independence between groups. For example, for weight (kg), we calculate an effect of −1.00 (95% CI: −7.82, 5.82), whereas Ghaedi et al. reported −1.00 (95% CI: −3.15, 1.15).

b) For treatment effects from Jönsson et al. (10), we were also unable to calculate the CIs from Ghaedi et al. Here we used a correlation of 0.8 within group and between the 2 conditions in the crossover study. For example, for weight (kg), we calculate an effect of −3.00 (95% CI: −6.53, 0.53), whereas Ghaedi et al. reported −3.00 (95% CI: −3.55, −2.45).

We ask that Ghaedi et al. address our questions and revise the meta-analyses accordingly.

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XC and SLD: reviewed the original article, recalculated effects, and noted discrepancies; and all authors: discussed the errors identified and how to present them, and read and approved the final manuscript.

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Abbreviations used: CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

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Reply to X Chen et al.

Dear Editor:

We thank Chen et al. for their interest in reading our work entitled "Effects of a Paleolithic Diet on Cardiovascular Disease Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." In that study (1), we evaluated the effects of a Paleolithic diet on cardiovascular disease risk factors using data from randomized controlled trials. However, Chen et al. raised some questions that must be addressed.

According to their classification regarding possible questions, we answer those questions in the same order accordingly:

1) Discrepancies in effect sizes reported:

a) In the study of Irish et al. (2), only the baseline data, but not after-intervention data, were reported in Table 1. Only the percentage change in the mean was reported in the Result section, meaning that this percentage cannot be used to calculate the SE. Therefore, data on C-reactive protein were extracted from Figure 5E in that article using Plot Digitizer (http://plotdigitizer.sourceforge.net/). This kind of figure-based estimation is a routine procedure to derive the means and their variations.

b) In all included studies in our meta-analysis, the unit of lipids was mmol/L except for the study of Masharani

et al. (3) and the unit conversion from mg/dL to mmol/L was performed for this study. Therefore, the correct unit of lipids is mmol/L, whereas unfortunately it has been reported in mg/dL for lipid markers. The effect size of −0.20 mmol/L for triglycerides is correct. However, the findings from reanalysis did not tangibly change from those reported in the article [weighted mean difference (WMD) = −0.22 mmol/L; 95% CI: −0.43, −0.02 mmol/L; $P = 0.031$ compared with WMD = −0.24 mmol/L; 95% CI: −0.46, −0.01 mmol/L; $P = 0.037$] (Figure 4B). We thank Chen et al. for their precise point.

c) As observed in Figure 4B, we used a mean difference of −0.14 for the study of Genoni et al. (4). In fact, the effect size of −0.41, which is seen in Table 1, was written by mistake. Unfortunately, this is a typing error in Table 1; however, the effect size used for the meta-analysis is right.

d) and e) It can be seen in Figure 2C (BMI) that we used an effect size of −1.8 from the study of Mellberg et al. (5) and −0.8 from the study of Boers et al. (6), but these were swapped by mistake (−0.8 for Mellberg et al.'s study and −1.8 for Boers et al.'s study in Table 1); unfortunately this is a typing error in Table 1. In fact the effect sizes reported in Figure 2C are right.

2) Selection of effect sizes included

a) and b) Stomby et al.'s article (7) is a substudy of the larger main study of Mellberg et al. (5), and therefore they have the same design. In these 2 studies, we extracted data on all outcomes from the first period only (6-mo period) and no data were extracted from the other intervention periods (12, 18, and 24 mo). We reported the whole follow-up period for the studies of Stomby et al. (7) and Mellberg et al. (5) (720 d) in Table 1. However, all outcomes were extracted over a 6-mo period in both articles. Maybe it would have been better had we reported the 6-mo intervention period for both studies in Table 1 to prevent misconceptions. Data on body weight were also extracted from Figure 2B for the 6-mo period (intervention group: baseline, 87 kg; end, 79.1 kg; control group: baseline, 86.8 kg; end, 83.8 kg).

c) Stomby et al.'s article (7) is a substudy of the larger main study of Mellberg et al. (5). Indeed, Stomby et al. (sample size = 49) replicated data from Mellberg et al.'s study (sample size = 61), and so we only included Mellberg et al.'s study in our meta-analysis. But because the data on body fat percentage had not been reported in this study, we only extracted the body fat data from Stomby et al.'s study, and the other outcomes were only extracted from the study of Mellberg et al. (the main study).

d) We sent an email to 2 authors of this study (B Ahrén and T Jönsson) and asked them to send us data on other outcomes, if possible. Finally, on 16 January, 2018, T Jönsson responded to our request and sent us the data on blood pressure and lipid profiles.

3) CIs that could not be reproduced

a) The reason for these differences is related to the correlation coefficient. In the study of Boers et al. (6), we did not use the assumed constant correlation coefficient (e.g., 0.5 and 0.8) to calculate the mean differences between end of study and baseline. If we can calculate the correlation coefficient from available data from studies included in the analyses, it is more accurate than the assumed constant correlation coefficient. Therefore, using the studies that reported mean ± SD values pre and post intervention and also change from baseline to endpoint for outcomes, we calculated the correlation coefficient via SD baseline (SD_E), SD final (SD_C), and SD change (SD_{diff}) by the following formula:

$$\text{corr} = \frac{SD_E^2 + SD_C^2 - SD_{\text{diff}}^2}{2 \times SD_E \times SD_C} \quad (1)$$

Finally, we estimated the SD for mean change from baseline to endpoint by averaging the calculated correlation coefficients.

b) In the study of Jönsson et al. (8), we did not use the assumed constant correlation coefficient (e.g., 0.5 and 0.8) to calculate the mean differences between end of study and baseline. In this study, mean ± SD values pre and post intervention for outcome measures were reported, and we could impute SD for the mean change from baseline to endpoint using the P value for means of outcomes in the intervention and control groups. To resolve the concerns in this regard, we performed reanalyses by using a constant correlation coefficient of 0.8, such that for the studies that did not report the changes from baseline to follow-up values, the correlation coefficient of 0.8 was used to compute the SDs for the mean change values. The findings from this reanalysis did not tangibly change from those reported previously.

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Update on the Acute Effects of Ketone Supplements in Athletes

Dear Editor:

We have read with interest the study entitled "Utility of ketone supplementation to enhance physical performance: a systematic review" (1), where Margolis and O'Fallon summarize the evidence on the potential ergogenic effects of ketone supplements and nicely discuss potential biological mechanisms. The authors conclude that there are discrepancies across studies in the effects of ketone supplements on exercise performance (1). Based on this heterogeneity, they conclude that there is currently insufficient evidence to support a recommendation of using ketone supplements for athletes. It must be noted, however, that the authors reviewed at the same time the effects of *chronic* (i.e., several weeks) and *acute* (i.e., before exertion) administration of ketone supplements on sports performance.

From the 3 studies (2–4) considered as "positive" for athletic performance by Margolis and O'Fallon, only the study by Cox et al. (3) actually reported a significant improvement in performance with acute ketone supplementation. The study by Waldman et al. (4) did not find an enhanced performance after acute ketone supplementation. Although these authors reported an increased fatigue index (i.e., a lower reduction of power output per unit of time) during the Wingate anaerobic test, no improvements were found for actual performance (as reflected by the lack of differences for peak and mean power output during the test) (4). In turn, the performance benefits reported by Poffé et al. (2) were found after 3 wk ketone supplementation, but no acute effects were observed. Therefore, acute ketone supplementation does not improve exercise performance, at least in efforts lasting ≤1 h. In fact, a recent meta-analysis by our group—including 13 studies in total—found that acute ketone supplementation exerts no effects on overall performance (Hedges' $g = -0.05$; 95% CI: −0.30 to 0.20; $P = 0.682$) (5). The lack of performance-enhancing effect was confirmed when analyzing separately endurance time-trial performance (Hedges' $g = -0.04$; 95% CI: −0.35 to 0.28; $P = 0.820$), the effects of ketone esters (Hedges' $g = -0.07$; 95% CI: −0.38 to 0.24; $P = 0.660$), or those of ketone salts (Hedges' $g = -0.02$; 95% CI = −0.45 to 0.41; $P = 0.928$). Of note, no heterogeneity was found for any of these results ($I^2 = 0\%$) (5). Except for the study by Cox et al., the rest of the available reports to date have found no benefits of acute ketone supplementation or even negative effects on athletic performance (6, 7).

Future studies should analyze the acute effects of ketone supplements on other types of exercise (e.g., ultra-endurance sports), and further research is warranted to confirm its potential benefits as a recovery drink or when consumed in the longer term—such as in the study by Poffé et al. (2). For the time being, there is insufficient evidence to recommend acute supplementation with ketone supplements in athletes.

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