

Cigarette smoking and thyroid eye disease: a systematic review

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REVIEW

Abstract

Purpose To evaluate the epidemiological evidence for a causal association between tobacco smoking and thyroid eye disease (TED).

Methods Systematic review, including quality assessment, of published epidemiological studies and evaluation of the evidence using established causality criteria.

Results Fourteen papers describing 15 studies were included. There was a positive association between smoking and TED in four case-control studies when compared with control patients with Graves' disease but no ophthalmopathy (odds ratio (OR) 1.94–10.1) and in seven case-control studies in which control subjects did not have thyroid disease (OR 1.22–20.2). Two cohort studies examined the occurrence of new cases of TED; one study found an increased incidence of TED with smoking. Four cohort studies investigated progression or outcome of treatment in patients with established TED, three finding an association between smoking and poorer outcome. The quality of the studies was variable, but the association with smoking was strong in the most methodologically rigorous studies. Other evidence supporting a causal link was a consistent association across studies, a dose-response effect, a reduced risk of TED in ex-smokers, and a temporal relationship.

Conclusion This systematic review provided strong evidence for a causal association between smoking and development of TED. Current-smokers were also more likely to experience disease progression or poorer outcome of treatment. Patients with Graves' disease and the general public should be educated about the risk of smoking and TED. These findings suggest that patients with Graves' disease or TED who are smokers

should be given effective support to stop smoking.

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Introduction

Thyroid eye disease (TED), also known as Graves' ophthalmopathy or thyroid-associated ophthalmopathy, is the most frequent extrathyroidal manifestation of autoimmune hyperthyroidism (Graves' disease); 25–50% of patients with Graves' disease have eye involvement, of whom 3–5% develop severe disease.^{1,2} The aetiology of TED is complex. Genetic susceptibility and endogenous and environmental factors play a role in its development.^{2–4} The genetic factors are poorly defined but appear to have the lesser role.² The risk of developing TED increases with age and women are more likely to develop Graves' disease than men.⁴

An association of tobacco smoking with TED was first described in 1987⁵ and the evidence to support a causal link is growing.⁶ Three recent reviews concluded there is a causal association.^{7–9} However, none of these previous reviews included non-English language papers or an appraisal of the quality of the included studies and two did not state the methods for the literature search and identification of studies.^{7,8} Therefore, we aimed to expand on this previous work and undertake a systematic review of the evidence, including a rigorous quality assessment of studies and application of standard criteria for causality, to robustly assess the relationship between smoking and TED.

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Materials and methods

Identification of studies

MEDLINE (on Ovid from 1966) and EMBASE (on Ovid from 1980) were searched as well as ISI Web of Science (from 1990). Keywords and MESH terms for 'randomised controlled trials' or 'observational studies' were combined with 'tobacco smoking' and 'thyroid eye disease' or its similes. The final list of titles and abstracts was screened by two reviewers (JT and RE) and full publications obtained where articles were thought to be potentially relevant. Bibliographies of included studies and review papers were screened to identify other relevant studies. The main searches were run in September 2003 and March 2005 and updated in October 2005.

Inclusion and exclusion criteria

Analytical observational epidemiological studies (case-control and cohort studies) and intervention studies with comparison groups were included if they had measurements of tobacco-smoking status, and reported the association between smoking and the development, progression, or treatment outcomes of TED after appropriate statistical analysis. We excluded cross-sectional studies as they are less appropriate for assessing evidence of association where the temporal relationship between exposure and outcome and direction of causality is uncertain.¹⁰ We excluded conference abstracts as they contain insufficient detail. Non-English language papers were translated as necessary.

Quality assessment and data extraction

We did not use an established quality assessment tool. A previous review of quality assessment tools for non-randomised studies found that none addressed all the key dimensions of quality.¹¹ We investigated a range of possible tools for observational epidemiological studies, but found none which addressed all the key areas of the design and conduct of studies, nor included detailed and specific enough criteria and scoring systems to assess the quality of studies investigating the link between smoking and TED. For example, we considered that precise detailed criteria were essential for evaluating key quality dimensions such as the adequacy of the process of identifying and defining cases or progression of disease, and of smoking exposure status assessment. We therefore developed separate case-control and cohort study appraisal tools adapted initially from existing instruments.¹²⁻¹⁵ We further refined these tools through a process of discussion and review within our team,

which was carrying out a series of systematic reviews of the link between smoking and eye disease. This team had relevant epidemiology and ophthalmology expertise.

The resulting review tools (available on request) aimed to assess all the key dimensions of quality graded generally as 'fully', 'partially', or 'not' met. The tools included detailed descriptions of the methodological quality criteria required for a study to 'fully' or 'partially' meet each quality criteria. There were 12 quality criteria for case-control studies and 14 for cohort studies (Table 1). Five of these criteria (marked in bold in Table 1) were classed as 'key criteria' based on discussions within the team and review of standard epidemiological texts to identify critical potential areas of weakness of each design.

Two authors (JT and RE) independently reviewed the identified papers, extracted the data, and completed the quality assessment. Results were compared and discrepancies discussed with adjudication by the third reviewer (SPK) if required. We set *a priori* eligibility criteria to determine if studies were eligible for inclusion in a meta-analysis. Studies that included suitable data and at least partially met all five key quality criteria were eligible. Meta-analysis was not possible because only one study¹⁶ was of adequate quality. Findings were summarised using tables and narrative synthesis.

Results

Literature search

We identified 181 papers from the literature databases and five additional papers from screening bibliographies. After initial screening, 44 potential studies were identified, but 26 of these studies did not meet the inclusion criteria. We excluded a further four studies during the quality review process because measures of association between smoking and TED were not presented and there was insufficient data provided for them to be calculated by the reviewers.¹⁷⁻²⁰ One of the included papers described two separate cohort studies.²¹ Therefore, the review included 14 papers describing 15 studies (nine case-control and six cohort).

Description of included studies

Eleven studies were conducted in Europe,^{5,16,21-28} two in the US,^{29,30} and one each in Taiwan³¹ and Japan.³² Most included more female than male subjects. Ages of subjects ranged from around 20 years to around 80 years. Seven papers did not present odds ratios (ORs) and unadjusted ORs were calculated by reviewers (RE/RH) from data in the papers.^{21,22,24-27,29} In addition, the 95% confidence intervals (CIs) were calculated for one study.³²

Table 1 Quality criteria for assessment of case-control and cohort studies included in the review: key quality criteria are marked in bold

Case-control studies	Cohort studies
Degree to which study base and time period described	Degree to which study base and time period described
Representativeness of controls of the study base	Representativeness and comparability of the cohort(s)
Adequacy of process for identification and definition of cases or progression/response to treatment	Adequacy of process for identification and definition of cases or progression/response to treatment
Representativeness of cases eligible for inclusion	Equivalence of case ascertainment procedures for exposure groups
Adequacy of response rates	Adequacy of response rates
Adequacy of data collection methods	Adequacy of data collection methods
Adequacy of data on smoking history	Adequacy of data on smoking history
Equivalence of data collection methods in cases and controls	Adequacy of allocation into exposure groups by smoking status
Adequacy of main analysis methods	Equality of follow-up between exposure groups
Adequacy of exposure variables used in analysis.	Adequacy of length of follow-up period
Adequacy of dealing with potential confounders through design or analysis	Adequacy of main analysis methods
	Adequacy of exposure variables used in analysis.
	Adequacy of dealing with potential confounders through design or analysis

Two studies presented *P*-values from another acceptable method of analysis of association, Kaplan-Meier life-table analysis.^{28,30}

Eight of the case-control studies (Table 2) recruited patients with prevalent TED. One case-control study recruited incident cases.²⁴ Incident cases are preferred because with prevalent cases smoking status or recall of smoking status may change after development of TED.

In the case-control studies, two main comparisons were used: comparing smoking status or history between TED cases and non-Graves' disease controls (eight studies), and between TED cases and patients with Graves' disease but no TED (five studies). Several studies included both types of comparison by using more than one control group. The comparison of smoking in TED cases and patients with Graves' disease but without TED is much more informative as it provides specific evidence of whether smoking is associated with the development of TED in patients with Graves' disease. Comparisons of smoking between TED cases and non-Graves' disease controls are more difficult to interpret as a positive association could imply a relationship of smoking with the development of Graves' disease or TED or both. The studies which recruited controls without Graves' disease did so from either the community^{24,29,31} or from hospital clinics^{22,23,25,32} or from both.⁵ The studies which used Graves' disease controls recruited controls from hospital clinics.^{5,22,24-26}

Four prospective and two retrospective cohort studies investigated the incidence, progression, or treatment outcomes by smoking status among cohorts of patients with Graves' disease (Table 3). One study assessed the incidence of TED in patients with Graves' disease of recent onset.¹⁶ Another reported both the incidence of

TED and progression of existing TED.²⁷ Four studies examined progression and response to treatment of TED by smoking status.^{21,27,28,30}

Quality assessment

The quality of the included studies varied and was often poor. None of the case-control studies met all five key quality criteria. Of the five case-control studies which used controls with Graves' disease without TED, one fully or partially met all of the key quality criteria except, the method of analysis;²² three studies fully or partially met three criteria²⁴⁻²⁶ and one met only two criteria.⁵ Of the other four case-control studies which only used controls without Graves' disease, one fully or partially met four key criteria and also at least partially met 11 out of 12 of all the quality criteria.²³

Across all nine case-control studies, the smoking variable used in the analysis was adequate in only one study.²² The main problem was that smoking status was very crudely and inadequately categorised with ex-smokers combined with current-smokers, or split between current- and non-smokers according to when quitting occurred. If there is an association of TED with smoking that is attenuated by quitting smoking, these approaches will tend to reduce the size of the observed association between TED and smoking.

Only two studies fully met the criterion for the quality of the analysis.^{5,31} All but one of the studies at least partially met the criterion for case identification and definition, although none fully met this criterion because all but one study used prevalent rather than incident cases and only four studies reported use of a standard classification system for TED.^{5,23,31,32} All seven of the

Table 2 Thyroid eye disease and smoking: summary of case-control studies

Study	Study population, location	Case characteristics	Control characteristics	Exposure measurement, assessment smoking status	Analysis variables	Confounders addressed through design or analysis	Association of smoking with thyroid eye disease
Hagg and Asplund ⁵	<i>Cases:</i> University Hospital, Sweden <i>Controls:</i> 1. Community (population register), Sweden 2. Hospital clinic, Sweden	Prevalent 12 endocrine ophthalmopathy (≥ 3 Werner's classification), 2 M 10 F, mean age onset ophthalmopathy 38 (range 24–51) years	1. Forty-two community controls (no thyroid disorder) 2. Twenty-four subjects with GD but slight or no eye disease, matched for age and sex	Questionnaire Current smoking status and at onset of disease	Current-smokers (those who had smoked for some period during the past year) <i>vs</i> non-smokers. Current-smokers plus ex-smokers (those who had been smokers but had not smoked in the past year) <i>vs</i> never-smokers	Sex, age	Current-smokers <i>vs</i> non-smokers, TED cases and GD controls: adjusted OR 10.0 (95% CI 1.4–74.3) Current-smokers plus ex-smokers <i>vs</i> never-smokers, TED cases and GD controls: adjusted OR 4.5 (95% CI 0.8–24.5) Current-smokers <i>vs</i> non-smokers, TED cases and community controls: adjusted OR 20.2 (95% CI 2.8–144.8) Current-smokers plus ex-smokers <i>vs</i> never-smokers, TED cases and community controls: adjusted OR 8.9 (95% CI 1.3–60.2)
Shine <i>et al</i> ²²	<i>Cases:</i> Specialist Eye Hospital (London, UK) <i>Controls:</i> Specialist Eye Hospital (London, UK) and Teaching Hospital (Cambridge, UK)	Prevalent 85 severe TED (van Dyck classification), median age 68 (range 21–80) years	1. Sixty-two subjects with GD median age 56 (range 15–81) years 2. Eighty-one subjects with other thyroid disease or no thyroid disease, median age 61 (25–91) years	Questionnaire Lifelong smoking status	Current-smokers <i>vs</i> never-smokers (no definitions)	None	TED cases and GD controls: OR 3.78 (95% CI 1.63–9.05) (calc by reviewer) TED cases and GD plus other controls: OR 9.42 (95% CI 3.85–23.7 (calc by reviewer)
Prummel and Wiersinga ²³	<i>Cases:</i> Endocrinology Clinic, the Netherlands <i>Controls:</i> General Medicine Clinics, the Netherlands	Prevalent 100 TED with onset of disease within 10 years of study and no thyrotoxicosis, 16 M 84 F, mean age 46.4 \pm 12.8 years	Four hundred hospital and community controls 1. Patients visiting general ophthalmic outpatient clinic. 2. Individuals accompanying patients to endocrine clinic	Self-completion questionnaire Smoking status assessed at onset of disease	Smokers (current-smokers and those who had stopped within 5 years) <i>vs</i> non-smokers (non-smokers or ceased more than 5 years previously)	Sex, age	Adjusted OR 6.5 (95% CI 3.8–11.2)

Table 2 (Continued)

Study	Study population, location	Case characteristics	Control characteristics	Exposure measurement, assessment smoking status	Analysis variables	Confounders addressed through design or analysis	Association of smoking with thyroid eye disease
Winsa <i>et al</i> ²⁴	<i>Cases:</i> County hospitals, Sweden <i>Controls:</i> Community, Sweden	Incident 62 TED (grades I–IV), 13 M 49 F, mean age 44 ± 12 years	Three hundred and seventy-two healthy community controls; 142 GD and no ophthalmopathy	Self-completion questionnaire Time of smoking status assessment not stated	Ever-smokers (current and former smokers) <i>vs</i> non-smokers	Sex, age	Current-smokers <i>vs</i> non-smokers TED cases and GD no TED controls: OR 1.53 (95% CI 0.83–2.80) (calc by reviewer) Ever-smokers <i>vs</i> never-smokers, TED cases and GD no TED controls: OR 2.07 (95% CI 1.12–3.84) (calc by reviewer) Current-smokers <i>vs</i> non-smokers, TED cases and community controls: OR 2.20 (95% CI 1.28–3.80) (calc by reviewer) Ever-smokers <i>vs</i> never-smokers, TED cases and community controls: OR 2.35 (95% CI 1.35–4.09) (calc by reviewer)
Nunery <i>et al</i> ²⁹	<i>Cases:</i> University Eye Institute, US <i>Controls:</i> Community, US	Prevalent TED categorised as type I (no restrictive diplopia) or type II (restrictive diplopia present). Type I: 56 F 9 M, mean age 36 ± 12.5 years Type II: 38 F 21 M, mean age 52 ± 11.7 years	Community controls identified through random telephone number dialling. Age range 25–64 years	Questionnaire for cases, telephone interview for controls Smoking status assessed at onset for cases, current status for control	Current-smokers (within 2 years of onset) <i>vs</i> non-smokers	Sex, age	Type I TED cases and community controls: OR 3.91 (calc by reviewer) Type II TED cases and community controls: OR 13.5 (calc by reviewer)
O'Hare and Geoghegan ²⁵	<i>Cases:</i> Endocrinology Clinic, Ireland <i>Controls:</i> Orthopaedic and Trauma Clinic, Ireland	Prevalent 34 TED cases : 5 M 29 F, mean age 37 ± 16 years	Hospital: 168, 26 M 142 F with other thyroid diseases mean age 43 ± 17 years GD no TED controls: 34, 8 M 41 F, mean age 44 ± 16 years	Structured interview Lifelong assessment of smoking status	Ever-smokers <i>vs</i> never-smokers, smoker before onset disease <i>vs</i> never-smokers	Sex, age, thyrotoxicosis	TED cases and GD controls. Smoking at onset <i>vs</i> non-smokers: OR 1.40 (95% CI 0.5–4.03) (calc by reviewer) TED cases and non GD controls. Ever-smokers <i>vs</i> never-smokers: OR 2.29 (95% CI 1.03–5.08) (calc by reviewer)

Table 2 (Continued)

Study	Study population, location	Case characteristics	Control characteristics	Exposure measurement, assessment smoking status	Analysis variables	Confounders addressed through design or analysis	Association of smoking with thyroid eye disease
Bartalena <i>et al</i> ²⁶	<i>Cases:</i> Endocrinology Clinic, University Hospitals, Italy <i>Controls:</i> Endocrinology Clinics, Italy	Prevalent 307 TED cases, all F, mean age 46.2 (range 16–74) years	Hospital 167 GD without TED. All F. Mean age 45.4 (range 17–73) years, 486 F endocrine clinic attenders with no thyroid abnormality mean age 37.3 (range 15–77) years	Questionnaire Lifelong assessment of smoking status	Ever-smokers <i>vs</i> never-smokers	Sex, age	TED cases and non-GD controls. Smoking at onset <i>vs</i> never-smokers: OR 3.48 (95% CI 1.61–7.52) (calc by reviewer) TED cases and GD controls, OR 1.94 (95% CI 1.3–2.91) (calc by reviewer) TED cases and non GD hospital controls: OR 4.65 (95% CI 3.39–6.4) (calc by reviewer) TED cases and all controls: OR 4.22 (95% CI 3.17–5.66) (calc by reviewer)
Shiraishi <i>et al</i> ³²	<i>Cases:</i> Hospital Clinics, Japan <i>Controls:</i> Internal Medicine Department, Japan	Prevalent 102 TED cases, 18 M 84 F, mean age M 46.1 (range 17–77) years, mean age F 39.4 (range 17–77) years	Hospital controls (unspecified). 102, 18 M 84 F. Mean age M 46.1 (range 17–77) years, mean age F 39.5 (range 17–77) years	Clinical record, or if absent questionnaire Lifelong assessment of smoking status	Smoker/recent ex-smoker (<5 years before onset) <i>vs</i> never-smoker/long-term ex-smoker (>5 years before onset)	Sex, age	OR 1.22 (95% CI 0.66–2.26) (95% CI calc by reviewer)

GO = Graves' ophthalmopathy, GD = Graves' disease, TED = thyroid eye disease.

Table 3 Thyroid eye disease and smoking: summary of cohort studies

Study	Study population, location	Study type and follow-up period	Cohort characteristics	Outcomes assessed	Exposure measurement	Analysis variables	Confounders addressed through design or analysis	Association of smoking with thyroid eye disease
Tallstedt <i>et al</i> ²⁷	Hospital Clinics, Sweden	Prospective study of patients within GD clinical trial, >2 years follow-up	One hundred and seventy-one GD patients with and without TED from clinical trial Smokers: 89 total, 70 without TED at baseline. 18 M 71 F, age range 25–55 years Non-smokers: 82 total, 77 without TED at baseline. 11 M 71 F, age range 25–55 years	Incidence of new cases of TED and progression existing disease	Self-completion questionnaire Lifelong assessment of smoking status	Current-smokers (including ex-smokers <1 year) <i>vs</i> non-smokers (including ex-smokers >1 year)	Thyroid dysfunction	RR 1.59 (95% CI 0.72–3.49) (calc by reviewer)
Pfeilschifter and Ziegler ¹⁶	University Department of Endocrinology and Metabolism, Germany	Prospective ≥1 year follow-up	Two hundred and fifty-three patients with GD of recent onset. 212 F 41 M, mean age 36.8 ± 12.4 years. Smokers: 87 F 17, mean age 35.9 ± 10.8 years. Never-smokers: 107 F 17, mean age 36.8 ± 13.3 years Ex-smokers: 18 F 7 M 40.0 ± 13.7 years.	Incidence of new cases of TED: total ophthalmopathy, proptosis, diplopia	Questionnaire Lifelong assessment of smoking status	Current-smokers <i>vs</i> never-smokers, ex-smokers >20 cigs/day <i>vs</i> never smoker	Sex, age ethnicity, surgery/radiotherapy	Total ophthalmopathy: Current-smokers <i>vs</i> never-smokers: RR 1.32 (95% CI 1.06–1.64) <i>P</i> = 0.011 Proptosis: current-smokers <i>vs</i> never-smokers: RR 2.64 (95% CI 1.79–3.90) <i>P</i> < 0.0001 Diplopia: Current-smokers <i>vs</i> never-smokers: RR 3.14 (95% CI 1.65–5.98) <i>P</i> < 0.0001
Bartley <i>et al</i> ³⁰	Population-based, cohort from Rochester Epidemiology Project, Minnesota, USA	Retrospective, 14 years follow-up	One hundred and twenty TED patients, 17 M 103 F, mean age at diagnosis 44.7 ± 17.4 years.	Progression/treatment effect, surgery	Record review and follow-up questionnaire, time period of smoking assessment status not stated	Current-smokers <i>vs</i> non-smokers (not defined)	Sex, age, thyroid dysfunction, years since diagnosis	No significant difference in outcomes, after adjustment for confounders: <i>P</i> = 0.73
Bartalena <i>et al</i> ²¹	University Hospital Eye Centre, Italy	Prospective study nested in RCT of treatment for GD. Time period not stated	Three hundred patients undergoing radioiodine treatment for Graves' hyperthyroidism, mild or no ophthalmopathy.	Outcome of treatment: progression/improvement of known cases	Method of data collection not stated. Lifelong assessment of smoking status	Current-smokers plus ex-smokers <1 year <i>vs</i> nonsmokers plus ex-smokers >1 year	Radioiodine treatment	Increased progression following radioiodine treatment: RR 3.94 (95% CI 1.41–11.02) <i>P</i> = 0.003 (calc by reviewer) Decreased improvement with radioiodine and steroid treatment: RR 0.23 (95% CI 0.14–0.40) <i>P</i> < 0.001 (calc by reviewer)
		Retrospective cohort study of patients with severe TED. Time period not clear	Patients with severe TED treated with orbital radiation therapy and high-dose steroids, 110 F 40 M, mean age 41 (range 30–63) years	Response/nonresponse or progression (responder = good/excellent/moderate, nonresponder = no response or progression)	Method of data collection not stated. Lifelong assessment of smoking status	Current-smokers plus ex-smokers <1 year <i>vs</i> non-smokers plus ex-smokers >1 year	Radioiodine treatment	Reduced response to therapy: RR 0.73 (0.62–0.85) <i>P</i> = 0.001 (calc by reviewer)
Eckstein <i>et al</i> ²⁸	University Department of Ophthalmology, Germany	Prospective, 1 year follow-up of patients with TED	Sixty patients 41 smokers, 11 M 30 F, mean age 46 (range 18–70) years. 19 non-smokers, 4 M 15 F, mean age 47 (range 30–69) years.	Response to treatment, clinical activity score (CAS), motility, proptosis	Level of biomarker, N-2-hydroxyethylvaline (HEV)	Current-smokers <i>vs</i> non-smokers defined by HEV levels: current-smoker = HEV >2.9 µg/l, non-smoker = HEV <2.9 µg/l	Age, thyroid function, duration, and severity of thyroid eye disease	Less improvement in CAS at 12 months 53% of smokers and 74% non-smokers, <i>P</i> < 0.05 Less improvement in motility at 12 month 24% smokers and 60% non-smokers, <i>P</i> < 0.017 No significant difference in improvement in proptosis at 12 months, 9% smokers and 5% non-smokers, <i>P</i> = NS

GO = Graves' ophthalmopathy, GD = Graves' disease, TED = thyroid eye disease.

case-control studies where a quality assessment could be made, at least partially met the criterion for the appropriateness of the controls, although none fully met this criteria. The most common problem was the use of hospital/clinic controls that may have higher rates of smoking than in the true source population for the cases, potentially reducing the size of the observed association between smoking and TED.

Among the cohort studies, only one was considered to at least partially meet all five key criteria assessed.¹⁶ The other cohort studies only met two or three key quality criteria. The main analysis method was considered adequate in only two studies.^{16,28} The process of allocating subjects to distinct smoking categories was particularly poorly performed in the cohort studies. The strongest approach is to divide subjects into current-smokers, ex-smokers, and never-smokers, and compare current- and ex-smokers separately with never-smokers in the analysis. Only one study did this,¹⁶ whereas combining ex-smokers with smokers in a comparison of ever-smokers and never-smokers, or combining ex-smokers with non-smokers in a comparison of current-smokers and current non-smokers was common. Three studies categorised smokers who had stopped within 5 years of the study as current-smokers and those who had stopped more than 5 years previously as non-smokers.^{23,31,32} Three studies categorised patients who had stopped more than 1 year previously as non-smokers.^{21,27,29}

Imprecision in exposure assessment causing nondifferential misclassification is a frequent problem in epidemiological studies and tends to bias the observed association of smoking and TED towards the null. The limited nature of the smoking data was a key weakness of the cohort and case-control studies. Lifelong smoking status was assessed in seven studies.^{16,21,22,25-27,32} The other studies only assessed current smoking status or status at the onset of disease^{5,23,29,31} or the method was not stated.^{24,30} A further potential bias in cohort is measurement imprecision where smokers and non-smokers are categorised at baseline only. This will not allow for the effect of changed exposure status, such as quitting smoking, over time. Changes in exposure status are especially likely with prolonged follow-up, and will bias the measure of association towards the null. Only one of the cohort studies re-assessed smoking status during follow-up,¹⁶ although in most studies where it was described, the follow-up period was short.

The presence of confounding factors presents a problem for all observational studies. Ten studies addressed confounding by sex^{5,16,23-26,29-32} and 11 by age,^{5,16,23-26,28-32} through design or adjustment in analysis. Other confounders addressed were degree of

thyroid dysfunction^{16,28,30} and, in studies examining progression of TED in relation to smoking, the duration and severity of eye disease.^{28,30} Two cohort studies adjusted the analysis for radio-iodine and other treatments.^{16,21}

Association between smoking and TED

Overall, eight of the nine case-control studies found a positive association between smoking and the development of TED for current-smokers compared with non-smokers or never-smokers: OR from 1.94 to 20.2, depending on sex of patients, type of ophthalmopathy, and whether controls had thyroid disease or not (Table 2). In all five case-control studies with the methodologically stronger comparison between TED cases and controls with Graves' disease but no ophthalmopathy, there was a positive association between smoking and TED: OR from 1.94 to 10.1.^{5,22,24-26} Of these, in the study by Shine *et al*,²² which met the most key quality criteria, the OR for developing TED in current-smokers compared with never-smokers was 3.78 (95% CI 1.63-9.05). For seven case-control studies in which control subjects did not have thyroid disease, positive associations between TED and smoking with ORs of up to 20.2 were recorded,^{5,22-24,26,29,31} with an OR of 6.5 in the study in which the highest number of quality criteria were at least partially met.²³ Only one of these seven studies found no association of TED with smoking.³²

The cohort studies included a retrospective study with 14 years follow-up³⁰ and three prospective studies with 1 or 2 years follow-up.^{16,27,28} One of the cohort papers described two studies: an observational study nested in a randomised controlled trial of treatment for Graves' disease and a retrospective cohort study of patients with severe ophthalmopathy; the time period for follow-up was not clear in this study.²¹

Two of the cohort studies examined the occurrence of new cases of TED in patients with Graves' disease.^{16,27} One study at least partially met all five of the key quality criteria and at least 13 of the 14 quality criteria.¹⁶ This study found an increased risk of total ophthalmopathy (RR 1.32, 95% CI 1.06-1.64), proptosis (RR 2.64, 95% CI 1.79-3.90) and diplopia (RR 3.14, 95% CI 1.65-5.98) in smokers compared with never-smokers. The other study found no association between smoking and eye disease but included ex-smokers in the non-smoker comparison group.²⁷

The remaining four cohort studies examined the effects of smoking on progression or on the outcome of treatment in patients with established TED.^{21,28,30} Three studies found a positive association with current-smokers having a poorer outcome compared with

current non-smokers (including former smokers).^{21,28} Bartley *et al*,³⁰ found no evidence of poorer outcome among smokers after following patients for 14 years, although the smoking status of the comparison groups was poorly defined.

Effects of smoking dose

Nine studies investigated for a dose–response effect of smoking^{5,16,22,23,26–28,31,32} and seven found evidence of a dose response. The strongest analyses were in three studies which assessed the association between a measure of smoking dose (severity and/or duration) and outcome.^{16,27,28} Two cohort studies examined the effect of smoking dose on the development of TED in patients with Graves' disease.^{16,27} The most comprehensive analysis was conducted by Pfeilschifter and Ziegler,¹⁶ who divided current-smokers by severity of smoking: 1–10 cigarettes/day, 11–20 cigarettes/day, 11–20 cigarettes/day with <100 000 total, 11–20 cigarettes/day with >100 000 total, and >20 cigarettes/day. Compared with never-smokers, in linear trend analysis, there was a significant increase in RR for the development of total symptoms and proptosis ($P < 0.05$) and for diplopia ($P < 0.01$) as smoking dose increased. However, a second methodologically weaker study²⁷ found no correlation between development of TED and a smoking index, calculated as the number of daily cigarettes smoked at study entry multiplied by number of years smoking. Eckstein *et al*²⁸ followed patients with pre-existing TED and found a significant correlation between *N*-2 hydroxyethylvaline (a marker that reflects the smoking dose over several months previously) and progression as measured by a clinical activity score (a measure of TED progression) and reduced eye motility at 1.5, 4.5, and 7.5 months.

Two studies noted that there were more heavy smokers in groups with severe or moderate/severe TED compared with those with less severe ophthalmopathy.^{5,22} Three studies observed that the OR for development were higher when more severe forms of TED were considered.^{23,26,32} In contrast, one study noted no difference in the percentage of smokers in slight or moderate to severe ophthalmopathy patients.³¹

Evidence for reversibility on smoking cessation

Reversibility of the association between smoking and TED can be inferred from reduced associations with TED among ex-smokers compared with current-smokers. Among the case–control studies with a comparison between TED cases and Graves' disease controls, Hagg and Asplund⁵ found an OR of 10.0 for the association of TED and smoking for current-smokers *vs* non-smokers.

This dropped to an OR of 4.5 when current-smokers were combined with ex-smokers and compared with never-smokers. O'Hare and Geoghegan²⁵ found a stronger association with current smoking (OR 3.48) at the onset of TED than with ever-smoking (OR 2.29). One cohort study,¹⁶ the strongest methodologically, examined the effect of stopping smoking on TED and found no increased risk for ophthalmopathy in ex-smokers compared with never-smokers for a variety of indicators: total ophthalmopathy (RR 1.45, 95% CI 0.90–2.33, $P = 0.122$), proptosis (RR 0.90, 95% CI 0.24–2.33, $P = 0.873$), and diplopia (RR 1.88, 95% CI 0.46–7.73, $P = 0.382$). This contrasted with the strong association with current smoking.

Discussion

We found 15 case–control and cohort studies which investigated an association between tobacco smoking and TED. The quality of the studies was variable, with many studies having deficiencies in key quality criteria, and many of the case–control studies having an inappropriate control group to assess the research question adequately. However, most of the studies, particularly those with the strongest designs and methodologies, supported an association between smoking and the development and progression of TED.

Our review had important strengths. In comparison with three previous reviews on this topic,^{7–9} we used a more rigorous search strategy and identified studies not included in these previous reviews.^{25,26,28,30,32} We included non-English studies. We only included evidence from study designs that are the strongest for investigating causality, and unlike previous reviews, we included a comprehensive assessment of study quality. Because of the small number of high-quality studies, meta-analysis was not considered to be appropriate.

Criteria for the assessment of causality were advanced by Hill³³ and subsequently modified by Susser.³⁴ The criteria of causality advocated include a strong and consistent association, evidence of dose response and reversibility, a clear temporal relationship, and biological plausibility.

We found evidence of a strong and consistent association between smoking and TED. Eight of nine case–control studies found a positive association with an up to 20-fold increased risk of TED for current-smokers compared with non- or never-smokers. However, in four studies, analysis was restricted only to a comparison of cases with TED and controls without Graves' disease, which makes the results more difficult to interpret. All five of the case–control studies which carried out the more appropriate comparison of smoking among patients with Graves' disease with and without TED

found evidence of an association, including the study which met the greatest number of the key quality criteria.

Prospective cohort studies are the best placed to demonstrate unequivocally that smoking preceded the development or progression of TED. Of the two prospective studies investigating causes of incident TED, the study which was judged to be of highest quality found a strong positive association between smoking and the incidence of TED in patients with Graves' disease.¹⁶ The second such study found no association, but was methodologically weaker. There was also an association of smoking with greater progression of TED and/or poorer response to treatment in established TED: three of four studies finding a positive association.

Evidence came from studies which were heterogeneous in setting, design, and analysis. Studies assessed the association of smoking in populations from Europe, America, and the Far East; in case-control and cohort studies; for incident or prevalent TED; and progression or treatment outcome. Controls for the case-control studies included hospital and community controls with or without Graves' disease. TED is not a homogeneous diagnosis and definitions of disease varied between studies, with different classifications, symptoms, and severities of disease.

Most studies which investigated for it showed a dose-response effect with increased incidence of TED and severity of eye disease symptoms as smoking intensity increased and stronger associations with smoking in patients with severe TED compared with less severe disease. Only three studies examined the effects of quitting smoking. All found evidence of reduced risk for TED among ex-smokers compared with current smokers.

The biological mechanisms by which smoking contributes to the development of TED remain unclear. Several theories have been proposed. For example, smoking may have a direct irritant action on the eye. This would explain the inflammatory changes, but does not explain the increased volume of extraocular muscle and retrobulbar fibroadipose tissues.¹ Smoking has been linked to other autoimmune diseases including rheumatoid arthritis and Crohn's disease; this suggests there may be a generalised stimulation of the autoimmune process in smokers.² Cytokines are believed to play an important role in the pathogenesis of TED and smoking might influence cytokine secretion and activity by causing hypoxia in the retrobulbar space.¹⁻³ Other postulated mechanisms include smoking affecting immunological reactions involved in the pathogenesis of eye disease by altering TSH and making it more immunogenic, or by sensitising the orbital tissue to an as yet unidentified trigger for TED.¹

In conclusion, we found strong epidemiological evidence for a causal association between tobacco

smoking and TED, with RR/OR >2 in most studies. The quality of the studies was variable but evidence of association was most consistently present in the higher quality studies. Similar associations have also been found for smoking and the development of age-related macular degeneration³⁵ and cataract.³⁶ In our judgement on the balance of the evidence available, particularly from the higher quality studies, there is sufficient evidence of causality and hence justification for educational and smoking cessation interventions with patients and the public who are often unaware that smoking has adverse ocular effects.³⁷ Patients with Graves' disease should be encouraged to stop smoking in order to both help prevent development of TED and to reduce the general physical harm that smoking causes. Patients with existing TED should also be advised to stop smoking, as smoking cessation is likely to slow or stop progression of eye disease and improve the outcome of treatment. Many diabetes, cardiac, and respiratory clinics have incorporated smoking cessation support into their routine services. UK ophthalmology or optometry services and endocrine clinics should likewise routinely assess smoking status and offer smoking cessation support for patients with or at risk of eye diseases related to smoking.

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