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DOI:

[10.1161/CIRCRESAHA.120.316748](https://doi.org/10.1161/CIRCRESAHA.120.316748)

*Document Version*

Publisher's PDF, also known as Version of record

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*Citation for published version (APA):*

Floyd, C. N., Shahed, F., Ukah, F., McNeill, K., O'Gallagher, K., Mills, C. E., Evangelopoulos, D., Lim, S., Mudway, I., Barratt, B., Walton, H., & Webb, A. J. (2020). Acute Blood Pressure-Lowering Effects of Nitrogen Dioxide Exposure from Domestic Gas Cooking via Elevation of Plasma Nitrite Concentration in Healthy Individuals. *Circulation Research*, 127(6), 847-848. <https://doi.org/10.1161/CIRCRESAHA.120.316748>

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# Acute Blood Pressure-Lowering Effects of Nitrogen Dioxide Exposure From Domestic Gas Cooking Via Elevation of Plasma Nitrite Concentration in Healthy Individuals

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**A**ir pollution is a major cause of cardiovascular and all-cause mortality. Disentangling the relative contributions of pollutants is challenging, as epidemiological data measuring exposure to one (eg, nitrogen dioxide [NO<sub>2</sub>]) is inevitably confounded by exposure to others (eg, particulate matter). Animal studies suggest that inhaled NO<sub>2</sub> has the potential to increase plasma [nitrite]<sup>1</sup>; a chemical originally considered to be physiologically inert before we found that its reduction to nitric oxide protects the myocardium against ischemia-reperfusion injury and lowers blood pressure in humans.<sup>2</sup>

We conducted an acute, randomized, controlled, crossover study to assess the impact of 90 minutes exposure to NO<sub>2</sub> (from sitting next to a domestic gas cooker with gas hobs lit and uncovered) versus control (room air) on plasma [nitrite] (primary end point) and blood pressure (secondary end points) in 12 healthy participants. All underwent both interventions/visits (interval 7–108 days) in a computer-generated randomized order. Baseline characteristics (mean±SD): 26±4 years, 10/12 female, body mass index 21.9±3.0 kg/m<sup>2</sup>, systolic blood pressure 113.8±7.9 mmHg, diastolic blood pressure 72.8±5.7 mmHg. The exposure phase was followed by a 90 minutes washout phase at background [NO<sub>2</sub>]. Participants fasted for 12 hours before each visit and received 250 mL low-nitrate water at time 0 h/1.5 h. The study was powered for a difference in plasma [nitrite] of 27±40 nmol/L on repeated-measures, 2-way ANOVA

( $\alpha$ , 0.05 and  $\beta$ , 0.2) following D'Agostino-Pearson normality-confirmation, with Sidak post-test (GraphPad Prism v8.2.1).<sup>3</sup>

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Relative to control, exposure increased ambient [NO<sub>2</sub>]: 276.3±38.5 versus 27.6±2.8 ppb ( $P<0.001$ ). Plasma [nitrite] was increased through both the 90 minutes NO<sub>2</sub> exposure and 90 minutes washout ( $P<0.001$ ; Figure [A]). NO<sub>2</sub> exposure decreased both systolic blood pressure and diastolic blood pressure (both  $P<0.001$ ; Figure [B] and [C]). The largest decrease in systolic blood pressure relative to control occurred at 45 minutes (4.6 mmHg [95% CI, 0.2–8.9];  $P=0.032$ ) and 90 minutes (5.5 mmHg [95% CI, 1.2–9.9];  $P=0.005$ ). The effect of NO<sub>2</sub> on diastolic blood pressure was maximal at 45 minutes (5.7 mmHg [95% CI, 0.9–10.5];  $P=0.009$ ).

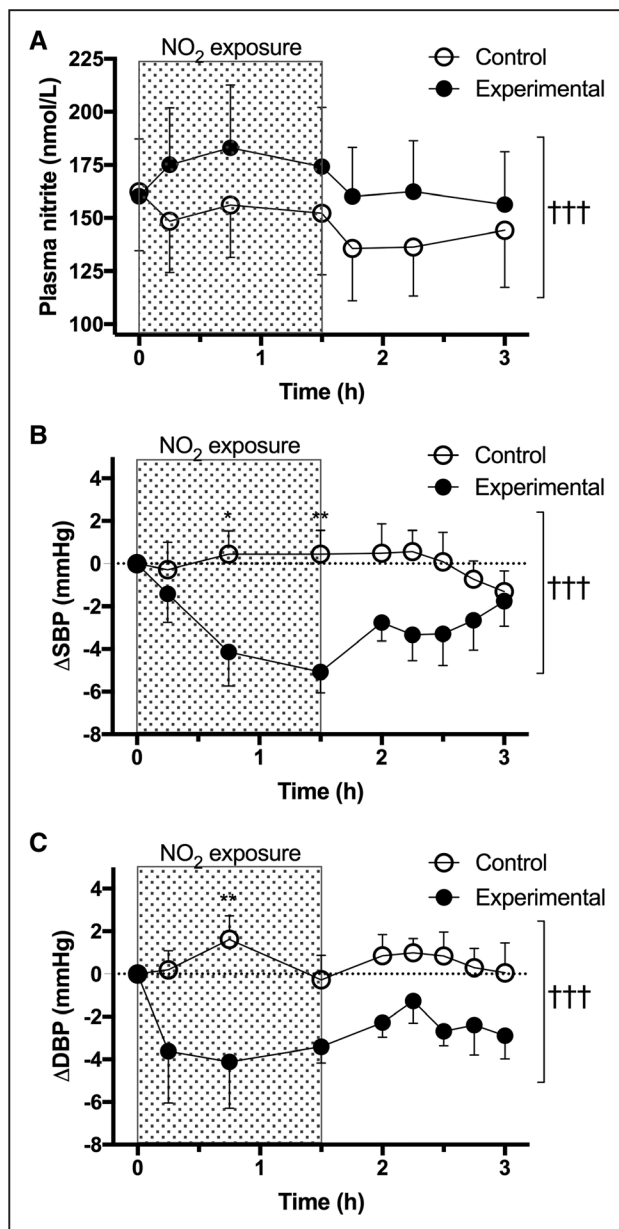
The temporal relationship between the increase in plasma [nitrite] and systolic blood pressure/diastolic blood pressure reduction ( $\approx 5$  mmHg) is consistent with studies investigating dietary nitrate.<sup>2</sup> Furthermore, whilst the level of NO<sub>2</sub> exposure (276.3±38.5 ppb) was  $\approx 2.5$ -fold greater than recommended limits for exposure (eg, World Health Organization guideline 105 ppb 1-hour mean), it is less than that recorded adjacent to busy roads or in some domestic kitchens ( $\approx 2000$  ppb).

**Key Words:** air pollution ■ blood pressure ■ nitrite ■ nitrogen dioxide ■ particulate matter

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For Sources of Funding and Disclosures, see page 848.

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**Figure.** Effect of nitrogen dioxide (NO<sub>2</sub>) exposure on plasma [nitrite] and blood pressure.

Plasma [nitrite] (A), systolic blood pressure (ΔSBP; B), diastolic blood pressure (ΔDBP; C). Comparison between experimental and control shown as ††† $P < 0.001$  and individual timepoints as \* $P < 0.05$  and \*\* $P < 0.01$ . Data expressed as mean ± SEM (n=12).

Our model is, therefore, conservative relative to real-world exposure.

Previously, an increase in plasma [nitrite] at 2 hours following diesel exhaust inhalation was thought to be due to particulate matter-mediated induction of inflammatory pathways.<sup>3</sup>

However, our data suggest a more rapid increase in plasma [nitrite] which favors chemical conversion from NO<sub>2</sub> (eg, via a nitrous acid intermediary) and presents a plausible mechanism through which inhaled NO<sub>2</sub> increases plasma [nitrite].<sup>1</sup> This novel ecophysiological

NOx cycle may directly feed into the established nitrate-nitrite-nitric oxide pathway and contribute nitric oxide-mediated cardiovascular effects.<sup>2</sup> Adverse respiratory effects of inhaled NO<sub>2</sub> were not investigated here.<sup>1</sup>

These data must be considered in the context of the strong epidemiological association between NO<sub>2</sub> exposure and cardiovascular mortality.<sup>1</sup> However, particulate matter-free NO<sub>2</sub> does not appear to impair either vascular function, fibrinolysis, or affect heart rate variability in patients with coronary heart disease: parameters adversely affected by increased ambient NO<sub>2</sub> exposure in epidemiological studies.<sup>4,5</sup> This study expands our understanding of how inhaled NO<sub>2</sub> might impact the cardiovascular system, and the role of diet in disease: it is not just what you eat, but how you cook it that matters.

## ARTICLE INFORMATION

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### Sources of Funding

King's Together Multi and Interdisciplinary Research Scheme (Wellcome Trust Institutional Strategic Support Fund [204823/Z/16/Z]). H. Walton and D. Evangelopoulos's posts part-funded by NIHR-HPRU on Health Impacts of Environmental Hazards at KCL in Partnership with PHE and ICL, London, UK. Internal infrastructure financial support: KCL-BHF Centre, NIHR-CRF/NIHR-BRC at GSTFT/KCL. Views expressed are authors' (not necessarily NHS/NIHR/DHSC/PHE).

### Disclosures

None.

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