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Respiratory manifestations of hypothyroidism

A systematic review

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33 **Abstract**

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

37

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

43

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

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

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

57 between subjects and controls.

58

59 Conclusion: Mechanistic data, linking hypothyroidism and respiratory function are at best limited.

60 This area of research is therefore open for retesting hypotheses, using appropriate study designs and
61 methods.

62 Systematic review registration number on PROSPERO: CRD42015016815.

63

64

65 **Introduction**

66 Overt hypothyroidism is a common endocrine condition, which affects 1-2% of adults
67 (1), while subclinical hypothyroidism has been reported in 4-20% (2). It is most often caused by
68 autoimmunity, but may also be a consequence of radioiodine treatment or thyroid surgery as the
69 most prominent other causes (3-5). Hypothyroidism may give rise to many physical (6) and mental
70 symptoms (6, 7) and is associated with increased mortality (8). The increased mortality might, at
71 least partly, be explained by increased pre-existing pulmonary morbidity, or excess pulmonary co-
72 morbidity after the diagnosis of hypothyroidism (8, 9). In the extremely rare but potentially deadly
73 case of myxedema coma, the severe thyroid failure has a direct effect on the respiratory function via
74 the ventilator control system (carotid glomus and brain stem respiratory centers) (10, 11). Upper
75 airway obstruction (UAO) may also contribute to the pulmonary morbidity, either by the presence
76 of a goiter in classical Hashimoto's thyroiditis or from macroglossia, thickening of vocal cords, and
77 mucopolysaccharide deposits in the respiratory tract, as observed in patients with severe myxedema
78 (11-13). However, several other factors probably contribute to the link between hypothyroidism, the
79 respiratory system, and increased mortality.

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

83

84 **Methods**

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

89 English-language publications on the relationship between respiratory function and
90 hypothyroidism, accessible in PubMed and EMBASE databases (January 1 1950 – January 31
91 2015), were identified. We used the PICOS approach (Population, Intervention, Comparison,
92 Outcome and Study design) for setting the research question (15). All studies dealing with overt or
93 subclinical hypothyroid patients were considered if the outcome was related to the respiratory
94 function. Both observational and interventional studies were accepted, irrespective of whether the
95 design was retrospective, cross sectional, or prospective. No comparator group was necessary. We
96 performed the last search on February 20, 2015. The full search strategy is provided in the
97 appendix.

98

99 **Literature search**

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

113

114 **Results**

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

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

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

130

131 **INSERT FIGURE 1, TABLE 1 AND TABLE 2 AROUND HERE**

132

133 **Respiratory symptoms and ventilation**

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

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

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

145 A study of overt hypothyroid patients found that the response to hypercapnia and
146 hypoxia was reduced initially, improved seven days after either triiodothyronine (LT3) or
147 levothyroxine (LT4) treatment, and normalized in most patients after 12-24 weeks of LT4 treatment
148 only (20). That study, however, was hampered by 25% of the patients being lost to follow-up.
149 Another study failed to reproduce these results (21), may be due to a sample size half of that used in
150 the previous study. In a non-blinded study, including patients with overt or subclinical
151 hypothyroidism, the end-tidal CO₂ was reduced (22). This finding is surprising, but most likely
152 explained by hyperventilation at the time of examination.

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

159

160 **Pulmonary function**

161 The results from the eleven studies addressing the influence of overt or subclinical
162 hypothyroidism on pulmonary function are contradictory. Nine of the eleven studies have study
163 designs with considerable risk of bias (Table 1). Three studies addressed the impact of overt
164 hypothyroidism on the diaphragmatic and abdominal muscle strength, and offer contradictory
165 results (21, 23, 24). Two studies, one with 43 patients (23) and another with 24 patients (24), found
166 that the diaphragmatic muscle strength improved by either LT4 or LT3 treatment. A third study,
167 including 20 patients, found no improvement after LT4 treatment (21). All three studies included a
168 limited number of participants and can therefore not be the foundation of strong conclusions (21,
169 23, 24).

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

174 Two studies comprising 267 (25) and 120 patients (27) suffering from subclinical
175 hypothyroidism, found the Forced Vital Capacity (FVC) reduced by more than 250 ml, and the
176 Forced Expiratory Volume in 1 second (FEV₁) reduced by 190 ml, as compared with healthy
177 participants. A study of 20 overt hypothyroid patients showed similar findings compared to healthy
178 participants (28). Although the results may seem unequivocal, they should be interpreted with
179 caution, as the study and control groups were not comparable with respect to sex, age, and BMI.

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

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

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

190

191 **Obstructive sleep apnea syndrome**

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

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

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

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

211

212 **INSERT TABLE 3 AROUND HERE**

213

214 **Discussion**

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

221

222 **Overt and subclinical hypothyroidism**

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

230 In case of subclinical hypothyroidism, patients may have reduced diaphragmatic
231 muscle strength and lower FVC and FEV₁, according to two studies (25, 27), but these results
232 should be interpreted with caution since the male/female ratio was higher in the control groups.

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

235

236 **Thyroid hormone substitution**

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

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

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

248

249 **Upper airway obstruction and hypothyroidism**

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

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

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

266

267 **Hypothyroidism and respiration in experimental animal models**

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

277 A reduced diaphragmatic muscle strength - as seen in some human studies (23-25) -
278 may be explained by studies in thyroidectomized rats (60). Here, a decreased capacity for energy
279 transduction and glycolysis due to diminished enzyme levels (succinate dehydrogenase, hexokinase,
280 3-hydroxyl-CoA dehydrogenase, and phosphofructokinase) in the thoracic diaphragm has been found
281 (60). Another study analyzing diaphragmatic muscle fibers from propylthiouracil-induced

282 hypothyroidism in rats showed a decreased maximum force and myosin heavy chain_{2B/2X} content
283 (61).

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

287

288 **Limitations**

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

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

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

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

311

312 **Implications for the future**

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

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

326

327 **Conclusions**

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

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

334

335

336

337 **Author Disclosure Statement**

338 There are no conflicts of interest in this study

339

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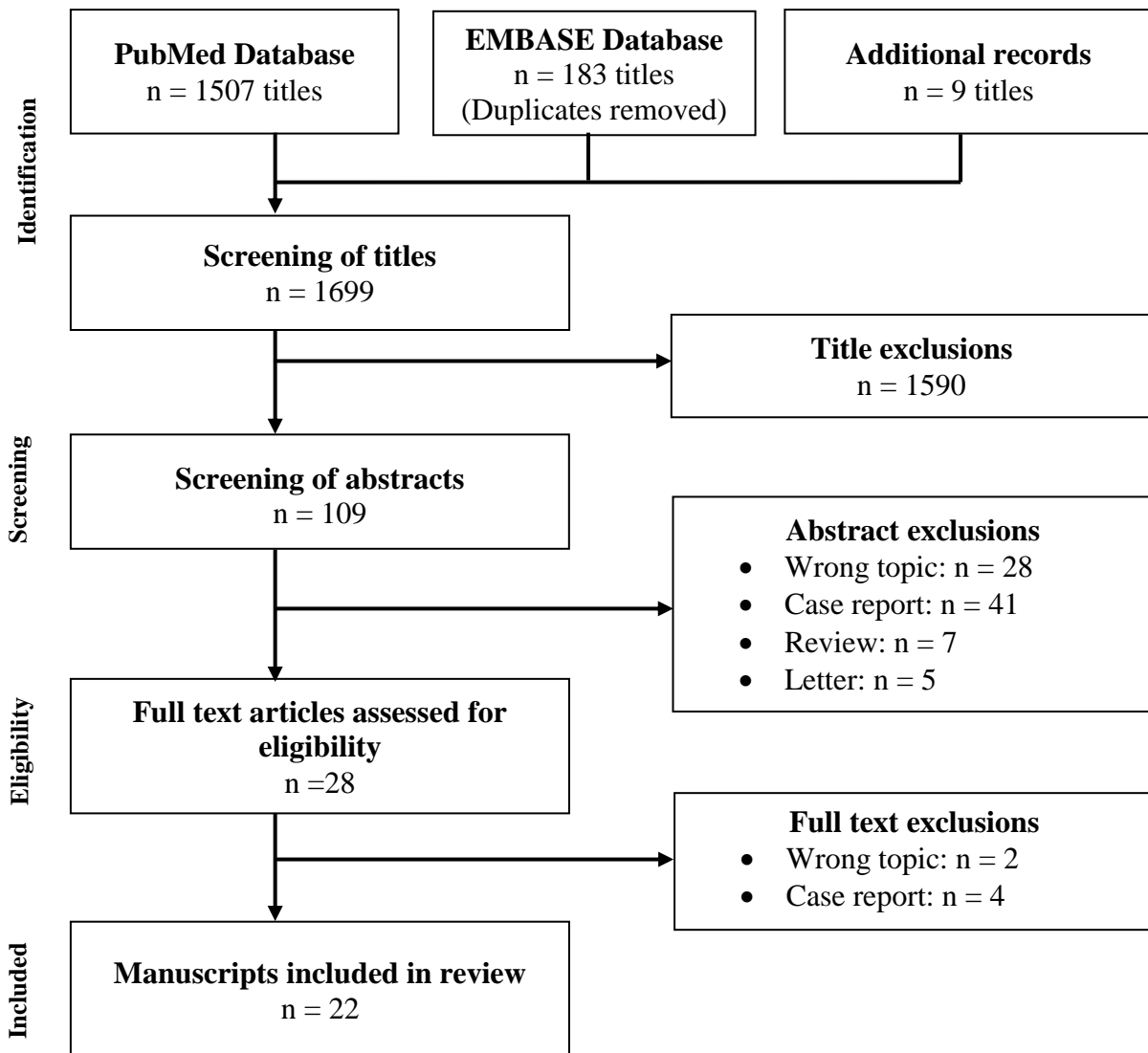


Table 1:

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 (CO₂), Carbon monoxide (CO), Manovacuumeter (MVM), Pulmonary function test (PFT), Forced Vital Capacity (FVC), Forced Expiratory volume 1 second (FEV₁), 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	<i>n</i>	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 _i Max 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 (FEV₁).

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)	