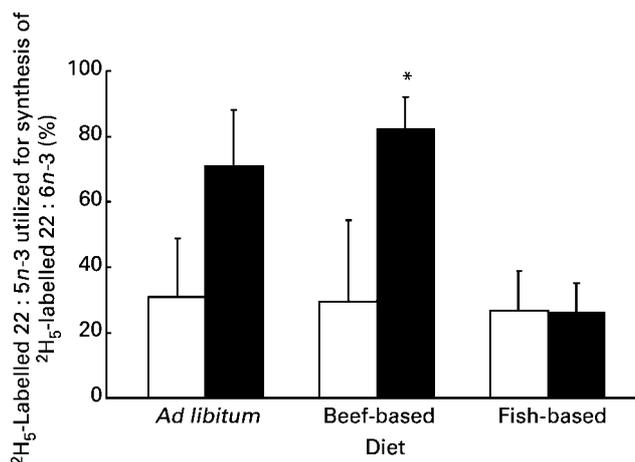


## Nutrition Discussion Forum

### *n*-3 Fatty acid metabolism in women

Using a stable-isotope tracer technique, Burdge & Wootton (2002) noted that women of child-bearing age (about 28 years) had a much greater capacity to convert  $\alpha$ -linolenic acid (18:3*n*-3) to docosahexaenoic acid (22:6*n*-3) compared with men of a similar age (Burdge *et al.* 2002). Based on their analysis of the plasma  $^{13}\text{C}$ -labelled fatty acids, they reported that there was approximately a 9% excursion of  $^{13}\text{C}$ -labelled 18:3*n*-3 into  $^{13}\text{C}$ -labelled 22:6*n*-3 in women. In men, however, they found essentially no excursion of the label into plasma 22:6*n*-3 (0% excursion). However, they did show excursion of the tracer into both eicosapentaenoic (20:5*n*-3) and docosapentaenoic (22:5*n*-3) acids in both groups of subjects (Burdge *et al.* 2002).

Using similar isotope tracer procedures, we previously reported that both men (*n* 4) and women (*n* 4) were capable of converting  $^2\text{H}_5$ -labelled 18:3*n*-3 ethyl ester into  $\text{C}_{20}$  and  $\text{C}_{22}$  polyunsaturated fatty acids, including  $^2\text{H}_5$ -labelled 22:6*n*-3 (Pawlosky *et al.* 2001). Moreover, we found that both male (*n* 5) and female (*n* 5) subjects were able to synthesize 22:6*n*-3 from 18:3*n*-3 when they subsisted on various diets (fish- or beef-based, or *ad libitum*) that had different concentrations of long-chain polyunsaturated fatty acids (Pawlosky *et al.* 2003). We derived the *in vivo* rate constant coefficients for the individual transformations of *n*-3 fatty acids beginning with 18:3*n*-3 and calculated the percentage utilization of each precursor *n*-3 fatty acid for product formation (e.g. the percentage of 20:5*n*-3 converted to 22:5*n*-3 was calculated using the rate constant coefficients describing this transformation) using a compartmental modelling procedure. The differences between men and women in their capacities to utilize 18:3*n*-3 for 22:6*n*-3 production observed by Burdge & Wootton (2002) prompted us to analyse data from our dietary study (Pawlosky *et al.* 2003) in respect of gender. In evaluating the effects of the beef- or fish-based or *ad libitum* diets on the kinetics of *n*-3 fatty acid metabolism, we observed that gender exerted a profound influence in the determination of a rate constant coefficient involved in one of the steps in the biosynthesis of 22:6*n*-3. During the period when subjects subsisted on a beef-based diet, the rate constant coefficient for the conversion of 22:5*n*-3 to 22:6*n*-3 was much greater ( $P=0.001$ ) in women ( $k$  0.041 (SD 0.007)) compared with men ( $k$  0.012 (SD 0.004)). The larger rate constant coefficient in women led to a nearly 3-fold greater amount of 22:5*n*-3 utilized for 22:6*n*-3 synthesis compared with men (Fig. 1). This was also observed during the *ad libitum* dietary phase of study, but did not reach statistical significance ( $P=0.08$ ). Very interestingly, while subjects subsisted on the fish-based diet, both groups showed about equal capability in their utilization of 22:5*n*-3 for 22:6*n*-3 synthesis (Fig. 1).



**Fig. 1.**  $^2\text{H}_5$ -Labelled 22:5*n*-3 (%) utilized for synthesis of  $^2\text{H}_5$ -labelled 22:6*n*-3 in male (□) (*n* 5) and female (■) (*n* 5) subjects maintained on each of three different diets (*ad libitum*, beef-based and fish-based) for a period of 3 weeks. Values are means with standard deviations shown by vertical bars. Values are derived from the *in vivo* kinetic rate constants of *n*-3 fatty acid metabolism. Mean value was significantly different from that of male subjects (Student's *t* test): \* $P=0.03$ .

The effect of gender on the percentage excursion of labelled *n*-3 fatty acids observed by Burdge & Wootton (2002) in human subjects may be largely explained by the differences in the magnitude of the rate constant coefficient that describes the synthesis of 22:6*n*-3 from 22:5*n*-3 in male and female subjects. Gender appears to be a strong determinant that influences the synthesis of 22:6*n*-3 in human subjects. It is possible that Burdge & Wootton (2002) failed to detect excursion of the tracer into plasma 22:6*n*-3 in male subjects because of the lower conversion rate of 22:5*n*-3 to 22:6*n*-3, demanding highly sensitive analytical procedures. It is noteworthy that the beef-based diet did not appear to stimulate the synthesis of 22:6*n*-3 in male subjects compared with a fish-based diet (Fig. 1). This suggests that the regulation of *n*-3 fatty acid metabolism in women is more sensitive to dietary alterations and this may possibly be due to hormonal factors.

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## *n*-3 Fatty acid metabolism in women – Reply

The findings reported by Pawlosky *et al.* (2003a) are in good agreement with our results, which show greater conversion of  $\alpha$ -linolenic acid (LNA; 18: 3*n*-3) to docosahexaenoic acid (DHA; 22: 6*n*-3) in women compared with men consuming their habitual diet (Burdge *et al.* 2002; Burdge & Wootton, 2002). It has long been known that greater oestrogen exposure increases dihomo- $\gamma$ -linolenic acid and arachidonic acid concentrations in women, which implies increased  $\Delta$ 6- and  $\Delta$ 5-desaturase activities (Ottosson *et al.* 1984). This is consistent with the observation that women taking 30–35  $\mu$ g ethinyloestradiol/d in a contraceptive pill, which represents an increase in oestrogen exposure compared with the menstrual cycle, had 2.5-fold greater conversion of  $\alpha$ -[ $^{13}$ C]LNA to DHA than those who did not take synthetic oestrogens (Burdge & Wootton, 2002). One additional important implication of our findings and those of Pawlosky *et al.* (2003a) is that the conversion of docosapentaenoic acid (DPA) to DHA, which uniquely requires both  $\Delta$ 6-desaturase activity and peroxisomal  $\beta$ -oxidation, is also modified by gender. This suggests that DHA synthesis may be regulated independently from the activity of earlier steps in the pathway.

There appears to be a reciprocal relationship between partitioning of  $\alpha$ -[ $^{13}$ C]LNA towards  $\beta$ -oxidation, measured as excretion of  $^{13}$ CO<sub>2</sub> on breath and C recycling into saturated and monounsaturated fatty acids, and conversion to eicosapentaenoic acid (EPA), DPA and DHA (Burdge & Wootton, 2003). Women, who preferentially use carbohydrate as an energy source (Jones *et al.* 1998), would have a greater availability of  $\alpha$ -LNA for conversion to EPA, DPA and DHA. In men, who use fatty acids as an energy source to a greater extent than women (Jones *et al.* 1998), less  $\alpha$ -LNA would be available for conversion to long-chain polyunsaturated fatty acids. Together with greater fractional conversion of DPA, preferential partitioning of fatty acids away from  $\beta$ -oxidation may further increase the overall capacity of women for DHA synthesis.

Although there appear to be differences in the sensitivity of the techniques used, these are not so great as to produce differing conclusions about the effects of gender upon  $\alpha$ -LNA metabolism. In fact, when [ $^{13}$ C]DHA enrichment exceeded background abundance, we could readily detect it (Burdge & Wootton, 2002). We suggest that conversion below this level would be of questionable biological importance. Kinetic analysis of the type described by Pawlosky *et al.* (2003b) uses concentrations of labelled

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DOI: 10.1079/BJN2003985

fatty acids in plasma as an indirect measure of  $\alpha$ -LNA conversion, which is an intracellular process. Since such models ignore partitioning of individual intermediates between lipid pools and different metabolic fates ( $\beta$ -oxidation, storage or further metabolic transformation), there is a tendency towards underestimation of conversion and limited precision.

The key question that remains to be addressed is the biological significance of differences in capacity for DHA synthesis between men and women. It is possible that maintenance of DHA concentrations in tissues in men may depend on dietary sources or recycling to a greater extent than in women. Capacity to up-regulate DHA synthesis under hormonal control in women may be important for satisfying fetal demands for DHA during pregnancy. Plasma phospholipid DHA concentration increases in pregnant women: this may facilitate supply of DHA to the fetus (Postle *et al.* 1995). Up-regulation of DHA synthesis due to rising circulating oestrogen levels may be an important source of DHA to support this increase in maternal plasma DHA concentration. One potential implication is that differences in capacity for DHA synthesis may contribute to the 50 % variation in plasma DHA concentration between women at term (Postle *et al.* 1995). If true, infants born to mothers with a lower capacity for DHA synthesis may be at greater risk of deficit in DHA assimilation. It would then be important to characterise in detail factors that determine capacity for DHA synthesis in women.

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DOI: 10.1079/BJN2003986