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THE INCREASE IN PLASMA IL-6 FOLLOWING SPRINT INTERVAL TRAINING DOES NOT DEPEND ON TOTAL SPRINT VOLUME

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ABSTRACT

The magnitude of the beneficial increase in plasma interleukin-6 (IL-6) with exercise is greater with continuous exercise of higher intensity and longer duration. However, it is unknown whether a greater volume of supramaximal interval exercise also enhances the IL-6 response. Therefore, the aim of this study was to compare the effects of two sprint interval training (SIT) protocols involving different volumes of sprint exercise on plasma IL-6 levels. Nine healthy young men (age: 24±4 y, BMI: 23.3±3.1 kg·m-2, V̇O2max: 42±6 mL·kg-1·min-1) completed three experimental trials in randomised order, including 'classic' SIT (4x30-s 'all-out' cycle sprints within a 22-min session), reduced-exertion high-intensity interval training (REHIT; 2x20-s 'all-out' cycle sprints within a 10-min session), and a control condition (seated rest). Blood samples were collected before exercise and at 0-, 30-, and 90-min post-exercise, and analyzed for lactate and IL-6. Blood lactate levels peaked directly post-SIT (1.5±0.2 mM to 11.9±2.5 mM; p<.001) and REHIT (1.7±0.4 to 9.1±3.1 mM; p<.001). Plasma IL-6 levels peaked 30-min post-exercise (0.84±0.12 to 1.31±0.17 pg·mL-1 for SIT, p=.003; 0.75±0.09 to 1.18±0.36 pg·mL-1 for REHIT, p=.028). Compared to the control trial, IL-6 iAUC was significantly higher for both SIT (p=.002) and REHIT (p=.013), with no significant difference between SIT and REHIT. In conclusion, we demonstrate that the increase in plasma IL-6 levels is similar for the two SIT protocols involving a 3-fold difference in sprint exercise volume (120 s vs. 40 s). Our data provide support for a possible role of glycogenolysis in the IL-6 response to SIT.

Keywords: *interleukin-6, lactate, Reduced-exertion high-intensity interval training, REHIT, SIT*

INTRODUCTION

The pleiotropic cytokine interleukin 6 (IL-6) can exhibit distinctly contrasting effects on health. On the one hand, chronically elevated plasma IL-6 levels act in a pro-inflammatory manner and have been implicated in the development of a range of diseases, including cancer, autoimmune disorders, and atherosclerosis (Orange, Leslie, Ross, Mann, & Wackerhage, 2023). Conversely, the short-lived spike in IL-6 release from skeletal muscle during and after exercise (which makes IL-6 a prime example of a myokine) is thought to have acute anti-inflammatory effects (Pedersen, Steensberg, & Schjerling, 2001) and has been proposed to be at least partly responsible for a range of health benefits of regular exercise, including improved insulin sensitivity (Benrick, Wallenius, & Asterholm, 2012), improved lipid metabolism (Lin et al., 2023), appetite regulation (Islam et al., 2017), acute suppression of cancer cell proliferation (Or-

ange et al., 2022), and attenuation of cancer cachexia progression (Daou, 2020).

The magnitude of the increase in plasma IL-6 has been shown to be greater with exercise of longer duration and with greater exercise intensity (Cullen, Thomas, Webb, & Hughes, 2016; Ostrowski, Schjerling, & Pedersen, 2000). Thus, it is not surprising that sprint interval training (SIT; an exercise intervention involving repeated supramaximal sprints (Weston, Wisloff, & Coombes, 2014)) has been demonstrated to be effective at increasing circulating IL-6 levels (Ferreira et al., 2018; Harnish & Sabo, 2016; Islam et al., 2017). SIT provides an interesting experimental model that can help us understand the effects of exercise performed at the highest intensities that individuals can achieve. However, the 'classic' SIT protocol involving 4-6 repeated 30-s 'all-out' cycle sprints within a 22-31-min exercise session (Burgomaster, Hughes, Heigenhauser, Bradwell, & Gibala, 2005) is not generally regarded as a feasible real-world exercise intervention because of its excessively intense nature and associated negative affective responses (Biddle & Batterham, 2015; Ekkekakis, Vallance, Wilson, & Ewing Garber, 2023; Hardcastle, Ray, Beale, & Hagger, 2014).

Nonetheless, over the past decade, we have demonstrated that the number and duration of supramaximal sprints in the classic SIT protocol can be substantially reduced without attenuating the magnitude of various acute physiological responses, associated chronic training adaptations, and health benefits (Metcalfe et al., 2020; Metcalfe, Babraj, Fawkner, & Vollaard, 2012; Metcalfe, Tardif, Thompson, & Vollaard, 2016; Nalçakan et al., 2017; Thomas et al., 2020; Vollaard, Metcalfe, & Williams, 2017). Specifically, we have developed the reduced-exertion high-intensity interval training (REHIT) protocol, involving two 20-s 'all-out' cycle sprints within a 10-min low-intensity exercise session (Metcalfe et al., 2012). The reduced total sprint volume attenuates negative affective responses (Metcalfe et al., 2022; Songsorn et al., 2020), making REHIT a manageable and acceptable intervention (Metcalfe et al., 2020; Metcalfe & Vollaard, 2024). Moreover, despite the low total sprint volume, REHIT has been demonstrated to be effective at improving key health markers such as maximal aerobic capacity ($\dot{V}O_{2max}$) (Metcalfe et al., 2012; Metcalfe et al., 2016; Metcalfe & Vollaard, 2021), insulin sensitivity (Gillen et al., 2016; Metcalfe et al., 2012), and blood pressure (Cuddy, Ramos, & Dalleck, 2019; Gillen et al., 2014; Ruffino et al., 2017). This suggests that the health benefits associated with SIT are predominantly due to achieving supramaximal intensities during the initial supramaximal sprints, rather than requiring a large volume of sprint exercise (Metcalfe & Vollaard, 2024). However, to date, it remains unknown whether reducing the volume of sprint exercise attenuates the plasma IL-6 myokine response.

In a seminal study, Hojman et al. (2019) established that: i) the increase in plasma IL-6 levels is tightly correlated with the increase in plasma lactate, ii) injecting mice with lactate leads to an increase in plasma IL-6 levels, iii) buffering the lactate-associated decrease in pH during exercise attenuates the increase in plasma IL-6 levels, and iv) blocking pH-sensitive proteases attenuates the exercise-induced increase in plasma IL-6 levels. Accordingly, the authors proposed that the increase in blood lactate with exercise leads to matrix metalloproteinase-dependent release of IL-6 from skeletal muscle (Hojman et al., 2019). This model may explain why IL-6 secretion is augmented during high-intensity exercise, and it leads us to hypothesize that different interval protocols associated with similar increases in blood lac-

tate levels will also result in similar increases in plasma IL-6 levels. As REHIT is expected to result in similar levels of glycogenolysis, glycolysis, and skeletal muscle lactate production compared to classic SIT (Metcalfe et al., 2015; Parolin et al., 1999), we expect REHIT also to be associated with a similar IL-6 response compared to SIT. Thus, the objective of this study was to compare the IL-6 response to classic SIT, REHIT, and a no-exercise control condition, to establish the effect of total supramaximal sprint volume on changes in plasma IL-6 levels.

METHODS

Participants

Thirteen healthy young men volunteered to participate in this study. Exclusion criteria were age: < 18 y or > 40 y, BMI > 35 kg·m^{-2}, participation in a structured exercise training programme at any time in the preceding 6 months, suffering from acute (e.g., common cold, COVID-19, flu, etc) or chronic disease (e.g., diabetes, heart disease, cancer, etc), answering 'yes' to one or more questions of a standard physical activity readiness questionnaire (PAR-Q), resting heart rate ≥ 100 beats·min^{-1}, and/or clinically significant hypertension (>140/90 mm Hg). Data are presented for 9 participants (mean ± SD age = 24 ± 4 years; BMI = 23.3 ± 3.1 kg·m^{-2}; $\dot{V}O_{2max}$ = 42 ± 6 mL·kg^{-1}·min^{-1}) because full blood sample sets could not be obtained for three participants due to technical issues with the cannula (n = 2) and haemolysis (n = 1), and one participant did not adhere to pre-test instructions (i.e., did not attend the lab after an overnight fast). The study received local University ethics approval (NHS, Invasive or Clinical Research Committee; NICR 14395), and all participants provided written consent after full written and verbal explanation of the study protocol.

Experimental design

Prior to the experimental trials, each participant completed a maximal incremental cycling test to volitional exhaustion to assess maximal aerobic capacity ($\dot{V}O_{2max}$). Participants started cycling on a stationary bike at an intensity of 50 W for 1 min, after which the intensity increased by 1 W every 3 s until volitional exhaustion or inability to maintain a pedalling frequency of >60 rpm. Expired O_2 and CO_2 were continuously measured breath-by-breath using an online gas analyser (K5, Cosmed, Banbury, UK). $\dot{V}O_{2max}$ was determined as the highest value for a 15-breath rolling average of $\dot{V}O_2$ and was accepted if at least two of the following criteria were met: (i) volitional exhaustion, (ii) respiratory exchange ratio >1.15, and (iii) maximal heart rate within 10 beats min^{-1} of the age-predicted maximum (i.e., 220-age).

On a separate day, each participant performed a familiarization session involving one 30-second Wingate sprint and one 20-second Wingate sprint, with 4 min of unloaded cycling after each sprint. The subsequent experimental trials were performed in a randomised order using a counterbalanced Latin square design, with trials separated by ≥1 week. The three trials included a resting control session (control; no exercise) and two exercise sessions: 1) 'classic' SIT (a 4-min unloaded warm-up followed by four 30-s bouts of 'all-out' cycling against a resistance of 7.5% of body mass, interspersed with 4 min unloaded pedalling), and 2) REHIT (a 2-min unloaded warm-up followed by two 20-s bouts of 'all-out' cycling against a resistance of 7.5% of body mass, interspersed with 3 min (after the first sprint) or 4 min (after the seconds sprint) of unloaded pedalling). Participants were asked to record their dietary intake for the day prior to the first trial and replicate this for the days before the remain-

ing two trials. Furthermore, participants were asked to avoid any prolonged and/or strenuous exercise, as well as alcohol intake, for at least 48 hours prior to each trial.

For each experimental trial, participants attended the laboratory at approximately 09:00 a.m. after an overnight fast. Participants received a standardised breakfast consisting of an energy bar (Trek High Protein Flapjack; 50 g, 976 kJ, 12.6 g fat, 20.3 g carbohydrate, 9 g protein) and 500 mL of water. Participants remained seated after completing breakfast for 30 minutes before starting the SIT protocol, for 42 minutes before starting the REHIT protocol (to account for the difference in exercise duration between the SIT and REHIT protocols), or for the remainder of the session for the control trial. Power output was measured continuously during each exercise bout. Following completion of each exercise protocol, participants remained seated for an additional 90 min. Venous blood samples were collected from a cannula inserted in a superficial forearm vein (BD Nexiva, BD, Helsingborg, Sweden), directly before exercise, directly post-exercise, and 30- and 90-min post-exercise, or at equivalent time points for the control trial. Samples were collected into EDTA Vacutainer tubes and stored on ice prior to centrifugation at 4 °C for 10 min at 3000 x g. After centrifugation, the plasma was dispensed into Eppendorf tubes and stored at −80 °C until analysis. Haematocrit (Hct; Hawksley & Sons Ltd, Sussex, UK) and haemoglobin (HemoCue 201+ System, Hemocue Ltd, Ängelholm, Sweden) were determined from EDTA-treated whole blood at each time-point. Changes in plasma volume from pre-exercise were calculated using published equations by Dill & Costill (1974). Blood lactate was analysed using the Lactate Pro meter (Arkray, Kyoto, Japan). A commercially available ELISA kit was used to determine plasma concentrations of IL-6 (Quantikine HS Human IL-6, R&D Systems, Minneapolis, USA). Analyses were done in duplicate, and IL-6 levels were corrected for changes in plasma volume.

Statistical analysis

All data are presented as mean ± SD. Incremental area under the curve (iAUC) for IL-6 was calculated using the trapezoid rule. Data were tested for normality using the Shapiro-Wilk test. As plasma IL-6 data significantly deviated from a normal distribution for some trials, IL-6 data were analysed using a nonparametric test. Changes between time-points (pre-exercise and 0-, 30-, and 90-min post-exercise) for blood lactate and plasma IL-6 were analysed using repeated measures ANOVAs (with Tukey pairwise comparisons) and Friedman tests (with Durbin-Conover pairwise comparisons), respectively, for each trial. Differences between the three trials for IL-6 iAUC were analysed using the Friedman test with Durbin-Conover pairwise comparisons. Significance was accepted at $p < .05$.

RESULTS

All participants completed both exercise sessions and the control condition. During the first sprint, peak power output (PPO) and mean power output (MPO) were 258% and 176% of W_{max} for SIT and 278% and 200% of W_{max} for REHIT. Both PPO and MPO decreased with successive sprint repetitions during SIT and REHIT (see Table 1). Plasma volume was significantly decreased immediately post-exercise for both SIT (-11.5 ± 7.2%; $p < .001$) and REHIT (-9.5 ± 5.6%; $p < .001$) but had returned to baseline by 30 min post-exercise for both trials. The magnitude of decrease in plasma volume was not significantly different for SIT and REHIT.

Table 1. *Power data for the SIT and REHIT trials (n=9)*

	SIT				REHIT	
	Sprint 1	**Sprint 2**	**Sprint 3**	**Sprint 4**	**Sprint 1**	**Sprint 2**
PPO (W)	622±117	579±69	525±68	500±78	672±123	652±114
MPO (W)	489±75	419±32	372±31	365±34	555±102	508±81

Values shown are means±SD

Blood lactate levels increased significantly immediately following SIT and REHIT ($p < .001$), remained higher above the baseline at 30 min post-exercise ($p < .001$ for SIT, $p = .002$ for REHIT), but were no longer significantly different from baseline at 90 min post-exercise (Figure 1A). Plasma IL-6 levels corrected for plasma volume change (Figure 1B) were significantly increased from baseline and directly post-exercise at the 30 min post-exercise time point for both SIT ($p = .003$ vs. baseline, $p = .002$ vs. immediately post-exercise, $p < .001$ vs. 90 min post-exercise) and REHIT ($p = .028$ vs. baseline, $p = .004$ vs. immediately post-exercise). By 90 min post-exercise, plasma IL-6 levels were no longer significantly different from baseline and immediately post-exercise following either SIT or REHIT (Figure 1B). Compared to Control, IL-6 iAUC was significantly higher for both SIT ($p = .002$) and REHIT ($p = .013$). However, IL-6 iAUC was not significantly different between SIT and REHIT (Figure 2).

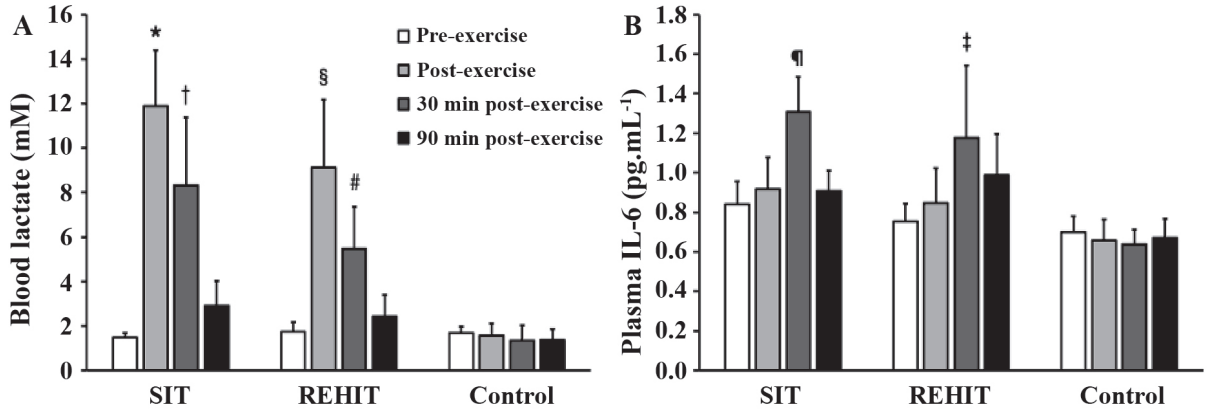

Figure 1. *The effects of SIT, REHIT and Control on blood lactate (A) and plasma IL-6 (B; n=9).*
*Significant differences: *p < .001 vs. pre-exercise and 90 min post-exercise, p = .003 vs. 30 min post-exercise; † p < .001 vs. pre-exercise and 90 min post-exercise; § p < .001 vs. pre-exercise and 90 min post-exercise, p = .001 vs. 30 min post-exercise; # p = .002 vs. pre-exercise and 90 min post-exercise; ¶: p = .003 vs. pre-exercise, p = .002 vs. post-exercise, p < .001 vs. 90 min post-exercise; ‡: p = .028 vs. pre-exercise, p = .004 vs. post-exercise.*

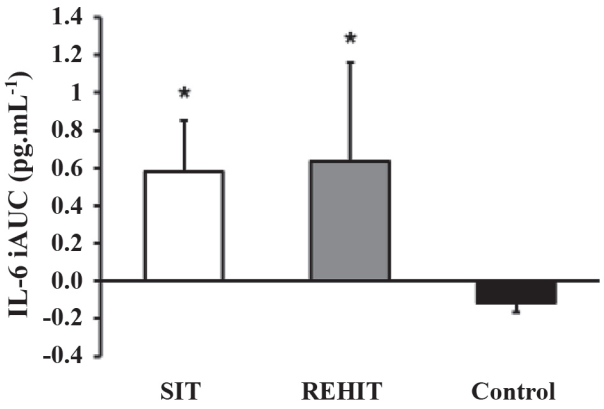

Figure 2. *IL-6 incremental area under the curve (iAUC) for SIT, REHIT and Control (n = 9). *: significantly different from Control (p = .002 vs. SIT; p = .013 vs. REHIT).*

DISCUSSION

The aim of this study was to compare the blood lactate and plasma IL-6 responses between classic SIT and REHIT to confirm whether the physiological responses were similar in protocols involving different volumes of sprint exercise. Our main finding was that neither the increase in blood lactate nor the increase in plasma IL-6 was significantly different between SIT and REHIT. This was despite the 3-fold difference in supramaximal sprint volume between the two protocols (120 s for SIT *vs*. 40 s for REHIT). These novel findings support our previous conclusions (Metcalfe & Vollaard, 2024; Vollaard et al., 2017) that using the classic SIT protocol, which involves four or more 30-s supramaximal sprint repetitions, is unnecessarily strenuous for improving health markers, as similar effects can be achieved with protocols involving fewer and shorter sprints.

Our finding that SIT and REHIT are associated with similar increases in both blood lactate and plasma IL-6 is in line with the model linking exercise intensity, lactate production, and IL-6 release during strenuous exercise as previously proposed by Hojman et al. (2019). It has been shown that the rapid glycogenolysis occurring during supramaximal exercise is limited to the first half of the initial sprints in a SIT session (Parolin et al., 1999). Glycogenolysis and glycolytic rates are strongly attenuated in the second half of the sprints and from 3 sprints onwards. Thus, glycogen depletion and blood lactate levels are expected to be of similar magnitudes with REHIT and classic SIT, despite the 3- to 4.5-fold larger sprint volume in the latter protocol (Metcalfe et al., 2015; Parolin et al., 1999). The lactate and/or hydrogen ions released from active skeletal muscle have been proposed to activate pH-sensitive proteases (e.g., metalloproteinases (MMP) 2 and 9), which in turn release IL-6 stored in preformed intramyocellular IL-6 depots (Hojman et al., 2019). Our present data suggest that a similar amount of glycogen breakdown and lactate production during SIT and REHIT may lead to similar activation of these mechanisms.

In this study, we took a blood sample immediately after completing the SIT and REHIT sessions. This was 4 minutes after the completion of the last sprint for both protocols, but 17 min and 30 s after completing the first sprint for SIT, and 7 min and 20 s after completing the first sprint for REHIT. Despite the 17 min and 30 s between completing the

first sprint in the SIT protocol and taking the post-exercise blood sample, plasma IL-6 levels had not yet significantly increased at this time point. Thus, it appears that IL-6 is not rapidly released during or directly after supramaximal exercise, but rather that there is a lag in the response. This finding is supported by most (Dos Santos Quaresma, Campos, Tavares-Silva, Marques, & Thomatieli-Santos, 2021; Ferreira et al., 2018; Islam et al., 2017; Kouvelioti et al., 2019; Proschinger et al., 2023; Wadley, Chen, Lip, Fisher, & Aldred, 2016), but not all (Casuso, Aragon-Vela, Huertas, Ruiz-Ariza, & Martinez-Lopez, 2018; Nemet et al., 2009; Wu, Deng, & Gao, 2023), previous studies investigating the effects of HIIT or SIT. The reason for this discrepancy between studies is unclear.

Considering the difference between SIT and REHIT in the timing of blood sampling relative to the completion of the first sprint, it could be expected that the time-course of the changes in plasma IL-6 for REHIT further lags those for SIT by ~10 min. However, as we only took blood samples immediately, 30 min, and 90 min after completing the bouts, we cannot determine exactly when peak IL-6 levels occurred, and this may have occurred at different time points for the two trials. Notably, at the 90 min post-exercise time point, plasma IL-6 levels were significantly decreased compared to 30 min post-exercise in the SIT trial, but not in the REHIT trial. Another observation is that plasma IL-6 levels were significantly increased just over half an hour after completing the first sprint during the REHIT session. This short time period suggests that IL-6 gene transcription is not essential for the plasma IL-6 response to supramaximal exercise, and that IL-6 may be released from preformed intramyocellular IL-6 depots, as previously proposed by Hojman et al. (2019).

The magnitude of the increase in plasma IL-6 levels we observed following SIT and REHIT was similar to that reported in previous studies investigating HIIT and SIT protocols (Casuso et al., 2018; Ferreira et al., 2018; Kouvelioti et al., 2019; Nemet et al., 2009; Wadley et al., 2016; Wu et al., 2023; Zwetsloot, John, Lawrence, Battista, & Shanely, 2014). However, far larger increases have been reported following continuous exercise of longer duration—for example, a 19-fold increase following 5 hrs of knee extension exercise at 40% W_{max} (Steensberg et al., 2000), a 100-fold increase following marathon running (Bernecker et al., 2013), and a >10,000-fold increase following completion of a 246-km ultramarathon running race (Goussetis et al., 2009). This raises questions about whether the more modest increase in plasma IL-6 following SIT and REHIT is sufficient to exert health benefits. However, it has been suggested that the plasma IL-6 response to very long-duration exercise may represent muscle damage rather than a health-promoting myokine response (Starkie, Rolland, Angus, Anderson, & Febbraio, 2001). Furthermore, whereas it is feasible for inactive or sedentary individuals to regularly perform REHIT sessions as an exercise intervention for improving general health and well-being (Metcalfe & Vollaard, 2024), this is not the case for these types of endurance exercise sessions that have been demonstrated to be associated with very large increases in plasma IL-6 levels.

Some limitations to our study should be highlighted. First, our protocol had insufficient temporal resolution to determine the exact timepoints at which plasma IL-6 levels peaked following SIT and REHIT, and whether the magnitude of the increase was similar at peak levels. Second, while we did not find a significant difference in IL-6 iAUC between

SIT and REHIT, a study with a larger sample size is required to determine if the two interventions result in the same increase. Future studies should incorporate additional timepoints between 0 and 30 min post-exercise to confirm whether our findings are applicable to different populations, including women and older individuals. Third, PPO was lower for SIT compared to REHIT, suggesting some pacing, presumably due to participants' awareness of how much exercise was yet to come. This means that the sprints during the SIT protocol were not technically 'all-out', and this may have reduced the plasma IL-6 response. However, the difference in PPO between SIT and REHIT was less than 10%, so this difference may not have been sufficient to alter the physiological responses.

CONCLUSION

In conclusion, we demonstrate that there is no significant difference in the increase in plasma IL-6 levels between SIT involving 4x30-s supramaximal sprints and REHIT involving 2x20-s supramaximal sprints. Our data support a link between the release of lactate from active skeletal muscle and the increase in plasma IL-6 levels, adding to the accumulating body of evidence that demonstrates very low volumes of supramaximal exercise can elicit physiological responses proposed to be associated with positive health effects.

Author contributions

NBJV, RSM, ECRH, KLB, and JZ conceived of and designed the study. JZ, JB, DK, and MH recruited participants and collected the data. KLB performed the IL-6 ELISA. NBJV performed statistical analysis. NBJV drafted the manuscript. All authors contributed to editing and revising the manuscript in its final version. All authors read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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