

Burden of Cough in Refractory Chronic Cough Population Enrolled in a Phase 2b Study of the P2X3 Antagonist BLU-5937

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Introduction

- Refractory Chronic Cough (RCC) is a cough that persists for 8 weeks or more despite adequate treatment of all identifiable associated diseases or without identifiable cause^{1,2}.
- RCC results from a sensory nerve dysfunction¹, in which the ATP-gated ion channel P2X3 is suggested to play a key role (Fig 1.).

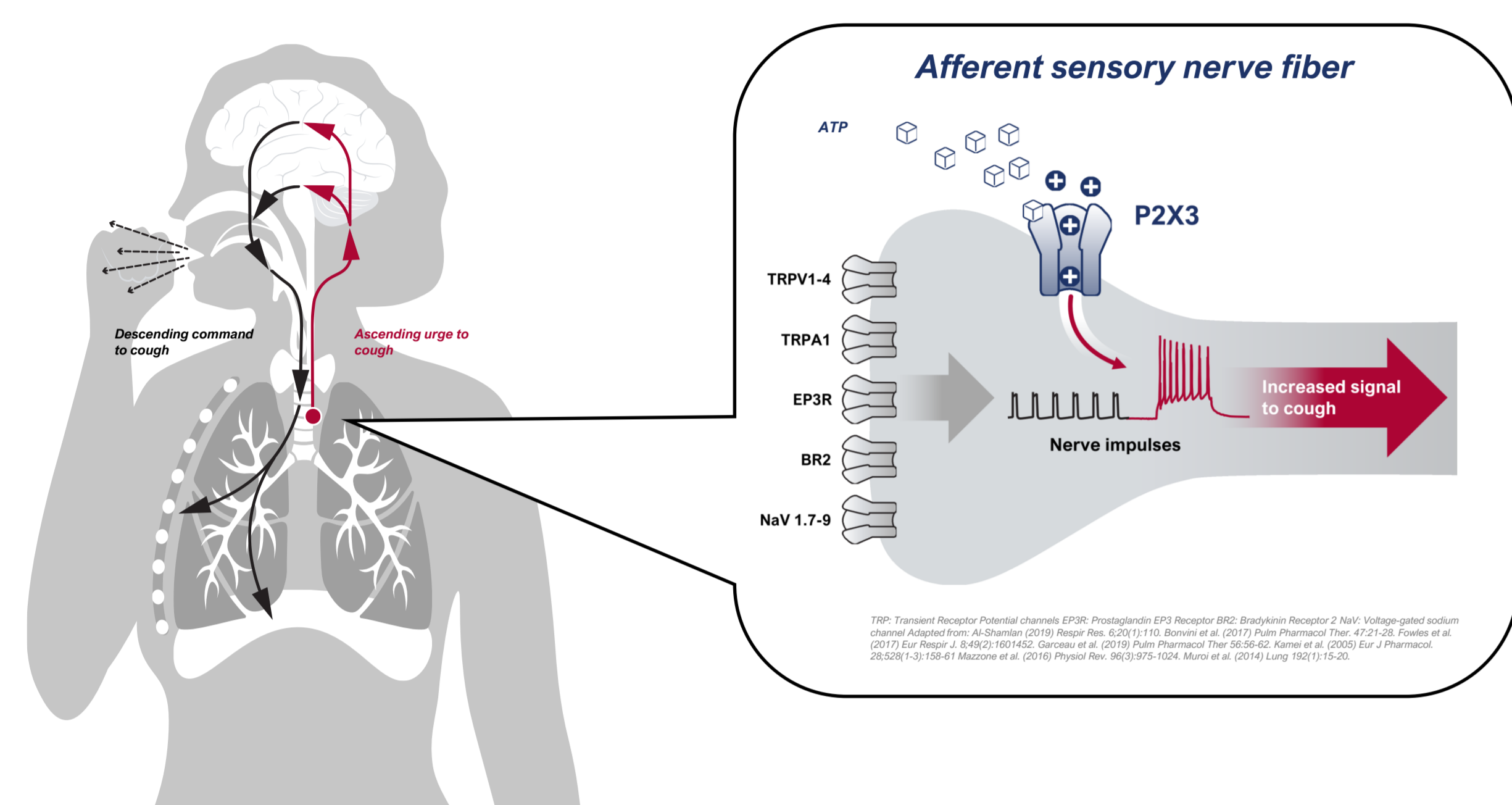


Figure 1. Model of the Role of P2X3 in Cough Signaling

- The frequent and exaggerated cough of RCC patients may have significant impact on quality of life, including social isolation, difficulty conversing, emotional distress, anxiety, guilt, fatigue, urinary incontinence and sleep disturbances³.
- These burdens are further exacerbated by the lack of indicated treatment: there is no treatment for RCC currently approved by the FDA.
- The Leicester Cough Questionnaire (LCQ) reflects the impact of cough on quality of life across physical, social and psychological subdomains. Each of the 19 item reports the impact of cough over the last 2 weeks with a 7-point Likert scale, with higher scores representing a better quality of life, over a total aggregated score of 21⁴.
- We report the burden of cough on quality of life at baseline measured by the LCQ in participants tiered by cough frequency enrolled in a phase 2b trial of the P2X3 antagonist BLU-5937.

Methods

- SOOTHE (NCT04678206) was a multi-center phase 2b, randomized, placebo-controlled, parallel arm clinical dose-finding study in participants diagnosed with persistent cough for ≥ 1 year and a cough severity of at least 40 mm on a 100 mm visual analog scale.
- A FEV₁/FVC score of at least 60% was also necessary for inclusion. Patients with a diagnosis of COPD, bronchiectasis or IPF were excluded from the study.
- Participants who maintained an awake cough frequency ≥ 25 or ≥ 10 to < 25 coughs/h after a run-in period were randomized respectively to a main (n=249) or exploratory (n=61) population for a double-blind treatment period.
- Burden on quality of life was assessed at the start of the double-blind treatment period using the LCQ.

Results

Overall Demographics And Cough Characteristics

- The population enrolled in SOOTHE, enriched for baseline cough frequency, had a demographic profile consistent with other non-enriched studies in RCC (Tab 1).^{5,6}
- The main (n=249) and exploratory (n=61) populations showed broadly similar demographic profiles, with the exception of a lower proportion of women (main: 82% vs exploratory: 61%).
- Partition by cough frequency between the main and exploratory populations had broadly similar cough characteristics, apart from the expected difference in mean cough frequency at baseline.

Leicester Cough Questionnaire

- The small difference in total LCQ scores (10.6 \pm 3.1 and 11.8 \pm 3.0) at baseline suggested similar reported burdens on quality of life in the main and exploratory populations, respectively (Fig 2a).
- Similar burdens are also reported across all three LCQ subdomains in the main vs exploratory populations (Fig 2b). Average physical subdomain scores of 4.1 \pm 1.0 vs 4.6 \pm 1.1, psychological subdomain score of 3.3 \pm 1.2 vs 3.6 \pm 1.2 and social subdomain scores of 3.2 \pm 1.2 vs 3.7 \pm 1.2.
- Specific items reported as most burdensome were also similar between populations (Tab. 2). Most frequent burdens reported included a lack of control of their cough, their perception by other people, annoyance of partner family or friends, interruption of conversations and calls, as well as embarrassment and frustration due to cough.

Table 1. Baseline Demographics And Characteristics

	Main	Exploratory	
Participants, n	249	61	
Female, n (%)	204 (82%)	37 (61%)	
Age (years), mean (SD)	60.9 (10.6)	61.3 (9.4)	
BMI (kg/m ²), mean (SD)	28.1 (6.0)	30.1 (5.3)	
FEV ₁ /FVC, mean (SD)*	0.77 (0.07)	0.77 (0.07)	
Race, n (%)	White	240 (96%)	57 (93%)
	Black	3 (1%)	3 (5%)
	Asian	4 (2%)	1 (2%)
	American Indian/ Alaska Native	2 (1%)	0
	24H Cough Frequency** (coughs/h), mean _{geo}	38.9	11.2
LCQ, mean (SD)	10.6 (3.1)	11.8 (3.0)	
CS-VAS (mm), mean (SD)	72.9 (14.8)	69.5 (16.0)	
Cough Duration (years), mean (SD)	11.7 (9.9)	11.8 (11.7)	

* Measured at Day -16 (screening) or within 2 years prior to screening and after the onset of cough
 ** Measured at baseline

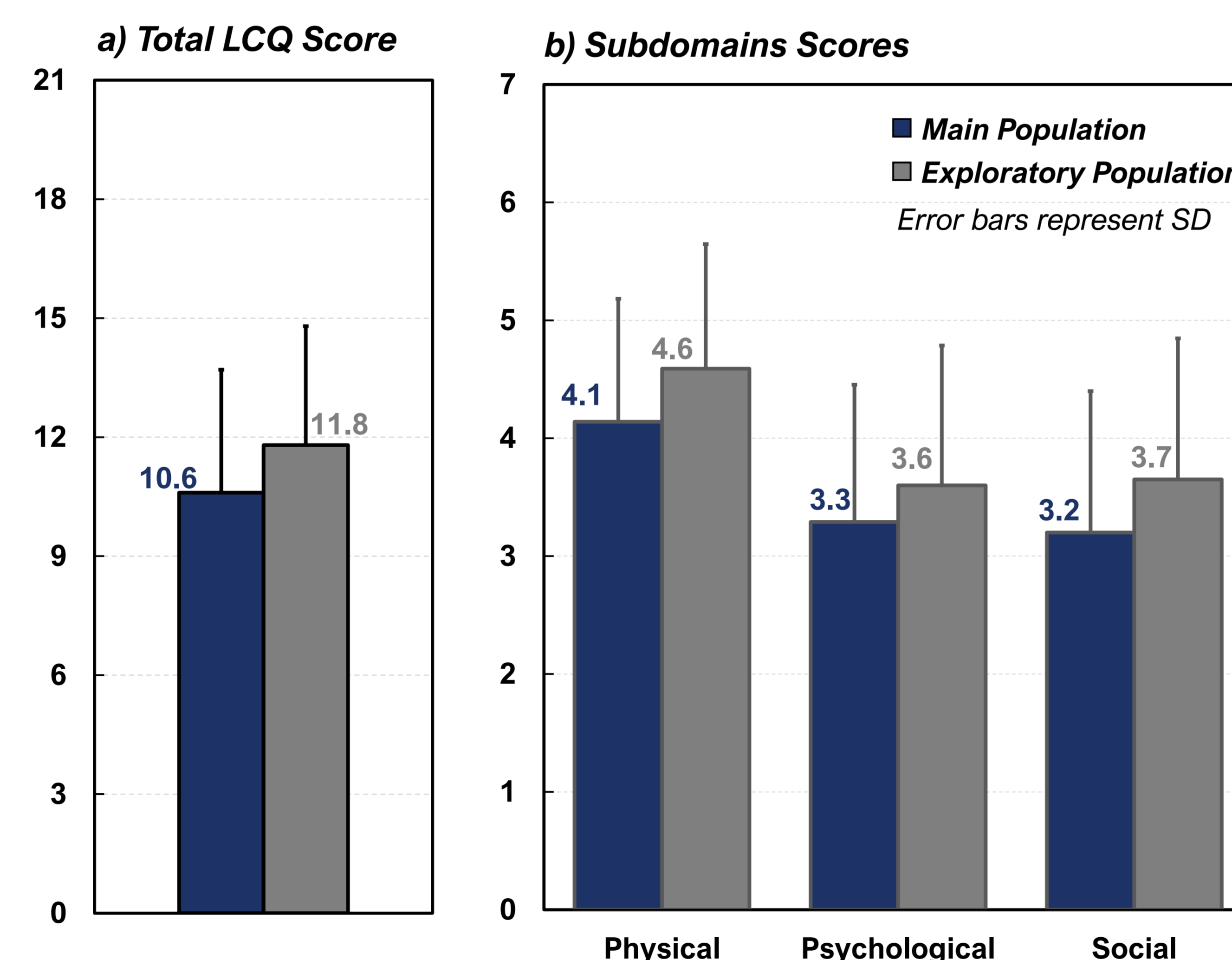


Figure 2. Leicester Cough Questionnaire Score

Table 2. Leicester Cough Questionnaire Items Reported As Most Burdensome*

In the last 2 weeks...	Mean Item Score (SD)	Main Item responses (area size represents % of answers)		Mean Item Score (SD)	Exploratory Item responses (area size represents % of answers)	
		Highest Burden	No Burden		Highest Burden	No Burden
... have you felt in control of your cough?	2.4 (1.4)	1	7	2.8 (1.3)	1	7
... have you been concerned that other people think something is wrong with you because of your cough?	2.6 (1.5)	1	7	3.2 (1.6)	1	7
... I feel that my cough has annoyed my partner, family or friends	2.8 (1.6)	1	7	3.2 (1.7)	1	7
... my cough has interrupted conversation or phone calls	2.9 (1.3)	1	7	3.4 (1.3)	1	7
... how often have you felt embarrassed by your coughing?	3.0 (1.5)	1	7	3.4 (1.5)	1	7
... my cough has made me feel frustrated	3.1 (1.6)	1	7	3.2 (1.5)	1	7
... my cough has made me feel fed up	3.1 (1.7)	1	7	3.6 (1.8)	1	7
... how many times a day have you had coughing bouts?	3.2 (1.2)	1	7	3.6 (1.4)	1	7
... I felt that my cough interfered with the overall enjoyment of my life	3.4 (1.5)	1	7	3.9 (1.5)	1	7

* Lower scores represent a greater burden on quality of life

Conclusions

- Differences in the size of populations enrolled in SOOTHE limit comparisons, as no statistical analyses were pre-specified. However, the small difference in total LCQ score indicates an important burden of cough, regardless of cough frequencies of either population enrolled in SOOTHE. An important burden is also reflected in all subdomains of the LCQ, highlighting the broad negative impact RCC imposes on patients.
- Review of LCQ items also highlight the important social and emotional impacts of RCC independent of baseline cough frequency tiers.

References

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