



Deciphering Unique and Shared interactions between the Human Gut Microbiota and Oral Antidiabetic Drugs

Huahui Ren^{1,2}, Zhun Shi¹, Fangming Yang¹, Shujie Wang^{3,4}, Fengyi Yuan⁵, Tingting Li^{3,4}, Min Li¹,
Jiahui Zhu¹, Junhua Li^{1,6}, Kui Wu^{1,7}, Yifei Zhang^{3,4}, Guang Ning^{3,4},
Karsten Kristiansen^{1,2*}, Weiqing Wang^{3,4*}, Yanyun Gu^{3,4*}, Huanzi Zhong^{1*}

1 BGI Research, Shenzhen 518083, China.

2 Laboratory of Genomics and Molecular Biomedicine, Department of Biology, University of Copenhagen, 2100 Copenhagen, Denmark

3 Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases

4 Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the PR China, Shanghai National Center for Translational Medicine

5 Department of Endocrinology and Metabolism, Shenzhen People's Hospital

6 Shenzhen Key Laboratory of Unknown Pathogen Identification

7 Guangdong Provincial Key Laboratory of Human Disease Genomics

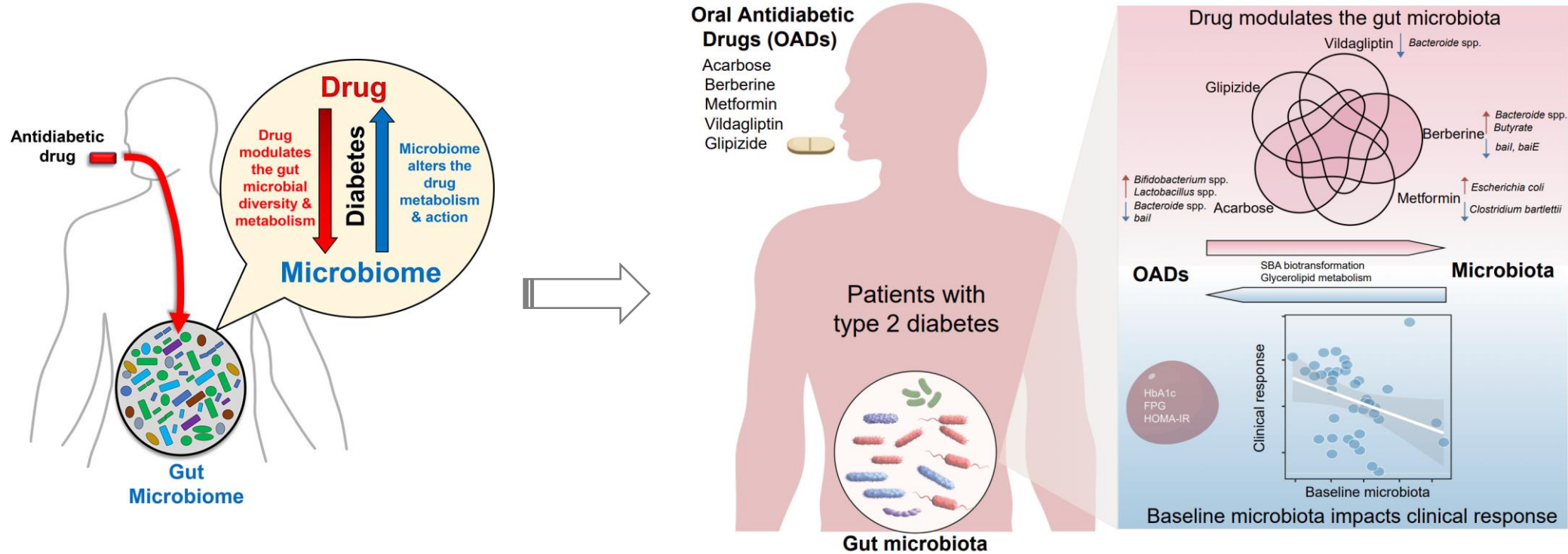


Huahui Ren, Zhun Shi, Fangming Yang, Shujie Wang, Fengyi Yuan, Tingting Li, Min Li, Jiahui Zhu, Junhua Li, Kui Wu, Yifei Zhang, Guang Ning, Karsten Kristiansen, Weiqing Wang, Yanyun Gu, Huanzi Zhong. 2024. Deciphering Unique and Shared interactions between the Human Gut Microbiota and Oral Antidiabetic Drugs.

iMeta e179. <https://doi.org/10.1002/imt2.179>



Background



- Diabetes is a crucial global public health concern.
- Numerous studies have demonstrated the bidirectional interactions between oral antidiabetic drugs (OADs) and the gut microbiota in patients with type 2 diabetes; however, a comprehensive evaluation is still warranted.



Results

◆ Metagenomic and clinical data from six clinical intervention studies

Table 1 Details of oral-antidiabetic drugs (OADs) related metagenomic datasets included in this study.

Dataset [↵]	Disease [↵]	Drug (Participant/ Sample) [↵]	Drug dosage/Duration [↵]	Sampling (days) [↵]	Age (years) [↵]	Sex (male/female) [↵]	BMI (kg/m ² , Pre) [↵]	HbA1c (% Pre- treatment) [↵]	HbA1c (% Post- treatment) [↵]	Location [↵]	Accession number [↵]
Gu et al. 2017 [4] [↵]	ND-T2D [↵]	Acarbose (51 / 102) [↵]	100 mg tid p.o. (minimum) / 3-month [↵]	90 [↵]	52.96 ± 0.95 [↵]	17/34 [↵]	26.32 ± 0.45 [↵]	7.53 ± 0.11 [↵]	6.39 ± 0.07 # [↵]	China, Multicenter [↵]	PRJEB12124 [↵]
		Glipizide (43 / 86) [↵]	5 mg tid p.o. /3-month [↵]	90 [↵]	53.96 ± 1.03 [↵]	24/19 [↵]	26.01 ± 0.52 [↵]	7.67 ± 0.14 [↵]	6.32 ± 0.10 # [↵]		
Wu et al. 2017 [5] [↵]	ND-T2D [↵]	Metformin (22 / 65) [↵]	1,700 mg tid p.o. / 4- month [↵]	60,120 [↵]	52.6 ± 2.0 [↵]	8/14 [↵]	36.54 ± 1.44 [↵]	6.67 ± 0.11 [↵]	5.97 ± 0.08 # [↵]	Spain [↵]	PRJNA361402 [↵]
Zhang et al.2020 [6] [↵]	ND-T2D [↵]	Berberine (85 / 170) [↵]	600 mg bid p.o./ 12- week [↵]	84 [↵]	52 ± 1.17 [↵]	52/33 [↵]	25.86 ± 0.37 [↵]	7.68 ± 0.08 [↵]	6.68 ± 0.07 # [↵]	China, Multicenter [↵]	PRJNA643353 [↵]
		Placebo (96 / 192) [↵]	600 mg bid p.o./12- week [↵]	84 [↵]	52.23 ± 0.99 [↵]	56/40 [↵]	26.32 ± 0.35 [↵]	7.83 ± 0.08 [↵]	7.22 ± 0.10 # [↵]		
Zhang et al.2022 [7] [↵]	ND-T2D [↵]	Acarbose (42 / 84) [↵]	100 mg tid p.o. / 24- week [↵]	168 [↵]	52.19 ± 1.48 [↵]	27/15 [↵]	26.87 ± 0.27 [↵]	7.82 ± 0.09 [↵]	6.40 ± 0.09 # [↵]	China, Bei Jing [↵]	PRJNA826552 [↵]
		Vildagliptin (40 / 80) [↵]	50 mg bid p.o /24- week. [↵]	168 [↵]	51.17 ± 1.4 [↵]	19/21 [↵]	27.11 ± 0.28 [↵]	7.78 ± 0.10 [↵]	6.36 ± 0.10 # [↵]		
Ren et al. 2023 [↵]	ND-T2D [↵]	Metformin (47 / 94) [↵]	1500 mg tid p.o. /3- month [↵]	90 [↵]	47.83 ± 1.38 [↵]	26/21 [↵]	25.26 ± 0.42 [↵]	8.20 ± 0.22 [↵]	6.36 ± 0.11 # [↵]	China, Shen Zhen [↵]	CNP0004692 [↵]
Zhao et al. 2018 [9] [↵]	T2D [↵]	Acarbose + U (16 / 64) [↵]	100 mg tid p.o. /12- week [↵]	28, 56, 84 [↵]	59.7 [↵]	7/9 [↵]	NA [↵]	8.31 ± 0.38 [↵]	7.01 ± 0.27 # [↵]	China, Shang Hai [↵]	PRJEB14155 [↵]
		Acarbose + W (27 / 108) [↵]	100 mg tid p.o./ 12- week [↵]	28, 56, 84 [↵]	58.4 [↵]	11/16 [↵]	NA [↵]	8.27 ± 0.27 [↵]	6.36 ± 0.11 # [↵]		

Continuous data are presented as mean ± sem (standard error of mean)[↓]

Acarbose + U: Acarbose + usual care[↵]

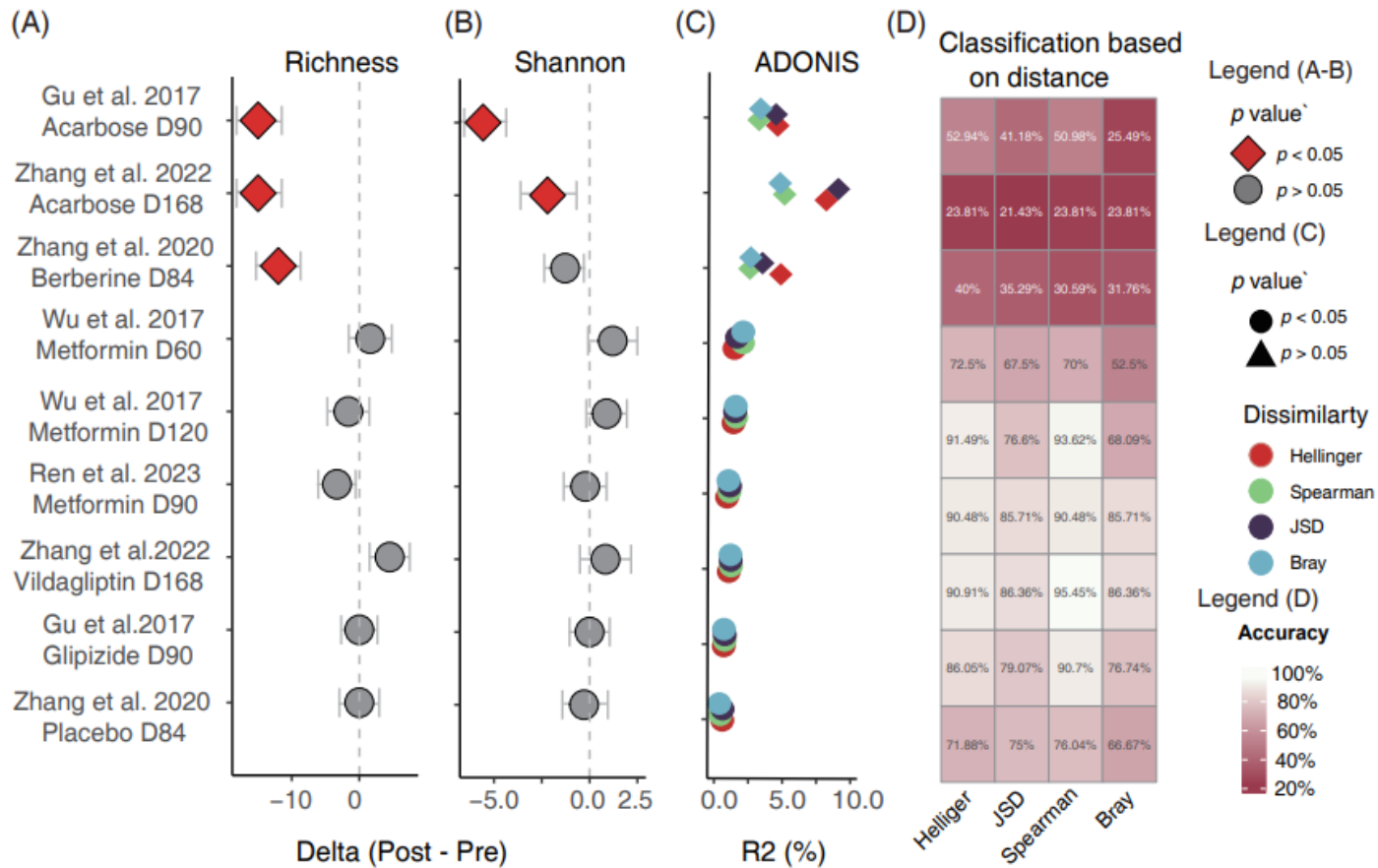
Acarbose + W: Acarbose + WTP (whole grains, traditional Chinese medicinal foods, and prebiotics)[↵]

#: HbA1c reported significantly decreased in the study ($p < 0.05$)[↵]



Results

◆ Impact of five OADs on microbial diversity in T2D patients

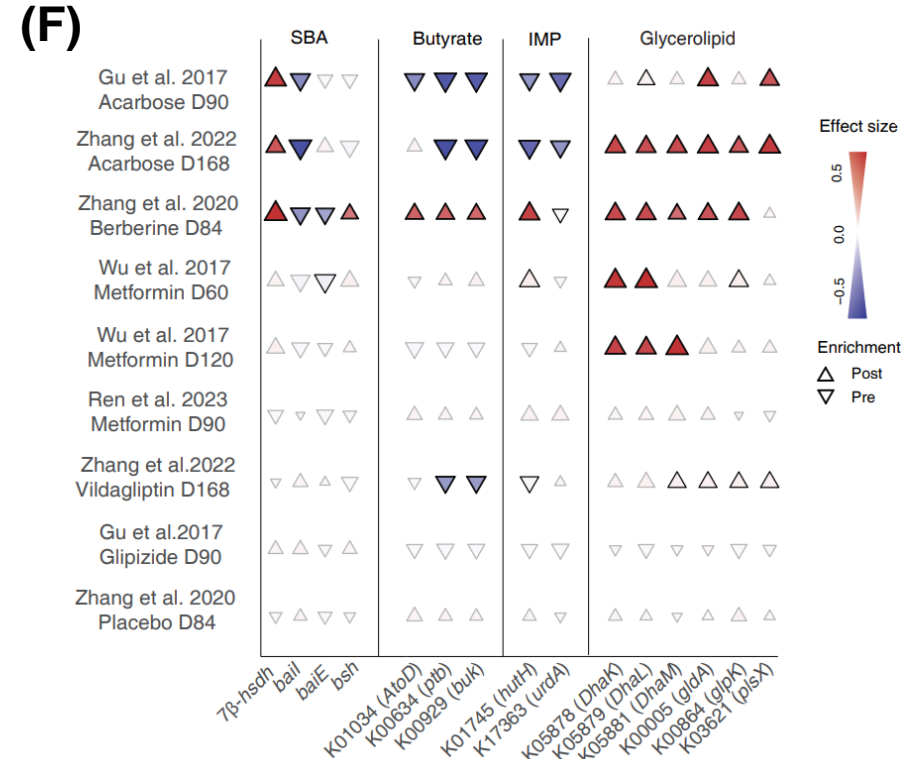
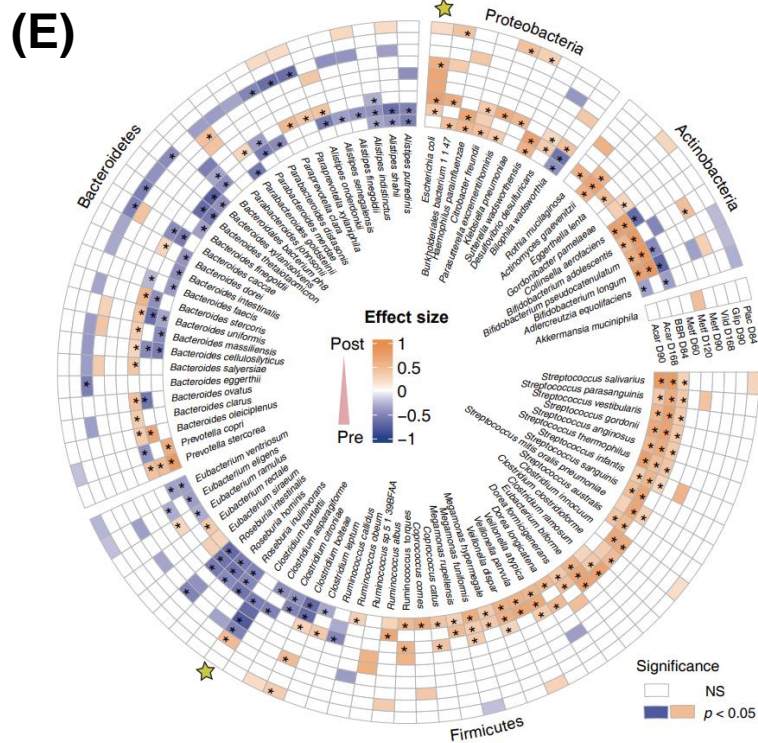


- Both **acarbose** and **berberine** treatments significantly reduced species-level richness and Shannon index and altered community composition.
- Treatment with **metformin, vildagliptin, glipizide, or placebo** did not result in significant changes in gut microbial diversity.



Results

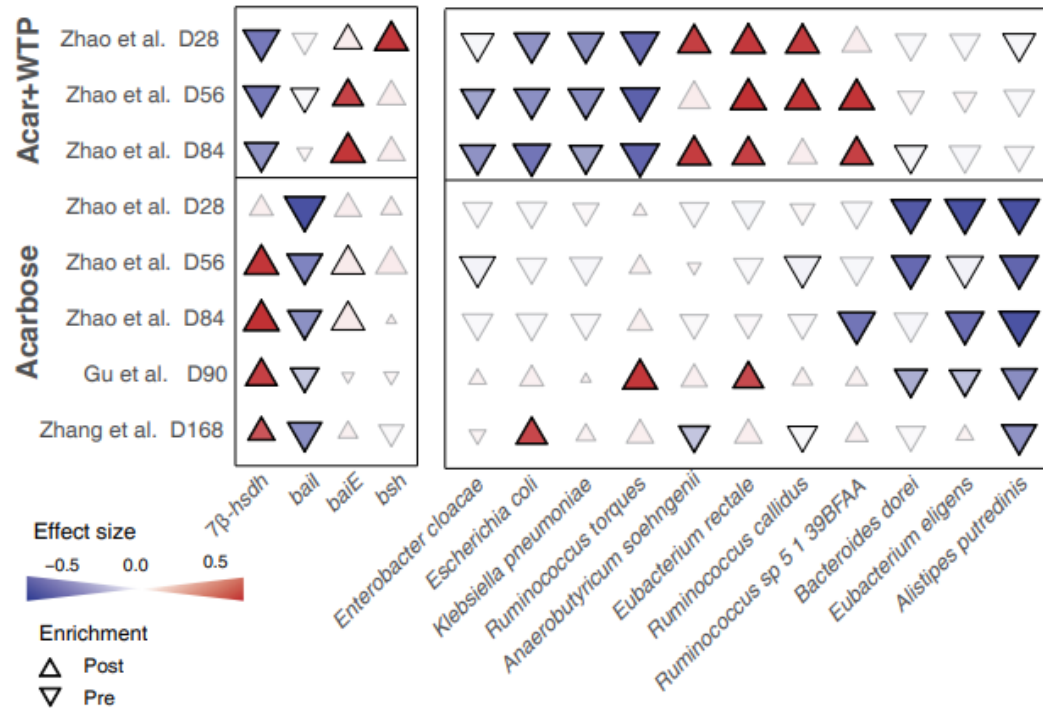
◆ Impact of OADs on microbial taxonomic and functional composition in T2D patients



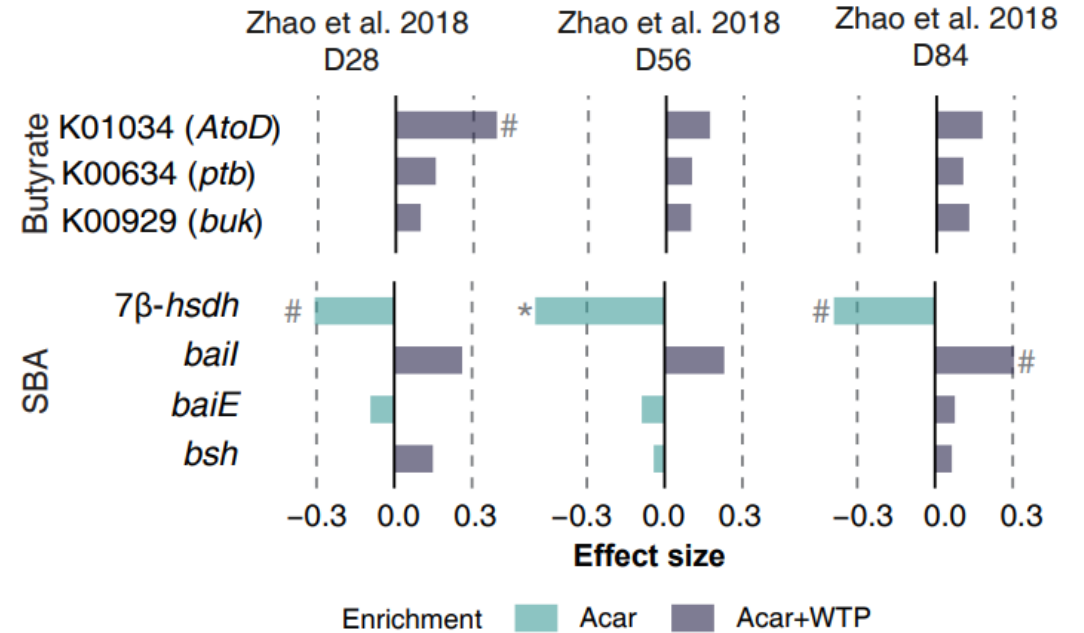
- **At the species level**, both acarbose and berberine significantly increased the relative abundances of multiple Firmicutes species, while acarbose and vildagliptin treatments significantly decreased the relative abundance of Bacteroidetes species. Following treatment with berberine and metformin, there was an increase in the relative abundance of *Escherichia coli* and a decrease in the relative abundance of *Clostridium bartlettii*.
- **At the functional level**, both acarbose and berberine significantly increased the relative abundance of the 7β -*hsdh* gene and decreased the relative abundance of genes involved in SBA transformation. Except for glipizide, all other OADs increased the abundances of genes involved in glycerolipid metabolism.

Results

◆ Impact of acarbose combined with a high-fiber diet intervention on secondary bile acid metabolism in T2D patients



(H)



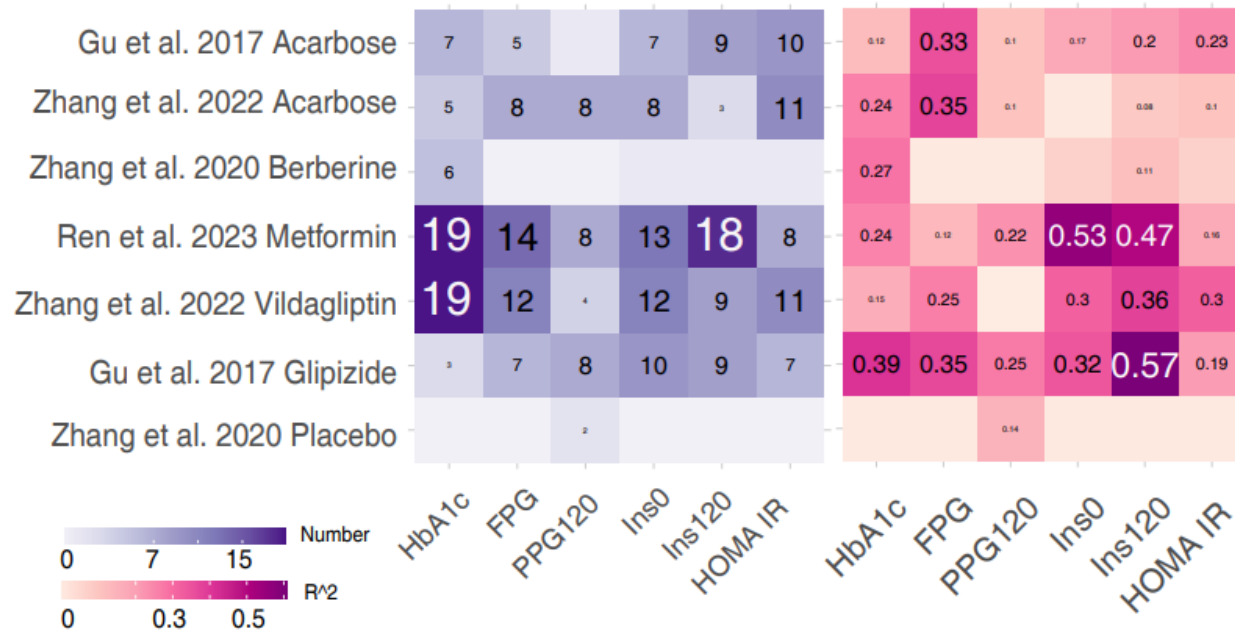
- Acar + WTP significantly decreased while Acar significantly increased the relative abundance of **the *7 β -hsdh* gene**.
- Post-treatment samples from the Acar+WTP group showed higher abundations of **the butyrate producing gene (K01034) and *bail***, and lower relative abundations of **the *7 β -hsdh* gene** compared to the Acar group alone.



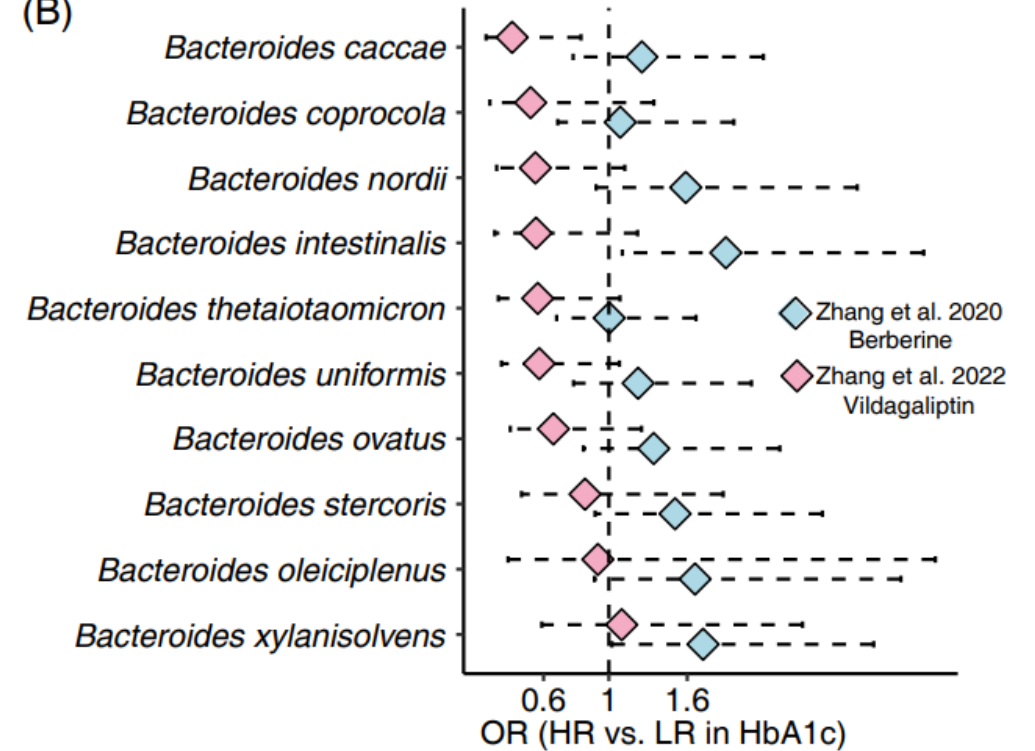
Results

◆ Baseline microbial features associate with treatment responses of OADs

(A)



(B)

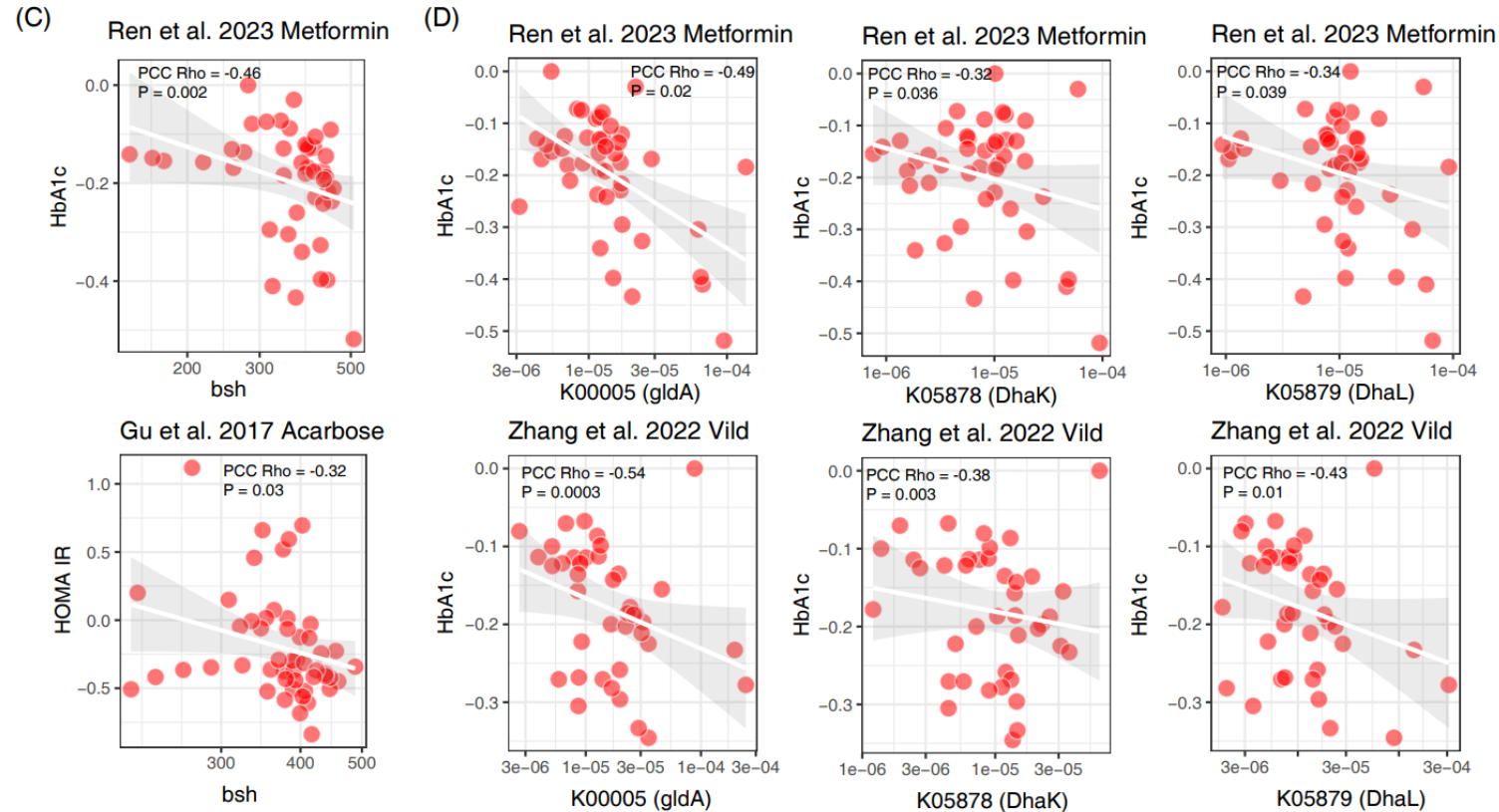


- Baseline microbial features explained 12% to 39% of the response variance in HbA1c, 12% to 35% of the variance in FPG, and 6% to 30% of the variance in HOMA-IR across OADs groups.
- Higher baseline abundance of *Bacteroides spp.* was associated with a tendency for low responders to vildagliptin, while it was associated with a tendency for high responders to berberine.



Results

◆ Baseline microbial features associate with glucose improvements of OADs



- **In the metformin and acarbose treatment groups**, higher abundances of *bsh* genes were associated with greater improvements in metformin(HbA1c) and acarbose groups(HOMA-IR).
- **In the metformin and vildagliptin treatment groups**, higher abundances of glycerolipid metabolism genes (*gldA*, *DhaK* and *DhaL*) and were linked to more significant reductions in HbA1c.



Conclusion

- Comprehensive analyses uncover distinct and shared changes in the gut microbiota of patients with type 2 diabetes receiving treatment with different oral antidiabetic drugs.
- Acarbose and berberine exhibit more pronounced impacts on the gut microbiota than metformin, vildagliptin, and glipizide.
- Combining acarbose with a high-fiber diet mitigates drug-induced reduction in microbial genes involved in the production of secondary bile acids.
- Baseline gut microbiome strongly associates with treatment responses of oral antidiabetic drugs.

Huahui Ren, Zhun Shi, Fangming Yang, Shujie Wang, Fengyi Yuan, Tingting Li, Min Li, Jiahui Zhu, Junhua Li, Kui Wu, Yifei Zhang, Guang Ning, Karsten Kristiansen, Weiqing Wang, Yanyun Gu, Huanzi Zhong¹. 2024. Deciphering Unique and Shared interactions between the Human Gut Microbiota and Oral Antidiabetic Drugs. *iMeta* e179. <https://doi.org/10.1002/imt2.179>



“iMeta” is an open-access Wiley partner journal launched by scientists of the Chinese Academy of Sciences. iMeta aims to promote metagenomics, microbiome, and bioinformatics research by publishing original research, methods, or protocols, and reviews. The goal is to publish high-quality papers (Top 10%, IF > 15) targeting a broad audience. Unique features include video submission, reproducible analysis, figure polishing, APC waiver, and promotion by social media with 500,000 followers. Three issues were released in [March](#), [June](#), and [September](#) 2022.



Society: <http://www.imeta.science>

Publisher: <https://wileyonlinelibrary.com/journal/imeta>

Submission: <https://mc.manuscriptcentral.com/imeta>



office@imeta.science



[iMeta](#)



[iMetaScience](#)



[iMetaScience](#)