Effect of diuretics on plasma renin activity in primary hypertension: A systematic review and meta-analysis

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Aims: Plasma renin activity (PRA) is regarded as a marker of sodium and fluid homeostasis in patients with primary hypertension. Whether effects of diuretics on PRA differ according to class of diuretic, whether diuretics lead to a sustained increase in PRA, and whether changes in PRA relate to those in blood pressure (BP) is unknown. We performed a systematic review and meta-analysis of trials investigating the antihypertensive effects of diuretic therapy in which PRA and/or other biomarkers of fluid homeostasis were measured before and after treatment.

Methods: Three databases were searched: MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials. Titles were firstly screened by title and abstract for relevancy before full-text articles were assessed for eligibility according to a predefined inclusion/exclusion criteria.

Results: A total of 1684 articles were retrieved of which 61 met the prespecified inclusion/exclusion criteria. PRA was measured in 30/61 studies. Diuretics led to a sustained increase in PRA which was similar for different classes of diuretic (standardised mean difference [95% confidence interval] 0.481 [0.362, 0.601], 0.729 [0.181, 1.28], 0.541 [0.253, 0.830] and 0.548 [0.159, 0.937] for thiazide, loop, mineralocorticoid receptor antagonists/potassium-sparing and combination diuretics respectively, Q = 0.897, \( P = .826 \), and did not relate to the average decrease in blood pressure.

Conclusion: In antihypertensive drug trials, diuretics lead to a sustained increase in average PRA, which is similar across different classes of diuretic and unrelated to the average reduction in blood pressure.

KEYWORDS
blood pressure, hypertension, plasma renin activity, renin

1 | INTRODUCTION

Hypertension is the single most common cause of morbidity and mortality worldwide.\(^1\) Retention of body sodium and water is thought to contribute to hypertension and diuretics are 1 of the major classes of antihypertensive treatment.\(^2\) Plasma renin activity (PRA) or renin mass is thought to be a marker of sodium and fluid homeostasis and diuretics may be more effective in individuals with suppressed renin indicative of sodium retention.\(^3\) Diuretic therapy leads to an increase
in PRA, but it is not known whether this differs according to the class of diuretic or whether the rise in PRA after treatment varies over time, since compensatory mechanisms may lead to sodium and fluid re-accumulation. Finally, it is not known whether the diuretic induced fall in blood pressure (BP) relates to the increase in PRA. The objective of the present study was to perform a systematic review and meta-analysis of randomised clinical trials (RCTs) where diuretics were used to treat hypertension and measurements of PRA and/or another biomarker of sodium and fluid homeostasis were available to address these questions at the level of metadata for individual RCT.

2 | METHODS

2.1 | Search strategy

This systematic review and meta-analysis was carried out in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A systematic literature search was performed on 3 databases; Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, (1946 to 20 February 2018), EMBASE (1974 to 2018 week 12), and The Cochrane Central Register of Controlled Trials databases (up to 19 March 2018). Studies included were trials of diuretics used either as mono- or multitherapy, which examined how they affected PRA, renin mass, and other markers of fluid homeostasis including plasma volume, brain-type natriuretic peptide, echocardiographic markers of circulating blood volume and measures of body water by electrical bioimpedance. The keywords used included ‘thiazide’, ‘thiazide-like’, ‘potassium-sparing’ and ‘diuretic’. Medical subject headings (MeSH) and non-MeSH terms were used to search the databases for relevant publications. The full search strategy for MEDLINE is provided in the supplementary material.

2.2 | Study selection and eligibility criteria

Papers were initially screened by title and abstract. Studies were eligible for inclusion if they were a RCT performed in hypertensive human subjects aged ≥18 years, examining antihypertensive effects of either a thiazide, thiazide-like, loop, mineralocorticoid receptor antagonist (MRA) or potassium-sparing diuretic with a duration of at least 1 week. Studies investigating novel diuretics not licensed for clinical use were excluded as were studies in which subjects had pulmonary arterial hypertension or heart failure. All studies were required to have examined PRA or another volume biomarker with results available before and during diuretic treatment or, in the case of placebo-controlled trials, during treatment with placebo. Studies were eligible if diuretic therapy was added to either no previous therapy or to stable background treatment. The search was limited to the English language only and review articles were disregarded. Titles and abstracts were screened by 1 author (R.J.M.), and the same author reviewed the full-text articles.

2.3 | Data collection process

Data were extracted independently by 1 author (R.J.M.) using a standard form. This included: author, year of publication, class of diuretic(s) and dose used, protocol (including presence of background therapy and whether placebo controlled), sample size, average age, sex distribution, ethnicity (if available), and prevalence of diabetes (if available). Outcome measurements were: mean (+ standard deviation/standard error) of values for BP and PRA or other volume biomarker before and during diuretic (and before and during placebo treatment in placebo-controlled studies) and the difference between values on and before treatment. If standard deviations were not reported, these were calculated from standard errors. P-values or confidence intervals. The duration of diuretic treatment at the time of measurement was also recorded. Where only graphical reports of measurements such as PRA and BP were available, an estimation from the graph was taken if it was judged to be accurate to within 10%. Units of PRA were converted to ng/mL/h if other units were used.

2.4 | Quantitative data synthesis and statistical analysis

Meta-analysis was conducted using Comprehensive Meta-Analysis Software Version 3 (Biostat, Englewood, NJ, USA). Meta-analysis was performed only for PRA as there were too few studies using other volume markers to allow a meaningful analysis. Net changes in PRA were obtained as the difference from baseline after treatment with either diuretic or placebo. If there was no standard error of the mean change stated, it was estimated from the P-value, number of observations and size of the change. A random-effects model was used to compensate for between-study heterogeneity in terms of demographic inconsistencies and different diuretic dose with calculation of the standardised mean difference in PRA and its 95% confidence interval (CI). Statistical heterogeneity was assessed using Cochran’s Q test. P < .05 was considered statistically significant and all tests were 2-tailed.

2.5 | Metaregression

Random-effects metaregression was performed using the method of moments to evaluate the association between standardized difference in PRA and duration of study at the time of measurement of PRA and between the standardized difference in PRA and change in systolic BP (SBP).

2.6 | Publication bias

Potential publication bias was assessed by inspection of Begg’s funnel plot asymmetry and Egger’s asymmetry tests.
RESULTS

3.1 Description of studies

The study selection process is detailed in a flow chart as per PRISMA guidelines (Figure 1). The initial MEDLINE search returned 451 results, Embase 466 and Central 767 (1684 in total). After removal of duplicates there were 920 articles of which 727 were excluded based on title and abstract. The remaining 193 full-text articles were assessed for eligibility and 132 were excluded for various reasons (Figure 1). The remaining 61 articles were included in the qualitative synthesis. The most common biomarker measured was PRA (30/61 studies) and the most commonly used diuretics were the thiazide class. For trials in which PRA was measured, the mean age was 50.7 ± 8.37 years, and % of male subjects was 54.3 ± 21.5%. Classes of diuretic were thiazide/thiazide-like (22/30, 73%), MRA/potassium-sparing (5/30, 17%, 4 spironolactone, 1 amiloride), loop (2/30, 3.3%) and combination (3/30, 10%). Individual diuretics were hydrochlorothiazide, amiloride, indapamide, bendroflumethiazide, chlorthalidone, cyclopenthiazide, chlorothiazide, furosemide, spironolactone, torsemide and triamterene. Details of individual trials are summarised in Table 1.

3.2 Meta-analysis: Effect of placebo and diuretic on PRA

Placebo had a negligible effect on PRA in the present analysis (Figure 2A). Standardized difference in mean PRA after placebo was −0.055 (95% CI −0.23, 0.12). With diuretic therapy, all diuretic classes led to a significant increase in PRA but there was neither between-class heterogeneity nor between-drug heterogeneity (Figure 2B). The average standardised difference in mean PRA change was: thiazide/thiazide-like 0.481 (0.362, 0.601), loop 0.729 (0.181, 1.28), MRA/potassium-sparing 0.541 (0.253, 0.830) and combination 0.548 (0.159, 0.937), Q = 0.897, P = .826. For between-drug analysis, the average standardised difference in mean PRA change was: hydrochlorothiazide 0.446 (0.296, 0.597), bendroflumethiazide 0.676 (0.209, 1.144), chlortalidone 0.544 (0.207, 0.882), indapamide 0.499.
| Study ID, year | Diuretic, dose | Study design, sample size | Time measured (wk) | PRA before (ng/mL/h) | PRA after (ng/mL/h) | SBP before (mmHg) | SBP after (mmHg) |
|----------------|----------------|--------------------------|-------------------|---------------------|---------------------|------------------|------------------|
| Ubaid-Girioli 2007 | HCTZ 25 mg | Parallel, 18 49.3 ± 7.2 46.03 | 12 | 0.9 ± 0.2 | 1.7 ± 0.2 | 136 ± 11.1 | 128.3 ± 11.1 |
| Villamil 2007 | HCTZ 6.25 mg | Parallel, 41 55.2 56.2 | 8 | 0.65 | 0.67 | 153.4 | 142.4 |
| Villamil 2007 | HCTZ 12.5 mg | Parallel, 41 55.4 54.8 | 8 | 0.38 | 0.55 | 153.4 | 139.5 |
| Villamil 2007 | HCTZ 25 mg | Parallel, 41 55.1 52.3 | 8 | 0.4 | 0.69 | 154.5 | 140.2 |
| Villamil 2007 | Placebo | Parallel, 41 54.4 55.9 | 8 | 0.36 | 0.362 | 152.7 | 145.2 |
| Vasavada 2003 | FUR 80 mg or TOR 40 mg | Crossover, 14 67 ± 11 | 93 | 3 | 0.37158 | 1.51 (1 wk), 1.32 (3 wk) | 147 (F), 143 (T) | 138 (F), 133 (T) |
| Sawathiparnich 2002 | SPIRO 100 mg | Crossover, 9 49.4 ± 4.1 | 100 | 2 | 1.5 ± 0.3 (SE) | 1.8 ± 0.3 (SE) | 131.8 ± 3.8 | 125 ± 2.8 |
| Roman 1998 | HCTZ 12.5-50 mg | Parallel, 28 50.1 ± 7.7 | 86 | 12 & 24 | 0.73 ± 0.92 | 2.06 ± 2.08 (12 wk), 1.51 ± 1.75 (24 wk) | 146 | 136 (12 wk), 136 (24 wk) |
| Trenkwalder 1996 | HCTZ/TRI 25/50–50/100 mg | Parallel, 27 80 ± 6 | 15.15 | 24 | 1.8 ± 1.9 | 3.1 ± 2.8 | 194 ± 21 | 166 ± 24 |
| Jounela 1994 | HCTZ 3 mg | Parallel, 22 48 | 36 | 6 | 2.17 | 2.66 | 147.4 | 143.7 |
| Jounela 1994 | HCTZ 6 mg | Parallel, 22 49.8 | 41 | 6 | 2.03 | 1.74 | 152.7 | 146.3 |
| Jounela 1994 | HCTZ 12.5 mg | Parallel, 21 47.2 | 41 | 6 | 1.97 | 2.34 | 152.8 | 146.4 |
| Jounela 1994 | HCTZ 25 mg | Parallel, 22 46.4 | 41 | 6 | 1.58 | 3.13 | 147 | 134.9 |
| Jounela 1994 | Placebo | Parallel, 22 48.5 | 41 | 6 | 1.65 | 1.6 | 152.5 | 150.4 |
| Gerber 1990 | HCTZ 50 mg (added to placebo or indomethacin) | Crossover, 13 53.8 | 1 & 2 | 1.7 ± 0.4 (SE) | 5.5 ± 0.9° (1 wk + placebo), 5.3 ± 1.1° (2 wk + placebo) | 148 | 137 [1 wk] | 136 [2 wk] |
| Gerber 1990 | HCTZ 50 mg | Crossover, 13 53.8 | 1 & 2 | 0.9 ± 0.25 (SE) | 2.4 ± 0.5° (1 wk + indomethacin), 1.9 ± 0.6° (2 wk + indomethacin) | 156 | 140 [1 wk] | 142 [2 wk] |
| Obel 1989 | CTD 20-50 mg | Crossover, 53 44.11 ± 9.76 45.28 | 12 | 0.74 ± 0.97 | 1.85 ± 1.84 | 1178.3 ± 26.6 | 144 ± 18.5 |
| Freis 1988 | HCTZ 50 mg | Parallel ... | 100 | 10 | 0.77 ± 1.26 | 3.21 ± 4.04 | ... | ... |
| Freis 1988 | HCTZ 100 mg | Parallel ... | 100 | 10 | 0.86 ± 1.02 | 3.92 ± 2.99 | ... | ... |
| Freis 1988 | HCTZ 200 mg | Parallel ... | 100 | 10 | 1.2 ± 0.94 | 7.91 ± 5.23 | ... | ... |
| Freis 1988 | HCTZ unknown | Parallel ... | 100 | 10 | 1.15 ± 1.19 | 6.97 ± 6.56 | ... | ... |
| McVeigh 1988 | CYC 50 μg | Parallel, 15 59 | 38.46 | 8 | 0.8 ± 0.4 | 0.9 ± 0.6 | 167 ± 19 | 159 ± 19 |
| McVeigh 1988 | CYC 125 μg | Parallel, 13 56 | 33.33 | 8 | 1.2 ± 0.6 | 1.2 ± 0.8 | 163 ± 23 | 149 ± 22 |
| McVeigh 1988 | CYC 500 μg | Parallel, 13 55 | 38.46 | 8 | 1.8 ± 1.3 | 5.4 ± 4.1 | 164 ± 18 | 140 ± 20 |
| McVeigh 1988 | Placebo | Parallel, 12 58 | 58.33 | 8 | 0.9 ± 0.5 | 1.1 ± 0.5 | 157 ± 17 | 156 ± 17 |
| Study ID, year   | Diuretic, dose  | Study design, sample size | Age (y) | Male % | Time measured (wk) | PRA before (ng/mL/h) | PRA after (ng/mL/h) | SBP before (mmHg) | SBP after (mmHg) |
|-----------------|----------------|--------------------------|---------|--------|-------------------|---------------------|---------------------|------------------|------------------|
| Koopmans 1986  | HCTZ 50 mg     | Crossover, 25            | 44 ± 11 | 50     | 4                 | 1.36 ± 0.89         | 3.63 ± 2.37         | 143 ± 15         | 132 ± 13         |
| Johnson 1986   | HCTZ 50 mg     | 8                        | 54      | 62.5   | 8                 | 0.45 ± 0.44         | 1.42 ± 1.31         |                  |                  |
| Giudicelli 1987 | HCTZ 25 mg     | Parallel, 10             | 51.7 ± 3.6 [SE] | 30    | 6.43              | 0.822 ± 0.174 [SE]  | 2.52 ± 0.954        |                  |                  |
| Muiesan 1985   | HCTZ/AMIL 50/5 mg |                     | 15      | 47.3 ± 17 | 50   | 4                 | 1.2 ± 0.12 [SE]    | 2.32 ± 0.16        | 171.7 ± 2.3      | 157.5 ± 2.1      |
| reeft 1983     | SPIRO 400 mg   | Crossover, 19            | ...     | 52.63  | 8                 | 1.22 ± 0.8          | 7.18 ± 7           |                  |                  |
| Kreeft 1983    | CTD 100 mg     | Crossover, 19            | ...     | 52.63  | 8                 | 1.22 ± 0.8          | 6.81 ± 8           |                  |                  |
| Chalmers 1982  | IND 2.5 mg     | Crossover, 16            | 53 ± 10 | 43.75  | 8                 | 0.79                | 142               | 165              | 157              |
| Bing 1981      | IND 2.5 mg     | Parallel, 8              | ...     | 50     | 16                | 4.4 ± 1 [SE]        | 7.4 ± 2.3          |                  |                  |
| Bing 1981a     | BFZ 5 mg       | Parallel, 7              | ...     | 50     | 16                | 3.3 ± 0.6           | 5.6 ± 1.2          |                  |                  |
| Bing 1981b     | IND + BFZ      | Parallel, 15             | ...     | 50     | 16                | 7.2 ± 1.4           | 10.9 ± 2.4         | 159 ± 8.6        | 142.8 ± 7.3      |
| Lawton 1979    | CTD 50 mg      | Parallel, 37             | 37 ± 8  | 71.43  | 4                 | 2.3 ± 1.8           | 7.4 ± 7.1          |                  |                  |
| Lawton 1979a   | Placebo        | Parallel, 38             | 37 ± 8  | 71.43  | 4                 | 2.1 ± 1.9           | 1.6 ± 1.3          |                  |                  |
| Dawson 1979    | BFZ 10 mg      | Crossover, 10            | 49      | ...    | 8                 | 0.86 ± 0.48         | 3.8 ± 2.76         | 173.6 ± 25       | 148 ± 18.7       |
| Holland 1979   | FUR 40 mg BD   | Crossover, 12            | ...     | ...    | 4                 | 0.8 ± 0.2 [SE]      | 2.5 ± 0.7          | 178.5            | 118d            |
| Holland 1979a  | HCTZ 50 mg BD  | Crossover, 11            | ...     | ...    | 4                 | 0.8 ± 0.2           | 4.7 ± 0.8          | 178.5            | 139d            |
| Oh 1978        | CTZ 500 mg BD  | Parallel, 7              | 43.6    | 14.29  | 14                | 0.21 ± 0.11         | 1.38 ± 1.37        |                  |                  |
| Wilcox 1977    | BFZ 2.5 mg BD  | Crossover, 26            | ...     | 75.86  | 4                 | 1.18 ± 0.15 [SE]    | 1.45 ± 0.21        | 183              | 159              |
| Chalmers 1976  | HCTZ 50 mg     | 20                       | 44.4 ± 3 | 35   | 8                 | 1.67                | 3.18               |                  |                  |
| Karlberg 1976  | SPIRO 200 mg   | Crossover, 27            | 47      | 33.33  | 8                 | 1.9 ± 1.2           | 5.9 ± 4            | 188              | 154              |
| Karlberg 1976a | Placebo        | Crossover, 27            | 47      | 33.33  | 8                 | 1.9 ± 1.2           | 2 ± 1.6            |                  |                  |
| Taniguchi 2006 | SPIRO 25 mg    | 51                       | 69 ± 9  | 47.06  | 24                | 1.7 ± 1.5           | 4.4 ± 4.6          | 144 ± 19         | 135 ± 19         |
| Cubeddu 1986   | HCTZ 25-100 mg | Parallel, 6             | 40 ± 5  | 33     | 4                 | 3 ± 0.5             | 3.3 ± 1.2          | 173              | 147              |
| Cubeddu 1986a  | Placebo        | Parallel, 6              | 41 ± 2  | 50     | 4                 | 3.8 ± 0.7           | 3.5 ± 0.7          | 151              | 147              |
| Ferrara 1987   | CTD 25 mg      | Parallel, 8              | 50 ± 8  | 50     | 6                 | 4.7 ± 2.6           | 9.9 ± 9.4          | 151              | 139              |
3.3 | Metaregression: Relation of change in PRA after diuretic to duration of treatment and change in BP

Random-effects metaregression was performed to examine whether the increase in PRA varied with duration of diuretic treatment and whether change in SBP was associated with change in PRA. The increase in PRA was not significantly related to duration of treatment (slope \(-0.0001\), 95% CI \(-0.02, 0.02\), \(P = .99\), Figure 3) and changes in SBP were independent of changes in PRA (coefficient \(-0.004\), 95% CI \(-0.02, 0.007\), \(P = .45\), Figure 4).

3.4 | Publication bias

The funnel plot of standard error vs effect size was asymmetric and suggestive of potential publication bias. Presence of publication bias was also suggested by Egger’s linear regression (\(P \leq .001\)). After adjustment of effect size for potential publication bias using the trim and fill correction, 10 potentially missing studies on the left side of the funnel plot were imputed leading to a corrected effect size that was slightly but not significantly less than the initial estimate (0.34 [95% CI 0.231, 0.45]; Figure 5).

3.5 | Effects of diuretic on markers of sodium and fluid homeostasis other than PRA

Of the other trials identified in which markers of sodium and fluid homeostasis other than PRA were used, other measures of renin (including prorenin, direct renin and active renin), weight/bio-impedance, echocardiographic measures and natriuretic peptides were measured in 29, 20, 9 and 4 trials, respectively.

4 | DISCUSSION

As far as we are aware, this is the first study to systematically review the effect of diuretic therapy on PRA and biomarkers of volume status in hypertensive individuals. Diuretics have been used in treatment of hypertension for many years, both as monotherapy and in combination with other antihypertensive agents. The ALLHAT trial demonstrated that thiazide-like diuretic treatment is among the most effective forms of antihypertensive therapy both in terms of blood pressure lowering efficacy and reduction in clinical events, particularly in black-African individuals who tend to have low-renin salt-sensitive hypertension. However, the short- and long-term mechanisms of action of the various classes of diuretics has been
debated and it is not clear whether diuretics lead to a sustained reduction in body sodium and intravascular volume because of compensatory mechanisms leading to sodium and fluid re-accumulation.

For example, 4–6 weeks after initiation of thiazide diuretic therapy, plasma and extracellular fluid volume have been found to return to near the original level despite continued reduction in BP.41–43

The main finding of the present analysis is that diuretics lead to a sustained increase in PRA, consistent with a sustained reduction in body sodium and volume. The mean change in PRA did not differ according to class of diuretic. This finding needs to be interpreted with caution since different doses were employed in the studies analysed. It might be expected that effects of the different diuretic classes on PRA would be related to their diuretic efficacy (i.e. loop > thiazide > MRA/potassium-retaining).44 Activation of compensatory systems may attenuate medium to longer-term effects of potent diuretics on PRA and it is notable that the antihypertensive effect of diuretics is dissociated with diuretic efficacy. We did not observe an association of rise in PRA with fall in BP. This could be because of the duration of action of different diuretic classes leading to different degrees of sympathetic activation and hence a dissociation between effects on sodium homeostasis and BP. Alternatively (or in addition) it might be because of pleiotropic effects of diuretics such as direct vasodilator action of thiazide/thiazide-like diuretics45 and specific effects of MRA/potassium retaining diuretics (aldosterone antagonism, effects of potassium).2

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It has been proposed that PRA might be useful for guiding diuretic therapy with regard initial selection of diuretic or non-diuretic therapy and dose titration of diuretic therapy. Whilst there is evidence that PRA is helpful in selecting patients who will benefit
from diuretic therapy, the potential use of change in PRA in guiding dose titration, selecting class of diuretic or in guiding use of combination diuretic therapy remains speculative. Such use of PRA depends on whether a rise in PRA is a reliable marker of response to diuretic and whether change in PRA varies according to class of diuretic and relates to the BP response to diuretic. At first sight the dissociation of change in BP with that of PRA in the present study would suggest that change in PRA, as opposed to pretreatment PRA is not a particularly useful marker to guide diuretic therapy (for example by increasing diuretic dose, changing class of diuretic or adding further diuretics if there is inadequate rise in PRA). However, it should be stressed that the present results relate to mean values obtained in the different trials and individual patient data are required to fully test this hypothesis.

This review is subject to several limitations. We were unable to stratify results by ethnicity which could be an important determinant of sodium homeostasis since the majority of studies were performed in Caucasians and, in many studies, ethnicity was not reported. Studies in specific ethnic groups will be required to determine if effects of diuretics on PRA differ according to ethnicity. The use of background therapy in some studies and a variable dose in others prevent a useful estimate of the effect size relating to a standard dose of diuretic. The duration of studies was relatively short. There were relatively few studies performed on nonthiazide or nonthiazide-like diuretics and therefore there was limited power to detect a difference between different classes of diuretic. The MRA/potassium sparing group was mostly composed of spironolactone which in many trials was used at high dose unrepresentative of its current use in primary hypertension.

In conclusion, this systematic review and meta-analysis demonstrated that diuretic therapy in hypertension leads to a sustained increase in PRA that does not differ between classes of diuretics and is unrelated to the fall in BP. This may be due to of homeostatic mechanisms limiting effects of diuretics on sodium and fluid retention and
pleiotropic effects of diuretics leading to a dissociation between change in sodium homeostasis and BP.

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COMPETING INTERESTS
There are no competing interests to declare.

CONTRIBUTORS
All authors developed the study concept and designed the research. R.J.M. conducted the electronic searches, study selection and extraction. R.J.M., M.C. and C.N.F. performed data analysis with L.F. and B.F. helping interpret the results. R.J.M., L.F. and P.J.C. wrote the majority of the manuscript. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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