

Glucosamine and mortality: a note of caution

I read with interest the paper by Li *et al*¹ reporting the association of regular glucosamine use with lower mortality. The authors report significantly lower all-cause mortality HR 0.85 (95% CI 0.82 to 0.89), cardiovascular mortality HR 0.82 (95% CI 0.74 to 0.90), cancer mortality HR 0.94 (95% CI 0.88 to 0.99), respiratory mortality HR 0.73 (95% CI 0.66 to 0.81) and digestive mortality HR 0.74 (95% CI 0.62 to 0.90). The magnitude of the reported reduction in mortality is striking, as is the consistency across major disease categories. The results reported by the authors are consistent with other prior epidemiological studies looking at glucosamine and mortality.²⁻⁴

The biological plausibility for glucosamine having such pronounced causative effects on mortality, particularly across the entire spectrum of disease, is somewhat tenuous. The authors suggest inhibition of NF- κ B (nuclear factor-kappa B) thereby reducing inflammation and glucosamine triggering a mimic response of low carbohydrate diet in animal models as potential explanations.¹ While there is validity to these hypotheses it is difficult to envisage the translation of these pathways with such marked improvements in mortality.

We have seen such beneficial associations with mortality reported for other supplements previously, perhaps most notably with vitamin D. Later detailed analyses have revealed that these associations appear to be due to other factors including unmeasured confounders and reverse causation. In the current work the authors have attempted to correct for important potential confounding factors including deprivation, lifestyle behaviours and non-steroidal anti-inflammatory drug use. However, despite such efforts it is likely that residual unmeasured confounders remain when using observational data such as this. Whether these unmeasured factors are important determinants of outcomes may be difficult to ascertain. As an illustration of this point, we recently reported an analysis of broadband Internet access as a predictor of emergency medical admission rates.^{5,6} We chose broadband access for this purpose as an example of a clear non-causative association, yet despite controlling for other measures of deprivation, it remained a significant predictor of admission rates, almost certainly as a surrogate of other socioeconomic factors. Similarly, I suggest it is more likely that the association between mortality and glucosamine use reflects unmeasured underlying healthcare behaviours or other confounders. For example, those taking regular glucosamine supplements may be more likely to engage in a multitude of other beneficial health-related behaviours which have a cumulative effect on decreasing mortality.

Randomised controlled trials (RCTs) represent the ideal setting to clarify these issues. To my knowledge, previous RCTs of glucosamine have not suggested any evidence of a beneficial effect on mortality. One could argue that any such RCT would need to be so large and of such long duration as to be

unfeasible, however, given the magnitude of benefit of glucosamine suggested by the current report, this is not the case and a RCT to assess this degree of benefit should be manageable.

In conclusion, while it would be gratifying to believe that glucosamine could be a panacea for a longer life, the current data are more likely to reflect regular glucosamine use as a surrogate marker for other unmeasured factors.

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