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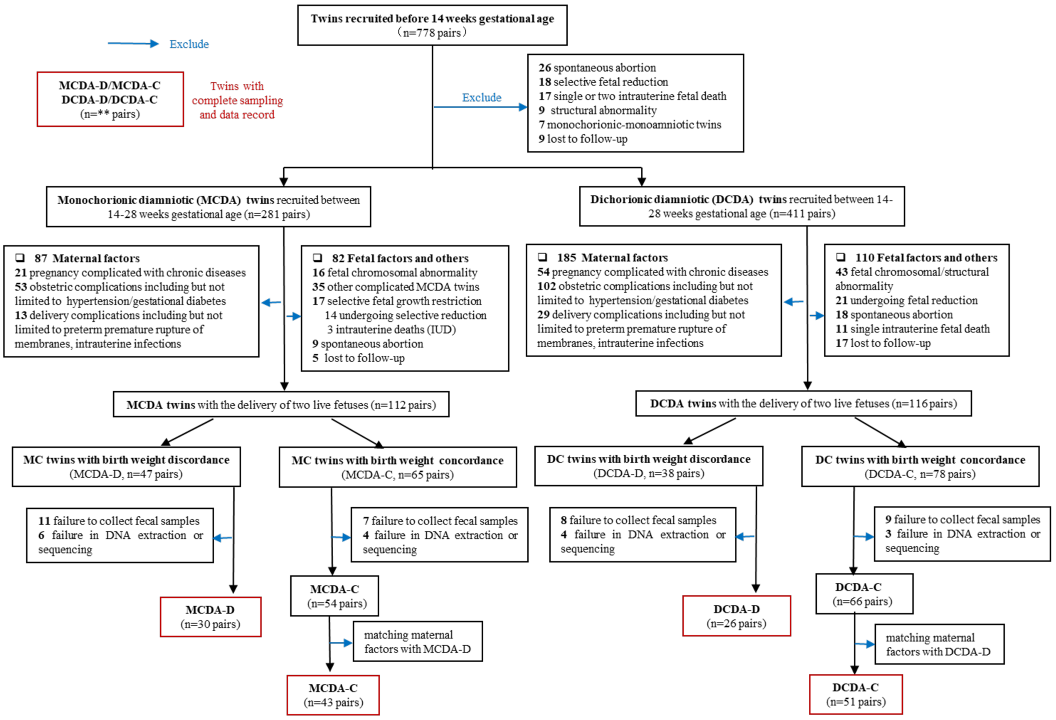
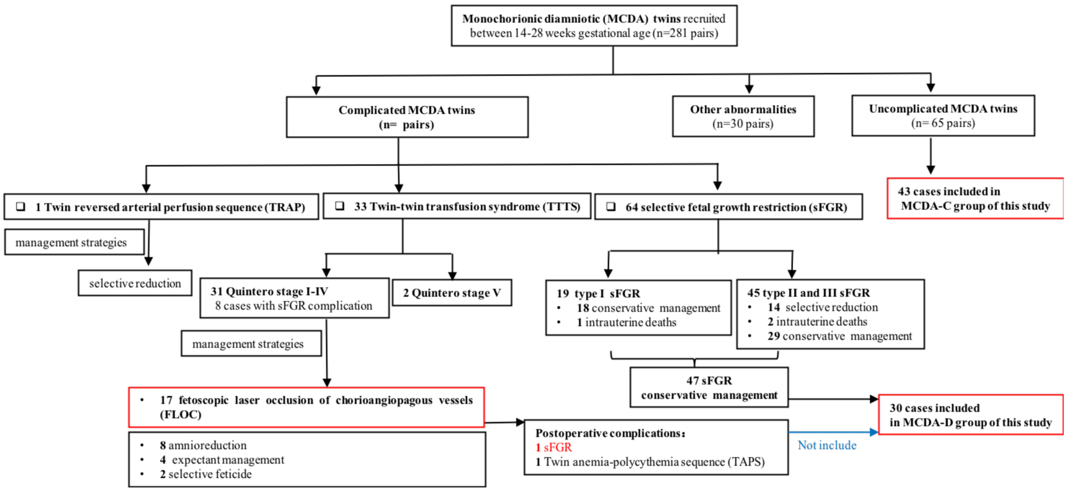
Supplementary Figures S1 to S15

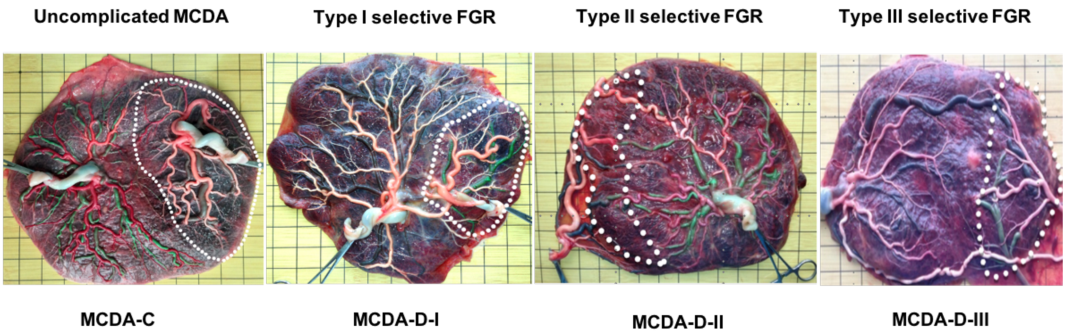


Supplementary Figure S1. Flowchart of volunteer recruitment and grouping. DCDA-D and DCDA-C represent DCDA twins with birth weight discordance and concordance, respectively. MCDA-D and MCDA-C represent MCDA twins with birth weight discordance and concordance, respectively.



Supplementary Figure S2. Occurrence and management of complicated MCDA twins.

sFGR represents selective fetal growth restriction.



Supplementary Figure S3. Placenta infused with placental vascular dye injection in MCDA-C and MCDA-D groups. The white dotted lines connect the smallest diameter vascular anastomoses points on the surface of the chorionic plate and divide the placenta into larger and smaller twin portions. Compared to MCDA-C, unequal placental sharing and discordance cord insertion are displayed as the features of placenta in MCDA-D-I, -II and -III groups.

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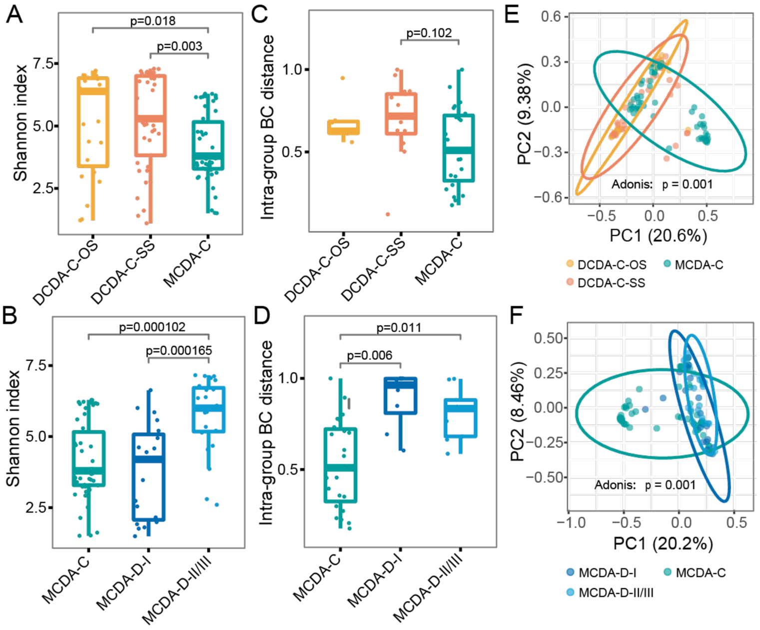
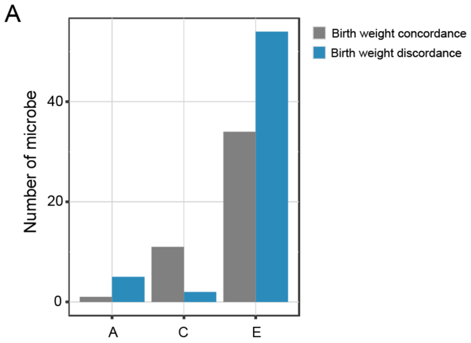


Supplementary Figure S4. The severity of the adverse intrauterine environment and genetics in shaping newborn gut microbiota. DCDA-SS and DCDA-OS represent DCDA with the same sex of each twin pair and DCDA with opposite sex of each twin pair, respectively. **(A-B)** Alpha diversities of neonatal gut microbiota compared among three groups. **(C-D)** Bray–Curtis (BC) distances of neonatal gut microbiota compared among three groups. **(E-F)** Principal component analysis (PCoA) plot of neonatal gut microbiota compared among three groups.



B

	Birth weight concordance			Birth weight discordance		
	A	**C**	**E**	**A**	**C**	**E**
Kocuria	0.89	0.00	0.11	0.00	0.00	1.00
Bifidobacterium	0.52	0.00	0.48	0.00	0.42	0.58
Bilophila	0.50	0.00	0.50	0.00	0.00	1.00
Desulfovibrio	0.46	0.00	0.54	0.00	0.00	1.00
Rothia	0.46	0.00	0.54	0.00	0.29	0.71
Megasphaera	0.45	0.00	0.55	0.00	0.00	1.00
Eubacterium	0.36	0.64	0.00	0.00	0.18	0.82
Klebsiella	0.36	0.00	0.64	0.00	0.00	1.00
Bacillus	0.33	0.09	0.58	0.00	0.00	1.00
Pseudomonas	0.29	0.00	0.71	0.00	0.00	1.00
Leptotrichia	0.21	0.00	0.79	0.00	0.11	0.90
Odoribacter	0.16	0.74	0.10	0.00	0.00	1.00
Fusobacterium	0.15	0.46	0.39	0.00	0.00	1.00

Supplementary Figure S5. Identified nascent microbes influenced by intrauterine environment and genetic factors. (A) A, C, and E in X-axis represents additive genetics, common environment, and unique environment, respectively. The grey bar represents the number of microbes from the sample of the control twins with birth weight concordance and the blue bar refers to the number of microbes from the sample of the twins with birth weight discordance. The height of grey bar at A in X-axis reflects the effect extent of genetic factors on bacterial taxa of birth weight concordance groups and, accordingly, the height of blue bar at A in X-axis reflects the effect extent of genetic factors on bacterial taxa of birth weight discordance groups. The grey and blue bars corresponding to the horizontal coordinate at E in X-axis are significantly higher than two bars at A or C. (**B**) The corresponding values of A, C and E of the genera with high heritability are showed in the groups with birth weight concordance and with birth weight discordance, respectively.

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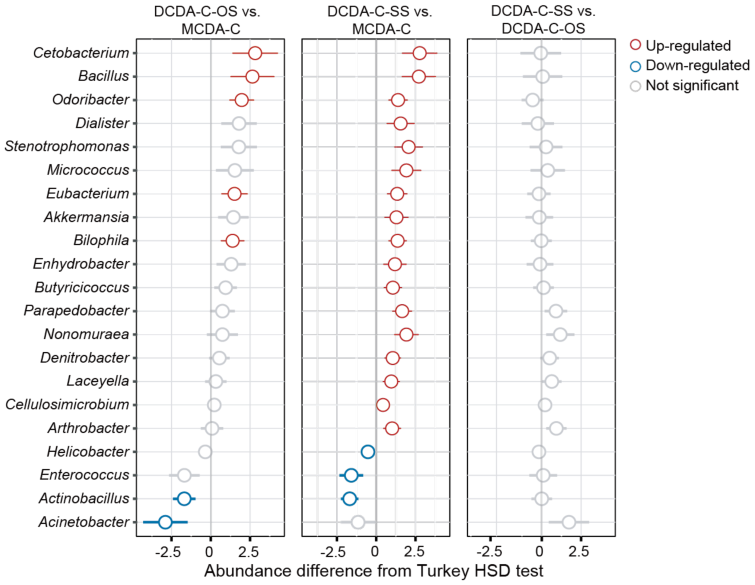

Supplementary Figure S6. Taxonomic differences related to genetic factors. The discriminatory bacteria were identified and ranked between the DCDA-C-OS and MCDA-C groups, between the DCDA-C-SS and MCDA-C groups or between the DCDA-C-OS and DCDA-C-SS groups, respectively. Co-variance between the differences of two groups was shown. Red dots represent genera showing significantly higher abundance in DCDA-C-OS or DCDA-C-SS than in MCDA-C, while blue dots represent genera showing lower abundance in DCDA-C-OS or DCDA-C-SS than in MCDA-C.

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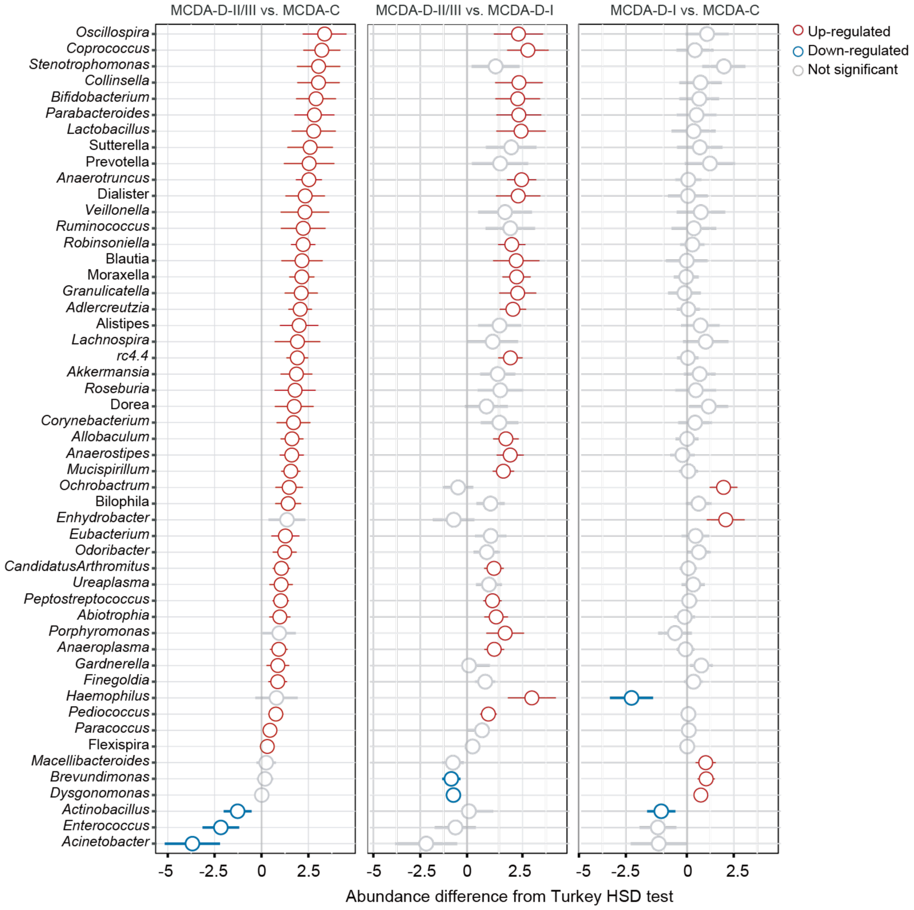

Supplementary Figure S7. Taxonomic differences related to fetal birth weight discordance. The discriminatory bacteria were identified and ranked between the MCDA-D-II/III and MCDA-C groups, between the MCDA-D-II/III and MCDA-D-I groups or between the MCDA-D-I and MCDA-C groups, respectively. Co-variance between the differences of two groups was shown. For each comparison, red dots represent genera showing significantly higher abundance in the *right* group than the *left* group, while blue dots represent genera showing lower abundance in the *right* group than the *left* group.

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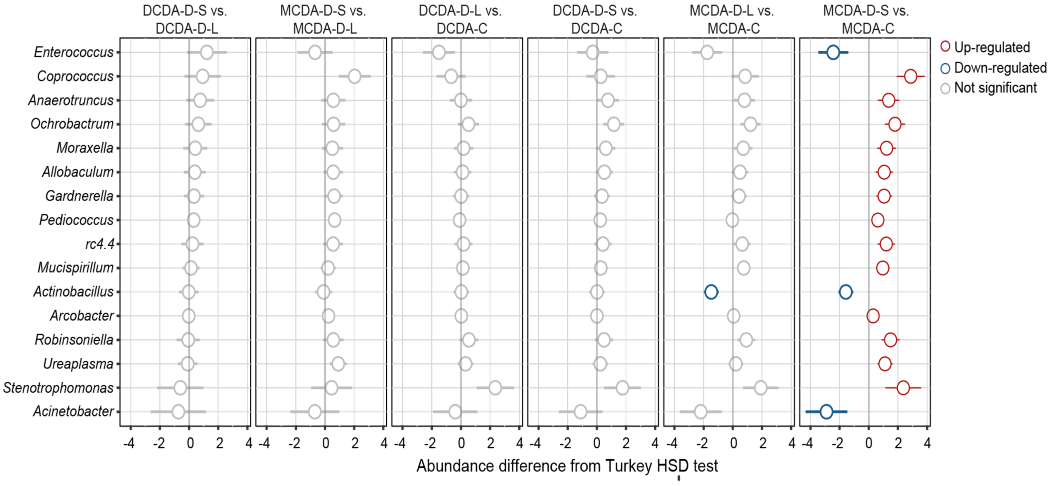

Supplementary Figure S8. sFGR-induced gut microbiota dysbiosis. The comparisons were preformed between larger and smaller twin pairs in MCDA-D or DCDA-D groups, and comparisons of larger or smaller twin pairs to their controls were also performed. The discriminatory bacteria were identified and ranked comparing DCDA-D-S group vs DCDA-C group, DCDA-D-L group vs DCDA-C group and DCDA-D-S group vs DCDA-D-L group, respectively. The same comparison was performed among MCDA-D-L, MCDA-D-S and MCDA-C groups. Co-variance between the differences of two groups was shown. For each two-group comparison, red dots represent genera showing significantly higher abundance in the *right* group than the *left* group, while blue dots represent genera showing lower abundance in the *right* group than the *left* group.

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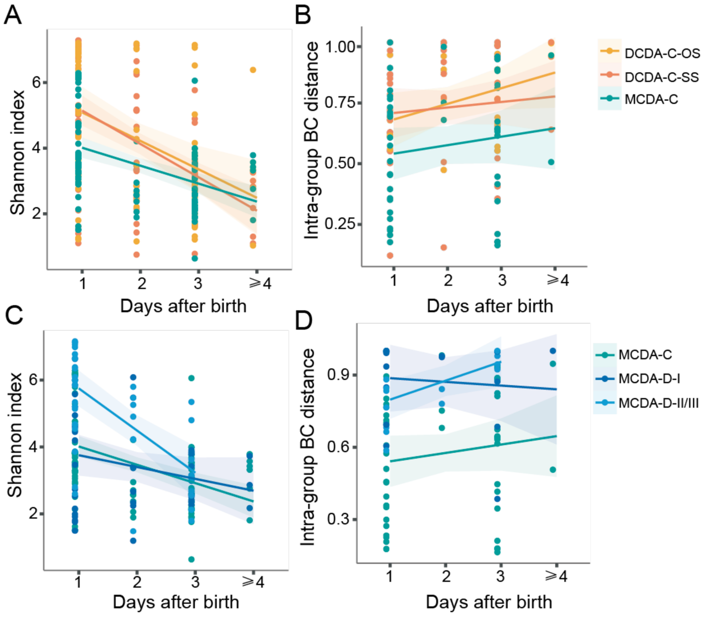

Supplementary Figure S9. The longitudinal effect of adverse intrauterine environment on microbial colonization patterns. (A) The variation of alpha diversity presented gradual decline in DCDA-C-SS (P=4.06E-09), DCDA-C-OS (P=0.0018) and MCDA-C (P=1.25E-06) groups within a few days after birth by the analysis of linear model of time series. **(B)** The BC distance of the microbial communities gradually increased in DCDA-C-SS (P=0.51), DCDA-C-OS (P=0.076) and MCDA-C (P=0.35) groups within a few days after birth. **(C)** The decreased alpha diversity showed in MCDA-D-I (P=0.11), MCDA-D-II/III (P=7.50E-06) and MCDA-C (P=1.25E-06) groups across the first few days. **(D)** The BC distance gradually increased in MCDA-C (P=0.35), rapidly increased in MCDA-D-II/III(P=0.026) and decreased steadily in MCDA-D-I (P=0.74) group across the first few days.

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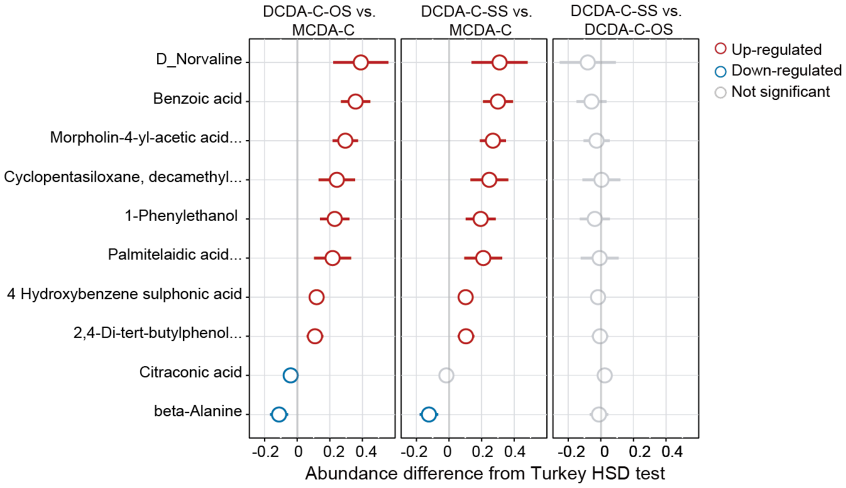

Supplementary Figure S10. Meconium metabolites influenced by genetic factors. The discriminatory metabolites were identified and ranked comparing the DCDA-C-OS group vs MCDA-C groups, DCDA-C-SS group vs MCDA-C group and DCDA-C-OS group vs DCDA-C-SS group, respectively. For each two-group comparison, red dots represent discriminatory metabolites showing significantly higher abundance in the *right* group than the *left* group, while blue dots represent metabolites showing lower abundance in the *right* group than the *left* group.

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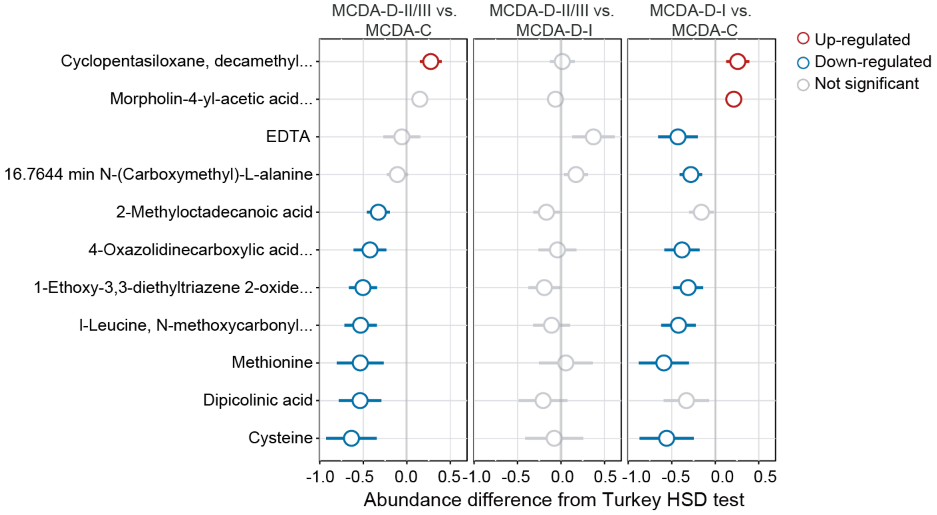
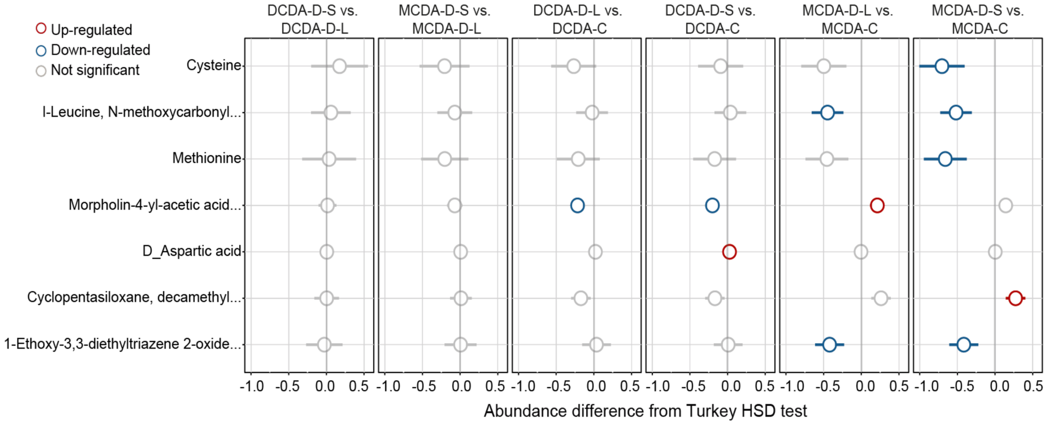
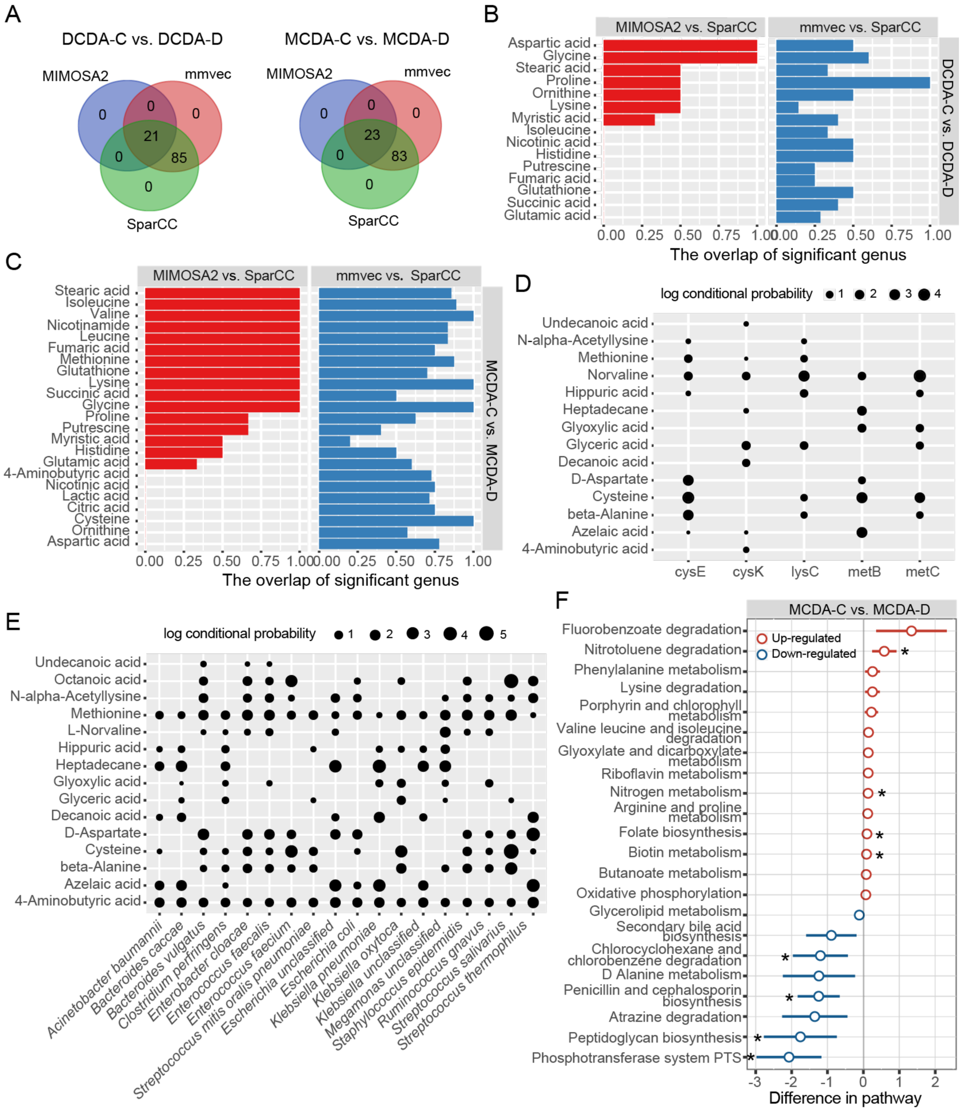


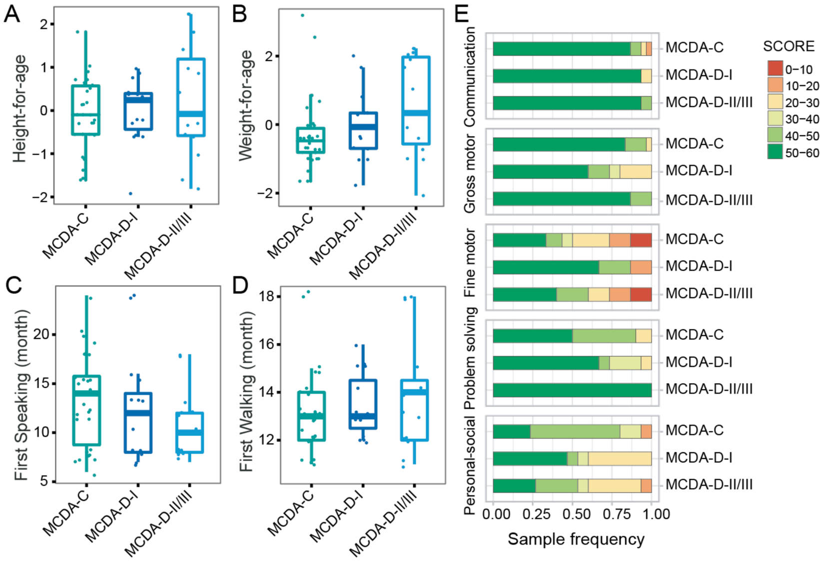
Supplementary Figure S11. The differences in the meconium metabolome related to fetal birth weight discordance. The discriminatory metabolites were illustrated successively according to the extent of difference by comparing MCDA-D-II/III group vs MCDA-C group, MCDA-D-II/III group vs MCDA-D-I group and MCDA-D-I group vs MCDA-C group, respectively. For each two-group comparison, red dots represent discriminatory metabolites showing significantly higher abundance in the *right* group than the *left* group, while blue dots represent metabolites showing lower abundance in the *right* group than the *left* group.



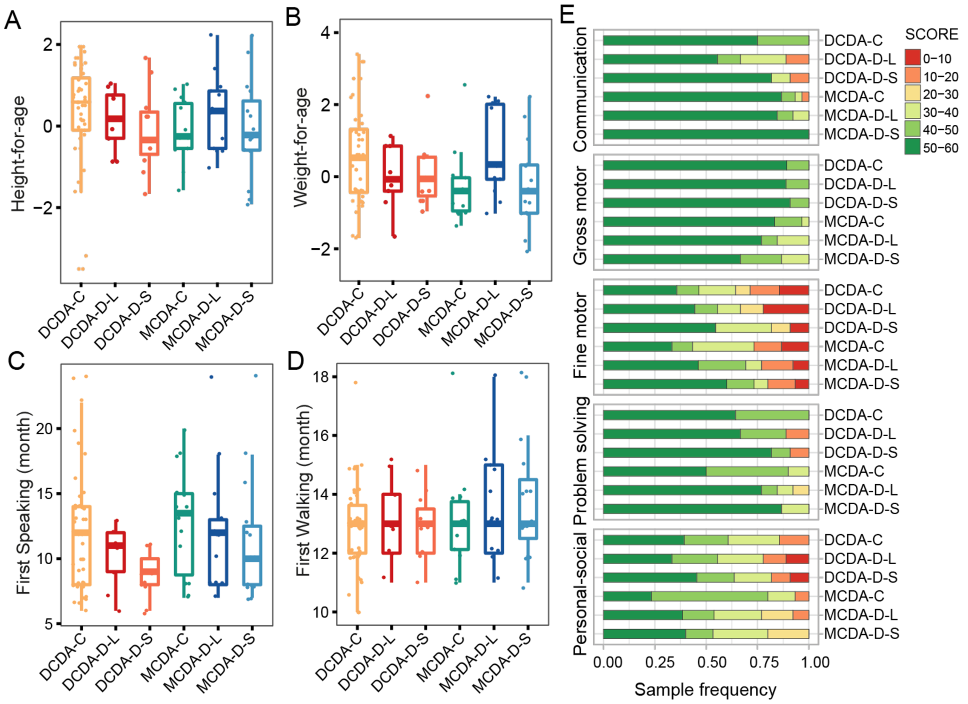
Supplementary Figure S12. Metabolic alternation associated with sFGR. MCDA-C, MCDA-D-L, and MCDA-D-S represent MCDA twins with birth weight concordance, the larger twin and smaller twin with birth weight for each MCDA-D twin pair, respectively. DCDA-C, DCDA-D-L, and DCDA-D-S represent DCDA twins with birth weight concordance, the larger twin and smaller twin with birth weight for each DCDA twin pair, respectively. The comparisons of meconium metabolome profiles were preformed between larger and smaller twin pairs in MCDA-D or DCDA groups, and comparisons between larger or smaller twin pairs and their controls were also performed. Differential metabolites were illustrated successively by comparing DCDA-D-S group vs DCDA-C group, DCDA-D-L group vs DCDA-C group and DCDA-D-S group vs DCDA-D-L group, respectively. The same comparison was performed between MCDA-D-L, MCDA-D-S and MCDA-C groups. For each two-group comparison, red dots represent discriminatory metabolites showing significantly higher abundance in the *right* group than the *left* group, while blue dots represent metabolites showing lower abundance in the *right* group than the *left* group.



Supplementary Figure S13. Correlation between bacteria and metabolites using three different methods. (A) The overlap of metabolites that were significantly correlated with bacteria identified by SparCC, MIMOSA2 and mmvec ($P < 0.05$; left, DCDA-C vs DCDA-D; right, MCDA-C vs MCDA-D). **(B)** The overlap of significantly differential bacteria identified by three different methods ($P < 0.05$; DCDA-C vs DCDA-D). **(C)** The overlap of significantly differential bacteria identified by three different methods ($P < 0.05$; MCDA-C vs MCDA-D). **(D-F)** Co-occurrence of metabolites and genes (D), metabolites and bacteria (E), and difference in metabolic pathway between MCDA-C and MCDA-D (F) calculated with metagenomic data. For two-group comparison in (F), red dots represent discriminatory metabolic pathways enriched in MCDA-D, while blue dots represent metabolic pathways enriched in MCDA-C (Tukey's HSD test in line model).



Supplementary Figure S14. The differences of physical and neurocognitive development in later life related to fetal birth weight discordance. (A-D) Comparisons of height-for-age, weight-for-age, first speaking time and first walking time among the MCDA-C, MCDA-D-I and MCDA-D-II/III groups by Wilcoxon's rank-sum test. **(E)** Comparisons of the percentage of score areas among the MCDA-C, MCDA-D-I and MCDA-D-II/III groups for each developmental domain of the ASQ-3 subscale.



Supplementary Figure S15. Variations of physical and neurocognitive development associated with FGR in the infanthood. (A-D) Comparisons of height-for-age, weight-for-age, first speaking time and first walking time among the DCDA-C, DCDA-L and DCDA-S groups, respectively. The same comparisons were performed among the MCDA-C, MCDA-D-L and MCDA-D-S groups, respectively, by using Wilcoxon's rank-sum test. **(E)** Comparisons of the percentage of score areas among the DCDA-C, DCDA-L and DCDA-S groups for each developmental domain of the ASQ-3 subscale. The same comparisons were performed among the MCDA-C, MCDA-D-L and MCDA-D-S groups, respectively.

Supplementary Tables S1 to S6

Supplementary Table S1. Placental characteristics of MCDA twin groups

	MCDA-D-I (n=10)[a]	**MCDA-D-II/III (n=20)[b]**	**MCDA-C (n=43)[c]**	**P value a vs c**	**P value a vs b**	**P value b vs c**
Placental territory discordance	0.49±0.20	0.63±0.14	0.23±0.11	0.0001[1***]	0.010[1*]	0.000[1***]
Placental sharing discordance (%)	8 (80.0%)	18 (90.0%)	19 (44.2%)	0.076	0.584	0.001[2**]
Velamentous or marginal cord insertion in larger twin (%)	1 (10.0%)	1 (5.0%)	5 (11.6%)	1.000	1.000	0.655
Velamentous or marginal cord insertion in smaller twin (%)	6 (60.0%)	16 (80.0%)	10 (23.2%)	0.050	0.384	0.000[2***]

[1] Analysis of variance (ANOVA); [2] Chi-square test; *P<0.05; ***P<0.001

Supplementary Table S2. Placental characteristics of DCDA twin groups

	DCDA-D (n=26)	DCDA-C (n=26)	P value
Placental territory discordance	0.17±0.05	0.14±0.05	0.032[1]*
Placental sharing discordance (%)	4 (15.4%)	2 (6.1%)	0.390[2]

[1] Analysis of variance (ANOVA); [2] Chi-square test; *P<0.05

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Supplementary Table S3. Placental characteristics among DCDA-D-S, DCDA-D-L and DCDA-C groups

	DCDA-D-S (n=26)^{a}	**DCDA-D-L (n=26)^{b}**	**DCDA-C (n=66)^{c}**	**P value a vs b**	**P value a vs c**	**P value b vs c**
Placental Weight (g)	327.3±61.6	394.8±59.8	373.7±47.0	0.0001**	0.0001**	0.091
Placental Vascular-Thrombotic Lesions (%)	6 (23.1%)	2(7.7%)	6 (9.1%)	0.248	0.091	1.000
Paracentral or centralcord insertion (%)	19 (73.1%)	23(88.5%)	59 (89.4%)	0.159	0.0102*	0.399
Velamentous or marginalcord insertion (%)	7 (26.9%)	3 (11.5%)	7 (10.6%)	0.159	0.061	1.000

[1] Analysis of variance (ANOVA); [2] Chi-square test

Supplementary Table S4. Maternal characteristics

	MCDA-D (n=30)[a]	**MCDA-C (n=43)[b]**	**DCDA-D (n=26)[c]**	**DCDA-C (n=51)[d]**	**P value a vs b**	**P value c vs d**
Maternal age (years)	30.7±3.9	31.2±4.3	33.4±4.4	33.5±4.4	0.606[1]	0.979[1]
Maternal BMI (kg/m^2)	22.1±3.4	22.6±3.8	22.4±2.4	22.2±3.2	0.556[1]	0.700[1]
Weight gain during pregnancy (kg)	13.8±5.0	15.4±5.8	17.0±6.5	16.6±4.7	0.227[1]	0.777[1]
Primigravida	/	/	/	/	0.213[2]	0.526[2]
Yes	19 (63.3%)	33 (63.3%)	21 (80.8%)	44 (86.3%)	/	/
No	11 (36.7%)	10 (63.3%)	5 (19.2%)	7 (13.7%)	/	/
Employment	/	/	/	/	0.510[2]	0.079[2]
Yes	27 (90%)	36 (83.7%)	20 (76.9%)	47 (92.2%)	/	/
No	3 (10%)	7 (16.3%)	6 (23.1%)	4 (7.8%)	/	/

[1] Student's T-test; [2] Chi-square test; DCDA-C and DCDA-D represent DCDA twins with birth weight concordance and birth weight discordance, respectively. MCDA-C and MCDA-D represent MCDA twins with birth weight concordance and birth weight discordance, respectively. BMI= Body Mass Index.

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Supplementary Table S5. Neonatal clinical outcomes of MCDA twin groups

	MCDA-D-S (n=30)[a]	**MCDA-D-L (n=30)[b]**	**MCDA-C (n=86)[c]**	**P value a vs b**	**P value a vs c**	**P value b vs c**
Birth Weight (g)	1385 ± 396	1999 ± 414	2098 ± 326	0.000***	0.000***	0.000***
Height (cm)	38.5± 3.8	42.4± 3.3	45.5± 2.4	0.000***	0.000***	0.000***
AC (cm)	25.4± 3.4	29.3± 2.8	30.9± 1.4	0.000***	0.000***	0.001**
HC (cm)	28.0± 2.7	31.5± 1.1	32.7± 1.1	0.000***	0.000***	0.000***
Apgar score at 1 min	8.9±1.6	9.1±1.4	9.5±0.4	0.305	0.000***	0.000***
Apgar score at 5 min	9.6±0.7	9.6±0.7	9.8±0.2	1.000	0.002**	0.002**
Umbilical blood pH	7.34±0.07	7.36±0.05	7.31±0.06	0.115	0.188	0.545

Analysis of variance (ANOVA); *P<0.05; **P<0.01; ***P<0.001; MCDA-C, MCDA-D-S and MCDA-D-L represent MCDA twins with birth weight concordance, the larger and the smaller of MCDA twins with birth weight discordance, respectively.

AC= Abdominal circumference; HC= Head circumference.

Supplementary Table S6. Neonatal clinical outcomes of DCDA twin groups

	DCDA-D-S (n=26)[a]	DCDA-D-L (n=26)[b]	DCDA-C (n=102)[c]	P value a vs b	P value a vs c	P value b vs c
Birth Weight (g)	2048 ± 447	2721 ± 460	2493 ± 362	0.000***	0.000***	0.009**
Height (cm)	43.7± 4.1	47.3± 2.7	45.9± 2.3	0.000***	0.000***	0.024*
AC (cm)	28.7± 3.3	31.9± 2.0	31.3± 1.6	0.000***	0.000***	0.168
HC (cm)	30.9± 2.7	33.4± 1.7	33.2± 1.5	0.000***	0.000***	0.549
Apgar score at 1 min	9.6±0.9	9.7±0.7	9.9±0.2	0.774	0.001**	0.003**
Apgar score at 5 min	9.9±0.3	9.9±0.3	10.0±0.0	1.000	0.006**	0.006**
Umbilical blood pH	7.35±0.05	7.36±0.05	7.35±0.03	0.507	0.905	0.473

Analysis of variance (ANOVA); *P<0.05; **P<0.01; ***P<0.001; DCDA-C, DCDA-D-S and DCDA-D-L represent DCDA twins with birth weight concordance, the larger and the smaller of DCDA twins with birth weight discordance, respectively.

AC= Abdominal circumference; HC= Head circumference.