Sleep patterns, docosahexaenoic acid, and gestational length

Dear Sir:

It was with great interest that we read in the Journal the recent article by Cheruku et al (1), which indicated that the maternal plasma docosahexaenoic acid (DHA) concentration during pregnancy is positively correlated with a more mature neonatal sleep-state pattern. The study involved 17 women who were divided into 2 groups (high-DHA group, \( n = 10 \); low-DHA group, \( n = 7 \)) on the basis of the percentage of DHA in their plasma phospholipids. The sleep patterns of the infants in the 2 groups were analyzed by analysis of variance, and maternal age and education were tested as covariates and found to be nonconfounding. The authors suggest that “differences in the prenatal supply of LCPUFAs [long-chain polyunsaturated fatty acids], especially DHA, may modify brain phospholipids and affect neural function.” We agree that this is a plausible suggestion because DHA is very important for brain function (2), but at the same time we believe that increased gestational length may also be responsible for the findings of Cheruku et al, assuming that longer gestation will also lead to a more mature central nervous system.

We previously showed that the dietary intake of fish oil containing DHA and eicosapentaenoic acid by pregnant women can prolong gestation and increase birth weight (3). As expected in the study by Cheruku et al, it is evident from Table 1 of their article that the high-DHA group tended to have a longer gestation, to have infants with higher birth weights, and to have infants who were longer in length at birth. None of these variables were significantly different from those of the low-DHA group, but this was also to be expected because of the low number of subjects.

We therefore wondered whether the observed association between DHA and sleep patterns might, in part or even fully, be mediated through a prolonging effect of DHA on gestation. This contention can be easily tested by examining 2 associations: 1) whether sleep patterns correlate with length of gestation and 2) whether the association between DHA and sleep patterns is weakened, or even abolished, when length of gestation is adjusted for by including the variable as a covariate in the analysis of variance. A condition for making these analyses in an optimal way is that gestation length, an inherently imprecise variable, is assessed is therefore needed to enable full evaluation of the results.

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REFERENCES
TABLE 1

Correlations between docosahexaenoic acid (DHA) and sleep measures, gestational age (GA) and sleep measures, partial correlations of DHA and sleep measures with GA removed (DHA − GA), and partial correlations of GA and sleep measures with DHA removed (GA − DHA) on postnatal days 1 and 2.

<table>
<thead>
<tr>
<th>Sleep measures</th>
<th>AS-d1</th>
<th>AS/QS-d1</th>
<th>Ar/QS-d1</th>
<th>Ar/AS-d1</th>
<th>AS-d2</th>
<th>AS/QS-d2</th>
<th>Ar/QS-d2</th>
<th>W-d2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>0.491</td>
<td>0.572</td>
<td>0.515</td>
<td>0.407</td>
<td>0.678</td>
<td>0.736</td>
<td>0.392</td>
<td>−0.574</td>
</tr>
<tr>
<td>GA</td>
<td>−0.599</td>
<td>−0.598</td>
<td>−0.737</td>
<td>−0.694</td>
<td>−0.462</td>
<td>−0.807</td>
<td>−0.703</td>
<td>0.306</td>
</tr>
<tr>
<td>DHA − GA</td>
<td>0.071</td>
<td>0.227</td>
<td>0.099</td>
<td>−0.254</td>
<td>0.561</td>
<td>0.374</td>
<td>−0.237</td>
<td>−0.536</td>
</tr>
<tr>
<td>GA − DHA</td>
<td>−0.399</td>
<td>−0.307</td>
<td>−0.620</td>
<td>−0.654</td>
<td>0.056</td>
<td>−0.588</td>
<td>−0.660</td>
<td>−0.193</td>
</tr>
</tbody>
</table>

1 AS, active sleep; AS/QS, active sleep/quiet sleep; Ar/QS, arousals in quiet sleep; Ar/AS, arousals in active sleep; W, wake; d1, day 1; d2, day 2.
2 DHA − GA correlation on day 1 = −0.758; on day 2 the correlation = −0.723.
3 P < 0.05.

Correlations between DHA values (with the use of the ratio of the long-chain polyunsaturated fatty acids n−6 and n−3) in pregnancy and sleep measures on days 1 and 2 are shown in Table 1. In recalculating these correlations, we found, to our embarrassment, that we had failed to delete the data from 3 infants on day 2 because they lacked sufficient time in their cribs to give us reliable sleep measures. Therefore, the correlations in Table 1 are based on data from 17 infants on day 1 and from 14 infants on day 2. (Importantly, in our reanalysis without the data from the 3 infants who had insufficient crib time, we found no significant differences in the sleep measures or in the correlations. In fact, some of the correlations were even greater. Thus, our interpretation of the original data remains unaffected by our reanalysis.) We then obtained correlations between GA (determined by ultrasound in all but 2 cases) and the sleep measures. The first 2 rows of Table 1 list all of the significant correlations (P < 0.05) obtained with either DHA or GA. The third row lists the partial correlations of DHA and sleep measures with the linear effects of GA removed, and the fourth row lists the partial correlations of GA and sleep measures with the effects of DHA removed.

In our original article, we correlated 2 DHA measures—DHA and the ratio of the long-chain polyunsaturated fats n−6 and n−3, with the sleep measures. In our new analyses we ran both sets of correlations and found that the DHA correlations were redundant with the n−6:n−3 correlations. This was expected because the 2 measures had a correlation of −0.92. Because the DHA measure yielded no new information, the correlations with this measure are not included.

The partial correlations fell into 2 patterns. Two sleep states—active sleep and wake—remained correlated with DHA concentrations after the effects of GA were removed, whereas 2 measures of arousal—arousal in active sleep and in quiet sleep—and the ratio of active sleep to quiet sleep remained associated with GA after the association with DHA concentrations was removed. On day 1, the partial correlations of 2 sleep measures with both of the predictor variables (DHA and GA) were not significant. This finding indicates that DHA indirectly affects these sleep measures via an increase in GA.

These analyses suggest the existence of 2 independent pathways and 1 interdependent pathway that relate DHA and GA to sleep measures in infants. Further research is necessary to determine the validity and generality of these conclusions, particularly in light of the lack of effect of DHA supplementation on GA in the study of Olsen et al, in which the comparison of fish-oil supplementation was made with women who received no oil (1), and in other studies (3, 4).

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REFERENCES

Bioelectrical impedance analysis for predicting body composition: what about the external validity of new regression equations?

Dear Sir:

In a recent issue of the Journal, Sun et al (1) emphasized the importance of bioelectrical impedance analysis (BIA) for large-scale epidemiologic studies. In their well-designed and detailed investigation, the authors combined several methods to assess different body compartments in 1474 whites and 355 blacks. In a multistep procedure, they used these results to develop a model for predicting total body water and fat-free mass (FFM) from BIA resistance. First, total body fat was calculated by using body weight, body volume derived from hydrostatic weighing, total...
body water calculated with the deuterium dilution method, and total-body bone mineral content determined with dual-energy X-ray absorptiometry (DXA). Second, in a regression analysis, these data were used to develop preliminary equations for calculating FFM from BIA resistance. After cross-validation, final equations were derived that were fitted to FFM calculated from the multi-compartment model with a very high precision ($R^2 = 0.90$ for males and 0.83 for females).

We are well aware of the limitations of previous BIA prediction equations. In recent studies we showed that the widely used equations of Deurenberg et al (2) and Lukaski et al (3) produced large differences in calculations of FFM (4). These differences increased with increasing age and body mass index and were higher in females than in males.

Thus, because we were enthusiastic about having new and better equations for calculating total body water and FFM from BIA measures, we recalculated a data set obtained from 708 white Germans between 18 and 65 y of age (4). In a subsample of 89 subjects, we also calculated FFM from a DXA scan (QDR2000; Hologic Inc, Bedford, MA).

Our results were not very satisfying. FFM calculated according to the equation provided by Sun et al was $4.2 \pm 1.9$ kg ($\pm$ SD) higher than that calculated according to the equation of Deurenberg et al (2), $2.3 \pm 1.3$ kg higher than that calculated according to the equation of Lukaski et al (3), and $3.7 \pm 2.5$ kg higher than that measured by DXA (Figure 1). The overprediction by the equation of Sun et al relative to the DXA measures and other BIA equations was more pronounced in males than in females ($P < 0.001$) and increased with increasing age ($P < 0.001$) and body mass index ($P < 0.001$).

In conclusion, FFM calculated with the new prediction equation of Sun et al was substantially overestimated compared with FFM calculated with other prediction equations and with DXA. This overestimation was higher than the marginal overestimation of $\approx 0.3$ kg observed by Sun et al. What did we learn from our recalculations? The study by Sun et al took advantage of 3 factors: a large population, qualified equations confirmed by subsequent cross-validation, and gold standard methods. However, after applying their model in our study population, we found the external validity to be questionable. Are BIA prediction equations applicable in general or do we need to have different equations for different populations or devices?

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**Reply to U Trippo et al**

Dear Sir:

We appreciate the comments by Trippo et al regarding the application of the bioelectrical impedance analysis (BIA) equa-
tions from our article “Development of bioelectrical impedance analysis prediction equations for body composition with the use of a multicomponent model for use in epidemiologic surveys” (1). In their letter, the authors applied our sex-specific BIA equations for fat-free mass (FFM) to a sample of 89 Germans between 18 and 65 y of age. Trippo et al compared the estimated FFM from our equations with estimated FFM from the BIA prediction equations of Deurenberg et al (2) and of Lukaski et al (3) and with FFM measured with dual-energy X-ray absorptiometry (DXA) with a Hologic QDR2000 (Hologic Inc, Bedford, MA). Trippo et al concluded that our equations produced greater FFM values than did DXA and the equations of Deurenberg et al and Lukaski et al. These findings were as expected and point out the importance of deriving body composition from a multicomponent model.

The equations of Deurenberg et al and Lukaski et al used FFM from underwater weighing based on a 2-component body-composition model in which a constant density of FFM of 1.1 g/mL based on Siri’s equation (4) and a constant density of a reference body of 1.064 g/mL based on the equation of Brozek et al (5) was assumed. The QDR2000 DXA technology assumes that the percentage of water in FFM is 73%, which implies an approximate constant density of FFM. Our BIA equations were validated and cross-validated against criterion methods by using Heymsfield et al’s (6) multicomponent model of FFM, which includes measures of body volume from underwater weighing, total body water, bone mineral content measured by DXA, and body weight. This multicomponent body-composition model does not assume a constant fat-free density or reference body, whereas the 2-component models of Siri and Brozek et al and DXA both assume constant densities. The density of FFM changes with age and is greater in males than in females, and these differences reflect variation in the concentrations of water, protein, and minerals in FFM. FFM obtained from a multicomponent body-composition model is greater than if FFM obtained from a 2-component model in children, young adults, and women (7–9). This is consistent with the finding of Trippo et al that FFM derived from our multicomponent body-composition model is larger than that estimated by DXA or derived with the use of the BIA equations of Deurenberg et al and Lukaski et al. In these 2 studies, the average age was the late 20s.

Trippo et al did not specify the BIA methods that were used to predict FFM; therefore, the machine, the frequency, and the electrode configurations used to collect the BIA data from these 89 persons are unknown. The BIA data in our study were collected under standardized protocols that were identical in each laboratory.

Our equations were designed specifically for application to the BIA data from the third National Health and Nutrition Examination Survey and were not to serve as the “final answer” for all BIA equations. Therefore, our sample included non-Hispanic whites and non-Hispanic blacks. The sample of Trippo et al included only German adults. It may not be possible to produce universal BIA equations because there are differences between populations. These differences cannot be detected without the use of a 4-compartment model, and they require calibration of each population with the use of BIA.

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REFERENCES
Vitamin B-12 and folate deficiency in elderly persons

Dear Sir:

In May 2002, the Food Standards Agency in the United Kingdom decided against endorsing the recommendation of the Committee on Medical Aspects of Food and Nutrition Policy that universal folic acid fortification of flour be introduced to prevent neural tube defects, but the agency also indicated a willingness to reconsider the decision in the light of further evidence. In coming to its decision, the Food Standards Agency was influenced by a recently completed study claiming that vitamin B-12 deficiency among the elderly is more common than had been previously suspected. The investigators linked this claim to the theoretical concern that folic acid fortification might delay the diagnosis of vitamin B-12 neuropathy or even precipitate its onset.

The report of that study, recently published in the Journal (1), does not distinguish serum vitamin B-12 concentrations that are sufficiently low to cause clinical disease (eg, symptomatic anemia or neuropathy) from those that may be low relative to the average but are not low enough to cause clinical disease. Somewhat arbitrary cutoffs were used, so that, for example, a serum vitamin B-12 concentration <150 pmol/L was regarded as "low," and a person with that concentration was considered to be "at high risk of vitamin B-12 deficiency." Serum methylmalonic acid is also used as a test for vitamin B-12 deficiency. As the authors acknowledged, and as their data showed, elevated serum methylmalonic acid may be associated with decreased renal function as well as with vitamin B-12 deficiency.

Clarke et al (1) did not quantify or define high risk. Few clinicians in the United Kingdom report having seen a case of irreversible vitamin B-12 neuropathy in the past decade, which indicates that, even in the vitamin B-12-"deficient" group, the likelihood of vitamin B-12 neuropathy (which results only from very severe vitamin B-12 deficiency) is negligible. Anemia was defined in men as a hemoglobin concentration <130 g/L, and, on this basis, the prevalence of anemia in men with "normal" vitamin B-12 concentrations was as high as 25%. No evidence was given that, in any of the subjects tested, vitamin B-12 deficiency was responsible for the anemia, and the prevalence of symptoms attributable to vitamin B-12 deficiency was not considered.

Unfortunately, the report does not provide information that would be helpful in determining the prevalence of illness in a population that is due to vitamin B-12 deficiency. If there were a problem, the solution would not be population screening for vitamin B-12 deficiency among the elderly, because that would be expensive and unwieldy, would create anxiety, and is unlikely to be specific. The use of the cutoffs reported by Clarke et al would result in 10% of people aged 65–74 y and 20% of those aged >75 y being under regular medical supervision and taking vitamin B-12 supplements in sufficiently high doses to treat neuropathy, in an attempt to prevent a problem (irreversible vitamin B-12 neuropathy) that may not exist. There may, however, be a case for fortifying flour with vitamin B-12 as well as with folate if it could be shown that this step would improve the nutritional status and health (eg, would reduce cardiovascular disease) of the elderly.

The report by Clarke et al provides no new evidence to suggest any concern about the folic acid fortification of flour (as introduced in North America in 1998) to prevent neural tube defects. New evidence shows that this fortification has not led to the "masking" of vitamin B-12 deficiency by correcting the anemia due to the lack of vitamin B-12 (2). It provides no information as to whether relatively low serum vitamin B-12 concentrations in the community represent a medical problem, and the proposal to introduce nationwide screening for vitamin B-12 (and folate) deficiency is unwarranted.

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REFERENCES


Reply to NJ Wald et al

Dear Sir:

Vitamin B-12 deficiency caused by either intrinsic factor deficiency or hypochlorhydria chiefly affects the elderly. Vitamin B-12 deficiency may present as macrocytic anemia, but it also causes neuropathy, including (if the deficiency is severe) subacute combined degeneration of the spinal cord (1). The neurologic symptoms may occur in the absence of anemia in 20–30% of cases (1). The diagnosis of vitamin B-12 deficiency is complicated by the limitations of the current vitamin B-12 assay techniques, whereby a low serum vitamin B-12 concentration does not always indicate vitamin B-12 deficiency. Persons with biologically significant vitamin B-12 deficiency almost always have elevated plasma concentrations of homocysteine or methylmalonic acid (1). Consequently, measurement of blood concentrations of either metabolite among persons with low or borderline concentrations of vitamin B-12 may be used to identify those at high risk of vitamin B-12 deficiency. Using these assays to identify persons with vitamin B-12 deficiency, we found that, among those aged 65–74 y, respectively, 10% and 20% were at high risk of vitamin B-12 deficiency (2).

Folic acid supplementation can prevent anemia among persons with vitamin B-12 deficiency, but it does not prevent damage to the nerves, spinal cord, or brain. Hence, universal, mandatory, folic acid fortification may delay the diagnosis of vitamin B-12 deficiency (ie, result in the "masking" of vitamin B-12 deficiency) and allow the progression of vitamin B-12-related damage to
peripheral nerves, spinal cord, and brain. It is not correct, as Wald et al (3) suggest, to dismiss the hazards of masking vitamin B-12 deficiency among elderly persons.

There is a biochemical basis for the masking of vitamin B-12 deficiency by folic acid (4). The methylenetetrahydrofolate reductase enzyme is responsible for the formation of 5-methyltetrahydrofolate, the primary circulating form of folate and carbon donor for homocysteine remethylation to methionine. The reaction catalyzed by this enzyme is irreversible, and the only way the product, once formed, can be recycled in the cell is to be converted back to tetrahydrofolate by the vitamin B-12–dependent enzyme methionine synthase. If folic acid is supplied to vitamin B-12–deficient persons, it can be converted directly to dihydrofolate and tetrahydrofolate in the bone marrow, which allows hematopoesis, but not in cells elsewhere. Thus, folic supplementation of vitamin B-12–deficient persons can prevent anemia and thereby mask the diagnosis of neuropathy.

A relevant document on folic acid fortification in the United Kingdom is the report from the Committee on Medical Aspects of Food and Nutrition Policy, entitled “Folic Acid and the Prevention of Disease” (5). This study concluded that mandatory fortification of flour with 240 µg folic acid/100 g flour could be beneficially and safely introduced, subject to 2 conditions. The first condition is that technical means be devised to ensure fortification at a target range and were positively associated with OGI (P = 0.03) but not with GL (P = 0.5). No significant associations were found between body mass index and either GL or OGI.

We studied the relations of dietary glycemic load (GL) and overall glycemic index (OGI) with glucose and insulin concentrations in a healthy pediatric population and whether the type of relation between glycemic load and blood insulin concentrations had been investigated.

We read with interest the letters by Mendosa (1) and Brand-Miller et al (2) in the April 2003 issue of the Journal. In those letters, the authors wondered whether data on glycemic load were available in a healthy pediatric population and whether the type of relation between glycemic load and blood insulin concentrations had been investigated.

Dear Sir:

We studied the relations of dietary glycemic load (GL) and overall glycemic index (OGI) with glucose and insulin concentrations in a population of healthy 8-y-old children. The trial design, eligibility criteria, and sampling methods were described previously (3). Of 164 healthy newborns who were randomly selected from all live births that occurred from August to December 1991, data at the age of 8 y were available for 111 children (105 were classified as normal weight and 6 were classified as overweight on the basis of criteria from the International Obesity Task Force; 4). Anthropometric variables (body weight and length), body mass index, nutritional habits, and biochemical data on serum insulin and glucose were evaluated. The children’s dietary habits were evaluated on the basis of a previously validated (5), age-adjusted food-frequency questionnaire, which was designed according to Block’s approach (6). Dietary GL and OGI were calculated by using the method of Liu et al (7) and reference tables for glycemic index (8). Student’s t test and the nonparametric Mann-Whitney U test were used to analyze between-sex differences in continuous variables. Analysis of variance and the Kruskal-Wallis test were used to analyze differences in continuous variables between tertiles of GL or OGI.

In agreement with the significantly higher energy and carbohydrate intakes found in the boys than in the girls, GL values were significantly higher in the boys than in the girls, but the boys and the girls did not differ significantly in OGI. Mean (±SD) values of GL and OGI were 145 ± 37 and 58 ± 2, respectively. The distribution of percentage of energy intake from macronutrients did not differ significantly between the boys and the girls, and the average values were 15% of energy from protein, 56% from carbohydrates, and 29% from fats. Serum insulin concentrations were in the normal range and were positively associated with OGI (P = 0.03) but not with GL (P = 0.5). No significant associations were found between body mass index and either GL or OGI.

We calculated mean daily dietary intake according to tertiles of GL and OGI. After adjustment for total energy intake, body mass

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REFERENCES


Dietary glycemic load, overall glycemic index, and serum insulin concentrations in healthy schoolchildren

Dear Sir:

We read with interest the letters by Mendosa (1) and Brand-Miller et al (2) in the April 2003 issue of the Journal. In those letters, the authors wondered whether data on glycemic load were available in a healthy pediatric population and whether the type of relation between glycemic load and blood insulin concentrations had been investigated.

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We calculated mean daily dietary intake according to tertiles of GL and OGI. After adjustment for total energy intake, body mass
We are writing in reference to the article by Joki et al (1) that was recently published in the Journal. The reported objective of the study was to investigate lipid and sterol metabolism in children with food allergy who were given restricted diets. Outcome measurements included concentrations of serum cholesterol precursors, plant sterols, and lipids. The authors concluded that allergic children have low dietary intakes of cholesterol and low serum cholesterol concentrations. The authors also concluded that serum plant sterol concentrations increased, probably as a result of plant sterols in the rapeseed oil supplement. A careful review of the article by Joki et al identified certain fundamental problems in the study design that severely compromise accurate interpretation of the results.

First, the inclusion of rapeseed oil supplementation confounds the hypothesis of the study. As the authors themselves stated, rapeseed oil is known to contain substantial amounts of plant sterols. Plant sterols are widely known to significantly lower plasma cholesterol concentrations and alter plasma plant sterol concentrations when consumed with the diet. Therefore, what this study actually examined was lipid and sterol metabolism in allergic children supplemented with or without plant sterol–containing rapeseed oil for 3 mo in combination with a restricted diet. This question is very different from the originally intended question about the metabolic effects of a restricted diet alone.

Second, interpretation of the results raises some important questions. The authors report that only 40 of the 52 children were supplemented with the rapeseed oil. It remains unclear to the reader why the supplement was given at all and why only a portion of the children received the supplement. More troubling is the fact that, as the data are presented, we do not know how many children in each group (food allergic and nonallergic) received the supplement or whether those children were the ones contributing the most to the decreased mean cholesterol concentrations. The authors do state that the subjects who received supplementary rapeseed oil had higher plant sterol concentrations than those who did not, but, in the Discussion section, changes in plant sterol concentrations are discussed by comparing allergic subjects with nonallergic subjects. Therefore, it is not clear from the results how many of the allergic and nonallergic subjects were supplemented, which makes it impossible to conclude whether it was the supplementation or the allergic condition that influenced serum plant sterol concentrations.

Third, the authors discuss the importance of cholesterol as an essential lipid molecule for growing children and state that one of the goals of their study was to determine whether the low concentrations of serum cholesterol in their subjects were due to insufficient cholesterol synthesis or absorption or to low intakes of cholesterol and saturated fat. In patients whose cholesterol absorption and intake may be compromised, it seems even more illogical that a supplement with known cholesterol-inhibitory properties would be prescribed. Not only would that predispose the patient to even lower serum cholesterol concentrations, but it also would no longer allow the researcher to accurately assess the hypothesis regarding cholesterol absorption and serum concentrations in allergic children given restricted diets.

Fourth, the authors’ rationale for using serum plant sterol concentrations to predict changes in cholesterol absorption is not scientifically sound. Under steady state conditions, plant sterol concentrations in serum are positively related to the efficiency of cholesterol absorption (2–4). However, plant sterol concentrations cannot be used as predictors when the serum concentrations of sterols are in a state of flux as a result of supplementation. When stanols are supplemented in the diet, there is a resultant decrease in plasma campesterol concentrations, which appears to mimic the decrease in cholesterol absorption. Similarly, when sterols are supplemented, cholesterol absorption decreases, but serum concentrations of plant sterols actually increase. Some researchers in the field of phytosterols have inappropriately used the campesterol-to-cholesterol ratio as an

Limitations of plasma plant sterols as indicators of cholesterol absorption

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Fourth, the authors’ rationale for using serum plant sterol concentrations to predict changes in cholesterol absorption is not scientifically sound. Under steady state conditions, plant sterol concentrations in serum are positively related to the efficiency of cholesterol absorption (2–4). However, plant sterol concentrations cannot be used as predictors when the serum concentrations of sterols are in a state of flux as a result of supplementation. When stanols are supplemented in the diet, there is a resultant decrease in plasma campesterol concentrations, which appears to mimic the decrease in cholesterol absorption. Similarly, when sterols are supplemented, cholesterol absorption decreases, but serum concentrations of plant sterols actually increase. Some researchers in the field of phytosterols have inappropriately used the campesterol-to-cholesterol ratio as an
indicator of changes in cholesterol absorption efficiency after plant stanol supplementation (5–7). Joki et al also incorrectly refer to this method when assessing changes in cholesterol absorption. In addition, they draw 2 contradictory conclusions regarding cholesterol absorption. First, they conclude that, because the campesterol-to-cholesterol ratio was higher in the allergic subjects than in the nonallergic subjects, cholesterol absorption was not affected, from which they draw the inference that the allergic subjects had no bowel inflammation. Second, they conclude that, because there was an increase in cholesterol synthesis, cholesterol absorption must have been reduced. The authors cannot have it both ways—either cholesterol absorption was altered or it was not.

We feel that the results of the study by Joki et al do not reflect the hypothesis and that this discrepancy is due to flaws in the study design. Moreover, the discussion regarding serum plant sterol concentrations and cholesterol absorption is inconsistent through the article and shows a poor understanding of the metabolic effects of plant sterols. To render this study meaningful to the scientific community, the authors need to restate the hypothesis so that it includes plant sterol supplementation, express the data clearly in terms of allergic and nonallergic subjects and in terms of which subjects from each group were supplemented, and, finally, rework the discussion with a stronger understanding of the effects of plant sterol consumption on metabolism generally and on cholesterol metabolism specifically.

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REFERENCES

Assessment of resting energy expenditure in mechanically ventilated patients

Dear Sir:

A recent study by Faisy et al (1) provided an equation for predicting energy expenditure (EE) in mechanically ventilated patients. Like Irton-Jones and Jones (2), Swinamer et al (3), and Frankenfield et al (4), Faisy et al speculated that the addition of factors such as minutes of ventilation and body temperature to the traditional indexes (ie, sex, age, weight, and height) used for EE prediction (5) would result in a better correlation.

To assess the validity of this equation, I screened the indirect calorimetry database of the University of Chicago Hospitals (6) and found 77 patients with complete records. Weight for the Harris-Benedict equation was adjusted by 50% (6), and a stress factor of 1.3 was used (7). The correlation (r) was assessed by using Pearson’s coefficient, bias was the difference between mea-

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Measuring bone mass accumulation

Dear Sir:

I thank Lehtonen-Veromaa et al (1) for their response to my letter (2) but feel that, to some extent, the additional analyses they offer are not yet quite on target. The authors provide the requested bone mineral content data, but only after adjusting for such variables as increases in bone area, height, and weight. The hypothesis involved in a nutrition and growth study is that the nutrient concerned influences the amassing of tissue and the increase in its size. If one adjusts the observed increases in mass for the increase in bone area (or height), then one has in effect simply produced another variable akin to bone mineral density.

Density, as I tried to indicate in my letter, is not a relevant outcome variable in a growth study because the hypothesis involved relates to mass, not packing. If one wanted to follow the growth trajectories for fat mass or muscle mass and how they might be influenced by nutrition, one certainly would not use an areal density measure. Instead, one would measure total-body fat mass or total-body lean mass. Bone mineral density or its equivalent, bone mass, adjusted for area is not a proper measure of bone mass accumulation. In contrast, bone mineral content unadjusted for growth-related variables is.

Thus, with the data supplied to date, we cannot tell whether in the study of Lehtonen-Veromaa et al (3) there was or was not an association of vitamin D status and bone mass accumulation. At the very least, we cannot estimate its magnitude.

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sured and calculated EEs, and agreement was assessed by using Bland-Altman analysis (8).

The data validate the equation of Faisy et al as a tool for EE prediction in mechanically ventilated patients. However, the Harris-Benedict equation (multiplied by 1.3) gave a better correlation and agreement with the measured EE and the smallest mean bias (Table 1). EE should be measured whenever possible. This analysis shows that, when the EE measurement is not available, the Harris-Benedict equation with a stress factor of 1.3 is the most accurate tool for EE prediction.

<table>
<thead>
<tr>
<th>Equation</th>
<th>Harris-Benedict²</th>
<th>Faisy et al (1)</th>
<th>Ireton-Jones and Jones (2)</th>
<th>Swinamer et al (3)</th>
<th>Frankenfield et al (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \bar{x} \pm SD )</td>
<td>2048 ± 479</td>
<td>2000 ± 548</td>
<td>1678 ± 339</td>
<td>1825 ± 745</td>
<td>1381 ± 1125</td>
</tr>
<tr>
<td>Correlation (r)</td>
<td>0.74</td>
<td>0.60</td>
<td>0.59</td>
<td>0.55</td>
<td>0.63</td>
</tr>
<tr>
<td>Mean bias</td>
<td>41 ± 372</td>
<td>82 ± 485</td>
<td>412 ± 436</td>
<td>264 ± 633</td>
<td>708 ± 893</td>
</tr>
<tr>
<td>Agreement</td>
<td>0.013</td>
<td>0.04</td>
<td>0.20</td>
<td>0.19</td>
<td>0.52</td>
</tr>
</tbody>
</table>

1 The measured energy expenditure value used was 2090 ± 540 kcal.
2 Multiplied by 1.3.

REFERENCES
Erratum


In the second paragraph of the Results section, we erroneously reported that “neither macro- nor micronutrient intakes significantly differed between groups before the study.” In actuality, the percentages of energy from carbohydrates and fat differed significantly between the groups ($P < 0.05$, Student’s $t$ test). The SEM values for iron intake were also misreported in that paragraph. The correct SEM values were 1.4 and 2.6 mg/d for the iron and placebo groups, respectively.

Erratum


On page 704, column 1 (paragraph 2, line 15), the ratio of diethylether to acetic acid is incorrect. The sentence should read as follows: The cartridge was eluted with 3 mL eluent I and then with 3 mL diethylether:acetic acid (98:2, vol:vol), 1 mL acetonitrile, and 8 mL acetonitrile:$n$-propanol (3:1, vol:vol) to recover the phosphatidylcholine fraction.

Erratum


Page 113, column 1, paragraph 1: The following sentence should have been inserted just after the sentence that ends with “when site was adjusted for.”: Honduran mothers had significantly lower mean ($\pm$ SD) plasma zinc concentrations than did Swedish mothers (0.61 $\pm$ 0.09 compared with 0.94 $\pm$ 0.11 mg/L, respectively; $P < 0.001$), whereas mean maternal plasma copper concentrations were similar at the 2 study sites (1.02 $\pm$ 0.23 compared with 1.04 $\pm$ 0.18 mg/L, respectively; $P = 0.52$).