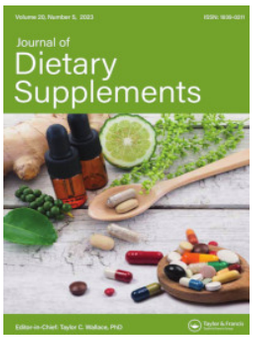

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ARTICLE COMMENTARY

Comment On: "A Double-Blind, Randomized, Placebo-Controlled Pilot Study Examining an Oxygen Nanobubble Beverage for 16.1-km Time Trial and Repeated Sprint Cycling Performance."

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To The Editor,

We read with equal parts interest and concern the paper by King and colleagues (King et al. 2023) which explored the effect of an 'oxygen-nanobubble beverage' on exercise physiology and performance in a small group of cyclists. Relative to placebo, the oxygenated beverage appeared to improve performance by 2.4% in a 16.1-km time-trial, and peak power output by 7.1% in a series of Wingate tests. The authors concluded that the oxygenated beverage "may provide a practical and effective ergogenic aid for competitive cyclists". The study was commissioned and funded by Avrox—a prominent vendor of oxygen containing beverages—and is displayed on the manufacturer's website alongside several commercial claims.

The findings by King et al. (2023) contradict a string of studies showing no effect of oxygenated beverages on exercise O_2 uptake (Hampson et al. 2003; Leibetseder et al. 2006; McNaughton et al. 2007; Willmert et al. 2002), exercise performance at sea-level (Fleming et al. 2017; Mielke et al. 2005), or exercise performance at altitude (Wing-Gaia et al. 2005). And although these data have been criticized for using the Haldane Transformation, which measures gas exchange at the nose/mouth and does not account for ingested O_2 which is purportedly absorbed through the GI tract, other studies rebut such criticism by showing no effect of oxygenated beverages on either muscle or peripheral O_2 saturation during exercise (Fleming et al. 2017). A narrative review in the *BJSM* concluded that *"Ergogenic claims for oxygenated water cannot be taken seriously"* (Piantadosi 2006).

We are not concerned that the data contradict the historical precedent—science thrives on debate and ongoing challenges to pre-existing norms. However, oxygenated beverages allegedly improve performance *via* a mechanism which is physiologically implausible. The drink was estimated to have provided ~15 mL of O_2. This is an inconsequential amount when contrasted against the O_2 inspired by the respiratory system. Indeed, from the cohort's $\dot{V}O_2$peak of ~57 mL/kg/min (~4.2 L/min), we calculated that the 30-minute exercise bout at 60% $\dot{V}O_2$peak would have required about 75 L (75,000 mL) of inspired O_2. A further ~80 L (80,000 mL) would likely have been inspired during the subsequent 16.1-km time trial. The O_2 provided by the beverage,

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assuming the full amount was successfully absorbed through the GI tract (an assumption that was not tested), represents just 0.01% of the O_2 derived during exercise *via* pulmonary ventilation. What's more, the healthy respiratory system is generally considered to be *overbuilt* for its demands (Dempsey et al. 2020), such that bypassing the airways and lungs *via* the gut is redundant. Expressed another way, if 1 L of O_2 yields between 4.85 and 5.02 calories (depending on substrate use; [Jeukendrup and Wallis 2005]), we can calculate that 15 mL of O_2 yields just 0.073 – 0.075 calories, or 304–315 joules. During 60 min of exercise (which is the approximate combined duration of the steady-state exercise bout and time trial), such an energy yield would equate to an additional 0.091 – 0.094 W, not 10 W as the authors reported during the time trial, and certainly not 63 W as was reported during the Wingate tests.

The authors' own data corroborate this speculation. Had the oxygenated beverage increased O_2 availability by a meaningful amount, it would have manifested in perturbations, however slight, in physiological responses. But there were no beverage effects on blood lactate, heart rate, or RPE during steady-state exercise, no effects on pH, PCO_2, $[HCO_3^-]$, TCO_2, or oxygen saturation into the time-trial recovery, and no blood gas, lactate, or SpO_2 differences during the Wingate tests.

There is also no explanation provided for why the oxygenated beverage provided such a potent ergogenic effect during Wingate testing: ~7% greater peak power output with the O_2 beverage versus placebo (with a medium effect size). Wingate tests measure anaerobic power and capacity, i.e. they comprise exercise bouts in which muscle contractions are fueled by the breakdown of high-energy phosphates and glucose molecules in the absence of oxygen, outside the mitochondria. It is unclear how ~15 mL of additional O_2 provided by the oxygenated beverage could possibly have influenced the Wingate tests in such a profound manner.

Occam's Razor, the often misused and misquoted principal of parsimony, points to placebo effects as perhaps the *only* rational explanation for the published outcomes, although we would be interested to hear alternative hypotheses. It is disappointing that the authors discussed the notion of placebo effects so timidly in their paper, offering just two sentences to question the efficacy of their blinding protocol and the potential "expectancy of positive outcomes". In fact, they repeatedly called for more resources to be devoted to the study oxygenated beverages: to clarify the physiological mechanisms responsible for the ergogenic effect, to investigate the bioavailability of oxygen-loaded nanobubbles, to determine if oxygen-nanobubble beverages affect physiological control during more sustained vigorous-intensity exercise, and to explore timing and dosage effects of oxygen-enriched water in relation to post-exercise recovery.

While we advocate that scientists remain open-minded to new ideas and experimental approaches, it would require some extremely robust and convincing data to (i) overturn such an unfavorable preexisting evidence profile and (ii) contradict the physiologically implausible mechanism of action. To paraphrase the French scholar Pierre-Simon Laplace, "Extraordinary claims require extraordinary evidence". The data from King et al. (2023) do not meet this criterion.

We invite the authors to address our concerns, review their conclusions, and offer some much-needed clarity to the scientific record.

Sincerely,
Dr Nicholas B. Tiller
Prof Asker Jeukendrup

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