

### Lower body mass index cutoff is required for Chinese as a risk factor for coronary artery disease and other obesity-related metabolic disorders

Dear Sir:

I agree with Pan et al (1) that there is a need to set a lower body mass index (BMI; in kg/m<sup>2</sup>) cutoff for Chinese in Taiwan as a risk factor for various obesity-related metabolic disorders. They proposed a BMI of slightly below 24 for Taiwan Chinese (1). This is very similar to that suggested for Hong Kong Chinese in 1999 by Ko et al (2), who used a BMI of 23 to define overweight in screening for diabetes, hypertension, dyslipidemia, or albuminuria in that population.

The BMI cutoff for Chinese is indeed much lower than that for other populations: the normal mean for mainland Chinese is 18.5–23.9 (3). Because Chinese have a lower baseline BMI to begin with, fewer increments are needed to reach obesity, so that BMIs of 24–27.9 are considered to indicate overweight and BMIs  $\geq 28$  are considered to indicate obesity (3). Risk factors increase with BMIs higher than the baseline value of 21.0: at BMIs of 23.0–24.9, the risk of hypertension, hypertriglyceridemia, and coronary artery disease is doubled, and at BMIs of 25.0–26.9, the risk is tripled (4).

Therefore, whether Taiwan, Hong Kong, or mainland Chinese, all Chinese have a lower BMI as a risk factor for coronary heart disease and other obesity-related metabolic disorders than do people in the West (5, 6). This fact has immense clinical and public health implications, because 1 of every 4 persons living today is Chinese (7).

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#### Reply to TO Cheng

Dear Sir:

We appreciate Dr Cheng's letter. He echoes our point (1) that there may be a need to set lower body mass index (BMI; in kg/m<sup>2</sup>) cutoffs for Chinese adults, and he raises the possibility that a decision to lower the cutoff could affect the well-being of Chinese, who make up a large proportion of the world's population. A World Health Organization (WHO) expert consultation also concluded recently that a substantial proportion of Asians with BMIs lower than the existing WHO cutoffs for overweight (BMI >25) are at high risk of type 2 diabetes and cardiovascular disease (2). We would like to go beyond this point to emphasize that screening for obesity is a complex issue. The most appropriate and useful cutoffs may vary with time and circumstances in any given population or race. Additional complexities are related to considerations such as the availability of resources and the negative effect of misclassification.

Our article (1) provided evidence that, relative to American whites and blacks surveyed during a similar period (1988–1994), Taiwanese had a higher excess risk associated with several obesity-related metabolic disorders at each fixed BMI level than did other populations. In addition, for each increment of BMI, the relative risk for several metabolic disorders was higher in Taiwanese than in other populations. Although evidence (3) shows that this phenomenon can be explained in part by the higher percentage body fat at a specific BMI in Chinese, the reasons for a higher percentage body fat and for a higher risk of metabolic diseases in Taiwanese are not altogether clear. It is possible that both genetic background and environmental factors such as lack of physical activity (4), intrauterine malnutrition (5), and poor magnesium status (6) could affect a person's susceptibility to metabolic disorders. If, for example, improving living standard and public health efforts were to increase physical activity or reduce exposure to intrauterine malnutrition and mineral deficiency, the susceptibility of Chinese to metabolic diseases at a given BMI might change even without changes in genetic make-up.

It is crucial to understand the meaning of BMI cutoffs for different age, sex, and ethnic groups so that one can apply BMI cutoffs effectively for screening. Lowering the BMI cutoff for obesity screening in Chinese may well be appropriate at the present time, but the susceptibility to metabolic disorders may change in either direction for Chinese in the future. This complex situation may be addressed more comprehensively when technological developments lead to more convenient and accurate ways to measure obesity.

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## Formulas containing live probiotic bacteria

Dear Sir:

In a recent issue of the Journal, Saavedra et al (1) reported on the safety and potential benefits resulting from the addition of the live probiotic bacteria *Bifidobacterium lactis* and *Streptococcus thermophilus* to infant formula. We agree that the rationale for the use of probiotics in infant formula is theoretically valid. The results of the study showed that infants fed formula containing live probiotic bacteria had a significantly lower frequency of colic or irritability and a lower frequency of antibiotic use than did infants who consumed standard formula. A number of issues cause us to question the validity and applicability of the reported results to clinical practice.

An exclusion criterion of the study was a breastfeeding frequency of  $\geq 3$  times/d. It is well established that breastfeeding is a major contributor to the immunologic health of infants. Therefore, breastfeeding has the potential to act as a major confounder in this study. In a child consuming probiotic-supplemented formula who is also breastfed, it is possible that any advantages gained are due primarily to the benefits of breastfeeding alone. The 3 formula groups in the study were unbalanced in terms of the percentage of infants who were breastfeeding at study entry (high-supplement formula: 23%; low-supplement formula: 28%; and standard formula (placebo): 15%). Although it is unfortunate that randomization did not prevent this from occurring, it is questionable whether breastfeeding should

have been permitted at all or whether the study population should have included formula-fed infants only.

A statistically significant difference between the standard and probiotic formula groups was the frequency of reported colic or irritability. The infants studied ranged in age from 3 to 24 mo (mean age: 7 mo). By definition, colic is a term used to describe frequent prolonged bouts of fussing, crying, and restlessness in an otherwise healthy infant that may persist into the second half of the first year of life, but tends to improve or disappear in most cases after 3–4 mo of age (2). Thus, it is difficult to interpret the reported decrease in colic or irritability in the probiotic-supplemented group as a direct consequence of the type of formula administered. It appears possible that those infants out of the colic phase (eg, infants  $>6$  mo of age) would benefit from probiotic supplementation. A group of infants with a narrower, younger age range would have been a more appropriate group to study.

The frequency of antibiotic use was also found to be significantly different between the probiotic formula and the standard formula groups. The group with the lowest antibiotic use, the low-supplement group, averaged 2.47 d of antibiotic use per 100 subject days (95% CI: 2.11, 2.84), whereas the standard formula group averaged 3.60 d of antibiotic use per 100 subject days (95% CI: 3.17, 4.02). Although the difference was statistically significant, one could argue that a reduction of 1 d out of 100 d is not clinically significant.

This study offers insight into the use of infant formulas supplemented with probiotic bacteria and the challenges encountered in designing these trials. We feel that further study in this area is warranted before any changes to current practice take place as a result of the study's findings.

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## Reply to J Falk et al

Dear Sir:

We thank Falk et al for their comments and pertinent questions, which should help us to clarify the validity of our study results, better understand their potential application, and adequately assert the contribution of this study to the probiotic literature in infant nutrition.

Of course, we agree with Falk et al that breastfeeding is a major contributor to the immunologic health of infants, even when provided in limited amounts, and that this is a confounding variable. Nevertheless, exclusive formula feeding in this population would shorten the time that infants receive the formula, limit the range and total time of observation, and raise ethical concerns. Because the primary goal of this trial was to assess safety and tolerance in this population of infants attending day care, a design was considered that maximized the number of infants and length of follow up.

The children were included in the study on the basis of their parents' willingness to participate in the trial after being approached by the research team. Although still far from ideal, breastfeeding rates and length of breastfeeding in the United States have increased. Given that the longest possible length of follow-up of infants consuming study formulas is essential to reasonably assess their safety and potential health effects, a compromise in design was reached to allow the entry of infants who were already in the process of weaning from breastfeeding (ie, had started taking formula) before being approached for participation. Breastfeeding  $\geq 3$  times/d was a study exclusion criterion. For obvious ethical reasons, the study did not discourage the amount or the frequency of breastfeeding, which was determined entirely by the parents. This design allowed infants in the process of weaning to participate, thus increasing our recruitment rate, allowing for a longer duration of follow-up during the weaning period and beyond, and resulting in observations that were actually closer to a "real-life situation" for most of the infants.

Careful randomization yielded homogeneous groups relative to all baseline anthropometric and demographic characteristics. There were differences between the groups in the percentage of infants being breastfed at the time of randomization: 23% in the high-supplement group, 28% in the low-supplement group, and 15% in the placebo group. These differences were not statistically significant. However, we also analyzed the potential for breastfeeding as a confounder in several other ways.

First, we assessed in each study group the average number of times that infants who were still being breastfed were being put to the breast at the time of enrollment: 2.2, 2.7, and 2.2 times for the high-supplement, low-supplement, and placebo groups, respectively. Second, we analyzed in each group the average number of days of continued breastfeeding (duration of weaning) during study participation: 56.2, 53.3, and 49.5 d for the high-supplement, low-supplement, and placebo groups, respectively. Finally, we analyzed the average actual number of times per day that each infant in each group was being put to the breast while participating in the study, until they weaned completely to formula: 1.8 (range: 1.5–2.2), 2.2 (1.0–2.6), and 1.8 (1.0–2.1) times/d for the high-supplement, low-supplement, and placebo groups, respectively. None of these differences were significant.

In total, the infants studied were at least partially breastfed for a grand total of 1070 subject-days, or only 4.3% of the total 24 830 subject-days of follow-up. Although, ultimately, the true effect of breastfeeding cannot be ascertained, the effect on the outcomes observed could be reasonably considered minimal if at all contributory to any differences in outcomes.

With regard to colic and irritability, Falk et al are correct that definitions of *colic* vary, as does the age at which infants can be diagnosed as having colic. The purpose of the inclusion of "colic or irritability" in the weekly questionnaire was to identify—as perceived and reported by the parents—any potential and apparent abdominal discomfort not attributable to other changes in the child's routine. The ultimate reason for this was to identify any potential gastrointestinal intolerances (in conjunction with the other questions related to upper and lower gastrointestinal symptoms). Given the age

span of the group in the study, we preferred to use the term "colic or irritability" to better describe the responses given by the parents to the standardized questionnaire. This is how the results and conclusions are reported.

Regarding antibiotic use, although a 1-d difference in antibiotic use per 100 subject-days may not appear to some to be "clinically significant," for a child in their first 2 y (730 d) of life, this equates to 7 d of antibiotic use or one standard course of antibiotic treatment for common illnesses requiring antimicrobials. Although this is obviously an extrapolation of the results, a decrease of one course of antibiotic treatment in a child receiving a formula containing probiotics in their first 2 y of life is not only clinically significant and relevant but is of potentially great epidemiologic effect, particularly in our current environment of indiscriminate antibiotic prescription and growing antibiotic resistance.

This is the most detailed and carefully controlled study yet to follow infants consuming a probiotic-supplemented formula for an extended period of time and to document safety and tolerance. The purpose of this single study was not to recommend changes across the board in standard clinical practice but to add to the growing body of evidence of safety and potential beneficial effects of specific agents for their use as probiotics in infant nutrition.

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## **Vitamin E from supplements has good bioavailability**

Dear Sir:

The results of a study published in the January 2004 issue of the *Journal* suggest that synthetic vitamin E in capsules is less bioavailable than is synthetic vitamin E in fortified cereal (1). As the manager of VERIS, a nonprofit information service on vitamin E and other antioxidants, I had the opportunity to review the results of numerous studies on vitamin E for  $> 15$  y. Several of these studies have shown benefits of supplemental vitamin E in amounts higher than are regularly consumed in the diet. The results have been somewhat variable, however, most likely due to differences in the dosages and forms of the vitamin E supplements evaluated. For example, research suggests that the bioavailability of natural-source vitamin E is approximately twice that of synthetic vitamin E (2–4).

Although it is recommended that vitamin E supplements be taken with a meal containing fat (because dietary fat generally promotes vitamin E absorption), no fat was provided with the vitamin E supplements in the study by Leonard et al. In addition, the physical form of the vitamin E added to the cereal differed from the vitamin E capsules used in the study. In contrast with the results of this study,

the results of other published studies have shown a high bioavailability of vitamin E from capsules when consumed with a meal providing adequate fat (2, 5)

Fortification of foods with vitamin E is of course a means of significantly increasing vitamin E intake, and the results of the study by Leonard et al suggest that formulation characteristics can affect the absorption of fat-soluble nutrients. Unfortunately, the study does not provide a meaningful comparison of the bioavailability of vitamin E from fortified cereal and that from capsules, because no fat was consumed with the vitamin E supplements. Further research is needed to provide a valid comparison of the bioavailability of vitamin E from fortified cereal and that from supplements consumed with fat.

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#### Reply to S Landvik

Dear Sir:

Landvik states that “results [of vitamin E studies] have been somewhat variable, ...most likely due to differences in the dosages and forms of the vitamin E supplements evaluated.” We concur that the outcomes of vitamin E supplementation studies have been variable, but the question is why. Studies of patients with fat malabsorption have shown that vitamin E absorption requires normal digestive processes involved in the absorption of dietary fats (1). However, the amounts and forms of fat required for optimal vitamin E absorption are unknown, and the causes of the variability in responses to supplements are also unknown. The purpose of our study was not to compare the bioavailability of vitamin E consumed with different amounts or kinds of dietary fat, but to design a study to evaluate the bioavailability of vitamin E in commonly consumed sources of the vitamin, namely, supplements and fortified breakfast cereal (2). Indeed, we anticipated that fortified breakfast cereal might not be an ideal vitamin E source because of its low fat content; therefore, one arm of our study included cereal that was intentionally suprafortified with vitamin E (eg, 400 IU per serving).

In an effort to make our results applicable to typical consumers, we considered that many persons take vitamins as part of their definition of a healthy lifestyle and thus take vitamins with breakfast

or in the morning while they remain fasting. Thus, vitamin and mineral supplements, including vitamin E, are commonly consumed on an empty stomach in the morning with juice, tea, coffee, or nonfat milk. On the basis of these observations, the question we wanted to answer was, Is there a difference in the bioavailability of vitamin E when consumed as part of a low-fat breakfast cereal compared with that of a supplement consumed with a nonfat drink?

Landvik also states that “it is recommended that vitamin E supplements be taken with a meal containing fat.” Two studies in humans have shown that plasma vitamin E increases to a greater extent when vitamin E supplements are taken with fat-containing foods (3, 4). Our study showed that vitamin E supplements are not effectively absorbed if they are taken on an empty stomach with a glass of nonfat milk (2). Therefore, we believe that our data support the advice that vitamin E supplements should not be taken alone, but rather should be consumed with food, perhaps foods containing higher amounts of fat in an effort to improve absorption.

Landvik claims that “the physical form of the vitamin E added to the cereal differed from the vitamin E capsules.” In point of fact, the same deuterium-labeled vitamin E ( $d_9$ -*all-rac*- $\alpha$ -tocopheryl acetate) was added to the cereal as was in the capsule. The study cereal was fortified in a manner identical to the commercially available cereal (Total; General Mills Inc, Minneapolis, MN) and was prepared by the same manufacturer so that the results of the study would be applicable to cereal available for purchase by average consumers. The vitamin E used was dissolved in the commercially used emulsion (Hoffmann-La Roche, Nutley, NJ), sprayed on the cereal, and then dried. The emulsion applied to the cereal was not included in the encapsulated vitamin E, but neither is it in commercially encapsulated vitamin E supplements. The differences in vitamin E absorption when the pill was consumed along with cereal suggest that the emulsion on the surface of the cereal does not increase vitamin E absorption from the supplement. Moreover, Roxborough et al (5) also observed a large degree of variability in subjects who consumed deuterium-labeled vitamin E with toast for breakfast. Thus, our findings concerning the lack of consistency in vitamin E absorption when the supplement is consumed with a low-fat meal are not unique.

From our results, we conclude that consumers wishing to increase their vitamin E intakes would benefit from eating their vitamin E supplement after a fat-containing meal, eating a vitamin E-fortified food such as breakfast cereal, or a combination of both. Food fortification with vitamin E appears to optimize vitamin E bioavailability from a low-fat diet, because we showed that the breakfast, which contained <5% fat (consisting of vitamin E-fortified cereal plus fat-free milk), unexpectedly increased vitamin E bioavailability. These findings are significant because fortified breakfast cereals are a major source of vitamin E in the American diet (6, 7). Further efforts to educate consumers regarding the consumption of vitamin E through fortified foods or supplements should be considered.

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## Estimates of renal net acid excretion and bone health

Dear Sir:

The recent Journal article by New et al (1) concerning positive associations of indexes of bone health with lower dietary acidity in a large group of premenopausal and perimenopausal women appears to provide further evidence of a relevant link between acid-base status and bone health. The authors estimated renal net acid excretion (NAE) as an index of net endogenous noncarbonic acid production by using a simple algorithm proposed by Frassetto et al (2) that includes daily dietary potassium and protein intakes. New et al calculated an estimated average energy-corrected NAE of  $0.161 \text{ mEq} \cdot \text{d}^{-1} \cdot 8.29 \text{ MJ}^{-1}$  for the whole study population. However, with the use of the mean values for protein (82.5 g/d) and potassium (3395 mg/d) intakes provided by New et al, the Frassetto algorithm

$$\text{NAE} = -10.2 + 54.5 \times (\text{protein/potassium}) \quad (1)$$

yields  $5 \text{ mEq} \cdot \text{d}^{-1} \cdot 8.29 \text{ MJ}^{-1}$ , ie, a value >30-fold that reported by New et al. It is interesting that the latter value corresponds closely to the individually energy-adjusted renal NAE values that we, on the one hand, analyzed in 24-h urine samples and, on the other hand, estimated from dietary records in 16–18-y-old adolescents participating in the Dortmund Nutritional and Anthropometric Longitudinally Designed Study (3; range of means:  $5.1\text{--}5.6 \text{ mEq} \cdot \text{d}^{-1} \cdot \text{MJ}^{-1}$ ). Thus, it appears that New et al may not have converted potassium intake (mg/d) to mEq/d as is required for use of the algorithm of Frassetto et al (2). In this case, the corrected overall mean estimate as well as the (corrected) estimates used for grouping the data set into quartiles should be reported to the interested reader to allow better understanding of the NAE values at which a possible influence on bone might become apparent (4).

Another important question raised by New et al concerns possible consequences of long-term low intakes of protein and dietary acid. The use of the minimum values for protein (20 g/d) and potassium (1475 mg/d) intakes (as reported for the study population; 1) in the formula of Frassetto et al results in an NAE estimate of

$2.2 \text{ mEq} \cdot \text{d}^{-1} \cdot 8.29 \text{ MJ}^{-1}$ . Should potassium intake increase, the estimate would be even smaller. In this context, it is of interest to learn what percentage of the women with a low protein intake [ $<45 \text{ g/d}$  (reference nutrient intake for protein)] and with consequently lower dietary acid loads did show bone mineral densities (BMD) or “areal BMDs” above the median value at the bone sites studied in this population. Several recent studies (eg, 5) suggested that low dietary protein intakes might exert detrimental effects on skeletal health.

Finally, it should be taken into consideration that the compensatory effect of a base (eg, potassium bicarbonate) on an acid that is metabolically released (eg, sulfuric acid) is additive (1 mEq sulfate – 1 mEq potassium) and not multiplicative. Additional dietary components (eg, phosphorus, magnesium, and calcium) are also involved, and they can be relatively easily included in an additive estimation model (the potential renal acid load model), which—according to our own results (3)—can provide a better fit with the analyzed NAE in 24-h urine samples than can the ratio of protein to potassium.

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## Reply to T Remer

Dear Sir:

Dr Remer's pertinent response to our recent publication on associations between estimates of net endogenous (noncarbonic) acid production (NEAP) and bone health indexes in the population of the Aberdeen Prospective Osteoporosis Screening Study (1) is most timely. We have reexamined our findings in light of the 3 important points he raises.

First, although we analyzed the association between NEAP and markers of bone health by using potassium intake converted to mEq/d, we reported NEAP estimates by measuring potassium intake in mg/d and not in mEq/d, which, as correctly pointed out by Remer, is required for the Frassetto algorithm (2). The correct estimates (mean  $\pm$  SD; median and range) for NEAP and the values used for grouping the data set into quartiles are shown in **Tables 1** and **2**, respectively.

**TABLE 1**

Net endogenous (noncarbonic) acid production (NEAP) and potential renal acid load (PRAL) estimates of the study population<sup>1</sup>

	Mean ± SD	Value
NEAP <sup>1</sup>	5.02 ± 0.78	4.97 (2.0–8.29)
PRAL <sup>2</sup>	3.68 ± 10.51	3.20 (–46.72 to 84.29)

<sup>1</sup> Estimate of NEAP obtained by using Frassetto et al (2) algorithm in mEq · d<sup>-1</sup> · MJ<sup>-1</sup>.

<sup>2</sup> Estimate of PRAL obtained by using Remer et al (6) equation in mEq/d.

**TABLE 2**

Net endogenous (noncarbonic) acid production (NEAP) estimates for quartile classification

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
NEAP	2.00–4.534	4.534–4.979	4.979–5.456	5.456–8.29

<sup>1</sup> Estimate of NEAP obtained by using Frassetto et al (2) algorithm in mEq · d<sup>-1</sup> · MJ<sup>-1</sup>.

The second point raised by Remer is a critical one, given the current controversy concerning the relation between dietary protein and bone (3, 4). We have examined our extensive data set to determine the percentage of women with an intake of protein below the reference nutrient intake (RNI), ie, <45 g/d (5), and we examined their respective bone mineral density (BMD) values. Only 24 women (2.3%) were below the RNI for protein and had a mean estimate for NEAP of 3.94 ± 0.95 mEq · d<sup>-1</sup> · MJ<sup>-1</sup> (range 2.04–5.50 mEq · d<sup>-1</sup> · MJ<sup>-1</sup>) and a mean estimate of potential renal acid load (PRAL) of -7.90 ± 9.44 mEq/d (range -33.6 to 4.58 mEq/d). Of these subjects, 50% had a lumbar spine BMD below the median value for the population. Figures for the other BMD sites were as follows: 67% (*n* = 16) for femoral neck BMD; 50% (*n* = 12) for femoral trochanter BMD; and 71% (*n* = 17) for femoral Ward's BMD. The numbers of subjects with low protein intake are too small to allow us to comment further on the growing body of evidence that long-term low dietary protein consumption may be harmful to skeletal integrity. It is important also to note that subjects with a low dietary protein intake are likely to be deficient in other nutrients that may be of benefit to bone.

In response to the third point, we estimated the PRAL by using Remer's calculation model (6), and these estimates are shown in Table 1. Furthermore, we investigated the association between estimates of PRAL and measurements of bone metabolism and BMD. The correlation between NEAP and PRAL was 0.93 (*P* < 0.001). Lower estimates of PRAL were associated with a higher peripheral cortical forearm bone mass (*P* < 0.03) and lower deoxypyridinoline excretion (*P* < 0.048), with similar nonsignificant trends for peripheral total bone mass and pyridinoline excretion (*P* < 0.07 and *P* < 0.1, respectively). However, correlations were weaker than those we reported for NEAP and bone. There was a nonsignificant trend for the lumbar spine and hip BMD to decrease across increasing tertiles of PRAL (*P* < 0.1), with similar findings for forearm bone mass.

We thank Dr Remer for providing us with this opportunity for extensive discussion of estimates of renal net acid excretion and its subsequent effects on bone health, and we encourage other groups to reanalyze existing dietary intake and bone health data sets to enable further exploration of the effect of dietary acidity and alkalinity on skeletal integrity.

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## Iron and zinc interactions

Dear Sir:

In a letter to the Editor in the December issue of the Journal, Sreedhar (1) raises the question whether iron supplementation has a negative effect on zinc concentrations, because the data from various studies seem to be conflicting. Although Lind et al (2) already pointed out several reasons that could explain the differences between the studies, we think that there is a more important reason for such differences.

Note that the results of the study by Lind et al (3) and of our study (4) were similar. Both studies reported a significant effect of interaction between iron and zinc supplementation on hemoglobin concentrations (*P* = 0.021 and *P* = 0.06, respectively) but not on zinc concentrations (*P* value not reported and *P* = 0.13, respectively). The main difference between the studies is that iron supplementation had a modest negative effect on the prevalence of low zinc concentrations in the study by Lind et al, whereas iron supplementation appeared to have a slight positive effect in our study.

Whereas Lind et al attribute this difference to differences in initial zinc status, we believe that the most important reason for this difference is that we controlled for the effect of the acute phase response by excluding infants with a C-reactive protein concentration > 10

mg/L in the analysis of the prevalence of deficiency and by controlling for the acute phase response in the analysis of covariance. The acute phase response strongly influences the concentrations of many indicators of micronutrient status, including ferritin and zinc concentrations (5). In the study by Lind et al, it is conceivable that the morbidity in the iron group was higher than in the placebo group, which led to lower zinc concentrations in the iron group. Iron supplementation is known to affect morbidity (6, 7).

Rather than the results, it is the interpretation of the outcomes that differs between the reports because of the importance given to outcomes by the 2 sets of authors. For example, Lind et al report that the prevalence of iron deficiency anemia was reduced to 2% and 3% after supplementation with iron and iron combined with zinc, respectively: these prevalence values are similar to those reported by us (3% and 8%, respectively). Our conclusion is that supplementation with iron and zinc combined is as effective in reducing iron deficiency anemia as is supplementation with iron alone. Thus, combined supplementation should be recommended in populations with a high risk of both iron and zinc deficiency. However, Lind et al concluded that combined iron and zinc supplementation is not optimal, because the increase in hemoglobin concentrations in the combined supplementation group was not significant. From a physiologic point of view, this is completely correct. However, note that in the study by Lind et al, the prevalence of low serum zinc after supplementation was 9% higher in the iron-only group and 24% lower in the iron plus zinc group than in the placebo group. To us, this provides clear evidence of the benefit of combined supplementation with iron and zinc.

The discussion between Sreedhar and Lind et al again shows the need for defining what is meant by interactions, because several different definitions are currently used. One definition is based on statistical arguments, with an interaction being significant when the combined effect of 2 interventions on an outcome variable does not equal the additive effect of the 2 interventions alone. To take a hypothetical example, iron and zinc interact according to this definition when combined supplementation reduces the prevalence of anemia by 30%, while the single supplements reduce anemia prevalence by 40% and 15%, respectively. If the reduction of anemia prevalence had been 55% after combined supplementation, there is no interaction in the statistical sense. However, interactions can also be physiologically defined. This means that 2 nutrients are surmised to play a role in the same metabolic pathway. Using the same example, a 55% reduction in anemia prevalence by the combined supplement would signify an interaction in the physiologic sense, because both nutrients contribute to the effect.

However, with Bob Dylan in mind, it is clear that "all definitions can't be right all of the time." On the basis of the first definition, how should the occurrence of an effect of interaction between iron and zinc on ferritin concentrations in the absence of an effect on hemoglobin concentrations be interpreted? It would be very unsatisfactory if only the outcome measured would determine whether an interaction between 2 nutrients exists. In contrast, in the example of iron and zinc, a physiologic interaction is surmised, but we are not sure. Iron and zinc may contribute to higher hemoglobin concentrations via 2 completely separate pathways.

It is not surprising that this situation leads to confusion in discussions and interpretation of results. The term *interaction* needs to be clearly defined, not only whether it is used in the statistical or physiologic sense but also whether the interaction is antagonistic, synergistic, or additive in nature.

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## Reply to FT Wieringa et al

Dear Sir:

I appreciate the comments of Wieringa et al in response to my letter to the Editor (1). In their letter, Wieringa et al search for explanations of the conflicting evidence of iron and zinc interactions (2, 3).

In my letter, I agreed with the convincing evidence that exclusion of acute phase reactants can correct for underestimation or overestimation of serum ferritin, retinol, and zinc, which are the most commonly used indicators of iron status, vitamin A status, and zinc status, respectively. Wieringa et al have rightly pointed out the caveats of using serum ferritin, retinol, and zinc as indicators of their respective micronutrient status during inflammation. However, it should be reemphasized that other factors like age, sex, and a variety of other host and environmental factors, such as pregnancy, genetic condition, overall nutrition, and force of infection, may influence the inflammatory process and hence micronutrient status. Plasma concentrations of these micronutrients may bear little relation to tissue status or the storage pool during inflammation, and data on nutritional status should be carefully examined and interpreted. In this respect, it is essential to understand the dynamics of both inflammation and micronutrient indexes.

In general, the interactions of micronutrients, especially iron and zinc, are believed to involve both preabsorptive (divalent metal transporter 1) and postabsorptive (ferritin, transferrin, and cytosolic aconitase) stages. Accumulating evidence suggests that these interactions can sometimes be beneficial rather than deleterious. For example, zinc can act as an antioxidant and prevent peroxidative damage during oral repletion of iron, either by induction of metallothionein or by stabilization of cell membranes (4). Therefore, investigations should examine the pros and cons of trace element interactions, which may provide information relevant to nutritional prophylaxis programs.

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## Reply to FT Wieringa et al

Dear Sir:

In their letter, Wieringa et al raise questions concerning definitions of iron and zinc deficiency and interpretation of interactions in the case of combined iron and zinc supplementation. The definitions of anemia, iron deficiency, zinc deficiency, and iron deficiency anemia (IDA) used in articles by Dijkhuizen et al (1) and us (2) are a hemoglobin concentration < 110 g/L, a serum ferritin concentration < 12 µg/L, a serum zinc concentration < 10.7 µmol/L, and a combination of anemia and low serum ferritin, respectively. These cutoffs comply with those suggested by the World Health Organization for anemia, iron deficiency, and IDA (3), whereas the cutoff for zinc deficiency was chosen as the value for serum zinc concentration 2 SDs below the mean for adult persons sampled in the morning after an overnight fast (4). One should remember that these definitions do not imply functional consequences. There are few population-based studies on normal serum zinc concentrations in infants and children. The only 2 studies published to our knowledge suggest a 2.5 percentile at 9–10 µmol/L (5, 6). Thus, both the study by Dijkhuizen et al (1) and our study (2) may have overestimated the problem of zinc deficiency in the populations studied. In addition, the use of serum zinc concentrations in the estimation of zinc status is not optimal, although it has been suggested to be of value in the estimation of zinc status in groups (7). In our study, only single

supplementation with iron improved anemia. Both the iron-only supplement and the combined iron and zinc supplement decreased IDA prevalence, although the definition of IDA mentioned above must be pointed out here. Although the iron-only supplement improved both hemoglobin and serum ferritin concentrations, the combined iron and zinc supplement increased only serum ferritin concentrations but had no effect on hemoglobin concentrations in comparison with placebo. From a physiologic point of view, it must then be argued which iron-status measure more accurately depicts improved iron status. We argue that although an increase in hemoglobin concentration shows that ingested iron has in fact been absorbed and used for production of hemoglobin, an increase in only serum ferritin concentration says little about actual improvement of iron status.

Of greater importance to the issue of whether iron supplementation affects zinc status or vice versa are the functional consequences of zinc and iron deficiency. In the second part of our Indonesian study to be published in a forthcoming article (8), we found that combined supplementation with iron and zinc had a significant antagonistic effect on weight gain in Indonesian infants. The interpretation of this result is that adding iron to zinc abolishes the positive effect of zinc supplementation on weight gain. In the same article, we also found that combined supplementation with iron and zinc had a significant negative effect of interaction on psychomotor development, and the interpretation of this result is that adding zinc to iron abolishes the positive effect of iron supplementation on infant psychomotor development. From a public health point of view, these findings are more important than whether iron and zinc supplementation affects the prevalence of suboptimal micronutrient status.

As Wieringa et al suggest, several levels of interaction are possible: from competition for absorptive pathways in the intestine to differences in compliance due to side effects of the combined supplement. From our data, we can determine only that an interaction has occurred, but not which type of interaction is most important. Because of the negative functional consequences, we believe that our conclusion that combined iron and zinc supplementation administered as in the studies by both Dijkhuizen et al (1) and us (2) cannot be routinely recommended remains valid. However, both iron deficiency and zinc deficiency remain important public health problems in low-income settings, and finding solutions to improve iron and zinc nutrition in vulnerable groups, such as infants, children, and pregnant women, remains imperative.

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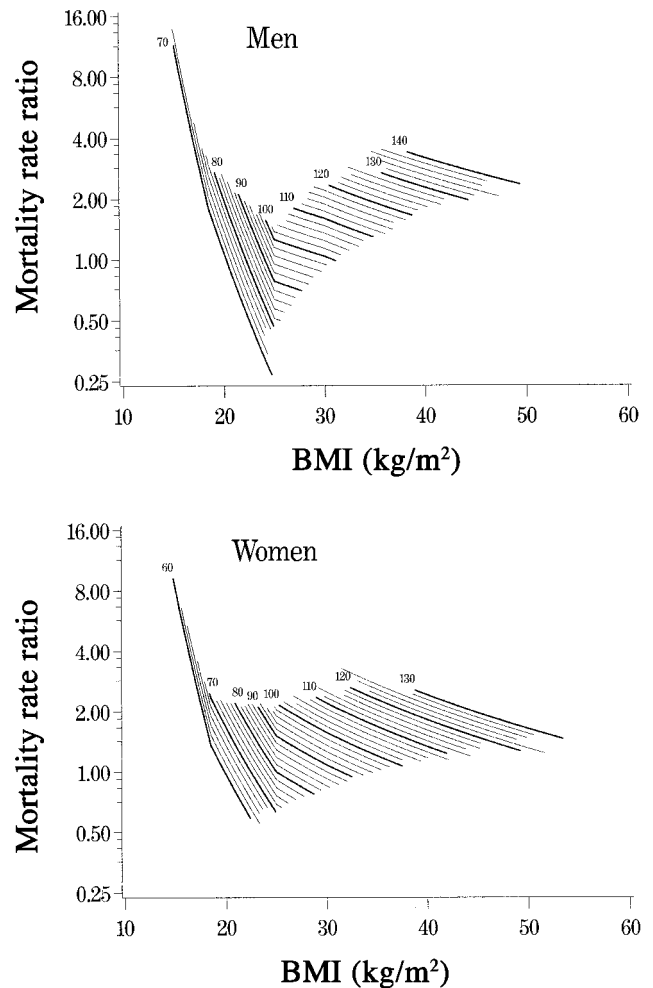
### Does waist circumference alone explain obesity-related health risk?

Dear Sir:

In an editorial related to an article by Janssen et al (1), Bray recommended that we be reluctant toward replacing body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) with waist circumference as the only clinical measurement for indicating health risks associated with overweight and obesity (2). We agree with Bray. In their article, Janssen et al (1) called for prospective studies. We published such a paper last summer (3). Our results support both the hypotheses of Janssen et al and Bray's reluctance toward ignoring BMI.

Between 1993 and 1997, 57 053 men and women aged 50–64 y were recruited for a Danish prospective study, the Diet, Cancer, and Health study. The cohort represents 7% of the entire Danish population in this age group. From recruitment until 31 December 2002, 2323 deaths (1461 men and 862 women) were identified in the Civil Registration System by using the unique personal identification numbers assigned to all Danish inhabitants. Missing information about variables of interest led to the exclusion of 628 participants, and 4 were lost to follow-up.

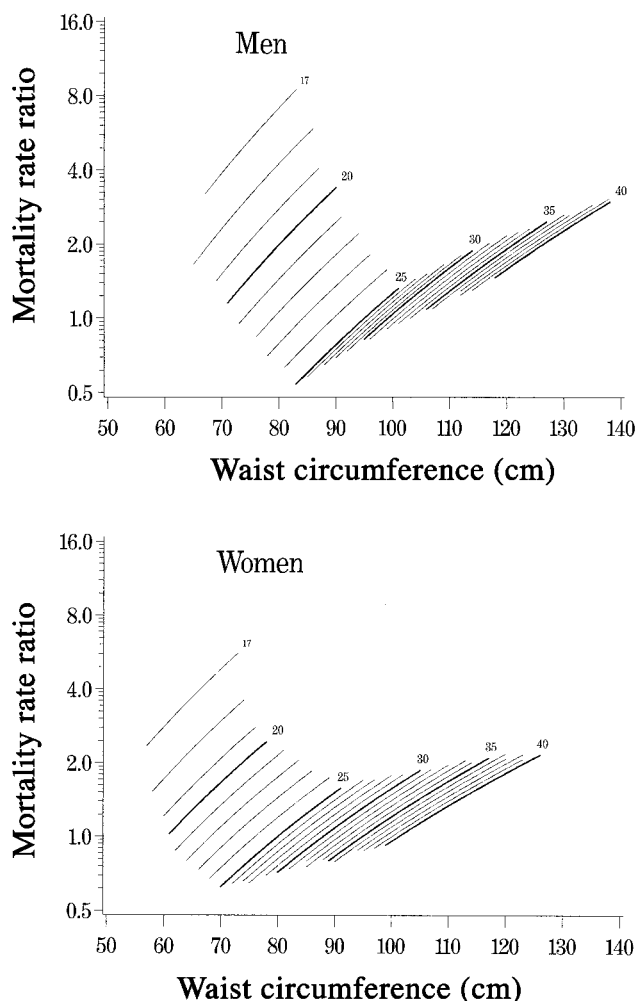
We examined the independent associations of waist circumference and BMI with all-cause mortality in this cohort of middle-aged men and women (3). We showed how BMI predicted mortality for given values of waist circumference and how waist circumference predicted mortality for given values of BMI (3). No sign of interaction was found (3). Our findings are summarized in the 2 new figures



**FIGURE 1.** Mortality risk associated with BMI (in  $\text{kg}/\text{m}^2$ ) for different values of waist circumference (in cm) among men ( $n = 26\,916$ ) and women ( $n = 29\,505$ ) in the Diet, Cancer, and Health study (1993–2002). The reference waist circumferences for the men and the women were 95 and 80 cm, respectively, and the reference BMI was 25. The vertical axis is log scaled.

presented here, which show the estimated associations for each of the obesity measures for fixed values of the other measure. The estimated association with mortality is displayed for a 95% normal range of variation in the obesity measure among subjects with a fixed value of the other measure (eg, for waist circumference = 130 cm, the 95% prediction limits for BMI were 35.7–44.3 for men and 38.8–53.4 for women). As shown in **Figure 1**, the estimated mortality rate ratio decreased with increasing BMI for all values of waist circumference between 60 and 130 cm in women and between 70 and 140 cm in men. The decrease in mortality was strongest for the lowest BMI values. The general increase in mortality with BMI among obese subjects seems to be caused by the fact that high BMI values are observed for subjects with a high waist circumference only, which can be seen from the horizontal extent of the waist circumference-specific curves. As shown in **Figure 2**, the estimated mortality rate increased log-linearly with waist circumference for BMI values between 17 and 40 in both men and women. Furthermore, increasing mortality with increasing waist circumference was found even for BMI values < 25 (3).

Thus, the importance of BMI for mortality depends on the World Health Organization's classifications of BMI (4). For overweight



**FIGURE 2.** Mortality risk associated with waist circumference for different values of BMI (in  $\text{kg}/\text{m}^2$ ) among men ( $n = 26\,916$ ) and women ( $n = 29\,505$ ) in the Diet, Cancer, and Health study (1993–2002). The reference waist circumferences for the men and the women were 95 and 80 cm, respectively, and the reference BMI was 25. The vertical axis is log scaled.

(BMI of 25–29.9) and obese (BMI  $\geq 30$ ) persons, waist circumference alone captures the increase in the mortality rate and replaces BMI as a risk indicator in a graded fashion, as suggested by Janssen et al (1). In contrast, for underweight (BMI  $< 18.5$ ) persons, BMI dominates the mortality rate, and in the normal weight range (BMI of 18.5–24.9), both waist circumference and BMI predict the mortality rate (3), but in opposite directions.

In summary, when BMI is  $>25$ , waist circumference alone is a very good predictor of mortality, whereas when BMI is  $<25$ , BMI is also important for the mortality rate, and waist circumference cannot fully replace BMI (3). Further studies investigating other endpoints related to obesity are needed.

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## Reply to J Bigaard et al

Dear Sir:

We appreciate the editorial by Bray (1) that accompanied our recent article examining the independent relations of body mass index (BMI) and waist circumference (WC) with obesity-related health risk (2). We also appreciate the letter by Bigaard et al that was written in response.

The article (3) that is referred to in the letter by Bigaard et al is an important longitudinal analysis that complements and extends our cross-sectional observations (2). A key finding from both of these articles is that higher WC values predict an increase in morbidity or mortality after control for BMI. These observations show the importance of including WC as a routine clinical measure. The 2 articles differed in that BMI was not a significant predictor of obesity-related health risk after control for WC in our cross-sectional analysis (2), whereas BMI was negatively associated with mortality after control for WC in the study by Bigaard et al (3). This result is supported by the results of an earlier longitudinal study in which BMI was negatively associated with mortality after adjustment for WC in men (4). In other words, in both of these longitudinal studies, higher BMI values indicated a lower mortality risk once the risk attributable to WC was accounted for (3, 4). This observation is far from intuitive, because most researchers and clinicians would argue that higher BMI values indicate a greater health risk. This is an important observation, which suggests that after statistical control for WC, BMI may represent a unique aspect of body composition—one that decreases health risk.

It is important to clarify that at no point in our article (2) did we indicate that clinicians should not obtain height and weight measurements to calculate BMI, as may have been interpreted from the letter by Bigaard et al or from the editorial by Bray (1). Rather, we suggested “that BMI coupled with WC did not predict obesity-related health risk better than did WC alone when these 2 anthropometric measures were examined on a continuous scale. . . However, when WC was dichotomized into the normal and high-risk categories advocated by the NIH [National Institutes of Health], BMI remained a significant predictor of health risk.” On the basis of these findings, we suggested “that WC is a better marker of health risk than is BMI, and consequently a greater emphasis should be placed on

WC in the obesity classification system.” We also proposed that “future studies are required to determine whether WC alone can be used as an indicator of health risk in clinical and research settings if a greater number of WC risk strata are developed, much as are currently used for BMI.”

Together the findings from our study and those of Bigaard et al support the observation that the use of WC measures identifies persons at increased risk of morbidity (2) and mortality (3) independently of BMI. These observations do not suggest that BMI should be withdrawn from the clinician’s office as a tool for identifying health risk. However, they do suggest that emphasis be placed on WC as a routine measure to identify obesity-related health risk. Whether the time has come to use WC as the first measure of obesity-related health risk and to use BMI as a supplement to WC warrants serious consideration.

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## Reply to J Bigaard et al

Dear Sir:

The letter by Bigaard et al discusses their article (1) that examined body mass index and waist circumference in relation to mortality in a Danish population and that appeared in print as I was writing my editorial to accompany the article by Janssen et al (2). I am happy to see the concurrence between my view and that of Bigaard et al. The figures that Bigaard et al add to their letter are helpful in pointing out the interaction between body mass index and waist circumference and the greater value of one over the other at different ends of the body mass index distribution.

The articles by Janssen et al (2) and Bigaard et al (1) focused on mortality, most of which was cardiovascular in nature. For cardiovascular mortality, the relation to body mass index is less pronounced than that for mortality from diabetes and gall bladder disease. Analysis of a large data set with information about mortality, cardiovascular disease, and diabetes would be most instructive. Until there is new information, however, I still maintain that the appropriate clinical steps for evaluating the risk associated with body weight are measurement of body mass index and waist circumference coupled with other laboratory measurements related to the metabolic syndrome (3).

The one point that I would like to stress from my editorial is that the current recommendations for waist circumference cutoffs do not adequately reflect the ranges that could help clinicians make judgments when evaluating their patients. Adoption of new cutoffs would be a step forward.

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## Erratum

Rozen GS, Rennert G, Dodiuk-Gad RP, et al. Calcium supplementation provides an extended window of opportunity for bone mass accretion after menarche. *Am J Clin Nutr* 2003;78:993-8.

On page 994, Table 1 erroneously contains data that represent values obtained at the end of the study period. The correct data, which represent values obtained at the time of inclusion in the study only, are represented in the revised table below.

**TABLE 1**

Baseline characteristics of the placebo and calcium-supplemented groups at the time of inclusion to the intervention study<sup>1</sup>

	Placebo group (n = 51)	Calcium-supplemented group (n = 49)
Age (y)	14.83 ± 0.11	14.86 ± 0.09
BMI (kg/m <sup>2</sup> )	20.39 ± 0.44	20.75 ± 0.41
Height (cm)	160.83 ± 0.73	161.26 ± 0.94
Weight (kg)	52.87 ± 1.32	54.04 ± 1.23
Time since menarche (mo)	26.04 ± 1.33	26.25 ± 1.71
Calcium intake (mg/d)	578.76 ± 22.55	580.22 ± 24.49
Energy intake (kcal)	1720.68 ± 83.97	1836.21 ± 98.84
BMD (g/cm <sup>2</sup> )		
Total-body	1.05 ± 0.01	1.04 ± 0.01
Lumbar spine (L2–L4)	1.09 ± 0.02	1.08 ± 0.02
Femoral neck	0.99 ± 0.02	0.99 ± 0.01
BMC (g)		
Total-body	819.96 ± 16.56	820.53 ± 18.48
Lumbar spine (L2–L4)	42.12 ± 0.98	40.69 ± 1.11
Femoral neck	4.43 ± 0.09	4.34 ± 0.09
PTH (pg/mL)	30.14 ± 1.45	31.37 ± 1.88
BAP (ng/mL)	23.43 ± 1.39	24.72 ± 1.39
Osteocalcin (ng/mL)	12.96 ± 0.44	13.41 ± 0.45
DPD (nmol DPD:mmol creat)	11.92 ± 0.63	12.19 ± 0.56
25(OH)D <sub>3</sub> (ng/mL)	13.74 ± 0.64	14.07 ± 0.74

<sup>1</sup> All values are  $\bar{x} \pm \text{SEM}$ . BMD, bone mineral density; BMC, bone mineral content; PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase; DPD, deoxypyridinoline cross-links; creat, creatinine; 25(OH)D<sub>3</sub>, 25-hydroxyvitamin D<sub>3</sub>. There were no significant differences between groups by *t* test.