

Author's response to reviews

Title: Dietary and other lifestyle correlates of serum folate concentrations in a healthy adult population in Crete, Greece: a cross-sectional study

Authors:

Christos Hatzis (kafatos@med.uoc.gr)
George K Bertias (gbert@med.uoc.gr)
Manolis Linardakis (linman@med.uoc.gr)
John M Scott (jscott@tcd.ie)
Anthony G Kafatos (kafatos@med.uoc.gr)

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Preventive Medicine & Nutrition Clinic,
University of Crete School of Medicine,
P.O. Box 1352, 71110
Heraklion, Greece

Hiromichi Kumagai, M.D.
Deputy-Editor-in-Chief,
Nutrition Journal

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Dear Dr. Kumagai,

Attached please find the revised version of the manuscript **MS: 1853228168825706** (“Dietary and other lifestyle correlates of serum folate concentrations in a healthy adult population in Crete, Greece: a cross-sectional study”), to be considered for publication in the Nutrition Journal. The manuscript has been amended according to the Reviewers’ comments, and a point-by-point response letter to the Reviewer’s comments is attached. The study (or any part of it) is not being considered for publication elsewhere, and all authors have read and approved the manuscript.

We look forward to hearing from you.

The Authors.

Point-by-point response to the Reviewers' comments:

1) Following the Reviewer's comment, we have repeated the statistical analyses presented in Tables 4-6, including both unadjusted and multivariate-adjusted values. More specifically, in **Table 4** an extra column has been added, presenting serum folate concentrations (geometric mean, 95% confidence interval) adjusted for: district of residence (urban, semi-urban, or rural), energy intake, and dietary intakes of the indicated nutrients in Table 5 (multivariate adjusted). Collinearity was assessed by calculation of variance inflation factors (VIF). Similarly, in **Table 5** correlation coefficients have been calculated controlling for age, gender, district of residence, body mass index, energy intake, and consumption of tobacco, coffee, and alcohol (multivariate adjusted). To adjust for possible effects of tobacco, alcohol, and coffee consumption in the associations between foods intake and serum folate status (**Table 6**), logistic regression was applied. Thus, the odds ratios for low folate status (serum concentration <1st quartile, age- and gender-specific) according to levels of foods intake (i.e. none, below, or above median consumption) has been calculated, adjusting for: district of residence, body mass index, energy intake, consumption of tobacco, coffee, and alcohol (multivariate adjusted).

The "Statistical analyses" paragraph in the "Methods" section has been rewritten to include the aforementioned changes. Also, parts of the "Results" referring to Tables 4-6 have been elaborated accordingly. The use of multivariate analysis is also emphasized in the "Discussion".

The "Abstract" has been amended to indicate that associations between tobacco or coffee consumption and serum folate were confounded by differences in nutrient intakes.

2) Footnote #3 applies to all dietary variables included in **Table 1**. This is now indicated by adding the footnote next to all dietary variables.

3) Indeed, although 75% of the study individuals consumed folate <400 µg/d, only 4.5% of them had suboptimal serum folate concentrations (≤ 7 nmol/l). Although our food database was up to date (ref. 11), this result may be due in part to methodological bias, as food intake was calculated from a single previous day, which on an individual basis is not accurate enough for quantitative assessment of vitamin intake. Such a discrepancy between serum folate

concentrations and dietary folate intake has been reported in several other surveys (e.g. refs 20, 23-25), including those where dietary folate intake was assessed by 3-day dietary records or food-frequency questionnaires, and is also explained by insufficient capturing of important sources of dietary folate. In addition, the use of vitamin supplements was not recorded in our survey (as already discussed), which may have resulted in underestimation of dietary folate intake. Finally, some researchers argue that total homocysteine is a more sensitive indicator of folate status than is serum (or erythrocyte) concentration of the vitamin (refs 20, 26). Yet, it was not in the aims of the present study to test this hypothesis. These lines of discussion have now been added in the manuscript (page 11, Discussion, paragraph 3). Citations have been renumbered accordingly.

- 4) The unit for dietary cholesterol intake presented in **Table 1** has been corrected to “mg/day”.