Nutrition Discussion Forum

Vitamin C intake and susceptibility to the common cold - Invited commentaries

Hemilä (1997) has carried out a literature review and a meta-analysis to determine whether there is convincing evidence that supplements of vitamin C can decrease human susceptibility to natural common cold infections. He concludes that although the evidence from six major studies gave no evidence of such benefit, for daily vitamin C supplements ≥1 g, the evidence from five other studies supported a hypothesis that British males may enjoy a significant benefit from vitamin C supplements. He therefore suggests that 'there are dose-dependent effects of vitamin C intake on health outcomes even in the absence of scurvy', and 'the potential effect of vitamin C intake on susceptibility to the common cold seems important as regards nutritional recommendations'. It seems to me, however, that there may be weaknesses in some of his arguments.

First, the data analysis focusing on British males involved selection from a much larger group, *a posteriori.* A small subset, selected from a much larger set, might exhibit some significantly atypical response patterns entirely by chance, and the justification for their selection in terms of possible reduced vitamin C intakes and status is not altogether convincing.

Second, the use of one-tailed *P* values because 'there is no theoretical or experimental reason to expect the vitamin C supplementation could increase the incidence of the common cold' seems statistically risky; most intervention trials employ the two-tailed test, which is more conservative. If the one-tailed test is used, then for consistency the upper limit of the 95 % confidence interval should be given an infinity.

Third, the argument (p. 62) that 'small studies with negative results may remain unpublished, while there is much less risk of publication bias in the case of large-scale studies' seems to have been applied less rigorously to the studies in Hemilä's Tables 2 and 3, than to those in Table 1. For two of the studies on male subjects listed in Table 2 the number of episodes observed were only 68 and 118, considerably less than the criterion of ≥200 episodes used for the analysis in Table 1. Publication bias is, of course, impossible to quantify, but I suspect that it may be a real problem for such meta-analysis studies.

Fourth, the intervention group in the study by Baird *et al.* (1979) was a mixture of two sub-groups, one of which received a synthetic drink with 80 mg vitamin C, and the other received natural orange juice containing 80 mg vitamin C plus flavonoids etc. By combining these two sub-groups in his analysis, Hemilä fails to recognize the possible non-vitamin C-related effects of orange juice. Of the two studies quoted from Clegg's laboratory, the first, by Charleston & Clegg (1972), was only briefly described; it did not employ a double-blind protocol, and the number of colds recorded by the male subjects in the placebo group seems surprisingly high. Over a 16-week period, seventeen of the thirty subjects recorded two or more colds, and three of the thirty recorded four colds (Clegg, 1974). The study by Clegg & Macdonald (1975) used L-ascorbic acid for only half of the 'Vitamin C' group in Hemilä's Table 2, and D-isoascorbic acid for the other half of this group. Nutritionally these are very different substances. In any case, this particular study yielded no evidence for benefit either from L-ascorbic acid, or from L-ascorbic acid plus D-isoascorbic acid. Hemilä himself clearly tended to discount the older 'poorly described'

study of Glazebrook & Thomson (1942) which lacked a placebo group, and which in any case failed to demonstrate a significant benefit for the males. Thus the evidence of any benefit for British male subjects rests almost entirely on the studies of Charleston & Clegg (1972) and of Baird *et al* (1979), neither of which seems a very reliable candidate for inclusion.

Fifth, as Hemilä has demonstrated in his opening paragraph, the mechanism, or mechanisms, whereby vitamin C might affect human susceptibility to common cold viruses remain speculative and poorly defined.

A more general question is: what is the minimum evidence upon which it would be reasonable to base a revised estimate of human vitamin C requirements, and do the accumulated data on susceptibility to the common cold meet these minimal criteria?

This problem is not, of course, confined solely to vitamin C. It seems reasonable to suggest that for most micronutrients there may be three theoretical zones of intake: zone (a), a low intake range associated with an unacceptably high risk of classical clinical or functional deficiency; zone (b), a wider range above this, associated with a low risk of overt deficiency, but with a gradually increasing level of protection against intermittent and subtle stresses; and finally zone (c), a higher range of intakes where some unwanted or toxic side effects may begin to outweigh any possible further benefits. Dietary recommendations (qv: National Research Council, 1989) or dietary reference values in the UK (Department of Health, 1991) have traditionally and perhaps necessarily focused on ensuring the avoidance of any risk of the overt deficiency which is associated with zone (a), usually plus an increment designed to ensure that most members of the population will attain a status typical of zone (b), but with no risk of encroaching into zone (c). If we then try to subdivide range (b) into segments with greater or lesser advantage: risk ratios, we often find that the data currently available are usually too weak and uncertain to permit such a calculation and that it is thus very difficult to measure the transition point (or range) between zones (b) and (c).

Each micronutrient undoubtedly needs to be considered on the merits of its individual evidence, coming mainly from human intervention studies. At one extreme, for example, it seems intuitively unlikely that niacin requirements will need to be increased to take account of the fact (Figge *et al.* 1988) that huge daily doses of nicotinic acid can have some beneficial pharmacological effects in atypical subjects with hyperlipidaemia. At the other extreme, it seems more than likely that human requirements for folate will need to take account of recent research on prevention of neural tube defects (Wald, 1993) and the reduction of hyperhomocysteinaemia (Boushey *et al.* 1995). Other vitamins, including vitamin C, remain intermediate and controversial with regard to the strength and interpretation of the available evidence. Vitamins E, K, and B_{12} probably also fall into this category. Vitamin E supplements have recently been reported to reduce the rate of non-fatal myocardial infarction in British subjects with established ischaemic heart disease (Stephens *et al.* 1996), but neither this evidence nor that from other recent studies on vitamin E can yet reliably define a specific daily vitamin E requirement unequivocally suitable for the entire population. Vitamin K research is also revealing new functions (Shearer, 1995), but these too probably cannot yet redefine human requirements. The elderly may need more than the current RDA (or RNI) of vitamin B_{12} (Van Goor *et al.* 1995), but how much more is required, and how many people would benefit?

Probably there will always be a need for dietary reference values, or RDA, that are based on the traditional model of the avoidance of overt clinical and functional deficiencies, partly because these are somewhat less difficult to choose and define and somewhat less difficult to measure than are the tenets of ‘optimum nutrition’. Ultimately,

however, a new goal may be to define the mean and population range of intakes for each nutrient, representing the transition between intake zones (b) and (c). Meta-analysis of the kind provided by Dr Hemilä may help us to achieve this objective, but at the present time I think we still have a long way to go!

C. J. BATES
MRC Dunn Nutrition Unit
Milton Road
Cambridge CB4 1XJ

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The review by Hemilä (1997) on vitamin C intake and susceptibility to the common cold, and the invited commentary by Bates (1997) raise some important principles on the adequacy of micronutrient intake in general and on vitamin C in particular. In essence, Hemilä's paper confirms what has been known for some time, that increased ascorbic acid intake has little effect on susceptibility to the common cold unless vitamin C intake is in the lower quartile of the reference range, when there may be a slight beneficial effect (Basu & Schorah, 1982). Because any effects are probably only meaningful in a limited group of people, and Bates successfully challenges even this by pointing out the weaknesses in the data supporting any role for vitamin C in the prevention of the common cold, it would probably be difficult to justify a recommendation for increased vitamin C intakes from this evidence alone. There is, however, much more evidence that ascorbic acid intakes above those that will prevent clinical scurvy do have an impact on the severity of cold symptoms (Basu & Schorah, 1982; Hemilä, 1992, 1994). There are also studies suggesting that more serious infections than the common cold may benefit from high ascorbate intakes (Hunt *et*

al 1994). These findings, together with the evidence for the potential role of antioxidants such as vitamin C in preventing free radical damage (Frei *et al.* 1989; Halliwell, 1994), provide considerable, although not conclusive, support for the idea that vitamin C intakes should be significantly higher than those preventing the development of clinical scurvy.

Studies in healthy individuals have indicated that intakes above 60 mg/d, with averages around 100 mg/d, will saturate metabolic processes and maximize vitamin C content in white cells (Kallner *et al.* 1979; Basu & Schorah, 1982; Newton *et al* 1983; Levine *et al.* 1996), and could, therefore, potentially maximize protection against diseases such as cancer, atherosclerosis and serious infections. Bates (1997) claims that, within the intake range for potential benefit, neither efficacy nor harm can be accurately gauged because there is insufficient evidence for either, in contrast to folate for the prevention of neural tube defects, where the evidence of benefit is overwhelming. Whilst I agree with regard to folate, I believe that Bates is being over-cautious in the case of ascorbic acid. If we were considering a range of beneficial intake reaching to over 500 mg/d then he would be right in urging caution because of the potential risk. However, the evidence suggests that adequate antioxidant effectiveness for ascorbate can be achieved by average increases in intake of about 50 mg/d. Here risk is minimal because with this increase in intake almost all the population (except those who choose to take supplements) would remain below 300 mg/d. Here there is no evidence of any adverse health effects of the vitamin (Diplock, 1995).

This does not mean that we should stop searching for possible harm. Indeed, perhaps the focus should now shift from the difficult studies which investigate whether small increases in intake of vitamin C are effective at maintaining health to those examining whether intakes of around 300 mg/d have any harmful effects. Such studies could be directed towards high risk groups, such as kidney-stone formers, women in early pregnancy, individuals with iron overload and haemolytic anaemia, and patients with gut problems, where there are some reported adverse effects of vitamin C (Basu & Schorah, 1982; Buettner & Jurkiewicz, 1996). Outcomes in these studies would need to assess indices capable of reflecting molecular and physiological changes, such as techniques for measuring DNA and lipid damage, and assessing early changes in organ function.

These studies would need large numbers and require careful monitoring, and would, therefore, be relatively expensive. However, as the current evidence suggests that a modestly increased intake of micronutrients could make some contribution to the prevention of chronic disease, there is the potential for cheap non-toxic prophylaxis. This makes it timely for some of the funding that supports 'genetic manipulation' research, which has yet to prove its cost-effectiveness in terms of health benefits, to be redirected towards solving the harm:benefit ratio generated by increasing intakes of certain micronutrients. Evidence is slowly accruing in favour of benefit, but harm is under-investigated. If evidence for absence of harm can be provided, recommendations for increased intake of vitamin C to average 100 mg/d could be made with confidence. We have been debating these issues for over 30 years. It is now time to put funding where our concerns are.

C. J. SCHORAH
Division of Clinical Sciences
The Old Medical School
University of Leeds
Leeds LS2 9JT

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Reply by Hemilä

Dr Bates makes five specific criticisms of my recent paper (Hemilä, 1997*a*) to which I shall respond separately:

1. When a person carries out twenty different subgroup analyses and finds that only one yields a statistically significant result ($P \leq 0{\cdot}05$), the finding must be interpreted very cautiously as it is likely to be caused by chance alone. However, to use the same logic to explain the *P* value in my Table 2 for the British male studies would imply that I had carried out some 1,000,000 kinds of selections of vitamin C studies and simply picked the best one. Such an explanation of the small *P* value is improbable in the extreme.

A highly significant difference in common cold incidence between vitamin C and placebo groups ($P = 0{\cdot}00003$) was also found in a meta-analysis of three randomized double-blind trials involving subjects under heavy acute physical stress (Hemilä, 1996*a*). Furthermore, a diet deficient in vitamin C increases the susceptibility of guinea pigs to infections, and in several controlled studies with human subjects vitamin C supplementation had effects on infections other than the common cold (Hemilä, 1997*b,c*). Thus the British male studies do not constitute an isolated group inconsistent with all other available data, but form one piece in a larger mosaic indicating that vitamin C influences the function of the immune system.

2. In examining the results of several studies on the same topic concurrently the direction of the effect being considered must be decided on, and one-tailed *P* values are thus appropriate (Rosenthal, 1978; Wolf, 1986). For example, if one study finds a decrease and another finds an increase in the same phenomenon, it makes no sense to compare the two

studies on the basis of two-tailed *P* values. If there are results pointing strongly in opposite directions there is obviously no wisdom in combining them formally or informally. Nevertheless, I am not aware of studies in which a significantly higher number of colds was observed in a group administered vitamin C.

In my paper I provided confidence intervals (CI) as a measure of precision and not as a test of the null hypothesis. One-tailed $P = 0{\cdot}05$ corresponds to two-tailed $P = 0{\cdot}10$, which itself corresponds to the 90 % CI with one limit at the null hypothesis level (Altman, 1991). While the 95 % CI is most commonly used and the 90 % CI is slightly narrower, the difference has no practical relevance in my tables.

3. In a long-lasting controversy, positive and negative findings are both newsworthy. For example, while Glazebrook & Thomson (1942), Walker *el al.* (1967), Carson *et al.* (1975), Elwood *et al.* (1976) and Tyrrell *et al.* (1977) all explicitly drew rather negative conclusions as to their findings on vitamin C and the common cold, the papers were nevertheless written and published.

The possible role of publication bias can be quantified by calculating the fail-safe *N,* which refers to the number of similar studies finding no difference which should remain unpublished with the effect of collectively reversing the conclusion that a statistically significant difference exists (Rosenthal, 1979; Light & Pillemer, 1984; Wolf, 1986). In the case of the four male studies in my Table 2, the fail-safe *n* is 31 unpublished studies finding no difference. Although this kind of measure is imprecise, publication bias seems not to be of major concern. Finally, it seems incomprehensible that publication bias would generate the substantial difference between the sexes.

4. There is only a slight difference between the two male groups of Baird *et al.* (1979) who were administered 80 mg vitamin C/d, and the difference is not in favour of orange juice. The number of cold episodes was ninety-one and ninety-three among the male subjects administered 80 mg/d in orange juice (*n* 62) and in synthetic drink (*n* 71) respectively, yielding $RR = 0{\cdot}89$ (95 % CI: 0·67, 1·19) in favour of the synthetic drink. Since the difference is small and statistically insignificant, it seems appropriate to combine the two groups who were administered the same vitamin C dose. The comparison between the synthetic drink containing 80 mg vitamin C/d and the synthetic drink lacking the vitamin yields $RR = 0{\cdot}59$ (95 % CI: 0·45, 0·77) for males, which is essentially the same as in my Table 2.

Bates claims that the incidence of colds was extraordinarily high in the study by Charleston & Clegg (1972), but the data in my Tables 1 and 2 contradict such a suggestion. The incidence rate was 6·2/year in the Charleston & Clegg (1972) male placebo group, but 11·2/year in the Baird *et al.* (1979) male placebo group and 7·2/year in the Elwood *et al.* (1976) female placebo group. The incidence was also higher in the large-scale trials by Ludvigsson *et al.* (1977) and Pitt & Costrini (1979).

Since there is evidence indicating that the effects of vitamin C on the immune system are based on its antioxidant role (Hemilä, 1992*a*, 1991*b*), the L- and D-isomers may both affect the immune system. In particular, Bissell *et al.* (1980) found similar suppression of viral replication in cell culture with L- and D-ascorbic acid. Accordingly, in the current state of knowledge it seems reasonable to combine the Clegg & Macdonald (1975) L- and D-isomer groups.

I do not discount the study by Glazebrook & Thomson (1942). As a form of sensitivity analysis I tested the effect of excluding their study as it is technically the most deficient among those in Table 2. However, the exclusion did not reduce the difference between the vitamin C and control groups, but made it greater. The Glazebrook & Thomson trial does have shortcomings but I see no reason to disregard it. The authors explicitly paid careful

attention to the comparability of the study groups. Neither does it seem likely that vitamin C added to food in a kitchen would generate a substantial placebo effect in the dining hall. Furthermore, they did find a statistically significant decrease in the number of colds in their vitamin C group ($P = 0{\cdot}048$; one-tailed χ^2-test).

Finally, Bates's commentary ignored the randomized double-blind trial by Tyrrell *et al.* (1977) which found a significant decrease in the number of men with recurrent colds when vitamin C was administered during their first cold episode ($P = 0{\cdot}018$; one-tailed χ^2-test).

5. Since what is biologically plausible depends upon the biological knowledge of the day, the understanding of a physiological mechanism usually is not crucial in drawing inferences on causal relationships in epidemiology. For example, the notion that smoking causes lung cancer was originally derived from observational epidemiological studies and the earliest conjectures on the biological mechanism were completely erroneous (Hennekens & Buring, 1987). Moreover, it took some five decades after the emergence of the first epidemiological findings before a direct aetiological link between smoking and lung cancer could be shown at the biochemical level (Denissenko *et al.* 1996).

Nevertheless, in my paper I explicitly cite studies reporting effects of vitamin C on the immune system and there are several other similar publications (Hemilä, 1997*b*). Bates' opinion that the mechanism whereby vitamin C might affect susceptibility to infections is merely speculative misses the point entirely.

The biochemical mechanism whereby vitamin C deficiency produces the pathological defects in scurvy is not well understood, and in particular the usual textbook reference to poor hydroxylation of collagen is a gross oversimplification, if valid at all (Englard & Seifter, 1986). However, I do not think it would be appropriate to describe the present understanding as purely speculative or to conclude that vitamin C has no effect on scurvy because the biochemistry has not yet been completely elucidated.

After his specific criticisms, Bates offered some general opinions on nutritional recommendations. He suggested that the effects of micronutrients should be considered primarily in the light of human intervention studies, a viewpoint which I heartily endorse. However, such an approach has not been applied in the official monographs on these issues.

In the British recommendations no mention is made of the vitamin C and common cold link (Department of Health, 1991) although more than sixty intervention studies have been published on the issue (Kleijnen *et al.* 1989). In fact, one of the studies cited in the UK recommendations reported that the geometric mean duration of colds was 6·4 days in vitamin C-deprived subjects and 3·3 days in non-deprived subjects, and the authors concluded that the absence of vitamin C tended to cause colds to last longer (Bartley *et al.* 1953). The brief comment on the vitamin C and plasma cholesterol relationship is based on one single uncontrolled study (Department of Health, 1991) although over thirty intervention studies have been published, eleven of which were placebo-controlled (Hemilä, 1992*b*).

The lack of thoroughness in reviewing the literature is not a problem restricted to the UK recommendations but is also apparent in the US recommendations (National Research Council, 1989). For example, the conclusion that vitamin C has no meaningful effect on the common cold is based on the reviews by Chalmers (1975) and by Dykes & Meier (1975). However, both reviews contain serious errors which should have been recognized by the authors of the monograph had they been familiar with the intervention study reports (Hemilä & Herman, 1995; Hemilä, 1996*b*). The conclusion that vitamin C has no effect on cholesterol metabolism is based on a single uncontrolled study (National Research Council,

1989) and no reference is given to the placebo-controlled trials, some of which reported a significant difference between the vitamin C and placebo groups (Hemilä, 1992&, 1993).

Because of the prominent political dimension of the nutritional recommendations there is evidently considerable incentive to oversimplify these complex issues and to be conservative as regards new findings. In the popular literature there are numerous, obviously false, claims about the benefits of vitamin C supplementation and such claims are utilized commercially; in this respect a conservative attitude in the nutritional recommendations is understandable. Nevertheless, such political concerns should not bias investigation of the actual scientific questions and provide no valid reason to ignore the intervention studies examining the effect of vitamin C on the common cold and on plasma cholesterol level, and a large number of intervention studies on other topics, some of which were reviewed by Basu & Schorah (1982). Furthermore, when a large number of studies have examined the same issue there is considerable risk that important points are not recognized easily, which underscores the importance of a systematic approach (Light & Pillemer, 1984; Wolf, 1986). However, in the case of vitamin C a systematic method of reviewing the literature was not applied (National Research Council, 1989; Department of Health, 1991).

As regards the safety of vitamin C supplementation, much speculation about potential harm has been advanced, but it has been shown to be unfounded (Rivers, 1987; Marks, 1989; Hemilä, 1994; Bendich & Langseth, 1995). Since none of the common cold studies (Hemilä 1992*a*) in which 1–3 g vitamin C/d was regularly administered to over 3000 subjects in all reported any meaningful difference in the occurrence of adverse symptoms between the vitamin and placebo groups, the safety of vitamin C in the 0·1–1 g/day range is no real concern. Obviously, argument for higher intakes cannot be based on safety alone, but must include sound evidence of benefit.

There are findings suggesting that in doses higher than those officially recommended, vitamin C may be beneficial for certain population groups as regards conditions other than scurvy. Nevertheless, we have no real understanding of who these subpopulations are, what the magnitude of the effect is, and what kind of dose would be best. If the subpopulations are small there is no point in recommending higher intakes for the general population. Table 1 of my paper indicates that the British male studies should not produce over-optimism as to the effect of vitamin C on the incidence of colds (Hemilä, 1997*a*). The effect of vitamin C on the symptoms of colds has usually been modest (Hemilä, 1992*a*). Nonetheless, the common cold is such a ubiquitous ailment that even quite a modest effect may be worth exploitation, and it is possible that there are effects on other conditions to be considered (Stone, 1972; Basu & Schorah, 1982; Hemilä, 1992*b*; Bielory & Gandhi, 1994; Bendich & Langseth, 1995; Hemilä, 1997*b,c*).

The possibility of publication bias and various technical shortcomings in the published studies should not discourage us from planning and carrying out carefully designed trials which address these questions more explicitly. The findings of such trials would provide a more solid scientific basis for further discussions about the appropriate intake levels.

H. HEMILÄ
Department of Public Health
University of Helsinki
Helsinki, Finland

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