Peer Review File
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Reviewer 1

This is a well-designed and clinically relevant study, the message is clear, but more insight is needed.

Comment 1: Do the authors have data on PIF via EH in patients with exacerbation of asthma or COPD?

Reply 1: In this study, we do not have or did not seek any measurements during exacerbations. Use of EH has been studied in ER setting for asthma exacerbation in pediatric population by Direkwatanachai et al. (Asian Pac J Allergy Immunol 2011;29:25-33). It was a clinical efficacy study and thus they did not measure flow rates. However, they found the effect of salbutamol to be similar when administered from pMDI with spacer or EH indicating sufficient flow rate even during exacerbations.

Comment 2: Is the repeatabilty of PIF via EH in these patient populations known?

Comment 3: It was shown that repeatability of inhaler manouvres is great in stable and exacerbated COPD, Erdeelyi T et al. J Aerosol Med Pulm Drug Deliv 2020.

Reply 2-3: In this study, we did not measure inspiratory parameters during exacerbation, and therefore, cannot analyse repeatability during exacerbation. However, we share the view that repeatability of inhaler maneuvers is good. This have been shown earlier for Easyhaler in patients with asthma and COPD by Malmberg *et al.* (J Aerosol Med Pulm Drug Deliv. 2014 Oct;27(5):329-40.).

Comment 4: For proper drug delivery, PIF is only one parameter to be considered. Do the authors have data on breath-hold time?

Reply 4: We do not have data on breath-hold time. However, we acknowledge the importance of other factors in the inhalation maneuver also. As proposed by Kamin *et al.* and Haidl *et al.* **(**J Aerosol Med**.** 2002;15:65–73, J Aerosol Med. 2003;16:21–29 and Respir Med. 2016;118:65–75) we have also looked at initial acceleration of the flow rate as well as volume inhaled after PIF. It is quite rare for patients to fail in the latter two parameters and therefore, we have concentrated on PIF in this work.

Comment 5: Did the type of regular inhalers used by patients influence PIF values measured through EH?

Reply 5: We have collected the information of inhaler used by patients, but as there is a large variability, the data is not easy to combine. Majority of patients had several inhalers in regular use and it is not straightforward to discern which one would be the most influential.

Comment 6: As describe in Ref16 in the manuscript, gender affects PIF in COPD. I do not see that gender vs. PIF was analyzed in the current manuscript. I suggest the use of a regression model to analyze the independent factors associated with PIF in asthma and COPD.

Reply 6: We have included the PIF results for males and females. Previous effort of regression analysis for independent factors for PIF through EH has found a poor coefficient of determination (predictive value) (Malmberg 2010), suggesting that such modeling is not clinically useful.

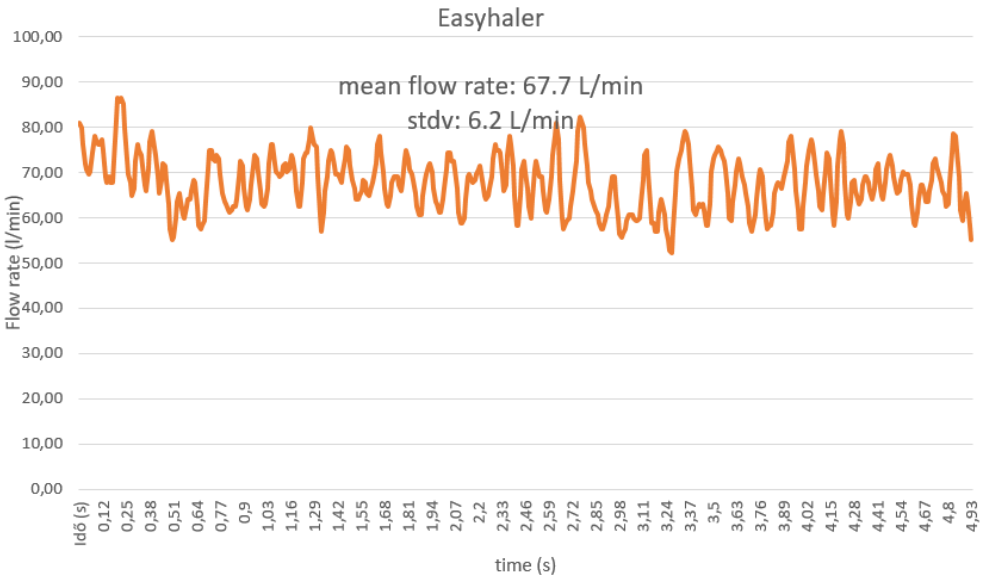
Changes in the text: We have added this in the Results section of the manuscript (page 12, line 244-247).

Reviewer 2

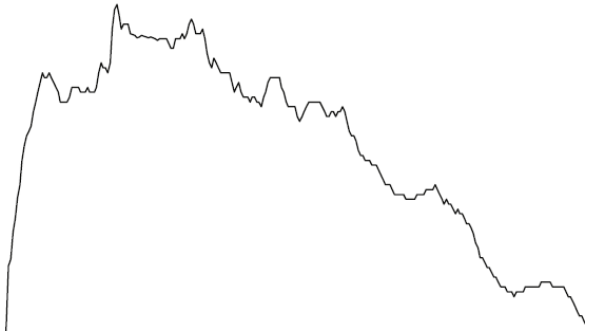
The topic of the manuscript is of high importance from the perspective of successful management of asthma and COPD. The idea to use two existing measured datasets both with relatively high number of patient to reveal correlations between peak inspiratory flow and native spirometric parameters or demographic data is good, the total number of patients provides an improved statistical power to the present analysis compared to previous similar studies (usually with 40-100 subjects).

However, there are some major questions and issues to be clarified:

Comment1: Spirometers are designed and optimized to measure the lung function parameters based on strict protocols. When performing native spirometry there is no flow resistance (or at least it is much lower than the resistance of the inhaler). However, if an inhaler is inserted between the mouth of the subject and the spirometer the measured flow is disturbed (even turbulent). The oscillating nature of the measured PIF may induce some error if data reading is automatic. To exemplify the above statement, consider the following plot, which is a result of constant flow measurement (the pump provided constant flow rate):



In the above case, if the reading is automatic, the flow rate could be any value between 52 -86 L/min. Similar problem arises when the flow is not constant.



So, the question is whether the authors verified/validated the spirometer for the special task and observed or not similar patterns? If yes, how did they treat this uncertainty? **This is a crucial question potentially affecting all the results of the work.**
Reply 1: The reviewer points outs an important and potentially detrimental question in measurement technology. In fact, in Easyhaler the flow is turbulent inside the aerosolization engine of the flow channel. In the measurements the sampling frequency is 10ms and we consider it sufficient to reliably detect oscillations described by the reviewer. Our measurement setup was developed in collaboration with the spirometer manufacturer and we have high confidence in their proficiency in measurement technology.

Comment 2: Another major issue regards the interpretation of the correlation analysis. In my opinion, based on the conclusions emerging from previous similar works:

1) the correlation of PIF through the device with age for children (positively) and for the old people (say over 70 years) is probably universal and not due to disease. The interpretation of current results should be made accordingly.
   Reply: We agree that the age has an effect on PIF which is unrelated to the disease status of the patient. The effect of age is described in table 2 and included in the Discussion section.

2) gender seems to be a significant parameter, men have significantly higher PIF through inhalers than women (see for instance the previous work on Easyhaler, Malmberg et al 2010). Why it is not studied here?
   Reply: We have included the PIF results for males and females.
   Changes in the text: We have added this in the Results section of the manuscript (page 12, line 244-247).

3) disease severity based on spirometry (see the old GOLD classification) seems to not correlate strongly with PIF, but this is still under debate. This would be an interesting issue to explore (actually the FEV1% and FVC% correlations were analysed here but not deeply interpreted. It would be worth looking at FEV1/FVC as well. I see this issue more interesting than the dependence on FEV1 (L), the authors focused on.
   Reply: This is important issue, but unfortunately this study was not designed to specifically look at this question. In contrast, we did not seek for association between FEV1 (L) and PIF, but with FEV1 % predicted as described in the Methods section.

FEV1/FVC is an important parameter in the definition of COPD. We feel that FEV1 % predicted reflects better the disease severity in COPD patients, than FEV1/FVC.

4) The main result of the work is that almost everyone can achieve 30 L/min through Easyhaler. However, as flow measurements through the inhaler are not routinely performed in the medical practice, it would be equally important to assess who is the person who cannot exceed 30 L/min based on available data (native spirometric parameters, demographic data etc.) and this is possible from the current data. I would suggest to look for independent predictors of PIF-through-the-device and provide the relationship between PIFdevice and its predictors (analytical function).
Reply: We have studied this carefully, but unfortunately have not found predictive tool. While there are general trends to be found, there is large variation in individual patients which is poorly reflected by the models. In clinical practice each patient must be treated and assessed individually. Luckily, the flow rate rarely poses any difficulties as seen from the results.

A few less crucial, but important issues:
Comment 3: A lot of flow measurements through different inhalation devices have been performed so far, but only a fraction of them dealt with correlations between these parameters and baseline spirometric data, demographic data or anthropometric data. It would be useful to include in the Introduction section a brief summary of these works. Suggestions: Jansens et al, 2008, Eur Resp J 31:78-83; Jarvis et al, 2007, Age and Aeging 36: 2013-218; van der Palen, 2003, Resp Med 97: 285-289; Dewar et al, 1999, Resp Med 93: 342-344; Kawamatawong et al. 2017, J Asthma Allergy 10: 17-21; Farkas et al. 2019, 154:133-140 and so on…
Reply 3: Thank you for these good reference suggestions. As the Introduction section is already quite long and includes the most relevant aspect of the study background, we would like to suggest adding some of the reference to the Discussion section to describe the strengths of the study.
Changes in the text: We have revised discussion section and added references accordingly (page 16, line 339-347)

Comment 4: The authors named the inhaled volume a secondary endpoint and determined its values without any interpretation of the results. Previous papers on drugs emitted by Easyhaler (Budesonide, Formoterol, Buventol, Bufomix, Safumix) demonstrated that inhaled volume did influence the amount and size distribution of emitted drugs and the consequent lung deposition. Therefore, it would be recommended to pay more attention to this parameter as well. A correlation analysis similar to that for PIF would be perfect (is FIVC the main predictor of IV through the device?), but at least some comments on this issue.
Reply 3: A correlation analysis for inhaled volume has been added.
Changes in the text: We have added mention of the analysis in the statistical section (page 10, line 202) and added table 3. Results given (page, line) and discussed (page 15-16, line 329-332).

Comment 5: There is increasing evidence that besides PIF and IV the flow ramp-up (acceleration) is also a crucial parameter. At least some comments on this should be included.
Reply 5: We have analysed this parameter, but in general it is relatively rare for patient not to achieve sufficient flow acceleration. As proposed by Kamin *et al.* and Haidl *et al.* (J Aerosol Med. 2002;15:65–73, J Aerosol Med. 2003;16:21–29 and Respir Med. 2016;118:65–75) sufficient acceleration is consider to be 0.7 L/s2. 98.4% of the patients achieved that in our study.

Disease group	N	Acceleration (l/s^2)	Std Dev
Asthmatic 6 to 17	93	4.1	2.4
Asthmatic 18 or more	185	4.0	3.2
COPD	87	3.4	2.5

Acceleration could not be defined for all the subjects

Comment 6: How the present PIF and IV data compares with similar data on Easyhaler measured by other investigators (e.g. Azouz et al 2014, J Aerosol Med Pulm Drug Deliv, 27). Can the differences be due to the fact that the flow resistance of the device was decreased before the release of Bufomix?
Reply 6: Currently, there are two variants of Easyhaler ("standard" and "centre slot") on the market. Standard configuration is used in the mono products and centre slot in combination products. The device resistance was therefore not lowered, but there are in fact two Easyhaler variants with different resistances available. Taken this into account we feel that the data is quite consistent with data found in the literature.

Reviewer 3
In the present study, the authors conducted a post hoc analysis of pooled peak inspiratory flow rate (PIF) data via Easyhaler (EH) from the two RCTs, and concluded that over 99% of patients with asthma and/or COPD were able to inhale through EH with an

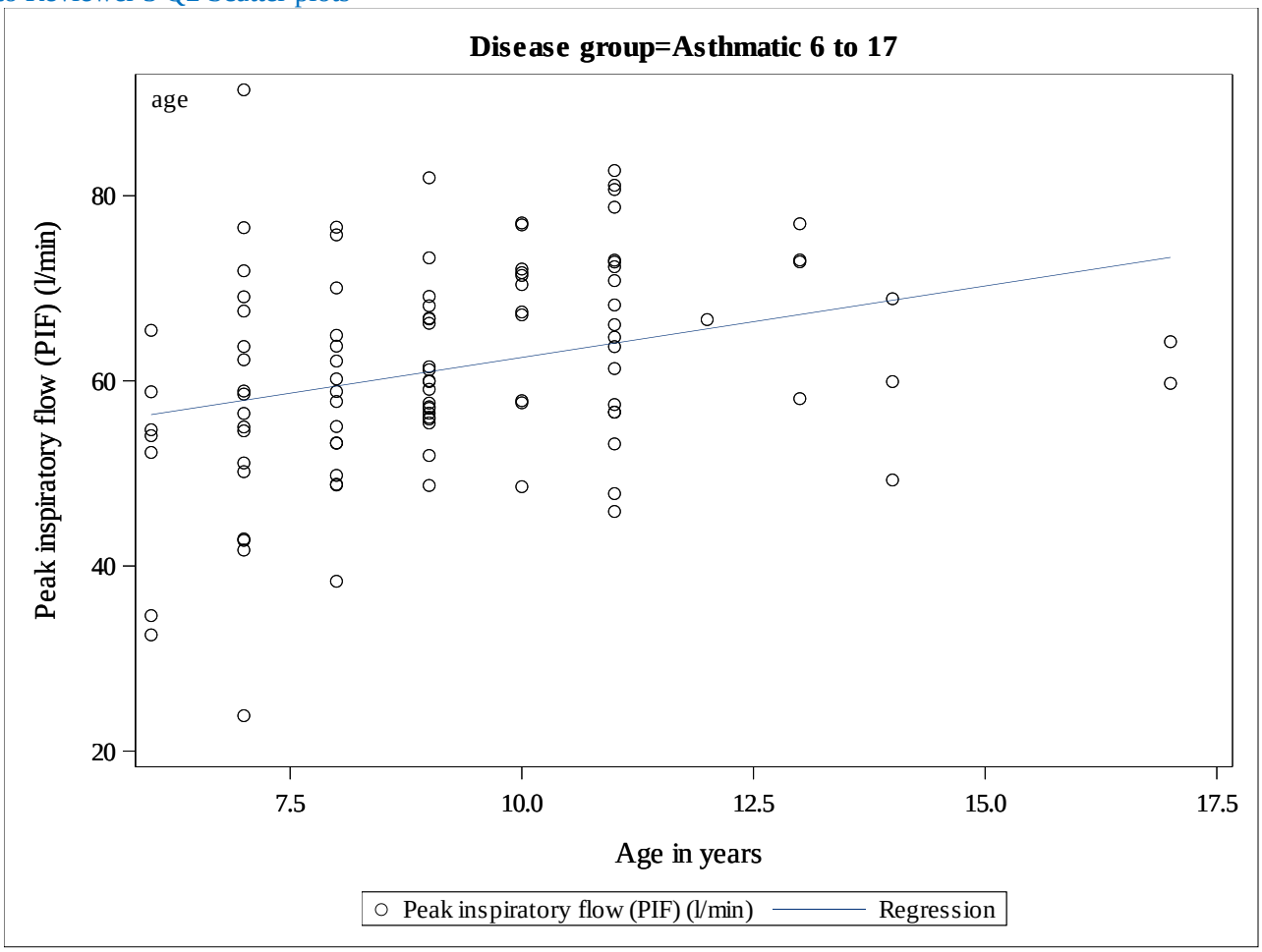
adequate PIF. Although these information may be useful to achieve the appropriate inhalation therapy using EH, adequate analyses were not carried out instead of enough data. The author should describe the details of following points.

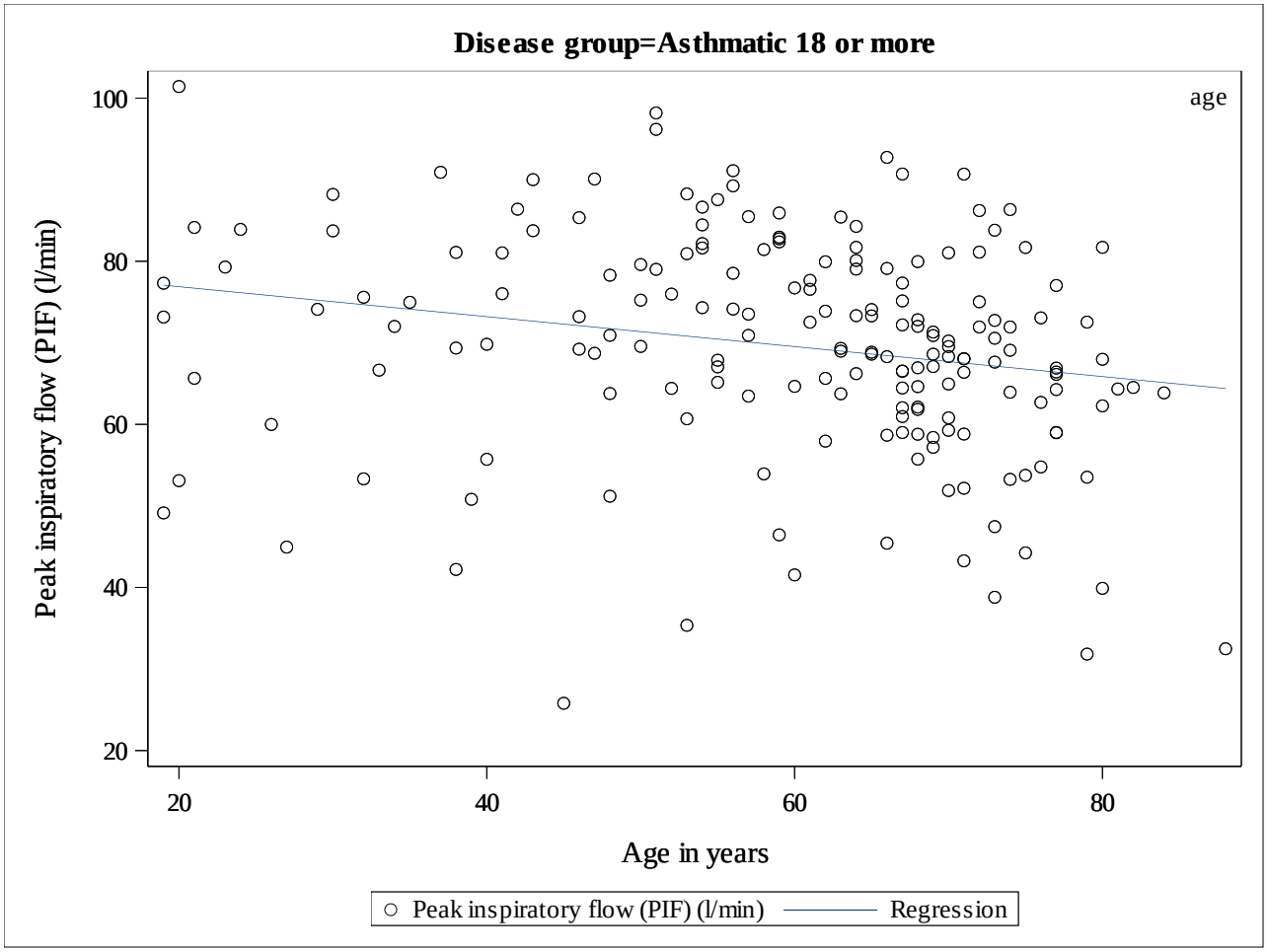
Comment1: The cutoff value for adequate PIF via EH was set at >30 L/min. But the evidence was not described in the manuscript. The information indicated in Page 3, Lines 12-14 is not EH specific data. The authors should describe the evidence.
Reply 1: Most comprehensive analysis on required flow rates to our knowledge has been conducted by Haidl et al. It describes the evidence and flow rates for many marketed inhalers. Changes in the text: We have added Haidl et al. 2016 as reference to the manuscript (page 6, line 101-104).

Comment 2: Table 2. Pearson's "linear" correlation analysis was used to analyze the relationship between PIF and patients' characteristics. The readers cannot judge that these relations are linear or not.
The scatter plots of these relationships should be described in Figure.
In the case of non-linear correlation, the author should use a categorization.
Reply 2: These scatter plots are provided for reviewers. However, we feel that they do not convey the main results and suggest that they shouldn't be included in the manuscript.
Changes in the text: Scatter plots attached to this response.

Comment 3: As indicated in Table 2, many patients' characteristics correlated the PIF via EH. In clinical practice, how could medical professionals detect a patient with insufficient PIF from their characteristics. The authors should add some discussion about the application of these data in clinical practice.
Reply 3: We have constructed several models for this purpose, but unfortunately, their predictive value is not good enough for clinical practice. Each patient must be assessed individually, but fortunately, PIF limit of Easyhaler is rarely a problem as demonstrated in this work.

Response to Reviewer 3 Q2 Scatter plots

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age
Peak inspiratory flow (PIF) (l/min)
100
80
60
40
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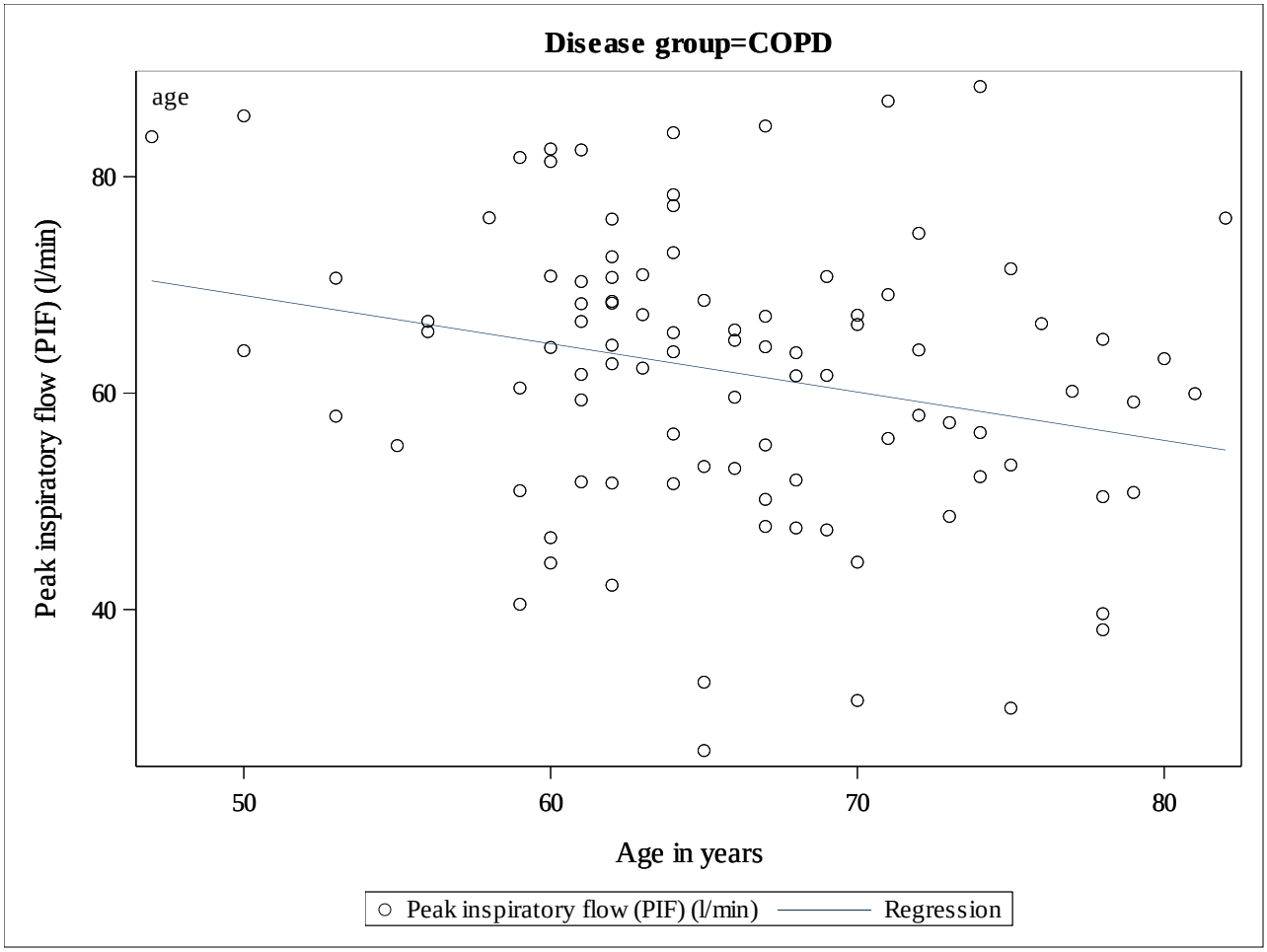
20
40
60
80
Age in years
Peak inspiratory flow (PIF) (l/min)
Regression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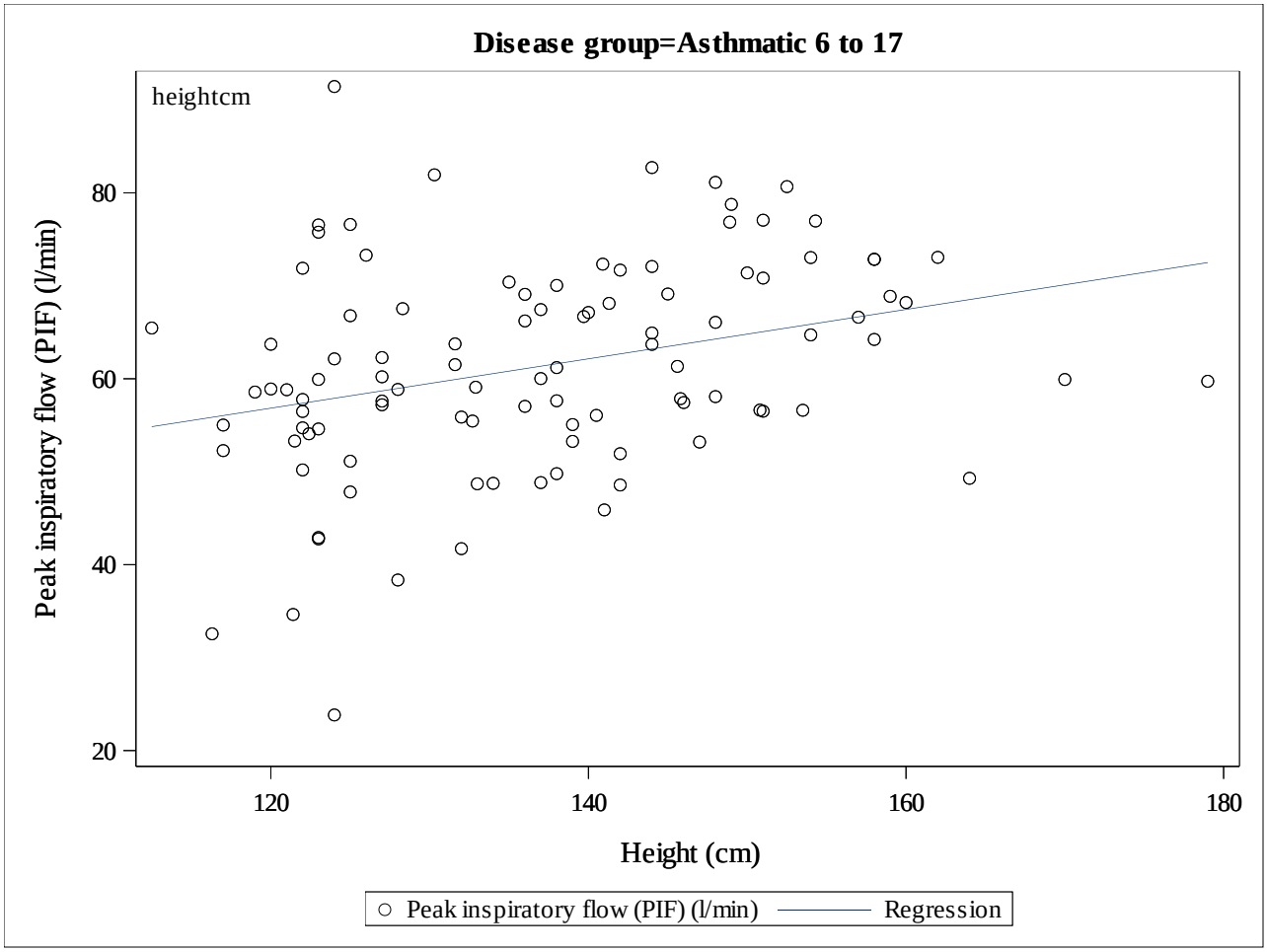
age
Peak inspiratory flow (PIF) (l/min)
80
60
40
50
60
70
80
Age in years
Peak inspiratory flow (PIF) (l/min)
Regression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heightcm
Peak inspiratory flow (PIF) (l/min)
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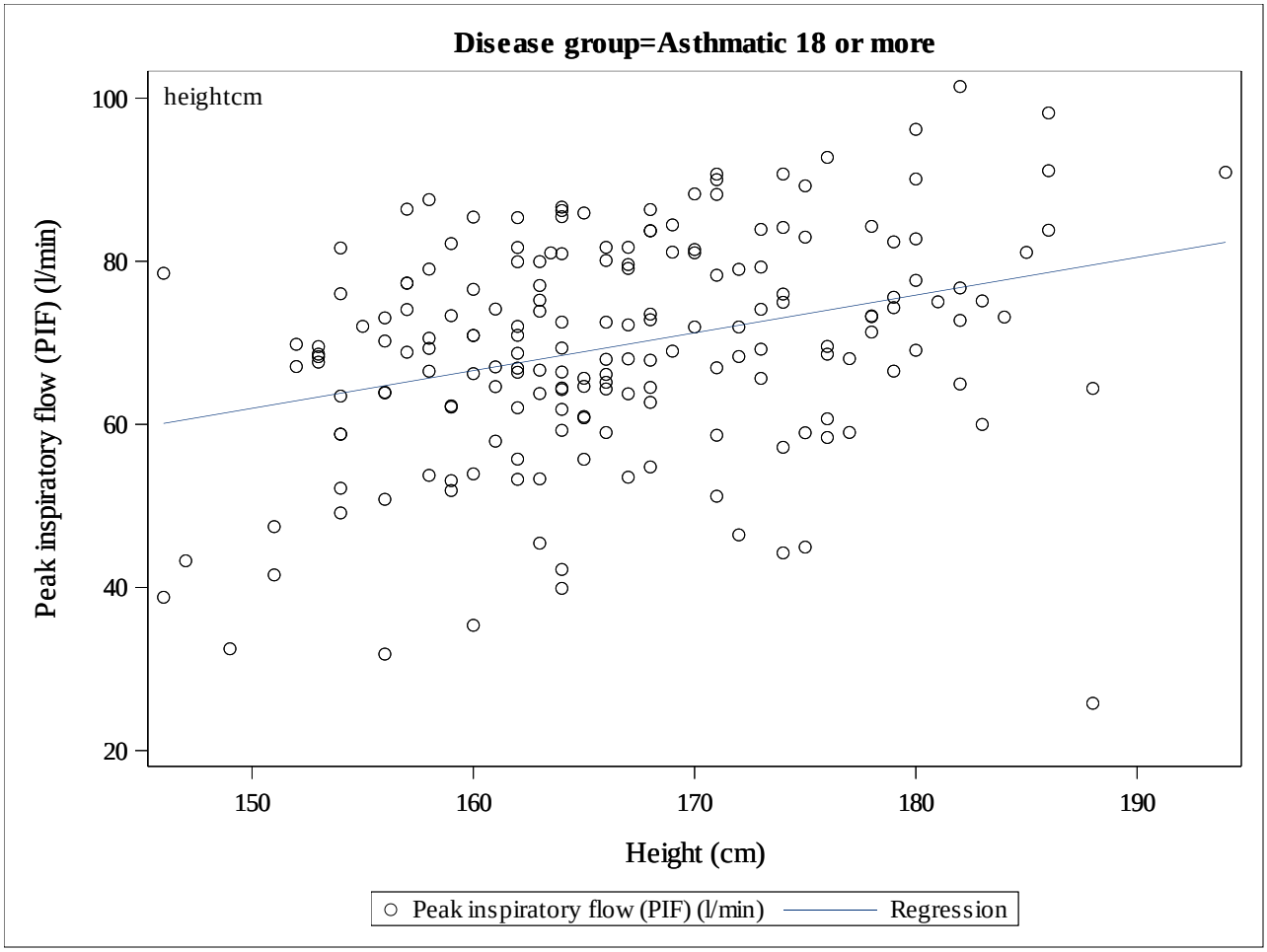
60
40
20
120
140
160
180
Height (cm)
Peak inspiratory flow (PIF) (l/min)
Regression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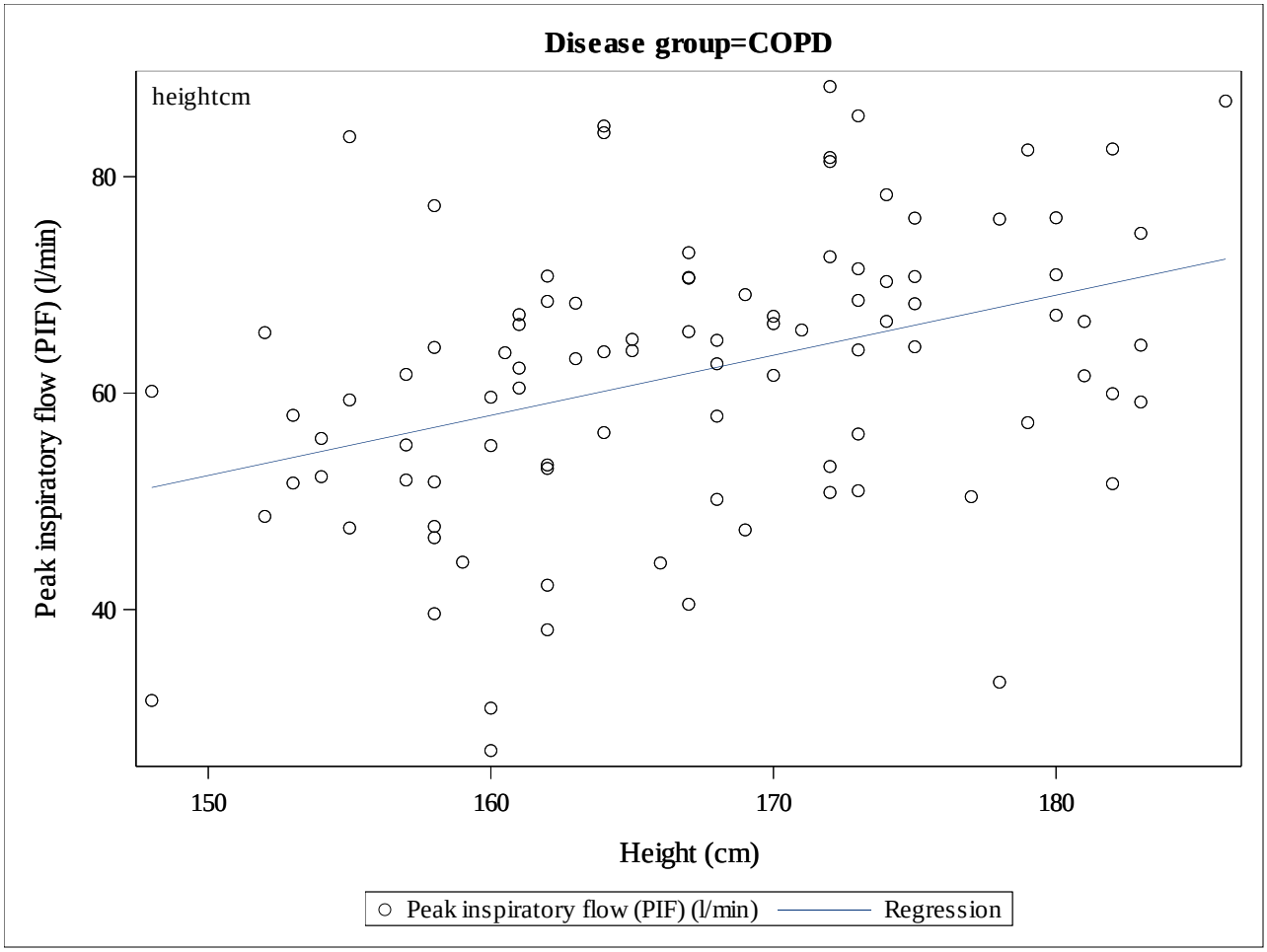
150
160
170
180
190
Height (cm)
Peak inspiratory flow (PIF) (l/min)
Regression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Peak inspiratory flow (PIF) (l/min)
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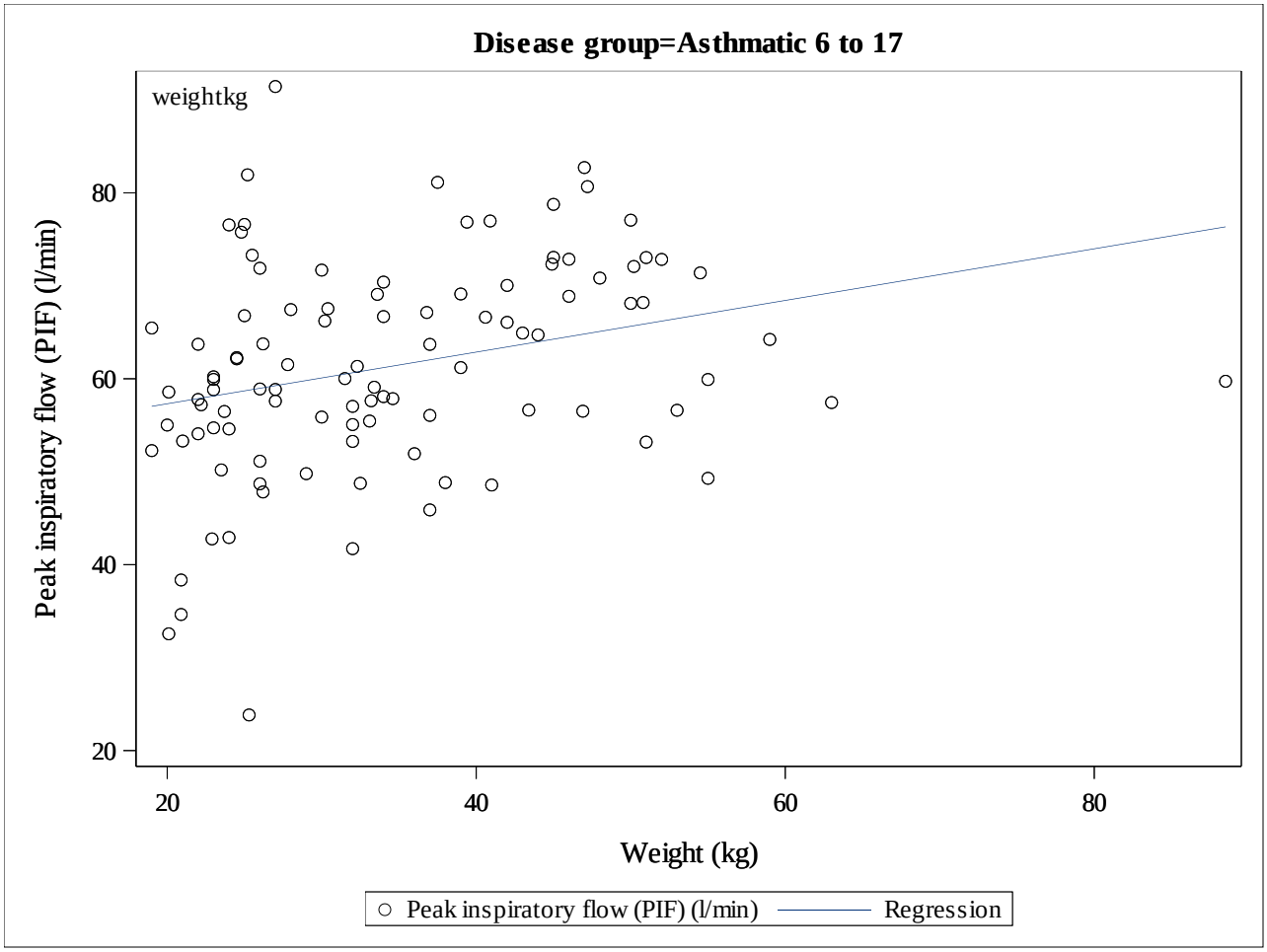
Height (cm)
Peak inspiratory flow (PIF) (l/min)
Regression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weightkg
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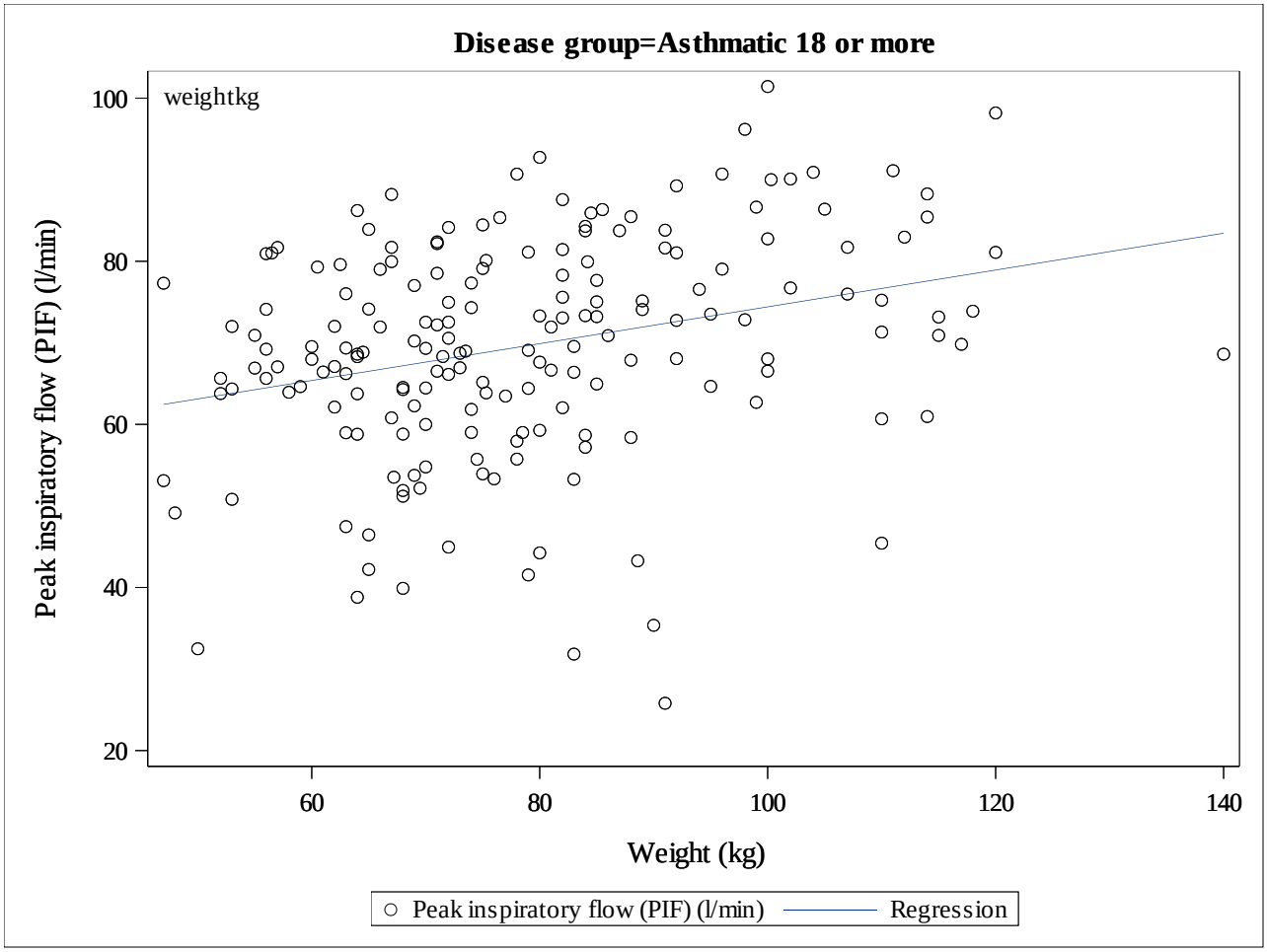
60
40
20
20
40
60
80
Weight (kg)
Peak inspiratory flow (PIF) (l/min)
Regression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weightkg
Peak inspiratory flow (PIF) (l/min)
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80
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120
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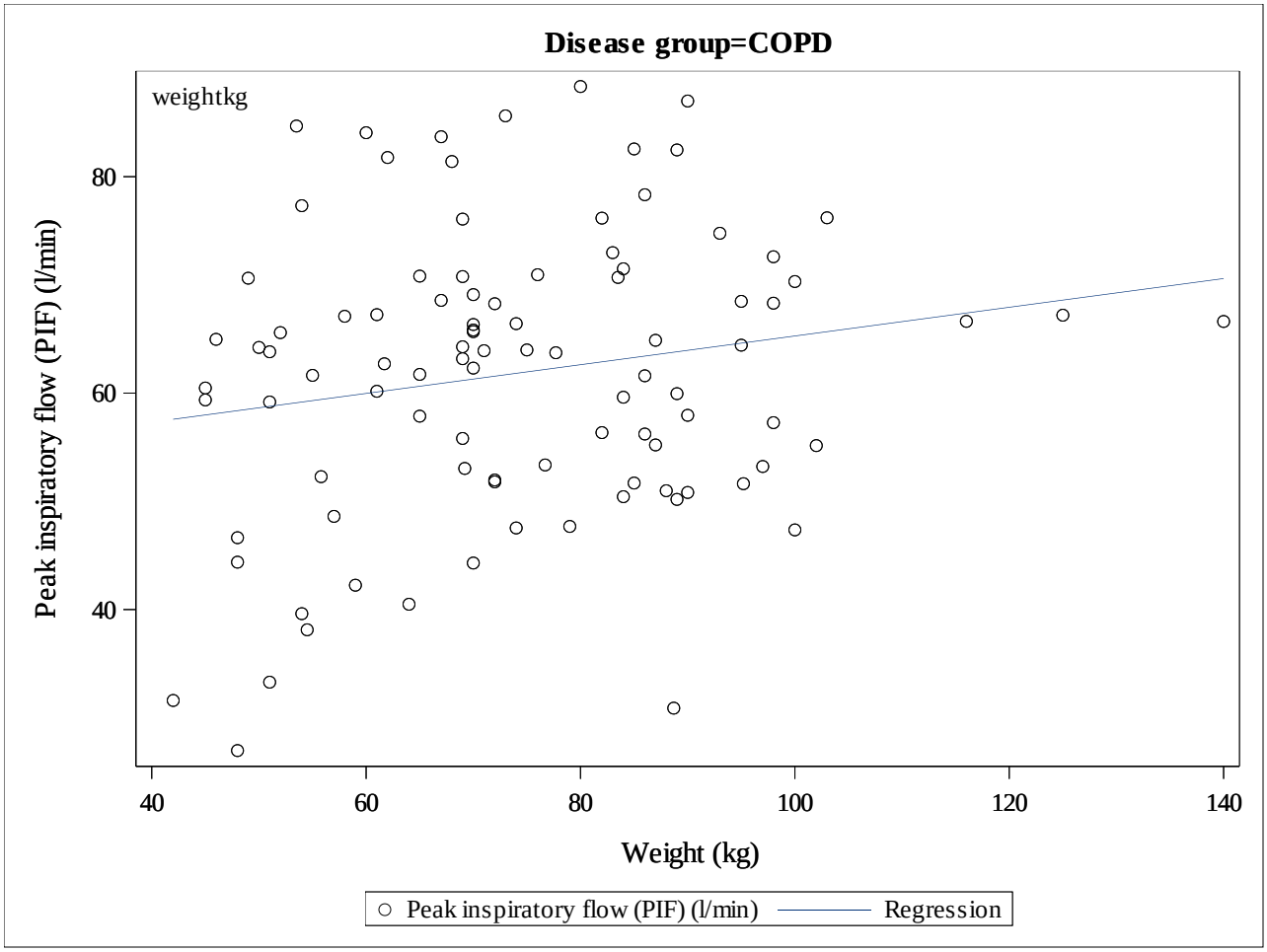
Weight (kg)
Peak inspiratory flow (PIF) (l/min)
Regression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weightkg
Peak inspiratory flow (PIF) (l/min)
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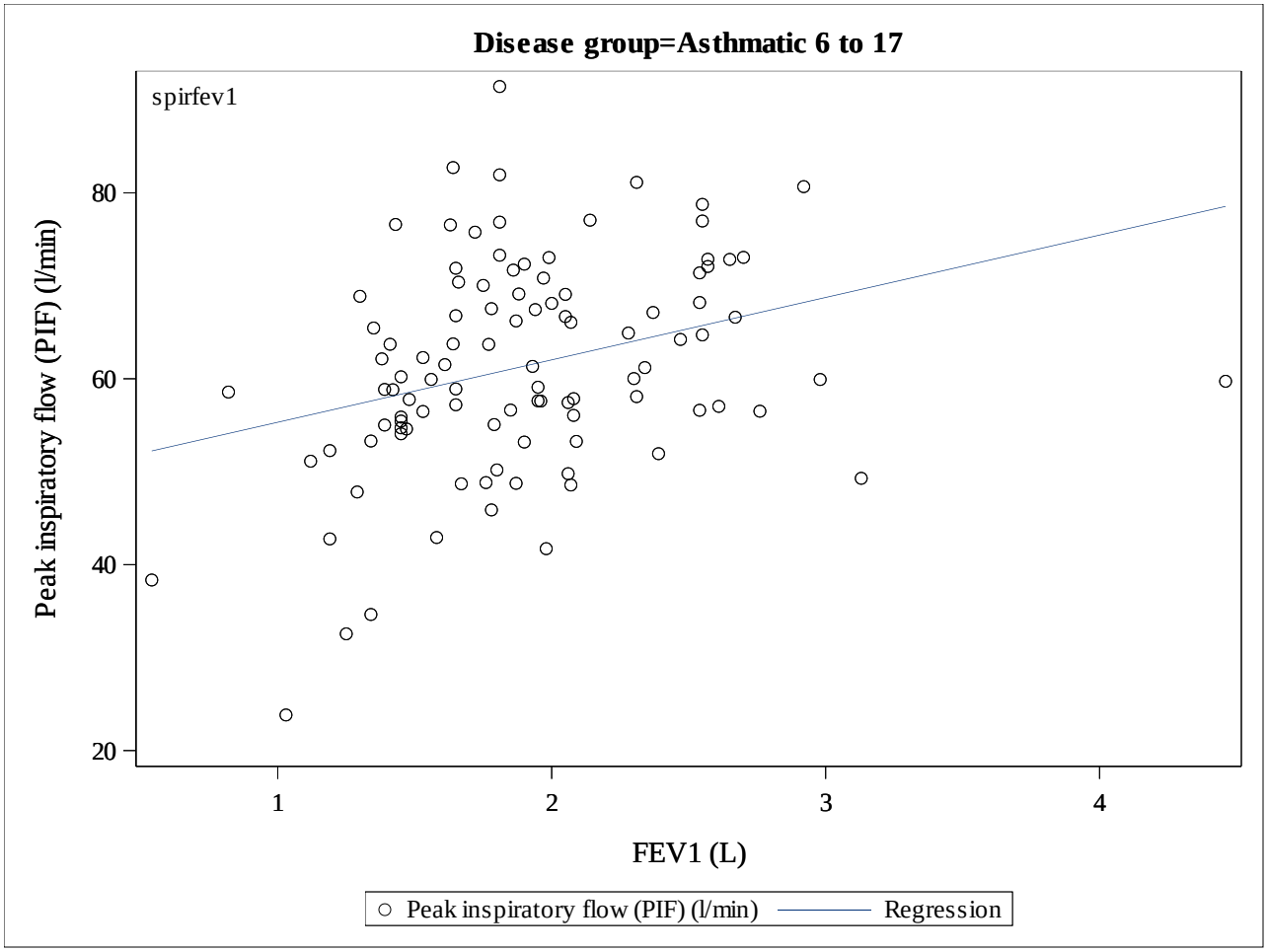
Weight (kg)
Peak inspiratory flow (PIF) (l/min)
Regression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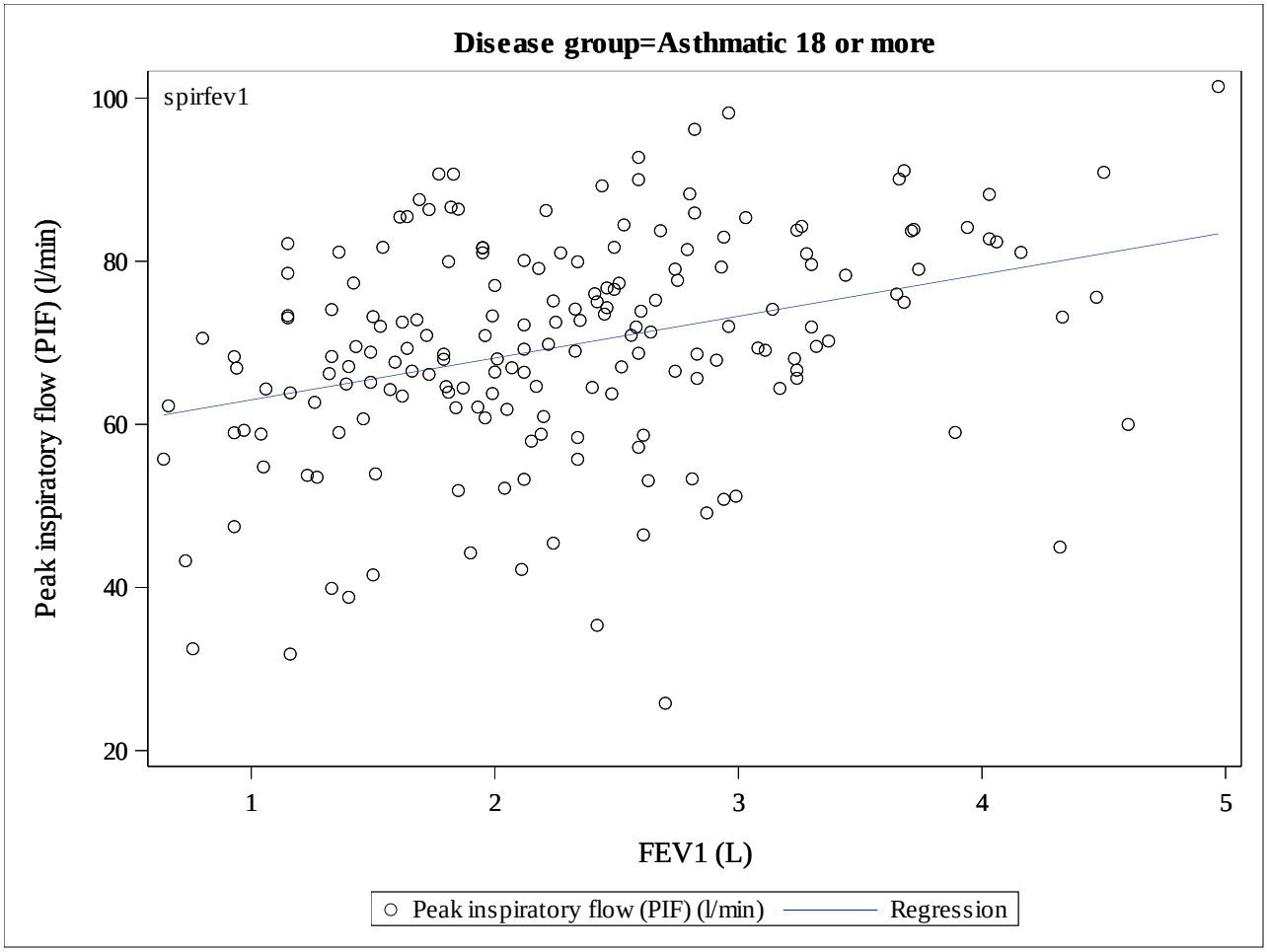
60
40
20
1
2
3
4
FEV1 (L)
Peak inspiratory flow (PIF) (l/min)
Regression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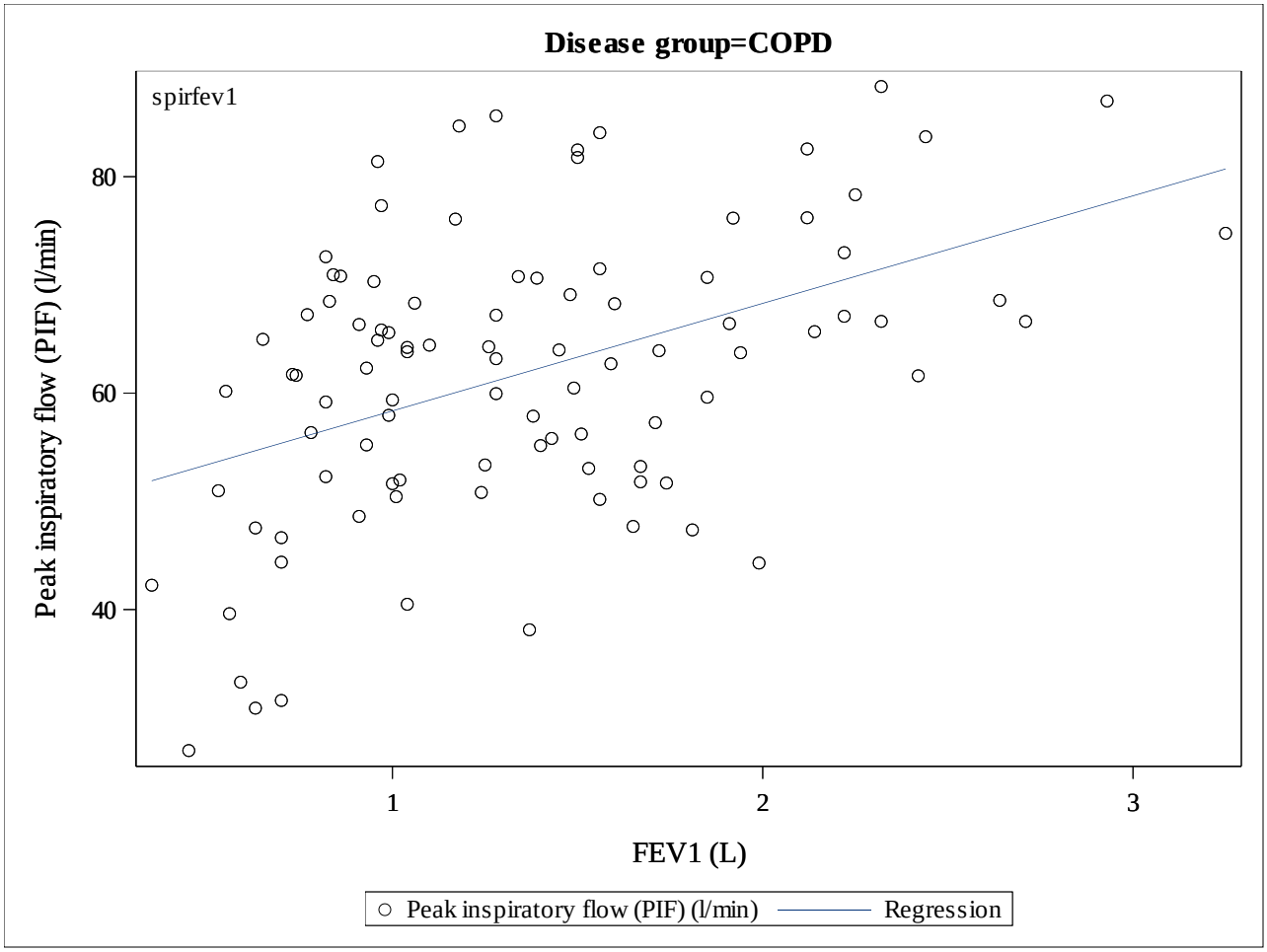
5
FEV1 (L)
Peak inspiratory flow (PIF) (l/min)
Regression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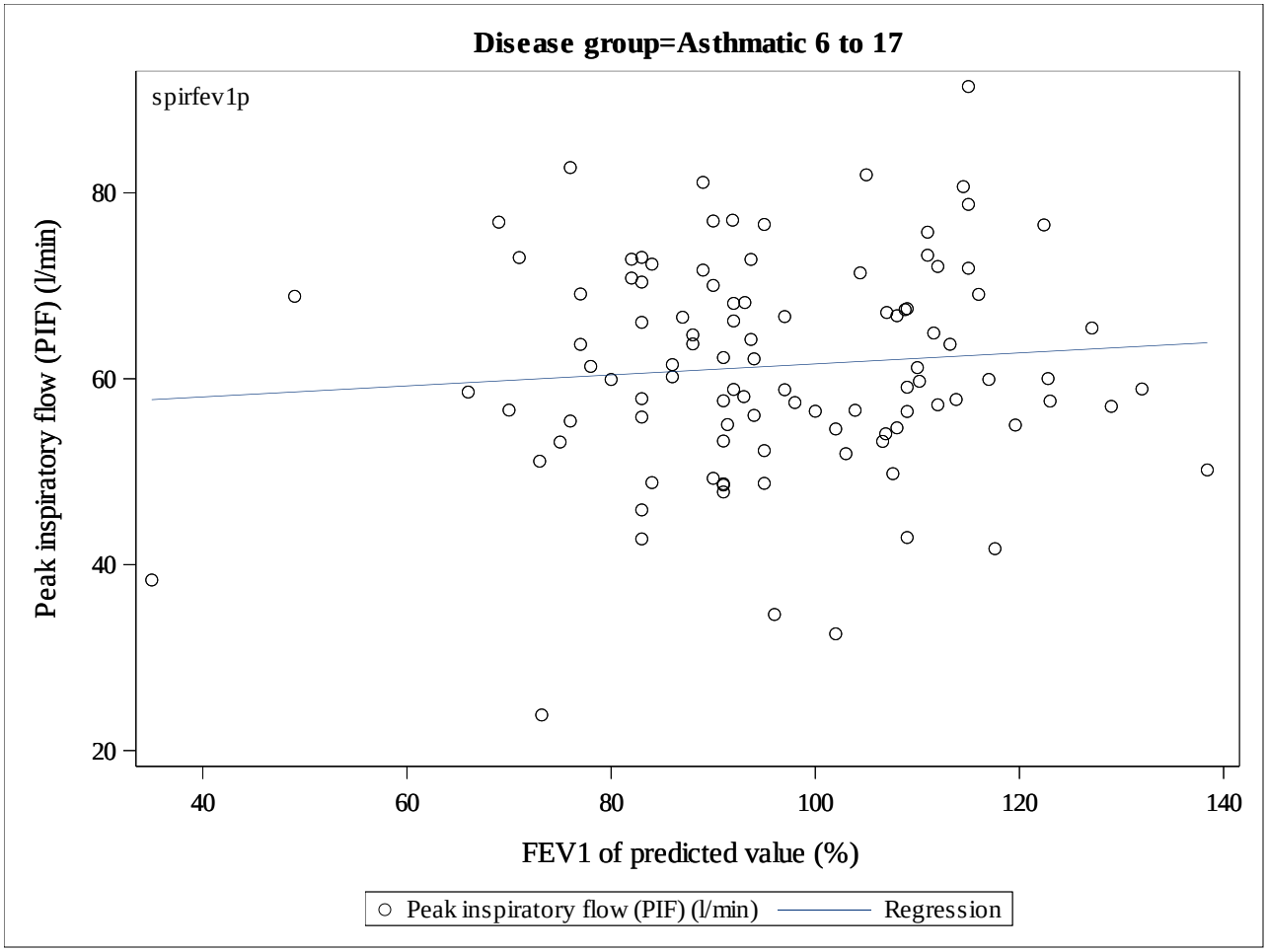
FEV1 (L)
Peak inspiratory flow (PIF) (l/min)
Regression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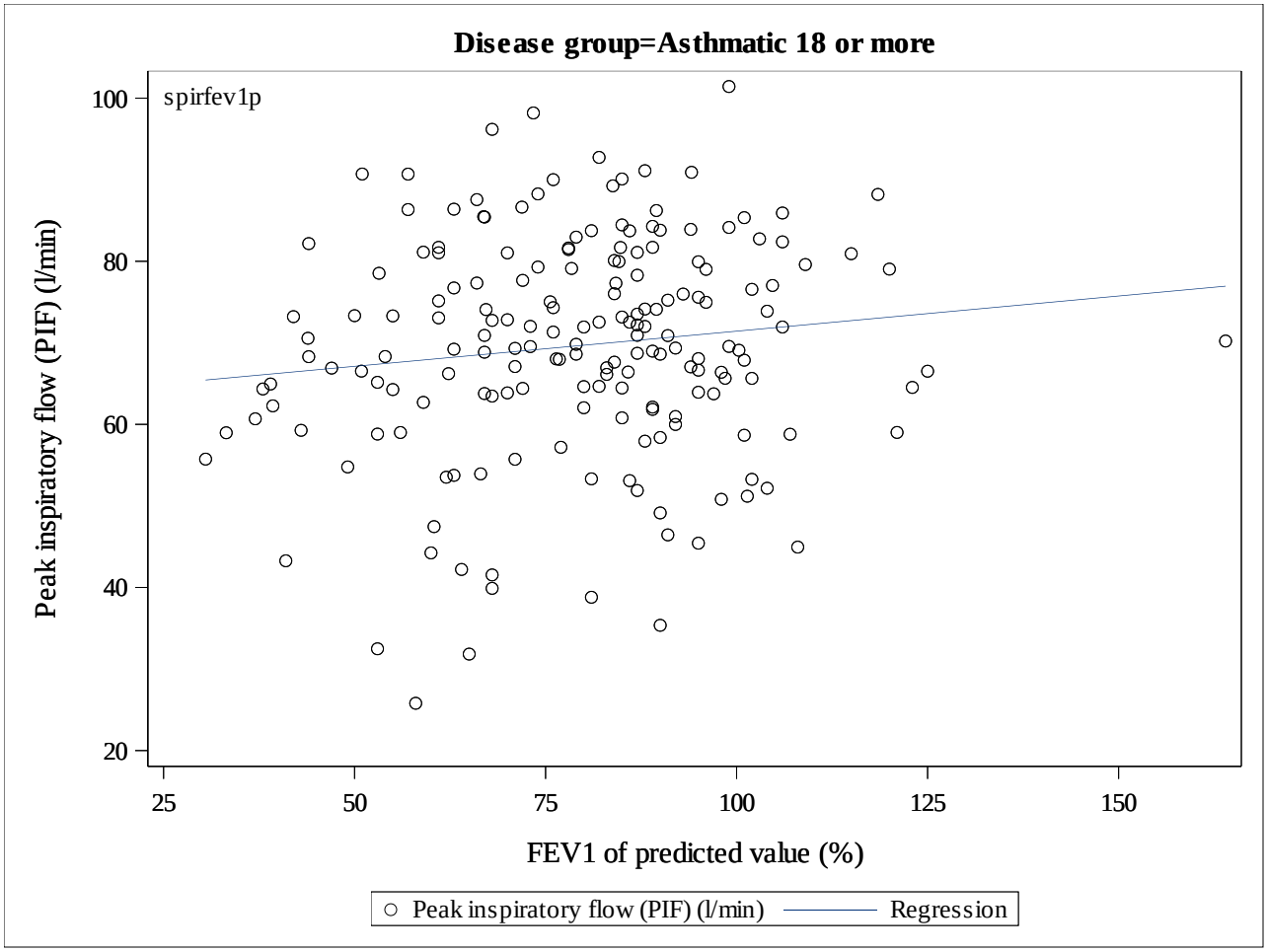
140
FEV1 of predicted value (%)
Peak inspiratory flow (PIF) (l/min)
Regression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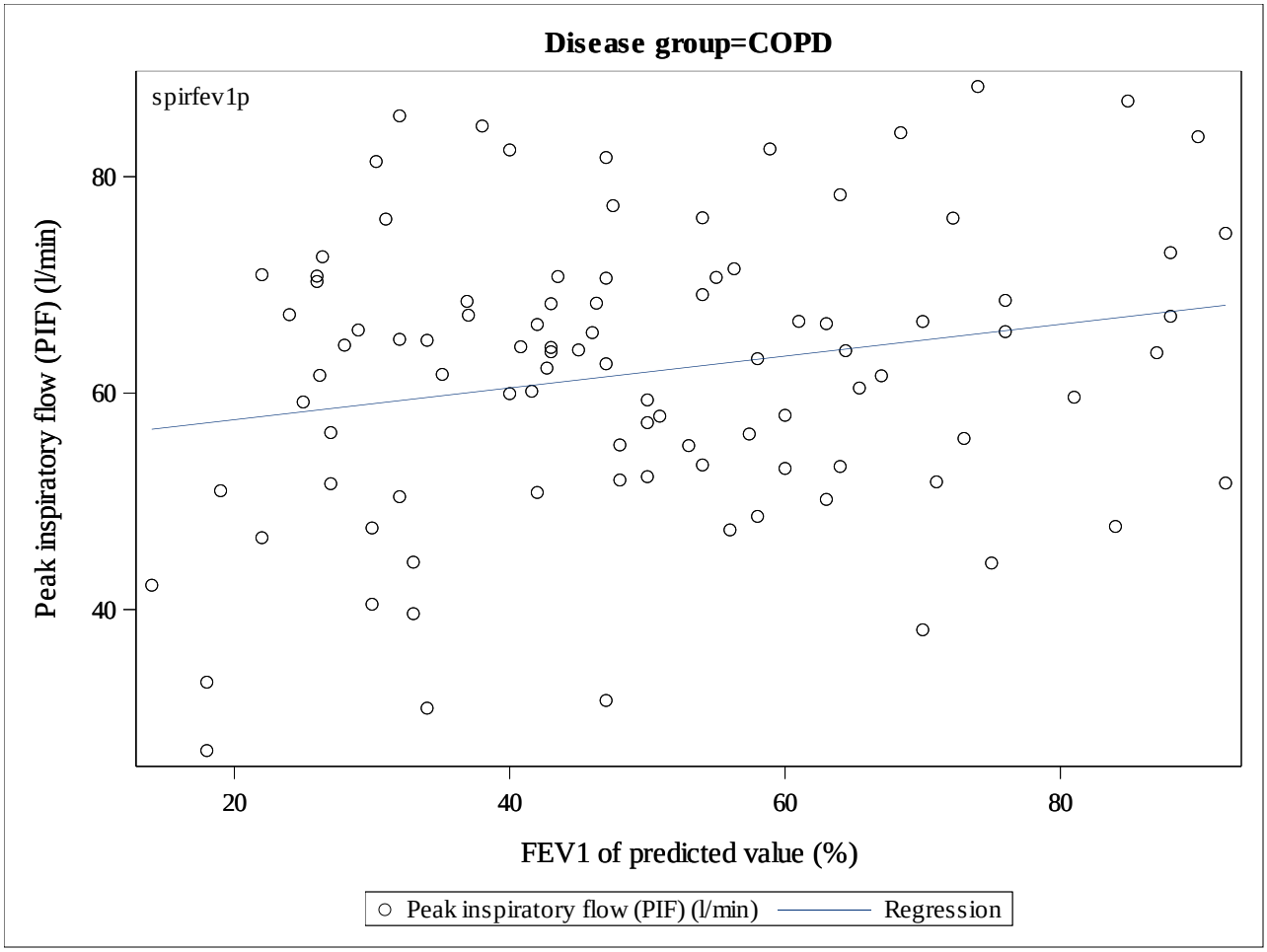
150
FEV1 of predicted value (%)
Peak inspiratory flow (PIF) (l/min)
Regression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Peak inspiratory flow (PIF) (l/min)
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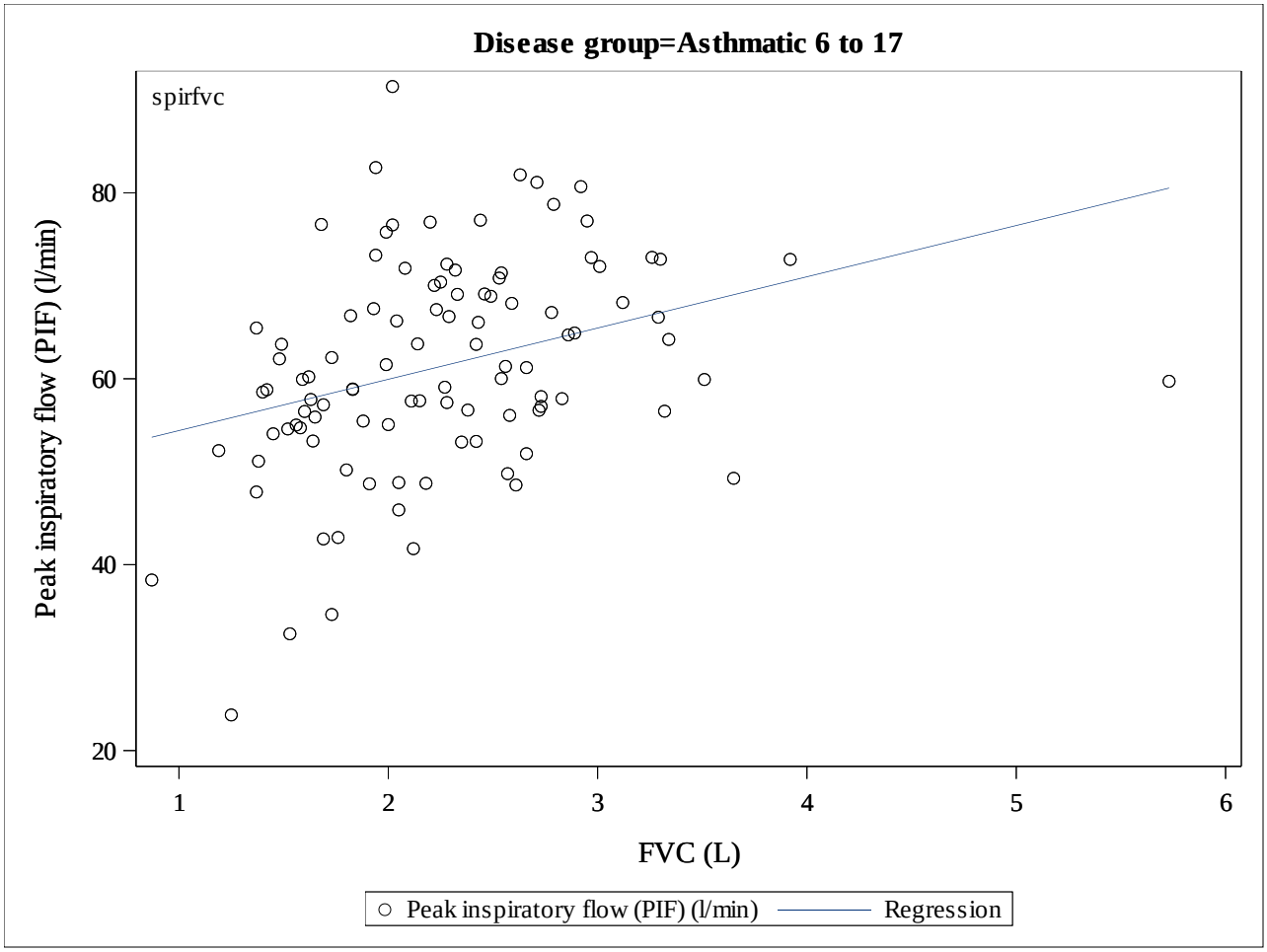
FEV1 of predicted value (%)
Peak inspiratory flow (PIF) (l/min)
Regression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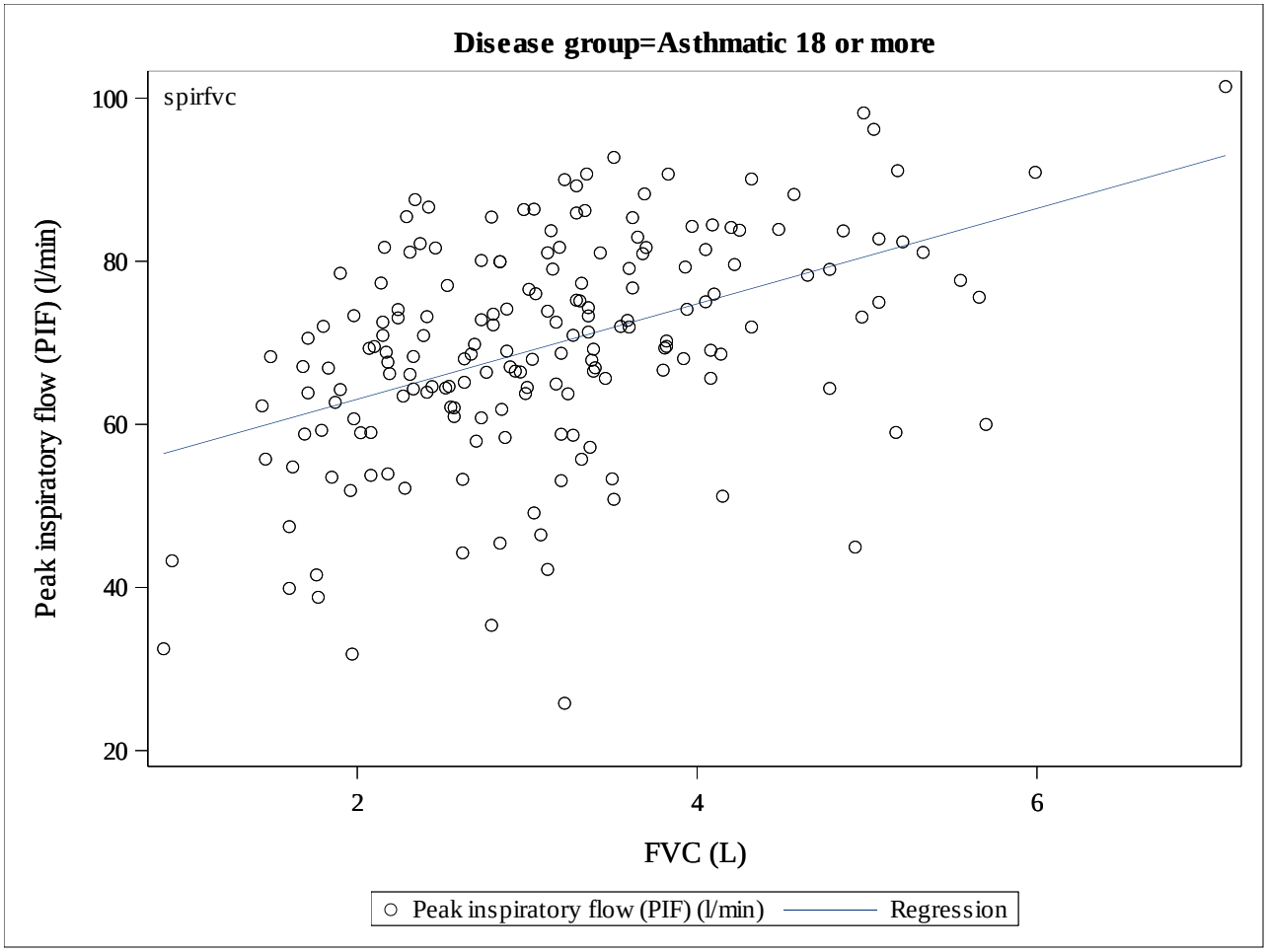
FVC (L)
Peak inspiratory flow (PIF) (l/min)
Regression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Peak inspiratory flow (PIF) (l/min)
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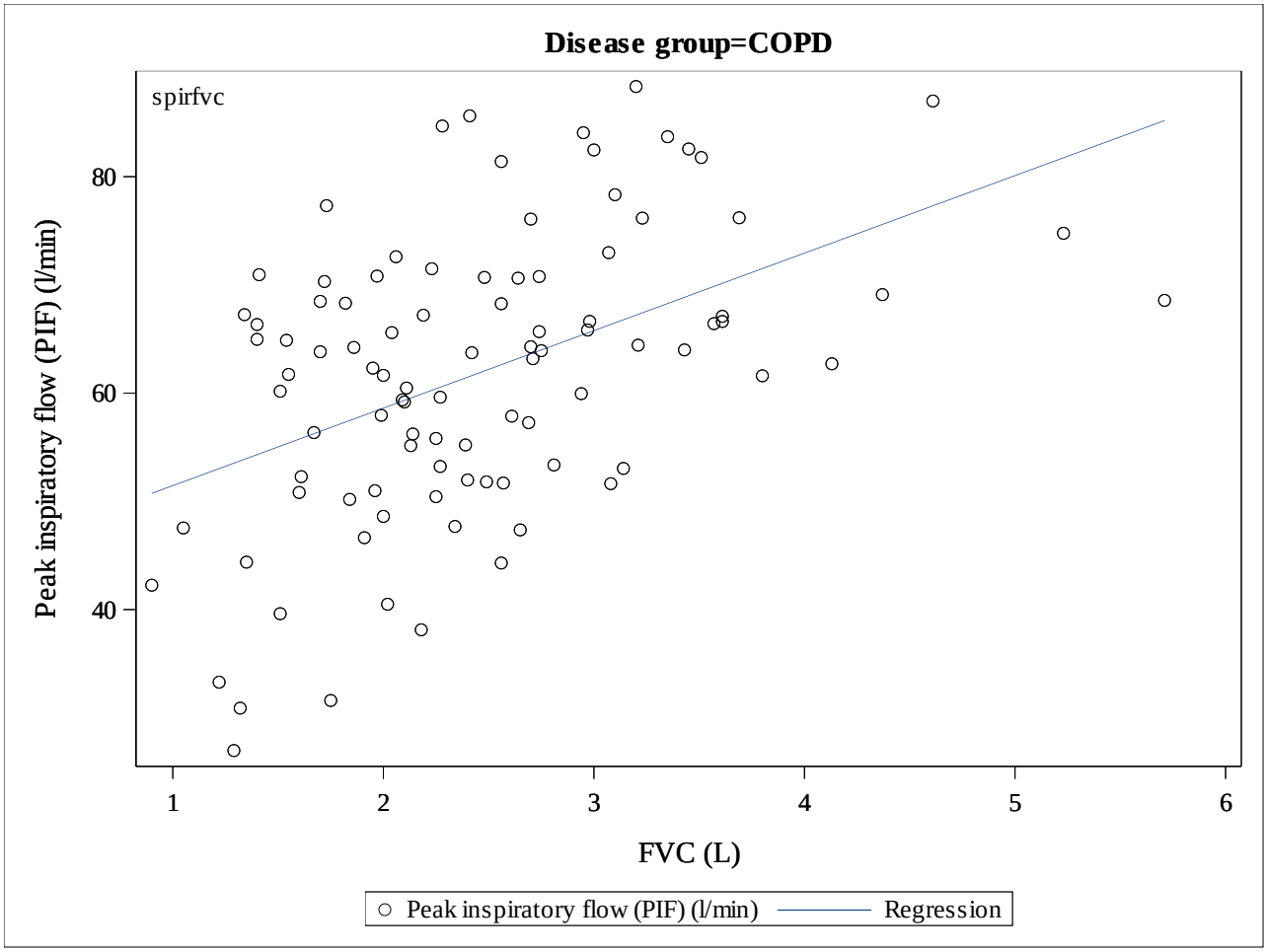
Peak inspiratory flow (PIF) (l/min)
Regression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Peak inspiratory flow (PIF) (l/min)
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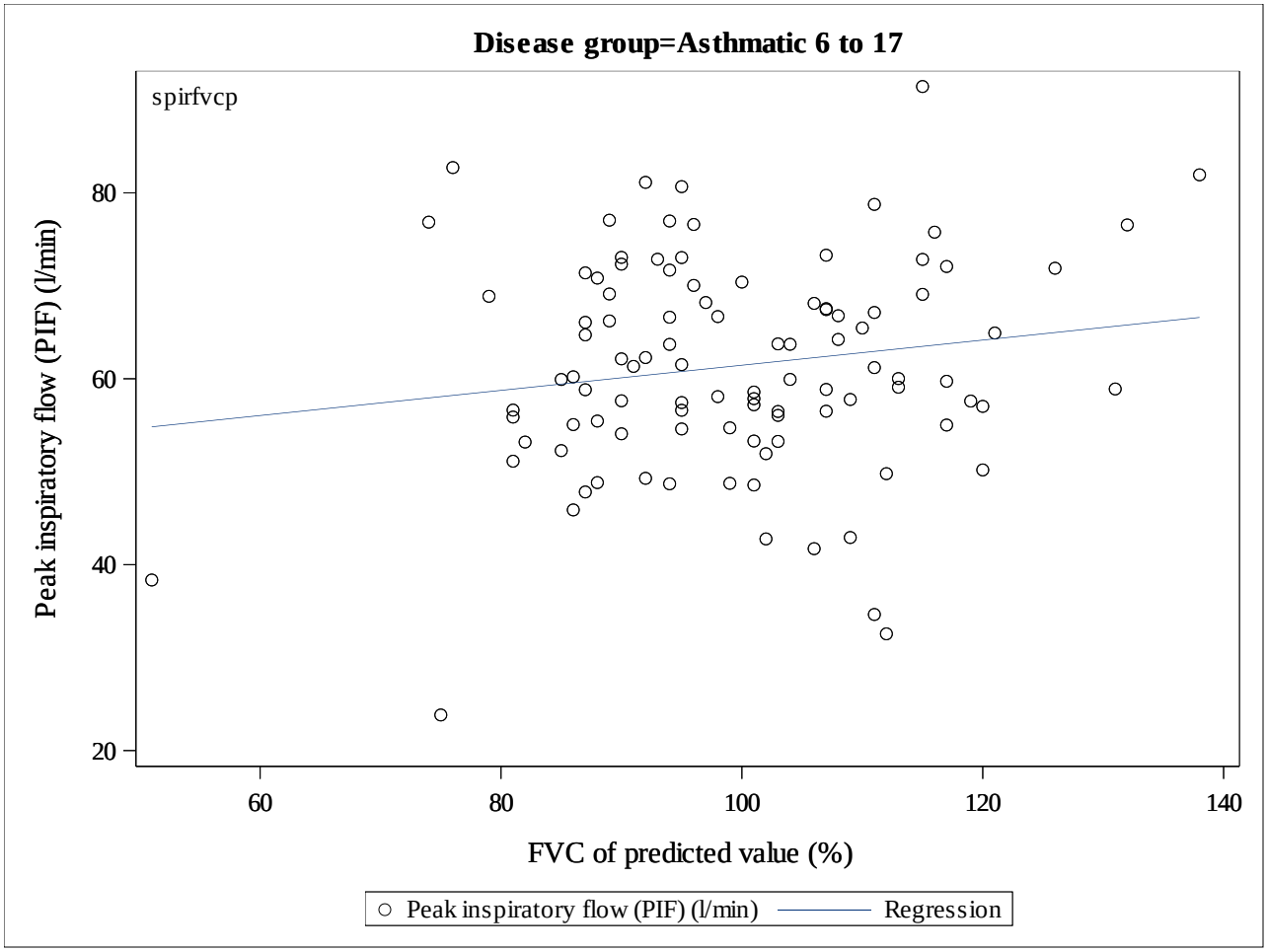
Peak inspiratory flow (PIF) (l/min)
Regression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Peak inspiratory flow (PIF) (l/min)
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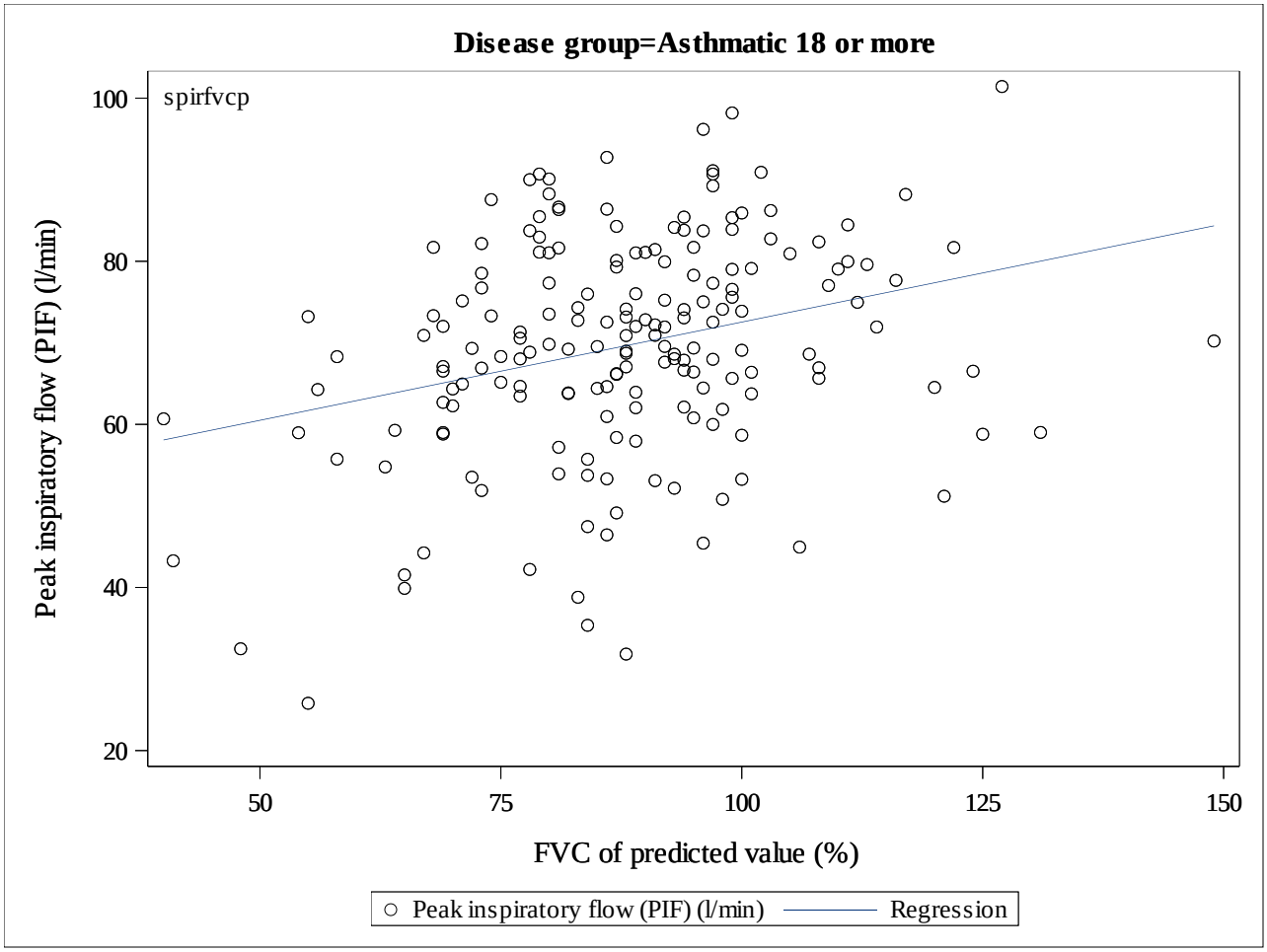
FVC of predicted value (%)
Peak inspiratory flow (PIF) (l/min)
Regression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spirfvcp
Peak inspiratory flow (PIF) (l/min)
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75
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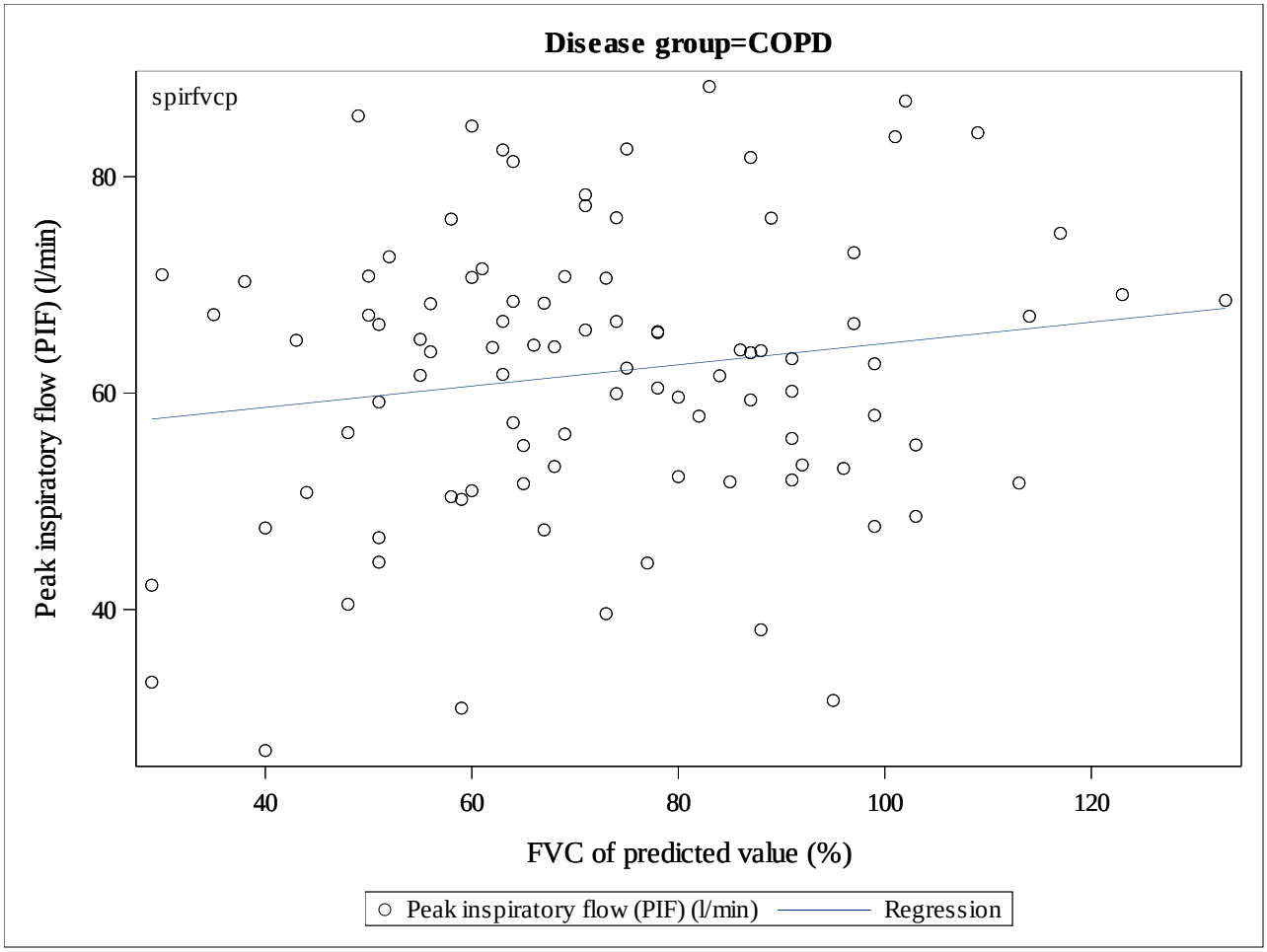
125
150
FVC of predicted value (%)
Peak inspiratory flow (PIF) (l/min)
Regression


Disease group=COPD
spirfvcp
Peak inspiratory flow (PIF) (l/min)
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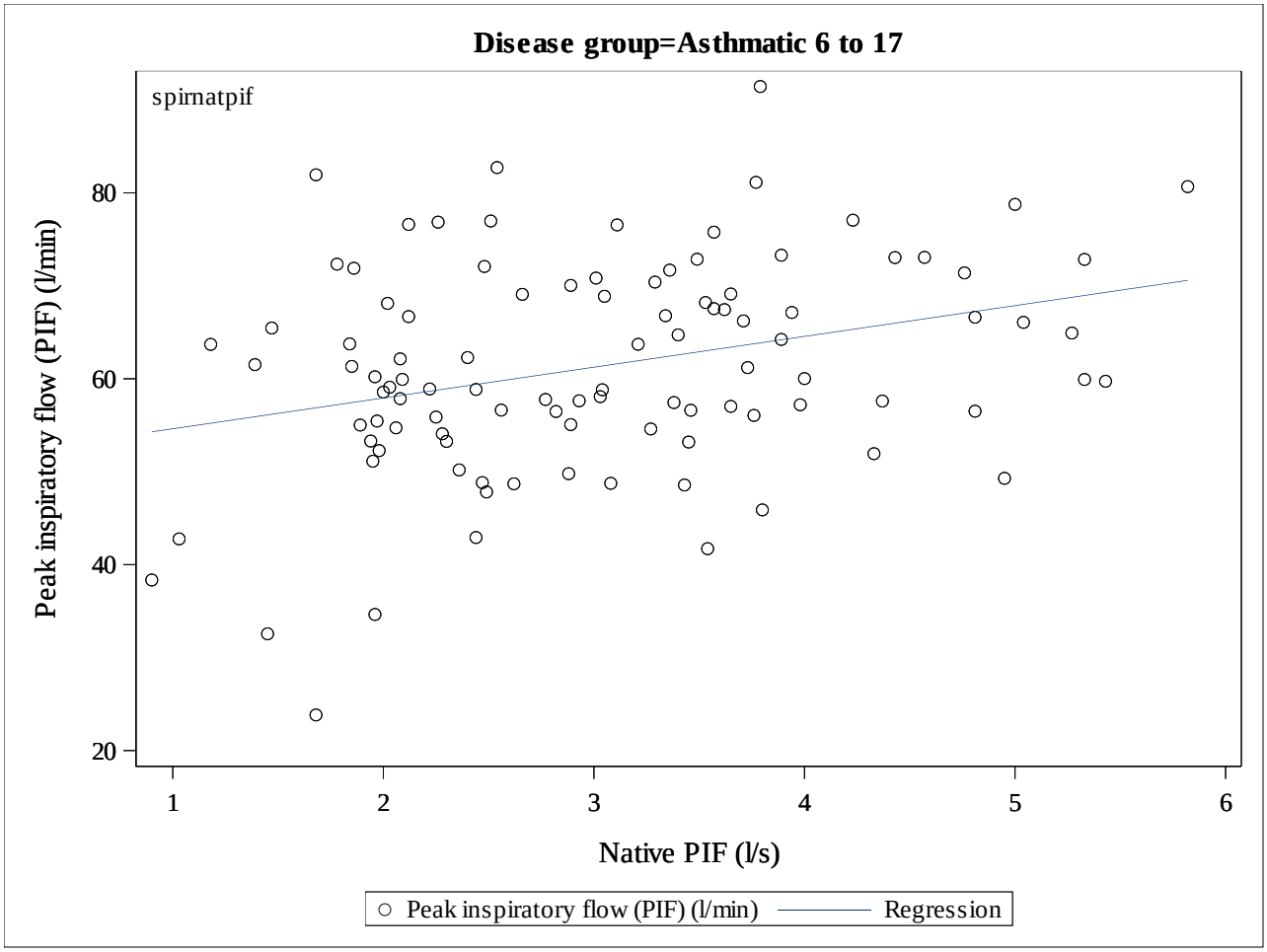
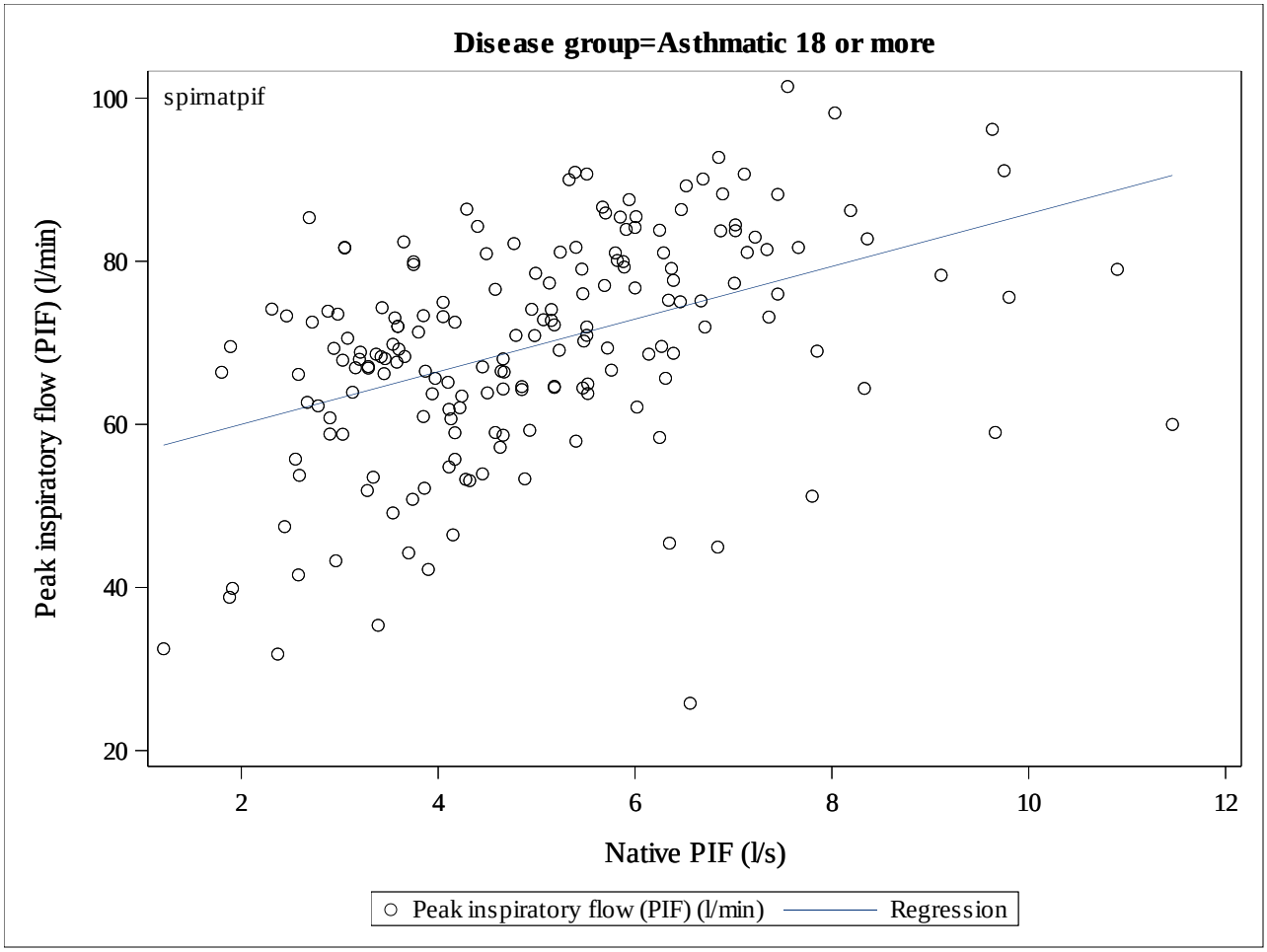
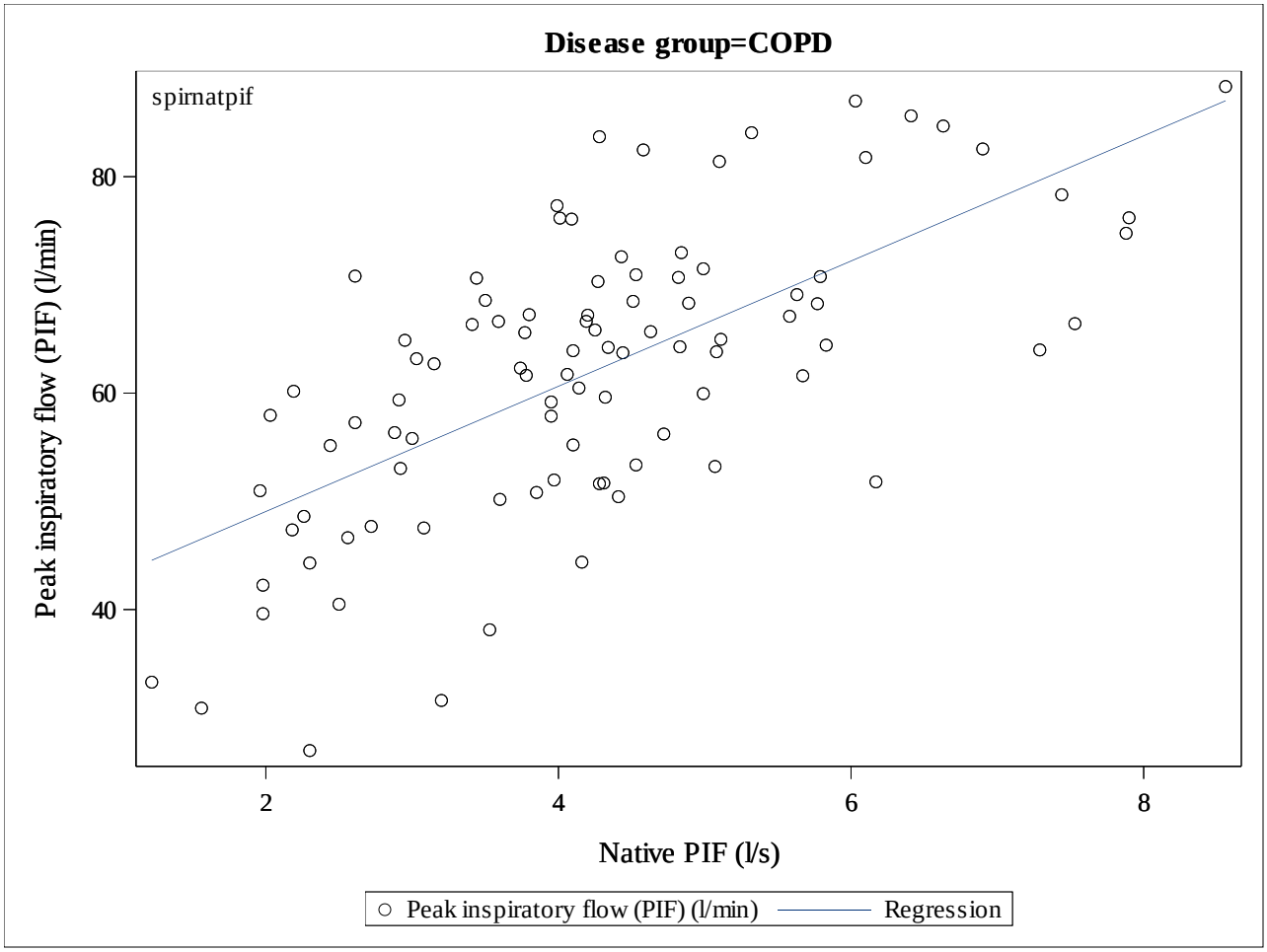
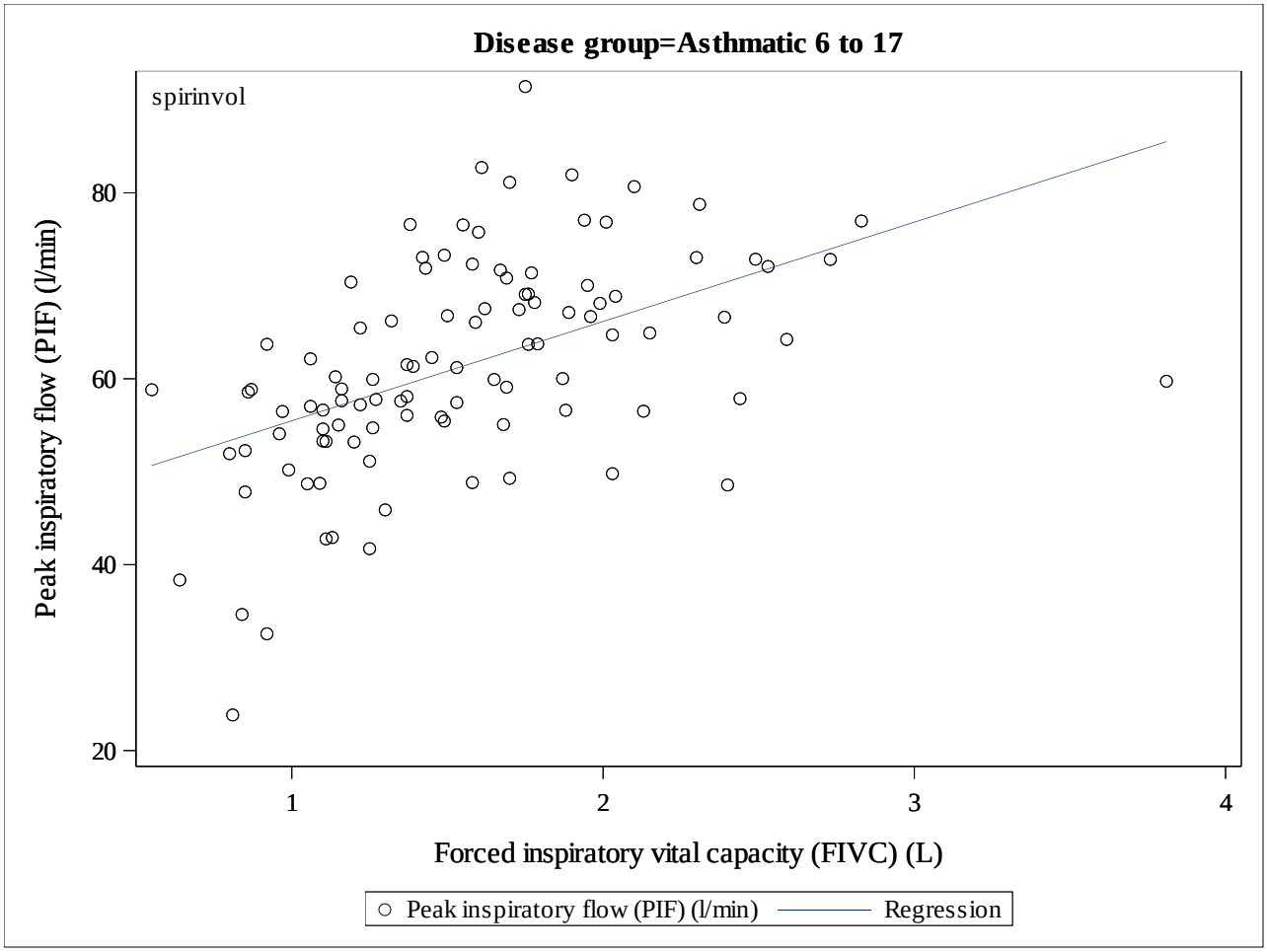
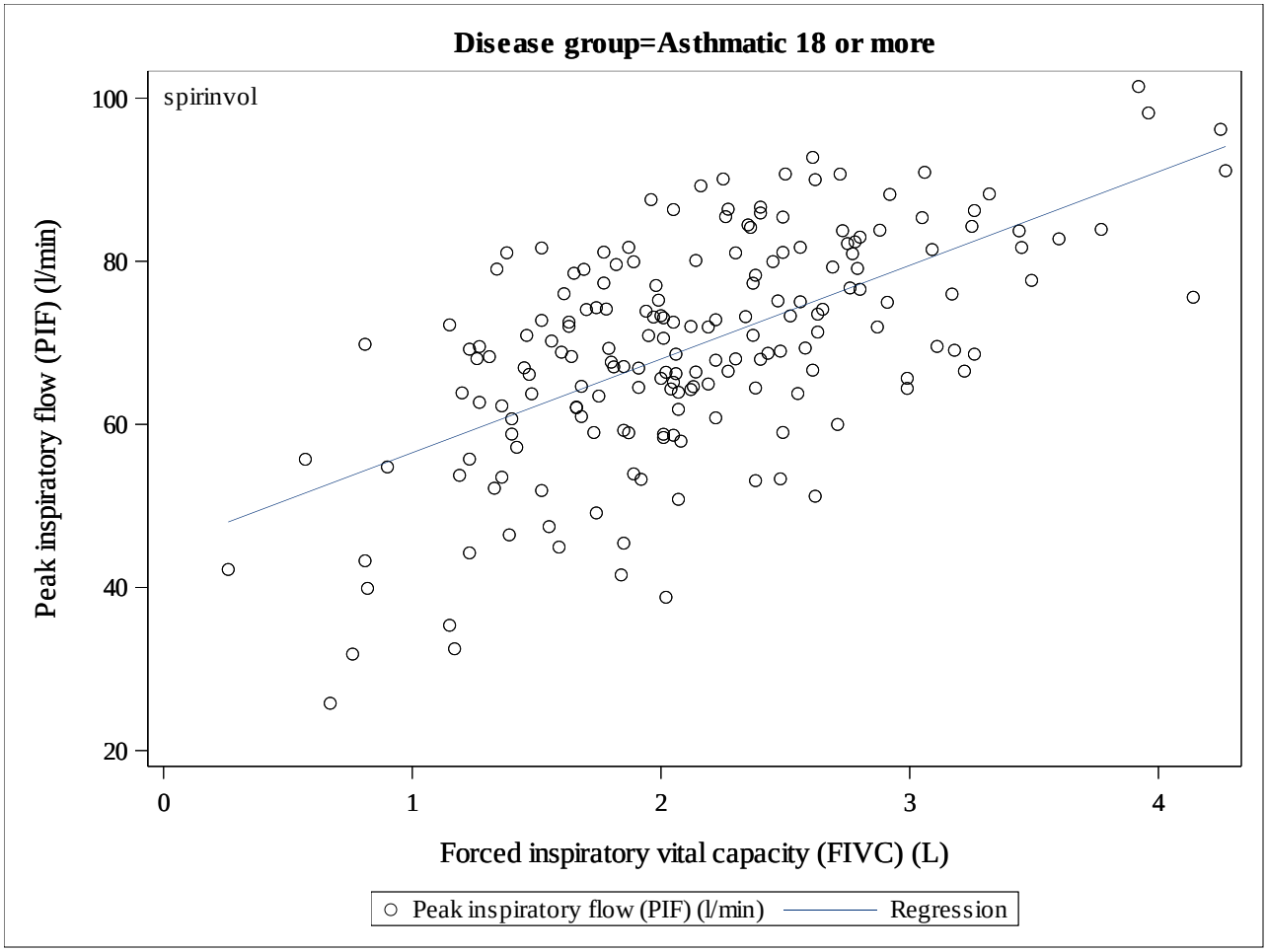
60
40
40
60
80
100
120
FVC of predicted value (%)
Peak inspiratory flow (PIF) (l/min)
Regression

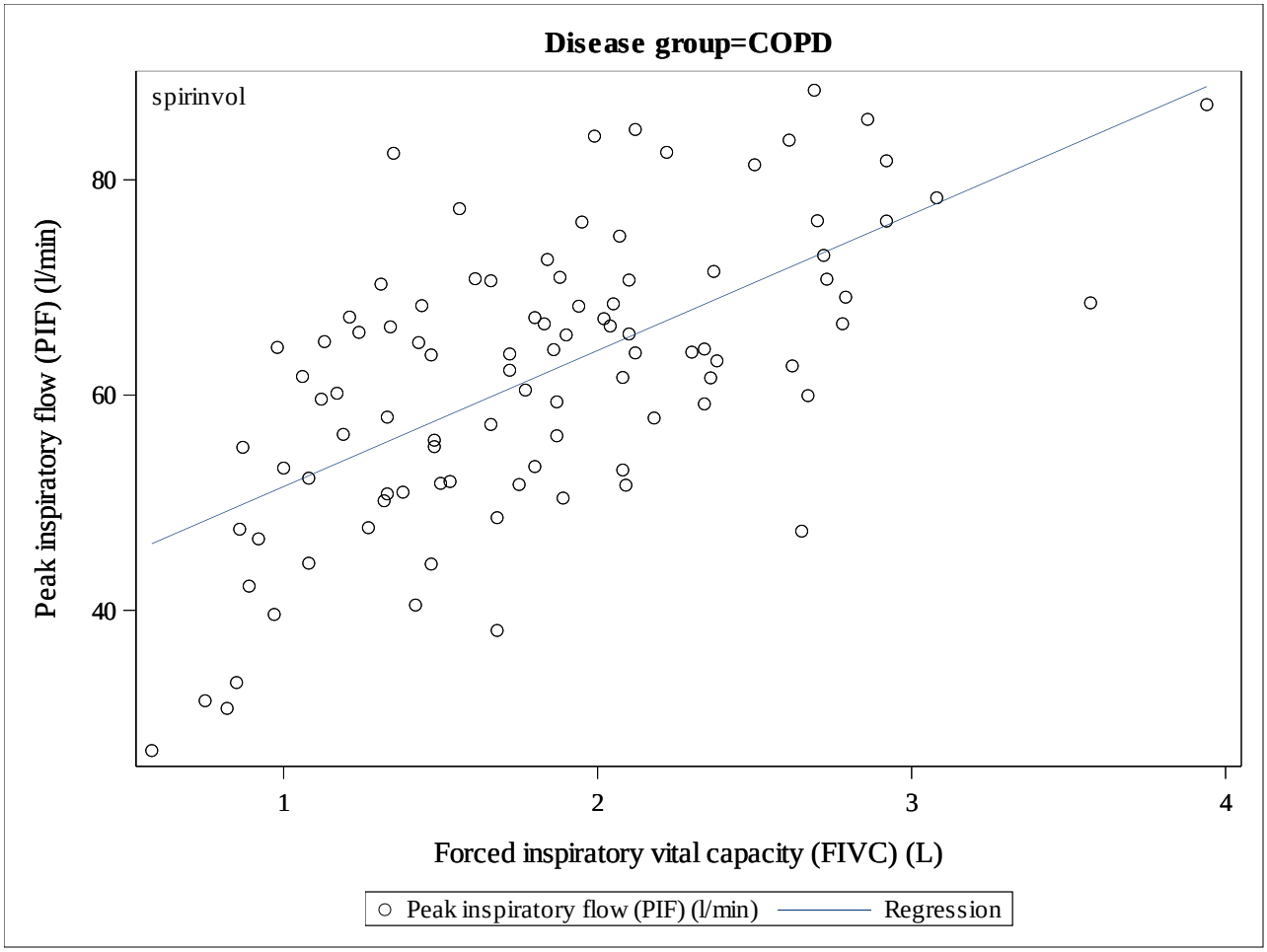

Disease group=Asthmatic 6 to 17
spirnatpif
Peak inspiratory flow (PIF) (l/min)
80
60
40
20
1
2
3
4
5
6
Native PIF (l/s)
Peak inspiratory flow (PIF) (l/min)
Regression

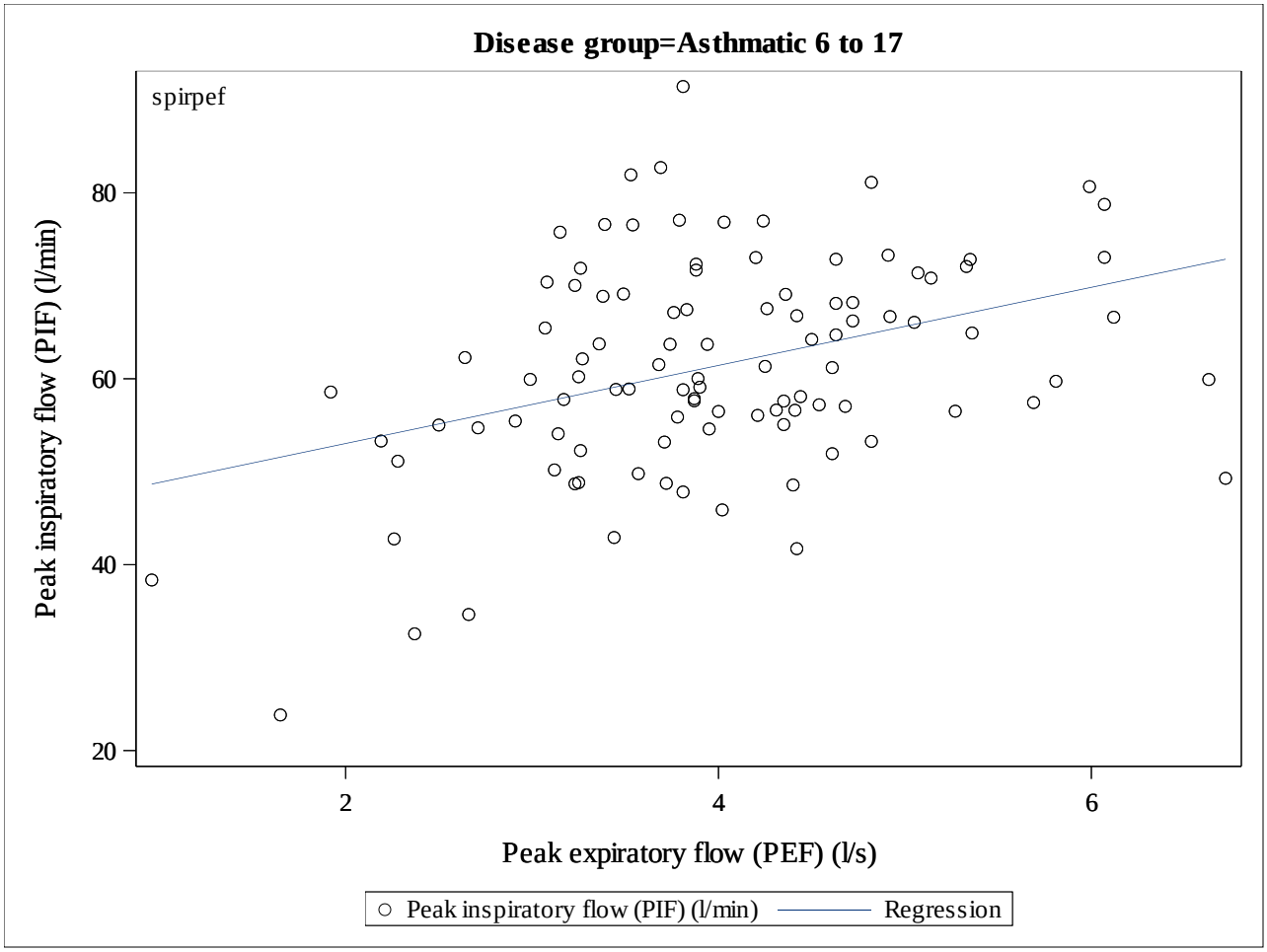

Disease group=Asthmatic 18 or more
spirnatpif
Peak inspiratory flow (PIF) (l/min)
100
80
60
40
20
2
4
6
8
10
12
Native PIF (l/s)
Peak inspiratory flow (PIF) (l/min)
Regression

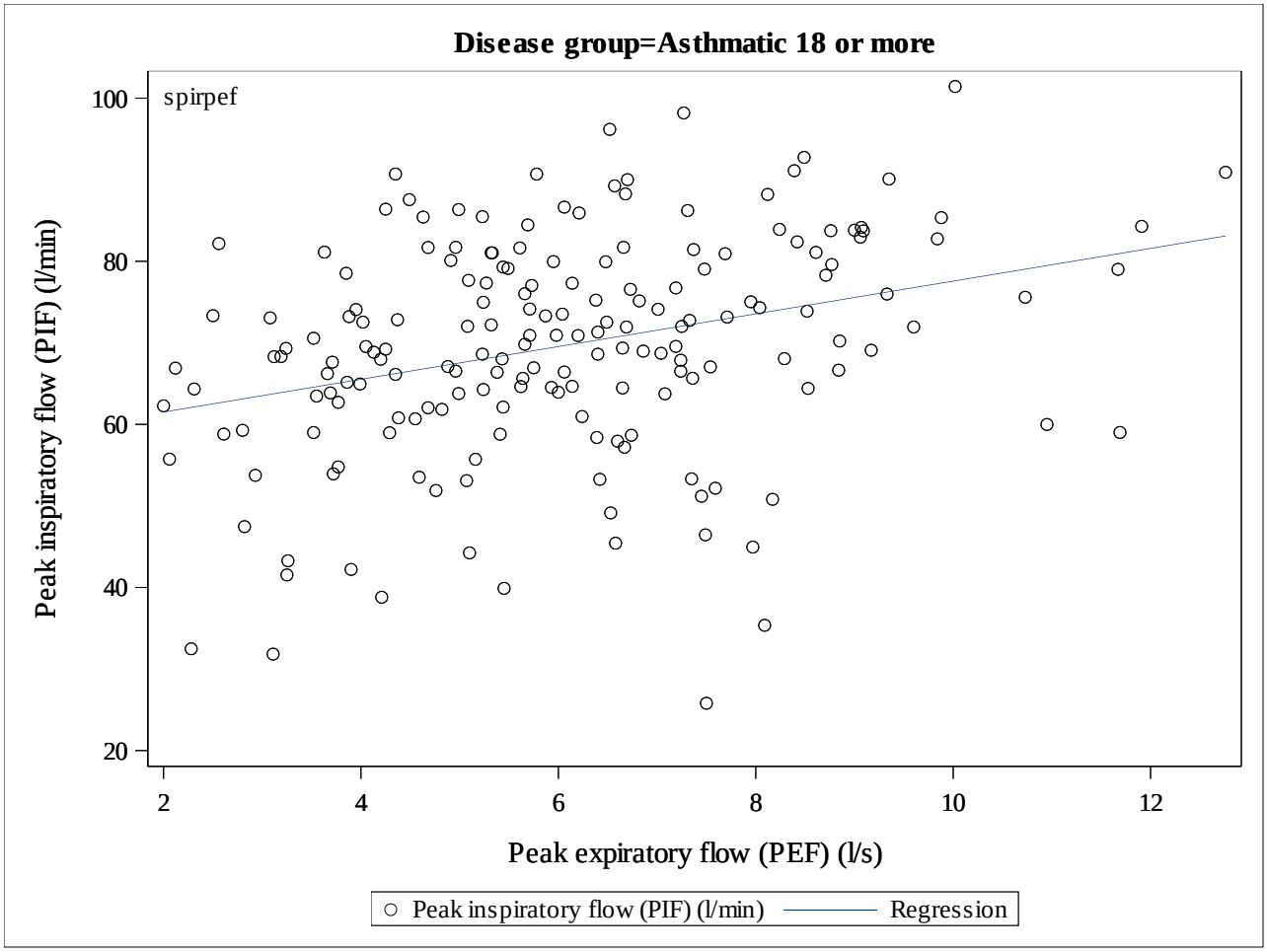

Disease group=COPD
spirnatpif
Peak inspiratory flow (PIF) (l/min)
80
60
40
2
4
6
8
Native PIF (l/s)
Peak inspiratory flow (PIF) (l/min)
Regression


Disease group=Asthmatic 6 to 17
spirinvol
Peak inspiratory flow (PIF) (l/min)
80
60
40
20
1
2
3
4
Forced inspiratory vital capacity (FIVC) (L)
Peak inspiratory flow (PIF) (l/min)
Regression


Disease group=Asthmatic 18 or more
spirinvol
Peak inspiratory flow (PIF) (l/min)
100
80
60
40
20
0
1
2
3
4
Forced inspiratory vital capacity (FIVC) (L)
Peak inspiratory flow (PIF) (l/min)
Regression


Disease group=COPD
spirinvol
Peak inspiratory flow (PIF) (l/min)
80
60
40
1
2
3
4
Forced inspiratory vital capacity (FIVC) (L)
Peak inspiratory flow (PIF) (l/min)
Regression


Disease group=Asthmatic 6 to 17
spirpef
Peak inspiratory flow (PIF) (l/min)
80
60
40
20
2
4
6
Peak expiratory flow (PEF) (l/s)
Peak inspiratory flow (PIF) (l/min)
Regression


Disease group=Asthmatic 18 or more
spirpef
Peak inspiratory flow (PIF) (l/min)
100
80
60
40
20
2
4
6
8
10
12
Peak expiratory flow (PEF) (l/s)
Peak inspiratory flow (PIF) (l/min)
Regression

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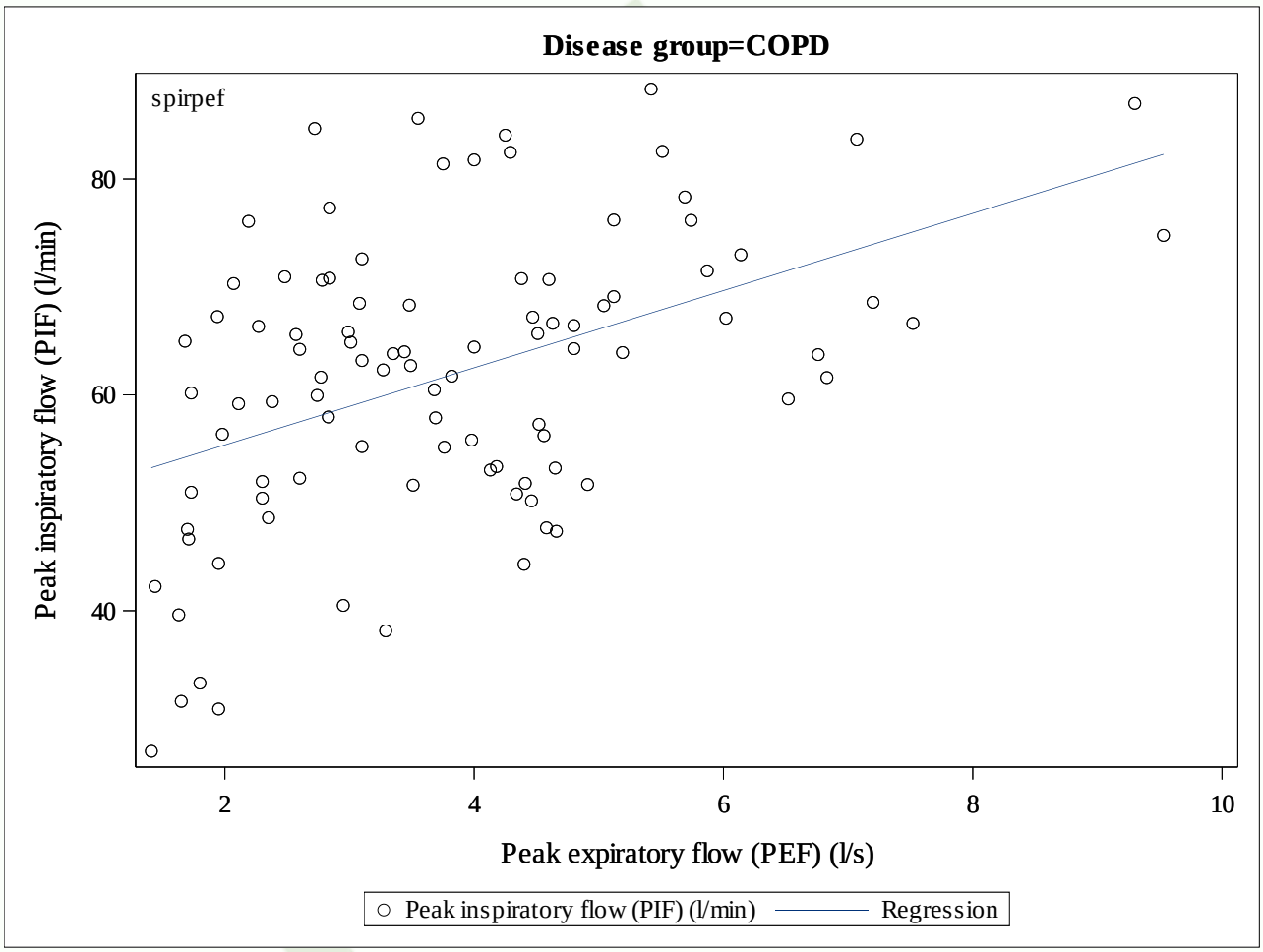

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