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LETTER TO THE EDITOR

Vitamin C and sex differences in respiratory tract infections

In their systematic review of sex differences in respiratory tract infections (RTIs), Falagas et al. concluded that males develop RTIs more frequently than females, in particular lower RTIs, and the course of the infection is often more severe in males than in females.[1]

In 1997, I reported a meta-analysis of British trials on vitamin C and the common cold which gives a complementary viewpoint on sex differences in RTIs.[2] In four trials with males, vitamin C supplementation reduced common cold incidence by 30% (95% CI: −40% to −19%), but had no effect in four trials with females (estimate −5%; 95% CI: −14% to +4%). The divergence in the confidence intervals suggests different effects on males and females. Three studies reported data for both males and females and the largest of these, by Baird et al.,[3] found highly significant interaction between sex and vitamin C effect on common cold incidence (Table 1). The two smaller trials had wide confidence intervals that overlapped between males and females.[2] Furthermore, in four trials with British males, vitamin C reduced recurrent colds during the study period by 46% (−60% to −26%), but had no effect on females.[2] In particular, Tyrrell et al.[4] found that therapeutic vitamin C during the first cold episode reduced subsequent colds in males by 40% (−63% to −3%),[2] but not in females (−7%; −45% to +54%). The Baird et al.[3] and Tyrrell et al.[4] studies were randomised placebo-controlled double-blind trials and their findings cannot be dismissed on methodological grounds.

Because large-scale trials give no evidence that high-dose vitamin C supplementation ($\geqslant$1 g/day) decreases common cold incidence,[2] the findings with British males call for special explanations. Several surveys had reported low dietary vitamin C intake in the UK and thus the benefit of supplementation may be explained by treating marginal deficiency.[2] This explanation is consistent with the estimated low daily vitamin C intake in Baird's study, 50 mg/day, and the particularly low dosage of vitamin C supplementation, 80 mg/day.[3] Usually plasma and leucocyte vitamin C concentrations are lower in males than in females although it is not clear to what extent this is due to dietary and physiological differences between the sexes.[2] Concluding from the British studies,[2–4] it seems that sex differences in RTIs may be generated by variations in dietary vitamin C intakes, in addition to the factors mentioned by Falagas et al.[1]

Furthermore, in a recent Cochrane review we identified three prophylactic vitamin C trials and each of them reported an 80% or greater decrease in pneumonia incidence in the vitamin C group.[5] All these trials examined males only and the incidence of pneumonia was particularly high. The benefit of vitamin C supplementation seemed to be explained by marginal deficiency and by increased requirement caused by heavy exertion.[5]

It is obvious that the findings of the common cold trials with British males[2] and pneumonia trials with males[5] cannot be extrapolated to the general population of the western countries. Nevertheless, further vitamin C trials are warranted among males with low dietary vitamin C intake.

Table 1 Interaction between sex and the effect of vitamin C on common cold incidence in British students (Baird et al., 1979).[3]

	Vitamin C		Placebo		RR (95% CI)	Interaction *P*
	Participants	No. of colds	Participants	No. of colds		
Males	133	184	61	135	0.63 (0.50–0.78)	0.0001
Females	105	199	51	78	1.24 (0.95–1.61)	

These data are from Refs. 2 and 3. The statistical significance of interaction was calculated from the change in $-2 \times \log(\text{likelihood})$ when the interaction term was added to the model (STATA program Poisson).

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