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ANH FEATURE: Iowa Women's Health Study: Do supplements kill older women more quickly?

ANH exposes the deception that lies behind the latest anti-supplement study

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KEY POINTS

1. The research, published in the *Archives of Internal Medicine's Less is More* series, was based on self-reported questionnaires completed by older women over an approximately two decade period and data from registers of death
2. The findings are one element, linked to vitamin and mineral supplements, taken from the Iowa Women's Health Study that looked at numerous lifestyle factors which may affect risk of death from heart disease, cancer and other causes
3. The study generated negative headlines about supplements around the world, yet the negative findings are mainly contentious, were only evident following data adjustment (massage) and may be anomalous
4. The study shows the strongest associations for calcium, which appeared to reduce the risk of death, and iron, which appeared to increase the risk of death
5. The study actually finds that vitamin and mineral supplement usage is associated with healthier lifestyles and the authors fail to indicate the outcome of the combined effect of healthy lifestyles and supplement usage
6. The study is a good example of some of the problems that can result from scientific reductionism, which can then be used, with inadequate scientific basis, to dissuade the general public from using supplements that could be vital to their health and longevity
7. At the ANH, we don't believe the study offers any evidence that supplement usage may be dangerous - and we are aware of copious research, and decades of clinical experience, suggesting quite the opposite

A study published in the prestigious *Archives of Internal Medicine* on October 10 proposes that women over the age of 55 who take vitamin or mineral supplements may die sooner than their supplement-free counterparts. The authors of the paper, led by Finnish researcher Jaako Mursu PhD, set out to test their hypothesis that supplementation would not reduce the risk of death. However, they were only able to generate findings that concurred with their hypothesis by heavily massaging the data, and most of their findings run contrary to previous and higher quality research findings.

"Promoting natural and sustainable healthcare through the use of good science and good law"

The data used in the study were derived from three self-reporting questionnaire surveys starting in 1986 and running over a period of 22 years through to 2008. The starting population of subjects was 38,772 Iowa (USA) women from rural and non-rural settings. Two subsequent surveys of the same cohort were conducted in 1997 and 2004, and, while in all three surveys supplement use was queried, food intake was not queried in the 1997 survey (reasons for this were not given by the authors). Women taking part in the study had to be between 55 and 69 years of age (their average age was 62).

In reading the paper, it is apparent that the authors found that supplement use was often associated with more healthy lifestyle indicators, such as lower body mass index (BMI), lower hip/waist ratio, higher vegetable intake and more exercise. This association has been reported previously by other researchers, and it's interesting that very few commentaries about the study in mainstream media have made any mention of this.

Data message

In Dr Mursu et al's study, it was only when some of the available confounding factors had been 'adjusted' out that a few trends for particular vitamins and minerals, hinting at possible increased risk of death, became apparent. In the firing line were vitamins like B6 and folic acid, as well as the minerals iron and copper.

The key question is: do the adjustments adequately account for the rash of confounding factors, some of which were not even considered by the authors? In other words, are the statistical findings biologically meaningful? And are the conclusions drawn by the authors really warranted? At the ANH, we think not, but more on this below.

Key factors not accounted for by the authors include:

- Drug intake and adverse reactions or interactions (the single factor most likely to be associated with risk of death)
- Nutrient status of the subjects (e.g. as derived by blood and urine tests)
- Duration of supplementation prior to the initial baseline in 1986
- Form of supplemental vitamin or mineral taken
- Other ingredients taken as supplements (such as essential fatty acids, botanicals and amino acids)
- The possibility that increased use of supplements may have been related to perceived or diagnosed ill health, and
- Whether sub-clinical signs of chronic disease, such as cancer or heart disease, could have already been present in some subjects at the start of the study, over which supplementation would have had little or no effect

Note: On top of this, let's not forget that the food questionnaire was not completed in the intermediate survey (1997), vitamin and mineral intake in food being critical because the nutrients studied are delivered both in conventional foods and in supplements.

While the study has generated negative headlines about vitamin and mineral use by older women around the world, the authors, in their final comment on the study, did indicate possible factors that could have compromised their findings, stating, "*We cannot exclude the possibility that some supplements were taken for reasonable cause in response to symptoms or clinical disease. We did not have data regarding nutritional status or detailed information of supplements used.*" But, having been able to support their null hypothesis, the authors appear to have had little interest in looking any further at their study's profound inadequacies.

Perusing the adjusted data closely, this is what we found: For the 15 vitamin or mineral categories studied in each of their three follow-up periods (1986-1996, 1997-2003 and 2004-2008), the mean hazard ratio (HR) for 20 out of 45 of the categories was less than 1. This

may suggest that for 20 categories there would be a lower risk of death among supplement users as compared with non-users, while in 25 categories, the risks would be greater the other way around. But such conclusions can't be drawn because of the variance (spread) of data. Here we must look at the confidence limits, and these were never, in each category, consistently either above or below 1. The exceptions were in calcium, where the HR was always less than 1, and in iron, where it was always greater than 1.

Therefore, in order to take anything away from the analysis of adjusted data, we need to take a closer look only at these two ingredients, calcium and iron. When we do this, warnings immediately start being flagged, given that other studies - supported by plausible mechanisms - suggest that very high intakes of simple calcium supplements, especially in the absence of vitamin D, may increase risk of heart attack and therefore death. Conversely, iron supplements have been shown to be beneficial for pre-menopausal women or those prone to anaemia. However, the possibility of an adverse effect of high intakes of particular forms of iron supplement on older women cannot be ruled out, as there are insufficient data available.

What do the data look like before adjustment?

It must be born in mind that this is an observational study where lifestyle factors, which are known to have a far greater influence on survival outcome than typical vitamin and mineral supplementation, have been 'adjusted out'. Before this data massage process has occurred, the findings are quite different, and appear to have been largely ignored by a mass media ever keen to find ways of damning supplements to appease their pharmaceutical industry advertisers.

So here you have it; this is what the study actually found before the data were adjusted...

Supplement users were significantly (statistically) more likely than non-users to:

- Be non-smokers
- Be more educated (graduates)
- Have lower risk of diabetes mellitus
- Have a lower body mass index (BMI)
- Have a lower mean hip-to-waist ratio
- Be more physically active
- Ingest fewer calories
- Consume more protein
- Consume less total fat
- Consume more polyunsaturated fatty acids
- Consume more fruit
- Consume more vegetables
- Consume more whole grain products

Frustratingly, the authors don't tell us how these supplement users fared over the years. However, we can assume it's quite likely that they did rather better than the non-users, and that's why the researchers have left us only with adjusted data that's meant to have removed the influence of these all-important lifestyle factors. For those of us more interested in integrated, whole-body, and functional models of medicine, this is of course nonsensical. We are actually more interested in trying to evaluate what combinations of factors deliver the best outcomes, be they best lifestyle practices combined with the best dietary and supplemental practices.

The bottom line

This study is a classic example of scientific reductionism being used to fulfil a particular need. In this case, it's supplement bashing, a well-known preoccupation of Big Pharma — and an approach that appears to be central to the protection of Big Pharma's profit margins.

Our view is that the self-reporting questionnaires, and lack of any supporting data on nutrient status of the study's subjects, means that the majority of the trends emerging from the adjusted data on which the study's conclusions were based are likely to be anomalous. This is especially the case given that the most powerful trend, the apparent benefit of calcium supplements, contradicts other findings from much more robust studies.

Another very important point is that many factors were not controlled for, and these likely contributed to uncontrolled sources of variation and confounding that were simply ignored. Among these is the crucial issue of the forms of nutrients taken, none of which were recorded in questionnaires. For example, there are several studies that suggest that long-term use of high doses of synthetic vitamin E, beta-carotene and folic acid may increase the risk of death, these generally having at least some plausible mechanisms. But, where the natural forms are consumed, especially where these nutrients are obtained from dietary sources, quite the reverse is found.

The lack of any clear dose/response trends suggests that high levels of variance and statistical noise have played havoc with the data, and the authors have mistakenly assumed that statistical significance of results should be interpreted as implying biological significance. Worse than this, the authors, by massaging the data in a weak observational study, have tried to attribute the trends they claim to have found as establishing cause and effect. This is, put simply, just bad science, especially when it's so obvious how the findings will be used by the media. At the time of writing, just two days after the study was published, 299 links to media claiming harmful effects of vitamins could be found on Google news.

A very clear example that should ring alarm bells for any scientist, practitioner or doctor reading the study is that in the case of vitamins, such as vitamin D, where there is overwhelming evidence of benefit, no positive findings emerged. But no, the authors could quietly ignore the huge tranche of empirical and published evidence that abounds, and publish their findings in the knowledge that they had satisfied their null hypothesis. In doing so, they have knowingly, or unknowingly, played into the hands of the pharmaceutical industry, the single biggest contributor to, and controller of, medical research.

Perhaps most damaging in the longer term is that the study's results provide further ammunition for regulators to clamp down even harder on consumer access to efficacious supplements — interfering with their ability to manage their own health. As we have seen many times in the past, legislators — most notably the European Commission, as well as the German, Danish and Finnish governments (note that Dr Mursu hails from Finland) — are only too keen to refer to this kind of evidence when developing needlessly restrictive laws on food supplements. In the EU, we've already seen many vitamin and mineral forms rendered illegal because companies have not been able to afford to compile dossiers justifying their safety. Harmonisation of vitamin and mineral maximum (and minimum) levels across all 27 EU Member States is now imminent. Regulators have taken it upon themselves to engage in a particular, and we argue, flawed approach to risk analysis that seeks to remove any risk to the consumer. The unfortunate reality is that — in the process assuming no changes to the European Commission's approach — regulators will also prevent large sectors of the public from consuming amounts of vitamins and minerals that are known both to be beneficial and that millions have consumed safely over many decades.

Our advice

Our advice is simple: Don't let this study influence your decisions about supplementation. We have always upheld that high doses of particular synthetic vitamins, notably synthetic vitamin E (alpha-tocopherol), beta-carotene and folic acid (pteroylmonoglutamic acid) may pose some risk to health in some individuals. But to avoid these risks, simply make sure you supplement with the right forms, at least of these vitamins, such as mixed tocopherols (and tocotrienols) in the case of vitamin E, mixed natural carotenoids in the case of beta-carotene and natural folate (including the 5-methyltetrahydrofolate form) in the case of folic acid.

And remember to maintain that healthy lifestyle: don't smoke, get plenty of sleep, manage your stress, eat lots of fruit and especially vegetables, drink plenty of clean, unadulterated water — and exercise regularly. Oh, and don't forget to supplement, as contrary to what most health authorities try to tell us, it's increasingly difficult to get enough nutrients from our food alone to keep us in optimum health.

But don't bother telling Dr Mursu and colleagues about this — they've closed their minds and shackled themselves firmly to the doctrine of scientific reductionism, which has failed so abysmally to deal with the ever-increasing chronic disease burden. Those who are the forefront of solution-based healthcare, whether they are members of the public or health professionals, have already turned their back on this type of reductionism, realising that, on its own, it leads nowhere other than to a dead end.