Vitamins and Mortality: An Interview With Jaakko Mursu

Linda Brookes, MSc; Jaakko Mursu, PhD

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An Expert Interview With Jaakko Mursu, PhD

The Study

Jaakko Mursu, PhD, is the lead author of the following study:

Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2011;171:1625-1633.

About the Interviewee

Jaakko Mursu, PhD, is a nutritional epidemiologist affiliated with the University of Eastern Finland, Kuopio, and the School of Public Health, University of Minnesota, Minneapolis.

Background to the Interview

A recently published analysis of data from the Iowa Women's Health Study by Dr. Mursu and his colleagues concluded that in older women, several commonly used dietary vitamin and mineral supplements, including multivitamins, folic acid, iron, and copper, may be associated with increased total mortality risk.[1] They also found that, in contrast to the findings of many previous studies, calcium was associated with decreased risk.

Previously, researchers in the same group showed that the use of dietary supplements in the United States had increased markedly between 1986 and 2004.[2] The long-term health consequences of many of these supplements remained unknown. On the basis of the previous studies, researchers hypothesized that use of dietary supplements is not associated with a reduced rate of total mortality.

In a study supported by the National Cancer Institute, the Academy of Finland, the Finnish Cultural Foundation, and the Fulbright program, Dr. Mursu and his colleagues examined the association between vitamin and mineral supplements and mortality rate among 38,772 older women (99% white, average age 61.6 years) who provided information about diet and supplement use in 1986, 1997, and 2004 via questionnaires. Self-reported supplement use increased substantially between 1986 and 2004, with 62.7% of women reporting use of at least 1 supplement daily in 1986, 75.1% in 1997, and 85.1% in 2004. Through December 31, 2008, a total of 15,594 deaths (40.2%) were identified through the State Health Registry of Iowa and the National Death Index.

Dr. Mursu's group found that, consistent with their original hypothesis, the use of most dietary supplements was not associated with a reduced rate of total mortality. In contrast, in this multivariable-adjusted analysis, many supplements were associated with increased risk for total mortality compared with corresponding nonuse:

- multivitamins (hazard ratio [HR], 1.06 [95% confidence interval [CI], 1.02-1.10]; absolute risk increase [ARI], 2.4%)
- vitamin B_6 (HR, 1.10 [95% CI, 1.01-1.21]; ARI, 4.1%)
- folic acid (HR,1.15 [95% CI, 1.00-1.32]; ARI, 5.9%)

- iron (HR,1.10 [95% CI, 1.03-1.17]; ARI, 3.9%)
- magnesium (HR,1.08 [95% CI, 1.01-1.15]; ARI, 3.6%)
- zinc (HR,1.08 [95% CI, 1.01-1.15]; ARI, 3.0%)
- copper (HR,1.45 [95% CI, 1.20-1.75]; ARI, 18.0%)

Of note, use of calcium was consistently *inversely* related to total mortality rate (HR, 0.91 [95% CI, 0.88-0.94]; absolute risk reduction, 3.8%), in contrast to the findings of previous studies.[3-5] The findings for iron and calcium were replicated in separate analyses across shorter follow-up intervals (10, 6, and 4 years) starting in 1986, 1997, and 2004; during each interval, approximately 15% of the original participants died. A dose-response relationship was seen for supplemental iron, with significantly increased risk for mortality at progressively lower doses as women aged throughout the study. There was no dose-response relationship for calcium.

The researchers acknowledged that their findings did not exclude the possibility of benefits of supplements, such as improved quality of life, but they concluded that the study raised concern about their long-term safety. "Based on existing evidence, we see little justification for the general and widespread use of dietary supplements. We recommend that they be used with strong medically based cause, such as symptomatic nutrient deficiency disease," they concluded

In an invited commentary published with the study,[6] Goran Bjelakovic, MD, DMSc (University of Nis, Nis, Serbia), and Christian Gluud, MD, DMSc (Copenhagen University Hospital, Denmark), noted that its findings added to "the growing evidence demonstrating that certain antioxidant supplements, such as vitamin E, vitamin A, and beta-carotene, can be harmful," while highlighting the difference in the result with respect to calcium, "which may require further study." They also concluded that "We cannot recommend the use of vitamin and mineral supplements as a preventive measure, at least not in a well-nourished population," adding, "Those supplements do not replace or add to the benefits of eating fruits and vegetables and may cause unwanted health consequences."

Dr. Mursu spoke with Linda Brookes, MSc, for Medscape Cardiology, to discuss the implications of the study results for Medscape readers.

The Interview

Medscape: **How did you come to study the effects of supplementation in this population?**

Dr. Mursu: The main goal of our original study was to look at different dietary patterns. The part of the study about supplementation was supposed to be a small side project, but it turned out to be bigger. Previous findings for supplement use were so dramatic[2] that we wanted to study them further. Supplement use is very common, especially in the United States, so the aim of our study was to determine whether there was any justification for their use. Even though supplements are not necessarily very expensive, if you use them for years, then there should be some justification for their use, and studies as a whole do not seem to support that view or that use.

Medscape: How did your study of supplement use tie in with the study of the dietary patterns?

Dr. Mursu: One of the ideas that we had originallywas that nutritionists tend to believe that in cases where the diet is deficient in nutrients, supplementing with multivitamins or with some other vitamin product or supplement would be beneficial or provide some additional health benefit. The next step was to investigate whether the quality of the diet affects how the supplements affect individuals,

because that is the theory. Usually nutritionists, physicians, or health experts recommend supplements, or at least they feel that it would be the most logical scenario, where they could provide some benefits if the diet is not good. However, although this seemed to be a very sound theory to start with, there are hardly any studies based on it.

Medscape: Were the women in the Iowa Women's Health Study asked the reasons why they were taking vitamin and other supplements?

Dr. Mursu: That is a very good question. Actually, no, and that is one of the limitations of the study. It would have been very interesting to know that because, for example for supplemental iron, we do not know why the women in the study were using it. My feeling is that supplemental iron is most often used for a specific reason, usually for an underlying illness that causes anemia. However, we could not study this further, so that was a limitation of the study. I would like to study whether iron itself is toxic or otherwise harmful or whether it is just an indicator of underlying disease. Basically, there are 2 options for iron: It could be harmful, but we could not exclude the possibility that it could be just a marker of something else.

Medscape: In your study, the supplement users actually had a healthier lifestyle than the nonusers at baseline. So, they were unlikely to be taking supplements to make up for a deficiency in diet, but for prevention and treatment.

Dr. Mursu: That seems to be the case, and that has been noticed in other studies as well, so usually the supplement users are the ones who do not really need them. Usually, they have healthier lifestyles and they are not taking them to make up for a dietary deficiency.

In our study, among the supplement users, their diet was better, they were exercising more, they were less likely to be smokers, and they were better educated -- so, if you did not adjust for these factors, the findings would be that these supplements are beneficial. Taking these factors into account in the statistical models, then, is a crucial part of the study. I was surprised to see that, after adjustment for these factors, supplements seemed to be harmful. I remember early findings in the 1980s, when such factors were not always that carefully adjusted for or taken into account, the findings were a little more optimistic or positive. I have heard it suggested quite often that these women were sick in the first place, but that did not seem to be the case in our study.

Medscape: Was this finding that healthier women use more supplements different from other studies, then?

Dr. Mursu: No, actually it was not; it is very common. Usually the health-conscious people are the ones using supplements. The logic is a little twisted: The ones who might need them are the ones who do not even consider using them, and the ones who would need them the least are using them.

Medscape: So, you think that in this type of population, it is related to awareness of the negative effects of the menopause on, for example, cardiovascular risk?

Dr. Mursu: I think that is exactly the case. As you get older, if you know that cardiovascular disease runs in your family, then of course you try to prevent it from getting worse or from happening in the first place. I think that is one of the reasons people are using supplements.

One of the limitations of the study was that although we had some information about the health status of these women, it is still possible that some received a diagnosis at some point, and when they got sick they changed their behavior. However, when the study started, the health status for each participant was assessed extensively, and so we were able to include only women who were healthy at the start -- and our findings were the same. It is a problem that we do not have all the details of what happened during the study, so in some instances it could be a potential factor that we were not able to not address.

Medscape: Did quality of diet modify any effects of the supplements used?

Dr. Mursu: I have done the analysis and am writing the report on that, but the findings were the same. I was expecting that at least, on the basis of previous theories or hypotheses, supplements in people with a worse diet could provide some benefits, but that did not seem to be the case. So, despite the quality of the diet, the findings were the same. They rather contradict the theory that supplements would be beneficial in cases of deficient diets. We have to look at that further. In this study, even the worst diets were still good enough so that the women did not have any clinical deficiencies of nutrients or vitamins.

Medscape: This contradicts the previously widely held belief that taking vitamin and mineral supplements would be beneficial for health.

Dr. Mursu: When the Iowa Women's Health Study started in the 1980s, there was a good theory that antioxidants and supplements could be beneficial because they provide additional nutrients. However, most studies -- especially the clinical trials, which are more reliable -- have found that there is really no benefit. The majority of those studies reported no beneficial effects on risk for cardiovascular disease or cancer, and some found that some of the supplements could be harmful. So, most of our findings were in line with those of previous studies, basically providing further evidence that supplements are not very useful if you want to prevent cardiovascular disease or cancer.

Medscape: Except for the result for calcium. Most previous studies didn't support your finding of a beneficial effect of calcium on total mortality. In the main, they concluded that there is a small but significant elevated risk for cardiovascular disease associated with calcium supplementation.

Dr. Mursu: That was the only one. Calcium was very strongly associated with a healthy lifestyle, despite doing all we did, adjusting for the other factors. Two possibilities may explain this result. Calcium itself could be beneficial -- that is, it protects bones and various other functions in the human body. The other possibility, which cannot be excluded, is that calcium is just a marker. Not being able to exclude this is a limitation of a study like this, and that is the challenge. For a long time people, including experts, felt that calcium should be beneficial for bone health and that it is safe, but now even that setting has become more blurry. There have been a few meta-analyses of the effects of calcium, and now there have been some concerns about potential harmful effects regarding myocardial infarction. In some studies, it has been found to increase the risk for myocardial infarction.

Medscape: Your finding for calcium wasn't affected by whether it was used with vitamin D or not? Some studies have suggested that this combination might have a beneficial effect on mortality.[7-9]

Dr. Mursu: We would have liked to study whether combining calcium with vitamin D produced different findings, but in 1986, hardly anyone used that combination.

Medscape: From the hazard ratios for the supplements you studied, some of the increases in risk seemed quite small.

Dr. Mursu: Yes. We studied 15 different supplements, and out of those, 7 were associated with increased risk for mortality -- but, as you said, the risk increase was relatively small. That is one of the reasons we have tried to tone down the message that supplements are not providing any benefit. Some of the headlines in the newspapers went too far in describing the risks. There is a potential for harm, but supplements are not killing you. In most cases, the risk increase was between 6% and 10%. So, it is not a dramatic increase. And you have to remember, this is relative risk. The absolute risk takes into account how common these diseases were, and those numbers were even smaller. So for example, for a multivitamin, the relative increase in risk was 6%, but the absolute risk was 2.4%. I would put more emphasis on his number as the more reliable estimate.

Medscape: From your study, could you exclude the possibility that dietary supplements could still be beneficial?

Dr. Mursu: We cannot exclude the possibility that in some cases for some diseases, these supplements would be beneficial. The aim of our study was to take a broader look, but the main causes of mortality in this population are still cardiovascular disease and cancer. If supplements were beneficial, then you would have expected to see an effect with the simple approach that we used. They may be beneficial against some specific rare diseases, so that would not have a big impact at a population level. We cannot exclude that in some cases supplement use would be beneficial, but for the main causes of death, that does not seem to be the case.

The Finnish Vitamin D Trial (FIND)

Medscape: Supplementation with vitamin D has previously been shown to have a beneficial effect on mortality.[9-11] Such studies as the VITamin D and omegA-3 triaL (VITAL) trial in the United States are under way to investigate whether vitamin D supplementation reduces the risk for cardiovascular disease or cancer.

Dr. Mursu: Vitamin D could be an exception in that sense, but in our study, for some reason -- I do not know why -- we did not find any benefit for vitamin D. I know that from similar studies and even clinical trials, there is some evidence that it could help prevent cardiovascular disease, but as I said, it was an exception in our study.

However, the theory is that because vitamin D is formed with the help of the sun, the further north you go, the more likely you are to be lacking in vitamin D. In such countries as Finland, where there are long periods during which the sun is hardly visible above the horizon at all, most people could be vitamin D deficient. So at the University of Eastern Finland in Kuopio, we are just starting a large-scale trial, the Finnish Vitamin D Trial (FIND), to determine whether vitamin D supplementation helps in the primary prevention of cardiovascular and cancer -- because if it helps anywhere, Finland would be the place to study that.

Medscape: That will be a randomized clinical trial?

Dr. Mursu: FIND will be a large-scale clinical trial that will start recruiting participants in early 2012.[12] It will be conducted by the University of Eastern Finland in Kuopio and funded by the Academy of Finland, University of Eastern Finland, the Juho Vainio Foundation, and the Finnish Foundation for Cardiovascular Research. We need to recruit about 20,000 people, men older than 60 years and women older than 65 years, to tackle this issue. They will be randomized to 3 groups of daily supplementation with either 40 µg/day (1600 IU) or 80 µg/day (3200 IU) of vitamin D_3 or placebo. Adherence, use of nonstudy drugs or supplements, diet, development of endpoints, and cardiovascular disease and cancer risk factors will be assessed by questionnaires. We will collect blood samples to assess effect modification by baseline 25-hydroxyvitamin D, and for future studies of genetic and biochemical hypotheses. Event data will be obtained by record linkage from the national computerized hospitalization registry. Trials such as this are needed, despite the high costs, to reliably determine whether there is an effect or not. Otherwise, observational studies have too many limitations to provide definite proof about whether supplements are effective or not.

Medscape: How long should a trial like that last?

Dr. Mursu: Usually a minimum of 5 years, as in the FIND study. Ten years would be better. Of course, usually for studies like that, you have to recruit people who are a little older. It is a kind of mathematical fact that you need enough people who get sick during the study to see the effects; that is the reason why most of the studies are done with older people. The young tend to stay healthier despite what they do, so if they seem to be lacking in a number of nutrients, they still manage somehow to stay well, although they usually pay the price later in later life.

Medscape: Will you be returning to Finland to work on the FIND trial?

Dr. Mursu: I am going to help our group to launch the trial, and I am going to study this issue further. I will continue to work on whether the quality of the diet would affect the outcome. The plan is to go back and forth between Finland and the United States and continue this collaboration. The study we just published was a unique opportunity to study diet and vitamins.

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