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Elevation of One Hour Plasma Glucose During Oral Glucose Tolerance Testing

Saba Sheikh, MBBS, MSCE[1,2,*], **Mary E. Putt, PhD, ScD**[3], **Kimberly A. Forde, MD, MHS**[3,4], **Ronald C. Rubenstein, MD, PhD**[1,2], **Andrea Kelly, MD, MSCE**[2,5]

[1]Division of Pulmonary Medicine and Cystic Fibrosis Center, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

[2]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

[3]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

[4]Division of Gastroenterology, Hospital of University of Pennsylvania and Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

[5]Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Summary.

Objectives: In cystic fibrosis (CF) patients, elevations in 1 hr plasma glucose (PG1) during a 75 g oral glucose tolerance test are common, but of unclear long-term clinical relevance. Thus, we examined associations of PG1 with percent-predicted forced expiratory volume in 1 sec (FEV_1% predicted), CF exacerbations, and CF related diabetes (CFRD) development.

Study Design: We conducted a retrospective cohort study of 80 pediatric patients with CF (43 males) followed over 5 years in a single CF center. We considered the association between elevated versus normal PG1 (greater vs. no greater than 160 mg/dl) and linear changes in FEV_1% predicted over time for males and female, as well as the odds of a CF exacerbation and the odds of developing CFRD.

Results: No significant difference in FEV_1% predicted between normal versus elevated PG1 was found at baseline, or over time in males or females. However, males with elevated PG1 tended to have worse FEV_1% predicted over time than those with normal PG1 (reduction of 0.9 FEV_1% predicted/year, 95%CI: 2.5, 0.6). Subjects with PG1 > 160 mg/dl were more likely to develop CFRD (OR 4.5, 95%CI: 1.7, 18.7, $P = 0.04$) but CF exacerbation risk was similar in both groups.

*Correspondence to: Saba Sheikh, MBBS, MSCE, Division of Pulmonary Medicine and Cystic Fibrosis Center, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, 34th Street and Civic Center Blvd., Philadelphia, PA 19104, sheikhs@email.chop.edu.

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Conclusion: The risk of CFRD increases with PG1 > 160 mg/dl. No statistically significant evidence of an association between elevated PG1 and pulmonary function was found, yet our results do not exclude the possibility that in males, elevated PG1 may signal adverse changes in FEV_1% predicted over time. This possibility requires further study with a larger sample size.

Keywords

cystic fibrosis; oral glucose tolerance test; cystic fibrosis related diabetes

INTRODUCTION

Cystic fibrosis related diabetes (CFRD) is an increasingly recognized complication of cystic fibrosis (CF); its prevalence increases with age, and it affects approximately 40–50% of adults with CF.[1] Untreated CFRD is associated with worse pulmonary function, worse nutritional status, and decreased survival.[2–4] Data from the 1980s found that untreated CFRD increases mortality in CF almost twofold by the age of 30.[5] More recent data demonstrate that early treatment of CFRD improves morbidity and mortality, and that the excess clinical decline with CFRD is partially reversible with administration of insulin.[6] These findings highlight the importance of early detection and management of CFRD.

As CFRD can occur in the absence of noticeable clinical signs and symptoms,[7] current standard of care guidelines published by the Cystic Fibrosis Foundation (CFF) recommend annual screening for CFRD with a 75 g oral glucose tolerance test (OGTT) starting by age 10.[8] The diagnosis of CFRD during the OGTT is based upon an elevated 2 hr plasma glucose (PG2) (>200 mg/dl). However, glucose intolerance falls along a spectrum, and less dramatic derangements such as elevations of 1 hr PG (PG1) and milder elevations of PG2 [>140 mg/dL & <200 mg/dL, defined as impaired glucose tolerance (IGT)] may not be benign. In fact, those with IGT demonstrate significantly lower percent predicted forced expiratory volume in 1 sec (FEV_1% predicted) and body mass index (BMI) compared to those with normal glucose tolerance (NGT).[9] Moreover, IGT has been associated with increased mortality and receipt of lung transplant at a younger age.[10] However, the clinical benefits derived from treatment of IGT remain unclear with small studies showing conflicting results.[6,11,12]

The North American CFRD Consensus Conference in 2009 defined glucose tolerance in individuals with PG1 >200 mg/dl as indeterminate (INDET), the significance of which is not completely understood. In the general population, both INDET and IGT are associated with a high risk of future development of diabetes mellitus (DM).[13] In adults without CF, a PG1 as low as 155 mg/dl is associated with increased risk of developing Type 2 DM and its associated complications including atherosclerosis.[14,15] In CF, isolated elevations of PG1 during OGTT are common, and cross-sectional data suggest higher PG1 may be associated with worse lung function.[16] Longitudinal changes in FEV_1% predicted were thus evaluated to test the hypothesis that elevations in PG1 are associated with a faster decline in pulmonary function in CF patients.

MATERIALS AND METHODS

Study Design

This retrospective study includes CF patients followed at the Children's Hospital of Philadelphia (CHOP) Cystic Fibrosis Center and who underwent screening OGTT between August 2005 and July 2009. Additional inclusion criteria were: age >8 years, a confirmed diagnosis of CF, and an OGTT performed in the well state (defined as no hospitalizations, oral or intravenous glucocorticoid exposure, or change in intravenous antibiotic therapy within the 4 weeks prior to the performance of the OGTT). Subjects were excluded if pulmonary function tests (PFTs) or OGTT PG1 were unavailable, if FEV_1% predicted at study entry was ≤40%, or if the OGTT was performed during a CF exacerbation as PG may be transiently elevated during periods of CF exacerbation. For the purpose of this study, only subjects with PG2 <140 mg/dl (i.e., having neither IGT nor CFRD) were included. Data collection ceased once subjects developed CFRD, operationally defined as 1) abnormal OGTT, 2) hyperglycemia (PG >200 mg/dl) persisting >48 hr during hospitalization, and/or 3) treatment initiation with an anti-diabetic agent; or became pregnant; or received an organ transplant. Data including pulmonary function as measured by forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC), OGTT results, height, weight, BMI, CF mutations, and colonizing pathogen were collected from the electronic medical record and the CFF patient registry, PortCF over 6 years: 1 year prior to and up to 5 years following the date of the baseline OGTT or until September 2013.

Percentiles for height, weight, and BMI were calculated using current reference data.[17] FEV_1 and FVC were reported as percentage of predicted value (FEV_1%- and FVC% predicted, respectively).[18,19] Glucose tolerance was defined by OGTT as normal glucose tolerance (NGT), IGT, indeterminate (INDET), and CFRD based on current CFF guidelines.[7]

Statistical Analyses

FEV_1% predicted over a 5 year follow-up period was the primary outcome, and PG1 at baseline was the primary exposure of interest. Mixed effects models using a random slope and intercept were developed to consider the linear change in FEV_1% predicted as a function of time in the entire cohort. We used this model to determine whether PG1 was associated with differences in FEV_1% predicted at baseline, as reported previously in cross-sectional studies, and whether elevated PG1 was associated with a more rapid decline in FEV_1% predicted. These hypotheses were considered for the cohort as a whole and for males and females separately. In the CF literature, female sex has been shown to modify risk of morbidity and mortality, which has been shown to extend to CFRD, and an initial exploration of the data suggested qualitatively that this could be the case here as well.[20] Therefore separate models for males and females were examined. The associations of PG1 with FEV_1% predicted were assessed using PG1 as a continuous variable as well as a binary variable using a cutoff of ≥ 160 mg/dl to define an elevated PG1. PG1 >155mg/dl portends increased risk of T2DM development and cardiovascular disease in non-CF people,[14,15] and therefore the threshold for abnormal PG1 was chosen at 160 mg/dl. Potential confounders of interest included BMI percentile, pancreatic insufficiency status (based on 72 hr fecal fat

analyses with <93% absorption or stool trypsin concentration <80 μg/g), age at baseline, pseudomonas colonization, and Cystic Fibrosis Transmembrane Receptor (CFTR) mutation. Confounder variables were included in the adjusted model if they had at least a 10% affect on the estimates for FEV_1% predicted over time. Logistic regression analysis adjusted for sex, age at baseline, BMI percentile, and FEV_1% predicted at study entry was used to assess association between elevated PG1 and the risk of developing CFRD over the subsequent 5 year period.

The sample size was based on a power calculation that indicated a total sample size of 80, with a 1:1 ratio of those with normal versus elevated PG1 was needed to detect a difference in trajectory of 1.5 FEV_1% predicted per year between the two PG1 groups assuming 80% power and a two-sided Type I error rate of 0.05.

The odds of CF exacerbation by PG1 group (> or ≤ 160 mg/dl) were estimated using generalized estimating equations with a logit link function. We assessed the risk of a first exacerbation following an observed elevation in PG1 using a Cox proportional hazard model and the log-rank test.

All analyses were performed using STATA 12 (StataCorp LP, College Station, TX). All tests were two-sided and used a Type I error rate of 0.05. The Institutional Review Board of The Children's Hospital of Philadelphia approved the study protocol under which these data were collected. Informed consent and assent (where age-appropriate) were obtained.

RESULTS

Initial screening of patients at the CHOP CF Center identified 110 patients who underwent a clinically indicated (baseline) OGTT during the screening period, August 2005 through July 2009. Of these, 14 were excluded because the baseline OGTT was not performed during a well state, one had severe CF lung disease (FEV_1% predicted <40% predicted) and three patients declined to participate. One patient who was unable to perform PFTs and two patients who did not have a PG1 reported were also excluded. Two subjects with an OGTT consistent with CFRD and seven with IGT were also excluded. Analyses were therefore performed on data from 80 subjects (43 male), age 5–20 years over a median study period of 4.8 years (range: 0.5–5.2 years) (Table 1). Loss to follow-up was primarily due to subjects transferring to other CF Centers. The majority (85%) was Caucasian, and 78% had at least one F508del CFTR allele.

At baseline, 73 subjects had NGT and seven had indeterminate glucose tolerance (INDET, PG1 >200 mg/dl). Fifteen males (35%) and 13 females (35%) had PG1 greater than 160 mg/dl. The incidence of CFRD in the study cohort during the subsequent five years was 15% (12/80 subjects).

In the cohort as a whole, FEV_1 predicted per year improved by 1.0% ($P = 0.001$) after adjustment for BMI percentile and age at study entry (Table 2). In males, after adjustment for BMI percentile and age at study entry, FEV_1 predicted/year increased by 1.1% per year ($P = 0.004$). However, in females, there was no detectable change in FEV_1 predicted per year (0.6%, $P = 0.2$) after similar confounder adjustment was made.

In males, after adjustment for BMI percentile and age at study entry, there was no significant difference in mean baseline FEV_1% predicted between subjects with normal versus elevated baseline PG1 (93 vs. 92%, $P = 0.9$, Table 3) but FEV_1% predicted improved over time by 0.6% per year in the normal versus elevated PG1 subjects ($P = 0.001$). Subjects with elevated PG1 had a smaller improvement in FEV_1% predicted/year compared to subjects with normal PG1 (0.6 vs. 1.5 FEV_1% predicted/year). This difference of close to 1% FEV_1% predicted/year (PG1 > 160, 95%CI: 2.5, 0.6, $P = 0.2$), is not statistically significant, and is smaller than what we anticipated based on our power calculation. In a model using PG1 as a continuous variable and adjusting for covariates, similar results were seen in males. Differences in mean baseline FEV_1% predicted between subjects with elevated PG1 defined per CFF criteria for INDET (>200 mg/dl) versus normal PG1 (≤200 mg/dl), were not statistically significant either (93 vs. 84%, $P = 0.3$) but FEV_1% predicted improved similarly over time ($P = 0.001$). Subjects with PG1 > 200 mg/dl also had a smaller improvement in FEV_1% predicted/year compared to subjects with PG1 ≤ 200 mg/dL (1.0 vs. 1.2 FEV_1% predicted/year) although not statistically significant and results may be affected by the small number of individuals with PG1 > 200 (n = 7).

In females, similar models revealed no significant difference in mean baseline FEV_1% predicted between subjects with normal versus subjects with elevated PG1 (FEV_1% predicted: 113 vs. 106%, $P = 0.2$), and no significant change in mean FEV_1% predicted over time (FEV_1% predicted/year 0.6, $P = 0.2$). Females with elevated PG1 did not have a significantly different change in FEV_1% predicted/year compared to females with normal PG1 (1.1 vs. 0.7 FEV_1% predicted/year, $P = 0.5$). In a model using PG1 as a continuous variable, higher PG1 was associated with lower FEV_1% predicted in females (decline of 1% in FEV_1% predicted per 10 mg/dl increase in PG1, $P = 0.05$). When using PG1 cutoff per CFF criteria and at 200 mg/dl, similar results were seen. Additional covariates added to the model, i.e., CFTR mutation, pancreatic insufficiency, pseudomonas status, or mean FEV_1% predicted in the year prior to OGTT did little to alter these estimates.

We note however that subjects with baseline PG1 ≥ 160 mg/dl were over four times more likely to subsequently develop CFRD compared to those with PG1 < 160 mg/dl (OR 4.5, 95%CI: 1.7, 18.7, $P = 0.04$). Those subjects with PG1 > 200 mg/dl were 10 times more likely to develop CFRD over the study period compared to those with PG1 ≤ 200 mg/dl ($P = 0.005$). Subjects with elevated PG1 at baseline were no more likely to have a CF exacerbation than subjects with normal PG1 (OR 1.2, CI: 0.9, 1.6, $P = 0.1$). The median time to CF exacerbation from baseline OGTT in this cohort was 928 days for those with normal PG1 versus 1380 days for those with elevated PG1. Thus, the median time to CF exacerbation did not differ by PG1 group (Log-rank χ^2 0.6, $P = 0.4$), and the relative hazard of CF exacerbation among subjects with elevated baseline PG1 did not differ from those with normal PG1 (Hazard ratio: 0.8; 95%CI 0.4, 1.5, $P = 0.4$).

CONCLUSIONS

In this study, the temporal relationship of an isolated elevated PG1, defined as plasma glucose >160 mg/dl in the setting of normal PG2 (<140 mg/dl), and pulmonary function over the subsequent 4–5 years was assessed in predominantly adolescent-aged CF patients

with normal baseline FEV_1% predicted and BMI percentiles. Somewhat unexpectedly, the overall cohort and particularly males, showed some improvement in FEV_1% predicted. Strictly speaking, no evidence of differences at either baseline or over time were associated with elevated PG1 in either males or females. However, the estimates suggested that males with elevated baseline PG1 might have less improvement in FEV_1% predicted than those with lower baseline PG1. Our sample size of only 43 males may have been insufficient to detect a significant result. A sample of 80 males with approximately half having elevated PG1 would be needed to show a significant difference of 1.5% per year in FEV_1% predicted over a 5 year period based on the power calculation we performed in advance of the study. We included all eligible subjects at our CF Center, but because we analyzed the data for males and females separately, our sample size was only half of what we anticipated, and the proportion of subjects with elevated PG1 was closer to a third than a half of the sample size. Additionally, the largest difference in the change in FEV_1% predicted that we observed (0.9% in males with versus without PG1 >160) was considerably smaller than what we anticipated the effect size to be. These three factors may have contributed to our study being underpowered. Our results however, while not statistically significant with respect to the association between PG1 elevation and loss in FEV_1% predicted, are the first to estimate changes in FEV_1% predicted over time in a pediatric CF population. As such they provide valuable estimates of possible effect sizes that might be used to design a larger study, particularly in male CF subjects.

The majority of our subjects had multiple OGTTs performed over the study period and therefore PG1 exposure was time varying. Additional analyses assessing the impact of varying PG1 (using annual OGTTs during the study period) on FEV_1% predicted were performed and yielded similar results (data not included).

We confirmed previous knowledge[21] that PG1 > 200 mg/dl, used to define Indeterminate glucose tolerance, is associated with an increased risk of CFRD development. However, a lower threshold of 160 mg/dl was also associated with a greater likelihood of developing CFRD over the subsequent 5 years. In 2010, the CFF defined indeterminate glucose tolerance as PG1 > 200 mg/dl during an OGTT, thereby acknowledging that these “early” glucose abnormalities are common in CF but that their clinical relevance was not known.[8] These isolated abnormalities likely reflect loss of early phase insulin secretion in CF.[22] In our group’s previous cross-sectional study, elevations in the PG1 were associated with lower FEV_1% predicted.[15] A similar association was seen in these data using continuous PG1 rather than a cutoff of 160 mg/dl and when stratified by sex, the results were primarily driven by lower FEV_1% predicted with PG1 in females. The University of Minnesota group subsequently found that in children, INDET was associated with a greater likelihood of developing CFRD over the subsequent 5 years.[21] This current study now begins to suggest that in a relatively healthy CF population, even more subtle glucose abnormalities may be associated with less well preserved pulmonary function in males as well as progression to CFRD. These early findings beg important clinical questions 1) does treatment of these early abnormalities improve CF relevant outcomes and 2) can β-cell function be preserved.

The threshold for worrisome hyperglycemia may in fact be lower than 200 mg/dl. The threshold for the diagnosis of CFRD by OGTT are partly adopted from Type 2 DM, which

focuses on the likelihood of developing diabetes related microvascular complications. In people with CF, while these concerns are relevant in the presence of fasting hyperglycemia, [23] pulmonary function and nutrition are of greater and more immediate concern. The ADA recognizes that PG1 ≥ 200 mg/dl is not normal in an otherwise healthy population. DeFronzo's group[14,24] suggests that the threshold for defining abnormal PG1 is even lower than 200 mg/dL: 1) in the non-CF population, adults with PG1 > 150–155 mg/dl during the OGTT are at greater risk of developing Type 2 DM and 2) these lower values are associated with early cardiovascular effects.[15] In children and adolescents with marked obesity and normal glucose tolerance, average PG1 was 120 mg/dl and in those with IGT 140 mg/dl.[25] These data and the recognition that insulin secretion defects arise early in CF and worsen over time along the continuum to IGT and CFRD suggest PG1 in the range of 150–199 mg/dl are indicative of these subtle insulin secretion defects. Accordingly, this study identified that a lower PG1 threshold, lower than the traditional 200 mg/dl, increases the likelihood of developing CFRD. This information is important as studies are designed to prevent or delay progression to CFRD.

Tofe et al.[9] demonstrated significantly lower FEV_1% predicted and BMI in subjects with CF and IGT versus those with normal glucose tolerance. Diminished insulin secretion and increased insulin resistance were also present in patients with IGT compared to NGT.[9] Despite these cross-sectional findings, limited studies testing the use of insulin treatment in the pre-diabetic state have yielded conflicting results. Bizarri et al.[11] reported improvements in BMI and FEV_1% predicted with glargine treatment (median dose = 0.3 U/kg/day) in a small population of CF patients with IGT. Moran et al.[6] treated 20 patients with IGT with aspart insulin at meals and found no improvements in BMI. Minicucci et al.[12] treated 16 patients with glargine and did not demonstrate improvements in BMI and FEV_1% predicted. These data are limited by small sample sizes with a high proportion of dropouts, and also differed in the insulin dosages used. In the absence of data confirming better clinical outcomes, insulin treatment of these early glucose abnormalities is not yet advocated. Additionally, none of these studies directly examined preservation of β-cell function.

The frequency of CF exacerbations affects short-term morbidity but also has long term affects on pulmonary function. In fact, recent data suggest that these episodic exacerbations are the primary drivers of pulmonary function decline,[26] as well as increase risk of mortality. [27] Hyperglycemia may be directly detrimental to the CF lung, as people with Type 1 and 2 DM have an increased risk of lower respiratory tract infections.[28,29] While the respiratory epithelium maintains lower glucose levels in airway mucous than in plasma,[30] hyperglycemia upsets this balance and increases the likelihood of serious bacterial and fungal infections.[31,32] Hyperglycemia in Type 2 DM may alter regulation of inflammatory pathways and chronic inflammation is implicated in declining lung function in individuals with diabetes.[33] Similar to CFRD, PG1 abnormalities may confer a similar risk. Therefore, the odds of a CF exacerbation in subjects with elevated PG1 were explored, but no association was found in this study.

This study is clearly limited by its small sample size from a single center. Other potential limitations exist. Evaluation of large populations of individuals with CF reveals declines in FEV_1% predicted over time. In contrast, our study population's FEV_1% predicted increased

over the 5 year period of study, and this overall improvement may mask the ill effects of elevated PG1. These improvements in pulmonary function may be explained by improvements in CF care over the previous decade including adoption of aggressive airway clearance, addition of hypertonic saline, better nutritional status, improved CFRD screening, and earlier treatment of CF exacerbations. Other explanations include improved physical activity, increased skill at personal disease management and/or increased ownership of disease among adolescents. Additional complexity may arise from closer follow-up, as well as added vigilance and care in CF subjects with worse CF pulmonary disease as well as early glucose abnormalities.

To avoid bias, OGTTs and pulmonary function tests performed during periods of identified poor health (such as hospitalization for pulmonary exacerbation) were excluded from these analyses. Therefore, this cohort is comprised of a relatively healthy CF population (Table 1). Important covariates such as pancreatic insufficiency status, pseudomonas colonization, and CF mutation were included in multivariable models as well to avoid confounding. Given these considerations and the sample size, a significant association or causal relationship between early hyperglycemia and declining pulmonary function over time was not established. While these largely negative data do not support the hypothesis that in children and young adults with CF, an elevated PG1 is associated with a more rapid decline in pulmonary function over time, a larger study is required to more definitively test this hypothesis and to test the benefits of interventions targeting PG1.

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TABLE 1—

Subject Characteristics at Baseline, Medians and IQR Reported for Continuous Variables, Number and Percent Reported for Categorical Variables

	All (N = 80)	Male (n = 43)	Female (n = 37)
Age	12 (9.0, 14.5)	11.1 (8.5, 14.7)	12.4 (9.3, 14.5)
Race			
White	76 (95)	41 (95)	35 (95)
African American	2 (2.5)	2 (5)	0 (0)
Unknown/missing	2 (2.5)	0 (0)	2 (5)
Pancreatic insufficient	68 (85)	38 (88)	30 (81)
CF mutation			
DeltaF508 homozygous	37 (46)	25 (58)	12 (32)
DeltaF508 heterozygous	25 (31)	8 (19)	17 (46)
Other	18 (23)	10 (23)	8 (22)
BMI percentile	59 (35, 74)	58 (36, 71)	60 (34, 79)
FEV_1% predicted	93 (84, 110)	93 (84, 110)	93 (82, 112)
Outcome			
Completed study period	55 (69)	28 (65)	27 (73)
Lost to follow-up	11 (14)	7 (16)	4 (11)
Developed CFRD	12 (15)	6 (14)	6 (16)
Late entry[1]	2 (2)	2 (5)	0 (0)
Follow-up time (years)	4.8 (4.1, 5.0)	4.7 (4.0, 5.0)	4.9 (4.2, 5.0)

[1] Study entry later than September 2008.

TABLE 2—

Mean (95%CI) Increase in FEV_1 Predicted (Per Year); Negative Values Indicate a Decrease

	Cohort		Male		Female	
Model	**Mean increase/year (95%CI)**	***P*-value**	**Mean increase/year (95%CI)**	***P*-value**	**Mean increase/year (95%CI)**	***P*-value**
Unadjusted	0.6 (0.03, 1.2)	0.04	0.8 (0.1, 1.6)	0.03	0.4 (−0.6, 1.3)	0.5
Adjusted[1]	1.0 (0.4, 1.5)	0.001	1.2 (0.5, 1.9)	0.001	0.7 (−0.2, 1.5)	0.2

[1]Adjusted for BMI percentile and age at study entry.

TABLE 3—

Mean (95%CI) Differences in FEV_1% Predicted at Baseline and Change in FEV_1 Predicted Over Time as a Function of Baseline PG1

FEV_1% predicted at baseline and as a function of PG1 and time					
		Male		Female	
Model	**FEV_1% predicted**	**Mean (95%CI)**	***P*-value**	**Mean (95%CI)**	***P*-value**
	Model allowing FEV_1% predicted to differ by constant across all times based on baseline PG1				
Unadjusted	Baseline PG1 < 160	98 (92, 104)	NA	102 (95, 108)	NA
	Baseline PG1 > 160	96 (88, 104)	NS[2]	86 (78, 95)	0.004[2]
	Change (per year)	0.8 (0.1, 1.5)	0.03[3]	0.3 (−0.6, 1.3)	NS[3]
Adjusted[1]	Baseline PG1 < 160	93 (78, 107)	NA	113 (95, 131)	NA
	Baseline PG1 > 160	92 (74, 110)	NS[2]	106 (85, 127)	0.20[2]
	Change (per year)	0.6 (0.5, 1.9)	0.001[3]	0.3 (−0.3, 1.5)	0.20[3]
	Model allowing FEV_1% predicted to differ over time as function of PG1[4]				
Adjusted[1]	Baseline PG1 < 160	92 (78, 106)	NA	113 (91, 131)	NA
	Baseline PG1 > 160	94 (76, 112)	NS[2]	106 (84, 127)	0.16[2]
	Changer for baseline < 160	1.5 (0.6, 2.3)	0.001[3]	0.7 (−1.2, 2.6)	NS[3]
	Change for baseline >160	0.6 (−0.8, 1.9)	0.20[3]	1.1 (−0.5, 2.7)	NS[3]

[1] Adjusted for BMI percentile and age at study entry.

[2] For the test of whether mean FEV_1% predicted at baseline differed as a function of PG1.

[3] For the test of whether the rate of change in FEV_1% predicted changes over time.

[4] Model includes interaction term for PG1 × time in study.