Tobacco Smoking and Thyroid Function

A Population-Based Study

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Background: The association between tobacco smoking and thyroid function is incompletely understood.

Methods: In a cross-sectional, population-based study conducted between August 15, 1995, and June 18, 1997, of 20,479 women and 10,355 men without previously known thyroid disease, we calculated the geometric mean serum concentration of thyrotropin and the prevalence of hypothyroidism and hyperthyroidism among current, former, and never smokers.

Results: Among women, the mean thyrotropin level was lower in current (1.33 mIU/L; 95% confidence interval [CI], 1.29-1.36 mIU/L) and former smokers (1.61 mIU/L; 95% CI, 1.56-1.65 mIU/L) compared with never smokers (1.66 mIU/L; 95% CI, 1.63-1.70 mIU/L). Similarly, among men, the mean thyrotropin level was lower in current (1.40 mIU/L; 95% CI, 1.36-1.44 mIU/L) and former smokers (1.61 mIU/L; 95% CI, 1.57-1.66 mIU/L) compared with never smokers (1.70 mIU/L; 95% CI, 1.66-1.75 mIU/L). In former smokers, thyrotropin levels increased gradually with time since smoking cessation (P for trend < .001). Among current smokers, moderate daily smoking was associated with higher thyrotropin levels than heavier smoking. In women, the prevalence of overt hypothyroidism was lower in current smokers compared with never smokers (odds ratio, 0.60; 95% CI, 0.38-0.95), whereas the prevalence of overt hyperthyroidism was higher among current smokers (odds ratio, 2.37; 95% CI, 1.34-4.20). The associations related to subclinical thyroid dysfunction were similar to those for overt thyroid disease.

Conclusions: These findings indicate that smoking is negatively associated with hypothyroidism but positively associated with hyperthyroidism. The associations with smoking cessation suggest that smoking may have reversible effects on thyroid function. Notably, we report for the first time, to our knowledge, a lower prevalence of overt hypothyroidism among current smokers.

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Methods

All inhabitants 20 years or older of Nord-Trøndelag County in Norway were invited to participate in the Nord-Trøndelag Health Study (HUNT) between August 15, 1995, and June 18, 1997. A total of 92,936 individuals were eligible to participate, and 66,140 (71.2%) attended. The study has been described in detail elsewhere.13 Briefly, the participants were asked to complete a self-administered questionnaire, which included questions about thyroid disease and smoking habits. They were asked if they had ever had hyperthyroidism, hypothyroidism,
goiter, or disease in the thyroid gland; if they had been receiving treatment with thyroxine, carbimazole, or radioactive iodine; or if they had undergone thyroid surgery. They were also asked if they currently smoked cigarettes, cigars, or a pipe daily, if they had never smoked daily; or, if they had previously been daily smokers, when they stopped smoking. Current and former smokers were asked at what age they started smoking, the average number of cigarettes per day, and how many years they had been smoking. On the basis of these questions, we classified the participants as never smokers, former smokers, or current smokers.

A nonfasting venous serum sample was obtained from each individual in the study, and analysis of thyrotropin was performed in subsamples, including all women older than 40 years and 50% of men older than 40 years. In addition, thyrotropin levels were measured in 5% random samples of men and women 20 to 40 years of age. In total, 34,851 individuals from these samples were selected for thyrotropin analysis. If the thyrotropin level was lower than 0.20 mIU/L, free thyroxine (FT₄) and total triiodothyronine (T₃) levels were also measured, and if the thyrotropin level was higher than 4.0 mIU/L, the FT₄ level was measured. Among the 34,851 individuals who were selected for thyrotropin analysis, we excluded people with previously known thyroid disease (n=2904) and people with missing information on thyrotropin level or smoking status (1113), leaving 30,834 people (20,479 women and 10,355 men) eligible for the present study.

LABORATORY MEASUREMENTS

Serum concentrations of thyrotropin, FT₄, and total T₃ were analyzed at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity, 0.03 mIU/L; total analytical variation, <5%), DELFIA FT₄ (total analytical variation, <7%), and AutoDELFIA T₃ (total analytical variation, <5%), respectively, all from Wallac Oy, Turku, Finland. Reference ranges for thyrotropin from this population have been published previously. On the basis of these results, the reference range for thyrotropin in the present study was defined as 0.30 to 3.5 mIU/L. The laboratory’s reference ranges were 0.62 to 1.55 ng/dL (to convert to picomoles per liter, multiply by 0.0154) for total T₃.

STATISTICAL ANALYSES

In a general linear model, we calculated geometric mean thyrotropin for never smokers, current smokers, and former smokers. In former smokers, we assessed whether mean thyrotropin levels differed according to time since smoking cessation (0-1, 2-3, 4-7, 8-12, 13-17, 18-22, and ≥23 years). In current smokers, we assessed whether mean thyrotropin levels differed according to the average number of cigarettes smoked per day (0-3, 4-7, 8-12, 13-17, and ≥18 cigarettes) or according to what age they started smoking (<16, 16-20, 21-25, and ≥26 years). When reporting the number of years since quitting or the number of cigarettes smoked per day, the participants tended to round off the numbers to 5, 10, 15, and so on; we therefore used categories of smoking that were centered around these numbers. Serum thyrotropin concentrations were log-transformed because of nonnormal distribution. Using a logistic regression model, we calculated the odds ratios (ORs) for thyroid dysfunction in current and former smokers compared with never smokers. Thus, overt hypothyroidism was defined as a thyrotropin level higher than 4.0 mIU/L combined with an FT₄ level less than 0.62 ng/dL, and subclinical hypothyroidism was defined as a thyrotropin level higher than 4.0 mIU/L combined with an FT₄ level of 0.62 ng/dL or higher. Overt hyperthyroidism was defined as a thyrotropin level lower than 0.20 mIU/L combined with an FT₄ level above the reference range, and subclinical hyperthyroidism was defined as a thyrotropin level lower than 0.20 mIU/L combined with neither an FT₄ level nor a total T₃ level above the reference range. In former smokers, we also assessed whether the prevalence of hypothyroidism or hyperthyroidism differed according to time since smoking cessation (0-3, 4-12, and ≥13 years).

We analyzed women and men separately, and all results were adjusted for age. The data were analyzed using SPSS statistical software, version 14.0, for Windows (SPSS Inc, Chicago, Illinois). The HUNT Study is a collaborative effort of the Faculty of Medicine, the Norwegian University of Science and Technology, the Norwegian Institute of Public Health, and Nord-Trøndelag County Council. The study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate.

RESULTS

Among women, the mean thyrotropin level was lower in current (1.33 mIU/L; 95% confidence interval [CI], 1.29-1.36 mIU/L) and former smokers (1.61 mIU/L; 95% CI, 1.56-1.65 mIU/L) compared with never smokers (1.66 mIU/L; 95% CI, 1.63-1.70 mIU/L). Among men, the mean thyrotropin level was similarly lower in current (1.40 mIU/L; 95% CI, 1.36-1.44 mIU/L) and former smokers (1.61 mIU/L; 95% CI, 1.57-1.66 mIU/L) compared with never smokers (1.70 mIU/L; 95% CI, 1.66-1.75 mIU/L) (Table 1).

In former smokers, the thyrotropin level increased gradually with time since smoking cessation (P for linear trend across categories < .001 in both women and men). Thus, women who had quit smoking approximately 5 to 10 years ago had similar mean thyrotropin levels as never smokers, whereas in men, the mean thyrotropin level was similar to never smokers among former smokers who had quit 18 or more years ago (Figure 1).

Among current smokers, moderate daily smoking was associated with higher thyrotropin levels compared with heavier smoking. Thus, the mean thyrotropin level was higher in women who reported smoking fewer than 4 cigarettes per day (1.46 mIU/L; 95% CI, 1.35-1.59 mIU/L) compared with those who reported smoking 8 to 12 cigarettes per day (1.30 mIU/L; 95% CI, 1.26-1.34 mIU/L). In

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Table 1. Age-Adjusted Geometric Mean Thyrotropin Levels by Sex in Never Smokers, Former Smokers, and Current Smokers

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of Participants</th>
<th>Thyrotropin (95% CI), mIU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>10,662</td>
<td>1.66 (1.63-1.70)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>4,240</td>
<td>1.61 (1.56-1.65)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>5,577</td>
<td>1.33 (1.29-1.36)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>3,295</td>
<td>1.70 (1.66-1.75)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>4,037</td>
<td>1.61 (1.57-1.66)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>3,023</td>
<td>1.40 (1.36-1.44)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
men, the mean thyrotropin level was higher among those who reported smoking fewer than 4 (1.53 mIU/L; 95% CI, 1.39-1.68 mIU/L) or 4 to 7 cigarettes (1.48 mIU/L; 95% CI, 1.40-1.56 mIU/L) per day compared with those who reported smoking 8 to 12 cigarettes per day (1.38 mIU/L; 95% CI, 1.33-1.44 mIU/L). In these data, smoking more than 12 cigarettes per day was not related to further reduction in the concentration of thyrotropin (Figure 2). In current smokers, age when they started smoking was not associated with thyrotropin (data not shown).

In current smokers, age when they started smoking was not associated with thyrotropin (data not shown).

Current smoking in women was related to nearly half the prevalence of overt (OR, 0.60; 95% CI, 0.38-0.95) and subclinical (OR, 0.54; 95% CI, 0.45-0.66) hypothyroidism compared with never smokers. In men, the ORs for overt and subclinical hypothyroidism were 0.51 (95% CI, 0.15-1.73) and 0.37 (95% CI, 0.26-0.52) among current smokers compared with never smokers (Table 2).

In relation to hyperthyroidism, the prevalence of overt (OR, 2.37; 95% CI, 1.34-4.20) and subclinical (OR, 1.83; 95% CI, 1.10-3.06) disease among women was approximately twice as high in current smokers compared with never smokers. For men, there were too few individuals with hyperthyroidism to yield meaningful estimates (Table 3).

In former smokers, the prevalence of thyroid dysfunction was not substantially different from that of never smokers. Analyses related to time since smoking cessation suggest that the prevalence of thyroid dysfunction gradually approached that of never smokers after smoking cessation (Tables 2 and 3). Notably, the lower prevalence of overt hypothyroidism that we found among current smokers was not present among former smokers who had recently quit smoking.

In a separate analysis, we included people with thyrotropin levels of 3.6 to 4.0 mIU/L or 0.20 to 0.49 mIU/L as subclinically hypothyroid or hyperthyroid, respectively. The associations with smoking were similar to the associations in the original analysis, except that the greater number of individuals allowed analysis of subclinical hyperthyroidism among men. Compared with never smoking men, the prevalence of subclinical hyperthyroidism was higher among current smokers (OR, 2.10; 95% CI, 1.39-3.17) and among former smokers who had quit smoking 4 to 12 years ago (OR, 1.95; 95% CI, 1.11-3.44).

The estimates were not substantially different when we restricted the analyses to individuals older than 40 years.

In this large population-based study of people without previously known thyroid disease, current smokers had lower levels of thyrotropin, a lower prevalence of hypothyroidism, and a higher prevalence of hyperthyroidism compared with never smokers. Our findings indicate essentially similar associations between tobacco smoking and thyroid function in women and men, except that there were too few men with hyperthyroidism to allow meaningful estimates for that group.

The cross-sectional design may not allow us to draw conclusions for causality, but we consider an effect of tobacco smoking on thyroid function biologically more plausible than an effect of thyroid function on smoking habits. Previous population-based studies have also reported lower thyrotropin levels among current smokers, and some of these studies found correspondingly higher FT₄ levels, free thyroxine indices, or free T₃.
levels, suggesting that smokers may have increased levels of thyroid hormones that are not mediated by thyrotropin.

The results of population-based studies have consistently shown that smokers have a lower prevalence of elevated thyrotropin levels, which is consistent with our finding related to subclinical hypothyroidism. We also found that current smoking was associated with a lower prevalence of overt hypothyroidism, which is at variance with previous studies that have reported either no association or an increased risk of hypothyroidism among smokers. Also, in a study of patients with Hashimoto thyroiditis, smoking was associated with a higher prevalence of overt hypothyroidism.

Current smoking has been shown to increase the risk of Graves hyperthyroidism, and this evidence was recently strengthened by a prospective study among women. Also, the investigators of a large cross-sectional study found that smokers were more likely to have relatively low thyrotropin concentrations. Thus, the higher prevalence of overt and subclinical hyperthyroidism that we found among current smokers is consistent with previous results.

Neither the components in tobacco that may cause the thyroid effects nor their mechanisms of action are clear. Knudsen et al found that the associations between smoking and thyrotropin and FT₄ levels disappeared after adjustment for thyroid volume and thyroid nodularity and suggested that the differences in thyrotropin and FT₄ levels were secondary to, or parallel with, changes in thyroid structure. Recently, a lower prevalence of thyroid autoantibodies was associated with current smoking, suggesting that tobacco smoke may reduce the risk of chronic autoimmune thyroiditis, which

Table 2. Age-Adjusted ORs for Overt Hypothyroidism and Subclinical Hypothyroidism by Sex in Never Smokers, Former Smokers, and Current Smokers, With Former Smokers Subdivided by Years Since Smoking Cessation

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants</td>
<td>Overt Hypothyroidism</td>
<td>Subclinical Hypothyroidism</td>
<td>No. of Participants</td>
<td>Overt Hypothyroidism</td>
<td>Subclinical Hypothyroidism</td>
</tr>
<tr>
<td>Never</td>
<td>10 662</td>
<td>89 1 [Reference]</td>
<td>620 1 [Reference]</td>
<td>3295</td>
<td>8 1 [Reference]</td>
<td>141 1 [Reference]</td>
</tr>
<tr>
<td>Former</td>
<td>4240</td>
<td>42 1.27 (0.87-1.85)</td>
<td>221 0.99 (0.84-1.17)</td>
<td>4037</td>
<td>11 0.97 (0.38-2.48)</td>
<td>179 0.88 (0.69-1.11)</td>
</tr>
<tr>
<td>Current</td>
<td>5577</td>
<td>25 0.60 (0.38-0.96)</td>
<td>157 0.54 (0.45-0.66)</td>
<td>3023</td>
<td>4 0.51 (0.15-1.73)</td>
<td>48 0.37 (0.26-0.52)</td>
</tr>
</tbody>
</table>

Time since smoking cessation, y

| 0-3    | 694 | 9 1.71 (0.85-3.43) | 25 0.71 (0.47-1.07) | 527 | 3 2.31 (0.61-8.78) | 13 0.59 (0.33-1.06) |
| 4-12   | 1082 | 13 1.57 (0.87-2.85) | 61 1.09 (0.83-1.44) | 914 | 3 1.16 (0.30-4.45) | 25 0.58 (0.37-0.89) |
| ≥ 13   | 2300 | 16 0.87 (0.51-1.50) | 127 1.03 (0.84-1.26) | 2492 | 5 0.68 (0.21-2.13) | 136 1.03 (0.80-1.32) |

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Age-Adjusted ORs for Overt Hyperthyroidism and Subclinical Hyperthyroidism by Sex in Never Smokers, Former Smokers, and Current Smokers, With Former Smokers Subdivided by Years Since Smoking Cessation

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants</td>
<td>Overt Hyperthyroidism</td>
<td>Subclinical Hyperthyroidism</td>
<td>No. of Participants</td>
<td>Overt Hyperthyroidism</td>
<td>Subclinical Hyperthyroidism</td>
</tr>
<tr>
<td>Former</td>
<td>4240</td>
<td>9 0.95 (0.44-2.06)</td>
<td>16 1.19 (0.66-2.16)</td>
<td>4037</td>
<td>2 . . .</td>
<td>10 . . .</td>
</tr>
<tr>
<td>Current</td>
<td>5577</td>
<td>28 2.37 (1.34-4.20)</td>
<td>29 1.83 (1.10-3.06)</td>
<td>3023</td>
<td>2 . . .</td>
<td>1 . . .</td>
</tr>
</tbody>
</table>

Time since smoking cessation, y

| 0-3    | 694 | 5 3.39 (1.27-9.08) | 5 2.58 (1.00-6.68) | 527 | 1 . . . | 1 . . . |
| 4-12   | 1082 | 1 0.43 (0.06-3.16) | 3 0.88 (0.27-2.88) | 914 | 0 . . . | 2 . . . |
| ≥ 13   | 2300 | 3 0.58 (0.18-1.94) | 7 0.94 (0.42-2.11) | 2492 | 1 . . . | 7 . . . |

Abbreviations: CI, confidence interval; OR, odds ratio.

Overt hyperthyroidism is defined as a thyrotropin level less than 0.20 mIU/L combined with a free thyroxine level greater than 1.55 ng/dL (to convert to picomoles per liter, multiply by 12.871). Subclinical hyperthyroidism is defined as a thyrotropin level less than 0.20 mIU/L combined with a free thyroxine level of 1.55 ng/dL or less and a total triiodothyronine level of 173.5 ng/dL or less.
is the most common cause of hypothyroidism in iodine-sufficient areas. Other studies have suggested that tobacco smoking is negatively associated with autoimmune diabetes\(^1\) and ulcerative colitis.\(^2\)

The dose of smoking, assessed by serum cotinine concentration, has been negatively associated with thyrotropin and also with the presence of thyroid autoantibodies,\(^3\)\(^4\) but others have failed to confirm any association between number of cigarettes per day and thyrotropin levels.\(^5\)\(^6\) Our results showed a gradual decline in thyrotropin level related to moderate smoking (from 0 to 12 cigarettes per day), but we observed no further decline related to heavier smoking.

We found gradually higher levels of thyrotropin with time since smoking cessation, and approximately 10 to 20 years after quitting, the thyrotropin level in former smokers did not differ from that of never smokers. Also, those who had quit smoking long ago had a prevalence of hypothyroidism or hyperthyroidism that did not differ from that of never smokers. For overt hypothyroidism, the lower prevalence among current smokers was not present in former smokers, not even among those who had recently quit. These results suggest that the effects of smoking that appear to influence thyroid function may be reversed if the smoking habit is discontinued. This possibility is supported by the results of other studies\(^1\)\(^2\)\(^7\) that have reported lower thyrotropin levels among current compared with former smokers. A prospective study\(^8\) found a decreasing risk of Graves hyperthyroidism related to time since smoking cessation. Nonetheless, our findings related to smoking cessation should be further tested in prospective studies.

In conclusion, we found that among people without previously known thyroid disease, smoking is associated with lower concentrations of thyrotropin, a lower prevalence of hypothyroidism, and a higher prevalence of hyperthyroidism. Our findings indicate that smoking tobacco influences thyroid function, that smoking is related to the risk of developing both hypothyroid and hyperthyroid disease, and that the thyroid effects of smoking may be reversible. The lower prevalence of overt hypothyroidism among current smokers has not previously been reported.

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Author Contributions: Dr Åsvold had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Åsvold, Bjørno, and Vatten. Acquisition of data: Bjørno and Vatten. Analysis and interpretation of data: Åsvold, Bjørno, Nilsen, and Vatten. Drafting of the manuscript: Åsvold and Vatten. Critical revision of the manuscript for important intellectual content: Bjørno, Nilsen, and Vatten. Statistical analysis: Nilsen and Vatten. Obtained funding: Bjørno. Study supervision: Bjørno, Nilsen, and Vatten.

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REFERENCES