

# Cigarette Smoking and Thyroid Hormone Levels in Males

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**Background.** Cigarette smoking has been linked to thyroid disease, although studies of this problem have not shown consistent effects, with some studies linking smoking to increased thyroid hormone levels, and others to decreased thyroid hormone levels.

**Methods.** We performed a secondary analysis of information collected from 4462 Vietnam-era male US Army veterans aged 31–49 years who participated in the Vietnam Experience Study in 1985–1986. The study group consisted of 1962 current smokers and 2406 current non-smokers who had no thyroid abnormalities on physical examination, no current use of thyroid medicine, and no history of thyroid disease.

**Results.** We found that current smokers have higher thyroxine levels and lower thyroid stimulating hormone levels than never smokers and former smokers. The higher thyroxine levels that we detected in smokers, compared to non-smokers, diminished when we controlled for thyroxine-binding globulin and testosterone. We also found that heavy smokers had a smaller increase in thyroxine levels than did light smokers, when compared to non-smokers.

**Conclusions.** Our findings suggest at least two distinct mechanisms for the effect of tobacco smoke on thyroid function; one related to higher levels of thyroxine-binding globulin and testosterone among smokers compared to non-smokers and another related to higher levels of thyrotoxins in tobacco smoke in heavy smokers compared to light and moderate smokers.

**Keywords:** thyroid, thyroxine, cigarette smoking, epidemiology, toxicology

Graves' disease, Graves' ophthalmopathy, and thyroid hormone abnormalities have been linked to cigarette smoking.<sup>1–8</sup> Results from some studies have shown that smokers have higher levels of thyroid hormones than non-smokers,<sup>4,9</sup> whereas results from other studies have not shown this effect.<sup>3,10</sup> Certain compounds detectable in the serum of people who have smoked recently, such as thiocyanate and 2,3-hydroxypyridine, interfere with normal thyroidal physiology.<sup>3,11,12</sup>

In this study, a secondary analysis of data obtained in the historical cohort of the Centers for Disease Control

Vietnam Experience Study conducted in 1985–1986, we compare levels of thyroxine ( $T_4$ ), free thyroxine index (FTI), and thyroid stimulating hormone (TSH) among smokers with those among former and never smokers. We repeated these analyses after controlling for other factors that affect thyroid hormone levels, including body mass index (BMI), age and serum testosterone levels, which has not been done in previous studies,<sup>3,4,9,10</sup> to further assess the effect of cigarette smoking on thyroid hormone levels.

## METHODS

Complete medical history and physical examination data were obtained in 1985 and 1986 from 4462 randomly selected Vietnam-era US Army veterans as part of The Centers for Disease Control Vietnam Experience Study.<sup>13–15</sup> As described in detail elsewhere,<sup>14,16</sup> the men examined were randomly selected from more than 14 000 veterans who participated in a large telephone interview study. All participants were required to have enlisted in the Army between 1965 and 1971 and to have served only a single tour of duty before being discharged.

All subjects completed medical questionnaires that were administered by trained physician's assistants.

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Subjects were asked, 'Did a doctor ever tell you that you have an overactive thyroid?' and 'Did a doctor ever tell you that you have an underactive thyroid?' All subjects were also asked to report all of the medications that they were currently taking and to report their complete cigarette smoking histories (subjects were not asked about cigar or pipe smoking). We searched the database for subjects who were currently taking thyroid medication, antihypertensives, and anticonvulsants. We also searched the database for all subjects who reported physician-diagnosed liver damage caused by alcohol consumption, hepatitis, or cirrhosis.

A physical examination was completed on each subject.<sup>17</sup> All subjects were examined for the presence of thyroid enlargement, tenderness, or nodules. All subjects had their height and weight measured. We calculated their BMI by dividing the subjects' weight in kilograms by the square of their height in centimetres.

Following an overnight fast, all veterans had blood drawn to measure their T<sub>4</sub>, T<sub>3</sub>U (triiodothyronine uptake), and TSH levels. The T<sub>4</sub> and TSH levels were measured by double antibody radioimmunoassay (the lower detection limit for TSH in this study is 0.5 mu/l), and T<sub>3</sub>U was measured using 125-I triiodothyronine tracer and reference serum.<sup>17</sup> Analyses were completed within 24 h of collection.<sup>17</sup> All laboratory results were monitored using bench and 'blind' repeat quality control procedures.<sup>18</sup> The FTI was calculated for each sample by the following formula:  $FTI = T_4 \times (T_3U/100 - T_3U)/0.418$ . In some analyses, we used serum testosterone levels as a covariate. Because the T<sub>4</sub>, FTI, and TSH values had a positively skewed distribution, we used natural logarithms to transform the data prior to analyses.

We excluded 94 men who had a history of thyroid disease, who currently used thyroid medications or anabolic steroids, or who had an abnormal thyroid gland on physical examination (Table 1).

Statistical analysis was performed with the SAS statistical package (SAS Institute, Cary, North Carolina). We used general linear models with Bonferoni t-tests to compare means of T<sub>4</sub>, FTI, and TSH between current smokers, former smokers and never smokers. We used clinical limits for 'high' values (141.6 nmol/l [11.0 µg/dl] for T<sub>4</sub> and 135.1 [10.5 µg/dl] for FTI) and 'low' values (0.5 mU/l for TSH). We performed linear regression with T<sub>4</sub>, FTI, and TSH as the dependant variables and cigarette smoking, antihypertensive drug use, anticonvulsant drug therapy, age, liver disease, low socioeconomic status (as determined by either a family income <US\$20 000 annually or ≤12 years of education), BMI, and serum testosterone levels as independent variables. We analysed the data for a dose-response effect by

TABLE 1 Number of men excluded from the study because they used thyroid medication or anabolic steroids or because they had abnormal results on thyroid examination, or a history of hypothyroidism or hyperthyroidism, stratified by smoking category. From the Vietnam Experience Study, 1985–1986

	Never smokers N = 1162	Former smokers N = 1292	Current smokers N = 2008
Taking thyroid medication	3 (0.3%)	3 (0.3%)	6 (0.3%)
Taking anabolic steroids	1 (0.1%)	0 (0.0%)	1 (0.1%)
Abnormal thyroid examination	9 (0.8%)	9 (0.7%)	15 (0.8%)
History of hyperthyroidism	7 (0.6%)	8 (0.6%)	14 (0.7%)
History of hypothyroidism	9 (0.8%)	9 (0.7%)	17 (0.9%)
Any reason for exclusion	23 (1.9%)	25 (1.9%)	46 (2.3%)

limiting the analysis to current smokers and including cigarettes per day as an exposure category. In some analyses we also included the square of cigarettes per day as a quadratic term.

## RESULTS

We analysed data on 4368 men, of whom 1962 were current smokers, 1267 were former smokers, and 1139 were never smokers. Among the current smokers, 265 (13.5%) smoked <11 cigarettes per day (light smokers), 780 (39.8%) smoked 11–25 cigarettes per day (moderate smokers), and 917 (46.8%) smoked >25 cigarettes a day (heavy smokers). Former smokers had stopped smoking, on average, 8 years prior to the study. The mean age was 38.0 years among current smokers, 38.5 years among former smokers, and 38.7 years among never smokers.

The mean T<sub>4</sub> level was higher among current smokers than among former smokers (100.4 nmol/l [7.8 µg/dl] versus 96.5 nmol/l [7.5 µg/dl],  $P < 0.05$ ) and never smokers (100.4 nmol/l [7.8 µg/dl] versus 94.0 nmol/l [7.3 µg/dl],  $P < 0.05$ ). Overall, T<sub>4</sub> levels greater than 141.6 nmol/l (11.0 µg/dl) were found among 2.6% of current smokers, 1.2% of former smokers, and 1.2% of never smokers ( $P = 0.002$ , Figure 1). In the analysis restricted to current smokers, T<sub>4</sub> levels greater than 141.6 nmol/l (11.0 µg/dl) were found among 3.4% of light smokers, 3.0% of moderate smokers, and 2.2% of heavy smokers ( $P = 0.444$ , Figure 2).

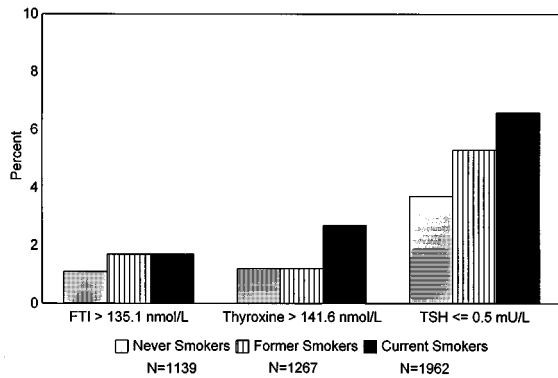


FIGURE 1 The percentage of never smoking, former smoking and current smoking men with thyroxine levels >141.6 nmol/l (11.0 µg/dl), free thyroxine index >135.1 nmol/l (10.5 µg/dl), or thyroid stimulating hormone level ≤0.5 mU/l. From the Vietnam Experience Study, 1985–1986

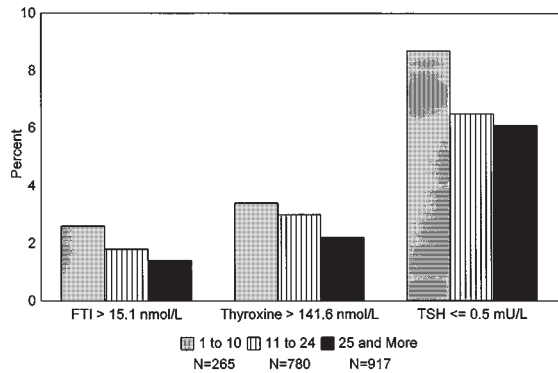


FIGURE 2 The percentage of light smoking, intermediate smoking, and heavy smoking men with thyroxine levels >141.6 nmol/l (11.0 µg/dl), free thyroxine index >135.1 nmol/l (10.5 µg/dl), or thyroid stimulating hormone level ≤0.5 mU/l. From the Vietnam Experience Study, 1985–1986

The mean FTI was higher among current smokers than among never smokers (97.6 nmol/l [7.6 µg/dl], versus 95.9 nmol/l [7.4 µg/dl],  $P < 0.05$ ) but not among former smokers (97.6 nmol/l [7.6 µg/dl], versus 97.3 nmol/l [7.6 µg/dl],  $P > 0.05$ ). Free thyroxine index >135.1 nmol/l (10.5 µg/dl), were found among 1.7% of current smokers, 1.7% of former smokers and 1.1% of never smokers ( $P = 0.386$ , Figure 1). In the analysis restricted to current smokers, FTI >135.1 nmol/l (10.5 µg/dl), were found among 2.6% of light smokers, 1.8% of moderate smokers, and 1.4% of heavy smokers ( $P = 0.399$ , Figure 2).

The mean TSH level was lower among current smokers than among former smokers (1.9 mU/l versus 2.3 mU/l,  $P < 0.05$ ) and never smokers (1.9 mU/l versus 2.3 mU/l,  $P < 0.05$ ). Thyroid stimulating hormone levels ≤0.5 mU/l were found among 6.6% of current smokers, 5.3% of former smokers, and 3.7% of never smokers ( $P = 0.002$ , Figure 1). In the analysis restricted to current smokers, TSH levels <0.5 mU/l were found among 8.7% of light smokers, 6.5% of moderate smokers, and 6.1% of heavy smokers ( $P = 0.330$ , Figure 2).

In the linear regression models, current cigarette smoking was associated with a significant increase in the  $T_4$  level and the FTI and a decrease in the TSH level (Table 2, Model A). When testosterone levels were added to the model (Model B) the effect of current smoking was decreased by 20% to 40%, suggesting that part of this effect may be related to increased testosterone levels in smokers.<sup>19</sup> The effect of current smoking on the FTI was much less than it was on the  $T_4$  level, demonstrating that much of the effect of smoking on thyroid hormone levels is related to increased levels of thyroxine-binding globulin.

In the models limited to current smokers, both the  $T_4$  level and the FTI were positively related to the packs of 20 cigarettes smoked per day and negatively related to the square of the number of packs smoked (Table 3). Using Model A for  $T_4$  levels, we calculated that  $T_4$  levels would increase 2.7 nmol/l (0.2 µg/dl), in smokers of 10 cigarettes per day, 3.9 nmol/l (0.3 µg/dl), in smokers of 20 cigarettes per day, 6.2 nmol/l (0.5 µg/dl), in smokers of 40 cigarettes per day, and 2.4 nmol/l (0.2 µg/d), in smokers of 60 cigarettes per day. The estimates did not change when testosterone or BMI was added to the model (Table 3, Models B and C). Thyroid stimulating hormone levels were not significantly affected by the smoking dose.

## DISCUSSION

We found that current smokers have higher  $T_4$  levels and lower TSH levels than never smokers and former smokers. Some researchers have reported similar results,<sup>2,4,9</sup> whereas other researchers have detected similar or lower thyroid hormone levels in smokers compared to non-smokers.<sup>3,10</sup> Our data suggest that several different toxicological mechanisms may explain these results. Part, but not all, of the higher levels of thyroid hormones among smokers is related to increased levels of thyroxine-binding globulin among smokers. Among current smokers, the mean  $T_4$  level was 6.8% higher than the level among never smokers and 4.0% higher than the level among former smokers, whereas the mean FTI among current smokers was 1.8%

TABLE 2 Results of linear regression models predicting the natural logarithms of thyroxine levels, free thyroxine indices and thyroid stimulating hormone levels with current smoking, use of antihypertensive or anticonvulsant medication, age, body mass index, testosterone level, and presence of liver disease. From the Vietnam Experience Study, 1985–1986

Variable	Model <sup>a</sup>	Intercept	Current smoking	Standard error	P
Thyroxine	A	4.659	0.048	0.006	<0.001
	B	4.282	0.040	0.006	<0.001
	C	4.224	0.040	0.006	<0.001
Free thyroxine index	A	4.590	0.012	0.005	0.020
	B	4.247	0.005	0.005	0.366
	C	4.440	0.004	0.005	0.508
Thyroid-stimulating hormone	A	0.390	-0.130	0.018	<0.001
	B	1.527	-0.106	0.019	<0.001
	C	1.195	-0.104	0.019	<0.001

<sup>a</sup> Model A—Current smoking, antihypertensive medication, anticonvulsant medication, age, low socioeconomic status and liver disease.

Model B—Model A plus testosterone level.

Model C—Model A plus body mass index and testosterone level.

TABLE 3 Results of linear regression models predicting the natural logarithms of thyroxine levels, free thyroxine indices and thyroid stimulating hormone levels with packs of 20 cigarettes per day, square of packs smoked per day, use of antihypertensive or anticonvulsant medication, age, low socioeconomic status, body mass index, testosterone level, and presence of liver disease in an analysis limited to current smokers. From the Vietnam Experience Study, 1985–1986

Variable	Model <sup>a</sup>	Intercept	Cigarettes/day	P	(Cigarettes/day) <sup>2</sup>	P
Thyroxine	A	4.761	0.069	0.005	-0.020	0.015
	B	4.358	0.067	0.006	-0.019	0.017
	C	4.349	0.067	0.006	-0.019	0.017
Free thyroxine index	A	4.598	0.049	0.020	-0.014	0.047
	B	4.288	0.048	0.023	-0.013	0.055
	C	4.446	0.043	0.039	-0.012	0.094
Thyroid stimulating hormone	A	0.105	-0.053	0.452	0.011	0.622
	B	1.342	-0.038	0.583	0.006	0.785
	C	1.366	-0.040	0.567	0.007	0.746

<sup>a</sup> Model A—Cigarette packs/day, cigarette packs squared/day, antihypertensive medication, low socioeconomic status, anticonvulsant medication, age, liver disease.

Model B—Model A plus testosterone level.

Model C—Model A plus body mass index and testosterone level.

higher than the FTI among never smokers and 0.3% higher than the FTI among former smokers. Another possible mechanism for our findings might be related to testosterone levels, which are higher among current smokers.<sup>19</sup> Results of a previous study showed an increase in FTI among women receiving androgen therapy for breast cancer.<sup>20</sup> In that study, the increase in T<sub>4</sub> was thought to be related to a decrease in thyroid-binding globulin that was associated with androgen therapy. In our analysis, the serum testosterone level was related to the T<sub>4</sub> level and the FTI when we compared current non-smokers with current smokers (Table 2), but not when

we limited our analysis to current smokers (Table 3). This finding suggests that testosterone levels may be an important factor in explaining differences between smokers and non-smokers, but that other mechanisms may be more important in explaining differences between subgroups of smokers.

In our study, heavy smokers had a smaller increase in T<sub>4</sub> levels and the FTI than did moderate smokers and light smokers, when compared to non-smokers. This finding is consistent with results from other studies that demonstrate lower levels of T<sub>4</sub> or the FTI in heavy smokers when compared with light smokers.<sup>3,10</sup> This

finding also suggests another mechanism by which smoking can affect thyroid hormone levels, perhaps related to the many toxins, including thiocyanate, 2,3-hydroxypyridine, 3,4-benzpyrene and hydroxyquinones, present in tobacco smoke.<sup>21,22</sup> Thiocyanate, which has a serum half-life of more than 6 days, has been studied extensively as a potential goitrogen.<sup>3,11,12</sup> Thiocyanate inhibits iodide transport and organification and, in the presence of iodine deficiency, can cause goitre.<sup>11</sup>

Another tobacco smoke constituent, 2,3-hydroxypyridine, inhibits T<sub>4</sub> deiodination by limiting iodothyronine deiodinase activity.<sup>23,24</sup> The effect of 2,3-hydroxypyridine is similar to that of propylthiouracil. Like propylthiouracil, 2,3-hydroxypyridine may slightly and temporarily elevate serum T<sub>4</sub> levels as a consequence of its deiodinase-altering activity prior to decreasing these levels. Thyroxine deiodination, however, is accelerated by other agents in tobacco smoke, such as 3,4-benzpyrene, a polynuclear aromatic hydrocarbon.<sup>25</sup>

Hydroxyquinones, also found in tobacco smoke, increase intracellular calcium and cause hepatotoxicity.<sup>26</sup> This disruption could impair degradation of T<sub>4</sub> resulting in elevated serum levels. Thyroid hormone abnormalities might be important aetiological factors in disturbances found in smokers and people with hyperthyroidism. For example, both cigarette smoking<sup>27</sup> and subclinical hyperthyroidism<sup>28</sup> have been linked to osteoporosis.

Thyroid abnormalities are more prevalent in women than men, and their prevalence increases with age.<sup>2</sup> We found the prevalence of self-reported thyroid disease (hyperthyroidism or hypothyroidism) to be less than 1% in our population, with no difference among people in different smoking categories. Other researchers have reported the prevalence of thyroid disease among men to be less than 1%. In one study, current cigarette smokers had a higher prevalence of toxic diffuse goitre and non-toxic diffuse goitre than non-smokers.<sup>2</sup>

An unexpected finding in this study was that the FTI was higher among current smokers than among never smokers, but not former smokers. We cannot determine whether this finding is related to long-term effects of smoking that exist even after smoking cessation or other factors.

Several potential biases may affect our ability to generalize from the results of this study. Study participants were all Vietnam-era Army veterans and may not be representative of the American male population. These results may also not be generalizable to women, as results of some research has shown that smoking may not affect thyroid hormone levels in clinically euthyroid women.<sup>29</sup> Standardized questionnaires such as those we used might elicit fewer reports of thyroid

disease than would clinical interviews and examinations. Smoking history was not validated by objective measures, such as serum cotinine levels. Subjects were not asked about cigar or pipe smoking, which also may affect thyroid hormone levels. Despite these limitations, however, we believe this study provides valuable information on how cigarette smoking affects thyroid function in males.

We conclude that cigarette smoking affects thyroid function in middle-aged men. In general, men who smoke have slightly higher T<sub>4</sub> levels and FTI and slightly lower TSH levels, than men who do not smoke, and these findings are probably related to higher levels of thyroxine-binding globulin and testosterone among smokers. Among current smokers, however, heavy smokers have slightly lower T<sub>4</sub> levels than light smokers, suggesting that higher levels of toxins in tobacco smoke in heavy smokers may be affecting thyroid hormone levels. In smokers with normal clinical examinations, mildly elevated T<sub>4</sub> levels and FTI and suppressed TSH levels may represent a smoking effect and not intrinsic thyroid disease.

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