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Exercise-induced metabolomics and its association with metabolic health in adolescents

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Abstract

Background While exercise training has been shown to improve various aspects of adolescent metabolic health, such as blood pressure, insulin resistance, and dyslipidemia, the underlying metabolic mechanisms remain poorly understood. No study has examined the metabolomic changes to identify potential mechanisms and explore biomarkers that predict exercise benefits in adolescents.

Methods We used propensity score matching to select 54 pairs of adolescents (ages 12–14 years) with and without long-term exercise training. Body mass index (BMI), waist circumference (WC) and metabolic indicators including blood pressure, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and triglycerides (TGs) were assessed at enrollment and 1-year follow-up. Untargeted metabolomics was analyzed at enrollment. The associations between metabolites and clinical metabolic indicators were tested.

Results Metabolomic analysis revealed 73 differential metabolites between exercise and non-exercise groups, with 59 metabolites associated with metabolic health indicators. Among them, a group of eicosanoids were consistently upregulated and negatively associated with diastolic blood pressure (DBP), HOMA-IR, or TGs, suggesting their potential roles in exercise-related improvements. Receiver operating characteristic analysis showed better predictive performance for exercise benefits on DBP and TGs using papaverine and azelaic acid compared to BMI and WC.

Conclusions Adolescents with long-term exercise are associated with improved metabolic health. Metabolomic profiles provide novel insights into the underlying mechanisms and offer useful biomarkers for predicting exercise benefits.

Keywords Long-term exercise, Adolescents, Metabolomic profiling, Adolescent metabolic health, Predictive biomarkers

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Introduction

Adolescent health is significantly impacted by the rising prevalence of metabolic disorders. Elevated blood pressure affects 12–20% of children and adolescents [1], with 3–12% diagnosed with hypertension [1–4]. Insulin resistance peaks during puberty, affecting 3.1–44% of adolescents [5, 6]. Furthermore, 20–30% of children have dyslipidemia, with hypertriglyceridemia being the most common type in adolescents [7–10]. Impaired cardiometabolic health during childhood is a strong predictor of future cardiovascular disease [11, 12], highlighting the need for early interventions to promote metabolic health and reduce long-term risk.

Long-term exercise has been shown to improve metabolic health in children and adolescents, including blood pressure, insulin resistance, dyslipidemia [13, 14]. With growing evidence of exercise benefits, the World Health Organization recommends 60 min of moderate to vigorous physical activity daily to support general health and prevent metabolic diseases [15]. However, the mechanisms behind exercise's benefits are not yet fully understood. These mechanisms generally include the regulation of exerkines, defined as humoral factors responsive to exercise [16–18], improvements in redox health [17], adaptations to the gut microbiota [19], and reduced inflammation [20], but research gaps remain regarding the detailed regulatory processes involved.

Moreover, there is a lack of effective methods to monitor and assess the effects of exercise on metabolic health, which would allow individuals to adjust their exercise plans accordingly. Current obesity markers, such as body mass index (BMI) and waist circumference (WC), could be useful, as weight loss often leads to metabolic improvements [21]. However, these markers have inherent limitations, as obesity and metabolic health are not always negatively correlated [22]. Additionally, both BMI and WC have their own drawbacks. A high BMI is not always associated with obesity or poor health, especially in physically active populations with high lean body mass [23]. While WC may better predict abdominal obesity, its effect size after exercise interventions in children and adolescents is small, with a pooled reduction of just 0.95 cm shown in a recent meta-analysis [24]; yet the measurement error can be significant, ranging from 0.7 cm to 15 cm [25]. Thus, there is a need for more reliable biomarkers to assess the benefits of exercise on metabolic health.

Metabolomics is the study of small molecules in biological samples. These molecules are produced through complex physiological processes in the body and can reflect past exposures, current metabolic states, and even predict future health outcomes [26]. Untargeted metabolomics provides a comprehensive, unbiased perspective, making it a powerful tool for understanding the processes occurring in adolescents with long-term exercise and for discovering potential biomarkers. While previous studies have explored the metabolomes of adults with long-term exercise [27, 28], fewer have focused on adolescents. Given the dramatic physical changes during adolescence, adolescents likely have distinct metabolomic profiles compared to adults, warranting focused research.

This study aims to investigate the serum metabolomic profiles of adolescents with and without long-term exercise training, and explore their associations with metabolic health both cross-sectionally and longitudinally. By using propensity score matching, we aim to control for potential confounding factors and identify biomarkers and mechanisms underlying exercise benefits on metabolic health.

Materials and methods

Participants

We used baseline and 1-year follow-up data from the TED (Teenager Exercise and Development) cohort, an ongoing, observational, prospective study of Chinese adolescents. Participants were recruited from two schools in Jining, Shandong Province, China: 169 students from Jining No. 7 Middle School (a general high school with students born or raised in Jining) and 192 students from the Jining Sports Training Center (an exercise training school with students also born or raised in Jining, who were interested in exercise training). Of these, 158 adolescents from the general high school and 111 adolescents from the exercise training school attended the 1-year follow-up. The remaining participants dropped out due to school transfers or discontinuation of exercise training. Baseline data were collected in June 2023, and follow-up data were collected in June 2024. All participants were from Jining, ensuring a similar dietary and genetic background to minimize the influence of these factors on metabolism.

The inclusion criteria for this study were: (1) aged 12 to 14 years at enrollment; (2) apparent health, with no history of chronic systemic diseases such as liver, lung, or heart conditions, tumors, or endocrine disorders (e.g., hypothyroidism or diabetes); (3) for the general high school group, participants had only received standard physical education and had not engaged in any structured exercise training program or exercise club; (4) for the exercise training group, participants had undergone at least 8 weeks of structured exercise training, as this duration has been shown to improve metabolic health in children and adolescents [14)]. Participants who had taken nutritional supplements or undergone treatments that could influence growth and metabolism (e.g., recombinant human growth hormone) were excluded. A total of 291 adolescents met the inclusion criteria, with 166

from the general high school and 125 from the exercise training school at enrollment.

The exercise training details for the two groups of students are as follows: All exercise training sessions are fully supervised throughout the entire course by experienced trainers to ensure the completion of the training. General high school students received standard physical education twice a week, for about 40 min per session, which included 10 min of teaching and warm-up followed by 30 min of actual exercise. They participated in general physical fitness activities aimed at improving overall fitness (e.g., running, sit-ups, standing long jump, etc.). In contrast, exercise training school students underwent structured training five days a week, with more than 2 h of exercise each day. This included physical fitness training (aerobic and resistance training, e.g., running, weightlifting, etc.) as well as specialized sports skills training (e.g., rugby, rowing, handball, tennis, badminton, fencing, boxing, judo, archery, and Taekwondo).

All participants volunteered, and informed consent was obtained from both the subjects and their guardians. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Peking Union Medical College Hospital (No. K3298).

Propensity score matching

Propensity score matching was used to balance covariates between the two groups, so that correlation analysis should not be significantly biased. Matching variables included age, sex, dietary habits, and target height. Dietary habits were matched because diet can strongly influence metabolic health and metabolomic outcomes. Target height was also matched because differences in hereditary height potential could affect whether adolescents participated in exercise training and might lead to inherent metabolomic differences. Propensity scores were calculated using logistic regression with the MatchIt package in R. A 1:1 greedy nearest neighbor matching method with a caliper of 0.02 was applied, where each unit in one group was matched to a control unit based on the distance between units.

Ultimately, 54 matched pairs were generated from the 291 adolescents who met the inclusion criteria. 54 participants from the general high school were classified as the non-exercise group, while 54 participants from the exercise training school were classified as the exercise group. 51 participants from the non-exercise group and 31 participants from the exercise group attended the 1-year follow-up. A flowchart of the study design is shown in Fig. 1.

Data collection and laboratory tests

Demographic data were collected using questionnaires, including information on parental height, dietary habits (e.g., intake of Western-style fast food, soda drinks, and desserts), physical activity patterns (e.g., duration of exercise training, daily exercise time, and frequency of 60-minute physical activity sessions, including both exercise and non-exercise activities), birth history (e.g., premature birth, cesarean delivery) and socioeconomic factors (e.g., parental education level and household income). Target height was calculated by adding (for boys) or subtracting (for girls) 6.5 cm from half of the combined parental height [29].

Height and weight were measured three times by the same trained physician in the morning using a standard anthropometer. Measurements were taken with differences between measurements not exceeding 0.2 cm for height and 0.1 kg for weight. Participants wore light clothes, removed shoes, and placed items such as mobile phones aside before measurements. BMI was calculated

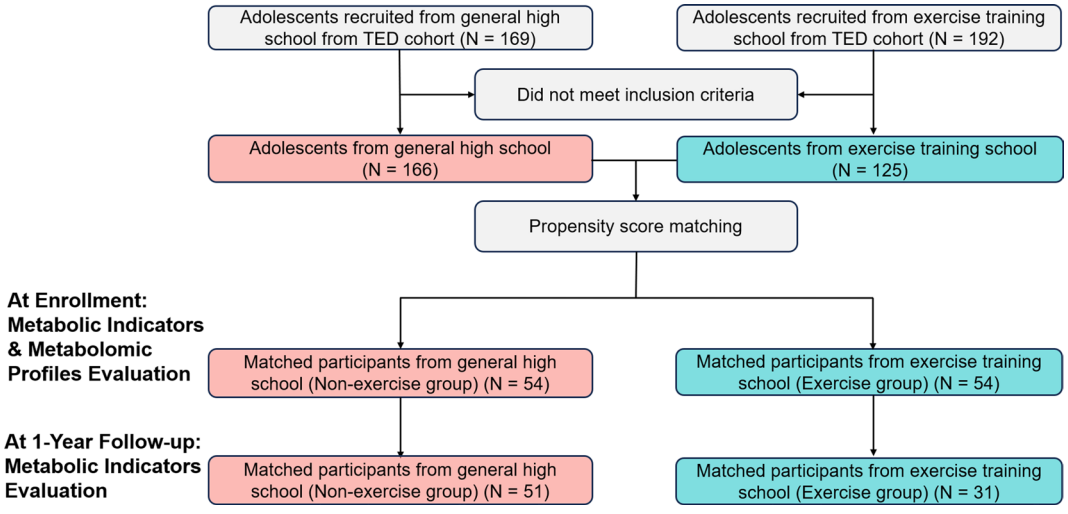

Fig. 1 Flowchart of the study design

as weight divided by height squared. Overweight or obesity status was classified according to Chinese standards for school-age adolescents [30]. WC was measured twice using a non-stretchable tape at the midpoint between the iliac crest and the costal margin, with differences between measurements not exceeding 0.2 cm. Blood pressure was recorded after a 5-minute rest, measured three times on the right arm while seated, using an Omron HBP 1300 electronic sphygmomanometer (Omron, Dalian, Japan). The average of the two most similar measurements was used in the analysis. Adolescents were classified as having elevated blood pressure if systolic blood pressure (SBP) exceeded 120 mmHg or diastolic blood pressure (DBP) exceeded 80 mmHg. Pubertal status was assessed by an experienced pediatric physician using the Tanner criteria. Bone age was determined by radiograph of the left hand and wrist (Ysio, Siemens, Germany), and radiographs were analyzed by two experienced radiologists blinded to chronological age using the Greulich and Pyle method.

Intravenous blood samples were collected after an overnight fast of at least 8 h in standard 5 mL vacutainer vials, placed on ice and transported to the laboratory of the Affiliated Hospital of Jining Medical University. Samples were immediately centrifuged at 1500 g for 10 min and separated for laboratory tests. The rest was stored at − 80 °C until metabolomic analysis. Laboratory tests included fasting blood sugar (FBS), insulin and triglycerides (TGs). These were analyzed using standard methods in the clinical laboratory of the Affiliated Hospital of Jining Medical University. FBG and TGs were measured with a biochemical automatic analyzer (Cobas c702, Roche; Shanghai, China), and insulin levels were determined using a chemiluminescence method. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated using the formula: HOMA-IR = [(fasting blood sugar (mmol/L) × fasting serum insulin (pmol/L)]/22.5. Adolescents with TGs greater than 1.01 mmol/L were classified as having elevated TGs [31]. Due to a lack of widely accepted cut-off values for HOMA-IR specific to adolescents, those in the highest quartile of HOMA-IR (HOMA-IR > 3.67) were classified as insulin resistant [32, 33].

Ultra-High performance liquid Chromatography - Tandem mass spectrometry (UHPLC-MS/MS) analysis

Serum samples (100 μL) were processed by resuspending in pre-chilled 80% methanol, followed by vortexing and incubation on ice for 5 min. After centrifugation at 15,000 g at 4 °C for 20 min, the supernatant was diluted to a final concentration of 53% methanol and centrifuged again under the same conditions. The final supernatant was injected into the UHPLC-MS/MS system for analysis.

Quality control (QC) samples were prepared by pooling aliquots from all samples and were injected every 10 samples to monitor method stability and reproducibility. To ensure method accuracy, internal standards were added to each sample prior to extraction. Intra-run and inter-run reproducibility were validated by analyzing QC samples in triplicate across multiple runs. The coefficients of variation (CV) for peak areas in QC samples were consistently below 15%, demonstrating the robustness of the method.

UHPLC-MS/MS analyses were performed using a Vanquish UHPLC system (Thermo Fisher, Germany) coupled with an Orbitrap Q Exactive™ HF mass spectrometer (Thermo Fisher, Germany). Separation was achieved on a Hypersil Gold column (100 × 2.1 mm, 1.9 μm) with a 12-minute linear gradient at a flow rate of 0.2 mL/min. For positive polarity, the eluents were: eluent A (0.1% formic acid in water) and eluent B (methanol); for negative polarity, eluent A (5 mM ammonium acetate, pH 9.0) and eluent B (methanol). The gradient program was as follows: 2% B for 1.5 min; 2–85% B over 3 min; 85–100% B over 10 min; 100-2% B over 10.1 min; and 2% B for 12 min. The mass spectrometer was operated in positive/negative polarity mode with a spray voltage of 3.5 kV, a capillary temperature of 320 °C, a sheath gas flow rate of 35 psi, and an auxiliary gas flow rate of 10 L/min.

Data processing and metabolite identification

Raw data was processed using Compound Discoverer 3.3 (Thermo Fisher) for peak alignment, peak picking, and quantitation. Key parameters included: peak area correction with the first QC, actual mass tolerance of 5 ppm, signal intensity tolerance of 30%, and minimum intensity. Peak intensities were normalized to the total spectral intensity and internal standards. Molecular formulas were predicted based on additive ions, molecular ion peaks, and fragment ions. Metabolites were identified by matching peaks with the mzCloud, mzVault, and MassList databases. Blank samples were used to exclude background noise. Compounds with a CV of relative peak areas greater than 30% in QC samples were excluded as potential low-quality data. Pearson correlation coefficients for QC samples were consistently close to 1, and principal component analysis (PCA) showed that QC samples clustered together, indicating high stability of the data. Final metabolite identification and relative quantification were performed using the Human Metabolome Database (HMDB) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases.

Statistical analyses

PCA and Partial Least Squares Discriminant Analysis (PLS-DA) was performed using MetaX. To validate the PLS-DA model and assess potential overfitting,

permutation testing was performed with 200 iterations. A model is considered valid if the R^2Y and Q^2Y values of the original model are significantly higher than those of the permuted data, and the Q^2 intercept on the Y-axis is less than 0.05. Variable importance in projection (VIP) was used to reflect the significance of variables. Univariate analysis (t-test) was used to assess statistical significance. Metabolites with VIP value greater than 1, the Benjamin-Hochberg false discovery rate (FDR) less than 0.05, and fold change greater than 1.5 or less than 0.667 were considered differential metabolites. The heatmap of differential metabolites was generated by the pheatmap package in R. Functional analysis and metabolic pathway enrichment were performed using the KEGG. Pathway enrichment was considered significant when ratio was satisfied by x/n greater than y/N and P-value of metabolic pathway was less than 0.05. In this context, N represents the total number of metabolites involved in the KEGG metabolic pathway, n is the number of differential metabolites within N, y is the number of metabolites annotated to a specific KEGG pathway, and x is the number of differential metabolites enriched in that pathway.

Other data analysis was performed using SPSS 26.0 software (IBM Corp., Armonk, N.Y., USA). Continuous data are presented as mean ± SD or median with interquartile range (IQR), and categorical variables as percentages. Student's t tests, Wilcoxon rank-sum, Spearman's rank correlation tests, χ^2 tests and Fisher's exact tests were used for unmatched baseline characteristics, while paired t tests, Wilcoxon signed-rank and McNemar tests were used for matched characteristics. Associations between differential metabolites and clinical metabolic indicators were analyzed using the cor() function in R, with significance set at P-value < 0.05. Association plots were generated using the corrplot package in R. MedCalc 23.0 was used to perform receiver operating characteristic (ROC) curve analysis.

Results

Clinical characteristics at enrollment and 1-Year Follow-up

After propensity score matching, 54 pairs of participants from non-exercise group and exercise group were selected. As shown in Table 1, no significant differences were observed between the two groups in terms of age, sex, target height, dietary habits, birth history, parental education, or household income. At enrollment, the exercise group had a median exercise duration of 4.5 months and demonstrated significantly greater daily exercise time and frequency of 60-minute physical activity sessions compared to the non-exercise group. The exercise group also had a lower BMI and WC than the non-exercise group. Among metabolic indicators, DBP, HOMA-IR, and TGs levels were significantly lower in the exercise group, while no significant differences were observed in SBP. These differences persisted at the 1-year follow-up. When comparing the changes in these indicators from enrollment to follow-up, no significant differences were found between the two groups (Table 2).

Serum metabolomics profile between exercise and Non-exercise groups at enrollment

PCA and PLS-DA were used to investigate the metabolic profiling variations between exercise and non-exercise group. Unsupervised PCA revealed some separation between the groups, with a degree of overlap (Fig. 2A). Supervised PLS-DA showed a clearer distinction between the two groups, with high model performance metrics ($R^2Y = 0.88$, $Q^2Y = 0.76$) (Fig. 2B). Permutation tests confirmed the model's validity (Fig. 2C).

A total of 73 differential metabolites were identified, of which 69 were upregulated and 4 were downregulated (Fig. 3 and Supplementary Table S1). Lipids and lipid-like molecules were the most prominent category (26 metabolites, 35.6%), followed by benzenoids (13 metabolites, 17.8%), organic acids and derivatives (8 metabolites, 11.0%), and organoheterocyclic compounds (8 metabolites, 11.0%). Among those lipids and lipid-like molecules, 10 were eicosanoids and 5 were phospholipids. Although not statistically significant, enrichment was observed in the steroid hormone biosynthesis pathway, phenylalanine metabolism pathway, and arachidonic acid metabolism pathway (Fig. 4 and Supplementary Table S2).

Associations between differential metabolites at enrollment and clinical metabolic indicators at enrollment and 1-Year Follow-up

Given that DBP, HOMA-IR, and TGs were significantly lower in the exercise group, Spearman's correlation tests were conducted to explore the associations between differential metabolites and these clinical indicators. As shown in Fig. 5 and Supplementary Table S3, 59 of the 73 metabolites were identified as being associated with DBP, HOMA-IR, or TGs. At enrollment, 43 metabolites were associated with DBP, including 12 benzenoids, 11 lipids and lipid-like molecules, and 7 organic acids and derivatives, among others. 45 metabolites were associated with HOMA-IR, including 16 lipids and lipid-like molecules, 9 benzenoids, and 7 organoheterocyclic compounds, among others. 39 metabolites were associated with TGs, including 15 lipids and lipid-like molecules, 8 benzenoids, and 6 organoheterocyclic compounds, among others. At follow-up, 23 metabolites were still associated with DBP, 24 with HOMA-IR, and 33 with TGs (Fig. 5 and Supplementary Table S3).

Interestingly, 42 of 73 metabolites were associated with more than one indicator, suggesting their roles in overall metabolic health regulation. A group of eicosanoids were found negatively correlated with DBP, HOMA-IR, or TGs

Table 1 Characteristics of exercise and non-exercise group at enrollment and 1-year follow-up after propensity score matching

Characteristics	Enrollment			1-Year Follow-up		
	Non-exercise (*n* = 54)	Exercise (*n* = 54)	*P* value	Non-exercise (*n* = 51)	Exercise (*n* = 31)	*P* value
Age, y	13.2 ± 0.4	13.3 ± 0.6	0.324	14.3 ± 0.4	14.4 ± 0.6	0.316
Male, n (%)	38 (70.4%)	35 (64.8%)	0.537	36 (70.6%)	21 (67.7%)	0.786
Target height, cm	174.3 (166.3-176.6)	174.0 (163.8-177.5)	0.787	174.0 (166.5-176.5)	175.5 (166.0-178.0)	0.509
High-fat and high-sucrose diet, n (%)	34 (63.0%)	33 (61.1%)	0.843	31 (60.8%)	19 (61.3%)	0.964
Western-style fast food intake ≥ 2 times per week, n (%)	3 (5.6%)	3 (5.6%)	1.000	3 (5.9%)	1 (3.2%)	1.000
Daily desserts, n (%)	6 (11.1%)	5 (9.3%)	0.750	5 (9.8%)	2 (6.5%)	0.705
Daily sodar drinks, n (%)	34 (63.0%)	31 (57.4%)	0.555	31 (60.8%)	18 (58.1%)	0.808
Premature birth, n (%)	2 (3.7%)	2 (3.7%)	1.000	2 (3.9%)	1 (3.2%)	1.000
Cesarean delivery, n (%)	22 (40.7%)	23 (42.6%)	0.845	21 (41.2%)	11 (35.5%)	0.608
Parental highest education level, n (%)	-	-	0.129	-	-	0.678
Junior high or less	15 (27.8%)	20 (37.0%)	-	14 (27.5%)	9 (29.0%)	-
Secondary high	20 (37.0%)	23 (42.6%)	-	20 (39.2%)	14 (45.2%)	-
College	12 (22.2%)	6 (11.1%)	-	11 (21.6%)	4 (12.9%)	-
University or higher	7 (13.0%)	5 (9.3%)	-	6 (11.8%)	4 (12.9%)	-
Household income, n (%)	-	-	0.513	-	-	0.748
<1000 Yuan/month	4/37 (10.8%)	9/41 (22.0%)	-	4/35 (11.4%)	3/23 (13.0%)	-
1000-<3000 Yuan/month	18/37 (48.6%)	17/41 (41.5%)	-	18/35 (51.4%)	10/23 (43.5%)	-
3000-<5000 Yuan/month	6 (16.2%)	4/41 (9.8%)	-	4/35 (11.4%)	3/23 (13.0%)	-
>5000 Yuan/month	9 (24.3%)	11/41 (26.8%)	-	9/35 (68.6%)	7/23 (30.4%)	-
Training duration, m	-	4.5 (2.4-9.0)	-	-	18.0 (14.5–20.0)	-
Daily exercise time, min/d	32 (13–51)	206 (120–223)	< 0.001	10 (6–26)	167 (103–240)	< 0.001
Frequency of 60-minute physical activity sessions, d/w	3 (2–5)	7 (6–7)	< 0.001	3 (1–4)	7 (5–7)	< 0.001
Bone age, y	15 (14–16)	15 (14–17)	0.415	16 (15–17)	16 (15–16)	0.774
Puberty, n (%)	52 (96.3%)	51 (94.4%)	1.000	51 (100.0%)	31 (100.0%)	1.000
Height, cm	165.8 ± 8.0	170.6 ± 8.9	0.004	169.5 ± 7.6	172.5 ± 8.3	0.104
Weight, kg	64.7 ± 18.8	60.1 ± 10.4	0.118	69.6 ± 21.5	62.3 ± 9.6	0.039
BMI, kg/m^2	22.3 ± 5.3	20.5 ± 2.6	0.001	24.0 ± 6.1	20.9 ± 2.3	0.002
Overweight or obese, n (%)	27(50.0%)	15(27.8%)	0.018	25 (49.2%)	7 (22.6%)	0.017
WC, cm	78.6 ± 14.0	71.2 ± 7.0	0.001	80.5 ± 14.9	73.0 ± 6.1	0.002
SBP, mmHg	119 ± 13	117 ± 10	0.321	116 ± 11	118 ± 11	0.303
DBP, mmHg	76 ± 9	68 ± 8	< 0.001	74 ± 9	68 ± 9	0.005
FBG, mmol/L	4.59 ± 0.35	4.53 ± 0.34	0.393	4.12 ± 0.42	4.56 ± 0.34	< 0.001
Insulin, uU/ml	16.50 (13.88–22.38)	10.60 (8.12–14.03)	< 0.001	17.3 (13.8–24.3)	11.7 (8.5–13.3)	< 0.001
HOMA-IR	3.43 (2.78–4.73)	2.16 (1.58–2.99)	< 0.001	3.24 (2.45–4.61)	2.20 (1.78–2.87)	< 0.001
TGs, mmol/L	1.13 (0.73–1.46)	0.74 (0.56–1.10)	< 0.001	0.87 (0.66–1.41)	0.69 (0.53–0.9)	0.003

Data are presented as means ± SD for normal distribution and median with interquartile range for non-normal distribution. Paired t tests, Wilcoxon signed-rank and McNemar tests were used for matched characteristics (age, target height, sex and dietary habits) while Student's t tests, Wilcoxon rank-sum, Spearman's rank correlation tests, χ^2 tests and Fisher's exact tests were used for unmatched characteristics (other characteristics). BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TGs, triglycerides;

(shown in the red box in Fig. 5), and most of them correlated with more than one indicator. Specifically, 6 eicosanoids were associated with DBP ($r = -0.199$–-0.372, $P = 0.002$–0.038), 8 were associated with HOMA-IR ($r = -0.372$–-0.199, P = < 0.001–0.038), and 8 were associated with TGs ($r = -0.424$–-0.229, P = < 0.001–0.017), suggesting a potential role of eicosanoids for exercise in improving overall metabolic health.

Differential metabolites as biomarkers for predicting clinical metabolic indicators after 1 year

To evaluate the potential of differential metabolites as biomarkers, ROC curve analysis was performed for metabolites associated with metabolic indicators at the 1-year follow-up. Among the 23 metabolites associated with DBP, papaverine was found to discriminate elevated DBP at follow-up with an AUC of 0.711 (95% CI: 0.545–0.877), outperforming BMI (AUC: 0.676, 95% CI:

Table 2 Key metabolic health changes within the 1-year follow-up period

	Non-exercise ($n=51$)	Exercise ($n=31$)	*P* value
ΔBMI, kg/m^2	0.26 ± 1.61	0.64 ± 1.62	0.313
ΔWC, cm	1.07 ± 4.97	1.83 ± 5.30	0.514
ΔDBP, mmHg	−1.78 ± 9.62	−0.16 ± 10.82	0.482
ΔHOMA-IR	−0.34 ± 2.38	0.27 ± 1.00	0.172
ΔTGs, mmol/L	−0.08 ± 0.41	−0.05 ± 0.32	0.699

Data are presented as means ± SD for normal distribution and median with interquartile range for non-normal distribution. Student's t tests were used. BMI, body mass index; WC, waist circumference; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; TGs, triglycerides;

0.511–0.841) and WC (AUC: 0.696, 95% CI: 0.541–0.850) (Fig. 6A).

For HOMA-IR, BMI and WC remained the best predictors of insulin resistance, with AUCs of 0.782 (95% CI: 0.681–0.882) and 0.740 (95% CI: 0.616–0.864), respectively.

Among the 33 metabolites associated with TGs at follow-up, prostaglandin K2 (AUC: 0.784, 95% CI: 0.678–0.889), 5-phenyl-N-(4-(trifluoromethyl)phenyl) oxazol-2-amine (AUC: 0.753, 95% CI: 0.644–0.861), and azelaic acid (AUC: 0.736, 95% CI: 0.628–0.844) showed superior performance in discriminating elevated TGs at follow-up compared to BMI (AUC: 0.717, 95% CI: 0.582–0.851) and WC (AUC: 0.723, 95% CI: 0.591–0.855). The combination of these three metabolites yielded the best prediction performance, with an AUC of 0.861 (95% CI: 0.774–0.948) (Fig. 6B).

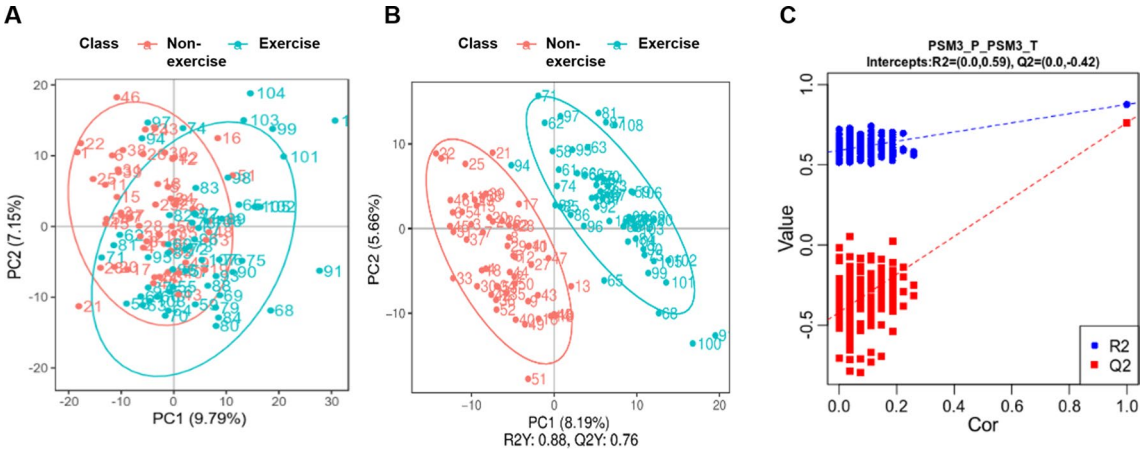

Fig. 2 Multivariate analysis of untargeted serum metabolomics research in non-exercise group ($n=54$) and exercise group ($n=54$) at enrollment. **A**. Principal component analysis of 2 groups. **B**. Partial least squares discriminant analysis (PLS-DA), $R^2Y=0.88$, $Q^2Y=0.76$. **C**. Corresponding permutation analyses for the statistical validation of PLS-DA

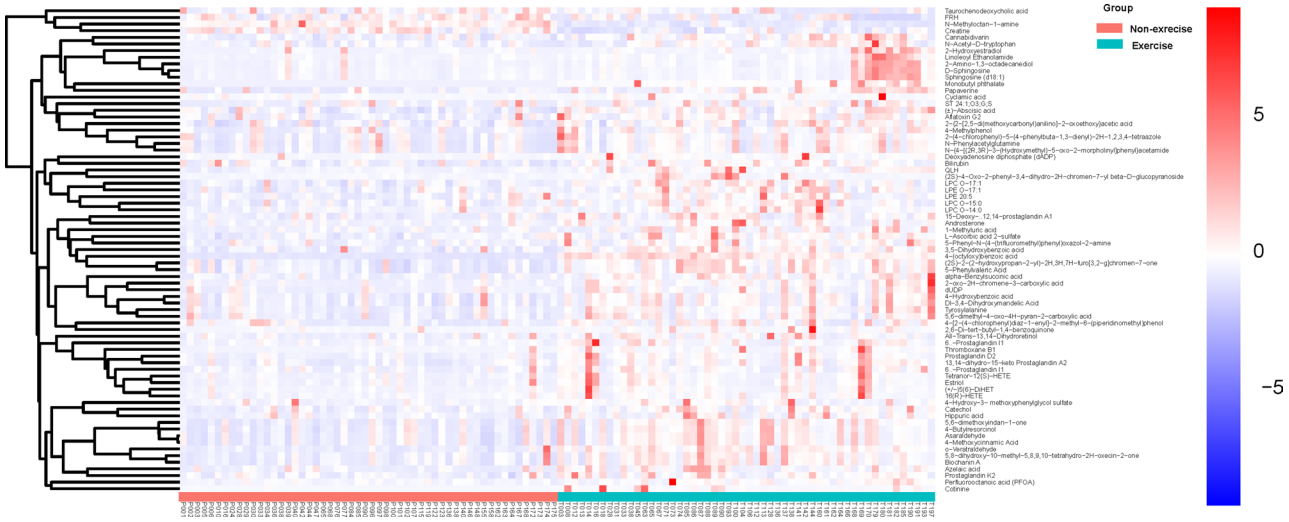

Fig. 3 Heat map of differential metabolites in non-exercise group ($n=54$) and exercise group ($n=54$) at enrollment. High peak intensity is represented in red, and low peak intensity is represented in blue. Hierarchical clustering, based on Euclidean distance, is shown with the dendrogram. A total of 73 differential metabolites were identified, of which 69 were upregulated and 4 were downregulated in exercise group compared to the non-exercise group

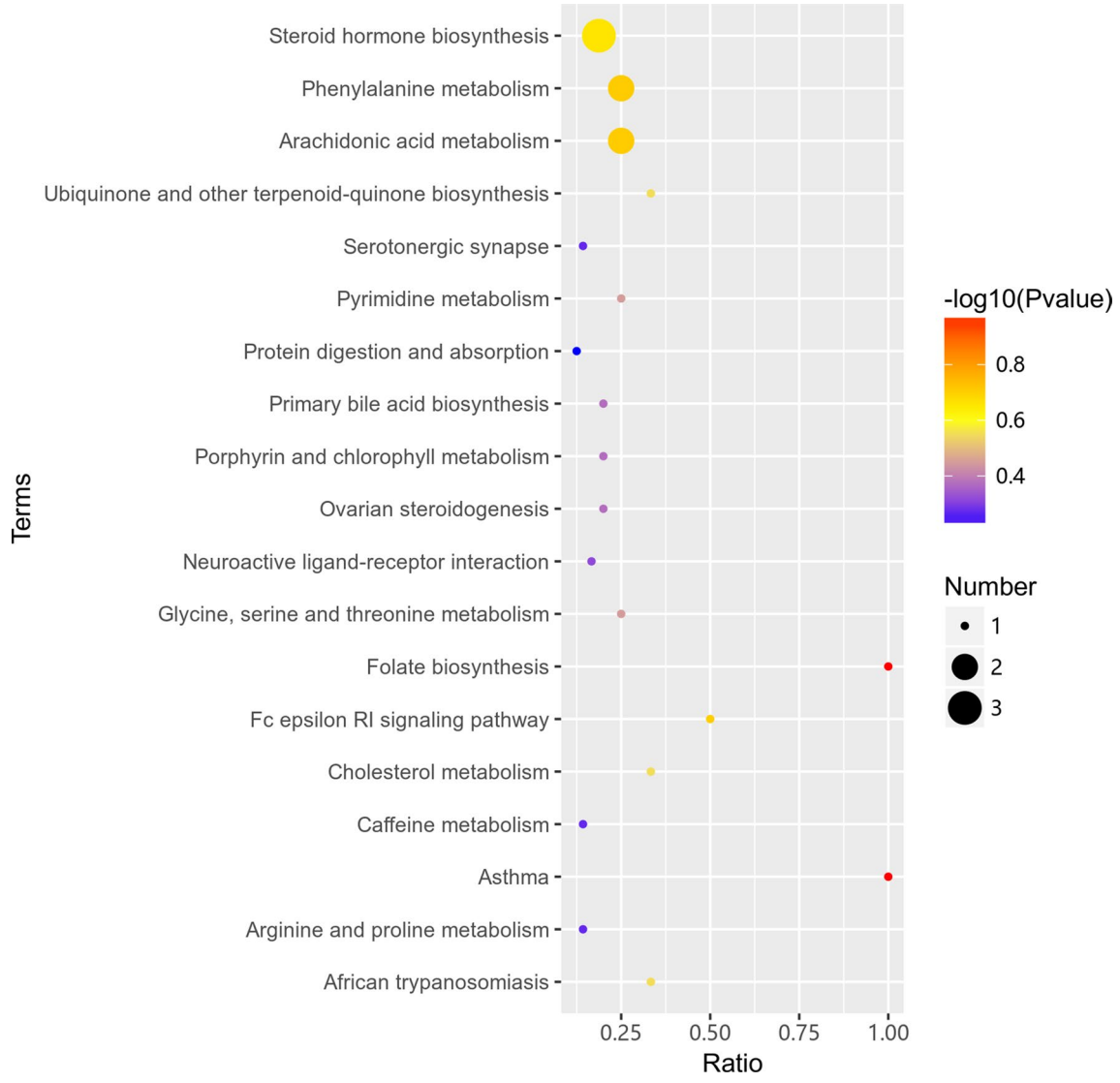

Fig. 4 Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment pathways of differential metabolites. The ratio represents the number of differential metabolites in a given metabolic pathway divided by the total number of identified metabolites in that pathway. The size of the dots reflects the number of metabolites in the pathway, while the color of the dots indicates the P-value obtained from the hypergeometric test. Top 3 pathways: steroid hormone biosynthesis pathway, phenylalanine metabolism pathway, and arachidonic acid metabolism pathway

Discussion

In this study, we employed propensity score matching to compare clinical metabolic indicators and serum metabolomic profiles between 54 pairs of adolescents engaged in exercise training and their matched peers who did not participate in sports. Propensity score matching allowed us to compare two groups with different exercise backgrounds but similar age, sex, dietary habits, hereditary target height and other characteristics, thus minimizing the impact of confounding factors on the exercise benefits related to metabolic health. High-throughput metabolomics provided new insights into the mechanisms behind exercise benefits building on existing knowledge, and helped identify potential biomarkers for predicting the effects of exercise on metabolic health (shown in Fig. 7).

Our findings showed that long-term exercise reduced BMI, WC, DBP, HOMA-IR and TGs levels at enrollment and 1-year follow up. Previous systematic reviews have demonstrated the benefits of exercise training for BMI, WC, SBP, DBP, HOMA-IR or TGs [13, 14, 34, 35]. Exercise durations of less than 2 months have shown benefits, although longer durations (more than 2 or 3 months) might produce stronger effects [13, 14]. Our results at enrollment were consistent with previous studies regarding DBP, HOMA-IR, and TGs, highlighting the beneficial effects of exercise on metabolic health. SBP did not differ significantly between the groups, which could be

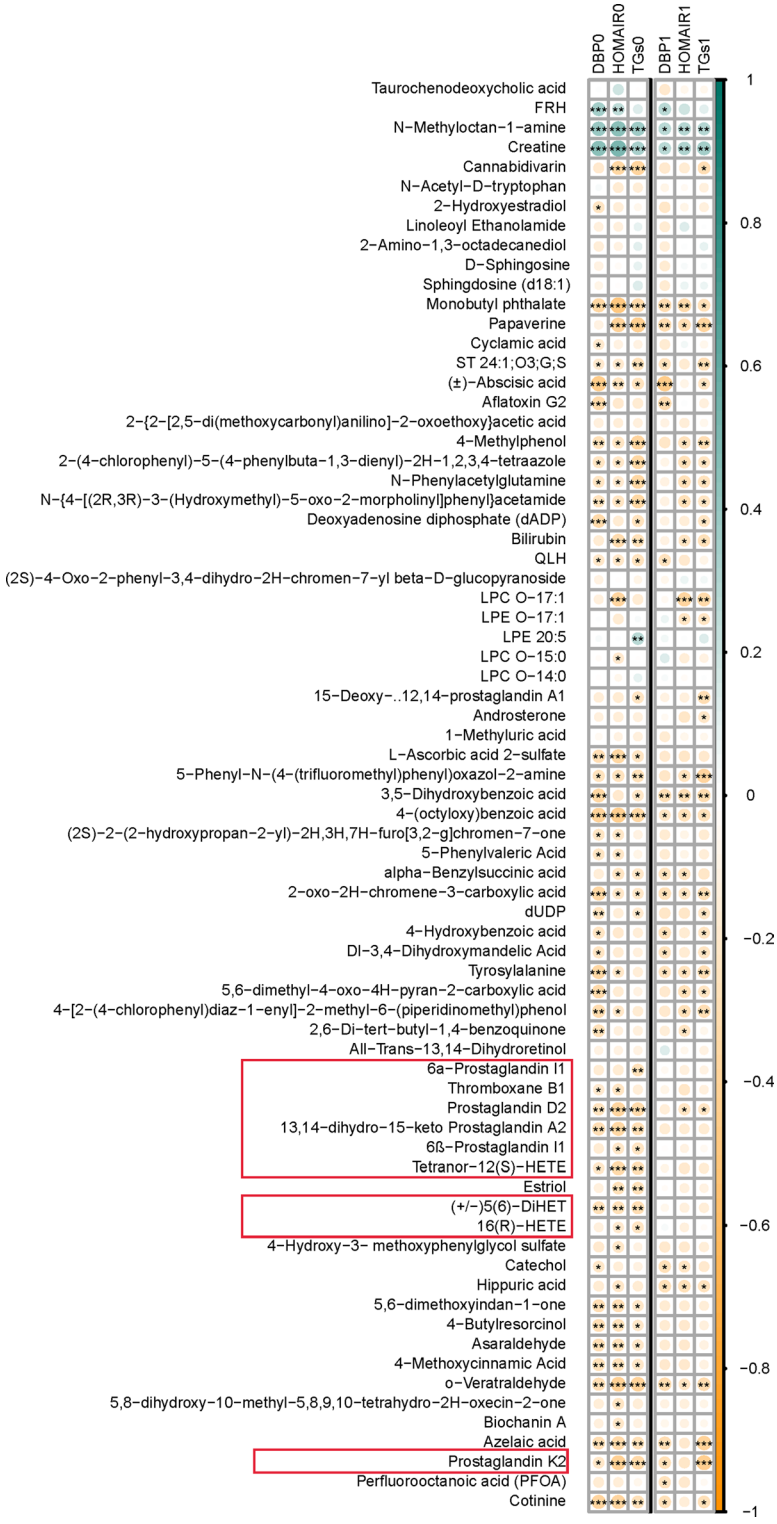

Fig. 5 Association between different metabolites and clinical metabolic indicators of interest at enrollment and 1-year follow-up. The red box showed a group of eicosanoids associated with clinical metabolic indicators. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. DBP0 & DBP1, diastolic blood pressure at enrollment and follow-up; HOMAIR0 & HOMAIR1, homeostasis model assessment of insulin resistance at enrollment and follow-up; TGs0 & TGs1, triglycerides at enrollment and follow-up

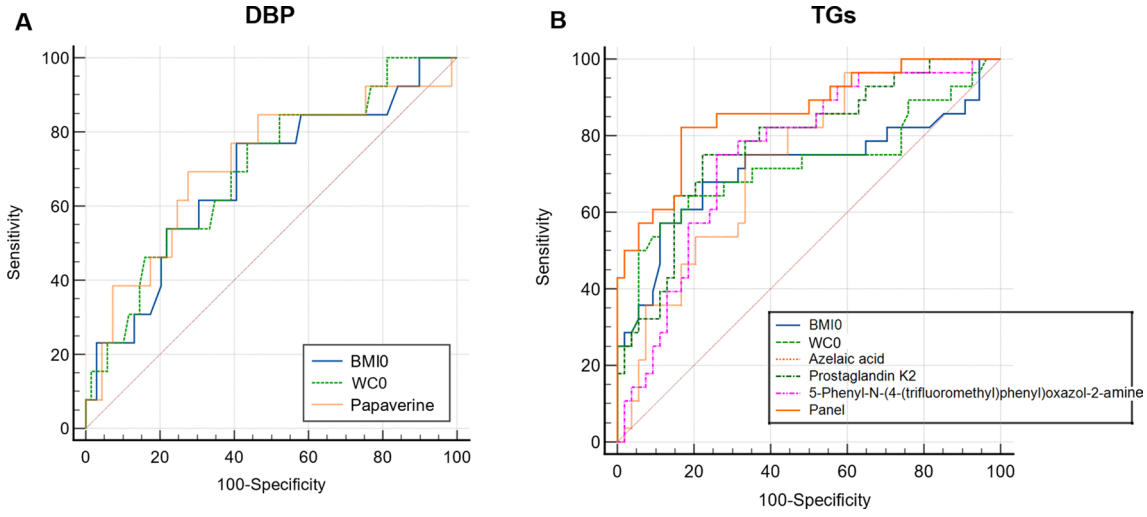

Fig. 6 Receiver operating characteristic analysis of potential biomarkers compared with body mass index (BMI) and waist circumference (WC) at enrollment for high diastolic blood pressure (DBP) and triglycerides (TGs) at follow-up. (**A**) Papaverine: area under curve (AUC): 0.711 (95%CI: 0.545–0.877), compared with BMI (AUC: 0.676, 95%CI: 0.511–0.841) and WC (AUC: 0.696, 95%CI: 0.541–0.850). (**B**) Azelaic acid (AUC: 0.736, 95%CI: 0.628–0.844), prostaglandin K2 (AUC: 0.784, 95%CI: 0.678–0.889), 5-phenyl-N-(4-(trifluoromethyl)phenyl) oxazol-2-amine (AUC: 0.753, 95%CI: 0.644–0.861) and panel: 0.861 (95%CI: 0.774–0.948) compared with BMI (AUC: 0.717, 95%CI: 0.582–0.851) and WC (AUC: 0.723, 95%CI: 0.591–0.855)

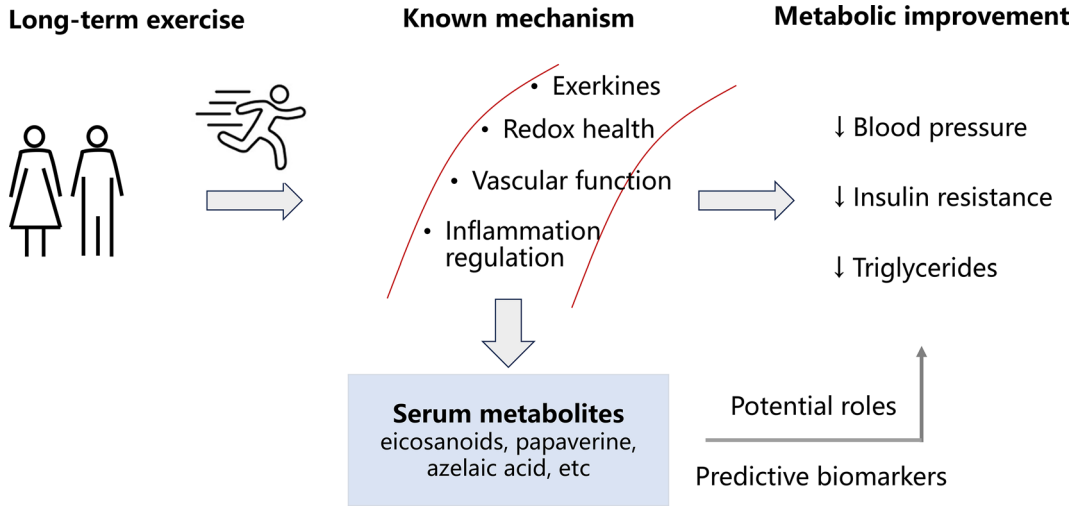

Fig. 7 Metabolomics offers new insight into exercise benefits on metabolic health in adolescents

explained by the greater average height in our exercise group, as SBP reflects the pressure generated when the heart beats, and taller individuals require higher SBP to circulate blood throughout the body. The results at the 1-year follow-up showed consistent metabolic health improvements in the exercise group, further validating the exercise effect. Interestingly, the changes in metabolic indicators over the year were not significant between the two groups. This is reasonable, as participants in the exercise group had undergone a median of 4.5 months of exercise training at enrollment, and metabolic indicators might have already decreased initially and then stabilized at healthy levels, as observed in adult studies [36]. Moreover, the exercise effect on health can diminish or even rebound if exercise is stopped [37, 38], emphasizing the need for continued exercise to sustain metabolic benefits during the follow-up period.

Untargeted metabolomics, which involves the comprehensive characterization of small molecules, provided an unbiased perspective to explore the overall physiological changes after long-term exercise and the potential mechanisms underlying the exercise effect on metabolic health. In this untargeted metabolomic study using UHPLC-MS/MS, we observed distinct differences in metabolomic profiles between adolescents with and without long-term exercise training. Differential metabolites were involved in pathways such as steroid hormone biosynthesis, phenylalanine metabolism, and arachidonic

acid metabolism, although the differences were not statistically significant. Previous untargeted metabolomic studies on long-term exercise have yielded varied results, likely due to differences in technological platforms, sample types, and exercise protocols [28]. Adult studies generally report changes in response to exercise in fatty acid metabolism, lipolysis, the tricarboxylic acid cycle, glycolysis, amino acid metabolism, and steroid metabolism, etc [27, 28, 39]. In our study the 3 enriched pathway could be related to steroid metabolism, amino acid metabolism and inflammation response after exercise. Similar pathways were also found in another UHPLC-MS/MS study of type 2 diabetes adults after aerobic exercise [40]. However, due to the limited number of metabolites identified in these pathways in our study, the specific relevance of these changes remains difficult to interpret.

Our study identified 59 differential metabolites associated with reductions in DBP, HOMA-IR, or TGs, with 42 of them correlated with more than one clinical indicator, suggesting that they may play a role in common and upstream pathways regulating DBP, HOMA-IR, and TGs simultaneously. A group of eicosanoids stood out among the identified metabolites, as they were consistently negatively associated with DBP, HOMA-IR, or TGs. Eicosanoids are bioactive lipids known to play a key role in the emergence and progression of metabolic diseases, primarily through their immune and inflammation-regulating functions [41]. In our study, we observed upregulation of eicosanoids that have shown potential anti-inflammatory effects in previous research. For example, 6α – prostaglandin I1 and 6β – prostaglandin I1 are prostaglandin I2 analogs known for mediating inflammation and vasodilation [42]. Prostaglandin D2 and 16 (R) – HETE have been implicated in vasodilation and the regulation of cardiovascular homeostasis and blood pressure [43, 44]. (+/-)5(6)-DiHET is an anti-inflammatory lipid mediator that can suppress vascular hyperpermeability during inflammation [45]. Except for eicosanoids, abscisic acid [46], papaverine [47], azelaic acid [48], 4-methoxycinnamic acid [49] have also been found to play roles in anti-inflammation and are strongly associated with metabolic indicators. While inflammation regulation is one of the known mechanisms through which exercise promotes metabolic health [20], these metabolites provide more specific insights into this process.

Interestingly, eicosanoids are mainly endogenous, while both papaverine and azelaic acid are thought to be primarily derived from plants, and obtained through dietary intake, therefore called "xenometabolites". Previous untargeted metabolomic studies have also found increases in "xenometabolites" associated with physical activity or exercise [50, 51], even under a highly controlled, equivalent diet [51], suggesting that exercise may regulate the metabolism of "xenometabolites" to improve metabolic health. The potential mechanisms could include exercise releasing xenometabolites from storage, exercise decreasing renal excretion of xenometabolites, exercise influencing xenometabolites from the digestive tract, or the possibility that these xenometabolites are not truly exogenous but are misclassified due to technological limitations [51]. This offers a novel perspective on the mechanisms behind the benefits of exercise, though the exact regulatory processes require further investigation.

Among the correlated metabolites, we aimed to identify potential biomarkers for predicting metabolic health. Biomarkers are valuable for assessing health and recovery during exercise, but most are used to improve performance in athletes [52], not to track exercise-induced health improvements. Developing a monitoring system to help individuals adjust their exercise interventions could greatly improve their metabolic health through exercise. Obesity markers like BMI and WC are potential markers and have been widely used for prediction of cardiometabolic diseases [53]. However, these markers are more likely to reflect the results of exercise rather than the intermediate processes, limiting their ability to predict future metabolic improvements. Additionally, BMI and WC can be influenced by lean body mass or measurement errors, further restricting their applicability.

Metabolites reflecting the physiological effects of exercise could offer more reliable biomarkers for predicting health improvements. In this study, we identified several potential biomarkers, such as papaverine and azelaic acid, which better predicted exercise-induced improvements in DBP and TGs than BMI or WC. Papaverine is an alkaloid with a variety of biological activities, including peripheral vasodilation, anti-inflammatory effects, and potential roles in cardiovascular health [47]. Its vasodilatory effect has been well established, leading to its clinical use in treating peripheral vascular spasm [47]. Azelaic acid, an α, ω-dicarboxylic acid, is known for its anti-inflammatory and antioxidant properties. It has been shown to improve metabolic health in high-fat diet-induced obese mice and overweight male adults, including reducing TGs [54, 55]. Our findings suggest these metabolites increase in response to long-term exercise, highlighting their role in exercise-induced metabolic improvements. For individuals aiming to improve metabolic health through exercise, these biomarkers reflect the effects of their current exercise plans and can be monitored throughout training to help adjust or customize exercise prescriptions. Additionally, prostaglandin K2 and 5-phenyl-N-(4-(trifluoromethyl)phenyl) oxazol-2-amine could also potentially predict future reductions in TGs, and offered even better predictive value when combined with azelaic acid. However, as prostaglandin K2 and 5-phenyl-N-(4-(trifluoromethyl)phenyl) oxazol-2-amine could not be annotated with current knowledge,

further investigation is needed to confirm their roles as biomarkers.

In conclusion, our metabolomic study highlights that exercise is associated with beneficial metabolic effects, and identifies associated metabolite changes, providing novel insights into how exercise improves adolescent health, including anti-inflammatory mediators like eicosanoids. Papaverine and azelaic acid emerged as potential biomarkers for predicting exercise benefits on DBP and TGs. To our knowledge, this is the first study to identify biomarkers for monitoring exercise effects on metabolic health and adjusting exercise prescriptions in practice. The strengths of our study include the careful matching of confounding factors, but there are limitations. The sample size was relatively small, and the AUC of potential markers showed broad 95% CI, suggesting instability in predictive power. Due to the absence of an independent cohort for validation, we were unable to address this limitation in our study. Future research should include larger sample sizes and validate the potential biomarkers in independent cohorts using targeted methods.

Supplementary Information

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Supplementary Material 1

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Author contributions
All authors read and approved the final manuscript. SC and HP designed the study. XG, ZZ, YW, SL, YH analyzed and interpreted data. XG conducted the analysis and drafted the manuscript. HS, HD revised the manuscript. HY, HZ, MZ, BB, SC and HP finalized the manuscript. The corresponding authors attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All participants volunteered, and informed consent was obtained from both the subjects and their guardians. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Peking Union Medical College Hospital (No. K3298).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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