

1

Breast-feeding as 'personalized nutrition'

2

3 Jonathan CK Wells

4 Professor of Anthropology and Pediatric Nutrition

5 Childhood Nutrition Research Centre

6 UCL Institute of Child Health

7 30 Guilford Street

8 London WC1N 1EH

9

10

11

12 **Introduction**

13

14 Health benefits of breast-feeding have been recognised since antiquity,¹ and yet with every
15 passing decade, our scientific understanding of breast-feeding as a mode of nutrition seems
16 to accelerate rather than reach a ‘final plateau’. We already have compelling evidence that it
17 matters, yet we also have much to discover about *how* exactly breast-feeding functions as a
18 biological process, how and why it varies between mother-infant dyads, and what this
19 means for promoting successful breast-feeding to the benefit of mothers and infants.
20 Breastfeeding is arguably the ultimate ‘biosocial’ trait, simultaneously linking complex
21 physiological processes with multiple components of behaviour in both mother and
22 offspring that are amenable to cultural influences.²

23

24 Breastfeeding provides nutrition for functions that extend far beyond somatic growth, and
25 has implications for development of the brain, gut and immune function, as well as cellular
26 health.³ Breast-feeding confers multiple health benefits on the offspring, including
27 protection from infections, increased intelligence, and probable protection against obesity
28 and diabetes, as well as reducing risks of breast cancer and diabetes in the mother.⁴

29

30 From an evolutionary perspective, breastfeeding represents ‘maternal investment’, through
31 which the mother can promote her genetic fitness by increasing the quality of her offspring.⁵

32 On the one hand, maternal fitness is promoted by allocating key nutrients and energy to
33 each offspring, a process honed for success over millions of years of evolution.⁶ On the other
34 hand, mothers often allocate resources across multiple offspring, who to some extent are
35 competitors for that investment. While each offspring might benefit from being breastfed

36 for longer, the mother may wean it earlier, in order to start investing in the next. Thus
37 breastfeeding may also be considered to represent a dynamic ‘tug-of-war’ between parties
38 with a genetic ‘conflict of interest’.⁷ **Figure 1** illustrates breast-feeding as the context for two
39 related optimisation games, through which both mother and offspring seek to maximise
40 their own genetic fitness.⁸ Importantly, the phenotypic characteristics of both mothers and
41 offspring, and their behavioural and physiological interactions, influence the outcomes of
42 these connected optimization games.⁷

43

44 *Insert Figure 1 near here*

45

46 Within both biomedical and evolutionary frameworks, a consolidating theme has been that
47 of breastfeeding as ‘personalised nutrition’. Poor maternal nutritional status may constrain
48 the delivery of both macronutrients and micronutrients to the offspring,⁹ while maternal
49 body composition is associated with the concentrations of hormones in breast-milk such as
50 leptin that may influence early programming of infant appetite.¹⁰ Breast-feeding also
51 exposes the infant to food flavours resulting from the maternal diet.¹¹ These experiences
52 may then shape later food preferences and acceptance of the solid foods available to the
53 family and culture during the process of weaning.¹¹

54

55 Breast-feeding also enables mothers to transfer immunity to the infant, whose own immune
56 function is immature at the time of birth. First, breast-milk contains large quantities of
57 secretory IgA antibodies, which are representative of the mother’s own history of
58 infections.³ Second, breast-milk, and particularly colostrum, contains leukocytes
59 (macrophages and neutrophils) that can destroy microbial pathogens by phagocytosis.³

60 Third, breast-milk contains antimicrobial factors such as lysozyme and lactoferrin.³
61 Intriguingly, the quantity of leukocytes in breast-milk increases not only if the mother has an
62 infection, but also if the offspring has an infection,¹² supporting the concept of dynamic
63 interaction between these parties illustrated in Figure 1.

64

65 Finally, breast-milk also contains microRNAs and stem cells, which may exert tissue-specific
66 effects on gene expression relating to immune and developmental functions in the
67 offspring.^{12, 13} However, studies are only beginning to produce evidence for differential
68 methylation of offspring DNA through breast-feeding.^{4, 14}

69

70 Collectively, these elements of ‘personalisation’ highlight how breast-feeding functions as an
71 early protective niche, during which the offspring can adapt to ecological stresses under the
72 mediating influence of maternal phenotype’, a scenario known to ecologists as the ‘safe
73 harbour’ hypothesis.¹⁵ During pregnancy, and to some extent during lactation, mammalian
74 offspring do not experience ecological stresses directly, but are rather exposed to the
75 magnitude of ‘maternal capital’, ie diverse aspects of phenotype which reflect the mother’s
76 relationship with her physical and social environment (**Figure 2**).¹⁶ It is within this overall
77 protective niche that the maternal-offspring dynamic interactions described in Figure 1 play
78 out.

79

80 *Insert Figure 2 near here*

81

82 So far, however, variability in breast-feeding has generally been conceptualised in relatively
83 narrow terms, referring to the direct biological characteristics of mother and offspring. It has

84 recently become clear that many of the genes that act most influentially on human
85 metabolism derive not from our own species, rather from those of our microbiomes. On this
86 basis, we must reconsider how breast-feeding links maternal and offspring biologies, and
87 how it may promote health.

88

89 **Present research activities**

90

91 Until recently, the microbiome was considered primarily in terms of pathogens, but there is
92 growing recognition that it represents an ecological system incorporating beneficial
93 commensals and symbionts that play critical roles in immune and metabolic health.¹⁷ Exactly
94 how the microbiome contributes to human metabolism is still rapidly unfolding. At a broader
95 level, a striking finding is that the transplantation of gut microbiota from adult male to
96 immature female mice resulted in elevated testosterone in the females,¹⁸ suggesting that
97 even a biological trait as fundamental as gender may in part be contingent on the activity of
98 the microbiome.

99

100 The human gut contains diverse microbes that play a key role in homeostasis under the
101 selective pressures generated both by host diet and appetite, and by competition from other
102 species.¹⁹ On the one hand, the microbiome shapes the capture of energy from the diet,
103 while on the other, the resulting metabolites shape numerous signalling systems that impact
104 appetite, inflammation and immune function, and various organs and tissues including the
105 brain.¹⁹ Collectively, the microbiome contributes millions of genes to human metabolism,
106 and variability in the underlying mix of species translates directly into variable metabolic

107 effects. A wide range of forms of malnutrition have been associated with a perturbed gut
108 microbiome, known as dysbiosis.

109

110 One crucial mother-offspring transfer of microbiota occurs at the time of delivery, but
111 breast-feeding also plays a key role in the establishment of the gut microbiome, promoting
112 both the colonization and the maturation of the infant gut.¹⁷ The bacteria present in breast-
113 milk vary in association with the stage of lactation, gestational age at delivery, and maternal
114 nutritional status.^{20, 21} Through these influences, the infant microbiome undergoes a process
115 of maturation, during which its changing composition assists the shift from digesting breast-
116 milk itself to digesting solid foods.²² This process of maturation continues through the period
117 of complementary feeding, and only reaches a composition similar to that of adults by
118 around 3 years of age.²³

119

120 Formula-feeding, and the early introduction of solid foods, have long been understood to
121 impact body composition in the short term, and may potentially impact long-term obesity
122 risk.^{24, 25} These associations may be mediated by their disruptive effects on the colonization
123 and maturation of the infant microbiome, which may in turn propagate long-term metabolic
124 effects.¹⁰

125

126 Researchers in the 19th-century had already learned that human milk contained
127 carbohydrates other than lactose, subsequently termed human milk oligosaccharides
128 (HMOs). These molecules contain lactose but are more complex and occur in multiple
129 different forms, and while evident in the milk of other species they are especially varied in
130 humans.²⁶ HMOs were soon recognised to provide metabolic substrates that promoted

131 healthy development of the infant intestinal microbiome, but more recent research has
132 shown that they also prevent pathogen attachment on mucosal surfaces, lower the risk of
133 infections, and provide important nutrients for brain development. Moreover, they may also
134 protect against mastitis in the mother.²⁶

135

136 If breast-feeding promotes growth and immune function, why do some breast-fed infants
137 nevertheless become severely malnourished? A study in Malawi demonstrated that HMO
138 variability may play a key role. Compared to the breast-milk of mothers whose infants
139 demonstrated severe growth retardation, that of healthy mothers contained greater
140 sialylated oligosaccharide concentrations.²⁷ The researchers transplanted the microbiome of
141 a growth-retarded infant into germ-free mice and piglets. By feeding these animals dietary
142 ingredients similar to those in a typical Malawian human diet, whilst also randomizing some
143 of the animals to receive sialylated bovine milk oligosaccharides, they showed that the
144 oligosaccharides increased lean tissue accretion in the growth-stunted animals.²⁷ This study
145 thus demonstrated a causal growth-promoting role of HMOs, mediated by their effects on
146 the microbiome.

147

148 However, the role of the microbiome in breast-feeding may be much broader, and might for
149 example contribute to infant appetite, and hence drive variability in infant vocalisation and
150 suckling.

151

152 **Need of future research**

153

154 Such work on the microbiome is just one component of recent work emphasising biological
155 variability within breast-feeding. Historically, breast-feeding has been promoted largely as a
156 single entity, on the grounds that it generically represents the optimum form of infant
157 nutrition. Substantial effort has been made to generate an evidence base demonstrating its
158 health benefits, and to establish how its promotion can be maximised. The introduction of
159 baby-friendly hospitals to maximise the initiation of breast-feeding, and efforts to provide
160 mothers with the time, resources and social support to continue breast-feed through infancy
161 have all been crucial.

162

163 It is something of a paradox, given the unique importance of this mode of nutrition, that
164 much of the research on which policy is based remains observational. Those mothers
165 electing, or enabled, to breast-feed are not necessarily identical in terms of their background
166 characteristics to those who do not breast-feed. This makes it difficult to partition biological
167 differences between these groups to social factors, the behavioural act of breast-feeding, or
168 the composition of breast-milk itself. Formal randomisation between breast- and formula-
169 feeding is clearly unethical, but recognising the variability *within* breast-feeding offers new
170 opportunities for health-promoting experimental work.

171

172 By focusing on the ‘personalized’ nature of breast-feeding, the characteristics of individual
173 mothers and offspring are drawn to the forefront of scientific enquiry. Likewise, by
174 considering breast-feeding to be a responsive process, it becomes reasonable to expect that
175 interventions targeting one or other party might change the *experience* of breast-feeding,
176 potentially altering its health impacts for both mothers and offspring. The notion that we

177 could not only promote breast-feeding *per se*, but also promote 'better' breast-feeding,
178 represents a major new avenue in nutritional research.

179

180 I will very briefly mention two broad strands of research that are already emerging in this
181 context, though they are by no means the only examples. The first relates to maternal
182 behaviour. For example, post-partum anxiety among mothers is common, in particular
183 among first-time mothers, and this anxiety may reduce the likelihood of mothers initiating
184 breast-feeding, or maintaining exclusive breast-feeding. Randomized trials are starting to
185 show that this effect can be countered by forms of relaxation therapy.²⁸

186

187 The second strand relates to the microbiome. The Malawian study described above
188 suggested that a narrow maternal dietary range impacted the maternal microbiome,
189 thereby steering the infant microbiome towards an unhealthy profile. This suggests that
190 changes in the maternal diet might benefit offspring development. A related issue is the
191 potential for maternal antibiotics transmitted by breast-milk to impact the infant
192 microbiome. Though research is still in its early stages, studies have already linked
193 pregnancy exposure to antibiotics with greater child BMI at 2 years.²⁹ Collectively, this work
194 suggests that targeting the microbiome may be a valuable new way to maximise the health
195 benefits of breast-feeding.

196

197 In summary, we need to reconceptualise breast-feeding as not only a form of personalized
198 nutrition, but also as a dynamic process between mothers and offspring that offers
199 opportunities to improve maternal and child health through interventions on diverse
200 relevant traits. Such efforts must not intrude on maternal autonomy, or negate the interests

201 of women in their own right. Rather, the opportunity is to target various environmental
202 constraints that may detract from the quality of breast-feeding. If we consider maternal
203 phenotype as a 'safe harbour' for the offspring in early life,¹⁵ then we must also
204 acknowledge that the mother may herself be exposed to external stresses or threats,
205 including poor diet, infection and psychosocial stress.¹⁶ If the mother has type 2 diabetes,
206 then she can still breast-feed successfully, but may need additional support to do so.
207 Improved understanding of the physiological, psychological and cultural variability
208 associated with breast-feeding will help meet these aims.

209

210 **Conflict of interest statement**

211 The author declares no conflict of interest.

212

213 **Legends for illustration**

214

215 **Figure 1.** Schematic diagram illustrating a two ‘allocation games’ played across generations,
216 whereby each of the mother and the offspring optimize their inclusive fitness. In the first
217 game, the mother optimizes her allocation of parental investment (PI) across competing
218 offspring (O1–O4). In the second game, which is sensitive to the first game, each offspring
219 optimizes its allocation of that investment between competing functions, such as
220 homeostatic maintenance (M), growth (G), immune function (I) and energy stores (E). In
221 post-natal life, breast-feeding is the primary context in which these two games are played.
222 Adapted with permission from reference 8.

223

224 **Figure 2.** Components of maternal phenotype, including dietary intake, that contribute to
225 the ‘personalized’ element of breast-feeding. While many maternal traits provide protection
226 against external stresses and threats (the ‘safe harbour’), maternal infection or metabolic
227 disease such as type 2 diabetes represent the incorporation of stresses within the protective
228 shell.

229

230 **References**

231

232 1. Papastavrou M, Genitsaridi SM, Komodiki E, Paliatsou S, Kontogeorgou A, Iacovidou N.
233 Breastfeeding in the Course of History. *J Pediatr Neonatal Care* 2015; **2**(6): 00096.

234

- 235 2. Wells JC. The role of cultural factors in human breastfeeding: Adaptive behaviour or biopower? In:
236 Bose K (ed) *Ecology, culture, nutrition, health and disease*. Kamla-Raj Enterprises: Delhi, India
237 2006, pp 39-47.
- 238
- 239 3. Jackson KM, Nazar AM. Breastfeeding, the immune response, and long-term health. *J Am*
240 *Osteopath Assoc* 2006; **106**(4): 203-207.
- 241
- 242 4. Victora CG, Bahl R, Barros AJ, Franca GV, Horton S, Krasevec J *et al*. Breastfeeding in the 21st
243 century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; **387**(10017): 475-490. doi:
244 10.1016/S0140-6736(15)01024-7
- 245
- 246 5. Trivers RL. Parental investment, and sexual selection. In: Campbell B, (ed). Chicago: Aldine, 1972.
247 pp 139-179.
- 248
- 249 6. Hinde K, German JB. Food in an evolutionary context: insights from mother's milk. *J Sci Food Agric*
250 2012; **92**(11): 2219-2223. doi: 10.1002/jsfa.5720
- 251
- 252 7. Wells JC. Parent-offspring conflict theory, signaling of need, and weight gain in early life. *Q.Rev*
253 *Biol* 2003; **78**(2): 169-202.
- 254
- 255 8. Wells JC. Adaptive variability in the duration of critical windows of plasticity: Implications for the
256 programming of obesity. *Evolution, medicine, and public health* 2014; **2014**(1): 109-121. doi:
257 10.1093/emph/eou019
- 258
- 259 9. Alvarez de Acosta T, Rossell-Pineda M, Cluet de Rodriguez I, Fuenmayor E. [Macronutrients in milk
260 of undernourished mothers]. *Arch Latinoam Nutr* 2009; **59**(2): 159-165.

261

262 10.Yasmin F, Tun HM, Konya TB, Guttman DS, Chari RS, Field CJ *et al.* Cesarean Section, Formula
263 Feeding, and Infant Antibiotic Exposure: Separate and Combined Impacts on Gut Microbial
264 Changes in Later Infancy. *Front Pediatr* 2017; **5**: 200. doi: 10.3389/fped.2017.00200

265

266 11.Ventura AK. Does Breastfeeding Shape Food Preferences? Links to Obesity. *Ann Nutr Metab* 2017;
267 **70 Suppl 3**: 8-15. doi: 10.1159/000478757

268

269 12.Witkowska-Zimny M, Kaminska-El-Hassan E. Cells of human breast milk. *Cell Mol Biol Lett* 2017;
270 **22**: 11. doi: 10.1186/s11658-017-0042-4

271

272 13.Alsaweed M, Hartmann PE, Geddes DT, Kakulas F. MicroRNAs in Breastmilk and the Lactating
273 Breast: Potential Immunoprotectors and Developmental Regulators for the Infant and the
274 Mother. *International journal of environmental research and public health* 2015; **12**(11): 13981-
275 14020. doi: 10.3390/ijerph121113981

276

277 14.Hartwig FP, Loret de Mola C, Davies NM, Victora CG, Relton CL. Breastfeeding effects on DNA
278 methylation in the offspring: A systematic literature review. *PLoS One* 2017; **12**(3): e0173070. doi:
279 10.1371/journal.pone.0173070

280

281 15.Shine R. Propagule size and parental care: the "safe harbor" hypothesis. *J Theor.Biol* 1978; **75**(4):
282 417-424.

283

284 16.Wells JC. Maternal capital and the metabolic ghetto: An evolutionary perspective on the
285 transgenerational basis of health inequalities. *Am J Hum Biol* 2010; **22**(1): 1-17.

286

- 287 17. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome
288 development: mom matters. *Trends Mol Med* 2015; **21**(2): 109-117. doi:
289 10.1016/j.molmed.2014.12.002
290
- 291 18. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U *et al.* Sex
292 differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science*
293 2013; **339**(6123): 1084-1088. doi: 10.1126/science.1233521
294
- 295 19. van de Wouw M, Schellekens H, Dinan TG, Cryan JF. Microbiota-Gut-Brain Axis: Modulator of Host
296 Metabolism and Appetite. *J Nutr* 2017; **147**(5): 727-745. doi: 10.3945/jn.116.240481
297
- 298 20. Khodayar-Pardo P, Mira-Pascual L, Collado MC, Martinez-Costa C. Impact of lactation stage,
299 gestational age and mode of delivery on breast milk microbiota. *J Perinatol* 2014; **34**(8): 599-605.
300 doi: 10.1038/jp.2014.47
301
- 302 21. Cabrera-Rubio R, Collado MC, Laitinen K, Salminen S, Isolauri E, Mira A. The human milk
303 microbiome changes over lactation and is shaped by maternal weight and mode of delivery. *Am J*
304 *Clin Nutr* 2012; **96**(3): 544-551. doi: 10.3945/ajcn.112.037382
305
- 306 22. Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R *et al.* Succession of microbial
307 consortia in the developing infant gut microbiome. *Proc Natl Acad Sci U S A* 2011; **108 Suppl 1**:
308 4578-4585. doi: 10.1073/pnas.1000081107
309
- 310 23. Yatsunencko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M *et al.* Human gut
311 microbiome viewed across age and geography. *Nature* 2012; **486**(7402): 222-227. e-pub ahead of
312 print 2012/06/16; doi: 10.1038/nature11053

313

314 24.Gale C, Logan KM, Santhakumaran S, Parkinson JR, Hyde MJ, Modi N. Effect of breastfeeding
315 compared with formula feeding on infant body composition: a systematic review and meta-
316 analysis. *Am J Clin Nutr* 2012; **95**(3): 656-669. doi: 10.3945/ajcn.111.027284

317

318 25.Daniels L, Mallan KM, Fildes A, Wilson J. The timing of solid introduction in an 'obesogenic'
319 environment: a narrative review of the evidence and methodological issues. *Australian and New*
320 *Zealand journal of public health* 2015; **39**(4): 366-373. doi: 10.1111/1753-6405.12376

321

322 26.Bode L. Human milk oligosaccharides: every baby needs a sugar mama. *Glycobiology* 2012; **22**(9):
323 1147-1162. doi: 10.1093/glycob/cws074

324

325 27.Charbonneau MR, O'Donnell D, Blanton LV, Totten SM, Davis JC, Barratt MJ *et al.* Sialylated Milk
326 Oligosaccharides Promote Microbiota-Dependent Growth in Models of Infant Undernutrition. *Cell*
327 2016; **164**(5): 859-871. doi: 10.1016/j.cell.2016.01.024

328

329 28.Mohd Shukri NH, Wells JCK, Fewtrell M. The effectiveness of interventions using relaxation
330 therapy to improve breastfeeding outcomes: A systematic review. *Maternal & child nutrition*
331 2018; **14**(2): e12563. doi: 10.1111/mcn.12563

332

333 29.Cassidy-Bushrow AE, Burmeister C, Havstad S, Levin AM, Lynch SV, Ownby DR *et al.* Prenatal
334 antimicrobial use and early-childhood body mass index. *Int J Obes (Lond)* 2018; **42**(1): 1-7. doi:
335 10.1038/ijo.2017.205

336

337

