent CVD, by conducting a review of numerous clinical trials [9]. As fish is rich in omega-3 PUFA, the

Table 1. Risk of side effects from ingestion of omega-3 PUFA [6].

	Gastrointestinal upset	Clinical bleeding	Fishy aftertaste	Worsening glycemia[a]	Rise in LDL-C[b]
Up to 1 g/d	Very low	Very low	Low	Very low	Very low
1 to 3 g/d	Moderate	Very low	Moderate	Low	Moderate
>3 g/d	Moderate	Low	Likely	Moderate	Likely

LDL-C, low density lipoprotein–cholesterol.
[a]Usually only in patients with impaired glucose tolerance and diabetes.
[b]Usually only in patients with hypertriglyceridemia.

American Heart Association recommends at least two fish meals per week to healthy people, and a supplemental therapy with 1 g of omega-3 PUFA per day to those with myocardial infarction [6]. Omega-3 PUFA may treat NAFLD and CVD simultaneously, killing two birds with one stone [10].

In this review, the average dose of omega-3 PUFA was 4 g/day (range: 0.8–13.7 g/day), and the authors found no reports of adverse effects of omega-3 PUFA supplementation in the studies reviewed. We should be cautious about this conclusion, because side effects of omega-3 PUFA supplementation do exist (Table 1).

We agree to adopt therapeutic regimen for NAFLD. However, we sincerely hope that the researchers take the CVD risk and the side effects of omega-3 PUFA in NAFLD into account when they determine the optimal dose of omega-3 PUFA. Because omega-3 PUFA could treat NAFLD and CVD, it is promising to consider that the optimal dose of omega-3 PUFA could be applied for NAFLD associated risk of CVD. Of course, the hypothesis needs to be validated by well-designed randomized controlled trials.

Conflict of interest

The authors declared that they do not have anything to disclose regarding conflict of interest with respect to this letter.

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Reply to: "The optimal dose of omega-3 supplementation for non-alcoholic fatty liver disease"

To the Editor:

We read with interest the letter by Drs. Li and Chen regarding our systematic review and meta-analysis of omega-3 supplementation in non-alcoholic fatty liver disease (NAFLD) [1]. We showed that, when compared with a control therapy, dietary omega-3 supplementation led to beneficial changes in liver fat in adults. On the basis of the pooled results of studies, which employed omega-3 supplementation of 0.83–13.7 g per day, we observed a statistically significant benefit on liver fat, which persisted even when only randomized controlled trials were examined.

Due to the strong association between NAFLD and cardiovascular disease (CVD), the importance of CVD to mortality in patients with NAFLD, and the benefit of omega-3 supplementation in CVD risk reduction, Li and Chen suggest that the optimal dose of omega-3 should be higher than 0.83 g per day. We point out that pooling of data by meta-analysis is a useful tool for objectively evaluating the consensus of a therapy such as omega-3 supplementation (*vs.* a suitable control). However, the heterogeneity and relative paucity of data entail that these results should not be used to inform clinical recommendations on issues such as optimal dosage in NAFLD Using the data from trials in cardiovascular disease of omega-3 supplementation to recommend a particular omega-3 dose for NAFLD would be an inference, not supported by the NAFLD data we have presented. As stated in our manuscript, more data from randomized controlled trials are required for this. While our meta-analysis substantiates the efficacy of omega-3 supplementation for modifying liver fat *per se*, the choice of dose in an individual with