Edith Cowan University

Research Online

2016

Iron supplementation and altitude: Decision making using a regression tree

Laura A. Garvican-Lewis

Andrew D. Govus
Edith Cowan University

Peter Peeling

Chris R. Abbiss
Edith Cowan University

Christopher J. Gore

Iron Supplementation and Altitude: Decision Making Using a Regression Tree

Dear Editor-in-chief

Altitude exposure increases the body's need for iron (Gassmann and Muckenthaler, 2015), primarily to support accelerated erythropoiesis, yet clear supplementation guidelines do not exist. Athletes are typically recommended to ingest a daily oral iron supplement to facilitate altitude adaptations, and to help maintain iron balance. However, there is some debate as to whether athletes with otherwise healthy iron stores should be supplemented, due in part to concerns of iron overload. Excess iron in vital organs is associated with an increased risk of a number of conditions including cancer, liver disease and heart failure. Therefore clear guidelines are warranted and athletes should be discouraged from 'self-prescribing" supplementation without medical advice.

In the absence of prospective-controlled studies, decision tree analysis can be used to describe a data set, with the resultant regression tree serving as guide for clinical decision making. Here, we present a regression tree in the context of iron supplementation during altitude exposure, to examine the association between pre-altitude ferritin (Ferritin-$_{Pre}$) and the haemoglobin mass (Hbmass) response, based on daily iron supplement dose.

De-identified ferritin and Hbmass data from 178 athletes engaged in altitude training were extracted from the Australian Institute of Sport (AIS) database. Altitude exposure was predominantly achieved via normobaric Live high: Train low (n = 147) at a simulated altitude of 3000 m for 2 to 4 weeks. The remaining athletes engaged in natural altitude training at venues ranging from 1350 to 2800 m for 3-4 weeks. Thus, the "hypoxic dose" ranged from ~890 km.h to ~1400 km.h. Ethical approval was granted by the AIS Human Ethics Committee, and athletes provided written informed consent. An in depth description and traditional analysis of the complete data set is presented elsewhere (Govus et al., 2015).

Iron supplementation was prescribed by a sports physician based on Ferritin-$_{Pre}$. Fifteen athletes were not supplemented based on medical advice or because of already high Ferritin-$_{Pre}$. Oral iron (FerroGrad C, 325 mg ferrous sulphate and 1,000 mg ascorbic acid, equivalent to 105 mg elemental iron; Abbott Laboratories, Botany Bay, Australia) was provided to the remaining athletes daily for the duration of altitude exposure. Nineteen athletes ingested two iron tablets per day (210 mg elemental iron) owing to Ferritin-$_{Pre}$ of <35 µg·L^{-1}. Hbmass was measured via CO-rebreathing pre and post altitude.

A regression tree was constructed in JMP (JMP® Pro 11.0, SAS Institute Inc., 2013, Cary, NC, USA) to describe the relationship between Ferritin-$_{Pre}$ (as a continuous predictor variable), supplement dose (as a categorical predictor variable) and the Hbmass response (%) following altitude exposure (as a continuous response variable). This approach uses a binary recursive partition algo-rithm to split the parent node into two daughter nodes, based on a partition of data that maximises group separation (Strobl et al., 2009). Group separation is character-ised by maximising the sum of squares for the difference between the parent node and child nodes, determined by the Log Worth score [(-log$_{10}$ (p-value)]. We chose to manually split these data to model the Hbmass response for athletes with Ferritin-$_{Pre}$ either > or < 100 µg·L^{-1}, based on current AIS guidelines. Next, these data were split by athletes' daily supplement dose (0, 105, or 210 mg), and then on the variable (split candidate) with the highest sum of squares.

The regression tree (Figure 1) contained seven splits, explaining ~12% of the variance (R^2 = 0.12) in the Hbmass response. Hbmass increased by 3.4±2.9% (mean±SD) in athletes with Ferritin-$_{Pre}$ <100 µg·L^{-1}, inde-pendent of supplement dose. More specifically, athletes with Ferritin-$_{Pre}$ >34.6 µg·L^{-1} who were supplemented with 105 mg·d^{-1} increased Hbmass by 3.4±2.8%, whilst those with Ferritin-$_{Pre}$ <34.6 µg·L^{-1} increased by 1.5±2.1%. In comparison, athletes with Ferritin-$_{Pre}$ >20 µg·L^{-1} who were supplemented with 210 mg·d^{-1} increased Hbmass by 3.3±3.4%, whereas those with Ferritin-$_{Pre}$ <20 µg·L^{-1} increased by 7.0±1.9%. In athletes with Ferritin-$_{Pre}$ >100 µg·L^{-1}, non-supplemented athletes increased Hbmass by 1.2±3.2%, compared with 3.4±3.3% in those who ingested 105 mg·d^{-1}.

Our regression tree suggests daily iron supplemen-tation may support Hbmass production during altitude exposure (Govus et al., 2015), particularly in athletes with low Ferritin-$_{Pre}$. Interestingly, supplemented athletes with low Ferritin-$_{Pre}$, tended to exhibit a greater Hbmass re-sponse than athletes with otherwise "healthy" iron stores. In fact, iron deficient (ID) athletes (ferritin <20 µg·L^{-1}) who ingested 210 mg·d^{-1} increased their Hbmass after altitude exposure by 7%, which is substantially larger than expected (Gore et al., 2013). Improved iron availa-bility (arising from supplementation), combined with enhanced iron absorption at altitude (Reynafarje and Ramos, 1961) and an accelerated erythropoietic drive may explain this observation. Prolonged altitude exposure suppresses the iron regulatory hormone hepcidin, thereby aiding intestinal iron absorption (Goetze et al., 2013). Iron deficiency may also elevate erythropoietin (EPO), therein 'priming' the erythropoietic system in anticipation of iron delivery (Mast et al., 2014). In combination, these factors may improve the efficacy of iron supplementation in ID athletes at altitude. In contrast, since Hbmass did not increase in the 8 athletes with Ferritin-$_{Pre}$ <35 µg·L^{-1} who were supplemented with 105 mg·d^{-1}, it is possible that in these athletes this dose was insufficient to support eryth-ropoiesis. Furthermore, athletes with higher Ferritin-$_{Pre}$, but large daily iron requirements, may also benefit from supplementation at altitude. The lack of improvement in Hbmass in non-supplemented athletes, may be related to
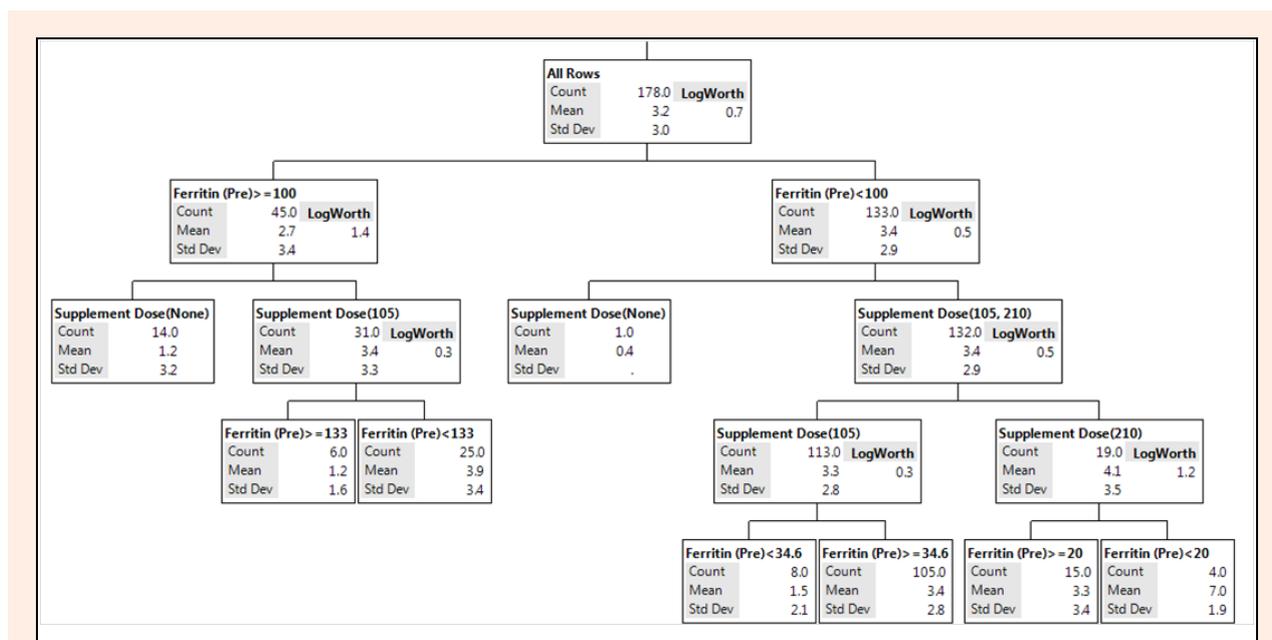
Figure 1. Regression tree estimating the Hbmass response to altitude (%) based on athletes' pre-altitude serum ferritin levels and their prescribed oral iron supplement dose during altitude exposure. Each parent node is split into child nodes based on the maximal Log Worth score [$-\log_{10}$ (*p* value)].

reduced iron *availability* and *mobility,* despite plentiful iron stores, perhaps due to an increase in hepcidin post-exercise (Peeling, 2010).

In summary, our regression tree suggests if sufficient iron is made available (via supplementation), even ID athletes can improve Hbmass in response to altitude. Some athletes with otherwise normal ferritin may also require supplementation to maintain an iron balance capable of supporting both the haematological and non-haematological adaptations to altitude. We recommend an individualised approach when deciding whether iron supplementation is appropriate, particularly concerning the dose provided.

Laura A. Garvican-Lewis [1]✉, Andrew D. Govus [2], Peter Peeling [3], Chris R. Abbiss [2] and Christopher J. Gore[1]

[1]Department of Physiology, Australian Institute of Sport, ACT, Australia; [2]Centre for Exercise and Sports Science Research, School of Exercise and Health Science, Edith Cowan University, WA, Australia; [3]School of Sport Science, Exercise and Health, University of Western Australia, WA, Australia

References

Gassmann, M. and Muckenthaler, M.U. (2015) Adaptation of iron requirement to hypoxic conditions at high altitude. *Journal of Applied Physiology (1985)* **119(12),** 1432-1440.

Goetze, O., Schmitt, J., Spliethoff, K., Theurl, I., Weiss, G., Swinkels, D.W., Tjalsma, H., Maggiorini, M., Krayenbuhl, P., Rau, M., Fruehauf, H., Wojtal, K.A., Mullhaupt, B., Fried, M., Gassmann, M., Lutz, T. and Geier, A. (2013) Adaptation of iron transport and metabolism to acute high-altitude hypoxia in mountaineers. *Hepatology* **58,** 2153-2162.

Gore, C.J., Sharpe, K., Garvican-Lewis, L.A., Saunders, P.U., Humberstone, C.E., Robertson, E.Y., Wachsmuth, N.B., Clark, S.A., Mclean, B.D., Friedmann-Bette, B., Neya, M., Pottgiesser, T., Schumacher, Y.O. and Schmidt, W.F. (2013) Altitude training and haemoglobin mass from the optimised carbon monoxide rebreathing method determined by a meta-analysis. *British Journal of Sports Medicine* **47(Suppl 1),** i31-9.

Govus, A.D., Garvican-Lewis, L.A., Abbiss, C.R., Peeling, P. and Gore, C.J. (2015) Pre-Altitude Serum Ferritin Levels and Daily Oral Iron Supplement Dose Mediate Iron Parameter and Hemoglobin Mass Responses to Altitude Exposure. *PLoS One* **10,** e0135120.

Mast, A.E., Kiss, J., Cable, R.G., Glynn, S. and Brambilla, D. (2014) Effects of Storage Iron on Erythropoietin and Hepcidin Responses to Acute Hemorrhage. *Blood* **124,** 1351-1351.

Peeling, P. (2010) Exercise as a mediator of hepcidin activity in athletes. *Eurpean Journal of Applied Physiology* **110,** 877-883.

Reynafarje, C. and Ramos, J. (1961) Influence of altitude changes on intestinal iron absorption. *The Journal of Laboratory and Clinical Medicine* **57,** 848-855.

Strobl, C., Malley, J. and Tutz, G. (2009) An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. *Psychological Methods* **14,** 323-348.

✉ **Laura Garvican-Lewis**
Australian Institute of Sport, Bruce, ACT, Australia
E-mail: laura.garvican@ausport.gov.au