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Longitudinal analysis of lung function in pregnant women with and without asthma.

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Online Repository Text

Methods

Data were collected from four prospective cohorts of pregnant women with asthma, conducted from 2004 to 2017: *Phase II Asthma in Pregnancy Study (Phase II) (2004-06)*,²⁶ the *Managing Asthma in Pregnancy (MAP) Study*²⁷ and the concurrent *Viral Exacerbations in Pregnancy Study (VEAP) (2007-10)*,²⁸ and the ongoing *Breathing for Life Trial (BLT) (2013-17)*.²⁹ The majority of participants were recruited via the antenatal clinic at the John Hunter Hospital (NSW Australia); a portion from MAP were recruited at Maitland Hospital (NSW Australia) and a portion from BLT recruited from five additional sites in Brisbane (QLD Australia), Canberra (ACT Australia) and Sydney (NSW Australia).

Inclusion/exclusion criteria

Women aged ≥ 18 years, with physician-diagnosed asthma, plus asthma symptoms or asthma medication use in the past year, were enrolled between 12 and 22 weeks gestation and followed regularly throughout their pregnancy until delivery. Women were excluded if they had a chronic lung disease other than asthma, were unable to perform spirometry, or had drug/alcohol dependence. Additional exclusion criteria for *MAP* were more than three courses of oral corticosteroids (OCS) in the past year, hospital admission for an asthma exacerbation in the past three months, or regular use of prednisolone/theophylline.²⁷ Women were excluded from participation in *BLT* if they had used OCS consecutively for 14 days or more in the past three months.²⁹

Women without respiratory disease, between 12-22 weeks gestation, served as healthy controls. Women were excluded as a control if they had a history of asthma, concomitant chronic illness, and drug or alcohol dependence, were unable to attend study visits or were unable to perform spirometry.

Results

Sensitivity analysis – gestational weight gain

For FVC% predicted, the baseline value increased for non-asthmatics (99.9% vs. 96.5% in main analysis) and asthmatics (97.2% vs. 93.9% in main analysis) when weight at each visit was included in the model (*Table E1, Online Repository Tables*). The decline in FVC% over gestation marginally decreased to -2.4% (-2.8% in main analysis) and the asthma*gestational age interaction term in the FVC% predicted model increased but remained non-significant (-0.11 95%CI -0.005-0.23, $p=0.06$). For FEV₁% predicted, the improvement in lung function over 40 weeks gestation doubled in asthmatics (1.6% vs 0.8% in main analysis) when gestational weight gain was included as a confounder, and for non-asthmatics the decline increased by 1.6% (-7.2% vs. -5.6% in main analysis). Also, by including gestational weight gain, obesity had a significant negative effect on FEV₁% predicted (-2.7%, $p=0.045$). For FEV₁:FVC%, the effect of obesity was no longer significant when including gestational weight gain as a confounder (1.22%, $p=0.079$).

Sensitivity analysis - Asthma control

There was a slight increase in baseline FVC (controlled asthma 97.2% and uncontrolled asthma 95.4%, vs. 93.9% in main analysis; and controls 99.4% vs. 96.5% in main analysis) when asthma control was included in the model (*Table E2, Online Repository Tables*). For baseline FEV₁ and FEV₁/FVC, there was a slight decrease for uncontrolled asthma (85.0% and 83.9%, respectively) but slight increase for controlled asthma (88.0% and 85.2%, respectively) vs. the main analysis (FEV₁ 86.8%, FEV₁/FVC 84.9%). The decline in FVC% over gestation marginally increased to -3.2% vs. -2.8% in the main analysis, with no significant interaction term for asthma (controlled or uncontrolled)*gestational age. Also, by including asthma control, the negative effect of obesity was slightly reduced (3.0% vs. 3.1% in main analysis). The decline in FEV₁ remained unchanged for non-asthmatics, when asthma control was included in the model; however, the improvement in FEV₁ increased in uncontrolled asthma (1.6% vs. 0.8% in main analysis) whilst FEV₁ did not change over gestation for controlled asthma (0%). For FEV₁/FVC, the improvement reduced to 1.6% over gestation for controlled asthma and increased to 3.6% for uncontrolled asthma (compared to 2.4% in main analysis). However, there were no statistically significant difference in lung function trajectories between controlled, and uncontrolled asthma.

Figure Legend

Figure E1: Changes in forced vital capacity (FVC)% predicted, forced expiratory volume in 1 second (FEV1)% predicted and FEV1:FVC% during pregnancy among women without asthma (dashed) and women with asthma (solid line). Figures depict scatterplot of individual values and regression lines based on the coefficients of the variables 'asthma', 'gestational age' and, if significant, the interaction term of 'asthma*gestational age' found in Table II.

Table E1: Mixed model regression coefficients for FVC% predicted, FEV₁% predicted and FEV₁:FVC% across gestation in women with and without asthma including gestational weight gain as confounder

	FVC% predicted (n=490, obs=1731)		FEV ₁ % predicted (n=490, obs=1749)		FEV ₁ :FVC (n=490, obs=1731)	
Variable	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	99.87 [94.54, 105.21]	<0.001	96.08 [90.23, 101.94]	<0.001	89.38 [86.29, 92.46]	<0.001
Asthma	-2.66 [-4.49, -0.83]	0.004	-10.08 [-13.22, -6.94]	<0.001	-4.17 [-6.02, -2.33]	<0.001
Gestational age (weeks)	-0.06 [-0.11, -0.01]	0.015	-0.18 [-0.28, -0.07]	<0.001	-0.01 [-0.08, 0.05]	0.649
Asthma*Gestational age†	-	-	0.22 [0.10, 0.33]	<0.001	0.08 [0.02, 0.15]	0.014
Maternal age at study entry	0.03 [-0.11, 0.18]	0.640	0.17 [0.02, 0.32]	0.027	-0.18 [-0.25, -0.10]	<0.001
<i>Smoking status at study entry</i>						
Never Smoker	Reference		Reference		Reference	
Ex-Smoker	-0.29 [-2.68, 2.10]	0.812	-1.74 [-4.20, 0.72]	0.165	-1.18 [-2.44, 0.09]	0.068
Current Smoker	1.51 [-0.28, 3.30]	0.098	0.70 [-1.14, 2.54]	0.456	-0.08 [-1.67, 0.15]	0.102
ECO (ppb)	-0.04 [-0.12, 0.05]	0.392	-0.13 [-0.22, -0.04]	0.006	-0.10 [-0.15, -0.04]	<0.001
<i>BMI category at study entry</i>						
Non-Overweight*	Reference		Reference		Reference	
Overweight	-0.59 [-2.65, 1.46]	0.572	-0.65 [-2.76, 1.47]	0.550	0.19 [-0.87, 1.25]	0.727
Obese	-3.15 [-5.71, -0.59]	0.016	-2.68 [-5.30, -0.06]	0.045	1.22 [-0.14, 2.57]	0.079
Weight (kg)	0.002 [-0.04, 0.05]	0.939	0.02 [-0.03, 0.07]	0.357	-0.003 [-0.03, 0.02]	0.831

†The interaction term for gestational age and asthma was not significant for FVC% predicted (0.11, 95%CI:-0.005, 0.23, p=0.060), the results from the FVC model without interaction term are presented.

*Includes underweight (n=14; range 16.64 – 18.5kg/m²) and healthy weight. BMI, body mass index; ECO, exhaled carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table E2: Mixed model regression coefficients for FVC% predicted, FEV₁% predicted and FEV₁:FVC% across gestation in women with controlled asthma, uncontrolled asthma and no asthma (n=921).

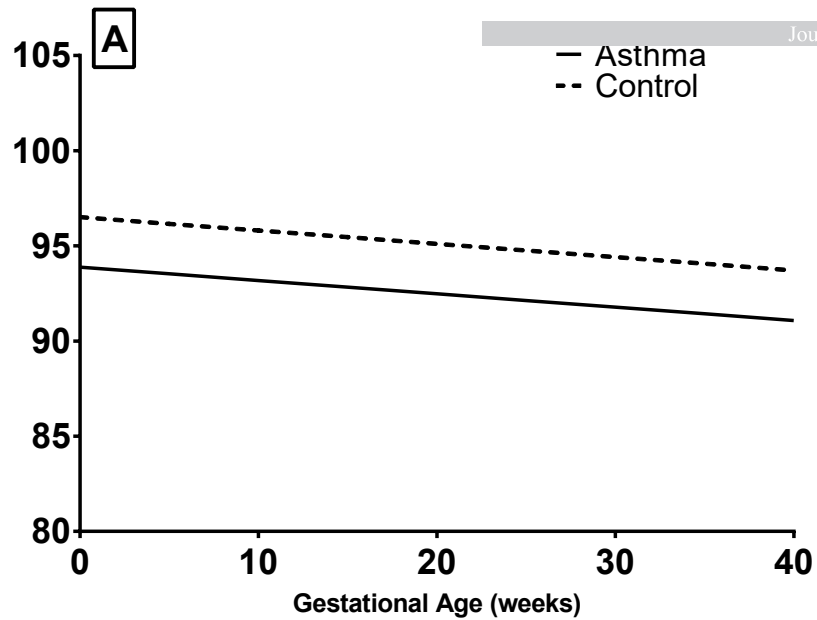
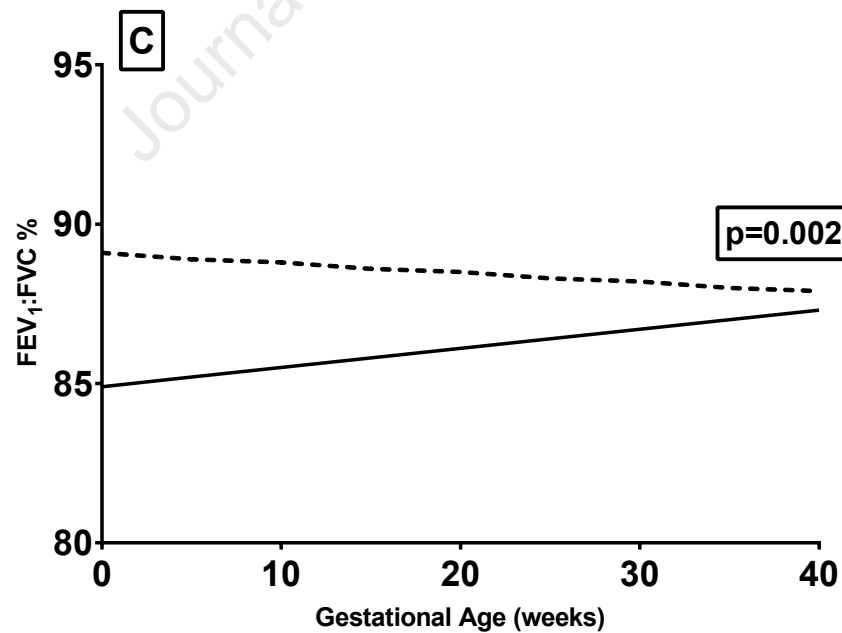
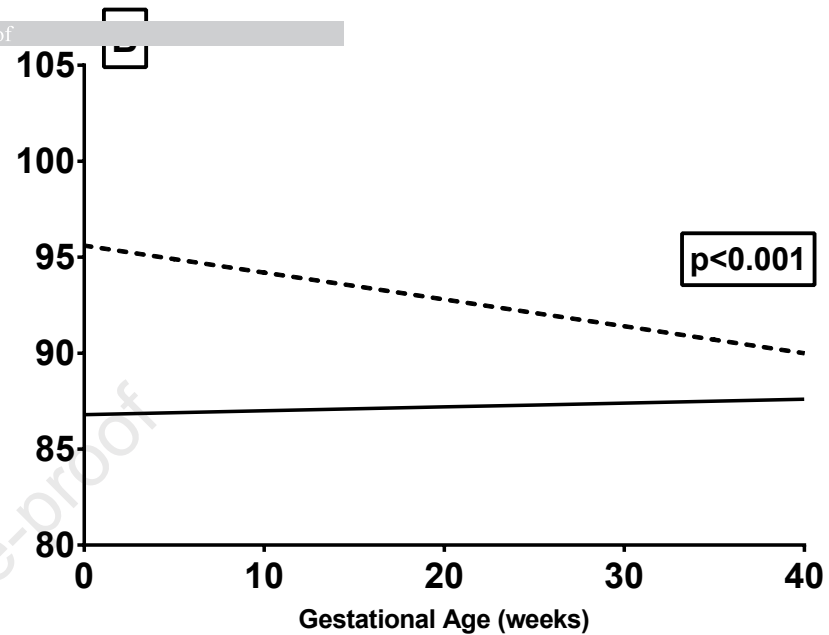
	FVC% predicted (3226 observations)		FEV ₁ % predicted (3244 observations)		FEV ₁ :FVC (3226 observations)	
Variable	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	99.42 [94.83, 104.01]	<0.0001	95.67 [90.70, 100.63]	<0.0001	89.06 [86.55, 91.58]	<0.0001
<i>Asthma status</i>						
No asthma	Reference		Reference		Reference	
Controlled (ACQ6 <1.5)	-2.16 [-3.95, -0.37]	0.018	-7.72 [-10.50, -4.94]	<0.0001	-3.83 [-5.55, -2.11]	<0.0001
Uncontrolled (ACQ6 ≥1.5)	-3.99 [-5.83, -2.15]	<0.0001	-10.64 [-13.72, -7.56]	<0.0001	-5.21 [-7.17, -3.25]	<0.0001
Gestational age (weeks)	-0.08 [-0.11, -0.05]	<0.0001	-0.14 [-0.22, -0.06]	0.0004	-0.03 [-0.08, 0.02]	0.299
<i>Asthma*Gestational age†</i>						
No asthma	Reference		Reference		Reference	
Controlled (ACQ6 <1.5)	-	-	0.14 [0.05, 0.22][#]	0.002	0.07 [0.02, 0.13][#]	0.009
Uncontrolled (ACQ6 ≥1.5)	-	-	0.18 [0.08, 0.28]	0.001	0.12 [0.05, 0.19]	0.0004
Maternal age at study entry	0.06 [-0.08, 0.20]	0.377	0.19 [0.04, 0.33]	0.010	-0.17 [-0.24, -0.10]	<0.0001
<i>Smoking status at study entry</i>						
Never Smoker	Reference		Reference		Reference	
Ex-Smoker	-0.90 [-3.19, 1.38]	0.438	-2.42 [-4.73, -0.11]	0.040	-1.32 [-2.46, -0.18]	0.024
Current Smoker	1.52 [-0.23, 3.26]	0.089	0.71 [-1.08, 2.50]	0.436	-0.74 [-1.59, 0.10]	0.086
ECO (ppb)	0.05 [-0.02, 0.13]	0.161	-0.04 [-0.11, 0.03]	0.259	-0.09 [-0.14, -0.05]	<0.0001
<i>BMI category at study entry</i>						
Non-Overweight [‡]	Reference		Reference		Reference	
Overweight	-0.98 [-2.89, 0.93]	0.316	-0.70 [-2.66, 1.26]	0.484	0.25 [-0.68, 1.18]	0.593
Obese	-3.00 [-4.84, -1.17]	0.001	-1.45 [-3.33, 0.42]	0.129	1.60 [0.72, 2.49]	0.0004

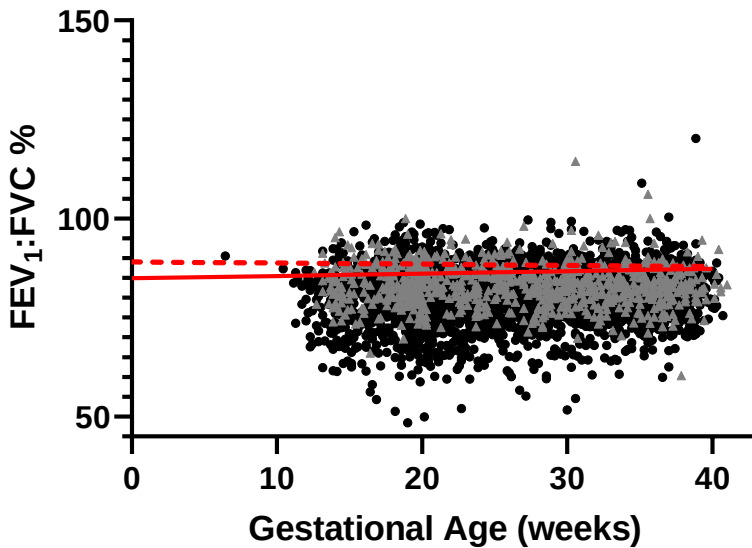
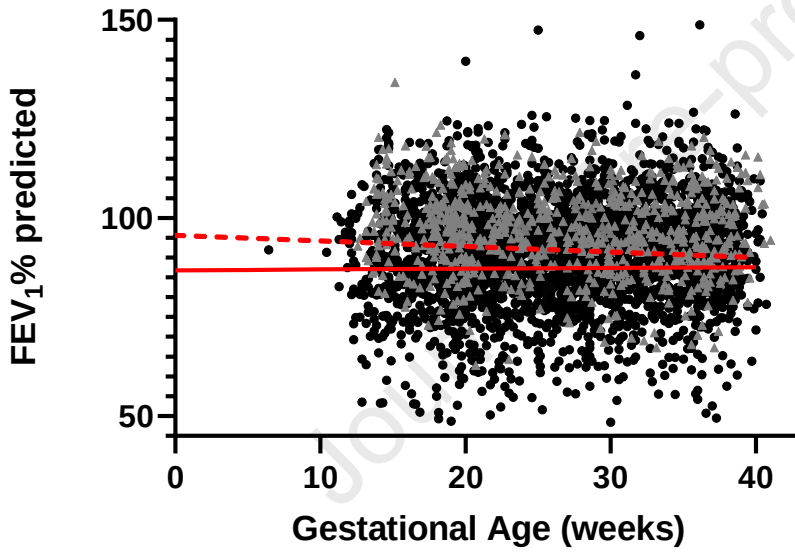
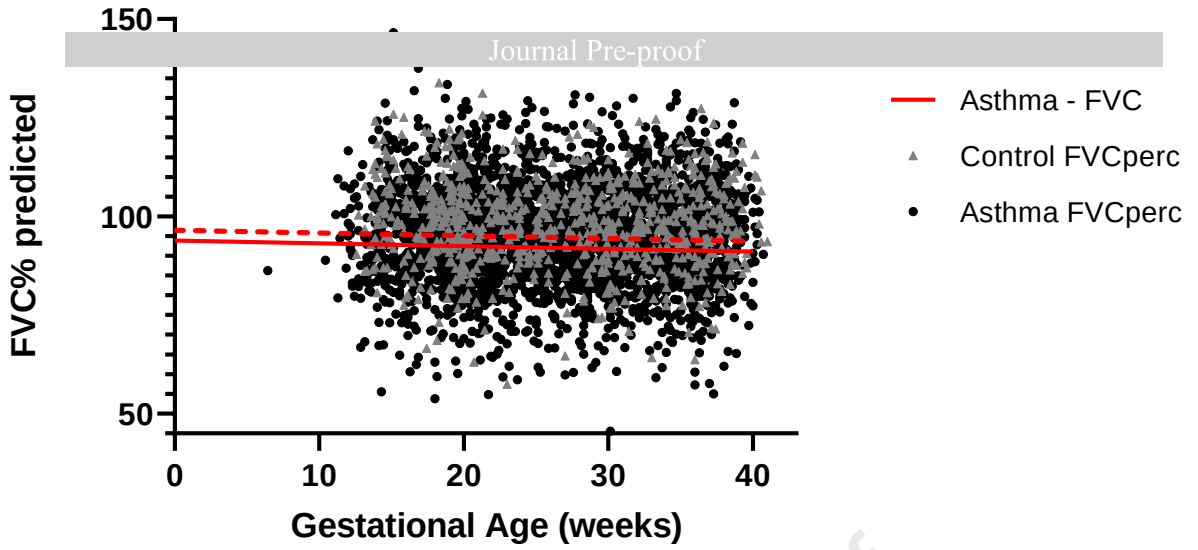
†The interaction term for gestational age and asthma was not significant for FVC% predicted: the results from the FVC model without interaction term are presented.

‡Includes underweight (n=14; range 16.64 – 18.5kg/m²) and healthy weight. ACQ, Asthma Control Questionnaire; BMI, body mass index; ECO, exhaled carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

[#]Not statistically significantly different to uncontrolled asthma.

FVC% predicted

FEV₁% predicted



1 **Title Page**

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4 **Longitudinal analysis of lung function in pregnant women with and without asthma.**

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25 PGG reports personal fees from AstraZeneca, GlaxoSmithKline, Novartis, and grants from
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Abstract

Background: Spirometry is commonly used to assess and monitor lung function. It may also be a useful tool to monitor maternal health during pregnancy. However, large studies examining lung function across gestation are limited. Secondly, whether spirometry values follow the same pattern during pregnancy in women with and without asthma is unknown.

Objective: This study investigates the effect of advancing gestation, and its interaction with asthma, on lung function, in a large well-defined cohort of pregnant women.

Methods: Data were obtained from prospective cohorts involving women with (n=770) and without (n=259) asthma (2004-2017), recruited between 12-22 weeks gestation. Lung function (forced vital capacity, FVC; forced expiratory volume in one second, FEV₁; FEV₁:FVC%) was assessed periodically during pregnancy using spirometry. Multilevel mixed-effect regression models were used to assess changes in lung function over gestation.

Results: Asthma had a significant effect on baseline lung function (FEV₁% -9%, FVC% -3%, FEV₁:FVC% -4%). FVC% decreased with advancing gestation (-0.07% /week [95% confidence interval, CI: -0.10, -0.04]), as did FEV₁%, but only among those without asthma (non-asthmatics: -0.14%/week [95%CI: -0.22, -0.06%]; compared to asthmatics: 0.02%/week [95%CI: -0.01, 0.06]). FEV₁:FVC% remained relatively stable for non-asthmatics (0.03%/week [95%CI: -0.08, 0.02]), but increased for asthmatics (0.06%/week [95%CI: 0.04, 0.16]).

Conclusion: Data suggest that advancing gestation negatively affects FVC% and FEV₁%. This is consistent with extrapulmonary restriction from advancing pregnancy. Yet, the presence of asthma altered the trajectories of FEV₁% and FEV₁:FVC%. Optimal asthma management during pregnancy might have opposed the negative effects of gestation on lung function.

Australian and New Zealand Clinical Trials Registry: ACTRN12607000561482 & ACTRN12613000202763.

91 Highlights box:

92 1. What is already known about this topic?

93 Spirometry is a useful clinical asthma management tool; yet its utility in pregnancy is
94 unclear.

95

96 2. What does this article add to our knowledge?

97 Pregnancy and mild asthma have limited impact on spirometry.

98

99 3. How does this study impact current management guidelines?

100 Spirometry can be used in clinical assessment and education during pregnancy.

101

102 Key Words:

103 Pulmonary function tests; Pregnancy; Asthma; Gestation; Spirometry; cohort studies

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118 Abbreviations list:

- 119 ACQ: asthma control questionnaire
- 120 BMI: body mass index
- 121 ECO: exhaled carbon monoxide
- 122 FEV₁: forced expiratory volume in one second
- 123 FVC: forced vital capacity
- 124 GWG: gestational weight gain
- 125 ICS: inhaled corticosteroids
- 126 LABA: long-acting beta-agonists
- 127 OCS: oral corticosteroids
- 128 SABA: short-acting beta-agonists

129 Introduction

130 Lung function has been associated with multiple disease outcomes,¹⁻⁶ in addition to being a
131 key component in respiratory disease diagnosis and monitoring.⁷ Spirometry is the most
132 commonly used technique to assess lung function, with values compared to a relevant
133 reference population to aid interpretation.⁸ Several reference values exist, which account for
134 age-, gender- and ethnicity- related differences, including the third National Health and
135 Nutrition Examination Survey (NHANESIII)⁹ and the Global Lung Index 2012 (GLI12).¹⁰
136 Existing reference datasets are based on healthy non-pregnant populations; thus, whether
137 advancing gestation influences spirometric values, and therefore their interpretation in the
138 context of pregnancy, is unclear.

139 Lung function may affect perinatal outcomes, with forced expiratory volume in one second
140 (FEV₁) in women with asthma negatively associated with gestational hypertension, preterm
141 birth, and fetal growth.^{11,12} Notably, perinatal outcomes were not associated with other
142 measures of asthma symptom control during pregnancy (i.e. symptoms, activity limitation,
143 sleep loss) in this study;¹¹ although an earlier study has suggested that daily asthma
144 symptoms are related to risk of intrauterine growth restriction.¹³ This highlights the
145 significance of monitoring lung function during pregnancy, particularly in women with
146 asthma, who are at increased risk of adverse perinatal outcomes and in whom the course of
147 asthma is unpredictable during pregnancy.¹⁴⁻¹⁷

148 Existing lung function reference values derived from cross-sectional studies of healthy non-
149 pregnant individuals do not elucidate whether spirometry indices change during pregnancy;
150 hence, research examining the impact of advancing gestation on lung function, and therefore
151 the utility of spirometry and its interpretation, during pregnancy is needed. Hormonal and
152 physiological adaptations that occur during pregnancy may affect maternal lung function,
153 notably the lower chest wall circumference and subcostal angle of the rib cage increase and
154 the diaphragm elevates.¹⁸ However, a lack of adequately-designed large-scale prospective
155 studies of spirometry in pregnancy, limits our understanding regarding the pattern of lung
156 function during pregnancy. Previous studies are limited by sample size, study design/
157 methodological flaws, including statistical methods, number of data collection points and
158 methods, and/or lack of inclusion of both asthmatics and controls.¹⁹⁻²⁷ Hence, longitudinal
159 changes in lung function during pregnancy are yet to be examined in a large cohort of
160 women, with and without asthma.

This study aimed to examine the effect of advancing gestation, and its interaction with asthma, on FEV₁, forced vital capacity (FVC) and FEV₁:FVC% in pregnancy.

Methods

Population

Data were collected from four prospective cohorts of pregnant women, recruited between 12-22 weeks gestation and followed until delivery, via the antenatal clinics of several Australian hospitals (2004-2017).²⁸⁻³¹ As previously described, women without respiratory disease served as healthy controls; women with asthma were defined as having a physician-diagnosis plus recent symptoms/ medication use. Ethics approval was obtained for all studies and written informed consent obtained prior to participation (see *Online Repository Text*).

Measurements

Baseline weight and height were measured and body mass index (BMI) calculated (kg/m²) and categorized as non-overweight (<25.0 kg/m²), overweight (25.0-29.9 kg/m²) and obese (≥30.0 kg/m²). Gestational weight gain (GWG) was calculated in a subset with repeat weight measurements. Current medication use (self-report), smoking status and tobacco exposure (self-report and exhaled carbon monoxide [ECO], measured with piCO Smokelyzer Breath CO Monitor (Bedford, UK)), and Asthma Control Questionnaire (ACQ) score³² were recorded at recruitment and throughout the study period; asthma was classed as 'controlled' (ACQ6 score <1.5) or 'uncontrolled' (ACQ6 score ≥1.5).³³ Self-reported medication adherence was recorded at each visit, as the % doses missed in the previous week.

Lung function was assessed using spirometry (*Phase II*: Spirotac IV, Vitalograph, Buckingham UK; MAP/VEAP and BLT: EasyOne Spirometer, NicheMedical, North Sydney Australia). FVC and FEV₁ were measured by a trained respiratory research nurse or research midwife according to ATS/ERS guidelines, expressed as a percentage of predicted values (NHANESIII⁹), and FEV₁:FVC ratio (%) calculated.

Statistical Analysis

Analysis was performed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). Data are presented as mean ± SD or n (%). Multilevel mixed-effect regression models were used to analyze lung function changes (FVC%, FEV₁%, FEV₁:FVC%), with gestational age (fixed effect) used as the time scale³⁴ and an interaction term for gestational age*asthma to determine whether the trend differed by asthma status. Random participant-level intercepts

accounted for repeated measures on participants and random slopes were included to model heterogeneity in trends; random intercepts and slopes were allowed to be correlated. Restricted maximum likelihood was used for parameter estimation. Models were adjusted for potential confounders (maternal age, smoking status, ECO measurement and BMI category at baseline), and their interaction with asthma status; thus, participants with non-missing confounders comprised the analysis sample. Potential confounders were considered for removal in an augmented backward selection approach, if they did not improve the model fit compared to the full model with all confounders (measured by a decrease in Akaike Information Criterion or non-significant Wald p-value), and if their removal did not alter the regression coefficient for the trend (the “change in estimate” approach). Model assumptions were assessed using histograms and residual plots. Additional (sensitivity) analyses were performed to assess the influence of each GWG and asthma control status. Significance was accepted when $p < 0.05$.

Results

A total of 1029, predominately Caucasian (89% [n=917]), women were included, of whom 259 (25%) were healthy controls and 770 (75%) had asthma (**Table I**). The mean number of visits during pregnancy was 4.1 ± 1.9 , with recruitment at a mean 18.1 ± 3.7 weeks gestation. Most were overweight (31% [n=317]) or obese (35% [n=361]) at baseline; 29% [n=288] were ex-smokers and 16% [n=163] current smokers.

At baseline, women with asthma had a median ACQ6 of 1.0 (0.33, 1.83), with 37% [n=282] classed as 'uncontrolled'³³ and 37% [n=283] taking ICS at a median dose of 500µg (400, 1000). Of the 283 women using ICS medication, most (69% [n=196]) were using an ICS/LABA combination. The majority of women with asthma (95% [n=730]) used SABA medication.

The regression analysis datasets for the outcome variables FVC%, FEV₁% and FEV₁:FVC% included 921 participants (90%) with ≥ 1 outcome assessment and non-missing maternal age, smoking status, ECO measurement and BMI category at baseline (**Table II**). **Figure 1** depicts lung function trajectories by asthma status (see also *Online Repository Figure E1*).

Women with, versus without, asthma had 2.7% lower FVC% at baseline ($p=0.004$). The interaction term indicated that the difference in FVC% trends were not statistically significant by asthma status (0.05% per week, 95%CI: -0.03 to 0.14, $p=0.215$) and as such was removed from the model with results showing FVC% decreased for both groups by 0.07% per week, $p<0.001$, **Table II**).

Baseline FEV₁% was 9% lower in women with, versus without, asthma ($p<0.001$). The interaction term indicates differential trends in FEV₁% during gestation ($p<0.0001$) where non-asthmatics had a significant decrease in FEV₁% (0.14% per week, 95%CI: 0.06, 0.22, $p<0.0001$, **Table II**) and asthmatics had a non-significant increase of 0.02% per week (95%CI: -0.01 to 0.06, $p=0.055$).

Women with, versus without, asthma had 4.2% lower FEV₁:FVC% at baseline ($p<0.001$). The interaction term ($p=0.002$) indicates that FEV₁:FVC% trends during gestation differed

for non-asthmatics (decrease of 0.03% per week, 95%CI: -0.08 to 0.02, $p=0.299$, **Table II**) and asthmatics (increase of 0.06% per week, 95%CI: 0.04 to 0.08, $p<0.0001$).

Sensitivity analyses

GWG was calculated for the 490 (48%) women with repeat weight measurements (controls: $n=93$ (36%); asthmatics: $n=397$ (52%)). Median GWG did not differ between groups ((0.50 kg/week [IQR 0.40-0.68] vs 0.48 kg/week [IQR 0.31-0.65], $p=0.23$). The inclusion of weight at each visit changed the estimates marginally (but not the direction), with an increase in baseline FVC (asthma and controls) and an increase in the interaction term for FEV₁; however, the number of observations reduced by approximately 46%, reducing the power of the models (*Online Repository Text; Table E1, Online Repository Tables*). Notably, the effect of baseline obesity on reducing FEV₁ became statistically significant, whilst the positive effect of obesity on FEV₁/FVC became non-significant, after adjusting for weight at each visit. These results suggest the analysis findings that were presented for the larger cohort, without adjusting for gestational weight gain, are potentially understating the differences in lung function observed between asthmatics and non-asthmatics during pregnancy.

ACQ6 was calculated at baseline and at each visit throughout pregnancy for women with asthma. Using a linear mix-model, the within-person change in ACQ6 was calculated at $<1\%$ over 40 weeks gestation. The inclusion of asthma control (uncontrolled and controlled, based on an ACQ6 cut-point of 1.5) during pregnancy changed the estimates only slightly (but not the direction), particularly for FVC (increase in baseline values). There was a significant difference between baseline values for lung function between uncontrolled and controlled asthma (as well as each compared to no asthma), and a significant interaction term with gestational age for both uncontrolled, and controlled, asthma; however, the rate of change over gestation did not differ between uncontrolled and controlled asthma (*Online Repository Text; Table E2, Online Repository Tables*). This suggests that asthma control during pregnancy did not significantly impact lung function trajectory in this population with predominantly mild asthma.

In exploring the effect of asthma control on lung function trajectories, controlling for medication adherence, the number of observations dropped dramatically (approximately 25% of total), which drastically reduced the power of the models (data not shown); thus this variable was not included in the final models.

Discussion

This study examined the effects of advancing gestation, and its interaction with asthma, on lung function, using repeat spirometry measures from a large cohort of well-characterised pregnant women with and without asthma. FVC% and FEV₁% declined with advancing gestation; however, whilst FVC% declined at the same rate in women with and without asthma, the trajectories for FEV₁% and FEV₁:FVC% differed by asthma status. FEV₁% remained relatively stable in women with asthma, whilst FEV₁:FVC% increased marginally. Conversely, FEV₁% decreased significantly for women without asthma. Results translate to lung function changes of between -5.6% and +2.4% over 40 weeks gestation; thus, advancing gestation impacts spirometry indices, although of seemingly limited clinical importance, and is altered by the presence of mild asthma.

Prior to our study, the trajectory of lung function over the course of pregnancy had not been adequately described. Our results indicate that advancing gestation impacts lung function, totalling a 5.6% decrement in FEV₁% and 2.8% decrement in FVC% over 40 weeks gestation; FEV₁:FVC% was unaffected. Similarly, a Brazilian study of 120 healthy women observed a statistically significant decline in FVC% (~4%) and FEV₁% (~3.5%), from the 1st to 3rd trimester, while FEV₁:FVC% remained stable.²⁵ In contrast, *Grindheim et al* reported a 3.1% increase in FVC% from 15-36 weeks gestation (4 measurements) in 87 non-smoking women without asthma, with no change detected in FEV₁% or FEV₁:FVC%.²⁰ Alternatively, gestational age did not affect spirometry indices in a study of 20 women with, and 20 women without, asthma; there was no significant difference within either group, across the three measurements (16, 25, and 35 weeks).²⁷ Similarly, a study of 51 healthy women did not detect a difference across trimesters in FEV₁, FVC or their ratio.²³ However, these studies are largely limited by sample size.^{20,23,27} Our results suggest that pregnancy-induced changes in lung function occur, in line with extrapulmonary lung restriction caused by an enlarging uterus as pregnancy progresses; however, the clinical importance is questionable.

As expected, asthma was associated with significantly lower baseline lung function compared with controls, with the greatest effect on FEV₁%, particularly in those with uncontrolled asthma at baseline. Interestingly, there was a significant interaction effect between asthma and gestational age on FEV₁% and FEV₁:FVC%, but not FVC%, such that FEV₁:FVC% marginally increased in women with asthma over the course of pregnancy, whilst FEV₁% declined in controls. Only one previous study has examined the interaction effect between asthma and gestational age on lung function.²⁷ This longitudinal study reported significantly

higher FEV₁% and FEV₁:FVC% in asthmatics [n=20] vs. controls [n=20] (~3% difference) at 35 weeks gestation, but not at 16 and 25 weeks.²⁷ Similar to our findings, authors reported a significant group*time effect on FEV₁% (p=0.04) and FEV₁:FVC% (p=0.01) in mixed-effect models; however, the strength and direction of these associations were not reported, limiting comparisons with our results.²⁷ Another study measured spirometry at approximately 18, 28 and 29 weeks gestation in non-smoking women with asthma and allergic rhinitis.³⁵ No significant change in FEV₁% or spirometry classification ('normal', 'mild/moderate obstruction', 'small airway obstruction') was observed; however, this study was limited by its small sample of 42 women [n=22 at the third assessment], a relatively narrow assessment period, and no healthy control group.³⁵ In our large cohort, using statistical methods that account for the increase in precision through taking repeated measures during pregnancy, and controlling for key confounders, we were able to detect a statistically significant interaction effect between asthma status and gestational age on spirometry parameters. Although information on medication adherence was collected, its inclusion in the models dramatically reduced the sample size and was therefore not included in the present analyses; however, given the impact of medication adherence on asthma management, the collection of this variable should be an important consideration for further research in this area.

The observed positive interaction effect between asthma and gestational age on lung function may reflect the fact that participants received active asthma management during pregnancy, suggesting that optimal asthma management, and/or use of asthma medications, modifies the negative impact of advancing gestation on lung function. Indeed, participants were not instructed to withhold asthma medications prior to assessment; thus, results may reflect recent asthma medication use, specifically bronchodilators. Moreover, analyses did not account for changes in medication use or adherence throughout pregnancy, due to a reduction in power of the models; however, sensitivity analyses including asthma control (ACQ6) revealed no difference in lung function trajectories during pregnancy between 'controlled' and 'uncontrolled' asthmatics. This may be expected in our population given that a <1% total change in ACQ6 score over pregnancy was observed. The effect may differ in women whose asthma is not actively managed throughout pregnancy, or whose asthma control fluctuates significantly and/or whom are non-adherent to their asthma medication. Further research is needed to explore these aspects.

Although it is well established that lung function deficits are associated with obesity, this has only been examined during pregnancy in one prior study which specifically excluded women

with asthma.²⁰ In their study of 87 women, *Grindheim et al* found no effect of pre-gestational BMI >25kg/m², nor excessive GWG, on FEV₁, FVC or PEF during pregnancy.²⁰ In contrast, our results demonstrate that an elevated BMI alone can contribute to an altered lung function trajectory during pregnancy, in women with and without asthma. Obesity in early pregnancy was a significant negative predictor of FVC% (-3.1%), compared to a BMI <25kg/m², having a marginally greater influence than asthma (-2.6%). A limitation of our study is that data on pre-pregnancy BMI was not available for our cohort. Nevertheless, the high rates of obesity in women of child-bearing age and the notably higher prevalence in pregnant women with asthma,³⁶ mean our findings are highly relevant to this population group. GWG was not available for approximately half of our sample, limiting our ability to explore the effect of this modifiable factor; yet, although reduced in power, our sensitivity analysis suggests that GWG may be an important factor to consider in future studies.

Monitoring lung function during pregnancy may be relevant to perinatal outcomes, as well as asthma outcomes. Early work by *Schatz et al* detected a direct relationship between mean FEV₁% during pregnancy and infant birth weight ($r=0.11$, $p<0.04$)¹² in 352 women with asthma. A lower maternal FEV₁% was associated with a 3-fold increased odds of birth weight in the lowest quartile (<3150g), and women with a mean FEV₁% <90%, vs. ≥90%, were 2.5 times more likely to have an infant with low ponderal index.¹² A second study by *Schatz et al* reported a weak, but statistically significant, correlation ($r=0.08$, $p<0.001$) between average FEV₁% during pregnancy and infant birth weight in 2123 women with asthma, whilst no relationship between birth weight and mean asthma symptoms, sleep disturbance or activity limitation during pregnancy existed,¹¹ supporting the utility of spirometry. Mean FEV₁% was also significantly lower (by 2.2-2.4%) for women who developed gestational hypertension, delivered pre-term or had a LBW infant, compared to women without this outcome.¹¹ However, whether these associations are observed in women without respiratory disease remains unknown.

A major strength of this study is the relatively large sample of well-defined women, with and without asthma, with repeat spirometry measures collected prospectively during pregnancy. Previous studies were limited by methodological design; were of small sample size, reducing statistical power; collected few repeat lung function measurements and/or during a narrow time frame; and/or did not include women with and without asthma to assess the disease impact.¹⁹⁻²⁷ Furthermore, evaluation of an interaction effect between asthma status and gestational age had not been adequately examined prior to our study.

The same reference equation was used within the prospective cohorts included in this analysis, allowing assessment of within-participant changes. However, the use of NHANESIII, not GLI12³⁷ reference values, may be deemed a limitation. Previous studies demonstrate good agreement in FEV₁, FVC and FEV₁:FVC predicted values between GLI12 and alternatives, including NHANESIII.^{8,10,37} Our in-house comparison between NHANESIII and GLI12 values for the spirometry results obtained in our population sample, also demonstrated a strong agreement (correlation coefficients: FEV₁% 0.98; FVC% 0.97).

A limitation in the interpretation of the results is the possibility that women with asthma had previously performed spirometry and therefore performed the technique better; however, the quality of all spirometry tests were evaluated against guidelines, therefore a training effect within the asthma group should not be present within our population (although could be present over time within both groups). In addition, the definition of asthma was participant report of physician diagnosis and recent history of medication and/or symptoms; we did not perform pre- and post-SABA spirometry to confirm asthma diagnosis, nor is provocation testing for research acceptable in pregnancy. Although this is representative of the population in the antenatal clinics, the absence of spirometric confirmation of asthma may have led to contamination of the asthma group with non-asthmatic women. If so, the effect of asthma on lung function in pregnancy would be diluted; therefore our results would *underestimate* the effect of asthma. Furthermore, it is unclear whether any participants were affected by respiratory infections or asthma exacerbation on the date of testing.

The inclusion of ECO and smoking status in the models strengthened the coefficient of primary interest, hence both variables were retained; however, interpretation of the effect of smoking on lung function in the models is limited given the collinearity between these two variables. Lastly, our cohort received regular contact and active asthma management during pregnancy, which may limit the generalizability of results. Although the sensitivity analysis did not show an effect of asthma control status on the interaction with gestational age, this may reflect the fact that most women had relatively mild asthma at baseline, that asthma control remained relatively unchanged throughout pregnancy (<1% change in ACQ6), and that all women received a form of asthma management. It is possible that an analysis of less well-controlled women would provide different results. Thus, further research examining the effect of asthma on lung function in pregnancy in women with more severe or poorly controlled asthma, and further elucidation of the effect of tobacco smoke exposure, is warranted.

In summary, FVC% and FEV₁% declined significantly over gestation, consistent with extrapulmonary restriction from an increasingly gravid uterus; FEV₁:FVC% was unaffected. FVC% declined at the same rate in women with and without asthma, yet, asthma status altered FEV₁% and FEV₁:FVC% trajectories. In women with asthma, FEV₁% remained relatively stable, whilst FEV₁:FVC% increased marginally, despite lower baseline values. This may reflect active asthma management during pregnancy, which raises the question of whether optimal asthma management can oppose the observed negative effects of advancing gestation on lung function. Research examining the difference between lung function measures collected during the pregnant and non-pregnant state would further elucidate the impact of pregnancy on lung function. This research provides evidence to support use of spirometry in clinical assessment, and education, of pregnant women with asthma in the context of FENO/asthma symptom assessment.

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Figure legend

Figure 1. Lung function changes during pregnancy among women without asthma (dashed) and women with asthma (solid line); a) forced vital capacity (FVC) % predicted, b) FEV₁% predicted and c) FEV₁:FVC%. Displayed p-values are from the interaction term gestational age*asthma in mixed model.

Table I. Baseline characteristics of pregnant women with and without asthma

	Control (n=259)	Asthma (n=770)	p-value
Maternal age, years (mean $\pm$ SD)	29.3 $\pm$ 4.9	29.0 $\pm$ 5.4	0.330
Gestational age, weeks (mean $\pm$ SD)	19.3 $\pm$ 5.3	17.7 $\pm$ 2.9	<0.001
Parity (median, IQR)	0 [0, 1] n=258	1 [0, 2] n=598	0.001
Ethnicity (n, %)			0.202
Caucasian	240 (92.7)	677 (87.9)	
Indigenous*	4 (4.5)	33 (4.3)	
Asian	3 (1.2)	16 (2.1)	
Hispanic	-	5 (0.7)	
African	-	3 (0.4)	
Other	3 (1.2)	6 (0.8)	
Unknown	9 (3.5)	30 (3.9)	
BMI (mean $\pm$ SD) [†]	27.6 $\pm$ 6.2	29.4 $\pm$ 7.5	<0.001
BMI Categories (n, %)			0.002
Non-Overweight [#]	114 (44.0)	245 (31.8)	
Overweight	77 (29.7)	240 (31.2)	
Obese	72 (27.8)	289 (37.5)	
Current Smoker (n, %)	25 (9.8) n=256	138 (18.3) n=756	0.001
Ex-Smoker (n, %)	81 (32.0) n=253	207 (27.8) n=746	0.195
ECO (mean $\pm$ SD)	3 $\pm$ 5	4 $\pm$ 6 n=748	0.009
FVC % predicted (mean $\pm$ SD)	99.0 $\pm$ 11.5 n=254	95.8 $\pm$ 13.0 n=660	<0.001
FEV ₁ % predicted (mean $\pm$ SD)	97.5 $\pm$ 10.9 n=254	90.9 $\pm$ 13.8 n=666	<0.001
FEV ₁ /FVC % (mean $\pm$ SD)	83.4 $\pm$ 5.3 n=255	80.5 $\pm$ 7.5 n=661	<0.001
Number of visits during pregnancy (mean $\pm$ SD)	3.2 $\pm$ 2.1	4.5 $\pm$ 1.7	<0.001
* Indigenous included Aboriginal, Torres Strait Islander and Maori; [†] data missing n=3 in asthma cohort and n=3 in non-asthma cohort; [#] Fourteen women (7 in both control and asthma group) had a BMI <18.5kg/m ² (range 16.6-18.4 kg/m ²) and were combined with women with a 'healthy' BMI at baseline as 'non-overweight'. BMI, body mass index; ECO, exhaled carbon monoxide; FEV ₁ , forced expiratory volume in 1 second; FVC, forced vital capacity.			

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Table II: Mixed model regression coefficients for FVC% predicted, FEV ₁ % predicted and FEV ₁ :FVC% across gestation in women with and without asthma (n=921).						
	FVC% predicted (3229 observations)		FEV ₁ % predicted (3247 observations)		FEV ₁ :FVC (3229 observations)	
Variable	Estimate	p-value	Estimate	p-value	Estimate	p-value
Constant	96.51 [92.08, 100.94]	<0.001	95.64 [90.65, 100.63]	<0.001	89.06 [86.54, 91.58]	<0.001
Asthma	-2.63 [-4.42, -0.83]	0.004	-8.82 [-11.58, -6.06]	<0.001	-4.19 [-5.88, -2.51]	<0.001
Gestational age (weeks)	-0.07 [-0.10, -0.04]	<0.001	-0.14 [-0.22, -0.06]	<0.001	-0.03 [-0.08, 0.02]	0.299
Asthma*Gestational age†	-	-	0.16 [0.08, 0.25]	<0.001	0.09 [0.03, 0.14]	0.002
Maternal age at study entry	0.07 [-0.08, 0.21]	0.362	0.19 [0.05, 0.33]	0.009	-0.18 [-0.24, -0.10]	<0.001
Smoking status at study entry	0.0935		0.037		0.0403	
Never Smoker	Reference		Reference		Reference	
Ex-Smoker	-1.02 [-3.31, 1.28]	0.386	-2.51 [-4.83, -0.19]	0.034	-1.31 [-2.45, -0.17]	0.024
Current Smoker	1.52 [-0.24 3.27]	0.090	0.75 [-1.05, 2.54]	0.415	-0.74 [-1.59, 0.11]	0.086
ECO (ppb)	0.04 [-0.03, 0.12]	0.273	-0.05 [-0.12, 0.02]	0.134	-0.09 [-0.14, -0.05]	<0.001
BMI category at study entry	0.0035		0.2607		0.0006	
Non-Overweight‡	Reference		Reference		Reference	
Overweight	-1.01 [-2.93, 0.91]	0.303	-0.73 [-2.70, 1.24]	0.466	0.24 [-0.69, 1.17]	0.610
Obese	-3.10 [-4.94, -1.26]	0.001	-1.57 [-3.45, 0.31]	0.102	1.60 [0.71, 2.49]	<0.001
†The interaction term for gestational age and asthma was not significant for FVC% predicted (0.05, 95%CI:-0.03, 0.14, p=0.215), the results from the FVC model without interaction term are presented.						
‡Includes underweight (n=14; range 16.64 – 18.5kg/m ²) and healthy weight. BMI, body mass index; ECO, exhaled carbon monoxide; FEV ₁ , forced expiratory volume in 1 second; FVC, forced vital capacity.						