

Description of Additional Supplementary Files

File Name: Supplementary Data 1

Description: Details of the 157 final study-cohort considered for our analysis. Studies with accession as HACK refers to those investigated in our study (Goel et al 2025). The accession number or source of these study-cohorts can be obtained from our Goel et al 2025 publication. Studies with Reference tagged as CMD refer to those which were obtained from curatedMetagenomicData but utilized by us only in this analysis (and not in Goel et al 2025). For those cohorts for which the sequenced that were mined separately, we have explicitly provided the accession number.

File Name: Supplementary Data 2

Description: Rank-scaled Feature Importance values of different non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index, Pielou's Evenness and Microbial Load obtained for Random Effect Models created separately for study/sub-cohort containing only infant gut microbiomes for the prediction of A. Overall *Bifidobacterium* detection and for the relative-abundance of *Bifidobacterium* B. *Longum* C. *Adolescentis* D. *Pseudocatenulatum* E. *Bifidum* F. *Dentium* G. *Breve* and H. *Catenulatum*. Random Forest models were evaluated using out-of-bag (OOB) correlations. Feature-wise associations were assessed using Spearman rank correlation (two-sided), with p values indicating strength of association. No multiple testing correction was applied, as analyses were conducted independently within each cohort.

File Name: Supplementary Data 3

Description: Rank-scaled Feature Importance values of different non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index, Pielou's Evenness and Microbial Load obtained for Random Effect Models created separately for study/sub-cohort containing only adult gut microbiomes for the prediction of A. Overall *Bifidobacterium* detection and for the relative-abundance of *Bifidobacterium* B. *Longum* C. *Adolescentis* D. *Pseudocatenulatum* E. *Bifidum* F. *Dentium* G. *Breve* H. *Catenulatum* and I. *Animalis*. Random Forest models were evaluated using out-of-bag (OOB) correlations. Feature-wise associations were assessed using

Spearman rank correlation (two-sided), with p values indicating strength of association. No multiple testing correction was applied, as analyses were conducted independently within each cohort.

File Name: Supplementary Data 4

Description: Rank-scaled Feature Importance values of different non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index, Pielou's Evenness and Microbial Load obtained for Random Effect Models created separately for study/sub-cohort containing only senior gut microbiomes for the prediction of A. Overall *Bifidobacterium* detection and for the relative-abundance of *Bifidobacterium* B. *Longum* C. *Adolescentis* D. *Pseudocatenulatum* E. *Bifidum* F. *Dentium* G. *Breve* H. *Catenulatum* and I. *Animalis*. Random Forest models were evaluated using out-of-bag (OOB) correlations. Feature-wise associations were assessed using Spearman rank correlation (two-sided), with p values indicating strength of association. No multiple testing correction was applied, as analyses were conducted independently within each cohort.

File Name: Supplementary Data 5

Description: Directionality of Association of non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index and Pielou's Evenness Index with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of eight major Bifidobacteria) study-cohorts from Infant age-group and 16S profiling strategy.

File Name: Supplementary Data 6

Description: Directionality of Association of non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index and Pielou's Evenness Index with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of eight major Bifidobacteria) study-cohorts from Adult age-group and 16S profiling strategy.

File Name: Supplementary Data 7

Description: Directionality of Association of non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index and Pielou's Evenness Index with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of eight major Bifidobacteria) study-cohorts from Senior age-group and 16S profiling strategy.

File Name: Supplementary Data 8

Description: Directionality of Association of non-*Bifidobacterium* taxa and other microbiome properties like Shannon Index, Pielou's Evenness Index and predicted Microbial Load with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of eight major Bifidobacteria) study-cohorts from Infant age-group and WGS profiling strategy.

File Name: Supplementary Data 9

Description: Directionality of Association of non-*Bifidobacterium* taxa as well as microbiome properties viz. Shannon Index, Pielou's Evenness Index and predicted Microbial Load with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of eight major Bifidobacteria) study-cohorts from Adult age-group and WGS profiling strategy.

File Name: Supplementary Data 10

Description: Directionality of Association of non-*Bifidobacterium* taxa as well as microbiome properties like Shannon Index, Pielou's Evenness Index and predicted microbial Load with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of eight major Bifidobacteria) study-cohorts from Senior age-group and WGS profiling strategy.

File Name: Supplementary Data 11

Description: Association-Scores of non-*Bifidobacterium* taxa along with the three microbiome properties (Shannon Index, Pielou's Evenness Index and estimated Microbial Load) with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of different Bifidobacterial species) in A. Infants B. Adults C. Seniors D. IndustrializedUrban E.

UrbanRuralMixed and F. RuralTribal population using study-cohorts from WGS profiling strategy.

File Name: Supplementary Data 12

Description: Association-Scores of non-*Bifidobacterium* taxa along with three different microbiome properties (Shannon Index, Pielou's Evenness Index and estimated Microbial Load) with Bifidobacterial features (overall *Bifidobacterium* detection and the abundance of different Bifidobacterial species) in A. Infants B. Adults C. Seniors D. IndustrializedUrban and E. Others population (including UrbanRuralMixed and RuralTribal) using study-cohorts from 16S profiling strategy.

File Name: Supplementary Data 13

Description: Graded Association-Scores between each Bifidobacterial taxa and other taxa (from different taxonomic groups) in six different diseases and control individuals.

File Name: Supplementary Data 14

Description: Pairwise Spearman rank correlation (two-sided) underlying Supplementary Figure 16: (A) correlation coefficients and (B) corresponding exact p values, shown for all nine *Bifidobacterium* features (A–I) across seven conditions (six diseases and matched controls). No multiple testing correction was applied, as analyses were conducted independently within each cohort.

File Name: Supplementary Data 15

Description: Graded Association-Scores between each Bifidobacterial taxa and other taxa (from different taxonomic groups) after adjusting for Shannon Index, Pielou's Evenness Index and Microbial Load (in WGS) stratified by age-group and cohort-life-style category in A. WGS and B. 16S.

File Name: Supplementary Data 16

Description: Details of the cohorts utilized in Diet/Medication/Clinical Adjusted Association-Scores as well as their robust PCA and PCoA components.

File Name: Supplementary Data 17

Description: Graded Association-Scores between each Bifidobacterial taxa and other non-Bifidobacterial taxa (from different taxonomic groups) after adjusting for Diet, Medication and Clinical stratified by sequencing-type A. WGS and B. 16S.

File Name: Supplementary Data 18

Description: Details of the 8 unseen (validation) intervention study-cohorts considered for analysis.

File Name: Supplementary Data 19

Description: Association-Scores of non-*Bifidobacterium* taxa with 8 *Bifidobacterium* taxa in the Adult/Seniors Validation Cohorts A. WGS B. 16S.

File Name: Supplementary Data 20

Description: Spearman Correlation (ρ) of non-*Bifidobacterium* taxa with 7 *Bifidobacterium* taxa in the Infant 16S Validation Cohort. Feature-wise associations were assessed using Spearman rank correlation (two-sided), with p values indicating strength of association. No multiple testing correction was applied, as analyses were conducted independently within each cohort.

File Name: Supplementary Data 21

Description: Associations between baseline Receptive-Scores and post-treatment increases in target *Bifidobacterium*-associated features with and without adding Microbiome properties like

Shannon Index, Pielou's Evenness Index and predicted Microbial Load (in WGS cohorts where at least 70% of the taxa were mapped with taxa present in the training model) as covariates. The results have been shown using two different approaches viz., Robust Linear Regression (RLR) and Leave-One-Out Cross Validation (LOOCV). Associations were assessed using robust linear regression (two-sided), with p values derived for regression coefficients. Model performance was evaluated using leave-one-out cross-validation (LOOCV). No multiple testing correction was applied, as analyses were performed independently across features and model configurations.

File Name: Supplementary Data 22

Description: List of 162 functional groups and their corresponding annotations along with the associations between the groups and nine different Bifidobacterial features are also mentioned. The major phylogenetic sources (non-Bifidobacterial taxa) of each functional group are also mentioned. Furthermore, the “type” column denotes the enrichment toward *longum/adolescentis* (positive) and enrichment towards *breve/dentium* (negative) and 0 indicates no enrichment in association.