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Opinion

Insights into endogenous *Bifidobacterium* species in the human gut microbiota during adulthood

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Bifidobacteria are among the earliest and most abundant bacterial colonizers of the neonatal gut in many mammals, where they elicit purported host health benefits. While early life-associated dynamics and diversity, as well as the metabolic and beneficial activities, of *Bifidobacterium* species have been well studied, functional contributions of bifidobacteria to health and well-being of adults remain less explored. In this opinion piece, we discuss the current knowledge regarding the relevance of endogenous *Bifidobacterium* species associated with adulthood. We identify knowledge gaps and discuss opportunities for microbiota enrichment with rationally selected strains of *Bifidobacterium* more adapted to the adult host. We propose that current knowledge and future studies in this area will help us to better understand the ecological, metabolic, and functional roles played by *Bifidobacterium* in the gut ecosystem across various host ages.

Highlights

There has been an increase in knowledge pertaining to the association between human health and the gut microbiota, including *Bifidobacterium*.

Endogenous bacterial species are of major interest for application in human health.

In contrast to early life, there is limited application of *Bifidobacterium* species known to be endogenous during adulthood.

In adulthood, there are bifidobacterial species that are particularly prevalent during this host life stage, while also being associated with host health.

Bifidobacterium longum subsp. *longum*, *Bifidobacterium adolescentis*, and *Bifidobacterium pseudocatenulatum* are prevalent species in the adult gut, are metabolically adapted towards particular dietary carbohydrate components of their host, and exhibit features pertinent to both gut microbiota and host interactions.

Carbohydrates represent an important host colonization factor for *Bifidobacterium*, and metabolic diversity among species and strains may explain differential adaptation, integration, and interaction with resident microbes.

The short- to long-term depletion of *Bifidobacterium* species following antibiotics or (dietary) exclusion may provide routes to understand how bifidobacteria can be re-established.

Bifidobacterium: a relevant genus in the adult gut microbiome

Bifidobacteria represent highly abundant and prevalent members of the mammalian gut microbiota, especially during host infancy [1]. Multiple studies have shown that a variety of metabolic, immune, and intestinal disease states coincide with *Bifidobacterium* depletion in the human gut microbiota [2]. Their positive association with health and well-being across the human lifespan has prompted a flurry of research activities aimed at assessing beneficial activities elicited by bifidobacteria [3], with extensive use of strains of *Bifidobacterium animalis* subsp. *lactis*, mostly because of their favorable technological properties [4]. Based on **shotgun metagenomics** (see Glossary), recent observational studies involving large population-based cohorts or based on meta-analysis have reinforced their association with health, in particular for certain bifidobacterial species, including *Bifidobacterium adolescentis* [5,6]. In the most recent decade, several research efforts have been directed towards identification of human-gut isolates as potential next-generation probiotics or live biotherapeutics [7]. The relative abundance of *Bifidobacterium* may reach up to 15% in the adult gut microbiota [8], with higher average levels detected in Japanese individuals (17.9 ± 15.2%) [9]. This variation may be driven by analytical parameters, genetic (specifically lactase non/persistency) [10], and environmental factors such as diet [11], among others. However, while there is increasing knowledge of the contribution of endogenous *Bifidobacterium* to human health, this has not yet translated into the exploitation of particular bifidobacterial strains to the same extent as that seen for such applications aimed at early life, especially with regard to human milk oligosaccharide metabolism [12]. Nonetheless, there is a growing body of literature that underwrites the rational selection of bifidobacteria in the context of their administration to adults, though this will require further assessment of their diversity, metabolism, and associated (beneficial) functionalities of such endogenous (i.e., autochthonous or resident), adult host-associated *Bifidobacterium* species.

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In this opinion piece, we discuss the endogenous communities of *Bifidobacterium* in adults, and specifically those that are present as prevalent species. We consider opportunities to enrich the adult gut microbiota with *Bifidobacterium* and discuss knowledge gaps to bridge for future studies. We propose that ecology-based understanding of the diversity and functionalities of *Bifidobacterium* as part of the human gut microbiome will provide opportunities to identify *Bifidobacterium* strains for specific age categories to support short- and long-term human health.

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Diversity and dynamics of *Bifidobacterium* species in adulthood

Bifidobacterial communities present in the human gut are essentially represented by 12 bifidobacterial (sub)species, whose detection, abundance, and prevalence vary with age. Previous studies have referred to this as **adult-type** versus **infant-type** (bifido)bacterial taxa [8,13], where it should be said that such species are not exclusive to a specific host age but, rather, differ in prevalence and/or abundance. The age association of variable prevalence of bifidobacterial species appears to reflect extensive adaptation to the gut environment, and especially dietary habits, with differential specificity between species and even subspecies. For instance, the infant gut microbiota typically harbors a higher abundance and prevalence of *Bifidobacterium bifidum, Bifidobacterium breve*, and *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) when compared with that of adults or the elderly. In healthy adults, the prevalence of *Bifidobacterium* generally exceeds 90% with just a few species present per subject [14,15] (Figure 1). *B. adolescentis* and *B. longum* subsp. *longum* (*B. longum*) appear to represent the most abundant and prevalent species [14,16–18] with *Bifidobacterium pseudocatenulatum* being detected at high prevalence and abundance in some Asian populations [9,19–21]. Besides being globally the most prevalent subspecies irrespective of age [22], strain transmission of *B. longum* is commonly observed among family members or even between unrelated subjects [19,23] (Box 1). Other species, such as *B. bifidum*

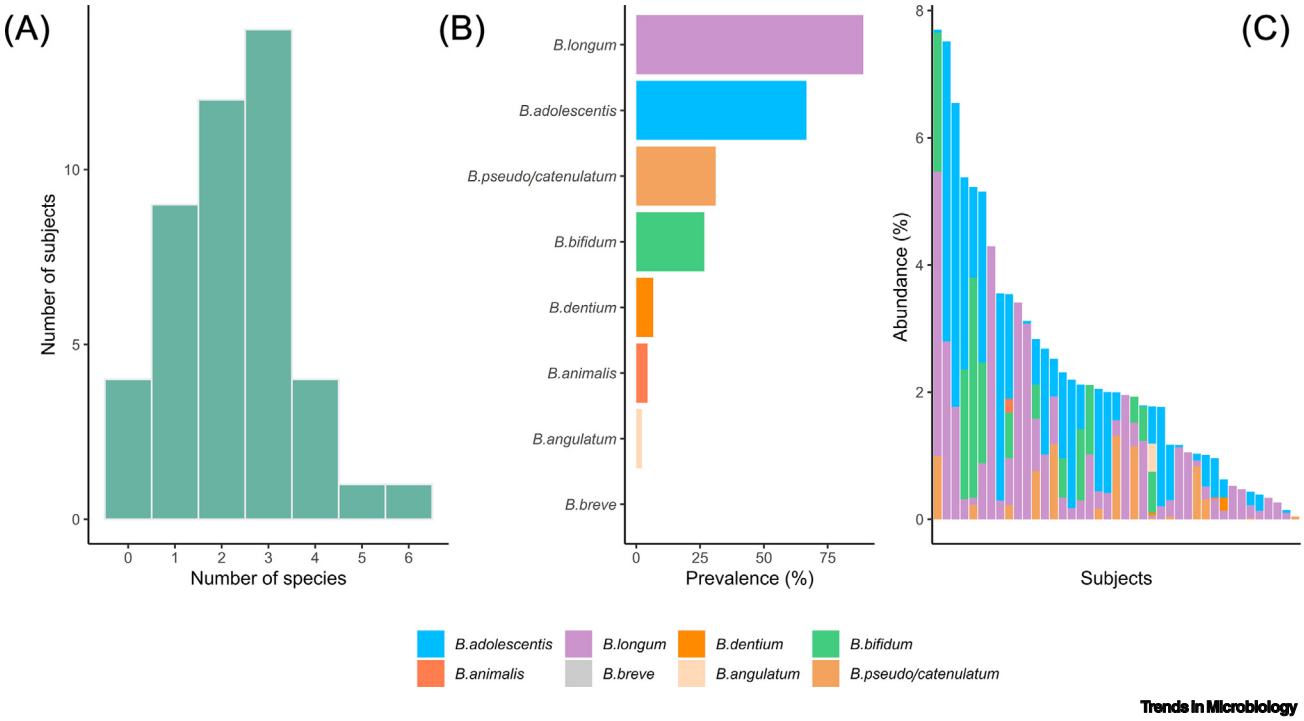

Figure 1. Example of the diversity of the *Bifidobacterium* community in a cohort of healthy adults. Number (panel A), prevalence (panel B), and abundance (panel C) of *Bifidobacterium* species (when detected) in fecal samples from 45 healthy adults. Data from [61] based on shotgun metagenomic sequencing data.

Box 1. Ecological fitness of *B. longum* subsp. *longum* (*B. longum*)

The *B. longum* taxon consists of three subspecies, that is, two human-associated subspecies – *B. longum* subsp. *infantis* (*B. infantis*) and *B. longum* – and one pig-associated subspecies (*B. longum* subsp. *suis*). *B. infantis* is highly adapted to human milk oligosaccharide metabolism and seems to be restricted to early-life hosts. In contrast, *B. longum* is a key member of bifidobacterial communities, displaying high persistence across the human lifespan, and subject to mother-to-infant and within-family transmission [23,62], while persistence of some *B. longum* strains was reported from infancy to 6 years of age [63] and up to 10 years [64]. *B. longum* strains and the functional adaptation of *Bifidobacterium* species/strains to diet, such as that associated with breast-feeding and weaning in early life [65] and with adult life [23], suggests that carbohydrates play a critical role in the establishment and persistence of *B. longum* strains across the human lifespan. In adults, a strain of *B. longum* was shown to persist for more than 6 months in a third of subjects of a study cohort [26], which is not a common property of most lactic acid bacteria/bifidobacteria [66]. The persistence of an ingested strain of *B. longum* was, in some subjects, associated with both composition and metabolic features of the initial gut microbiome, such as the absence of certain features of carbohydrate metabolism (such as galactose), and an apparent absence of any resident *B. longum*, suggesting an available metabolic niche for the ingested strain. The study illustrates the capacity of such a *Bifidobacterium* strain to colonize and persist in subjects with low/no endogenous *Bifidobacterium* species and the importance to identify carbohydrates to sustain colonization of specific supplemented strains.

Glossary

Adult-type: (bifido)bacterial taxa that are more prevalent and abundant in adults (compared with infants).
Dietary carbohydrates: carbohydrates that are part of the human diet (but are not those that are present in human milk) and that typically represent glycans present in/or derived from vegetables, cereals, and legumes.
Exopolysaccharides (EPSs): extracellular, bacteria-produced long-chain polysaccharides which comprise repeating units of sugars, commonly containing glucose, galactose, and rhamnose, and which are excreted as a tightly bound capsule or a loosely attached slime layer in microorganisms.
Infant-type: (bifido)bacterial taxa that are more prevalent and abundant in infants (compared with adults).
Metabolic cross-feeding: interaction between microorganisms in which molecules resulting from the metabolism of one microorganism are further metabolized by another.
Resistant starch: a fraction of starch that is not digested by human amylases in the small intestine and that therefore can reach the colon to be fermented by microbiota. There are currently five types of resistant starch.
Shotgun metagenomics: a DNA sequencing approach that allows the decoding of genomes of microbial consortia members and thus a detailed taxonomic profiling and functional assessment.

and *B. breve*, are commonly less prevalent in adults, however, with variation among studies [21], and *B. animalis*, specifically subsp. *lactis*, is mostly associated with intake of dairy products [24]. Metagenomic analysis has revealed intraindividual temporal stability of *B. longum*, *B. adolescentis*, and *B. bifidum* strains compared with the more dynamic microbiome [16]. A recent study further identified *B. longum* and *B. breve* associated with gut microbiome stability in healthy subjects over 1 year [25]. Coexistence of strains has been reported mostly for *B. longum* within a given individual [23,26], but overall, little is known about strain diversity among different *Bifidobacterium* species as well as their persistence within the adult gut microbiota.

Bifidobacterium-associated functions relevant to the adult human gut

Bifidobacterium species contribute to the production of a variety of metabolites (summarized in Figure 2). Here, we focus specifically on prevalent bifidobacterial species, that is, *B. adolescentis*, *B. longum*, and *B. pseudocatenulatum*, and their adaptation to the adult gut environment with specific reference to **dietary carbohydrates** they utilize and some of their cell envelope components, and how these factors may affect gut microbiota and microbe–host interactions.

Metabolism of dietary carbohydrates

Diet is one of the major determinants of the composition and function of the gut microbiota [27]. Notably, *B. adolescentis* was identified among gut microbiota species as being the most significantly associated with dietary habits [11]. Among dietary factors, dietary carbohydrates represent the most frequently reported dietary component being positively associated with *Bifidobacterium* species [11,28]. The 'Bifid shunt' is the central and unique metabolic pathway for carbohydrate fermentation used by bifidobacteria, resulting in comparably high ATP generation with concomitant production of acetate and lactate, without gas production. Human-derived *Bifidobacterium* species encode an extensive set of glycan-hydrolyzing enzymes which are responsible for species- or strain-specific carbohydrate-metabolizing abilities (recently reviewed in [29]). While most bifidobacteria can metabolize mono-, di-, and oligosaccharides, there is more variability in the metabolism of polysaccharidic dietary carbohydrates between species such as **resistant starch**, (arabino)xylans, (arabino) galactans, and arabinans, which are major components of the human diet [29]. The genomes of *B. longum, B. adolescentis*, and *B. pseudocatenulatum* encode a wide range of glycan-active enzymes which are predicted to target plant-based carbohydrates [20,30–32]. Genetic, biochemical, and metabolic information is nonetheless limited for these species, and we have focused mainly on *B. adolescentis* and *B. longum* [29,31,33,34] with growing scientific data regarding *B. pseudocatenulatum* [20,32]. *B. adolescentis* metabolism seems to be specialized towards utilization of plant-derived carbohydrates, specifically starch and starch-like polysaccharides [31,34,35], a

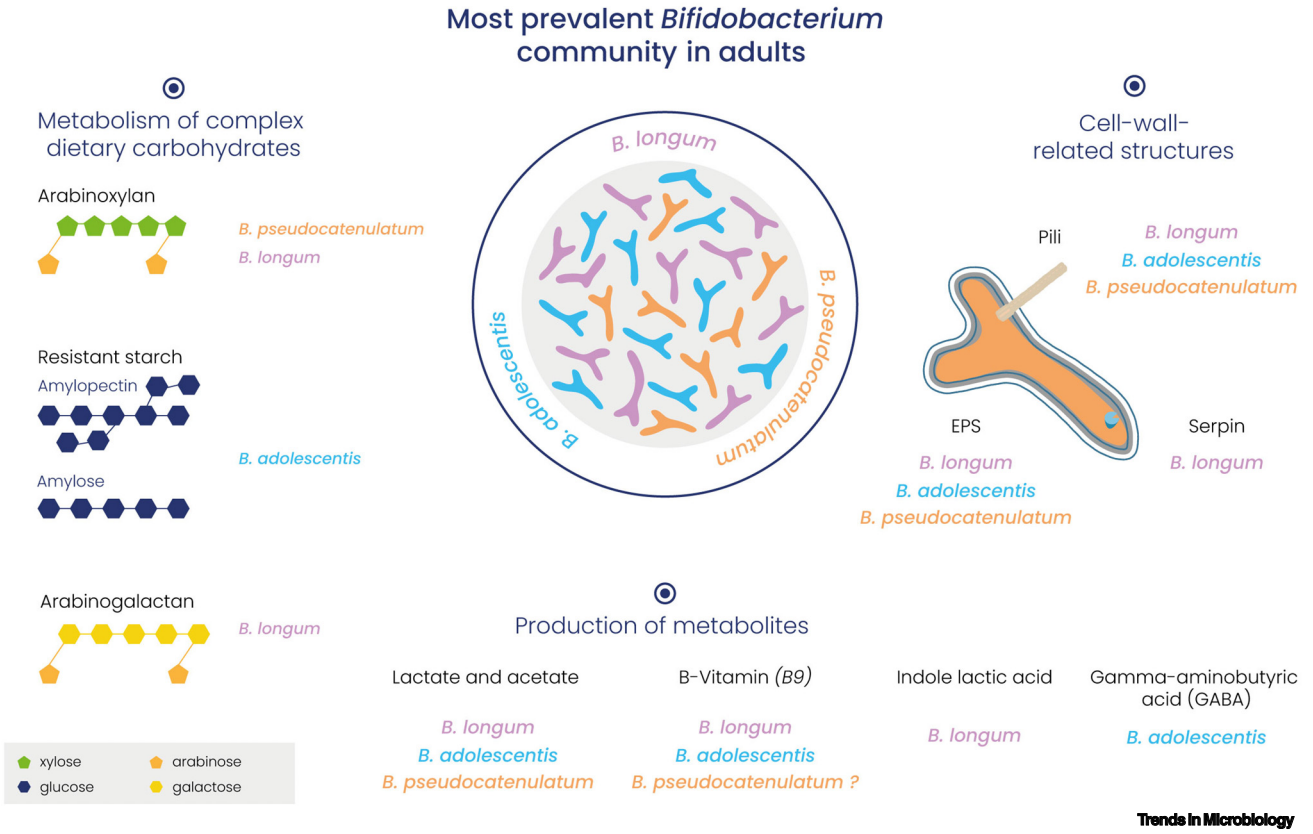

Figure 2. Example of metabolic capacities of prevalent adult-type *Bifidobacterium* species that are relevant to microbe–microbe and microbe–host interactions. The capacities do not indicate if they are species-specific, or conferred by all strains, but rather indicate that they appear to be present more frequently for some species. Abbreviation: EPS, exopolysaccharide.

property reflected in its core genome, encompassing a set of genes required for the uptake and metabolism of such glycans [31,36]. Variation between strains for their preference for a resistant starch type has been reported; this could at least partially explain the variable response of *Bifidobacterium* species in human intervention trials (recently reviewed in [37]). In contrast, *B. longum* strains prefer to metabolize arabinogalactan, arabinoxylan, or arabinan [38–40]. The genomes of *B. longum* strains isolated from elderly individuals display a higher abundance of genes predicted to encode extracellular α-L-arabinofuranosidases, being important for the metabolism of various arabinose-containing glycans. Consistent with its genomic content, it has been shown that the dietary intake of arabinoxylan results in an increase of *B. longum* [41]. Lastly, a recent study showed that certain *B. pseudocatenulatum* strains encompass an endo-1,4-β-xylanase-encoding gene that allows metabolism of plant-derived long-chain xylans, while it also enhanced the occurrence of this species in the gut of adults taking a diet rich in long-chain xylans [32].

Overall, both established and emerging evidence substantiates the capacity of certain *Bifidobacterium* species/strains to act as primary degraders of complex dietary, plant-based carbohydrates, which in turn would facilitate **metabolic cross-feeding** with secondary degraders and lead to higher production of particular host health-associated metabolites such as short-chain fatty acids (reviewed in [42] and references therein), perhaps providing a clue towards the health-associated benefits of bifidobacteria.

Bifidobacterial cell envelope components, secreted proteins, and metabolites as mediators of microbe–host interactions

Bifidobacterium has been negatively associated with particular markers of low-grade inflammation, such as lipopolysaccharide and C-reactive protein [43]. Based on association between gut microbiota composition/function and *ex vivo* cytokine response, two studies involving several hundred healthy subjects identified *B. pseudocatenulatum, B. adolescentis*, and *B. longum* as the species with clear immunomodulatory effects [44,45].

Given the association between certain *Bifidobacterium* species and immune parameters in adults, various cell wall components, secreted proteins, and metabolites from *Bifidobacterium* allow host interactions which have not been extensively studied in species that are prevalent in adulthood. An extracellular polymer with important bifidobacterial–host interactions is represented by **exopolysaccharides** (**EPSs**) [46]. Notably, genes responsible for EPS biosynthesis have been identified in all bifidobacterial genomes, except for *B. bifidum*, thus representing a common genetic feature irrespective of their ecological origin [46]. Among bifidobacteria associated with adults, EPS knowledge is centered around *B. longum,* where these structures are believed to be pivotal for the establishment and persistence in the gut [47]. Specifically, EPS produced by *B. longum* 35624 has been shown to induce immunoregulatory responses in the host and to suppress proinflammatory responses in inflammatory preclinical models [48]. While EPS of some bifidobacterial strains may serve as a source of nutrients for resident gut microbiota [49], there is currently limited knowledge on the effect of bifidobacterial EPSs on the human gut microbiota.

All known bifidobacteria are predicted to encode long filamentous structures known as pili or fimbriae, which are required for host adhesion and communication with the host [50]. Notably, a recent survey of all genes involved in pilus production in bifidobacteria, that is, the bifidobacterial fimbriome, which include genes for sortase-dependent and type IVb or Tad (tight-adherence) pilus production, revealed that the latter pili are universally conserved in bifidobacterial genomes. Conversely, sortase-dependent pilus loci display high genetic variability and are absent in some bifidobacterial genomes [51].

Extracellular bifidobacterial proteins involved in microbe–host interactions include eukaryotic-type serine protease inhibitors (serpins), which control various signaling pathways in eukaryotes, and may dampen inflammatory responses by inhibiting elastase activity. Genes encoding serpin-like proteins are present among *B. longum* [52]. It has recently been proposed that serpin production by *B. longum* plays a key role in microbe–host interaction through serpin-mediated inhibition of human intestinal serine proteases, thus allowing this species to persist in the human gut through protection against proteolytic attack [53].

Various other molecules (Figure 2) produced by bifidobacteria have been identified to be involved in host–microbe interactions, though in many cases this involved infant-type bifidobacterial species/strains. Whether, and to what extent, such molecules also play a role in the adult host–microbe interactions will need to be further assessed.

Bridging the *Bifidobacterium* gap in adult gut microbiota: insights into specific conditions and opportunities

Acute stressors, such as antibiotics or exclusion diets – both of which have been shown to deplete *Bifidobacterium* – may provide easier routes to understand how bifidobacteria can be re-established when compared with long-term conditions such as diseases or aging. Bifidobacterial abundance decreases, both relatively and quantitatively, by treatment with several classes of

commonly prescribed antibiotics, including macrolides and ampicillin [54]. A recent study identified *B. adolescentis* among various other species associated with gut microbiota recovery following antibiotic intake [55]. These species were shown to have a more elaborate coding capacity for enzymes involved in carbohydrate degradation. Notably, the inoculation of one particular strain of *B. adolescentis* and *Bacteroides thetaiotaomicron* was shown to result in a synergistic action with regard to microbiota diversity recovery. However, given that *B. adolescentis* strains differ in their ability to metabolize carbohydrates [31], a targeted isolation of strains might be relevant. Exclusion diets, especially those low in gluten and carbohydrates, such as low-FODMAP (Fermentable Oligo, Di, Monosaccharides And Polyols) and low-lactose, which have been designed to alleviate gastrointestinal-related symptoms, are other examples in which depletion of *Bifidobacterium* has been observed [56,57]. Such exclusion diets are increasingly adopted by the general population [58]. Mitigation of *Bifidobacterium* depletion has been the target of some studies for subjects consuming low-FODMAP diets. Administration of a multistrain product consisting of three lactic acid bacteria and three strains of *Bifidobacterium* (*B. breve* DSM 24732, *B. longum* DSM 24736, *B. infantis* DSM 24737) was shown to compensate for the loss observed in subjects who follow a low-FODMAP diet [59]. However, it is unknown whether the intake of the multistrain product results in higher abundance of either the exogenous strains or other *Bifidobacterium* species, and whether functions carried out by the ingested strains compensate for those from endogenous strains of *Bifidobacterium* which were depleted due to the low-FODMAP diet. For example, the intake of a strain of *B. adolescentis*, as opposed to a *B. animalis* subsp. *lactis* strain, by adult subjects resulted in a higher abundance of *Bifidobacterium* [60], suggesting that they differ in their capacity to stimulate endogenous *Bifidobacterium* and to colonize the gut. Notwithstanding this, to the best of our knowledge, no human studies have been published that used rationally selected *Bifidobacterium* strains to fill a functional gap. Whether preventive intake of *Bifidobacterium* strains rather than post-challenge administration is associated with a differential permissively of the gut microbiome to (temporarily or permanently) accommodate these strains warrants future research.

Concluding remarks

We have witnessed a staggering rise in microbiome-based approaches to support human health, in particular through administration of commensal bacteria. Recent approaches to identify strains with health benefits rely on a thorough understanding of their functions and modes of action. However, despite the growing availability of omics data, we still know little about the metabolic and functional contributions of individual microbial players within an ecological niche and the extent and directionality of interactions among them. Advances with genome-scale modeling represent an invaluable approach to dissect the underexplored role played by gut commensals, including *Bifidobacterium* species, pertaining to their positive contributions to human health. Access to large cross-sectional and longitudinal data sets across populations is expected to facilitate more in-depth exploration of metabolic and functional contributions of strains and species of *Bifidobacterium* in the gut microbiome as a function of host age, lifestyle, and health status. More detailed microbiome–diet studies and targeted screening of *Bifidobacterium* strains from adults will help to better guide precision approaches to both design the most effective mixture of strains with specific functional features and dietary ingredients to sustain their colonization and more precisely modulate and protect endogenous *Bifidobacterium* gut populations and ultimately human health. The application of these approaches in the context of aging, during which depletion of *Bifidobacterium* has been substantiated, will require more elaborate host–microbiome approaches given the variety of intrinsic and extrinsic factors associated with old age. The rational identification of strains to mitigate the decline of *Bifidobacterium* is critical and warrants knowledge expansion on their role and the underlying mechanisms of aging. Overall, increased availability of human microbiome data along the human lifespan and obtained from

Outstanding questions

What fraction, if any, of *Bifidobacterium* species/strains is retained throughout life?

Is the depletion of any *Bifidobacterium* species/strains during adulthood always associated with (long-term) clinical outcomes?

What, if any, are the functional differences in subjects enriched or depleted in *Bifidobacterium*?

Can supplementation of specific bifidobacterial strains fill functional gaps in the adult gut microbiota?

What is the variability between bifidobacterial strains in response to dietary intervention, and what functions determine their responsiveness to such interventions?

What factors drive the decline of *Bifidobacterium* in older age, and is this reversible?

Should persistent *Bifidobacterium* strains form a scientific pursuit in order to identify highly gut-adapted strains?

How does *Bifidobacterium* species prevalence and abundance in pregnant mothers affect their transfer to their offspring?

What is the relevance, if any, of the low-abundance/low-prevalence *Bifidobacterium* species?

various geographical locations across the world, coupled with deep phenotyping, should shed light on the factors associated with specific *Bifidobacterium* configurations, including the high- and low-prevalence/abundance species, and facilitate the development of more precise microbiota-based strategies for human health specifically targeting adults and the elderly (see Outstanding questions).

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Declaration of interests

M.D. is an employee of Danone Nutricia Research.

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