

**Online Supplementary Table 1: Summary of study characteristics of the included studies**

<b>First author</b>	<b>Year</b>	<b>Study type</b>	<b>Sample Size</b>	<b>Fatigue Assessment Tool</b>	<b>Fatigue Primary Outcome</b>
Antoniou (1)	2019	Cross-sectional	47	ESAS	Yes
Elbehairy (2)	2020	Cross-sectional	45	ESAS-R	Yes
Goertz (3)	2019	Cross-sectional	1290	CIS-F	Yes
Ji (4)	2019	RCT	52	MFI-20	Yes
Kallivoka (5)	2019	Cross-sectional	31	FAS	Yes
Lal (6)	2019	Cross-sectional	412	One item from FOSO	Yes
Lewthwaite (7)	2019	Longitudinal	95	CRQ-SAS	No
Ozoglu Aytac (8)	2019	RCT	85	CAFS	Yes
Patel (9)	2019	Cross-sectional	213	CRQ	Yes
Tomruk (10)	2019	Cross-sectional	27	MBS	No
Van Herck (11)	2019	Cross-sectional	446	CIS-F	Yes
Vardar-Yagli (12)	2019	Cross-sectional	31	FSS	No
Wu (13)	2019	Cross-sectional	154	MSAS	Yes

Yang (14)	2019	Cross-sectional	210	FACIT-F	Yes
Yohannes (15)	2019	Cross-sectional	273	MCFS	Yes
Blackstock (16)	2018	RCT	276	CRQ	No
Boer (17)	2018	Cross-sectional	166	CRQ	Not reported
Chen (18)	2018	Cross-sectional	91	BFI	Yes
Diago (19)	2018	Cross-sectional	51	CRQ	No
Economou (20)	2018	Case-control	38	FSS	Yes
Ekren (21)	2018	Cross-sectional	76	CRQ	No
Fijacko (22)	2018	Cross-sectional	51	FAS	No
Hamada (23)	2018	RCT	33	VAS	No
Lee (24)	2018	Cross-sectional	282	CRQ SF-36	Yes
Lopez (25)	2018	RCT	39	FSS	No
Mazzarin (26)	2018	Cross-sectional	39	FSS	No
Mi (27)	2018	Cross-sectional	119	CRQ	No
Seyedi Chegeni (28)	2018	RCT	91	FSS	Yes
Strandkvist (29)	2018	Cross-sectional	389	FACIT-F	Yes
Stridsman (30)	2018	Cross-sectional	367	FACIT-F EQ-5D-VAS	Yes

				CAT	
Van Dam van Isselt (31)	2018	Cross-sectional	Not reported	NRS	No
Vardar-Yagli (32)	2018	Cross-sectional	62	FSS	No
Yi (33)	2018	Cross-sectional	337	EORTC QLQ-C30	No
Alibašić (34)	2017	Cross-sectional	501	LCQ	No
Lim (35)	2017	Cross-sectional	130	FACIT-F	No
Limpawattana (36)	2017	Cross-sectional	121	Part of the FRAIL-Scale	No
Luk (37)	2017	Prospective	70	CRQ	No
Mi (38)	2017	Cross-sectional	119	One item	No
Martinez (39)	2017	Cross-sectional	880	CAT	No
Polat (40)	2017	Cross-sectional	60	VAS-Fatigue	Yes
Rehman (41)	2017	Cross-sectional	50	CRQ	No
Steurer-Stey (42)	2017	Cross-sectional	467	CRQ	No
Strassmann (43)	2017	Cohort	408	CRQ	Yes
Thakur (44)	2017	Cross-sectional	172	CRQ	No
Yilmaz (45)	2017	RCT	68	CAFS	Yes
Antoniou (46)	2016	Non randomised control explorative	20	FACIT-F SF-36	Yes

Arslan (47)	2016	RCT	65	CAFS	Yes
Benzo (48)	2016	Cross-sectional	310	CRQ	No
Cella (49)	2016	Longitudinal	125	PROMIS	Yes
Chen (50)	2016	Prospective cross-sectional	96	BFI	No
Chen (51)	2016	Prospective and retrospective	91	BFI	Yes
Christensen (52)	2016	Cross-sectional	258	LFS	No
Christensen (53)	2016	Cross-sectional	267	MSAS	No
Duruturk (54)	2016	RCT	47	FIS FSS	No
Javadzadeh (55)	2016	RCT	73	CRQ	No
Johnson-Warrington (56)	2016	RCT	78	CRQ	No
Kentson (57)	2016	Cross-sectional	101	3 structured questions about the experience of fatigue	Yes
Nguyen (58)	2016	Cross-sectional	302	CRQ	No
Polat (59)	2016	Cross-sectional	60	VAS	Yes
Ranjita (60)	2016	RCT	36	BORG	Yes
SooKyung (61)	2016	Longitudinal	152	QWB-SA	Yes

Yilmaz (62)	2016	Cross-sectional	30	BORG	No
Akgün (63)	2015	Cross-sectional	45	CAFS	Yes
Andersson (64)	2015	Cross-sectional	470	FACIT-F	No
Arikan (65)	2015	Cross-sectional	28	FIS	No
Canga (66)	2015	RCT	68	CRQ-SR	Yes
Garrow (67)	2015	Development and validation	203	FACIT-F	No
Herigstad (68)	2015	Cross-sectional	41	FSS	No
Irwin (69)	2015	Cross-sectional	185	PROMIS	Yes
Luk (70)	2015	Prospective cohort	88	CRQ	Yes
Mkacher (71)	2015	Cross-sectional	62	MFI-20	No
Parreira (72)	2015	Retrospective	80	CRQ	No
Stridsman (73)	2015	Cross-sectional	434	FACIT-F	Yes
Todt (74)	2015	Cross-sectional	101	3 items	Yes
Blumenthal (75)	2014	RCT	326	SF-36 BFI	No
Calik-Kutukcu (76)	2014	Cross-sectional	20	FIS FSS	Yes
Eckerblad (77)	2014	Cross-sectional	91	MSAS	No

Howard (78)	2014	RCT	222	CRQ	No
Lewko (79)	2014	Longitudinal	37	MFI-20	Yes
Lin (80)	2014	Cross-sectional	670	PROMIS-SF	No
Mitchell (81)	2014	RCT	184	CRQ-SR	No
Ortega (82)	2014	Prospective clinical trial	198	CRDQ	No
Schroedl (83)	2014	Retrospective	36	Not reported	Yes
Talwar (84)	2014	Cross-sectional	15	FSS	No
Theander (85)	2014	Cross-sectional	273	3 items MSAS FIS	Yes
Zwerink (86)	2014	Longitudinal	77	CRQ-SAS	Yes
Akinci (87)	2013	Cross-sectional	102	PFS	No
Apps (88)	2013	Cross-sectional	37	CRQ-SR	No
Beauchamp (89)	2013	Longitudinal	29	CRQ	No
Bentsen (90)	2013	Cross-sectional	100	BPQ	Yes
Bhatt (91)	2013	RCT	30	CRQ	No
Deng (92)	2013	RCT	64	MFI-20	Yes
Jones (93)	2013	Cross-sectional	1817	FACIT-F	No

Karakurt (94)	2013	Cross-sectional	255	VAS	Yes
Miravittles (95)	2013	Observational and cross-sectional	408	CAFS	No
Miravittles (96)	2013	Cross-sectional	450	CAFS	No
Paddison (97)	2013	Cross-sectional	100	ICFS	Yes
Park (98)	2013	Cross-sectional	596	MOS-36	No
Regueiro (99)	2013	Cross-sectional	301	CRQ	No
Román (100)	2013	RCT	26	CRQ	Yes
Stridsman (101)	2013	Cross-sectional	564	FACIT-F	Yes
Todt (102)	2013	Cross-sectional	54	3 items	Yes
Valderramas (103)	2013	Observational and cross-sectional	50	FSS	Yes
Al-shair (104)	2012	Observational and prospective	2107	FACIT-F	Yes
Janssen (105)	2012	Cross-sectional	73	VAS	Yes
Waschki (106)	2012	Prospective	134	FACIT-F	No
Al Moamary (107)	2011	Psychometric	45	CRQ-SAS	Yes
Al-shair (108)	2011	Cross-sectional	120	MCFS	No
Baltzan (109)	2011	Observational	251	SF-36V2	Yes

Hanania (110)	2011	Prospective and longitudinal	2118	FACIT-F	No
Janssen (111)	2011	Cross-sectional	105	VAS	No
Jones (112)	2011	Cross-sectional	1817	FACIT-F	No
Kapella (113)	2011	Cross-sectional and RCT	18	CRF-F POMS-F	No
Kapella (114)	2011	Prospective and longitudinal	88	CRQ	No
Meng (115)	2011	Cross-sectional	40	CRQ SF-36	No
Mollaoglu (116)	2011	Cross-sectional	98	VAS	Yes
Peters (117)	2011	Longitudinal	168	CIS-F	Yes
Theander (118)	2011	Cross-sectional	150	FIS	Yes
Vigil (119)	2011	RCT	23	CRQ	Yes
Zakerimoghadam (120)	2011	Cross-sectional	60	FSS	Yes
Borge (121)	2010	Cross-sectional	154	LFS	Yes
Cinar (122)	2010	Cross-sectional	114	BFI	Yes
Fong (123)	2010	Cross-sectional	41	CRQ	No
Ige (124)	2010	Prospective	44	CRDQ	No



Inal-Ince (125)	2010	Cross-sectional	22	FSS FIS	No
Laviolette 1 (126)	2010	RCT	12	CRQ	No
Sundararajan (127)	2010	Retrospective	102	CRQ-SR	Yes
Wong (128)	2010	Cross-sectional	42	MFI-20	No
Al-shair (129)	2009	Psychometric	122	MCFS	Yes
Baghai-Ravary (130)	2009	Cohort	107	FACIT-F	Yes
Blinderman (131)	2009	Observational and prospective	100	MSAS	No
Du Moulin (132)	2009	RCT	20	CRQ	No
Hospes (133)	2009	RCT	35	SF-36-V DEFS	No
Lewko (134)	2009	Cross-sectional	74	MFI-20	Yes
Mador (135)	2009	RCT	41	CRQ	No
Moore (136)	2009	RCT	20	CRQ	No
Nishimura (137)	2009	Prospective	156	CRQ	No
Theander (138)	2009	RCT	12	FIS	Yes
Duiverman (139)	2008	RCT	72	CRQ	No

Nguyen (140)	2008	Cross-sectional	115	CRQ	No
Ozalevli (141)	2008	Cross-sectional	130	CRQ	No
Ramachandran (142)	2008	RCT	114	CRQ	No
Theander (143)	2008	Cross-sectional	151	30 items FIS	Yes
Tsai (144)	2008	Prospective cohort	301	CRQ-SF	Yes
Walke (145)	2007	Observational cohort	74	ESAS	Yes
Carr (146)	2007	Observational	60	CRDQ	Yes
Jablonski (147)	2007	Cross-sectional	72	MSAS	No
McCarley (148)	2007	Pilot	10	VAS	No
Nonoyama (149)	2007	RCT	27	CRQ	Yes
Vandevoorde (150)	2007	Case study	68	One item	No
Guell (151)	2006	RCT	35	CRQ	No
Hill (152)	2006	RCT	33	CRDQ	No
Kapella (153)	2006	Cross-sectional	130	POMS NRS FAI	Yes
Mador (154)	2005	RCT	29	CRQ	No
Norweg (155)	2005	RCT	43	CRQ	No

Reishtein (156)	2005	Cross-sectional	100	VAS	No
Trappenburg (157)	2005	Cross-sectional	81	CRDQ	No
Cochrane (158)	2004	Cross-sectional	103	SF-36 CRQ	No
Eaton (159)	2004	Prospective and longitudinal	68	CRQ	No
Lacasse (160)	2004	RCT	23	CRQ SF-36-v	No
Man (161)	2004	RCT	42	SGRQ CRQ SF-36	Yes
Oga (162)	2004	Longitudinal	224	CRQ	No
Puhan (163)	2004	Psychometric	71	CRQ	No
Rea (164)	2004	Prospective RCT	71	CRQ	No
Walke (165)	2004	Cross-sectional	81	ESAS	Yes
Yeh (166)	2004	Cross-sectional	138	SF-36	No
Theander (167)	2002	Cross-sectional	36	FIS	Yes
Mok (168)	2003	Retrospective	53	CRQ	No
Singh (169)	2003	RCT	20	CRQ	Yes

Williams (170)	2003	Cross-sectional	80	CRQ-SR	Yes
Crockett (171)	2002	Prospective and longitudinal	157	CRQ	No
De Torres (172)	2002	Prospective	37	CRQ SF-36-v	No
Yuet (173)	2002	Cross-sectional	54	PFSQ-M	No
Boueri (174)	2001	Prospective	37	SF-36	No
Cook (175)	2001	RCT	53	CRQ SF-36	No
Foy (176)	2001	RCT	118	CRQ	Yes
Meek (177)	2001	Longitudinal	30	Self-reported diaries PFSQ-M BESC-F	Yes
Williams (178)	2001	Cross-sectional	52	CRQ-SR CRQ-IL	Yes
Güell (179)	2000	RCT	60	CRQ	No
Miyahara (180)	2000	Cross-sectional	18	CRQ	No
Woo (181)	2000	Cross-sectional	22	POMS	Yes
Woo (182)	2000	Cross-sectional	39	POMS	Yes
Berry (183)	1999	Trial	151	CRQ	No

Gift (184)	1999	Cross-sectional	104	SF-36	Yes
Lox (185)	1999	RCT	40	CRQ	No
Young (186)	1999	Longitudinal	51	CRDQ	Yes
Breslin (187)	1998	Cross-sectional	41	MFI-20	Yes
Breukink (188)	1998	Cross-sectional	19	MFI-20	Yes
Güell (189)	1998	Cross-sectional	60	CRQ	Yes
White (190)	1997	Cross-sectional	42	CRDQ	Yes
Graydon (191)	1995	Prospective and longitudinal	71	BESC	No
Martin (192)	1994	RCT	15	CRQ	No
Moody (193)	1993	Cross-sectional	19	CDAT	No
Moody (194)	1991	Cross-sectional	45	CDAT	No
Janson-Bjerklie (195)	1986	Cross-sectional	68	POMS	No
Kinsman (196)	1983	Cross-sectional	146	89 items	Yes

**Table 2: Prevalence of Fatigue in COPD**

First author	Population/ Study Type	COPD Sample Size	Fatigue Assessment Tool	Fatigue Primary Outcome	Fatigue Prevalence
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Goërtz (2019) (3)*	Secondary care population/ non-COPD control, Retrospective	1290	CIS- Subscale Fatigue	Yes	<i>COPD patients:</i> Normal: 25% Mild: 26% Severe: 49% <i>Non-COPD subjects:</i> Normal: 73% Mild: 17% Severe: 10%
Peters (2011) (117)*	Secondary care population, Longitudinal cross-sectional	168	CIS- Subscale Fatigue	Yes	Normal: 54% Mild: 25% Severe: 21%
Antoniou (2016) (46)	Secondary care population, Cross-sectional	12	SF-36- Vitality Domain	Yes	In this study 60% of COPD patients reported fatigue (clinically significant fatigue was defined at score of 50 or less)
Baltzan (2011) (109)	Pulmonary rehabilitation population, Cross-sectional	251	SF-36- Vitality Domain	Yes	Low fatigue: 61% High level: 39% (authors divided patients in two groups based on a score that was below 2 standard deviations from published mean age-adjusted normal vitality scores for the general Canadian population)
Gift (1999) (184)	Secondary care population, Cross-sectional	104	SF-36- Vitality Domain	Yes	In this study 58% of COPD patients reported fatigue (this number is calculated by % of responders that positively answered to the question about feeling a lack of energy during the past week)
Elbehairy (2020) (2)	Tertiary care population, Cross-sectional	45	ESAS-r Tiredness/Fatigue Symptom	No	In this study 49% of COPD patients reported a score of $\geq 5$ on Tiredness symptom of ESAS-r questionnaire
Walke (2007) (145)**	Secondary care population, Cross-sectional	74	ESAS- Tiredness/Fatigue Symptom	Yes	Normal: 31% Mild: 19% Severe: 50%

Walke (2004) (165)**	Secondary care population, Cross-sectional	81	ESAS- Tiredness/Fatigue Symptom	Yes	In this study 49% of COPD patients reported moderate or severe fatigue. Authors modified the original visual analog scale, so that Symptoms were rated on a 4-point scale (not present, mild, moderate, and severe), and only examined symptoms rated as moderate or severe.
Antoniou (2019) (1)	Secondary care population, Cross-sectional	47	ESAS- Tiredness/Fatigue Symptom	Yes	In this study 95% of COPD patients reported fatigue. (fatigue was considered as clinically significant (bothersome for the patient if scored at least 4)).
Yang (2019) (14)	Secondary care population, Cross-sectional	210	FACIT- Fatigue Scale	Yes	Mild: 51% Moderate: 31% Severe: 17%
Strandkvist (2018) (29)	Secondary care population, Cross-sectional	304	FACIT-Fatigue Scale	Yes	Prevalence clinically relevant fatigue (CRF) COPD women 36%; non-COPD women: 27.7% ( $p > 0.05$ ) COPD men; 38% non-COPD men 28% ( $p = 0.016$ ) (In this study clinically relevant fatigue (CRF) was defined as a FACIT-Fatigue score of $\leq 43$ )
Stridsman (2018) (30)	Secondary care population, Cross-sectional	367	FACIT-Fatigue Scale	Yes	<i>COPD 37%; Non-COPD subjects 28%</i> ( $p = 0.005$ ). (In this study clinically relevant fatigue has been defined as a score $\leq 43$ )
Stridsman (2013) (101)	Secondary care population, Cross-sectional	261	FACIT-Fatigue Scale	Yes	Clinically significant fatigue <i>COPD patients: 46%</i> <i>non-COPD subjects: 39%</i> ( $p = 0.008$ ) (In this study 3-4 units change in score has been used to identify clinically significant differences)

Andersson 2015 (64)	Secondary care population, Cross-sectional	470	FACIT-Fatigue Scale	Yes	COPD patients: 42.6% Non-COPD subjects:39% (p > 0.05)
Chen (2018) (18)	Pulmonary rehabilitation population, Cross-sectional	91	BFI	Yes	In this study 77% of COPD patients reported fatigue (information on cut-off scores is not reported)
Bentsen (2013) (90)	Tertiary care population, Cross-sectional	100	BPQ - Fatigue Item	Yes	In this study 72% of COPD patients reported fatigue
Valderramas (2013) (103)	Secondary care population, Cross-sectional	30	FSS	Yes	In this study 60% of COPD patients reported fatigue
Wong (2010) (128)	Pulmonary rehabilitation population, Cross-sectional	42	MFI- All Dimensions	No	Mental fatigue: 69% General fatigue: 54% Physical fatigue: 95% Reduced activity: 88% Reduced motivation: 83% (information on cut-off scores is not reported)
Kentson (2016) (57)	Secondary care population, Cross-sectional	101	3 Structured Questions on Fatigue	Yes	<i>COPD-patients: 72%</i> <i>Non-COPD subjects:56%</i> (patients and control subjects reporting fatigue score $\geq 1$ were classified as those with fatigue, and 0 scores with no fatigue)
Theander (2004) (167)	Secondary care population, Cross-sectional	44	FIS- All Dimensions	Yes	<i>COPD patients: 47%</i> <i>Non-COPD subjects:13%</i> report to experience fatigue every day during preceding month (information on cut-off scores is not reported). In this study COPD patients reported significantly greater impact of fatigue on Cognitive, Physical and Psychosocial functioning in comparison to control group
Blinderman	Secondary care	100	MSAS-Lack of	No	In this study 71% of COPD patients reported fatigue (this



(2009) (131)	population, Observational prospective		energy Symptom		number is calculated by taking % of patients reporting scores (3 or 4 on a scale of 0 to 4)
Vandevoorde (2007)(150)	Primary care population/non COPD control, Cross-sectional	68	one item on fatigue	No	<i>COPD all: 47%</i> <i>COPD known: 68%</i> <i>COPD newly detected: 35%</i> <i>Non-COPD: 47%</i>
Kinsman (1983) (196)	Secondary care population and tertiary care population, Cross-sectional	146	BESC- Fatigue Scale	Yes	In this study 95% of COPD patients reported

\* data (partially) obtained from the same set of data

\*\* data obtained from the same set of data

Abbreviations: COPD = chronic obstructive pulmonary disease, CIS = Checklist Individual Strength, SF-36 = Short Form-36 Health Survey, ESAS = Edmonton Symptom Assessment Scale, FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue scale, BFI = Brief Fatigue Inventory, BPQ = Breathing Problem Questionnaire, FSS = Fatigue Severity Scale, MFI = Multidimensional Fatigue Inventory, FIS = Fatigue Impact Scale, MSAS = Memorial Symptom Assessment Scale, BESC = Bronchitis-Emphysema Symptom Checklist

**Table 3: Socio-demographic factors associated with fatigue**

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
<b>COPD related fatigue – Socio-demographic factors</b>								

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
Goërtz (3)	2019	COPD diagnosis - secondary care population	1290	CIS-Fatigue	rs = -0.087 p = 0.002	rs = 0.113 p < 0.001	Education: p > 0.10  Work: p > 0.10	rs = -0.096 p = 0.001
Yohannes (15)	2019	at least 40 years old, COPD diagnosis, FEV1%pred < 70% - rehabilitation population	273	MCFS	r = 0.27 p = 0.04			
Chen (18)	2018	COPD, age ≥ 40 years - rehabilitation population	91	BFI	r = -0.23 p < 0.05			
Stridsman (30)	2018	COPD – primary care population	367	FACIT-Fatigue	Unadjusted OR = 1.04 (1.02–1.07)  Adjusted OR = 1.02 (0.98–1.05) p < 0.05  Adjusted for age, sex, smoking habits, any respiratory symptoms, anxiety/depression, heart disease and health care contacts	Unadjusted OR = 1.02 (0.67–1.55) p > 0.05		

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
Benzo (48)	2016	COPD diagnosis, age $\geq 18$ years, FEV1% $< 80\%$ - tertiary care population	310	CRQ	$r = 0.116$ $p > 0.05$			
Kentson (57)	2016	Stable COPD – secondary care population	101	3-items on fatigue (FIS)	<i>FIS-physical:</i> $r = -0.02$ $P > 0.05$  <i>FIS-psychosocial:</i> $r = -0.16$ $p < 0.20$  <i>FIS- cognitive:</i> $r = -0.17$ $p < 0.20$			
Bentsen (90)	2013	Stable COPD, age $\geq 35$ years, reported symptoms of breathlessness and a chronic cough and sputum production, able to write and read Norwegian – tertiary care population	100	BPQ	OR(95%CI) = 0.94 (0.87-1.01) $p = 0.075$  Adjusted for age, gender, lung function, comorbidity, and exacerbations	OR(95%CI) = 0.42 (0.15-1.21) $p = 0.108$  Adjusted for age, gender, lung function, comorbidity, and exacerbations		
Karakurt (94)	2013	COPD diagnose $\geq 6$ months, residing in central Erzincan and Kirsehir, hospitalization $\geq 2$	255	VAS		Women:  Mean $\pm$ SD = 75.36 $\pm$ 18.70	<i>Education level:</i> $p < 0.001$	$p < 0.05$

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
		days, no serious complications, no psychiatric history of illness – secondary care population				Men: Mean±SD = 50.57±20.11  p = 0.05		
Miravittles (96)	2013	Moderate or severe COPD, age 40 years, >10 pack years, COPD diagnose ≥ 5 years – secondary care population	408	CAFS	r = 0.10 p - not reported	Women: Mean±SD = 43.7±21.6  Men: Mean±SD = 35.0±24.9  p = 0.027	<i>Educational level:</i> p = 0.002	
Paddison (97)	2013	Stable COPD, participation in PR – rehabilitation population	100	ICFS	OR (95% CI) = 0.75 (0.27–2.05) OR (95% CI) = 0.98 (0.93–1.04)* p > 0.05 *Adjusted for age and sex	Men: OR (95% CI) = 1.88 (0.53–6.59) OR (95% CI) = 1.17 (0.37–3.70)* p > 0.05 *Adjusted for age and sex		
Al Moamary (107)	2011	Stable COPD, age ≤75 years, free of significant handicapping diseases –	45	CRQ	r = 0.07 p = 0.65			

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
		secondary care population						
Baltzan (109)	2011	COPD patients – rehabilitation population	251	SF-36	<p>Low fatigue Mean±SD = 67.1±8.2 p &gt; 0.05</p> <p>High fatigue Mean±SD = 63.7±9.2 p &lt; 0.01</p>	<p>Low fatigue Mean (%) males = 62 (40) Mean (%) female = 92 (60)</p> <p>High fatigue Mean (%) males = 48 (49) Mean (%) female = 92 (51)</p>		
Mollaoglu (116)	2011	All COPD patients – secondary care population	98	VAS	<p>65-69 years: Mean±SD = 70.8±27.6</p> <p>70-74 years: Mean±SD = 78.4±27.9</p> <p>&gt;75 years: Mean±SD = 82.6±18.4 p = 0.330</p>	<p>Women: Mean±SD = 85.32 ± 18.80</p> <p>Men: Mean±SD = 78.59 ± 22.22 p = &lt;0.12</p>	<p>Education level: p = 0.28</p>	p = 0.02
Borge (121)	2010	All COPD stages, age ≥30 years, able to write and read Norwegian – primary care population	154	LFS	r = -0.1 p > 0.05	r = 0.1 p > 0.05	<p>Educational level: r = -0.12 p &gt; 0.05</p>	
Wong (128)	2010	COPD diagnosis by a physician, age ≥18	42	MFI-20	<p>General fatigue: r = -0.01</p>			

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
		years – rehabilitation population			<p><math>p &gt; 0.05</math></p> <p><i>Mental fatigue:</i></p> <p><math>r = -0.09</math></p> <p><math>p &gt; 0.05</math></p> <p><i>Physical fatigue:</i></p> <p><math>r = 0.11</math></p> <p><math>p &gt; 0.05</math></p>			
Al-shair (129)	2009	Stable COPD for at least 4 weeks prior to the visit – secondary care population	122	MCFS	<p>&lt;65 years:</p> <p>31.9</p> <p>&gt;65 years:</p> <p>24.4</p> <p><math>p = 0.004</math></p>			
Kapella (153)	2006	Stable COPD, age $\geq 45$ years, > 10 pack years, no PR in the previous 6 months, no exacerbation within the previous 2 months, no asthma, no lung transplantation, no lung volume reduction surgery – secondary care population	130	POMS NRS FAI	<p><math>r = 0.22</math></p> <p><math>p &lt; 0.05</math></p>	<p><i>POMS:</i></p> <p>Women: Mean<math>\pm</math>SD = 11.6 <math>\pm 6.5</math></p> <p>Men: Mean<math>\pm</math>SD = 11.5 <math>\pm 6.4</math></p> <p>p-value = 0.02</p> <p><i>NRS:</i></p> <p>Women: Mean<math>\pm</math>SD = 9.4 <math>\pm 2.6</math></p> <p>Men: Mean<math>\pm</math>SD = 8.5 <math>\pm 2.6</math></p> <p><math>p &gt; 0.05</math></p> <p><i>FAI:</i></p> <p><math>p &gt; 0.05</math></p>		

First author	Year	Population	Sample size	Fatigue assess. tool	Factors associated with fatigue			
					Age	Sex	SES	Marital status
Reishtein (156)	2005	Stable COPD, FEV1 $\leq$ 60% predicted for age/sex/height, ability to speak and read English – secondary care population	100	VAS	r = -0.10 p > 0.05	R = 0.03 p > 0.05		
Yeh (166)	2004	COPD diagnosis – secondary care population	138	SF-36	r = 0.02 p > 0.05			
Crockett (171)	2002	COPD assessed by the FMCR Unit as being suitable candidate for the prescription of LTOT, age < 80 years – primary care population	157	CRQ		Women: Mean $\pm$ SD = 12.4 $\pm$ 5.9  Men: Mean $\pm$ SD = 14.2 $\pm$ 5.3  p < 0.05		
Woo (182)	2000	COPD with FEV1 < 60% of predicted values – secondary care population	39	POMS	<i>Regression analyses:</i> R square = 0.02 Beta = 0.09 t-value = 0.60 p > 0.05			

**Table 4: Disease-severity factors associated with fatigue**

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue					
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications	
<b>COPD severity-related factors</b>										
Goërtz (3)	2019	COPD diagnosis – secondary care population	1290	CIS-Fatigue	<i>mMRC</i> : Median (IQR) = 2(1-3) <i>rs</i> = 0.347 <i>p</i> < 0.001	Mean±SD = 55.5 ± 18.9 <i>rs</i> = -0.076 <i>p</i> = 0.006	Median(IQR) = 1(0-2) <i>rs</i> = 0.199 <i>p</i> < 0.001	Median(IQR) = 2(1-3) <i>rs</i> = 0.104 <i>p</i> = 0.016	Median(IQR) = 7(5-11) <i>rs</i> = 0.353 <i>p</i> < 0.001	LTOT n(%) <i>rs</i> = 0.146 <i>p</i> = 0.043
Yohannes (15)	2019	at least 40 years old, COPD diagnosis, FEV1%pred <70% - rehabilitation population	273	MCFS	<i>mMRC</i> : Mean±SD = 3.02±1.13 <i>r</i> = 0.26 <i>p</i> = <0.001	Mean±SD = 59.56±21.06 <i>r</i> = -0.07 <i>p</i> = 0.35				
Boer (17)	2018	spirometry-confirmed COPD, percentage of predicted FEV1 between	166	CRQ-Fatigue			<b>Exacerbation frequency/year</b> mean±SD = 4.0±2.1 <i>rs</i> = -0.069			



First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
		30 and 80%, age ≥ 40 – primary and secondary care population					<i>p</i> = 0.506 <b>Exacerbation free weeks/year</b> Mean±SD = 33.4±12.5 <i>r</i> <sub>s</sub> = 0.232 <i>p</i> = 0.023		
Chen (18)	2018	COPD, > 40 years – rehabilitation population	91	BFI	<i>Dyspnoea Inventory (DI)</i> : <i>r</i> <sub>s</sub> = 0.78 <i>p</i> < 0.01	Mean±SD = 51.1±21.2 <i>r</i> = -0.19 <i>p</i> > 0.05			
Lee (24)	2018	COPD, age ≥40 years, > 10 pack-years, stable disease with no acute exacerbations in the past four weeks, ability to speak, read and write English – primary, secondary and tertiary care	282	CRQ -Fatigue SF-36-Vitality	<i>CRQ-D</i> : Mean±SD = 23.83 ± 6.74 <i>r</i> = 0.37 <i>p</i> < 0.001 ( <i>SF-36-Vitality</i> )  <i>r</i> = 0.53 <i>p</i> < 0.001 ( <i>CRQ-Fatigue</i> )				

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
		population							
Stridsman (30)	2018	Not reported – primary care population	367	FACIT-Fatigue		Mean±SD = 78.7±16.9 Unadjusted OR(95%CI) = 0.97(0.96–0.98)  Adjusted* OR(95%CI) = 0.98(0.96–1.00)  *Adjusted for age, sex, smoking habits, any respiratory symptoms, anxiety/depression, heart disease and health care contacts			

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
Alibašić (34)	2017	stage I or II COPD, with productive cough for a period longer than three months a year – secondary care population	501	LCQ					Carbocisteine usage during 15 days Result: during the first observation 65% of patients experienced fatigue, at observation 3 15%. p < 0.001
Benzo (48)	2016	Older than 18, diagnosis of COPD, FEV1% = <80% - tertiary care population	310	CRQ-Fatigue		Mean±SD = 42.48±15.85 r = 0.129 p > 0.05			
Kentson (57)	2016	COPD, clinically stable condition - secondary care population	101	3 structured questions about the experience of fatigue (FIS)	<i>mMRC:</i>  <i>FIS-physical (0-40)</i> mMRC≤1(median) = 14 mMRC≥2(med	Median(IQR) = 50(17)  <i>FIS-physical</i> r = -0.16 p < 0.20  <i>FIS-</i>			

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					<p>ian) = 23 p = 0.004</p> <p><i>FIS- psychosocial (0-80)</i> mMRC≤1( median) = 20.5 mMRC≥2( median) = 30.0 p = 0.10</p> <p><i>FIS cognitive (0-40)</i> mMRC≤1( median) = 15.5 mMRC≥2( median) = 9.0 p = 0.24</p>	<p><i>psychosocial</i> r = -0.17 p &lt; 0.20</p> <p><i>FIS-cognitive</i> r = -0.13 p &gt; 0.05</p>			
Calik-Kutukcu (76)	2014	Age 40-80 years, not taking antibiotics, no change in medications for at least 3 weeks – rehabilitation population	20	FIS FSS	<p><i>mMRC:</i> Mean±SD = 1.4±1</p> <p><i>FIS-physical</i> r = 0.70 p = 0.001</p> <p><i>FIS- psychosocial</i></p>				

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					$r = 0.72$ $p = 0.001$  <i>FIS-cognitive</i> $r = 0.66$ $p = 0.02$  <i>FIS-total</i> $r = 0.69$ $p = 0.001$  <i>FSS-total</i> $r = 0.78$ $p = 0.001$				
Lin (80)	2014	COPD, age > 40 years, completed EQ-5-DL and PROMIS – secondary care population	670	PROMIS short form-Fatigue	<i>mMRC:</i> Mean±SD = 1.50±0.99 $r = 0.43$ $p = <0.001$  <i>FACIT-dyspnoea:</i> Mean±SD = 44.6±8.4 $r = 0.58$ $p = <0.001$	$r = -0.09$ $p > 0.05$			
Bentsen (90)	2013	Age > 35 years, COPD - tertiary care population	100	BPQ		OR(95%CI) 0.98 (0.95, 1.02) P = 0.318	Exacerbations during previous 4 weeks n(%) =	OR(95%CI) 1.35 (0.41, 4.42) p = 0.617	

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
						Adjusted for age, gender, lung function, comorbidity, and exacerbations	10(10) OR = 3.73 (0.41-33.70) p = 0.242 Adjusted for age, gender, lung function, comorbidity, and exacerbations	Adjusted for age, gender, lung function, comorbidity, and exacerbations	
Deng (92)	2013	Existing fatigue, FEV1 60%-25% of predicted after bronchodilation – secondary care population	64	MFI-20	<i>mMRC</i>  <i>MFI total</i> r = 0.31 p > 0.05  <i>General fatigue</i> r = 0.24 p > 0.05  <i>Physical fatigue</i> r = 0.47 p > 0.05  <i>Mental fatigue</i> r = 0.11				

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					p > 0.05				
Miravittles (96)	2013	COPD at least 5 years, age > 40 years - secondary care population	408	CAFS	MRC: Mean±SD = 2.7±0.9  r = 0.54 p < 0.0001		r = 0.38 p < 0.05		
Todt (102)	2013	COPD, clinically stable condition, no change in medication in the previous 4 weeks – secondary care population	54	Three questions concerning frequency, duration, and severity during the past month		Men Mean±SD = 50.8±16.8 Women Mean±SD = 48.6±15.7  Adjusted for sex			
Valderramas (103)	2013	No medication changes for at least 3 months before the beginning of the study – secondary care	50	FSS	MRC: Median(IQR) = 3±2 r = 0.69 p < 0.01	Mean±SD = 46.5±20.4 r = -0.38 p = 0.01			

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
		population							
Al Moamary (107)	2011	age < 75 years, FEV1 <70% and free of significant handicapping diseases - secondary care population	45	CRQ-SAS-Fatigue		Mean±SD = 58.4±15.3 r = 0.18 p = 0.25	Mean±SD = 3.8±2.5 r = -0.02 p = 0.88		
Baltzan (109)	2011	Not reported - rehabilitation population	251	SF-36-Vitality	MRC: Low fatigue: M = 2.8 ± 0.8  High fatigue: M = 3.4 ± 1 p <0.01	Low fatigue mean±SD = 45.9±13.3  High fatigue mean±SD = 43.1±12.6  p>0.05	<i>Depression:</i>  Low fatigue n(%) = 10(6)  High fatigue 16(16) p <0.05 Other diseases no difference		
Jones (112)	2011	30-80 years, COPD, > 10 pack years – primary care population	1817	FACIT-Fatigue			Stable vs exacerbation p <0.001	Mean±SD = 2±1.6	



First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
Meng (115)	2011	COPD outpatients - secondary care population	40	CRQ-Fatigue SF-36		Mean±SD = 55.0±20.2 r = 0.098 p = 0.551			
Mollaoglu (116)	2011	COPD - secondary care population	98	VAS-Fatigue	<i>PIF:</i> Mild dyspnoea Mean±SD = 74.21 ± 20.43  Moderate dyspnoea: Mean±SD = 79.20 ± 22.08  Severe dyspnoea: Mean±SD = 86.20 ± 19.85  p < 0.0001				
Peters (117)	2011	Diagnosed with COPD – secondary care population	168	CIS-Fatigue	<i>Dyspnoea emotions</i> r = 0.29 p < 0.01  <i>dyspnoea expectation:</i> r = 0.34	Mean±SD = 51.6 ± 13.6 r = 0.07 p > 0.05			

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					p = <0.01				
Borge (121)	2010	COPD, able to write and read Norwegian, aged > 30 years - primary care population	154	LFS	<i>Respiratory quality of life questionnaire (breathlessness):</i> Mean±SD = 2.4±1.4 r = 0.51 p = 0.001	Mean±SD = 59.1±22.6 r = -0.07 p > 0.05		0 diseases n(%): 29(18.8) 1 disease n(%): 37(24) 2 diseases n(%): 39(25.3) 3 diseases n(%): 31(20.1) 4 diseases n(%): 11(7.1) 5 diseases n(%): 4(2.6) 6 diseases n(%): 2(1.3) 7 diseases n(%): 1(0.6) r = 0.11 p < 0.001	

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue					
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications	
Inal-Ince (125)	2010	Clinically stable COPD – primary care population	22	FSS FIS		Mean±SD = 49.7±28.5  Total FIS score  r = -0.55 p < 0.05  <i>FIS physical</i> r = 0.56 p < 0.05  <i>FIS cognitive</i> r = -0.43 p < 0.05  <i>FIS psychosocial</i> r = -0.52 p < 0.05				
Wong (128)	2010	COPD, age >18 years - rehabilitation population	42	MFI-20	<i>MRC:</i> Mean = 2.6  <i>General</i>			Mean±SD = 2.6±1.4  <i>General</i>		

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					<i>fatigue</i> $r = 0.11$ $P > 0.05$			<i>fatigue</i> $r = 0.20$ $p > 0.05$	
					<i>Physical fatigue</i> $r = -0.33$ $p > 0.05$			<i>Physical fatigue</i> $r = 0.17$ $p > 0.05$	
					<i>Mental fatigue</i> $r = -0.04$ $p > 0.05$			<i>Mental fatigue</i> $r = 0.05$ $p > 0.05$	
Al-shair (129)	2009	Clinically stable COPD for at least 4 weeks prior to the visit - secondary care population	122	MCFS	<i>MRC:</i> Median(IQR) = 1(1) $r = 0.51$ $p < 0.001$				

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
Baghai-Ravary (130)	2009	FEV1% > 20%, stable condition at least 4 weeks from their last exacerbation – primary and secondary care population	107	FACIT-Fatigue	MRC: Median(IQR) = 3(2-4) p < 0.001  VAS: Mean±SD = 4.4±2.3 r = -0.34 p < 0.001	Mean±SD = 53.1±21.1 r = 0.1 p = 0.2	Mean±SD = 2±0-3 r = -0.27 p = 0.005	No correlation (p > 0.05)	
Nguyen (140)	2008	age ≥ 40, absence of other active symptomatic diseases which would interfere with exercise and ability to complete exercise tests – primary and secondary care population	115	CRQ	SOBQ <i>dyspnoea</i> : Mean±SD = 50±16.4 ( <i>good health</i> ) Mean±SD = 59.1±17.9 ( <i>poor health</i> ) r = -0.41 p < 0.05  CRQ <i>dyspnoea</i> : Mean±SD = 16.9±5 ( <i>good health</i> ) Mean±SD = 15.1±4.6 ( <i>poor health</i> ) r = 0.32				

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					p < 0.05				
Tsai (144)	2008	COPD, presenting to ED for treatment of COPD exacerbation, age > 55 years – secondary care population	301	SF-CRQ-Fatigue	VAS <i>dyspnoea</i> : Median(IQR) = 3(2-4) r = 0.13 p < 0.05				
McCarley (148)	2007	COPD, percentage of predicted FEV1 ≤ 60% - primary care population	10	VAS-Fatigue	VAS <i>scale dyspnea</i> : Mean±SD = 26±23 r = 0.48 p < .01	Mean±SD = 44±14  No significant association (p > 0.05)			
Kapella (153)	2006	COPD, > 45 years, > 10 pack years - secondary care population	130	POMS NRS FAI	Men: Mean±SD = 9.2±2.3 Women: Mean±SD = 9.6±2.1  <i>POMS</i> r = 0.74	Men: Mean±SD = 44.5±17.9  Women: mean±SD = 46.1±18.4  <i>POMS</i>	Men: Mean±SD = 1.5±1.6 Women: Mean±SD = 1.8±1.7		

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
					<p><math>p &lt; 0.001</math></p> <p><i>NRS</i>  <math>r = 0.59</math>  <math>p &lt; 0.001</math></p>	<p><math>r = 0.03</math>  <math>p &gt; 0.05</math></p> <p><i>NRS</i>  <math>r = -0.04</math>  <math>p &gt; 0.05</math></p>	<p><math>r = 0.27</math>  <math>p &lt; 0.01</math></p>		
Reishtein (156)	2005	COPD, FEV1 $\leq 60\%$ - secondary care population	100	- Horizontal 100mm visual analog scale.	<p><i>VAS scale (100 mm):</i>  Mean<math>\pm</math>SD = 54.23<math>\pm</math>23.81  <math>r = 0.43</math>  <math>p &lt; 0.001</math></p>				<p><math>r = 0.11</math>  <math>p &gt; 0.05</math></p>
Yeh (166)	2004	Primary diagnosis of COPD - secondary care population	138	- SF-36 stamina fatigue	<p><i>Borg's scale and VAS:</i>  Mean<math>\pm</math>SD = 1.35<math>\pm</math>1.62  <math>r = 0.32</math>  <math>p &lt; 0.001</math></p>	<p>Mean<math>\pm</math>SD = 60.32<math>\pm</math>22.28  <math>r = -0.13</math>  <math>p &gt; 0.05</math></p>			
Boueri (174)	2001	Primary diagnosis of COPD – rehabilitation population	37	SF-36-Vitality		<p>Mean<math>\pm</math>SD = 29.6<math>\pm</math>1.8  <math>r = -0.26</math>  <math>p = 0.15</math></p>			
Woo (182)	2000	Primary diagnosis of COPD -	22	F-POMS	<p><i>VVAS:</i>  Mean<math>\pm</math>SD = 55.45<math>\pm</math>20.97</p>				

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
		secondary care population			r = 0.69 p <0.0001  Adjusted for FEV1				
Woo (181)	2000	Diagnosed with COPD with FEV1 < 60% of predicted values - secondary care population	39	F-POMS	VVAS: Mean±SD = 53.08±18.70  $\beta$ = 0.41 t-value = 2.65  <i>Controlled for age and FEV1</i>	Mean±SD = 46.28±12.33  $\beta$ = -0.17 t-value = -1.08  Adjusted for age and dyspnoea			
Gift (184)	1999	Not currently smoking, no history of psychologic disease – secondary care population	104	SF-36-energy/fatigue	<i>A self-report measure for dyspnea, usual frequency, intensity and distress during past week (numeric scale):</i> r = 0.63 p = <.01				



First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
Breslin (187)	1998	Not reported – secondary care population	41	MFI-20		Mean±SD = 35.8±16.6  <i>General fatigue</i> r = -0.320 p < 0.05 <i>Physical fatigue</i> r = -0.432 p < 0.01  <i>Mental fatigue</i> r = -0.020 p > 0.05			
Breukink (188)	1998	Age > 45 years, FEV1predicted <80%, reversibility <10%, > 5 pack years – secondary care population	19	- MFI-20		Mean±SD = 38±17  <i>General fatigue</i> r = -0.28 p = 0.25  <i>Physical fatigue</i> r = -0.37 p = 0.12  <i>Mental</i>			

First author	Year	Population	Sample size	Fatigue assessment tool	Factors associated with fatigue				
					Dyspnoea	FEV1 %	Number of exacerbations	Number of comorbidities	Number of medications
						<i>fatigue</i> r = -0.23 p = 0.35			
Güell (189)	1998	Age < 75 years, COPD in stable condition, FEV1 < 50% of predicted – rehabilitation population	60	- CRQ-Fatigue		Mean±SD = 35±14  r = 0.26 p <0.01			

Table 5: Physical factors associated with fatigue

First author	Year	Population	Sample size	Fatigue	Physical factors
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				assessment tool	BMI	Peripheral muscle strength	Exercise capacity
<b>COPD related fatigue – Physical factors</b>							
Goertz (3)	2019	COPD diagnosis - secondary care population	1290	CIS-Fatigue	Mean±SD (kg/m <sup>2</sup> ) = 26+5 r = 0.03 ( <i>not reported in article</i> ) p > 0.10		
Al Moamary (107)	2011	Stable COPD, age ≤75 years, FEV1≤70%, no handicapping diseases - secondary care population	45	CRQ-Fatigue	Mean±SD (kg/m <sup>2</sup> ) = 32.6±9.3 r = -0.026 p = 0.08		<b>6mwt</b> Mean±SD (meters) = 226.9±99.2 r = 0.06 p = 0.69
Baltzan (47)	2011	COPD patients – rehabilitation population	251	SF-36-Vitality	Low fatigue Mean±SD (kg/m <sup>2</sup> ) = 27±5.3  High fatigue Mean±SD (kg/m <sup>2</sup> ) = 27.8±6.3 p > 0.05		<b>6mwt</b> Low fatigue Mean±SD = 387±81  High fatigue Mean±SD = 340±88  P<0.01
Crockett (171)	2002	COPD, no LTOT, <80 years, not mentally unfit to complete questionnaires, no severe life-	157	CRQ-Fatigue	Males: Mean±SD (kg/m <sup>2</sup> ) = 24.4±5.4 r = 0.23 p ≤ 0.001		

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
		threatening illness - primary care population			Females Mean±SD (kg/m <sup>2</sup> ) = 25.2±7.4 r = -0.02 p ≤ 0.001		
Breukink (188)	1998	Stable COPD, no use of LTOT, age>45 years, FEV1<80%, reversibility <10%, smoker or ex-smoker with a minimal of 5 pack years, no major comorbidities – secondary care population	19	MFI-20		<i>Physical fatigue</i> <i>MFI-20 (see article for general fatigue, reduction activity, reduction motivation, mental fatigue)</i>  <b><u>Quadriceps left</u></b> Mean±SD (N m*) = 95±28 r = -0.49 p = 0.03  <b><u>Hamstrings left</u></b> Mean±SD (N m*) = 75±22 r = -0.49 p = 0.04  <b><u>Quadriceps right</u></b> Mean±SD (N m*) = 93±24 r = -0.54 p = 0.02	<b><u>Symptom-limited bicycle exercise test (maximum workload)</u></b> Mean±SD (W) = 78±45  <i>General fatigue</i> r = -0.28 p = 0.261  <i>Physical fatigue</i> r = -0.044 p = 0.064  <i>Reduction activity</i> r = -0.21 p = 0.398  <i>Reduction motivation</i> r = -0.39 p = 0.110 <i>Mental fatigue</i> r = -0.35

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
						<p><b><u>Hamstrings right</u></b>  <i>(Physical fatigue)</i>  Mean±SD (N m*)  = 76±22  r = -0.38  p = 0.11</p> <p><b><u>Triceps left</u></b>  Mean±SD (N m*)  = 43±12  r = -0.61  p = 0.01</p> <p><b><u>Biceps left</u></b>  Mean±SD (N m*) =  59±16  r = -0.46  p = 0.05</p> <p><b><u>Triceps right</u></b>  Mean±SD (N m*) =  45±12  r = -0.45  p = 0.05</p> <p><b><u>Biceps right</u></b>  Mean±SD (N m*)  = 63±17  r = -0.48</p>	p = 0.159

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
						<p><math>p = 0.04</math></p> <p>*N m = muscle torque</p>	
Calik-Kutukcu (76)	2014	Stable COPD, age 40-80 years, no physical disability to perform tests - rehabilitation population	20	FIS FSS		<p><i>FIS</i></p> <p><b>Shoulder abductor</b> Mean±SD (N) = 147±38 <math>r = -0.72</math> <math>p = 0.001</math></p> <p><b>Shoulder flexor</b> Mean±SD (N) = 168±53 <math>r = -0.78</math> <math>p = 0.001</math></p>	
Boueri (174)	2001	Pulmonary rehabilitation patients – rehabilitation population	37	SF-36-Vitality			<p><b>6mwt</b> Mean±SD (feet)= 1.016.0±70.9 <math>r = 0.1</math> <math>p = 0.59</math></p>
Breslin (187)	1998	Stable COPD – secondary care population	41	-MFI-20			<p><b>6mwt</b> Subsample (n=19)</p> <p><i>General fatigue</i> <math>r = -0.552</math> <math>p &lt; 0.05</math></p> <p><i>Physical fatigue</i> <math>r = -0.530</math></p>

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
							<p><math>p &lt; 0.05</math></p> <p><i>Reduced activity</i>  <math>r = -0.548</math>  <math>p &lt; 0.05</math></p> <p><i>Reduced motivation</i>  <math>r = -0.042</math>  <math>p &gt; 0.05</math></p> <p><i>Mental fatigue</i>  <math>r = -0.408</math>  <math>p &gt; 0.05</math></p>
Kentson (57)	2016	Stable COPD, no other lung disease or major comorbidities - secondary care population	101	3 questions about frequency, duration and severity of fatigue			<p><b>6mwt</b>  Mean±SD (meters) = 395±139</p> <p><i>FIS-physical</i>  <math>r = -0.27</math>  <math>p &lt; 0.05</math></p> <p><i>FIS-psychosocial</i>  <math>r = -0.28</math>  <math>p &lt; 0.05</math></p> <p><i>FIS-cognitive</i>  <math>r = 0.04</math>  <math>p &gt; 0.05</math></p>

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
Lee (24)	2018	Stable COPD, FEV<80%, age ≥ 40 years, a history of current or past cigarette smoking (>10 pack years), no other major comorbidities - primary, secondary and tertiary care population	282	CRQ-Fatigue SF-36-Vitality			<b>6mwt</b> Mean±SD (feet)= 1091±372  <i>SF-36 Vitality</i> <i>r = -0.15</i> <i>p &lt;0.05</i>  <i>CRQ-Fatigue</i> <i>r = -0.18</i> <i>p &lt;0.01</i>
Lin (80)	2014	Stable COPD, age ≥40 years, no cognitive impairment, not frail, acute illness, not receiving hospice care, not staying in long-term care facility - secondary care population	670	PROMIS-43			<b>6mwt</b> Mean±SD (meters) = 335.6±110.4 <i>r = -0.29</i> <i>p &lt; 0.05</i>
Meng (115)	2011	Stable COPD, no major disabling diseases influencing exercise ability and quality of life - secondary care	40	CRQ-Fatigue			<u><b>Symptom-limited cycle ergometer graded exercise test</b></u>  <i>VO<sub>2</sub>peak</i> Mean±SD (ml/min)



First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
		population					= 1140±330 r = -0.132 p = 0.456  <i>VEpeak</i> Mean±SD (liters) = 39.5±12.4 r = -0.044 p = 0.805  <i>VEpeak % pred</i> Mean±SD= 72.3±26.2 r = -0.178 p = 0.320  <i>VE/MVV % pred</i> r = -0.433 p = 0.015  <i>RER at AT</i> Mean±SD = 0.86±0.07 r = -0.408 p = 0.031  <i>RER peak exercise</i> Mean±SD = 0.96±0.12 r = -0.136

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
							<p><math>p = 0.443</math></p> <p><i>Oxygen pulse at peak exercise</i>  <math>r = -0.039</math>  <math>p = 0.826</math></p> <p><i>HR at rest</i>  <i>Mean±SD (bpm) = 86±12</i>  <math>r = -0.301</math>  <math>p = 0.307</math></p> <p><i>HR at AT</i>  <i>Mean±SD (bpm) = 110±16</i>  <math>r = -0.425</math>  <math>p = 0.024</math></p> <p><i>HR peak exercise</i>  <i>Mean±SD (bpm) = 130±19</i>  <math>r = -0.410</math>  <math>p = 0.016</math></p> <p><i>SatO2 at rest</i>  <i>Mean±SD (%) = 94.4±2.4</i>  <math>r = 0.224</math>  <math>p = 0.203</math></p>

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
							<p><i>SatO2 at AT</i>  Mean±SD (%) = 92.4±3.5  r = 0.034  p = 0.869</p> <p><i>SatO2 peak exercise</i>  Mean±SD (%) = 89.5±6.1  r = 0.080  p = 0.672</p>
Nguyen (140)	2008	Moderate to severe stable COPD, age ≥40, no participation in exercise training or pulmonary rehabilitation for at least 1 year, no other active symptomatic diseases - primary and secondary care population	115	CRQ-Fatigue			<p><b>6mwt</b>  Good or better self-rated health:  Mean±SD (feet) = 1437.3 ± 291.5</p> <p>Fair/poor self-rated health:  Mean±SD (feet) = 1316.4 ± 349.8</p> <p>r = 0.35  p &lt; 0.05</p>
Strandkvist (29)	2018		389	FACIT-F		<p><b>Hand grip strength</b>  <u>JAMAR</u></p> <p>Women, mean±SD</p>	

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
						= 22.8±5.5 Multiple linear regression: B[95%CI] = 0.085[-0.001 to 0.171]  Men, mean±SD = 41.1±9.5 Multiple linear regression: B[95%CI] = 0.249[0.131 to 0.367]. Also, independent of physical activity 0.190[0.061 to 0.319]  Adjusted for smoking habits, age, and height.	
Todt (102)	2013	Stable COPD, no other major comorbidities – secondary care population	121	3 questions about frequency, duration and severity of fatigue			<u>6mwt</u> Men: Mean±SD (meters) = 432±144 Women: Mean±SD (meters): 380±128 r = -0.304*

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
							<p><math>p &lt; 0.05</math></p> <p>*adjusted for sex</p>
Valderramas (103)	2013	Stable COPD, not being involved in any type of physical activity, no extrapulmonary disease causing functional limitation and fatigue - secondary care population	50	FSS			<p><b>6mwt</b></p> <p>Mean±SD (meters) = 357.2±92.6</p> <p><math>r = -0.77</math></p> <p><math>p &lt; 0.01</math></p>
Wong (128)	2010	Symptomatic COPD patients who completed pulmonary 53rehabilitation, aged ≥18 years - rehabilitation population	42	MFI-20			<p><b>6mwt</b></p> <p>Mean±SD (meters) = 356±90</p> <p><i>General fatigue</i></p> <p><math>r = -0.17</math></p> <p><math>p &gt; 0.05</math></p> <p><i>Physical fatigue</i></p> <p><math>r = -0.11</math></p> <p><math>p &gt; 0.05</math></p> <p><i>Reduced activity</i></p> <p><math>r = -0.25</math></p> <p><math>p &gt; 0.05</math></p>

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
							<i>Reduced motivation</i> $r = -0.07$ $p > 0.05$  <i>Mental fatigue</i> $r = 0.11$ $p > 0.05$
Woo (182)	2000	Chronic bronchitis and/or emphysema, reported feelings of dyspnea and fatigue over the past few days, independent in moving and living, no psychiatric problems and concomitant neuromuscular disease - secondary care population	22	F-POMS			<b>6mwt</b> Mean±SD (meters) = 351.67±170.62 $r = -0.63$ $p < 0.005$
Yeh (166)	2004	COPD - secondary care population	138	SF-36			<b><u>6mwt/exercise tolerance</u></b> Mean±SD (minutes) = 303.2±114.32

First author	Year	Population	Sample size	Fatigue assessment tool	Physical factors		
					BMI	Peripheral muscle strength	Exercise capacity
							$r = -0.33$ $p < 0.001$
Yohannes (15)	2019	COPD, referred for outpatient pulmonary rehabilitation, FEV1<70%, aged ≥40 years, no lung cancer, no pre-existing conditions rendering exercise unsafe, no psychiatric illness – rehabilitation population	273	MCFS			<b>ISWT</b> Mean±SD (meters) = 189.19±116.07  <i>Physical fatigue</i> $r = -0.12$ $p < 0.05$  <i>Cognition</i> $r = -0.10$ $p = 0.11$  <i>Psychosocial</i> $r = -0.18$ $p < 0.002$  <i>Total score</i> $r = -0.14$ $p = 0.01$

Table 6: Psycho-social factors associated with fatigue

First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
<b>COPD related fatigue – Psychological factors</b>						
Goërtz (3)	2019	COPD diagnosis – secondary care population	1290			CAT rs = 0.584 p = <0.001
Kallikova (5)	2019	Age > 18 and < 65 years and COPD diagnosis – rehabilitation population	31			MVQoLI-15: Physical fatigue r = -0.007 p = 0.970 Mental fatigue r = -0.437 p = 0.014 Total fatigue r = -0.239 p = .195
Yang (14)	2019	COPD diagnosis – secondary care population	210			SF-12v2: Total SF-12v2-overall FACIT r = 0.77 PCS domain-overall FACIT p < 0.001 r = 0.44 MCS domain-overall FACIT p < 0.01 r = 0.55 Total SF-12v2-general fatigue FACIT



First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
						<p>p &lt; 0.01  r = 0.70  <i>PCS-domain-general fatigue FACIT</i>  p &lt; 0.01  r = 0.32  <i>MCS-domain-general fatigue FACIT</i>  p = &lt;0.01  r = 0.55  p &lt; 0.01</p>
Yohannes (15)	2019	at least 40 years old, COPD diagnosis, FEV1%pred <70% - rehabilitation population	273	<p><i>AIR:</i>  Mean±SD = 4.97 ± 5.31  r = 0.41  p &lt;0.001</p>		
Stridsman (30)	2018	Not reported - primary care population	367	<p><i>One question ('Do you have anxiety or depression?'):</i>  Mean±SD = 54 ± 14.8  OR = 2.40 (1.33–4.30)  p &gt; 0.05</p> <p>Adjusted for age, sex, smoking habits, any respiratory symptoms, anxiety/depression, heart disease and</p>	<p><i>One question ('Do you have anxiety or depression?'):</i>  Mean±SD = 54 ± 14.8  OR = 2.40 (1.33–4.30)  p &gt; 0.05</p> <p>Adjusted for age, sex, smoking habits, any respiratory symptoms, anxiety/depression, heart disease and</p>	

First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
				health care contacts	health care contacts	
Kentson (57)	2016	Stable COPD - secondary care population	101	<i>HADS:</i> $r = 0.38$ <i>FIS-physical:</i> $p < 0.01$ <i>FIS-psychosocial:</i> $r = 0.50$ $p < 0.01$ <i>FIS-cognitive:</i> $r = 0.43$ $p < 0.01$	<i>HADS:</i> $r = 0.52$ <i>FIS-physical:</i> $p < 0.01$ <i>FIS-psychosocial:</i> $r = 0.61$ $p < 0.01$ <i>FIS-cognitive:</i> $r = 0.50$ $p < 0.01$	
Arikan (65)	2015	COPD – rehabilitation population	28			<i>LCQ:</i> $r = -0.557$ $p = 0.003$
Parreira (72)	2015	Stable COPD 4 weeks before measurement; no comorbidity – secondary care population	80	<i>HADS:</i> $r = -0.366$ $p = 0.002$	<i>HADS:</i> $r = -0.382$ $p = 0.001$	
Lin (80)	2014	Stable COPD, age $\geq 40$ years, completed EQ-5-DL and PROMIS - secondary care population	670	<i>PROMIS:</i> $r = 0.53$ $p = < 0.001$	<i>PROMIS:</i> $r = 0.59$ $p = < 0.001$	<i>EQ-5D:</i> $p = < 0.001$

First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
Bentsen (90)	2013	Stable COPD, age ≥35, FEV1<80%; - tertiary care population	100	<i>BPQ</i> : 64% OR = 1.23 (0.32- 4.73) p = 0.761 Adjusted for age, gender, lung function, comorbidity, and exacerbations	<i>BPQ</i> : 69% OR = 7.13 (1.87- 27.22) p = 0.004 Adjusted for age, gender, lung function, comorbidity, and exacerbations	
Karakurt (94)	2013	COPD diagnose ≥ 6 months - secondary care population	255	<i>HADS</i> : r = 0.32 p < 0.001	<i>HADS</i> : r = 0.36 p < 0.001	
Miravittles (96)	2013	Moderate or severe COPD, FEV1 ≤ 80%, age > 40 years, >10 pack years, COPD diagnose ≥ 5 years - secondary care population	408	<i>HADS</i> : p <0.0001	<i>HADS</i> : p < 0.0001	
Baltzan (109)	2011	Not reported-rehabilitation population	251		<i>GDS</i> : p <0.01	
Hanania (110)	2011	Age 40-75, FEV1<80%, >10 pack years – secondary care population	2118		<i>CES</i> : 26% Mean±SD = 11 ± 9 p <0.001	

First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
Meng (115)	2011	COPD outpatients – secondary care population	40			<i>SF-36:</i> <i>Physical functioning:</i> <i>r = 0.265</i> <i>p = 0.098</i> <i>Role physical:</i> <i>r = 0.243</i> <i>p = 0.131</i> <i>Bodily pain:</i> <i>r = 0.205</i> <i>p = 0.203</i> <i>General health:</i> <i>r = 0.399</i> <i>p = 0.011</i> <i>Vitality:</i> <i>r = 0.524</i> <i>p = &lt;0,001</i> <i>Social functioning:</i> <i>r = 0.329</i> <i>p = 0.038</i> <i>Role emotional:</i> <i>r = 0.208</i> <i>p = 0.197</i> <i>Mental health:</i> <i>r = 0.252</i> <i>p = 0.117</i>
Vigil (119)	2011	COPD – secondary care population	40			<i>SF-36:</i> <i>Physical fatigue</i> <i>r = 0.77</i> <i>p = 0.01</i> <i>Mental fatigue</i> <i>r = 0.47</i> <i>p = 0.05</i>

First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
Borge (121)	2010	All COPD stages; age ≥30 years; ability to write and read Norwegian - primary care population	154	<i>HADS:</i> r = 0.45 p = 0.001	<i>HADS:</i> r = 0.53 p = 0.001	
Wong (128)	2010	COPD diagnosis, age ≥18 years - rehabilitation population	42	<i>HADS:</i> 42.9% <i>General fatigue:</i> r = 0.23 <i>Physical fatigue</i> r = -0.23 <i>Mental fatigue</i> r = -0.22 p > 0.05	<i>HADS:</i> 21.4% <i>General fatigue:</i> r = 0.00 <i>Physical fatigue</i> r = -0.22 <i>Mental fatigue</i> r = -0.30 p > 0.05	
Baghai-Ravary (130)	2009	Stable COPD ≥4 weeks; FEV1% > 20% - primary and secondary care population	107		<i>CES:</i> r = -0.59 p = <0.001	
Nguyen (140)	2008	Stable COPD ≥ 4 weeks; FEV1% < 60%; age ≥ 40 years; no participation in any formal exercise training or PR < 1 year; no other active symptomatic diseases - primary and secondary care population	115		<i>CES:</i> r = -0.45 p < 0.05	<i>SF-36:</i> r = 0.40 ( <i>physical fatigue</i> ); r = -0.48 ( <i>mental fatigue</i> ) p < 0.05
Kapella (153)	2006	FEV1 < 70%, age ≥45 years, >10 pack years	130	<i>POMS:</i> r = 0.61	<i>POMS:</i> r = 0.57	

First author	Year	Population	Sample size	Factors associated with fatigue		
				Anxiety	Depression	Quality of life
		- secondary care population		p = < 0.001  <i>NRS</i> r = 0.49 p = < 0.001	p < 0.001  <i>NRS</i> r = 0.45 p < 0.001	
Yeh (166)	2004	COPD diagnosis - secondary care population	138		<i>HADS:</i> r = 0.50 p < 0.001	<i>SF-36:</i> r = 0.58 p < 0.001
Breslin (187)	1998	Not reported - secondary care population	41		<i>CES:</i> r = 0.442 ( <i>general fatigue</i> ) p < 0.01; r = 0.258 ( <i>physical fatigue</i> ) p < 0.05; r = 0.40 ( <i>mental fatigue</i> ) p < 0.05	
Martin (192)	1994	COPD diagnosis; PR – rehabilitation population	15		<i>CES:</i> r = 0.66 p < 0.05	
Moody (194)	1991	Age ≥40 years, literate, CBE: verified by history and spirometry results – primary care population	45	<i>NEO-PI:</i> r = 0.43 p = < 0.001	<i>NEO-PI:</i> r = 0.57 p < 0.05	

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