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CLINICAL STUDY

Smoking and thyroid disorders – a meta-analysis

Peter Vestergaard

The Osteoporosis Clinic, Aarhus Amtssygehus, Aarhus University Hospital, Tage Hansens Gade 2, DK-8000 Aarhus C, Denmark

(Correspondence should be addressed to Peter Vestergaard; Email: p-vest@post4.tele.dk)

Abstract

Background: Smoking has been associated with Graves' disease, but it remains unclear if the association is present in other thyroid disorders.
Outcome variables: Graves' disease, Graves' ophthalmopathy, toxic nodular goitre, non-toxic goitre, post-partum thyroid disease, Hashimoto's thyroiditis, or hypothyroidism.
Material and methods: A search of MEDLINE identified 25 studies on the association between smoking and thyroid diseases.
Results: In Graves' disease eight studies were available showing an odds ratio (OR) of 3.30 (95% confidence interval (CI): 2.09–5.22) in current smokers compared with never smokers. In ex-smokers there was no significant excess risk of Graves' disease (OR = 1.41, 95% CI: 0.77–2.58). The OR associated with ever smoking in Graves' ophthalmopathy (4.40, 95% CI: 2.88–6.73, six studies) was significantly higher than in Graves' disease (1.90, 95% CI: 1.42–2.55, two-sided *P*-value < 0.01). Ever smoking was not associated with toxic nodular goitre (OR = 1.27, 95% CI: 0.69–2.33, three studies), while there was an increased risk of non-toxic goitre in smokers if men were excluded (OR = 1.29, 95% CI: 1.01–1.65, eight studies). The risk associated with smoking was significantly lower in men than in women for both Graves' disease and non-toxic goitre. Hashimoto's thyroiditis and post-partum thyroid dysfunction were also associated with smoking while the association with hypothyroidism did not reach statistical significance.
Conclusions: Cessation of smoking seems associated with a lower risk of Graves' disease than current smoking. Smoking increases the risk of Graves' ophthalmopathy beyond the risk associated with Graves' disease alone. Smoking cessation may lead to a decrease in morbidity from Graves' disease, especially in women.

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Introduction

Previous studies have associated smoking with Graves' disease (GD) (1–8) and with Graves' ophthalmopathy (GO – also termed endocrine ophthalmopathy) (1, 4–7, 9–15), whereas the studies on the association between smoking and other forms of thyroid disease are limited. As smoking is frequent in some countries (16) even a limited association between smoking and thyroid diseases may have a significant impact on the occurrence of, for example, GD.

However, there are several unanswered questions: (1) Does cessation of smoking reduce the risk of GD and GO (17), i.e. is the potential damage attributed to smoking a permanent organ damage which would mean an equal increase in risk in current and previous smokers, or is the risk linked to a partly or totally reversible acute toxic effect of the tobacco? (2) Is GO more severe in smokers than in non-smokers? (3) Are other types of thyroid disorders (toxic nodular goitre (TNG), non-toxic goitre (NTG), autoimmune hypothyroidism (AIH), Hashimoto's thyroiditis (HT), and post-partum thyroid dysfunction (PPTD)) linked to smoking?

In GD, hyperthyroidism is linked to immunological factors whereas this is not the case in TNG (18). If smoking was linked to GD but not TNG, it would suggest that smoking only modulates immunological processes. On the other hand, it has been shown that thyroid volume increases in smokers (19, 20), and this could suggest a link to NTG and eventually both TNG and GD. If smoking modulates immunological processes in the thyroid, smoking could potentially also be linked to AIH and HT. As PPTD contains features of several of the thyroid disorders mentioned, smoking may also be involved in this disorder.

To answer the questions raised above, a meta-analysis was performed assessing the relationship

between smoking habits and different thyroid disorders.

Materials and methods

MEDLINE was searched on 14 August 2001 using the MESH words 'smoking', 'hyperthyroidism', 'hypothyroidism', 'Graves', 'thyrotoxicosis', 'post partum thyroid dysfunction', and 'Hashimoto', which yielded 273 references. The reference lists of these papers were then screened for further studies. The Cochrane library was also screened using the same MESH terms, but no studies were identified.

Studies were included in the meta-analysis if they reported clinical data on the association between smoking as the exposure variable and any of the thyroid disorders mentioned as outcome variable. Studies were included irrespective of design. This was done as only few studies were available. It was tested if certain designs (e.g. case control designs) gave rise to different risk estimates than others, but this did not seem to be the case. No difference in risk estimates could be shown between prospective studies and other types of studies, but the number of studies was limited.

The association was expressed as an odds ratio (OR), and this was re-calculated for all studies by the method of Miettinen (21) using the figures given in the papers as the risk estimates presented in the papers had been calculated using different risk estimates and different methods for calculating 95% confidence intervals (95% CI). Furthermore, some studies had adjusted the presented risk estimates for age and gender, making a direct comparison of crude risk estimates uncertain.

Calculated ORs for different subgroups were compared using Poisson regression (22).

Smoking status was subdivided into (1) current smokers, i.e. subjects who smoked at the time of the study, (2) ever smokers, i.e. subjects who were either current smokers or who had stopped smoking at the time of the study, and (3) previous smokers, i.e. subjects who had previously smoked but had stopped at the time of the study.

Age and gender distribution were also extracted as potential confounders. The iodine status of the population was assessed from the region where the study was performed (23).

Funnel plots were used to evaluate possible publication bias. $2P$ denotes two-sided P-values.

Results

From the 273 original studies and the reference lists of these, 25 studies with clinical data were retrieved (Tables 1–6). Most of the studies presented data that were either exclusively or predominantly on women.

Previous smokers did not have an increased risk of GD compared with normal controls (Table 1). The OR for current smoking was borderline significantly higher than the estimate for previous smokers ($2P = 0.047$ by Poisson regression).

The risk estimates all displayed heterogeneity (Table 1). Two studies allowed a comparison of males (pooled OR = 0.76, 95% CI: 0.27–2.16) and females (pooled OR = 2.82, 95% CI: 1.18–6.73), finding a borderline significantly higher risk among the latter ($P = 0.03$ by univariate Poisson regression). Limiting the analysis to women increased the OR for ever smoking to 2.62 (95% CI: 2.01–3.38).

Only one study addressed the question of dose–response (8), reporting an increasing risk of hyperthyroidism with increasing numbers of cigarettes smoked per day in current smokers (OR = 5.1 for 21–40 cigarettes per day vs never smokers, and OR = 3.7 for 1–10 cigarettes per day, $P < 0.01$ with test for trend).

Table 2 shows data for patients with GO compared with normal controls. The risk estimate was heterogeneous due to differences in severity of eye disease. In the two studies where the patients were subdivided according to severity of eye disease (9, 10), smokers had a much higher risk of the more advanced stages of eye disease than non-smokers ($2P < 0.05$ by Poisson regression in both cases). In ever smokers the risk estimate of GO was significantly higher than the risk estimate associated with GD, $2P < 0.01$ by Poisson regression.

One study allowed comparison of GO in females and males (4), reporting a significantly lower risk among the latter ($2P = 0.03$ by Poisson regression).

Table 3 shows the risk of GO among patients with GD in smokers compared with non-smokers. Despite the heterogeneity in study designs, the risk estimates were homogeneous, with no difference between current and ever smokers. The estimate for ever smokers (2.53, 95% CI: 1.70–3.77) was close to the ratio (4.28/1.90 = 2.25) in risk estimates from Tables 1 and 2.

Two studies reported a dose–response relationship between number of cigarettes smoked in current smokers and risk of hyperthyroidism (13, 15).

Tellez *et al.* (15) found a higher risk of GO in Europeans compared with Asians after adjustment for smoking (OR = 6.4, 95% CI: 1.8–22.7); however, the OR for GO associated with smoking could not be shown to differ significantly in Europeans (2.2, 95% CI: 1.0–4.7) and Asians (8.3, 95% CI: 0.9–78.7; $2P = 0.27$).

Table 4 shows a trend towards an increased risk of NTG in smokers, especially if males were excluded from the analysis. Two studies allowed comparison of male and female ever smokers (2, 4): males tended to have a reduced risk (pooled OR = 0.45, 95% CI: 0.19–1.08) in contrast to females (pooled OR = 1.35, 95% CI: 1.02–1.80), and this difference was statistically significant ($2P = 0.02$ by Poisson regression).

Table 1 Meta-analysis of studies on the risk of Graves' disease associated with smoking (patients compared to controls).

Group	Study type	*n* (cases/controls)	Smoking	Definition of smoking	Smokers (%) (cases/controls)	Age (years)	Women (%)	Time since diagnosis	OR (95% CI)	Ref.
GD without GO	CC	167/486	Ever	Current+previous (<3% previous)	48/28	45.4	100	Most <1 year	2.39 (1.67–3.42)	1
GD	CC	101/1600	Current	Current/never	44/26	45–65	100	1–5 years	3.10 (1.96–4.90)	3
			Ever	Ever/never	70/45				2.89 (1.90–4.41)	
GD without GO	CC	96/400 (F)	Ever	Current or ceased within 5 years	2/1 (F)	40.65	89	N/A	1.68 (0.33–8.66) (F)	4
		12/400 (M)			50/57 (M)	45.92			0.76 (0.24–2.40) (M)	
GD without GO	CC	100/200	Ever	Current or ceased within 5 years	56/41	40	84	Median 2.5 (range 0.2–10) years	1.83 (1.13–2.97)	5
GD	CC	62/81	Current	Current/never	27/14	56	N/A	3–13 years	2.46 (1.01–6.00)	6
			Ever	Ever/never	56/47				1.47 (0.75–2.86)	
GD	CC	208/372	Current	Current/never	41/30	47	83	Newly diagnosed	4.53 (2.80–7.31)	7
			Ever	Ever/never	51/42				1.44 (1.02–2.02)	
GD	CC	182/163	Current	Current/not current	34/18	37.4	100	Newly diagnosed	2.39 (1.45–3.93)	8
GD	Cr	21/2079 (F)	Current	Never: never or total duration <6 month	79/43 (F)	42 and 55 years	51	Prevalence at study base	4.97 (1.83–13.51)	2
			Ever		81/55 (F)				3.46 (1.24–9.66)	
		3/1997 (M)	Current		67/60 (M)				1.34 (0.12–14.71)	
			Ever		67/72 (M)				0.78 (0.07–8.54)	

Smoking*	Common OR†	*P*‡
Current	3.30 (2.09–5.22)	0.01
Ever	1.90 (1.42–2.55)	0.04
Previous	1.41 (0.77–2.58)	0.05

CC: case-control; Cr: cross-sectional; GD, Graves' disease (may include patients with GO); GO: GD with endocrine ophthalmopathy; M: male; F; female; N/A: not available.
* Compared with never smokers.
† DerSimonian and Laird Estimator.
‡ Test for heterogeneity.

Table 2 Meta-analysis of studies on the risk of Graves opthalmopathy associated with smoking (patients compared to normal controls).

Group	Study type	*n* (cases/controls)	Smoking	Definition of smoking	Smokers (%) (cases/controls)	Age (years)	Women (%)	Time since diagnosis	OR (95% CI)	Ref.
Severe GO (Werner ≥3)	CC	12/42	Ever	Current or smoked within last year	83/31	38	83	3–15 years	11.15 (2.55–48.72)	9
Less severe GO (Werner 0–2)		24/42			46/31				1.89 (0.67–5.33)	
GO (Ophthalmopathy index)	CC	307/486	Ever	Current+previous (<3% previous)	64/28	46.2	100	Most <1 year	4.66 (3.46–6.27)	1
GO (NO SPECS[c] ≥1)	CC	92/400 (F)	Ever	Current or ceased within 5 years	8/1 (F)	36.62	89	N/A	8.15 (2.81–23.64) (F)	4
		24/400 (M)			71/58 (M)	47.29			1.76 (0.72–4.30) (M)	
Type I GO[a]	CC	65/65	Ever	Current or ceased ≤2 years	63/30	36.1	86	0–7 years	1.96 (0.96–4.02)	10
Type II GO[b]		59/59			83/27	52.0	64		13.52 (5.88–31.07)	
GO (NO SPECS[c] ≥2)	CC	100/200	Ever	Current or ceased within 5 years	81/38	46.4	84	Median 2.5 (range 0.1–10) years	7.11 (4.13–12.21)	5
GO (Van Dyk classification)	CC	85/81	Current	Current	62/14	68	N/A	3–13 years	10.54 (5.14–21.60)	6
			Ever	Ever	74/45				3.24 (1.70–6.17)	
								Smoking	Common OR*	*P*†
								Ever	4.40 (2.88–6.73)	<0.01
								Ever	4.87 (3.16–7.52)‡	<0.01

CC: case-control; GD: Graves disease (may include patients with GO); GO: GD with endocrine ophthalmopathy; M: male; F: female; N/A: not available.
* DerSimonian and Laird Estimator.
† Test for heterogeneity.
‡ Excluding males.
[a] No diplopia in functional field of gaze and essentially normal ductions and versions, [b] diplopia in the primary position or within 20° of primary position secondary to extraocular muscle restriction, [c] eye impairment scored by the American Thyroid Association NO SPECS system.

Table 3 Meta-analysis of the risk of Graves' opthalmopathy associated with smoking among patients with Graves disease (comparison of patients with and without ophthalmopathy).

Group	Study type	*n* (GO/no GO)	Smoking	Definition of smoking	Smokers (%) (cases/controls)	Age (years)	Women (%)	Time since diagnosis	OR (95% CI)	Ref.
GO/GD	Cr	38/45	Yes/no	Yes/no	97/22	N/A	N/A	N/A	63.00 (18.35–216.35)	11
Progression of GO after RAI	RCT+C	All had GO	Ever	Current or ceased <1 year	83/55	N/A	N/A	–	3.86 (1.37–10.91)	12
Severe GO (Werner ≥3) vs Less severe GO (Werner 0–2)	Cr	12/24	Ever	Current or smoked within last year	83/38	38	83	3–15 years	8.33 (1.64–42.24)	9
Follow-up[a]	C	135/93	Current	Current/never	44/32	36.8	50	<0.5 year	2.02 (1.17–3.46)	13
			Ever	Ever/never	58/41				1.94 (1.17–3.23)	
Development of GO after treatment[b]	C	22/125	Ever	Current or ceased <1 year	59/46	25–55	83	Newly diagnosed	1.72 (0.69–4.31)	14
GO/no GO	Cr	52/103	Current	Current/never	44/28	42.7	73	Newly diagnosed	3.17 (1.46–6.88)	15
		52/103	Ever	Ever/never	71/42				3.44 (1.70–6.95)	
GO/no GO	Cr	62/142	Current	Current/never	48/38	46.1	82	Newly diagnosed	1.88 (0.99–3.58)	7
		62/142	Ever	Ever/never	63/45				2.07 (1.12–3.80)	
								Smoking	Common OR*	*P*†
								Current	2.18 (1.51–3.14)	0.54
								Ever	2.53 (1.70–3.77)	0.17

C: cohort study; Cr: cross sectional; RCT: randomised controlled study; GD: Graves disease (may include patients with GO); GO: Graves' disease with endocrine ophthalmopathy; N/A: not available.
* DerSimonian and Laird Estimator.
† Test for heterogeneity.
[a] Excluding patients with only lid retraction or lid lag, [b] excluding patients with GO at baseline.

Table 4 Meta-analysis of the risk of non-toxic goiter (NTG – diffuse or nodular) associated with smoking.

Group	Study type	Cases/controls	Smoking	Definition of smoking	Smokers (%) (cases/controls)	Age (years)	Women (%)	Time since diagnosis	OR (95% CI)	Ref.
NTG	CC	405/486	Ever	Current+previous (<3% previous)	30/28	37.2	100	Most <1 year	1.13 (0.85–1.52)	1
NTG	CC	114/400 (F)	Ever	Current or ceased within 5 years	6/1 (F)	46.31	91	N/A	6.48 (2.17–19.37) (F)	4
		11/400 (M)			38/60 (M)	51.45			0.25 (0.07–0.86) (M)	
NTG	CC	100/200	Ever	Current or ceased within 5 years	45/40	48	82	Median 5.2 (range 0.1–10) years	1.23 (0.76–1.99)	5
NTG	CC	238/166	Current	Current	13/16	45.3	100	N/A	0.74 (0.42–1.30)	25
			Ever	Ever	16/21				0.71 (0.43–1.18)	
NTG	Cr	186/1470 (F)	Current	Current	55/42 (F)	42 or 55 years	51	Prevalence	1.68 (1.24–2.28) (F)	2
		8/1388 (M)			50/60 (M)				0.67 (0.17–2.66) (M)	
		217/1883 (F)	Ever	Ever	61/55 (F)				1.31 (0.98–1.75) (F)	
		12/1988 (M)			67/72 (M)				0.78 (0.23–2.58) (M)	
NTG – PG	Cr	113/712	Current	Smoker/non-smoker	32/31	50–72	100	Prevalence	1.04 (0.68–1.59)	31
NTG – PG	Cr	43/318	Current	Current	58/45	48–53	100	Prevalence	1.68 (0.88–3.19)	32
		46/395	Ever	Ever	61/56				1.22 (0.66–2.29)	
NTG – CG	Cr	35/184	Current	Current >15 cigaretes/day or no smoking within last 5 years	91/41	18–77	51	Prevalence	15.50 (5.82–41.29)	28
								Smoking	CommonOR*	*P*†
								Ever	1.22 (0.96–1.55)	<0.01
								Ever	1.29 (1.01–1.65)‡	<0.01

CC: Case-control study; Cr: Cross-sectional study; CG: Clinical goiter; NTG: non-toxic goiter; PG: palpable goiter; M: male; F: female; N/A: not available.
* DerSimonian and Laird Estimator.
† Test for heterogeneity.
‡ Excluding males and the study by Hegedüs *et al.* (28).

Table 5 Meta-analysis of the risk of toxic nodular goiter (TNG) associated with smoking.

Group	Study type	Cases/controls	Smoking	Definition of smoking	Smokers (%) (cases/controls)	Age (years)	Women (%)	Time since diagnosis	OR (95% CI)	Ref.
TNG	CC	165/486	Ever	Current+previous (<3% previous)	24/28	55.7	100	Most <1 year	0.80 (0.53–1.21)	1
TNG	CC	28/1600	Current	Current	32/26	45–65	100	1–5 years	1.35 (0.61–3.00)	3
			Ever	Ever	61/45				1.89 (0.89–4.01)	
TNG	CC	75/150	Ever	Current or ceased within 5 years	45/35	62.4	85	Median 3.5 (range 0.1–10) years	1.56 (0.89–2.75)	5
								Smoking	Common OR*	*P*†
								Ever	1.27 (0.69–2.33)	0.03

CC: Case-control study.
* DerSimonian and Laird Estimator.
† Test for heterogeneity.

Table 6 Meta-analysis of the risk of other thyroid diseases (post-partum thyroid, dysfunction, Hashimoto's thyroiditis and hypothyroidism) assoicated with smoking.

Group	Study type	Cases/controls	Smoking	Definition of smoking	Smokers (%) (cases/controls)	Age (years)	Women (%)	Time since diagnosis	OR (95% CI)	Ref.
PPTD – CD	C	15/276 (9T, 5 HY, 1 T+HY)	Ever	Continued or stopped smoking in pregnancy	N/A	N/A	100	New cases	3.6 (1.2–11)	26
PPTD – LAB[a]	C	46/167 (21 T, 17 HY, 11 T+HY)	Current	Current	48/37	25.3	100	New cases	1.55 (0.80–3.00)	33
PPTD – LAB	C	12/30[b] (7 T)	Current	Regular cigarette smokers	33/23	30	100	New cases	1.64 (0.37–7.21)	34
PPTD – LAB	C	14/260 (14 T)	Yes/No	Smoking yes/no	43/24	25.8	100	New cases	2.35 (0.80–6.84)	35
								Smoking	Common OR*	*P*†
								All studies	1.97 (1.23–3.17)	0.59
HT	CC	200/486	Ever	Current+previous (<3% previous)	34/28	47.5	100	Most <1 year	1.31 (0.92–1.87)	1
HT	CC	387/166	Current	Current	28/16	50.5	100	N/A	2.04 (1.29–3.25)	25
			Ever	Ever	34/21				1.92 (1.25–2.93)	
								Smoking	Common OR*	*P*†
								Ever	1.56 (1.07–2.28)	0.17
CH	CC	51/138	Current	Current	27/21	57.2	100	N/A	1.42 (0.68–2.98)	36
SH		84/138			23/21	51.5			1.10 (0.57–2.12)	
HY	C	1309	Current	Current	44	38–60	100	New cases	3.56 (1.57–8.09)	37
AIH	CC	75/150	Ever	Current or ceased within 5 years	43/35	49.3	93	Median 4 (0.2–10) years	1.36 (0.77–2.40)	5
								Smoking	Common OR*	*P*†
								Current	1.71 (0.87–3.39)	0.08
								All studies	1.58 (0.99–2.51)	0.14

PPTD: Post-partum thyroid dysfunction (CD: clinical dysfunction; LAB: diagnosis based on laboratory measurements of thyroid hormones; T: hyperthyroidism; HY: hypothyroidism; T+HY: alternating T and HY); HT: Hashimoto's thyroiditis; CH: clinical hypothyroidism; SH: subclinical hypothyroidism; AIH: autoimmune hypothyroidism; CC: case-control; C: cohort study (follow-up); N/A, not available.
* DerSimonian and Laird Estimator.
† Test for heterogeneity.
[a] Cohort: 100 with thyroid antibodies, 120 without as controls; [b]all thyroid autoantibody positive.

If the estimate in women with NTG for ever smoking was compared with the corresponding estimate in GD, a significant difference was present ($2P < 0.01$ by Poisson regression).

In NTG, smokers had a trend towards more solid goitres and a higher prevalence of nodular versus diffuse non-toxic goitre (24).

Table 5 shows an insignificant trend towards a higher risk of TNG in smokers compared with non-smokers.

Table 6 summarises studies in patients with HT, PPTD and hypothyroidism. There were only few and heterogeneous studies for each category. Smoking attained statistical significance as a risk factor for PPTD and HT. Although there was a trend, it did not attain statistical significance for hypothyroidism.

In the two studies on HT, the diagnosis was based on clinical history, thyroid hormones, thyroid microsomal autoantibody determination, and thyroid ultrasound and/or scan.

Limiting the analysis of PPTD to the three studies with a laboratory definition changed the estimate to 1.73 (95% CI: 1.02–2.91), and this estimate was non-significantly lower than the estimate presented by Kuijpens *et al.* (26) based on clinical disease ($2P = 0.24$ by Poisson regression).

Publication bias did not seem to have influenced the results as estimated from funnel plots. Age did not influence risk estimates (Table 1–6).

Discussion

The risk of GO was significantly higher than the risk of GD, and in patients with GD smoking further increased the risk of GO (multiplicative relationship), which may suggest that other mechanisms may be involved in the pathogenesis of GO besides those leading to GD.

Upon cessation of smoking, the risk of GD seemed to return to the same level as in never smokers. In GO it was not possible to estimate the effects of smoking cessation.

The heterogeneity of risk estimates with smoking in GD (Table 1) was probably linked to heterogeneity in smoking patterns (amounts smoked per day in current smokers, duration of smoking, time since smoking cessation, total amounts smoked throughout life).

The higher risk of NTG in female smokers is in accordance with studies reporting higher thyroid volume in smokers than in non-smokers (27–29). The heterogeneity of the common OR in NTG was probably due to differences in smoking patterns and different definitions of goitre (diffuse or nodular–palpable, visible, etc.).

In TNG, no significant relationship with smoking was present, but the number of studies was limited.

The risk of both GD and NTG was lower in men than women, perhaps related to the fact that differences in autoantibody formation has been reported between male and female smokers (30).

The prevalence of PPTD differed between studies depending on the disease definition, and the prevalence of autoantibodies in the population, making the confidence interval wide in some cases.

The association with smoking was present both in study groups with a low smoking frequency (4) and in study groups with a high smoking frequency (5).

The relationship between smoking and GD was homogeneous across studies performed in iodine-replete (4, 5) and iodine-deficient regions (1). This could indicate that smoking acts independently of iodine status.

It should be noted that all studies, except the study by Tellez *et al.* (15), were performed in Caucasians. Despite reporting a higher OR of GO in Europeans compared with Asians after adjustment, the OR associated with smoking itself could not be shown to be different in the study by Tellez *et al.* (15). This apparent paradox could perhaps be linked to other differences besides smoking and iodine intake, such as differences in human leucocyte antigen (HLA) haplotypes (11) between ethnic groups.

It should be emphasised that several of the study groups were small and heterogeneous, and further studies are thus needed.

In conclusion, cessation of smoking was associated with a lower risk of GD than current smoking. Men seemed to be protected from the detrimental effects of smoking in GD and NTG.

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