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LONGITUDINAL ANALYSIS OF FEV1 MEASUREMENTS BY ASTHMATIC PATIENTS IN COMPARISON TO CLINIC SPIROMETRY MEASUREMENTS

A Thesis in

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by

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Abstract

Background: Spirometry is considered to be the "gold standard" for assessing lung function in a clinical setting[1]. Researchers have studied at-home monitoring as an alternative to spirometry to offset inflating fiscal costs of medical monitoring, help patients adhere to their treatment regimen, and in some respects improve their quality of life. In addition, very few clinical have focused on asthmatics who are smokers.

Objective: The objective of the research is to evaluate whether or not the FEV_1 measurements taken at home are comparable to the spirometry performed in a clinical setting.

Methods: The SMOG study data from all 44 nonsmokers and 39 light smokers will be obtained for evaluation. Of the original sample population, 34 non-smokers and 33 light smokers will be obtained for analysis. Linear mixed models will be conducted using the dependent variable, spirometry FEV_1 measurements in a clinical setting. The independent variables will be the following: diary FEV_1 measurements, age, height, weight, gender, race, and smoking history. Descriptive statistics were used to provide summary statistics of both dependent and independent variables. Concordance agreement and Pearson's correlation will be used to evaluate diary card FEV_1 measurements and spirometry FEV_1 measurements in a clinical setting.

Results: The Asthma Clinical Research Network conducted a study in asthmatics who smoke, called "Smoking Modulates Outcomes of Glucocortoid Therapy (SMOG)." The SMOG study had a mean age of 29.4 years (6.9). There were 34 females and 33 males. The overall average height was 67.3 inches (3.8). Overall, there were 15

(22.4%) Black (non-Hispanic Origin); 6 (9.0%) Hispanic; 6 (9.0%) Other; and 40 (59.7%) White (non-Hispanic Origin). The smoking status of the study population consisted of 33 (49.3%) smokers and 34 (50.7%) non-smokers. The average weight was 179 pounds (47.1). The linear mixed-effects model showed a statistically significance effect between the clinical spirometry FEV_1 measurement and each of the following variables: the morning FEV_1 diary measurement ($p<0.0001$); height ($p<0.0001$); gender ($p=0.0116$); Black (non-Hispanic Origin) race ($p<0.0001$); Hispanic race($p<0.0001$); and the intercept ($p=0.0378$). The linear mixed-effects model without morning FEV_1 diary measurement as a prognostic factor, showed a statistically significance effect between the clinical spirometry FEV_1 measurement and the evening FEV_1 diary measurement ($p<0.0001$). The linear mixed-effects model, without evening FEV_1 diary as a prognostic factor, showed a statistically significance effect between the clinical spirometry FEV_1 measurement and the morning FEV_1 diary measurement ($p<0.0001$). The weighted and un-weighted Pearson's Correlation Coefficient between the morning diary $FEV_{1\ \text{and}}$ Clinical Spirometry FEV_1 has a value of

0.81 (0.69, 0.89) and 0.81 (0.69, 0.89) respectively. The Concordance Agreement has a value of 0.66 (0.51, 0.76) and 0.66(0.51, 0.76), un-weighted and weighted, respectively between the morning diary FEV_1 and the Clinical Spirometry $FEV_{1.}$ The weighted and un-weighted Pearson's Correlation Coefficient between the evening diary $FEV_{1\ \text{and}}$ Clinical Spirometry FEV_1 has a value of 0.80 (0.67, 0.89) and 0.80 (0.68, 0.89) respectively. The Concordance Agreement has a value of 0.70 (0.55, 0.80) and 0.70 (0.55, 0.80), un-weighted and weighted, respectively between the morning diary FEV_1 and the Clinical Spirometry $FEV_{1.}$

Table of Contents

CHAPTER 1: INTRODUCTION

Asthma is a chronic lung disease that prevents normal functioning of the airways. During an asthma attack, a person experiences trouble breathing because the airways become constricted - making it difficult to breath. As the airways become inflamed, the cells in the airways produce mucus which makes it more difficult to breath. Certain triggers can cause an asthma attack such as tobacco smoke. When an asthmatic person inhales tobacco smoke, it damages the cilia which allow dust and mucus to accumulate in the airways. Damaged cells and increased mucus production eventually trigger an asthma attack. Surprisingly, there are a growing number of smokers who also suffer from asthma in the United States. Approximately 25 to 35% of asthmatics smoke some form of tobacco[2]. Despite the irritation of the airways due to tobacco smoke, asthmatic patients continue to expose themselves to its deteriorating affects. As a preventative measure, physicians have developed monitoring programs to improve the quality of life for asthmatics and encourage smoking cessation. One approach is to give the patient the responsibility of monitoring his or her lung function.

Spirometry is considered to be the “gold standard” for evaluating asthma in a clinical setting[1]. During a spirometry test, a technical professional takes a series of pulmonary measurements to evaluate different aspects of lung function. Multiple measurements may reveal effectiveness of treatment or airway constriction during exercise[6]. Unfortunately, multiple measurements translate to increasing fiscal costs for clinicians. According to one researcher, if we assumed 17 million Americans with asthma smoke, it would cost $2.2 billion for evaluation and administration of treatment[3]. Costly monitoring and treatment has motivated some doctors to find alternative methods for monitoring smokers and non-smokers with asthma. As a result, home monitoring has emerged as one appealing method of self-evaluation.

The peak flow meter is a portable spirometry device which patients may use in the home. The home pulmonary tests assess forced expiratory volume similar to the tests performed in the clinical setting. Home monitoring allows the patient to determine when his or her asthma is worse, whether treatment is working, and when he or she needs emergency care. One study revealed a statistically significant improvement in the quality of life as a result of home monitoring[1]. The evaluation of lung function has helped researchers and patients to gauge abnormal lung functioning.

Whether in the hospital setting or at home, the forced expiratory volume (FEV_1) measurement is a biomarker for the degree of obstruction with asthma. The FEV_1 measurement is used- to capture the maximal amount of air you can forcefully exhale in one second. A normal FEV_1 is greater than 80%; mild obstruction is 60-70 percent; Moderate obstruction is 40 to 59%; and Severe obstruction is less than 40% [7]. Researchers have studied the effects of smoking on asthma through prognostic factors such as the FEV_1 measurement. As a result, several studies have emerged to assess tobacco smoke on asthmatics with abnormal FEV_1 measurements[2].

The Asthma Clinical Research Network conducted the (Smoking Modulates Outcomes of Glucocorticoid Therapy(SMOG) trial, a placebo-controlled, double-blind, cross-over trial, was performed to study the effects of inhaled corticosteroid or leukotriene receptor antagonist in patients with asthma[3]. The study contained 44 nonsmokers and 39 light smokers between the ages of 18 and 50 years with a history of asthma. All subjects had pre-bronchodilator FEV_1 values between 70 and 90%. The non-smoking subpopulation was required to have less than 2 pack years of smoking history. A patient was classified as a smoker if he or she currently smoked 10 to 40 cigarettes a day. Patients were assessed for spirometry measurements over a period of 22 weeks or 10 visits (with 8 weeks on study treatment, 6 weeks on placebo washout, and 8 weeks on alternative treatment).

The SMOG trial is of particular interest to the asthma researchers, as inpatient and home monitoring both were conducted to evaluate asthmatic patients with pre-bronchodilator FEV_1 values of between 70 and 90%.

CHAPTER 2: METHODS

SMOG Study Population

The SMOG study data set was obtained from the Principal Investigator of the Data Coordinating Center for the Asthma Clinical Research Network (ACRN), the NIH-funded network that originally conducted the study[3]. The SMOG study contained 44 non-smokers and 39 light-smokers. Out of the original study population, 34 non - smokers and 33 light-smokers were obtained for analysis as missing FEV_1 measurements were removed from the study. The spirometry FEV_1 measurement in a clinical setting is the dependent variable under study. The independent variables are diary FEV_1 measurements and treatment and the following demographic: race, age, weight, height, and smoking history.

Linear Mixed-Effects Model Using SMOG Data

A linear-mixed effects model was invoked to evaluate the fixed and random effects on the dependent variable, clinical spirometry FEV_1 measurements . Let $Y_i = (y_{i1}, y_{i2}, y_{i3} \ldots\ldots y_{ij})$ be a j×1 vector for subject i for I = 1,2,…..n. The general linear mixed-effects model is $Y_i = X_i\beta + Z_i \gamma_i + \varepsilon_i$. The design matrix contains the fixed effects matrix, X_i as a j×b matrix. The regression coefficients matrix β is a b×1 vector. The random effects matrix , is an m 1 vector with a j m design matrix Z_i. The vector, , is a j×1 vector to capture within subject errors. The variance-covariance matrices of γ_i and ε_i are assumed to be independent of each other. For the purposes of analysis, it is assumed that the variance-covariance matrix of the random effect is unstructured because we assume unequal variances with no discernible pattern.

Measurements of Association

The Concordance Agreement Coefficient was used to evaluate the relationship between Clinical spirometry FEV_1 measurements and diary card FEV_1 values[9]. In particular, the Concordance Agreement Coefficient yields a value between -1 and 1 that assesses the level of agreement between two variables. The Pearson's correlation coefficient is a measure of the linear association between two continuous variables and yields a value between -1 and 1. If the correlation coefficient is negative, then the correlation indicates that as one variable increases the other decreases. If the correlation coefficient is equal to 0 then there is no relationship between the two variables. If the correlation coefficient is positive, then there both variables increase or decrease together[8].

Additional Information Regarding Analysis

A linear mixed-effects model was chosen due to the fact that some patients were missing their dairy card information. Descriptive statistics were used to provide summary statistics of both dependent and independent variables. The prognostic variables of height, weight, and age were used instead of the FEV_1 predicted factor, which is determined by those demographics. The statistical models and descriptives were generated by the Statistical Analysis System (SAS) software, version 9.3. The repeated measurements Concordance Agreement Coefficient did exclude individuals who did not provide paired data on more than one occasion.

CHAPTER 3: RESULTS

Descriptive Statistics for the Population Under Study

The SMOG study had a mean age of 29.4 years (6.9). There were 34 females and 33 males. The overall average height was 67.3 inches (3.8). Overall, there were 15 (22.4%) Black (non-Hispanic Origin); 6 (9.0%) Hispanic; 6 (9.0%) Other; and 40 (59.7%) White (non-Hispanic Origin). The smoking status of the study population consisted of 33 (49.3%) smokers and 34 (50.7%) non-smokers. The average weight was 179 pounds (47.1) (Table 1). There were 16 patients with missing FEV_1 measurements. The Clinical and Diary FEV_1 measurements values at each visit were between 2.5 and 3.0 for all visits (Table 2). However, the spirometry showed a trend towards higher across visits in comparison with evening and morning diary cards (Figure 1). The evening diary card values, in the same figure, showed a higher trend in FEV_1 measurements across visits. The morning diary card measurements reflected lower FEV_1 measurements.

Linear Mixed-Effects Model with Morning and Evening Diary FEV_1 Measurements

The linear mixed-effects model showed a statistically significant effect between the clinical spirometry FEV_1 measurement and the following variables: the morning FEV_1 diary measurement ($p<0.0001$), Black (Non-Hispanic Origin) race ($p<0.0001$), Hispanic race ($p=0.0107$), height ($p<0.0001$), and female gender ($p=0.0116$) , and Age ($p=0.0197$) (Table 3).

Linear Mixed-Effects Model without Evening Diary FEV_1 Measurements

The linear mixed-effects model showed a statistically significant effect between the clinical spirometry FEV_1 measurement and the following variables: the morning FEV_1

diary measurement ($p<0.0001$), Black (Non-Hispanic Origin) race ($p<0.0001$), Hispanic race ($p=0.0112$), height ($p<0.0001$), gender ($p=0.0129$), age ($p=0.0265$) (Table 4).

Linear Mixed-Effects Model without Morning Diary FEV_1 Measurements

The linear mixed-effects model showed a statistically significant effect between the clinical spirometry FEV_1 measurement and the following variables: the evening FEV_1 diary measurement ($p<0.0001$), Black (Non-Hispanic Origin) race ($p<0.0001$), Hispanic race ($p=0.0128$), height ($p<0.0001$),and gender ($p=0.0086$) , age ($p=0.0490$) (Table 5).

The Pearson's Correlation Coefficient and Concordance Agreement

The weighted and un-weighted Pearson's Correlation Coefficient between the morning diary $FEV_{1\ and}$ Clinical Spirometry FEV_1 has a value of 0.81 (0.69,0.89) and 0.81 (0.69,0.89), respectively (Table 6). The Concordance Agreement Coefficient has a value of 0.66 (0.51, 0.76) and 0.66(0.51,0.76), un-weighted and weighted, respectively, which suggests a strongly positive linear relationship between the morning diary FEV_1 and the Clinical Spirometry FEV_1.

The weighted and un-weighted Pearson's Correlation Coefficient between the evening diary FEV_1 Clinical Spirometry FEV_1 has a value of 0.80 (0.67, 0.89) and 0.80 (0.68, 0.89) respectively. The Concordance Agreement Coefficient has a value of 0.70

(0.56, 0.81) and 0.66 (0.56, 0.81), un-weighted and weighted, respectively, which suggests a strongly positive agreement between the evening diary FEV_1 and the Clinical Spirometry FEV_1 (Table 7).

In Figure 2, all of the Pearson's Correlation statistics showed a decreasing trend at visit 6. However, there was no discernable pattern across visits. The highest Pearson Correlation values were present at visits 2 and 10. In Figure 3, there were similar trends in agreement at visits 8 and 9 for all comparisons. The Concordance agreement appeared to be higher for evening and spirometry comparisons across visits.

CHAPTER 4: CONCLUSION

The morning FEV_1 diary card displayed statistically significant relationships with spirometry FEV_1 based on the linear mixed-effects model, suggesting that morning diary cards are significant predictors of spirometry in a clinical setting. The evening FEV_1 diary card also displayed statistically significant relationships with spirometry FEV_1 based on the linear mixed-effects model without the morning diary card in the model. However, we note that the morning diary card influences the evening diary card when both factors are considered in the model. The Pearson's Correlation showed a strong positive linear relationship between spirometry in a clinical setting and morning diary $FEV_{1.}$ The Concordance of Correlation Coefficient suggests a positive agreement between the morning diary FEV_1 measurement and the spirometry in a clinical setting. On the other hand, The Pearson's Correlation has shown a strong positive relationship between spirometry in a clinical setting and evening diary $FEV_{1.}$ The Concordance of Correlation Coefficient suggests a positive agreement between the evening diary FEV_1 measurement and the spirometry in a clinical setting. Because there is a similar result in correlation for peak flow measurements, we conclude there is an agreement between home monitoring of peak flow measurements (morning and evening) and the spirometry in a clinical setting.

Appendix

Tables and Figures

Table 1. Demographics

Age		29.4(6.9)
Gender	female	34(50.7%)
	male	33(49.3%)
Height		67.3(3.8)
Race	American Indian or Alaskan Native	2(3.0%)
	Asian or Pacific Islander	3(4.5%)
	Black, not of Hispanic Origin	15(22.4%)
	Hispanic	6(9.0%)
	Other	1(1.5%)
	White, not of Hispanic Origin	40(59.7%)
Smoker	no	34(50.7%)
	yes	33(49.3%)
Weight		179(47.1)

Table 1A. Demographics

Age		30.1(7.1)
Gender	female	10 (62.5%)
	male	6 (37.5%)
Height		67.2(4.3)
Race		
	Black, not of Hispanic Origin	4 (25.0%)
	Hispanic	1 (6.3%)
	White, not of Hispanic Origin	11 (68.8%)
Smoker	no	10 (62.5%)
	yes	6 (37.5%)
Weight		189(42.2)

*Note: Patients who are missing Morning and Evening Diary Card Measurements

Table 2. Spirometry by Visit

Visit Number	Spirometry	Mean (Std. Dev.)
2	Clinical FEV-1	3.0(0.5)
	Morning Diary FEV-1	2.6(0.5)
	Evening Diary FEV-1	2.8(0.5)
3	Clinical FEV-1	3.0(0.5)
	Morning Diary FEV-1	2.6(0.5)
	Evening Diary FEV-1	2.7(0.5)
4	Clinical FEV-1	3.0(0.6)
	Morning Diary FEV-1	2.6(0.6)
	Evening Diary FEV-1	2.7(0.6)
5	Clinical FEV-1	3.1(0.6)
	Morning Diary FEV-1	2.7(0.6)
	Evening Diary FEV-1	2.8(0.6)
6	Clinical FEV-1	3.1(0.6)
	Morning Diary FEV-1	2.7(0.6)
	Evening Diary FEV-1	2.7(0.6)
7	Clinical FEV-1	2.9(0.6)
	Morning Diary FEV-1	2.6(0.6)
	Evening Diary FEV-1	2.6(0.6)
8	Clinical FEV-1	2.9(0.6)
	Morning Diary FEV-1	2.5(0.6)
	Evening Diary FEV-1	2.6(0.6)
9	Clinical FEV-1	3.0(0.7)
	Morning Diary FEV-1	2.6(0.6)
	Evening Diary FEV-1	2.6(0.6)
10	Clinical FEV-1	3.0(0.6)
	Morning Diary FEV-1	2.6(0.6)
	Evening Diary FEV-1	2.6(0.6)

Table 3. Linear Mixed-Effects Model Results

Effect		Estimate	Standard Error	P-Value
Intercept		-2.1585	0.8061	0.0097
Race				
American Indian or Alaskan Native		-0.05572	0.1818	0.7594
Asian or Pacific Islander		-0.2237	0.1491	0.1345
Black, not of Hispanic Origin		-0.4929	0.09158	<0.0001
Hispanic		-0.2965	0.1158	0.0109
Other		0.1009	0.3203	0.7530
White, not of Hispanic Origin		0	.	.
Smoker	no	0.05222	0.06334	0.4102
	yes	0	.	.
Gender	female	-0.2170	0.08009	0.0071
	male	0	.	.
Age		-0.01173	0.005244	0.0259
Height (In.)		0.07463	0.01216	<0.0001
Morning Diary FEV1 (L)		0.3640	0.09369	0.0001
Evening Diary FEV1 (L)		-0.1083	0.09501	0.2550
Weight (lbs.)		0.000300	0.000886	0.7351

Table 4. Linear Mixed-Effects Model Results without Evening Diary FEV_1

Effect		Estimate	Standard Error	P-Value
Intercept		-2.1772	0.8050	0.0090
Race				
American Indian or Alaskan Native		-0.04689	0.1814	0.7962
Asian or Pacific Islander		-0.2142	0.1487	0.1506
Black, not of Hispanic Origin		-0.4754	0.09020	<.0001
Hispanic		-0.2943	0.1156	0.0114
Other		0.1231	0.3198	0.7006
White, not of Hispanic Origin		0	.	.
Smoker	no	0.05348	0.06326	0.3984
	yes	0	.	.
Gender	female	-0.2140	0.07997	0.0078
	male	0	.	.
Age		-0.01107	0.005206	0.0341
Height (In.)		0.07383	0.01213	<0.0001
Morning Diary FEV1 (L)		0.2715	0.04611	<0.0001
Weight (lbs.)		0.000280	0.000885	0.7517

Table 5. Linear Mixed-Effects Model Results without Morning Diary FEV_1

Effect		Estimate	Standard Error	P-Value
Intercept		-2.3317	0.8555	0.0086
Race	American Indian or Alaskan Native	-0.02717	0.1930	0.88881
	Asian or Pacific Islander	-0.2548	0.1583	0.1085
	Black, not of Hispanic Origin	-0.4600	0.09676	<0.0001
	Hispanic	-0.3073	0.1229	0.0129
	Other	0.1622	0.3333	0.6267
	White, not of Hispanic Origin	0	.	
Smoker	no	0.08421	0.06671	0.2077
	yes	0	.	
Gender	female	-0.2439	0.08470	0.0042
	male	0	.	
Age		-0.01035	0.005556	0.0632
Height (In.)		0.07834	0.01287	<0.0001
Evening Diary FEV_1 (L)		0.2043	0.04783	<0.0001
Weight (lbs.)		0.000202	0.000942	0.8300

Table 6. Correlation : Clinical Spirometry and Morning Diary FEV_1

Parameter	95% LCL	Estimate	95% UCL
Un-weighted Pearson	0.6876493	0.8111065	0.8918153
Weighted Pearson	0.6891204	0.8125407	0.8926116
Un-weighted Concordance	0.512806	0.6603858	0.7615501
Weighted Concordance	0.5148628	0.6613603	0.7621373

Table 7. Correlation : Clinical Spirometry and Evening Diary FEV_1

Parameter	95% LCL	Estimate	95% UCL
Un-weighted Pearson	0.6738092	0.8035137	0.8853354
Weighted Pearson	0.6759173	0.8047961	0.8857446
Un-weighted Concordance	0.5563109	0.7068832	0.8069497
Weighted Concordance	0.5583939	0.7079145	0.8063227

Figure 1: Mean and Standard Deviation of Clinical Spirometry, Morning and Evening Diary

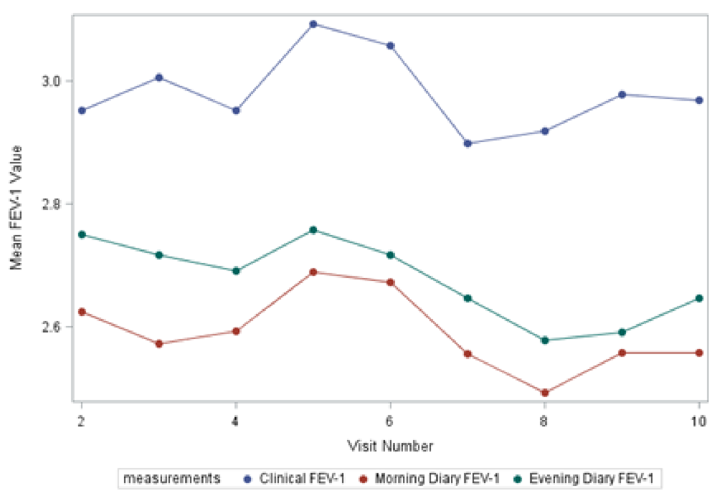


Figure 2: Pearsons Correlation Coefficient: Clinical Spirometry, Morning and Evening Diary

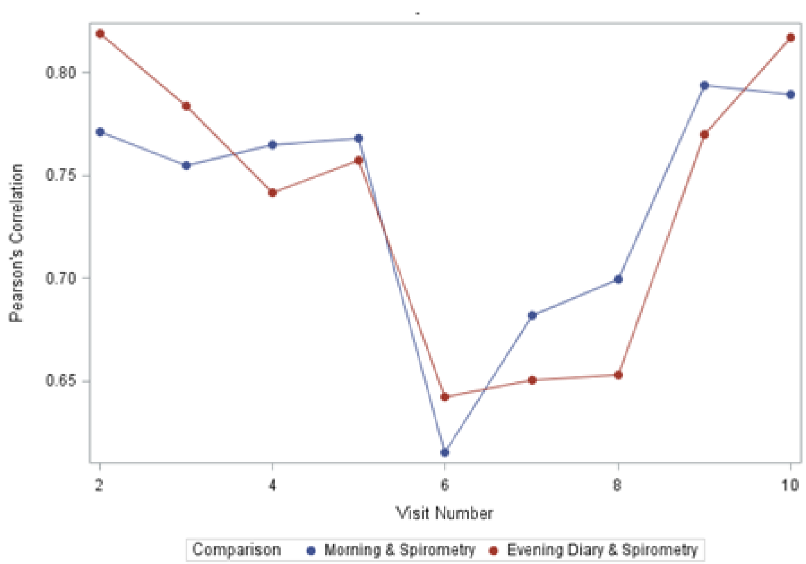
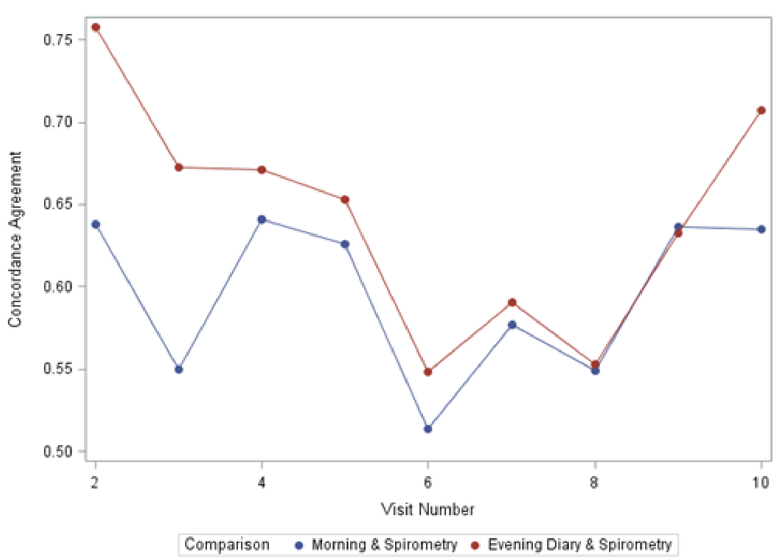


Figure 3: Concordance Agreement of Clinical Spirometry, Morning and Evening Diary



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