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Tailored effects of coarse grain substitution on blood pressure via gut microbiota-metabolite networks and host gene variants: a randomized controlled trial



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We previously reported inverse associations of coarse grain (CG) intake with blood pressure, mediated by metabolites and gut microbiota. In this 12-week randomized controlled trial among 172 prehypertension participants, both the CG (100 g/day) group and the control group (refined grain) showed significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) over 12 weeks, with no significant time by group interaction. In the exploratory analyses of secondary outcomes, significant time by group interactions were detected for 26 taxa (such as *g__Lactococcus* and *g__Faecalibacterium*), associated with 23 differential fecal metabolites, which in turn were correlated with blood pressure changes over the CG intervention. Microbial ATP-binding cassette transporter was highlighted in the pathway annotation for the CG-derived differential microbial taxa. Baseline gut microbiota exhibited predictive potential for blood pressure reduction, while host *ABO* variance rs514659 modulated the intervention effect on SBP and DBP (P interaction < 0.05), providing preliminary evidence for the tailored nutrition strategies optimizing blood pressure and gut microbiota profiles.

As a leading risk factor of cardiovascular mortality, hypertension has been increasingly prevalent globally¹. Approximately 33% of the world's adults were estimated as having hypertension², while in China, about a quarter of adults were hypertensive³. Moreover, a nationwide survey also estimated a prevalence of 41.3% for prehypertension⁴, associated with over 65% elevated risks of cardiovascular incidence, as compared to normotensive people⁵.

Dietary strategies with an emphasis on whole grain intake, such as Dietary Approaches to Stop Hypertension and Mediterranean Diet^{6,7}, were suggested to be effective in reducing blood pressure by interventional studies

among Western populations. Meanwhile, a few prospective cohort studies suggested increasing whole grain intake was associated with reduced hypertension incidence^{8,9}. Tighe et al. reported a 6-mmHg reduction in systolic blood pressure (SBP) over a 12-week whole-grain intervention¹⁰, and Pins et al. observed significant improvements in blood pressure control over a similar 12-week oat cereal trial¹¹, suggesting a beneficial effect on blood pressure by receiving 12-week grain-based interventions.

In Chinese dietary habits, coarse grain (CG) is an affordable and popular grain group, which refers to all grains other than wheat or rice

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products, but includes various dried beans, thus are rich in dietary fiber, minerals, and vitamins, benefiting from low processing degree¹². Recently, we found that CG intake frequency was inversely associated with blood pressure in 430,000 adults in China¹³. Meanwhile, we also observed that dried bean intake was inversely associated with the risk of hypertension, partially mediated by gut microbial alterations¹⁴. However, it was not clear whether partially substituting refined grain (RG) with CG would benefit blood pressure control and gut microbiota in individuals with prehypertension.

The gut microbiota plays significant roles in human health, with growing evidence linking microbial imbalances to cardiovascular diseases such as atherosclerosis and hypertension¹⁵. Individual differences in human responses to nutritional interventions have been well-recognized recently¹⁶, yet the determinants of the differences are to be elucidated. In our previous trial of dietary fiber supplementation (including polyglucose, oligosaccharides, psyllium husk, and/or wheat bran, up to 5 g/d), baseline gut microbiota profiles showed a strong predictive value in individual differences in the improvement of clinical outcomes¹⁷. Given prior evidence linking coarse-grain intake, gut microbiota, and hypertension, we hypothesized that gut microbiota may similarly predict blood pressure reduction upon a fiber-rich coarse-grain intervention. Interestingly, recent human genomic studies showed that genetic variants may somewhat determine gut microbiota composition, with a remarkable understanding of the effect of gene *ABO* and *LCT* variants, as compared to other genes, on fiber-consuming species^{18,19}. Revelation of microbial determinants of response differences and gene-intervention interactions, upon CG intervention, would provide new information for precision nutrition intervention strategies.

This open-label randomized controlled trial aimed to evaluate the effects of partially substituting RG with CG on blood pressure and gut microbiota profile among individuals with prehypertension. The effects of gut microbiota and host *ABO* and *LCT* variants on the intervention responsiveness were also examined.

Results

Participant characteristics and compliance

In total, 172 participants were enrolled and randomized into the CG group and RG group ($n = 86$ for each). Over the 12-week intervention, 4 participants and 17 participants dropped out in the CG and RG groups, respectively, due to long-time travel out of the city, unplanned pregnancy, lost interest, or lost contact (Supplementary Fig. 1). The mean $\pm$ standard deviation (SD) age of the participants was 39.8 ± 12.5 years, 42.44% were male (Table 1). There were no between-group differences in baseline characteristics. Among those who completed the CG intervention ($n = 82$), the mean daily CG intake was 121.2 ± 35.6 g (daily oat intake: 68.9 ± 28.9 g; daily buckwheat intake: 52.1 ± 30.1 g), with a mean adherence score of 1.21. A total of 69 participants in the RG group finished all the intervention follow-up visits.

Effects on blood pressure and other clinical outcomes

After 12 weeks of intervention, the intention-to-treat (ITT) analysis indicated significant decreases in SBP (CG: -5.32 ± 9.22 mm Hg, RG: -5.30 ± 9.95 mm Hg) and diastolic blood pressure (DBP) (CG: -2.58 ± 6.83 mm Hg, RG: -2.59 ± 6.16 mm Hg) in both groups ($P < 0.001$). Crucially, no significant time by group interaction effect was detected for either SBP or DBP, indicating that the magnitude of blood pressure reduction did not differ significantly between the CG and RG interventions (Table 2).

Regarding all the other metabolic outcomes, including glucose (GLU), insulin (INS), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP), and waist circumference, no significant time-by-group interactions was observed. Within-group changes were observed in the decrease in TC (CG group), waist circumference (both groups), and HDL-C (RG

group) ($P < 0.050$), but in a small magnitude. The results from the per-protocol analysis were similar (Table S1), while SBP reduction was -6.98 ± 8.00 and -6.14 ± 11.10 in the CG and RG group, respectively (both $P < 0.001$). Regarding lifestyle changes, the change in physical activity levels (Δ Metabolic equivalents of task, MET) from baseline to week 12 did not differ significantly between the two groups ($P = 0.500$), indicating balanced compliance with exercise recommendations.

Effects on gut microbiota and metabolites in relation to blood pressure change

Group difference was observed in α -diversity (invsimpson index) over the intervention period (Supplementary Fig. 2, $KSp = 0.026$). β -diversity difference was also observed at week 12 (Supplementary Fig. 3, $P < 0.050$). Over the intervention period, differential gut microbiota changes were identified in the relative abundance of 10 genera and 16 species (Fig. 1A, B, $P_{FDR} < 0.100$; Table S2), among which 5 genera and 6 species showed a $P_{FDR} < 0.050$. Notably, CG resulted in the largest increase in *g_Lactococcus* with a log fold change (FC) of 1.78, and *s_Lactococcus_garvieae* (log FC = 3.72) and the largest decreases in *g_Leuconostoc* (log FC = -2.31) and *s_Leuconostoc_lactis* (log FC = -2.63), respectively ($P_{FDR} < 0.100$; Table S2).

The mixed linear model detected 428 differential fecal metabolites ($P < 0.050$, all the $P_{FDR} > 0.100$) (Table S3), from which 23 metabolites were confirmed to have correlations with changes in either SBP or DBP (Table S4). Networks were illustrated for the correlations among feature metabolites, differential gut microbial taxa, and blood pressure over the CG intervention (Fig. 1C, D and Table S5). Overall, covariation patterns were identified among microbial genera/species, fecal metabolites, and host blood pressure upon CG intervention. Notably, 7-(5-pentylfuran-2-yl)heptanoylcarnitine in relation to SBP change exhibited covariations with 9 differential genera/species. Functional profiling of the differential genera/species using PICRUSt2 indicated that they were mainly associated with the ATP-binding cassette (ABC) transporter pathway, which showed the highest predicted abundance (Fig. 1E). Moreover, 11-dehydro-2,3-dinor thromboxane B2, gitoxigenin, and graveliferone, in relation to DBP, were linked with 3 differential genera/species each, while *s_Bifidobacterium_longum* was linked with 4 SBP-related metabolites: N-eicosapentaenoyl tyrosine, dihydroxylisinonoleucine, phe thr, and equol.

Baseline microbiota predict the responsiveness upon coarse grain intervention

Among the machine learning models, the highest Area under the Receiver Operator Characteristics curve (AUC) (95% CI) predicting responders of blood pressure reduction was 0.881 (0.666–1.000) from the random forest model (Fig. 2A). The top ten contributing features were presented in Fig. 2B. Notably, the relative abundance of *g_Bifidobacterium* and *g_Streptococcus* was lower in responders than in non-responders ($P < 0.050$). Moreover, the microbial predictive score (MPS) based on the Shapley additive explanation (SHAP) values of the top 10 contributing features was inversely correlated with the changes in both SBP and DBP ($P < 0.010$, Fig. 2C, D).

The genotype-intervention interaction on changes in blood pressure

Significant interactions were observed between the rs514659 genotype (*ABO* gene) and intervention on the reduction of both SBP ($P_{interaction} = 0.029$; Fig. 3A; Table S6) and DBP ($P_{interaction} = 0.040$; Fig. 3B; Table S6). In the CG group, we also detected associations between rs514659 genotype and changes in intervention-derived differential genera (*g_Dorea*, *g_Faecalibacterium*) and species (*s_Bacteroides_caccae*, *s_Faecalibacterium_prausnitzii*, and *s_Dorea_longicatena*), respectively (Fig. 3C, D, details are shown in Table S7). No interaction was detected for the *LCT* variant (Table S6).

Discussion

In this 12-week open randomized controlled trial, non-differential reductions of blood pressure were observed in both groups, whereas between-

Table 1 | Baseline characteristics of participants

Characteristic	Overall	Group		P
		CG	RG	
N	172	86	86	
Men [n (%)]	73 (42.44)	34 (39.53)	39 (45.35)	0.537
Age (y)	39.8 ± 12.5	38.9 ± 12.1	40.6 ± 12.9	0.368
Married [n (%)]	129 (75.00)	61 (70.90)	68 (79.10)	0.291
Education level [n (%)]				0.294
0–9 years	10 (5.81)	5 (5.81)	5 (5.81)	
10–12 years	23 (13.37)	8 (9.30)	15 (17.44)	
13–16 years	101 (58.70)	50 (58.14)	51 (59.30)	
>17 years	38 (22.09)	23 (26.74)	15 (17.44)	
Current smokers [n (%)]	24 (13.95)	10 (11.63)	14 (16.28)	0.509
Alcohol drinkers [n (%)]	7 (4.10)	2 (2.33)	5 (5.81)	0.440
BMI (kg/m ²)	25.11 ± 3.35	24.64 ± 2.94	25.59 ± 3.65	0.064
SBP (mmHg)	119.7 ± 11.2	120.9 ± 11.3	118.6 ± 11.1	0.186
DBP (mmHg)	82.4 ± 8.7	83.3 ± 8.9	81.5 ± 8.5	0.187
Waist circumference (cm)	86.02 ± 9.93	84.81 ± 9.27	87.24 ± 10.47	0.110
Glucose (mmol/L)	5.42 ± 0.81	5.51 ± 1.01	5.34 ± 0.54	0.167
Insulin (μU/mL)	12.74 ± 8.32	13.57 ± 8.82	11.93 ± 7.77	0.203
HOMA-IR	3.11 ± 2.25	3.36 ± 2.29	2.87 ± 1.99	0.141
TC (mmol/L)	4.64 ± 0.96	4.77 ± 0.95	4.52 ± 0.87	0.102
TG (mmol/L)	1.56 ± 0.97	1.61 ± 1.06	1.52 ± 0.87	0.544
LDL-C (mmol/L)	2.95 ± 0.85	3.07 ± 0.84	2.83 ± 0.85	0.675
HDL-C (mmol/L)	1.21 ± 0.31	1.20 ± 0.30	1.22 ± 0.31	0.069
hs-CRP (mg/L)	1.85 ± 4.57	2.30 ± 6.37	1.41 ± 1.34	0.207
Physical activity (MET-min-d ⁻¹)	207.43 ± 282.25	215.01 ± 302.98	199.86 ± 261.46	0.726

Data are means ± SD or numbers (percentage). Overall between-group difference was determined by the *t*-test, the Wilcoxon rank-sum test, and the Chi-square test when appropriate.

BMI body mass index, CG coarse grain group, DBP diastolic blood pressure, HDL-C high-density lipoprotein cholesterol, HOMA-IR homeostatic model assessment of insulin resistance, hs-CRP high-sensitivity C-reactive protein, LDL-C low-density lipoprotein cholesterol, MET metabolic equivalent task, RG refined grain group, SBP systolic blood pressure, TC total cholesterol, TG triglyceride.

group differential changes were detected in gut microbiota features. Covariations were identified among gut microbiota, fecal metabolites, and blood pressure over the CG intervention. Moreover, gut microbiota-based random forest models exhibited a prediction potential for the blood pressure responsiveness after CG intervention, and host *ABO* gene variants showed significant interactions with intervention on the blood pressure reduction. These findings do not demonstrate a superior blood pressure benefit of coarse grains in this population, but rather suggest distinct microbiota-dependent metabolic changes.

Both the CG and RG groups exhibited blood pressure reduction, with a similar magnitude (5.32 and 5.30 mmHg) in the ITT set, whereas in the per-protocol set, the changes in SBP were −6.98 and −6.14 mmHg, respectively. Our results may suggest no extra benefits on blood pressure by 12-week CG intervention, in addition to overall lifestyle modification among prehypertension participants. Xue et al. observed a significantly larger reduction of SBP and DBP with a 3-month oat bran intervention in stage-1 hypertension patients²⁰. One possible explanation could be that individuals having prehypertension are not as sensitive as those hypertension patients to the CG-derived effects on blood pressure control. Similarly, the effect magnitude of dietary fiber intervention on blood pressure also varies depending on the level of blood pressure at baseline²¹. Moreover, Sacks et al. found that dietary and behavioral modifications, including sodium reduction and healthy eating patterns, independently lead to substantial reductions in blood pressure, even in control arms²². Those results may highlight the power of integrated strategies in controlling blood pressure compared to single food interventions. Nevertheless, we did observe that the CG intervention may significantly reduce TC, while RG did not, although our

participants generally have baseline TC levels in the normal range. This result may indicate potential beneficial effects of oat plus buckwheat on lipid metabolism in prehypertension participants, as previously shown using either oat or buckwheat, individually^{23–25}. Importantly, since the change in physical activity was balanced between groups, the distinct metabolic improvements observed specifically in the CG group are likely driven by the dietary substitution rather than differential exercise habits. However, without tracking the changes in alcohol drinking and smoking over the intervention, we cannot fully rule out the possible influence driven by unmeasured variations in lifestyle modifications. Over the 12-week intervention, CG substitution resulted in between-group differential changes of gut microbiota, in both diversities and relative abundance at the genera and species levels. Differential fecal metabolites were also identified. By assessing the correlations among changes in gut microbial taxa, fecal metabolites, and blood pressure, we identified a series of covariations among them driven by CG intervention, some of which may provide new insights into the underlying mechanisms for the CG-gut microbiota metabolism-blood pressure regulation axis. For instance, CG led to an increase in *g_Faecalibacterium*, known for its promotion to short chain fatty acid production and anti-inflammatory properties^{26,27}. *g_Faecalibacterium* was also correlated with the change in fecal metabolite sophoraflavanone G, which was related to SBP change in our data and previously identified to have an anti-inflammatory effect in lipopolysaccharide-stimulated mouse macrophages²⁸. Moreover, the CG intervention led to an apparent increase in *s_Lactococcus_garvieae*, associated with DBP-related fecal metabolites Gitoxygenin. In supporting a stronger role of *g_Lactococcus* in blood pressure regulation, in a randomized controlled trial with prehypertensive

Table 2 | Outcomes over the intervention by group in intention to treat set^a

Outcome	Group		P ^b		
	CG	RG	Group	Time	Time by group
SBP (mm Hg)			0.116	0.943	0.379
Week 0	120.86 (11.29)	118.60 (11.08)			
Week 6	116.24 (11.57)	113.21 (11.32)			
Week 12	115.93 (11.17)	113.69 (11.79)			
P ^c	<0.001	<0.001			
ΔWeek 6	−4.80 (10.74)	−6.00 (9.42)			
ΔWeek 12	−5.32 (9.22)	−5.30 (9.95)			
DBP (mm Hg)			0.134	0.795	0.947
Week 0	83.28 (8.90)	81.52 (8.46)			
Week 6	80.60 (8.89)	78.81 (8.05)			
Week 12	80.84 (8.09)	78.79 (8.91)			
P ^c	<0.001	<0.001			
ΔWeek 6	−2.76 (7.13)	−2.82 (5.54)			
ΔWeek 12	−2.58 (6.83)	−2.59 (6.16)			
Waist circumference (cm)			0.154	0.074	0.816
Week 0	84.81 (9.27)	87.24 (10.47)			
Week 6	83.13 (9.87)	85.40 (11.09)			
Week 12	83.73 (9.94)	85.74 (10.60)			
P ^c	0.001	0.019			
ΔWeek 6	−1.74 (4.44)	−1.74 (4.40)			
ΔWeek 12	−1.10 (3.82)	−1.07 (4.27)			
Glucose (mmol/L)			0.350	0.440	0.901
Week 0	5.51 (1.01)	5.34 (0.54)			
Week 6	5.46 (0.91)	5.33 (0.55)			
Week 12	5.42 (1.11)	5.32 (0.62)			
P ^c	0.452	0.940			
ΔWeek 6	−0.06 (0.61)	−0.01 (0.50)			
ΔWeek 12	−0.10 (0.67)	−0.06 (0.49)			
Insulin (μU/mL)			0.350	0.660	0.590
Week 0	13.57 (8.82)	11.93 (7.77)			
Week 12	12.61 (10.84)	12.25 (9.42)			
P ^c	0.478	0.860			
ΔWeek 12	−0.79 (11.35)	0.04 (8.85)			
TC (mmol/L)			0.248	0.093	0.159
Week 0	4.77 (0.95)	4.52 (0.95)			
Week 6	4.51 (0.80)	4.40 (0.92)			
Week 12	4.65 (0.90)	4.45 (0.98)			
P ^c	0.002	0.200			
ΔWeek 6	−0.21 (0.59)	−0.07 (0.47)			
ΔWeek 12	−0.11 (0.70)	−0.12 (0.58)			
TG (mmol/L)			0.848	0.217	0.395
Week 0	1.61 (1.06)	1.52 (0.87)			
Week 6	1.53 (0.81)	1.66 (0.93)			
Week 12	1.73 (1.77)	1.69 (0.94)			
P ^c	0.471	0.099			
ΔWeek 6	−0.06 (0.81)	0.07 (0.69)			
ΔWeek 12	0.10 (1.34)	0.09 (0.66)			
HDL-C (mmol/L)			0.118	0.919	0.546
Week 0	1.20 (0.30)	1.22 (0.31)			
Week 6	1.19 (0.30)	1.14 (0.25)			

Table 2 (continued) | Outcomes over the intervention by group in intention to treat set^a

Outcome	Group		P ^b		
	CG	RG	Group	Time	Time by group
Week 12	1.20 (0.33)	1.13 (0.23)			
P ^c	0.972	<0.001			
ΔWeek 6	−0.00 (0.15)	−0.02 (0.10)			
ΔWeek 12	−0.01 (0.24)	−0.06 (0.16)			
LDL-C (mmol/L)			0.388	0.134	0.189
Week 0	3.07 (0.84)	2.83 (0.85)			
Week 6	2.95 (0.74)	2.86 (0.81)			
Week 12	3.05 (0.75)	2.92 (0.84)			
P ^c	0.083	0.370			
ΔWeek 6	−0.08 (0.45)	0.04 (0.40)			
ΔWeek 12	0.00 (0.50)	0.05 (0.54)			
hs-CRP (mg/L)			0.280	0.290	0.200
Week 0	2.30 (6.37)	1.41 (1.34)			
Week 12	1.50 (1.86)	1.50 (1.84)			
P ^c	0.220	0.720			
ΔWeek 12	−0.89 (6.39)	0.08 (1.91)			

Data are mean (SD).

CG coarse grain group, DBP diastolic blood pressure, HDL-C high-density lipoprotein cholesterol, hs-CRP high-sensitivity C-reactive protein, LDL-C low-density lipoprotein cholesterol, RG refined grain group, SBP systolic blood pressure, TC total cholesterol, TG triglyceride.

^aWeek 0 (CG: *n* = 86, RG: *n* = 86), week 6 (CG: *n* = 86, RG: *n* = 74), week 12 (CG: *n* = 82, RG: *n* = 69).

^bP values were determined by generalized estimating equation (GEE) adjusted for age, sex, batch, and baseline measurement.

^cGEE was used to assess the effect of time on variables across all visit times, adjusted for age, sex, and batch.

participants, fermented milk with *Lactococcus lactis* showed a significant effect on blood pressure reduction²⁹. Interestingly, we observed a lower level of SBP-related fecal 7-(5-pentylfuran-2-yl)heptanoylcarnitine after CG intervention, associated with a group of differential gut microbial features, with enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway emphasizing ABC transporter. In supporting our finding, a previous experiment reported that certain gut microbial species in *Bifidobacterium* highly depend on the ABC transporter to uptake α-(1,6)- oligosaccharides from legumes and starch, thereby affecting the competitive growth and function of gut microbiota³⁰. However, in order to establish the networks among fecal metabolites, gut microbiota, and blood pressure, false discovery rate (FDR) adjustment was not applied in identifying the metabolites and mutual correlations; those results should be considered as exploratory.

Notably, the findings from the predicted microbiome functions and metabolomics showed a high degree of convergence. The PICRUST2 analysis highlighted the enrichment of the ABC transporter pathway. This functional prediction aligns well with the metabolomics profile, which revealed significant changes in specific metabolites correlated with blood pressure. Since ABC transporters are the primary mechanism for the bacterial uptake of dietary oligosaccharides and the transport of lipid derivatives³⁰, the observed metabolic shifts likely represent a functional readout of this enriched transport activity, reflecting the microbiota's active utilization of coarse-grain substrates.

Although little knowledge can be tracked for the physiological role of 7-(5-pentylfuran-2-yl)heptanoylcarnitine in humans, serum heptanoylcarnitine was identified as a strong biomarker for coronary artery disease risk in patients with type 2 diabetes³¹. A meta-analysis of randomized controlled trials suggested L-carnitine supplementation was able to reduce DBP³². Our data may have extended the mechanism understanding, that gut microbiota may modulate the effect of CG intervention on blood pressure control through competitive substrate uptake. Interestingly, we observed that *s_Bifidobacterium_longum* was related to several blood pressure-related metabolites, including equol, a bacterial metabolite from the daidzein isoflavone, that has estrogenic and antioxidant activity³³. This may

indirectly support the beneficial effect of the CG intervention (containing black bean) via microbiome-metabolite interactions.

Our study also highlighted the potential predictive value of baseline gut microbiota in the responsiveness to the CG intervention. The random forest model showed a preliminary predictive ability of those responders in blood pressure reduction, with further confirmations from close relations between MPS and blood pressure changes driven by CG intervention. This finding suggests that specific gut microbiota profiles could serve as biomarkers for identifying individuals who are more likely to get vascular benefits from CG replacement, emphasizing a dominating role of microbiota features in personalized nutrition³⁴. We noticed lower baseline relative abundances of *g_Bifidobacterium* in responders than in non-responders. This may indicate a more sensitive potential with CG intervention for those having sub-optimal gut microbiota features, given that many species from the *g_Bifidobacterium* are well-recorded to promote cardiovascular health³⁵.

Genetic variations can influence dietary responses, further advocating for the integration of genetic information in dietary recommendations³⁶. In terms of the effect of dietary fiber intake on gut microbiota profiles, the host *ABO* locus has been replicated for its association with *Collinsella* species, *Bifidobacterium*, and *Faecalibacterium*³⁷, all related to dietary fiber utilization. *ABO* variant rs514659 is associated with the presence of the O blood phenotype, has been linked to myocardial infarction of coronary artery disease in a large genome-wide association studies³⁸. Another study also found that rs51465 was associated with plasma von Willebrand Factor, a factor related to inflammation or vascular tone, in 7856 participants of European descent³⁹. We verified an interaction between rs514659 and intervention on blood pressure changes. Moreover, rs514659 was related to the relative abundance of *g_Faecalibacterium* and *g_Dorea* in our participants, which were also differential genera upon CG intervention. Our data may not only support the genetic effect of the *ABO* gene on gut microbiota structure, but also highlight the host genetic predisposition on the vascular benefit of dietary modification, related to gut microbiota modulations.

It is important to note that these gene-diet interactions may be population-specific. The allele frequency of the *ABO* variant varies

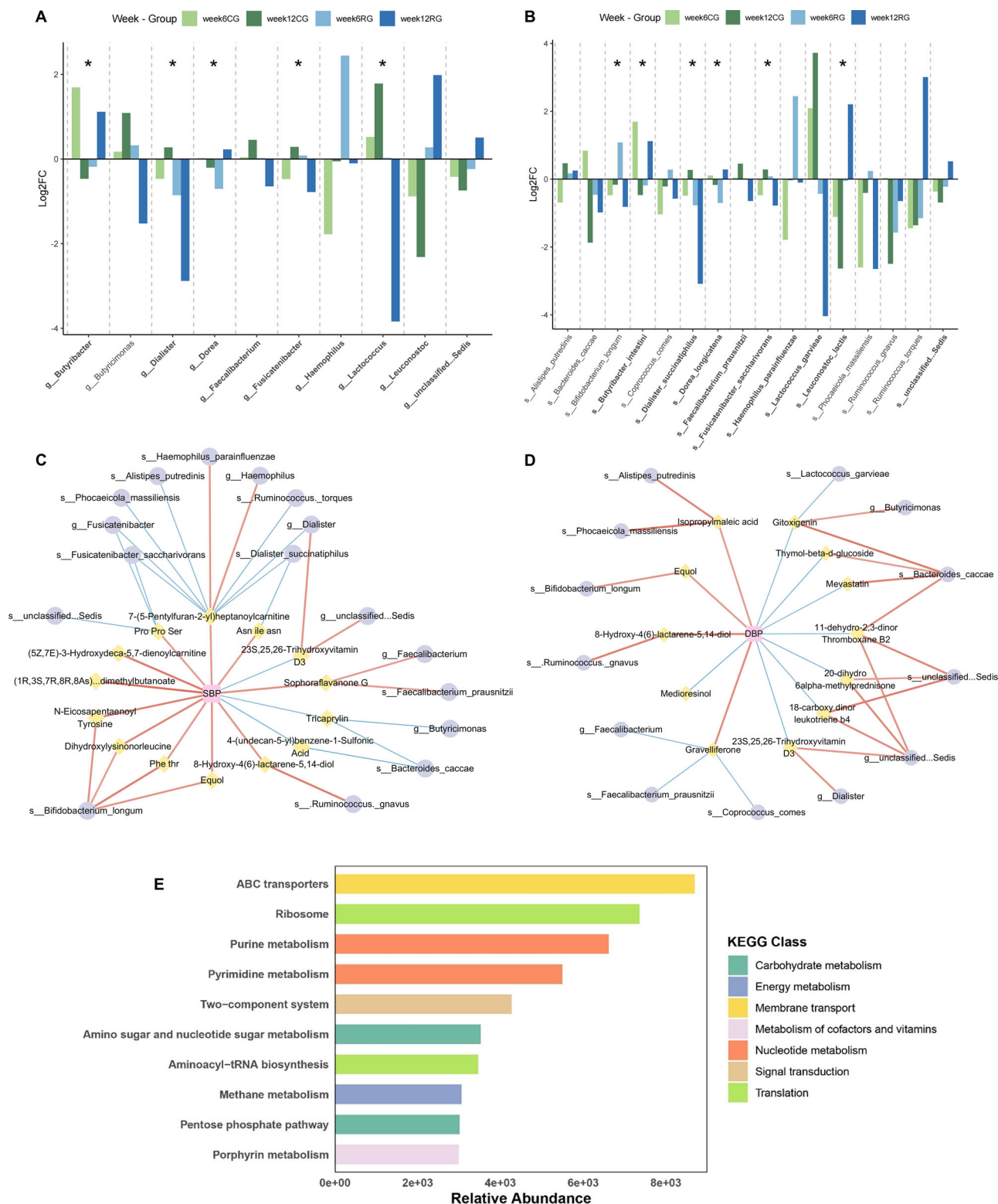


Fig. 1 | Effects on gut microbiota and correlation networks among microbiota, fecal metabolites, and blood pressure reduction. Log fold changes in differential genera (A) and species (B) are presented for week 6 and week 12, as compared to baseline levels. The differential gut microbiota was identified by checking the time by intervention effect using GEE, adjusted for age, sex, and batch. C, D The correlation networks among changes in differential microbiota, differential metabolites, and blood pressure in the CG group. Red lines indicate positive correlations, while blue lines represent negative correlations. The thickness of the lines reflects the strength of the correlations. E The top 10 KEGG pathways predicted by 7-(5-Pentylfuran-2-yl)heptanoylcarnitine related-gut microbe in the CG group at 12 weeks. CG, Coarse Grain group; DBP, diastolic blood pressure; FC, fold change; RG, Refined Grain

group; SBP, systolic blood pressure; ABC transporters, ATP-binding cassette transporters. *g__unclassified...Sedis* represents *g__unclassified_f__Eubacteriales_XIII_Incertae_Sedis*. *s__unclassified...Sedis* represents *s__unclassified_f__Eubacteriales_XIII_Incertae_Sedis*. (1R,3S,7R,8R,8As)...dimethylbutanoate represents (1R,3S,7R,8R,8As)-8-{2-[(2R,4S)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate. The gut microbiota analysis was conducted in the per-protocol set: CG: $n = 64$, RG: $n = 49$. The metabolites analysis in the CG group was carried out in 51 subjects with adequate stool samples available. * Differences with false discovery rate (FDR)-adjusted P value < 0.050 .

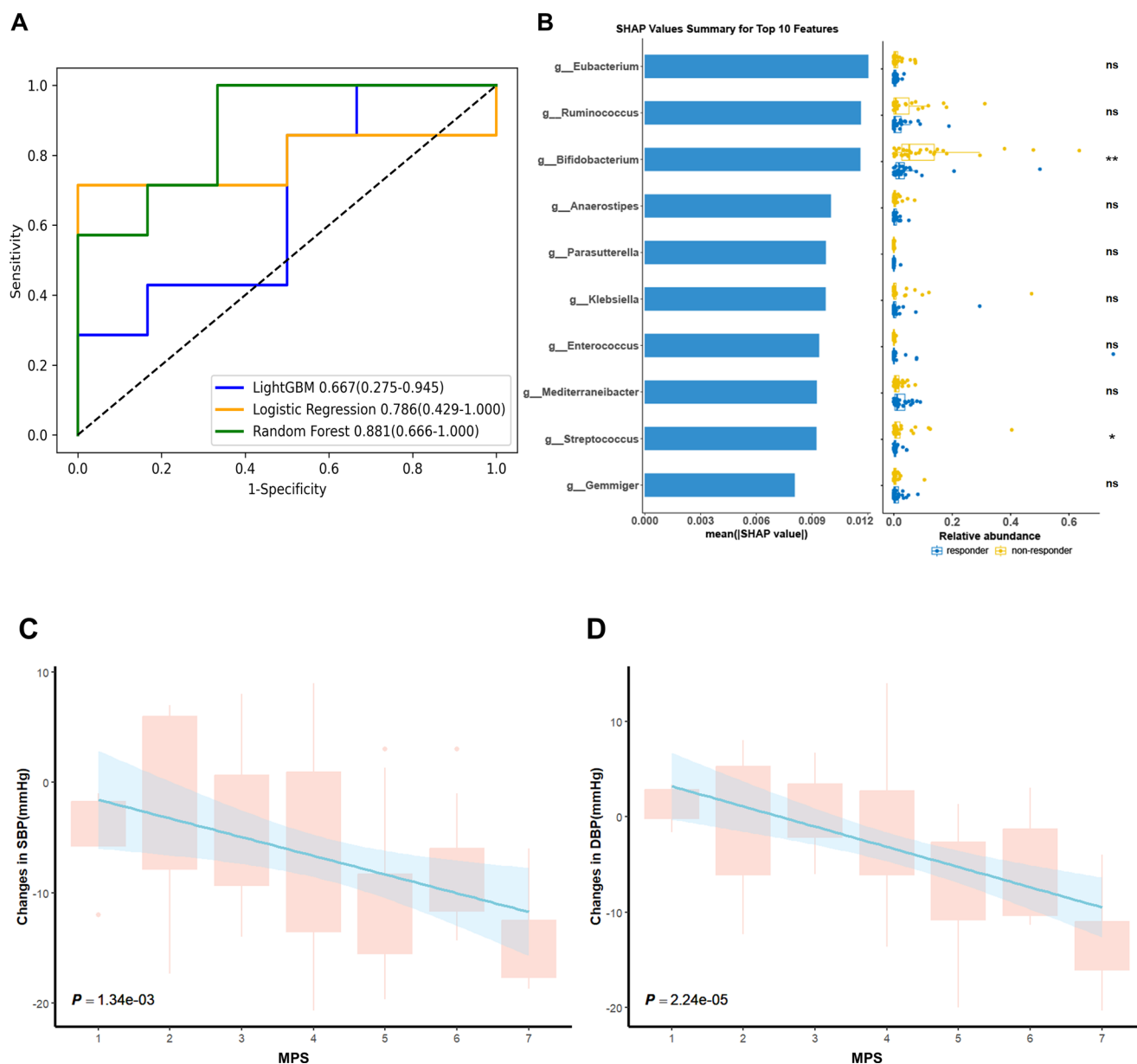


Fig. 2 | Baseline gut microbiota predispose the blood pressure reduction upon intervention. AUC of machine learning models (A) and the top ten contributing features (B) of the random forest model are presented. C, D The associations between MPS and the 12-week changes in SBP and DBP, respectively; multiple linear

regression was used to explore the associations between the variables, adjusting for age, gender, and batch. MPS microbial predictive score, SHAP Shapley additive explanation. The gut microbiota analysis was conducted in the per-protocol set of the CG group ($n = 64$). * $P < 0.050$, ** $P < 0.010$.

substantially across different ethnic groups⁴⁰. The traditional Chinese diet, characterized by higher carbohydrate intake compared to Western diets, shapes a distinct baseline gut microbiota profile. Consequently, the interplay we observed between host genetics, gut microbiota, and the coarse grain intervention may not be directly generalizable to populations with different genetic backgrounds or dietary habits. Future studies in diverse multi-ethnic cohorts are needed to validate the genotype-dependent responsiveness.

There are several limitations in our study. Firstly, blood pressure was measured only on the morning of the visiting day; day-to-day variations could not be captured. Secondly, the study was carried out from March 2023 to September 2023, the natural seasonal decline in blood pressure due to rising ambient temperatures and vasodilation⁴¹ may have contributed to reductions in both groups, potentially masking intervention-specific effects. Future studies with longer durations and larger sample sizes are needed to detect the net intervention effects. Third, only a survey-based approach was

applied to assess adherence, and different assessments were used for the CG group and RG group due to an open-label design with different intervention methods; thus, possible imbalance of the adherence between the two groups may have affected the results. Fourth, the generalizability and reliability of the predictive value of microbial signatures need further independent validation. Furthermore, the flexibility of choosing grain types and consuming time may preclude isolating grain or timing-specific effects, yet the internal validity of the coarse-vs-refined contrast remains robust, as all intervention grains shared high fiber content distinct from the control. Given the higher dropout rate observed in the control group, future gut microbiota trials should implement strategies to enhance retention, such as providing the intervention products to the control group post-trial, increasing engagement through frequent health feedback, and optimizing fecal sampling logistics to minimize participant burden.

In conclusion, we observed differential changes in gut microbiota-fecal metabolite networks by substituting RG with CG among Chinese

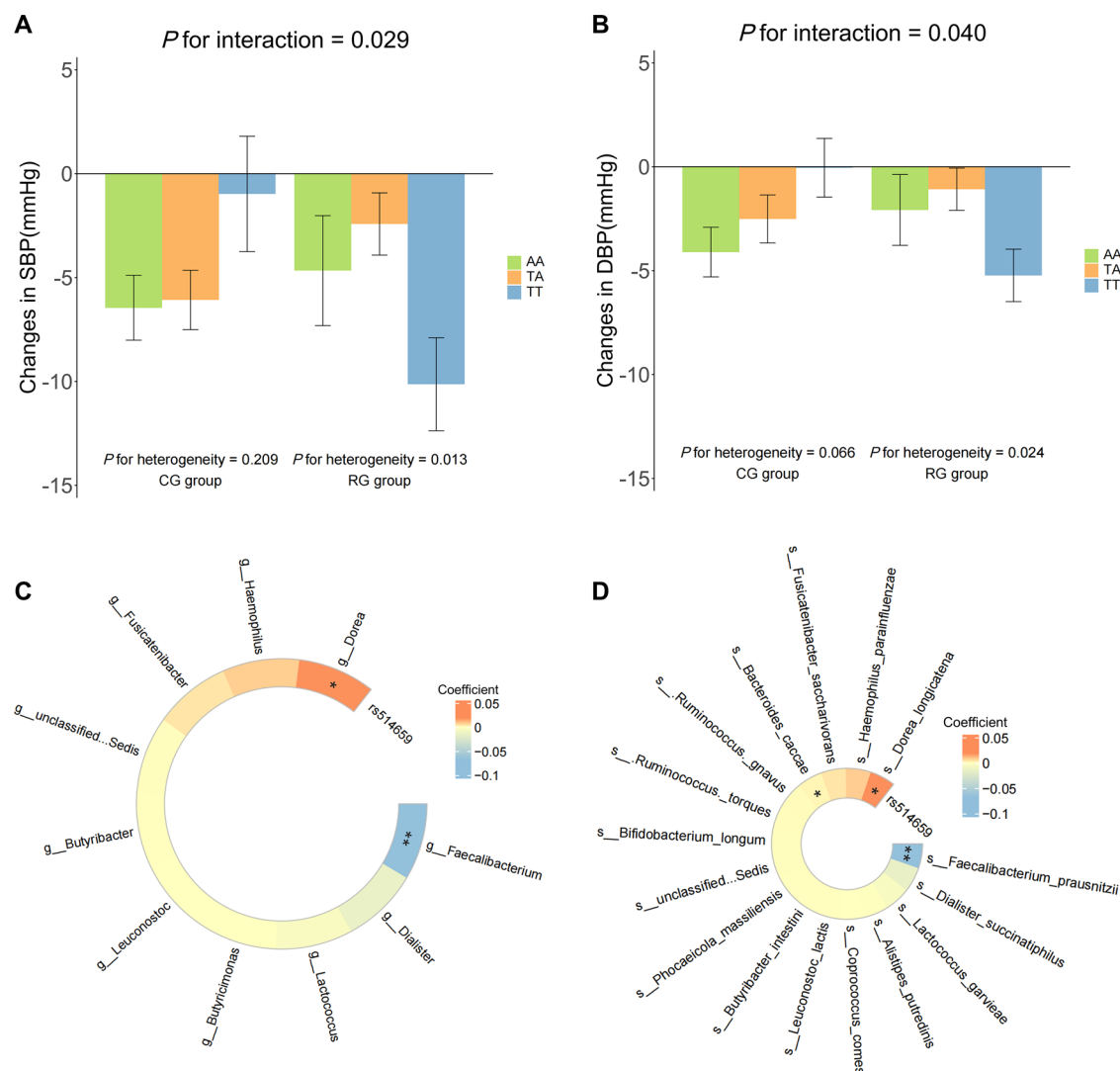


Fig. 3 | ABO genotype interactions with intervention on blood pressure and associations with differential gut microbiota. The effects of rs514659 genotype, intervention, and genotype-intervention interactions on the changes in SBP (A) and DBP (B) were examined using general linear models adjusted for age, sex, and batch. The associations between the rs514659 genotype and changes of differential genera (C) and species (D) were examined using a general linear model adjusted for age, sex, and batch. CG Coarse Grain group, DBP diastolic blood pressure, FC fold change,

RG Refined Grain group, SBP systolic blood pressure. g_unclassified...Sedis represents g_unclassified_f_Eubacteriales_XIII_Incertae_Sedis. s_unclassified...Sedis represents s_unclassified_f_Eubacteriales_XIII_Incertae_Sedis. The interaction analysis was conducted in participants with complete blood pressure data: CG: $n = 82$, RG: $n = 69$. The gut microbiota analysis was conducted in the per-protocol set: CG: $n = 64$, RG: $n = 49$. * P value < 0.050, ** P value < 0.010.

individuals with prehypertension, but did not find differential reductions in blood pressure between groups. Moreover, baseline microbiota profiles showed potential for predicting individual responsiveness in blood pressure. These findings provide preliminary insights into the microbiota-dependent effects of coarse grains, but larger, longer trials are warranted to validate these tailored nutrition strategies.

Methods

Study design and participants

This study is a 12-week open randomized controlled trial to evaluate the effects on blood pressure, cardiometabolic risk factors, and gut microbiota by partially substituting RG with CG among prehypertension subjects. Participants were recruited by advertisements posted by the Epidemiology Division, School of Public Health, Xi'an Jiaotong University Health Science Center or the Nutrition Department, Xi'an Daxing Hospital. The inclusion criteria were as follows: (1) age: 18~65 years old; (2) 18.5 kg/m² ≤ BMI < 40 kg/m²; (3) SBP: 120~139 mmHg; or DBP: 80~89 mmHg

(mean of three measurements at rest, 2 min apart). The exclusion criteria were as follows: (1) pregnancy or lactation; (2) abnormal liver or kidney function; (3) regular intake of CG with daily intake exceeding 60 g, which represents approximately three times the average daily intake of the Chinese population⁴², potentially indicating a distinct baseline gut microbiota profile established by long-term dietary habits⁴³; (4) having gastrointestinal diseases, such as severe diarrhea, constipation, severe peptic inflammation, active peptic ulcer, and acute cholecystitis or history of cholecystectomy; (5) having undergone gastrointestinal resection (except appendicitis and hernia surgery); (6) SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or taking anti-hypertensive drugs; (7) diagnosed with coronary heart disease, cerebral hemorrhage, cerebral thrombosis, stroke or hemiplegia; (8) diagnosed with cancer, hyperthyroidism, or hypothyroidism; (9) diagnosed with infectious diseases such as hepatitis B, tuberculosis or acquired immune deficiency syndrome; (10) diagnosed with any psychiatric disorder, epileptic or on antiepileptic and antidepressant treatment; (11) participated in other clinical trials within 3 months.

From March 2023 to September 2023, a total of 494 participants who finished an online screening questionnaire were invited to attend an onsite screening session at the Nutrition Department, Xi'an Daxing Hospital. After the exclusion of individuals who did not meet the inclusion criteria, refused to participate, or were lost to follow-up, 172 eligible participants were recruited (Supplementary Fig. 1). The study protocol was approved by the Ethical Committee of Xi'an Jiaotong University Health Science Center (approval number 2021-336) and the Ethics Committee of Xi'an Daxing Hospital (approval number KY2023-0001). The study was registered at the China Clinical Trial Registration Center (www.chictr.org.cn, ChiCTR2300069460). All the participants provided informed consents before the intervention.

Randomization

The randomization was conducted by a statistician who was not involved in any other step of the study using block randomization (block size = 4). On the baseline visit day, each participant was sequentially allocated to either the CG group or the RG group using the sealed allocation number.

Sample size

The sample size was calculated using Epicalc-2000 software, employing a method for comparing continuous variables in the context of a clinical trial outcome. We aimed to detect a 5-mmHg difference in SBP change between groups, as a clinically significant reduction that showed reduced risks of future stroke and coronary heart disease⁴⁴. The standard deviation of SBP was set at 9.60 mmHg based on prior data from local residents with high coarse grain intake frequency⁴⁵, and in consideration of the SBP range specified in our inclusion criteria. Setting the significance level at 0.05, a total of 77 participants in each group would obtain 90% power. Assuming a dropout rate of 10%, a total of 172 participants (86 participants in each group) were finally recruited.

Intervention

The intervention strategy was implemented by providing participants with grains, demo recipes showing how to incorporate intervention grains into their diets, as well as lifestyle counseling materials based on "Chinese Guideline on Healthy Lifestyle to Prevent Cardiometabolic Diseases" issued by the Chinese Society of Preventive Medicine in 2020⁴⁶. During the 1-week run-in period before the baseline visit, all participants were provided with the lifestyle counseling materials and were required to finish a 3-day dietary record. After group allocation at the baseline visit, participants started to receive their interventions. For the CG group, participants were provided with CG, including ready-to-eat oatmeal, 5-black grain oatmeal, oatmeal rice, rye buckwheat oat noodles, and raw buckwheat flour (detailed ingredients and major nutrient facts can be found in Table S8) (provided by Guilin Seasmild Food Co., Ltd). A short instruction along with demo recipes was provided to ensure a daily replacement of 100 g RG with CG (Table S9). Lifestyle counseling material was also provided: a balanced diet, moderate exercise, healthy sleep, and smoking and alcohol restriction (Table S10). For the RG group, participants were provided with equivalent RG, including rice and wheat flour (100 g/day), similar demo recipes without emphasis on CG, and lifestyle counseling materials same as the CG group. At baseline and 6-week visits, intervention grains sufficient for 6 weeks were dispensed to each participant. Over the 12-week intervention, a short online survey was carried out every 3 weeks for the CG group to monitor their CG intake. The adherence of the CG intervention was assessed by calculating the proportion of the daily intake amount of CG divided by 100 g, and completion of the intervention follow-up assessment, while the adherence of the RG group was evaluated by completion of the intervention follow-up assessment.

Outcomes, follow-up, and data collection

The primary outcome is the change in SBP. The secondary outcomes include changes in DBP, GLU, INS, TC, TG, HDL-C, LDL-C, and gut microbiota over the 12 weeks of intervention. The networks illustration, prediction of individual responses, and pathway enrichment analysis are exploratory.

Participants were required to visit the research center, the Nutrition Department of Daxing Hospital, at week 0, 6, and 12, to finish their baseline examination and follow-up assessment. The questionnaire information was collected using a Radcap-based online system⁴⁷. The baseline questionnaire mainly included demographic information, smoking and alcohol consumption, physical activity level (using the International Physical Activity Questionnaire), and disease history. A food frequency questionnaire was used to collect participants' habitual dietary intake at baseline.

All the physical examinations were conducted by trained health workers. Height and weight were measured using a calibrated electronic scale (Huaaju HJ-201), accurate to 0.10 cm and 0.10 kg, respectively. Waist circumference was measured with a non-stretchable tape (DSBLT-721) at the midpoint between the lowest rib and the iliac crest to the nearest 0.1 cm. Participants were required to remove their coats, shoes, and any heavy objects on their bodies and to wear lightweight clothing during the measurements. Blood pressure measurements (Omron U724J) were taken with the participants in a seated position in a quiet room, ensuring that the feet were flat on the floor and that the jacket and arm sleeve were removed. Participants were required to place their arms on a tabletop with their palms facing up, relax their whole body, and sit still for at least 5 min before measurement. Three measurements were carried out with an interval of 5 min between each measurement. The mean of the three values was used in the analyses.

Biological sample collection and measurement

Overnight fasting blood samples were collected at each visit by trained nurses at the research center. Blood samples were centrifuged (Eppendorf 5702R) at a speed of $2400 \times g$ for 15 min and allocated as plasma, buffy coat, and erythrocyte samples immediately on the day of blood sample collection, then stored at -80°C until measurement. GLU, TC, TG, INS, LDL-C, HDL-C, and hs-CRP in plasma were measured by an automated biochemical analyzer (Beckman Coulter AU680).

QIAampBlood Kit (QIAGEN) was used to extract DNA from buffy coat, and a customized Illumina Infinium[®] Asian Screening Array (Illumina, San Diego, CA, USA; Guoke Biotechnology, Beijing, China) was used to genotype and analyze the research samples. Our array included 24 single nucleotide polymorphisms (SNPs) on the *ABO* gene and 9 SNPs on the *LCT* gene (Table S11), which have been previously reported to be significantly associated with gut microbiota in the context of dietary fiber intake¹⁸. We selected one Tag-SNP from each of the gene *ABO* (rs514659) and *LCT* (rs2322659) for gene by group interaction analysis, both of which were linked to cardiovascular disease^{39,47}.

Fecal samples were collected at week 0, 6, and 12. A special fecal collection kit (including scoop-containing collection tubes, disposable collection boxes, self-filling ice packs, insulated bags, etc.) and a collection instruction card with a QR code linking to a short tutorial video were provided to subjects in advance. Participants were required to bring their fecal samples to the research center within 4 h after collection. If the participants could not bring it by themselves immediately, an express courier service was used to ensure the sample was delivered to the research center shortly. The fecal samples were preserved with ice packs during transportation, and immediately frozen in a -80°C refrigerator upon receipt.

Stool DNA was extracted from fecal samples using the PF Mag-Bind Stool DNA Kit (Omega Bio-tek, Georgia, USA) according to the manufacturer's instructions. Stool DNA extracts were assayed on 1% agarose gels, and DNA concentration and purity were determined using a NanoDrop 2000 UV-vis spectrophotometer (Thermo Scientific, Wilmington, USA). The bacterial 16S rRNA gene was amplified using primers 27F (5'-AGRGTTYGATYMTGGCTCAG-3') and 1492R (5'-RGY-TACCTTGTTACGACTT-3'). Purified SMRTbell libraries were sequenced on the Pacbio Revio System (Pacific Biosciences, CA, USA) by Majorbio Bio-Pharm Technology Co., Ltd (Shanghai, China). The processing of PacBio raw reads was conducted through the SMRTLink analysis software (version 11.0) to obtain high-quality Hifi reads after a minimum of three full passes with 99% sequence accuracy. Hifi reads were barcode-identified and length-filtered, and sequences <1000 bp or >1800 bp in length were

removed. The HiFi sequencing reads were processed using the DADA2 plugin in the QIIME 2 pipeline (version 2020.2) under recommended parameters to perform de-noised and generate amplicon sequence variants (ASVs).

The fecal metabolites were measured by LC-MS/MS on a Thermo UHPLC-Q Exactive HF-X system (ACQUITY HSS T3 column equipped) (Waters, USA). The generated raw data were processed using Progenesis QI software (Waters Corporation, Milford, USA) to identify metabolites. Initially, a 50 mg sample was added to a 2 mL centrifuge tube, and a 6 mm diameter grinding bead was added. For metabolite extraction, 400 μ L of extraction solution (methanol: water = 4:1 (v:v)) containing 0.02 mg/mL of internal standard (L-2-chlorophenylalanine) was used. Samples were ground using the Wombio-96c frozen tissue grinder (Shanghai Wanbo Biotechnology Co., LTD) for 6 min (-10°C , 50 Hz), then low-temperature ultrasonic extraction for 30 min (5°C , 40 kHz). After being left at -20°C for 30 min, the samples underwent centrifugation for 15 min (4°C , $13,000 \times g$), and the supernatant was transferred to the injection vial for LC-MS/MS analysis. The LC-MS/MS analysis was conducted on a Thermo UHPLC-Q Exactive HF-X system, which was equipped with an ACQUITY HSS T3 column (100 mm $\times$ 2.1 mm i.d., 1.8 μ m; Waters, USA) at Majorbio Bio-Pharm Technology Co. Ltd (Shanghai, China). A pooled quality control sample (QC) was prepared by mixing equal volumes of all samples and tested along with the analytic samples. The QC samples were disposed and tested in the same manner as the analytic samples. It helped to represent the whole sample set, which would be injected at regular intervals (every 5–15 samples) in order to monitor the stability of the analysis.

Statistical analyses

Both ITT and per-protocol principles were applied in the analyzes of the intervention effects. The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables with a normal distribution were described using mean $\pm$ SD, while categorical variables were presented as frequency (n) and percentage (%). The t -test, χ^2 test, or Wilcoxon rank sum test was used to compare baseline characteristics between two groups. To assess the effects of group, intervention duration (time), and their interactions on study outcomes, a generalized estimation equation (GEE) was used, in which group and intervention duration served as fixed effects and subjects as random effects. To account for the temporal correlation of repeated measures (Week 0, 6, and 12), an autoregressive (AR1) working correlation matrix was selected based on the Quasi-Likelihood under Independence Criterion. Baseline values were included as the initial time point in the longitudinal outcome vector to estimate changes over time. Between-group comparisons of changes in outcome variables were performed by analysis of covariance, while correlations between variables were explored by partial Spearman's correlation analysis.

The 16S rRNA sequencing results of fecal samples were pump-flattened according to the minimum sequence number (4129) to complete downstream diversity and microbiota composition analyzes. The α -diversity index of the gut microbiota (invsimpson index) was compared between the two groups at week 0, week 6, and week 12, using the Kolmogorov–Smirnov test. Principal coordinate analysis based on Bray–Curtis distance was performed to assess whether β -diversity at the genus level of each group differs between groups at three stages. After removing microbial genera with a low frequency of appearance (more than 10% of participants showing a relative abundance of 0) before analysis, the time by intervention effects on the gut microbial genera were assessed by GEE, adjusted for age, sex, and batch, to identify differential gut microbiota changes over the intervention. Taxa having a FDR-adjusted P value < 0.100 were considered as exploratory candidates and selected for downstream correlation analysis.

The fecal metabolites abundance was log-transformed and normalized using the sum normalization method. The mixed linear model was used to identify differential metabolites at the endpoint between two groups with the adjustment of the corresponding baseline levels of the metabolites, age, gender, and batch by the R package “nlme” and “lsmeans”. Partial

Spearman's correlation analysis adjusted for age, gender, and batch was used to identify feature metabolites related to the changes in blood pressure in the CG group from the differential metabolites, and the correlations between changes in metabolites and the changes in microbial taxa. Correlation networks were visualized as network maps using partial Spearman's correlation coefficients among the changes in the relative abundance of differential species/genera, feature metabolites, and blood pressure. PICRUSt2 (version 2.5.3) was used to predict KEGG pathways based on sequence count data of selected ASVs, characterizing microbial functional profiles.

Machine learning models (random forest analysis, lightGBM, and logistic regression) were used to assess the predictive ability of baseline gut microbiota on effective reduction of blood pressure (SBP reduction ≥ 5 mmHg and DBP reduction ≥ 0 mmHg) using packages ‘sklearn’ and ‘lightgbm’. Optimal models were determined based on the AUC. SHAP values > 0 were defined as 1, and those ≤ 0 as 0. The values of the top 10 contributing genera in the optimal model were then summed to derive MPS. The association between MPS and blood pressure changes was assessed using a linear regression model adjusted for age, sex, and batch.

The effects of genotype-intervention interactions on the changes in blood pressure were examined using general linear models adjusted for age, sex, and batch. The Kruskal–Wallis test was used to compare the changes in blood pressure between three genotypes. General linear models adjusted for age, sex, and batch were used to analyze the association between rs514659 genotypes and differential gut microbial genera and species.

Statistical analyzes in this study were done using R (version 4.1.0), Python (version 3.10), and Cytoscape (version 3.10.1). All reported P -values were two-sided, and $P < 0.050$ was considered a statistically meaningful difference. Post-hoc analyses were performed using FDR adjusted P -values when appropriate.

Data availability

The datasets analysed during the current study are available in the figshare repository. Dataset, on the following doi: 16S <https://doi.org/10.6084/m9.figshare.27337704.v1>.

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Author contributions

XLiu: Study concept and design. J.L., Y.H., J.H., J.X., C.H., K.J., M.W., W.L., X.F., G.M., A.T., K.X., H.N., XLiao, H.Y., L.L., F.C., B.M., and T.T.: Case collection and data acquisition. J.L., Y.H., and XLiu: Analysis and interpretation of data, statistical analysis, drafting of the manuscript. LShi,

LSi, T.T., and X Liu: Critical revision of the manuscript for important intellectual content. J.L., Y.H., and X Liu: Drafting of the manuscript revision. All the authors revised and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at

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