

Biomarker of CF lung disease: Lung clearance index

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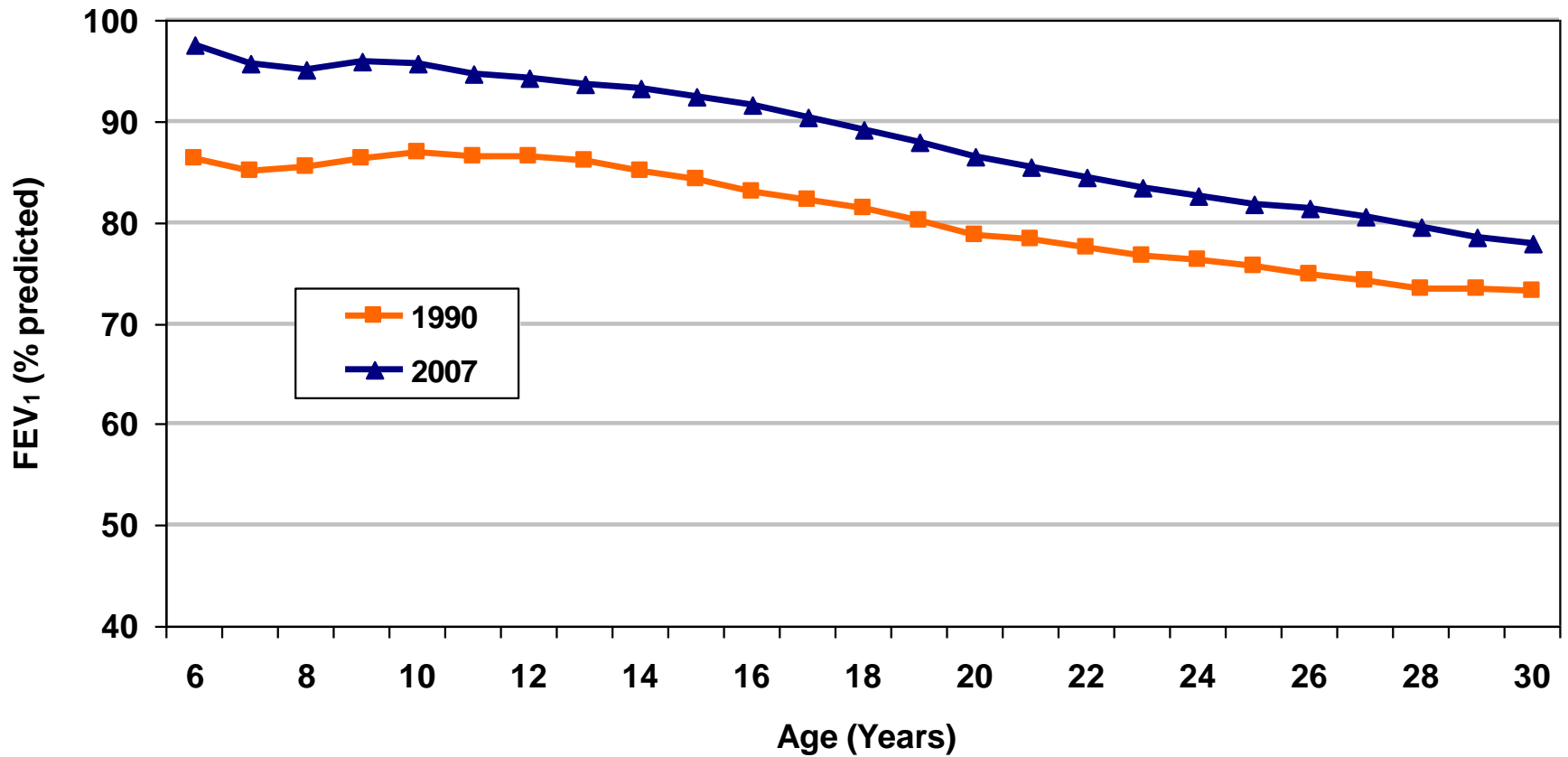
Toronto, Canada

SickKids®



The problem of success..

Median FEV₁ (% predicted) in Canada



Lung clearance index

why do we need another marker of lung function?

- Measured by multiple breath washout during tidal breathing; feasible in all age groups
- More sensitive than spirometry to detect abnormalities in the peripheral airways

Aurora P et al., *Thorax* 2004

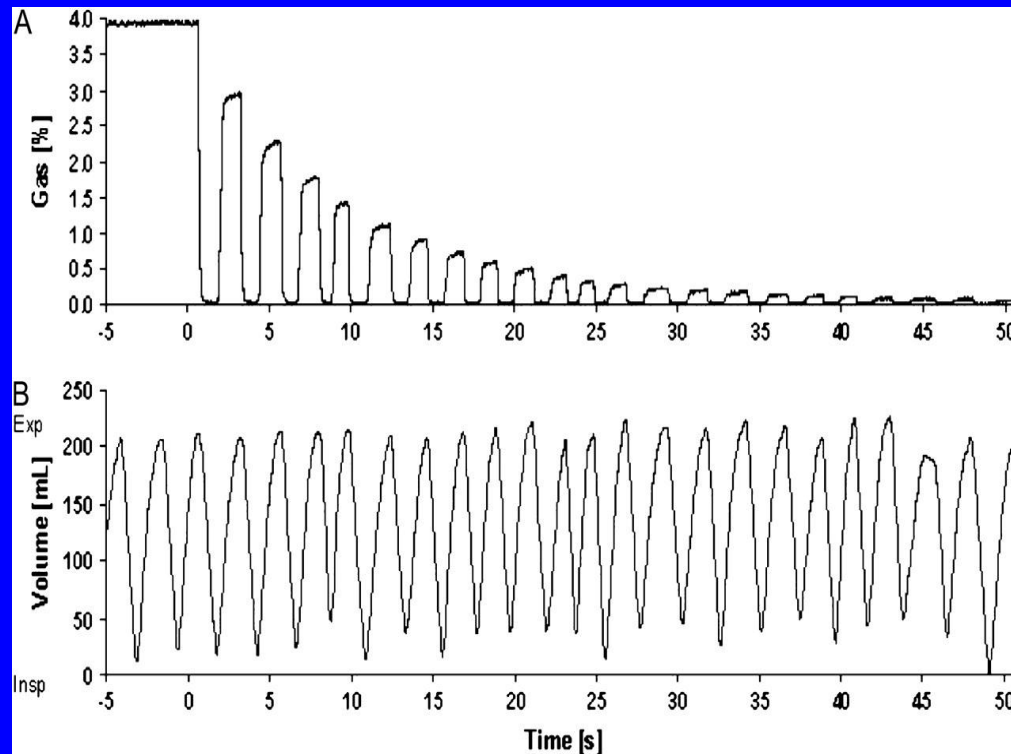
Gustaffson P et al., *ERJ* 2003

- Tracks abnormalities from early life and predicts spirometry in school age

Aurora P et al., *AJRRCM* 2011

Multiple breath washout setup

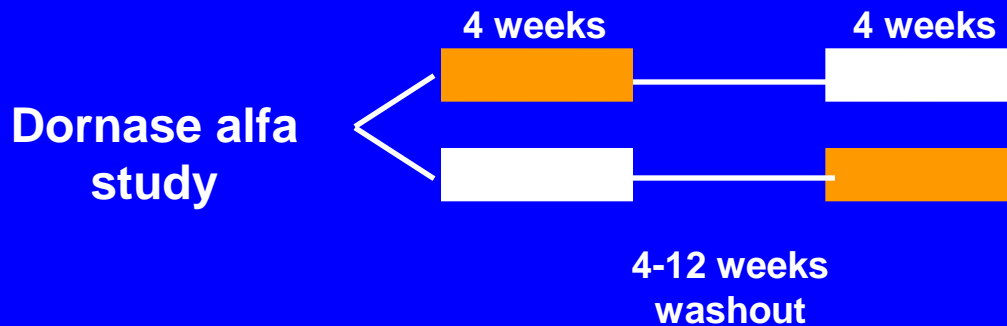
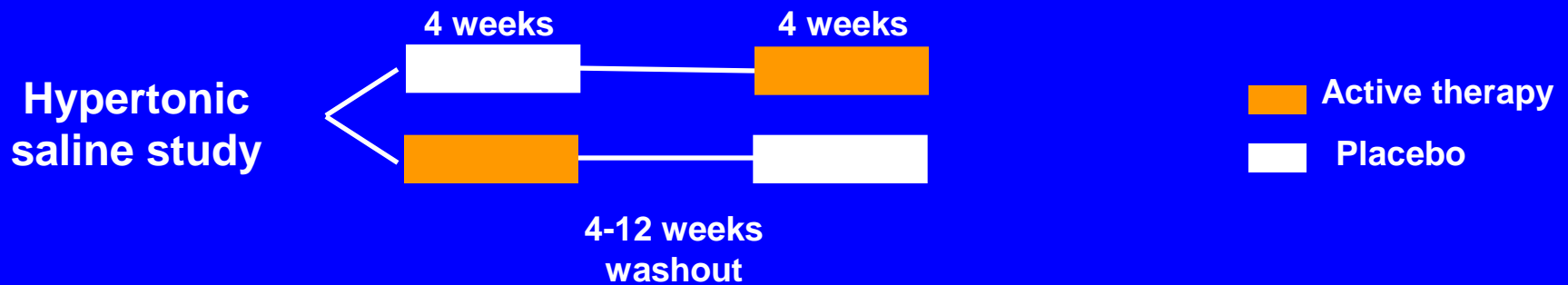
MBW tracing



$$\text{LCI} = \frac{\text{Cumulative Expired Volume}}{\text{Functional Residual Capacity}}$$

LCI responsiveness to interventions

HS/dornase alfa studies

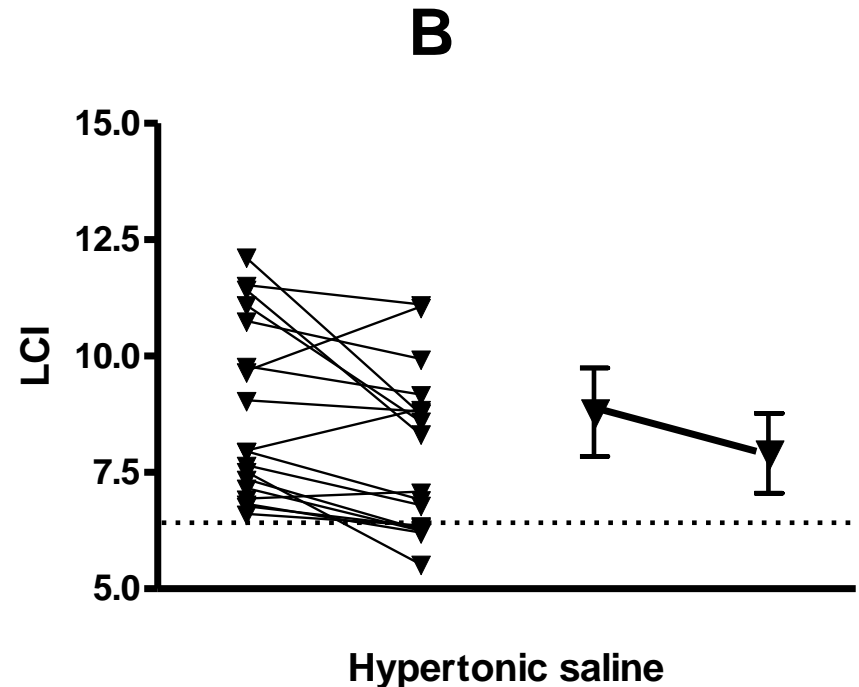
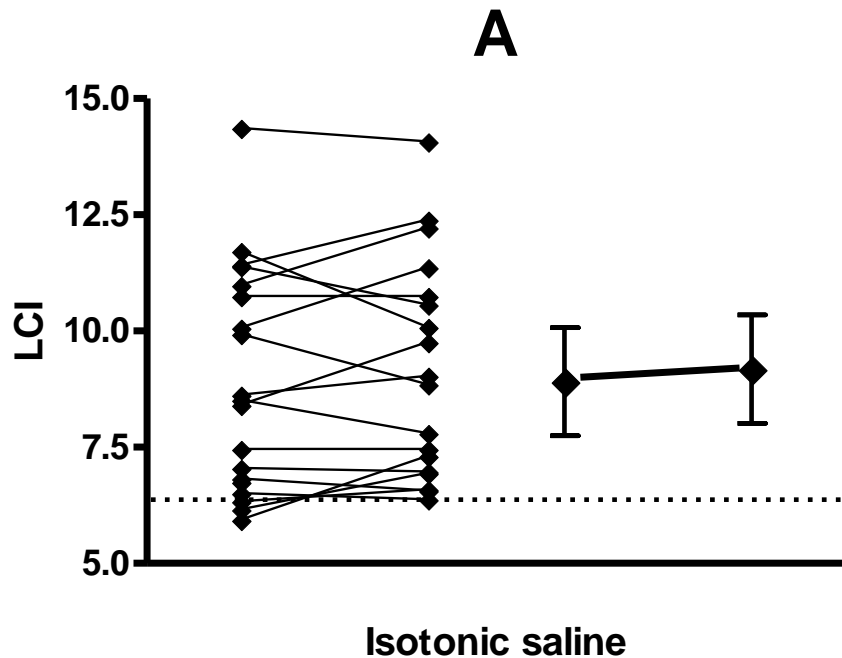


Key inclusion criteria

$FEV_1 > 80\%$
Age 6-18 years
Clinical stability

LCI in interventional studies

hypertonic saline



treatment effect size: 1.16 ± 0.94 [0.27, 2.05] $p=0.016$;

Amin et.al,
Thorax 2010

Post Hoc Sample Size Calculation

Outcome Analysis	Treatment Effect*	Required Sample Size
Spirometry		
FEV ₁ % predicted	1.78 ± 11.95	356
FEF ₂₅₋₇₅ % predicted	5.26 ± 22.26	143
CFQ-R Domains		
Respiratory	2.87 ± 14.22	195
CFQ-R Parent Domains		
Respiratory	5.91 ± 16.15	61

ISIS LCI substudy

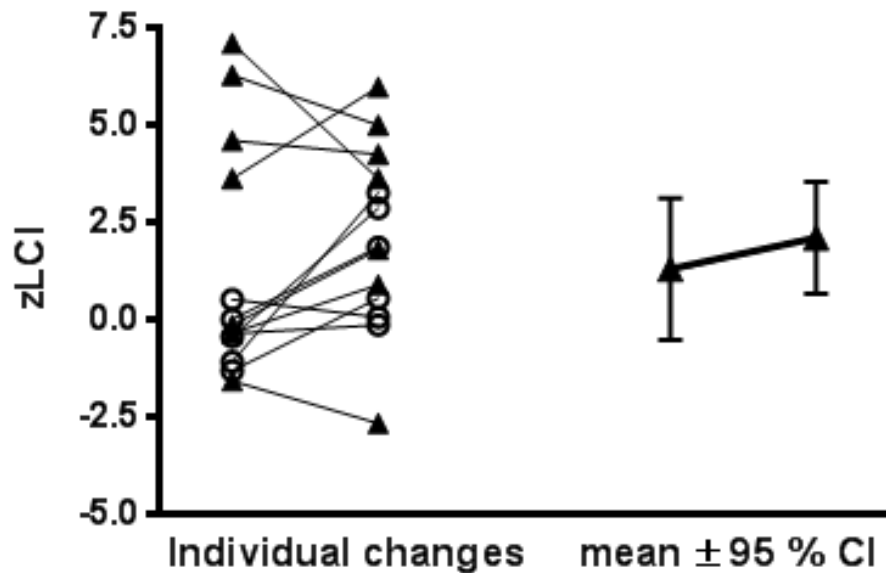
methods

- **48 week interventional study assessing the effect of hypertonic saline in infants and young children with CF**
- **MBW offered as additional lung function test to all participants of ISIS at Toronto site (separate IRB approval and consent)**
- **Measurements performed at baseline and week 48 (end of study)**
- **Measurements performed either during infant pulmonary function testing under sedation (n=11) or during spontaneous breathing while watching a video**

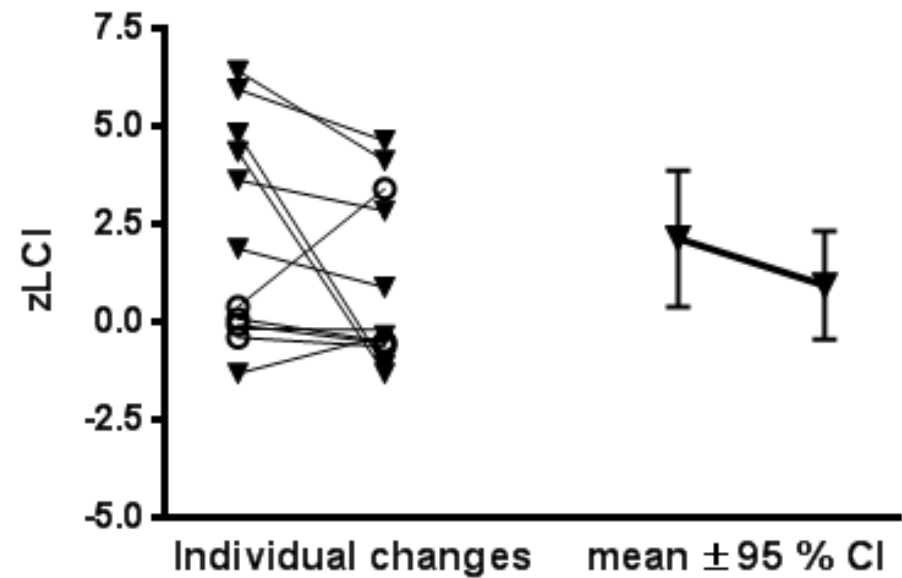
LCI in ISIS participants

isotonic versus hypertonic saline

Isotonic saline



Hypertonic saline



Mass spectrometry and SF₆

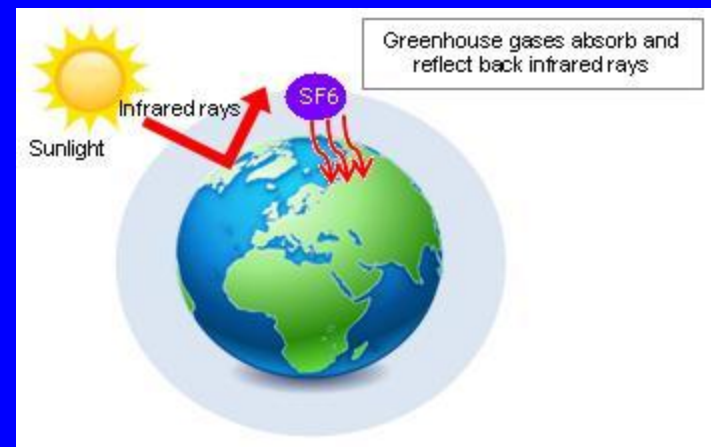
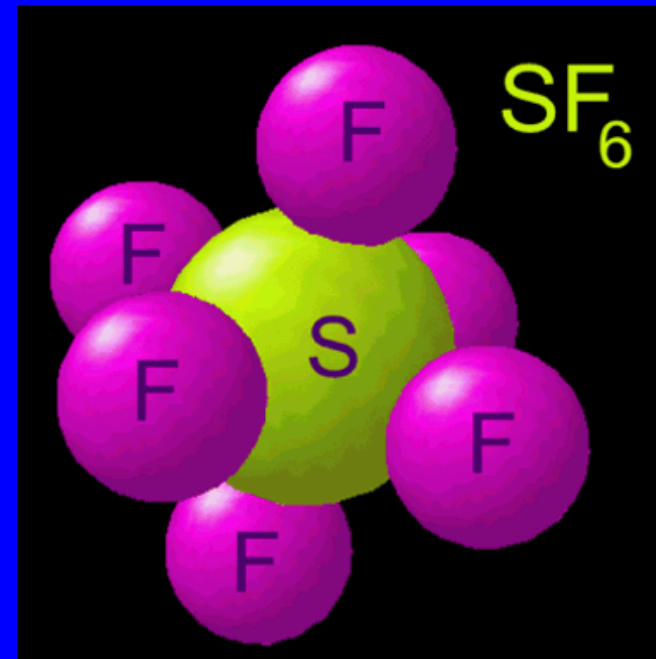
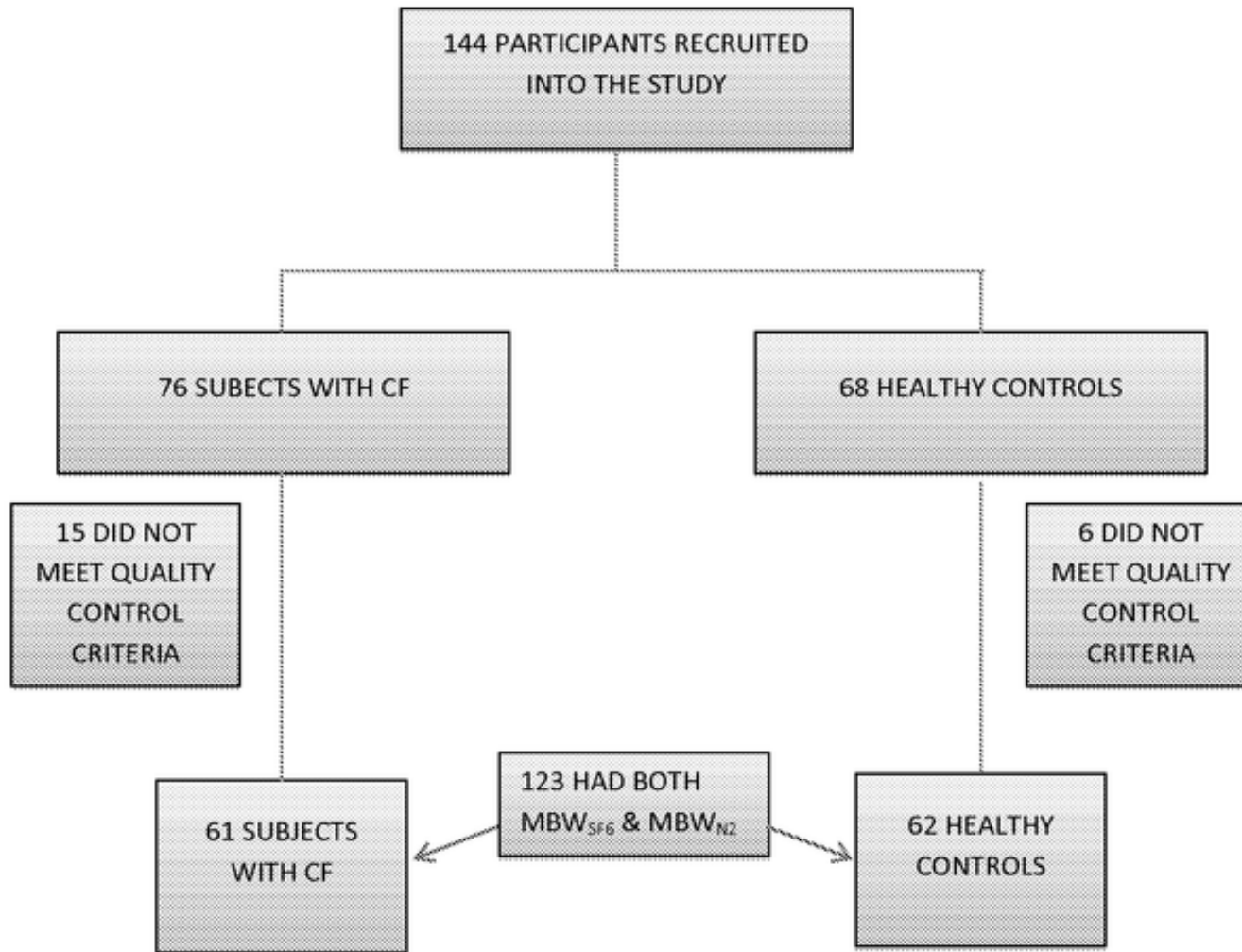


Figure 1. Study Participant Flow Diagram.



Jensen R, Stanojevic S, Gibney K, Salazar JG, et al. (2013) Multiple Breath Nitrogen Washout: A Feasible Alternative to Mass Spectrometry. PLoS ONE 8(2): e56868. doi:10.1371/journal.pone.0056868
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056868>

LCI in health and disease

Mass spectrometry versus nitrogen washout

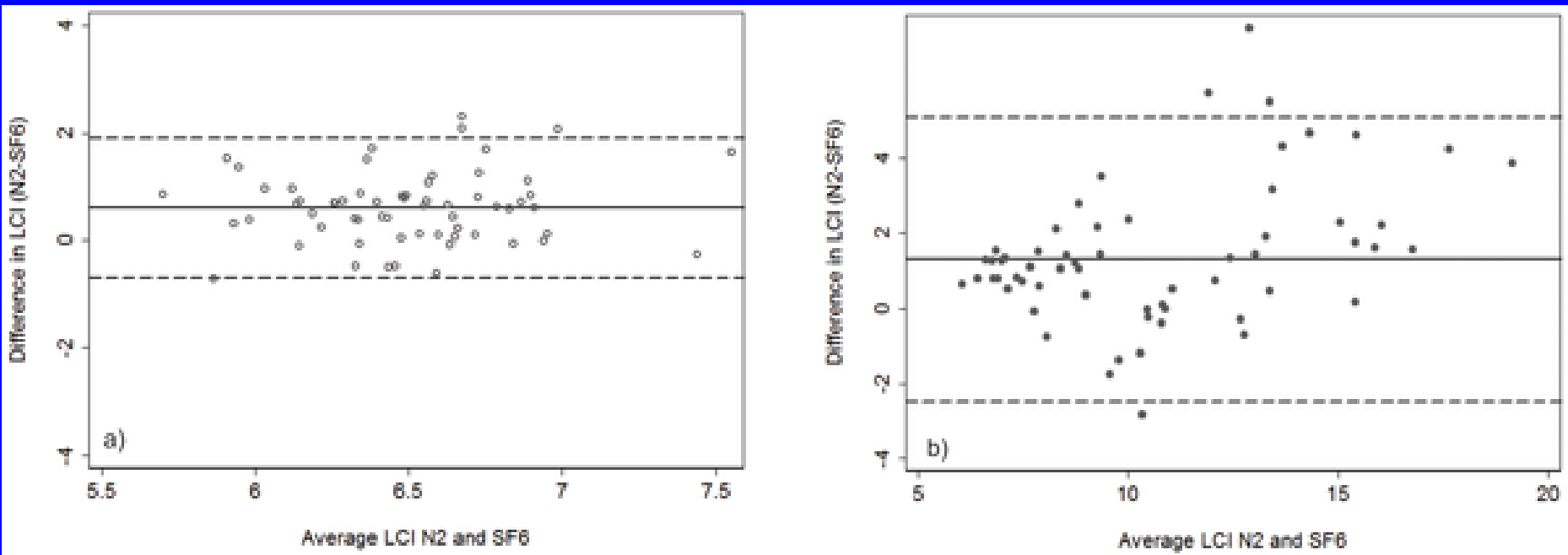
	HC mean (CV)	CF mean (CV)	P-value
Sample Size	61	62	
LCI_{SF6}	6.19 (0.05)	10.05 (0.05)	<0.001
LCI_{N2}	6.81 (0.05)	11.29 (0.05)	<0.001
FRC_{SF6} (L)	1.60 (0.06)	1.41 (0.06)	0.185
FRC_{N2} (L)	1.92 (0.07)	1.89 (0.05)	0.948
*FRC_{pleth} (L)	2.25 (0.79)	2.31(0.97)	0.471

*FRC_{pleth} measurements were obtained in n = 44 HC and n = 30 CF; results presented as mean (SD).
doi:10.1371/journal.pone.0056868.t002

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Summary

- **Multiple breath washout parameters hold great promise as an outcome measure in young children**
- **3 interventional studies CF patients > 6 years have demonstrated treatment effects requiring smaller sample sizes**
- **Data from ISIS suggest that LCI can be modified by treatment in infants and young children as well**
- **Nitrogen based washout technology is now validated and should facilitate the implementation of LCI as an outcome measure in multi-center studies**