读书报告分享

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Improved Glucose and Lipid Metabolism in the Early Life of Female Offspring by Maternal Dietary Genistein Is Associated With Alterations in the Gut Microbiota

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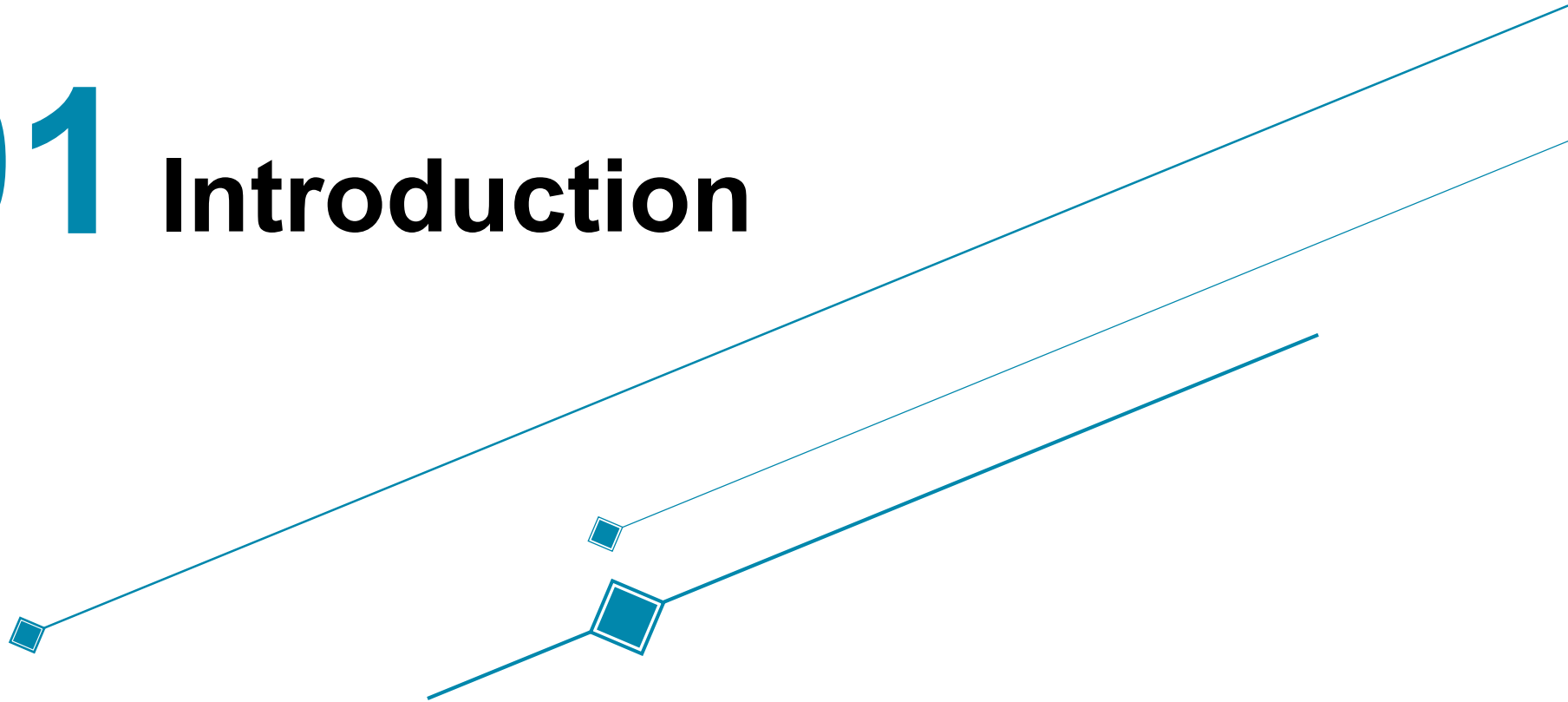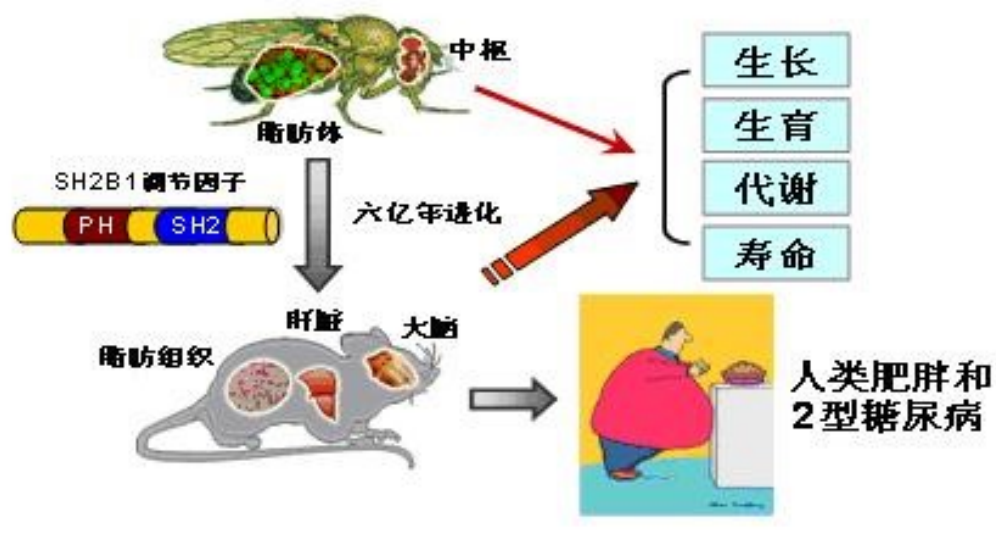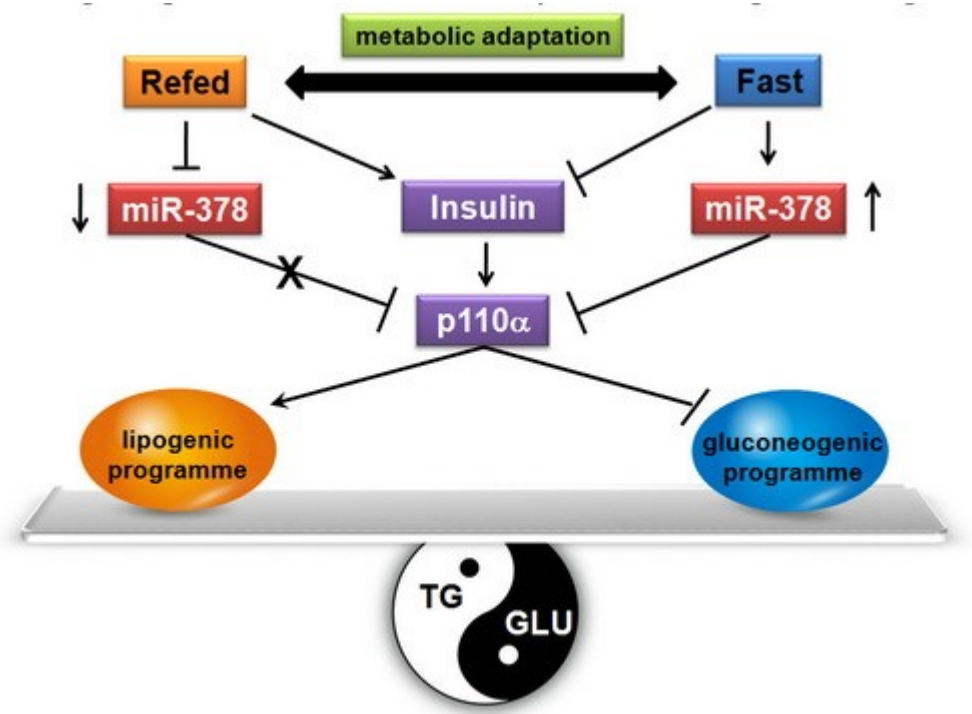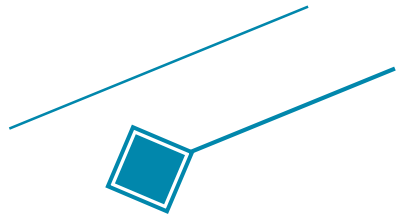
# CONTENTS

01 **Introduction**

肥胖症和2型糖尿病（T2DM）广泛流行，并给健康和经济带来巨大负担。然而，肥胖和糖尿病的病因和发病机制仍不清楚。最近的许多研究以及作者以前的研究表明，母体在怀孕和哺乳期间的高脂饮食可以显著增加后代对肥胖症，葡萄糖耐量和胰岛素抵抗的敏感性。因此，在生命早期进行干预可能会重设疾病轨迹并预防糖尿病的发作和发展。

膳食中的生物活性化合物在预防和治疗代谢紊乱方面发挥着有益作用，金雀异黄素是大豆中所含异黄酮的主要成分之一，近年来，越来越多的研究表明它可改善糖脂代谢，并已证明摄入金雀异黄素可以显著改善高脂肪饮食或糖尿病小鼠肠道微生物群的失衡。
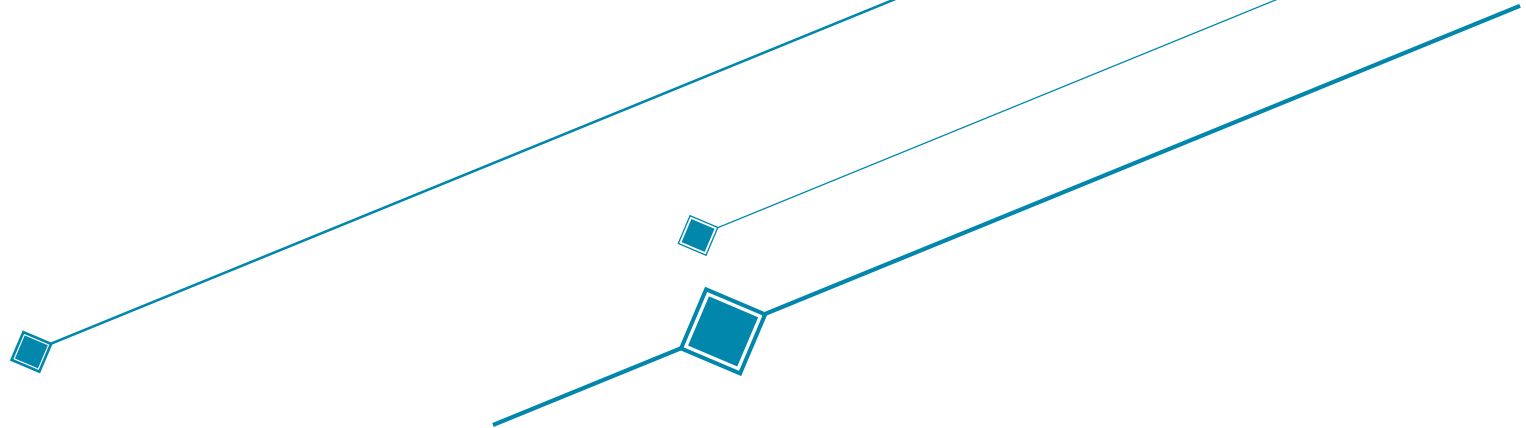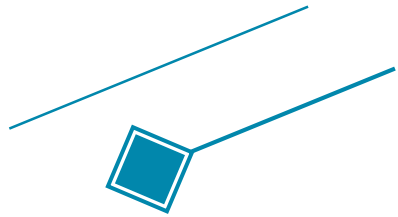
　　在过去的几十年中，肠道菌群已成为医学研究的重点。研究发现环境因素中肠道菌群与肥胖的发病有一定的相关性，此外，已有研究显示金雀异黄素对葡萄糖耐量的改善与肠道菌群改变有关联。然而，母体金雀异黄素干预后对后代肠道菌群的影响的研究是有限的。
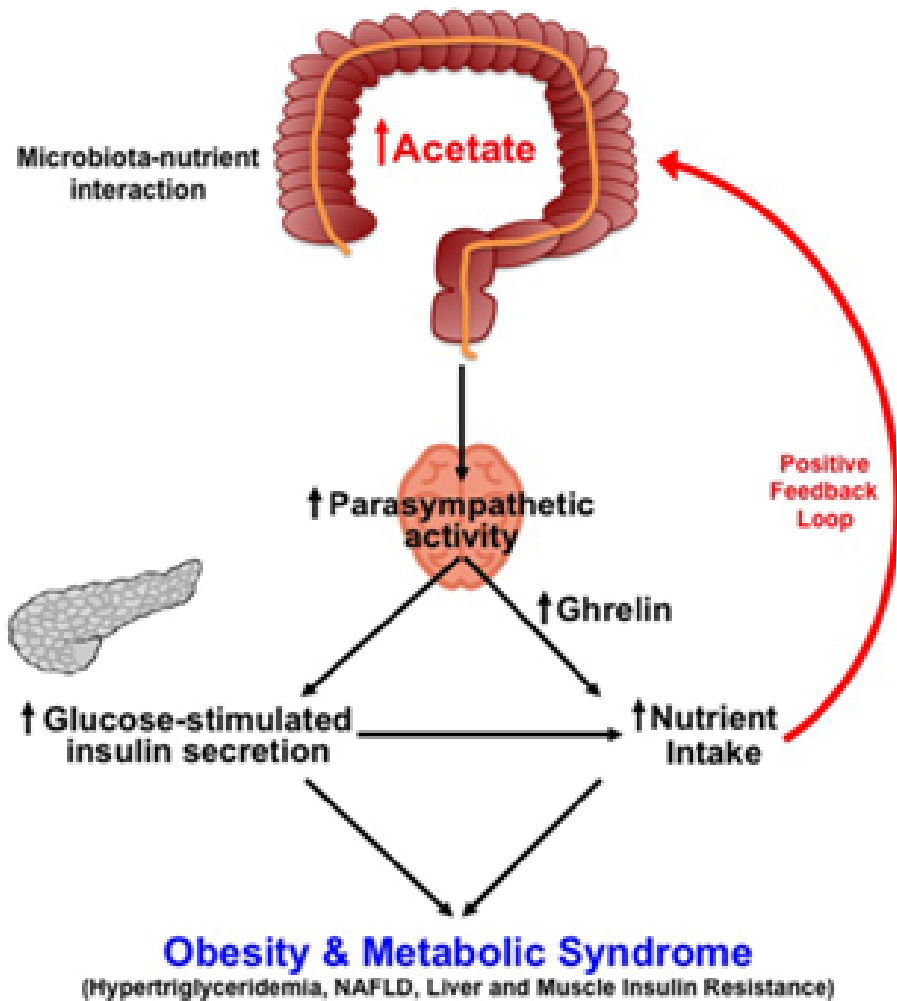
本研究意在探究母体膳食金雀异黄素对雌性后代早期生命代谢健康的影响，并确定母体金雀异黄酮摄入是否可以改变母体高脂饮食对雌性后代的有害代谢作用；此外，我们还进一步探讨肠道微生物的改变是否在雌性后代机体代谢健康中发挥关键作用。
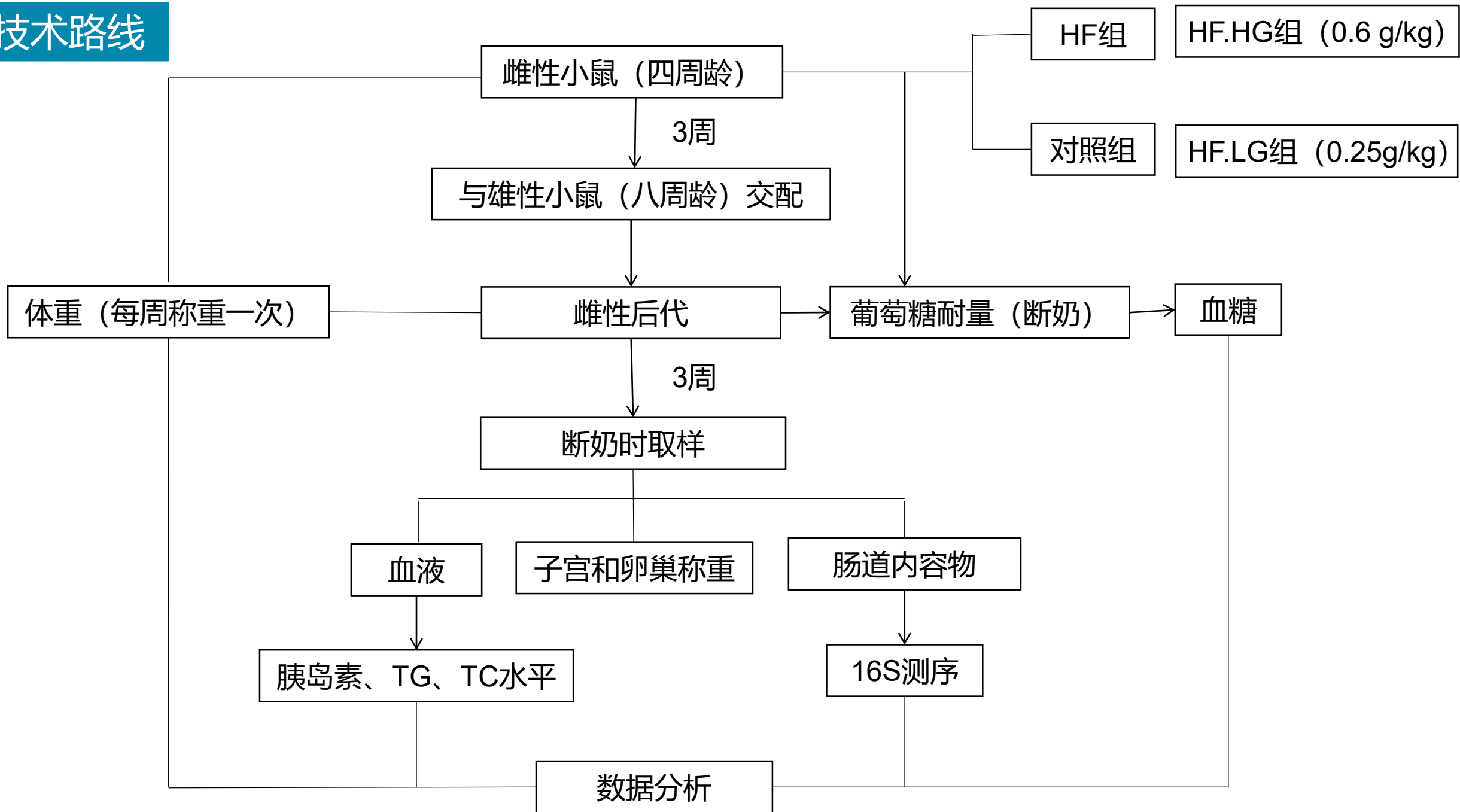
02 Materials and methods

技术路线

雌性小鼠（四周龄）

HF组 | HF.HG组（0.6 g/kg）

对照组 | HF.LG组（0.25g/kg）

3周

与雄性小鼠（八周龄）交配

体重（每周称重一次）

雌性后代

葡萄糖耐量（断奶）

血糖

3周

断奶时取样

血液

子宫和卵巢称重

肠道内容物

胰岛素、TG、TC水平

16S测序

数据分析

Ingredients	HF.LG(g)	HF.HG(g)	HF(g)	Control(g)
Casein	258	258	258	200
L-Cystine	4	4	4	3
Corn Starch	0	0	0	397
Maltodextrin	162	162	162	132
Sucrose	89	89	89	100
Cellulose	65	65	65	50
Soybean Oil	0	0	0	0
Corn Oil	32	32	32	70
t-Butylhydroquinone	0	0	0	0.014
Mineral Mix S10026	13	13	13	0
MinarelMix S10022G	0	0	0	35
Vitamin Mix V10001	13	13	13	0
Vitamin Mix V10037	0	0	0	10
Choline Bitartrate	2.6	2.6	2.6	2.5
Lard	316.6	316.6	316.6	0
DiCalcium Phosphate	16.8	16.8	16.8	0
Calcium Carbonate	7	7	7	0
Potassium Citrate, 1H2O	21	21	21	0
FD&C Blue Dye #1	0.06	0.06	0.06	0
Genistein	0.25	0.6	0	0
Total	1000	1000	1000	1000

Table S1. The nutritional compositions of four types of diet.

03 Results
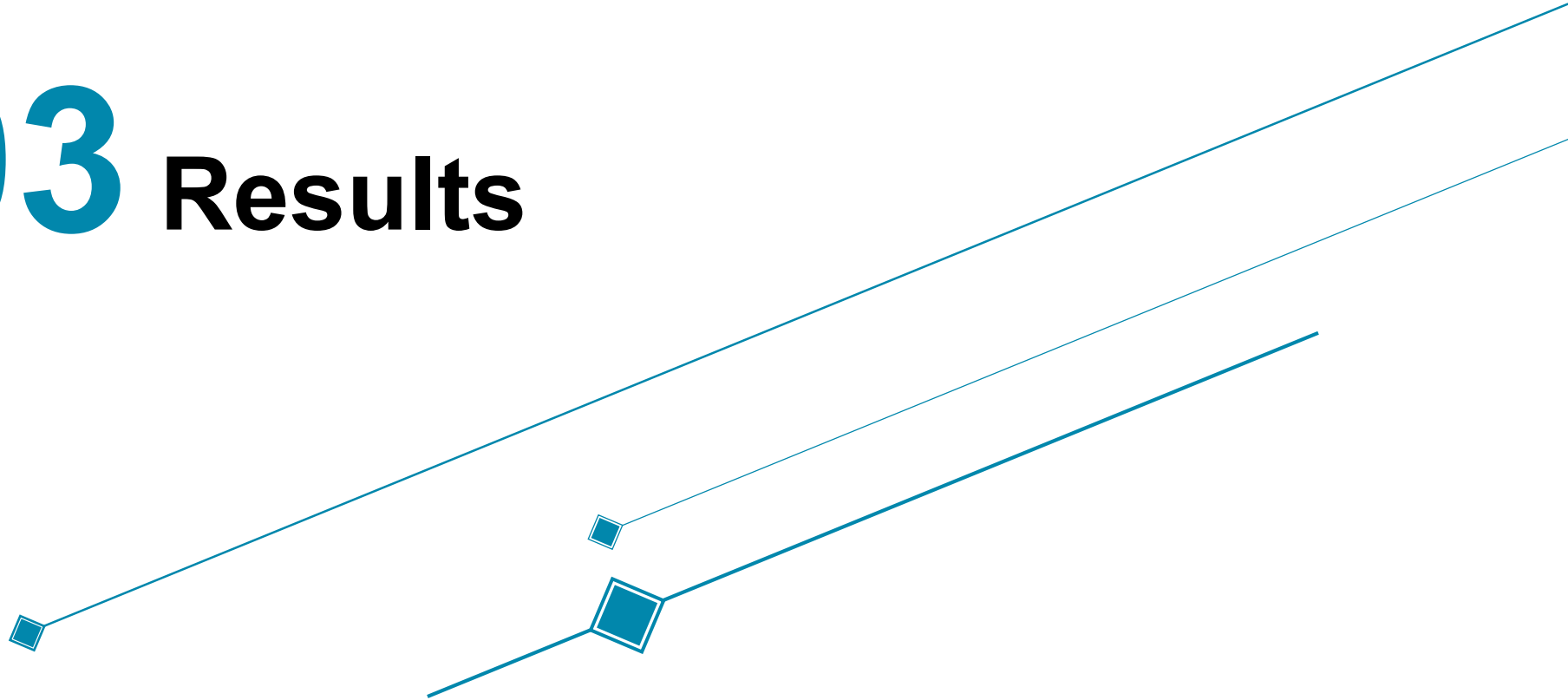
Table 1 Dam and liter characteristics.

Parameters	HF	HF.LG	HF.HG	Control
	(n = 6)	(n = 6)	(n = 8)	(n = 8)
Body weight(g)	31.5 $\pm$ 0.9	30.7 $\pm$ 0.6	30.2 $\pm$ 0.6	24.1 $\pm$ 0.6[*]
AUC of OGTT(mmol/l·h)	21.8 $\pm$ 1.2	19.7 $\pm$ 0.9	21.4 $\pm$ 1.2	17.5 $\pm$ 0.8[*]
Pups/litter	8.0 $\pm$ 0.6	6.8 $\pm$ 1.0	7.2 $\pm$ 0.5	7.0 $\pm$ 0.6
Uterus index (%) to body weight(%)	0.33 $\pm$ 0.1	0.42 $\pm$ 0.0	0.29 $\pm$ 0.1	0.39 $\pm$ 0.0
Ovary index (%) to body weight(%)	0.11 $\pm$ 0.0	0.13 $\pm$ 0.0	0.10 $\pm$ 0.0	0.12 $\pm$ 0.0

Data are expressed as means $\pm$ S.E.M (n = 6–8/group).[*]$p < 0.05$ vs.
Uterus index: weight ratio of uterus to body weight; Ovary index: weight ratio of ovaries to body weight.
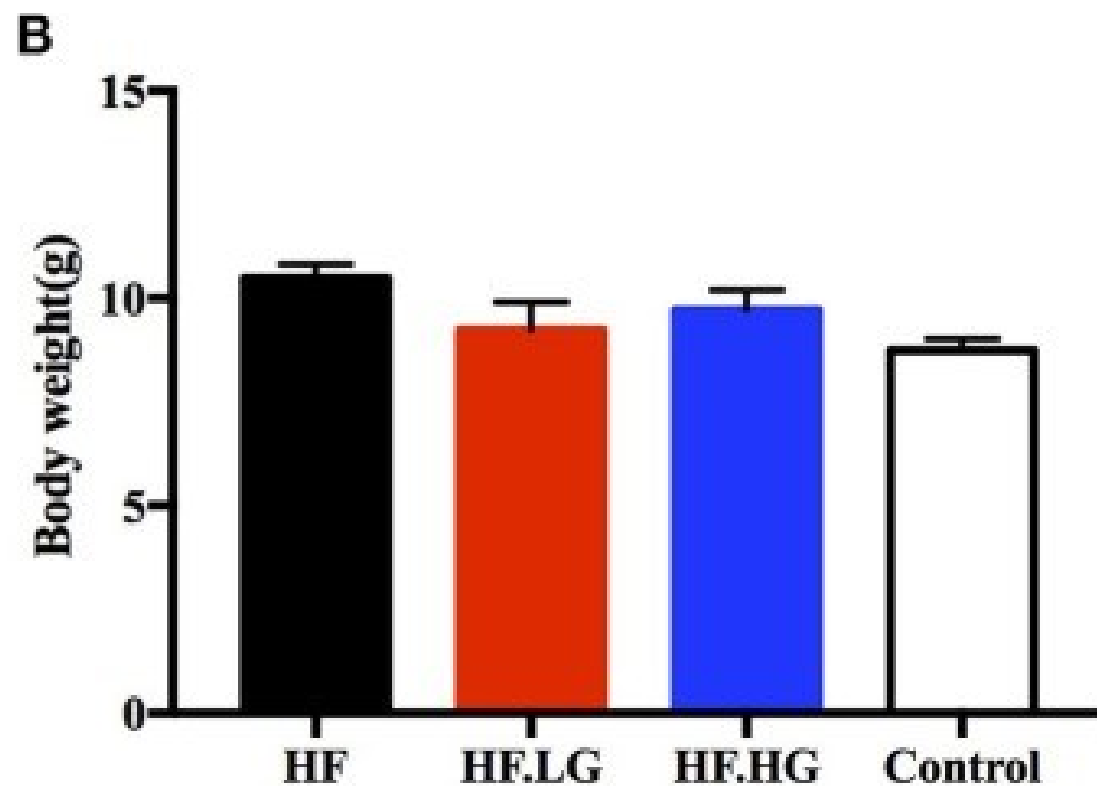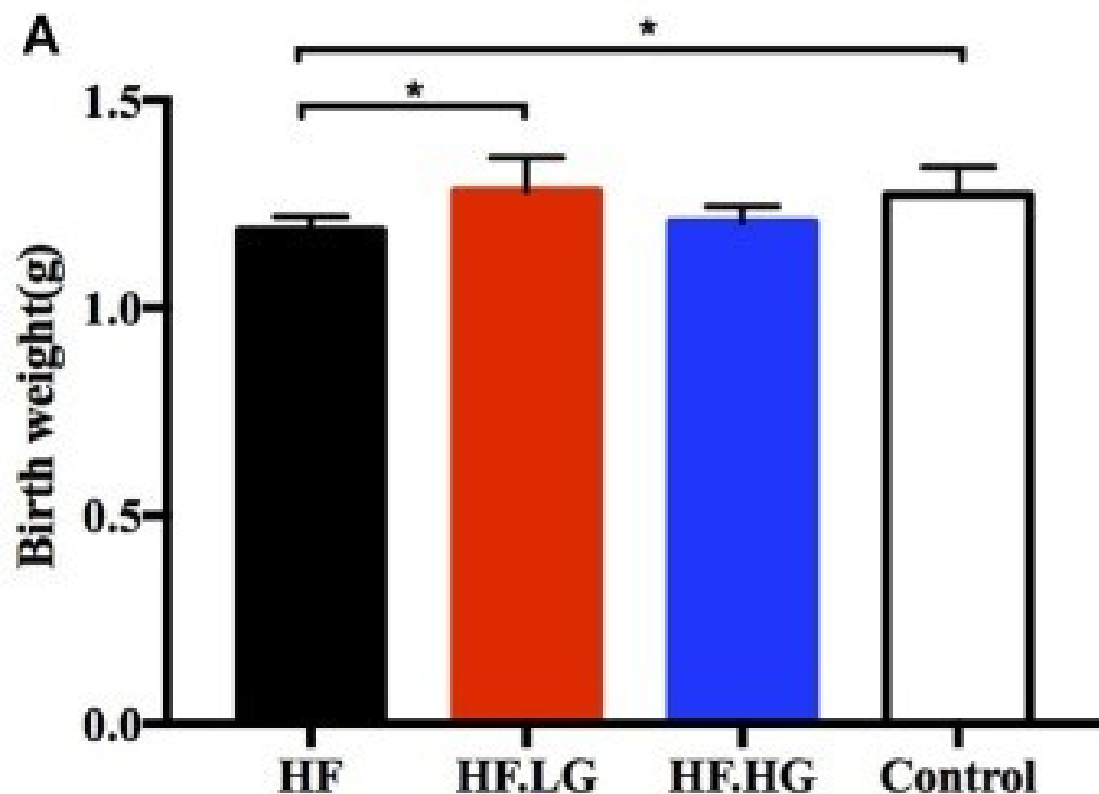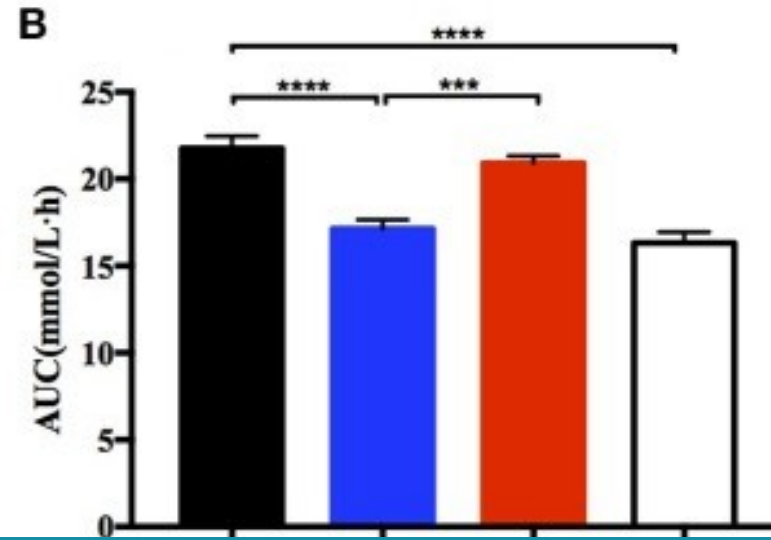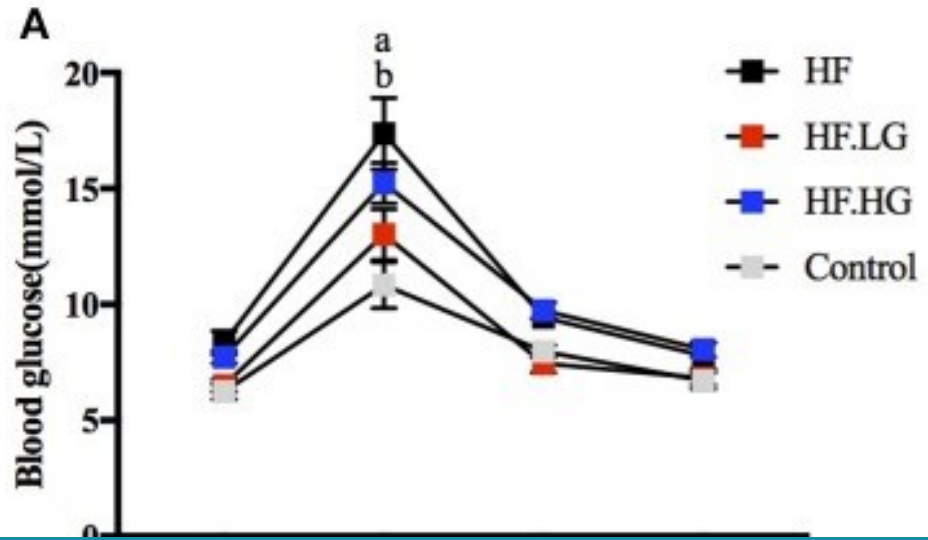
高脂饮食确实会引起母体体重增加、葡萄糖耐量降低

Figure 1. Birth weight and body weight at weaning in offspring.

高脂饮食会引起后代出生体重降低、但在高脂饮食中添加低剂量金雀异黄素可以使后代出生体重得到改善

Data are ex_____veen other group and the HF group: $p < 0.05$.

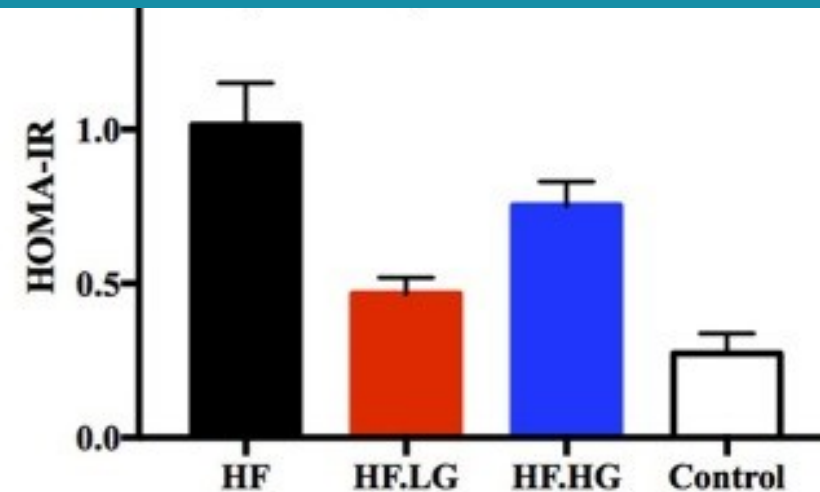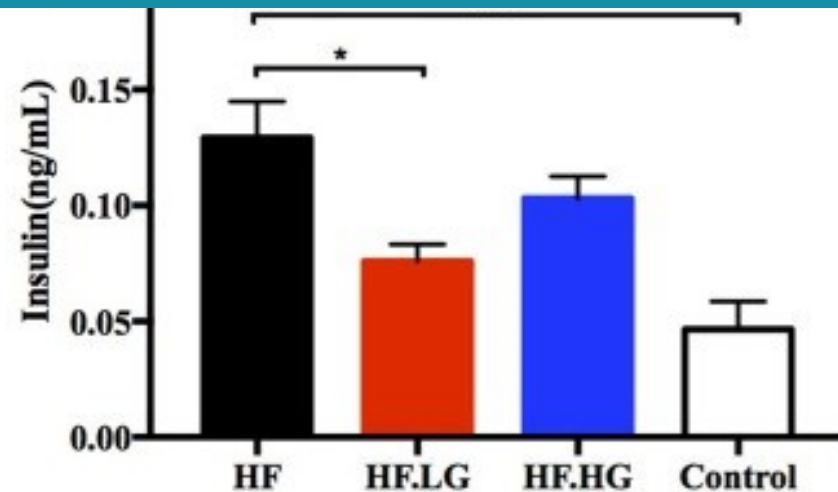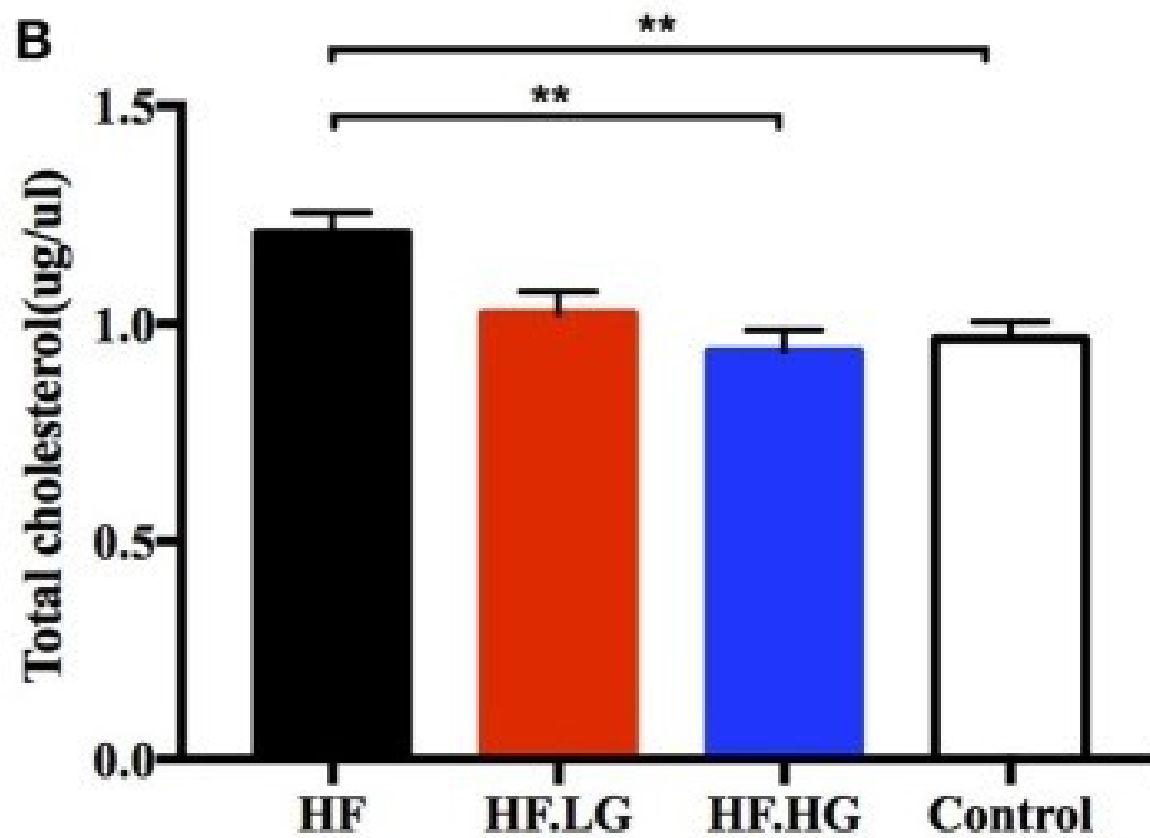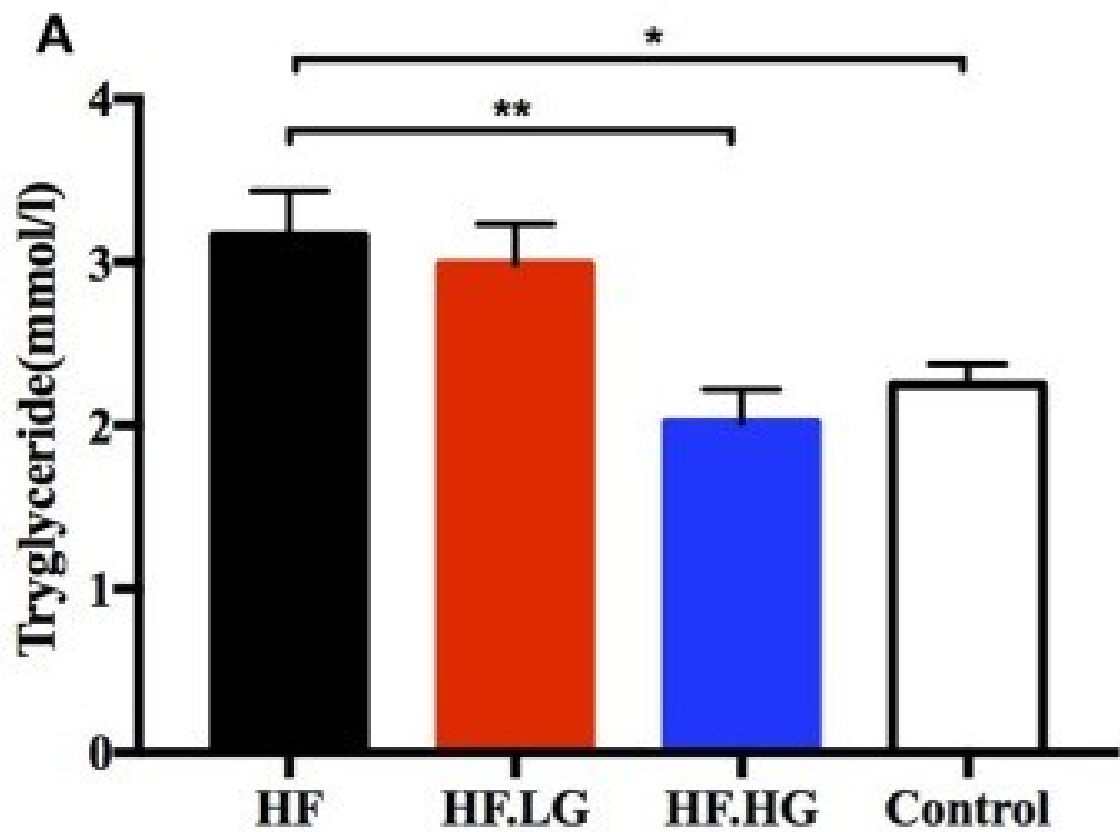高脂饮食会引起后代糖耐量降低、低剂量添加金雀异黄素后糖耐量水平显著上升；并且高脂饮食后代的胰岛素和胰岛素抵抗指数均显著上升，低剂量添加后后代胰岛素敏感性得到改善。

Figure 2 Glucose metabolism of the female offspring at weaning.
(A) OGTT; (B) AUC; (C) Serum insulin levels; (D)HOMA-IR.

Figure 2. Lipid metabolism of the female offspring stereoscopic

摄入高脂饮食会影响子代的血清TC、TG水平，但高剂量添加金雀异黄素后，二者均显著降低。

significantly different between other group and the HF group. *p < 0.05; **p < 0.01.

Table S2. Comparison of estimator indices of alpha diversity.

Estimators	HF.LG	HF.HG	HF	Control
Simpson	0.960±0.009	0.965±0.003	0.972±0.003	0.974±0.001
Chao1	376.5±12.5	383.8±5.4	395.5±11.6	392.2±9.9
Shannon	5.94±0.14	5.98±0.07	6.18±0.08	6.25±0.05

α多样性分析，表明四组之间物种丰富度以及多样性是相似，但添加金雀异黄素之后会有下降的趋势

Figure 4 PCA plots of gut communities in the female offspring at weaning (*n* = 6–8/group).
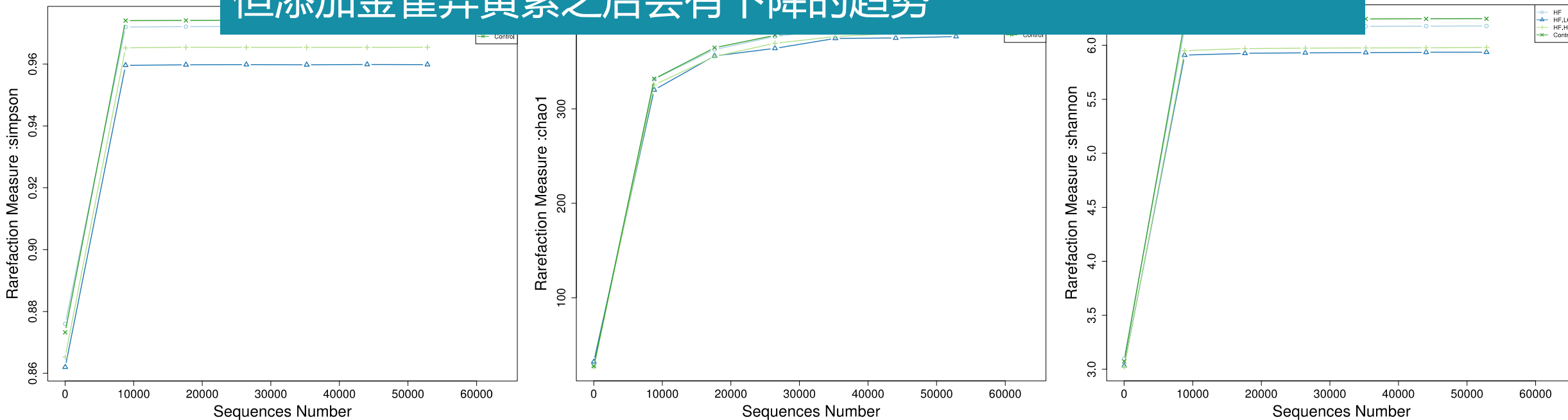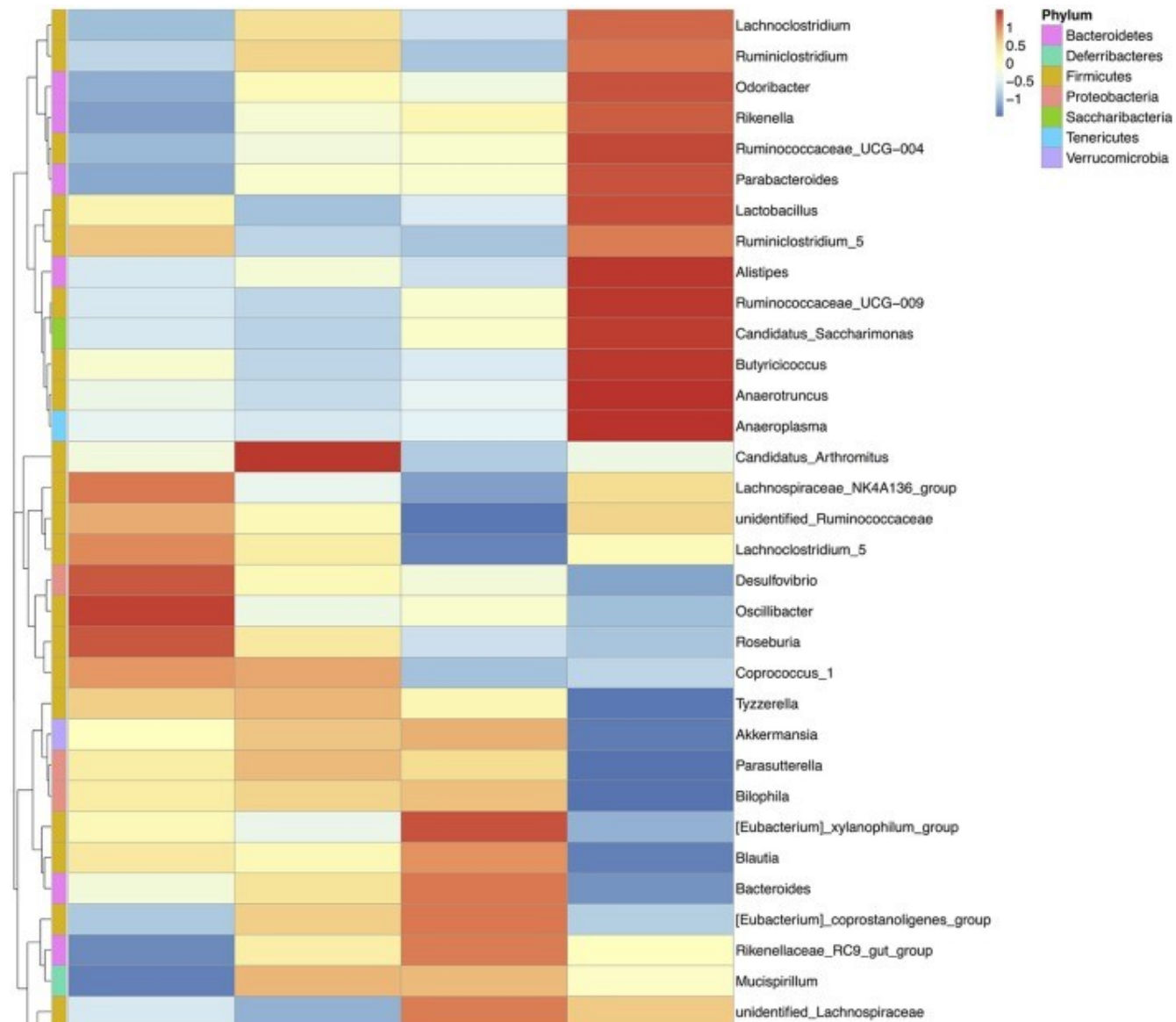
PCA以及热图分析表明，不同母体饮食造成后代肠道菌群的结构的改变存在显著性差异
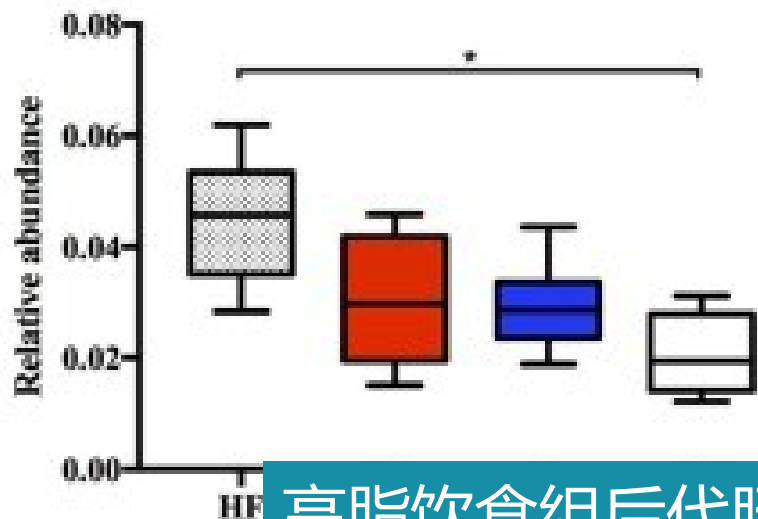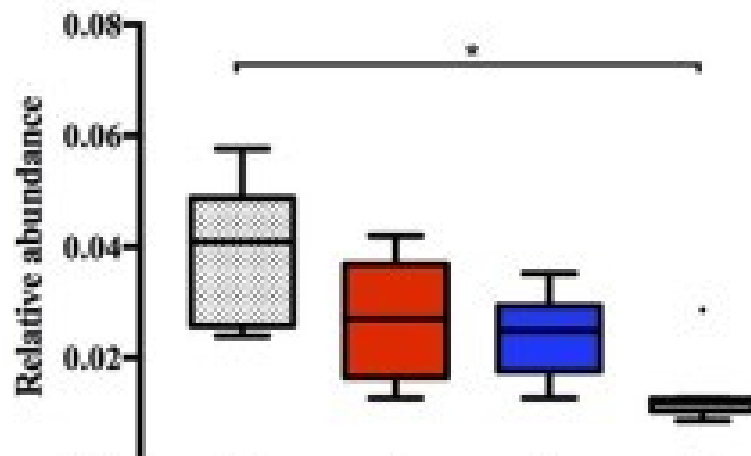
Figure 6 Relative abundance of bacterial taxa at different taxonomic levels in each group (*n* = 6–8/group)

(D) *Desulfovibrionaceae*; 弧菌科

(E) *Desulfovibrio*; 脱硫弧菌属

高脂饮食组后代肠道菌群中的变形菌门以及厚壁菌门比例都显著增加，添加金雀异黄素后子代的这些菌群比例有所改善

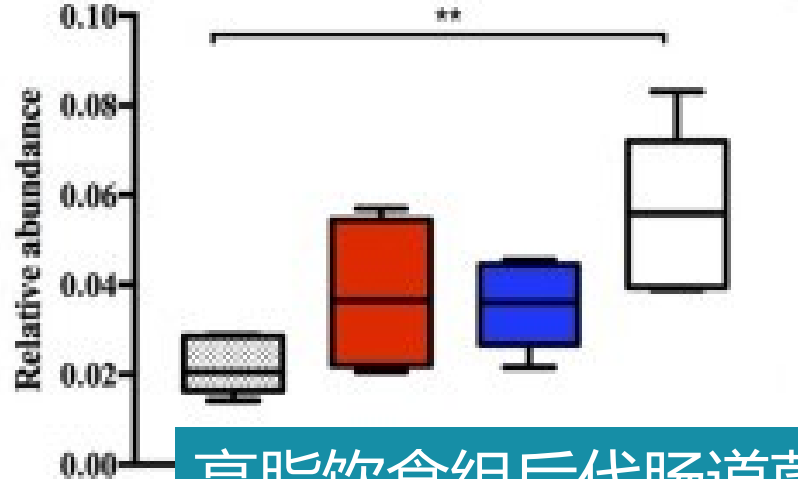Figure 6 Relative abundance of bacterial taxa at different taxonomic levels in each group. (*n* = 6–8/group) 紫单胞菌科
-004;

(H) *Rikenella*, 理研菌属

(I) *Rikenellaceae_RC9_gut_group*. 理研菌属*RC9肠道菌群*
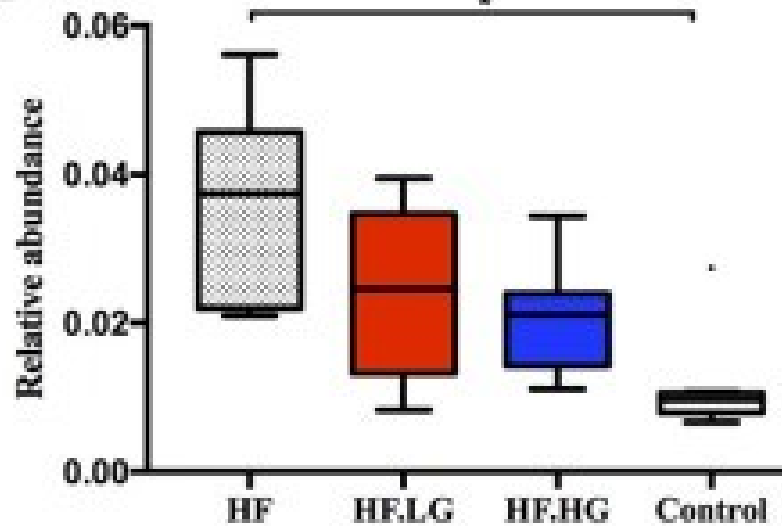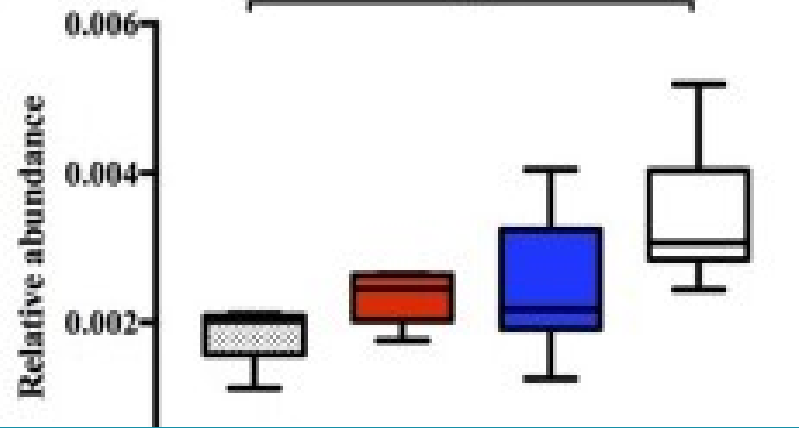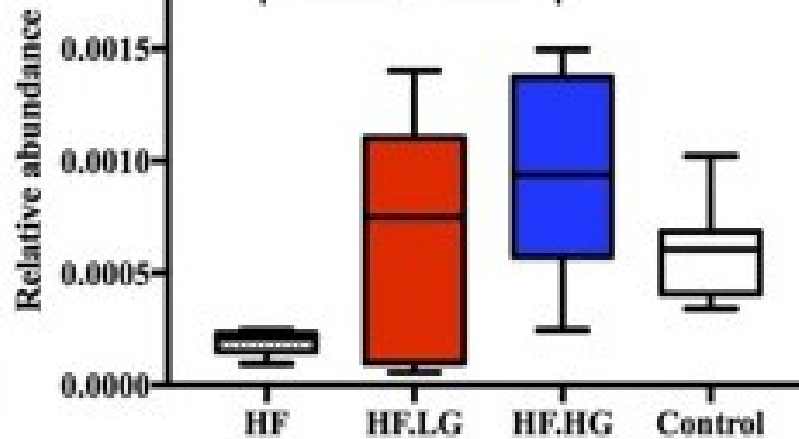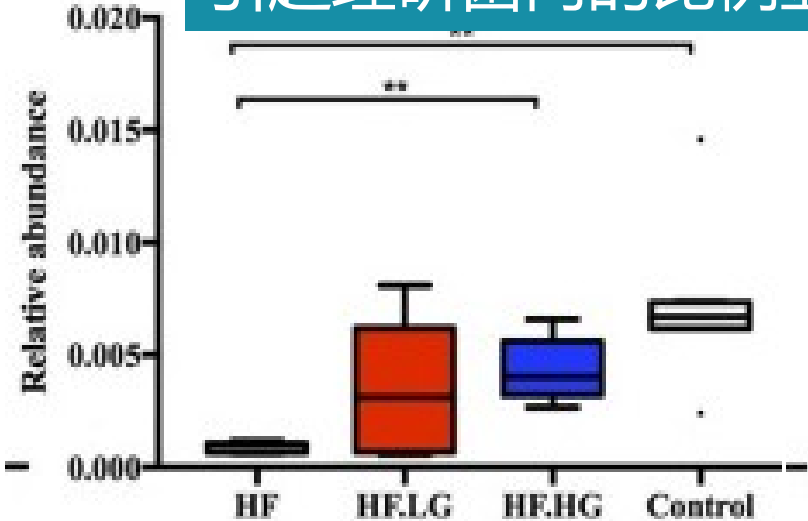
高脂饮食组后代肠道菌群中的拟杆菌门（有益菌）比例显著降低，添加金雀异黄素后子代的这些菌群比例均显著性增加；并且，高剂量添加会引起理研菌门的比例显著增加，这可能在脂代谢中起重要作用

Figure 7 The LEfSe analysis of the different gut microbiota from the phylum level down to the species level (*n* = 6–8/group).
(A) Differently enriched bacteria among the HF-HF.LG-Control group

B

高脂饮食会引起后代肠道中变形菌门和厚壁菌门丰度增加，从而造成肥胖，但添加金雀异黄素后，拟杆菌属以及AKK等有益菌丰度增加，抑制肥胖的发生，并且高剂量添加后生酸拟杆菌独特富集，促进金雀异黄素在肠道代谢中的作用

(B) Differently enriched bacteria among the HF-HF.HG-Control group.

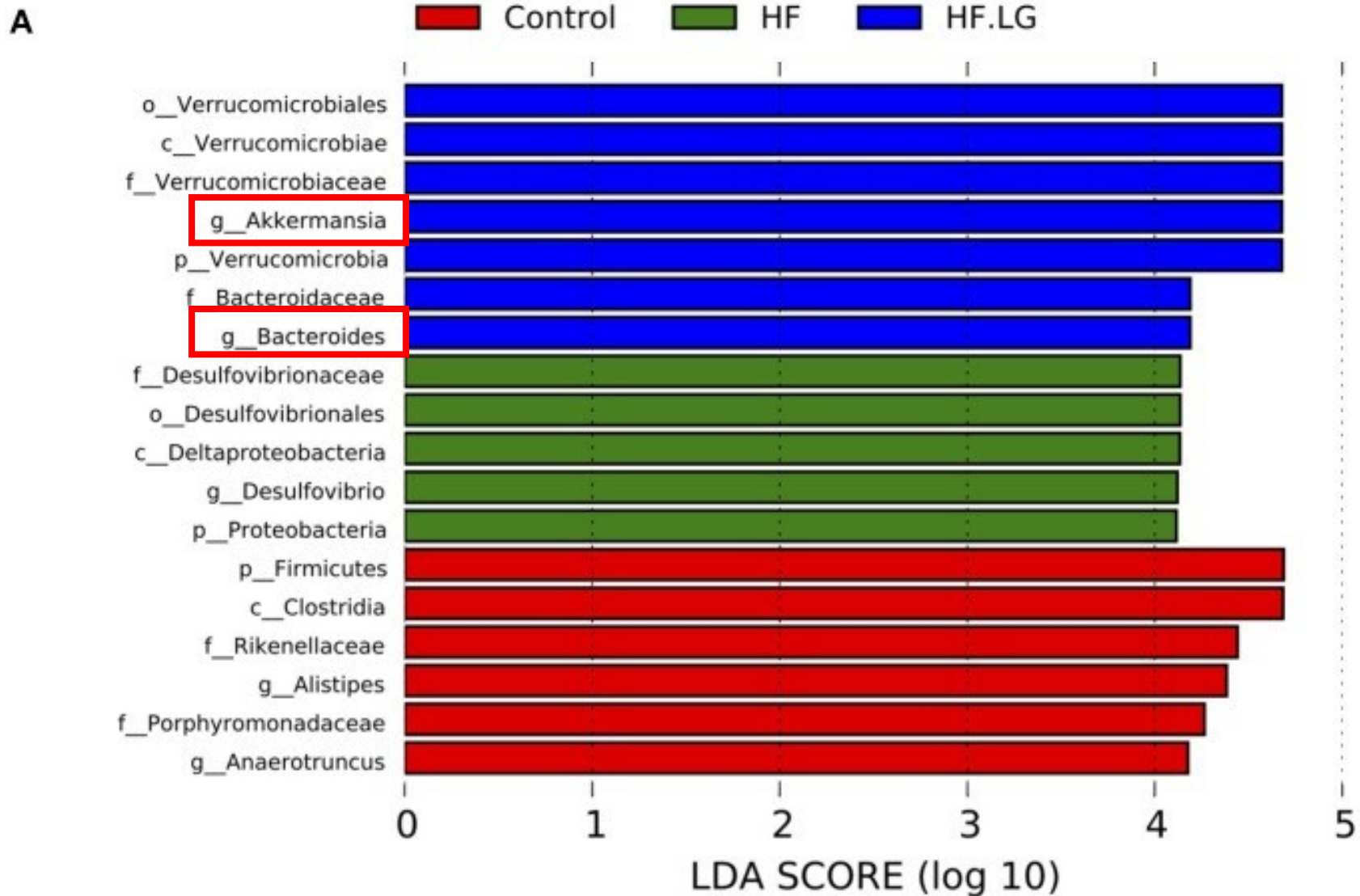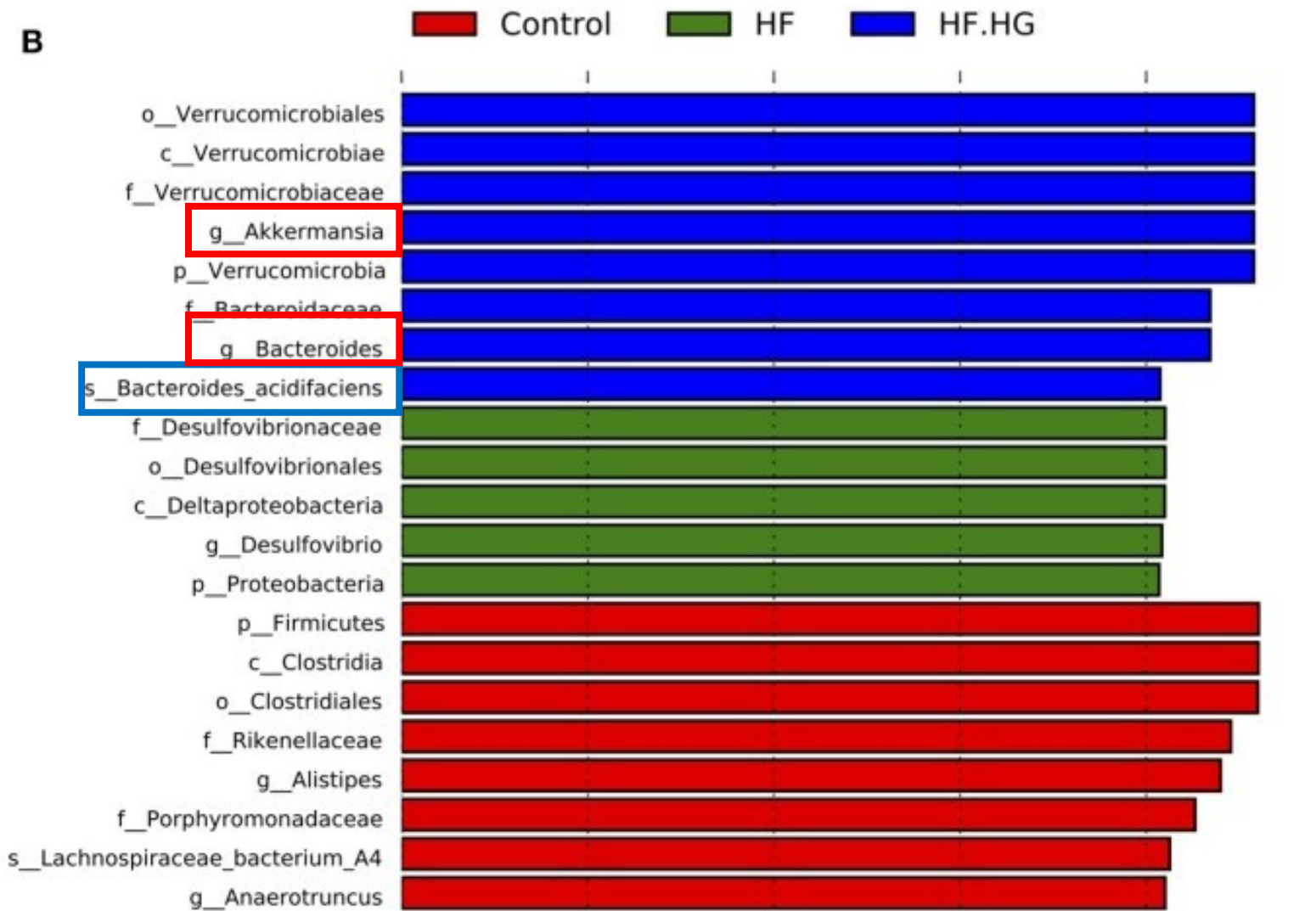**Table 2** Correlation analyses between relative abundance of bacterial taxa at different taxonomic levels and glucose and lipid metabolism parameters ($n = 6$–8/group).

Metabolic index	Taxonomic level	Specific Taxon	r	p-value	FDR
AUC	phylum	Proteobacteria	0.59	0.0009	0.0033
	class	Deltaproteobacteria	0.59	0.0010	0.0028
	family	*Desulfovibrionaceae*	0.60	0.0008	0.0044
	family	*Porphyromonadaceae*	−0.52	0.0043	0.0095
	genus	*Desulfovibrio*	0.61	0.0005	0.0055
Insulin	phylum	Proteobacteria	0.50	0.0067	0.0082
	class	Clostridia	−0.52	0.0044	0.0081
	class	Deltaproteobacteria	0.51	0.0057	0.0090
	family	*Desulfovibrionaceae*	0.53	0.0041	0.0090
	family	*Porphyromonadaceae*	−0.58	0.0013	0.0143
	family	*Rikenellaceae*	−0.53	0.0036	0.0099
	genus	*Alistipes*	−0.53	0.0034	0.0125
	genus	*Rikenella*	−0.54	0.0029	0.0160
	genus	*Desulfovibrio*	0.51	0.0061	0.0084
	species	*Bacteroides_acidifaciens*	0.38	0.0460	0.0506

Table 2 Correlation analyses between relative abundance of bacterial taxa at different taxonomic levels and glucose and lipid metabolism parameters ($n = 6$–8/group).

Metabolic index	Taxonomic level	Specific Taxon	r	p-value	FDR
HOMA-IR	phylum	Proteobacteria	0.58	0.0013	0.0024
	class	Clostridia	−0.47	0.0108	0.0132
	class	Deltaproteobacteria	0.60	0.0007	0.0026
	family	*Desulfovibrionaceae*	0.62	0.0005	0.0055
	family	*Porphyromonadaceae*	−0.62	0.0005	0.0028
	family	*Rikenellaceae*	−0.50	0.0071	0.0111
	genus	*Alistipes*	−0.49	0.0083	0.0114
	genus	*Rikenella*	−0.59	0.0010	0.0022
	genus	*Desulfovibrio*	0.59	0.0009	0.0025
	species	*Bacteroides_acidifaciens*	0.46	0.0130	0.0143
TC	phylum	Proteobacteria	0.45	0.0161	0.0443

相关性分析表明，肠道菌群从门水平到种水平上均在不同程度上与糖脂代谢有关，其中生酸拟杆菌的相对丰度与胰岛素抵抗指数正相关，这表明添加不同剂量的金雀异黄素对后代糖代谢以及胰岛素敏感性的影响存在差异

04 Discussion
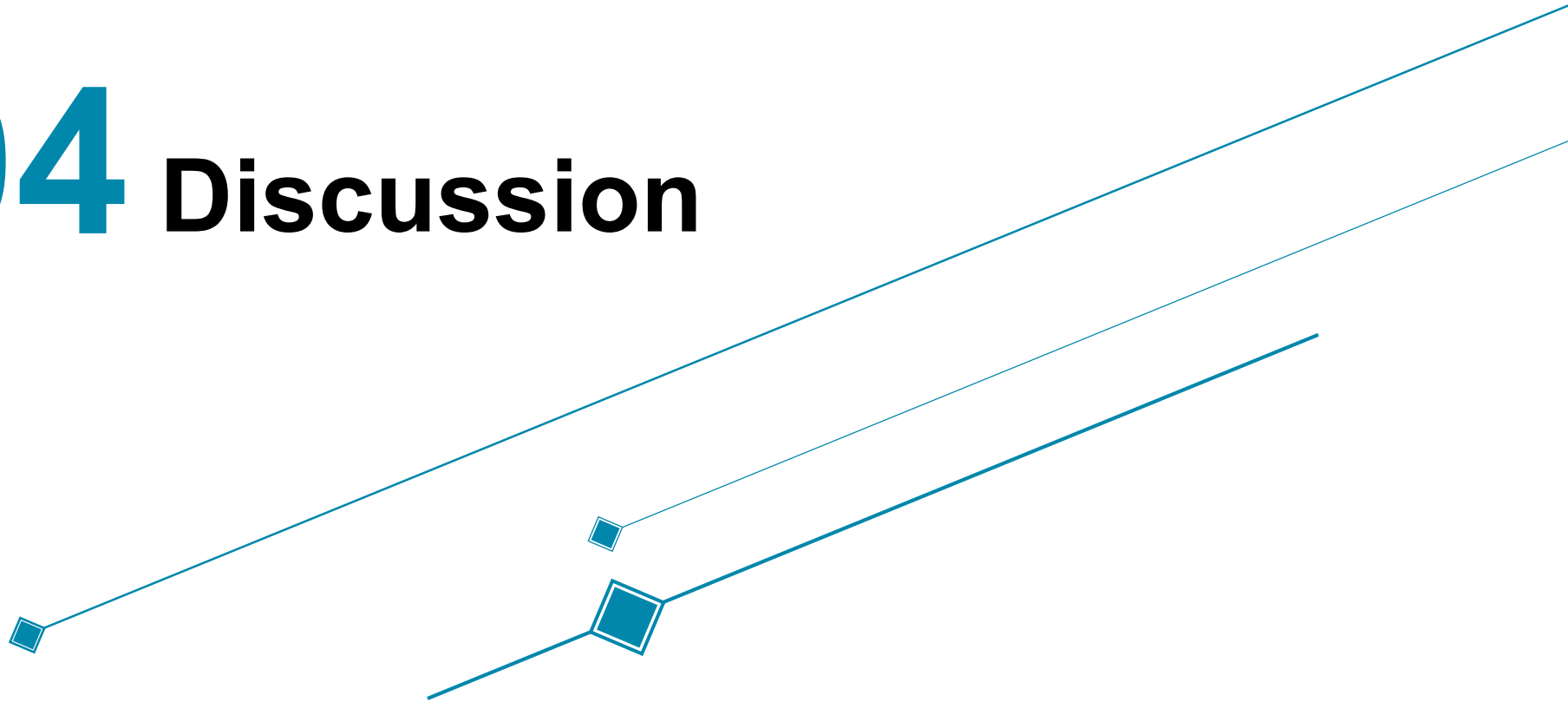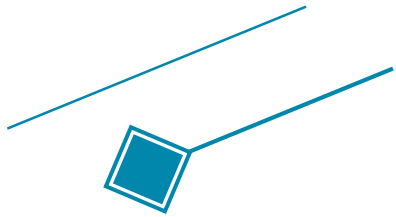
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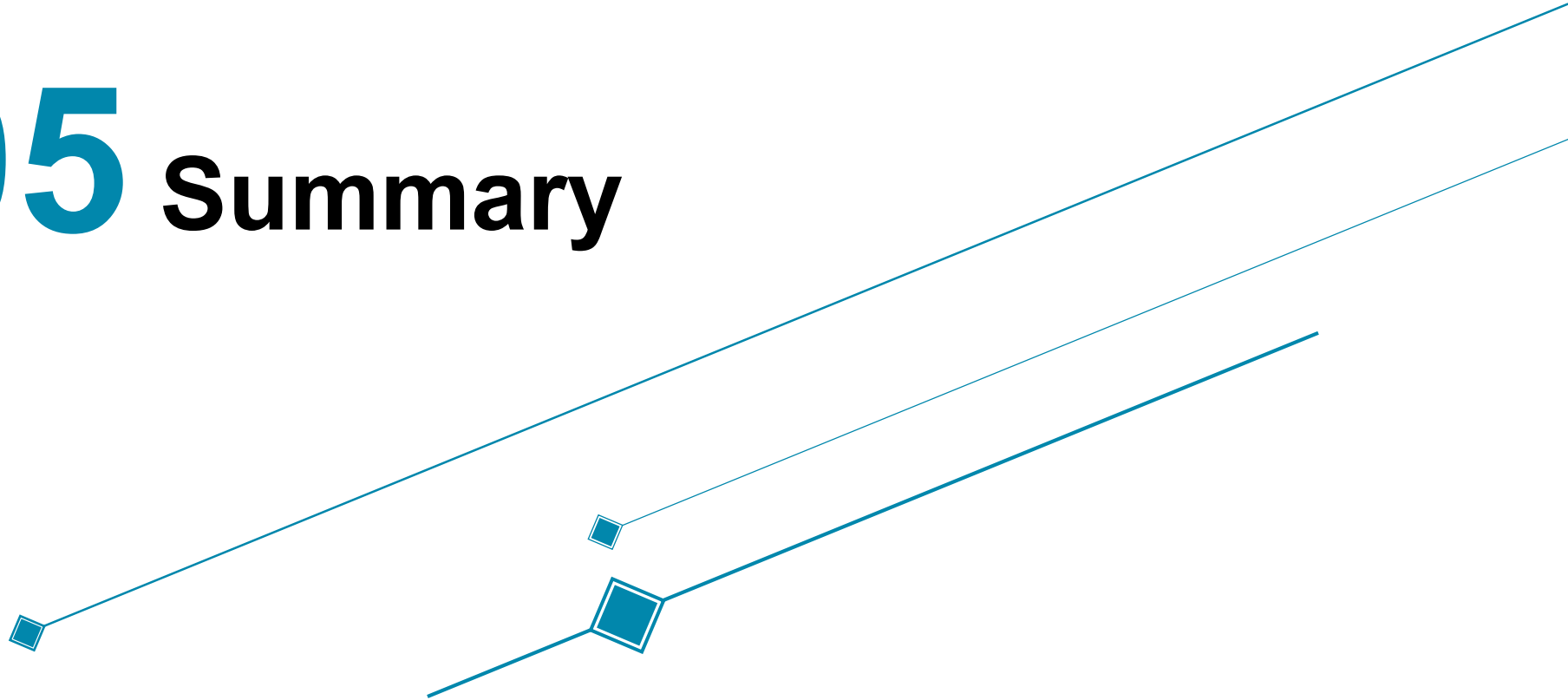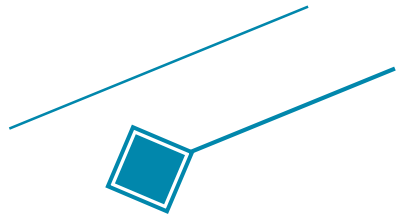在交配前3周及整个怀孕和哺乳期间摄入金雀异黄素可显著改善雌性后代生命早期的糖脂代谢，并逆转母体高脂饮食的对雌性后代的不利影响。

02

葡萄糖和脂质代谢的改善与后代肠道菌群的改变有关。（这是第一个报道肠道菌群在母体膳食金雀异黄素对雌性后代糖脂代谢影响中的作用的研究。）

03

结果表明，母体膳食干预可能是对抗后代肥胖和糖尿病的重要工具，这也明确了肠道菌群对后代糖脂代谢的作用。

05 Summary

本研究通过探讨在孕前、孕期以及整个哺乳期对母鼠饮食进行干预，对雌性子鼠的肠道微生物和糖脂代谢的影响，指出肠道微生物的改变确实会在雌性后代早期的机体代谢健康中发挥关键作用，这也为早期预防代谢性疾病的发生和发展提供一些证据和新的目标。

探索肠道菌群在介导跨代影响中的作用

C57BL/6 female mice were fed a HF, HF with genistein (0.6 g kg−1 diet) or normal control diet for 3 weeks before mating and throughout pregnancy and lactation. The offspring had free access to normal diet from weaning to 24 weeks of age.

Gut microbiota might be a crucial factor in deciphering the metabolic benefits of perinatal genistein consumption in dams and adult female offspring†

Check for updates

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THANKS

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