

Reply: Gut microbiota diversity and atopic disease: Does breast-feeding play a role?

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38 To the Editor:

39 We thank Azad and colleagues¹ for their important points regarding our article “Low diversity
40 of the gut microbiota in infants with atopic eczema”. Admittedly, we were satisfied with the
41 notion that all infants were breastfed until one month of age in the original paper.² The absent
42 increase in diversity from one week to one month of age also indicated that breastfeeding
43 inhibited diversity development. However, we did not relate microbiota diversity to exclusive
44 breastfeeding at one month of age. Reassessing the data, we identified three atopic and four
45 healthy infants who were not exclusively breastfed at one month of age. As requested, we
46 have analyzed whether exclusive breastfeeding was associated with lower gut microbiota
47 diversity, and if this affected the comparison between the atopic and healthy infants.

48
49 As hypothesized, exclusive breastfeeding was associated with low diversity of the total
50 microbiota in infant stool (Table 1). Interestingly, the results indicate that the difference was a
51 consequence of low Firmicutes diversity in the exclusively breastfed infants. Thus, although
52 the differences in Firmicutes diversity did not reach statistical significance and only seven
53 partially breastfed infants were included in this analysis, formula introduction seems to favour
54 the establishment of new Firmicutes strains. As expected, the relative abundance of
55 bifidobacteria was higher in the exclusively than the partially breastfed infants (39% vs. 15%,
56 $p=0.04$). The relative abundance of the other bacterial phyla and genera did not differ
57 significantly (data not shown).

58

59 Our results are consistent with previous reports.^{3,4} However, most studies have compared
60 breastfeeding with formula feeding, not with partial breastfeeding. What our findings and
61 those of Azad *et al* add to the field is that the diversity is higher also among partially
62 breastfed infants.¹

63

64 Secondly, we reassessed the diversity in the atopic and non-atopic infants, limiting the
65 comparison to infants who were exclusively breastfed at one month of age. The differences in
66 diversity of the total microbiota, Bacteroidetes and *Bacteroides* between atopic and healthy
67 infants in the original study² remained (Table 1), and there were still no significant
68 differences in relative abundance for any bacteria (data not shown).

69

70 There is poor evidence for an association between breastfeeding and allergy. Any allergy
71 preventive effects seem to be at most marginal.⁵ Azad and colleagues argue that the
72 exclusively breastfed infants in our study might run an increased risk for developing atopic
73 disease since their mothers had allergic disease. The atopic eczema incidence was, however,
74 similar between infants with maternal atopic heredity who were and were not exclusively
75 breastfed at one months of age in the original allergy prevention study⁶, 5/34 (15%) vs.
76 10/116 (9%), p=0.33.

77

78 In summary, exclusively breastfed infants subsequently developing atopic eczema had a lower
79 diversity of the total microbiota, the phyla Bacteroidetes and the genus *Bacteroides* than
80 infants who remained healthy. Furthermore, exclusive breastfeeding was associated with less
81 diversity. Other important sources of commensal bacteria than the nutrition seem to be
82 responsible for the higher diversity among infants who remained healthy. Potential sources
83 warrant further investigations.

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TABLE. Shannon diversity index of the total microbiota and dominant phyla and genera in stool samples obtained at one month of age in infants that were exclusively or partially breastfed, and exclusively breastfed infants that did or did not have atopic eczema during the first two years of life.

	<u>Exclusive breastfeeding at one month</u>			<u>Atopic eczema (only exclusively breastfed incl.)*</u>		
	<u>Yes</u> <u>median, (n=33)</u> <u>(iq range)</u>	<u>No</u> <u>median, (n=7)</u> <u>(iq range)</u>	<u>p-value **</u>	<u>Yes</u> <u>median, (n=17)</u> <u>(iq range)</u>	<u>No</u> <u>median (n=16)</u> <u>(iq range)</u>	<u>p-value **</u>
Total microbiota	1.57 (1.39-1.85))	1.93 (1.52-2.14)	0.03	1.45 (1.13-1.57)	1.63 (1.53-2.12)	0.002
Bacteroidetes	0.31 (0.00-0.53)	0.12 (0.00-0.56)	0.72	0.06 (0.00-0.42)	0.49 (0.08-0.61)	0.04
<i>Bacteroides</i> species	0.12 (0.00-0.48)	0.12 (0.00-0.47)	0.86	0.04 (0.00-0.35)	0.30 (0.08-0.49)	0.04
Actinobacter	0.38 (0.22-0.56)	0.33 (0.09-0.46)	0.42	0.38 (0.33-0.47)	0.41 (0.17-0.71)	0.63
<i>Bifidobacterium</i> species	0.35 (0.18-0.46)	0.32 (0.06-0.37)	0.38	0.34 (0.22-0.41)	0.37 (0.16-0.63)	0.53
Firmicutes	0.59 (0.35-0.87)	1.16 (0.43-1.80)	0.15	0.44 (0.34-0.85)	0.67 (0.48-0.92)	0.19
Proteobacteria	0.21 (0.09-0.35)	0.10 (0.06-0.42)	0.92	0.17 (0.04-0.35)	0.27 (0.17-0.33)	0.38

* only infants that were exclusively breastfed at one month of age were included in the analyses; ** Mann-Whitney *U* test