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Published in:
Current Anthropology

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2005

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Joordens, J. C. A., Kuipers, R. S., & Muskiet, F. A. J. (2005). On breast milk, diet, and large human brains. *Current Anthropology*, 46(1), 122-124.

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Discussion

On Breast Milk, Diet, and Large Human Brains

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19 VII 04

Robson, in "Breast Milk, Diet, and Large Human Brains" (CA 45:419–25), has tested the hypothesis that "greater proportions of animal products in human diet affect the composition of human milk" and Martin's hypothesis that "the unique pattern of human brain growth is due to the unique composition of human milk." Her conclusions are that "the wide variation in human diet has little impact on breast milk quantity and quality" and that Martin's hypothesis should be rejected. We agree with the latter conclusion (adding that we question whether Martin's hypothesis merited the effort) but would like to raise some points of discussion.

1. Robson states that AA and DHA levels in human milk are consistent despite variations in maternal diet. Contrary to this, however, she notes the dose-dependency of its DHA content indicated by several maternal-DHA or fish-oil-supplementation trials. Consequently, because of the sizable worldwide differences in maternal DHA (especially fish) intake, one may expect the DHA content of human milk to be subject to wide biological variation, and that is indeed what we have found in a data set of 465 human milk samples collected by the Groningen University Hospital in various countries of the world during the past 25 years (Smit et al. 2002). Analysis of 28 fatty acids in these samples revealed that the biological variation is greatest in DHA and EPA, amounting to 68% and 100%, respectively. The lowest DHA content was found in the breast milk of a mother living in Islamabad, northern Pakistan (0.03 mol%), and the highest in a counterpart living in one of the fish-eating Caribbean islands (1.63 mol%). The low DHA content of milk in northern Pakistan is a matter of special concern (Smit et al. 1999), since it undoubtedly reflects poor maternal DHA status in pregnancy, during which the initial part of brain growth occurs. Regarding the consistency of the AA content of human milk Rob-

son seems to have a point, since in line with this notion our data set indicates relatively low (i.e., 28%) biological variation. However, as yet unpublished data obtained from a fish-eating population living on Lake Kitangiri (a freshwater lake in northeastern Tanzania) has refuted this supposed consistency. The milk of these women was found to have the highest AA content encountered by us so far (median 0.70 mol%, range 0.50–0.90), which derives from the lifetime consumption of local AA- (and DHA-) rich freshwater fish as the only animal lipid source. We conclude that the fatty-acid composition of human milk is highly dependent on both short- and long-term maternal diet and that, in view of the variety of dietary habits, there is no such thing as consistency in its fatty-acid composition worldwide. We have at present little knowledge of the evolutionarily established "unique composition of human milk" or the interaction between this ancient human milk composition and our brain-building genome. It is, however very probable that early *Homo sapiens* had higher intakes of long-chain polyunsaturated fatty acids (LC-PUFA) (e.g., from game and fish) than modern Western humans, and recent experiments in rats have shown that dietary omega-3 fatty acids (ALA, EPA, and DHA) not only cause changes in brain phospholipid structure and composition but also modulate the expression of a sizable number of genes with functions in, for example, brain cell structure, energy metabolism, neurotransmission, signal transduction, and regulation (Kitajka et al. 2002).

2. Robson concludes that there is no evidence that LC-PUFA deficiencies during infancy cause smaller brain size. We would point out that many studies have shown a relation between DHA status and head circumference or calculated brain weight, though only within the range of normal human brain proportions (e.g., Hornstra 2000, Woltil et al. 1998). However, we regard brain size as irrelevant to the issue at hand. It is not brain size that matters here but brain quality. Therefore, we do not agree with Robson's support of Heird's observation that "formulas without LC-PUFA have been fed to infants for decades and have not resulted in epidemics of either poor vision or neurodevelopmental delays." It is well established (see, e.g., Muskiet et al. 2004) that feeding infants with standard formulas lacking DHA and AA causes biochemically demonstrable low status of LC-PUFA in various body compartments including the brain (notably DHA). Low LC-PUFA status coincides, especially in pre-term infants, with unfavorable neurodevelopment during the first four postnatal months, as derived from various tests of visual, perceptive, cognitive, and motor development (e.g., Larque, Demmelmair, and Koletzko 2002, Koletzko et al. 2001, Innis 2003). A recent study carried out by our Groningen group showed that term infants receiving formula without LC-PUFA had a higher

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frequency of mildly abnormal “general movements” at the age of three months, a condition which significantly increased risk of development of minor neurological dysfunction, attention problems, and aggressive behavior at school age (Bouwstra et al. 2003). In addition, epidemiological data and controlled trials with ALA and fish oil implicate subclinical omega-3 deficiency in cardiovascular disease, inflammatory disorders, attention deficit disorder (ADHD), dyslexia, (postpartum) depression, dementia, and schizophrenia (Muskiel et al. 2004 and references therein, Peet 2004). Corresponding with declining intake of omega-3 fatty acids during the past 100 years, some of these diseases have become widespread in the modern Western world and nowadays constitute a major public health concern. We realize that the consequences of subclinical (micro-) nutrient deficiencies are difficult to objectify and to prove according to rules of “evidence-based medicine,” since deficiencies usually operate over long periods, which hampers identification of causal relationships. However, we feel that the current lack of hard evidence on long-term effects of low LC-PUFA status in pregnancy and infancy is not to be taken as proof of lack of effect and therefore regret the misleading message transmitted by the quotation from Heird in Robson’s report.

Reply

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I thank Joordens, Kuipers, and Muskiel for their comments and appreciate the opportunity to continue discussion surrounding the mechanisms of human encephalization. While they contest the generalizations I make about the cross-cultural variation of human breast milk composition and its effects on infant development, they agree with my conclusion that human milk is similar to that of other primates and is therefore not a unique resource supporting the unique rapid postnatal brain growth in humans as Martin hypothesized. However, they question whether testing “Martin’s hypothesis merited the effort.” Both Martin’s hypothesis and meat eating as a “prime releaser” for large human brain size remain extremely influential propositions among anthropologists even in the absence of a pathway for diet to facilitate this expansion. If meat eating is to influence human brain growth, then it must be shown what biochemical properties affect brain growth, when ontogenetically these nutrients would be influential, and how meat eating would transfer these benefits. I addressed each of these lines of evidence and tested Martin’s (1983, 1995) hypothesis that human breast milk was unique in composition, conferring nutritional benefits to infants during the period of rapid postnatal brain growth. I

showed that, contrary to long-standing assumptions about the role of meat eating and breast milk composition in human encephalization, the long-chain fatty-acid (LC-PUFA) composition of human breast milk is not unique among anthropoid primates and that the two primary fatty acids in brain tissue, AA and DHA, are not “prime releasers” for encephalization.

Joordens et al. cite two studies to contend that brain size is positively correlated with DHA levels. However, neither Hornstra (2000) nor Woltil et al. (1998) show that full-term infants fed non-LC-PUFA formula milks have smaller adult brain sizes. Hornstra (2000) investigated the DHA levels of fetal tissue, not breast-feeding infants, and did not find a statistically significant correlation with smaller head circumference “after correction for gestational age” (p. 1264S). Woltil et al. (1998) studied low-birth-weight babies, over half of whom were premature. Low birth weight and prematurity are both variables known to have important confounding effects on infant outcome (Hack et al. 2002). Nevertheless, as Joordens et al. note, the brain weights of infants in both studies were within normal ranges, further underlining the lack of evidence linking infant LC-PUFA levels and resulting brain size.

Joordens et al. say that they “regard brain size as irrelevant to the issue at hand. It is not brain size that matters here but brain quality.” While brain size was exactly the issue at hand in my report, they focus on brain quality because they have two primary objections to generalizations I make about the consistency of fatty acids in human milk and the (superficial) effects of LC-PUFA during infant development. First, they cite the analyses of Smit et al. (2002) and unpublished data showing wide variation in the fatty-acid levels of human milk and “no such thing as consistency in its fatty-acid composition worldwide.” Smit et al. (2002) qualify the wide variation in their study as “somewhat artificial” (p. 551) because a few cases of very high DHA levels skew their distribution. In the data they used (table 1, p. 552) the populations’ range lows (0.08–0.10 mol%) and medians (0.16–0.33 mol%) are remarkably similar despite very different diets. DHA is always present in breast milk, regardless of maternal diet, and the median value of DHA in human milk is, in fact, very consistent cross-culturally. Second, Joordens et al. point to numerous studies showing negative health and neurological effects coincident with low LC-PUFA status and therefore find Heird’s (1999) conclusion that “the described benefits of LC-PUFA are subtle” and that “formulas without LC-PUFA have been fed to infants for decades and have not resulted in epidemics of either poor vision or neurodevelopmental delays” (p. 207) misleading. Though they note (as do I) a “lack of hard evidence” supporting the “long-term effects of low LC-PUFA status,” they argue that this should not be taken as proof of lack of effect. Innis (2003) recently reviewed the mixed results of studies exploring a relationship between DHA status and several mental or motor development tests. The available evidence is equivocal, and Innis reminds us that those studies which do find “associations between DHA and

visual and neurodevelopment in breast-fed infants should not be confused with demonstration of causality" (p. S5).

Recently, Muskiet et al. (2004) continued to draw attention to the improbability of linking meat eating, LC-PUFA dietary intake, and evolution of large human brain size. They agree that meat is a poor source of DHA and that, though "humans are rather poor DHA synthesizers . . . the low LC(n-3)P synthesis rate may still provide us with sufficient LC(n-3)P status" (p. 184). The ability of infants and adults to biosynthesize DHA makes dietary sources of LC-PUFA unnecessary for brain growth and development, even to achieve very large brain sizes.

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