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ORIGINAL ARTICLE

Cytokine, glycemic, and insulinemic responses to an acute bout of games-based activity in adolescents

Karah J. Dring[1] | **Simon B. Cooper**[1] | **John G. Morris**[1] | **Caroline Sunderland**[1] | **Gemma A. Foulds**[2] | **A. Graham Pockley**[2] | **Mary E. Nevill**[1]

[1]Department of Sport Science, Sport Health and Performance Enhancement (SHAPE) Research Centre, School of Science and Technology, Nottingham Trent University, Nottingham, UK

[2]John van Geest Cancer Research Centre, School of Science and Technology, Nottingham Trent University, Nottingham, UK

Correspondence
Simon B. Cooper, Department of Sport Science, School of Science and Technology, Nottingham Trent University, Clifton Campus, Nottingham, UK.
Email: simon.cooper@ntu.ac.uk

An acute bout of endurance exercise in adults stimulates a same-day anti-inflammatory response which may affect low-grade chronic inflammation and insulin resistance and benefit cardio-metabolic health. The anti-inflammatory responses to intermittent games-based exercise and to exercise in young people beyond 2 hours post-exercise are unknown. Thus, the purpose of the present study is to examine the anti-inflammatory, glycemic and insulinemic response to games-based activity in adolescents. Following ethical approval and familiarization, 39 adolescents (12.3 ± 0.7 years) completed an exercise (E) and rested (R) trial in a counterbalanced, randomized crossover design. Following a standardized breakfast, participants completed 1-hour games-based activity. Capillary blood samples were taken at baseline, immediately and 1 hour post-exercise, and 30, 60 and 120 minutes following a standardized lunch. A final blood sample was taken the next morning. Data were analyzed using repeated measures ANOVA. IL-6 concentration was higher on day one of the exercise trial (E:3.4 ± 0.4, R:2.7 ± 0.4 pg/mL; $P = 0.006$), as was the anti-inflammatory IL-6:TNF-α ratio (E:5.53 ± 0.93, R:3.75 ± 0.45; $P = 0.027$). Levels of the anti-inflammatory cytokine IL-10 increased on day two of the exercise trial (E:2.11 ± 0.23, R:1.66 ± 0.16 pg/mL; $P = 0.032$). Insulin sensitivity was enhanced on the exercise trial with a reduction in iAUC following the standardized lunch (E:2310 ± 834, R:3122 ± 1443 mU/L × 120 minutes; $P < 0.001$). Games-based activity stimulated an anti-inflammatory response up to 24 hours post-exercise and improved insulin sensitivity in response to a standardized meal in healthy adolescents. These novel findings suggest that games-based activity is an ecologically valid mode of exercise to elicit beneficial effects on cardio-metabolic risk factors in young people.

KEYWORDS

adolescents, cardio-metabolic health, games-based activity, glycemic, inflammation, insulinemic

1 | INTRODUCTION

Low-grade chronic inflammation is involved in the pathogenesis of several chronic diseases, including cardiovascular disease and type 2 diabetes.[1-4] Although such conditions typically present during adulthood, the development of cardio-metabolic risk factors for these diseases originate during childhood, with low-grade chronic inflammation, atherosclerotic plaques, and insulin resistance observed in pubertal children.[5-7] Low-grade chronic inflammation is defined as a twofold to threefold increase in systemic concentrations of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and the acute phase protein c-reactive protein (CRP).[3] The inflammatory response that follows an acute bout of exercise (reflected by increased IL-6 levels that are produced by the contraction of skeletal muscle and the subsequent stimulation of a systemic increase in the concentration of anti-inflammatory cytokines) is a mechanism that stimulates muscle regeneration and reduces low-grade chronic inflammation and insulin resistance in adults,[1,3] with in vitro studies reporting that IL-10 inhibits the synthesis of chronic pro-inflammatory mediators TNF-α and IL-1β.[3] Furthermore, in the plantaris muscle of mice increased levels of IL-6 post-exercise increases the expression of glucose transporter-4, which increases glucose uptake.[8] These findings suggest that a rise in IL-6 post-exercise triggers an anti-inflammatory response and enhances insulin sensitivity.

Despite the presence of low-grade chronic inflammation and insulin resistance in young people,[5] information on the inflammatory response to an acute bout of exercise in adolescents is limited. Previous studies examining the release of inflammatory mediators, IL-6, and TNF-α in response to an acute bout of endurance exercise have reported increases,[9,10] decreases,[11] or no changes.[12,13] However, young people do not typically participate in endurance exercise, with intermittent activity being both enjoyable (important for long-term adherence)[14] and replicative of their physical activity patterns.[15] Eccentric exercise is an alternative mode of physical activity that elicits an increase in the release of pro-inflammatory cytokines (IL-6 and IL-1β) in response to the muscle damage incurred.[16-18] Furthermore, games-based activities, such as basketball, are intermittent in nature and replicate the activity patterns of young people whilst also having previously been reported to induce muscle damage and an inflammatory response (increased IL-6 and IL-1β) in adults.[19] Therefore, it is important to determine whether intermittent games-based activity elicits a protective anti-inflammatory response which benefits cardio-metabolic health in young people.[1,3]

Only two studies in young people have assessed the effect of intermittent exercise on inflammatory mediators.[10,20] McMurray et al[20] reported that 10×2 minutes bouts of high intensity intermittent cycling in pubertal adolescents increased the anti-inflammatory IL-6:TNF-α ratio by 80% 2 hours post-exercise, whereas Scheet et al[10] observed that 90 minutes of soccer in pre-pubertal children increased IL-6 (125%) and TNF-α (18%) 2 hours post-exercise, yet did not affect anti-inflammatory mediator IL-10. The differences in exercise intensity and duration might explain these discrepant findings. Importantly, these studies have only assessed IL-6, TNF-α, and IL-10 for 2 hours post-exercise, despite in vitro studies reporting that inflammatory mediators (IL-10 and CRP) remain elevated for up to 24 hours post-exercise.[1,3] To fully examine the inflammatory response to exercise, a complete range of pro-inflammatory (IL-1β, TNF-α, and CRP) and anti-inflammatory (IL-6, IL-10 and IL-6:TNF-α) cytokines should be measured up to 24 hours post-exercise.

Another important aspect of cardio-metabolic health is the glycemic and insulinaemic responses following a meal. It has previously been reported that a 45-minute bout of aerobic exercise residually enhanced insulin sensitivity in adolescents for up to 17 hours, as demonstrated by reduced postprandial glycemic and insulinaemic responses following a high fat meal.[21] Furthermore, high intensity intermittent and moderate intensity cycling in adolescent boys reduced the glycemic and insulinemic responses by 24%-29% following an oral glucose tolerance test, in comparison with a rested control trial.[22] However, the impact of exercise on the glycemic and insulinemic responses to an ecologically valid meal remains unknown and no studies have examined the association between the inflammatory and glycemic/insulinemic responses post-exercise, despite the anti-inflammatory response being associated with insulin sensitivity.[23]

Therefore, the present study investigated if an acute bout of intermittent games-based activity stimulates an anti-inflammatory and metabolic response in young people.

2 | METHODOLOGY

2.1 | Study design

The institutional ethical advisory committee approved all procedures (approval number SST-417). Participants were recruited from secondary schools, and written informed parental consent alongside child assent was obtained. The following exclusion criteria were applied (a) a medical history of chronic diseases including, but not limited to, cardiovascular disease, diabetes, and hypertension, (b) prescription of regular medication that may affect participation in the study, and (c) any factor that would cause an inability to complete the exercise components of the study. A parent/guardian completed a health screen questionnaire on behalf of the participant to ensure there were no medical conditions affecting participation in the study.

The familiarization session preceded the main experimental trial by 7 days. During familiarization, the experimental

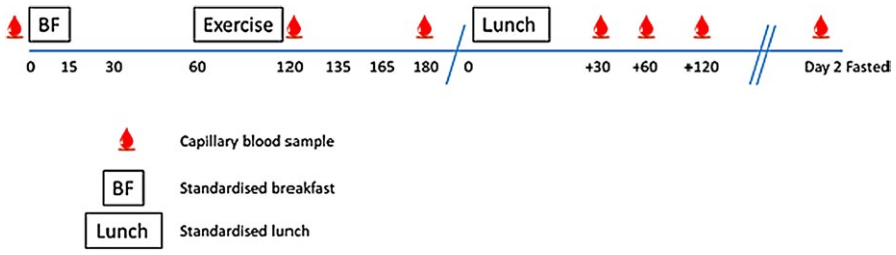

FIGURE 1 Experimental protocol

protocol was explained to participants and they were familiarized with the methods included in the main trials. Participants completed the multi-stage fitness test (MSFT) to predict peak oxygen consumption.[24] Predicted peak oxygen uptake was calculated using an adolescent-specific calculation,[25] and mean (±SD) peak oxygen consumption was 50.3 ± 4.4 mL/kg/min.

2.2 | Participant characteristics

Forty-one schoolchildren aged 11-13 years were recruited to the present study. Two participants did not complete the study, as a consequence of which 39 participants (20 males, 19 females) were included in the analysis. During familiarization, body mass (Seca 770 digital scale, Hamburg, Germany), height, and sitting height (Leicester Height Measure, Seca, Hamburg, Germany) were measured to determine age at peak height velocity.[26] Waist circumference was measured at the narrowest point of the torso using a standard tape measure. Four skinfold sites (tricep, subscapular, supraspinale, and front thigh) were measured by trained kinanthropometrists in line with ISAK guidelines.[27] The sum of skinfolds was the preferred measure of body composition, as estimated body fat from skinfolds is associated with large random and systematic error.[28] The participants' anthropometric characteristics were (mean ± SD) age 12.3 ± 0.7 years; height 155.7 ± 7.5 cm; body mass: 46.0 ± 9.5 kg; predicted years from peak height velocity: −0.37 ± 1.1 years; waist circumference: 65.4 ± 5.7 cm; and sum of skinfolds: 44.9 ± 19.5 mm.

2.3 | Main trials

The study employed a randomized, counterbalanced, crossover design consisting of an exercise and rested (control) trial, separated by 7 days. As one of the main trials incorporated an exercise session, participants were not blinded to the trial condition. The experimental protocol is displayed in Figure 1.

Participants recorded their dietary intake for 24 hours preceding the first main trial and during evening one of the study; recorded diets were replicated for the subsequent main trial. Participants arrived at school fasted from 9 PM the previous evening on day one and day two of the main trials. Participants were asked to refrain from physical activity 24 hours prior to and during all main trials. A telephone call was made to parents/guardians prior to each main trial to ensure compliance.

On arrival at school (8.30 AM), participants were fitted with a heart rate monitor (Team Sports System, Firstbeat Technologies Ltd, Jyvaskyla, Finland) which was worn during main trials. A standardized breakfast (cornflakes, milk, toast, margarine) and lunch (chicken sandwich (cheese alternative for vegetarians), baked crisps, apple) were provided, each containing 1.5 g carbohydrate per kg body mass, as used in previous research.[24] Participants had 15 minutes to consume each meal.

2.4 | Capillary blood sample

Capillary blood samples were taken at baseline, immediately post-exercise, and 60 minutes post-exercise (Figure 1). Additional blood samples were taken 30, 60 minutes (2 hours post-exercise), and 120 minutes (3 hours post-exercise) following a standardized lunch. A final fasted capillary blood sample was taken the following morning (day two) using previously described methods.[29]

Blood glucose and plasma insulin concentrations were measured in duplicate using commercially available kits (glucose: GOD/PAP method, GL364, Randox, Crumlin, Ireland; insulin: ELISA, Mercodia Ltd, Uppsala, Sweden). The intra-assay coefficient of variation (CV) of the assays, based on eight repeat measurements, was 2.3% for blood glucose and 3.2% for plasma insulin concentration. Blood glucose and plasma insulin iAUC following the standardized lunch were calculated.[30,31]

Cytokine (IL-1β, IL-6, TNF-α, and IL-10) concentrations were determined using a flow cytometry-based multiplex bead approach (AimPlex™ multiplex assay, YSL, Pomona, CA, USA) using a Beckman Coulter Gallios™ flow cytometer and Kaluza™ data acquisition and analysis software (Beckman Coulter, London, UK). CRP concentrations were determined using the same approach, but in a separate assay due to a greater sample dilution being required. In line with manufacturer guidelines, a minimum of 50 events per bead population were acquired. The intra-assay CV based on eight repeat measurements was in line with the CV of ~16% reported in the literature for these analytes[32] (IL-6:15.9%; IL-10:13.2%; TNF-α: 14.7%, IL-1β: 17.4%; CRP: 10.2%).

A comparison between cytokine concentrations determined from capillary (C) and venous (V) blood was performed on 20 samples obtained from healthy adults. There was no difference for any analytes (IL-6: C 1.41 ± 1.17, V 1.41 ± 1.49 pg/mL, $P = 0.999$; IL-10: C 0.69 ± 0.30, V 0.66 ± 0.29 pg/mL, $P = 0.750$; TNF-α: C 1.20 ± 1.79, V 1.52 ± 2.26 pg/mL, $P = 0.234$; IL-1β: C 2.66 ± 2.19, V 1.41 ± 1.43 pg/mL, $P = 0.187$; CRP C 0.32 ± 0.61, V 0.31 ± 0.56 mg/L, $P = 0.767$). The 95% limits of agreement were calculated[33]: IL-6 −0.923, +0.823 pg/mL; IL-10 −0.969, +0.929 pg/mL; TNF-α −1.208, +1.458 pg/mL; IL-1β −2.102, +0.868 pg/mL; and CRP −0.471, +0.434 mg/L.

2.5 | Exercise protocol

The exercise trial incorporated a 60-minute basketball session, which commenced 1 hour after breakfast on day 1 (Figure 1). An experienced basketball coach delivered the sessions to groups of 10 participants in a school sports hall. The basketball session consisted of a warm-up (5 minutes of jogging on the court followed by dynamnic stretches), skill-based drills (30-minute passing, dribbling and shooting drills), and small-sided games (25 minutes) to finish. Immediately post-exercise, participants returned to the classroom and rested quietly for the remainder of the day. During the control trial, participants rested in the classroom throughout the day.

2.6 | Statistical analysis

A power calculation was performed using GPower 3.1.9.2 based on the previously reported effects of exercise on IL-6 in young people[34] and an estimated effect size of 0.3 (two-tailed significance). This yielded a required total sample size of 38.

Data were assessed for normality using the Shapiro-Wilk test, and all dependent variables were normally distributed (all $P > 0.05$). Inflammatory cytokine, blood glucose, and plasma insulin concentration data were analyzed in SPSS (Version 24, SPSS Inc, Chicago, IL, USA) via three-way (trial * time * sex) Analysis of Variance (ANOVA) with repeated measures for trial and time. Separate ANOVAs were conducted for day one and between resting measures on day one and day two. Where significant interactions were observed, post-hoc pairwise comparisons were performed using a Bonferroni correction. Blood glucose iAUC, plasma insulin iAUC, and heart rate were compared using a paired samples *t* test. Where significant effects existed for main effect of trial and trial by time interactions, effect sizes were calculated as Cohen's *d*. For all analysis, significance was accepted as $P < 0.05$ and data are presented as mean ± SEM.

TABLE 1 Summary of the inflammatory responses following 60-min high intensity, intermittent, games-based activity and during the rested control trial

	Rest	Post-exercise	1 h post-exercise	2 h post-exercise	3 h post-exercise	Day 2 rest
IL-6 (pg/mL)						
Exercise	2.07 ± 0.34	2.46 ± 0.35	3.51 ± 0.56	4.28 ± 0.49	4.81 ± 0.84	2.30 ± 0.45
Control	1.98 ± 0.33	2.06 ± 0.35	2.88 ± 0.50	3.19 ± 0.70	3.77 ± 0.42	2.14 ± 0.33
IL-10 (pg/mL)						
Exercise	1.45 ± 0.14	1.63 ± 0.19	1.43 ± 0.14	1.74 ± 0.15	1.75 ± 0.19	2.11 ± 0.23*
Control	1.80 ± 0.17	1.73 ± 0.18	1.44 ± 0.12	1.60 ± 0.14	1.72 ± 0.13	1.66 ± 0.16
TNF-α (pg/mL)						
Exercise	1.08 ± 0.21	1.00 ± 0.19	0.98 ± 0.20	1.28 ± 0.33*	1.17 ± 0.24	1.18 ± 0.26
Control	1.17 ± 0.19	0.99 ± 0.14	0.93 ± 0.14	0.98 ± 0.17	0.96 ± 0.14	1.02 ± 0.15
IL-1β (pg/mL)						
Exercise	3.13 ± 0.29	2.95 ± 0.31	3.05 ± 0.31	3.08 ± 0.35	3.02 ± 0.35	3.17 ± 0.34
Control	2.85 ± 0.23	2.68 ± 0.22	2.85 ± 0.25	3.01 ± 0.37	2.94 ± 0.27	2.73 ± 0.23
CRP (mg/L)						
Exercise	0.24 ± 0.06	0.25 ± 0.06	0.20 ± 0.04	0.21 ± 0.06	0.23 ± 0.06	0.25 ± 0.08
Control	0.26 ± 0.05	0.25 ± 0.05	0.22 ± 0.05	0.20 ± 0.04	0.19 ± 0.04	0.17 ± 0.04
IL-6: TNF-a						
Exercise	2.38 ± 0.30	5.21 ± 1.80	5.48 ± 0.90	7.25 ± 1.83	7.27 ± 2.61	2.66 ± 0.37
Control	2.19 ± 0.28	3.06 ± 0.50	3.95 ± 0.85	4.58 ± 0.68	4.94 ± 0.81	3.15 ± 0.85

Levels of inflammatory mediators reported as Mean ± SEM.
*Significant difference between trials, $P < 0.05$.

3 | RESULTS

3.1 | Heart rate

Mean heart rate during the basketball was 157 ± 11 beats/min (76 ± 5% of maximum heart rate achieved during the MSFT; HR_{max}), and maximum recorded mean heart rate was 197 ± 9 beats/min (96 ± 4% HR_{max}). Consequentially, mean heart rate was higher during the exercise trial than the control trial (exercise: 104 ± 14 beats/min, 51 ± 7% HR_{max}; resting: 90 ± 10 beats/min, 44 ± 5% HR_{max}; $t_{(38)} = -7.2$, $P < 0.001$).

3.2 | Inflammatory and metabolic responses

At baseline, there was no difference in inflammatory cytokine, blood glucose, or plasma insulin concentration between the exercise and control trials (all $P > 0.05$). When considering the effect of sex, there were no differences in inflammatory cytokine concentrations between the boys and girls at baseline or post-exercise (all $P > 0.05$).

3.2.1 | Inflammatory variables

The response of the inflammatory variables can be found in Table 1. Overall, IL-6 concentration was higher during day one of the exercise trial when compared with the control trial (exercise: 3.4 ± 0.4, resting: 2.7 ± 0.4 pg/mL; main effect trial, $F_{(1,35)} = 8.7$, $P = 0.006$; $d = 0.3$). Furthermore, IL-6 concentration increased across time during both trials on day one (main effect time, $F_{(1,35)} = 11.3$, $P < 0.001$). No trial * time interaction effect was observed for IL-6 concentration on day one ($P = 0.604$), nor were there any differences 24 hours post-exercise (main effect trial, $P = 0.422$; trial*time interaction, $P = 0.852$).

Overall, IL-10 concentration did not differ between the exercise and control trial on day one (main effect trial, $P = 0.569$), nor were there changes across time (main effect time, $P = 0.151$), nor a trial*time interaction ($P = 0.161$). However, when considering the response of IL-10 24 hours post-exercise, there was a trial*time interaction ($F_{(1,38)} = 5.9$, $P = 0.020$; $d = 0.4$) whereby IL-10 concentration was higher on day two of the exercise trial than the control trial ($t_{(34)} = -2.2$, $P = 0.032$).

Overall, there were no differences in TNF-α concentration between the exercise and control trials on day one (main effect trial, $P = 0.400$), nor were there changes across time (main effect time, $P = 0.197$). There was a trial * time interaction for TNF-α concentration during day one ($F_{(4,108)} = 2.5$, $P = 0.048$), whereby 2 hours post-exercise there was a tendency for TNF-α concentration to increase during the exercise trial in contrast to the control trial ($t_{(27)} = 2.3$, $P = 0.076$, $d = 0.2$). When considering the response of TNF-α 24 hours post-exercise, there was no difference between trials (main effect trial, $P = 0.680$; trial*time interaction, $P = 0.083$).

Overall, IL-1β concentration did not differ between the exercise and control trials on day one (main effect trial, $P = 0.220$), nor were there any differences in IL-1β concentration across time (main effect time, $P = 0.647$). Furthermore, the pattern of change in IL-1β concentration was similar between trials during day one (trial*time interaction, $P = 0.952$). When considering the response of IL-1β 24 hours post-exercise, there was no difference between trials (main effect trial, $P = 0.068$; trial * time interaction, $P = 0.621$).

Overall, CRP concentration did not differ between the exercise and control trials on day one (main effect trial, $P = 0.967$), nor were there any differences in CRP concentration across time (main effect time, $P = 0.190$). The pattern of change in CRP concentration was similar between

TABLE 2 Summary of the glycemic and insulinemic responses following 60-min high intensity, intermittent, games-based activity and during the rested control trial

	Rest	Post-exercise	1 h post-exercise	30 min post-lunch	60 min post-lunch	120 min post-lunch	Day 2
Blood glucose (mmol/L)							
Exercise	4.38 ± 0.06	5.82 ± 0.16*	4.25 ± 0.07*	5.89 ± 0.13	5.01 ± 0.07	4.93 ± 0.08	4.38 ± 0.06
Control	4.54 ± 0.08	5.07 ± 0.10	4.74 ± 0.13	6.07 ± 0.17	5.09 ± 0.12	4.90 ± 0.08	4.72 ± 0.12
Plasma insulin (mU/L)							
Exercise	7.26 ± 0.86	35.95 ± 4.03 *	7.83 ± 1.60*	36.64 ± 3.90*	28.84 ± 2.31*	20.11 ± 2.05	7.22 ± 0.72
Control	8.17 ± 0.94	25.98 ± 3.39	10.50 ± 1.98	59.01 ± 7.84	33.26 ± 2.81	26.28 ± 3.19	8.70 ± 1.18
HOMA-IR							
Exercise	1.55 ± 0.63	-	-	-	-	-	1.40 ± 0.75
Control	1.64 ± 0.86	-	-	-	-	-	1.59 ± 0.93

Glycemic and insulinemic responses reported as Mean ± SEM.

*Significant difference between trials, $P < 0.05$.

trials during day one (trial*time interaction, $P = 0.593$). When considering the response of CRP 24 hours post-exercise, there was no difference between trials (main effect trial, $P = 0.716$; trial*time interaction, $P = 0.116$).

Overall, the IL-6:TNF-α ratio was higher during day one of the exercise trial when compared with the control trial (exercise: 5.53 ± 0.93, resting 3.75 ± 0.45; main effect trial, $F_{(1, 24)} = 5.5$, $P = 0.027$; $d = 0.5$). Furthermore, the IL-6:TNF-α ratio increased across time during both trials on day one (main effect time, $F_{(4, 96)} = 3.3$, $P = 0.043$). There was no trial * time interaction effect observed for the IL-6:TNF-α ratio on day one ($P = 0.764$), nor was there a difference between trials 24 hours post-exercise (main effect trial, $P = 0.827$; trial * time interaction, $P = 0.348$).

3.2.2 | Metabolic variables

The response of the metabolic variables can be found in Table 2. Overall blood glucose concentration did not differ between the exercise and control trial (main effect trial, $P = 0.087$), yet did differ over time (main effect time, $F_{(6,210)} = 61.2$, $P < 0.001$). Furthermore, the pattern of change in blood glucose concentration differed between trials (trial * time interaction, $F_{(6,210)} = 8.8$, $P < 0.001$), whereby blood glucose concentration was higher immediately post-exercise during the exercise trial compared to the control trial ($t_{(35)} = 3.1$, $P < 0.001$, $d = 0.9$). Blood glucose concentration was also lower 1 hour post-exercise on the exercise trial compared to the control trial ($t_{(35)} = 2.3$, $P < 0.001$, $d = 0.8$). No differences were evident at any other time point on day one (all $P > 0.05$). On day two, fasting blood glucose concentration was lower for the exercise trial compared to the control trial ($t_{(35)} = 3.3$, $P = 0.027$, $d = 0.6$). When considering the effect of sex, blood glucose concentration was higher at baseline and immediately post-exercise in females compared with males (trial * sex interaction, $F_{(1,35)} = 6.5$, $P = 0.016$).

Blood glucose iAUC did not differ between the exercise and the control trial (main effect trial, $P = 0.084$), nor was there an effect of sex on blood glucose iAUC following the standardized lunch (trial * sex interaction, $P = 0.083$).

Overall, plasma insulin concentration was lower during the exercise trial than the control trial (exercise: 20.8 ± 2.5, resting: 24.2 ± 1.7 mU/L; main effect trial, $F_{(1,23)} = 6.7$, $P = 0.016$, $d = 0.3$) and changed across time (main effect time, $F_{(6, 138)} = 55.9$, $P < 0.001$). The pattern of change in plasma insulin concentration differed between trials (trial * time interaction, $F_{(6,138)} = 7.9$, $P < 0.001$). Specifically, during the exercise trial plasma insulin concentration reached a higher peak than the control trial immediately post-exercise ($t_{(23)} = -1.33$, $P = 0.011$, $d = 0.5$), whereas plasma insulin concentration 1 hour post-exercise was lower on the exercise trial when compared to the control trial ($t_{(23)} = 0.29$, $P = 0.039$, $d = 0.3$). Plasma insulin concentration was lower during the exercise trial compared to the control trial 30 minutes post-lunch ($t_{(23)} = 1.35$, $P < 0.001$, $d = 0.7$) and 60 minutes post-lunch ($t_{(23)} = 0.61$, $P = 0.048$, $d = 0.4$). When considering the effect of sex, the response to exercise did not differ between boys and girls (trial * sex interaction, $P = 0.082$).

Plasma insulin iAUC following the consumption of the standardized lunch was lower during the exercise trial compared to the control trial (exercise: 2310 ± 834, resting: 3122 ± 1443 mU/L × 120 minutes, $t_{(24)} = 3.0$, $P < 0.001$, $d = 0.7$), but this effect was not different between the sexes (trial * sex interaction, $P = 0.170$).

HOMA-IR was calculated for the fasted blood samples on day one and day two, with no difference between trials (main effect trial, $P = 0.136$), or between day one and day two (main effect time, $P = 0.519$). Furthermore, the change in HOMA-IR between day one and day two was similar between trials (trial * time interaction, $P = 0.439$).

4 | DISCUSSION

The primary finding of the present study was that an acute bout of intermittent games-based activity elicited an anti-inflammatory response with a 132% increase in IL-6 concentration and a 200% rise in the anti-inflammatory IL-6:TNF-α ratio 3 hours post-exercise when compared with the rested trial. Furthermore, there was a 27% increase in concentration of anti-inflammatory cytokine IL-10 24 hours post-exercise in comparison with the rested trial. The pro-inflammatory cytokine IL-1β and acute phase protein CRP were unaffected by the 60-minute bout of games-based activity, whereas the concentration of TNF-α increased following exercise. In addition, the insulinemic response to a standardized lunch was reduced by 35% following the games-based exercise when compared with the control trial. This is the first study to examine a range of inflammatory cytokines and the glycemic and insulinemic responses up to 24 hours following games-based activity in adolescents.

The observed response of IL-6 in the present study is consistent with the findings of the only other study which has examined games-based activity in young people, in which a 91% increase was observed 1 hour post-exercise in pre-pubertal boys.[10] The present study is novel as it is the first to report that the IL-6 concentration continues to increase in healthy adolescents 3 hours post-exercise, whereas previous studies suggested IL-6 concentration increased transiently and returned to resting levels 1 hour post-exercise.[1] The increase in IL-6 concentration stimulated a twofold increase in the anti-inflammatory IL-6:TNF-α ratio 3 hours post-exercise and a 27% increase in IL-10 concentration 24 hours post-exercise. The 200% increase in the IL-6:TNF-α ratio was greater than the 80% increase following 10 × 2 minutes

bouts of high intensity intermittent cycling in adolescents,[20] whilst the present study is the first to report an increase IL-10 concentration 24 hours post-exercise in young people. The greater inflammatory response observed in the present study may relate to the longer duration of the exercise session compared to previous studies. Alternatively, this might relate to the mode of exercise undertaken, as basketball has an intense eccentric component, which in adults induces muscle damage that stimulates an inflammatory response of similar magnitude to that observed in the present study.[19] However, these suggestions are speculative and future research should examine the optimum duration and intensity of games-based activity for eliciting an inflammatory response.

The increase in IL-6 concentration post-exercise has both pro- and anti-inflammatory role in exercise-induced inflammation,[3] as indicated by the 31% increase in pro-inflammatory cytokine TNF-α 2 hours post-exercise. The increase in TNF-α concentration in the present study is consistent with the ~10%-30% increase reported in young people following moderate-to-vigorous exercise.[9,20,34] Although a chronic increase in TNF-α is suggested to increase cardio-metabolic disease risk in adults,[35] the transient increase in TNF-α following exercise in adolescents in the present study may also elicit cardio-metabolic health benefits. Previous research has suggested that following damage to skeletal muscle during moderate-to-vigorous exercise, the transient increase in pro-inflammatory cytokine TNF-α advances muscle regeneration and augments glucose uptake with the increased expression of GLUT-1,[36] potentially contributing to the enhanced insulin sensitivity associated with regular participation in exercise.

IL-1β and CRP were the only inflammatory markers in the present study to be unaffected by the acute bout of games-based activity. The lack of an effect of exercise on IL-1β concentration is consistent with one previous study that reported no change following 90-minute games-based activity in prepubertal boys.[10] The present study is the first, to the authors' knowledge, to assess the response of CRP following an acute bout of exercise in adolescents. However, one previous study in adults reported a small increase in CRP concentration the day following a marathon race.[3] It is therefore possible that longer duration bouts of exercise lead to greater increases in the systemic concentration of inflammatory mediators. Further research is required to determine the relationship between exercise intensity, duration, and the subsequent inflammatory response. However, it is important to note that the mileu of cytokine responses observed in the present study is likely to arise from the release of IL-6 as a result of the contraction of skeletal muscle during the games-based activity.

In the present study, the glycemic response to a standardized lunch was similar between trials, with no difference in blood glucose iAUC observed. Yet, postprandial plasma insulin iAUC was 35% lower and peak plasma insulin was 61% lower following the games-based activity. An acute bout of high intensity intermittent exercise (lasting ~22 minutes) has previously resulted in a 29% reduction in postprandial blood glucose iAUC and a 24% reduction in plasma insulin iAUC in adolescent boys.[22] It is important to note that the present study is the first to report an exercise-induced reduction in peak plasma insulin concentration following an ecologically valid meal and a reduction in insulin iAUC as a result of games-based activity which was of greater magnitude than in previous studies using different types of exercise.[22]

The greater enhancement in insulin sensitivity may relate to the training status and higher peak oxygen uptake of participants in the present study[21,22] which may have enabled exercise at higher absolute intensities. Although it has previously been proposed that the capacity for insulin sensitivity to change following exercise is reduced in well-trained participants,[22] the present study suggests that if adolescents having a greater level of fitness sustain overall higher absolute exercise intensities, then they experience a greater enhancement in insulin sensitivity post-exercise. Nonetheless, the enhanced insulin sensitivity observed in the present study reduces the risk of developing chronic diseases such as type 2 diabetes, thereby highlighting the importance of games-based activity for adolescent health.

Finally, the intermittent games-based activity employed in the present study is considered an enjoyable mode of exercise for adolescents[14] and can be undertaken during the school day, thereby facilitating participation for all young people. These issues of appropriateness and accessibility of physical activity are particularly important given that only 23% of adolescents currently meet the recommended guidelines of 60-minute moderate-to-vigorous physical activity per day.[15]

5 | PERSPECTIVES

The present study shows that an acute bout of games-based activity in adolescents elicits anti-inflammatory effects, as evidenced by the increase in systemic concentrations of anti-inflammatory cytokines (IL-6, IL-10) and a higher anti-inflammatory IL-6:TNF-α ratio, alongside a reduced insulinemic response to a standardized lunch. These findings demonstrate a beneficial effect across these cardio-metabolic disease risk factors and have important implications for the health of young people, especially given that the anti-inflammatory effects are evident up to 24 hours post-exercise. If such exercise was repeated regularly then it would elicit beneficial effects on cardio-metabolic health in adolescents. These findings will inform those responsible for designing and implementing physical activity interventions in schools. Such interventions are particularly important given that less than one in four young people currently meet physical activity guidelines[15] and adherence

may be enhanced with games-based activity. Future research should aim to further quantify the optimum intensity and duration of exercise for cardio-metabolic health in young people and identify effective interventions for the implementation of this in practice.

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CONFLICTS OF INTEREST

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ORCID

Karah J. Dring https://orcid.org/0000-0002-9647-3579
Simon B. Cooper https://orcid.org/0000-0001-5219-5020
John G. Morris https://orcid.org/0000-0001-6508-7897
Caroline Sunderland https://orcid.org/0000-0001-7484-1345
Gemma A. Foulds https://orcid.org/0000-0002-2503-7580
A. Graham Pockley https://orcid.org/0000-0001-9593-6431
Mary E. Nevill https://orcid.org/0000-0003-2498-9493

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