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**Vitamin/mineral supplementation, cause-specific (cancer, cardiovascular disease) incidence and mortality, and total mortality in the EPIC-Heidelberg cohort study**

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In the EPIC-Heidelberg cohort, taking vitamin/mineral supplements is a common but rather unstable behavior. Our findings reveal that vitamin/mineral supplementation is a behavioral marker of a set of favorable health characteristics, such as higher educational level, lower BMI, and healthier diet. However, vitamin/mineral supplementation might also relate to several unfavorable factors, such as older age and pre-existing health conditions, particularly cancer.

Currently available evidence suggests no or very limited protective effects of any vitamin/mineral or multivitamin supplements on cancer and cardiovascular incidence and mortality. From the present study we draw the same conclusion. Although several significant inverse associations were observed among certain subgroups of the cohort, the small effect sizes and non-significant interaction terms suggest that these associations might be due to chance.

The present study suggests potential beneficial effects of antioxidant vitamin supplements on cancer mortality and all-cause mortality. However, it is notable that the number of antioxidant vitamin supplement users was limited. Although vitamin A, C, and E have similar antioxidant properties, it is still a limitation of the present study that their individual effects could not be evaluated.

The present study supports the previous finding that calcium supplements might increase MI risk. The next tasks may be to investigate if even a short-term calcium

supplementation could also substantially increase the MI risk and to understand the underlying mechanisms.

The present study observed a statistically significantly increased cancer mortality and all-cause mortality in baseline non-users who started taking supplements during follow-up, suggesting an “unhealthy-user effect,” which researchers should be cautious of in future observational studies.

There are a large number of challenges for a prospective cohort study to evaluate the effects of vitamin/mineral supplementation on cancer and CVD incidence and mortality in free-living populations, mainly because of the difficulties in accurate measurement of duration and dosage and complete elimination of residual bias. For this reason, a randomized placebo-controlled trial may be a better choice. Given that multivitamin supplements are the most readily available commercial preparation and are being widely used by adult populations, future clinical trials should address the efficacy of multivitamin supplements in primary prevention of chronic diseases so that an evidence-based recommendation can be made for the public.

Calcium supplements are widely recommended to elderly populations for promoting bone health. Recently, however, a safety concern over its potential adverse effect on MI risk has arisen. If calcium supplements indeed increase MI risk, it will be of interest for future studies to find out good companions for calcium supplements so that their combination can be used to reduce the risks of bone fracture without increasing the MI risk.

Overall, at the current stage, the most appropriate recommendation for adult populations in economically developed countries might be that one should increase intakes of vitamins and minerals through healthy diet, rather than from supplements. On the other hand, it needs to be noted that majority of the previous observational and interventional investigations were performed in affluent countries, where deficiencies of important vitamins and minerals are supposed to be rare. In future, more epidemiological studies, in

particular clinical trials, should evaluate the effects of vitamin/mineral supplements in countries where dietary intakes of vitamins and minerals are generally suboptimal.