Clinical implications of abnormal thyroid function during smoking cessation: a systematic review

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ABSTRACT

Introduction: Smoking has been reported to have multiple effects on the hypothalamus–pituitary–thyroid axis and the functioning of the thyroid gland. However, the association between smoking cessation and thyroid function is poorly understood. We conducted a systematic review to determine the impact of smoking cessation on thyroid function. Methodology: A comprehensive search was performed using Pubmed, Embase and Cochrane Central Register for Controlled Trials, using the following query (date of the last search 30th September 2017): [“cessation tabágico” OR “tabagismo”] AND (“thyroid”). Results: A strategy of initial search identified a total of 1935 articles. After removal of duplicates and screening, 56 articles were considered potentially eligible and selected for analysis. Discussion: The current evidence is inconclusive regarding smoking cessation effect on thyroid function. Smoking cessation is associated with mild changes in thyroid function tests, with TSH elevation, increased levels of thyroid autoantibodies, increasing the risk of developing autoimmune hypothyroidism. This negative impact on thyroid function could mediate the weight gain, constipation and negative changes in cognition and mood associated with smoking cessation. Conclusions: This dysfunction thyroidia is often consulted when patients with mental disorders should be a priori considered. Professional motivation to work in this field is increasing positive and long-term health benefits resulting in improved general health and a reduced risk of smoking-related diseases. Although smoking cessation was traditionally the province of the family physician, nowadays the psychiatrist is often consulted when patients with mental disorders consider smoking cessation, or when patients have difficulty in achieving abstinence. Structured psychotherapeutic interventions such as motivational interview, specialized behavioral techniques and neuropsychopharmacological treatments should constitute additional sources of professional motivation to work in this field. Smoking affects pituitary, adrenal, testicular and ovarian function, calcium, lipid, and glucose metabolism and the action of insulin. It has been reported to have...
multiple effects on the hypothalamus–pituitary–thyroid axis and the functioning of the thyroid gland. The evidence concerning the impact of smoking on thyroid function is scarce, and less is known about adverse endocrine effects that patients may experience while quitting smoking. In fact, smoking cessation isn’t devoid of side effects, which include nicotine withdrawal syndrome and weight gain. The primary goal of this paper was to review existing evidence of the inextricable link between smoking cessation and thyroid. The research question was “Does smoking cessation result in sustainable changes in thyroid function?” Given the nonspecific cognitive and metabolic changes that may occur in some patients during smoking cessation, this is immensely appealing and clinically relevant. To answer this question we systematically reviewed the evidence regarding thyroid function changes in patients undergoing smoking cessation.

**METHODOLOGY**

A comprehensive search was performed using Pubmed, Embase and Cochrane Central Register for Controlled Trials, using the following query (date of the last search 30th September 2017): [“smoking cessation” OR “smoking”) AND ( “thyroid”). All references cited were also reviewed to identify additional studies not covered by the above-mentioned electronic databases.

The study population consisted of smokers or secondhand smokers undergoing smoking cessation, or controlled smoking exposures, without history of thyroid diseases. Primary outcomes were thyroid function test measurements. Studies were considered eligible if they were 1) experimental, prospective or cross-sectional studies, 2) they provided data on thyroid function (i.e., TSH, ft3, ft4, TPOab) in case and control groups, and/or 3) they provided data on the relationship between thyroid levels and smoking status. Studies were excluded if 1) they contained insufficient data; 2) they were reviews, case reports, editorials, in vitro and non-human studies. Only papers written in English, Spanish and Portuguese were evaluated. In the first phase, titles and abstracts were independently screened by two reviewers to determine whether the inclusion criteria were satisfied. Any disagreement or discrepancy between the studies selected was solved by consensus. When necessary, a third reviewer was consulted.

General characteristics of each study such as first author, year of publication, setting, population, principal findings and main conclusion were retrieved. Although the use of quality scoring systems or quality scales in observation studies is controversial, the quality of individual studies was assessed using the Newcastle–Ottawa Scale (NOS). As an overall quality check and in order to ensure transparent reporting, this systematic review was conducted in accordance with PRISMA guidelines.

**RESULTS**

The initial search strategy identified a total of 1935 articles. After duplicates removal and screening, 56 articles were considered potentially eligible and selected for full-text reading. Of these, 34 studies did not meet the inclusion criteria and were excluded from the qualitative synthesis (Figure 1).

A total of 22 studies that enrolled 99142 participants investigated smoking effect (either smoking exposure or smoking cessation) on thyroid function tests. Of these, three were experimental studies, three consisted of prospective studies, and sixteen were cross-sectional studies.

Overall, smoking was associated with decreased serum TSH concentrations and/or increased thyroid hormone synthesis. There were however conflicting results which could be explained by the direct inhibitory effect of thiocyanate on the thyroid gland. Some studies have suggested this increased thyroid activity could be secondary to changes in thyroid structure promoted by smoking (thyroid volumes and thyroid nodularity). Other studies convey the effect of smoking on thyroid volume is dependent on iodine intake whereas the effect on function is likely to depend on other factors.

During pregnancy, smoking was associated with higher ft3 levels, lower ft4 levels, without significant differences in TSH concentration. Secondhand Smoke exposure was also accompanied by an increase in thyroid hormone secretion but with relevant gender differences, suggesting the participation of estrogens in this effect.

Smoking appears to be negatively associated with thyroid autoimmunity and hypothyroidisms, although with discordant results. In a prospective study, incident hypothyroidism was very common in former smokers and within two years after smoking cessation, the percentage of hypothyroid cases attributable to cessation of smoking was 85%. Likewise, tobacco discontinuation was associated with decreased serum T3, elevation of serum TSH and increased occurrence of TPO-Ab and/or TG-Ab in serum.

The study samples were located in several countries: United States of America, Sweden, Denmark, Finland, Norway, Netherlands, Iran, South Korea, Greece, Italy, Poland and Germany. Their general characteristics are summarized in Table 1.

As reflected in Table 1, the included studies had moderate to high methodological quality, assessed by NOS. Most patients were randomly recruited from community samples and recruitment strategies were well defined. However, ascertainment of the exposure differed across studies. In the vast majority of cases, smoking history was not validated by objective measures, relying on data obtained by self-disclosure. Nevertheless, in one study smoking status was assessed by assays of carbon monoxide hemoglobin saturation and in other studies, serum cotinine was used to determine smoking status. Confounding factors such as BMI and age were relevant in some studies, influencing the interpretation of results. The representativeness of samples...
was variable, in few studies the generalization of results could be hampered (war veterans\textsuperscript{44}, infants\textsuperscript{23}).

The limited number of the studies and the wide range of the primary outcomes prevented the conduct of a meta-analysis.

**DISCUSSION**

Thyroid hormones are critical on neurodevelopment and are widely distributed in the brain with a multitude of effects on the central nervous system including a putative effect in the pathogenesis of psychiatric disorders\textsuperscript{32}. Entering neurons by crossing the endothelial cells of the blood–brain barrier, thyroid hormones regulate brain development, contributing to synaptic plasticity, learning, and memory, sharing processes with nicotine cholinergic mechanisms\textsuperscript{35}.

Nicotine modulates indeed a wide range of aspects of the endocrine system. These effects are mainly mediated by the pharmacological action of nicotine and also by toxins such as thiocyanate and 2,3-hydroxypropyridine\textsuperscript{113}. Thiocyanate leads to increased excretion of iodine, seeming to inhibit iodine uptake by the thyroid and can have a goitrogenic effect in the absence of sufficient iodine\textsuperscript{42}, 2,3-hydroxypropyridine prevents deiodination and activation of T\textsubscript{3}. However, thyroid hormone treatment can in certain situations improve cognition, raising the question of self–medication hypothesis in smokers\textsuperscript{43}. In an animal study, twice daily nicotine for 4–6 weeks reversed a deficit in water radial arm maze performance in thyroidectomized-induced hypothyroid rats\textsuperscript{156}. In the same rat model, thyroidectomies caused impairments in Long–Term Potentiation (LTP), reversed by nicotine administration\textsuperscript{157}. Interestingly, in a rat model of Alzheimer’s disease (characterized by loss of cholinergic function), levothyroxine prevented cognitive impairment and improved memory function\textsuperscript{138}. Enhancement of the cholinergic system with Varenicline is the standard treatment of smoking cessation\textsuperscript{159}. Considering that in Alzheimer patients a higher T\textsubscript{4} predicts a favorable response to Donepezil\textsuperscript{38}, supplementation with levothyroxine could potentiate the therapeutic response to Varenicline, which is still unsatisfactory in a vast proportion of cases. Thus, thyroid hormone agonists may be novel treatments for smoking cessation therapies (Figure 2).

Smoking has detrimental effects on a wide range of endocrine and metabolic functions. Overall, smoking is associated with higher T\textsubscript{4} and T\textsubscript{3} and lower TSH serum concentrations\textsuperscript{65}. This suggests that there is a stimulatory effect of cigarette smoke exposure on thyroid hormone release, likely induced by activation of the sympathetic nervous system from nicotine, with fall of serum TSH\textsuperscript{11,41}. The increased levels of thyroxine–binding globulin among smokers could also play a role. Another possible mechanism could be related to testosterone levels which are higher among current smokers\textsuperscript{16}. Smoking also induces a variety of effects on the immunoregulatory system (immune suppression, alteration of cytokine balance, induction of apoptosis\textsuperscript{42}) and circulating inflammation markers, particularly IL–1β, which have been shown to inhibit differentiated thyroid cell functions including human thyroid cell adenylate cyclase and thyroglobulin release\textsuperscript{163}.

On the other hand, smoking could also inhibit thyroid hormone production and have a goitrogenic effect due to the presence of thiocyanate. Thiocyanate has demonstrated antithyroid activity in experimental studies. It tends to oppose the stimulatory effect of smoking which could explain some of the discrepant results\textsuperscript{25–26}. With a higher intake of iodine and thus a higher supply of iodine to the thyroid, the competitive inhibition on uptake by thiocyanate would likely play a less important role, as seen in one of the studies\textsuperscript{124}.

On the clinical level, thyroid volume and goiter prevalence were associated with smoking habits with the strongest association found in areas with pronounced iodine deficiency\textsuperscript{31}. Vejbjerg P (2008) showed that the effect of smoking on thyroid volume seems to be dependent on iodine intake\textsuperscript{134}. Smoking increases the risk of Graves’ disease\textsuperscript{44} and the outcome of Graves Ophthalmopathy has shown to be considerably poorer in smokers than in non-smokers\textsuperscript{155}. Smoking is also associated with relapse of thyrotoxicosis and even smoking history was an independent risk factor associated with impaired response to intravenous corticosteroids in patients with Graves Ophthalmopathy\textsuperscript{46}.

On the other hand, smoking might have a protective factor towards autoimmune hypothyroidism\textsuperscript{57}. Although in the beginning smoking was thought to increase the risk of hypothyroidism in patients with Hashimoto thyroiditis\textsuperscript{48}, recent studies have shown that smoking may protect against the development of thyroid peroxidase antibodies, which may result in a decreased risk of Hashimoto’s hypothyroidism\textsuperscript{47–48}. Decreased thyroid autoimmunity may result from smoke’s interference with iodide transport, decreased TSH secretion, or smoke’s suppressive effects on immune function\textsuperscript{30}. Accordingly, smoking cessation could increase the risk of Hashimoto hypothyroidism. In a prospective cohort study of euthyroid women discontinuation of smoking was associated with an increased risk for occurrence of TPO–Ab and Tg–Ab in serum\textsuperscript{152}, translated in an increased incidence of overt autoimmune hypothyroidism (more than 6-fold increased the first two years after smoking cessation\textsuperscript{30}). A probable explanation of these findings is that smoking inhibits the development of TPO–Ab and thereby protects, to a certain extent, against the occurrence of chronic lymphocytic thyroiditis and consequently against an elevated
TSH\textsuperscript{32}. Smoking was also found to be protective of thyroiditis in interferon–alpha induced thyroid dysfunction\textsuperscript{48}.

Additionally, current smoking reduces dose–dependently the risk of thyroid cancer\textsuperscript{41}. The protective effect of smoking may be due to different mechanisms, including an impact on thyroid stimulating hormone and estrogen metabolism. Some of these changes appear to be reversible on cessation of smoking. In fact, on long term, smoking cessation reverses at least part of smoking’s effects on thyroid disorders, reducing the association between severity of eye disease and Grave’s disease (Figure 2).

We have presented a critical review of 22 studies which evaluated smoking exposure or discontinuation on thyroid function. This systematic review demonstrates that smoking cessation may be associated with mild thyroid dysfunction. This is timely considering that the deleterious consequences of tobacco on the thyroid systems are often overlooked and that this mild thyroid dysfunction could have several clinical implications.

Methodological differences may in part explain the discrepancy in some findings. In most studies, smoking was evaluated through a questionnaire based on self-report, without collateral verification or objective measures such as serum cotinine confirmation. Although several studies have shown the reliability of these self-reported assessments, this method raises concern about recall bias and overall it could underestimate the prevalence of smoking\textsuperscript{49}.

Similarly, other discrepancies in results across studies may be due to the large heterogeneity among the studies and different laboratory measurement techniques (assays) and cut-offs. The complexity of tobacco type, the variable thiocyanate content, the subjective criteria of "former smoker", the numbers of cigarettes smoked and duration of smoking are potential confounding factors very hard to address in this kind of studies. Additionally, the cross-sectional design of most studies precludes concluding for causality.

In the vast majority of studies, patients with known or previous thyroid disorders (hyperthyroidism, goiter, nodules, cancer, and hypothyroidism) or taking thyroid medications were excluded, given the potential confounding effect. However, these patients are likely a clinically significant group and their management constitute one of the greatest challenges in smoking cessation consultation.

**CONCLUSION**

In summary, smoking affects almost all aspects of the functioning of the thyroid gland. Even if tobacco use could have some protective effects regarding autoimmune hypothyroidism, it is unequivocal that every smoker should be effectively encouraged to discontinue. Hypothyroidism is easily treatable and can’t compete with the cardiovascular and oncological hazards of smoking.

The current evidence is inconclusive regarding smoking cessation effect on thyroid function. Smoking cessation seems to induce mild changes in thyroid function tests namely a decreased thyroid hormones synthesis and a slight increase in TSH levels. These subnormal TSH levels are still of clinical uncertainty. Altered thyroid levels during nicotine withdrawal could be linked to the metabolic changes that lead to weight gain, constipation and negative changes in cognitive function and mood. This subclinical or clinical hypothyroidism could be therefore a potential biological predictor of successful quitting. Addressing and treating it could mean significantly higher rates of smoking abstinence which has remained low despite all the available pharmacological and psychotherapeutic interventions. This subclinical hypothyroidism could explain as well (at least theoretically) the lower rates of successful smoking cessation in women. The sustainability of altered thyroid function in the long term warrants further research. A randomized clinical trial investigating the effect of smoking cessation on thyroid function is desirable to present the highest evidence. Nevertheless, these findings offer another perspective in clinicians seeking to understand and treat tobacco use disorder.

**Clinical Implications**

From a practical point, there isn’t evidence yet to advise clinical monitoring of thyroid function during or after smoking cessation. However, at least two exceptions should be allowed: patients with a history of any thyroid disorder or being on thyroid medication and patients presenting symptoms or signs compatible with hypothyroidism following successful smoking cessation. A high degree of clinical suspicion for hypothyroidism should be considered in patients with a recent history of smoking cessation, so they could be correctly diagnosed and properly treated.

![Figure 1: Flowchart describing the process of article selection](image-url)
Explanation:
Smoking cessation seems to induce mild changes in thyroid function tests namely a decreased thyroid hormones synthesis and a slight increase in TSH levels. On long-term, smoking cessation could reverse the higher risk of Graves’ disease and thyroid eye disease in smokers.
Altered thyroid levels during nicotine withdrawal could be linked to weight gain, constipation and negative changes in cognitive function and mood. Thyroid hormone agonists and/or iodine supplementation may add value to current smoking cessation protocols.

Abbreviations: T\textsubscript{3}: Tri-iodothyronine; T\textsubscript{4}: thyroxine; TSH: Thyroid stimulating hormone; TPO Ab: Thyroperoxidase antibody; TG Ab: Thyroglobulin antibody.
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13. Wells, George & She, Beverly & O’Connell, Diane & Peterson, je & Welch, Vivian & Losos, M & Tugwell, Peter. (2000). The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis


17. Belin RM, Astor BC, Poe NR, Ladenson PW. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotopin concentration elevation and a higher prevalence of mild hypothyroperoxidase antibody suppression in the third National Health and Nutrition Examination Survey (NHANESIII). J Clin Endocrinol Metab. 2004 Dec;89(12):6077–86.


19. Aasvold BO, Bjørto T, Nilsen TI. The endocrine effects of cigarette smoking on thyroid activity. [Internet]. 2013 Sep;23(9):1151–9.


31. Mammosen J, Ghazarian SR, Rosen A, Ladenson PW. Patterns of Interferon-Alpha–Induced Thyroid Dysfunction Vary with Ethnicity, Sex, Smoking Status, and Pretreatment Thyroxin in an International Cohort of Patients Treated for Hepatitis C. Thyroid [Internet]. 2013 Sep;23(9):1151–8.


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Table 1: Selected studies of smoking and thyroid function

<table>
<thead>
<tr>
<th>First Author, Year, and Reference Country and Setting</th>
<th>Type of Study and Population</th>
<th>Principal Findings</th>
<th>Appraisal/Limitations</th>
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<tr>
<td>Melander11, 1981 Sweden</td>
<td>Cross-Sectional N= 57: 32 ♂ and 25 ♂ Age: 35 years</td>
<td><strong>Before SC:</strong> T&lt;sub&gt;3&lt;/sub&gt; (nmol/l): 2.21±0.05 rT&lt;sub&gt;3&lt;/sub&gt; (nmol/l): 0.55±0.02 T&lt;sub&gt;4&lt;/sub&gt; (nmol/l): 100.3±2.1 TSH (mU/l): 91.7±1.9. <strong>After SC:</strong> T&lt;sub&gt;3&lt;/sub&gt;: 2.23 ± 0.06 rT&lt;sub&gt;3&lt;/sub&gt;: 0.51±0.02 T&lt;sub&gt;4&lt;/sub&gt;: 96.6±2.3 TSH: 1.91±0.10*</td>
<td>Following smoking cessation there were small decreases in serum T&lt;sub&gt;4&lt;/sub&gt;, rT&lt;sub&gt;3&lt;/sub&gt; and a slight increase in serum TSH</td>
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<tr>
<td>Sepkovic24, 1984 USA Community Setting</td>
<td>Cross-Sectional N= 200: 101 ♂ and 99 ♂</td>
<td>Controls: T&lt;sub&gt;3&lt;/sub&gt;: 204 ng/dL ± 5.9 (p&lt;0.05); T&lt;sub&gt;4&lt;/sub&gt;: 7.3 μg/dL ± 0.2 (p&lt;0.05); TSH: 2.4 μU/mL ± 0.1 <strong>Heavy Smokers:</strong> T&lt;sub&gt;3&lt;/sub&gt;: 181.0 ± 10.4 (p&lt;0.05); T&lt;sub&gt;4&lt;/sub&gt;: 6.4 ± 0.2 (p&lt;0.05); TSH: 2.9 ± 0.2 Substantial decreases in serum thyroxine T&lt;sub&gt;3&lt;/sub&gt; and T&lt;sub&gt;4&lt;/sub&gt; in heavy smokers.</td>
<td>A limited number of patients. Blood carboxyhemoglobin and plasma cotinine as assessment of smoker status. NOS:5/10</td>
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<tr>
<td>Christensen11, 1984 Sweden Community Setting</td>
<td>Cross-Sectional N= 441 ♂ Age: 48 or 53 years</td>
<td>Heavy smokers had higher serum T&lt;sub&gt;3&lt;/sub&gt; and lower rT&lt;sub&gt;3&lt;/sub&gt; than never smokers (data unavailable) (p&lt;0.01). Serum TSH was also higher in smokers. Women taking estrogen supplements had higher serum T&lt;sub&gt;3&lt;/sub&gt; and T&lt;sub&gt;4&lt;/sub&gt; levels than those not receiving such supplements (p&lt;0.05) while rT&lt;sub&gt;3&lt;/sub&gt; and TSH levels were unaffected by estrogens.</td>
<td>Random sample The presence of recall bias regarding the assessment of smoking status NOS:6/10</td>
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<tr>
<td>Ericsson11, 1991 Sweden Community Setting</td>
<td>Cross-Sectional N= 4100: 1555 smokers (836 ♂, 719 ♀), 1048 ex-smokers (604 ♂, 444 ♀) and 1497 non-smokers (560 ♂, 937 ♀), Age: 42 or 55 (2 cohorts).</td>
<td>Men: T&lt;sub&gt;3&lt;/sub&gt; (nmol/L) (cohort 1928) smokers: 1.74 ± 0.30; non-smokers: 1.69±0.32 T&lt;sub&gt;4&lt;/sub&gt; (cohort 1941) smokers: 1.85±0.36; non-smokers: 1.70±0.36; TSH (cohort 1941) smokers: 2.10±0.09; non-smokers: 2.19±0.12*** Women: T&lt;sub&gt;3&lt;/sub&gt; (cohort 1928) smokers: 1.88 ± 0.31 non-smokers: 1.83±0.30; T&lt;sub&gt;4&lt;/sub&gt; (cohort 1941) smokers: 1.67±0.36; non-smokers: 1.70±0.36; TSH (cohort 1941) smokers: 2.58±0.38; non-smokers: 2.53±1.47; TSH (cohort 1941) smokers: 2.04±0.94; non-smokers: 2.32±1.26**</td>
<td>No randomization. No control for confounding variables. The presence of recall bias regarding the assessment of smoking (solely by questionnaires). NOS:6/10</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>N</th>
<th>Age</th>
<th>Smoking Status</th>
<th>TSH (mIU/L)</th>
<th>Free T4 (nmol/L)</th>
<th>FTI (µg/dL)</th>
<th>T3 (µg/dL)</th>
<th>Passive smoking</th>
<th>Clinical Findings</th>
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<tr>
<td>Fisher, 1997</td>
<td>USA</td>
<td>Community Setting (War Veterans)</td>
<td>4368</td>
<td>1962 current smokers, 1267 former smokers and 1139 never smokers</td>
<td>Age: 31-49 years</td>
<td>TS4 (current smokers): 100.4 (former smokers) and 96.5 (never smokers)</td>
<td>Mean FTI (current smokers): 9.76 (former smokers): 95.9</td>
<td>TSH (current smokers): 1.9 (former smokers): 2.3</td>
<td>Serum TSH concentration was positively and dose-dependently associated with the number of cigarettes per day.</td>
<td>Random sample. Study participants were Army veterans and may not be representative of the Portuguese male population. The presence of recall bias regarding the assessment of smoking solely by questionnaires. NOS: 8/10</td>
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<tr>
<td>Knudsen, 2002</td>
<td>Denmark</td>
<td>Cross-sectional setting</td>
<td>4649</td>
<td>2 areas in Denmark with mild and moderate iodine deficiency.</td>
<td>In heavy smokers serum TG was the double of never smokers (unavailable data). There was a strong association between smoking and serum TG level (p&lt;0.001), the association was strongest in the area with the lowest iodine intake. The increased risk of thyroid enlargement associated with smoking was most pronounced among women aged 40 to 45 years.</td>
<td>There was a random selection of subjects. Iodine status was biochemically confirmed. NOS: 8/10</td>
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<td>Belin, 2004</td>
<td>USA</td>
<td>Cross-sectional setting</td>
<td>15,592</td>
<td>Age: 12 to 90 years</td>
<td>TS4 nonsmokers: 8.7 µg/dL; mild smokers: 8.7 and active smoking: 8.7 Fewer smokers had TPOAb and/or TgAb presence compared with nonsmokers. Smokers were found to have 43% lower odds of presence of thyroid autoantibodies compared with nonsmokers. The odds of having thyroid autoantibodies present was lower by 1.1% for every 10ng/mL increase in serum cotinine. The OR of TSH elevation in smokers compared with nonsmokers was 0.5. Greater odds of TSH elevation were increasing age, female gender and high urinary iodine.</td>
<td>Large sample size. The use of cotinine as an objective serum biomarker to determine the smoking status instead of self-reporting parameters. Subjects with serum cotinine levels greater than 15 ng/mL were classified as smokers. NOS: 9/10</td>
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<td>Jorde, 2006</td>
<td>Norway</td>
<td>Cross-sectional setting</td>
<td>6085 subjects not using thyroxine</td>
<td>141 subjects (92 smokers) using thyroxine</td>
<td>Not using thyroxine, TSH (mIU/L) smokers: 1.59 ± 0.87 and nonsmokers: 1.90 ± 1.03* Using Thyroxine, TSH (mIU/L) smokers: 2.05 ± 1.76 and nonsmokers: 1.78 ± 1.53 Serum TSH levels were significantly lower in the smokers than in the nonsmokers both in males and females. Serum free T4 and free T3 levels were significantly higher in smokers than non-smokers. In those not using thyroxine, no relation was found between number of cigarettes smoked and serum TSH.</td>
<td>The presence of recall bias regarding the assessment of smoking solely by questionnaires. NOS: 7/10</td>
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<td>Asvold, 2007</td>
<td>Norway</td>
<td>Cross-sectional setting</td>
<td>3485</td>
<td>(20479 smokers and 14372 nonsmokers)</td>
<td>Women TSH levels: 1.33 mU/L (current smokers): 1.66 (never smokers). Men TSH levels: 1.40 mU/L (current smokers): 1.70 (never smokers). Smoking negatively associated with hypothyroidism but positively associated with hyperthyroidism. Among current smokers, heavier smoking was associated with lower TSH levels compared with moderate smoking. In former smokers, the prevalence of thyroid dysfunction was not substantially different from that of never smokers.</td>
<td>There was randomization on epidemiological selection. The presence of recall bias regarding the assessment of smoking by questionnaires. NOS: 6/10</td>
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<td>Vejbjerg, 2008</td>
<td>Denmark</td>
<td>Cross-sectional setting</td>
<td>3372</td>
<td>Age: 18-22, 25-30, 40-45, 60-65 years old.</td>
<td>Non-Smoker: TSH: 1.57 fT4: 16.07 fT3: 4.86 Former Smoker: TSH: 1.42 fT4: 16.29 fT3: 4.94 Moderate current smokers: TSH: 1.33 fT4: 16.47 fT3: 5.00 Heavy current smokers: TSH: 1.32 fT4: 16.64 fT3: 5.06 The effect of smoking on hormonal levels was unchanged after the iodization. There was a lower overall impact of smoking on mean thyroid volume after mandatory iodization of salt.</td>
<td>The presence of recall bias regarding the assessment of smoking solely by questionnaires. The region of inhabitancy used as a proxy for iodine status (it wasn’t biochemically confirmed). NOS: 9/10</td>
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<td>Malepeas, 2008</td>
<td>Netherlands</td>
<td>Community Setting</td>
<td>1853</td>
<td>985 smokers and 868 nonsmokers</td>
<td>Current Smokers: TSH: 1.31 mU/L fT4 (pmol/L): 16.59±2.59 Never Smokers: TSH: 1.46 fT4:16.52±2.76 Serum TSH was lower in current smokers than nonsmokers. Free T4 concentrations did not differ significantly between smoking groups.</td>
<td>Large sample size. The presence of recall bias regarding the assessment of smoking. Lack of data of duration since smoking cessation for former smokers. NOS: 7/10</td>
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<td>Soldin, 2009</td>
<td>USA</td>
<td>Community Setting</td>
<td>267</td>
<td>Age between 18 and 44 years.</td>
<td>Active smokers: TSH (mU/L): 1.40; T4 (µg/dL): 7.6; T3 (µg/dL): 99.1 Passive smokers: TSH: 1.30; T4: 7.9; T3: 87.6 Nonsmokers: TSH: 1.50 T4: 8.7 T3: 106.6 Active and passive exposure to cigarette tobacco smoke was associated with a mild inhibitory effect on the thyroid reflected in higher serum T4 and T3 in nonsmokers compared to smokers.</td>
<td>The use of cotinine as an objective serum biomarker to determine the smoking status instead of self-reporting parameters. NOS: 8/10</td>
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<td>Cho, 2010</td>
<td>South Korea</td>
<td>Cross-sectional setting</td>
<td>3399: 1540 smokers and 1859 nonsmokers</td>
<td>Age: 55 years</td>
<td>Current smoking was negatively associated with subclinical hypothyroidism compared with never or former smokers. Smoking and iodine showed a negative interaction term, which means that current smoking is associated with a low prevalence of subclinical hypothyroidism by inhibiting the effect of iodine on the thyroid in people living in iodine-sufficient areas. No association between smoking status or iodine intake and positive anti-TPO Ab.</td>
<td>The presence of recall bias regarding the assessment of smoking solely by questionnaires. There was a random selection of subjects. NOS: 7/10</td>
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<td>Location</td>
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<td>Denmark</td>
<td>Clinical Sample</td>
<td>Incident hypothyroidism was very common in people who had recently stopped smoking. Within two years after smoking cessation, the percentage of hypothyroid cases attributable to cessation of smoking was 85%.</td>
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<td>Iran</td>
<td>Community Sample</td>
<td>Serum TSH levels were significantly associated with BMI both in adolescent smokers and in adolescent nonsmokers. Likewise, serum TSH levels were strong associated with BMI in adolescents exposed to ETS than in adolescents not exposed to ETS. Active and passive smoking may mediate the association between thyroid function and BMI in adolescents. In smoking adolescents, hypothyroidism may lead to an increase of the BMI, whereas this was not the case in nonsmoking adolescents.</td>
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<td>Poland</td>
<td>Hospital Staff</td>
<td>Measurements 30 minutes before and 60 minutes after smoking: TSH (mU/L) (control): 3.92±0.52 (obese ♀) and 8.53±2.33 (lean ♂). TSH (after smoking): 4.12±0.56 (obese ♀) and 9.57±2.51 (lean ♂). There was no statistically significant difference in TSH secretion between the lean and obese group during smoking.</td>
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<td>Greece</td>
<td>Community Setting</td>
<td>Baseline: T3 (ng/mL): 1.11 ± 0.11 ng/mL: 1.36 ± 0.14 TSH (mU/L): 2.45 ±1.68. After SHS: T3: 1.17 ± 0.09** fT4: 1.54 ± 0.18* TSH: 2.12 ± 1.66 One hour of passive smoking was accompanied by significant increases in T3 and fT4. TSH showed a nonsignificant decrease.</td>
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<td>Greece</td>
<td>Community Sample</td>
<td>SHS exposure was accompanied by an increase in thyroid hormone secretion (T3 in both sexes and fT4 only in males). In men, SHS was accompanied by increased T3-to-fT4 ratios. Absence of a significant change in the T3-to-fT4 ratio in women.</td>
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<td>Italy</td>
<td>Hospital Setting</td>
<td>The OR of smoking for developing TPO-Ab and/or TG-Ab were 0.62 one year before seroconversion and 0.59 at seroconversion. Discontinuation of smoking was associated with an increased risk for occurrence of TPO-Ab and/or TG-Ab in serum.</td>
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<td>Netherlands</td>
<td>Family members of thyroid patients</td>
<td>The presence of recall bias regarding the assessment of smoking by questionnaires. Ever smokers were significantly younger and leaner than never smoker (p&lt;0.05). Very low rate of female smokers in comparison with the males ones.</td>
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<td>Germany</td>
<td>Community Setting</td>
<td>Absence of randomized. Both groups were regular smokers, however there was a wide range of smoking habits (5 to 22 cigarettes daily for 8 to 36 years).</td>
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**Notes:**
- NOS: 8/10
- NOS: 7/10
- NOS: 8/9
- NOS: 6/9
- NOS: 0/10
Clinical implications of abnormal thyroid function during smoking cessation: a systematic review

| Prospective Study | Smokers before pregnancy: TSH 1.06 mU/L, fT₄ 15.02 pmol/L e fT₃ 5.26 pmol/L. Nonsmokers before pregnancy: TSH 1.03 mU/L, fT₄ 15.17 pmol/L** e fT₃ 5.05 pmol/L** Those who smoke before pregnancy had a lower prevalence of TG-Abs but no difference in levels of TPO-Abs. Smoking during pregnancy associated with higher fT₃ levels and lower fT₄ levels. Cessation of smoking during early pregnancy had no influence on maternal TSH or thyroid hormone levels compared with smokers. The presence of recall bias regarding the assessment of smoking solely by questionnaires. Nonsmokers mothers were older compared to smokers (p<0.05). NOS: 8/9 |
| Community Sample | Abbreviations: T₃: Tri-iodothyronine T₄: Thyroxine fT₄: Free Thyroxin fT₃: Free Tri-iodothyronine TBG: Thyroid-binding globulin TSH: Thyrotropine // Thyroid stimulating hormone TG: Thyroglobulin TC: Thiocyanate FTI: Free thyroxine index ETS: Environmental Tobacco Smoke TPO Ab: Thyroperoxidase antibody TG Ab: Thyroglobulin antibody rT₃: Reverse tri-iodothyronine SHS: Secondhand Smoke SC: Smoking Cessation OR: Odds Ratio FU: Follow-up ♂: males ♀: females BMI: Body Mass Index *p <0.001 ** p<0.05 |

Männistö, 2012 Finland Community Sample Prospective Study FU: 8 years N=4640 ☻: 1335 prepregnancy smokers and 3305 nonsmokers, mean age 26 and 28 years respectively