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Reply to OM Shannon et al

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

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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 (NaNO₃; KNO₃)

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

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

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

69 **Disclosures:** None.

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