[illegible]

## 2. Materials and methods

### 2.1. Animals

[illegible]

### 2.2. MS and CUMS modeling

[illegible]

### 2.3. wt of dams and pups

[illegible]

### 2.4. Behavioral tests

[illegible]

### 2.5. Quantitative RT-PCR

[illegible]

### 2.6. Immunohistochemistry

[illegible]

### 2.7. Enzyme-linked immunosorbent assay (ELISA)

[illegible]

### 2.8. 16S rDNA sequencing

[illegible]

### 2.9. Statistical analysis

[illegible]

## 3. Results

### 3.1. Comparisons of behaviors between MS model and CUMS model

[illegible]

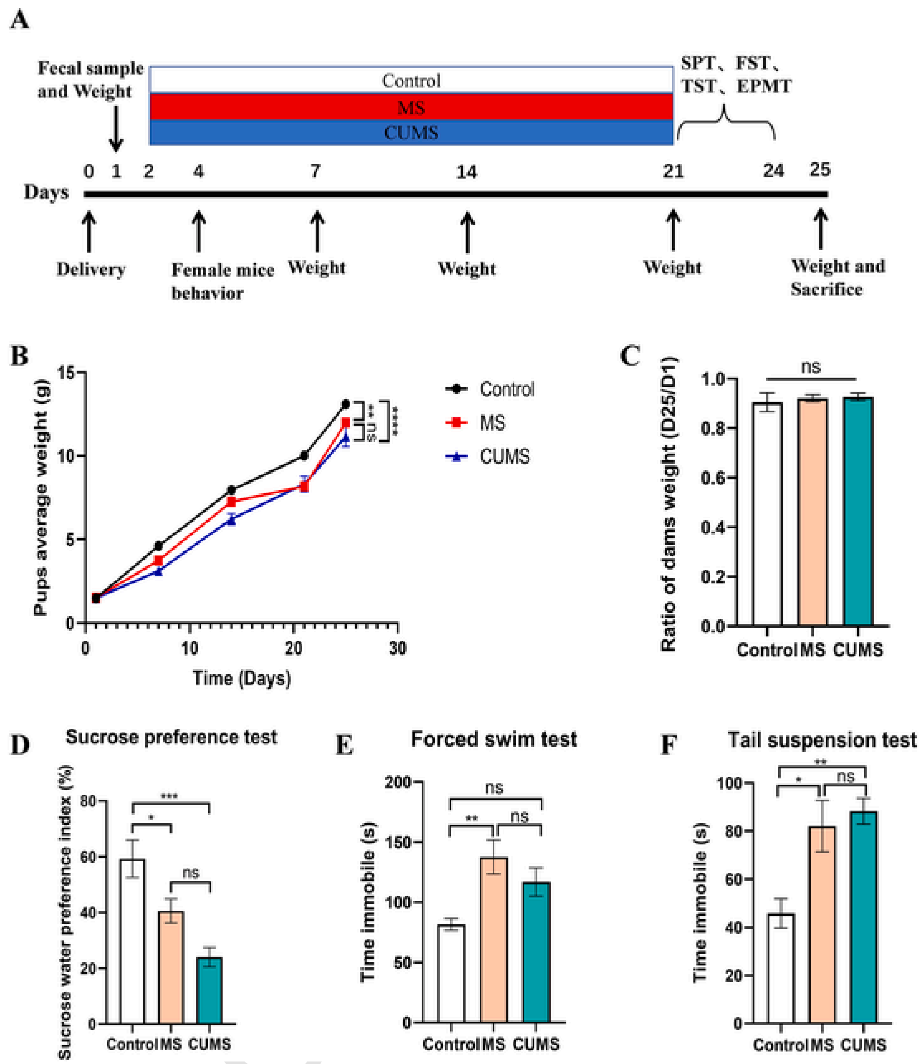


Fig. 1.

### 3.2. The expression of PPD related genes in brain were detected by RT-qPCR

Crh Crhr1

Il1b Caspase1 Nlrp3 Il6 Tnfa Bdnf

### 3.3. The contents of related substances in plasma and cortex were detected by ELISA

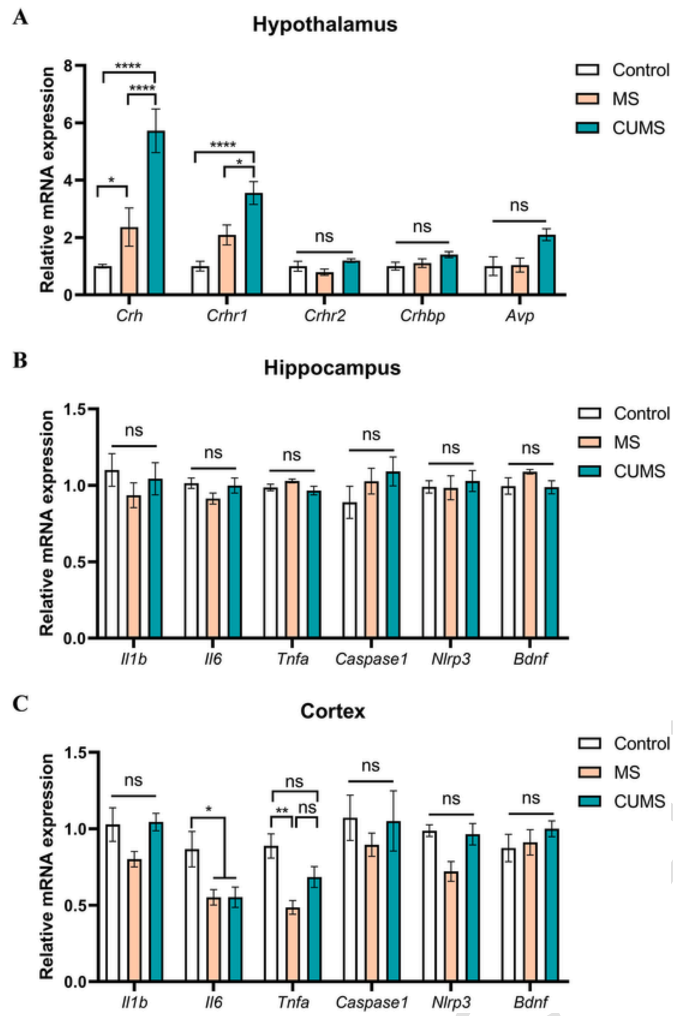


Fig. 2. [illegible] n [illegible] n [illegible] n [illegible] *P [illegible] **P [illegible] ***P [illegible] ****P [illegible]

[illegible]

## 3.4. CUMS model and MS model showed different changes in BDNF

[illegible]

## 3.5. 16s rDNA sequencing

### 3.5.1. Alpha diversity

[illegible]

### 3.5.2. Beta diversity

[illegible]

### 3.5.3. Composition of bacterial community structure

[illegible] Bacteroidetes [illegible] Firmicutes [illegible] proteobacteria [illegible] Muribaculaceae [illegible] Alistipes [illegible] Lactobacillus [illegible]

### 3.5.4. Significant species differences

[illegible] Bacteroidetes [illegible] Firmicutes [illegible] Proteobacteria [illegible] Lactobacillus [illegible] Desulfovibrio [illegible] Mucispirillum [illegible] Bacteroidetes [illegible]

[illegible] Bacteroides [illegible] Lactobacillus [illegible] Robinsoniella [illegible] Erysipelatoclostridium [illegible] Clostridioides [illegible] Empedobacter [illegible] Mucispirillum [illegible] Deferribacteres [illegible]

## 4. Discussion

[illegible]

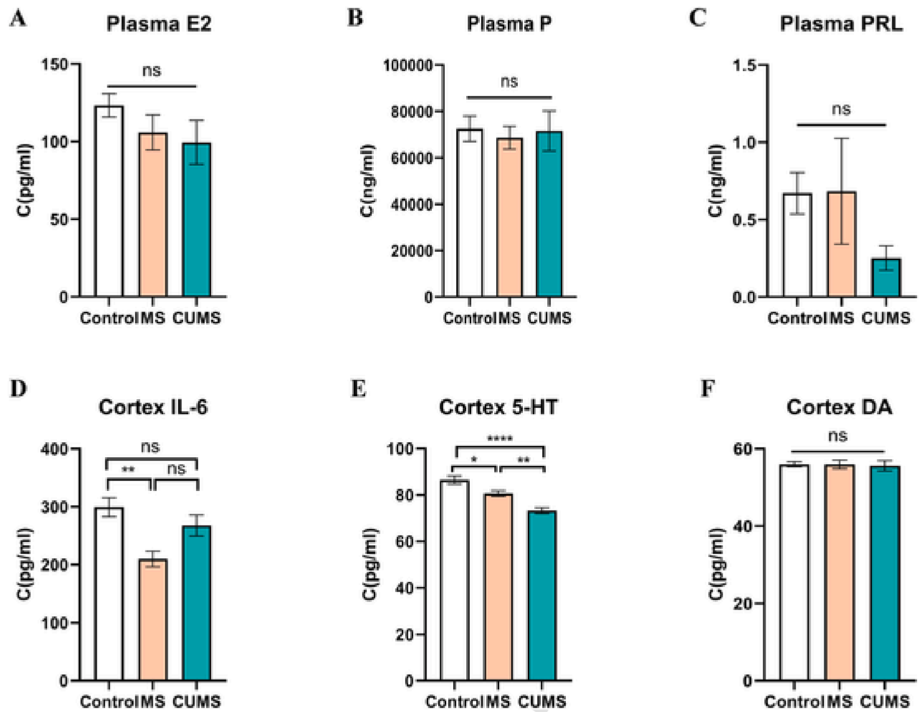


Fig. 3. '- 8E; / '- @E :<; I<C8K<; JL9JK8E<J:?8E><J @E GC8JD8 8E; :FIK<O;<K<:K<; 9P &#- (F J@E@@8EK;@=<I<E:< <O@JK<; @E C<M<C n (F J@E@@8EK;@=<I<E:< <O@JK<; @E C<M<C n (F J@E@@8EK;@=<I<E:< <O@JK<; @E, &C<M<C n #& C<M<C@EFIK<OK@L< n ". C<M<C@E :FIK<OK@L< n (F J@E@@8EK;@=<I<E:< <O@JK<; @E C<M<C@EFIK<OK@L< n 8 K8@JK@:8C K<JK<; 8J K?< D<8E W - ' *P ** P ** ** P EJD<8EJ EFE J@E@@8EK

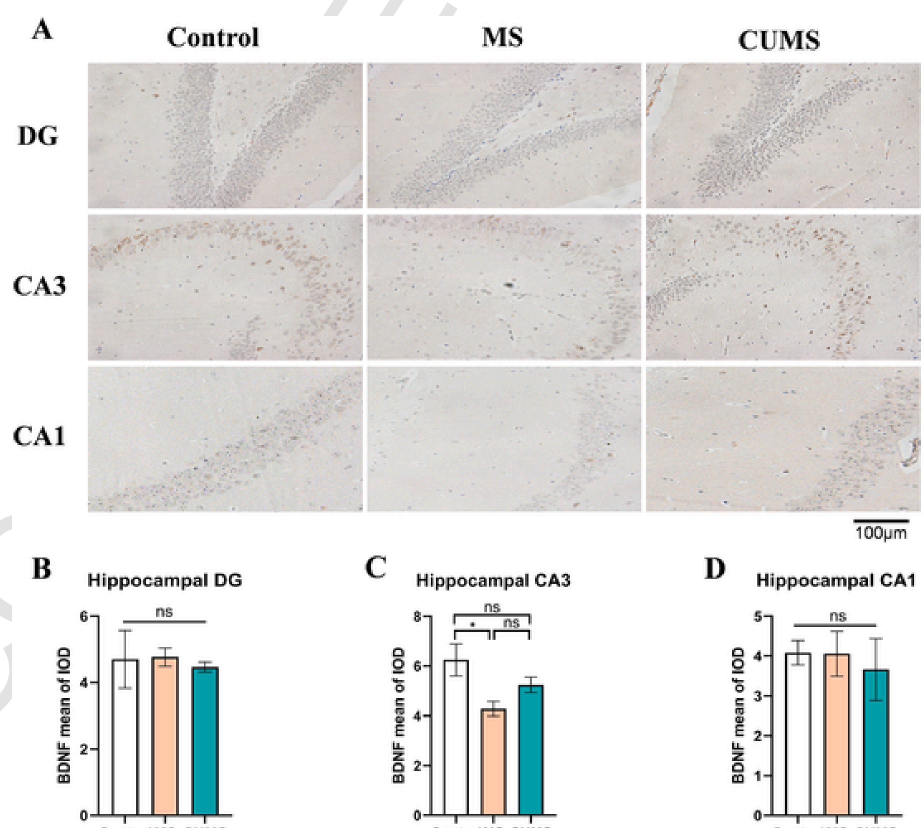


Fig. 4. (L D9<I F= ( GFJ@K@M<<CC@EK?< ?@GGF:8DG8CJL9 I<>@FEJ ! 8E; F=EFI D8C8E; JK<JJD@:< ,< GI<J<EK8K@M<@D8><JF= ( F=K?< ?@GGF:8DG8CJL9 I<>@FEJ ! 8E; @EK?< K?I<< <OG<I@D<EK8C>IFLGJ -: 8C< 98I üD Y +L8EK@K8K@M<;< K<:K@FE F=?@GGF:8DG8C ( :FEK<EK @EK?< ! N8J G<I=FID<; #) @EK<>I8C FGK@:8C ;<EJ@KP 8 K8@JK@:8C K<JK<; 8J K?< D<8E W - ' n *P EJD<8EJ EFE J@E@@8EK

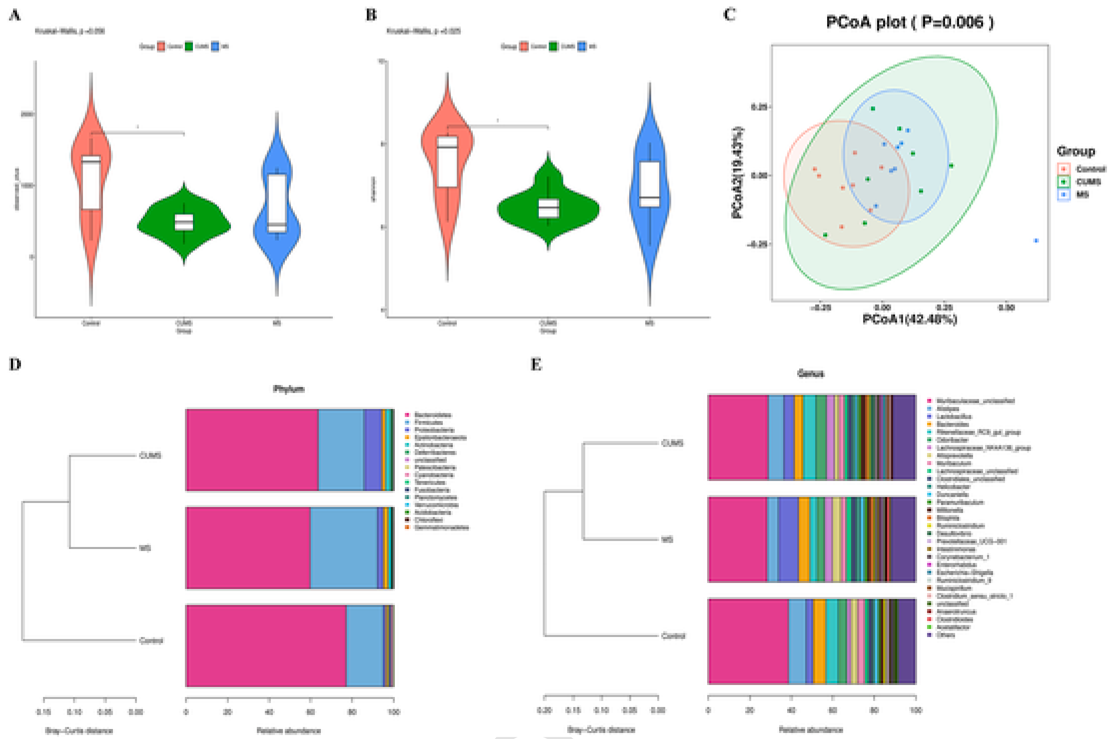


Fig. 5. þ ;@M‹J@RKý ;@M‹J@RK8E; -G<:@J<8E8CPJ<J F=>LKD@ F9@RK8 )9 J<M<; 7JG<@J@E O n -?8EEFE @E O n * F 8E8CPJ@F=>LK 98:K‹@ ;8 K8 n CLJK‹ >I8G? 8E8CPJ@F=G?PCID C‹M<C n CLJK‹ >I8G? 8E8CPJ@F=><ELJ C‹M<C n *P

.? <I<=F< :?8E><J @ED8K‹E8C9F;P N<@?K:8EEFK9< LJ<; 8J 8 D<8 JLI< F=K?< JL:<JJ F=;< GI<JJ@E DF;<C 5 6 .? < JL:I FJ< GI<=<I<E< @E O@E '- DF;<C;<:I <8J<; DFI< F9M@LJC .? @@E@8 K‹J K?8KK?< / '- DF;<C @DFI< F9M@LJ @E E?<;F E@ #E - . 8E; .- . '- DF;<C 8E; / '- DF;<C G‹=FD <; ;@=‹<EK .? < '- DF;<C J?FN<; CE><I @DF9@C@K @E . 8E; K?< / '- DF;<C J?FN<; CE><I @DF9@C@K K@< @E . .? <I< N8J EF ;@=‹<E< @E K?< JK8P K@< @E K?< :FJ<; 8ID 8I<8 9<KN<E K?< KNF >IFLGJ N?@? JL>><JK<; K?8K & D@< N<I< D<<B8E; K@@ 8E; N<I< DFI< @B JK< F=8M@8E< 8E; 8EO@@ @E K?< E<N <EM@ED<EK 5 6

#DDLE< JPJK<D 8E; :PKFB@E<J 8I< @DDFCM< @E K?< ;<M<CFGD<EKF= ** 5 Ð 6 (&,* @E8DD8JFD< ;<=@E<P @D GIFM< ;< GI<JJ@E C@9<?8M@F@D< 8E; Caspase1 8E; Nlrp3 D, ( C‹M<C @E<8J<; @E K?< 9CFF; :<CDF=;< GI<JJ< G8K@EKJ 5 6 #KJL>><JK K?8K** D8P 8CF 9< I<C8K<; KF@E8DD8KF@E -F N< D<8JLI<; K?< @E@8 KFJ +* , I< JLCKJ J?FN<; K?8KI<C8K@M<Il1b, Il6, Tnfa, Caspase1 8E; Nlrp3 D, ( <OGI<JJ@EJ J?FN<; EF JK8K@K@C;@=‹<E< @E K?< ?@GF:8DGLJ N?@C< 8K@M<Il6 8E; Tnfa D, ( <OGI<JJ@E;<:I <8J<; @E K?< :FIK<O F=K?< JK<JJ DF;<C &#- I<JLCK8CF J?FN<; K?8K#& C‹M<CN8J ;<:I <8J<; @E K?< :FIK<OF=JK<JJ<; ;8DJ <JG<@8CCP@E K?< '- DF;<C CK?FL>?K?<J< I< JLCKJ;@=‹ =FD JFD< GL9C@<; JKL; @J K?<I< 8I< 8CF :FE=C@K@E I< GFIKJ F=@E8DD8KFP :?8E><J 8JJF:@K< N@K?** 8E; K?< C@@K ELD9<I F=I<GFIKJ D8B<J @K@=@ CKKF;< K‹D@E< 8 IFC<F=E<LIF@E8DD8KF@E @E K?< LE;<I CP@E E<LIF9@CF>P F=** 5 6 1< JG<:LC8K< K?8K E<LIF@E8DD8KF@E I<C8K<; :PKFB@E<J @EK<JJ<; ;8DJ N<I< @EJK<F= =<<; 98:B I<>LC8KFE FE GFJKG8KLD ;8P 8E; K?< 9F;P @E@8K<; K?< 8EK@E8DD8KFP I<JGFEJ< @EM@F JF K?8KK?< @E8DD8KFP =8KFJ ;<:I <8J<; J?8IGCP

*I <M@LJ JKL; @J<?8M<J?FNE ;<:I <8J<; ". 8E; ( C‹M<C @EG8K@EKJ N@K?** 5 6 .? < I<C8K@M< Bdnf D, ( <OGI<JJ@E J?FN<; EF J@E@8 EK;@=‹<E< 9<KN<E :FIK<O 8E; ?@GF:8DGLJ "F N<M<I @DLEF?@KF? <D@8C JK8@E@E I<JLCK F= ?@GF:8DGLJ J?FN<; K?8KK?< <OGI<JJ@E F= ( J@E@8 EKCP;<:I <8J<; @E K?< '- DF;<C8E; J@E@8 EKCP;<:I <8J<; @E K?< / '- DF;<C .? @JKL; P ?8J 9<<E LE89C<KF;< DFEJK8K<K?< :?8E><J F= @E K?< :FIK<O .? < C‹M<CF=

". @E K?< :FIK<O J?FN<; 8 ;F NEN8I; KE; @E K?< JK<JJ DF;<C8E; / '- DF;<C;<:I <8J<; J@E@8 EKCP

.? < G8JD8 C‹M<C F=<JK8;@FC GIF><JK<FE<8E; GIFC8K@E I<;<:K‹D@E<; @E K?@JKL; P J@:< :?8E><J @E K?< C‹M<C F=I<GIF;L :KM<?FI DFE<J 8I< 8CF 8 I@B =8KF =FI ** 5 6 .? < I<JLCKJ J?FN<; K?8K <JK8;@FC 8E; GIFC8K@E8 ;<:I <8J@EKE; @E K?< JK<JJ DF;<C 9LK K?< ;<:I <8J< N8J DFI< F9M@LJ @E K?< / '- DF;<C )E < @EK<I<JK@E =@E;@E @E K?8KGIF><JK<FE< C‹M<C 8I< G8K@C8CP ?@?< 8=K‹ ;<C@M<IP 1< ;@CK< K?< G8JD8 KF K@<J ;L I@E D<8JLI<D<EK #K@J ;L I@E GFJJ@C< K?8KK?@JKLCKJ@D8P ?8M<9<<EJK<N<; 9P <O<JJ@M< ;@CLK@FE I8K@F

.? < "* 8O@J@E @DGFIK8EK G8KF=K?< E<LIF<E;F :I @E<JPJK<D @E MF CM< @E EKFCC@E> I<JGFEJ<J KF JK<JJ 8E; I<>LC8K@E D8EP GJP?@8C 8:KM@K@J #EI <8J< JK<JJ @E<8J<J K?< J<I <K@E F=I<C8K<; ?FIDFE<J 5 6 1< N<I< JLIGI@J<; KF=@E K?8KK?< D, ( <OGI<JJ@EJ F=Crh 8E; Crhr1 @E '- DF;<C N<I< J@E@8 EKCP@E<8J<; @E K?< ?PGFK?8CDLJ K?8E '- DF;<C 1< ?PGFK?<J@<; K?8K / '- D@?K:8LJ< ;8DJ KF=<<C DFI< JK<JJ<;

#K@9<:FD@E @E<8J@EKCP I<:F>E@<; K?8KK?< >LKD@ F9@D< :8E G8P 8 IFC< @E GI<J@E I<C8K<; DFF; ;@FI;<I J #EK?< - J<HL<E @E I<JLCK K?< þ ;@M‹J@KPF=JK<JJ DF;<C N8J CFN<I K?8E K?8KF=:FEKFC >IFLG N?@CK?< ý ;@M‹J@KPN8J EF ;@=‹<EK .? < IFL>? K?< ;@K8E:< :CLJK‹@E >K<JK:KLI< 8E8CPJ@ K?< 98:K‹@8CFDDLE@KPJKL:KLI< F= K?< JK<JJ DF;<C N8J J@D@8 )E < LE8EK@@G8K<; I<JLCKN8J K?8KLacto-bacillus @E<8J<; @E K?< DF;<C>IFLG Lactobacillus @J <E<I8CCP FEJ@ <I<; 8 9<E<=@@C98:K‹@8 8E; @K89LE;8 E:< ;<:I <8J<; @E K?< ;<GI<J J@E DF;<C>IFLG 5 6 )= :FLIJ< JFD< J:?FC8IJ 8CF J?FN<; K?8K Lactobacillus @E<8J<; @E K?< JK<JJDF;<C>IFLG 5 6 C‹N I8K@F F= Firmicutes KFBacteroidetes I8K@F @JF EJ@<I<; 8 EFD8C ?<8CK?P JK8K< F=K?< @EK<JK@8CD@ F9@D< 5 6 #EFLI JKL; P K?< I8K@F @E :I <8J<; @E K?< DF;<C>IFLG @E@8 K@E K?8KK?< @EK<JK@8CD@ F9@D< :FD GFJ@K@E F=K?< DF;<C>IFLGN8J ;<M<CFG@E @E 98; ;@<:K@E #E K‹E8KF@8CPK?<I< 8I< JFD< ;@=‹<E<J @E K?< 89LE;8 E:< 8E; ;@M‹J@KP F=@EK<JK@8CD@ F9@D< @E =<I<EK:FEKFC >IFLGJ @E GFJKG8KLD ;<GI<JJ@E 5 Ð 6 #EK<JK@8CD@ F9@D< @8=<:K<; 9P D8EP =8:KFJ @E:CLJ@E> ;@<K=8KF<KF8=<:KC<E >K?F=DF;<C :F E D8P C8;; KF;@=‹<E:<J @E K?< I<JLCKJ @ 8E; 8><JK=FDF;<C <GP@E >KF;@=‹<E<J @E K?< @E

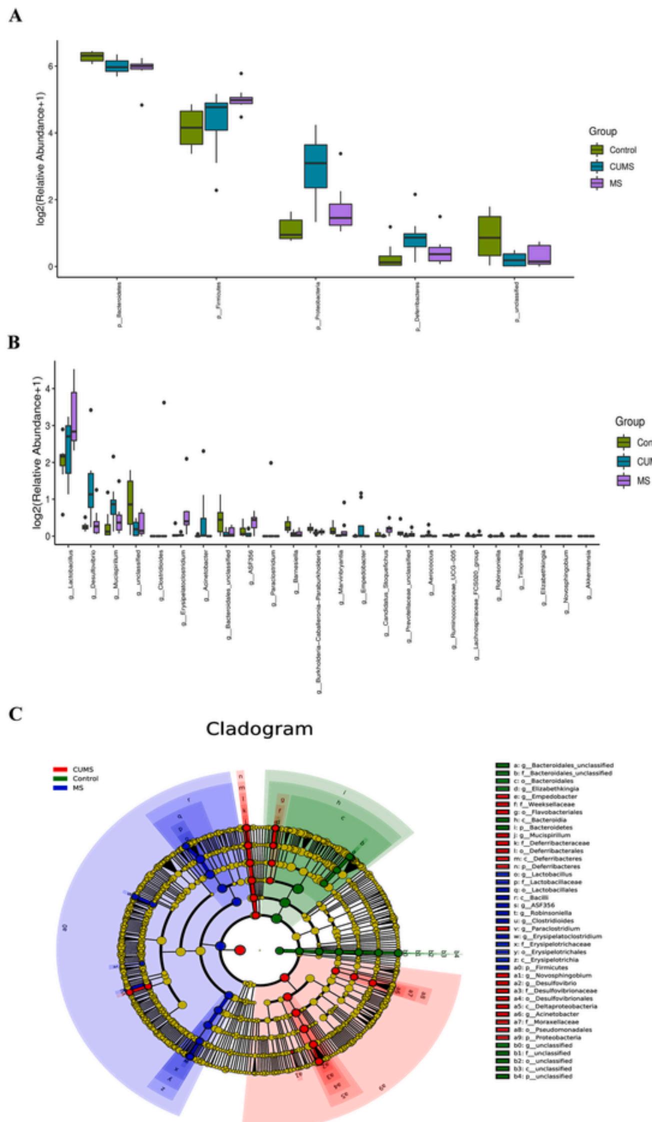


Fig. 6. E 8CPJ@F=J@E@8 EK;@=<<E< F=>LKD@ F9@K8 8 IGCK;@=< <E< 8E8CPJ@F=G?PCD C<M<C n 8 IGCK;@=<<E< 8E8CPJ@F=><ELJ C<M<C n & =<;@=<<E< 8E8CPJ@ n

K<JK@8CD@ F9@D<5 6 -<:FE; =<;@E<EMI@ED<EKF=DF;<CD@< @EL; @E ;@<K :C@8K< K<D G<8KL< 8E; ?LD@@PK N@C8CJF 8=<K :?8E><J @E@KK<JK@8CD@ F9@D< @E8CPC ;@=<<EKDF;<C@EED<K F;J 8I< 8; FGK<; .?< KPG< @K<EJ@KP8E; ;L I8K@E F=JK<JJFJ 8CF C<8; KF ;@=<<EK :?8E><J @E8E@8C GPJ@FCF>P 8E; @K<JK@8C D@ F9@D< 5 6

)L I JK; P GIFM@J K?< =@K<M@< E:< KFFLI BEFNG;>< K?8KK?<J KNF DF;<CJ ?8; JFD< ;@=<<EK;<GK<JJ@M<9<?8M@IBC ?@GF8 DG8C ( :?8E><J :FIK@8C ". :?8E><J "* 8C@J?8E><J 8E; @K<JK@8C D@ F9@D< :?8E><J <O<GK=F JFD< :FDDFE =<8KL<J .?<P 8C J?FN<; ;<GK<JJ@E C@<9<?8M@IF 9LK / '- DF;<C?8; DFI< F9M@LJ G8 8E?<;F E@ @E* . 8E; CE><I @DF9@<K@< @E . N?@C- DF;<C ?8; CE><I @DF9@<K@< @E . / '- DF;<C?8; K?< CF<JK:FIK@8C ". :FEK<EK N?@C- DF;<C?8; K?< CF<JK?@GF8 DG8C ( <O G<JJ@E / '- DF;<C,@G8P<; 8 ?@?<I ?PGFK?8C8DLJ I<C8K<; D, ( <OG<JJ@E Crh Crhr1 K?8E '- DF;<C #E ><E<I8C '- DF;<C 8E; / '- DF;<C?8M<;@=<<EKG<=FD8E:< @E9<?8M@IF8E; GP J@FCF>P .?< / '- DF;<CJ?FN<; DFI< F9M@LJ G8 8D<K<:?8E><J N?@? D8P 9< DFI< JL@8KC<=F ** @E :<; 9P M8@@LJ JF:@8C<EM@ED<EK8C=8 KFJ

## Funding source

.? @J<J<8I:? N8J JLGGFK<; 9P >I8EKJ =IFD K?< "L E8E *I FM@E8C-: @E< .<:?EFCF>P < G8KD<EK $$ 8E; , 8E; K?< ? 8E>J?8 -: @E< .<:?EFCF>P < G8KD<EK B?

## Author contribution statement

38E 4?8E> '< E>?L8 &@ &@4?8E> 8E; 1< @4FL ;<J@E<; K?< <O G<I@D<EK 38E 4?8E> G<=FD <; DFJKF=K?< <OG<I@D<EK 8E8CPQ<; K?< I<JLCK 8E; NI FK< D8ELJ:I@GK @L @? @G<=FD <; K?< <OG<I@D<EK 8E; D8ELJ:I@GK<M@J@EJ '< E>?L8 &@ &@4?8E> 8E; 1< @4FL I<M@<; K?< D8ELJ:I@GK CC8LK?FIJ :FEKI@9LK<; 8E; ?8M<8GGIFM<; K?< =@8C D8ELJ:I@GK

## Declaration of competing interest

.? < 8LK?FIJ ;<:C8I< K?8KK?<P ?8M<EF BEFNE :FDG<K@E> =@8E:@8C @K<I<JKJ FI G<JFE8CI<C8K@EJ?@GJK?8K:FLC; ?8M<8GG<8I<; KF@EC<E< K?< NFIB I<GFK<; @EK?@JG8G<

## Acknowledgements

(F E<

## Appendix A. Supplementary data

-LGGC<D<EK8P ;8K8KFK?@J8IK@C< :8E 9< =FLE; FEC@E< 8K ?KKGJ ;F @FI> A99I:

## References

5 6 ' F O -8E;D8E * 8 M@&' !CP E CE>@LK@E:JK; P F=NFD<EÕ ;<G<JJ@E JFDGKFD GIF=@C;L I@E> 8E; 8=K< K?< GFJKG8KLD G?8J< < G<JJ E O@P Ð ?KKGJ ;F @FI> ;8
5 6 &@8 &@8 ? <E " &@8 -?< 2 4?8E> - ? <E 1 ? <E ! +@ " "L 8E> - 4?8E> (< LIFGFK<K@E F=I<;L :<; K?PIF@ ?FID FE< N@K?@E<8J< <JKF><E 8E; GIF><JKF< E@E GFJKG8KLD ;<G<JJ@E @FJ@,< G ?KKGJ ;F @FI> 9JI
5 6 $& *8 NCLJB@$- &FEJK<@E - C<D@E .? < E<LIF9@CF>P F=GFJKG8KLD 8E O@P 8E; ;<G<JJ@E .I <EJ (< LIFJ@ Ð ?KKGJ ;F @FI> AK@
5 6 3 " .8 E> ! , 4<E> & 1L 3 " 18 E> $ $@E> ,< J<8I:? GIF><JJ FE 8E@D8CDF;<C=F GFJKG8KLD ;<G<JJ@E 8E; K?<@9<?8M@ <M8C8K@E D<K?F; J : K8&8 E @D-: @-@E Ð
5 6 ! ? <M8C@< -@FG@& !L <E@E :S ' *8J:8C. &8M8C ,@<EK #! F E<8 < D8E<C F CJ? *I LMFJK ? L 08E '< JJ8>I &<L@<! &<GFLJ<Q! 9 <IC* ' &C; F ==<K F=>LKD@ F9@K8FE ;<G<JJ@M<C@< 9<?8M@J @D@< @D<;@8K<; 9P K?< <E F :8EE89@E@ JPJK<D (8 K F DD LE ?KKGJ ;F @FI> J
5 6 3 4?8E> , "L 8E> ' ? <E> & 18 E> $ ? 8F $ &@* 4?<E> * 2@ 4 4?8E> " 38F !L KD@ F9@K8=FD (& ,* ;< =@@<EKD@< 8D<C@@8K<J ;<G<JJ@M<C@< 9<?8M@J 9P I<>LC8K@E 8JK F:PK<J ;P J=LE:K@E M8 @ "#*% '@:I F9@D< ?KKGJ ;F @FI> J
5 6 3 ' &@ 3 "L $ -?<E - " 1L 3 &@&. 3@ C<M8K@E F=JFE8 G@: GIF<@E @8JJF:@8K<; N@K? K?< 8EK@G<JJ8EK<C@<=<KJ F==<L C@8:@;@B :? IFE@ DF;<C F=;<G<JJ@E *? PJ@F <?8M Ð ?KKGJ ;F @FI> AG?PJ<?
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5 6 3 & "8 F " 3 2L 2 " -L 2 4?8E> ! " 3L8E & $@E> 4 <@==<K F= D8K<E8C<G I@8K@E FE <G<I8K@IP 9<?8M@ 8E; , <G<JJ@E @P @GF:8DGLJ F=I8KJ ? @E (< LIFJLI> @J ,< J Ð
5 6 $ 0<KLC<E@8 I@P D8K<E8CJ<G8 8K@E 8 IF;<EKDF;<CF=;<G<JJ@E 8E; 8 G<M8C@EK ?LD8E :F E;@K@E *? 8ID8:FC,<G *, Ð ?KKGJ ;F @FI> J
5 6 ' & F :: @8 ,8 Q@@- * 08;C8DL; @1 .I LD 9LCC 8 C<@< *<;<IJ<E ,< G8K< CE>J<G8 8K@E =ID GLGJGIF; L:<;<G<JJ@E C@<9<?8M@ @EK DFK?<IJ *JP:?FE<LIF<E; F:I@EFCF>P Ð ?KKGJ ;F @FI> AGJP E<L<E
5 6 1 -?@- 4?8E> 3 &L 3 18 E> $ 4?8F & &@ :<C@JGFEJ<J @E G<JJ< D@< @E :<; 9P :? IFE@LEGK<; @K8C< D@; JK<JJ $ ==<K @JF; Ð ?KKGJ ;F @FI> AA8
5 6 . 2L< &- 1L 2 ' &@ + 18 E> ,< J<8I:? GIF><JJ FE 8E@D8CDF;<C=

[illegible]