



THE ASSOCIATION OF VITAMIN E SUPPLEMENTATION AND MORTALITY – FINALLY CONSISTENT RESULTS OF STATISTICAL ANALYSIS. RE: THE QUESTIONABLE ASSOCIATION OF VITAMIN E SUPPLEMENTATION AND MORTALITY – INCONSISTENT RESULTS OF DIFFERENT META-ANALYTIC APPROACHES

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Dear Sirs,

In a recently published paper we investigated the association of vitamin E supplementation and mortality [1]. We applied two distinct methodological meta-analytical approaches: the first one, using a classical meta-regression with random effects, modelling univariate effect measures by way of the study-specific mortality odds ratios. In the second one, we applied hierarchical logistic regression analyses, modelling the mortality risks in different treatment groups within a certain trial separately in a bivariate approach. We concluded that both methodological approaches yield inconsistent results. The hierarchical logistic regression approach showed an increased mortality risk of patients who received vitamin E in high dosage compared to a control group of patients not receiving vitamin E. In contrast, the classical approach shows that the increased mortality risk in certain trials was not due to a high dose of supplemented vitamin E. That could be explained by a higher proportion of male patients that were included in these trials. In this latter approach the study patients' sex distribution turned out to be a confounder that causally impacts mortality. As this confounder additionally is associated with the supplemented vitamin E doses, the impact of (high dose) vitamin E supplementation tends to over-estimated the data.

In this letter I would like to give important information concerning the findings reported

above. I performed further analyses of the same data source, using new available software tools that allowed to enhance the applied statistical methodology. Beyond main effects of predictive factors on mortality, interactions were investigated. In particular, an interaction of vitamin E dosage with the study patients' mean age as well as with the sex distribution proved to be significant. If the corresponding interaction terms are included in the newly established models, the corresponding results partly differ from those reported in [1]. These new results are consistent in that different methodological approaches coincide. The figures reported in the following table result from the application of hierarchical logistic regression. These data agree with those resulting from the classical meta-regression approach (not shown).

These data show that low doses of vitamin E are associated with a significantly decreased mortality risk in most populations, comparing vitamin E treated patients with the control group. If high doses of vitamin E are included, an increased mortality risk may actually exist. The odds ratio of vitamin E treated versus control patients increases along with decreasing mean age of study patients as well as along with a decreasing proportion of male patients. Thus the harmful effect of high dose vitamin E supplementation increases with decreasing baseline mortality risk of a population. The effect reaches statistical significance (OR=1.87 of high dose vitamin E versus control patients, $p=0.0411$) in an extreme "low risk population", i.e. a

relatively young population with a large proportion of females. Noteworthy this effect is established in multivariate statistical models providing adjustment for possible confounding

factors. These findings can not be explained by confounding effects and a causal harmful impact of high-dose vitamin E supplementation seems to exist.

Mean age	Proportion of male patients	Vitamin E <400IU/d vs. Control			Vitamin E \geq 400IU/d vs. Control		
		OR	95% CI	p-value	OR	95% CI	p-value
70 years	75%	0.98	0.93-1.04	0.5331	0.92	0.80-1.05	0.2207
70 years	25%	0.90	0.85-0.95	0.0010	1.22	1.02-1.46	0.0342
50 years	75%	0.95	0.92-0.98	0.0027	1.41	0.91-2.18	0.1157
50 years	25%	0.87	0.83-0.91	<.0001	1.87	1.00-3.39	0.0411

Yours sincerely,

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Abbreviations: **IU/d:** international units per day; **CI:** confidence interval; **OR:** odds ratio.

REFERENCES

1. Gerß, J., Köpcke, W., The questionable association of vitamin E supplementation and mortality – Inconsistent results of different meta-analytic approaches. *Cellular and Molecular Biology* 2009, **55** Suppl: OL1111-1120.