UNIVERSITY OF AUCKLAND
Waipapa Taumata Rau
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES

# Latte Dosage Trial

## Caffeine for the prevention of intermittent hypoxaemia in late preterm babies


Elizabeth Oliphant

For the Latte Dosage Study Group

(Elizabeth Oliphant, Chris McKinlay, David McNamara, Jane Alsweiler)


NWH Report Day 2022

# Background

*"On a global level, given their relatively larger numbers, babies born at 34 to 36 weeks are likely to have the greatest public health impact and to be of the most importance in the planning of services"*

- World Health Organisation

In: *Born Too Soon: The Global Action Report on Preterm Birth* [2012]

Image: vermont.momcollective.com/2013/11/13/34-weeks-premature/

# Background

## Intellectual disability

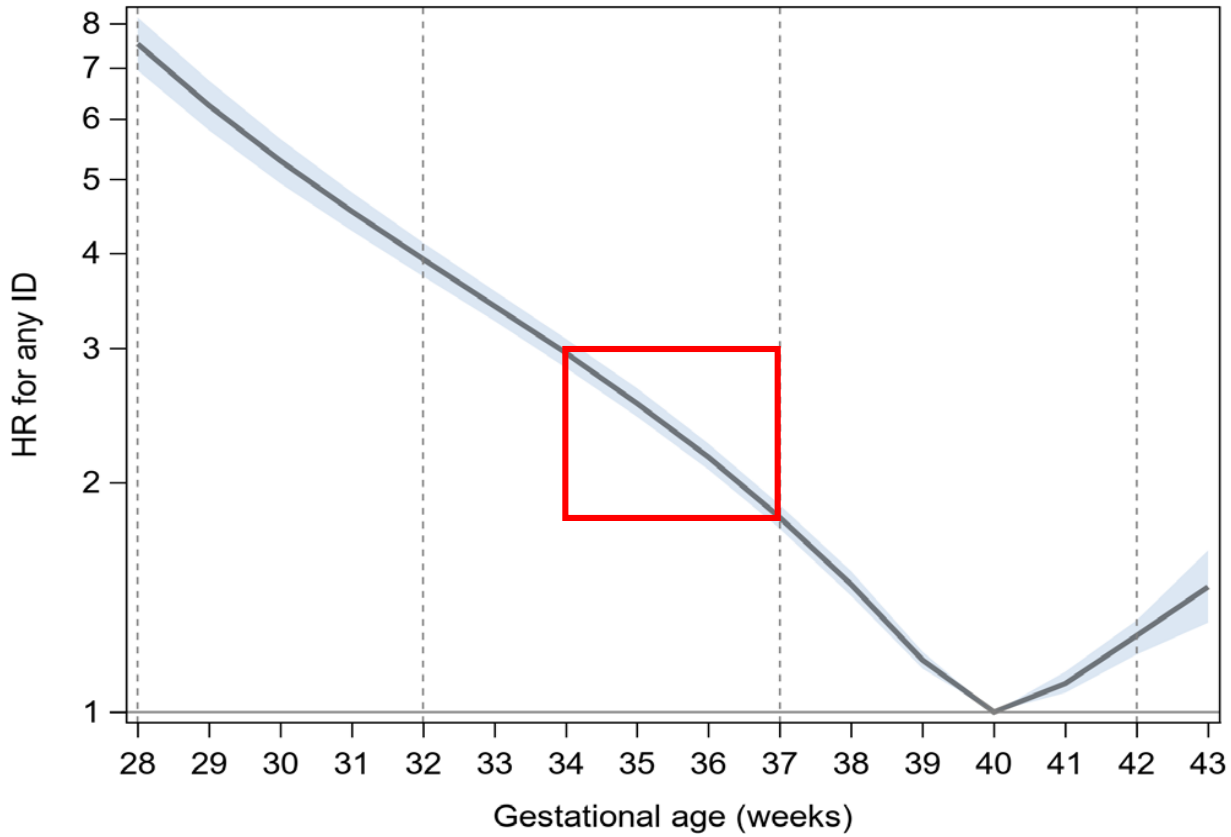
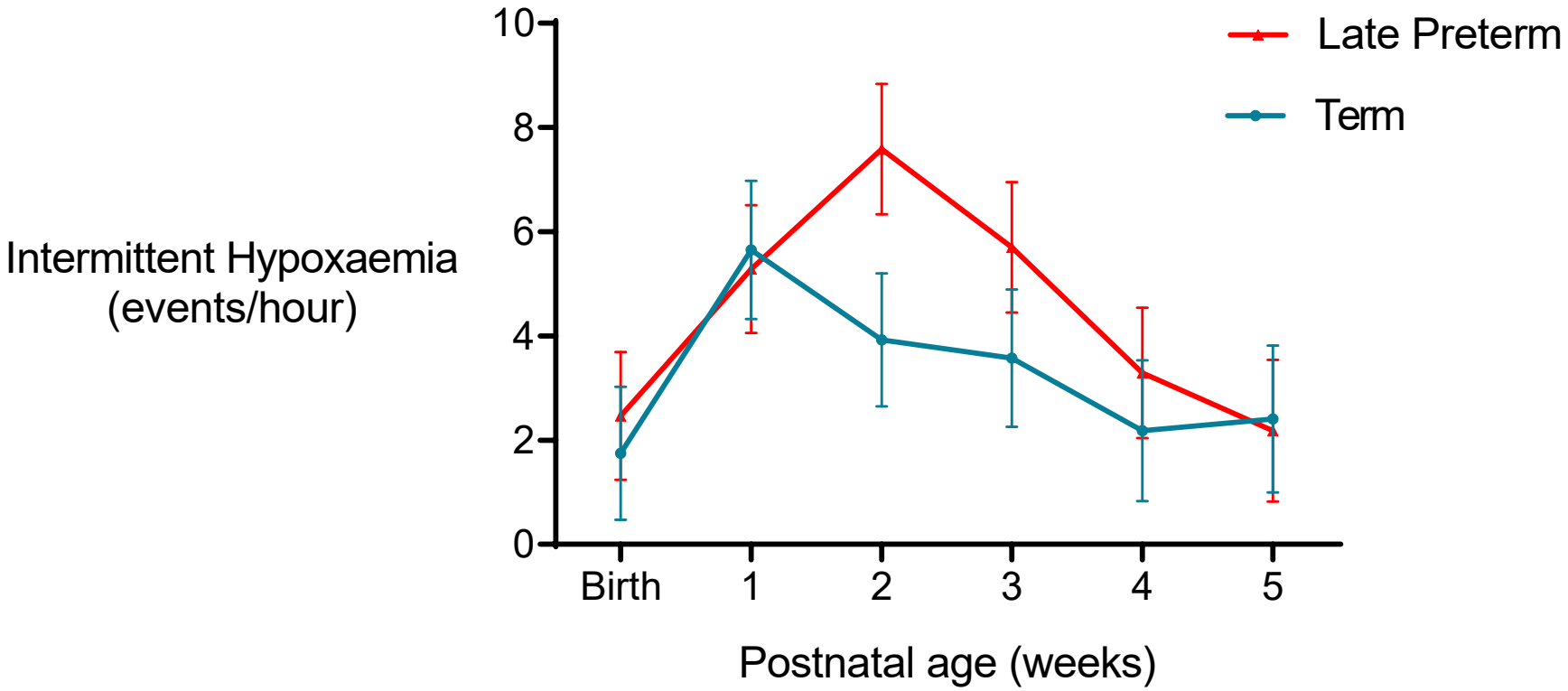



**Figure**: Hazard Ratio (HR) for intellectual disability (ID) according to gestational age

Yin W, et al. Arch Dis Child 2022;**0**:1–7

# Background

## LaP study




Williams et al. J Pediat. 2019. 204: 89–95.e1

# Background

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## Caffeine for Apnoea of Prematurity trial

| Outcome | Caffeine group n/N (%) | Placebo group n/N (%) | Odds Ratio | 95% CI | P-value |
|---|---|---|---|---|---|
| Composite death / neurodevelopmental disability at **18-21 months** N= 1869 (Schmidt et al., 2007) | 377/937 (40.2) | 431/932 (46.2) | 0.77 | 0.64-0.93 | 0.008 |
| Composite death / neurodevelopmental disability at **5 years** N=1640 (Schmidt et al., 2012) | 176/833 (21.1) | 200/807 (24.8) | 0.82 | 0.65-1.03 | 0.09 |
| Composite functional impairment at **11 years** N= 920 (Schmidt et al., 2017) | 145/457 (31.7) | 174/463 (37.6) | 0.78 | 0.59-1.02 | 0.07 |
| *Poor academic performance* | 66/458 (14.4) | 61/462 (13.2) | 11.1 | 0.77-1.61 | 0.58 |
| *Motor impairment* | 90/457 (19.7) | 130/473 (27.5) | 0.66 | 0.48-0.9 | 0.009 |
| *Behaviour problems* | 52/476 (10.9) | 40/481 (8.3) | 1.32 | 0.85-2.07 | 0.22 |

Schmidt et al, NEJM 2007; 357: 1893-1902; Schmidt et al, JAMA 2012; 307: 275; Schmidt et al, JAMA Pediatrics 2017; 564: 171

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# Latte Dosage Trial

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## Aim

To determine the most effective dose of caffeine citrate to reduce intermittent hypoxaemia in late preterm babies.

## Study design

Multi-centre, double blind, dosage, randomised controlled trial

## Setting

NICUs and postnatal wards at 2 Auckland hospitals

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# Latte Dosage Trial

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## Population

Infants born between $34^{+0}$ – $36^{+6}$ weeks' GA

### Exclusion criteria

- Major congenital abnormality
- Minor congenital abnormality likely to affect respiration, growth or development
- Previous caffeine treatment
- Renal or hepatic impairment
- Tachyarrhythmia
- Seizures

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# Latte Dosage Trial

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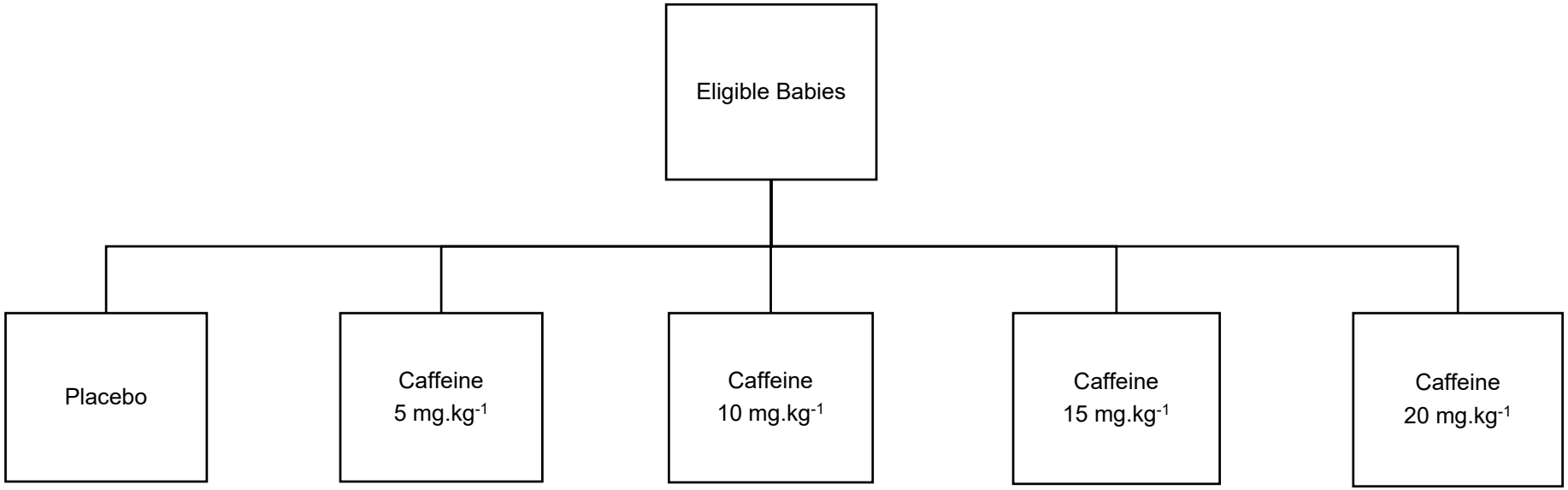
## Randomisation




- Randomised, stratified by site and gestational age (GA) (34/35/36 weeks)
- <72 hours after birth to 40 weeks GA
- Multiples randomised to same group
- Loading dose 2 $mL.kg^{-1}$, then daily dose of 1 $mL.kg^{-1}$

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# Latte Dosage Trial

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## Outcome

- **Primary outcome:** Intermittent hypoxaemia ($SpO_2$ ≥10% below baseline for <2 minutes) at 2 weeks after randomisation

- **Secondary outcomes:**
  - Intermittent hypoxaemia at term equivalent age
  - Growth
  - Tachycardia
  - Feed intolerance
  - Sleeping
  - Maternal Depression
  - Salivary caffeine concentration in mothers and babies

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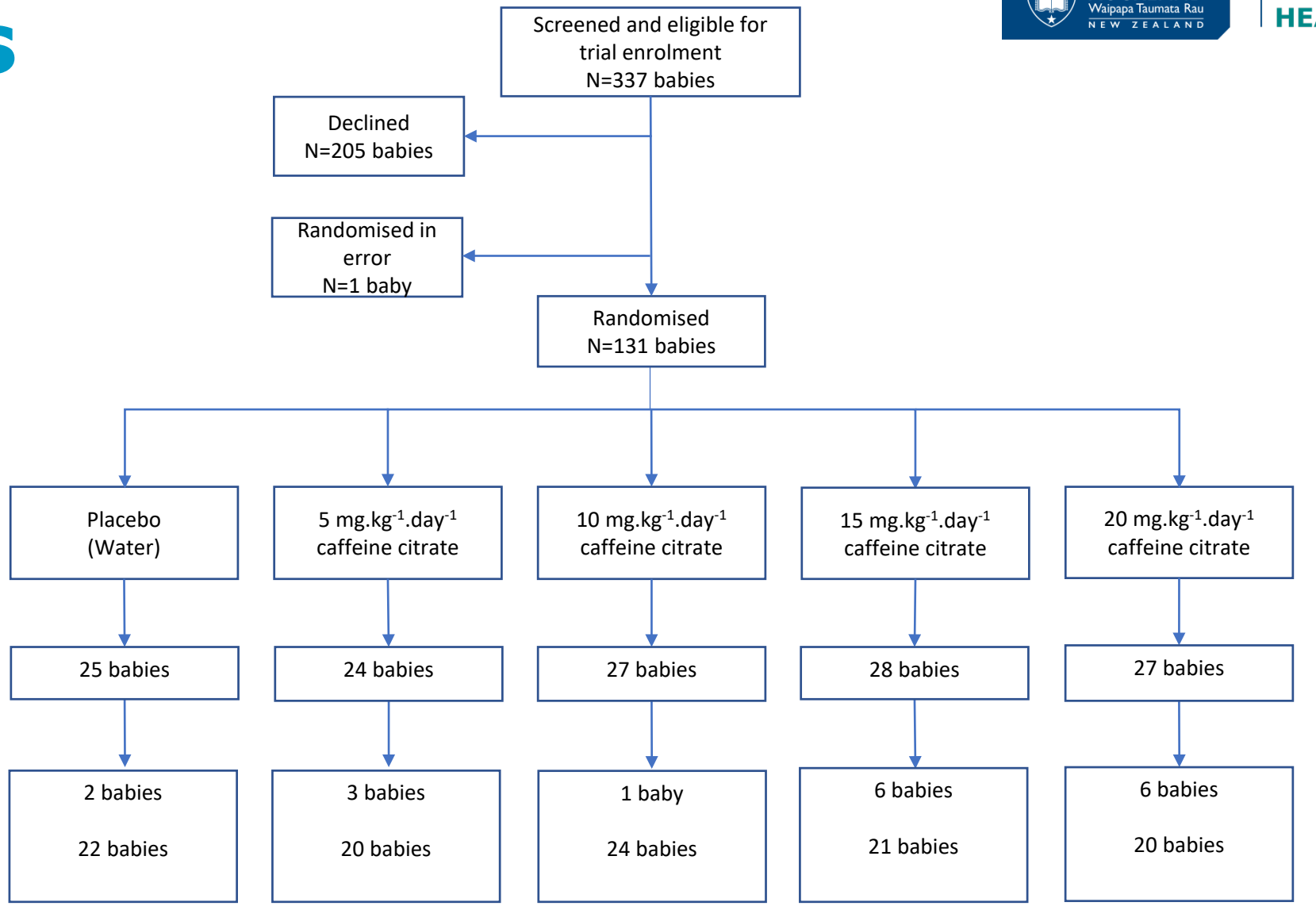
# Sample size

To detect a 50% reduction of 3.5 episodes per hour, and allowing a 10% drop out rate and 90% power we require 23 babies in each arm x 5 arms = 120 babies, with two-sided alpha of 0.05.

# Results


Screened and eligible for trial enrolment N=337 babies
Declined N=205 babies
Randomised in error N=1 baby
Randomised N=131 babies
Placebo (Water)
5 mg.kg-1.day-1 caffeine citrate
10 mg.kg-1.day-1 caffeine citrate
15 mg.kg-1.day-1 caffeine citrate
20 mg.kg-1.day-1 caffeine citrate
Allocated
25 babies
24 babies
27 babies
28 babies
27 babies
Withdrew (baseline to 2 weeks)
2 babies
3 babies
1 baby
6 babies
6 babies
Primary outcome measured
22 babies
20 babies
24 babies
21 babies
20 babies

# Results:
## Baseline maternal characteristics

| | Placebo | Caffeine citrate 5 mg.kg$^{-1}$.day$^{-1}$ | Caffeine citrate 10 mg.kg$^{-1}$.day$^{-1}$ | Caffeine citrate 15 mg.kg$^{-1}$.day$^{-1}$ | Caffeine citrate 20 mg.kg$^{-1}$.day$^{-1}$ | All caffeine groups |
|---|---|---|---|---|---|---|
| **Number of mothers (% of total)** | 24 (20) | 23 (19) | 24 (20) | 25 (21) | 25 (21) | 97 (80) |
| **Age (years; mean (SD)** | 31 (6) | 32 (5) | 31 (6) | 32 (6) | 31 (6) | 31 (6) |
| **Primiparaous** | 9 (38) | 11 (48) | 16 (67) | 15 (60) | 13 (52) | 55 (57) |
| **BMI (kg/m$^2$); median (IQR)** | 26.1 (23.5, 30.7) | 27.9 (24.2, 31.5) | 26.3 (23.3, 30.6) | 24.9 (21.9, 28.4) | 28.6 (23.4, 32.5) | 26.5 (23.2, 30.1) |
| **Multiple pregnancy** | 0 (0) | 1 (4) | 3 (13) | 2 (8) | 2 (8) | 8 (8) |
| **Antenatal corticosteroids** | 5 (21) | 4 (17) | 8 (33) | 8 (32) | 4 (16) | 24 (25) |
| **Caesarean delivery** | 8 (33) | 10 (42) | 15 (56) | 12 (44) | 10 (37) | 47 (45) |

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# Results: Baseline infant characteristics

| | Placebo | Caffeine citrate 5 $mg.kg^{-1}.day^{-1}$ | Caffeine citrate 10 $mg.kg^{-1}.day^{-1}$ | Caffeine citrate 15 $mg.kg^{-1}.day^{-1}$ | Caffeine citrate 20 $mg^{-1}.kg^{-1}.day$ | All caffeine groups |
|---|---|---|---|---|---|---|
| **Number of babies (% of total)** | 24 (19) | 24 (19) | 27 (21) | 27 (21) | 27 (21) | 105 (82) |
| **Gestational Age** | | | | | | |
| **34 weeks** | 6 (25) | 5 (21) | 6 (22) | 5 (19) | 6 (21) | 22 (21) |
| **35 weeks** | 7 (29) | 8 (33) | 9 (33) | 10 (37) | 9 (32) | 36 (34) |
| **36 weeks** | 11 (46) | 11 (46) | 12 (44) | 12 (44) | 12 (46) | 47 (45) |
| **Sex (male)** | 14 (58) | 17 (71) | 12 (44) | 18 (67) | 16 (60) | 63 (60) |
| **Singleton** | 24 (100) | 22 (92) | 21 (78) | 23 (85) | 23 (85) | 89 (85) |
| **Birth Weight (Z-score)** | -0.0 (1) | 0.2 (1) | -0.1 (1) | 0.1 (1) | -0.5 (1) | -0.1 (1) |
| **Admitted to NICU** | 12 (50) | 12 (50) | 13 (48) | 13 (48) | 17 (63) | 55 (52) |
| **Ethnicity (Prioritised)** | | | | | | |
| **Māori** | 2 (8) | 6 (25) | 1 (4) | 2 (7) | 7 (25) | 16 (15) |
| **Pacific Islander** | 7 (29) | 5 (21) | 2 (7) | 5 (19) | 5 (18) | 17 (16) |
| **Asian** | 7 (29) | 5 (21) | 13 (48) | 11 (41) | 7 (26) | 36 (34) |
| **Other** | 1 (4) | 1 (4) | 1 (4) | 1 (4) | 1 (4) | 4 (4) |
| **NZ European** | 7 (29) | 7 (29) | 10 (37) | 8 (30) | 7 (25) | 32 (30) |

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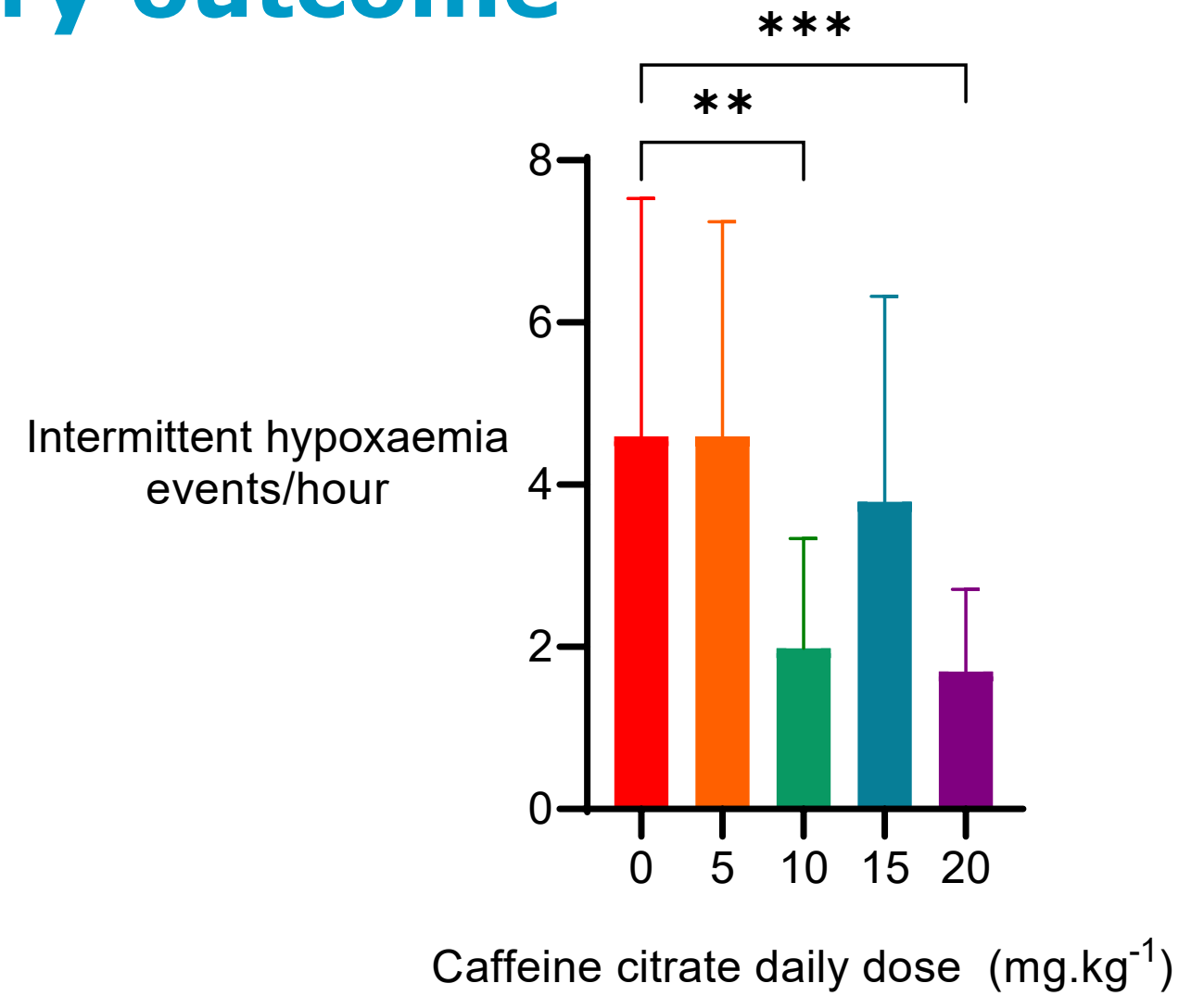
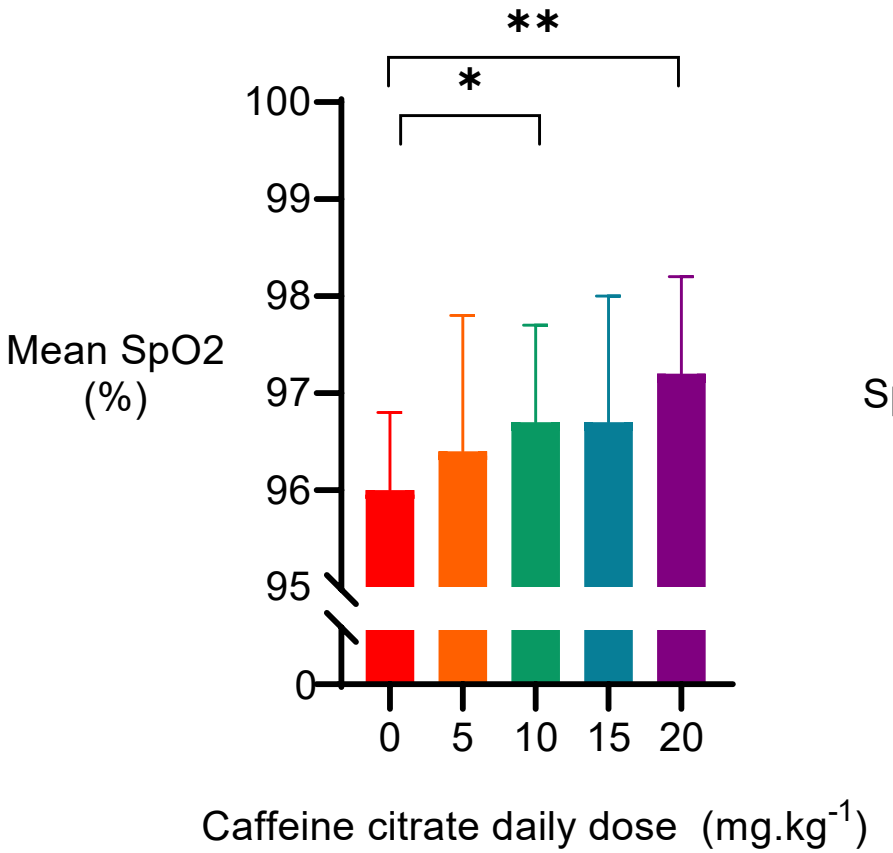
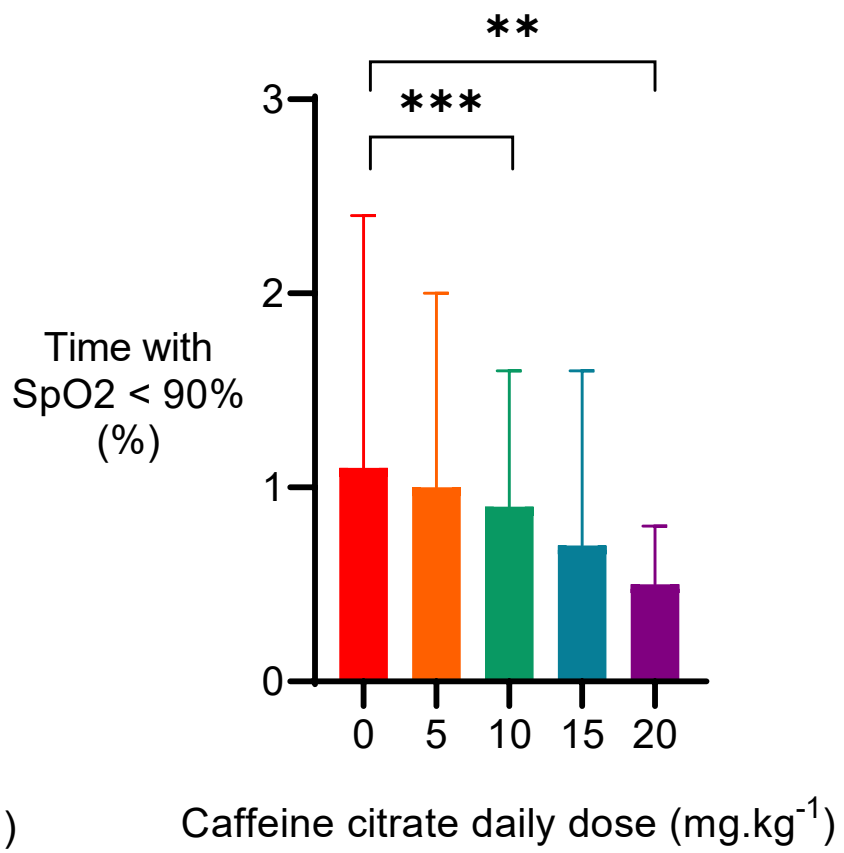
# Results:
## Primary outcome




** p <0.01
***p <0.005

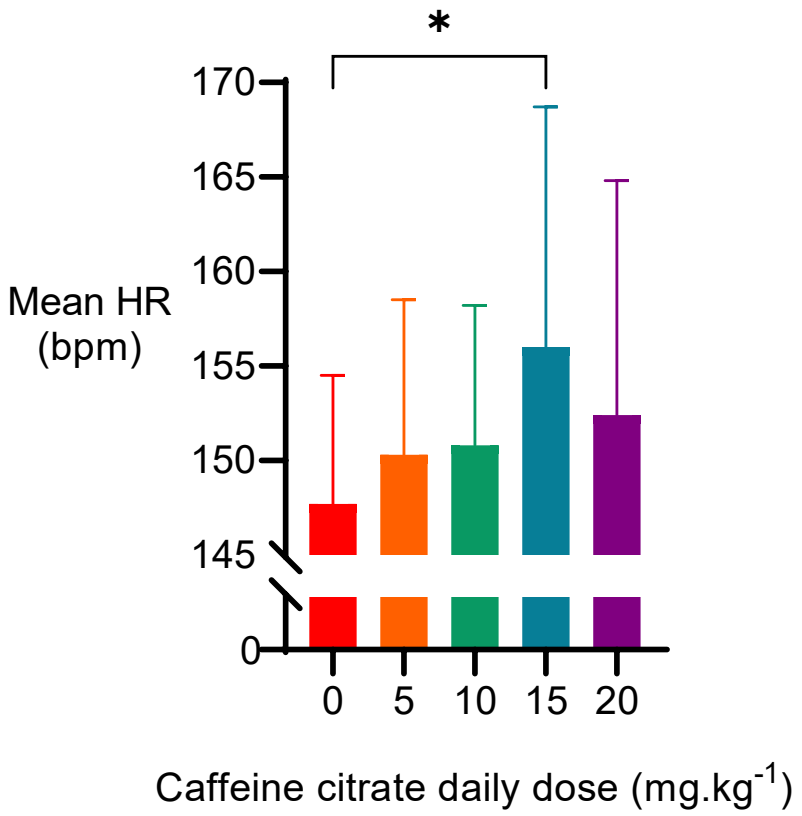
# Results: Respiratory Outcomes

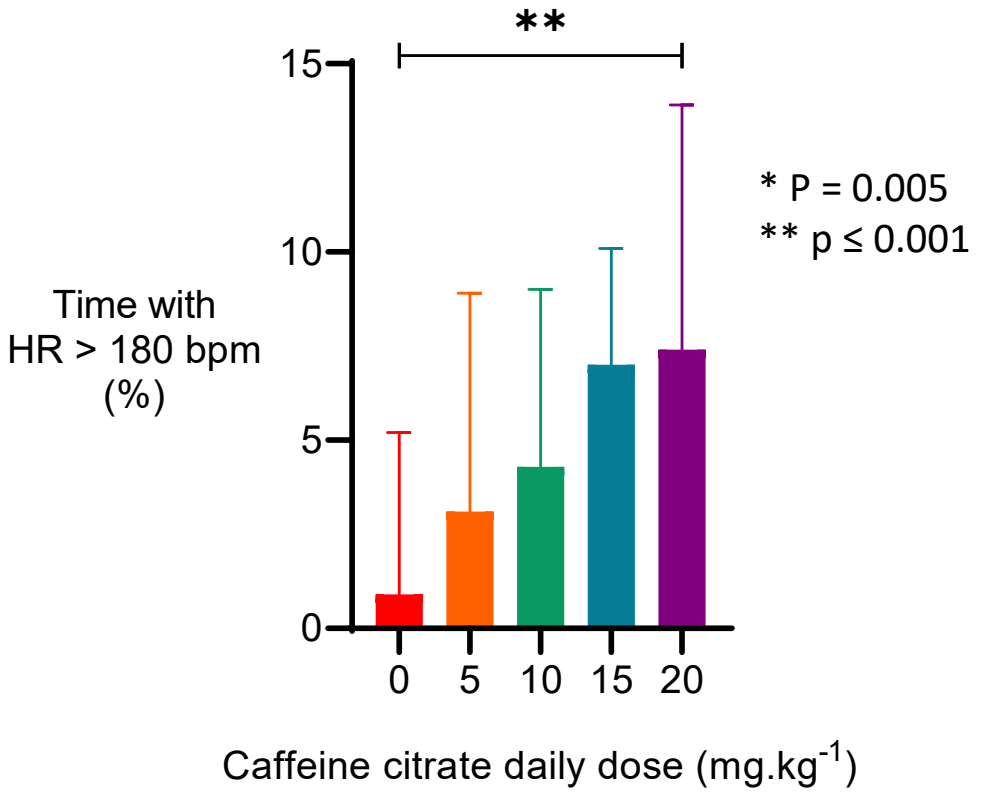



* $p < 0.05$
** $p < 0.005$
*** $p < 0.001$

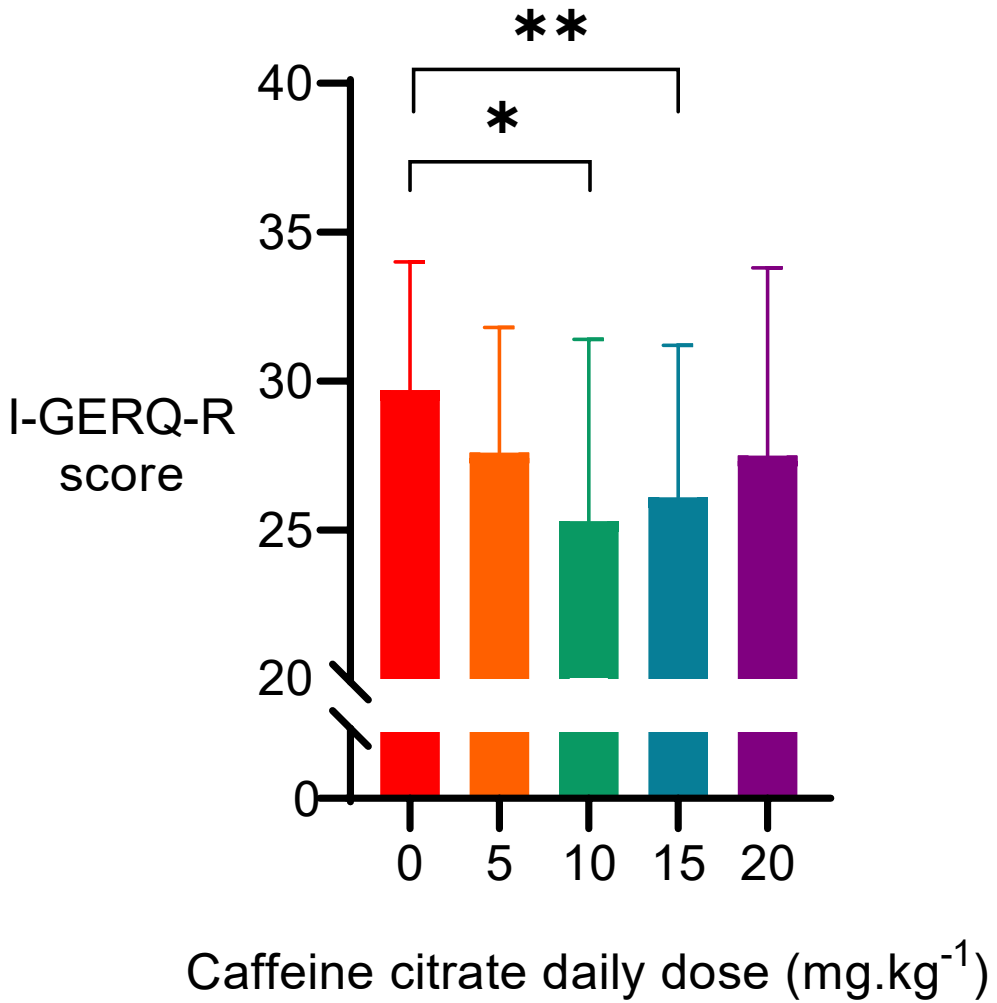
# Results: Heart rate




* P = 0.005
** p ≤ 0.001

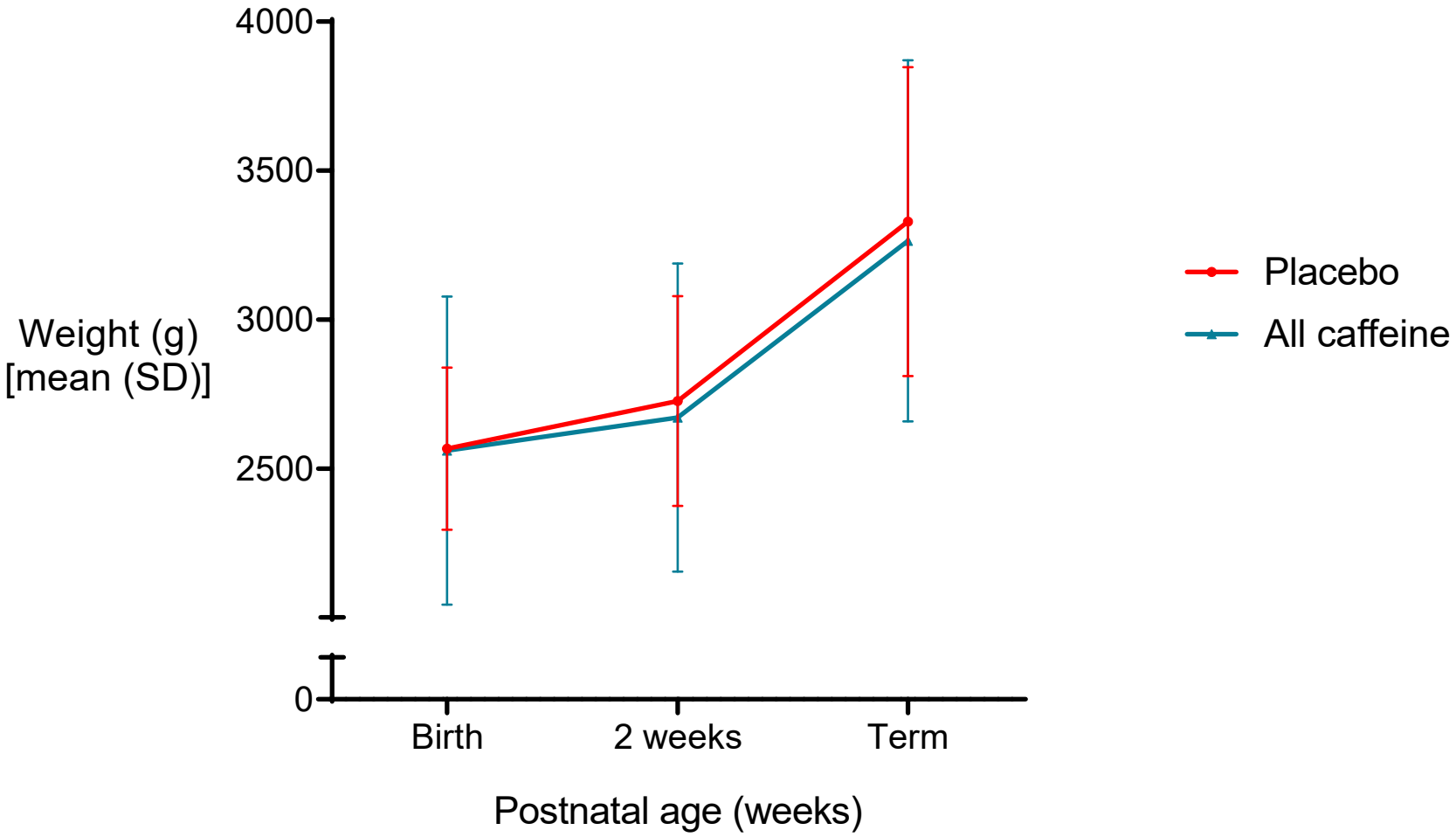
# Results: GI Symptoms



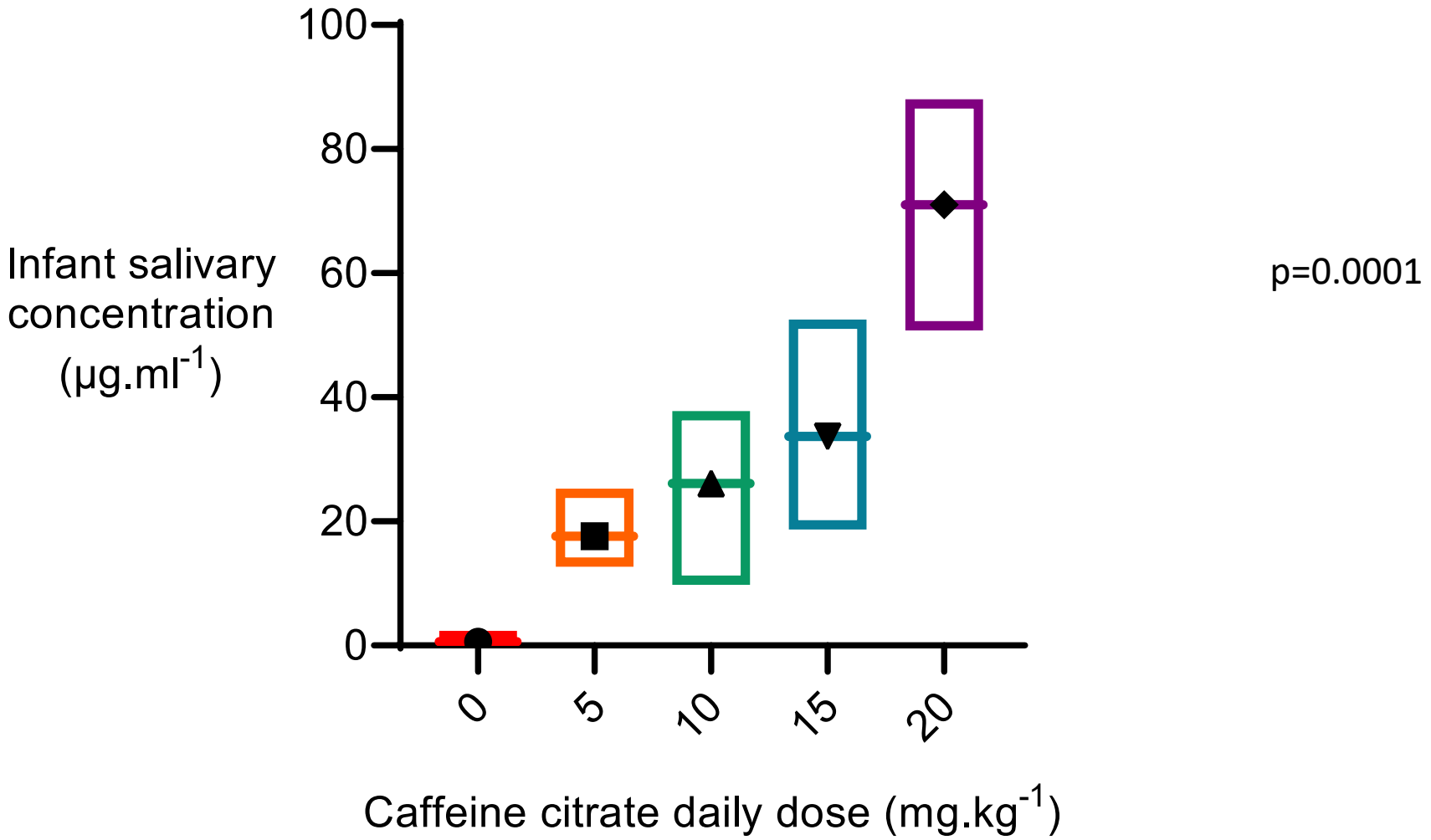

* p = 0.019
** p = 0.045

**Note:**
Lower score indicates less reflux symptoms
Minimally important difference = 3 points

# Results: Growth



# Salivary caffeine




p=0.0001

# Conclusions

20 mg.kg$^{-1}$.day$^{-1}$ is the most effective dose at reducing intermittent hypoxaemia in late preterm babies; 10 mg.kg$^{-1}$.day$^{-1}$ was also effective.

Further research is needed to determine if this dose of caffeine in late preterm babies will improve neurodevelopmental outcomes

# Acknowledgements

Babies and their whānau who participated in the study

Alana Cavadino

Logan Williams

Sarah Philipsen

Sabine Huth

Florella Keen

Lisa Mravicich

# Withdrawal reasons

| | Placebo | Caffeine citrate 5 mg.kg$^{-1}$.day$^{-1}$ | Caffeine citrate 10 mg.kg$^{-1}$.day$^{-1}$ | Caffeine citrate 15 mg.kg$^{-1}$.day$^{-1}$ | Caffeine citrate 20 mg.kg$^{-1}$.day$^{-1}$ | All caffeine groups |
|---|---|---|---|---|---|---|
| **Total in group; N** | 24 | 24 | 27 | 27 | 27 | 105 |
| **Number withdrew (%)** | 4 (13%) | 5 (21%) | 6 (22%) | 8 (30%) | 7 (26%) | 26 (25%) |
| | | | | | | |
| **Withdrawal reason; N** | | | | | | |
| Administration difficulties | 0 | 0 | 2 | 3 | 2 | 7 |
| Parents changed mind | 4 | 1 | 1 | 3 | 3 | 8 |
| Side effects or drug not tolerated | 0 | 3 | 3 | 1 | 1 | 8 |
| Other^ | 0 | 1 | 0 | 1 | 1 | 3 |

^Including: investigators discretion (n=1), moved outside study follow-up area (n=1), inability to follow up due to the COVID lockdowns (n=1)