Ageing trajectory of the gut microbiota is associated with metabolic diseases in a chronological age-dependent manner

We read with interest the recent article by Ng *et al*. (*Gut*, 2022; 71:910–8), who reported inhibition of the gut microbiota trajectory in patients with autism spectrum disorder.[1] Similarly, the human gut microbiota ages in adults.[2 3] Transplantation of gut microbes from elderly hosts, compared with their younger counterparts, deteriorates recipients' age-related metabolic alternations.[4 5] However, the gut microbiota in humans could differ in its pace of ageing, namely, accelerated or delayed microbiota ageing, even among those with similar chronological ages (figure 1A); this process is analogous to biological ageing.[6] Therefore, we wondered whether the gut microbiota ageing trajectory could be used as a biomarker for metabolic diseases in adults. We analysed the gut microbiota compositions of 6376 participants of a population-level survey[7] with Quantitative Insights Into Microbial Ecology (QIIME),[8] among whom the median chronological age of the healthy participants is 43 (IQR, 31–45, online supplemental table S1). A random forest algorithm was applied to the data of 1083 healthy individuals to model gut microbiota ageing in relation to chronological age. The model was then applied to subjects with metabolic diseases, matching healthy individuals by chronological age. See the online supplemental file 1 for additional information.

At the modelling phase, the microbiota age of the 1083 healthy individuals showed a significant and positive correlation with chronological age (online supplemental figure S1). The microbiota age in the healthy individuals was not significantly associated with gender or residing sites (developed vs less developed), but is significantly associated with grain, fruits and rice wine consumption (online supplemental table S2 and online supplemental figure S2). When the model was applied to individuals with metabolic diseases, the ageing trajectory of their microbiota was neither accelerated nor delayed but intersected with that of healthy individuals at nearly 50 years old (figure 1B–D). In individuals with metabolic disease, the microbiota age was older than that in healthy individuals at younger chronological ages, comparable with that in healthy individuals at middle chronological ages, and younger than that in healthy individuals at older chronological ages (online supplemental figure S3). Metabolic diseases (including hypertension, diabetes and metabolic syndrome) patients who took antibiotics or medication showed significantly lower microbiota age than the treatment-naive patients (online supplemental figure S4). We removed the medicated patients and the above intersecting patterns could still be reproduced (online supplemental figure S5).

To dissect the random forest ageing model, we analysed the ageing trajectories of the top 20 model-contributing taxa (figure 2A). The heatmap clearly showed that the relative taxonomic abundances correlated positively (upper half) or negatively (lower half) with chronological ageing in the healthy individuals, but the trajectories were disordered in hypertensive individuals. Typical microbial examples include *Clostridium* and *Parabacteroides distasonis*, with obvious intersecting patterns (figure 2B,C). Similar disordered taxonomic ageing trajectories were also observed in participants with diabetes, obesity, metabolic syndrome, hypercholesterolemia and hypertriglyceridaemia (online supplemental figure S6).

In conclusion, the results of the current and Ng's study suggest that the ageing trajectory of the gut microbiota could be a potential biomarker for both paediatric and adult chronic diseases. However, accelerated microbiota ageing should not be simply considered a risk factor for metabolic diseases in adults or vice versa, as it might be chronological-age dependent. Our finding corresponds to Wilmanski's observation that elderly individuals who carried younger microbiota signatures could have lower survival rates,[9] but analyses to understand covariates (lifestyle, diet, medication, etc), subpopulation differences and longitudinal disease risks of gut microbiota ageing are warranted. Moreover, whether a chronological age-dependent bacterial function could be observed and understood in mechanism studies is worth investigating. Interestingly, a common practice in faecal microbiota transplantation (FMT) is to

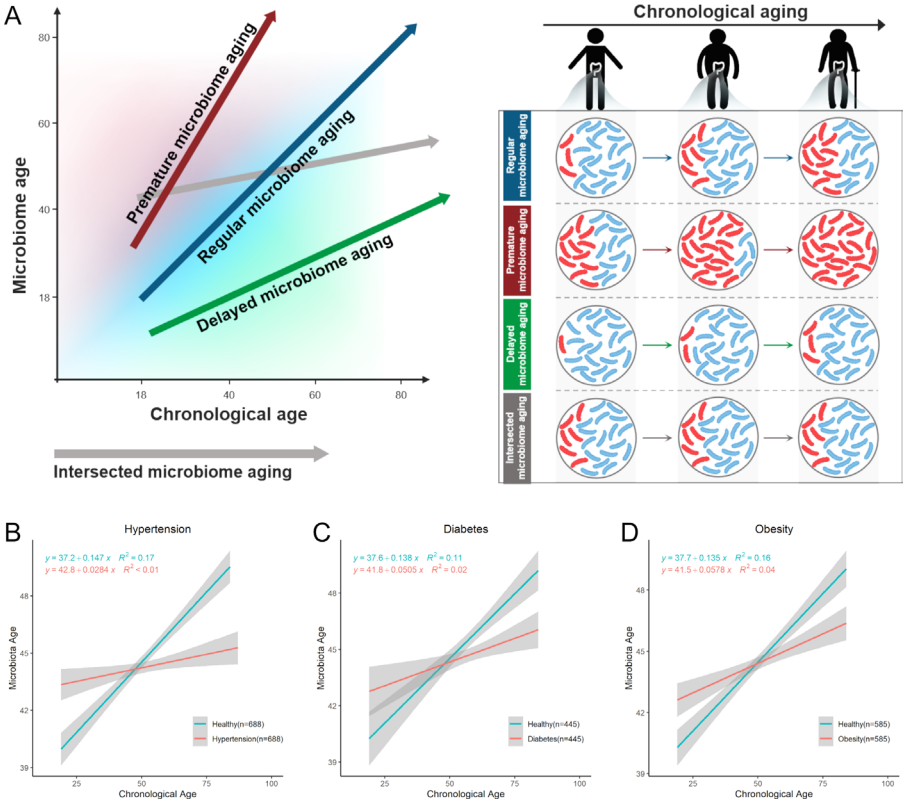

Figure 1 Gut microbiome ageing patterns in participants with metabolic diseases and their healthy counterparts. (A) Three different patterns of ageing trajectories of the gut microbiota. (B–D) Gut microbiota ageing trajectory in patients with hypertension, diabetes and obesity versus healthy individuals. The random forest model was trained with the microbiota features of healthy individuals and then applied to predict the microbiota age of participants with hypertension, diabetes and obesity in relation to their chronological their age separately.

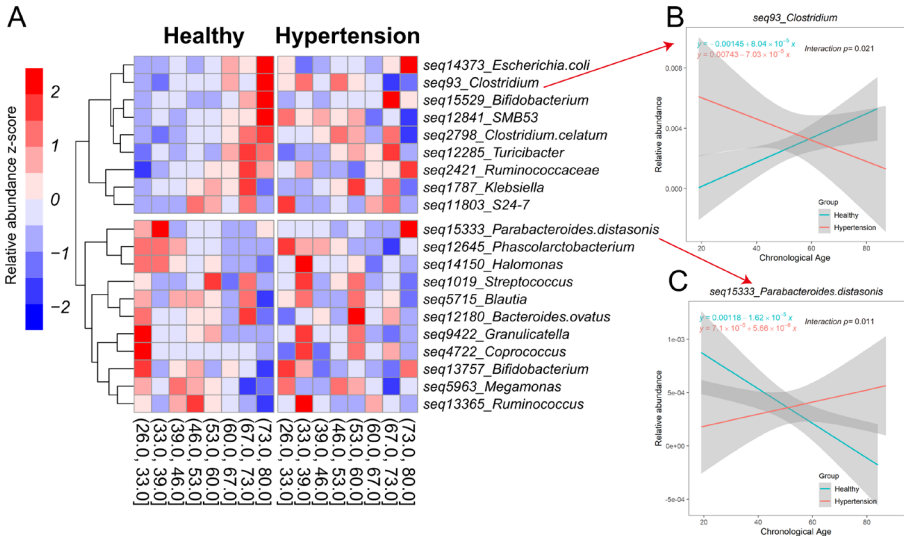

Figure 2 Significant intersecting trajectories of taxonomic relative abundances in healthy and hypertensive participants. (A) Heatmap of the top 20 important amplicon sequence variant from the random forest regression model plotted against chronological age in healthy and hypertensive individuals. Significant intersecting patterns of the relative abundances of (B) *seq93_Clostridium* and (C) *seq15333_Parabacteroides distasonis* in healthy individuals and hypertensive participants. The interaction p indicates the significance of interaction term in the multivariable linear regression model.

choose young donors for health reasons. Analysing whether a chronological age-matched healthy donor for FMT could promote additional health benefits in the recipient is worth further investigation.

JingXiang Fu ,[1] **Wen Qiu**,[1] **Huimin Zheng**,[1] **Cancan Qi**,[1] **Shixian Hu** ,[2] **Wei Wu**,[3] **Huidi Wang**,[1] **Guangyan Wu**,[1] **Peihua Cao**,[4,5] **Zhenchao Ma**,[6] **Chao Zheng**,[6] **Wen-Jun Ma**,[7] **Hong-Wei Zhou** ,[1,8] **Yan He**[1,8]

[1]Microbiome Medicine Center, Division of Laboratory Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong, China
[2]Institute of Precision Medicine, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[3]Guangdong Provincial Institute of Public Health, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, China
[4]Clinical Research Center, Zhujiang Hospital, Southern Medical University, Guangzhou, China
[5]Department of Biostatistics, School of Public Health, Southern Medical University, Guangzhou, China
[6]Huzhou Central Hospital, School of Medicine, Zhejiang University, Huzhou, Zhejiang, China
[7]Department of Public Health and Preventive Medicine, School of Medicine, Jinan University, Guangzhou, Guangdong, China
[8]State Key Laboratory of Organ Failure Research, Southern Medical University, Guangzhou, China

Correspondence to Professor Yan He, Microbiome Medicine Center, Division of Laboratory Medicine, Zhujiang Hospital, Southern Medical University, Guanghzou, China; yanhe@i.smu.edu.cn

Correction notice This article has been corrected since it published Online First. The first author's name in the citationof reference 9 has been corrected.

Acknowledgements We thank Professor Lianmin Chen from Nanjing Medical University for an insightful discussion. YH (corresponding author) argued with Professor Lianmin Chen about whether a younger gut microbiota is always a healthier one, and then initiated the present analysis, in addition to the inspiration by Ng's study. Based on the present observations, YH could be wrong for insisting that a younger microbiota is always better, but might be chronological-age dependent.

Contributors JF, YH and H-WZ designed the study and prepared the manuscript. YH, WW, W-JM and H-WZ provided the data. JF, WQ, H-MZ, HW, GW and YH analysed the data. PC, ZM and CZ provided crucial advice in analysing and interpreting the data.

Funding This study was supported by the National Key R&D Program of China (2019YFA0802300 (YH), 2017YFC1310600 (H-WZ)); National Natural Science Foundation of China (NSFC82022044 (YH), NSFC81925026 (H-WZ), 81800746 (YH)); and Natural Science Foundation of Guangdong Province China, Project No.-2018A0303130118 (WW).

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by the ethical review committee of the Chinese Center for Disease Control and Prevention (no. 201519-A). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2022-328034).

JF and WQ contributed equally.

To cite Fu J, Qiu W, Zheng H, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2022-328034

Received 9 June 2022
Accepted 14 August 2022

Gut 2022;**0**:1–2. doi:10.1136/gutjnl-2022-328034

ORCID iDs
JingXiang Fu http://orcid.org/0000-0003-3009-5269
Shixian Hu http://orcid.org/0000-0002-1190-0325
Hong-Wei Zhou http://orcid.org/0000-0003-2472-8541

REFERENCES

1 Wan Y, Zuo T, Xu Z, *et al*. Underdevelopment of the gut microbiota and bacteria species as non-invasive markers of prediction in children with autism spectrum disorder. *Gut* 2022;71:910–8.
2 Yatsunenko T, Rey FE, Manary MJ, *et al*. Human gut microbiome viewed across age and geography. *Nature* 2012;486:222–7.
3 Zhang X, Zhong H, Li Y, *et al*. Sex- and age-related trajectories of the adult human gut microbiota shared across populations of different ethnicities. *Nat Aging* 2021;1:87–100.
4 Bárcena C, Valdés-Mas R, Mayoral P, *et al*. Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. *Nat Med* 2019;25:1234–42.
5 Boehme M, Guzzetta KE, Bastiaanssen TFS, *et al*. Microbiota from young mice counteracts selective age-associated behavioral deficits. *Nat Aging* 2021;1:666–76.
6 Hamczyk MR, Nevado RM, Barettino A, *et al*. Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol* 2020;75:919–30.
7 He Y, Wu W, Zheng H-M, *et al*. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. *Nat Med* 2018;24:1532–5.
8 Caporaso JG, Kuczynski J, Stombaugh J, *et al*. QIIME allows analysis of high-throughput community sequencing data. *Nat Methods* 2010;7:335–6.
9 Wilmanski T, Diener C, Rappaport N, *et al*. Gut microbiome pattern reflects healthy ageing and predicts survival in humans. *Nat Metab* 2021;3:274–86.