How maternal BMI modifies the impact of personalised asthma management in pregnancy.

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Conflicts of Interest

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Highlights Box:

What is already known about this topic?

F_ENO -based asthma management reduces exacerbations in pregnancy and infant bronchiolitis.

What does this article add to our knowledge?

Effects are attenuated among obese mothers and those with excess GWG.

How does this study impact current management guidelines?

Weight management is important for contributing to improved asthma management in pregnancy.

Keywords:

asthma; pregnancy; exhaled nitric oxide; fractional exhaled nitric oxide; FENO; bronchiolitis; wheeze; obesity; maternal BMI

Abbreviations: ACQ, Asthma Control Questionnaire; BMI, body mass index; ED, emergency department; F_ENO, fractional exhaled nitric oxide; GP, general practitioner; GWG, gestational weight gain; IRR, incidence rate ratio.

ABSTRACT

Background: Maternal asthma is associated with perinatal complications and respiratory illness in offspring. Obesity increases asthma exacerbation risk in pregnancy and risk of wheeze in offspring.

Objectives: In this secondary analysis of a randomised controlled trial (RCT), we investigated the influence of maternal body mass index (BMI), gestational weight gain (GWG) and fractional exhaled nitric oxide (F_ENO)-based management on asthma exacerbations in pregnancy and offspring wheeze.

Methods: 220 women were randomised to asthma treatment adjustment according to symptoms (control group), or F_ENO and symptoms (F_ENO group). Exacerbations were recorded prospectively. Height and weight were measured at baseline, and in late pregnancy. GWG was categorised according to Institute of Medicine (IOM) guidelines. A validated parent-completed questionnaire assessed infant wheeze-related outcomes.

Results: F_ENO based management was associated with a significantly lower incidence rate ratio (IRR) for maternal exacerbations in non-obese mothers (0.52, 95% CI 0.31–0.88, P=0.015, n=129), and women with GWG within recommendations (0.35, 95% CI 0.12-0.96, P=0.042, n=43), but not for obese mothers (0.59, 95% CI 0.32-1.08, P=0.089, n=88), or women with excess GWG (0.58, 95% CI 0.32-1.04, P=0.07, n=104). Recurrent bronchiolitis occurred in 5.3% (n=1) of infants born to non-overweight mothers, 16.7% (n=3) of infants of overweight mothers and 21.7% (n=5) of infants of obese mothers in the control group. In the F_ENO group, two infants of obese mothers had recurrent bronchiolitis (7.1%, P=0.031).

Conclusions: The benefits of F_ENO -based management are attenuated among obese mothers and those with excess GWG, indicating the importance of weight management in contributing to improved asthma management in pregnancy.

INTRODUCTION

Asthma is the most common chronic health disorder experienced during pregnancy (1), affecting 3-12% of women (1-3). Maternal asthma is associated with numerous perinatal and neonatal complications (4, 5), and increases the likelihood that offspring will develop respiratory illnesses such as bronchiolitis (6) and asthma (7). In those who suffer from asthma, 8-65% will experience an exacerbation during pregnancy (8, 9), which is associated with a greater risk of complications such as low birth weight (10).

Obesity increases the risk of asthma exacerbations in pregnancy (11, 12), and is also an independent risk factor for wheeze and asthma in offspring (13). This is of particular concern given that one third of Australian women are overweight, obese or morbidly obese during pregnancy (14). Obesity is particularly prevalent in women with asthma, who are more likely to be obese prior to (15) and during pregnancy (11) than women without asthma. Therefore, both asthma and obesity pose significant health risks for women during pregnancy and their offspring, and measures to attenuate these risks need to be assessed.

The fraction of exhaled nitric oxide (F_ENO) is a surrogate marker of IL-13 dependent type 2 airway inflammation, and can be used to guide the treatment of asthma (16). F_ENO-based management has been shown to reduce maternal exacerbations of asthma during pregnancy (17), and improve respiratory outcomes of offspring in early life, including lower rates of neonatal hospitalisation (17), bronchiolitis (18) and asthma (19). Some reports suggest that obesity may independently effect F_ENO levels, which suggests that obesity may confound the interpretation of F_ENO and F_ENO -based management. F_ENO levels are reported to be significantly lower in obese asthmatics compared to non-obese asthmatics (20-22). However, several studies report no association between obesity and F_ENO (23-26). We therefore questioned whether F_ENO-based management would be effective for obese pregnant women with asthma. We hypothesised that the efficacy of F_ENO-based management of asthma in pregnancy on maternal exacerbations, infant bronchiolitis and infant health care

88 utilisation for wheeze would differ based on maternal body mass index (BMI) category or gestational
89 weight gain (GWG).

90 Using data from the Managing Asthma in Pregnancy (MAP) study (17) and Growing Into Asthma
91 (GIA) birth cohort (18) (19), we investigated the influence of maternal BMI and GWG on F_ENO-based
92 asthma management on maternal exacerbations during pregnancy, and wheeze-related outcomes in
93 offspring during the first 12 months of life.

METHODS

Study design and participants

This is a secondary analysis of data from the MAP study (17) and GIA birth cohort (18) (19), the methods of which have been published in detail previously. The MAP study was a double-blind, parallel group, randomised controlled trial conducted between June 2007 and December 2010. Women aged over 18 years with doctor-diagnosed asthma, confirmed by a respiratory physician's diagnostic interview, and who required inhaled therapy for asthma in the past year were recruited (17). The GIA birth cohort was a prospective, double-blind, longitudinal, observational follow-up of the offspring of women enrolled in the MAP study (18).

Ethics statement

All participants gave written informed consent for participation in these studies. The Hunter New England Area Health Service and University of Newcastle Research Human Ethics Committees approved the studies (MAP approval number 07/02/21/3.06, GIA approval number 12/06/20/4.03) and the MAP study was registered with the Australian New Zealand Clinical Trials Registry ACTRN 12607000561482.

Procedures and outcomes of the MAP study

The primary outcome of the MAP study was total number of asthma exacerbations, defined as events for which the participant sought medical attention (unscheduled doctors visit, presentation to the emergency department [ED], admission to hospital, or use of oral corticosteroids [OCS]) (17). Eligible participants were randomised 1:1 to either the control or intervention group before 22 weeks gestation. The intervention group was managed with an algorithm that utilised F_ENO levels as well as clinical symptoms to adjust ICS and β2-agonist therapy, while the control group was managed with an algorithm that utilised clinical symptoms alone. Clinical symptoms were assessed using the Asthma Control Questionnaire (ACQ) (27). All exacerbations after randomisation were recorded

prospectively. Participants had ICS delivered as a budesonide turbuhaler (AstraZeneca, North Ryde, New South Wales, Australia). Participants were reviewed at monthly antenatal clinics by a research assistant who collected data on clinical symptoms, ACQ score, current treatment, F_ENO levels and FEV_1. Data were sent to a statistician who applied the relevant algorithm before sending the treatment recommendation back to the research assistant to inform the participant. If asthma symptoms remained uncontrolled despite maximum treatment, participants were seen in the antenatal clinic by a respiratory physician who was a member of the study team. Participants were contacted by telephone two weeks after each antenatal clinic visit to assess symptoms and exacerbations, and to encourage adherence to the study protocol.

Maternal height and weight were measured at the first visit, and BMI calculated and categorised as non-overweight (<25 kg/m^2), overweight (25-29.9kg/m^2) and obese (≥30kg/m^2). GWG was calculated as the average weight gain over the second and third trimester (kg/week) between the first and last study visit. GWG was compared with Institute of Medicine guidelines (28), which recommend that women with a healthy BMI gain up to 0.45 kg/week, overweight women gain up to 0.27kg/week and obese women gain up to 0.23kg/wk, and categorised as GWG below or within guideline recommendations, or above guideline recommendations.

Procedures and outcomes of the GIA cohort follow-up

Children, parents/carers and study personnel who undertook follow-up visits were blinded to the treatment group allocated during pregnancy. When infants were 6 and 12 months of age, the primary carer completed a validated parent-report questionnaire with 50 questions on patterns of wheeze and other respiratory symptoms, respiratory infections, family history of allergic diseases, breastfeeding, immunisation and socioeconomic status (29, 30). We analysed data on any health care utilisation for wheeze (hospital admission, emergency department presentation, attending or calling the GP in an emergency, or referral to a consultant), and episodes of infant bronchiolitis

(reported as none, once, or more than once), by maternal intervention group, BMI and GWG category.

Statistical methods

Data were analysed on an intention-to-treat basis. Statistical analysis was conducted using Stata version 14 (StataCorp LLC, College Station TX, USA). Participants were categorised based on treatment group allocation (F_ENO-group or control group), BMI category (non-overweight, overweight and obese) and GWG category (below/within recommendations or above recommendations). The number of women with at least one exacerbation was compared using Chi-Squared tests with Bonferroni adjusted p-values for multiple comparisons. The exacerbation rate difference (incidence rate ratio, IRR) between the treatment groups and the interaction with BMI or excessive GWG was compared with a Poisson regression model; after which the aforementioned a priori determined groups were used in the Poisson regression to identify attenuation of treatment effect. Potential confounders were identified and added to the regression analysis.

Quality-of-life variables as reported in the original RCT (17) were analysed using ANCOVA with adjustment for baseline values. For other continuous variables, ANOVA (Tukey-Kramer or Fisher-Hayter pairwise comparison) or Kruskal-Wallis tests were performed as appropriate. Categorical variables were analysed using Chi-Squared tests or Fisher's Exact test. Multiple comparisons were Bonferroni adjusted. Significance was accepted when $p<0.05$.

RESULTS

Effect of maternal BMI category

Table 1 shows the subject characteristics at baseline, when categorised by intervention group and maternal BMI. Data on BMI was available for 217 women, of whom 62 (29%) were non-overweight, while 67 (31%) were overweight and 88 (41%) were obese. Groups were balanced regarding maternal age, categorised GWG, smoking status, gestational age at randomisation, place of birth, atopy, asthma history and medication, lung function and quality of life.

The proportion of women with exacerbations during pregnancy was higher in overweight (39%) and obese (48%) women, compared to non-overweight women (34%) in the control group (Figure 1A, Table 2). Similarly, in the F_ENO group, the proportion of women with exacerbations was higher in the overweight (28%) and obese (31%) women compared to non-overweight women (15%, Figure 1A, Table 2, P=0.067 all six groups). The interaction between treatment group and BMI was not significant (p=0.419) and remained not significant after adjusting for parity (interaction p=0.474). The magnitude of the F_ENO-based management effect was summarised as the incidence rate ratio (IRR) for maternal exacerbations (adjusted for parity), and greatest in the non-overweight subgroup (IRR = 0.38, 95% CI 0.14 – 1.07, P=0.067, n=62), followed by the overweight sub-group (IRR = 0.48, 95% CI 0.24 – 0.99, P=0.048, n=67), and the obese sub-group (IRR = 0.59, 95% confidence interval (CI) 0.32 – 1.08, P=0.089, n=88).[Chi-squared for trend p=0.029]. When combined, the IRR for maternal exacerbations was different between management groups for non-obese (non-overweight and overweight) mothers (0.52, 95% CI 0.31–0.88, P=0.015, n=129).

Online Repository Table E1 outlines perinatal outcomes for the cohort, categorised by intervention group and maternal BMI. Data was available for 211 children, of whom 60 (28%) were born to mothers who were of non-overweight BMI, 66 (31%) to mothers who were overweight and 85 (40%) to mothers who were obese. Groups were balanced for infant sex, gestational age at birth, birth length and head circumference, and labour and delivery outcomes. Infants born to mothers in the

control group with a non-overweight BMI weighed significantly less at birth (median 3350g) compared to infants born to obese mothers in the F_ENO intervention group (median 3770g, Table E1, P=0.029).

Health care utilisation for wheeze in infancy occurred in 36% of infants of obese mothers in the control group (vs. 34% in the F_ENO group), 26% of infants of overweight mothers (vs. 15% in the F_ENO group) and 11% of infants of non-overweight mothers (vs. 8% in the F_ENO group, P=0.084 all six groups, Figure 1B). When combined, the proportion of health care utilisation for wheeze was 19% for non-obese (non-overweight and overweight) mothers in the control group (vs. 11% in the F_ENO group, P=0.038 all four groups).

Recurrent bronchiolitis (more than once) in infancy was reported for 5% of those of non-overweight mothers, 17% of overweight mothers and 22% of obese mothers in the control group. Conversely, in the FENO group, recurrent bronchiolitis only occurred in two infants (7%) of obese mothers (P=0.031, Figure 1C). When combined, the proportion of recurrent bronchiolitis was 11% for non-obese (non-overweight and overweight) mothers in the control group (vs. 0% in the F_ENO group, P=0.008 all four groups).

Effect of maternal GWG

Table 3 outlines baseline subject characteristics when categorised by intervention group and maternal GWG. Data were available for 147 women, of whom 43 (29%) were below or within recommended guidelines for GWG, while 104 (71%) were above the recommended guideline for GWG. Groups were balanced for maternal age, BMI, smoking history, gestational age at randomisation, employment status, atopy, lung function, asthma medication use and quality of life. A lower proportion of women in the F_ENO group experienced an exacerbation (24% below/within GWG recommendations; 28% above recommendations) compared to the control group (55% below/within GWG recommendations; 42% above recommendations, p=0.072 all four groups) across both GWG categories (Figure 2A, Table 4). The interaction between treatment groups and

excessive GWG was not significant (p=0.215) and remained not significant after adjustment for hospitalisations in the past 2 years (interaction p=0.389).

Women in the F_ENO group with GWG below/within recommendations had a significantly lower exacerbation rate compared to the control group (GWG below/within recommendations, IRR 0.35, 95% CI 0.12 – 0.96, adjusted for hospitalisations in past 2 years, p=0.042, n=43). Women in the F_ENO group with GWG above recommendations had a reduction in exacerbation rate compared to the control group with GWG above recommendations, but this failed to reach statistical significance (IRR 0.58, 95% CI 0.32 – 1.04, P=0.07, n=104). Women in the F_ENO intervention group, both those who were below/within or above GWG recommendations, had significantly fewer unscheduled doctor visits than women in the control group who had GWG below/within recommended limits (P=0.003, Table 4).

Online Repository Table E2 outlines perinatal outcomes for the cohort, categorised by intervention group and maternal GWG. Data was available for 144 children, of whom 41 (28%) were born to mothers below/within the recommended limits for GWG, while 103 (72%) were born to mothers above the recommended limit for GWG. Groups were balanced regarding infant sex, gestational age at birth, birth weight, length and head circumference, labour and delivery outcomes, and maternal and infant complications. There were no significant differences between sub-groups.

Health care utilisation for wheeze occurred in 20% of infants of mothers with GWG below/within recommendations and 24% of infants of mothers with GWG above recommendations, in the control group (vs. 11% and 9%, respectively, in the F_ENO group, P=0.297 all four groups, Figure 2B).

Recurrent bronchiolitis in infancy was reported for 14% of those in the control group with GWG below/within recommendations, compared to 11% of those in the F_ENO group (GWG below/within recommendations), and in 12% of the control group with GWG above recommendations compared to 0% in the F_ENO group (GWG above recommendations) (P=0.033 all four groups, Figure 2C).

DISCUSSION

This study examined the effect of maternal BMI and GWG on the efficacy of F_ENO-based management for pregnant women with asthma. The proportion of women who experienced an asthma exacerbation during pregnancy increased with maternal obesity but not with increasing GWG, as previously described (11, 12). However, this study contributes novel data showing that both obesity and excessive GWG attenuated the beneficial effects of F_ENO-based management on maternal exacerbations. This was demonstrated by a non-significant exacerbation rate (IRR) among obese women, and those with excess GWG. For maternal exacerbations, the biggest effects of F_ENO-based management (over symptoms-based management) were demonstrated in mothers with gestational weight gain within guideline recommendations (72% decrease), and those who were non-overweight (64% decrease). These effect sizes are greater than the overall effect reported in the original trial (50% decrease in exacerbation rate) (17). This suggests that optimal efficacy of the F_ENO-based asthma management approach may be achieved among women who are not obese, and who have GWG within recommendations, highlighting the importance of nutritional status in achieving optimal respiratory outcomes in pregnancy.

F_ENO is a marker of eosinophilic and corticosteroid-sensitive airway inflammation, with elevated levels suggesting uncontrolled disease, and can be used to adjust treatment and improve disease outcomes. F_ENO-based management has been shown to reduce maternal asthma exacerbations during pregnancy (17), and improve offspring respiratory outcomes, including lower rates of bronchiolitis in infancy (18) and asthma at pre-school age (19). The relationship between F_ENO (and F_ENO-based management) and obesity, however, remains unclear. While some studies indicate that obesity is associated with lower F_ENO levels in asthmatic adults (20-22) and children (31, 32), others report that there is no association between F_ENO levels and obesity in either adults (23-26) or children (33-37) with asthma. The picture is even less clear in non-asthmatic subjects, with obesity associated with a higher FeNO level (24, 33-35, 38-41), a lower (36, 42) F_ENO level, or no change in

F_ENO (21, 26, 43-45). These mixed results may be accounted for by differences in how obesity was classified, as well as by differences in the numerous confounding variables that influence F_ENO levels (46, 47). Furthermore, asthma is a heterogenous disease with different pathological phenotypes, including both eosinophilic and non-eosinophilic disease (48). Consequently, given that F_ENO is a measure of eosinophilic inflammation, some of the variation in the relationship between obesity and F_ENO may also be explained by differences in the proportion of eosinophilic and non-eosinophilic (neutrophilic) populations. Given these uncertainties, and the rising prevalence of obesity, especially in asthma, it is important to determine whether BMI might influence the efficacy of F_ENO-based management for asthma in pregnancy.

Maternal BMI, but not GWG, was associated with a greater risk of asthma exacerbation during pregnancy, regardless of symptom- or F_ENO-based asthma management, which is consistent with previous studies (11, 12). While F_ENO-based management reduced asthma exacerbations across all BMI and GWG categories, the effect was attenuated with increasing BMI and increasing GWG. Of interest, we observed an increase in the proportion of infants with recurrent bronchiolitis in parallel with maternal early-pregnancy BMI; yet, F_ENO-based management reduced both health care utilisation for wheeze and recurrent bronchiolitis in infancy across all maternal BMI and GWG categories. This may suggest that F_ENO-based asthma management during pregnancy partially mitigates the negative effects of overweight and obesity on both maternal and infant respiratory health. However, although F_ENO-based management remains beneficial, its efficacy appears to be reduced at a higher BMI and with GWG above the recommended limits. In order to improve the efficacy of this asthma management approach during pregnancy, early nutritional/lifestyle intervention is required to address obesity in early pregnancy and monitor GWG.

Obesity and excess GWG are both associated with an increased risk of a range of antepartum, intrapartum and postpartum complications for women, in addition to an increased risk of adverse outcomes for their offspring (49-52). Pre-pregnancy weight loss has been shown to reduce the risk of

284 several obesity-related complications such as gestational diabetes (53) and neonatal mortality (54).
285 Given the results of our study, targeted preconception counselling and the development of a weight
286 loss program for overweight and obese women with asthma may be beneficial in reducing
287 exacerbations during pregnancy and adverse infant outcomes. Our results also highlight the
288 importance of weight management during pregnancy in women with asthma. This is likely to pose a
289 challenge, however, as GWG recommendations are rarely discussed by health care providers (55),
290 and changing outcomes has proven difficult even with intensive intervention (56, 57).

291 An alternative approach to improving outcomes for pregnant women with asthma may lie in
292 addressing the question of why F_ENO-based management was less effective with maternal obesity or
293 excess GWG. The major change in obesity is an increase in adipose tissue, a recognised endocrine
294 organ, which produces pro-inflammatory cytokines, or "adipokines", such as TNF-α and IL-6 (49).
295 This is largely driven by a shift in adipose tissue macrophages to the pro-inflammatory M1
296 phenotype, and results in a low-grade systemic inflammatory state (49). sCD-163, a marker of
297 macrophage activation, is significantly elevated in obese women with asthma in pregnancy, and,
298 when elevated, is associated with significantly more exacerbations requiring oral corticosteroids
299 (12). Elevated sCD-163 has also been associated with worse asthma control in obese girls (58) and
300 other complications of pregnancy such as gestational diabetes mellitus (59). Asthma exacerbations
301 in obese individuals may therefore be driven, or at least contributed to, by systemic inflammation
302 from macrophages in adipose tissue rather than localised eosinophilic inflammation in the lungs.
303 Given that F_ENO is a marker of eosinophilic airway inflammation rather than systemic inflammation,
304 this could explain the lower F_ENO levels observed in obese asthmatics (20-22, 31, 32) and why F_ENO-
305 based management, which alters medication dosing according to F_ENO levels, is less effective with
306 increasing BMI. Monitoring systemic markers of macrophage activation, such as sCD-163, may
307 therefore prove useful in guiding the management of pregnant women with asthma, but further
308 research is needed to determine how this might influence treatment.

A major limitation of this was the small sample sizes within the sub-groups, and the lack of a control group of non-asthmatic women where infant outcomes were evaluated. The Breathing for Life Trial, a multi-centre, parallel group, randomised controlled trial of F_ENO-based management versus usual care (60), is currently underway, and may allow validation of these findings in a larger cohort (1200 pregnant women with asthma).

In summary, this study indicates that while F_ENO-based management remains beneficial in reducing adverse maternal and infant outcomes of asthma, its efficacy is attenuated with increasing BMI and excess GWG. Consequently, if issues of maternal obesity and GWG are addressed both prior to pregnancy, and during pregnancy, maternal and infant respiratory outcomes may be improved. Furthermore, given that monitoring F_ENO, a marker of eosinophilic inflammation, is less effective in obesity, our study supports the notion that asthma exacerbations may, at least in part, be driven by low-grade systemic inflammation.

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495 of asthma during pregnancy and its impact on perinatal outcomes and infant and childhood
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498

499 Table 1: Baseline subject characteristics of pregnant women with asthma, by intervention group and maternal BMI

	Control Group (C)			F_ENO Group (F)			
	Non-overweight (n=29)	Overweight (n=31)	Obese (n=46)	Non-overweight (n=33)	Overweight (n=36)	Obese (n=42)	p-Value
Demographics							
Maternal Age (years) ¶	29.0 (6.5)	29.2 (5.0)	28.6 (5.4)	26.3 (4.5)	28.6 (5.8)	29.0 (5.0)	0.264
Gestational Weight Gain - *	*n=18*	*n=22*	*n=31*	*n=22*	*n=20*	*n=33*	0.485
Below/Within Guideline Recommendations	5 (28%)	5 (23%)	12 (39%)	6 (27%)	3 (15%)	12 (36%)	
Above Guideline Recommendations	13 (72%)	17 (77%)	19 (61%)	16 (73%)	17 (85%)	21 (64%)	
Ex-Smoker ‖	10 (38%)	8 (32%)	22 (49%)	10 (30%)	16 (46%) *n=35*	15 (38%) *n=40*	0.601

Pack Years ǂ	3.0 [1.1, 8.0]	5.3 [3.5, 13.9]	2.1 [1.0, 6.0]	2.9 [2.0, 5.0]	2.5 [1.0, 7.0]	3.3 [1.0, 5.5]	0.642
Gestational age (weeks) at randomisationǂ	20 [18, 21]	20 [19, 21]	20 [19, 21]	20 [19, 21]	20 [18, 22]	21 [19, 22]	0.767
Parity ǂ	0 [0, 1]	1 [0, 1]	1 [0, 2]	0 [0, 1]	1 [0, 1]	1 [0, 2]	**<0.001**[1]
Australian bornǁ	25 (89%) *n=28*	28 (97%) *n=29*	39 (89%) *n=44*	27 (87%) *n=31*	31 (94%) *n=33*	38 (97%) *n=39*	0.470
Employed*	24 (86%)	22 (76%)	26 (59%)	18 (58%)	22 (67%)	16 (41%)	**0.004**[1]
Atopy ǁ	19 (76%) *n=25*	25 (81%)	31 (74%)	26 (79%)	23 (72%) *n=32*	30 (75%) *n=40*	0.971
Asthma History (past 2 years)¶						*n=41*	
Hospitalisations for asthma (per person)	0.10 (0.41)	0.06 (0.36)	0.04 (0.21)	0.09 (0.52)	0	0	0.598

Emergency Department visits (per person)	0.17 (0.60)	0.32 (0.70)	0.13 (0.40)	0.52 (1.80)	0.06 (0.23)	0.12 (0.64)	0.244
OCS courses (per person)	0.24 (0.58)	0.65 (1.11)	0.43 (1.33)	0.36 (0.78)	0.11 (0.32)	0.37 (0.83)	0.270
Lung Function ¶							
FEV_1 % predicted	95.4 (14.7)	92.4 (13.7)	97.1 (14.8)	92.5 (12.8)	94.6 (15.0)	96.5 (11.6)	0.579
FVC % predicted	104.7 [93.4, 113.6]	101.4 [95.5, 110.0]	105 [94.2, 112.8]	103.4 [92.0, 114.0]	106.0 [97.2, 113.0]	103.8 [97.2, 115.9]	0.918
FEV_1:FVC	0.83 [0.76, 0.87]	0.81 [0.74, 0.83]	0.82 [0.75, 0.85]	0.75 [0.71, 0.84]	0.78 [0.73, 0.83]	0.81 [0.76, 0.85]	0.239
F_ENO (ppb) ‡	15.0 [9.1, 33.0] 28	16.6 [9.1, 37.7]	13.4 [7.8, 26.1]	19.1 [7.2, 34.3]	20.3 [6.3, 53.5] 35	14.8 [6.0, 26.9]	0.837
Asthma Medication							
Beta-2 agonist use (days/week) n ‡	0 [0, 6] *n=28*	2 [0, 7] *n=30*	2 [0, 7] *n=44*	1 [0, 3]	1 [0, 7] *n=31*	0 [0, 3] *n=40*	0.292

ICS use*	8 (28%)	11 (35%)	15 (33%)	6 (18%)	9 (25%)	16 (38%)	0.465
ICS Dose (beclomethasone dipropionate equivalent) among users (µg/day) ‡	650 [450, 800]	800 [400, 1600]	800 [40, 2000]	800 [500, 1000]	1000 [800, 1000]	900 [800, 1400]	0.448
Quality of Life‡	*n=28*	*n=30*	*n=45*	*n=32*	*n=34*	*n=40*	
SF-12 Physical[§]	52.9 [40.7, 55.6]	46.3 [40.4, 53.6]	49.1 [43.4, 52.3]	49.3 [43.5, 54.8]	49.6 [45.9, 52.8]	49.0 [41.5, 51.8]	0.173
SF-12 Mental[§]	53.5 [46.0, 57.9]	49.5 [42.8, 56.2]	55.0 [49.1, 58.7]	55.2 [48.4, 57.8]	56.3 [54.9, 57.9]	56.4 [44.9, 59.9]	0.114
AQLQ-total[¥]	0.8 [0.3, 1.3]	1.3 [0.8, 2.0]	1.0 [0.5, 1.6] *n=42*	0.8 [0.5, 1.1] *n=30*	0.6 [0.4, 1.4] *n=33*	0.9 [0.4, 1.6] *n=38*	0.103

*Chi-squared; ‡Kruskal-Wallis; ‖Fisher Exact; ¶ANOVA; [§] Low=0, high=100; [¥] Good=0, Poor=10 [1]Control Non-Overweight vs FENO Obese significantly different ($p<0.05$)

Data are mean (sd), median [interquartile range] or n (%) as appropriate

501

502

503 Table 2: Efficacy outcomes according to intervention group and maternal BMI in women with asthma followed during pregnancy

	Control Group (C)			F_ENO Group (F)			
	Non-overweight (n=29)	Overweight (n=31)	Obese (n=46)	Non-overweight (n=33)	Overweight (n=36)	Obese (n=42)	p-value
Experienced ≥ 1 exacerbation during pregnancy*	10 (34%)	12 (39%)	22 (48%)	5 (15%)	10 (28%)	13 (31%)	0.067
Exacerbation types § (mean SD)							
Unscheduled doctor visits	0.37 (0.69)	0.59 (0.98)	0.67 (0.75)	0.17 (0.38)	0.34 (0.55)	0.37 (0.63)	0.183
OCS use	0.11 (0.32)	0.45 (1.0)	0.10 (0.30)	0.03 (0.19)	0.17 (0.38)	0.08 (0.27)	0.072
Hospitalisation	0.07 (0.27)	0	0.02 (0.15)	0	0	0	0.098

Emergency department (ED) presentation	0.04 (0.19)	0	0.02 (0.15)	0	0.03 (0.19)	0.05 (0.23)	0.433
Quality of Life ¶	*n=26*	*n=29*	*n=38*	*n=28*	*n=28*	*n=36*	
SF12-Physical[§]	50.9 [40.4, 54.7]	45.6 [35.5, 49.0]	46.1 [37.9, 50.7]	46.5 [43.4, 53.0]	48.9 [42.7, 52.2]	44.2 [37.4, 50.5]	0.802
SF12-Mental[§]	55.1 [47.3, 56.4]	53.3 [46.0, 57.8]	54.6 [44.6, 57.5]	55.8 [47.0, 59.2]	57.8 [55.5, 60.2]	56.6 [47.9, 59.3]	0.076
AQLQ-M-Total[¥]	0.63 [0.4, 1.3] *n=25*	1.1 [0.5, 1.9] *n=28*	1.0 [0.5, 1.6]	0.9 [0.4, 1.4]	0.6 [0.5, 1.0] *n=26*	0.9 [0.5, 1.0]	0.569
Lung Function ¶	*n=26*	*n=28*	*n=41*	*n=27*	*n=28*	*n=38*	
FEV_1 (L)	3.0 (0.4)	3.0 (0.4)	3.1 (0.6)	3.0 (0.5)	3.2 (0.5)	3.0 (0.4)	0.706
FEV_1 % predicted	95.8 (11.7)	93.9 (12.6)	96.2 (14.4)	94.6 (13.7)	96.6 (11.0)	97.7 (11.0) n=37	0.861

FVC (L)	3.7 (0.4)	3.8 (0.5)	3.8 (0.7)	3.8 (0.6)	3.9 (0.5)	3.7 (0.5)	0.493
FVC %	103.9 (11.3)	103.1 (13.2)	102.2 (14.2)	104.1 (13.5)	104.8 (11.0)	103.6 (11.0) n=37	0.971
FEV_1:FVC	0.80 (0.06	0.79 (0.04)	0.82 (0.06)	0.79 (0.06)	0.81 (0.07)	0.82 (0.04)	0.171
Inflammation							
F_ENO (ppb) ǂ	12.3 [5.6, 21.8]	14.9 [7.4, 23.8] *n=29*	8.6 [5.9, 14.2]	11.5 [5.4, 16.4] *n=29*	13.3 [6.5, 23.1] *n=29*	10.8 [5.6, 15.6]	0.279
Treatment	*n=27*	*n=29*	*n=42*	*n=29*	*n=29*	*n=38*	
Beta-2 use past week (days/week) ǂ	1 [0, 3] *n=25*	1 [0, 3]	1 [0, 5]	1 [0, 3]	1 [0, 5] *n=28*	1 [0, 3]	0.979
ICS use *	11 (41%)	15 (52%)	19 (45%)	22 (76%)	19 (66%)	27 (71%)	**0.017**[1]
ICS dose (beclomethasone dipropionate	800 [400, 800]	800 [400, 1600]	800 [400, 1600]	400 [200, 800]	400 [400, 1600]	400 [200, 1600]	0.068

equivalent, ICS users), µg/day ‡							
ICS/LABA use ‖	3 (11%)	5 (17%)	9 (21%)	10 (34%)	10 (34%) *n=29*	19 (50%)	**0.006**[2]

*Chi-squared; §Poisson regression; ‡Kruskal-Wallis; ¶ ANCOVA/ANOVA; ‖Fisher; [§] Low=0, high=100; [¥] Good=0, Poor=10 [1]No significant subgroups [2]Control Non-Overweight vs Feno Obese (p<0.01), Control Overweight vs Feno Obese (p=0.03), Control Obese vs Feno Obese (p=0.04). Data are mean (sd), median (interquartile range) or n (%) as appropriate

AQLQ-M: Asthma Quality of Life Questionnaire – Marks

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505

506 Table 3: Baseline subject characteristics by intervention group and maternal gestational weight gain (GWG), in women with asthma followed during

507 pregnancy

	Control Group (C)		F_ENO Group (F)		
	GWG below/within recommendation (n=22)	GWG above recommendation (n=50)	GWG below/within recommendation (n=21)	GWG above recommendation (n=54)	p-Value
Maternal Age (years) ¶	30.3 (4.6)	27.3 (5.5)	29.8 (5.4)	28.0 (5.2)	0.077
Gestational age (weeks) at randomisation‡	20 [19, 21]	20 [18, 21]	20 [18, 21]	20 [19, 21]	0.340
BMI category at randomisation*					0.577
Non-overweight	5 (23%)	13 (27%)	6 (29%)	16 (30%)	
Overweight	5 (23%)	17 (35%)	3 (14%)	17 (31%)	
Obese	12 (55%)	19 (39%)	12 (57%)	21 (39%)	
Ex-Smoker ‖	9 (43%) *n=21*	16 (36%) *n=45*	5 (24%)	22 (42%) *n=53*	0.517

Pack Years ǂ	6.0 [2.0, 7.0] *n=9*	2.6 [0.4, 4.6] *n=16*	1.0 [1.0, 2.0] *n=5*	3.0 [1.0, 6.0] *n=22*	0.198
Parity ǂ	1 [0,3]	0 [0, 1]	1 [0, 2]	1 [0, 1]	**0.017**
Australian born‖	17 (81) *n=21*	46 (94) *n=49*	13 (76) *n=17*	52 (98) *n=53*	**0.008**[1]
Employed*	12 (57) *n=21*	39 (80) *n=49*	9 (53) *n=17*	31 (58) *n=53*	0.065
Atopy ‖	17 (85%) *n=20*	33 (72%) *n=46*	19 (90%)	38 (73%) *n=52*	0.269
Asthma History in past 2 years¶					
Hospitalisations	0.1 (0.5)	0 (0)	0 (0)	0 (0)	**0.015**[2]
Emergency department visits	0.3 (0.6)	0.1 (0.5)	0 (0)	0.2 (0.7)	0.363
OCS courses	0.7 (1.6)	0.3 (1.0)	0.2 (0.5)	0.3 (0.7)	0.259
Lung Function ¶					
FEV_1 % predicted	90.8 (16.8)	96.0 (14.9)	92.9 (10.3)	95.3 (14.8)	0.609

FVC % predicted	99.0 (16.1)	104.8 (14.3)	101.7 (12.5)	106.4 (15.7)	0.382
FEV_1:FVC	80.2 (6.5)	79.9 (7.5)	79.3 (6.3)	78.4 (8.1)	0.686
Airway inflammation					
F_ENO (ppb) ǂ	18.3 [10.9, 34.5]	14.6 [6.7, 31.5] *n=49*	15.9 [7.6, 52.8] *n=20*	20.5 [7.1, 29.0]	0.742
Asthma Medication					
Beta-2 agonist use (days/week) ǂ	2 [0, 7] *n=21*	0 [0, 7] *n=47*	0.5 [0, 4] *n=20*	1 [0, 5]	0.583
ICS use*	8 (36%)	14 (28%)	10 (48%)	13 (24%)	0.217
ICS dose (beclomethasone dipropionate equivalent) among users, µg/day ǂ	500 [400, 900]	800 [400, 1000]	900 [800, 1600]	800 [600, 1000]	0.281
Quality of Lifeǂ	*n=22*	*n=49*	*n=21*	*n=52*	
SF-12 Physical§	48.6 [34.9, 52.8]	49.3 [44.1]	49.7 [43.9, 54.6]	49.6 [44.7, 53.6]	0.721
SF-12 Mental§	52.8 [48.2, 57.9]	52.8 [43.3, 57.9]	55.0 [42.2, 59.3]	55.6 [47.7, 58.3]	0.668

AQLQ-total[¥]	1.0 [0.5, 2.0] *n=21*	0.9 [0.4, 1.6] *n=48*	0.9 [0.19, 1.1] *n=20*	0.9 [0.4, 1.6] *n=49*	0.688

*Chi-squared; ‡Kruskal-Wallis; ‖Fisher Exact; ¶ANOVA; [§] Low=0, high=100; [¥] Good=0, Poor=10; [1]FENO within vs FENO above (p=0.0300; [2] Control within vs Control above (p<0.05) and Control within vs FENO above (p<0.05)

Data are mean (sd), median [interquartile range] or n (%) as appropriate

508

509

510 Table 4: Efficacy outcomes according to intervention group and maternal gestational weight gain (GWG), in women with asthma followed during pregnancy

	Control Group (C)		F_ENO Group (F)		
	GWG below/within recommendation (n=22)	GWG above recommendation (n=50)	GWG below/within recommendation (n=21)	GWG above recommendation (n=54)	p-value
Experienced ≥ 1 exacerbation during pregnancy *	12 (55%)	21 (42%)	5 (24%)	15 (28%)	0.072
Exacerbation types §					
Unscheduled Doctor visits	0.82 (1.01)	0.56 (0.76)	0.19 (0.40)	0.33 (0.58)	**0.003**[1]
OCS use	0.27 (0.88)	0.16 (0.42)	0.05 (0.22)	0.09 (0.29)	0.056
Hospitalisation	0.05 (0.21)	0.02 (0.14)	0	0	0.184
Emergency Department presentation	0.05 (0.21)	0.02 (0.4)	0.05 (0.22)	0.02 (0.14)	0.674

Quality of Life ¶	*n=22*	*n=47*	*n=20*	*n=51*	
SF12-Physical[§]	45.9 [40.8, 50.9]	47.7 [37.3, 51.7]	43.4 [37.0, 51.8]	47.8 [40.4, 52.5]	0.729
SF12-Mental[§]	56.3 [53.5, 57.8]	53.9 [42.8, 57.5]	57.2 [54.0, 59.2]	55.8 [48.5, 59.3]	0.953
AQLQM-Total[¥]	0.5 [0.3, 1.0] *n=22*	0.9 [0.5, 1.6] *n=46*	0.9 [0.4, 1.3]	0.9 [0.4, 1.4] *n=49*	0.409
Lung Function ¶	*n=21*			*n=53*	
FEV_1 (L)	2.9 (0.6)	3.1 (0.4)	2.9 (0.4)	3.1 (0.5)	0.138
FEV_1 %	92.0 (17.6)	96.8 (12.4)	92.9 (9.5)	97.2 (12.5) *n=52*	0.298
FVC (L)	3.6 (0.7)	3.9 (0.5)	3.6 (0.5)	3.8 (0.5)	0.082
FVC %	99.0 (17.2)	104.6 (12.3)	100.8 (9.8)	105.2 (12.3) *n=52*	0.184
FEV_1:FVC	80.7 (5.9)	80.7 (5.9)	80.3 (5.4)	80.5 (5.6)	0.996
Airway Inflammation					

F_ENO (ppb) ‡	10.8 [6.6, 22.2]	11.3 [6.7, 17.5]	11.0 [6.0, 15.7]	12.2 [6.0, 19.3]	0.949
Treatment					
Beta-2 use past week (no. days) ‡	0 [0, 2] *n=21*	1 [0,3]	0 [0, 2]	1 [0,3] *n=53*	0.374
ICS use *	12 (55%)	21 (42%)	16 (76%)	37 (69%)	**0.014**[2]
ICS dose (beclomethasone dipropionate equivalent, all women) µg/day ‡	400 [0, 800]	0 [0, 400]	400 [200, 800]	200 [0, 800]	0.128
ICS dose (beclomethasone dipropionate equivalent, ICS users) µg/day ‡	800 [600, 1200]	800 [400, 800]	800 [300, 1200]	400 [200, 1600]	0.274
ICS/LABA use ‖	4 (18%)	8 (16%)	7 (33%)	22 (41%)	**0.025**[3]
Symptom-free days ‡	7 [5, 7]	5 [1, 7]	7 [5, 7]	6 [4, 7]	0.080

*Chi-squared; §Poisson regression; ‡Kruskal-Wallis; ¶ ANCOVA/ANOVA; ‖Fisher; [§] Low=0, high=100; [¥] Good=0, Poor=10; [1] Control within vs Control above (p<0.01) and Control within vs FENO above (p<0.01); [2] Control above vs FENO within (p<0.05) and Control above vs FENO above (p<0.05); [3] Clinical above vs FENO above (p<0.05)

Data are mean (sd), median [interquartile range] or n (%) as appropriate

AQLQ-M: Asthma Quality of Life Questionnaire - Marks

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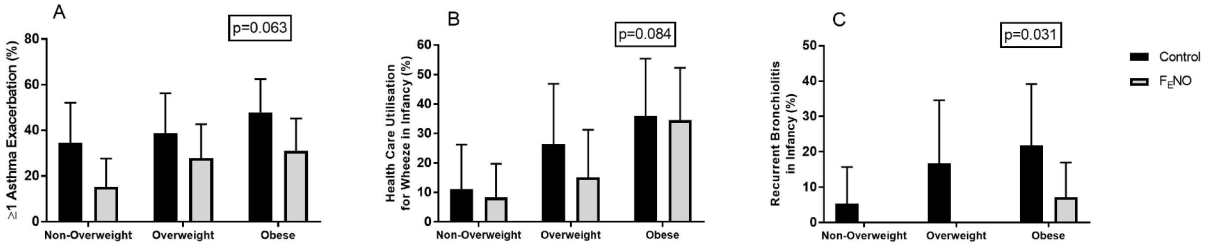
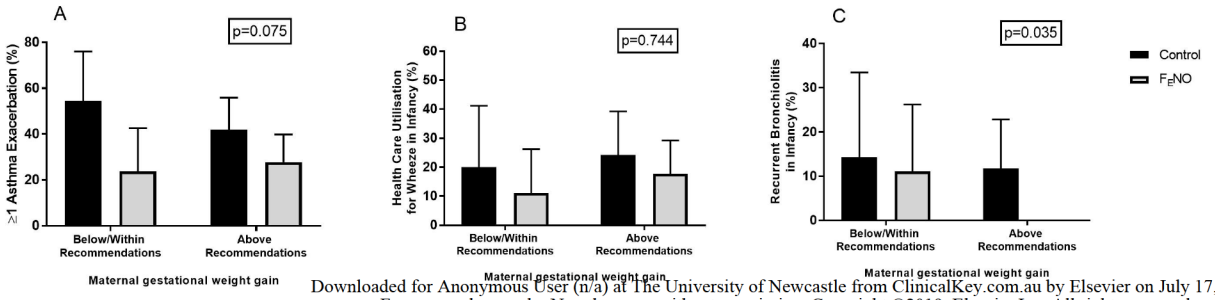
514 **FIGURE LEGENDS**

515 **Figure 1:** The proportion of women with asthma exacerbations (A), and children with health care
516 utilisation for wheeze in infancy (hospitalisation; emergency department visits; unscheduled GP
517 visits; oral corticosteroid use) (B) or recurrent bronchiolitis (more than once) in infancy (C) born to
518 mothers with non-overweight, overweight and obese BMIs who were managed throughout
519 pregnancy according to either a F_ENO-based or a symptoms-based (control) algorithm.

520 **Figure 2:** The proportion of women with asthma exacerbations (A), and children with health care
521 utilisation for wheeze in infancy (hospitalisation; emergency department visits; unscheduled GP
522 visits; oral corticosteroid use) (B) or recurrent bronchiolitis (more than once) in infancy (C) born to
523 mothers within and exceeding recommended gestational weight gain limits who were managed
524 throughout pregnancy according to either a F_ENO-based or a symptoms-based (control) algorithm.

525





Online Repository Table 1

Table E1. Perinatal outcomes according to intervention group and maternal BMI, in women with asthma followed during pregnancy							
	Control group			F_ENO Group			
	Non-overweight (n=29)	Overweight (n=33)	Obese (n=44)	Non-overweight (n=31)	Overweight (n=33)	Obese (n=41)	p-value
Male Infant *	18 (62.0%)	11 (33.3%)	22 (50%)	13 (41.9%)	16 (48.5%)	16 (39.0%)	0.354
Gestational age at birth (weeks) ‡	39.6 [38.4, 40.7]	39.9 [37.9, 40.3]	39.6 [38.6, 40.4]	39.6 [38.6, 40.9]	40.3 [38.9, 41.1]	39.6 [39.0, 40.3]	0.573
Birth weight (grams) ‡	3350 [2960, 3520]	3475 [2930, 3660] *n=32*	3535 [3280, 3980] *n=43*	3360 [3040, 3800]	3520 [3020, 3743] *n=32*	3770 [3260, 4010]	**0.029 (Control non-overweight vs F_ENO**

							Obese)
Birth length (cm) ‡	50.0 [49.0, 52.0] *n=24*	51.5 [49.5, 53.0] *n=25*	52.0 [50.0, 53.0] *n=41*	51.0 [49.5, 53.0] *n=26*	52.0 [51.0, 54.0] *n=31*	51.0 [50.0, 53.5] *n=37*	0.176
Birth Head circumference (cm) ‡	35.0 [33.8, 35.5] *n=28*	34.0 [33.0, 35.0] *n=31*	35.0 [34.0, 36.0] *n=43*	34.6 [34.0, 35.0] *n=30*	34.0 [33.0, 35.5] *n=32*	35.2 [34.0, 36.0]	0.097
Labour type	*n=28*	*n=31*	*n=44*	*n=31*	*n=33*	*n=40*	
Spontaneous *	13 (46%)	18 (58%)	21 (48%)	22 (71%)	22 (67%)	19 (48%)	0.168
Induced *	11 (39%)	9 (29%)	13 (30%)	7 (23%)	7 (21%)	13 (33%)	0.657
No labour ‖	3 (11%)	3 (10%)	8 (18%)	1 (3%)	4 (12%)	7 (18%)	0.416
Spontaneous and Augmented ‖	1 (4%)	1 (3%)	1 (2%)	1 (3%)	0 (0%)	1 (3%)	0.948
Delivery type ‖							
Vaginal	19 (68%)	21 (68%)	30 (68%)	25 (81%)	28 (85%)	25 (63%)	0.258
Forceps	2 (7%)	1 (3%)	4 (9%)	4 (13%)	3 (9%)	2 (5%)	0.767

Vacuum	2 (7%)	2 (6%)	0 (0%)	2 (6%)	1 (3%)	0 (0%)	0.160
C-section elective	3 (11%)	2 (6%)	8 (18%)	2 (6%)	2 (6%)	8 (20%)	0.271
C-section non-elective	4 (14%)	6 (19%)	4 (9%)	2 (6%)	3 (9%)	6 (15%)	0.635
Maternal Complications ‖							
Pre-eclampsia	1 (4%)	1 (3%)	3 (7%)	2 (6%)	0 (0%)	1 (3%)	0.727
Gestational Diabetes	1 (4%)	4 (13%)	6 (14%)	0 (0%)	1 (3%)	7 (18%)	**0.046**
Hypertension	2 (7%)	3 (10%)	6 (14%)	0 (0%)	0 (0%)	7 (18%)	**0.022**
Postpartum Hemorrhage	3 (11%)	0 (0%)	1 (2%)	2 (6%)	1 (3%)	2 (5%)	0.415
Premature rupture of membranes	3 (11%)	3 (10%)	2 (5%)	8 (26%)	2 (6%)	2 (5%)	0.065
Multiple pregnancy	1 (4%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0.546
Infant Complications ‖							
Stillbirth	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0.726

Preterm delivery	2 (7%)	5 (15%)	2 (5%)	1 (3%)	2 (6%)	3 (7%)	0.590
Intrauterine Growth Restriction	3 (10%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	**0.004**
Jaundice	1 (3%)	1 (3%)	1 (2%)	1 (3%)	1 (3%)	1 (2%)	1.000
Neonatal intensive care unit (NICU) admission	6 (21)	8 (24)	4 (9)	3 (10)	1 (3)	4 (10)	0.094
*Chi-squared; ‡Kruskal-Wallis; ‖Fisher Exact Data are mean (sd), median [interquartile range] or n (%) as appropriate							

Online Repository Table 2

Table E2. Perinatal outcomes according to intervention group and maternal gestational weight gain, in women with asthma followed during pregnancy					
	Control group		F_ENO group		
	GWG below/within recommendation (n=21)	GWG above recommendation (n=50)	GWG below/within recommendation (n=20)	GWG above recommendation (n=53)	p-value
Male infant *	8 (38%)	26 (52%)	6 (30%)	23 (43%)	0.317
Gestational age at birth (weeks) ǂ	39.0 [38.7, 40.0]	39.7 [38.4, 40.3]	39.6 [38.6, 40.6]	40.0 [39.0, 41.0]	0.157
Birth weight (grams) ǂ	3508 [3220, 3805] *n=20*	3430 [3000, 3710] *n=48*	3525 [3030, 3855]	3520 [3160, 3920]	0.615
Birth length (cm) ǂ	51.0 [50.0, 53.5] *n=20*	51.5 [49.0, 53.0] *n=40*	50.5 [49.0, 52.0] *n=18*	51.5 [50.0, 54.0] *n=49*	0.246
Birth Head Circumference (cm) ǂ	35.0 [34.0, 36.0]	34.5 [33.0, 35.5]	34.6 [34.0, 35.5]	35.0 [34.0, 36.0]	0.479

	n=20	*n=47*			
Labour type ‖					
Spontaneous	8 (38%)	27 (55%)	9 (45%)	35 (66%)	0.119
Induced	5 (24%)	15 (31%)	9 (45%)	10 (19%)	0.145
No labour	6 (29%)	6 (12%)	2 (10%)	6 (11%)	0.267
Spontaneous and Augmented	2 (10%)	1 (2%)	0 (0%)	2 (4%)	0.407
Delivery type ‖					
Vaginal	10 (48%)	35 (71%)	13 (65%)	40 (75%)	0.125
Forceps	0 (0%)	4 (8%)	1 (5%)	5 (9%)	0.669
Vacuum	1 (5%)	2 (4%)	1 (5%)	0 (0%)	0.324
C-section elective	5 (24%)	6 (12%)	2 (10%)	6 (11%)	0.504
C-section non-elective	6 (29%)	6 (12%)	4 (20%)	6 (11%)	0.235

Maternal Complications ‖					
Pre-eclampsia	2 (10%)	1 (2%)	0 (0%)	2 (4%)	0.407
Gestational Diabetes	2 (10%)	5 (10%)	2 (10%)	3 (6%)	0.805
Hypertension	4 (19%)	5 (10%)	2 (10%)	4 (8%)	0.527
Postpartum Hemorrhage	2 (10%)	1 (2%)	1 (5%)	2 (4%)	0.434
Premature rupture of membranes	1 (5%)	5 (10%)	1 (5%)	6 (11%)	0.863
Multiple pregnancy	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0.629
Infant Complications ‖					
Stillbirth	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1.000
Preterm delivery	1 (5%)	5 (10%)	1 (5%)	1 (2%)	0.301
IUGR	0 (0%)	2 (4%)	1 (5%)	0 (0%)	0.334
Jaundice	1 (5%)	2 (4%)	1 (5%)	2 (4%)	1.000

Neonatal intensive care unit (NICU) admission	2 (10%)	9 (18%)	1 (5%)	3 (6%)	0.208

*Chi-squared; ǂKruskal-Wallis; ‖Fisher Exact

Data are mean (sd), median (interquartile range) or n (%) as appropriate