

# THE LANCET

## Respiratory Medicine

### Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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## Supplementary Data

Demographics		Overall, N=2,320	Subjective, N=638	Device-based, N=729
Age (years)		58.0 (12.6)	58.4 (13.0)	59.2 (12.6)
Sex (% male)		61% (1,338/2,193)	60% (350/583)	63% (434/693)
BMI (kg/m <sup>2</sup> )		32.4 (7.3)	31.8 (6.7)	31.3 (6.6)
Ethnicity				
	<i>White</i>	75% (1,685/2,234)	71% (439/619)	75% (542/722)
	<i>South Asian</i>	12% (262/2,234)	17% (105/619)	13% (91/722)
	<i>Black</i>	6.9% (154/2,234)	6.3% (39/619)	6.1% (44/722)
	<i>Mixed</i>	2.1% (46/2,234)	2.6% (16/619)	2.2% (16/722)
	<i>Other</i>	3.9% (87/2,234)	3.2% (20/619)	4.0% (29/722)
Townsend IMD quintile				
	<i>1 - most deprived</i>	23% (517/2,288)	20% (127/629)	22% (159/727)
	<i>2</i>	23% (533/2,288)	19% (118/629)	20% (491/727)
	<i>3</i>	18% (404/2,288)	17% (108/629)	16% (116/727)
	<i>4</i>	17% (396/2,288)	22% (136/629)	20% (142/727)
	<i>5 - least deprived</i>	19% (438/2,288)	22% (140/629)	22% (161/727)
Smoking Status				
	<i>Never</i>	55% (1,151/2,105)	59% (373/631)	54% (359/667)
	<i>Ex-smoker</i>	44% (916/2,105)	40% (251/631)	45% (297/667)
	<i>Current smoker</i>	1.8% (38/2,105)	1.1% (7/631)	1.6% (11/667)
Average units of alcohol (per week)		4.9 (7.7)	4.9 (7.4)	4.9 (7.6)
Days admission was into pandemic		198 (125)	173 (119)	115 (82.9)
Days since discharge		156 (45.1)	162 (40.0)	162 (44.4)
<b>Comorbidities</b>				
Hypertension		35% (767/2,175)	37% (215/576)	34% (231/682)
Diabetes		22% (473/2,168)	22% (123/571)	22% (146/679)
Liver disease		3.1% (67/2,163)	2.6% (25/571)	3.8% (26/679)
Asthma		19% (408/2,173)	15% (88/574)	17% (118/680)
COPD		5.5% (121/2,171)	4.2% (24/573)	4.9% (33/680)
Chronic kidney disease		4.3% (94/2,172)	3.7% (21/572)	3.8% (26/682)
High cholesterol		20% (442/2,171)	23% (132/572)	19% (131/681)
Depression or anxiety		17% (373/2,168)	11% (63/572)	9.7% (66/679)
<b>COVID-19 severity</b>				
WHO clinical progression				

	<i>WHO – class 3-4</i>	17% (385/2,273)	21% (130/626)	19% (138/720)
	<i>WHO – class 5</i>	42% (959/2,273)	44% (273/626)	40% (290/720)
	<i>WHO – class 6</i>	23% (517/2,273)	17% (104/626)	16% (116/720)
	<i>WHO – class 7-9</i>	18% (412/2,273)	14% (119/626)	24% (176/720)
Length of stay (days)		13.9 (18.1)	13.9 (19.4)	15.5 (21.1)
ITU admission (% admitted)		33% (701/2,101)	32% (202/631)	39% (264/669)
<b>Pre-COVID-19 symptoms</b>				
Subjective sleep quality (10=best)		7.9 (2.6)	8.1 (2.5)	8.2 (2.4)
Subjective dyspnoea (0=best)		1.2 (2.1)	1.1 (2.0)	1.1 (2.0)
<b>Post-COVID-19 symptoms</b>				
Subjective sleep quality (10=best)		6.0 (3.1)	6.3 (3.1)	6.1 (3.0)
Subjective dyspnoea (0=best)		4.0 (2.9)	4.1 (2.8)	4.1 (2.8)
PHQ9 level				
	<i>None</i>		53% (329/622)	52% (369/704)
	<i>Mild</i>		21% (133/622)	22% (158/704)
	<i>Moderate</i>		14% (88/622)	13% (90/704)
	<i>Moderately Severe</i>		6.1% (38/622)	8.0% (56/704)
	<i>Severe</i>		5.5% (34/622)	4.4% (31/704)
GAD7 level				
	<i>Minimal</i>	59% (1,209/2,162)	61% (377/620)	61% (433/705)
	<i>Mild</i>	22% (466/2,162)	21% (133/620)	19% (134/705)
	<i>Moderate</i>	13% (276/2,162)	11% (67/620)	11% (81/705)
	<i>Severe</i>	9.8% (211/2,162)	6.9% (43/620)	8.1% (57/705)
Subjective sleep length (hours)		6.7 (1.9)	6.6 (2.0)	6.6 (1.9)

**Supplementary Table 1 Demographics of study participants:** Participant demographics are shown for three groups. The first group, termed *Overall*, are participants who consented to research following COVID-19 hospitalisation. The second group, termed *Subjective*, are participants who responded to both the Pittsburgh Sleep Quality Index and Numerical Rating Scale questionnaires. The third group, termed *device-based*, are participants who had their sleep assessed using actigraphy. Continuous values are presented as mean (SD). Categorical data are presented as % (n/N). If the value for a patient was missing, that patient was excluded from each specific comparison. PSQI=Pittsburgh sleep quality index. BMI=body mass index. IMD=Index of multiple deprivation. COPD=Chronic obstructive pulmonary disease. WHO=World health organisation. ITU=intensive therapy unit. PHQ9=Patient Health Questionnaire (9-questions). GAD7=Generalised Anxiety Disorder 7-item scale.

<b>Demographics</b>		<b>N</b>	<b>No deterioration, N = 300</b>	<b>Deterioration, N = 338</b>
Age (years)		629	61.0 (12.9)	56.1 (12.7)
Sex (% male)		583	66% (183/277)	55% (167/306)
BMI (kg/m <sup>2</sup> )		565	31.1 (6.4)	32.4 (6.8)
Ethnicity		619		
	<i>White</i>		71% (210/295)	71% (229/324)
	<i>South Asian</i>		16% (47/295)	18% (58/324)
	<i>Black</i>		6.8% (20/295)	5.9% (19/324)
	<i>Mixed</i>		3.4% (10/295)	1.9% (6/324)
	<i>Other</i>		2.7% (8/295)	3.7% (12/324)
Townsend IMD quintile		629		
	<i>1 - most deprived</i>		17% (51/296)	23% (76/333)
	<i>2</i>		18% (54/296)	19% (64/333)
	<i>3</i>		17% (51/296)	17% (57/333)
	<i>4</i>		24% (71/296)	20% (65/333)
	<i>5 - least deprived</i>		23% (69/296)	21% (71/333)
Smoking Status		631		
	<i>Never</i>		57% (168/297)	61% (205/334)
	<i>Ex-smoker</i>		42% (126/297)	37% (125/334)
	<i>Current smoker</i>		1.0% (3/297)	1.2% (4/334)
Average units of alcohol (per week)		605	5.4 (7.6)	4.3 (7.2)
Days admission was into pandemic		638	173 (121)	174 (117)
Days since discharge		638	165 (38.0)	159 (41.6)
<b>Comorbidities</b>				
Hypertension		576	34% (93/271)	40% (122/305)
Diabetes		571	24% (65/269)	19% (58/302)
Liver disease		571	1.9% (5/269)	3.3% (10/302)
Asthma		574	13% (36/270)	17% (52/304)
COPD		573	5.2% (14/270)	3.3% (10/303)
Chronic kidney disease		572	4.1% (11/268)	3.3% (10/304)
High cholesterol		572	28% (75/269)	19% (57/303)
Depression or anxiety		572	9.7% (26/268)	12% (37/304)
<b>COVID-19 severity</b>				
WHO clinical progression		626		
	<i>WHO – class 3-4</i>		17% (50/295)	24% (80/331)

	<i>WHO – class 5</i>		47% (139/295)	40% (134/331)
	<i>WHO – class 6</i>		18% (52/295)	16% (52/331)
	<i>WHO – class 7-9</i>		18% (54/295)	20% (65/331)
Length of stay (days)		635	13.4 (15.7)	14.4 (22.2)
ITU admission (% admitted)		631	31% (91/295)	33% (111/336)
<b>Pre-COVID-19 symptoms</b>				
Subjective sleep quality (10=best)		638	7.7 (2.9)	8.5 (2.0)
Subjective dyspnoea (0=best)		636	1.4 (2.3)	0.9 (1.6)
<b>Post-COVID-19 symptoms</b>				
Subjective sleep quality (10=best)		638	8.3 (2.4)	4.5 (2.5)
Subjective dyspnoea (0=best)		635	3.3 (2.8)	4.8 (2.7)
PHQ9 level		622		
	<i>None</i>		66% (194/293)	41% (125/329)
	<i>Mild</i>		20% (59/293)	22% (74/329)
	<i>Moderate</i>		7.5% (22/293)	20% (66/329)
	<i>Moderately Severe</i>		3.4% (10/293)	8.5% (28/329)
	<i>Severe</i>		2.7% (8/293)	7.9% (26/329)
GAD7 level		620		
	<i>Minimal</i>		74% (215/292)	49% (162/328)
	<i>Mild</i>		14% (41/292)	28% (92/328)
	<i>Moderate</i>		8.6% (25/292)	13% (42/328)
	<i>Severe</i>		3.8% (11/292)	9.8% (32/328)
Subjective sleep period duration (hours)		603	6.9 (1.8)	6.4 (2.0)

**Supplementary Table 2 Cohort demographics for Numerical Rating Scale participants:** Participants who answered the numerical rating scale were categorised according to whether their sleep quality had deteriorated or not. Continuous values are presented as mean (SD). Categorical data are presented as % (n/N). PSQI=Pittsburgh sleep quality index. BMI=body mass index. IMD=Index of multiple deprivation. COPD=Chronic obstructive pulmonary disease. WHO=World health organisation. PHQ9=Patient Health Questionnaire. PHQ9=Patient Health Questionnaire (9-questions). GAD7=Generalised Anxiety Disorder 7-item scale.

<b>Demographics</b>		<b>N</b>	<b>Regular, N = 110</b>	<b>Middle, N = 110</b>	<b>Irregular, N = 111</b>
Age (years)		330	57.4 (13.2)	59.4 (12.4)	59.6 (12.1)
Sex (% male)		304	71% (69/97)	61% (64/105)	67% (68/102)
BMI (kg/m <sup>2</sup> )		310	30.9 (6.4)	30.7 (5.8)	31.2 (8.1)
Ethnicity		326			
	<i>White</i>		84% (91/108)	76% (82/108)	62% (68/110)
	<i>South Asian</i>		9.3% (10/108)	14% (15/108)	15% (16/110)
	<i>Black</i>		2.8% (3/108)	3.7% (4/108)	15% (16/110)
	<i>Mixed</i>		0.9% (1/108)	1.9% (2/108)	4.5% (5/110)
	<i>Other</i>		2.8% (3/108)	4.6% (5/108)	4.5% (5/110)
Townsend IMD quintile		331			
	<i>1 - most deprived</i>		17% (19/110)	20% (22/110)	38% (42/111)
	<i>2</i>		18% (20/110)	26% (29/110)	16% (18/111)
	<i>3</i>		14% (15/110)	15% (17/110)	20% (22/111)
	<i>4</i>		27% (30/110)	15% (16/110)	15% (17/111)
	<i>5 - least deprived</i>		24% (26/110)	24% (26/110)	11% (12/111)
Smoking Status		295			
	<i>Never</i>		56% (55/99)	53% (52/98)	40% (39/98)
	<i>Ex-smoker</i>		44% (44/99)	47% (46/98)	54% (53/98)
	<i>Current smoker</i>		0% (0/99)	0% (0/98)	6.1% (6/98)
Average units of alcohol (per week)		283	6.0 (8.6)	5.2 (7.7)	3.5 (5.8)
Days admission was into pandemic		331	132 (94)	132 (94)	119 (78)
Days since discharge		331	161 (47)	155 (49)	161 (47)
<b>Comorbidities</b>					
Hypertension		299	24% (23/97)	32% (33/103)	43% (43/99)
Diabetes		297	12% (12/96)	16% (16/103)	32% (31/98)
Liver disease		298	2.1% (2/96)	2.9% (3/103)	6.1% (6/99)
Asthma		298	11% (11/96)	19% (20/103)	14% (14/99)
COPD		298	2.1% (2/96)	5.8% (6/103)	7.1% (7/99)
Chronic kidney disease		299	2.1% (2/96)	0% (0/103)	11% (11/100)
High cholesterol		299	14% (14/97)	19% (20/103)	24% (24/99)
Depression or anxiety		297	3.1% (3/96)	4.9% (5/103)	14% (14/98)
<b>COVID-19 severity</b>					
WHO clinical progression		326			
	<i>WHO – class 3-4</i>		17% (19/109)	22% (24/109)	15% (16/108)



	<i>WHO – class 5</i>		36% (39/109)	43% (47/109)	37% (40/108)
	<i>WHO – class 6</i>		22% (24/109)	13% (14/109)	15% (16/108)
	<i>WHO – class 7-9</i>		25% (27/109)	22% (24/109)	33% (36/108)
Length of stay (days)		330	14.5 (16.4)	15.3 (23.0)	22.1 (31.9)
ITU admission (% admitted)		298	45% (45/100)	34% (34/100)	48% (47/98)
<b>Pre-COVID-19 symptoms</b>					
Subjective sleep quality (10=best)		290	8.2 (2.7)	8.5 (2.2)	7.8 (2.7)
Subjective dyspnoea (0=best)		289	0.9 (1.7)	1.0 (2.1)	1.4 (2.1)
<b>Post-COVID-19 symptoms</b>					
Subjective sleep quality (10=best)		278	6.2 (3.2)	6.1 (2.8)	5.4 (3.1)
Subjective dyspnoea (0=best)		279	3.9 (2.7)	3.5 (2.8)	4.8 (2.9)
PHQ9 level		316			
	<i>None</i>		62% (63/102)	53% (56/105)	46% (50/109)
	<i>Mild</i>		20% (20/102)	30% (31/105)	17% (19/109)
	<i>Moderate</i>		14% (14/102)	9.5% (10/105)	17% (19/109)
	<i>Moderately Severe</i>		2.9% (3/102)	4.8% (5/105)	12% (13/109)
	<i>Severe</i>		2.0% (2/102)	2.9% (3/105)	7.3% (8/109)
GAD7 level		316			
	<i>Minimal</i>		64% (65/102)	66% (69/105)	54% (59/109)
	<i>Mild</i>		23% (23/102)	19% (20/105)	16% (17/109)
	<i>Moderate</i>		8.8% (9/102)	10% (11/105)	20% (22/109)
	<i>Severe</i>		4.9% (5/102)	4.8% (5/105)	10% (11/109)
Subjective sleep period duration (hours)		268	7.0 (1.3)	6.8 (1.5)	6.2 (2.1)

**Supplementary Table 3 Cohort demographics for Sleep Regularity Index:** Participants were placed into quintiles according to their Sleep Regularity Index (Top quintile= highest sleep regularity index (most regular), Lowest quintile= lowest sleep regularity index (least regular)). Continuous values are presented as mean (SD). Categorical data are presented as % (n/N). PSQI=Pittsburgh sleep quality index. BMI=body mass index. IMD=Index of multiple deprivation. COPD=Chronic obstructive pulmonary disease. WHO=World health organisation. PHQ9=Patient Health Questionnaire. GAD7=Generalised Anxiety Disorder 7-item scale.

		<b>Non-hospitalised n=553</b>	<b>Recently hospitalised n=553</b>	<b>Device-based n=553</b>
Age (years)		69.5 (8.3)	70.5 (8.0)	60.9 (9.0)
Sex (% male)		64% (354/553)	63% (349/553)	64% (379/553)
BMI (kg/m <sup>2</sup> )		30.5 (5.8)	30.3 (5.8)	31.1 (6.4)
Ethnicity				
	<i>White</i>	96% (533/553)	96% (531/553)	75% (415/553)
	<i>South Asian</i>	0.7% (4/553)	1.2% (7/553)	13% (72/553)
	<i>Black</i>	1.3% (7/553)	1.4% (8/553)	5.1% (28/553)
	<i>Mixed</i>	0.4% (2/553)	0.8% (3/553)	2.4% (13/553)
	<i>Other</i>	1.3% (7/553)	0.8% (4/553)	4.6% (25/553)
Smoker (%)				
	<i>Never</i>	49% (271/553)	51% (282/553)	53% (295/553)
	<i>Ex-smoker</i>	44% (243/553)	41% (227/553)	45% (249/553)
	<i>Current smoker</i>	7.1% (39/553)	7.8% (43/553)	1.7% (9/553)
Subjective sleep length (hours)		7.1 (1.1)	7.1 (1.2)	6.6 (1.9)
<b>Pre-morbid Comorbidities</b>				
Hypertension		30% (166/553)	33% (182/553)	35% (194/553)
Diabetes		6.0% (33/553)	9.1% (50/553)	21% (116/553)
Liver disease		0.4% (2/553)	0.6% (3/553)	3.9% (22/553)
Asthma		16% (88/553)	16% (88/553)	17% (94/553)
COPD		0% (0/553)	0% (0/553)	5.2% (29/553)
Chronic kidney disease		0% (0/553)	0.6% (3/553)	3.5% (20/553)
High cholesterol		15% (83/553)	15% (83/553)	20% (111/553)
Depression or anxiety		6.9% (38/553)	8.0% (44/553)	9.8% (54/553)

**Supplementary Table 4 Demographics of participants compared to the UK biobank:** The device-based cohort of COVID-19 participants was compared to participants in the UK Biobank. UK biobank participants were split into two groups according to whether they had been hospitalised in the 12 months before wearing the actigraphy device (*non-hospitalised*) or were hospitalised for at least overnight 2-11 months before wearing the actigraphy device (*recently hospitalised*). The final group, device-based, are participants who had been hospitalised with COVID-19 and had actigraphy measured after discharge. Groups were matched for age, sex, BMI and, if applicable, time from hospital discharge at an aggregated level. Continuous values are presented as mean (SD). Categorical data are presented as % (n/N). If the value for a patient was missing, that patient was excluded from each specific comparison. BMI=Body Mass Index. COPD=Chronic obstructive pulmonary disease.

	<b>Sleep Quality (Pittsburgh Sleep Quality Index)</b>	<b>Sleep Deterioration (Numerical Rating Scale)</b>	<b>Sleep Regularity</b>
Dyspnoea-12	3.15 (1.41; 7.10)	1.29 (0.53; 2.04)	1.09 (0.39; 1.79)
Predicted FEV <sub>1</sub> (%)	-2.94 (-5.93; -0.18)	-3.94 (-6.89; -0.99)	-3.17 (-5.74; -0.59)
Predicted FVC (%)	-3.79 (-6.83; -0.75)	-3.59 (-6.52; -0.65)	-4.09 (-6.62; -1.55)
Predicted TLCO (%)	2.36 (-4.72; 9.44)	2.04 (-4.53; 8.61)	-10.37 (-53.51; 32.77)
Predicted KCO (%)	-0.49 (-5.62; 4.64)	-0.14 (-4.90; 4.63)	0.39 (-4.10; 4.89)
MIP	-6.07 (-13.65; 1.51)	0.87 (-7.14; 8.88)	..
MEP	-8.66 (-19.04; 1.72)	5.00 (-5.76; 15.76)	..
SARC-F	0.66 (0.47; 0.84)	0.17 (-0.01; 0.36)	0.34 (0.16; 0.51)
GAD7 (Mild)	1.61 (1.17; 2.20)	1.34 (1.03; 1.73)	0.88 (0.67; 1.16)
GAD7 (Moderate)	4.66 (2.93; 7.42)	1.47 (1.04; 2.08)	1.38 (0.97; 1.96)
GAD7 (Severe)	9.68 (5.04; 18.62)	1.65 (1.10; 2.49)	1.23 (0.83; 1.82)

**Supplementary Table 5: Dyspnoea, muscle weakness and anxiety are associated with sleep disturbance:** In contrast to the rest of the paper, the evaluations (Pittsburgh Sleep Quality Index, numerical rating scale and device-based) for sleep disturbance were treated as a continuous variable. Multivariable linear regression was used to evaluate the standardised effect estimates for all variables except anxiety (GAD7); multinomial logistic regression was used to evaluate the relative risk with anxiety. In all cases, the estimates were standardised by centring and scaling (subtract mean, divide by standard deviation) the sleep variable and all models were adjusted for a minimally sufficient set of covariates. FEV<sub>1</sub>=Forced Exhaled Volume in 1 second. FVC=Forced Vital Capacity. KCO=Carbon monoxide transfer coefficient. TLCO=Transfer capacity of the lung. MIP=Maximum Inspiratory Pressure. MEP=Maximum Expiratory Pressure. GAD7=Generalised Anxiety Disorder 7-item scale. No results are presented for sleep regularity and MIP or MEP due to the sample size being too small to adjust for covariates.

Label	Effect size	Mediated effect	Proportion mediated, %
c' (Relationship between poor sleep quality and dyspnoea)	1.15 (-0.03; 2.27)		
a <sub>1</sub> (Relationship between poor sleep quality and anxiety)	0.65 (0.51; 0.80)	1.77 (1.04; 2.62)	38.70 (22.67; 57.17)
b <sub>1</sub> (Relationship between anxiety and dyspnoea)	2.73 (1.79; 3.71)		
a <sub>2</sub> (Relationship between poor sleep quality and muscle function)	1.00 (0.65; 1.38)	1.66 (0.97; 2.55)	36.22 (21.19; 55.56)
b <sub>2</sub> (Relationship between muscle function and dyspnoea)	1.66 (1.26; 2.11)		

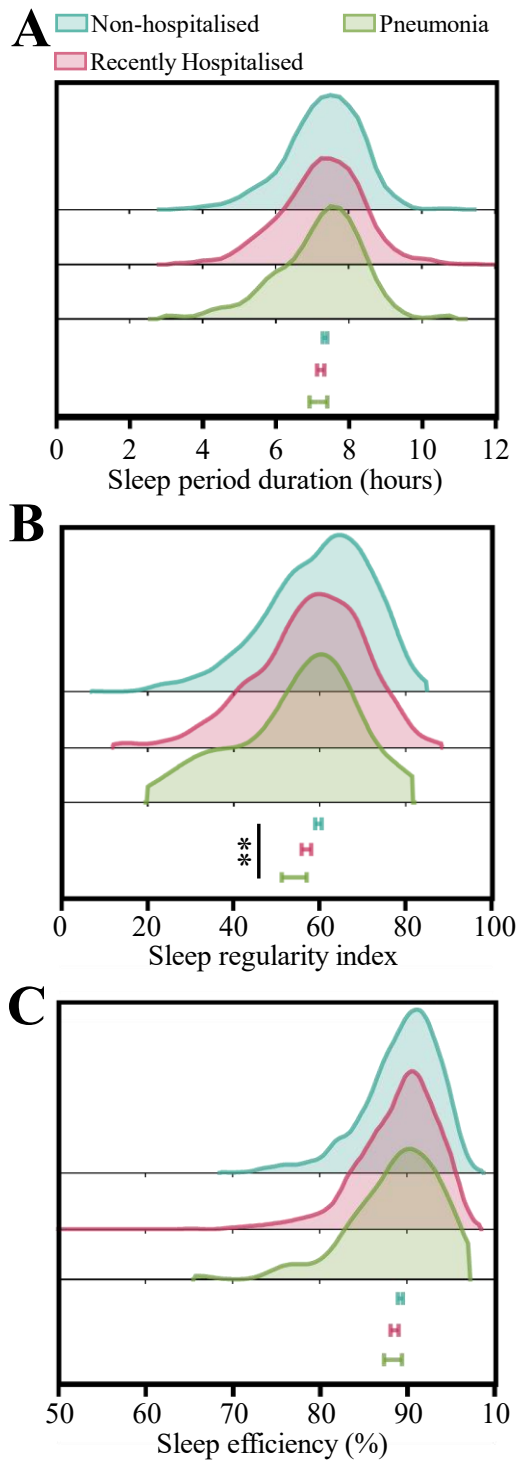
**Supplementary Table 6:** Results of the multiple mediation model using sleep quality (Pittsburgh Sleep Quality Index) as the exposure and dyspnoea as the outcome. Results show 95% confidence intervals calculated using a bootstrap with 1,999 resamples.

Label	Effect size	Mediated effect	Proportion mediated, %
c' (Relationship between sleep deterioration and dyspnoea)	1.07 (-0.07; 2.28)		
a <sub>1</sub> (Relationship between sleep deterioration and anxiety)	0.36 (0.18; 0.54)	1.01 (0.46; 1.69)	35.63 (16.14; 59.22)
b <sub>1</sub> (Relationship between anxiety and dyspnoea)	2.81 (1.89; 3.75)		
a <sub>2</sub> (Relationship between sleep deterioration and muscle function)	0.46 (0.07; 0.84)	0.76 (0.11; 1.49)	26.87 (3.91; 52.34)
b <sub>2</sub> (Relationship between muscle function and dyspnoea)	1.67 (1.27; 2.12)		

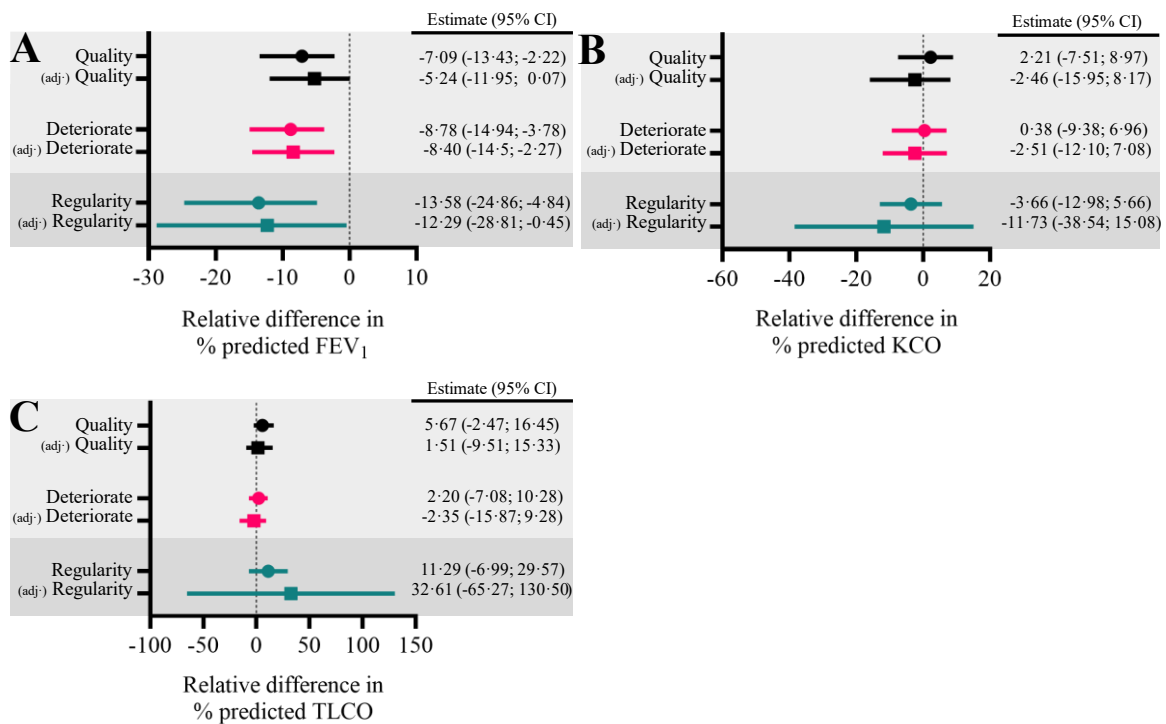
**Supplementary Table 7:** Results of the multiple mediation model using sleep deterioration (numerical rating scale) as the exposure and dyspnoea as the outcome. Results show 95% confidence intervals calculated using a bootstrap with 1,999 resamples.

Label	Effect size	Mediated effect	Proportion mediated, %
c' (Relationship between sleep irregularity and dyspnoea)	2.20 (-0.24; 4.63)		
a <sub>1</sub> (Relationship between sleep irregularity and anxiety)	0.34 (0.03; 0.62)	0.94 (0.07; 2.24)	17.69 (1.38; 42.27)
b <sub>1</sub> (Relationship between anxiety and dyspnoea)	2.76 (1.19; 4.51)		
a <sub>2</sub> (Relationship between sleep irregularity and muscle function)	1.28 (0.67; 1.90)	2.15 (0.80; 3.82)	40.62 (15.15; 72.34)
b <sub>2</sub> (Relationship between muscle function and dyspnoea)	1.68 (0.87; 2.44)		

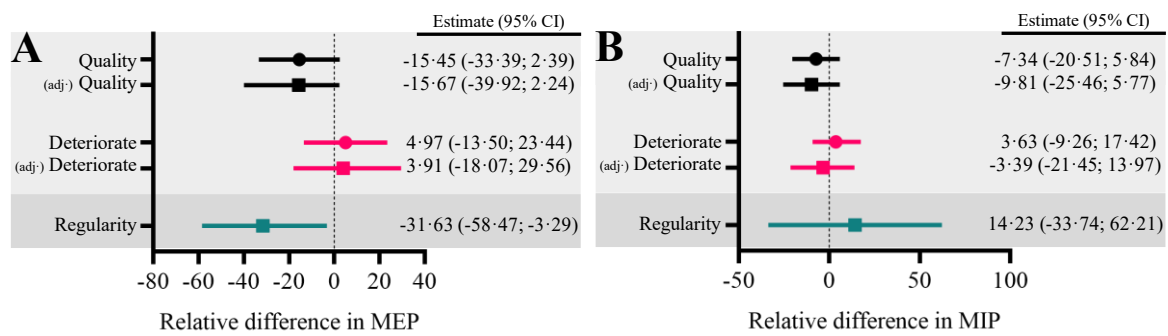
**Supplementary Table 8:** Results of the multiple mediation model using sleep regularity as the exposure and dyspnoea as the outcome. Results show 95% confidence intervals calculated using a bootstrap with 1,999 resamples.



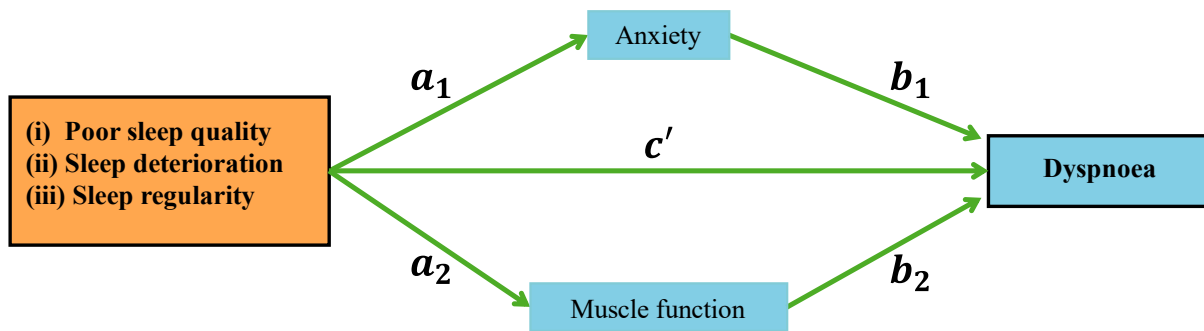
**Supplementary Figure 1: Sleep disturbance after hospitalisation:** Sleep traits were quantified in UK Biobank participants after hospitalisation with non-COVID-19 pneumonia. These data quantified (A) sleep period duration, (B) sleep efficiency and (C) sleep regularity index. UK Biobank participants with pneumonia (olive green, lower) were matched (age, sex, BMI and, if applicable, time from discharge) with *non-hospitalised* UK Biobank participants (sea green, upper) and *recently hospitalised* UK Biobank participants (red, middle). Mean $\pm$ 95% confidence intervals are shown underneath the graphs (\*= $p < 0.05$ , linear regression (appendix pp 26-28)).



**Supplementary Figure 2: Sleep disturbance is associated with altered lung function:** The associations between changes in the sleep parameters Sleep quality (PSQI, black); Sleep deterioration (NRS, Pink); Sleep regularity (Teal) and lung function were investigated. (A) Shows the association with percentage predicted FEV<sub>1</sub>. (B) Shows the association with KCO (C) Shows the association with TLCO. Both unadjusted (circles) or multivariable (squares) effect estimates are shown with 95% confidence intervals. In multivariable linear regression, the association was adjusted for age, sex, BMI, comorbidities, COVID-19 severity, length of stay, number of days into the pandemic and number of days since discharge. Light grey background indicates a subjective evaluation of sleep quality, and a dark-grey background indicates a device-based measurement of sleep. BMI=Body Mass Index. FEV<sub>1</sub>= Forced Expiratory Volume in 1 second, KCO= Carbon monoxide transfer coefficient, TLCO= Transfer capacity of the lung.



**Supplementary Figure 3: Sleep disturbance is associated with altered respiratory pressures:** Associations between changes in the sleep parameters Sleep quality (PSQI, black); Sleep deterioration (NRS, Pink); Sleep regularity (Teal) were investigated with altered respiratory pressures. **(A)** Shows the association with maximal expiratory pressure (MEP). **(B)** Shows the association with maximal inspiratory pressure (MIP). Both unadjusted (circles) or multivariable (squares) effect estimates are shown with 95% confidence intervals. In multivariable linear regression, the association was adjusted for age, sex, BMI, comorbidities, COVID-19 severity, length of stay, number of days into the pandemic and number of days since discharge. Light grey background indicates a subjective evaluation of sleep quality, and a dark-grey background indicates a device-based measurement of sleep.



**Supplementary Figure 4: Mediation model:** Mediation models investigated the association between sleep disruption and dyspnoea to investigate whether anxiety and muscle function could be considered mediators in the relationship. The results are reported in Supplementary Tables 6-8 (appendix p 19) as well as in **Figure 5**. The pathway labelled  $c'$  represents the direct effect of sleep disruption on dyspnoea. The pathways labelled  $a_i$  represent the effect of sleep disruption on the hypothesis mediators (Anxiety and Muscle Function). Lastly, the pathways labelled  $b_i$  represent the effect of the mediators on dyspnoea and are calculated whilst controlling for sleep disruption.



## Supplementary Methods

**Participants:** Participants who consented to research were enrolled in the study. For these participants, follow-up data were collected at two time points: an early time point 2-7 months after hospital discharge, and a later time point 10-14 months after hospital discharge. Participants were excluded from this analysis if:

1. They had pre-morbid conditions that have been linked to sleep disturbance. These were:
  - a. Obstructive sleep apnoea
  - b. Obesity hyperventilative syndrome
  - c. Chronic fatigue syndrome
  - d. Chronic neurological disorders
2. Benzodiazepines had been prescribed before hospital admission.
3. Their COVID PCR test result first became positive  $\geq 7$  days after hospital admission.

No participants in either the subjective or device-based cohort had an obstetric code associated with their admission. Although core information was collected at all sites, only certain sites offered participants the chance to fill in sleep questionnaires or wear actigraphy devices. Sex was classified as sex assigned at birth; age was categorised as < 40, 40–49, 50–59, 60–69, and  $\geq 70$  years; body mass index (BMI) was categorised as *underweight* (< 20 kg/m<sup>2</sup>), *normal weight* (20-24.99 kg/m<sup>2</sup>), *overweight* (25-29.99 kg/m<sup>2</sup>), *obese* (30-34.99 kg/m<sup>2</sup>) and *morbidly obese* (>34.99 kg/m<sup>2</sup>); ethnicity was recorded according to census definitions and categorised as the four most frequent classes in the dataset: *White*, *South Asian*, *Black*, *Mixed* and *Other*; the Townsend index of multiple deprivation (IMD) was obtained using postcode and was categorised as quintiles with the first quintile indicating the most deprived; Length of hospital stay was categorised as quartiles with the first quartile indicating the shortest stays; presence of pre-COVID-19 comorbid disease was also recorded for *hypertension*, *diabetes*, *asthma*, *high cholesterol* and *depression/anxiety*; number of days into the pandemic was defined as the number of days from 29/01/2020, the date of the first confirmed cases of COVID-19 in the UK; number of days since discharge was defined as the number of days from a patients discharge from hospital to the date of their early follow-up tests.

The presence of comorbid diseases was obtained from medical records before admission with COVID-19. Comorbid disease following admission with COVID-19 was obtained from the study's case report form combined with information from the medical record.

### Subjective assessment of sleep quality:

**Numerical rating scale:** Participants answered the question “*For each symptom, please rate your symptoms before you had COVID-19 and how you are now.*”. At the early assessment time point, participants rated their sleep quality and recalled their pre-COVID-19 sleep quality. At the late assessment time point, participants rated their current sleep quality.

**Actigraphy:** Tri-axial acceleration data were collected at a 30Hz sampling frequency and were processed using the GGIR package (version 2.2-0, <http://cran.r-project.org>) in R<sup>1-3</sup>. The GGIR package is a sleep detection algorithm validated with polysomnography (PSQ)<sup>2</sup> and has automated detection of the sleep period time window<sup>3</sup>. The R script used to produce estimates of sleep regularity index, sleep efficiency and sleep period duration has previously been described and is open source<sup>4</sup>. The definitions of these three variables are:

<b>Sleep metric</b>	<b>Definition</b>
<b>Sleep regularity index<sup>5</sup></b>	The sleep regularity index is the percentage probability that a participant is in the same state (asleep or awake) at any two time points exactly 24 hours apart.  A participant who is asleep/awake at the exact same times every day would score 100.
<b>Sleep period duration</b>	Sleep period duration is the length of the sleep period time window. That is the time between the onset of sleep and the final wake-up of the night.
<b>Sleep efficiency</b>	Sleep efficiency is the percentage of time in the sleep period duration that a participant was estimated to be asleep.  A participant who had no night-time arousals (e.g., never rolling over) would have 100% efficiency.

The same settings for the algorithms were used for the analysis in PHOSP and the UK Biobank cohort<sup>6</sup>.

**Symptom assessment:**

<b>Symptom</b>	<b>Assessment</b>	<b>Interpretation</b>
<b>Dyspnoea</b>	<b>Dyspnoea-12 questionnaire</b>  Dyspnoea was assessed using the dyspnoea-12 questionnaire <sup>7</sup> , incorporating both physical and affective aspects, consisting of 12 descriptor questions, each scored 0 – 3.	A higher score indicates worse dyspnoea
<b>Lung Function</b>	Performed according to local standard operating procedures dependent on the availability of local equipment. The highest reading recorded per participant was used in this study and percent predicted values were calculated using the Global Lung Function Initiative (GLI) reference equations <sup>8</sup>	

<b>Anxiety</b>	<b>Generalised Anxiety Disorder 7-item assessment<sup>9</sup></b> Anxiety was assessed using the generalised anxiety disorder 7-item assessment which has a scale ranging from 0 – 21.	The results were categorised: Minimal (0-4) Mild (5-9) Moderate (10-14) Severe ( $\geq 15$ ) <sup>9</sup>
<b>Muscle Function</b>	<b>SARC-F questionnaire</b> This was performed as previously described <sup>10</sup> .	A lower score indicates better muscle function.
<b>Depression</b>	<b>Patient Health Questionnaire (9-questions)</b> The PHQ9 is a tool for monitoring the severity of depression using 9 questions and has a scale ranging from 0 – 27.	The results were categorised: None (0-4) Mild (5-9) Moderate (10-14) Moderately Severe (15-19) Severe (20-27) <sup>11</sup>

**UK Biobank cohort:** Actigraphy was performed in the UK biobank between February 2013 and December 2015 when all participants with a valid e-mail address were invited to wear a wrist-worn accelerometer device (Axivity AX3) on their dominant wrist 24/day for seven days. Tri-axial acceleration data were collected at 100Hz. Of the total cohort, 21% (103,664/502,540) of participants were accepted. Further details of data collection and processing have been previously reported<sup>12</sup>. The traces were analysed using GGIR<sup>1</sup>, as described above, using identical parameters to the PHOSP analysis. Of the 103,664 participants, the UK Biobank flagged 25% (15,427/103,664) of individuals as having data problems (Field 90002), poor wear time (Field 90015), poor calibration (Field 90016 and 90017), or their recording period included a daylight-saving change (Field 90018) and were hence excluded. Moreover, individuals were excluded if the number of interrupted recording periods (Field 90180), the duration of interrupted recording periods (Field 90181), or the number of recording errors (Field 90182) was greater than the respective variable's  $Q_3 + 1 \cdot 5 \times IQR$ , where  $Q_3$  represents the 3<sup>rd</sup> quartile, as has been previously suggested<sup>4</sup>. A further 6% (5,743/103,664) of participants were excluded based on metrics determined from their detected sleep: either short (< 3h) or long (> 12h) mean sleep duration, too few (< 5) or too many (> 30) average sleep episodes per night, average wake-up in the afternoon, or had fewer than 2 days of valid data. These exclusions were to ensure individuals with extreme (and feasibly incorrect) sleep characteristics did not bias our analysis, as has been previously suggested<sup>4,13</sup>. This left a maximum of 82,503 participants with clean actigraphy data for analysis.

Three cohorts were created from this dataset: *non-hospitalised*, *recently hospitalised*, and *pneumonia*. Participants were placed in the *non-hospitalised* cohort if they did not have a recorded hospital admission any time prior to their actigraphy being recorded. Participants were placed in the *recently hospitalised* cohort if they were admitted to hospital at least overnight, for a reason other than pneumonia, 2-11 months before their actigraphy recording period (period chosen to match the PHOSP-COVID cohort). Participants were placed in the *pneumonia* group if they were admitted to hospital at least overnight with a diagnosis of pneumonia (ICD10 code J09 – J18 (not including J10·8, J11·1, or J11·8)) 2-11 months before their actigraphy recording period. These groups were generated using the Hospital Episode Statistics (HES) dataset which contains the date of admission, date of discharge, primary diagnosis for each hospital admission (coded as an ICD10 code), and method of discharge; methods of discharge from hospital that included *death*, *not applicable*, or *not known* were excluded. In total, 394,379 UK Biobank participants had at least one hospital admission recorded. Of these, 71% (280,107) of participants had at least one hospital admission that lasted at least overnight.

In total, 42,649 UK Biobank participants had both clean actigraphy data available and at least one overnight hospital admission recorded in HES. Of these, 7% (2,903/42,649) of participants were hospitalised at least overnight 2-11 months before their actigraphy recording period; only 3% (91/2,903) were admitted for pneumonia, leaving 97% (2,805/2,903) for the *recently hospitalised* cohort. For the *non-hospitalised* cohort, 66% (54,691/82,503) of participants were admitted to hospital at some point before their actigraphy recording leaving 34% (27,812/82,503) of participants in the *non-hospitalised* cohort.

Individuals were matched when comparing actigraphy data between UK Biobank or PHOSP cohorts. During matching, age was split into decades (as above), BMI was split into the following categories (< 20 kg/m<sup>2</sup>, 20-24·99 kg/m<sup>2</sup>, 25-29·99 kg/m<sup>2</sup>, 30-34·99 kg/m<sup>2</sup> and >34·99 kg/m<sup>2</sup>), and time from discharge was categorised as the following (2 – 5 months, 6 – 7 months, 8 months, 9 – 11 months). This was done due to limitations on what data could be extracted from the PHOSP-COVID database. These limitations, combined with the size of the cohort, precluded matching on length of stay. If participants could not be matched to the UK Biobank, then they were excluded from analysis; this occurred for 15% (94/647) participants due to their age. UK Biobank participants were matched at a 1:1 ratio with participants in PHOSP-COVID. This process was repeated 25 times with participants being selected at random, creating 25 separate cohorts. The results were the same for all 25 cohorts and therefore a single representative cohort is shown in the paper. Confidence intervals of the mean were constructed for actigraphy measures in each cohort using a Studentised bootstrap approach<sup>14</sup>.

Nearest neighbour propensity score matching without replacement was used to compare actigraphy traces after pneumonia hospitalisation in the UK Biobank. These cohorts were compared at a 10:10:1 (*non-hospitalised: recently hospitalised: pneumonia*) ratio and the propensity score was estimated from logistic regression of the cohort on age, sex, BMI, and, if appropriate, time from discharge using the R package `MatchIt`<sup>15</sup>. To estimate the cohort effect and its standard error, we fit a linear regression model with sleep disruption as the outcome and the cohort, covariates (age, sex, BMI, and time from discharge), and their interaction as predictors and included the full matching weights in the estimation. The `lm()` function was used to fit the linear regression and the `comparisons()` function in the `marginalEffects` package was used to perform g-computation in the matched sample to estimate the average treatment effect in the *pneumonia* cohort. A cluster-robust variance was used to estimate its standard error with matching stratum membership as the clustering variable.

### **PHOSP-COVID and the UK Biobank actigraphy data collection**

Actigraphy was collected in PHOSP-COVID by wearing a GENEActiv Original device on the non-dominant wrist for 14 days. Actigraphy was collected in the UK Biobank by wearing an Activity AX3 on the dominant wrist for 7 days. Other studies have suggested that these protocol differences, length of time worn, and device wear-location should not prevent comparisons<sup>16,17</sup>.

### **DAG and covariates:**

Potential covariates for associations between sleep disturbances and dyspnoea were selected using a Directed Acyclic Graph (DAG, appendix p 32, [www.dagitty.net](http://www.dagitty.net)<sup>18</sup>). This was constructed based on previous literature and consulting subject matter experts. The total covariates considered were *age, sex, BMI, comorbidities (pre-COVID), comorbidities (post-COVID), medication (pre-COVID), medication (post-COVID), sleep disturbance pre-COVID, deprivation, vaccination status (at admission), WHO COVID severity, length of stay, ICU admission, ethnicity, muscle function, anxiety, number of days into the pandemic, and number of days since discharge*. This suggested the minimally sufficient adjustment set:

- Age, sex, BMI, length of stay, WHO COVID severity, number of days into the pandemic, number of days since discharge, and pre-COVID comorbidities.

The remaining variables were not included in this minimal set due to the following reasons:

- a) Vaccination status: vaccination status was controlled by COVID-severity.
- b) Ethnicity: ethnicity was controlled by COVID severity (via vaccination status) and comorbidities (pre-COVID).
- c) ICU admission: ICU admission was controlled by the length of stay.
- d) Medication (pre-COVID): medications taken pre-COVID-19 hospital admission were controlled by COVID severity (via sleep disturbance (pre-COVID)).

- e) Medication (post-COVID): medications taken post-COVID-19 hospital admission were not linked to any of our outcomes due to the chance this would come temporally after.
- f) Social deprivation: deprivation was controlled by BMI.
- g) Comorbidities (post-COVID): comorbidities post-COVID were controlled by days since discharge and COVID severity.
- h) Sleep disturbance pre-COVID: sleep disturbance (pre-COVID) was controlled by age, sex, and COVID severity.

### Regression bootstrap confidence intervals

All associations were analysed using linear regression both unadjusted and adjusting for the minimally sufficient set of covariates. Due to the residual's departure from normality (assessed via QQ-plot), bootstrap 95% confidence intervals for the regression coefficients were used. The approach used here was to bootstrap the residuals of the fitted model. If you are seeking to estimate the coefficient  $\beta_1$  of the straight line  $y = \beta_0 + \beta_1 x$ , the method is:

1. Fit the model to the original data  $(x_1, y_1), (x_2, y_2), \dots, (x_n, y_n)$  to get coefficient estimates  $\hat{\beta}_0, \hat{\beta}_1$ , residuals  $r_1, r_2, \dots, r_n$  and the estimate for the error variance  $s^2 = (n - 2)^{-1} \sum_{j=1}^n r_j^2$ .
2. To generate your bootstrap sample:
  - a. Set  $x_j^* = x_j$ ;
  - b. Randomly sample  $\varepsilon_j^*$  from  $\{r_1 - \bar{r}, r_2 - \bar{r}, \dots, r_n - \bar{r}\} \times s$ , where  $\bar{r}$  is the mean of the residuals and  $s$  is the square root of the estimated error variance.
  - c. Set  $y_j^* = \hat{\beta}_0 + \hat{\beta}_1 x_j^* + \varepsilon_j^*$  (i.e., the fitted value from the original model plus a randomly selected  $\varepsilon_j^*$ ).
  - d. Repeat steps (a) – (c) until a full sample  $(x_1^*, y_1^*), (x_2^*, y_2^*), \dots, (x_n^*, y_n^*)$  has been generated.
3. Calculate the least squares estimate and standard errors,  $\hat{\beta}_1^*$  and  $SE(\hat{\beta}_1^*)$ , respectively, based on the bootstrap sample generated in step (2).
4. Calculate the Z-score

$$Z_i^* = \frac{\hat{\beta}_1^* - \hat{\beta}_1}{SE(\hat{\beta}_1^*)}$$

Repeat steps (1) – (4) to generate the desired number of bootstrap estimates (here,  $B = 1999$  bootstrap samples were calculated). This will result in the sample  $Z_1^*, Z_2^*, \dots, Z_B^*$ . To calculate the  $100(1 - 2\alpha)\%$  confidence interval for  $\beta_1$ , compute the empirical  $\alpha$ - and  $(1 - \alpha)$ -quantiles of  $Z_1^*, Z_2^*, \dots, Z_B^*$ . Due to the choice of  $B = 1999$ ,  $\hat{t}^{(\alpha)}$  is the  $(1999 + 1) \times 0 \cdot 025 = 50^{\text{th}}$  smallest  $Z_j^*$  and  $\hat{t}^{(1-\alpha)}$  is the  $(1999 + 1) \times 0 \cdot 975 = 1950^{\text{th}}$  smallest (i.e., the  $50^{\text{th}}$  largest)  $Z_j^*$ . This gives the  $100(1 - 2\alpha)\%$  confidence interval for  $\beta_1$  as:

$$\left( \hat{\beta}_1 - \hat{t}^{(1-\alpha)} SE(\hat{\beta}_1), \hat{\beta}_1 - \hat{t}^{(\alpha)} SE(\hat{\beta}_1) \right).$$

## Mediation analysis

A multiple mediation model was used to estimate the direct effect of sleep disturbance metrics, and the indirect effects of anxiety and muscle function, on dyspnoea. Three separate exposures were considered: (i) Poor sleep quality (PSQI), (ii) sleep deterioration (NRS), and (iii) sleep regularity. This led to three multiple mediation models (appendix p 23). Linear regression with the product of coefficients method was used which estimates the effect of the exposure on the mediators ( $a_i$ ;  $i = 1, 2$ ), the effect of the mediators on the outcome ( $b_i$ ;  $i = 1, 2$ ) and the direct effect of the exposure on the outcome after adjusting for the mediators ( $c'$ ). The average causal mediation effect (ACME) for each mediator is then calculated as  $\gamma_i = a_i \times b_i$ ;  $i = 1, 2$  and the proportion mediated by the  $i^{\text{th}}$  mediator is  $100 \times \gamma_i / (c' + \gamma_1 + \gamma_2)$ . Confidence intervals for the ACMEs were computed using a bootstrap approach to loosen the assumption of normally distributed residuals with 1,999 resamples. This was conducted using the R package `lavaan` version 0.6-12<sup>19</sup>.

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# Supplementary File

