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Letter to the Editor

Randomised trials on vitamin C

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Lykkesfeldt and Poulsen's review has a promising title, and in the introductory paragraph, they state that 'over the years, it has been suggested that vitamin C be used as a remedy against many diseases as different as common colds and cancers'[1]. Given their title and introduction, one would expect a discussion about randomised controlled trials (RCT) on vitamin C and the common cold. However, this topic is ignored in their review. This is an unfortunate omission because the common cold studies give interesting information on the issues that Lykkesfeldt and Poulsen discuss.

We have written a Cochrane review on vitamin C and the common cold[2]. We identified twenty-nine placebo-controlled comparisons on the effect of regular vitamin C supplementation on common cold incidence, twenty-nine comparisons on regular vitamin C and common cold duration and seven comparisons on therapeutic vitamin C and common cold duration. Most of the included trials were RCT, although that was not our inclusion criterion.

In our Cochrane review, we found significant heterogeneity in the effect of vitamin C on common cold incidence. In five RCT with participants under heavy acute physical stress – three of them with marathon runners – vitamin C halved the incidence of colds[2,3]. Lykkesfeldt and Poulsen suggest that RCT on vitamin C have been negative because the dietary vitamin C intake of participants has been high. However, there is no basis for assuming that the benefit of vitamin C for physically stressed participants is caused by low dietary vitamin C intake. In particular, Peters *et al.*[4,5] estimated that the marathon runners in their trial had a high level of dietary vitamin C intake, on average 0·5 g/d, yet 0·6 g/d vitamin C supplementation still reduced the incidence of colds. This refutes Lykkesfeldt and Poulsen's proposal that vitamin C cannot be beneficial if dietary vitamin C intake is high: 'we believe that it is imperative that enrolled subjects have hypovitaminosis C at study entry and that this condition is used as an entry-level inclusion criterion in order to ensure a possibility of effect' (p. 1256). Under some conditions, additional vitamin C may be beneficial even in the case of high dietary vitamin C intake.

Lykkesfeldt and Poulsen also state that 'it is striking that no study has used vitamin C deficiency as an inclusion criterion' (p. 1256), which is misleading. In this journal, I reported a systematic review on vitamin C and common cold incidence, which was restricted to trials carried out in the UK[6,7]. The rationale for including only UK trials was that several surveys in the 1970s and earlier had found a particularly low dietary vitamin C intake in the UK[6]. Thus, my restriction to the UK trials served as a surrogate for low dietary vitamin C intake. In one of the identified trials, the authors estimated that the average dietary vitamin C intake was 10–15 mg/d[5,8], in another trial, it was 50 mg/d[5,9], and in a third trial, the authors noted that the average intake in the UK was 44 mg/d, without estimating the intake of their own participants[10]. In four trials with UK males, vitamin C supplementation reduced common cold incidence by 30 % (rate ratio 0·70; 95 % CI 0·60–0·81), whereas in four trials with females, it had no effect (95 % CI 0·86–1·04)[6]. The strongest evidence for vitamin C and sex interaction was seen in the RCT by Baird *et al.*[9]. Low-dose vitamin C supplementation, 0·08 g/d, decreased the incidence of colds by 37 % in males but had no effect on females (test for vitamin C and sex interaction $P=0{\cdot}0001$[11]). Furthermore, Tyrrell *et al.*[12] found in a therapeutic RCT in the UK that vitamin C significantly reduced the number of recurrent colds in males but not in females, although the interaction was NS[5,6,11]. Thus, trials carried out in the UK in the 1970s and earlier are interesting for the question of whether vitamin C supplementation might be beneficial for people with rather low dietary vitamin C intake. The UK studies on the common cold suggest that there may be a vitamin C and sex interaction when dietary vitamin C intake is rather low.

Vitamin C has also reduced the duration of colds[2,5,13,14]. In regular supplementation trials, ≥0·2 g/d vitamin C shortened the mean duration of colds in adults by 8 % and in children by 13 %[2]. The largest RCT with adults was performed by Anderson *et al.*[5,15], and it found a 21 % decrease in the number of days confined indoors per episode ($P=0{\cdot}015$) with the dosage of 1 g/d each day and 3 g/d extra for 3 d when the participant caught the common cold. The largest RCT with children was by Ludvigsson *et al.*[16] who found a 14 % decrease per episode in absence from school because of the common cold by using 1 g/d ($P=0{\cdot}016$). The effect of vitamin C on the duration of colds is not restricted to people with low dietary vitamin C intake. Furthermore, there is

evidence suggesting dose dependency, so that higher-dose supplementation causes, on average, greater benefit[2,14]. These studies also refute Lykkesfeldt and Poulsen's proposal that vitamin C might be beneficial only if dietary vitamin C intake is low.

We have also written a Cochrane review on vitamin C and pneumonia[17,18]. We found three prophylactic trials, of which one was a RCT[19], and two therapeutic trials, of which one was a RCT[20]. In their prophylactic RCT, Pitt & Costrini[5,17,19] found that vitamin C significantly reduced the incidence of pneumonia in US Marine recruits during recruit training. The plasma vitamin C level of the recruits was high (56 μmol/l), and therefore low dietary vitamin C cannot explain the effect. Instead, the benefit of vitamin C may be explained by the high level of physical activity, the same explanation that was proposed for the group of five RCT in which vitamin C halved the common cold incidence[2,3]. Another prophylactic trial was carried out in the UK in the 1940s, and the particularly low dietary vitamin C intake, 10–15 mg/d, may explain the significant decrease in pneumonia incidence in schoolboys by low-dose vitamin C supplementation[5,8]. For practical reasons, the latter trial did not allocate participants by randomisation, but allocation to treatment groups was carried out by school 'divisions'. However, this is an unlikely explanation for the significant difference in the incidence of pneumonia[17].

In their therapeutic RCT with elderly hospitalised patients in the UK, Hunt *et al.*[20] found that 0·2 g/d of vitamin C significantly decreased the total respiratory clinical score in the most ill participants, but had no effect on the less ill participants[5,17]. One interesting difference between the most and less ill participants was at the plasma vitamin C levels, which were lower among the former (mean 20 *v.* 26 μmol/l). Thus, the benefit in this UK trial might be explained by the low vitamin C levels of the most ill participants, although low levels were not used as an inclusion criterion for the trial.

Thus, several RCT on vitamin C and respiratory infections have been published, and many of these are relevant to the questions considered by Lykkesfeldt and Poulsen. Furthermore, certain of these RCT were rather large, with over 600 participants[15,16,19], whereas 65 % (23/35) of the trials listed in Lykkesfeldt and Poulsen's Table 2 had less than 600 participants. Moreover, Lykkesfeldt and Poulsen's Table 2 contains trials that have no justification for inclusion. Chandra's 1992 trial[21] was shown to be fabricated several years ago[22,23]. In addition, several of the trials in Table 2 had low-dose vitamin C administered with a large number of other substances[1], including β-carotene, which increases mortality in some population groups[24]. Such trials are not relevant when considering the specific effects of vitamin C.

The PRISMA statement gives recommendations for the conduct of systematic reviews[25]. Transparency of reporting is very important. For example, the study and report characteristics of eligibility should be explicitly specified, all information sources should be described, and the number of studies screened and assessed for eligibility should be given. These recommendations were not followed by Lykkesfeldt and Poulsen. They excluded numerous RCT that seem to be relevant to their topic, whereas they included RCT that are definitely irrelevant. The rationale for their trial selection is ambiguous.

Finally, the title of Lykkesfeldt and Poulsen's paper emphasises RCT, whereas a large part of their text discusses cohort studies. Accordingly, the title and text are inconsistent. Dietary factors correlate strongly with each other and with numerous other lifestyle factors. Therefore, the correlations between dietary vitamin C intake and health outcomes can be explained by residual confounders[26,27]. The problem of residual confounders is the reason why the proponents of evidence-based medicine consider that conclusions about intervention effects should be based on controlled trials and not on cohort studies. In this respect, the title misleads the reader about the text that follows.

Harri Hemilä
Department of Public Health
University of Helsinki
PO Box 41
Helsinki FIN-00014
Finland
fax +358 9 191 27570
email harri.hemila@helsinki.fi

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