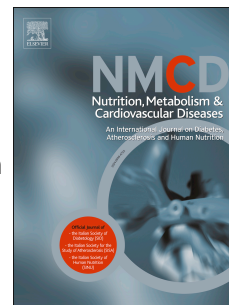


# Journal Pre-proof

The Effect of Dietary Fiber (Oat bran) Supplement on Blood Pressure in Patients with Essential Hypertension: a randomized controlled trial

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1 **The Effect of Dietary Fiber (Oat bran) Supplement on Blood Pressure in Patients**  
2 **with Essential Hypertension: a randomized controlled trial**

3 Running head: Dietary Fiber and Blood Pressure

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Journal Pre-proof

## 1 **Abstract**

### 2 **Background and aims**

3 Insufficient dietary fiber (DF) intake is associated with increased blood pressure (BP)  
4 and the mode of action is unclear. The intake of DF supplements by participants in  
5 previous interventional studies was still far below the amount recommended by the  
6 World Health Organization. Therefore, this study aims to explore the effect of  
7 supplementing relatively sufficient DF on BP and gut microbiota in patients with  
8 essential hypertension.

### 9 **Methods and results**

10 Fifty participants who met the inclusion criteria were randomly divided into the DF  
11 group (n=25) and control group (n=25). All the participants received education about  
12 regular dietary guidance for hypertension. In addition to dietary guidance, one bag of  
13 Oat bran (30g/d) supplement (containing DF 8.9g) was delivered to the DF group.  
14 The office BP (oBP), 24h ambulatory blood pressure and gut microbiota were  
15 measured at baseline and third month. After intervention, the oSBP( $P<0.001$ ), oDBP  
16 ( $P<0.028$ ) in the DF group were lower than those in the control group. Similarly, the  
17 changes in 24hmaxSBP ( $P=0.002$ ), 24hmaxDBP ( $P=0.001$ ), 24haveSBP ( $P<0.007$ )  
18 and 24haveDBP ( $P=0.008$ ) were greater in the DF group than the control group. The  
19 use of antihypertensive drugs in the DF group was significantly reduced ( $P=0.021$ ).  
20 The  $\beta$  diversity, including Jaccard ( $P=0.008$ ) and Bray-Curtis distance ( $P=0.004$ ),  
21 showed significant differences ( $P<0.05$ ) between two groups by the third month. The

1 changes of the *Bifidobacterium* ( $P=0.019$ ) and *Spirillum* ( $P=0.006$ ) in the DF group  
2 were significant.

### 3 **Conclusions**

4 Increased DF (Oat bran) supplement improved BP, reduced the amount of  
5 antihypertensive drugs and modulated the gut microbiota.

6 **Keywords:** Essential hypertension, dietary fiber, blood pressure, ambulatory blood  
7 pressure, gut microbiota.

8 *Trial registration number:* ChiCTR1900024055.

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## 1 **Introduction**

2 The prevalence of hypertension (HTN) is high and continues to increase in  
3 China[1-2]. A nationwide survey was performed to assess the prevalence of HTN  
4 from October 2012 to December 2015 in China, and the result showed that 23.2%  
5 ( $\approx$ 244.5 million) of the population  $\geq$ 18 years of age had HTN, and another 41.3%  
6 ( $\approx$ 435.3 million) had pre-HTN based on the Chinese guideline[2]. HTN is the leading  
7 risk factor for cardiovascular disease and premature death[1,3-4]. Therefore, HTN is  
8 considered one of the most serious public health problems in China[5,6].

9 The treatment of HTN mainly includes pharmacological treatment and  
10 non-pharmacological treatment[7]. At present, about 23.9-40.7% of people in China  
11 use antihypertensive medication, while only 3.9-15.3% meet the recommended target  
12 of blood pressure (BP)  $<$ 140/90 mmHg[1-2]. One of the reasons why so many  
13 patients do not take medication is because they are expensive, and the issue of  
14 drug-resistance can limit the effectiveness of these medications in some patients[8].  
15 Therefore, the major challenge is to develop effective, practical and sustainable  
16 prevention and treatment strategies for managing HTN in China.

17 Medical nutrition therapy, a spectrum of nutrition services aimed at optimizing  
18 individual well-being has been recognized as integral in managing the health of  
19 people with chronic conditions[9]. The importance of nutritional therapy in patients  
20 with HTN is crucial for the control of their BP level and this should involve healthy  
21 nutritionally balanced diet[10]. Dietary approaches to stop hypertension (DASH) diet  
22 is rich in fruits, vegetables, whole grains and low-fat dairy products, with reduced  
23 content of saturated and total fat, which is recommended for adults with elevated BP  
24 or HTN. DASH diet provides a means to enhance intake of potassium, calcium,  
25 magnesium, and dietary fiber (DF) [11]. DF is called the "seventh nutrient" and it is  
26 that fraction of the edible parts of plants including grains, fruits and vegetables or  
27 their extracts, or synthetic analogues that is neither digested nor absorbed in the small  
28 intestine[12-14]. Oat bran is rich in soluble DF[15], which has attracted wide attention  
29 because of its potential role in improving intestinal health[16,17]. Increasing the daily  
30 consumption of Oat bran can provide the required DF supplement. Some researchers

1 have carried out studies on the relationship between DF intake and BP levels, but  
2 there are some differences in the results. For example, increasing the DF supplement  
3 did not have favorable effect on BP in Japanese children with overweight and  
4 hypercholesterolemia[18]. A meta-analysis showed that after supplementing with DF  
5 amounting to average DF intake of 6g/d, the systolic blood pressure (SBP) and  
6 diastolic blood pressure (DBP) decreased by only 0.9mmHg and 0.7mmHg  
7 respectively in a healthy population[19]. However, Whelton et al.[20] conducted a  
8 meta-analysis of randomized controlled experiments on the effect of DF intervention  
9 in patients with HTN and found that compared with the control group, the SBP and  
10 DBP of the intervention group (the average DF intake reached 10.7g/d) decreased by  
11 5.95mmHg and 4.20mmHg, respectively. However, in the above studies, the average  
12 daily DF intake of the participants, whether in the normal populations or hypertensive  
13 populations, was still far lower than the DF intake recommended by the World Health  
14 Organization (25 ~ 35g/d). In addition, previous studies only collected the  
15 measurement of office BP (oBP) or self-reported BP, which did not allow for the  
16 identification of patients with white coat and masked HTN instead of 24h ambulatory  
17 blood pressure (ABP). These BP would have had a greater impact on the results of the  
18 studies. 24h ABP can reflect the overall BP level of the patient and 24h ambulatory  
19 average BP is also an important indicator of the prognosis of HTN[21,22]. Thus, the  
20 effect of increasing DF supplement on 24h ABP in patients with HTN requires further  
21 exploration.

22 In terms of the mechanism of the lowering effect of DF on BP, this is not fully  
23 understood. A few trials have found that DF can produce short-chain fatty acids  
24 (SCFAs) through fermentation by gut microbiota (mainly *thick-walled bacteria* and  
25 *bifidobacteria*). This is thought to activate G protein-coupled receptors and olfactory  
26 receptor 78 distributed in the kidneys and blood vessels, inhibits the release of renin,  
27 and thereby decrease BP[23-25]. SCFAs can also directly activate vagal afferents via  
28 G protein-coupled receptors, signaling to the brain. Finally, it can modulate brain  
29 function and influence BP[26]. In relation to the gut-brain pathways, SCFAs are  
30 directly or indirectly involved in BP regulation. Therefore, SCFAs-producing

1 microorganisms are essential for maintaining BP and cardiovascular health. So far,  
2 there is evidence in some human studies involving healthy populations, linking DF to  
3 gut microbiota[27]. But, there are few studies that report on the impact of relatively  
4 sufficient DF supplementation on gut microbiota in patients with essential HTN.

5 Based on the above, this study proposes the following assumptions:  
6 supplementing with sufficient amount of DF could (1) improve the oBP and 24h ABP  
7 in patients with essential HTN; (2) modulate the gut SCFAs-producing bacteria.

## 8 **2 Materials and Methods**

### 9 **2.1 Study Design**

10 This study was a prospective, randomized controlled trial that was conducted  
11 from March to December 2019. The clinical trial registration number of this study  
12 was ChiCTR1900024055. Eligible participants were randomly and blindly allocated  
13 to the DF or the control groups using computer-generated random numbers over a 3  
14 months (3m) intervention period[28]. Before the intervention, all subjects underwent a  
15 one-week washout period[29] to diminish the effect of background diets on the study.  
16 The study was approved by the ethics committee of the Soochow University  
17 (reference: ECSU-2019000116). All patients provided written informed consent.

### 18 **2.2 Subjects**

19 Patients with HTN were recruited from the First Affiliated Hospital of Soochow  
20 University and the Bai-Liang community in Suzhou. The inclusion criteria were as  
21 follows: patients (1) were between 18 and 65 years and had been diagnosed with HTN  
22 stage 1 [SBP=140-159mmHg and (or) DBP=90-99mmHg], according to the standard  
23 of the latest guidelines for the prevention and treatment of HTN in China[7], (2) were  
24 without adjustment of antihypertensive drugs within 2 weeks before the intervention,  
25 (3) were able to communicate, (4) had volunteered to participate in this study and  
26 signed informed consent. The exclusion criteria were as follows: patients (1) were  
27 allergic to Oat-bran or being treated by other dietary interventions, (2) ate DF  
28 regularly (25g/d), (3) had complications, (4) had serious diseases (e.g., heart failure or  
29 cancer), (5) had diarrhea, dysentery or other gastrointestinal diseases in the past 1  
30 month, (6) took microecological agents, antibiotics or hormones within the past 1



1 month, (7) with irregular living habits and often engaged in social activities, (8) were  
2 pregnant or lactating women, (9) had serious mental illness or cognitive impairment.

### 3 **2.3 Sample Size Calculation**

4 We have not been able to find a similar study that supplemented relatively  
5 high-DF diet in hypertensive patients. Before commencing the research, we designed  
6 a pre-experiment with 10 participants and calculated the sample size based on the  
7 results of the pre-experiment. The mean difference of office SBP at the end of the  
8 intervention between the two groups was 10.2 mmHg, and the standard deviation (SD)  
9 of the two groups was 8.5 mmHg. With  $\alpha = 0.05$  and power = 0.8, we calculated 20  
10 patients for each group. In view of the sample loss of 20%, the number for each group  
11 was 24. Finally, we recruited 25 patients for each group in the study.

### 12 **2.4 Intervention**

#### 13 **Control Group**

14 Dietary education is essential for the treatment of hypertensive patients. Based  
15 on ethical requirements, the control group was given dietary guidance for HTN at  
16 their first visit. We used DASH diet which is usually recommended to patients with  
17 HTN[11] as dietary guidance. Diet recommended: (1) <6g/d of sodium; (2) a low  
18 consumption of saturated fatty acids and cholesterol, such as animal viscera, cream  
19 products, animal oil, etc.; (3) 500g/d of vegetables and fruits, such as lettuce, celery,  
20 apple, banana, etc.; (4) 50-70g/w of nuts, such as almond and peanut; 400 g/w of fish;  
21 (5) 200ml/d of low-fat or fat free dairy milk.

#### 22 **DF group**

23 In addition to the dietary guidance, one bag of Oat bran (30g) supplement  
24 (containing 8.9g) was delivered to the DF group. The Oat bran (free of charge) was  
25 prepared in vacuum packing (30g/bag), which was provided by Fuzhiyuan company,  
26 Shijiazhuang, China. Researchers informed the patients to consume Oat bran 1 bag/d  
27 between meals or with breakfast. The patients recorded the Oat bran intake every day,  
28 and informed researchers in time if any adverse reactions occurred.

#### 29 **Follow-up**

30 Two researchers followed up patients regularly by phone, Wechat or face-to-face.

1 The frequencies and the contents of follow-up for the two groups were: (1) follow up  
2 frequency: once/w in the first month, once/2w in the second and third month, (2) the  
3 content: for the control group, researchers followed up the participants' diet, BP  
4 control, adjustment of medication, changes of exercise; for the DF group, researchers  
5 followed up the participants' compliance to Oat bran and whether there were any  
6 discomfort or reactions, in addition to contents mentioned above. Those whose diets  
7 did not meet the requirements of the dietary program (consumption of Oat bran <4d/w)  
8 in the intervention period were excluded from the study.

## 9 **2.5 Outcomes**

10 The primary outcomes included results from oBP, 24h ABP and the diversity of  
11 gut microbiota. The secondary outcomes were the compliance to taking Oat bran and  
12 the changes of antihypertensive drugs.

### 13 **2.5.1 Anthropometric Measurements**

14 The weight, height, waist and hip of participants were measured at baseline and  
15 3m by a unified measuring device at the First Affiliated Hospital of Soochow  
16 University or a community based clinic. Body mass index (BMI) was calculated as  
17 weight (kg) divided by square of height (m<sup>2</sup>); Waist-Hip Ratio (WHR) was calculated  
18 as waist circumference (cm) divided by hip circumference (cm).

### 19 **2.5.2 The International Physical Activity Questionnaire (IPAQ)**

20 In this study, we used IPAQ, the tool of international measure of physical activity,  
21 to assess physical activity of patients at baseline. The questionnaire was composed of  
22 four physical domains including: transportation, household chores, leisure-time and  
23 occupational physical activity. The frequency and cumulative time for each domain of  
24 physical activity were investigated in detail and used to evaluate the level of physical  
25 activity in a week. Xu et al.[31] tested the reliability and validity of IPAQ and the  
26 retest reliability coefficient was 0.71-0.93 and the criterion validity was 0.74. These  
27 values demonstrated evidence of the good reliability and validity of the tool. In IPAQ,  
28 using metabolic equivalent task (MET) minutes represents the amount of energy  
29 expended carrying out physical activity. Method of calculating MET minutes a week:  
30 multiply the MET value given (walking = 3.3, moderate activity = 4, vigorous activity

1 = 8) by the minutes the activity was carried out and again by the number of days that  
2 that activity was undertaken.

### 3 **2.5.3 Diet Record**

4 Dietary intakes were assessed using 3 days diet records. Two trained dietitians  
5 instructed the participants to record detailed dietary intake in 3 days (including 2  
6 working days and 1 weekend day) at baseline and 3m, which were completed at home.  
7 The composition and quantities of the diets including DF, carbohydrate, protein, fat,  
8 cholesterol, sodium, calcium, potassium intake and total energy were calculated by  
9 the *Fei Hua nutrition software V2.7.6.10* (Bowen Shixun Technology, Beijing, China).

### 10 **2.5.4 Oat bran intake record**

11 In this study, we evaluated the frequency of consuming Oat bran according to  
12 participant's Oat bran intake record. The records were taken mainly at the time of  
13 having the Oat bran and included the number of Oat bran bags every week. This also  
14 enabled an understanding of the patients' Oat bran consumption adherence.

### 15 **2.5.5 The office BP and 24h ABP**

16 The oBP was measured in the teaching room of hospital or community at  
17 baseline and 3m, including office systolic blood pressure (oSBP) and office diastolic  
18 blood pressure (oDBP). The researchers measured participants' BP using the corrected  
19 OMRON sphygmomanometer (HEM-8102) in the upper arm at sitting position, after  
20 taking a rest for at least five minutes. Repeated measurement was performed with a 5  
21 minute interval[32]. We took the average of these two values as the final BP value.  
22 The 24h ABP measurement included the 24h average, minimum and maximum SBP  
23 (24haveSBP, 24hminSBP, 24hmaxSBP) and 24h average, minimum and maximum  
24 DBP (24haveDBP, 24hminDBP, 24hmaxDBP). All participants were equipped with  
25 the ABP device (Mobil-O-Graph PWA, Germany) for 24h at baseline and 3m. 24h  
26 ABP encompassed taking BP measurements every 20 min during the day (8:00 a.m. to  
27 10:00 p.m.) and every 30 min at night (10:00 p.m. to 8:00 a.m.)[32]. The criteria for  
28 valid ABP recordings included successful recording of  $\geq 80\%$  of SBP and DBP during  
29 both the daytime and nocturnal periods, and at least one BP measurement per hour.  
30 When summarizing the 24h ABP report, researchers needed to strictly screen and

1 check the data obtained, and removed the abnormal BP value (SBP>260mmHg or  
2 <70mmHg, DBP>150mmHg or <40mmHg) [32].

### 3 **2.5.6 Gut microbiota**

4 Researchers collected the fecal samples of each patient at baseline and 3m, with  
5 sterile bags, gloves and tubes distributed to the patients. Information about  
6 precautions for sampling was also provided to the patients. A 5g fecal sample was  
7 collected from a sterile bag to sterile tube each time. After sample collection, the  
8 researchers put the aseptic collection tube into the liquid nitrogen tank as soon as  
9 possible. The aseptic collection tube was then transferred to the -80 °C refrigerator in  
10 the laboratory within 2h. We determined fecal microbiota composition by 16S rRNA  
11 gene sequencing and bacterial functions by metagenomic analysis[33]. Based on the  
12 results of Operational taxonomic units (OTUs) clustering, the representative  
13 sequences of OTUs were annotated to obtain the relative abundance of species. In  
14 addition, the  $\alpha$  diversity index of the samples was calculated by OTUs, including  
15 Chao1, Faith's PD, Simpson and Shannon indexes. Non-metric multidimensional  
16 scaling (NMDS), reflecting the sample in a multidimensional space in the form of  
17 points according to the information in the sample, was used to analyze  $\beta$  diversity of  
18 samples based on Jaccard and Bray Curtis distance. The degree of difference between  
19 different samples was reflected by the distance between points.

### 20 **2.5.7 Statistical Analysis**

21 Statistical analyses were performed using SPSS 18.0 software (SPSS, Inc.,  
22 Chicago, IL, USA). The analysis mainly included the following aspects:

23 (1) Description of demographic and clinical data: For categorical variables, the  
24 results were described as the frequency (percentages); For continuous variables, we  
25 determined if data was normally distributed by using the Kolmogorov-Smirnov test  
26 before analysis. If it was normal, it was expressed as mean $\pm$ standard deviation (SD),  
27 otherwise, it was expressed as median ( $P_{25}$ ,  $P_{75}$ ).

28 (2) Comparisons of the variables between the two groups were conducted at  
29 baseline and 3m: For categorical variables, the results were described using Pearson  
30 Chi-square test or Fisher's exact test. For continuous variables, if it was normally

1 distributed, the comparisons between groups were made using the Independent  
2 samples  $t$  test, otherwise, Mann-Whitney  $U$  test was used.

3 (3) Description of gut microbiota data: relative OTUs abundances were  
4 calculated using Quantitative Insights Into Microbial Ecology[34]. Venn diagram  
5 made by the abundance of OTUs was used to explore which species were shared or  
6 unique between groups[35]. The  $\beta$  diversity reflected the degree of difference between  
7 the groups and was examined using NMDS based on accard and Bray Curtis[36].  
8 Community richness and diversity were examined in each group using  $\alpha$  diversity,  
9 including Chao1, Faith's PD, Simpson, and Shannon indexes[37], which were  
10 calculated from OTUs. The relative abundance of the DF and control group were  
11 compared at the genus level.

12 (4) Intention-To-Treat (ITT) of BP was performed to ensure the reliability of  
13 research results.

14 (5) A  $p$  value of  $<0.05$  was considered statistically significant.

### 15 **3 Result**

#### 16 **3.1 Study Participants**

17 Based on the inclusion and exclusion criteria of the study, 56 hypertensive  
18 patients were initially recruited. Three of the participants could not be contacted,  
19 another three voluntarily withdrew. Finally, 50 patients were randomly allocated to  
20 the DF group ( $n = 25$ ) and the control group ( $n = 25$ ). During follow-up, three patients  
21 in the DF group and three patients in the control group withdrew from the study. In  
22 the DF group: one patient showed poor adherence (consumption of Oat bran  $<4d/w$ ),  
23 one patient withdrew due to gastrointestinal reaction at 2 weeks, and another patient  
24 could not be contacted; In the control group: two patients refused 24h ABP, and one  
25 patient could not be contacted. Finally, 22 subjects in the DF group and 22 subjects in  
26 the control group completed the 3m follow-up study. The selection process of patients  
27 is shown in Figure 1. The mean age of patients was  $47\pm 13$  years and 32 (72.7%) were  
28 men. While 86.4% were married, 93.2% had junior middle school or higher level of  
29 education. The mean sleep duration of patients was  $7.0\pm 1.1$  h/d, 43.2% of patients

1 exercised regularly, 27.3% smoked and 27.3% drank alcohol. The mean BMI of  
2 patients was  $24.9 \pm 2.5$  kg/m<sup>2</sup>, and while 40.9% were normal, 40.9% were overweight.  
3 The shortest duration of hypertension was onset, the longest was 22 years, with an  
4 average of  $5 \pm 6$  years. While 29 (65.9%) participants had a duration of fewer than 5  
5 years, 36 (81.8%) had a family history of HTN, 5 cases (18.2%) had comorbidity and  
6 none had complications. Furthermore, 14 (31.8%) were treated with one type of  
7 antihypertensive drug and 19 (43.2%) were not treated with medicine. The  
8 demographic and clinical characteristics of the enrolled patients in each group are  
9 shown in Table 1. There were no significant differences in any of the parameters  
10 between two groups at baseline ( $P > 0.05$ ).

11 Based on food diary analysis, nutrients consumed at baseline and 3m were  
12 compared between the two groups. There were no significant differences in daily  
13 energy and nutrient (except DF) intake between two groups at baseline and 3m  
14 ( $P > 0.05$ ), which are shown in Table 2.

### 15 **3.2 Compliance with dietary fiber (Oat bran)**

16 Compliance with DF (Oat bran) was evaluated according to the frequency of  
17 eating Oat bran. The results showed that the frequency of Oat bran consumption was  
18 stable (about 6.5 bags/w, Figure 2). Two independent samples *t*-test were used to  
19 compare the quality of DF intake between the two groups. The results showed that  
20 there was no statistically significant difference in the quality of DF intake at baseline  
21 ( $P > 0.05$ ). At 3m of intervention, the quantity of DF intake in the DF group was  
22 significantly higher than that of the control group ( $P < 0.001$ , Table 3).

### 23 **3.3 Effect of dietary fiber (Oat bran) supplementation on BP in patients with** 24 **essential hypertension**

#### 25 **3.3.1 Comparison of oBP and 24h ABP between the two groups**

26 At baseline, there were no significant differences in the oBP and 24h ABP. At  
27 3m, the oSBP ( $t = 4.233$ ,  $P < 0.001$ ) and oDBP ( $t = 2.283$ ,  $P < 0.028$ ) in the DF group were  
28 lower than those in the control group. The changes of 24hmaxSBP ( $t = -3.238$ ,

1  $P=0.002$ ), 24hmaxDBP ( $t=-3.582$ ,  $P=0.001$ ), 24haveSBP ( $t=-2.812$ ,  $P<0.007$ ) and  
2 24haveDBP ( $t=-2.781$ ,  $P=0.008$ ) between baseline and 3m in the DF group were  
3 greater than those in the control group. However, the 24hminSBP and 24hminDBP  
4 did not decrease, remaining stable in the DF group.

5 The analysis of ITT relating to oBP and 24h ABP was performed to ensure the  
6 stability of the results above. The results showed the changes of BP were consistent  
7 with the findings above (Table 5).

### 8 **3.4 Effect of dietary fiber (Oat bran) supplementation on gut microbiota in** 9 **patients with essential hypertension**

#### 10 **3.4.1 Sequencing results and quality control**

11 88 fecal samples were collected from 44 patients with essential HTN. All fecal  
12 samples were successfully sequenced and analyzed. 3,286,866 original gene  
13 sequences were obtained. After splicing, quality control, and chimeric filtration,  
14 2,952,730 high-quality gene sequences were obtained. Each sample contained 33,554  
15 sequences on average, with an average length of 444 bp.

#### 16 **3.4.2 Comparison of the diversity of gut microbiota between the two groups**

##### 17 **3.4.2.1 The $\alpha$ diversity of gut microbiota**

18 The  $\alpha$  diversity was mainly reflected by Chao1, Faith's PD, Simpson, and  
19 Shannon indexes. We compared the Chao 1, Faith's PD, Simpson, and Shannon  
20 indexes of the two groups at baseline and 3m. The results showed that there were no  
21 significant differences ( $P>0.05$ ) between the two groups.

##### 22 **3.4.2.2 The $\beta$ diversity of gut microbiota**

23 NMDS, including Jaccard and Bray-Curtis distance, was used to analyze the  $\beta$   
24 diversity of gut microbiota. There were no statistically significant differences with  
25 respect to the  $\beta$  diversity at baseline. However, the results of Jaccard ( $P=0.008$ ) and  
26 Bray-Curtis distance ( $P=0.004$ ) showed that there were significant differences  
27 between the two groups at 3m (Figure 3). This would indicate that the abundance of  
28 gut microbiota was significantly different between the two groups.

##### 29 **3.4.3 Comparison of relative abundance of the targeted gut microbiota between**

## 1 **the two groups**

2 The relative abundance of the targeted gut microbiota was compared between the  
3 two groups. The results showed that: at baseline, there were no significant differences  
4 ( $P>0.05$ ) in the relative abundance of *Bifidobacterium*, *Lactobacillus*, *Spirillum*,  
5 *Eubacterium*, *Escherichia coli* and *Enterococcus*. At 3m, the relative abundance of  
6 *Spirillum* in the DF group was higher than that in control group ( $t=-2.175$ ,  $P=0.035$ ).  
7 The changes of the relative abundances of *Bifidobacterium* ( $t=-2.437$ ,  $P=0.019$ ) and  
8 *Spirillum* ( $t=-2.175$ ,  $P=0.006$ ) between baseline and 3m in the DF group were  
9 significantly higher than those in the control group (Table 6).

## 10 **3.5 Adjustment of antihypertensive drugs after the intervention**

11 During the intervention, 9 (20.5%) patients adjusted their antihypertensive drugs.  
12 In the control group, 2 patients increased the antihypertensive drugs, while in the DF  
13 group, 6 patients decreased the antihypertensive drugs and one patient stopped taking  
14 the antihypertensive drugs. After analysis, we found that the differences were  
15 statistically significant ( $\chi^2=9.714$ ,  $P=0.021$ ) between the two groups (Table 7).

## 16 **Discussion**

17 Previous studies have shown that small doses of DF have a low protective effect  
18 on oBP[19,20]. However, only few studies have explored the effect of relatively  
19 sufficient DF on oBP and 24h ABP. In our study, hypertensive patients were provided  
20 with Oat bran supplements, ensuring a daily consumption of DF of  $21.8\pm 3.5$ g/d.  
21 Although it still did not reach the recommended quantity of DF by World Health  
22 Organization, it was a dose that had not been achieved in previous studies. The  
23 relationship between DF intake and the gut microbiome is well-established in healthy  
24 adults, so, in this study, we examined the relationship between DF and gut microbiota  
25 in hypertensive patients and this was based on supplementing a large amount of DF.

## 26 **4.1 Effect of increased dietary fiber (Oat bran) supplementation on oBP**

27 The results indicate that increased DF can lower BP. After 3m of Oat bran  
28 intervention, oSBP and oDBP in the DF group decreased by  $15.3\pm 8.4$  mmHg and



1 10.2±10.2 mmHg, respectively. These findings are inconsistent with the conclusions  
2 of the study conducted by Wright et al.[38]. They reported that 12 participants with  
3 HTN consumed a high-fiber diet (5g/d) for a six-week experimental period, but their  
4 mean BP did not decrease significantly. The differences in these results may be due to  
5 the unstable BP of the patients in the study by Wright et al.[38], and due to the fact  
6 that the DF supplement was less in that study. However, our results are consistent  
7 with the results of Keenan et al. [39]. In that study, DF-rich Oat  $\beta$  glucan (containing  
8 DF 5.5g/d, for 6 weeks) was provided to 18 hypertensive patients and the results  
9 showed that the patients' oSBP and oDBP decreased by 7.5 mmHg and 5.5 mmHg,  
10 respectively. Compared to the Keenan's study, the current study achieved better BP  
11 improvement which may be due to the larger amount of DF supplements (8.85g/d)  
12 and longer intervention period (12 weeks). Sufficient DF does not only provide the  
13 substrate for bacterial fermentation to produce SCFAs, but can also regulate the gut  
14 microbiota ecosystem to increase the number of SCFAs-producing bacteria, thereby  
15 further enhancing SCFAs production[17,40].

#### 16 **4.2 Effect of increased dietary fiber (Oat bran) supplementation on 24h ABP**

17 In this study, the values of 24h ABP were used as the main outcome indicators,  
18 since the oBP could reflect the true BP level of the patient at a certain time point and  
19 quiet state, while the 24h ABP which has many readings could more accurately reflect  
20 the patient's overall BP level in a 24-hour period.

21 The results of this study showed that after 3m of Oat bran intervention, the 24h  
22 maximum SBP and maximum DBP of the DF group decreased by 14.0±15.5 mmHg  
23 and 11.1±14.6 mmHg, respectively. In contrast, the control group had a 24h maximum  
24 SBP decrease of 1.9±8.0 mmHg. These findings showed that Oat bran intervention  
25 can significantly improve the peak BP of hypertensive patients, thereby delaying the  
26 development of HTN. Bastos et al.[41] conducted a 5-year follow-up study on 1,076  
27 patients with HTN and the results showed that the level of 24h average BP was  
28 positively correlated with the incidence of cardiovascular events. The results of this  
29 study revealed that the 24h average SBP and the 24h average DBP of the experimental  
30 group decreased by 4.5±8.1 mmHg and 3.1±5.6 mmHg, respectively, compared with

1 baseline values. In contrast, the values for the control group did not improve. This  
2 showed that Oat bran intervention can improve the overall BP level and it also  
3 demonstrates the effectiveness of Oat bran intervention on BP in patients with HTN.  
4 In addition, after 3m of Oat bran intervention, the 24h minimum SBP and minimum  
5 DBP of the experimental group did not decrease, which would suggest that Oat bran  
6 did not "blindly" reduce the minimum SBP and DBP, but effectively protected the  
7 blood supply to vital organs in the patients under study.

#### 8 **4.3 Effect of increased dietary fiber (Oat bran) supplementation in modulating** 9 **gut microbiota**

10 Recent studies have shown that gut microbiota plays an important role in the  
11 occurrence and development of HTN[12-13]. The diversity, uniformity and relative  
12 abundance of gut microbiota are important parameters reflecting the composition of  
13 gut microbiome[27].  $\alpha$  diversity is used for analyzing the complexity of species[19]  
14 and the diversity of a sample, while  $\beta$  diversity analysis is used to evaluate differences  
15 in samples, in terms of species complexity[42]. Li et al.[43] found that the  $\alpha$  diversity  
16 of gut microbiota in patients with HTN is lower than that in healthy people. We  
17 compared the diversity of gut microbiota in participants with HTN and the results  
18 showed that there were no significant changes at the third month in the  $\alpha$  diversity of  
19 gut microbiota. This would indicate that the 3m intervention with Oat bran failed to  
20 improve the species diversity and uniformity of gut microbiota in patients with HTN.  
21 This finding was consistent with the results of Li et al.[44], in which supplemented  
22 DF (mainly Oats and wheat) for 3 weeks did not significantly change the  $\alpha$  diversity  
23 of gut microbiota. On the other hand, Huang et al.[45] surveyed the people whose  
24 dietary habits had been maintained for more than 10 years and the results showed that  
25 the diversity of intestinal microbiota in the vegetarian group rich in DF was higher  
26 than that in the normal group. This finding was different from the result of this study  
27 and indicated that the period of Oat bran intervention in this study was shorter and not  
28 enough to increase the diversity of gut microbiota.

29 The effect of DF on BP in patients with HTN may be related to increasing the  
30 relative abundance of SCFAs-producing bacteria and beneficial bacteria in their

1 intestines[23,25]. *Bifidobacterium*, *Lactobacillus*, *Spirobacter* and *Eubacteria* can  
2 ferment DF in the intestine to produce SCFAs[46,47]. In addition, *Bifidobacterium*  
3 and *Lactobacillus* are important probiotic and dominant bacteria in human intestinal  
4 flora[48,49]. *Trichosporium* is a potential probiotic, which has the effect of  
5 anti-inflammatory and regulating the disorder of bacteria[29], while *E. coli* and  
6 *Enterococcus* are harmful bacteria[50]. In this study, these six bacteria were taken as  
7 the target bacteria and the results showed that the relative abundance of  
8 *Bifidobacterium* and *Trichosporium* in the DF group significantly increased after 3m  
9 of Oat bran intervention, which is consistent with the results of Kristeket al.[17]. In  
10 Kristek's study, they performed anaerobic batch-culture experiments in vitro and the  
11 results found that Oat bran resulted in significant increase in the relative abundance of  
12 *Bifidobacterium*. *Bifidobacterium* and *Lactobacillus* are the two main SCFAs  
13 producing bacteria genera[24-26]. Some mechanisms have been suggested to explain  
14 the potential effect of SCFAs on BP. In particular, it has been proposed that G  
15 protein-coupled receptors 43 and olfactory receptor 78 expressed in the kidney can be  
16 activated by SCFAs, which inhibits the release of renin, and thus play a crucial role in  
17 regulation of BP[23-25]. Vagal afferents also express receptors that can sense SCFAs,  
18 which provide another pathway for the BP modulating effects of SCFAs[23].  
19 Furthermore, SCFAs, in particular, butyrate, have anti-inflammatory effects that are  
20 presumed to be mediated by inhibition of histone deacetylase (HDAC), which may  
21 decrease BP[51]. A pre-clinical research found that butyrate administration to mice  
22 resulted in decreased BP levels by HDAC inhibition[52]. Although *Lactobacillus* and  
23 *Eubacterium* in our study did not show significant differences between the two groups,  
24 in the DF group at 3m they increased compared to the baseline. While Daniel et al.[27]  
25 analyzed 64 researches including 2,099 cases of healthy participants, the results  
26 showed DF intervention resulted in significantly higher abundance of *Lactobacillus*  
27 compared with placebo/low-fiber group. This may indicate that hypertensive patients  
28 with gut microbiota dysbiosis compared to the healthy participants will require a  
29 longer intervention period. Therefore, the study with prolonged intervention is needed  
30 to explore the effect of DF supplement on gut microbiota in patients with HTN. In

1 addition, due to fact that SCFAs and their downstream substances related to  
2 regulating BP were not examined, we could not assess the pathway of the effect of DF  
3 on BP.

#### 4 **4.4 Effect of increased dietary fiber (Oat bran) supplementation on** 5 **antihypertensive drugs**

6 At present, drug therapy is the most common management approach adopted by  
7 most patients with HTN. When patients develop drug resistance or their BP does not  
8 meet the target required, it is often necessary to appropriately increase the dose and  
9 types of antihypertensive drugs or replace the antihypertensive medications. However,  
10 the European Hypertension Management Guideline (2018) emphasizes that  
11 non-pharmacological treatment can delay the start of antihypertensive drugs or  
12 improve the effectiveness of antihypertensive medications[53]. Liu et al.[54]  
13 conducted a meta-analysis on the efficacy of non-pharmacological treatment of  
14 hypertension, and the results showed that the BP-lowering effect of antihypertensive  
15 drug combined with non-pharmacological treatment were significantly better than that  
16 of single medical treatment. The results of this study showed that 3m of DF (Oat bran)  
17 intervention could help reduce the amount of antihypertensive drugs. Therefore, as  
18 one of non-pharmacological treatments, supplementing with DF (Oat bran) could be  
19 beneficial for the control of BP in patients with HTN.

#### 20 **Limitations**

21 There are some limitations of our study. One of the limitations is that we did not  
22 measure the level of SCFAs, which may have explained whether *Bifidobacterium* and  
23 *Tricholoma* are associated with changes in SCFAs. Therefore, further studies are  
24 required to understand the current findings. After we supplemented with 30g Oat bran,  
25 the average daily DF intake of the DF group (21.83g/d) did not reach the DF intake  
26 recommended by the World Health Organization (25 ~ 35g/d). The DF intake needs to  
27 be increased in subsequent studies to find out whether it will lower BP further.

#### 28 **Conclusion**

29 Based on the results of this study, we conclude that supplementing the diets with  
30 a sufficient amount of DF is a useful strategy of effectively improving BP in

1 populations with HTN or pre-HTN. Therefore, in developing clinical nutritional  
2 therapy for patients with HTN, it is essential for health professionals to evaluate the  
3 nutrient intake including DF.

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#### 8 **Declaration of competing interest**

9 The authors declare no conflict of interest.

#### 10 **References**

- 11 [1] Bundy JD, He J. Hypertension and Related Cardiovascular Disease Burden in  
12 China. *Ann Glob Health*. 2016;82(2):227-233. doi:10.1016/j.aogh.2016.02.002.
- 13 [2] Wang Z, Chen Z, Zhang L, et al. Status of Hypertension in China: Results From  
14 the China Hypertension Survey, 2012-2015. *Circulation*. 2018;137(22):2344-2356.  
15 doi:10.1161/CIRCULATIONAHA.117.032380.
- 16 [3] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global  
17 burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365(9455):217-223.  
18 doi:10.1016/S0140-6736(05)17741-1.
- 19 [4] GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and  
20 national age-sex specific all-cause and cause-specific mortality for 240 causes of  
21 death, 1990-2013: a systematic analysis for the Global Burden of Disease Study  
22 2013. *Lancet*. 2015;385(9963):117-171. doi:10.1016/S0140-6736(14)61682-2.
- 23 [5] He J, Gu D, Wu X, et al. Major causes of death among men and women in  
24 China. *N Engl J Med*. 2005;353(11):1124-1134. doi:10.1056/NEJMsa050467.
- 25 [6] He J, Gu D, Chen J, et al. Premature deaths attributable to blood pressure in China:  
26 a prospective cohort study. *Lancet*. 2009;374(9703):1765-1772.  
27 doi:10.1016/S0140-6736(09)61199-5.
- 28 [7] Joint Committee for Guideline Revision. 2018 Chinese Guidelines for Prevention  
29 and Treatment of Hypertension-A report of the Revision Committee of Chinese  
30 Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol*.

- 1 2019;16(3):182-241. doi:10.11909/j.issn.1671-5411.2019.03.014.
- 2 [8] Lin XF, Dai HL, Guang XF. Advances in medication compliance in hypertensive  
3 patients. *Chinese Journal of Cardiovascular Research*. 2015; 13:202-203.
- 4 [9] Davison KM, D'Andreamatteo C, Smye VL. Medical nutrition therapy in  
5 Canadian federal correctional facilities. *BMC Health Serv Res*. 2019;19(1):89.  
6 Published 2019 Feb 1. doi:10.1186/s12913-019-3926-3.
- 7 [10] Fantin F, Macchi F, Giani A, Bissoli L. The Importance of Nutrition in  
8 Hypertension. *Nutrients*. 2019;11(10):2542. Published 2019 Oct 21.  
9 doi:10.3390/nu11102542.
- 10 [11] Whelton PK, Carey RM, Aronow WS, et al. 2017  
11 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for  
12 the Prevention, Detection, Evaluation, and Management of High Blood Pressure in  
13 Adults: A Report of the American College of Cardiology/American Heart Association  
14 Task Force on Clinical Practice Guidelines [published correction appears in  
15 *Hypertension*. 2018 Jun;71(6):e140-e144]. *Hypertension*. 2018;71(6):e13-e115.  
16 doi:10.1161/HYP.0000000000000065.
- 17 [12] Jones JM. CODEX-aligned dietary fiber definitions help to bridge the 'fiber  
18 gap'. *Nutr J*. 2014;13:34. Published 2014 Apr 12. doi:10.1186/1475-2891-13-34.
- 19 [13] Holscher HD. Dietary fiber and prebiotics and the gastrointestinal  
20 microbiota. *Gut Microbes*. 2017;8(2):172-184. doi:10.1080/19490976.2017.1290756
- 21 [14] Makki K, Deehan EC, Walter J, Bäckhed F. The Impact of Dietary Fiber on Gut  
22 Microbiota in Host Health and Disease. *Cell Host Microbe*. 2018;23(6):705-715.  
23 doi:10.1016/j.chom.2018.05.012.
- 24 [15] Talukder S, Sharma DP. Development of dietary fiber rich chicken meat patties  
25 using wheat and oat bran. *J Food Sci Technol*. 2010;47(2):224-229.  
26 doi:10.1007/s13197-010-0027-z.
- 27 [16] Nilsson U, Johansson M, Nilsson A, Björck I, Nyman M. Dietary  
28 supplementation with beta-glucan enriched oat bran increases faecal concentration of  
29 carboxylic acids in healthy subjects. *Eur J Clin Nutr*. 2008;62(8):978-984.  
30 doi:10.1038/sj.ejcn.1602816.

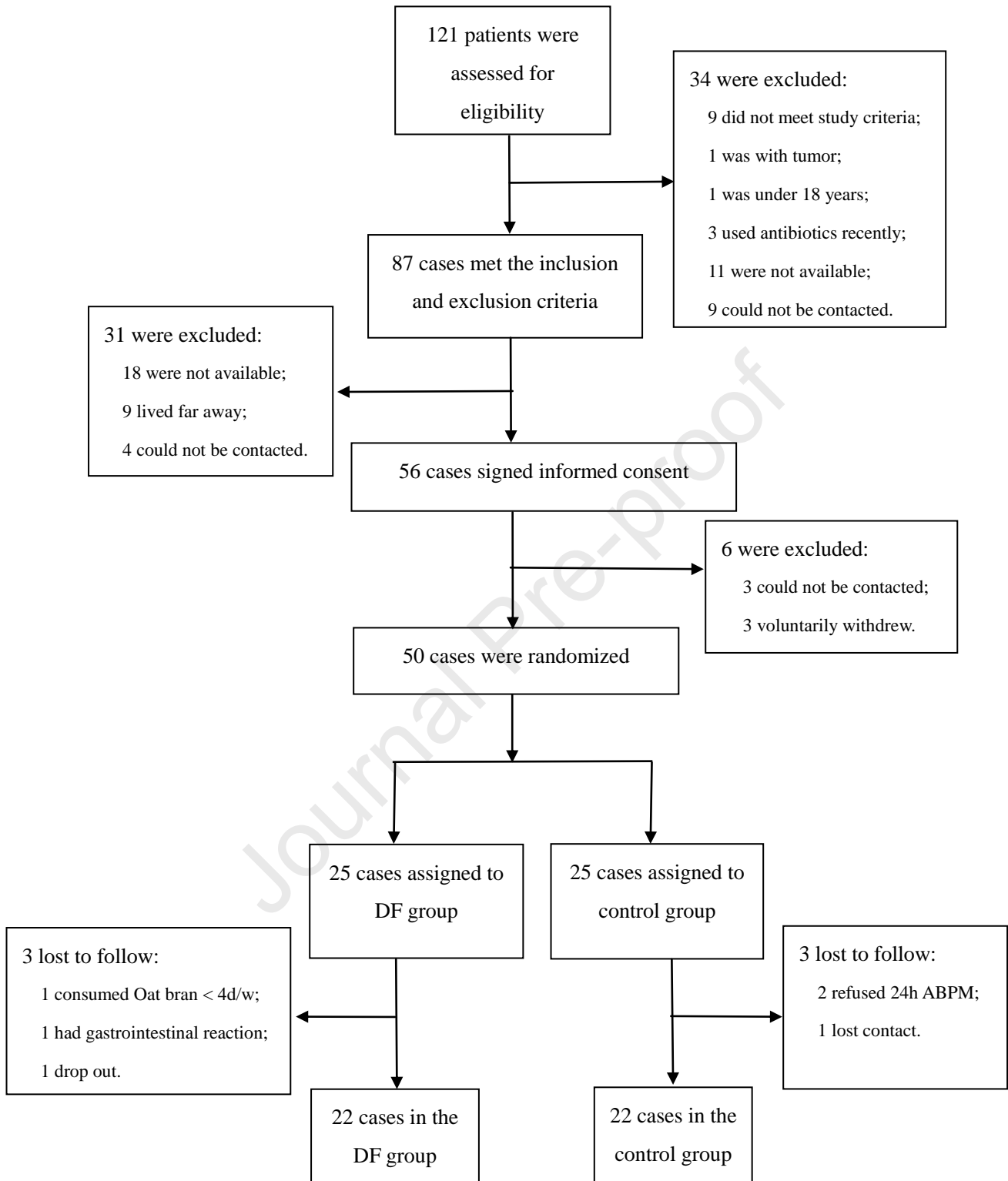
- 1 [17] Kristek A, Wiese M, Heuer P, et al. Oat bran, but not its isolated bioactive  
2  $\beta$ -glucans or polyphenols, have a bifidogenic effect in an in vitro fermentation model  
3 of the gut microbiota. *Br J Nutr.* 2019;121(5):549-559.  
4 doi:10.1017/S0007114518003501.
- 5 [18] Shinozaki K, Okuda M, Sasaki S, Kunitsugu I, Shigeta M. Dietary Fiber  
6 Consumption Decreases the Risks of Overweight and Hypercholesterolemia in  
7 Japanese Children. *Ann Nutr Metab.* 2015;67(1):58-64. doi:10.1159/000434634.
- 8 [19] Evans CE, Greenwood DC, Threapleton DE, et al. Effects of dietary fibre type on  
9 blood pressure: a systematic review and meta-analysis of randomized controlled trials  
10 of healthy individuals. *J Hypertens.* 2015;33(5):897-911.  
11 doi:10.1097/HJH.0000000000000515.
- 12 [20] Whelton SP, Hyre AD, Pedersen B, Yi Y, Whelton PK, He J. Effect of dietary  
13 fiber intake on blood pressure: a meta-analysis of randomized, controlled clinical  
14 trials. *J Hypertens.* 2005;23(3):475-481. doi:10.1097/01.hjh.0000160199.51158.cf.
- 15 [21] De la Sierra A. Advantages of Ambulatory Blood Pressure Monitoring in  
16 Assessing the Efficacy of Antihypertensive Therapy. *Cardiol Ther.* 2015;4(Suppl  
17 1):5-17. doi:10.1007/s40119-015-0043-1.
- 18 [22] Bastos JM, Bertoquini S, Silva JA, Polónia J. Relationship between ambulatory  
19 blood pressure monitoring values and future occurrence of ischemic cerebrovascular  
20 and coronary events in hypertensive patients. *Rev Port Cardiol.* 2006;25(3):305-316.
- 21 [23] Miyamoto J, Kasubuchi M, Nakajima A, Irie J, Itoh H, Kimura I. The role of  
22 short-chain fatty acid on blood pressure regulation. *Curr Opin Nephrol Hypertens.*  
23 2016;25(5):379-383. doi:10.1097/MNH.0000000000000246.
- 24 [24] Pluznick J. A novel SCFA receptor, the microbiota, and blood pressure  
25 regulation. *Gut Microbes.* 2014;5(2):202-207. doi:10.4161/gmic.27492.
- 26 [25] Natarajan N, Hori D, Flavahan S, et al. Microbial short chain fatty acid  
27 metabolites lower blood pressure via endothelial G protein-coupled receptor  
28 41. *Physiol Genomics.* 2016;48(11):826-834.  
29 doi:10.1152/physiolgenomics.00089.2016.
- 30 [26] Muralitharan RR, Jama HA, Xie L, Peh A, Snelson M, Marques FZ. Microbial

- 1 Peer Pressure: The Role of the Gut Microbiota in Hypertension and Its  
2 Complications. *Hypertension*. 2020;76(6):1674-1687.  
3 doi:10.1161/HYPERTENSIONAHA.120.14473.
- 4 [27] So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota  
5 composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr*.  
6 2018;107(6):965-983. doi:10.1093/ajcn/nqy041.
- 7 [28] Georg Jensen M, Kristensen M, Astrup A. Effect of alginate supplementation on  
8 weight loss in obese subjects completing a 12-wk energy-restricted diet: a randomized  
9 controlled trial. *Am J Clin Nutr*. 2012;96(1):5-13. doi:10.3945/ajcn.111.025312.
- 10 [29] Daving Y, Andrén E, Nordholm L, Grimby G. Reliability of an interview  
11 approach to the Functional Independence Measure. *Clin Rehabil*. 2001;15(3):301-310.  
12 doi:10.1191/026921501669986659.
- 13 [30] Keenan JM, Pins JJ, Frazel C, Moran A, Turnquist L. Oat ingestion reduces  
14 systolic and diastolic blood pressure in patients with mild or borderline hypertension:  
15 a pilot trial. *J Fam Pract*. 2002;51(4):369.
- 16 [31] Qu NN, Li KJ. [Study on the reliability and validity of international physical  
17 activity questionnaire (Chinese Vision, IPAQ)]. *Chinese journal of epidemiology*.  
18 2004; 3:87-90.
- 19 [32] Chinese Working Group on blood pressure measurement. Guidelines for blood  
20 pressure measurement in China. *Chinese Journal of Hypertension* 2011;  
21 19:1101-1115.
- 22 [33] Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut  
23 microbiome. *Science*. 2006;312(5778):1355-1359. doi:10.1126/science.1124234.
- 24 [34] Edgar RC. UPARSE: highly accurate OTU sequences from microbial amplicon  
25 reads. *Nat Methods*. 2013;10(10):996-998. doi:10.1038/nmeth.2604.
- 26 [35] Oksanen J, Blanchet FG, Kindt R, et al. Vegan: Community Ecology Package. R  
27 Package Version 2.2-1, 2015;2:1-2.
- 28 [36] Chen J, Bittinger K, Charlson ES, et al. Associating microbiome composition  
29 with environmental covariates using generalized UniFrac distances. *Bioinformatics*.  
30 2012;28(16):2106-2113. doi:10.1093/bioinformatics/bts342.



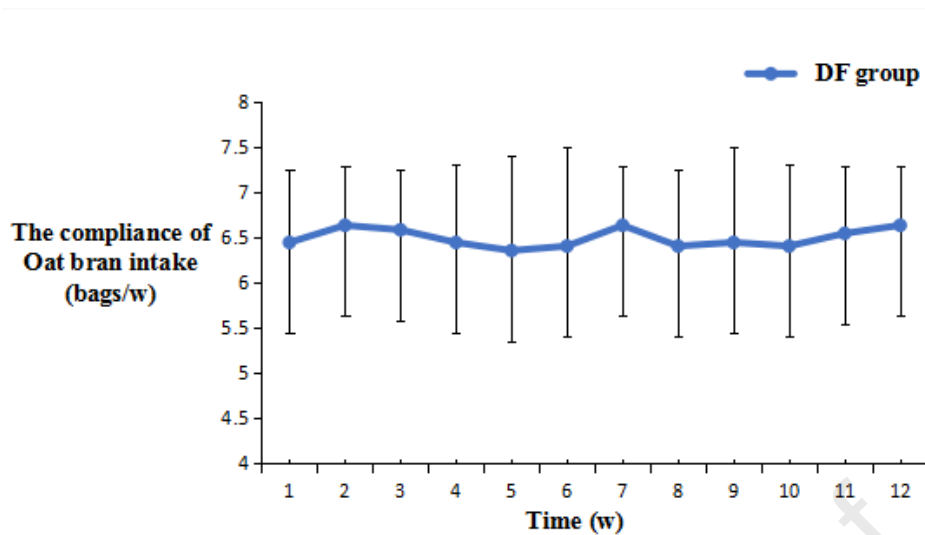
- 1 [37] Tuomisto, H. Ecography. In: Robert K. Colwell. Defining  $\beta$  diversity as a  
2 function of  $\alpha$  and gamma diversity. 2010. pp. 2–22.
- 3 [38] Wright A, Burstyn PG, Gibney MJ. Dietary fibre and blood pressure. *Br Med J*.  
4 1979;2(6204):1541-1543. doi:10.1136/bmj.2.6204.1541.
- 5 [39] Keenan JM, Pins JJ, Frazel C, Moran A, Turnquist L. Oat ingestion reduces  
6 systolic and diastolic blood pressure in patients with mild or borderline hypertension:  
7 a pilot trial. *J Fam Pract*. 2002;51(4):369.
- 8 [40] Robles-Vera I, Toral M, de la Visitación N, et al. Probiotics Prevent Dysbiosis  
9 and the Rise in Blood Pressure in Genetic Hypertension: Role of Short-Chain Fatty  
10 Acids. *Mol Nutr Food Res*. 2020;64(6):e1900616. doi:10.1002/mnfr.201900616.
- 11 [41] Bastos JM, Bertoquini S, Silva JA, Polónia J. Relationship between ambulatory  
12 blood pressure monitoring values and future occurrence of ischemic cerebrovascular  
13 and coronary events in hypertensive patients. *Rev Port Cardiol*. 2006;25(3):305-316.
- 14 [42] Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations,  
15 functions, and implications for health and disease. *Gastroenterology*.  
16 2014;146(6):1564-1572. doi:10.1053/j.gastro.2014.01.058.
- 17 [43] Li J, Zhao F, Wang Y, et al. Gut microbiota dysbiosis contributes to the  
18 development of hypertension. *Microbiome*. 2017;5(1):14. Published 2017 Feb 1.  
19 doi:10.1186/s40168-016-0222-x.
- 20 [44] Li J, Xu H, Sun Z, et al. Effect of dietary interventions on the intestinal  
21 microbiota of mongolian hosts[J]. *Sci Bull*, 2016, 61(20): 1605-1614.
- 22 [45] Huang XD. The relationship between the structure of intestinal microbiota and  
23 fecal fatty acids with different diet patterns. Northeast Agricultural university, 2018.
- 24 [46] Ren A, Tong Q, Zhang B. Formation and absorption mechanism of short-chain  
25 fatty acids. *Guangdong Feed* 2015; 24:28-29.
- 26 [47] Wan X, Wang XY, Li N. Research progression of short chain fatty acid. *Chin J*  
27 *Gastrointest Surg* September, 2015: 958-960.
- 28 [48] O'Callaghan A, van Sinderen D. Bifidobacteria and Their Role as Members of  
29 the Human Gut Microbiota. *Front Microbiol*. 2016;7:925. Published 2016 Jun 15.  
30 doi:10.3389/fmicb.2016.00925.

- 1 [49] Di Cerbo A, Palmieri B, Aponte M, Morales-Medina JC, Iannitti T. Mechanisms  
2 and therapeutic effectiveness of lactobacilli. *J Clin Pathol.* 2016;69(3):187-203.  
3 doi:10.1136/jclinpath-2015-202976.
- 4 [50] Fisher K, Phillips C. The ecology, epidemiology and virulence of *Enterococcus*.  
5 *Microbiology* 2009; 155:1749-1757.
- 6 [51] Schilderink R, Verseijden C, Seppen J, et al. The SCFA butyrate stimulates the  
7 epithelial production of retinoic acid via inhibition of epithelial HDAC. *Am J Physiol*  
8 *Gastrointest Liver Physiol.* 2016;310(11):G1138-G1146.  
9 doi:10.1152/ajpgi.00411.2015.
- 10 [52] Kumar P, Gogulamudi VR, Periasamy R, Raghavaraju G, Subramanian U,  
11 Pandey KN. Inhibition of HDAC enhances STAT acetylation, blocks NF- $\kappa$ B, and  
12 suppresses the renal inflammation and fibrosis in *Npr1* haplotype male mice. *Am J*  
13 *Physiol Renal Physiol.* 2017;313(3):F781-F795. doi:10.1152/ajprenal.00166.2017.
- 14 [53] Williams B, Mancia G, Spiering W, AgabitiRosei E, Azizi M, BurnierM,et al.  
15 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*  
16 2018; 39:3021-3104.
- 17 [54] Liu SX. Meta-analysis of the evaluation of the effect of non-drug treatment of  
18 hypertension. Shanxi Medical University, 2008.
- 19  
20  
21

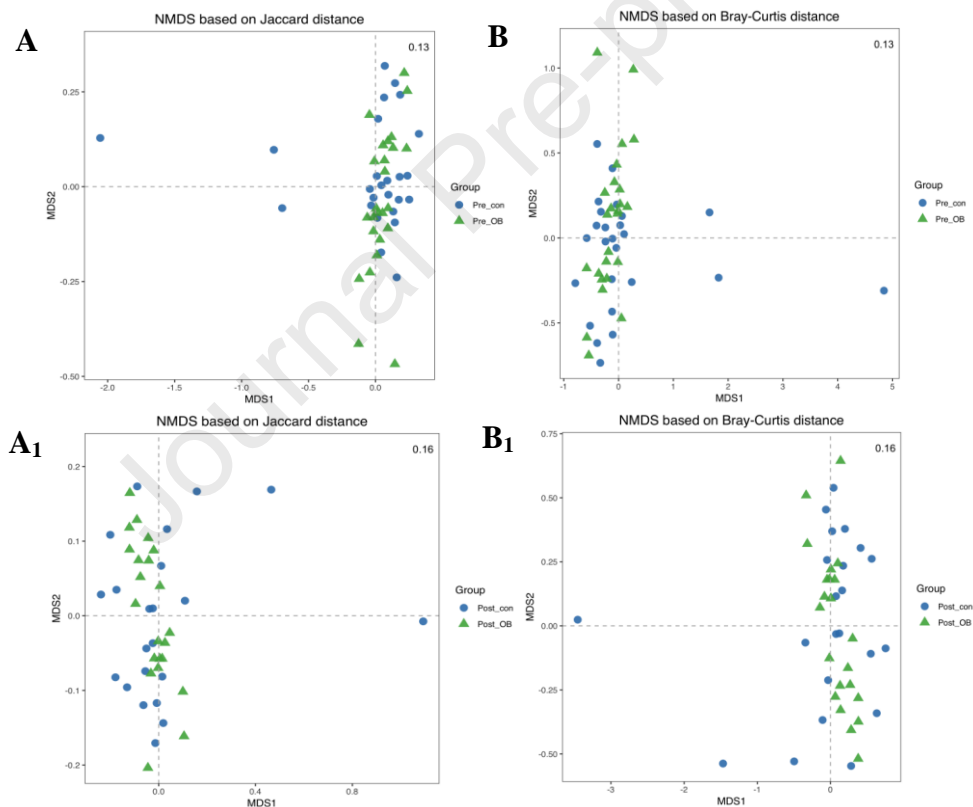


**Figure 1** Trial flowchart.

ABPM: Ambulatory blood pressure monitoring; DF: Dietary Fiber.



**Figure 2** The curve of frequency of Oat bran intake in the DF group ( $\bar{x} \pm s$ , bags/w). DF: Dietary Fiber.



**Figure 3** Comparison of the  $\beta$  diversity of gut microbiota.

**A and B:** comparison of the  $\beta$  diversity at baseline between two groups based on Jaccard and Bray-Curtis distance ( $P=0.102$ ,  $P=0.110$ ); **A<sub>1</sub> and B<sub>1</sub>:** comparison of the  $\beta$  diversity at 3 m between two groups based on Jaccard and Bray-Curtis distance ( $P=0.008$ ,  $P=0.004$ ). Pre\_con: Control group at baseline; Pre\_OB: DF group at baseline; Post\_con: Control group at 3 m; Post\_OB: DF group at 3 m; NMDS: Non-metric Multi-Dimensional Scaling; Points in plots represent samples. The degree of difference between different samples was reflected by the distance between points.  $P < 0.05$  indicated the difference was statistically significant.

**Table 1** Socio-demographic and clinical characteristics

Characteristic		Control group (n=22) $\bar{x}\pm s/n(\%)$	DF group (n=22) $\bar{x}\pm s /n(\%)$	$t / \chi^2$	$P$
Age (years)		49±14	46±13	0.903	0.372 <sup>a</sup>
Gender	Male	15(68.2)	17(77.3)	0.458	0.736 <sup>b</sup>
Marital status	Unmarried	2(9.1)	3(13.6)	1.202	1.000 <sup>c</sup>
	Married	19(86.4)	19(86.4)		
	Divorce	1(4.5)	0(0.0)		
Education	Primary school	3(13.6)	0(0.0)	7.229	0.060 <sup>c</sup>
	Junior middle school	8(36.4)	3(13.6)		
	High school/SSS	4(18.2)	5(22.7)		
	College or higher	7(31.8)	14(63.6)		
Medical payment	Medical insurance	21(95.5)	21(95.5)	1.870	1.000 <sup>c</sup>
	NRCMI	1(4.5)	0(0.0)		
	Self-funded	0(0.0)	1(4.5)		
Exercise	Never	5(22.7)	0(0.0)	5.726	0.070 <sup>c</sup>
	Irregular	8(36.4)	12(54.5)		
	Regular	9(40.9)	10(45.5)		
PA (MET.min/w)	Baseline	5833.0±2158.1	6071.9±1545.7	-0.422	0.675 <sup>a</sup>
	3 m	5952.7±2150.3	6092.3±1970.3	-0.224	0.824 <sup>a</sup>
DOS(h/d)		6.8±1.1	7.3±1.0	-1.613	0.114 <sup>a</sup>
Smoke	Yes	14(63.6)	18(81.8)	1.833	0.310 <sup>b</sup>
Alcohol intake	Yes	7(31.8)	5(22.7)	0.458	0.736 <sup>b</sup>
BMI (kg/m <sup>2</sup> )		24.7±3.0	25.1±2.8	-0.508	0.614 <sup>a</sup>
WHR		0.9±0.8	0.9±0.0	0.131	0.897 <sup>a</sup>
Constipation	Yes	20(90.9)	20(90.9)	-	1.000 <sup>b</sup>
DOH (years)		6.1±6.6	4.2±5.3	1.060	0.295 <sup>a</sup>
TAHD	≥2	4(18.2)	7(31.8)	2.014	0.404 <sup>b</sup>
	1	9(40.9)	5(22.7)		
	0	9(40.9)	10(45.5)		
Family history	Yes	18(81.8)	18(81.8)	-	1.000 <sup>b</sup>
Comorbidity	Yes	6(27.3)	3(9.1)	-	0.240 <sup>b</sup>

DF: Dietary Fiber; SSS: Secondary Specialized School; NRCMI: New Rural Cooperative Medical Insurance; PA: Amount of Physical Activity; DOS: Duration of Sleep; BMI: Body Mass Index; WHR: Waist-Hip Ratio; DOH: Duration of hypertension; TAHD: Types of Antihypertensive Drug. a: Independent samples t-test; b: Pearson Chi-square test; c: Fisher's exact test.

**Table 2** Comparison of qualities of dietary nutrition (except DF) intake between two groups

	Time	Control group (n=22) $\bar{x}\pm s$	DF group (n=22) $\bar{x}\pm s$	<i>t</i>	<i>P</i>
Total calories (kcal/d)	Baseline	2162.6±313.2	2099.5±245.2	0.751	0.457
	3 m	2188.1±311.8	2156.6±290.2	0.351	0.727
Protein (g/d)	Baseline	90.5±16.8	93.0±16.0	-0.495	0.623
	3 m	93.3±14.9	98.7±16.7	-1.155	0.254
Fat (g/d)	Baseline	68.6±10.6	66.5±7.7	0.780	0.440
	3 m	70.4±9.1	72.0±15.3	0.412	0.683
Carbohydrate (g/d)	Baseline	348.0±76.8	313.1±70.8	1.582	0.121
	3 m	342.1±61.4	333.1±46.3	0.556	0.581
Cholesterol (mg/d)	Baseline	284.6±167.2	313.32±163.1	-0.584	0.562
	3 m	281.6±158.3	325.8±161.6	-0.927	0.359
Sodium (mg/d)	Baseline	2158.4±610.3	1979.1±937.7	0.764	0.449
	3 m	2098.1±562.7	2017.93±781.1	0.396	0.694
Calcium (mg/d)	Baseline	383.4±192.0	466.5±248.8	-1.258	0.215
	3 m	434.3±199.4	477.8±177.3	-0.771	0.445
Potassium (mg/d)	Baseline	1685.5±334.7	1721.2±310.1	-0.370	0.713
	3 m	1754.1±402.9	1785.0±478.4	-0.235	0.816

DF: Dietary Fiber.

**Table 3** Comparison of the quality of DF intake between two groups

	Time	Control group (n=22) $\bar{x}\pm s$	DF group (n=22) $\bar{x}\pm s$	<i>t</i>	<i>P</i>
DF (g)	Baseline	12.5±4.3	12.5±4.4	-0.016	0.987
	3 m	13.5±4.7	21.8±3.5	-6.729	<0.001**

DF: Dietary Fiber; \*\*:  $P < 0.001$ .

**Table 4** Comparison of oBP and 24h ABP between two groups

BP	Time	Control group	DF group	<i>t</i>	<i>P</i>
		(n=22) $\bar{x}\pm s$	(n=22) $\bar{x}\pm s$		
oSBP	Baseline	137.2±10.1	138.0±11.1	-0.242	NS
	3 m	133.0±7.4	122.6±8.8	4.233	<0.001**
	MD	4.2±10.7	15.3±8.4	-3.837	<0.001**
oDBP	Baseline	86.8±9.9	91.7±11.0	-1.576	NS
	3 m	87.4±9.2	81.5±7.7	2.283	0.028*
	MD	-0.6±10.5	10.2±10.2	-3.466	0.001*
24hmaxSBP	Baseline	153.8±11.8	159.8±20.0	-1.215	NS
	3 m	151.9±11.1	145.9±13.5	1.622	NS
	MD	1.9±8.0	14.0±15.5	-3.238	0.002*
24hmaxDBP	Baseline	100.1±11.2	107.7±15.3	-1.903	NS
	3 m	100.8±10.5	96.6±9.7	1.378	NS
	MD	-0.7±5.4	11.1±14.6	-3.582	0.001*
24hminSBP	Baseline	107.5±12.2	104.0±13.1	0.918	NS
	3 m	108.6±15.8	106.0±12.6	0.602	NS
	MD	-1.1±11.1	-2.1±12.1	0.261	NS
24hminDBP	Baseline	65.9±11.3	62.5±9.0	1.094	NS
	3 m	67.1±11.7	63.4±9.4	1.148	NS
	MD	-1.2±6.9	-0.9±8.6	-1.136	NS
24haveSBP	Baseline	129.0±9.7	129.6±13.4	-1.180	NS
	3 m	130.4±11.2	125.1±11.1	1.558	NS
	MD	-1.4±5.5	4.5±8.1	-2.812	0.007*
24haveDBP	Baseline	83.9±11.1	85.1±9.2	-0.384	NS
	3 m	85.3±12.1	81.9±8.2	1.092	NS
	MD	-1.5±5.4	3.1±5.6	-2.781	0.008*

oBP: office blood pressure; ABP: Ambulatory blood pressure; DF: Dietary Fiber; BP: blood pressure; oSBP: office systolic blood pressure; oDBP: office diastolic blood pressure; 24hmaxSBP: 24h maximum systolic blood pressure; 24hmaxDBP: 24h maximum diastolic blood pressure; 24hminSBP: 24h minimum systolic blood pressure; 24hminDBP: 24h minimum diastolic blood pressure; 24haveSBP: 24h average systolic blood pressure; 24haveDBP: 24h average diastolic blood pressure. MD: Mean Difference; NS: the difference was not statistically significant; \*:  $P<0.05$ ; \*\*:  $P<0.001$ .

**Table 5** Intention-to-treat analysis of comparison of oBP and 24h ABP between two groups

BP	Time	Control group (n=25) $\bar{x}\pm s$	DF group (n=25) $\bar{x}\pm s$	<i>t</i>	<i>P</i>
oSBP	Baseline	135.8±10.5	136.8±10.9	-0.358	NS
	3 m	132.0±7.7	123.3±8.5	3.794	0.000**
	MD	3.7±10.1	13.5±9.3	-3.553	0.001*
oDBP	Baseline	86.4±9.8	90.8±10.8	-1.483	NS
	3 m	87.0±9.2	81.8±7.6	2.175	0.035*
	MD	-0.5±9.8	9.0±10.1	-3.373	0.001*
24hmaxSBP	Baseline	152.2±12.1	158.4±19.1	-1.354	NS
	3 m	150.6±11.3	146.1±12.6	1.322	NS
	MD	1.7±7.5	12.3±15.2	-3.122	0.003*
24hmaxDBP	Baseline	98.7±12.4	107.0±14.7	-2.176	0.034*
	3 m	99.3±11.9	97.2±9.7	0.680	NS
	MD	-0.6±5.1	9.8±14.1	-3.481	0.001*
24hminSBP	Baseline	107.6±12.3	105.0±13.0	0.714	NS
	3 m	108.6±15.5	106.8±12.4	0.444	NS
	MD	-1.0±10.3	-1.8±11.3	0.261	NS
24hminDBP	Baseline	65.5±10.9	63.8±9.2	0.604	NS
	3 m	66.5±11.3	64.5±9.5	0.677	NS
	MD	-1.0±6.4	-0.8±8.1	-1.136	NS
24haveSBP	Baseline	128.2±9.9	129.4±12.7	-0.373	NS
	3 m	129.4±11.3	125.4±10.5	1.284	NS
	MD	-1.2±5.2	4.0±7.7	-2.780	0.008*
24haveDBP	Baseline	82.9±11.2	85.2±8.9	-0.812	NS
	3 m	84.2±12.2	82.4±8.2	0.587	NS
	MD	-1.3±5.0	2.8±5.3	-2.760	0.008*

oBP: office blood pressure; ABP: Ambulatory blood pressure; DF: Dietary Fiber; BP: blood pressure; oSBP: office systolic blood pressure; oDBP: office diastolic blood pressure; 24hmaxSBP: 24h maximum systolic blood pressure; 24hmaxDBP: 24h maximum diastolic blood pressure; 24hminSBP: 24h minimum systolic blood pressure; 24hminDBP: 24h minimum diastolic blood pressure; 24haveSBP: 24h average systolic blood pressure; 24haveDBP: 24h average diastolic blood pressure. MD: Mean Difference; NS: the difference was not statistically significant; \*:  $P<0.05$ ; \*\*:  $P<0.001$ .



**Table 6** Comparison of the relative abundance (%) of the targeted microbiota between two groups

Gut microbiota (Genus)	Time	Control group	DF group	<i>t/Z</i>	<i>P</i>
		(n=22) $\bar{x}\pm s, M(P_{25}, P_{75})$	(n=22) $\bar{x}\pm s, M(P_{25}, P_{75})$		
Bifidobacterium	Baseline	1.2±2.4	0.4±0.5	1.596 <sup>a</sup>	NS
	3 m	0.5±0.8	1.4±2.4	-1.668 <sup>a</sup>	NS
	MD	-0.7±2.4	1.0±2.3	-2.437 <sup>a</sup>	0.019*
Lactobacillus	Baseline	0.1(0.0, 1.9)	0.1(0.0, 1.0)	-1.394 <sup>b</sup>	NS
	3 m	0.1(0.0, 1.0)	0.0(0.0, 0.2)	-1.649 <sup>b</sup>	NS
	MD	0.0(-0.8, 0.1)	0.0(-0.0, 0.1)	-0.799 <sup>b</sup>	NS
Spirillum	Baseline	11.7±6.5	10.8±5.8	0.458 <sup>a</sup>	NS
	3 m	9.3±6.6	14.3±8.4	-2.175 <sup>a</sup>	0.035*
	MD	-2.3±6.7	3.5±6.6	-2.889 <sup>a</sup>	0.006*
Eubacterium	Baseline	0.0(0.0, 0.0)	0.0(0.0, 0.0)	-0.618 <sup>b</sup>	NS
	3 m	0.0(0.0, 0.0)	0.0(0.0, 0.0)	0.000 <sup>b</sup>	NS
	MD	0.0(0.0, 0.0)	0.0(0.0, 0.0)	-0.300 <sup>b</sup>	NS
Escherichia coli	Baseline	0.5(0.2, 1.7)	0.4(0.2, 1.6)	-0.424 <sup>b</sup>	NS
	3 m	1.3(0.2, 3.1)	0.5(0.1, 2.9)	-0.211 <sup>b</sup>	NS
	MD	0.3(-0.3, 1.2)	0.0(-0.6, 1.0)	-0.622 <sup>b</sup>	NS
Enterococcus	Baseline	0.0(0.0, 0.1)	0.0(0.0, 0.0)	-1.418 <sup>b</sup>	NS
	3 m	3.9(1.1, 8.4)	4.5(2.2, 18.5)	-0.723 <sup>b</sup>	NS
	MD	0.0(-0.0, 0.1)	0.0(0.0, 0.1)	-1.249 <sup>b</sup>	NS

DF: Dietary Fiber; MD: Mean Difference; \*:  $P < 0.05$ ; a: Independent samples *t* test; b: Mann-Whitney *U* test. NS: the difference was not statistically significant; \*:  $P < 0.05$ .

**Table 7** Comparison of the antihypertensive drugs taken at 3 m [n(%)]

Changes of medication dosage	Control (n=22)	DF (n=22)	$\chi^2$	<i>P</i>
Withdrawal	0(0.0)	1(4.5)	9.714	0.021*
Reduce	0(0.0)	6(27.3)		
No change	20(90.9)	15(68.2)		
Increase	2(9.1)	0(0.0)		

\*:  $P < 0.05$ .

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**Highlights**

1. Increased dietary fiber (Oat bran) supplement significantly improved blood pressure and 24h ambulatory blood pressure, while reducing the amount of antihypertensive drugs in hypertensive patients.
2. Dietary fiber significantly modulated the gut microbiota and in particular increased the relative abundance of *Bifidobacterium* and *Spirillum*.
3. Dietary fiber (Oat bran) supplement is an effective and economical method of blood pressure management.

## ICMJE DISCLOSURE FORM

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