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Early life colonization of the human gut: microbes matter everywhere

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Microbes colonising the infant intestine, especially bacteria, are considered important for metabolic and immunological programming in early life, potentially affecting the susceptibility of the host to disease. We combined published data to provide a global view of microbiota development in early life. The results support the concept that the microbiota develops with age in an orchestrated manner, showing common patterns across populations. Furthermore, infants are colonised at birth by specific, selected maternal faecal bacteria and likely their bacteriophages. Therefore, infants are adapted to receiving specific bacterial signals, partly derived from the maternal microbiota, at successive immunological time windows during early development. Birth by caesarean section compromises the initial vertical transmission of microbes whereas antibiotic use shifts the microbiota away from the normal developmental pattern. These disruptions alter the microbial signals that the host receives, potentially affecting child development.

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Introduction

Infants are colonised by microbes at birth, and over the first years of life the microbes form stable communities, termed microbiota, on all body surfaces. The microbiota consists of bacteria, archaea, viruses and fungi, different species living in different parts of the body depending on the ecological requirements of the microbial species. The bacterial component of the microbiota has been extensively investigated, while considerably less is currently known on the other microbes colonising infants. The intestine is the largest body surface with a very high density of microbes, mainly anaerobic bacteria. The microbes in the gut are in constant contact and interaction with host cells [1]. The reciprocal interaction of bacteria and immune cells plays an important role during the time when the immune system is developing: signals from the gut microbiota are thought to be important for proper immune maturation and the development of tolerance towards benign microbes [1]. Furthermore, the gut microbiota has strong effects on host energy metabolism, especially in early life [2•,3•,4,5••], via degradation of non-digestible food components [2•,3•], production of short-chain fatty acids that the host cells use as an energy source [4], metabolism of hormone-like bile acids [6], production of inflammatory and anti-inflammatory signals to the host [1], and by influencing hormone levels [7], gene expression in the liver [8], and overall energy use and storage in adipose and muscle tissue [9]. Thus, the microbiota is considered important for metabolic and immunological programming in early life, potentially affecting both current growth [2•,3•,5••], and the long-term susceptibility of the host to diet-induced metabolic disease [10].

Materials and methods

Several dozens of recent studies have addressed the development of infant bacterial microbiota since birth (Supplementary Table 1). In order to effectively summarise the existing data, we collected data on the average relative abundance of the five most abundant bacterial classes from the early life microbiota studies ($N = 34$) where this information was available and accessible. In most studies it was possible to obtain the data separately for the different birth modes and antibiotic-treated and non-treated groups, but data from formula-fed and breastfed infants were usually not presented separately. When possible, we collected information on the proportion of breastfed (exclusively or partially) infants in the cohort. Information on the proportion of breastfed infants was available for 30 of the 34 studies.

Significance of associations between the relative abundance of selected bacterial taxa and age, proportion breastfed, birth mode, antibiotic use, and location were assessed using linear regression or analysis of variance models, weighted by the cohort size. The associations with age, breastfeeding and location were tested among the vaginally born, non-antibiotic-treated cohorts (termed 'normal' cohorts).

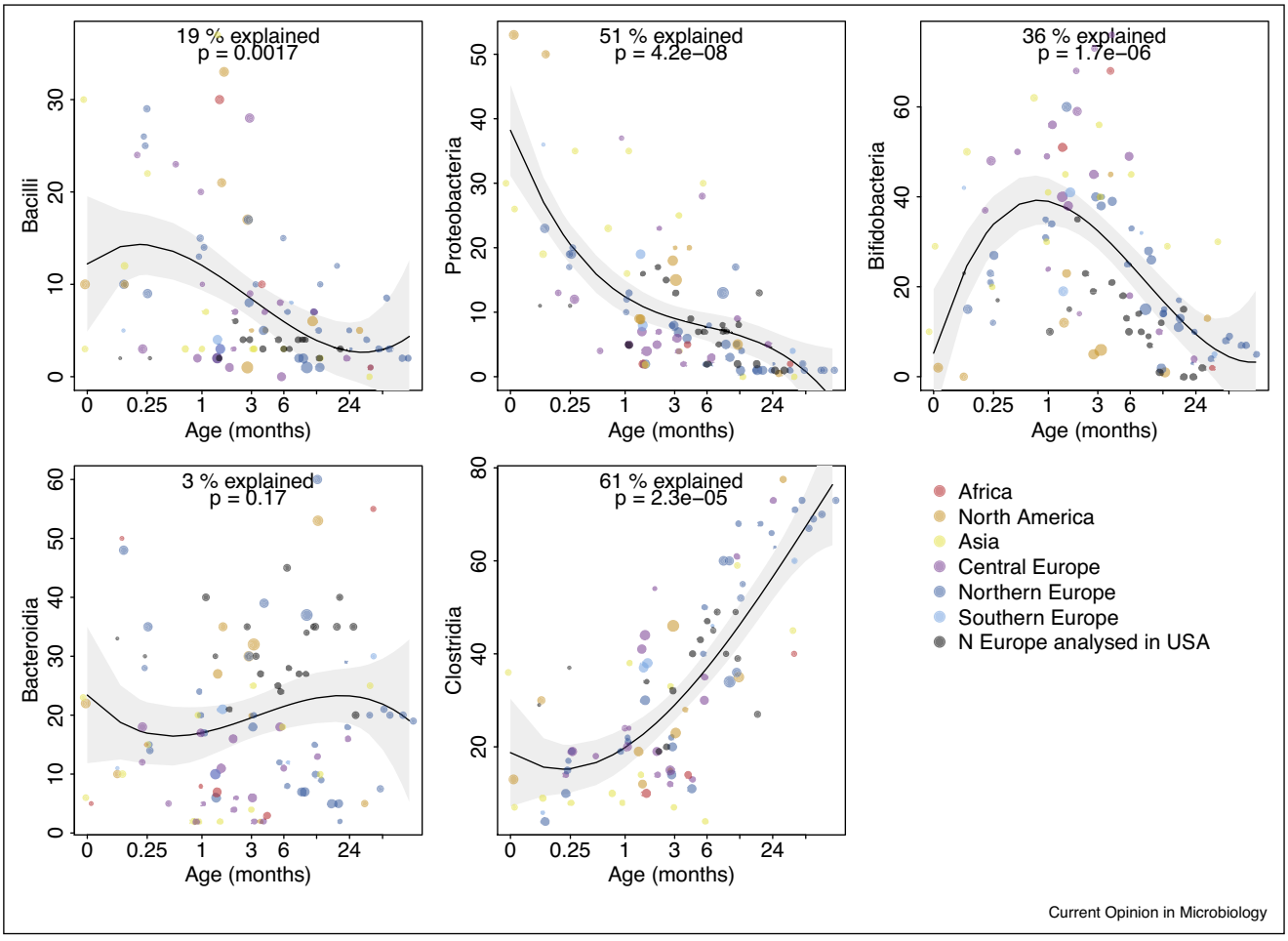
Temporal development of the gut microbiota

Already during birth, infants are exposed to a large diversity of maternal and environmental microbes, some of which find a suitable habitat on the infant body.

Immediately after birth, the bacterial communities that the infant has been exposed to, such as maternal vaginal or skin bacteria, can be detected on the infant [11]. However, these communities do not colonise the infant as such [12••]: only the microbes that are adapted to the conditions present in the different body sites of the infant can survive: the environment thus selects which microbes colonise which body surface.

After the initial colonisation, considerable temporal fluctuation of the gut microbiota composition takes place during the first years of life. In spite of different sample processing procedures, phylogenetic approaches, and geographic location of the cohorts, it is of interest to note that a common general picture emerges when data from different studies are combined (Figure 1). Typically during the first days of life, aerobic and facultative bacteria, such as streptococci and enterobacteria dominate the infant gut community (Figure 1a, b). It is assumed that the gut environment becomes increasingly anoxic with age, although actual luminal oxygen levels have not been determined in infants [13]. Presumably the reduction in oxygen levels enables anaerobic bacteria to grow, as bifidobacteria commonly become the most abundant member during the first weeks of life (Figure 1c). In some infants, *Bacteroides* spp. form a large fraction of the microbiota from early on (Figure 1d), while in others, these remain a minority and *Bifidobacterium* spp. dominate. Unlike the other taxa, *Bacteroides* spp. do not appear to follow an age-associated developmental pattern, but may be abundant at any age. Several *Bifidobacterium* and

Figure 1



Gut microbiota succession in early life. Data on the average relative abundance of the five most abundant bacterial taxa in vaginally born healthy children from different cohorts were collected from available literature (see Supplementary Table 1, references [3•,14,20,29•,34•,32•,36••,38–60]). The cohorts are coloured by continent, with Europe further geographically divided. Two studies [15,16•] contained samples from Northern Europe (N Europe), but were analysed in the US. As we found several similarities between the American data and these two cohorts, we chose to highlight them (black). The size of the symbols indicates the size of the cohort. The trend line, 95% confidence interval, proportion of variation explained, and the p-value are obtained from a regression model with the third degree polynomial of log-transformed age, weighted by the size of the cohort.