^{13}C labelled glucose-fructose show greater exogenous and whole-body CHO oxidation and lower O_2 cost of running at 120 vs 60 & 90 g·h^{-1} in elite male marathoners

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Running head: CHO oxidation from 60, 90 and 120 g·h^{-1} in male marathoners

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Abstract

We evaluated the effects of carbohydrate (CHO) ingestion at rates of 60 (maltodextrin:fructose ratio 1:0), 90 (2:1), and 120 (1:1) $g \cdot h^{-1}$ on whole body substrate metabolism, exogenous CHO oxidation (via U-^{13}C enriched glucose-fructose drinks) and gastrointestinal (GI) symptoms in elite male marathon runners (*n*=8; marathon PB, 02:22:54 ± 00:05:37). After 24 h of a high-CHO (8 $g \cdot kg^{-1}$) diet and pre-exercise meal (2 $g \cdot kg^{-1}$), participants completed 120-minute running trials comprising 15 mins at 95% lactate threshold (LT), 90 mins at 94% lactate turnpoint and a final 15 mins at 95% LT. Mean whole body CHO oxidation (120 $g \cdot h^{-1}$, 3.06 ± 0.19; 90 $g \cdot h^{-1}$, 2.46 ± 0.12; 60 $g \cdot h^{-1}$, 2.08 ± 0.03 $g \cdot min^{-1}$) and hour 2 mean exogenous CHO oxidation (120 $g \cdot h^{-1}$, 1.68 ± 0.16; 90 $g \cdot h^{-1}$, 1.31 ± 0.18; 60 $g \cdot h^{-1}$, 0.89 ± 0.11 $g \cdot min^{-1}$) were different between all trials ($P<0.01$ for all pairwise comparisons), such that 120 $g \cdot h^{-1}$ > 90 $g \cdot h^{-1}$ > 60 $g \cdot h^{-1}$. Running economy was improved in the 120 $g \cdot h^{-1}$ condition, with a 2.6% lower O_2 cost compared to 60 $g \cdot h^{-1}$ (P = 0.021). The incidence of moderate or severe (≥4) GI symptoms was high in all trials, though peak symptoms of nausea, stomach fullness and abdominal cramps were greatest for 120 $g \cdot h^{-1}$. We report for the first time that CHO ingestion at 120 $g \cdot h^{-1}$ confers a metabolic advantage to male marathoners by better maintaining whole-body rates of CHO oxidation, increasing exogenous CHO oxidation and improving running economy. However, gut training strategies, preceding practical application, are warranted.

Key Words

Marathon, maltodextrin, fructose, stable isotopes

New and Noteworthy

We used stable isotope methodology to evaluate exogenous rates of CHO oxidation in elite male marathoners. We report that 120 (maltodextrin:fructose ratio 1:1) $g \cdot h^{-1}$ CHO induces greater whole-body and exogenous CHO oxidation compared with 60 (1:0) – 90 (2:1) $g \cdot h^{-1}$ and reduces the O_2 cost of running. However, the performance implications of such doses remain to be determined. The prevalence of GI symptoms across the doses suggests targeted fuelling practice and gut training is warranted.

INTRODUCTION

The classical model of endurance performance suggests that key physiological determinants of marathon performance include a runner's $\dot{V}O_{2max}$, the percentage of $\dot{V}O_{2max}$ that can be sustained throughout the race (commonly associated with lactate threshold or critical speed), and the oxygen cost of submaximal running, referred to as running economy (mL $O_2 \cdot kg^{-1} \cdot km^{-1}$) (1-3). External factors (course profile, environment, pacing, drafting, nutrition, footwear) also significantly influence marathon performance (3). While the biomechanical (4-6), environmental (7), and physiological aspects (3, 8) of a sub-2-hour marathon have recently received increased research focus, research on nutritional demands remains underexplored.

One viewpoint emphasised that in addition to possessing a superior $\dot{V}O_{2max}$, lactate threshold (LT), and running economy, achieving optimal performance will require an individualised and meticulous fuelling strategy, a high aptitude for exogenous carbohydrate (CHO) oxidation, and an absence of gastrointestinal (GI) distress (9). Indeed, the depletion of finite glycogen stores within the muscle leads to a critical reduction in the rate at which adenosine triphosphate (ATP) can be re-synthesised within muscle cells, thereby compromising the energy supply required to sustain muscle contraction and force output, ultimately resulting in fatigue (10, 11). Therefore, in addition to glycogen supercompensation (12, 13), the consumption of CHO during exercise has consistently been shown to enhance capacity for exercise lasting >1 h (14-16). In events lasting >2.5h, that would otherwise be limited by glycogen depletion (12), the improvement in exercise capacity with CHO feeding is primarily achieved by maintaining plasma glucose, whole-body CHO oxidation rates (17) and sparing liver glycogen (18), playing a critical role for performance and endurance capacity (19). Additionally, increasing evidence suggests that hepatic overflow of exogenous CHO ingestion, can also contribute directly to skeletal muscle metabolism and reduce

endogenous CHO utilisation, particularly at low to moderate exercise intensities, when hepatic glycogen stores are sufficiently replete (20, 21). As a result, CHO intake during exercise, using a combination of CHO monosaccharides, is recommended for endurance athletes. It has been suggested that the use of a single source CHO (e.g glucose), particularly at high rates, can saturate the SGLT-1 transporter that aids in its absorption, after which no increase in exogenous CHO oxidation is observed (22). However, the addition of another monosaccharide such as fructose that uses a different transporter (GLUT5) results in higher exogenous CHO oxidation rates (23). This can be attributed to the recruitment of a different transporter that can maximise exogenous CHO oxidation. Therefore, multiple-transportable CHO formulations constitute a key strategy to enhance carbohydrate delivery and availability, mitigate liver glycogen depletion, and thereby sustain performance (24).

A recent modelling study (25) assessed the exogenous CHO intake required to run a sub-2-hour marathon across sexes and calculated that male runners would require 93 ± 26 $g \cdot h^{-1}$ of exogenous CHO to run a sub-2-hour marathon, suggesting that the current ≤ 90 $g \cdot h^{-1}$ recommendations are insufficient for 65% of modelled athletes (25). Though based on anecdotal practitioner experience and field observations, some reviews already recommend CHO intakes exceeding 100 $g \cdot h^{-1}$ if GI tolerance allows (14). However, the current ACSM recommendations for CHO intake are 30 – 60 $g \cdot h^{-1}$ for exercise lasting 1 – 2.5 h and up to 90 $g \cdot h^{-1}$ of multiple transportable CHO for exercise lasting >2.5h (19). While modelling data suggests that higher CHO intakes may be necessary to meet the metabolic demands of a sub-2-hour marathon, direct evidence assessing exogenous CHO oxidation rates at these higher intakes in elite endurance runners does not exist. Therefore, further research is needed to empirically evaluate whether CHO intake exceeding 90 $g \cdot h^{-1}$ can be effectively oxidised and tolerated in this population.

Recent data from our laboratory demonstrated that trained male cyclists can tolerate 120 g·h^{-1} of multiple transportable CHO blends with minimal GI discomfort, reaching peak exogenous CHO oxidation rates of 1.87 g·min^{-1} (26). This demonstrates that exogenous CHO bioavailability may surpass the currently recommended upper limit of 90 g·h^{-1} (27). Nonetheless, the feasibility of such doses in runners, particularly tier 3 (i.e. highly trained /national level) and 4 runners (elite / international level), exercising at an intensity within the heavy intensity domain, is unclear with limited research supporting such claims. This discrepancy may arise from the higher incidence of GI complaints in runners compared to cyclists (28), potentially stemming from the repetitive high-impact mechanics of running that can cause damage to the intestinal lining and gastric jostling (29). Amongst the studies that have implemented running as an exercise modality, the majority have used lesser trained subjects and/or lower relative exercise intensities (30-33). As a result, the absolute exercise intensities and metabolic requirements are lower than what would be observed in well-trained or elite marathon runners running at, or close to, marathon pace. Furthermore, CHO intakes >1.5 g.min^{-1} during running exercise have also been associated with GI symptoms, which can further hinder performance (30, 34-36).

The aim of the present study was, therefore, to evaluate the effects of CHO ingestion at rates of 60, 90, and 120 g·h^{-1} on whole body substrate metabolism, exogenous CHO oxidation and GI symptoms. We hypothesised that CHO feeding would support greater rates of whole-body CHO oxidation and exogenous CHO oxidation in a dose-dependent manner. To this end, we recruited eight male highly trained/elite runners from the England Athletics Endurance Programme all who had marathon personal bests that were faster than 2 h 30 minutes. According to the participant classification framework (37), these runners are representative of both tier 3 (highly trained/national level athletes) and tier 4 (elite/international level athletes). Runners consumed CHO at rates of 60, 90 and 120 g·h^{-1}

during 2 h of running, wherein 90 minutes corresponded to a running pace just below projected marathon pace i.e. 94% of lactate turn point (3, 38). To assess rates of exogenous CHO oxidation, CHO was ingested in fluid form and all drinks were enriched with both ^{13}C-glucose and ^{13}C-fructose.

METHODS

Participants

Eight male elite marathon runners participated in the study. Participant characteristics are presented in Table 1. Participants were defined as highly trained and elite (Tier 3 and 4) in accordance with the classification of Mckay et al., (37) in which Tier 3 denotes Highly Trained/National-level athletes and Tier 4 denotes Elite/International-level athletes. Participants were required to have completed a certified race within the 12 months prior to the study, with a qualifying time of 2:30:00 or faster for the marathon, or 1:13:00 or faster for the half-marathon. All provided written informed consent, after receiving a comprehensive explanation of all experimental procedures and risks. Sample size was determined according to our primary outcome variable (i.e., exogenous CHO oxidation) assuming an estimated mean exogenous CHO oxidation of 1.5 ± 0.3 g·min^{-1} and 1.0 ± 0.3 g·min^{-1} in the 120 and 60 g.h^{-1} CHO trials, respectively (estimated rates are taken from previous CHO dose studies from both running and cycling (26, 31, 39). These data give an effect size of dz = 1.2, where a sample size of 8 would provide an alpha value of 0.05 and a power of 0.80 (GPower, version 3.1.9.6). Participants presenting with musculoskeletal injuries, metabolic disease, gastrointestinal infections, diseases, and/or disorders, asthma, cardiovascular and cerebrovascular disease were excluded from the study. Furthermore, those on specific

medication (e.g., balcofen, methotrexate, tacrolimus and voriconazole, beta-blockers or diuretics) were also excluded from the study.

Ethical Approval

The study received approval from the Ethics committee of Liverpool John Moores University (23/SPS/055) and adhered to the standards outlined in the latest revision of the Declaration of Helsinki for Human Research Ethics.

Experimental Overview

A schematic illustration describing the experimental procedures is shown in Fig. 1. Utilising a double-blind randomised crossover design, each participant completed three experimental trials during which they were provided with either 60, 90 or 120 $g \cdot h^{-1}$ of a CHO drink in a random order. Each trial consisted of a 120-minute run and the intensities prescribed are presented in Fig. 1. Participants were given a standardised diet for the 24-h preceding each trial, consisting of 8.0 $g \cdot kg^{-1}$ CHO; 2.0 $g \cdot kg^{-1}$ protein and 1.0 $g \cdot kg^{-1}$ fat. This was repeated for each subsequent visit.

Preliminary Testing

At least one week before experimental trials, participants completed an incremental test on a motorised treadmill (Pulsar H/p, Cosmos, Germany) to determine their first and second lactate thresholds. The initial incremental step test began with the slope set at 1% (40) and an initial speed of 12-14 $km \cdot h^{-1}$, depending on each subject's fastest marathon time or equivalent. At the end of each 3-minute stage, a fingertip blood sample was collected and analyzed immediately for blood lactate concentration (Biosen C-Line analyser by EKF Diagnostics, Cardiff, UK). Sampling and analysis occurred while the athlete commenced the subsequent stage to minimize interruption. The second lactate turn point (LT2) was identified as the workload eliciting a sudden and sustained increase in [La^{-}] above preceding values. Once this rise was observed, participants completed the stage in progress, and the blood sample obtained at its conclusion was used to confirm LT2. Blood lactate concentration was

plotted against running speed, with LT defined as the initial elevation in blood lactate above the baseline value. Lactate turn point (LTP) was characterised by a subsequent and sudden increase in blood lactate concentration. Both were determined through visual inspection after being reviewed by 2 independent researchers (3). Heart rate (HR) (Polar H10; Polar, Kempele, Finland) and expired gas (Moxus modular metabolic system; AEI Technologies Inc, PA) were monitored throughout.

Following a 15-30-minute rest period, subjects underwent a 60-minute familiarisation protocol, during which they ran for 60 minutes at the prescribed speeds (corresponding to the first hour of the 120-minute experimental trial; see Figure.1). Participants received 125 mL of fluid at the start of exercise and every 15 minutes thereafter to replicate the CHO drink protocol used during the experimental trials. HR and ratings of perceived exertion (RPE) were monitored throughout, while expired gas was collected for 3 minutes at 15-minute intervals to calculate whole-body substrate utilisation. Blood lactate and body mass were measured at 0, 15, 45, and 60 minutes. The session was also used to evaluate the prescribed running speeds and, if necessary, adjust them, based on participant feedback and lactate trajectory to ensure the target exercise intensities were achieved.

Experimental trials

On the morning of the experimental trial participants reported to the laboratory at ~0900 h after consuming a standardised high CHO breakfast (2 $g \cdot kg^{-1}$ CHO; 0.25 $g \cdot kg^{-1}$ protein and 0.1 $g \cdot kg^{-1}$ fat). Prior to exercise, participants provided a resting finger prick blood sample to measure resting blood lactate concentration and haematocrit (Hirschmann™ Haematocrit Tubes, Germany). The same measures were collected post-exercise. A resting breath sample was also collected into a 10 mL exetainer (Labco, High Wycombe, UK). Participants then completed a modified visual analogue scale for GI

symptom assessment (41). Subjects were educated and advised to complete the 10-point GI symptom rating scale as follows: 1 to 4 indicated mild GI symptoms (i.e., sensation of GI symptoms, but not substantial enough to interfere with exercise), 5 to 9 indicated severe GI symptoms (i.e., GI symptoms substantial enough to interfere with exercise), and 10 indicated extreme GI symptoms warranting exercise cessation. If no specific GI symptom was experienced, participants reported zero. Perceived satiety, drink sweetness and desire to drink were assessed using a modified visual analogue scale (42). Body mass (BM) was measured at standardised 1-min pauses at prespecified time points (0, 15, 45, 75, 105, 120 mins) that were identical across all three trials. This was used to adjust running economy values for changes in body mass over time within each trial. Running economy was expressed as the oxygen cost of running (mL $O_2 \cdot kg^{-1} \cdot km^{-1}$), calculated from steady-state VO_2, adjusted for the speed required to cover 1 km, and corrected for body mass at 30-minute intervals. This was then converted to energetic cost ($kJ \cdot kg^{-1} \cdot km^{-1}$) (43). A calibrated floor scale (Seca, Germany) was positioned adjacent to the treadmill, and conscious efforts were made to minimise any additional time off the treadmill. This data was incorporated into running economy calculations to account for within-trial changes in body mass.

Participants completed 120 minutes running on a motorised treadmill with the incline set at 1% (40) at speeds corresponding to 95% LT for the first and final 15 minute intervals and 94% LTP for 90 minutes. Expired gas was collected for a 3-minute period every 15 minutes to calculate whole body substrate utilisation. The final minute of this period was used to collect expired gas into the evacuated exetainer tubes to determine the ^{13}C-to-^{12}C ratio in CO_2. Perceived satiety, drink sweetness and desire to drink, along with HR and RPE were also assessed every 15 minutes. A finger prick blood sample was collected, and GI symptoms and BM were recorded every 30 minutes.

CHO Drink

CHO drinks were formulated using maltodextrin and fructose (Science in Sport PLC, Blackburn, UK) in the following ratios for each condition: 60 $g \cdot h^{-1}$ (120 g maltodextrin, 0 g fructose, 0.08 g U-^{13}C glucose tracer), 90 $g \cdot h^{-1}$ (120 g maltodextrin, 60 g fructose, 0.08 g U-^{13}C glucose tracer, 0.04 g U-^{13}C fructose tracer), and 120 $g \cdot h^{-1}$ (120 g maltodextrin, 120 g fructose, 0.08 g U-^{13}C glucose tracer, 0.08 g U-^{13}C fructose tracer). Each formulation was made into a 1 L solution (total over 2 h), and 125 mL was consumed every 15 min (i.e., 500 $mL \cdot h^{-1}$). The maltodextrin dose was held constant across all conditions (120 g over 2 h); fructose was varied (0, 60, 120 g over 2 h) to achieve the target intakes and blend ratios. The resulting carbohydrate concentrations were 12% (60 $g \cdot h^{-1}$), 18% (90 $g \cdot h^{-1}$), and 24% (120 $g \cdot h^{-1}$) (w/v). A fixed fluid volume was used across conditions for ecological validity; therefore, dose and concentration varied jointly by design.

Indirect Calorimetry

Respiratory gas exchange variables were measured using a mixing chamber (Moxus modular metabolic system; AEI Technologies Inc, PA). Oxygen uptake (VO_2), carbon dioxide production (VCO_2) and respiratory exchange ratio (RER) were measured for 3 minutes at 15-minute intervals, prior to exercise and for the final 3 minutes every 15 minutes during exercise, with mean values calculated for each 30 s. Breath samples were extracted in duplicate directly from the mixing chamber during the final minute of each 3-minute gas analysis period, during which the sample line was briefly disconnected. Fat oxidation and CHO oxidation were calculated indirectly using previously established calculations of oxidation rates during moderate to high intensity exercise (Jeukendrup and Wallis, 2005). Urinary nitrogen was not measured, and values therefore reflect non-protein substrate partitioning. As a result, the following equations were used.

CHO oxidation ($g \cdot min^{-1}$) = $4.21 \times \dot{V}CO_2 - 2.962 \times \dot{V}O_2$

Fat oxidation ($g \cdot min^{-1}$) = $1.695 \times \dot{V}O_2 - 1.701 \times \dot{V}CO_2$

$^{13}C/^{12}C$ analysis of CHO drink

An elemental analyser-isotope ratio mass spectrometer (Europa Scientific 20-20; Iso-Analytical Ltd., Crewe, UK) was utilised to quantify the ^{13}C enrichment of freeze-dried (U-^{13}C glucose/ U-^{13}C fructose) drink samples and the natural ^{13}C background of the glucose-fructose drink, and this was expressed as $\delta^{13}C$ ‰ versus Pee Dee belemnite (PDB).

$^{13}C/^{12}C$ analysis of breath CO_2

An Iso Analytical 20-20 isotope ratio mass spectrometer (IRMS), linked to a Europa Scientific ANCA NT GC system and a Gilson 222 autosampler, was used to analyse breath samples. Breath samples were continuously transferred through a Valco sampling port in a helium flow, and carbon dioxide was separated from other gases using a capillary column (PoraPLOTQ; Agilent JW columns) with dimensions of 27.5 m × 0.32 mm × 10 μm. The oven temperature was maintained at 68°C. A magnesium perchlorate trap was used to remove water from the sample. Samples were analysed in multiples, with the contents of the sample loop switched to the gas chromatography (GC) column every 50 s, initiating a restart of the GC separation process. Ions with mass-to-charge ratios (m/z) of 44 and 45 were monitored for CO_2 and $^{13}CO_2$, respectively. Results for ^{13}C enrichment in breath samples were expressed as $\delta^{13}C$ ‰ versus PDB.

Exogenous CHO oxidation was calculated using the following formula:

Exogenous CHO oxidation ($g \cdot min^{-1}$) = $\dot{V}CO_2 \times (\delta Exp - \delta Expbkg) / (\delta Ing - \delta Expbkg)/k$,

In which δExp represents the ^{13}C enrichment observed in the expired air at various exercise time points, δIng signifies the [U-^{13}C] enrichment present in the ingested maltodextrin drink, δExpbkg denotes the ^{13}C enrichment in the expired air before exercise (background), and k is the quantity of CO_2 in litres (L CO_2) generated by the oxidation of 1 gram of glucose ($k = 0.7467$ L $CO_2 \cdot g^{-1}$ glucose).

Statistical Analysis

All statistical analyses were performed using R (The R Project for Statistical Computing, Version 4.3.0). Differences in mean exogenous CHO oxidation, whole body CHO and fat oxidation, HR, RPE, energy expenditure, running economy, and blood glucose and blood lactate concentrations were all analysed by two-way repeated-measures ANOVA. Peak exogenous CHO oxidation was analysed by one-way repeated measures ANOVA. Mauchly's test for sphericity was used, and in cases where this assumption was violated, the Greenhouse–Geisser correction was applied. Where a significant main effect was found, pairwise comparisons were conducted using the Holm post hoc test and Cohen's *d* was calculated (with 0.2, 0.5, >0.8 representing a small, moderate and large effect, respectively) and 95% confidence intervals (CI) for paired differences are also presented. Non-normally distributed data were analysed using Friedman's ANOVA, the non-parametric equivalent of a one-way repeated-measures ANOVA. Where a significant main effect was found pairwise comparisons were conducted used a Wilcoxon's Signed Ranks test. Differences in symptom prevalence across conditions were analysed using Cochran's *Q* test followed by pairwise McNemar tests with Holm adjustment. All data in text, figures, and tables are presented as means ± SD, with *P* values ≤ 0.05 indicating statistical significance.

RESULTS

Effects of dose of CHO ingestion on physiological, metabolic and perceptual responses to exercise

In regard to running velocity (i.e. differences between time points where participants ran at LT and 94% of LTP), there were significant differences between physiological measures collected at 15 and 120 minutes (i.e. running speed at 95% LT) compared to those during the 90-minute higher intensity portion of the protocol i.e. running at 94% of LTP (Fig 2). When considering the 90 minutes completed at 94% of LTP, there were progressive increases in heart rate (Fig 2 A) and RPE (Fig 2 B), a deterioration of running economy (Fig 2 D) but no difference in blood lactate (Fig 2 C) or caloric cost of running (Fig 2 E). Across the whole 2 h period, exercise significantly increased heart rate, blood lactate concentration, RPE, and impaired running economy (all P<0.001) (Fig 2). No differences were observed between CHO trials for these variables (P = 0.73, 0.11, 0.79, 0.10) with the exception of running economy (P=0.015), where there were significant differences in oxygen cost between the 60 and 120 $g \cdot h^{-1}$ trial (P = 0.047, Mean Difference 6.14, 95% CI [0.13, 12.10] $O_2 \cdot kg^{-1} \cdot km^{-1}$, Cohen's d = 0.85) but no differences between the 60 and 90 $g \cdot h^{-1}$ trials (P = 0.097, Mean Difference = 2.93, 95% CI [-1.12, 6.98] $O_2 \cdot kg^{-1} \cdot km^{-1}$, Cohen's d = 0.61) or 90 and 120 $g \cdot h^{-1}$ trials (P = 0.259, Mean Difference = 3.20, 95% CI [-2.97, 9.37] $O_2 \cdot kg^{-1} \cdot km^{-1}$, Cohen's d = 0.434) (Fig 2 D). The O_2 cost was 2.6% lower in the 120 $g \cdot h^{-1}$ trial and 1.12% lower in the 90 $g \cdot h^{-1}$ trial compared to the 60 $g \cdot h^{-1}$ trial, respectively.

Effects of dose of CHO ingestion on blood glucose concentration and whole-body substrate metabolism

In accordance with CHO provision during exercise, blood glucose significantly increased (P<0.001) during exercise (Figure 3A) and was also significantly different between trials (P=0.028). In relation to trial specific comparisons, blood glucose was greater in the

120 g·h^{-1} trial compared with 60 g·h^{-1} (P=0.036; Mean Difference = 0.81, 95% CI [0.27, 1.35] mmol.L^{-1}, Cohen's d = 1.24, mean concentrations of 5.94 ± 0.70 vs. 5.13 ± 0.24 mmol·L^{-1}, respectively). However, no differences were apparent between 120 and 90 g·h^{-1} (P=0.254; Mean Difference = 0.36, 95% CI [-0.37, 1.08] mmol.L^{-1}, Cohen's d = 0.41, mean concentration 5.59 ± 0.52 mmol·L^{-1}, respectively) or between 90 and 60 g·h^{-1} (P=0.127; Mean Difference = 0.45, 95% CI [0.04, 0.87] mmol.L^{-1}, Cohen's d = 0.932).

In relation to the effects of exercise, there was a progressive decline in both RER (P<0.001) and whole-body CHO oxidation (P<0.001) and an accompanying progressive increase in fat oxidation (P<0.001) (Figure 3). However, with increasing dose of CHO ingestion, RER (P<0.001), rates of whole-body CHO (P<0.001) and fat oxidation (P<0.001), and total CHO (P<0.001) and fat oxidation (P<0.001) during exercise were all significantly different between conditions (Figure 3B-F, respectively). Specifically, RER (mean ± SD: 0.83 ± 0.01, 0.86 ± 0.02, 0.89 ± 0.03), rate of CHO oxidation (mean ± SD: 2.09 ± 0.09, 2.46 ± 0.34, 3.07 ± 0.54 g·min^{-1}), rate of fat oxidation (mean ± SD: 1.07 ± 0.22, 0.90 ± 0.27, 0.67 ± 0.20 g·min^{-1}), total CHO (mean ± SD: 250 ± 11, 295 ± 41, 367 ± 65 g) and total fat oxidation (mean ± SD: 128 ± 26, 110 ± 29, 80 ± 24 g) all displayed significant pairwise differences (mean values reported for 60, 90 and 120 g·h^{-1} , respectively) between trials (all P<0.01), such that 120 g·h^{-1} > 90 g·h^{-1} > 60 g·h^{-1} (**RER**: Mean Difference 0.03, 95% CI [0.02, 0.05], Cohen's d = 2.00); Mean Difference 0.03, 95% CI [0.01, 0.04], Cohen's d = 1.48); **CHO oxidation**: Mean Difference 0.61, 95% CI [0.38, 0.83] g·min^{-1}, Cohen's d = 2.25); Mean Difference 0.37, 95% CI [0.09, 0.66] g·min^{-1}, Cohen's d = 1.11); **fat oxidation**: Mean Difference 0.23, 95% CI [0.10, 0.36] g·min^{-1}, Cohen's d = 1.45); Mean Difference 0.17, 95% CI [0.05, 0.29] g·min^{-1}, Cohen's d = 1.21; **Total CHO**: Mean Difference 73, 95% CI [46, 99] g, Cohen's d = 2.26; Mean Difference 45, 95% CI [11, 79] g, Cohen's d = 1.12; **Total fat**: Mean Difference 30, 95% CI [17, 43] g, Cohen's d = 1.90; Mean Difference 18,

95% CI [5, 31] g, Cohen's d = 1.20). All previous comparisons are reported for120 vs 90 $g \cdot h^{-1}$, and 90 vs 60 $g \cdot h^{-1}$, respectively.

No differences were apparent between trials (P=0.413) in rate of total energy expenditure during exercise (Figure 4 A), though energy expenditure was significantly greater (P<0.001) during the 90 minutes of exercise undertaken at 94% of LTP compared with the 2 x 15 min periods of exercise completed at 95% LT. Of note, the metabolic crossover point (i.e., the time-point during exercise at which fat provides the greater contribution towards total energy expenditure) was delayed by approximately 40 minutes when participants consumed 90 $g \cdot h^{-1}$ compared with consuming 60 $g \cdot h^{-1}$ (Figure 4 C and B, respectively), whereas 120 $g \cdot h^{-1}$ prevented the occurrence of a crossover point. When taken together, the results demonstrate that a dose of 120 $g \cdot h^{-1}$ maintained whole body CHO oxidation to a greater extent than both the 90 and 60 $g \cdot h^{-1}$ doses (Figure 4 D).

Effects of dose of CHO ingestion on exogenous CHO oxidation and efficiency

Exogenous rates of CHO oxidation during exercise are presented in Figure 5B. Exogenous CHO oxidation was significantly different between trials (P < 0.001) such that mean exogenous CHO oxidation *during hour 2* was greater with an ingestion rate of 120 $g \cdot h^{-1}$ (1.68 ± 0.16 $g \cdot min^{-1}$) compared with both 90 $g \cdot h^{-1}$ (1.31 ± 0.18 $g \cdot min^{-1}$; P = 0.0025, Mean Difference 0.37, 95% CI [0.23, 0.51] $g \cdot min^{-1}$, Cohen's d = 2.22) and 60 $g \cdot h^{-1}$ (0.89 ± 0.11 $g \cdot min^{-1}$; P <0.0001 Mean Difference 0.79, 95% CI [0.65, 0.92] $g \cdot min^{-1}$, Cohen's d = 5.01). Additionally, exogenous CHO oxidation *during hour 2* was also significantly greater with an ingestion rate of 90 $g \cdot h^{-1}$ compared with 60 $g \cdot h^{-1}$ (P = 0.0034, Mean Difference 0.41, 95% CI [0.24, 0.59] $g \cdot min^{-1}$, Cohen's d = 1.94) (Fig. 5 C). Similarly, peak exogenous CHO oxidation rates (Fig 5 D) also exhibited significant differences between conditions (P < 0.001) between all pairwise comparisons (all P < 0.001) such that 120 $g \cdot h^{-1}$ (1.77 ± 0.13 $g \cdot min^{-1}$) > 90 $g \cdot h^{-1}$ (1.41 ± 0.12 $g \cdot min^{-1}$) > 60 $g \cdot h^{-1}$ (1.00 ± 0.10 $g \cdot min^{-1}$) (Mean Difference 0.41, 95% CI [0.29,

386 0.53] g·min^{-1}, Cohen's d = 2.87; Mean Difference 0.41, 95% CI [0.29, 0.54] g·min^{-1}, Cohen's
387 d = 2.74 for 120 vs 90 g·h^{-1}, and 90 vs 60 g·h^{-1}, respectively).

388 There was no significant difference in oxidation efficiency (Fig 5E) between trials
389 during *hour* 2 (120 g·h^{-1}: 84 ± 8%; 90 g·h^{-1}: 87 ± 12 %; 60 g·h^{-1}: 89 ± 11%, P = 0.554)
390 (Figure 5D). The contribution of endogenous CHO oxidation, exogenous CHO oxidation and
391 fat oxidation towards energy expenditure during the second hour of exercise is also presented
392 in Figure 5F. The contribution of endogenous CHO oxidation was not different between
393 trials (P = 0.312). However, in accordance with the dose-response effect of CHO ingestion on
394 exogenous CHO oxidation, the contribution of exogenous CHO oxidation towards total
395 energy expenditure was also significantly different between trials (P < 0.001), where pairwise
396 comparisons (all P<0.001) again confirmed that ingestion rates of 120 g·h^{-1} (39 ± 5%) > 90
397 g·h^{-1} (30 ± 4%) > 60 g·h^{-1} (21 ± 4%) (Mean Difference 9, 95% CI [5, 13] %, Cohen's d =
398 1.73; Mean Difference 10, 95% CI [6, 14] %, Cohen's d = 1.97 for 120 vs 90 g·h^{-1}, and 90 vs
399 60 g·h^{-1}, respectively. In contrast, the contribution of fat towards total energy expenditure was
400 significantly lower in the 120 g·h^{-1} trial (35 ± 8 %) compared with both the 90 g·h^{-1} (49 ± 8
401 %) (Mean Difference 15 % CI [11, 18] %, Cohen's d = 3.57) and 60 g·h^{-1} trials (57 ± 6 %)
402 (Mean Difference 23 % CI [14, 31] %, Cohen's d = 2.11) *(*both P<0.001). Additionally, the
403 contribution of fat was significantly greater in the 60 g·h^{-1} trial compared with the 90 g·h^{-1}
404 trial (P<0.001) (Mean Difference 9 % CI [0.04, 16] %, Cohen's d = 0.83). Such data
405 collectively demonstrate that CHO dependency is only maintained with CHO ingestion rates
406 of 120 g·h^{-1} (i.e. 66% CHO contribution), whereas ingestion rates of 90 and 60 g·h^{-1} result in
407 a transition towards fat dependence during the second hour of exercise (Fig 5 F).

Effects of dose of CHO ingestion on gastrointestinal discomfort and drink palatability

The incidence of moderate or severe (≥4) GI symptoms was high across all conditions (see Figure 6). All runners reported experiencing one or more moderate or severe symptoms. Cumulative gastrointestinal (GI) symptom scores did not differ significantly (P = 0.357; between CHO doses (52 (30-126); (59 (30-153); (40-127) for 60, 90 and 120 g·h^{-1}, respectively). However, peak scores for nausea (P = 0.01), stomach fullness (P = 0.026), and abdominal cramps (P = 0.012) varied between conditions. Nausea scores were significantly higher at 120 g·h^{-1} compared to both 60 g·h^{-1} (P = 0.021, Mean Difference 3, 95% CI [2, 5] AU, r = 1) and 90 g·h^{-1} (P = 0.041, Mean Difference 3, 95% CI [2, 6] AU, r = 1). Stomach fullness was also reported to be greater at 120 g·h^{-1} than at 60 g·h^{-1} (P = 0.004, Mean Difference 4, 95% CI [2, 5] AU, r = 1) and 90 g·h^{-1} (P = 0.014, Mean Difference 2, 95% CI [1, 2] AU, r = 0.89). Additionally, abdominal cramps were significantly different between conditions, with higher scores at 120 g·h^{-1} compared to 60 g·h^{-1} (P = 0.005, Mean Difference 3, 95% CI [1, 5] AU, r = 0.89) and at 90 g·h^{-1} (P = 0.050, Mean Difference 2, 95% CI [1, 3] AU, r = 0.89). Cochran's Q test revealed a significant difference in symptom prevalence across conditions (Q = 6.4; P = 0.040) for nausea. Post-hoc McNemar comparisons (Holm-adjusted) were not significant: 60 vs 90 P = (1.00; Matched OR = 1.00, [0.03, 38.49]); 60 vs 120 P = (0.133; Matched OR = ∞, [0.90, ∞]); 90 vs 120 (P = 0.133; Matched OR = ∞, [0.90, ∞]). A greater proportion of participants reported nausea in the 120 g·h^{-1} trial (75%) compared to 90 g·h^{-1} (25%) and 60 g·h^{-1} (25%). Similarly, a significant difference was observed for abdominal cramps (Q = 6.33; P = 0.042), with no differences in Post-hoc McNemar comparisons (Holm-adjusted) 60 vs 90 P = (0.479; Matched OR = ∞, [0.29, ∞]); 60 vs 120 P = (0.073; Matched OR = ∞, [1.22, ∞]); 90 vs 120 (P = 0.371; Matched OR = 4.00, [0.52, 96.98]). Abdominal cramps were reported by 37.5% of participants in the 120 g·h^{-1} trial, compared to 12.5% in the 90 g·h^{-1} and 12.5% 60 g·h^{-1} trials. Notably, all 8

participants reported symptoms of stomach fullness above 4 for all conditions, resulting in 100% prevalence of moderate to severe symptoms across the 120 g·h^{-1}, 90 g·h^{-1}, and 60 g·h^{-1} trials for stomach fullness. Perception of drink sweetness was significantly greater at 120 g·h^{-1} 8 (5-9) compared to 60 g·h^{-1} 3 (1-6), P = 0.006, Mean Difference 4, 95% CI [3, 6] AU, r = 1) and 90 g·h^{-1} 5 (4-7), P = 0.020, Mean Difference 2, 95% CI [1, 3] AU, r = 1). The urge to drink and drink pleasantness were low across all conditions with no difference between conditions (Fig 7).

DISCUSSION

Confirming our hypothesis, we report for the first time that CHO ingestion during exercise increases whole-body and exogenous rates of CHO oxidation in elite male marathon runners in a dose dependent manner. In using an exercise duration (i.e., 2 hours) and intensity that is somewhat representative of marathon pace (i.e., the majority of the exercise stimulus was completed at 94% of LTP), we observed that whole body rates of CHO oxidation and CHO dependency is only maintained with CHO ingestion rates of 120 g·h^{-1}. In contrast, CHO ingestion rates aligned to the current CHO guidelines of 60-90 g·h^{-1} are associated with a reduction in whole body CHO utilisation and an accompanying transition towards fat dependence during the second hour of exercise (though we acknowledge the absence of isotopic or nitrogen balance markers does not account for protein oxidation). In using U-^{13}C glucose stable isotope tracers for glucose and fructose, we also report some of the highest rates of exogenous CHO oxidation observed to date in runners, with individual values ranging from 1.64 to 1.99 g·min^{-1} in the 120 g·h^{-1} trial. Of note, such changes in exercise metabolism were accompanied by differences in running economy such that higher CHO ingestion rates led to lower oxygen consumption rates. Taken together, this suggests a metabolic advantage of higher CHO doses. However, the high prevalence of GI symptoms

458 across the doses of 60-120 g·h^{-1} (with symptoms of nausea, stomach fullness and abdominal
459 cramps greatest with 120 g·h^{-1}), along with low urge to drink suggests that further
460 investigations of practical strategies for athlete fuelling are warranted.

461 The physiological requirements to run a sub-2-hour marathon (3) has led to increased
462 academic interest on the endogenous and exogenous carbohydrate requirements to sustain the
463 required absolute intensity. Indeed, recent modelling has suggested that exogenous CHO
464 requirements for males and females would be 93 ± 26 and 108 ± 22 g·h^{-1}, respectively (25).
465 In that study, 65% of modelled runners (regardless of sex, body mass and/or running
466 economy) were suggested to need more than the current CHO recommendations of 90 g·h^{-1}.
467 Nonetheless, the practicality and feasibility of consuming such doses are limited by the lack
468 of direct observations on elite athletes. Accordingly, we collaborated with the England
469 Athletics Endurance Program to recruit a cohort of male runners with personal best marathon
470 times all faster than 2 h 30 minutes. Whilst we acknowledge that our chosen exercise protocol
471 did not replicate the absolute running speeds required to run a sub-2 h marathon, our study
472 holds ecological validity considering we clamped the majority of the exercise stimulus close
473 to each participant's estimated race pace, i.e. 94% of LTP. Furthermore, participants
474 completed each 2 h running protocol in conditions of high CHO availability that is currently
475 recognised as best practice, as achieved by 24 h of a standardised high CHO diet (8 g·kg^{-1})
476 and pre-race meal (2 g·kg^{-1}). Our chosen CHO intervention utilised incremental doses of
477 CHO ingestion such that absolute doses of 60 g·h^{-1} (single source, maltodextrin), 90 g·h^{-1}
478 (dual source blend of maltodextrin and fructose in a 2:1 ratio) and 120 g·h^{-1} (dual source
479 blend of maltodextrin and fructose in a 1:1 ratio) were ingested. Importantly, our form of
480 CHO delivery was in fluid format so as to replicate the predominant method and frequency of
481 CHO delivery that elite runners typically utilise during racing (125 ml every 15 minutes).
482 The enrichment of drinks with both ^{13}C-glucose and ^{13}C-fructose tracers also allowed us to

directly assess exogenous rates of CHO oxidation and efficiency. Though our CHO solutions were formulated using maltodextrin, it is considered that the use of [U-^{13}C] glucose as a tracer remains appropriate in this context. In contrast to the utilisation of an insoluble starch tracee (44), the utilisation of maltodextrin (as a soluble α-1,4 glucose polymer) is rapidly hydrolysed by intestinal enzymes to free glucose prior to absorption. Once hydrolysed, maltodextrin-derived glucose and the ingested ^{13}C-glucose tracer enter the same systemic pool via SGLT1/GLUT2 and follow identical oxidative pathways (45). Indeed, previous data from our laboratory demonstrated that plasma U-^{13}C glucose enrichment reached a plateau within 30–120 min of exercise when participants ingested 60 g·h^{-1} of a maltodextrin solution, thereby excluding differences in appearance kinetics between the maltodextrin solution and the U-^{13}C tracer (46). Such data would appear to validate the use of a mixture of naturally enriched maltodextrins with U-^{13}C glucose tracer to estimate the oxidation of maltodextrin during exercise, an approach utilised in multiple studies evaluating exogenous CHO oxidation (26, 44, 47). Furthermore, although total CHO intake reached 120 g·h^{-1} in the present study, the absolute maltodextrin dose studied here (i.e. 60 g·h^{-1}) was constant across trials and matched the dose previously used by Pugh et al., (46). Moreover, we also observed that (i) breath ^{13}C-glucose enrichment reached and maintained a plateau during exercise across trials (Fig. 5 B), (ii) breath $^{13}CO_2$ exhibited the expected time course and dose–response (Fig. 5 A), and (iii) exogenous CHO oxidation increased with intake in a dose response manner (Fig. 5 B). Nevertheless, this remains a methodological limitation, and for definitive validation it is acknowledged that future studies should directly compare U-^{13}C glucose with a labelled maltodextrin tracer under identical ingestion rates (i.e. 60 g·h^{-1}).

To our knowledge, the present study represents the first direct assessment of exogenous CHO oxidation in elite male marathon runners. Our results clearly demonstrate a dose response effect whereby peak exogenous CHO oxidation rates increased in accordance

with absolute CHO ingestion (see Figure 5 B). Our study extends previous evaluations of exogenous CHO oxidation in runners (31, 33, 39, 48) and we report some of the highest exogenous oxidation rates observed in runners to date, with peak rates of 1.00 ± 0.10 g·min^{-1}, 1.48 ± 0.13 g·min^{-1} and 1.77 ± 0.13 g·min^{-1} with CHO ingestion rates of 60, 90 and 120 g·h^{-1}, respectively. While peak values provide useful context, we acknowledge that single time points can overestimate utilizable carbohydrate if considered in isolation. Accordingly, we also report mean values during hour 2 of exercise, (0.89 ± 0.11 g·min^{-1}, 1.31 ± 0.18 g·min^{-1} and 1.68 ± 0.16 g·min^{-1} for 60, 90 and 120 g·h^{-1}) which in our dataset closely aligned with the peak responses. In relation to the latter, these values are comparable to recent observations from our laboratory in trained male cyclists where we observed peak exogenous CHO oxidation rates of approximately 1.6 g·min^{-1} when 120 g·h^{-1} (1:0.8 ratio of maltodextrin to fructose) was administered in fluid format (26). High rates of exogenous CHO oxidation in cyclists (i.e. 1.5-2.0 g·min^{-1} with ingestion rates 90-120 g·h^{-1}) are now well documented within the literature (26, 49, 50).

An evaluation of existing studies clearly demonstrates that exogenous CHO oxidation rates do not equate to ingestion rates, with oxidation efficiencies typically reported in the range of 70–90% (51, 52). Recently, Podlogar et al. (50) reported higher oxidation efficiencies with 90 g·h^{-1} (86 ± 10%) using a 2:1 maltodextrin: fructose ratio compared to 120 g·h^{-1} of CHO (76 ± 11%) with a 1:0.8 ratio, with higher exercise intensities. In the present study, we observed high oxidation efficiencies across all conditions (89 ± 4% at 60 g·h^{-1}, 87 ± 4% at 90 g·h^{-1}, and 84 ± 3% at 120 g·h^{-1}), with no significant difference between doses. It is possible that during exercise above LT associated with increased (albeit stable) metabolic acidosis, the respiratory exchange ratio (RER) may provide an inaccurate estimation of substrate utilisation, primarily due to the increased release of non-respiratory CO_2 and depletion of the labile bicarbonate pool (53). However, stoichiometric calculations

remain valid under these conditions, as $\dot{V}CO_2$ continues to reflect tissue-level CO_2 production with reasonable accuracy up to intensities of 80 – 85% $\dot{V}O_{2max}$ (54). The high CHO oxidation efficiencies observed here may then be due to the participants' elite training status and associated metabolic adaptations, together with the running modality and high exercise intensity. Additionally, the use of a 1:1 ratio of maltodextrin and fructose (as opposed to 2:1 or 1:0.8 ratio) may have also contributed to the high oxidation efficiencies observed here (52).

The effects of increasing dose of CHO ingestion during exercise had profound effects on whole body substrate metabolism. Indeed, whilst it has long been posed that both half-marathon (55) and marathon running (56) are CHO dependent, the present study demonstrates that rates of whole-body CHO oxidation and CHO dependency (i.e., 65% CHO contribution during the 2nd hour of "simulated" marathon running) are only maintained with the higher CHO ingestion rate of 120 g·h^{-1}. Indeed, 120 g·h^{-1} prevented the occurrence of a metabolic crossover point (i.e., the time-point during exercise at which fat provides the greater contribution towards total energy expenditure). In contrast, ingestion rates of 90 and 60 g·h^{-1} resulted in an apparent transition towards fat dependence whereby fat provided 49 and 54% of the energy contribution during the second hour of exercise, versus 40 and 46% of the energy contribution in the first hour, respectively. Collectively, these results demonstrate that fat does not provide a negligible contribution to energy production at intensities close to marathon race pace but, rather, provides an obligatory role in sustaining ATP production. Nevertheless, it must be noted, that the reliance solely on indirect calorimetry to assess substrate oxidation does not account for potential protein oxidation as the RER for protein (~0.80) lies closer to fat (~0.75) than carbohydrate (1.00) (56). Accordingly, when nitrogen excretion is not quantified and non-protein stoichiometric equations are applied, any resultant lowering of RER may be partly attributable to protein oxidation (potentially biasing estimates

toward greater fat oxidation rates, particularly with low glycogen availability), giving rise to greater leucine oxidation and greater negative net balance (56, 57). However, in nitrogen-corrected protocols during 120-min of prolonged treadmill running, protein contributed ~4–5% of total energy and was not affected by carbohydrate feeding during exercise (2 $g \cdot min^{-1}$), indicating that under well-fed conditions the likely misclassification is small (58). Therefore, the capacity for high rates of fat oxidation (i.e. ≥1 $g.min^{-1}$) at these high relative intensities and absolute running speeds could also be due to the elite training status and extensive training history of the participants and, in the context of the present study, also reflects limited CHO availability during the second hour of exercise.

It is noteworthy that even with ingestion rates of 120 $g \cdot h^{-1}$, CHO dependency slightly decreased from hour 1 (69%) to hour 2 (65%). In relation to running a sub-2 h marathon (i.e., necessitating higher absolute running speeds and associated CHO requirement), this provides further support that CHO ingestion rates of 90-120 $g \cdot h^{-1}$ are likely to confer a metabolic advantage compared with traditional recommendations of 60-90 $g \cdot h^{-1}$. Furthermore, a significant metabolic advantage was also observed as the O_2 cost of running was lower in the 120 $g \cdot h^{-1}$. This preferential reliance on CHO is logical, as the energy yield from CHO oxidation is more efficient than that of fat, providing greater energy per litre of O_2 consumed (59). Minimising the decline in running efficiency over time would likely enhance physiological resilience and support the preservation of critical speed during prolonged efforts (60). Nonetheless, given the limited capacity for both muscle and liver glycogen storage in elite marathoners (and that is *accessible* to active muscle), the present results also suggest that elite runners must possess a high capacity for fat oxidation even at race pace. Indeed, unpublished observations from our laboratory on a male Ethiopian distance runner (body mass 53.2 kg) during incremental exercise testing demonstrated whole body CHO and fat oxidation rates of 3.79 (75% energy contribution) and 0.57 $g.min^{-1}$ (25% energy

583 contribution) with an RER of 0.96 when running at 21 km.h^{-1}, respectively. Clearly, further
584 research is needed to directly quantify the energetic requirements and associated CHO cost to
585 readily meet the physiological demands of running a marathon at the elite level. In this
586 regard, the interaction of training and nutritional strategies (i.e., models of CHO periodisation
587 aligned to the principle of fuelling for the work required) may permit the training adaptations
588 that are likely necessary to simultaneously oxidise both carbohydrate and fat at such high
589 intensities (61).

590 Despite the potential metabolic advantage associated with higher rates of CHO
591 ingestion, there remain questions over the feasibility and practical application of such doses,
592 largely due to issues regarding GI tolerability. Indeed, although we observed high incidence
593 of moderate or severe GI symptoms across the range of 60-120 g·h^{-1}, peak symptoms of
594 nausea, stomach fullness, and abdominal cramps were reported in the 120 g·h^{-1} trial.
595 Nonetheless, in considering that cumulative GI scores were not different between trials
596 alongside previous observations of minimal GI symptoms when runners ingest up to 90 g·h^{-1}
597 during lower intensity running protocols (31, 33, 48), it is possible that the GI disturbances
598 frequently reported are perhaps more driven by exercise intensity, as opposed to CHO intake
599 *per se* (62, 63). However, the CHO concentration could also play a role in symptom
600 progression (51). In this regard, perturbations to GI homeostasis, driven by splanchnic
601 hypoperfusion (64), altered gastric myoelectrical rhythms, and cumulative exercise stress (65)
602 likely underpin symptom escalation during prolonged high-intensity exercise, thus suggesting
603 that exercise-induced GI dysfunction, rather than CHO load alone, is a key modulator of
604 nutrient tolerance and ingestion behaviour.

605 Notwithstanding a lack of knowledge and awareness of CHO guidelines (66), such
606 physiological mechanisms may explain, in part, the consistently low CHO intake that is self-
607 reported during marathon running (67). For example, marathon runners reportedly consume

relatively modest amounts of CHO (35 ± 26 g·h^{-1}), though individual intakes vary widely from as little as 6 g·h^{-1} to 136 g·h^{-1}. This variability suggests that only a small proportion of runners (<15%) consume CHO at levels exceeding the upper limits of current guidelines (67). However, despite the runners in the present study having experience of CHO intakes 100 – 120 g·h^{-1}, the decline in drink pleasantness over time and the consistently low urge to drink reported here (as evident in all trials) further suggest that GI issues may also limit habitual in-race fuelling practices. To address potential gastrointestinal limitations, gut training (35, 68) and personalised CHO intakes (69) have been proposed to enhance CHO absorption, improve tolerance, and reduce symptoms. Notably, given that previous research from our laboratory has shown that CHO feeding forms do not affect exogenous CHO oxidation (26), behavioural strategies that promote an individualised approach to CHO intake (e.g. altering drink palatability through taste, temperature, fluid volume and inclusion of alternative feeding forms such as gels) may help to practically achieve higher CHO ingestion rates and potentially increase GI tolerance.

Despite the novelty and practical relevance of our data, we acknowledge that this study had several limitations. Indirect calorimetry, which does not explicitly quantify protein oxidation, can bias estimates toward fat since the RER of protein (~0.80) is closer to fat (~0.75) than carbohydrate (1.00). As such, future studies should incorporate tracer-based methodology to directly quantify whole-body protein oxidation. In addition, though we acknowledge an apparent upward trend in blood lactate during exercise (which may be interpreted as non-steady state conditions) it is noteworthy that this response was driven by participants 2 and 6 (Supplementary Data Figure 1) who lost steady steady-state during exercise. This is physiologically expected, as critical speed/LT2 declines with fatigue (70), but the majority remained in steady state, and inclusion or exclusion of these cases did not alter statistical inferences for either mean exogenous CHO oxidation during hour 2 or peak

exogenous CHO oxidation (Supplementary Tables 1 and 2). Therefore, stable blood lactate further supports the validity of indirect calorimetry based substrate partitioning in this context (54). Because our study was primarily powered to detect changes in exogenous CHO oxidation, we also acknowledge our inability to identify smaller differences in other measures such as GI symptoms between trials. It is noteworthy that CHO concentration varied across drinks (24%, 18%, 12% at a fixed 500 $mL \cdot h^{-1}$), hence differences between trials (i.e exogenous CHO oxidation and GI symptoms) cannot be attributed solely to dose given that concentration-dependent differences in gastric emptying may also have contributed to the findings reported here. Future studies should therefore further evaluate the effects of dose, ratio and concentration (71, 72) in an elite running cohort. Although we maintained a double-blind design, we also acknowledge that the choice to keep the flavour neutral meant that differences in sweetness and concentration likely made the CHO dose easily identifiable to participants. Furthermore, CHO was provided only in drink form, whereas athletes typically use a mix of drinks, gels, and other sources during competition. We also did not include a water-only trial, which would have served as a true placebo condition for comparison. The absence of performance-based measures also means that we were unable to directly assess the impact of CHO dose on exercise performance, and this clearly warrants future investigation.

In summary, the present data demonstrate for the first time a clear dose-response effect of CHO ingestion in trained male runners on both whole-body and exogenous CHO oxidation during simulated marathon running. Importantly, our results suggest that an ingestion rate of 120 $g \cdot h^{-1}$ may confer a metabolic advantage (as also evidenced by improved running economy) compared to currently recommended doses of 60 and 90 $g \cdot h^{-1}$. We also observed the highest rates of exogenous CHO oxidation yet reported in runners in the literature, with peak individual oxidation rates ranging from 1.64 to 1.99 $g \cdot min^{-1}$. Nonetheless, the potential performance implications of such higher CHO doses remain to be

658 evaluated and the high prevalence of GI symptoms across all conditions suggests that
659 marathon runners would likely benefit from strategies that enhance CHO tolerance and
660 mitigate GI distress.

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Author contributions

SR, KOJ, AMJ, JPM and JNP designed the study. SR, KGS and HJM performed experiments; SR, JNP, TMB, and JPM analysed the data and interpreted the results. SR, JNP, and JPM drafted the manuscript and DJO, JBL, TMB, KOJ AMJ, JPM and JNP edited and revised the manuscript. All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Supplemental Material

Supplementary Figure 1 - https://doi.org/10.6084/m9.figshare.30432313.v2

Supplementary Figure 1 – Legend - https://doi.org/10.6084/m9.figshare.30432313.v2

Supplementary Table 1 and 2 - https://doi.org/10.6084/m9.figshare.30432313.v2

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892 **Table 1.** Participant Characteristics.

893

894 **Figure 1**

895 Schematic overview of the experimental protocol employed in each trial. Following 24 h of a
896 high CHO diet, subjects consumed a high CHO pre-exercise meal before undertaking 120
897 min of running at 94% lactate turn point (LTP) with the first and final 15 minutes at 95%
898 lactate threshold (LT) during which they consumed 60, 90 and 120 $g \cdot h^{-1}$ CHO drinks.

899

900 **Figure 2**

901 (A) Heart rate, (B) RPE, (C) blood lactate, (D) running economy and (E) caloric cost of
902 running, during prolonged treadmill running with CHO ingestion at 60, 90, and 120 $g \cdot h^{-1}$.
903 Data are mean ± SD for n = 8 elite male marathon runners. Running economy was calculated
904 as the oxygen cost of submaximal exercise. Statistical differences were assessed by repeated-
905 measures ANOVA with Holm–Bonferroni correction. a–h denotes $P < 0.05$ vs. 15 (a), 30 (b),
906 45 (c), 60 (d), 75 (e), 90 (f), 105 (g), and 120 (h) min, respectively; # denotes $P < 0.05$ vs. 60
907 $g \cdot h^{-1}$ trial.

908

909 **Figure 3 (A)** Blood glucose concentration, (B) whole-body CHO oxidation rate, (C) fat
910 oxidation rate, (D) respiratory exchange ratio (RER), (E) total CHO use, and (F) total fat use
911 during prolonged treadmill running with CHO ingestion at 60, 90, and 120 $g \cdot h^{-1}$. Data are
912 mean ± SD for n = 8 elite male marathon runners. Statistical differences were analysed using
913 two-way repeated-measures ANOVA with Holm–Bonferroni correction; total carbohydrate
914 and fat use were analysed using one-way repeated measures ANOVA. a–h denotes $P < 0.05$
915 vs. 15 (a), 30 (b), 45 (c), 60 (d), 75 (e), 90 (f), 105 (g), and 120 (h) min, respectively; #
916 denotes $P < 0.05$ vs. 60 $g \cdot h^{-1}$ trial; † denotes $P < 0.05$ vs. 90 $g \cdot h^{-1}$ trial.

Figure 4

(A) Total energy expenditure during prolonged treadmill running. Energy expenditure derived from CHO and fat for (B) 60 $g \cdot h^{-1}$ (C) 90 $g \cdot h^{-1}$ and (D) 120 $g \cdot h^{-1}$. Data are mean ± SD for n = 8 elite male marathon runners. For total energy expenditure, statistical differences were analysed using two-way repeated-measures ANOVA with Holm–Bonferroni correction; a–h denotes $P < 0.05$ vs. 15 (a), 30 (b), 45 (c), 60 (d), 75 (e), 90 (f), 105 (g), and 120 (h) min, respectively.

Figure 5

(A) Breath $^{13}CO_2$ enrichment and (B) exogenous CHO oxidation (B) during prolonged treadmill running in the 60, 90 and 120 $g \cdot h^{-1}$ trials. (B) Individual participants' mean exogenous CHO during *hour 2* and (D) peak exogenous CHO oxidation during prolonged treadmill running (E) oxidation efficiency (F) and substrate contributions to total energy expenditure during hour 2 of exercise. Data are mean ± SD for n = 8 elite male marathon runners. Statistical differences in exogenous CHO oxidation during exercise were assessed by two-way repeated-measures ANOVA; hour 2 mean and peak exogenous CHO oxidation, oxidation efficiency, and substrate contribution were analysed using one-way repeated measures ANOVA. with Holm–Bonferroni correction; a–h denotes $P < 0.05$ vs. 15 (a), 30 (b), 45 (c), 60 (d), 75 (e), 90 (f), 105 (g), and 120 (h) min, respectively. # denotes $P < 0.05$ vs. 60 $g \cdot h^{-1}$ trial; † denotes $P < 0.05$ vs. 90 $g \cdot h^{-1}$ trial.

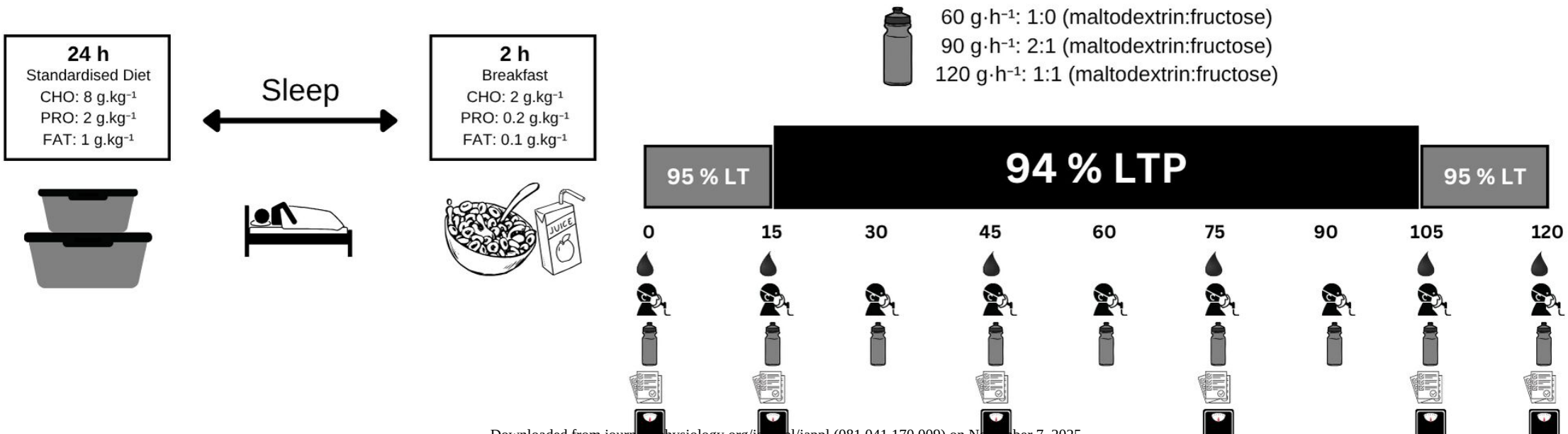
Figure 6

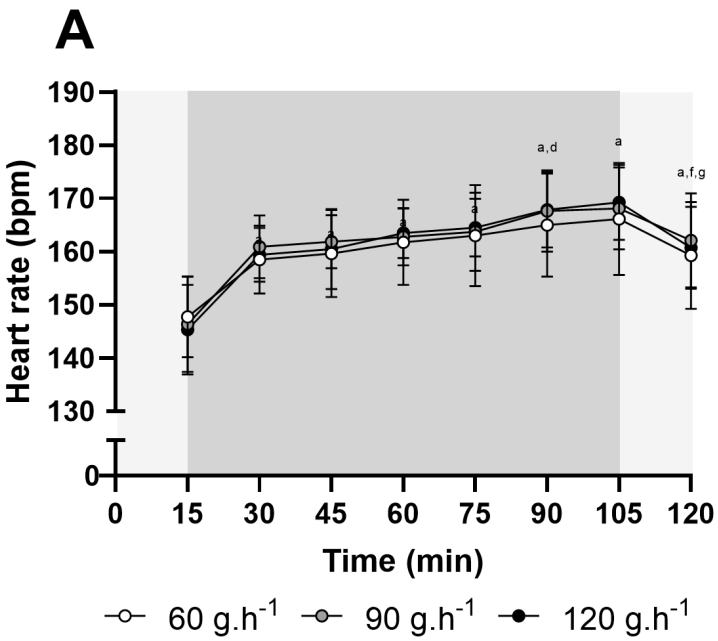
Gastrointestinal symptom progression during exercise in the (A) 60, (B) 90 and (C) 120 $g \cdot h^{-1}$ trials during prolonged treadmill running. Data are mean ± SD for n = 8 elite male marathon

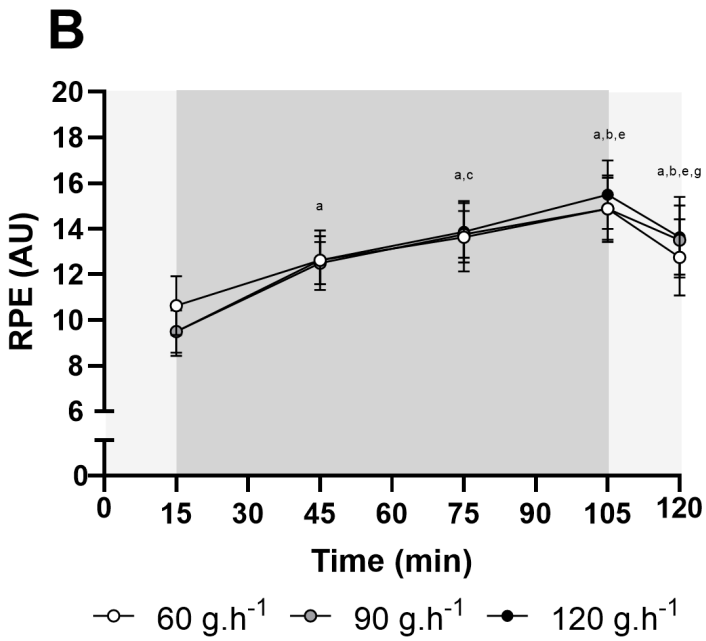
runners. Statistical differences in symptom progression across time were analysed using Friedman's ANOVA.

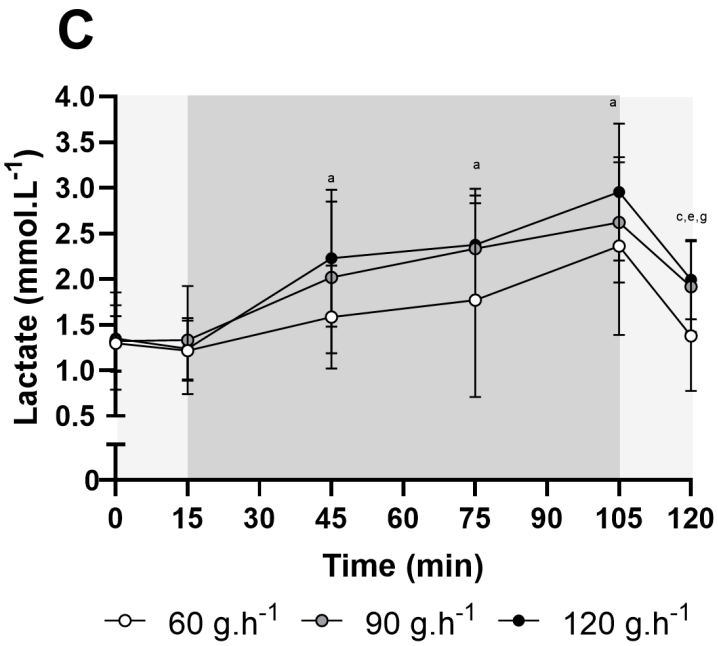
Figure 7

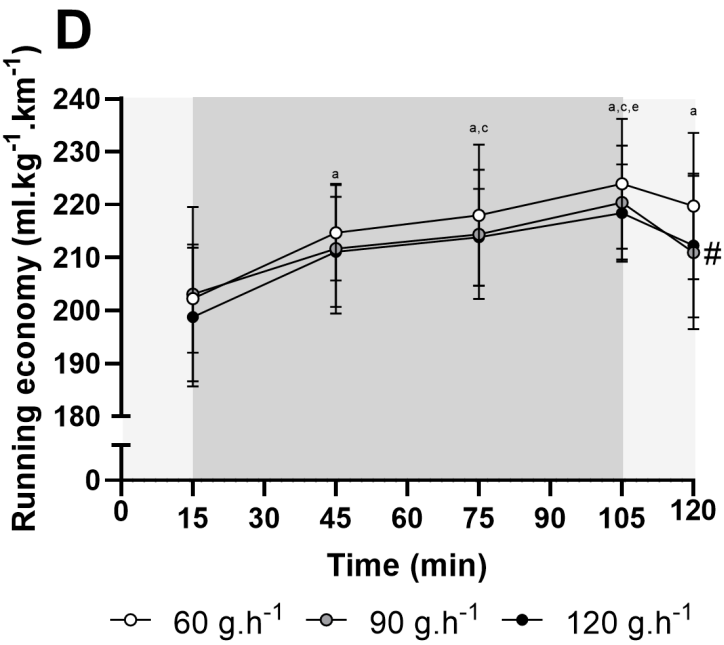
(A) Drink sweetness, (B) drink pleasantness and (C) urge to drink during the 60, 90 and 120 $g \cdot h^{-1}$ trials during prolonged treadmill running. Data are mean ± SD for n = 8 elite male marathon runners. Statistical differences in symptom progression across time were analysed using Friedman's ANOVA. # Denotes significance from the 60 $g \cdot h^{-1}$ trial and † denotes significance from the 90 $g \cdot h^{-1}$.

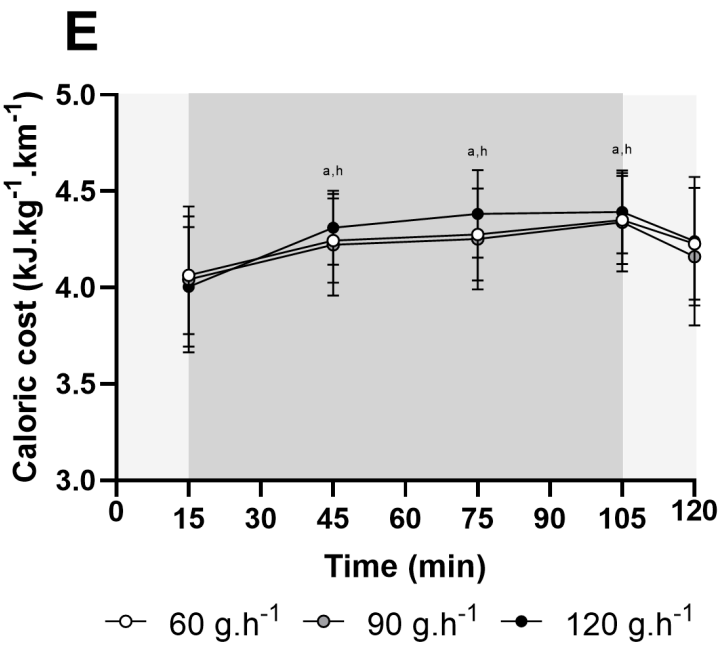


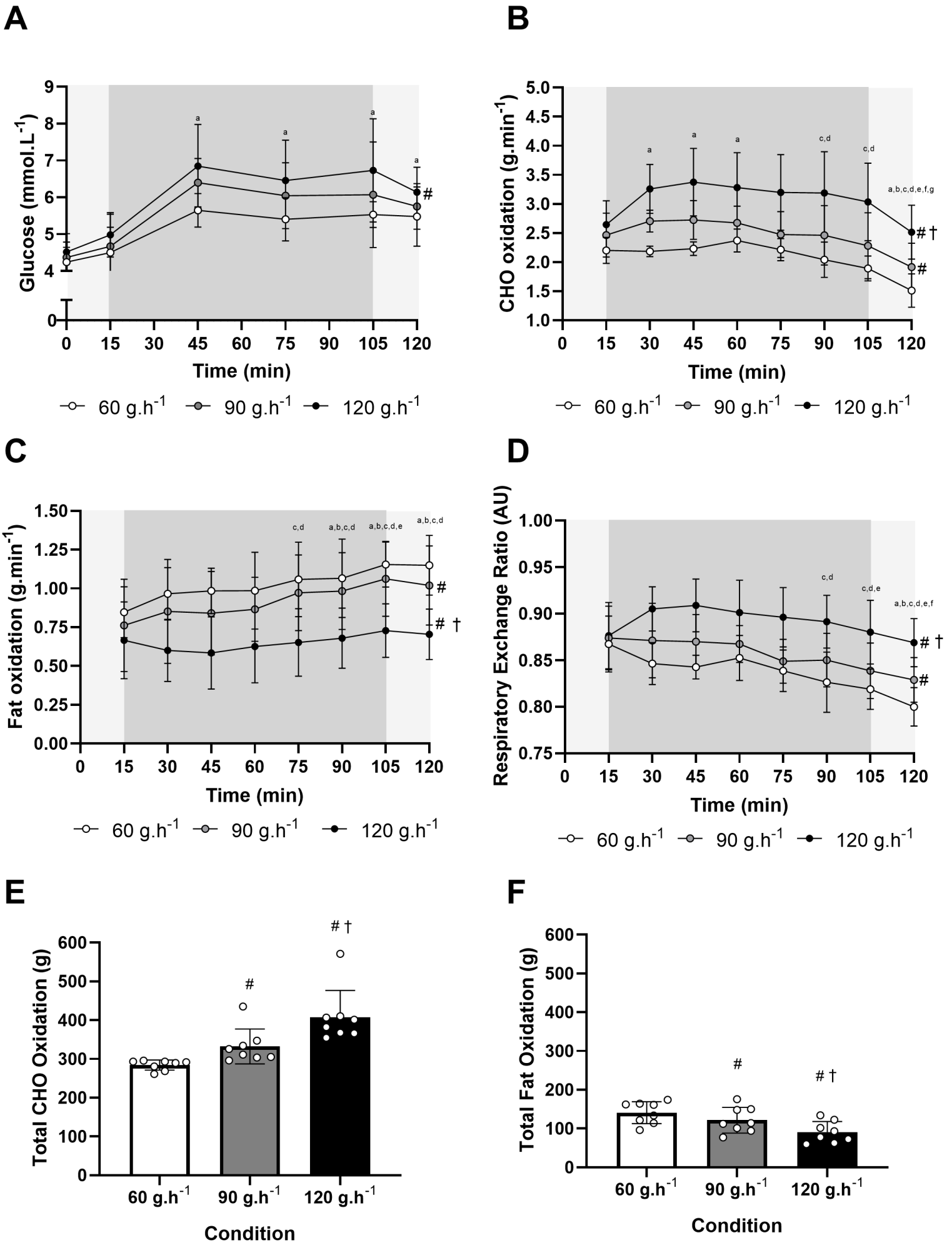


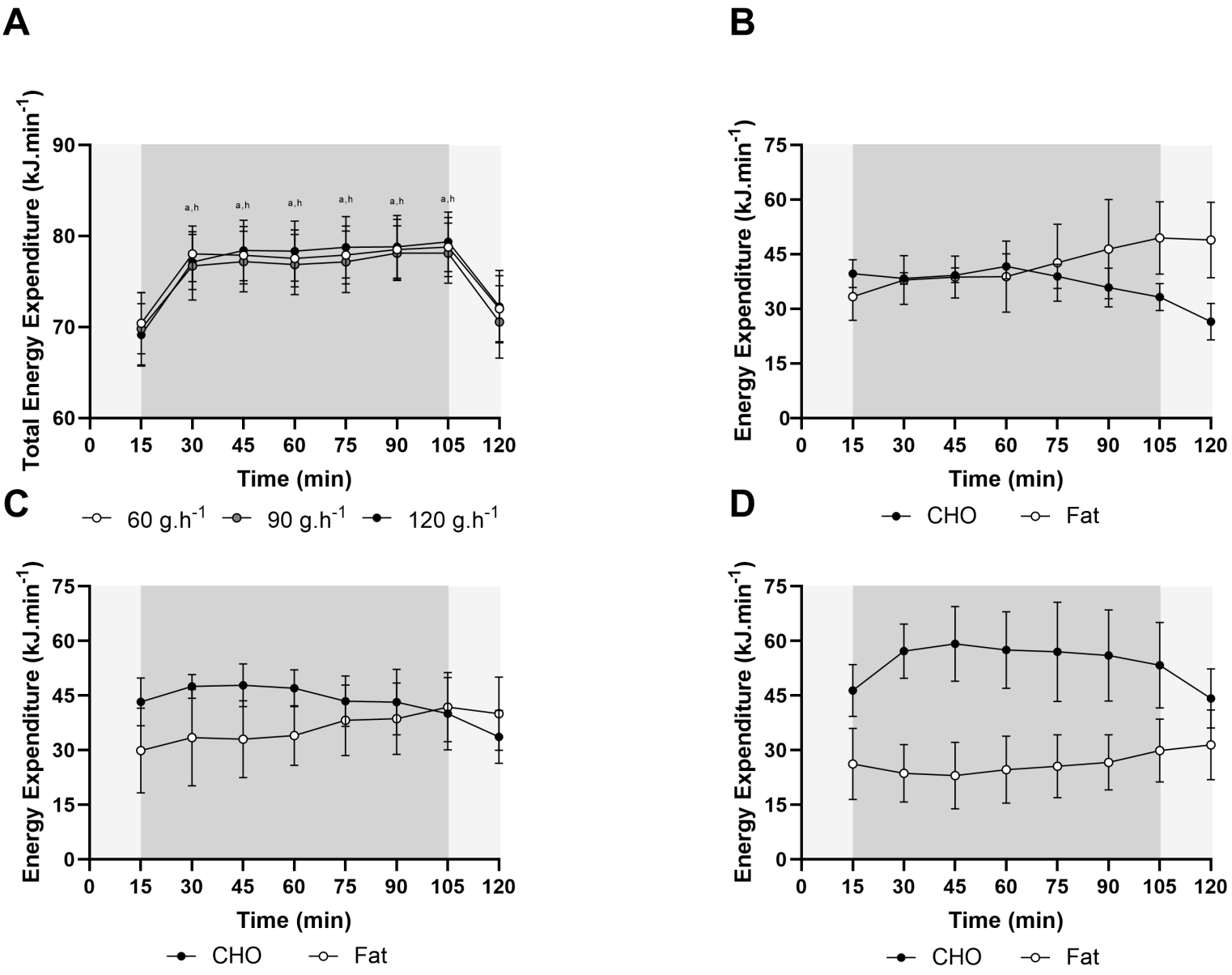


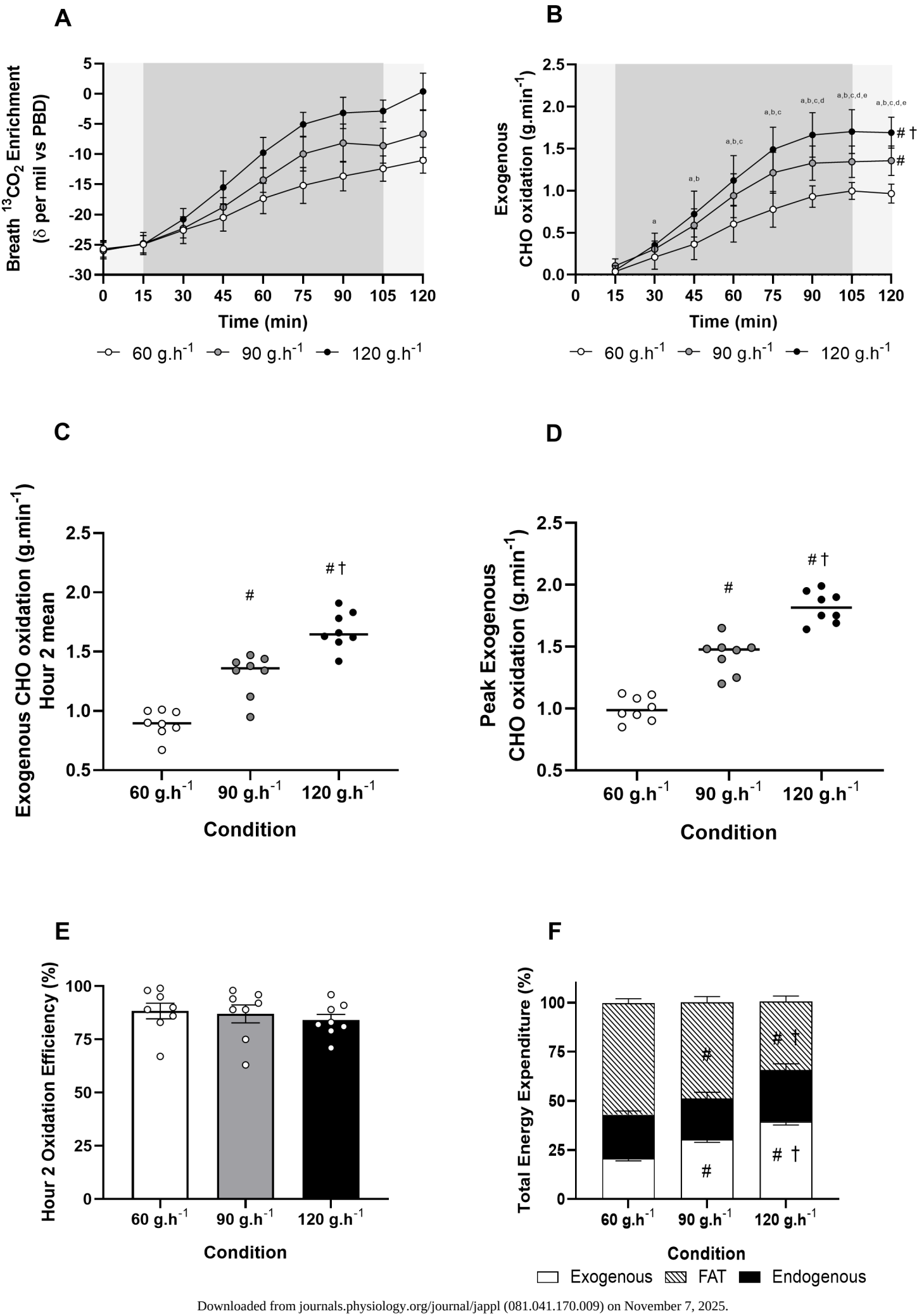


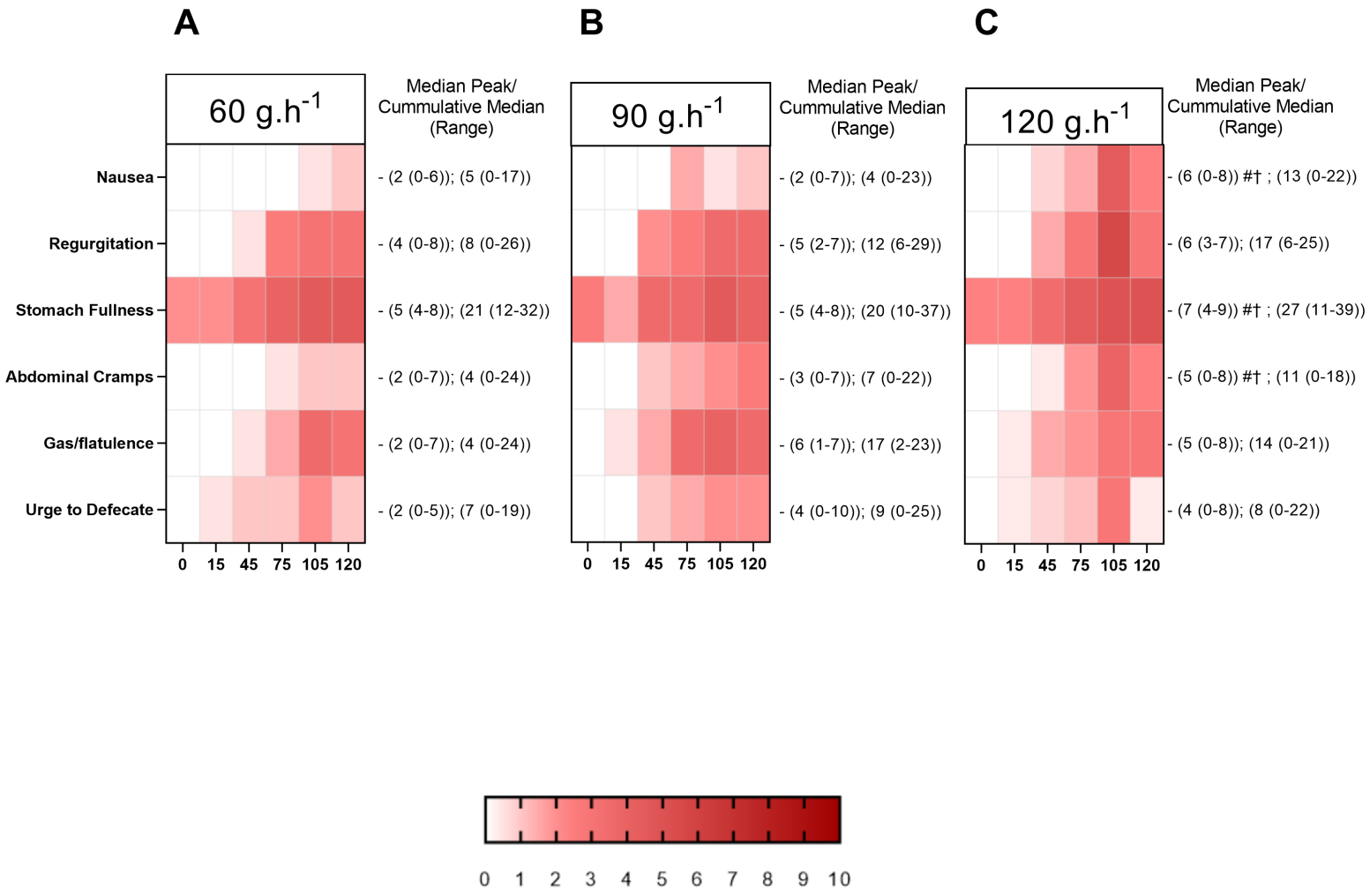


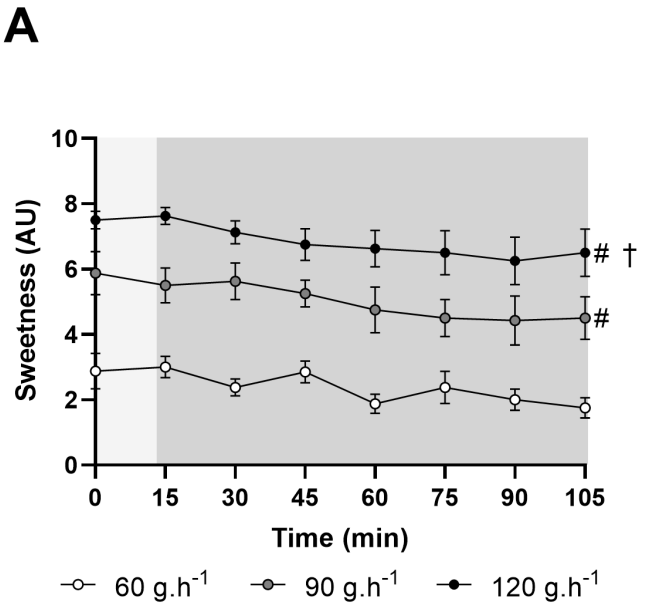


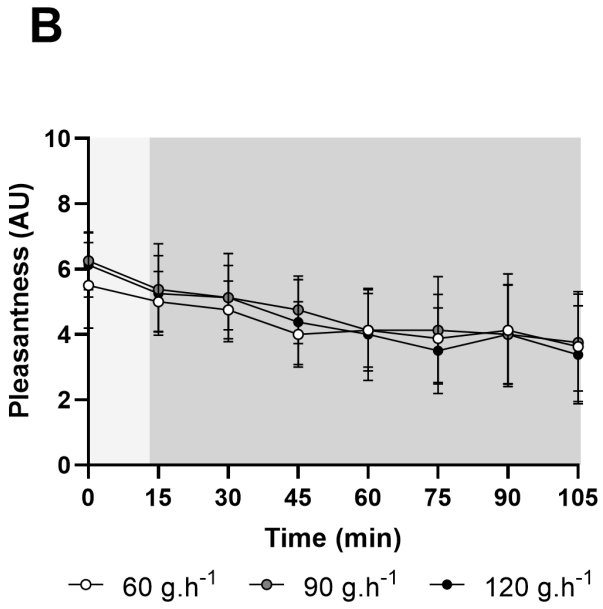


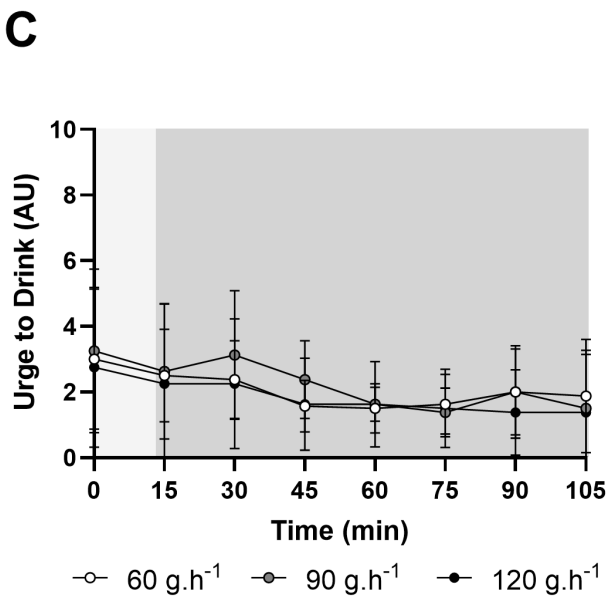












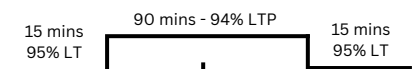
Participant Characteristics $n = 8$	
Age	33 ± 6
Height (cm)	177 ± 7
BM (kg)	67.4 ± 3
Marathon PB	2:22:54 ± 05:37
Speed at 95 % LT ($km.h^{-1}$)	15.3 ± 1
Speed at 94 % LTP ($km.h^{-1}$)	16.4 ± 1

120 g·h⁻¹ Maintains Whole-Body CHO oxidation, Increases Exogenous CHO oxidation and Lowers O_2 Cost of Running in Elite Male Marathoners

METHODS

n = 8 elite marathoners

Treadmill Running

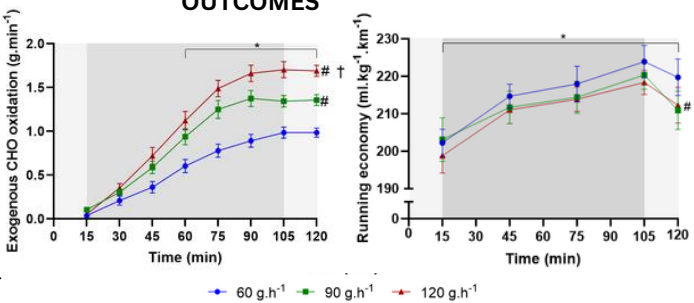


60 g·h⁻¹ | 90 g·h⁻¹ | 120 g·h⁻¹

125mL every 15 minutes

OUTCOMES

120 g·h⁻¹



CONCLUSION

- 120 g·h⁻¹ confers a metabolic advantage to male marathoners by better maintaining whole-body rates of CHO oxidation compared with 60-90 g·h⁻¹.
- 120 g·h⁻¹ of CHO lowers O_2 cost by 2.6% compared to 60 g·h⁻¹.
- Peak scores for nausea, stomach fullness and abdominal cramps were greatest for 120 g·h⁻¹.