Commentary: Vitamin supplement use and confounding by lifestyle

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The role of micronutrients in the development of chronic disease remains unclear. A number of observational studies have suggested a protective effect of various nutrients—e.g. folic acid and vitamin E with coronary heart disease, antioxidant vitamins, and cancer. However, recent reviews of the literature have described inconsistencies among studies and conflict between the results of observational research and clinical trials.1,2 One explanation for these discrepant findings is that results from observational studies of micronutrient intake and disease may be confounded by variables associated with a ‘healthy lifestyle’.3-6 As one review of supplement use and cancer put it, ‘[s]upplement use may be a behavioral marker for “healthy lifestyle”’.3-6 As one review of supplement use and cancer put it, ‘[s]upplement use may be a behavioral marker for “healthy lifestyle”’.3-6

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14 Ishihara J, Sobue T, Yamamoto S et al. Validity and reproducibility of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J Epidemiology 2003;13(Suppl.):S134–S147.

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major health-related behaviors may reduce this confounding effect, but completeness of adjustment can never be assured.\textsuperscript{1} The argument for confounding by lifestyle seems plausible—even in studies of total micronutrient intake, those with the highest intakes tend to be supplement users and numerous studies have shown that supplement use is associated with leading a healthier lifestyle. For example, research in Western populations has found that compared with non-users, supplement users tend to be older and leaner, have higher incomes and education, and are more likely to be female and Caucasian; in addition, they are less likely to smoke or drink heavily and generally consume healthier diets and exercise more than non-users.\textsuperscript{7–12}

Several recent studies have described supplement use in new populations and have expanded our understanding of supplement users (e.g. suggesting that supplement users tend to believe in a diet—cancer connection, are more likely to receive cancer-screening tests, take other medications for disease prevention, and have different underlying medical conditions than do non-users\textsuperscript{9,10,11}). The current article by Ishihara et al.\textsuperscript{14} is an interesting addition to the literature—it is one of the few conducted in an Asian population,\textsuperscript{15,16} and it reports associations for some factors that have not been widely studied, including several that are specific to a Japanese population. Of particular interest are the results suggesting that while supplement use in Japan tends to be associated with aspects of a Western lifestyle, the ‘... intakes of both energy and most nutrients were ... lower for users than non-users of dietary supplements after various factors were adjusted’. This contrasts with results in Western populations that suggest supplement users consume healthier diets than do non-users.\textsuperscript{8,11}

Adjusting for confounding by lifestyle is complicated, even with the information provided by studies such as the current one. For example, several studies suggest that those who take individual-vitamin supplements differ from those who take multivitamins or do not use supplements at all, and there may be differences between those who take one individual supplement versus another.\textsuperscript{9,17,18} Many researchers collect detailed data on supplement use as part of a comprehensive nutrition assessment. For example, the authors of the current study asked about ‘... general use of any vitamin supplements more than once a week, and use of specific supplements by five categories ... For each category, the brand names, frequency, and duration of use were asked.’ The authors also tried to ensure correct classification by ‘[re-categorizing supplements] using brand names according to the definition of dietary supplements in the Women’s Healthy Living Eating and Living Study’, and they validated this method in another study.\textsuperscript{19} Yet in their analyses, the authors considered only a binary ‘user versus non-user’ outcome, with users defined as anyone ‘... who used at least one category of dietary supplement one or more times a week for a year or more’. Results for ‘supplement users’ can obscure important differences, and when a comparison between high and low intake may be a comparison of those who take individual-vitamin supplements versus those who do not,\textsuperscript{20} this heterogeneity is important.

A factor related to supplement use (however ‘use’ is defined) may or may not be a confounder depending on what other variables are controlled in the model. The authors addressed this concern in their dietary-intake analyses (Table 2), stating ‘... the results [for the full multivariate models] did not change when adjustment was made only for biological factors (age and BMI)’. Their other results (Table 1) are derived from a model in which the variables are mutually adjusted (although the authors do not explain what this means, I assumed the results were from a multivariate model with all variables entered simultaneously). The authors do not say whether these findings would have changed upon using a different subset of the variables in the model. In describing their model selection, they state that they looked at 14 dietary behaviours in relation to supplement use, and ‘... included in the logistic model the only three variables as dietary habits associated with supplement use’. But they do not say how they decided what constituted an association. Their text hints that this decision was made by significance tests. In particular their Results section describes associations primarily as ‘statistically significant’ or not (presumably at the 0.05 level, although this is not stated). However, statistical significance says little about the magnitude or precision of an estimated association, and is especially misleading when its absence is misinterpreted as absence of an association. Absence of significance signifies only that the association was estimated too imprecisely to determine the direction with confidence, and often reflects more the limited size of the sample than the size of the association. This and numerous other problems with significance tests have led many methodologists and editors to actively discourage their use in favour of CI and related techniques.\textsuperscript{21–29} Table 1 presents CI for many associations, but the Results section suggests that the authors interpreted (and perhaps disregarded) certain associations based more on their ‘statistical significance’ than their magnitude or precision.

When a model selection strategy uses statistical significance as a criterion for including or excluding variables, it can lead to downwardly biased estimates for the coefficient standard errors (ref. 29, p. 402). In Table 1 we are only shown results from one final model, with little description of how the model was chosen or the sensitivity of the results to its specification; hence, in the present context we cannot know the severity of this bias. Nonetheless, based on methodological studies cited elsewhere (ref. 29, p. 402), I suspect that the results reported by Ishihara et al. are much less accurate (and less significant!) than their CI and P-values convey.

Finally, the authors give little detail on how their variables were measured, and they do not say whether the cutoff points used for the lifestyle variables reflect the categories used on the questionnaire or if they were chosen by some other criterion. For example, it is not clear how to use their finding that supplement use is associated with stress, when no detail is given on how they determined an individual’s stress level or what the categories ‘High’, ‘Medium’, and ‘Low’ represent. For other variables, the cutoff points reflect understandable quantities, but it is still not clear how they were chosen. (The authors do not say if these details are given in other papers based on these data, but they do give references for in-press articles that may have this information.)\textsuperscript{30,31} Poor category choices can obscure dose—response relations and leave unnecessary residual confounding (ref. 29, pp. 205–07). At a minimum, it would be helpful to know if their results were sensitive to their choice of categories.

Of course, the issues raised above apply to other studies of supplement use: many have employed a dichotomous supplement-use variable, and their results may have been
sensitive to how variables were measured, categorized, and modelled. The current study is valuable in providing results in a seldom-studied population of supplement users. As the authors point out, ‘[f]urther investigation should be done using available data on brand names, frequency, and duration of usage in our study’. Given the wealth of data the authors have collected, I will look forward to seeing future results.

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