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## Reply to OM Shannon et al

Lauren C. Blekkenhorst  
*Edith Cowan University*

Joshua R. Lewis  
*Edith Cowan University*

Richard L. Prince

Amanda Devine  
*Edith Cowan University*

Nicola P. Bondonno

*See next page for additional authors*

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## Authors

Lauren C. Blekkenhorst, Joshua R. Lewis, Richard L. Prince, Amanda Devine, Nicola P. Bondonno, Catherine P. Bondonno, Lisa G. Wood, Ian B. Puddey, Natalie C. Ward, Kevin D. Croft, Richard J. Woodman, Lawrence J. Beilin, and Jonathan M. Hodgson

**Response to Letter, “No effect of 4 weeks nitrate-rich vegetable consumption on blood pressure: Reflections for future research”**

Lauren C Blekkenhorst<sup>1</sup>, Joshua R Lewis<sup>1,2,3,4</sup>, Richard L Prince<sup>2,5</sup>, Amanda Devine<sup>1</sup>, Nicola P Bondonno<sup>2</sup>, Catherine P Bondonno<sup>1</sup>, Lisa G Wood<sup>7</sup>, Ian B Puddey<sup>2</sup>, Natalie C Ward<sup>2,8</sup>, Kevin D Croft<sup>2</sup>, Richard J Woodman<sup>9</sup>, Lawrence J Beilin<sup>2</sup>, Jonathan M Hodgson<sup>1</sup>

<sup>1</sup>School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia

<sup>2</sup>Medical School, The University of Western Australia, Perth, WA, Australia

<sup>3</sup>Centre for Kidney Research, Children's Hospital at Westmead, Westmead, NSW, Australia

<sup>4</sup>School of Public Health, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

<sup>3</sup>Centre for Kidney Research, Children's Hospital at Westmead, Westmead, NSW, Australia

<sup>4</sup>School of Public Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

<sup>5</sup>Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, WA, Australia

<sup>7</sup>School of Biomedical Science and Pharmacy, University of Newcastle, New Lambton Heights, NSW, Australia

<sup>8</sup>School of Biomedical Sciences & Curtin Health Innovation Research Institute, Curtin University, Bentley, WA, Australia

<sup>9</sup>Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide, SA, Australia

**Address for correspondence and reprint requests:**

- 23    Lauren C Blekkenhorst
- 24    School of Medical and Health Sciences
- 25    Edith Cowan University
- 26    270 Joondalup Drive JOONDALUP WA 6027
- 27    Tel: 61 8 6304 4604
- 28    Email: [l.blekkenhorst@ecu.edu.au](mailto:l.blekkenhorst@ecu.edu.au)

29 **Response to letter:**

30 We would like to thank Shannon and colleagues for their interest in our recent publication  
31 (1). Our approach to increasing nitrate intake was to have participants consume high nitrate  
32 vegetables, rather than supplements. The estimated increase in nitrate intake of ~150 mg/d  
33 was in addition to an estimated background intake of ~85 mg/d (1). This represents a  
34 substantial increase in habitual nitrate intake. With typical median habitual nitrate intakes of  
35 ~100 mg/d (2), a nitrate intake of >200 mg/d would represent high nitrate intake within most  
36 populations. We believe that an increase in nitrate intake of >100 mg/d is readily achievable  
37 for the wider population. Although a very high nitrate intake (>500 mg/d) can be achieved  
38 through dietary means, this is unrealistic on a long-term basis for the majority of the general  
39 population. Such intakes usually require supplementation with nitrate salts ( $\text{NaNO}_3$ ;  $\text{KNO}_3$ )  
40 or concentrated beetroot juice. The feasibility of translation of findings to shift behaviours of  
41 the wider population should be taken into account in designing future studies.

42 Many trials have now investigated the effects of increased nitrate intake on blood pressure (3-  
43 6). Results of acute studies are largely consistent and indicate dose-related blood pressure  
44 lowering with increased nitrate intake. The chronic effects following a sustained increase in  
45 nitrate intake are less consistent (3-5). Several previous trials indicate that a short-term  
46 increase in nitrate intake does not result in lower blood pressure (7-10): results that align with  
47 our recent trial (1). However, other short-term trials have demonstrated blood pressure  
48 lowering effects following sustained short-term increases in nitrate intake (3-5, 11).

49 The reasons for the inconsistent results from short-term trials are unclear. We agree that  
50 nitrate dose may be a factor, but counterintuitively, a meta-analysis of short-term studies  
51 indicated smaller effect sizes for blood pressure among trials with the highest nitrate intakes  
52 (3). This contrasts with data from acute studies (4), and suggests that factors other than dose

may account for the inconsistent findings. One explanation may be that sustained higher nitrate intakes can result in down-regulation of nitric oxide synthase leading to reduced endogenous nitric oxide production and/or reduced sensitivity of cellular targets to nitric oxide (12). Another possibility is an interaction between sulphur-containing compounds and nitrate (13, 14). In a study by Dewhurst-Trigg and others (14), the ingestion of vegetables with high thiocyanate (a sulphur-containing compound) attenuated the blood pressure lowering-effects of nitrate-rich vegetables. Several of the high nitrate vegetables consumed by the participants in our study were also likely to include sulphur-containing compounds. Furthermore, the age and health status of participants may be important. Older individuals and those at an increased risk of cardiovascular disease may respond differently to healthy populations (3-5, 7-9). This is supported by Ashor and colleagues who reported that when short-term trials that recruited active, healthy individuals were excluded from their meta-analysis, effects on blood pressure became non-significant (3).

In summary, we agree with Shannon and colleagues that dose of nitrate may be a contributing factor to the inconsistencies in nitrate intervention trials. However, we believe that factors other than nitrate dose are more likely to explain the inconsistent findings in this field.

69 **Disclosures:** None.

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