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LETTER TO THE EDITOR

# Reply to Bossi and Matta

Myrthe Stalmans,[1] Domen Tominec,[2] Wout Lauriks,[1] Ruben Robberechts,[3] Monique Ramaekers,[1] Tadej Debevec,[2,4] and Chiel Poffé[3]

[1]Exercise Physiology Research Group, Department of Movement Sciences, KU Leuven, Leuven, Belgium; [2]Faculty of Sport, University of Ljubljana, Ljubljana, Slovenia; [3]Rehabilitation Research Center (REVAL), Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium; and [4]Department of Automatics, Biocybernetics and Robotics, Jožef Stefan Institute, Ljubljana, Slovenia

REPLY: We appreciate the insightful Letter to the Editor formulated by Bossi and Matta (1) regarding our publication on the effects of exogenous ketosis (EK) during exercise under simulated hypoxia (2), and the related postpublication exchange with McCarthy et al. (3, 4). In our original study (2), participants completed a protocol at a simulated altitude of 4,000 m (fraction of inspired oxygen = 12.7%), and performed this protocol twice; once with regular intake of ketone ester supplements to establish a state of EK, and once with a placebo supplement as control. This study was part of a larger project, aiming to explore the impact of EK on hypoxic tolerance and acute mountain sickness development (5). After 1.5 h in hypoxia, participants cycled for 10 min at 1.5 $W \cdot kg^{-1}$ as warm-up, followed by a graded test until exhaustion that started at 100 W and increased by 20 $W \cdot min^{-1}$. Despite elevated blood and skeletal muscle oxygenation at the start of this maximal exercise with EK, peak power output obtained during the graded cycling test was, on average, 10 W lower than in their control session.

It was signified by McCarthy et al. (3) that both peak power output and physiological parameters showed large intersession variability. Their curiosity and commitment to the field of ketone research likely prompted the question of whether this might have resulted from distinct physiological responses rather than methodological noise. This, in turn, was countered by Bossi and Matta (1), who expressed concerns about the retrospective analysis of individual responses and correlations. They primarily urge caution with this approach, arguing that to identify and separate distinct response types and components of variation (i.e., interindividual, intra-individual, individual-by-treatment), more targeted and specialized experimental paradigms are required.

We support Bossi and Matta (1) in their argument that one cannot simply attribute all of the observed variability to meaningful differences in participants' responses, and that attempting to do so may substantially distort any conclusions resulting from such "nontargeted" analyses. Any incentive to characterize interindividual, intra-individual, and individual-by-treatment responses needs to be carefully considered already at the stage of protocol design, and requires a meticulously predefined and justified methodological framework. Nonetheless, this does not fully preclude the value of exploratory analyses. Importantly, such post hoc explorations should never substitute for more appropriate experimental paradigms and should never be interpreted as ignorant claims and or facts. However, they may contribute to the generation of novel insights that help to identify patterns and aid fellow researchers in the journey toward understanding the effects of EK on the physiological fingerprint during exercise and hypoxic exposure. As such, we wish to emphasize that we earlier presented these individual-level patterns solely to enable the exploration of novel hypotheses and to guide future research in this domain. In this light, we wish to underline the fact that our study only involved male participants, which needs to be carefully considered when interpreting any data resulting from this research project, averaged or individualized.

Altogether, the quickly growing amount of data and observations contributes to rapid progress in this remarkable field. It is of note that all of the relevant data from our study are available and we kindly invite the interested readers to further explore any hypotheses arising from this work. Finally, and in line with the insightful and valuable comments by Bossi and Matta (1), we are also very much looking forward to future studies targeted to expand our understanding of the individual physiological variability in response to ketone supplementation under hypoxic conditions—a topic that undoubtedly warrants further investigation.

All anonymized data are available at https://doi.org/10.6084/m9.figshare.30146047.

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Correspondence: C. Poffé (chiel.poffe@uhasselt.be).
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## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

M.S. and C.P. drafted manuscript; M.S., D.T., W.L., R.R., M.R., T.D., and C.P. edited and revised manuscript; M.S., D.T., W.L., R.R., M.R., T.D., and C.P. approved final version of manuscript.

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