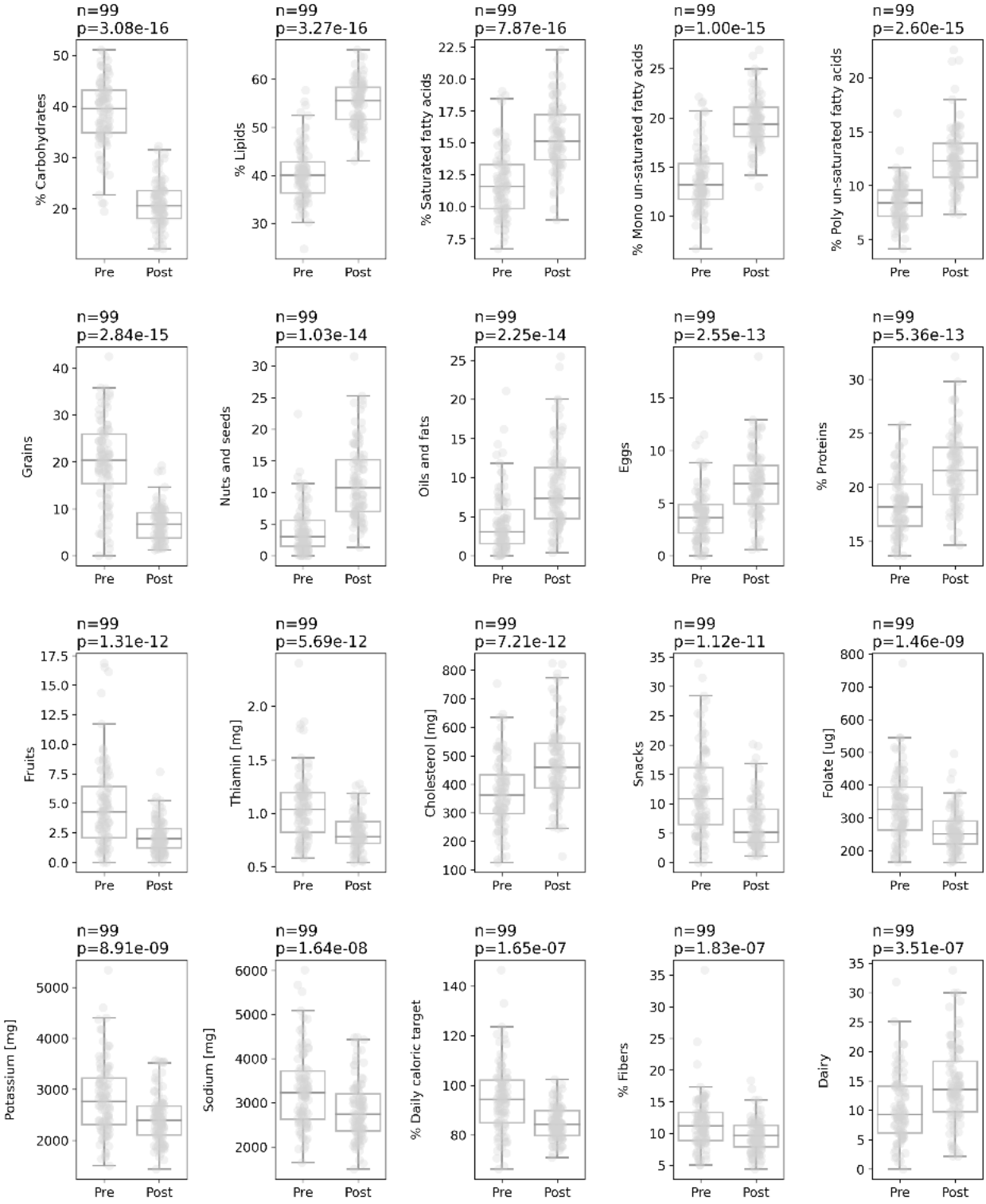
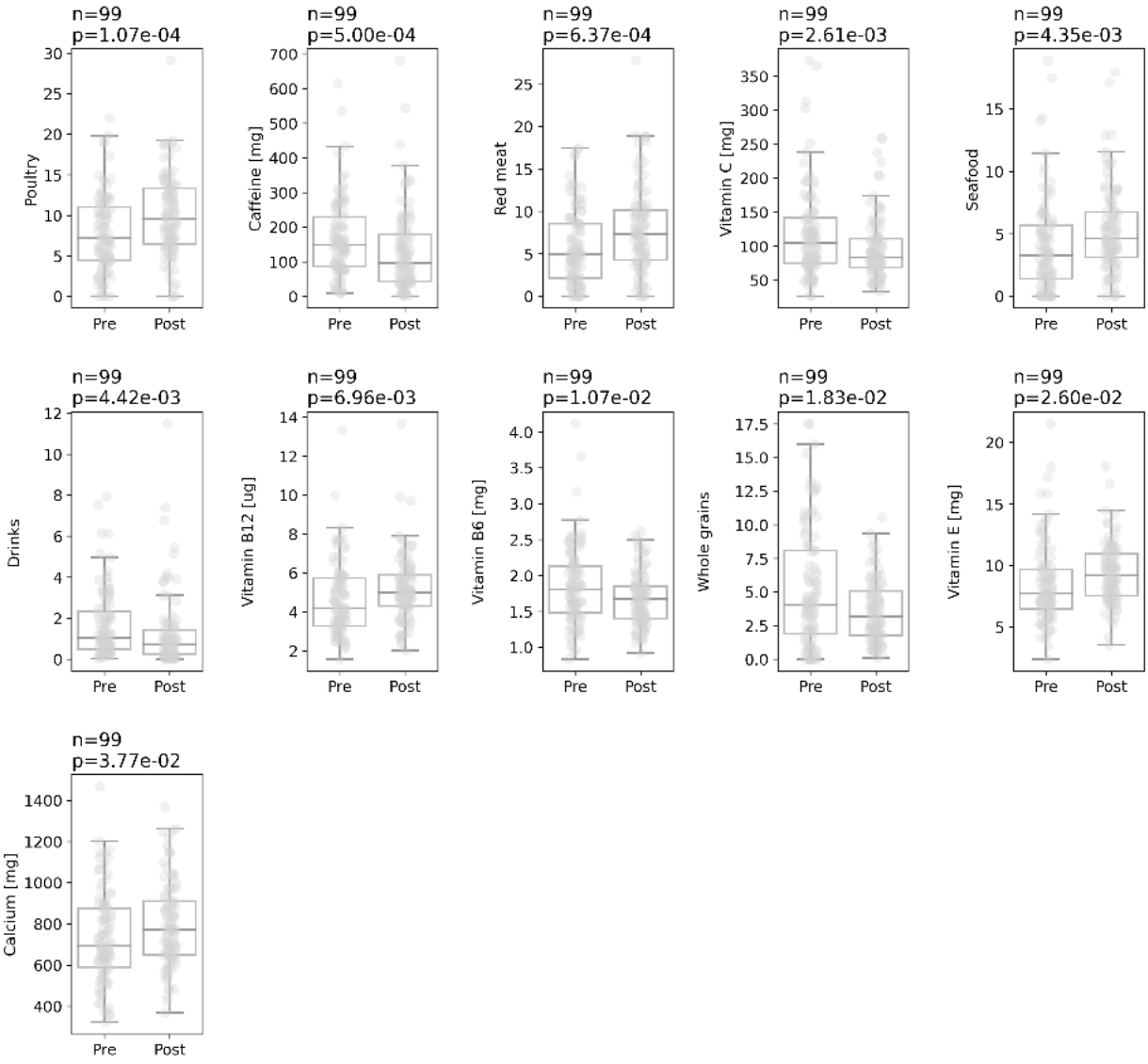
Impact of Dietary Interventions on Pre-diabetic Oral and Gut Microbiome, Metabolites and Cytokines

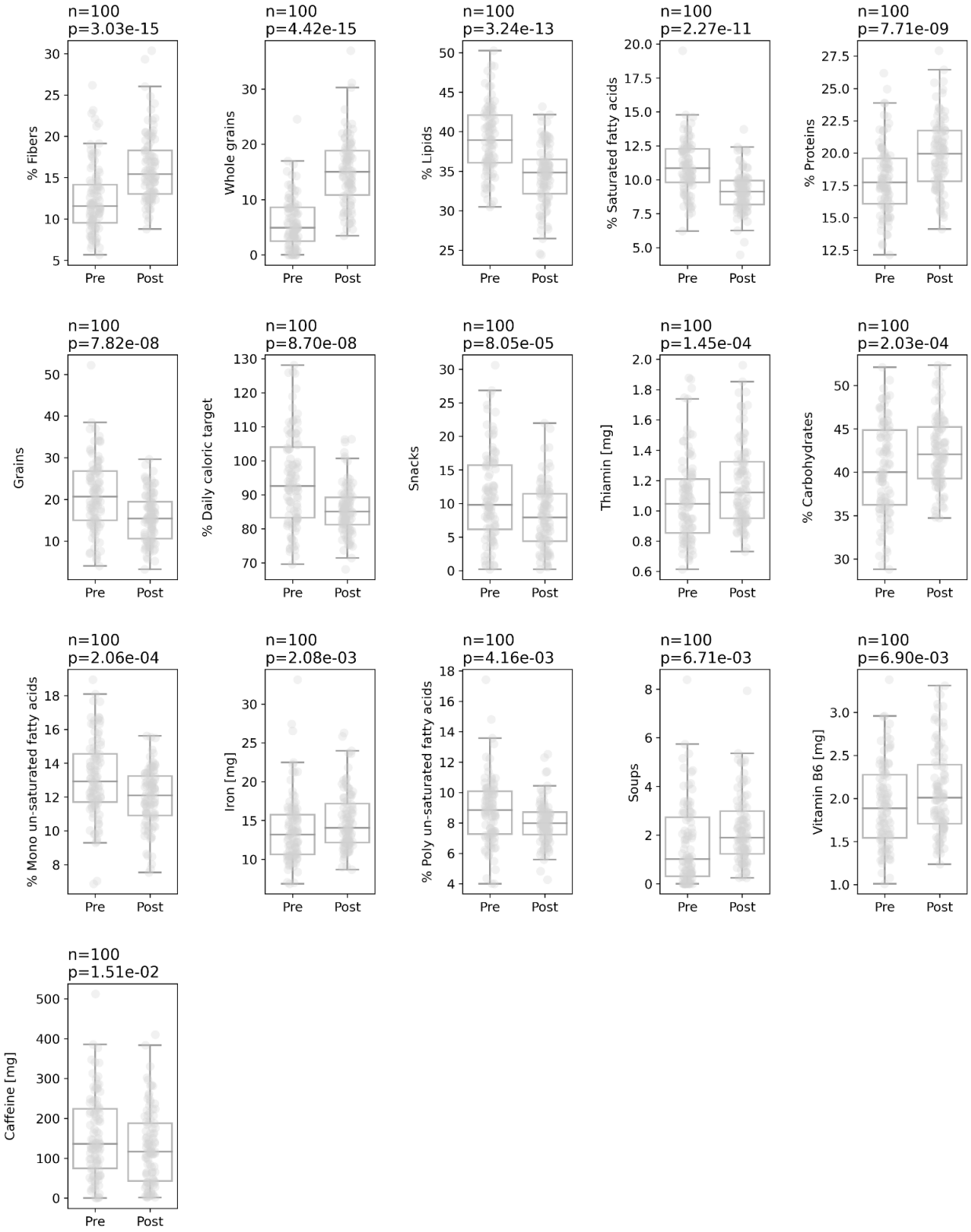
Supplementary Information

a Diet - PPT diet

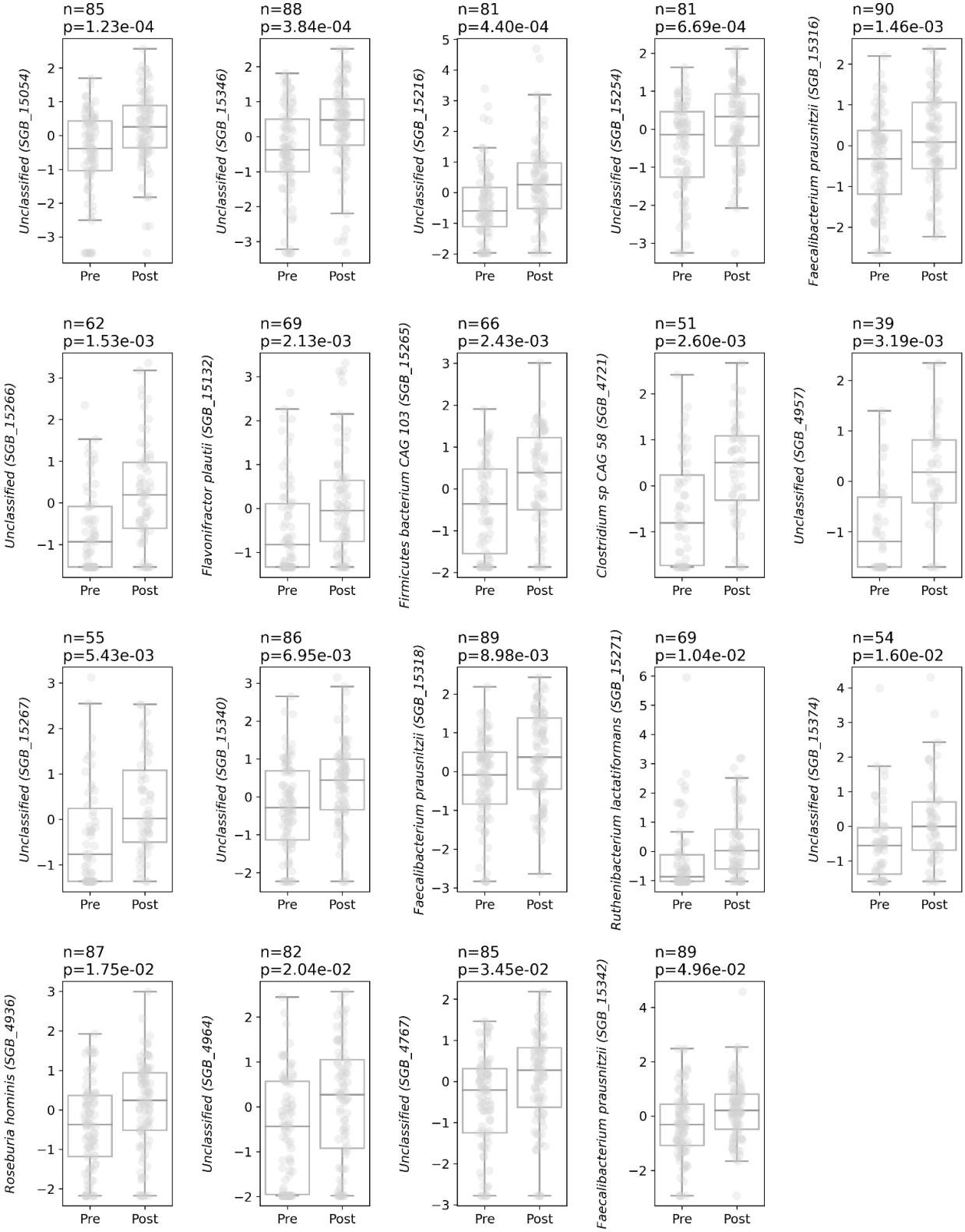



n=99
p=1.07e-04
Poultry
n=99
p=5.00e-04
Caffeine [mg]
n=99
p=6.37e-04
Red meat
n=99
p=2.61e-03
Vitamin C [mg]
n=99
p=4.35e-03
Seafood
n=99
p=4.42e-03
Drinks
n=99
p=6.96e-03
Vitamin B12 [ug]
n=99
p=1.07e-02
Vitamin B6 [mg]
n=99
p=1.83e-02
Whole grains
n=99
p=2.60e-02
Vitamin E [mg]
n=99
p=3.77e-02
Calcium [mg]
Pre
Post

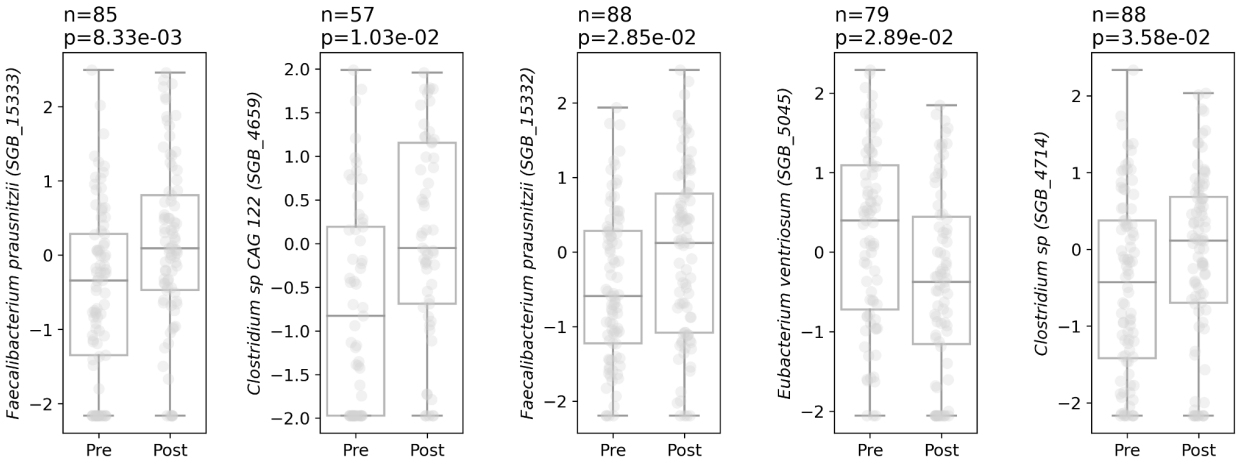
b Diet - MED diet

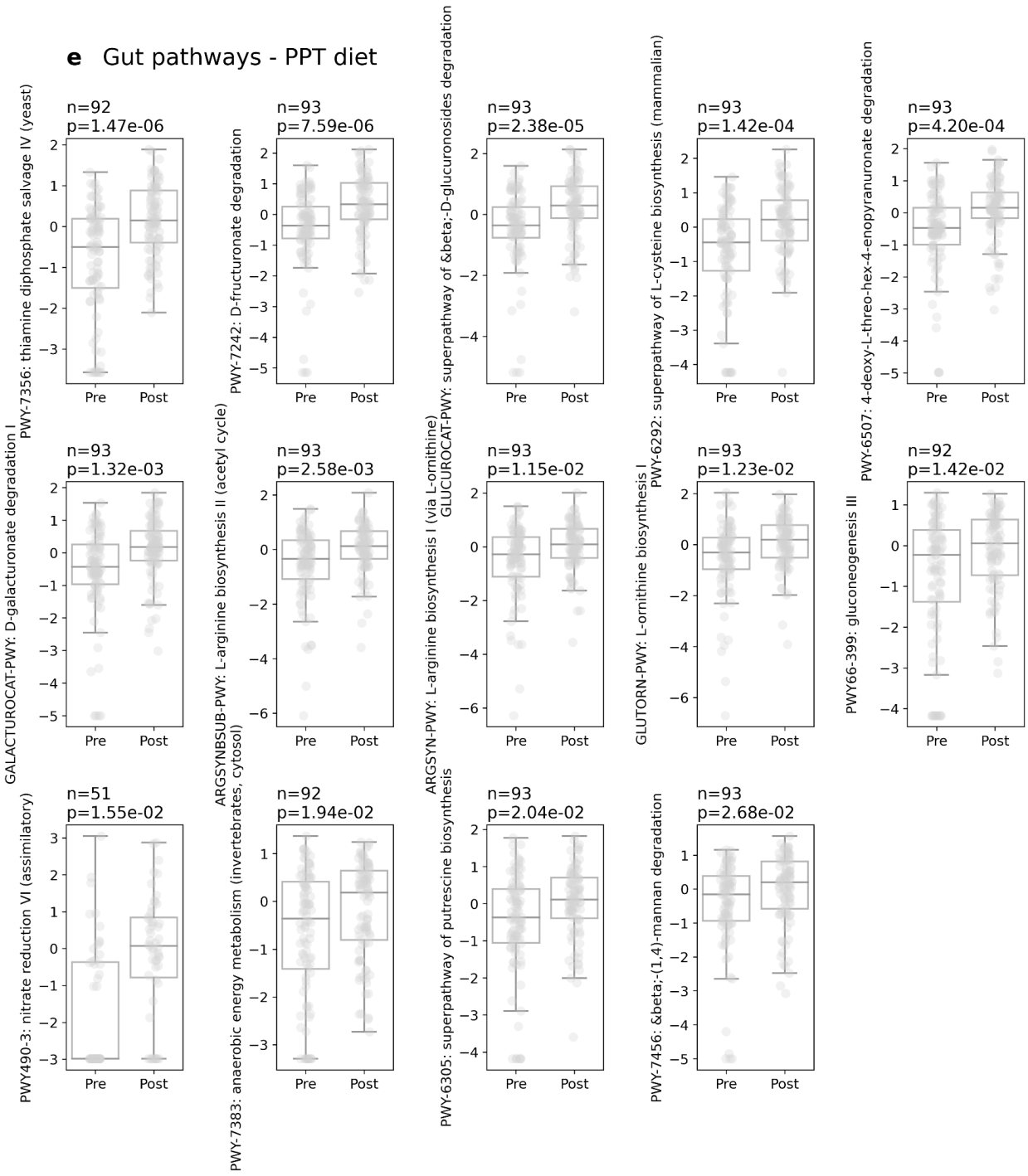


c Gut species - PPT diet



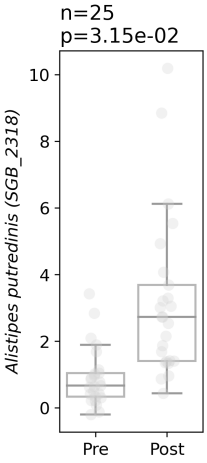
d Gut species - MED diet



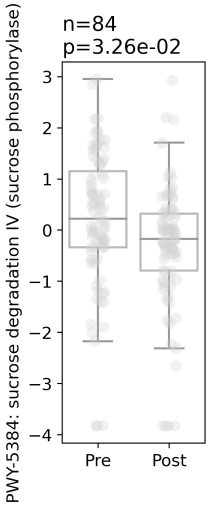

e Gut pathways - PPT diet
GALACTUROCAT-PWY: D-galacturonate degradation I
n=92
p=1.47e-06
PWY-7356: thiamine diphosphate salvage IV (yeast)
n=93
p=7.59e-06
PWY-7242: D-fructuronate degradation
n=93
p=2.38e-05
ARGSYNBSUB-PWY: L-arginine biosynthesis II (acetyl cycle)
n=93
p=1.32e-03
n=93
p=2.58e-03
ARGSYN-PWY: L-arginine biosynthesis I (via L-ornithine)
GLUCUROCAT-PWY: superpathway of β-D-glucuronosides degradation
n=93
p=1.15e-02
GLUTORN-PWY: L-ornithine biosynthesis I
n=93
p=1.42e-03
PWY-6292: superpathway of L-cysteine biosynthesis (mammalian)
n=93
p=1.23e-02
PWY66-399: gluconeogenesis III
n=92
p=4.20e-04
n=92
p=1.42e-02
PWY490-3: nitrate reduction VI (assimilatory)
n=51
p=1.55e-02
PWY-7383: anaerobic energy metabolism (invertebrates, cytosol)
n=92
p=1.94e-02
PWY-6305: superpathway of putrescine biosynthesis
n=93
p=2.04e-02
PWY-7456: β-(1,4)-mannan degradation
n=93
p=2.68e-02
Pre
Post

f Gut pathways - MED diet

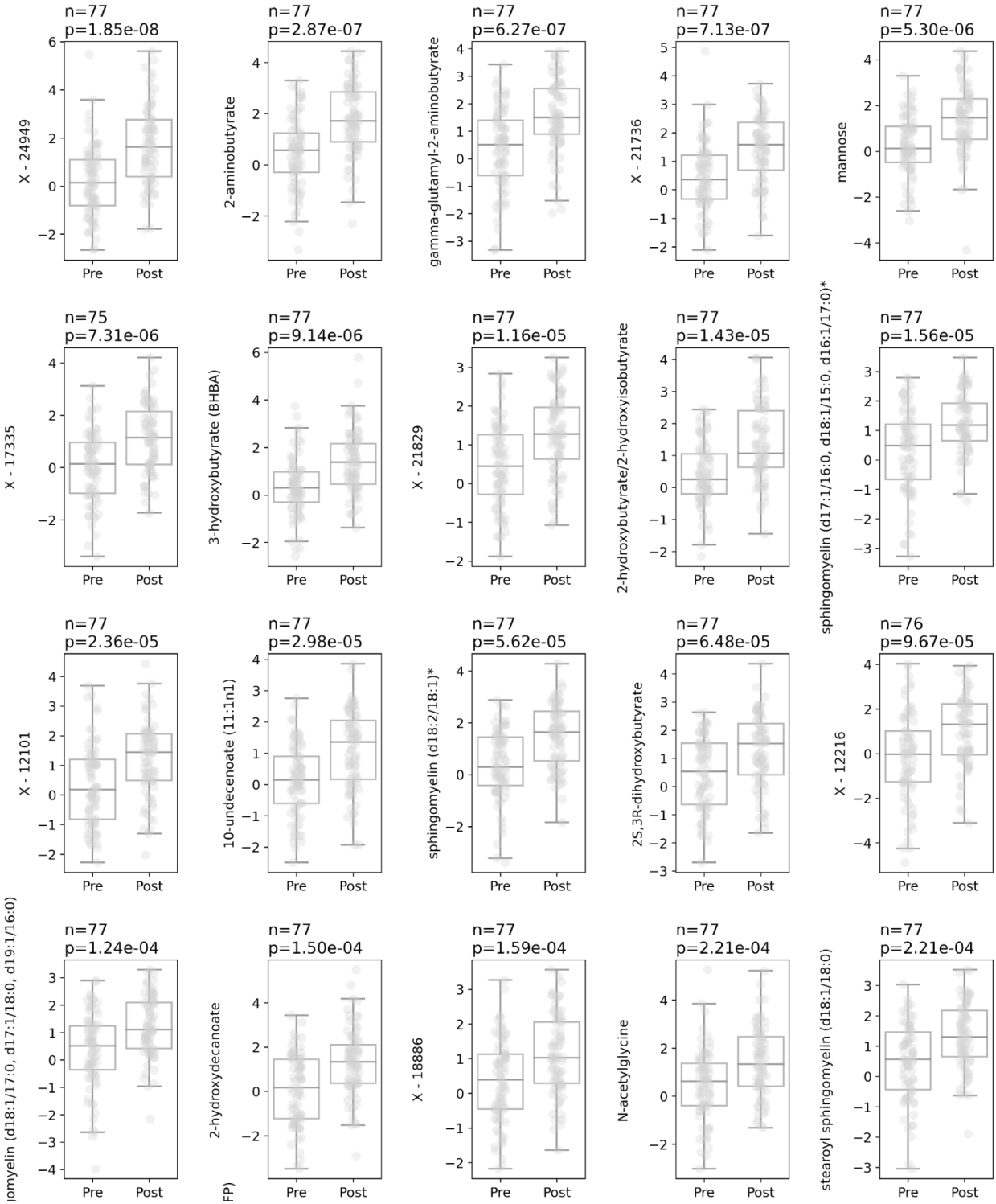
g Oral species - MED diet



h Oral pathways - PPT diet

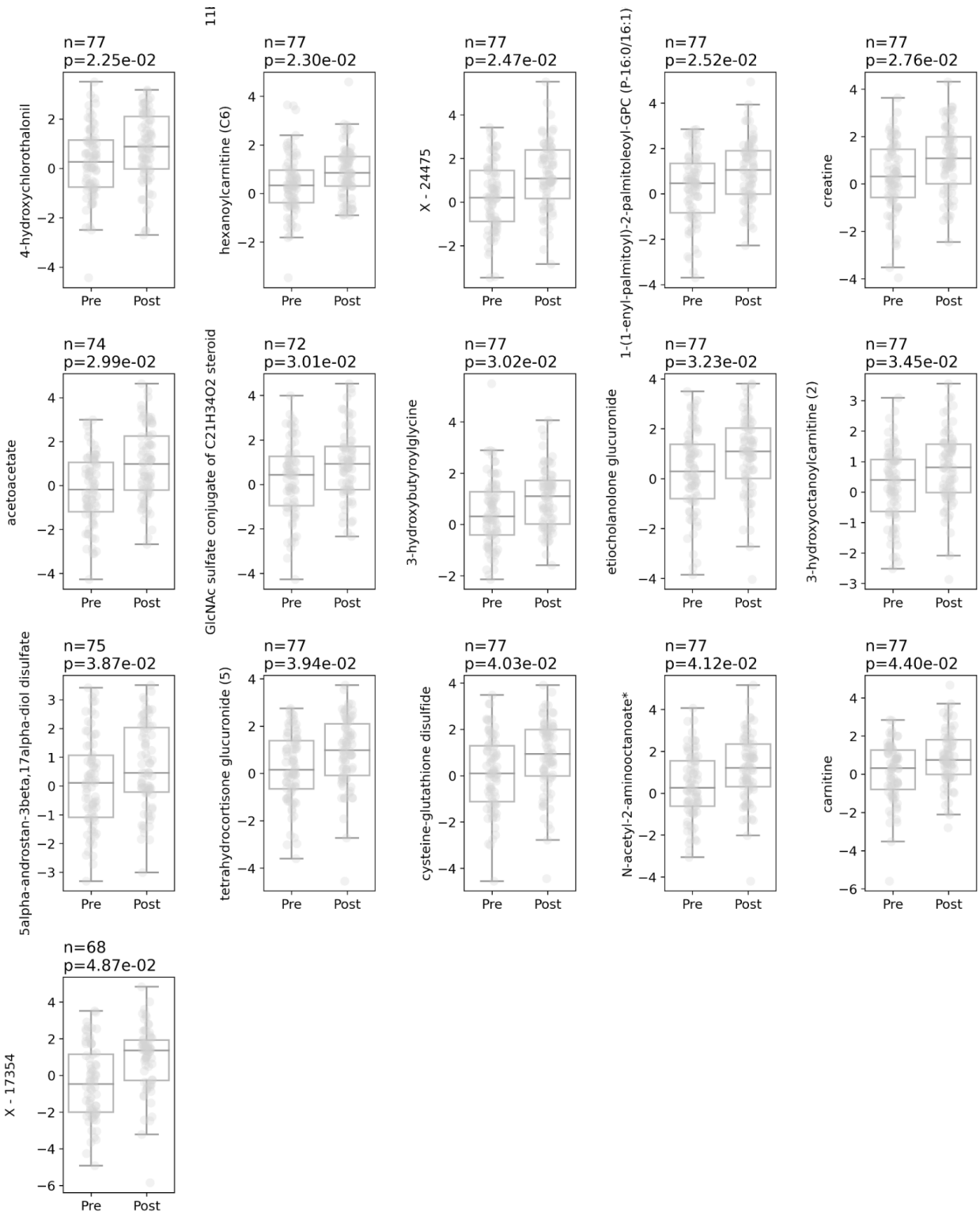


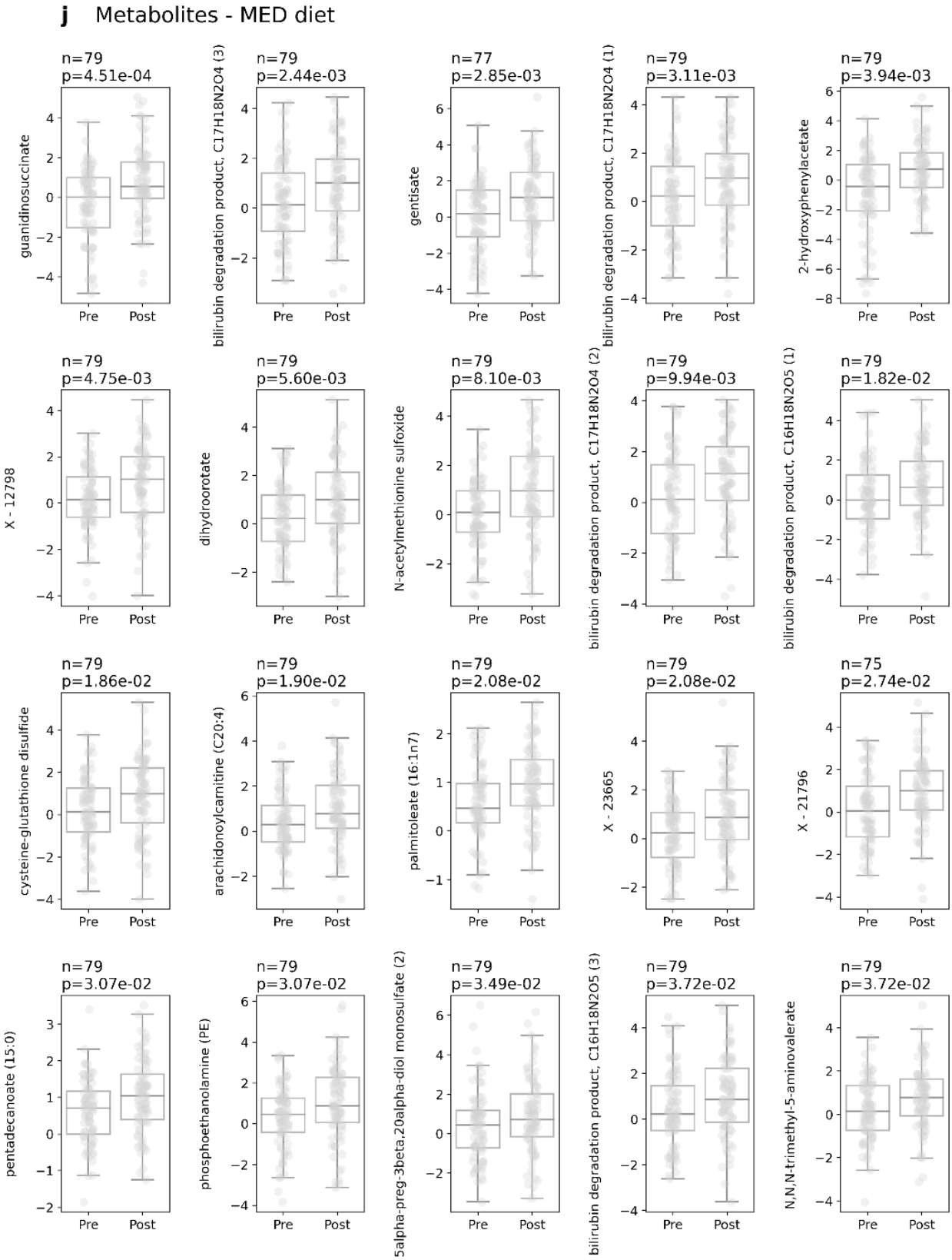
i Metabolites - PPT diet

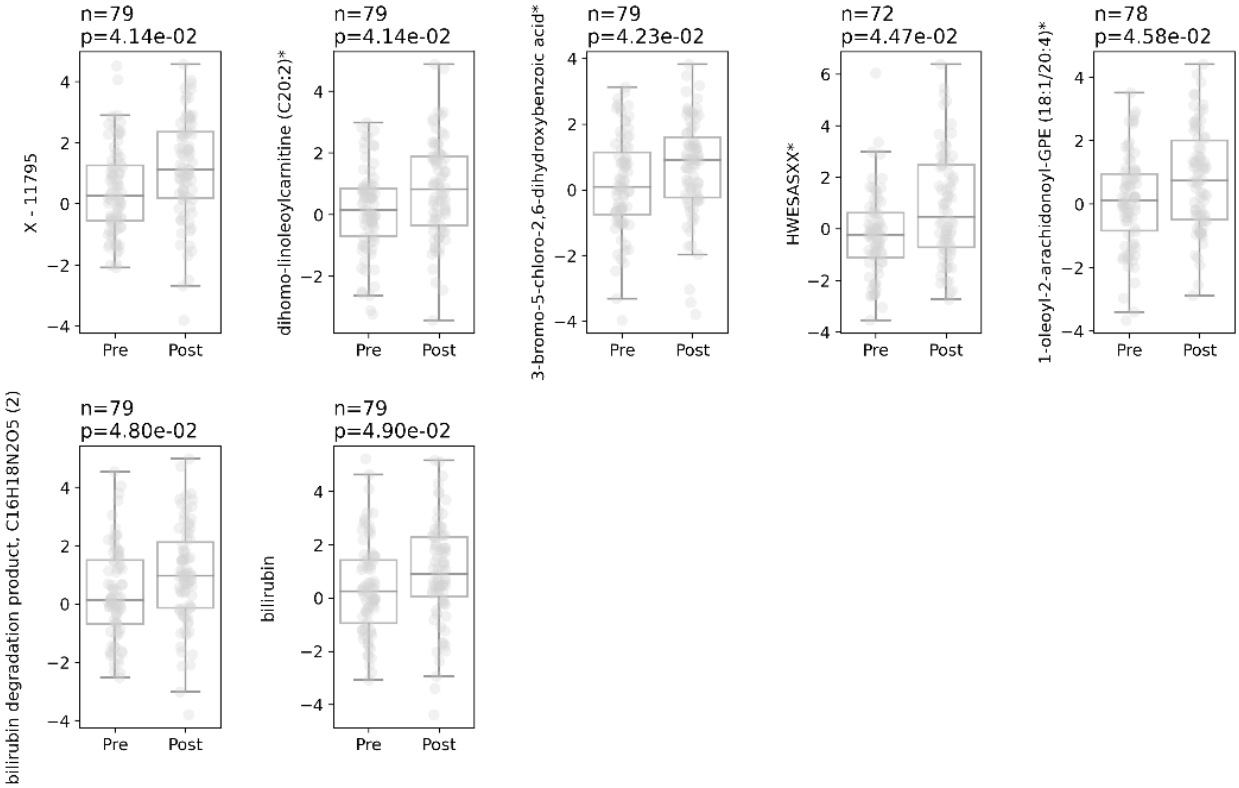


sphing
X - 12798
n=77
p=2.27e-04
3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMP
n=77
p=2.60e-04
hydroxypalmitoyl sphingomyelin (d18:1/16:0(OH))
n=77
p=2.67e-04
palmitoyl dihydrosphingomyelin (d18:0/16:0)*
n=77
p=2.67e-04
3,5-dichloro-2,6-dihydroxybenzoic acid
n=77
p=2.90e-04
sphingomyelin (d18:1/20:0, d16:1/22:0)*
n=77
p=3.32e-04
2-hydroxyphenylacetate
n=76
p=5.00e-04
X - 11315
n=77
p=5.36e-04
sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19:1/24:0)*
n=77
p=5.51e-04
3-hydroxyhexanoate
n=77
p=5.81e-04
X - 23665
n=77
p=6.80e-04
sphingomyelin (d18:1/20:1, d18:2/20:0)*
n=77
p=9.30e-04
hexanoylglutamine
n=77
p=1.20e-03
1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2)*
n=77
p=1.33e-03
glutamine conjugate of C6H10O2 (2)*
n=77
p=1.48e-03
3-hydroxyoctanoate
n=77
p=1.52e-03
X - 21661
n=77
p=1.56e-03
3-bromo-5-chloro-2,6-dihydroxybenzoic acid*
n=77
p=1.68e-03
3-aminoisobutyrate
n=77
p=1.68e-03
X - 11849
n=77
p=2.27e-03
gomyelin (d18:1/22:1, d18:2/22:0, d16:1/24:1)*
n=77
p=2.64e-03
1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)*
n=77
p=3.14e-03
(R)-3-hydroxybutyrylcarnitine
n=77
p=3.30e-03
X - 21607
n=77
p=3.55e-03
2-aminooctanoate
n=77
p=3.73e-03
Pre
Post

sp
n=77
p=3.83e-03
X - 11858
n=77
p=3.92e-03
3-hydroxy-2-ethylpropionate
n=67
p=4.13e-03
X - 13729
n=77
p=4.22e-03
X - 11470
n=77
p=4.43e-03
2-ketocaprylate
n=75
p=5.24e-03
anthranilate
n=76
p=5.27e-03
guanidinosuccinate
n=77
p=5.93e-03
sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)*
n=77
p=7.02e-03
palmitoyl-linoleoyl-glycerol (16:0/18:2) [1]*
n=77
p=7.54e-03
lignoceroylcarnitine (C24)*
n=77
p=7.72e-03
palmitoyl sphingomyelin (d18:1/16:0)
n=77
p=8.90e-03
(14 or 15)-methylpalmitate (a17:0 or i17:0)
n=77
p=9.79e-03
tricosanoyl sphingomyelin (d18:1/23:0)*
n=77
p=1.00e-02
1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (P-16:0/18:2)*
n=77
p=1.10e-02
palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*
n=77
p=1.27e-02
X - 11847
n=77
p=1.36e-02
1-(1-enyl-stearoyl)-2-linoleoyl-GPE (P-18:0/18:2)*
n=71
p=1.53e-02
X - 22509
n=77
p=1.63e-02
3-hydroxyisobutyrate
n=77
p=1.75e-02
branched-chain, straight-chain, or cyclopropyl 12:1 fatty acid*
n=77
p=1.79e-02
phosphocholine
n=72
p=2.02e-02
11beta-hydroxyetiocholanolone glucuronide*
n=77
p=2.06e-02
phytanate
n=77
p=2.06e-02
undecenoylcarnitine (C11:1)
n=77
p=2.15e-02
pregnenediol sulfate (C21H34O5S)*
Pre
Post
6:1)*


4-hydroxychlorothalonil
n=77
p=2.25e-02
11l
hexanoylcarnitine (C6)
n=77
p=2.30e-02
X - 24475
n=77
p=2.47e-02
1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)
n=77
p=2.52e-02
creatine
n=77
p=2.76e-02
acetoacetate
n=74
p=2.99e-02
GlcNAc sulfate conjugate of C21H34O2 steroid
n=72
p=3.01e-02
3-hydroxybutyroylglycine
n=77
p=3.02e-02
etiocholanolone glucuronide
n=77
p=3.23e-02
3-hydroxyoctanoylcarnitine (2)
n=77
p=3.45e-02
5alpha-androstan-3beta,17alpha-diol disulfate
n=75
p=3.87e-02
tetrahydrocortisone glucuronide (5)
n=77
p=3.94e-02
cysteine-glutathione disulfide
n=77
p=4.03e-02
N-acetyl-2-aminooctanoate*
n=77
p=4.12e-02
carnitine
n=77
p=4.40e-02
X - 17354
n=68
p=4.87e-02
Pre
Post


j Metabolites - MED diet
guanidinosuccinate
n=79
p=4.51e-04
bilirubin degradation product, C17H18N2O4 (3)
n=79
p=2.44e-03
gentisate
n=77
p=2.85e-03
bilirubin degradation product, C17H18N2O4 (1)
n=79
p=3.11e-03
2-hydroxyphenylacetate
n=79
p=3.94e-03
X - 12798
n=79
p=4.75e-03
dihydroorotate
n=79
p=5.60e-03
N-acetylmethionine sulfoxide
n=79
p=8.10e-03
bilirubin degradation product, C17H18N2O4 (2)
n=79
p=9.94e-03
bilirubin degradation product, C16H18N2O5 (1)
n=79
p=1.82e-02
cysteine-glutathione disulfide
n=79
p=1.86e-02
arachidonoylcarnitine (C20:4)
n=79
p=1.90e-02
palmitoleate (16:1n7)
n=79
p=2.08e-02
X - 23665
n=79
p=2.08e-02
X - 21796
n=75
p=2.74e-02
pentadecanoate (15:0)
n=79
p=3.07e-02
phosphoethanolamine (PE)
n=79
p=3.07e-02
5alpha-preg-3beta,20alpha-diol monosulfate (2)
n=79
p=3.49e-02
bilirubin degradation product, C16H18N2O5 (3)
n=79
p=3.72e-02
N,N,N-trimethyl-5-aminovalerate
n=79
p=3.72e-02
Pre
Post


n=79
p=4.14e-02
X - 11795
n=79
p=4.14e-02
dihomo-linoleoylcarnitine (C20:2)*
n=79
p=4.23e-02
3-bromo-5-chloro-2,6-dihydroxybenzoic acid*
n=72
p=4.47e-02
HWESASXX*
n=78
p=4.58e-02
1-oleoyl-2-arachidonoyl-GPE (18:1/20:4)*
n=79
p=4.80e-02
bilirubin degradation product, C16H18N2O5 (2)
n=79
p=4.90e-02
bilirubin
Pre
Post

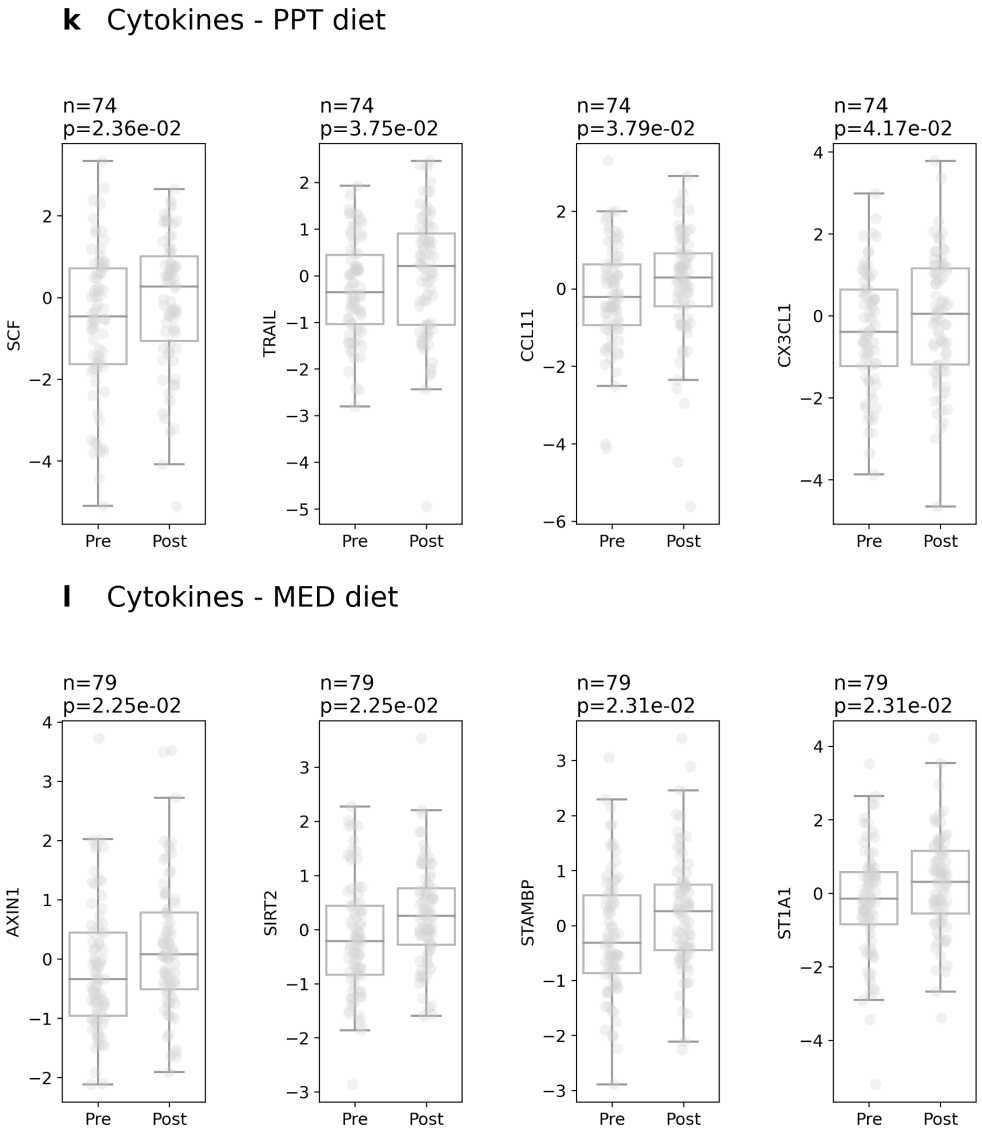
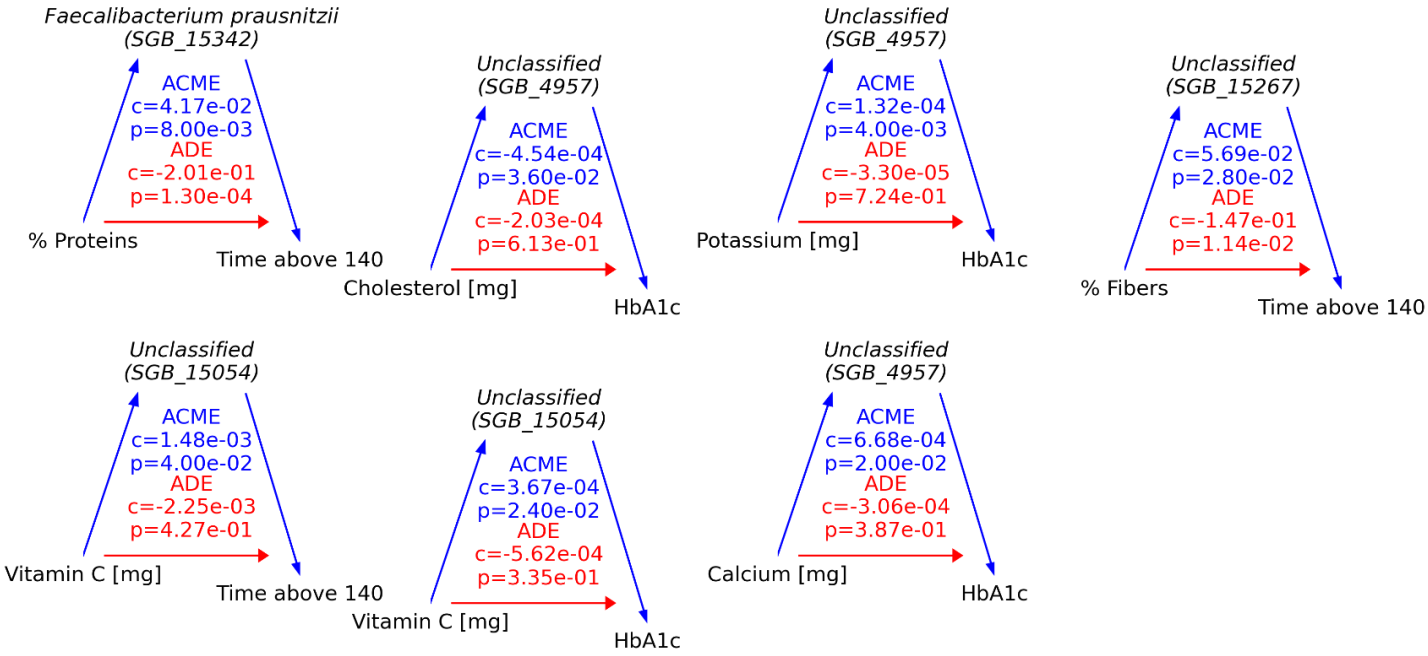


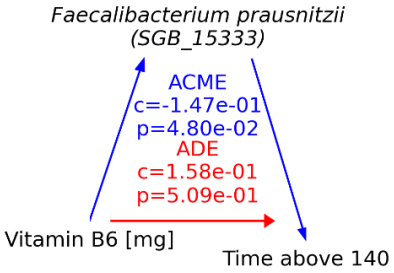
Figure S1. The PPT diet had bigger effect on the microbiome and metabolites than the MED diet

Features at baseline versus the end of the intervention that significantly changed (Bonferroni corrected p<0.05, two-sided Wilcoxon paired signed-rank test or false discovery rate correction solely in the cytokines). Units are standard deviations over the log10 transformed data (Methods). p - p-value, n - number of participants compared. Boxes show the quartiles of the data (0.25, 0.50, 0.75) while the whiskers extend to 1.5 of the inter quartile range, points beyond the whiskers are considered to be outliers. The title specifies the type of features (diet, microbial species, microbial pathways, metabolites or cytokines) and the diet group ("PPT" or "MED" diet). There was no significant difference between the two diet groups at baseline in any of the 2,803 molecular features tested (Bonferroni corrected p>0.05, two-sided Mann-Whitney U test). Source data are provided as a Source Data file.

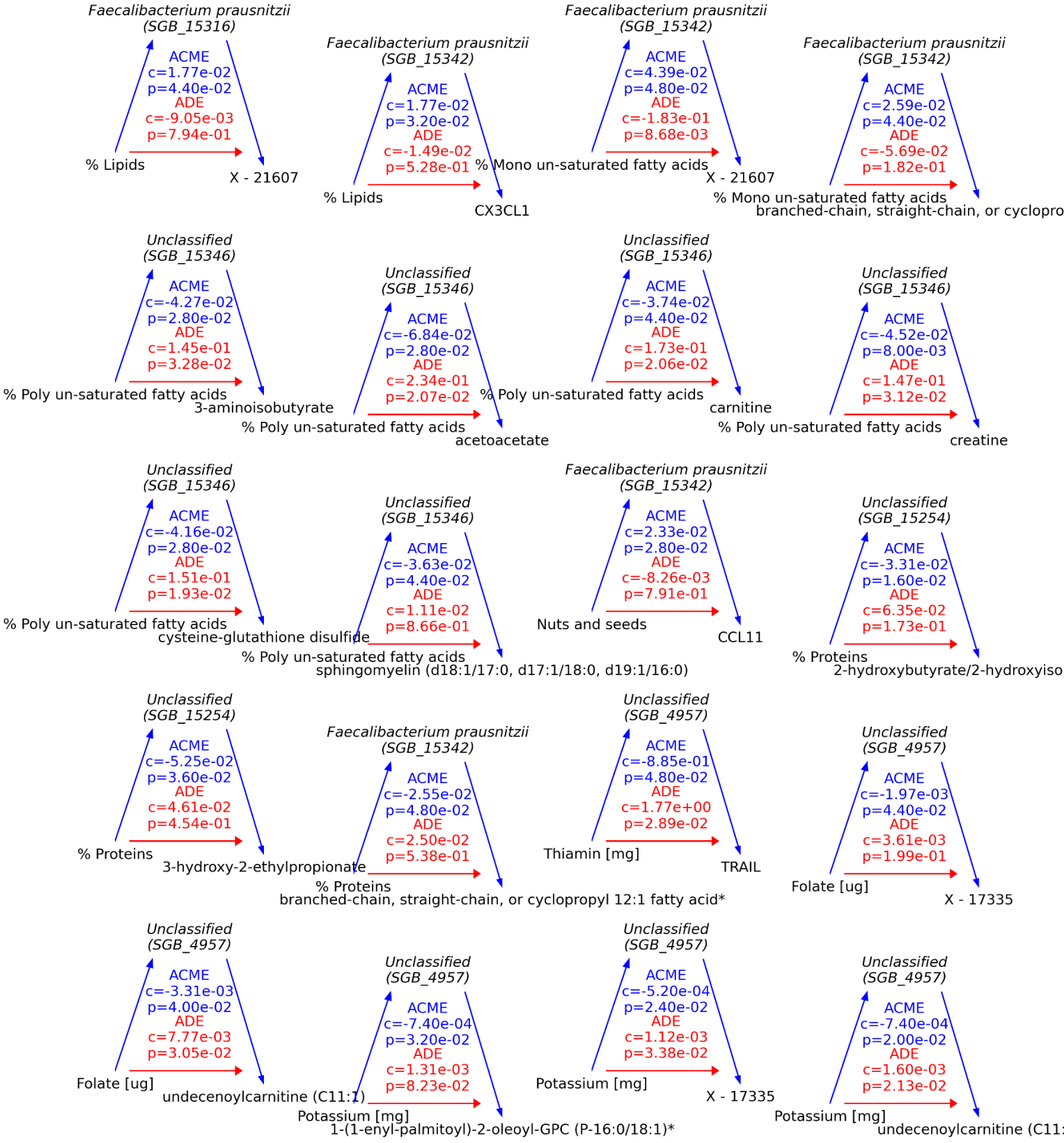
a PPT diet - Microbial species - Glycemic measurements

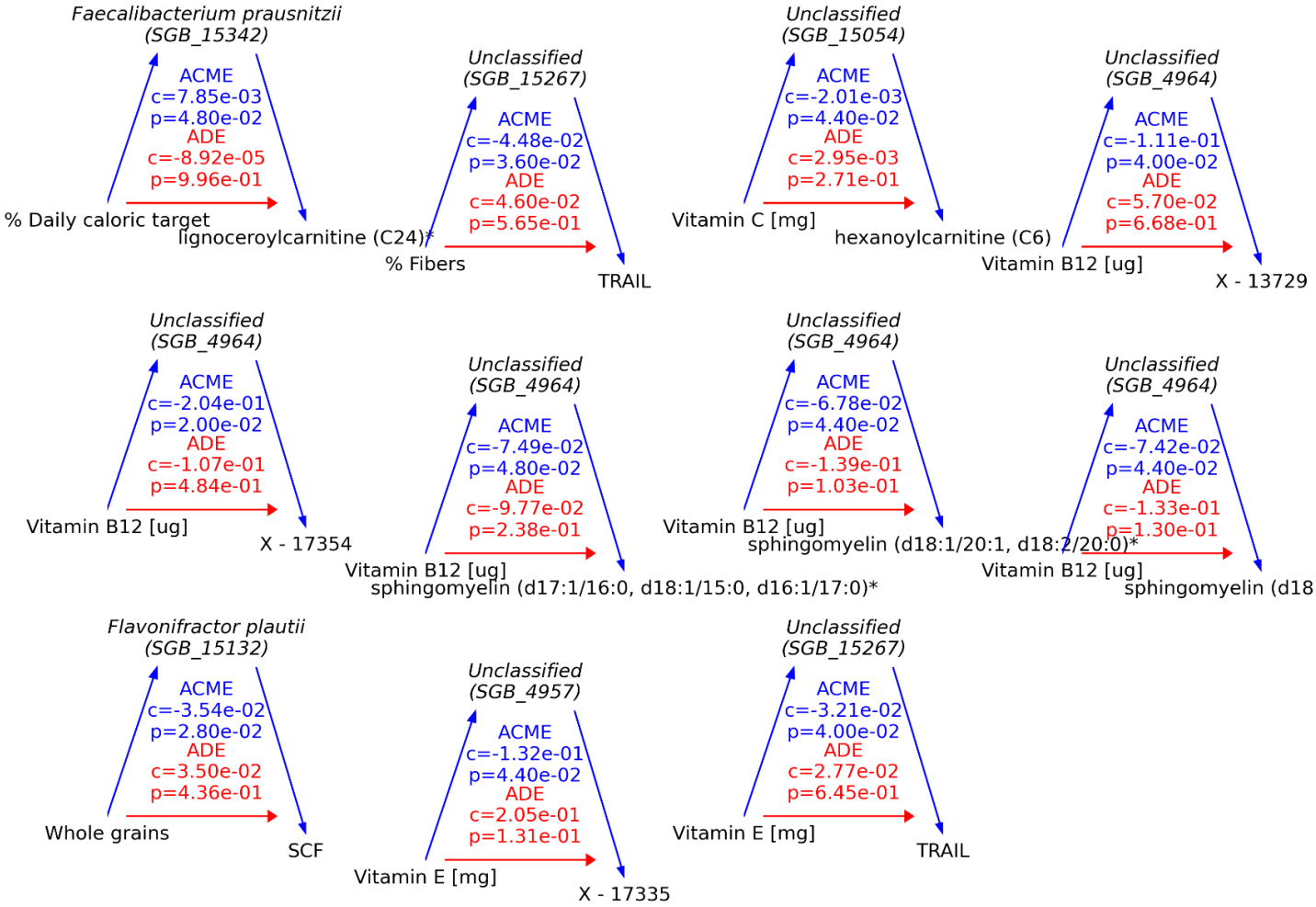


b MED diet - Microbial species - Glycemic measurements

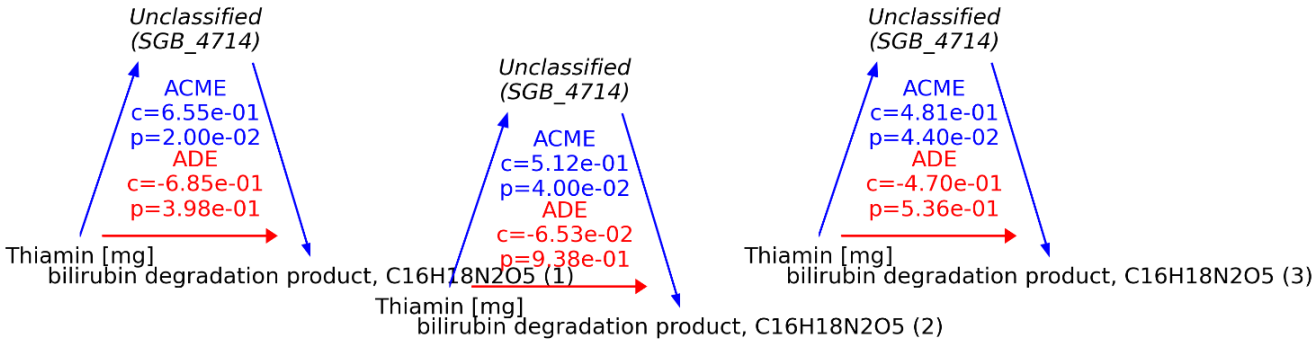


c PPT diet - Microbial species - Metabolites and Cytokines

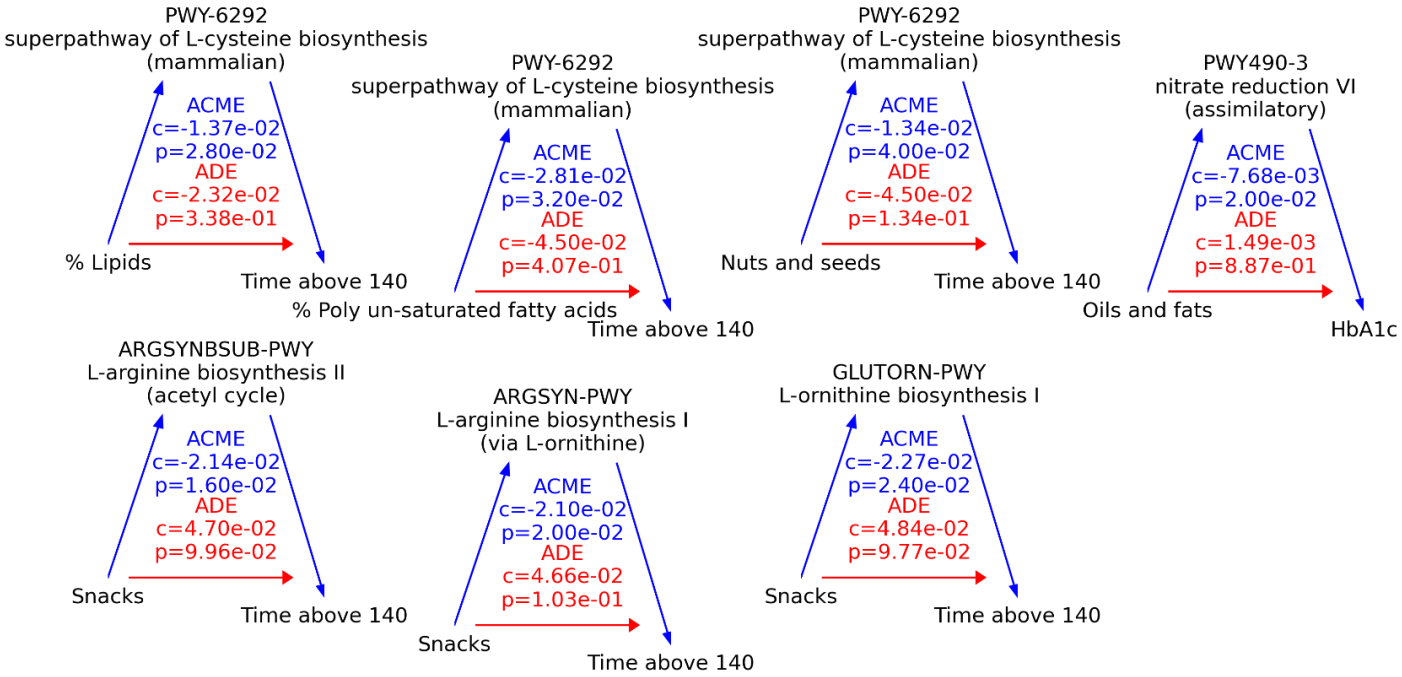




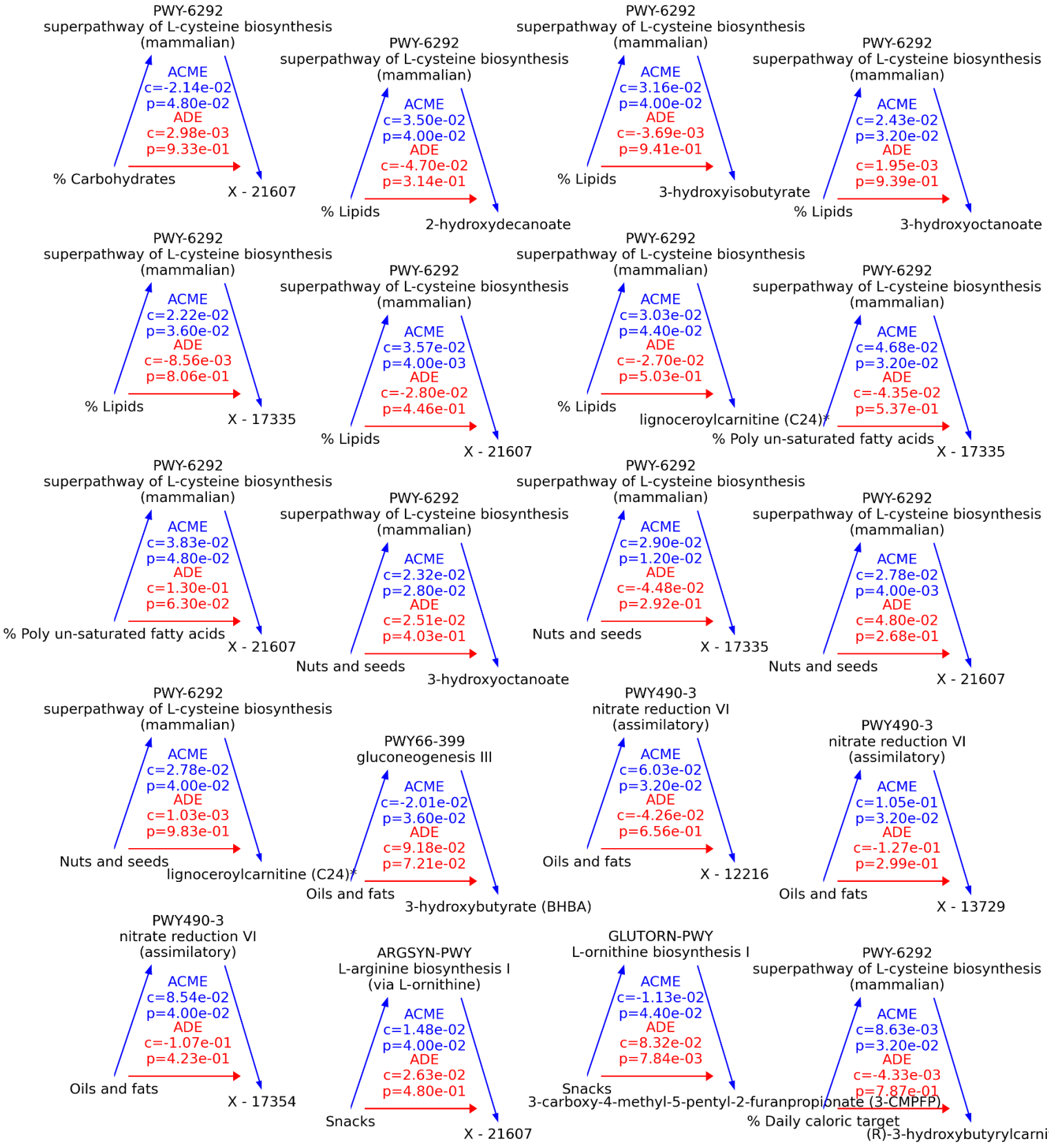
d MED diet - Microbial species - Metabolites and Cytokines

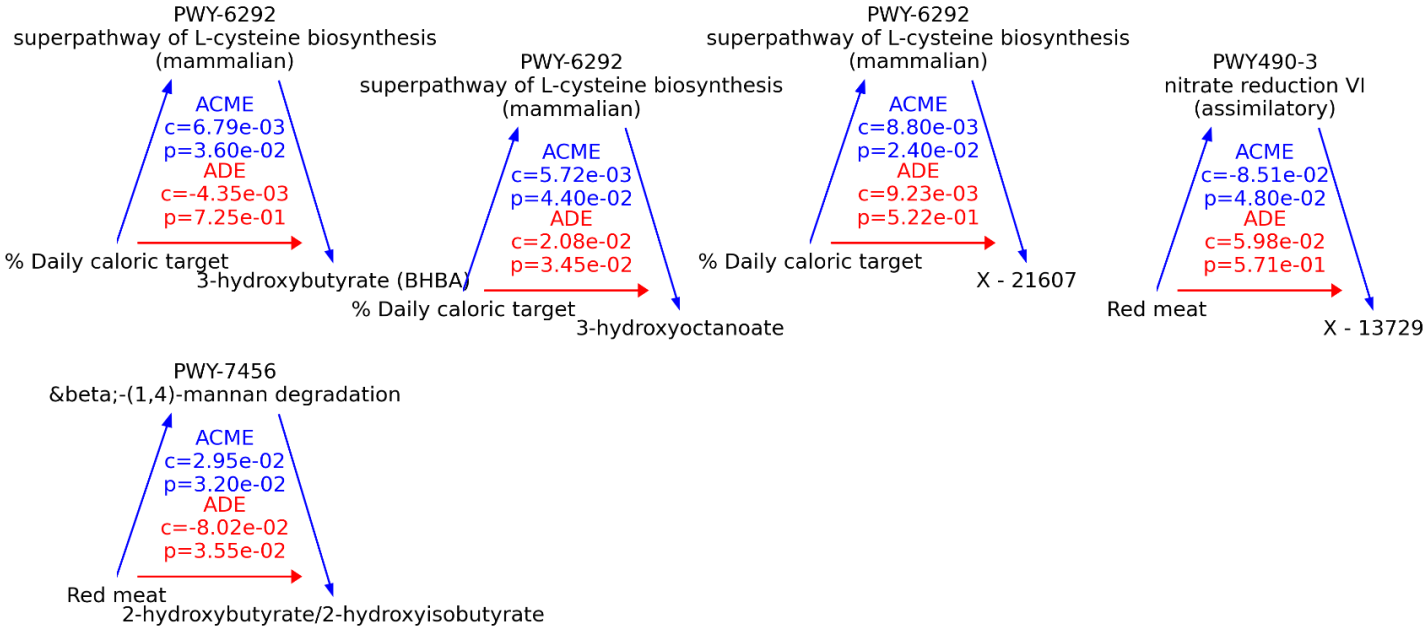


e PPT diet - Microbial pathways - Glycemic measurements

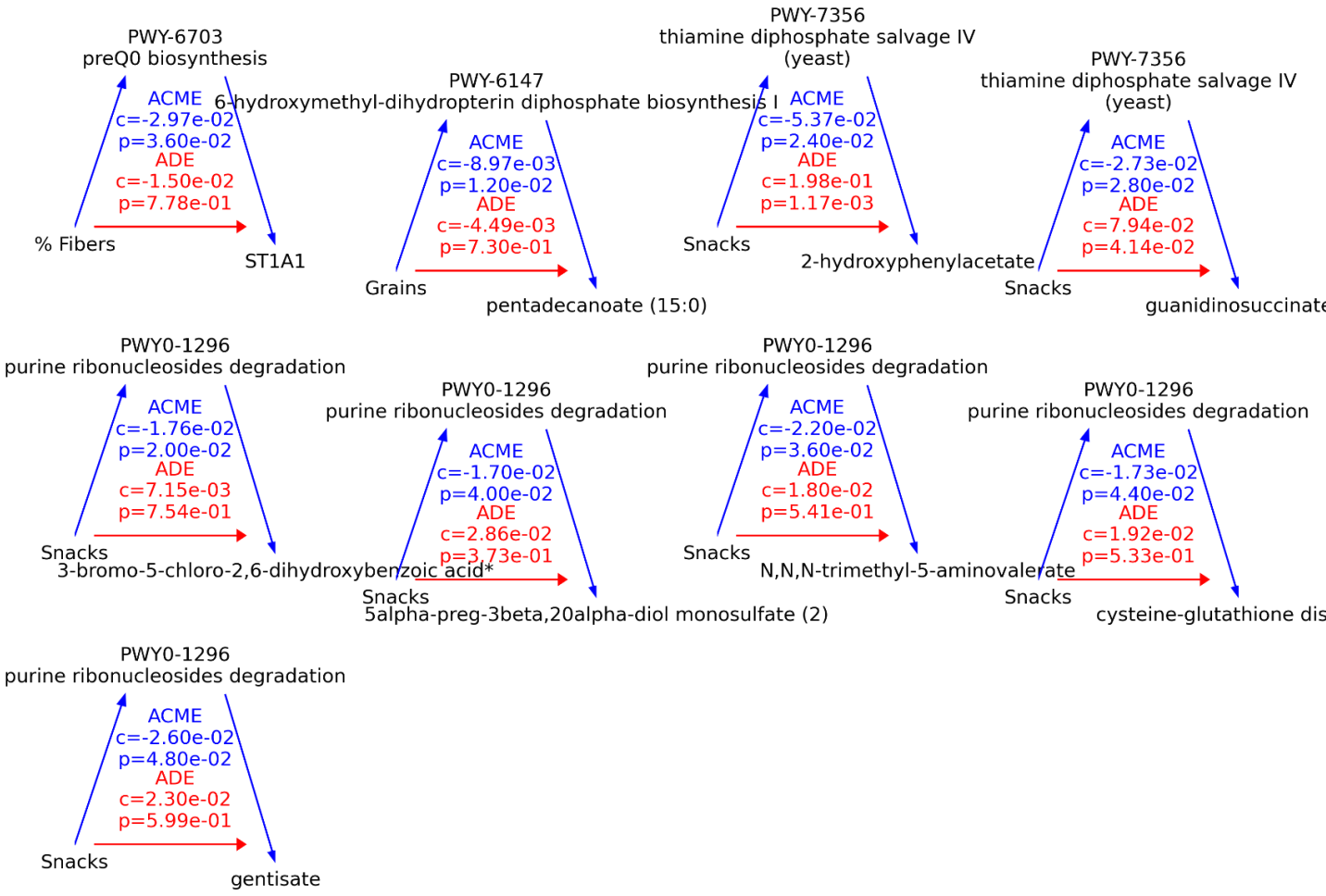


f PPT diet - Microbial pathways - Metabolites and Cytokines

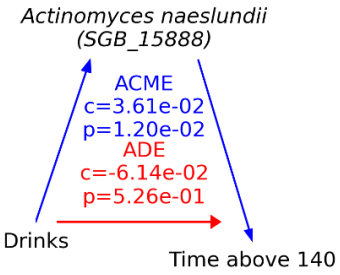



PWY-6292
superpathway of L-cysteine biosynthesis
(mammalian)
ACME
c=6.79e-03
p=3.60e-02
ADE
c=-4.35e-03
p=7.25e-01
% Daily caloric target
3-hydroxybutyrate (BHBA)
PWY-6292
superpathway of L-cysteine biosynthesis
(mammalian)
ACME
c=5.72e-03
p=4.40e-02
ADE
c=2.08e-02
p=3.45e-02
% Daily caloric target
3-hydroxyoctanoate
PWY-6292
superpathway of L-cysteine biosynthesis
(mammalian)
ACME
c=8.80e-03
p=2.40e-02
ADE
c=9.23e-03
p=5.22e-01
% Daily caloric target
X - 21607
PWY490-3
nitrate reduction VI
(assimilatory)
ACME
c=-8.51e-02
p=4.80e-02
ADE
c=5.98e-02
p=5.71e-01
Red meat
X - 13729
PWY-7456
β-(1,4)-mannan degradation
ACME
c=2.95e-02
p=3.20e-02
ADE
c=-8.02e-02
p=3.55e-02
Red meat
2-hydroxybutyrate/2-hydroxyisobutyrate

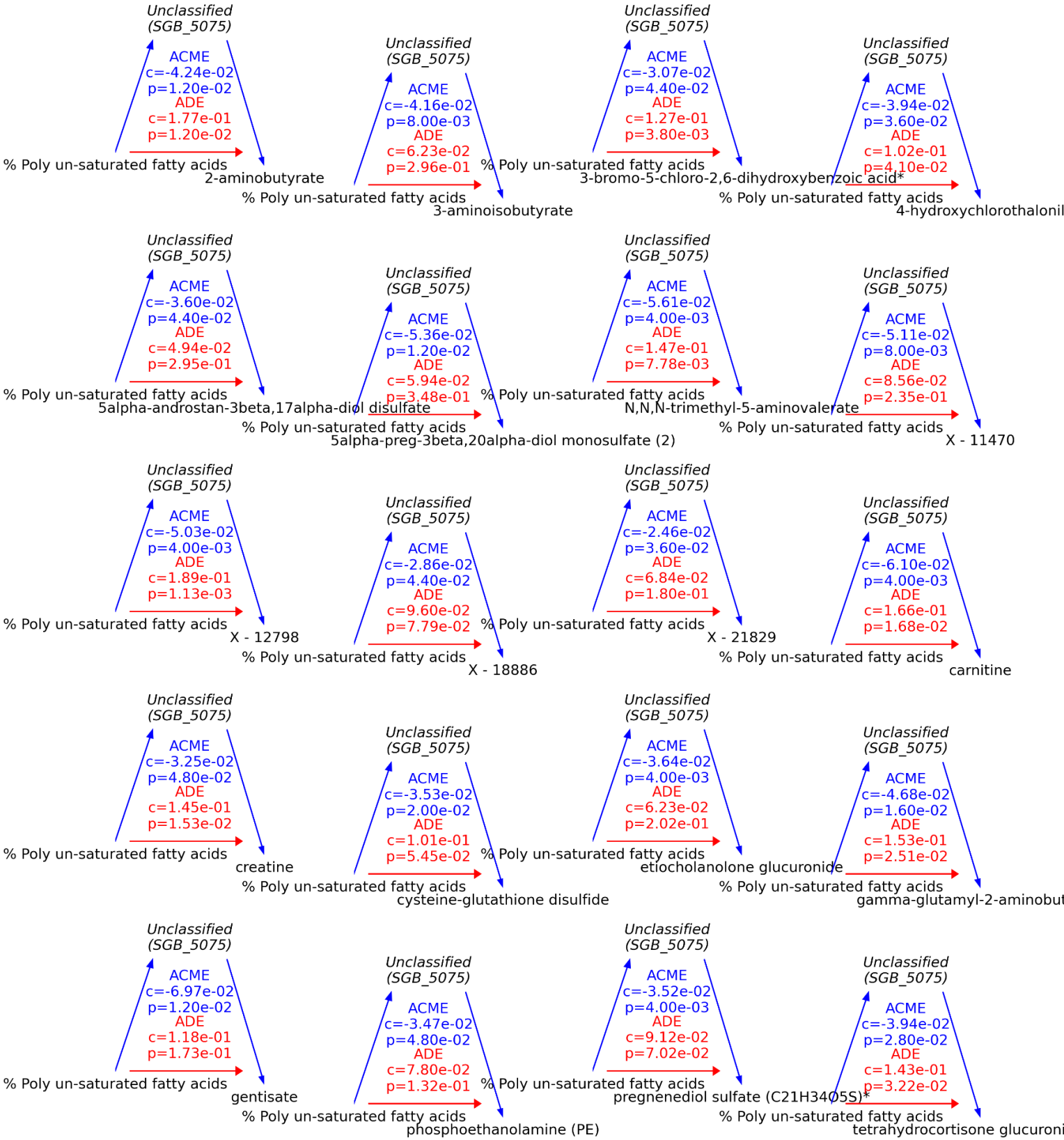
g MED diet - Microbial pathways - Metabolites and Cytokines

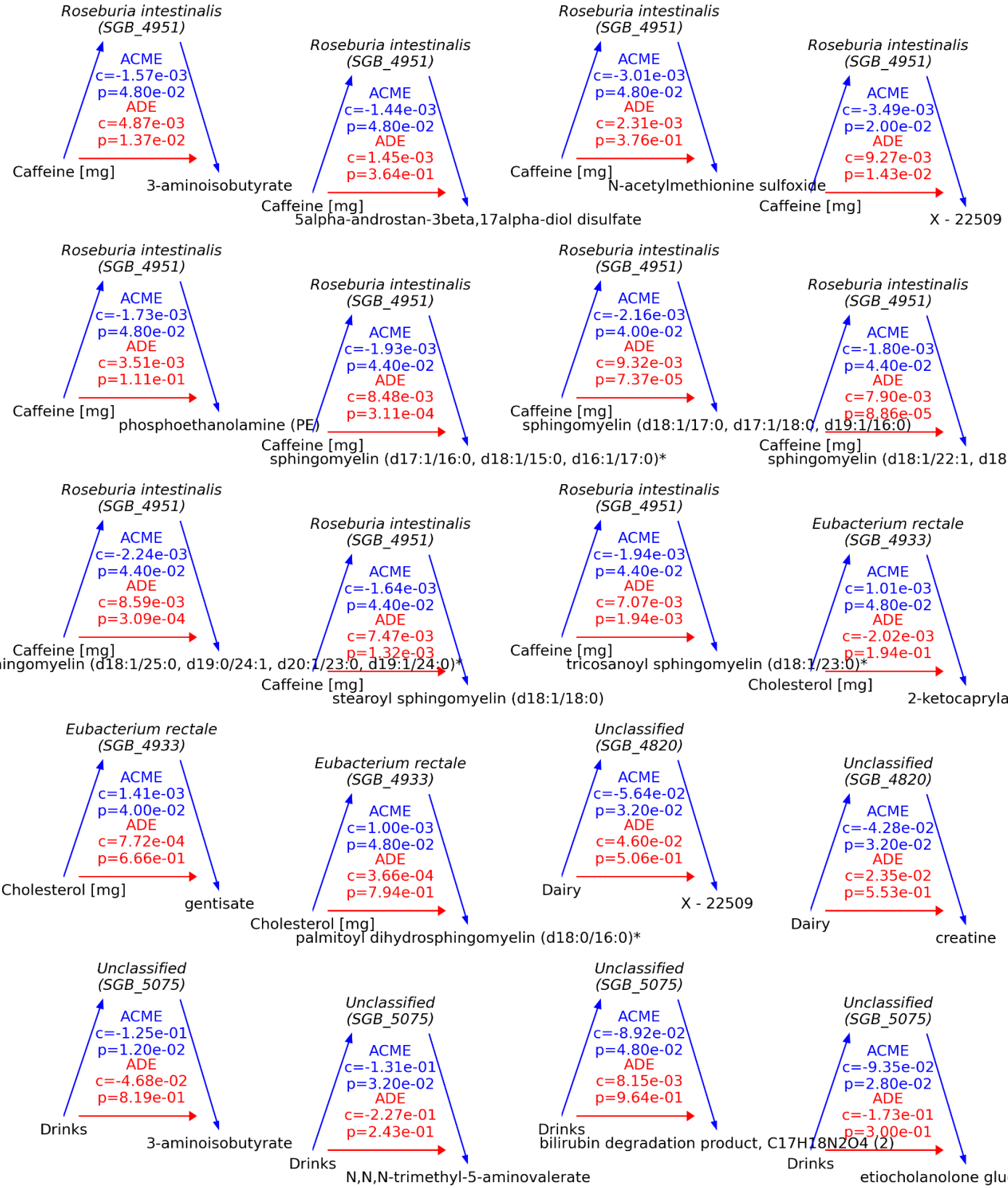


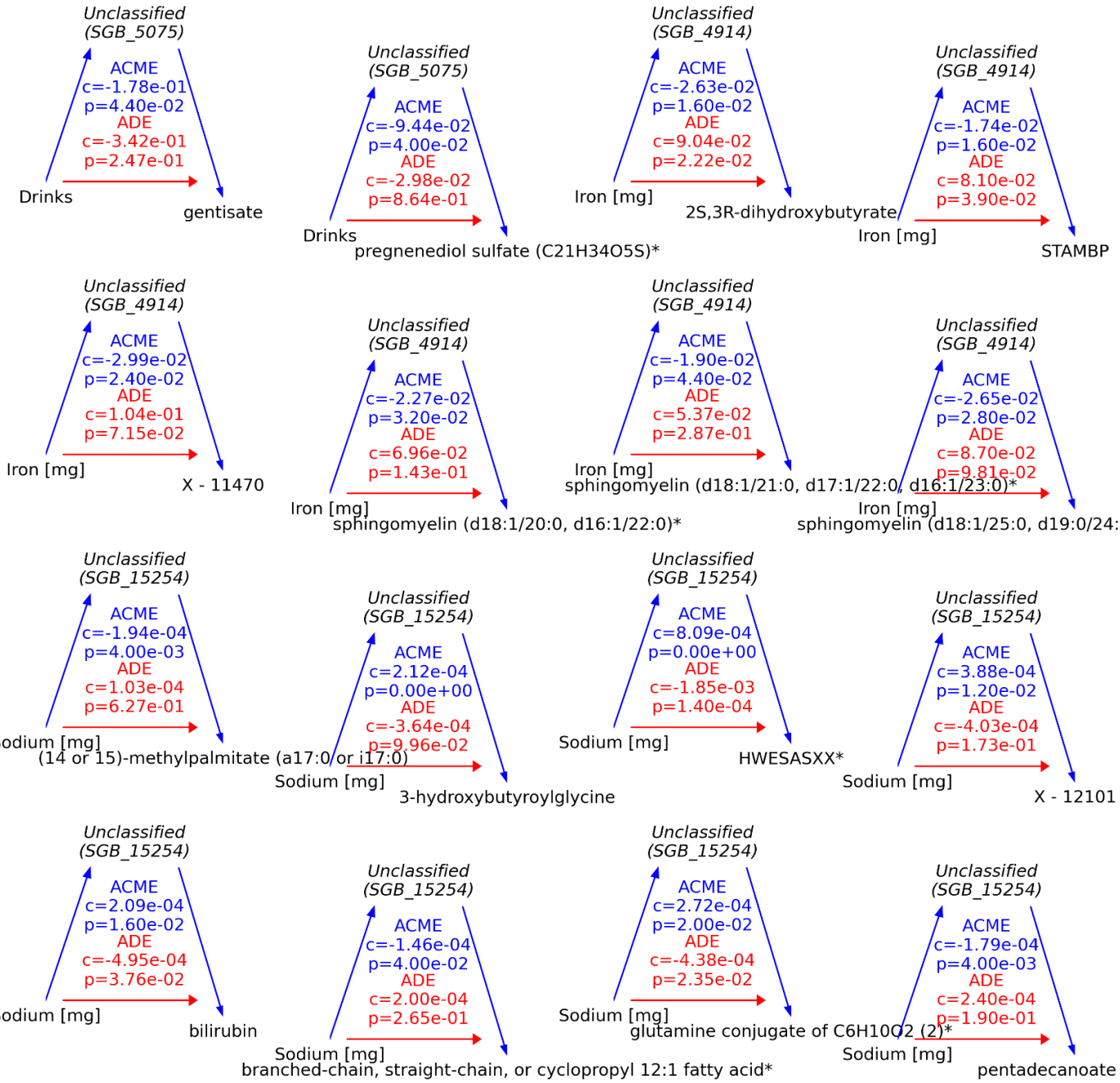
h Diet - Oral strains - Glycemic measurements



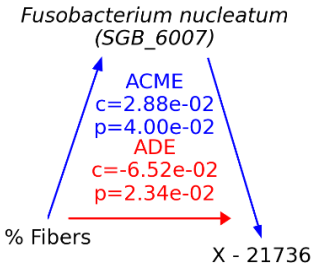
i Diet - Gut strains - Metabolites and Cytokines

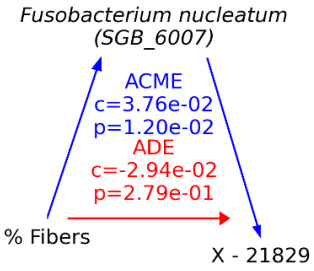


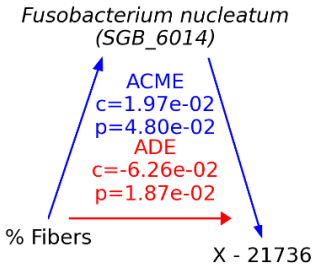

Roseburia intestinalis (SGB_4951)
ACME c=-1.57e-03 p=4.80e-02
ADE c=4.87e-03 p=1.37e-02
Caffeine [mg]
3-aminoisobutyrate
Roseburia intestinalis (SGB_4951)
ACME c=-1.44e-03 p=4.80e-02
ADE c=1.45e-03 p=3.64e-01
Caffeine [mg]
5alpha-androstan-3beta,17alpha-diol disulfate
Roseburia intestinalis (SGB_4951)
ACME c=-3.01e-03 p=4.80e-02
ADE c=2.31e-03 p=3.76e-01
Caffeine [mg]
N-acetylmethionine sulfoxide
Roseburia intestinalis (SGB_4951)
ACME c=-3.49e-03 p=2.00e-02
ADE c=9.27e-03 p=1.43e-02
Caffeine [mg]
X - 22509
Roseburia intestinalis (SGB_4951)
ACME c=-1.73e-03 p=4.80e-02
ADE c=3.51e-03 p=1.11e-01
Caffeine [mg]
phosphoethanolamine (PE)
Roseburia intestinalis (SGB_4951)
ACME c=-1.93e-03 p=4.40e-02
ADE c=8.48e-03 p=3.11e-04
Caffeine [mg]
sphingomyelin (d17:1/16:0, d18:1/15:0, d16:1/17:0)*
Roseburia intestinalis (SGB_4951)
ACME c=-2.16e-03 p=4.00e-02
ADE c=9.32e-03 p=7.37e-05
Caffeine [mg]
sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)
Roseburia intestinalis (SGB_4951)
ACME c=-1.80e-03 p=4.40e-02
ADE c=7.90e-03 p=8.86e-05
Caffeine [mg]
sphingomyelin (d18:1/22:1, d18:2/22:0, d
Roseburia intestinalis (SGB_4951)
ACME c=-2.24e-03 p=4.40e-02
ADE c=8.59e-03 p=3.09e-04
Caffeine [mg]
sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19:1/24:0)*
Roseburia intestinalis (SGB_4951)
ACME c=-1.64e-03 p=4.40e-02
ADE c=7.47e-03 p=1.32e-03
Caffeine [mg]
stearoyl sphingomyelin (d18:1/18:0)
Roseburia intestinalis (SGB_4951)
ACME c=-1.94e-03 p=4.40e-02
ADE c=7.07e-03 p=1.94e-03
Caffeine [mg]
tricosanoyl sphingomyelin (d18:1/23:0)*
Eubacterium rectale (SGB_4933)
ACME c=1.01e-03 p=4.80e-02
ADE c=-2.02e-03 p=1.94e-01
Cholesterol [mg]
2-ketocaprylate
Eubacterium rectale (SGB_4933)
ACME c=1.41e-03 p=4.00e-02
ADE c=7.72e-04 p=6.66e-01
Cholesterol [mg]
gentisate
Eubacterium rectale (SGB_4933)
ACME c=1.00e-03 p=4.80e-02
ADE c=3.66e-04 p=7.94e-01
Cholesterol [mg]
palmitoyl dihydrosphingomyelin (d18:0/16:0)*
Unclassified (SGB_4820)
ACME c=-5.64e-02 p=3.20e-02
ADE c=4.60e-02 p=5.06e-01
Dairy
X - 22509
Unclassified (SGB_4820)
ACME c=-4.28e-02 p=3.20e-02
ADE c=2.35e-02 p=5.53e-01
Dairy
creatine
Unclassified (SGB_5075)
ACME c=-1.25e-01 p=1.20e-02
ADE c=-4.68e-02 p=8.19e-01
Drinks
3-aminoisobutyrate
Unclassified (SGB_5075)
ACME c=-1.31e-01 p=3.20e-02
ADE c=-2.27e-01 p=2.43e-01
Drinks
N,N,N-trimethyl-5-aminovalerate
Unclassified (SGB_5075)
ACME c=-8.92e-02 p=4.80e-02
ADE c=8.15e-03 p=9.64e-01
Drinks
bilirubin degradation product, C17H18N2O4 (2)
Unclassified (SGB_5075)
ACME c=-9.35e-02 p=2.80e-02
ADE c=-1.73e-01 p=3.00e-01
Drinks
etiocholanolone glucuronide

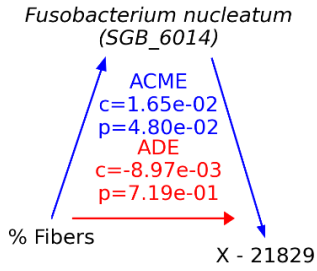

Unclassified (SGB_5075)
ACME c=-1.78e-01 p=4.40e-02
ADE c=-3.42e-01 p=2.47e-01
Drinks
gentisate
Unclassified (SGB_5075)
ACME c=-9.44e-02 p=4.00e-02
ADE c=-2.98e-02 p=8.64e-01
Drinks
pregnenediol sulfate (C21H34O5S)*
Unclassified (SGB_4914)
ACME c=-2.63e-02 p=1.60e-02
ADE c=9.04e-02 p=2.22e-02
Iron [mg]
2S,3R-dihydroxybutyrate
Unclassified (SGB_4914)
ACME c=-1.74e-02 p=1.60e-02
ADE c=8.10e-02 p=3.90e-02
Iron [mg]
STAMBP
Unclassified (SGB_4914)
ACME c=-2.99e-02 p=2.40e-02
ADE c=1.04e-01 p=7.15e-02
Iron [mg]
X - 11470
Unclassified (SGB_4914)
ACME c=-2.27e-02 p=3.20e-02
ADE c=6.96e-02 p=1.43e-01
Iron [mg]
sphingomyelin (d18:1/20:0, d16:1/22:0)*
Unclassified (SGB_4914)
ACME c=-1.90e-02 p=4.40e-02
ADE c=5.37e-02 p=2.87e-01
Iron [mg]
sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0)*
Unclassified (SGB_4914)
ACME c=-2.65e-02 p=2.80e-02
ADE c=8.70e-02 p=9.81e-02
Iron [mg]
sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0,
Unclassified (SGB_15254)
ACME c=-1.94e-04 p=4.00e-03
ADE c=1.03e-04 p=6.27e-01
Sodium [mg]
(14 or 15)-methylpalmitate (a17:0 or i17:0)
Unclassified (SGB_15254)
ACME c=2.12e-04 p=0.00e+00
ADE c=-3.64e-04 p=9.96e-02
Sodium [mg]
3-hydroxybutyroylglycine
Unclassified (SGB_15254)
ACME c=8.09e-04 p=0.00e+00
ADE c=-1.85e-03 p=1.40e-04
Sodium [mg]
HWESASXX*
Unclassified (SGB_15254)
ACME c=3.88e-04 p=1.20e-02
ADE c=-4.03e-04 p=1.73e-01
Sodium [mg]
X - 12101
Unclassified (SGB_15254)
ACME c=2.09e-04 p=1.60e-02
ADE c=-4.95e-04 p=3.76e-02
Sodium [mg]
bilirubin
Unclassified (SGB_15254)
ACME c=-1.46e-04 p=4.00e-02
ADE c=2.00e-04 p=2.65e-01
Sodium [mg]
branched-chain, straight-chain, or cyclopropyl 12:1 fatty acid*
Unclassified (SGB_15254)
ACME c=2.72e-04 p=2.00e-02
ADE c=-4.38e-04 p=2.35e-02
Sodium [mg]
glutamine conjugate of C6H10O2 (2)*
Unclassified (SGB_15254)
ACME c=-1.79e-04 p=4.00e-03
ADE c=2.40e-04 p=1.90e-01
Sodium [mg]
pentadecanoate (15:0)

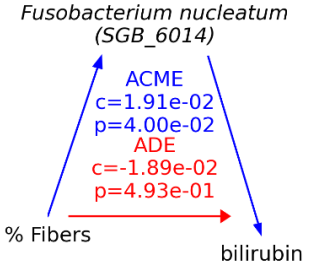
j Diet - Oral strains - Metabolites and Cytokines

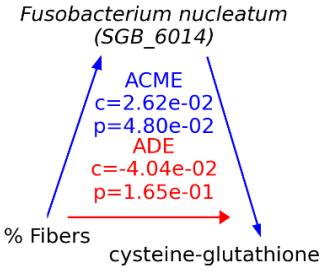


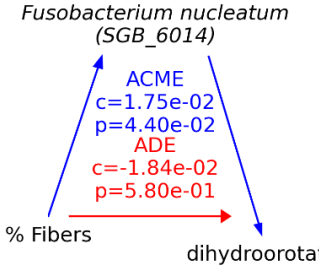


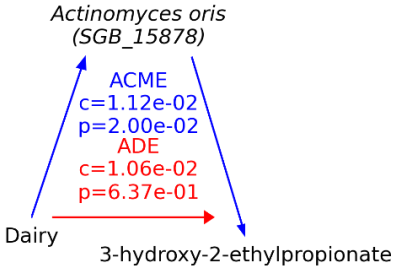


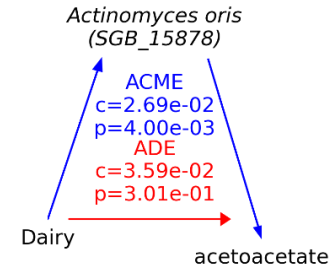


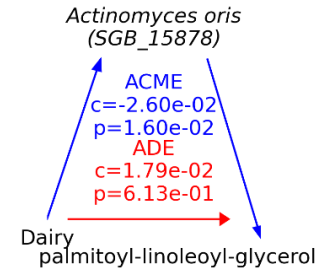


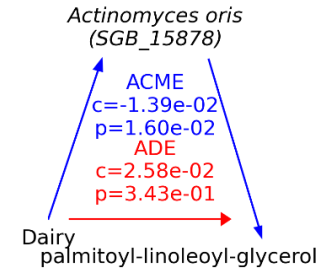


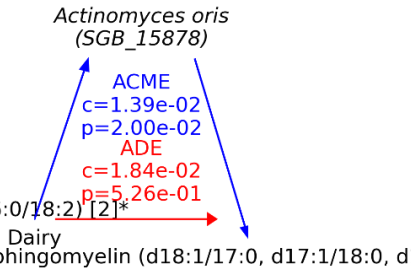


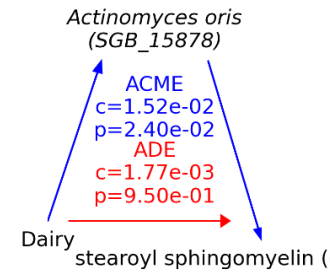


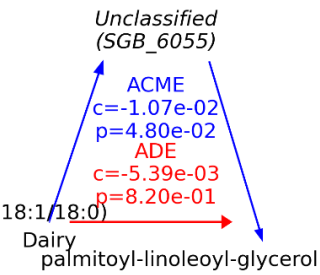


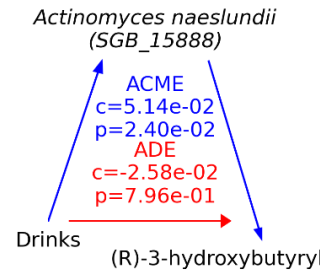


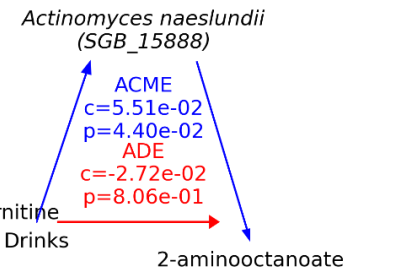


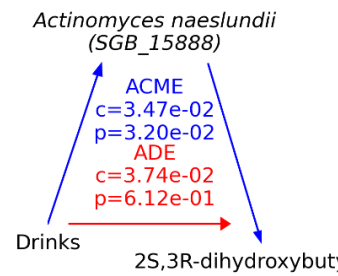


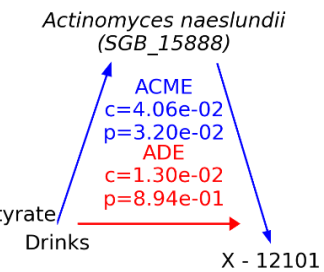


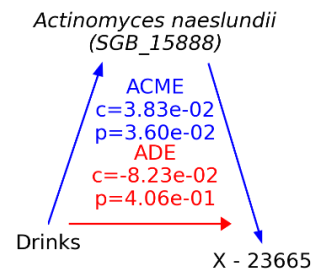


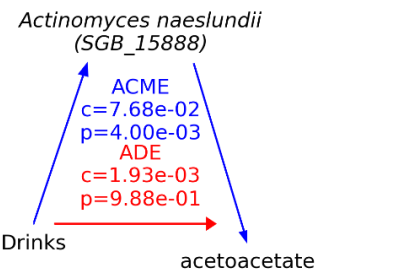


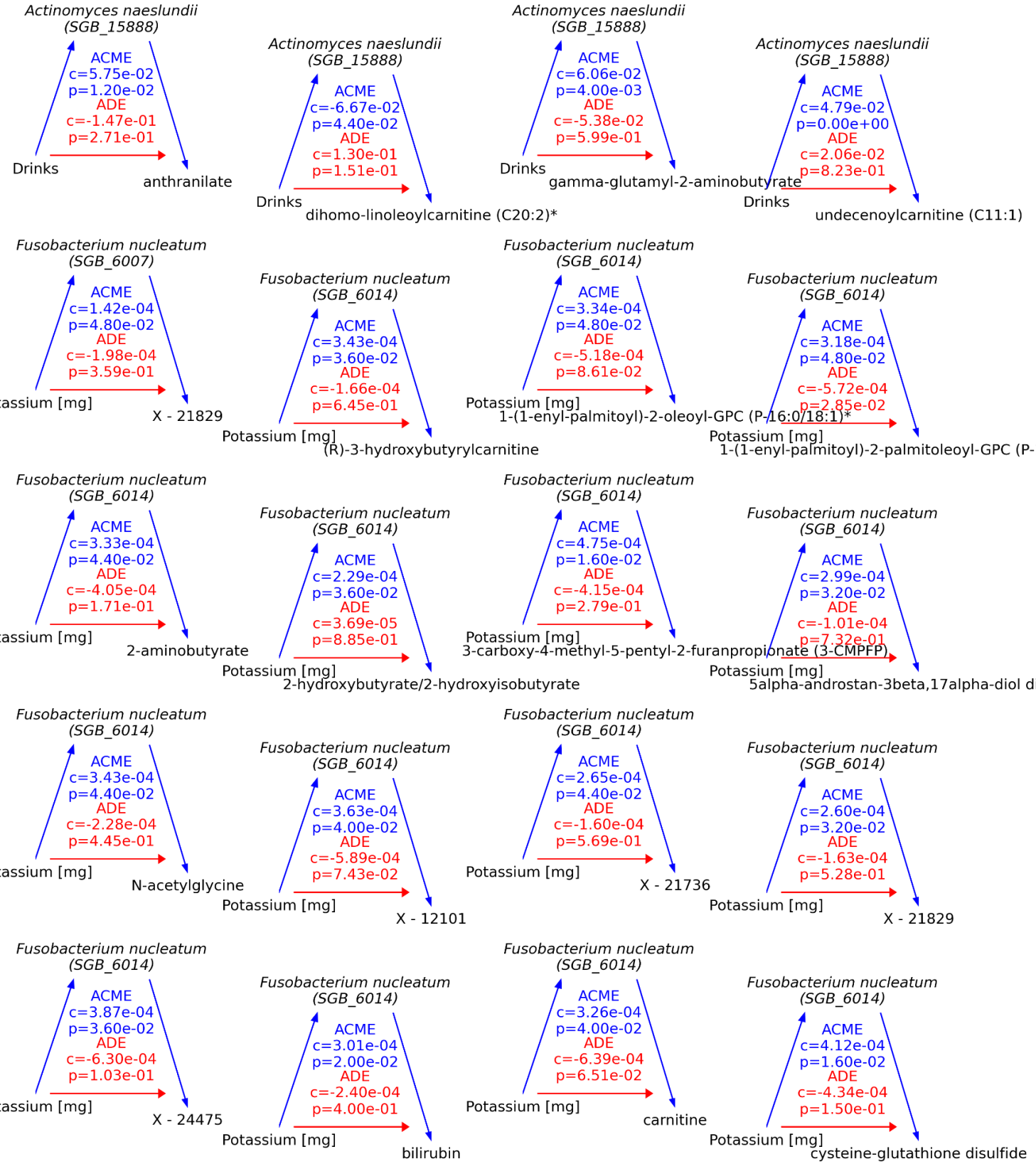


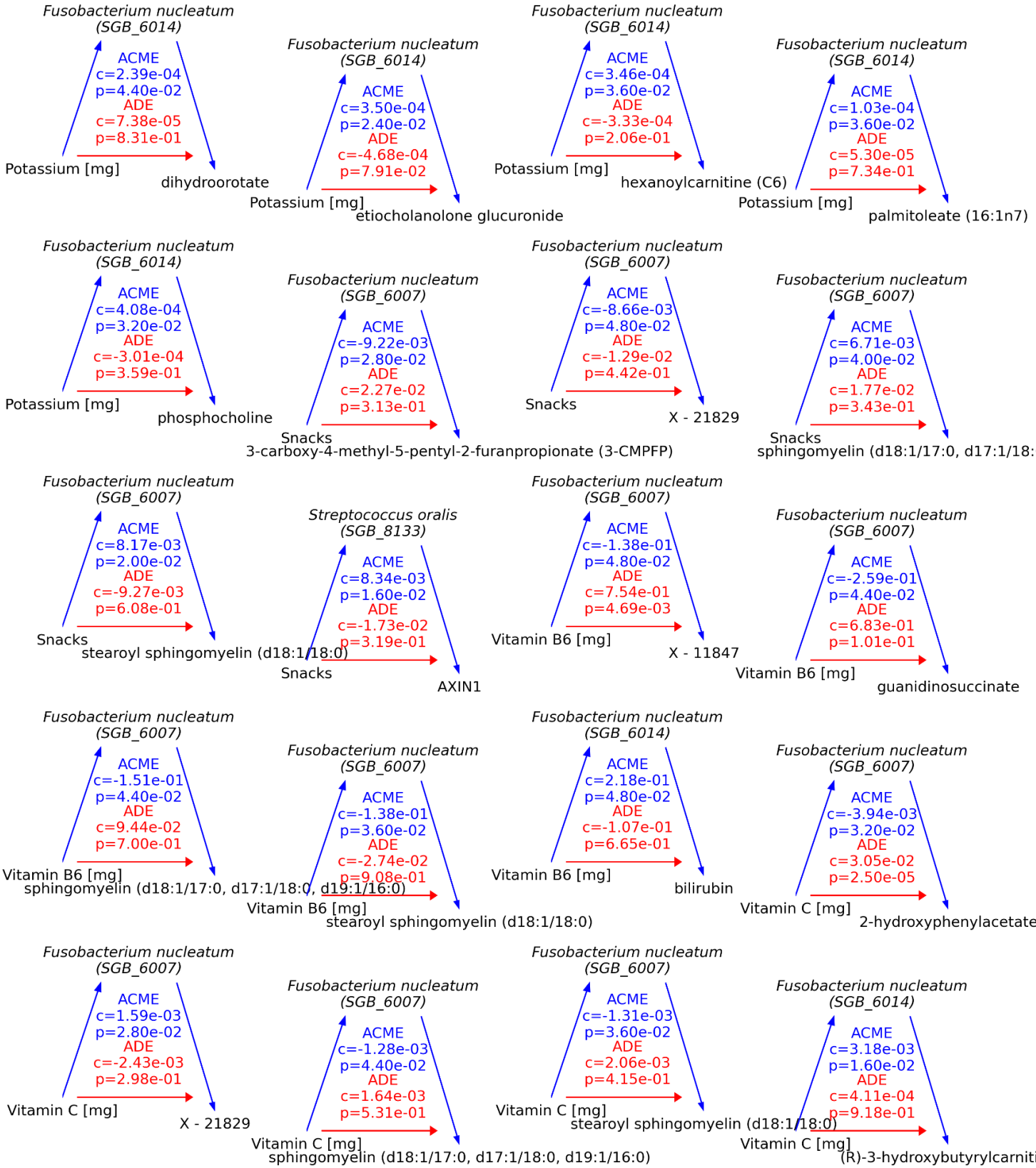









Actinomyces naeslundii (SGB_15888)
ACME c=5.75e-02 p=1.20e-02
ADE c=-1.47e-01 p=2.71e-01
Drinks
anthranilate
Actinomyces naeslundii (SGB_15888)
ACME c=-6.67e-02 p=4.40e-02
ADE c=1.30e-01 p=1.51e-01
Drinks
dihomo-linoleoylcarnitine (C20:2)*
Actinomyces naeslundii (SGB_15888)
ACME c=6.06e-02 p=4.00e-03
ADE c=-5.38e-02 p=5.99e-01
Drinks
gamma-glutamyl-2-aminobutyrate
Actinomyces naeslundii (SGB_15888)
ACME c=4.79e-02 p=0.00e+00
ADE c=2.06e-02 p=8.23e-01
Drinks
undecenoylcarnitine (C11:1)
Fusobacterium nucleatum (SGB_6007)
ACME c=1.42e-04 p=4.80e-02
ADE c=-1.98e-04 p=3.59e-01
Potassium [mg]
X - 21829
Fusobacterium nucleatum (SGB_6014)
ACME c=3.43e-04 p=3.60e-02
ADE c=-1.66e-04 p=6.45e-01
Potassium [mg]
(R)-3-hydroxybutyrylcarnitine
Fusobacterium nucleatum (SGB_6014)
ACME c=3.34e-04 p=4.80e-02
ADE c=-5.18e-04 p=8.61e-02
Potassium [mg]
1-(1-enyl-palmitoyl)-2-oleoyl-GPC (P-16:0/18:1)*
Fusobacterium nucleatum (SGB_6014)
ACME c=3.18e-04 p=4.80e-02
ADE c=-5.72e-04 p=2.85e-02
Potassium [mg]
1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:
Fusobacterium nucleatum (SGB_6014)
ACME c=3.33e-04 p=4.40e-02
ADE c=-4.05e-04 p=1.71e-01
Potassium [mg]
2-aminobutyrate
Fusobacterium nucleatum (SGB_6014)
ACME c=2.29e-04 p=3.60e-02
ADE c=3.69e-05 p=8.85e-01
Potassium [mg]
2-hydroxybutyrate/2-hydroxyisobutyrate
Fusobacterium nucleatum (SGB_6014)
ACME c=4.75e-04 p=1.60e-02
ADE c=-4.15e-04 p=2.79e-01
Potassium [mg]
3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP)
Fusobacterium nucleatum (SGB_6014)
ACME c=2.99e-04 p=3.20e-02
ADE c=-1.01e-04 p=7.32e-01
Potassium [mg]
5alpha-androstan-3beta,17alpha-diol disul
Fusobacterium nucleatum (SGB_6014)
ACME c=3.43e-04 p=4.40e-02
ADE c=-2.28e-04 p=4.45e-01
Potassium [mg]
N-acetylglycine
Fusobacterium nucleatum (SGB_6014)
ACME c=3.63e-04 p=4.00e-02
ADE c=-5.89e-04 p=7.43e-02
Potassium [mg]
X - 12101
Fusobacterium nucleatum (SGB_6014)
ACME c=2.65e-04 p=4.40e-02
ADE c=-1.60e-04 p=5.69e-01
Potassium [mg]
X - 21736
Fusobacterium nucleatum (SGB_6014)
ACME c=2.60e-04 p=3.20e-02
ADE c=-1.63e-04 p=5.28e-01
Potassium [mg]
X - 21829
Fusobacterium nucleatum (SGB_6014)
ACME c=3.87e-04 p=3.60e-02
ADE c=-6.30e-04 p=1.03e-01
Potassium [mg]
X - 24475
Fusobacterium nucleatum (SGB_6014)
ACME c=3.01e-04 p=2.00e-02
ADE c=-2.40e-04 p=4.00e-01
Potassium [mg]
bilirubin
Fusobacterium nucleatum (SGB_6014)
ACME c=3.26e-04 p=4.00e-02
ADE c=-6.39e-04 p=6.51e-02
Potassium [mg]
carnitine
Fusobacterium nucleatum (SGB_6014)
ACME c=4.12e-04 p=1.60e-02
ADE c=-4.34e-04 p=1.50e-01
Potassium [mg]
cysteine-glutathione disulfide


Fusobacterium nucleatum (SGB_6014)
ACME c=2.39e-04 p=4.40e-02
ADE c=7.38e-05 p=8.31e-01
Potassium [mg]
dihydroorotate
Fusobacterium nucleatum (SGB_6014)
ACME c=3.50e-04 p=2.40e-02
ADE c=-4.68e-04 p=7.91e-02
Potassium [mg]
etiocholanolone glucuronide
Fusobacterium nucleatum (SGB_6014)
ACME c=3.46e-04 p=3.60e-02
ADE c=-3.33e-04 p=2.06e-01
Potassium [mg]
hexanoylcarnitine (C6)
Fusobacterium nucleatum (SGB_6014)
ACME c=1.03e-04 p=3.60e-02
ADE c=5.30e-05 p=7.34e-01
Potassium [mg]
palmitoleate (16:1n7)
Fusobacterium nucleatum (SGB_6014)
ACME c=4.08e-04 p=3.20e-02
ADE c=-3.01e-04 p=3.59e-01
Potassium [mg]
phosphocholine
Fusobacterium nucleatum (SGB_6007)
ACME c=-9.22e-03 p=2.80e-02
ADE c=2.27e-02 p=3.13e-01
Snacks
3-carboxy-4-methyl-5-pentyl-2-furanpropionate (3-CMPFP)
Fusobacterium nucleatum (SGB_6007)
ACME c=-8.66e-03 p=4.80e-02
ADE c=-1.29e-02 p=4.42e-01
Snacks
X - 21829
Fusobacterium nucleatum (SGB_6007)
ACME c=6.71e-03 p=4.00e-02
ADE c=1.77e-02 p=3.43e-01
Snacks
sphingomyelin (d18:1/17:0, d17:1/18:0, d19:
Fusobacterium nucleatum (SGB_6007)
ACME c=8.17e-03 p=2.00e-02
ADE c=-9.27e-03 p=6.08e-01
Snacks
stearoyl sphingomyelin (d18:1/18:0)
Streptococcus oralis (SGB_8133)
ACME c=8.34e-03 p=1.60e-02
ADE c=-1.73e-02 p=3.19e-01
Snacks
AXIN1
Fusobacterium nucleatum (SGB_6007)
ACME c=-1.38e-01 p=4.80e-02
ADE c=7.54e-01 p=4.69e-03
Vitamin B6 [mg]
X - 11847
Fusobacterium nucleatum (SGB_6007)
ACME c=-2.59e-01 p=4.40e-02
ADE c=6.83e-01 p=1.01e-01
Vitamin B6 [mg]
guanidinosuccinate
Fusobacterium nucleatum (SGB_6007)
ACME c=-1.51e-01 p=4.40e-02
ADE c=9.44e-02 p=7.00e-01
Vitamin B6 [mg]
sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)
Fusobacterium nucleatum (SGB_6007)
ACME c=-1.38e-01 p=3.60e-02
ADE c=-2.74e-02 p=9.08e-01
Vitamin B6 [mg]
stearoyl sphingomyelin (d18:1/18:0)
Fusobacterium nucleatum (SGB_6014)
ACME c=2.18e-01 p=4.80e-02
ADE c=-1.07e-01 p=6.65e-01
Vitamin B6 [mg]
bilirubin
Fusobacterium nucleatum (SGB_6007)
ACME c=-3.94e-03 p=3.20e-02
ADE c=3.05e-02 p=2.50e-05
Vitamin C [mg]
2-hydroxyphenylacetate
Fusobacterium nucleatum (SGB_6007)
ACME c=1.59e-03 p=2.80e-02
ADE c=-2.43e-03 p=2.98e-01
Vitamin C [mg]
X - 21829
Fusobacterium nucleatum (SGB_6007)
ACME c=-1.28e-03 p=4.40e-02
ADE c=1.64e-03 p=5.31e-01
Vitamin C [mg]
sphingomyelin (d18:1/17:0, d17:1/18:0, d19:1/16:0)
Fusobacterium nucleatum (SGB_6007)
ACME c=-1.31e-03 p=3.60e-02
ADE c=2.06e-03 p=4.15e-01
Vitamin C [mg]
stearoyl sphingomyelin (d18:1/18:0)
Fusobacterium nucleatum (SGB_6014)
ACME c=3.18e-03 p=1.60e-02
ADE c=4.11e-04 p=9.18e-01
Vitamin C [mg]
(R)-3-hydroxybutyrylcarnitine

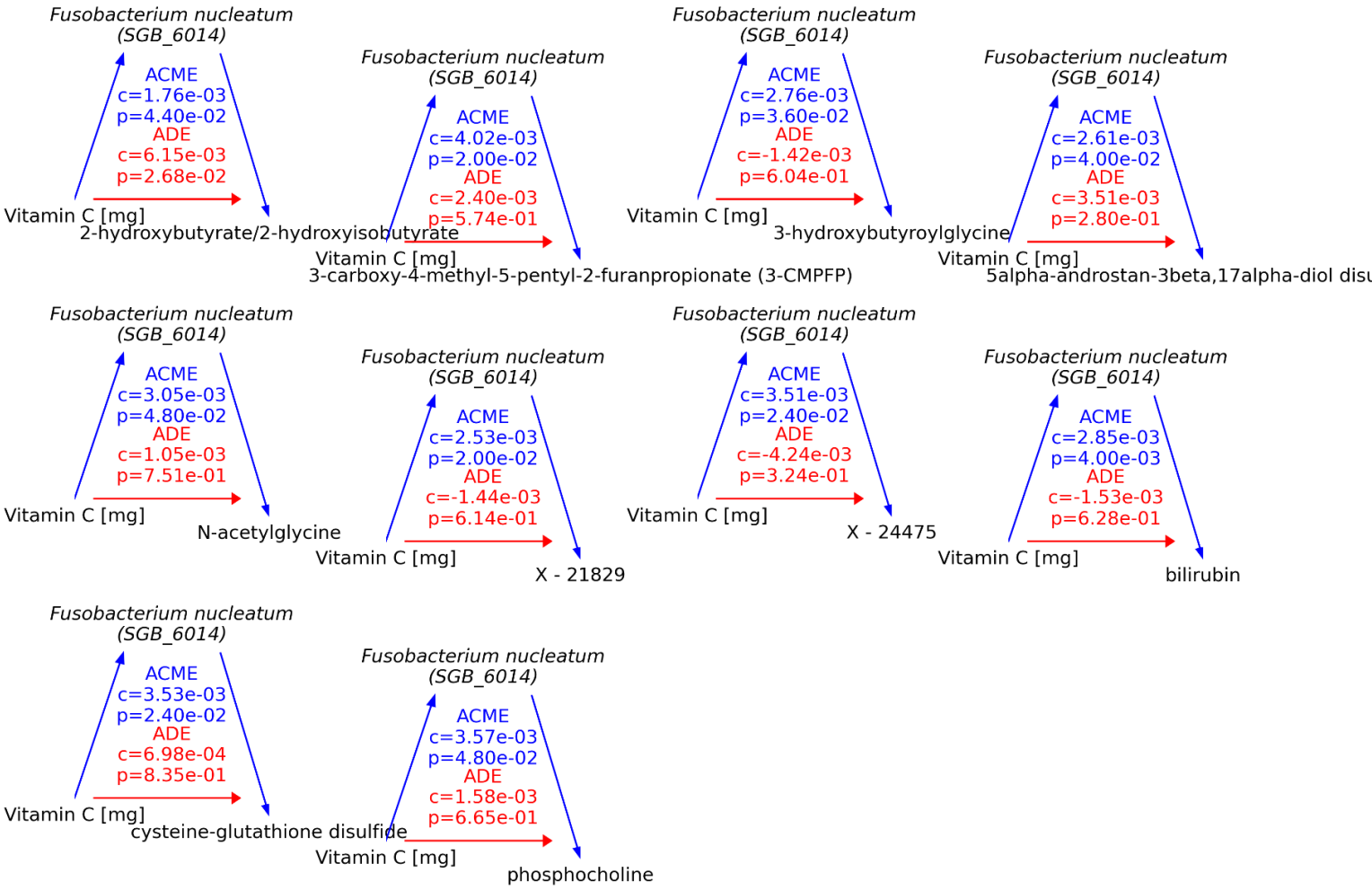


Figure S2. The microbiome mediates the diet's effect

Each plot shows a path from a dietary feature to an outcome that is mediated by the microbiome (two-sided bootstrap p<0.05). The left apex is the dietary feature, the right apex is the outcome and the upper apex is the microbial mediator. The title specifies the diet group ("PPT" or "MED" diet), type of microbial mediators (species, pathways or strains) and the type of outcome (glycemic measurements or metabolites and cytokines). The average direct effect (ADE) in red, the average causal mediated effect (ACME) in blue, c - effect size, p - p-value. Source data are provided as a Source Data file.

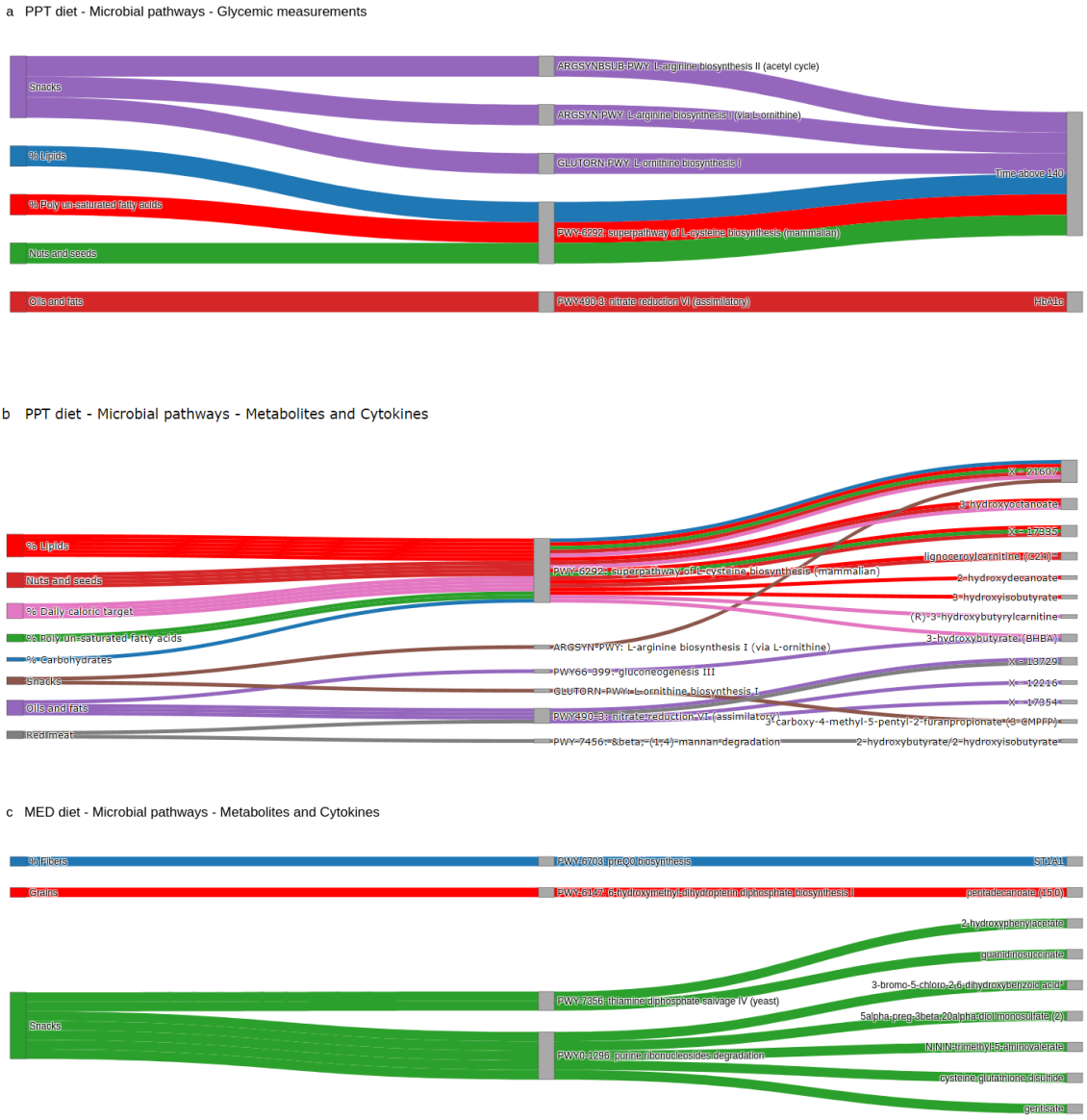


Figure S3. Microbial pathways mediate the diet's effect

Each alluvial plot shows paths from diet to outcomes that are mediated by oral and gut microbial pathways (two-sided bootstrap $p<0.05$). The outcomes in **a.** are glycemic measurements, and in **b.** and **c.** the outcomes are metabolites and cytokines. **a.** and **b.** show paths of the "PPT diet", while **c.** shows paths of the "MED diet". No mediating effect on glycemic measurements was found in the "MED diet". Source data are provided as a Source Data file.

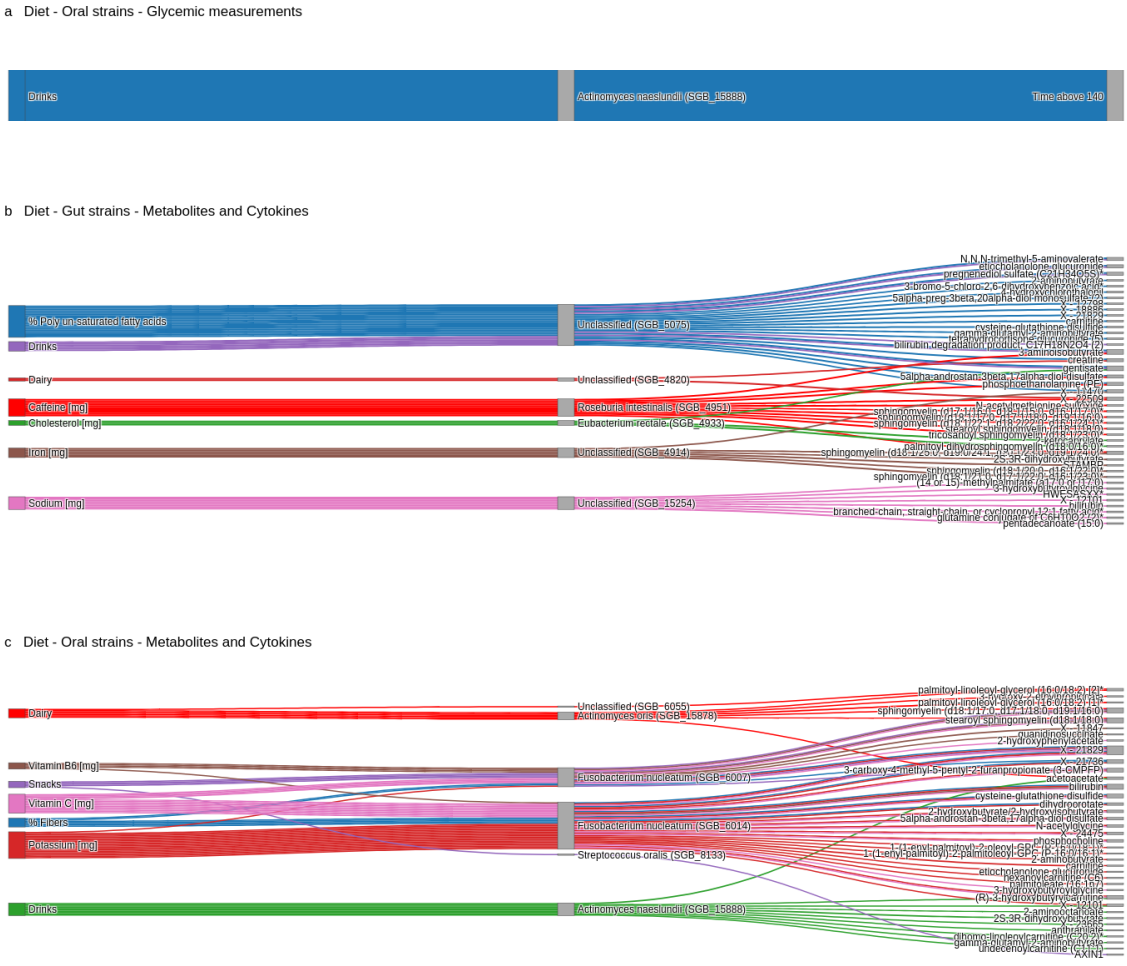


Figure S4. Microbial strains mediate the diet's effect

Each alluvial plot shows paths from diet to outcomes that are mediated by microbial strains (two-sided bootstrap p<0.05). The outcomes in **a.** are glycemic measurements, and in **b.** and **c.** the outcomes are metabolites and cytokines. **a.** and **c.** show paths of the oral environment, while **b.** shows paths of the gut environment. The "PPT diet" and "MED diet" were combined. No mediating effect on glycemic measurements was found in the gut environment. Source data are provided as a Source Data file.