Proponents of evidence-based medicine emphasize that conclusions about the effects of interventions should be based on controlled trials with clinically relevant outcomes, and not on studies measuring laboratory markers or on epidemiological studies. Studies with laboratory outcomes are often unreliable because the effects on surrogate outcomes (e.g. measurements of laboratory markers of the immune system) can substantially differ from the effects on clinically relevant outcomes. Epidemiological studies often measure clinically relevant outcomes, but unknown differences between the study groups could explain the observed differences in the outcome. Therefore, my work on vitamin C has focused on controlled trials with clinically relevant outcomes.

In our systematic review on vitamin C supplementation and the common cold (1), we combined the results of 24 trial comparisons involving 10,708 participants of the general community who had been administered prophylactically ≥0.2 g/day of vitamin C. The pooled risk ratio (RR) of colds, RR=0.97 (95% CI: 0.94 to 1.00), indicates that there is no evidence that regular vitamin C supplementation might reduce the risk of colds in the general community. However, five trials involving a total of 598 marathon runners, skiers, and soldiers on sub-arctic exercises yielded a pooled RR= 0.48 (0.35 to 0.64) for common cold incidence, indicating benefit for such people. Thus, there may be substantial heterogeneity in the effect of vitamin C supplementation, so that supplementation reduces the incidence of colds in people under heavy acute physical stress, but has no effect on the incidence of colds in the ordinary people.

29 comparisons examined the effect of prophylactic vitamin C on the duration of the common cold (9649 common cold episodes) (1). In adults, the duration of colds was reduced by 8% (3% to 12%), and in children by 13% (6% to 21%). The consistent effect of vitamin C supplementation on common cold duration suggests that therapeutic vitamin C might be useful for people who have caught the common cold. However, few trials have directly examined the therapeutic effect of vitamin C supplementation and their findings are not consistent.

In our systematic review on vitamin C supplementation and pneumonia (2), we identified three prophylactic trials which recorded 37 cases of pneumonia in 2,335 people. All three trials found significantly lower incidence of pneumonia in the vitamin C group. However, only one of the trials was a randomised, double-blind and placebo-controlled trial (RCT). Two of the trials examined military recruits and the third studied boys from "lower wage-earning classes" attending a boarding school in the UK during World War II. Thus, although the results of these trials suggest that vitamin C may affect susceptibility to pneumonia under some conditions, the findings should not be generalized for the general population. It does not seem reasonable to assume that vitamin C supplementation would reduce the incidence of pneumonia in the ordinary people in developed countries. In our systematic review, we also identified two therapeutic trials involving 197 pneumonia patients. One of the trials was an RCT; it studied elderly patients in the UK and found lower mortality and reduced respiratory symptom scores in the vitamin C group; however, the benefit was restricted to the most ill patients. The second therapeutic trial examined adults with a
wide age range in the former Soviet Union and found a dose-dependent reduction in the time to recovery with two vitamin C doses.

Although we cannot directly extrapolate the effects found in animal studies to humans, it is worth noting that vitamin C has prevented diverse viral and bacterial infections in animals (3). Thus, it is possible that the effect of vitamin C on humans is not restricted to the common cold and pneumonia.

A common feature of the discussions of the physiological effects of vitamins C and E has been the implicit assumption that their effects are similar in all people. If such an assumption was valid, it would allow extrapolation of any study findings widely, given that the trial is well conducted and so large that the results are accurate. However, the common cold studies suggest that the effect can depend on the kind of people and their living conditions (1). Furthermore, even stronger evidence of heterogeneity in the effect of vitamin E, another antioxidant, was recently shown (4). Among participants with a dietary vitamin C intake above the median of 90 mg/day, vitamin E supplementation increased mortality among those aged 50-62 years by 19%, whereas vitamin E decreased mortality among those aged 66-69 years by 41%. If the effects of vitamin C and E supplementation vary substantially between different subpopulations, the heterogeneity of the effect evidently means a need for careful consideration of goals when planning new trials on these vitamins. Assuming heterogeneity, further trials should try to identify and characterize the population groups or living conditions in which these vitamins might be beneficial, rather than re-examining the effects on ordinary Western people for whom the studies already available have not found any meaningful overall benefits from daily supplementation.

References
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Harri Hemilä
University of Helsinki
Finland
harri.hemila@helsinki.fi
http://www.mv.helsinki.fi/home/hemila
http://www.mv.helsinki.fi/home/hemila/vitc_colds.htm (Papers on vitamin C and the common cold)