Individual differences in apparent energy digestibility are larger than generally recognized

Dear Sir:

Disturbances in energy balance are responsible for 2 of the world’s major health problems: obesity and protein-calorie malnutrition. Even small positive or negative excursions in energy balance lead to relatively large changes in body weight over prolonged time periods (1).

An important current focus of clinical nutrition and physiology is on establishing if and to what extent individuals differ in their energy physiology. Although an abundance of research focuses on energy expenditure, until recently remarkably little attention has been directed at establishing the variability in net energy absorption or “apparent digestibility” observed among adult humans. Atwater et al. in the early 1900s developed the “average” or population metabolizable energy (ME) values that are now applied universally for protein (4 kcal/g), carbohydrate (4 kcal/g), and fat (9 kcal/g) that include adjustments in macronutrient gross energy values for stool and urinary urea energy losses (2). The average adult eating a mixed diet loses about 5% of gross ingested energy in stool.

Jumpertz et al. (3) recently reported the associations between gut microbes, caloric load, and nutrient absorption in humans. The investigators provided lean and obese men 2 energy intake amounts while subjects were closely monitored on a metabolic ward. Each supervised 3-d feeding period was preceded by a 3-d weight-maintenance diet. The gross energy contents of ingested foods and stools were then measured by bomb calorimetry. Although only a minor component of a larger investigative focus, the authors reported the percentage of energy lost in stools as ranging between 2.1% and 9.2% (2400-kcal/d diet) and 1.6% and 7.6% (3400-kcal/d diet). Even on the same diet, men thus varied by 6–7% or ±150–200 kcal/d in net energy retained. Such large individual differences in net energy retention have largely gone unnoticed as the fastidious metabolic ward conditions needed for this type of research largely disappeared since their heyday a half-century ago. Jumpertz et al detected short-term changes in gut microbiota with overfeeding and suggestive evidence of response differences between lean and obese subjects.

We similarly reported relatively large individual differences in apparent digestibility >20 y ago as part of a much larger clinical research facility energy physiology trial (4). Subjects were 8 healthy adult men participating in an overfeeding study in which the same liquid formula consisting of blender-processed foods was continuously fed through a thin nasoenteral tube for 3 wk. The initial week included a weight-maintenance (mean ± SD: −35 ± 147 g/d) energy intake followed by 1 wk of twice the maintenance energy intake. Energy intake was returned to baseline amounts during the third week as weight decreased (−142 ± 138 g/d) from the overfeeding period. Bomb calorimetry was used to measure the energy contents of food and stools collected under metabolic balance conditions during the last 4 d of each 1-wk period. Herein we emphasize the results only from weeks 1 and 3 during which subjects were infused with a weight-maintenance energy intake. The apparent digestibility during the initial maintenance week ranged from 93% to 99% (96.7 ± 2.1%) with corresponding findings for the second maintenance period nearly identical for each subject (96.6 ± 1.9%; r = 0.98, P < 0.001). We could find no significant correlations between apparent energy digestibility and subject age, BMI, fat mass, or fat-free mass. Hence, our findings in a very tightly controlled metabolic ward study show the same large range in net energy digestibility as observed by Jumpertz et al (3).

Other salient examples include a number of supervised inpatient clinical trials in adult men that examined apparent fat digestibility during evaluation of the weight-loss drug orlistat. Hussain et al (5) and Hartmann et al (6) reported respective fecal fat amounts ranging between 1.62–5.4 g/d and 1.32–5.52 g/d during 5-d control periods in subjects who consumed very similar diets.

These carefully controlled supervised studies of men fed identical or very similar diets show a remarkable range of apparent individual subject energy and fat digestibility. The between-subject variability is surprisingly large and within the range reported for between-subject variation in energy expenditure (1). Our balance study included a replicate maintenance-feeding week that showed these individual apparent digestibilities are remarkably consistent within subjects.

The question arises as to what mechanisms underlie these individual differences? Many factors determine macronutrient digestion and absorption, and stool losses also include energy-containing compounds from endogenous secretions and gut microbes. Establishing the basis of these individual differences in the net energy retained from food presents an important research question in the context of recent interest in the gut as a key organ in energy balance regulation. As with energy expenditure (1, 7), these individual differences in apparent digestibility are a key component of human phenotypic differences in energy metabolism.

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Dear Sir:

We read with interest the article by Catov et al (1) in a recent issue of the Journal, partly because this topic is extremely important in Hungary where there is a very high rate of preterm birth (~9%) (2), and partly because we have completed a number of studies regarding the possible association of folic acid–containing multivitamin or folic acid–alone supplementation during pregnancy with the risk of preterm birth (PTB) and low birth weight (LBW). Thus, we were surprised to read their sentence, “the timing and frequency of weekly supplement intake may be important in these associations, and to our knowledge, these factors have not been previously examined.”

The objective of our randomized controlled trial (RCT) was to test the efficacy of folic acid (0.8 mg)–containing multivitamin use in the periconception period on the reduction in first occurrence of neural tube defects (3). However, this RCT, which included 2367 and 2305 live-born babies in the multivitamin-supplemented and unsupplemented groups, respectively, did not show a difference between mean (±SD) birth weight (3291 ± 488 compared with 3288 ± 478 g) and gestational age at delivery (39.6 ± 1.7 compared with 39.6 ± 1.6 wk), thus there was no significant difference in the rate of PTB (7.5% compared with 7.2%) and LBW (4.3% compared with 3.5%) (4). These findings appeared to be reasonable because these pregnant women were supplied with this multivitamin from the 12th preconception week until the 12th postconception week, and major fetal growth occurs after the first trimester, mainly during the third trimester. The advantages of an RCT were obvious: only one type of multivitamin was used, with strict regulation of its intake; and after the 12th postconception week these pregnant women did not use multivitamins or folic acid. When this RCT was performed, the benefits of folic acid or folic acid–containing multivitamin supplements in the prevention of neural tube defects were not known, and appropriate multivitamins were not available in Hungary.

Unfortunately, the use of multivitamin and folic acid in the prevention of congenital abnormalities has not become widespread in Hungary. When we tried to ascertain why this was the case, women frequently mentioned that their doctors did not recommend the use of these pregnancy supplements due to the possibility of giving birth to “giant” infants. Thus, we decided to research this idea. The birth outcomes of singleton births to primiparous women with prospectively and medically recorded vitamin supplements in prenatal maternity log-books were compared in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities. This data set included 6293, 169, and 311 pregnant women receiving supplementation of folic acid alone, multivitamins, or folic acid plus multivitamins, respectively, and these data were compared with the data on 7319 pregnant women who were not receiving folic acid or folic acid–containing multivitamin supplementation (5). In general, the onset of the use of these pregnancy supplements was after the first visit in the prenatal care clinic—ie, between 7 and 10 wk gestation—and most women used them until the end of pregnancy. There were 3 primary multivitamins that were used [Elevit, 0.8 mg folic acid, 53.3% (Roche); Materna, 1.0 mg folic acid, 39.0% (Wyeth-Lederle); and Polyvitaplex-10, 0.1 mg folic acid, 2.9% (Chinoin)], and only one kind of folic acid tablet was marketed in Hungary during the study period, which contained 3 mg folic acid/tablet. Most pregnant women used 2 tablets/d; the estimated daily dose was 5.6 mg.

The mean gestational age was somewhat greater in the multivitamin-supplemented group (39.4 compared with 39.2 wk; \( P = 0.28 \)), with a mild increase in mean birth weight (3336 compared with 3262 g; \( P < 0.001 \)), but the rate of PTB was lower (6.4% compared with 11.1%; OR: 0.63; 95% CI: 0.46, 0.86), without a significant reduction in LBW rate (5.1% compared with 5.8%; OR: 0.87; 95% CI: 0.44, 1.51).

The effect of multivitamins on birth outcomes was evaluated according to the time of supplementation. These multivitamins were rarely used only during the first trimester of pregnancy (this supplementation corresponded to the periconception period), and this supplementation did not significantly change the birth outcomes of the mothers’ newborn infants. However, the use of these multivitamins during the third trimester (ie, use during only the third, the second and third, or the first through the third trimesters) resulted in a 75-g increase in mean birth weight with a significant reduction in the PTB rate (6.9%).

The mean gestational age was 0.3 wk longer \( (P < 0.0001) \) and the mean birth weight was increased by 32 g \( (P = 0.28) \) in the group of pregnant women with folic acid supplementation alone. The rate of PTB \( (7.6%) \) was significantly lower in this group compared with the reference group \( (11.1%); \) OR: 0.68; 95% CI: 0.63, 0.73), but the rate of LBW did not show a significant reduction \( (5.1% \text{ compared with } 5.8%); \) OR: 0.88; 95% CI: 0.62, 1.14). The use of folic acid alone in the third trimester (including the 3 subgroups mentioned previously, ie, the third, the second and third, or the first through the third trimesters) was associated with 0.6 wk longer mean gestational age \( (39.8 \text{ wk}) \) and a more significant reduction in the rate of PTB \( (4.8%); \) OR: 0.38; 95% CI: 0.33, 0.45). The mean birth weight \( (3253 g; \) OR: 0.86) and LBW rate \( (5.0%); \) OR: 0.88; 95% CI: 0.56, 1.27) did not show a significant difference from the reference values. In addition, folic acid supplementation only in the third trimester also resulted in a longer mean gestation age \( (39.5 \text{ wk}) \) and a lower PTB rate \( (7.6%); \) OR: 0.62; 95% CI: 0.45, 0.87).

Thus, the hypothesis regarding much larger infants after the use of these pregnancy supplements was not confirmed, but the reduction in PTB after multivitamin and particularly folic acid supplementation in the second part of pregnancy was shown. These important data were published not only in a periodical (5) but in the fourth edition of Preventive Nutrition as well (6). These new findings should stimulate the introduction of 2 different preventive strategies: periconceptional folic acid or folic acid–containing multivitamin supplementation for reduction in neural tube defects, and perhaps some other serious birth defects, and a higher dose of folic acid supplementation in the second half of pregnancy to reduce the risk of certain types of PTB. These 2 preventive efforts can significantly reduce the 2 major factors associated with infant mortality and disabilities: congenital abnormalities and PTB.