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Respiratory manifestations of hypothyroidism
- A systematic review

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Abstract

Background: Hypothyroidism has been associated with increased pulmonary morbidity and overall mortality. We conducted a systematic review to identify the prevalence and underlying mechanisms of respiratory problems among patients with thyroid insufficiency.

Methods: PubMed and EMBASE databases were searched for relevant literature from January 1950 through January 2015 with study eligibility criteria: English-language publications; Adult subclinical or overt hypothyroid patients; Intervention, observational or retrospective studies; and respiratory manifestations. We followed the PRISMA statement and used the Cochrane's risk of bias tool.

Results: A total of 1699 papers were screened by two independent authors for relevant titles. Of 109 relevant abstracts, 28 papers underwent full text analyses, of which 22 were included in the review. We identified possible mechanisms explaining respiratory problems at multiple physiological levels such as the ventilator control system, diaphragmatic muscle function, pulmonary gas exchange, goiter caused upper airway obstruction, decreased capacity for energy transduction, and reduced glycolytic activity.

Obstructive sleep apnea syndrome was found among 30% of newly diagnosed patients with overt hypothyroidism, and demonstrated reversibility following treatment. The evidence for or against a direct effect on pulmonary function was ambiguous. However, each of the above mentioned areas were only dealt with in a limited number of studies.

Therefore, we refrain from giving strong conclusions on any of these themes. Moreover, most studies were hampered by considerable risk of bias due to e.g. small numbers of patients, lack of control groups, randomization and blinding, and differences in BMI, gender, and age

between subjects and controls.

Conclusion: Mechanistic data, linking hypothyroidism and respiratory function are at best limited. This area of research is therefore open for retesting hypotheses, using appropriate study designs and methods.

Systematic review registration number on PROSPERO: CRD42015016815.

Introduction

Overt hypothyroidism is a common endocrine condition, which affects 1-2% of adults (1), while subclinical hypothyroidism has been reported in 4-20% (2). It is most often caused by autoimmunity, but may also be a consequence of radioiodine treatment or thyroid surgery as the most prominent other causes (3-5). Hypothyroidism may give rise to many physical (6) and mental symptoms (6, 7) and is associated with increased mortality (8). The increased mortality might, at least partly, be explained by increased pre-existing pulmonary morbidity, or excess pulmonary co-morbidity after the diagnosis of hypothyroidism (8, 9). In the extremely rare but potentially deadly case of myxedema coma, the severe thyroid failure has a direct effect on the respiratory function via the ventilator control system (carotid glomus and brain stem respiratory centers) (10, 11). Upper airway obstruction (UAO) may also contribute to the pulmonary morbidity, either by the presence of a goiter in classical Hashimoto's thyroiditis or from macroglossia, thickening of vocal cords, and mucopolysaccharide deposits in the respiratory tract, as observed in patients with severe myxedema (11-13). However, several other factors probably contribute to the link between hypothyroidism, the respiratory system, and increased mortality.

Here, based on the observed increased mortality and pulmonary co-morbidity, we aim at investigating – by a literature review - the impact of hypothyroidism on pulmonary function and the respiratory system, an issue very sparsely addressed previously.

Methods

We performed a systematic review according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (14). Methods as well as inclusion and exclusion criteria were specified in advance in a review protocol, which can be accessed at http://www.crd.york.ac.uk/PROSPERO/ by registration no. CRD42015016815.

English-language publications on the relationship between respiratory function and hypothyroidism, accessible in PubMed and EMBASE databases (January 1 1950 – January 31 2015), were identified. We used the PICOS approach (Population, Intervention, Comparison, Outcome and Study design) for setting the research question (15). All studies dealing with overt or subclinical hypothyroid patients were considered if the outcome was related to the respiratory function. Both observational and interventional studies were accepted, irrespective of whether the design was retrospective, cross sectional, or prospective. No comparator group was necessary. We performed the last search on February 20, 2015. The full search strategy is provided in the appendix.

Literature search

Two authors (JS and KW) independently screened the titles and abstracts. They decided, by consensus, which articles to evaluate in full text. We searched for outcomes related to neurological ventilatory control, pulmonary gas exchange, pulmonary function, respiratory strength, and sleep apnea. Only English language articles were included. The exclusion criteria were: case reports, expert opinions, letters, reviews, and studies conducted in pregnant patients or those with thyroid cancer. Multiple reports of the same set of data were assessed, and only the most representative or updated report was included. We screened the reference lists of included full text articles for missing publications. The same two authors extracted data independently, according to a pre-specified data collection sheet. Disagreements were resolved by discussion. The following data were extracted: type and design of the study, first authorship, country of origin, year of publication, number of patients, demographics, severity of hypothyroidism, type of intervention if relevant, time of post-intervention follow-up, and outcome parameters. The ‘Cochrane risk of bias tool’ was used to assess the risk of bias in each of the included articles (16).

Results

We identified 1690 relevant titles from PubMed and EMBASE and nine from the reference lists of included papers (Figure 1). We excluded 1672 titles, after review of titles and abstracts, leaving twenty-eight for full text evaluation. Six full text papers failed to meet the inclusion criteria resulting in twenty-two papers for the final analyses. No randomized double blind placebo controlled studies were identified.

Applying the 'Cochrane Risk of Bias tool' across studies, we found a considerable risk of bias as many studies failed to describe inclusion procedures, include control groups, randomize for treatment, blind observers or participants, or failed to report data previously described in the method section (Table 1). As a consequence, we made no attempt to perform a meta-analysis.

Most of the included studies (Table 2) were small, with fifty or fewer individuals in thirteen of the twenty-two studies. Sixteen studies included overt hypothyroid patients only, and four studies included subclinical hypothyroid patients only. The two remaining studies included both groups of hypothyroid patients. There were thirteen intervention studies, eight prospective observational studies, and one retrospective observational study.

INSERT FIGURE 1, TABLE 1 AND TABLE 2 AROUND HERE

Respiratory symptoms and ventilation

We identified six studies addressing the effect of overt or subclinical hypothyroidism on respiratory symptoms and ventilation. Four of the six studies had substantial risk of bias in their study design (Table 1), defined as using neither randomization, nor allocation concealment or

blinding. Among 124 (17) and 20 (18) patients with overt hypothyroidism, two observational studies with severe risk of bias (Table 1) found increased respiratory symptoms, including shortness of breath, sputum production, cough, wheezing, and airway hyper-responsiveness, with an odds ratio of 2.7-3.5, when compared to 1346 healthy controls.

It has been debated whether pleural effusion, due to overt hypothyroidism, causes some of the respiratory symptoms in patients with thyroid failure. A single study with high risk of bias (Table 1) found that the effusions in such patients were primarily due to other diseases than hypothyroidism (19).

A study of overt hypothyroid patients found that the response to hypercapnia and hypoxia was reduced initially, improved seven days after either triiodothyronine (LT3) or levothyroxine (LT4) treatment, and normalized in most patients after 12-24 weeks of LT4 treatment only (20). That study, however, was hampered by 25% of the patients being lost to follow-up. Another study failed to reproduce these results (21), may be due to a sample size half of that used in the previous study. In a non-blinded study, including patients with overt or subclinical hypothyroidism, the end-tidal CO_2 was reduced (22). This finding is surprising, but most likely explained by hyperventilation at the time of examination.

Based on these data, no clear conclusions can be made regarding the impact of hypothyroidism on respiratory symptoms and ventilation. The included studies all use different assessment techniques, and are hampered by substantial risk of bias. We therefore refrain from giving any conclusions on this topic. Only two studies have addressed the effects of LT4 substitution on ventilation (20, 21). Both studies suffer from a high risk of observer bias, and they present opposing results, which renders a conclusion impossible (Table 3).

Pulmonary function

The results from the eleven studies addressing the influence of overt or subclinical hypothyroidism on pulmonary function are contradictory. Nine of the eleven studies have study designs with considerable risk of bias (Table 1). Three studies addressed the impact of overt hypothyroidism on the diaphragmatic and abdominal muscle strength, and offer contradictory results (21, 23, 24). Two studies, one with 43 patients (23) and another with 24 patients (24), found that the diaphragmatic muscle strength improved by either LT4 or LT3 treatment. A third study, including 20 patients, found no improvement after LT4 treatment (21). All three studies included a limited number of participants and can therefore not be the foundation of strong conclusions (21, 23, 24).

In subclinical hypothyroidism, a single study found a reduced diaphragmatic inspiratory and expiratory strength, but the results were invalidated by 3.7 times more men being included in the control group than in the study group (25). As for the diaphragmatic inspiratory strength, no change in this parameter has been demonstrated in this group of patients (26).

Two studies comprising 267 (25) and 120 patients (27) suffering from subclinical hypothyroidism, found the Forced Vital Capacity (FVC) reduced by more than 250 ml, and the Forced Expiratory Volume in 1 second (FEV_1) reduced by 190 ml, as compared with healthy participants. A study of 20 overt hypothyroid patients showed similar findings compared to healthy participants (28). Although the results may seem unequivocal, they should be interpreted with caution, as the study and control groups were not comparable with respect to sex, age, and BMI.

Apart from these three reports, the majority of studies showed no impact of thyroid dysfunction on pulmonary function when using pulmonary function tests (18, 24, 29-31), most likely because of small sample sizes (21-45 patients). The lack of a control group - with a few exceptions (18, 24, 30) - is clearly another limitation of these studies. One study, with 43 overt hypothyroid patients (23), found that the pulmonary function improved after initiation of LT4,

despite the fact that it was not affected at baseline. Other studies with fewer patients could not reproduce this finding (24, 29-31), which might be due to limited power.

As the majority of the studies have serious methodological limitations, it is difficult, if not impossible, to make any clear conclusions regarding the impact of hypothyroidism, or the effect of LT4 therapy, on the diaphragmatic muscle strength and pulmonary function (Table 3).

Obstructive sleep apnea syndrome

We identified seven studies which investigated the impact of overt or subclinical hypothyroidism on obstructive sleep apnea syndrome (OSAS). Three of the seven studies carried a significant risk of bias. Comparison across studies is difficult as study designs, populations, and the employed techniques varied.

Nocturnal breathing abnormalities, such as restless sleep, snoring, choking, and in severe cases apnea periods, occurred among 25-50% of patients with overt hypothyroidism (32-35). One study found that 30% of patients with recently diagnosed primary overt hypothyroidism suffered from OSAS, according to well defined criteria (34). In these patients, OSAS was reversed by LT4 treatment (34). The other studies were limited by differences in BMI between control and patient groups, presence of goiter, small patient numbers, or missing data on thyroid hormone levels. After LT4 replacement therapy, all interventional studies demonstrated a significant reduction in apnea periods, oxygen desaturation events, and in snoring and choking (33-37). In subclinical hypothyroidism, one study from a specialized sleep clinic (38) found that 53% of the patients had OSAS. However, a similar high rate of OSAS was found among euthyroid subjects, probably reflecting selection bias in that study.

We conclude that overt hypothyroidism seems to be linked to sleep apnea syndrome, with improvement after LT4 substitution, as shown in four of six studies (Table 3). The evidence of

subclinical hypothyroidism being linked with sleep apnea syndrome is vaguer as only one study with serious methodological limitations addressed this issue.

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Discussion

We undertook a systematic review with the aim of elucidating the type and magnitude of respiratory problems among patients with hypothyroidism and, if possible, to identify the underlying physiological mechanisms. Unfortunately, many of the studies, on which we base this review, are hampered by considerable heterogeneity, generally low participant numbers, and high risk of observer and selection bias. We gave most credence to the studies with the least bias and weighted these highest in our conclusions, which, however, still are rather vague.

Overt and subclinical hypothyroidism

Overt hypothyroidism may be associated with an increased risk of respiratory symptoms (19). Such patients may also have a decreased control of breathing in response to hypercapnia and hypoxia (20), diminished diaphragmatic muscle strength (23, 24), and higher propensity to develop sleep apnea (34). These statements are, however, associated with great uncertainty as the evidence is sparse. Additionally, the few studies, conducted within this area, are hampered by considerable observer and selection bias as they rarely use blinding or randomization in their designs.

In case of subclinical hypothyroidism, patients may have reduced diaphragmatic muscle strength and lower FVC and FEV_1, according to two studies (25, 27), but these results should be interpreted with caution since the male/female ratio was higher in the control groups.

Whether patients with subclinical hypothyroidism suffer from unrecognized sleep apnea syndrome is unclarified (38).

Thyroid hormone substitution

In overt hypothyroid patients, both LT3 and LT4, taken separately, improved the response to hypercapnia and hypoxia as soon as seven days after initiation of treatment (20), with normalization after 2-5 months of LT4 therapy only (20). The diminished diaphragmatic muscle strength normalized within three months of LT4 or LT3 treatment, in both subclinical and overt hypothyroid patients (23-25). As the evidence of an effect of hypothyroidism on the pulmonary function is too weak to make a conclusion, the evidence of a direct effect of LT3 or LT4 substitution likewise becomes inadequate to allow any conclusion on this topic (24, 29-31).

In hypothyroid patients with sleep apnea, most studies demonstrate an effect of LT4 therapy in reducing or even eliminating nocturnal apnea periods (33-37).

No studies have investigated the treatment effects of LT3 compared to LT4 on respiratory symptoms, ventilation, pulmonary function, diaphragmatic function, or sleep apnea.

Upper airway obstruction and hypothyroidism

When hypothyroidism is caused by Hashimoto's thyroiditis, the effect of LT4 treatment can in part be explained by the reduction in thyroid size following restoration of euthyroidism (39, 40). UAO does not always lead to subjective symptoms and may therefore be overlooked in patients with thyroid disease (41). However, while thoroughly studied in nontoxic goiter (12), there are no studies on the pulmonary effect following goiter reduction in Hashimoto's thyroiditis.

The majority of Hashimoto's thyroiditis patients do not have a goiter. However, when present, a goiter can cause UAO by tracheal compression, as seen in 14-31% of patients referred for

evaluation of simple goiter (41, 42), and in 26-60% of patients referred to thyroidectomy (43-45). UAO, due to dislocation of the trachea or decrease of tracheal cross-sectional area, can have a pronounced effect on the airflow (41, 42, 46), which is significantly improved by goiter volume reduction (47, 48). Tracheal compression is somewhat more frequent when the goiter has a substernal location (35-73%), compared to a cervical location (9-58%) (49-53). Tracheal compression might not lead to symptoms, but is nevertheless a relevant consideration, as UAO may develop into life-threatening respiratory insufficiency (41, 54-56). The extent to which these factors are at play in hypothyroid individuals is unknown.

Hypothyroidism and respiration in experimental animal models

Based on studies in experimental animal models, the brain stem, peripheral chemosensors, ATP generating enzymes, and muscle function, seem to be affected by hypothyroidism. Studies in hamsters - as in man (20) - have identified a decreased response (breathing frequency) to hypoxia and hypercapnia three months after development of hypothyroidism (57-59). This is caused by diminished dopamine receptor (D1) protein levels in the respiratory centers of the brain stem (paraventricular nucleus of the hypothalamus [PVN] and solitary nucleus), and the carotid glomus (57). Dopamine receptor (D2) levels are increased in the striatum and carotid glomus in the hypothyroid state, contrasting with the reduction of these receptor levels in the PVN (58).

A reduced diaphragmatic muscle strength - as seen in some human studies (23-25) - may be explained by studies in thyroidectomized rats (60). Here, a decreased capacity for energy transduction and glycolysis due to diminished enzyme levels (succinate dehydrogenase, hexokinase, 3-hyroxyl-CoA dehydrogenase, and phosphofructokinase) in the thoracic diaphragm has been found (60). Another study analyzing diaphragmatic muscle fibers from propylthiouracil-induced

hypothyroidism in rats showed a decreased maximum force and myosin heavy chain$_{2B/2X}$ content (61).

From the aforementioned, there are many pathways to the diminished respiratory function, but it is clear that much remains to be explored in order to clarify how transient or permanent hypothyroidism, as well as LT4 treatment, affect the respiratory system.

Limitations

In our search for evidence of the impact of hypothyroidism on respiratory function, we encountered a paucity of high-quality data. No randomized controlled studies were conducted either in subclinical disease or in overt hypothyroidism in combination with medical treatment. Also many studies have a skewed balance between males and females, probably just reflecting the female preponderance of this disorder. Nevertheless, this, as well as the small study populations, questions whether the findings can be generalized to a broader population of hypothyroid individuals. Furthermore, many of the older studies do not address the potential confounding effect of the co-existence of goiter, if present.

We have not included patients with pre-existing pulmonary disease. Therefore, we cannot dissect whether hypothyroidism merely adds to the severity of pre-existing pulmonary disease or is the cause of *de novo* respiratory disease. There is some evidence that especially autoimmune hypothyroidism may be related to pulmonary diseases such as asthma and chronic obstructive pulmonary disease, but this area is sparsely investigated (62, 63).

As hypothyroidism affects multiple organ systems, the distinction between a primary pulmonary effect and an effect mediated via the nervous system, the cardiopulmonary system or the skeletal muscles is far from clear-cut. We did not include any data on cardiovascular or muscle function in our analyses, which might limit the generalizability of our findings. The impact of

hypothyroidism on exercise capacity has been covered in a recent systematic review by Lankhaar et al. (64), who identified multiple causes of exercise intolerance due to disturbances in the cardiovascular-, cardiopulmonary-, musculoskeletal-, neuromuscular-, and cellular metabolic systems (64). Persisting complaints of exercise intolerance was found in a subgroup of subclinical hypothyroid patients not responding with symptom relief, despite adequate treatment with LT4 (64).

Implications for the future

Regarding the impact of overt hypothyroidism on respiratory symptoms, ventilation, and diaphragmatic muscle strength, no conclusions can be provided due to the small number of studies and the significant methodological weaknesses. Thus, this area of research is open for retesting hypotheses regarding the effects of hypothyroidism on various features of the respiratory system, employing prospective study designs, validated methods, and blinded assessments. The influence of overt hypothyroidism on the diaphragmatic function should also be further explored, since this unique thoraco-abdominal muscle has an important role in forming the voice, cough, and for exercise capacity. As for subclinical hypothyroidism, it remains uncertain whether the ventilator response to hypoxia and hypercapnia is affected, or whether these patients are more prone to suffer from sleep apnea syndrome than the background population.

Importantly, as most patients diagnosed with hypothyroidism are substituted with LT4, data on the long-term impact of persistent hypothyroidism on the respiratory function is virtually non-existent.

Conclusions

The evidence of an impact of hypothyroidism on respiratory function is at best limited. We found no information linking the effect of hypothyroidism on respiratory function to the increased

mortality from pulmonary diseases, as reported previously from registry-based data (8). In contrast to the considerable knowledge regarding the influence of hypothyroidism on the cardiovascular system (65, 66), many aspects of the influence on the respiratory function have been inadequately addressed or not explored at all.

Author Disclosure Statement

There are no conflicts of interest in this study

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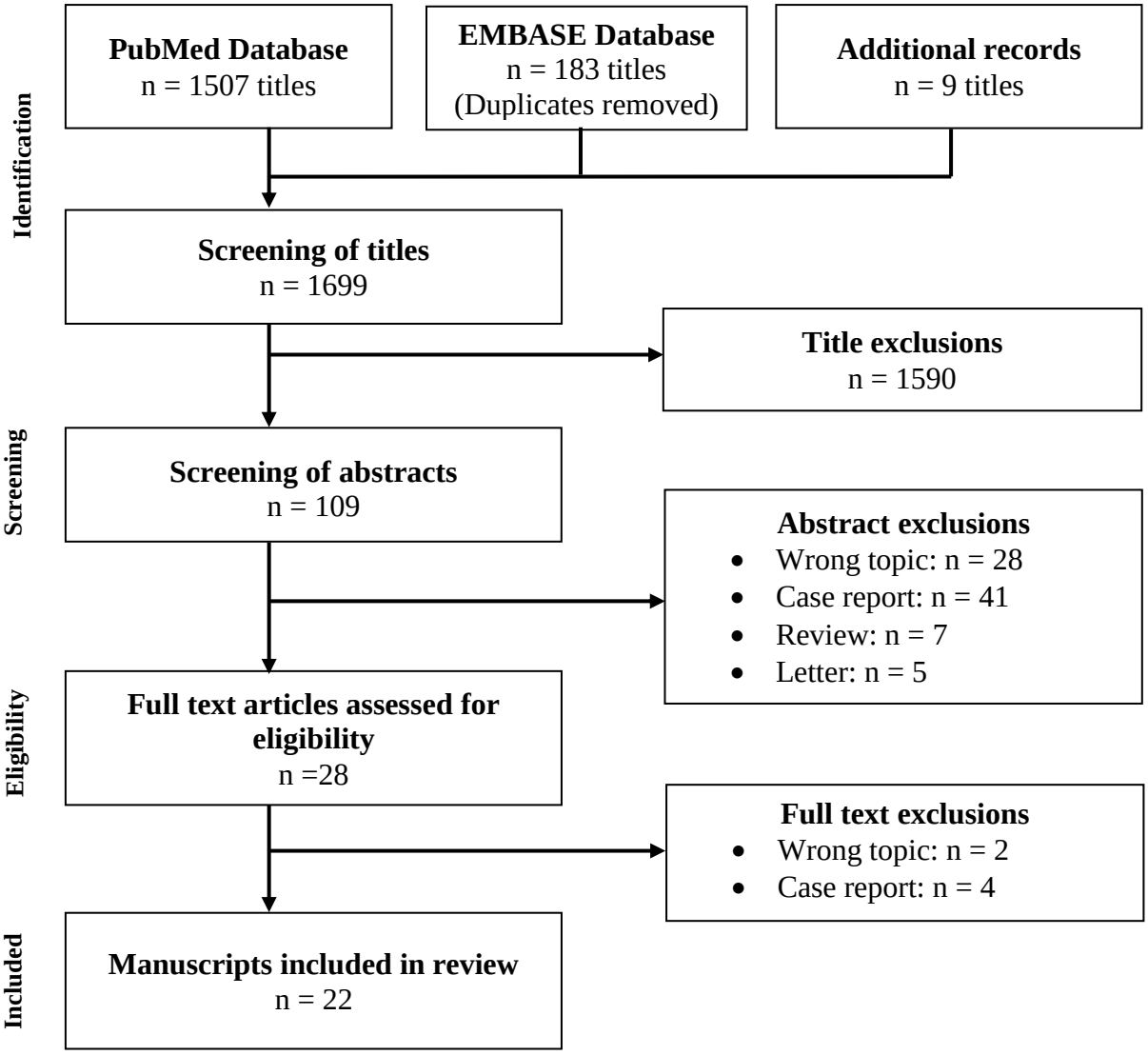
Identification
PubMed Database
n = 1507 titles
EMBASE Database
n = 183 titles
(Duplicates removed)
Additional records
n = 9 titles
Screening of titles
n = 1699
Title exclusions
n = 1590
Screening
Screening of abstracts
n = 109
Abstract exclusions
Wrong topic: n = 28
Case report: n = 41
Review: n = 7
Letter: n = 5
Eligibility
Full text articles assessed for eligibility
n =28
Full text exclusions
Wrong topic: n = 2
Case report: n = 4
Included
Manuscripts included in review
n = 22

Table 1:
Risk of bias summary in the 22 studies included for review. Unclear risk of bias (?), low risk of bias (+), and high risk of bias (-).

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data	Selective reporting	Other bias
Birring 2003 (17)	+	?	?	?	+	?	+
Birring 2005 (18)	+	?	+	+	+	?	+
Gottehrer 1990 (19)	?	?	?	?	+	?	+
Ladenson 1988 (20)	?	?	?	?	+	?	+
Duranti 1993 (21)	?	?	?	?	+	-	?
Ansarin 2011 (22)	?	?	?	?	+	?	+
Siafakas 1992 (23)	?	?	?	?	+	?	+
Gorini 1989 (24)	?	?	?	?	-	?	?
Cakmak 2011 (25)	-	?	?	?	+	?	-
Reuters 2009 (26)	?	?	+	+	+	?	+
Cakmak 2007 (27)	?	?	?	?	-	?	+
Swami 2010 (28)	?	?	?	?	+	?	-
Wilson 1960 (29)	-	?	?	?	+	?	?
Ambrosino 1985 (30)	?	?	?	?	-	?	+
Koral 2006 (31)	?	?	?	?	+	?	-
Pelttari 1994 (32)	?	?	+	+	+	?	-
Lin 1992 (33)	?	?	+	+	+	?	?
Jha 2006 (34)	?	?	+	+	+	?	+
Hira1999 (35)	?	?	+	+	-	?	+
Misiolek 2007 (36)	?	?	?	?	-	?	-
Rajagopal 1984 (37)	?	?	?	?	-	?	-
Resta 2005 (38)	?	?	?	?	+	?	-

Table 2:
Included studies regarding the respiratory manifestations of hypothyroidism. Observational (OB), Interventional (IN), Retrospective (RE), Overt hypothyroidism (HT), Subclinical hypothyroidism (sHT), Thyrotropin (TSH), Levothyroxine (LT4), Triiodothyronine (LT3) Questionnaire (Quest), Carbon dioxide measurements (CO_2), Carbon monoxide (CO), Manovacumeter (MVM), Pulmonary function test (PFT), Forced Vital Capacity (FVC), Forced Expiratory volume 1 second (FEV_1), Polysomnography (PSG), Obstructive sleep apnea (OSAS), Apnea Hypopnea Index (AHI) and Respiratory Disturbance Index (RDI). Age: mean (years). TSH is given as the mean value (mIU/l) at time of diagnosis. Non-available: NA

Study	Design	*n*	Age	Cohort	Methods	Results
Birring 2003 (17)	OB	1534	56	HT (primary), TSH: NA	Quest	Breathlessness, sputum and cough more prevalent.
Birring 2005 (18)	IN	45	52	HT (primary), TSH 2	PFT	No change in PFT. Increase in respiratory symptoms.
Gottehrer 1990 (19)	RE	128	NA	HT (primary), TSH: NA	X-ray	Pleural effusions rarely caused by hypothyroidism.
Ladenson 1988 (20)	IN	38	50	HT (primary), TSH: 97	MVM	Depressed response to hypoxia and hypercapnia. Improved within one week of LT3 or LT4 treatment in 75 % of patients. Normalized after LT4 for 12-24 weeks.
Duranti 1993 (21)	IN	20	54	HT (primary), TSH > 64	MVM, PFT	No change in ventilator control systems or diaphragmatic strength after LT4.
Ansarin 2011 (22)	OB	95	35	sHT/HT (NA), TSH: 8/44	CO_2	Reduced alveolar ventilation or hypoventilation in both groups.
Siafakas 1992 (23)	IN	43	54	HT (various causes), TSH: 55	MVM PFT	Diaphragmatic in- and expiratory strength, FVC and FEV_1 improved after LT4.
Gorini 1989 (24)	IN	24	42	HT (surgery), TSH: 44	PFT	No change in PFT. FVC and P_iMax improved after LT3.
Cakmak 2011 (25)	OB	184	46	sHT (NA), TSH: 11	PFT	Reduced diaphragmatic strength, FVC and FEV_1.
Reuters 2009 (26)	OB	68	47	sHT (various causes), TSH: 5	MVM	No difference in inspiratory strength.
Cakmak 2007 (27)	OB	267	43	sHT/HT (NA), TSH: 10/74	PFT	Reduced FVC and FEV_1.
Swami 2010 (28)	IN	40	40	HT (NA), TSH: 14	PFT	Reduced FVC and FEV_1.
Wilson 1960 (29)	IN	26	51	HT (NA), TSH: NA	PFT	No effect of LT3/desiccated thyroid on PFT.
Ambrosino 1985 (30)	IN	21	37	HT (surgery), TSH: 51	PFT	No change in PFT and no effect of LT3.
Koral 2006 (31)	IN	38	43	sHT (NA), TSH: 13	PFT	No effect of LT4 on PFT.
Pelttari 1994 (32)	OB	214	43	HT (NA), TSH > 10	PSG	50 % had nocturnal breathing abnormalities.
Lin 1992 (33)	IN	85	46	HT (NA), TSH > 25	PSG	25 % had mild to severe OSAS. Improved after LT4.
Jha 2006 (34)	IN	50	34	HT (primary), TSH: 100	PSG	30 % had AHI > 5. Reversible after LT4.
Hira1999 (35)	IN	20	33	HT (NA), TSH: NA	PSG	45 % had OSAS. Majority resolved after LT4.
Misiolek 2007 (36)	IN	15	50	HT (NA), TSH: 39	RDI	No change in RDI, but reduced sleepiness and snoring after LT4.
Rajagopal 1984 (37)	IN	9	49	HT (NA), TSH: NA	PSG	Reduced number of apneas after LT4.
Resta 2005 (38)	OB	108	52	sHT (NA), TSH: 8	PSG	53 % of patients had OSAS, which ameliorated after treatment.

Table 3:
Recommendations based on strength of evidence. Moderate level of evidence: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low level of evidence: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Levothyroxine (LT4), Forced Vital Capacity (FVC) and Forced Expiratory volume 1 second (FEV_1).

Theme	Physiological effect	Level of evidence	Sources
Ventilation in hypothyroid patients	Affected ventilation	Low (one or more studies with severe limitations)	(20-22)
	Ventilation normalizes after LT4 treatment	Low (one or more studies with severe limitations)	
Diaphragmatic muscle strength in hypothyroid patients	Reduced diaphragmatic muscle strength	Low (one or more studies with severe limitations)	(21, 23-26)
	Diaphragmatic muscle strength increases after LT4 treatment	Low (one or more studies with severe limitations)	
Pulmonary function tests in hypothyroid patients	No change in FVC and FEV_1	Low (one or more studies with severe limitations)	(18, 23-24, 25, 27-31)
	Increased FVC and FEV_1 after LT4 treatment	Low (one or more studies with severe limitations)	
Sleep apnea in hypothyroid patients	Nocturnal breathing abnormalities due to upper airway obstruction	Moderate (several studies with some limitations)	(32-38)
	Nocturnal breathing abnormalities reverses after LT4 treatment	Moderate (several studies with some limitations)	