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Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe

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ABSTRACT

Introduction: In the European Union, there are 180,000 new cases of upper aerodigestive tract (UADT) cancer cases per year – more than half of whom will die of the disease. Socioeconomic inequalities in UADT cancer incidence are recognised across Europe. We aimed to assess the components of socioeconomic risk both independently and through their influence on the known behavioural risk factors of smoking, alcohol consumption and diet.

Patients and methods: A multicentre case–control study with 2198 cases of UADT cancer and 2141 controls from hospital and population sources was undertaken involving 14 centres

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from 10 countries. Personal interviews collected information on demographics, lifetime occupation history, smoking, alcohol consumption and diet. Socioeconomic status was measured by education, occupational social class and unemployment. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using unconditional logistic regression.
Results: When controlling for age, sex and centre significantly increased risks for UADT cancer were observed for those with low versus high educational attainment OR = 1.98 (95% CI 1.67, 2.36). Similarly, for occupational socioeconomic indicators – comparing the lowest versus highest International Socio-Economic Index (ISEI) quartile for the longest occupation gave OR = 1.60 (1.28, 2.00); and for unemployment OR = 1.64 (1.24, 2.17). Statistical significance remained for low education when adjusting for smoking, alcohol and diet behaviours OR = 1.29 (1.06, 1.57) in the multivariate analysis. Inequalities were observed only among men but not among women and were greater among those in the British Isles and Eastern European countries than in Southern and Central/Northern European countries. Associations were broadly consistent for subsite and source of controls (hospital and community).
Conclusion: Socioeconomic inequalities for UADT cancers are only observed among men and are not totally explained by smoking, alcohol drinking and diet.

1. Introduction

Upper aerodigestive tract (UADT) cancer includes the subsites: oral cavity, pharynx (excluding nasopharynx), larynx and oesophagus. Collectively these cancers are among the most common in the world – with the greatest burden falling upon developing countries.[1] Although rarer in Europe, UADT cancers still account for 180,000 new cases per year,[2] and the incidence has been increasing in our most deprived communities.[2]

There is little doubt that tobacco smoking and excessive alcohol consumption are the major risk factors for UADT cancer[3], with diets low in fruits and vegetables,[4] and human oncogenic papillomavirus infection[5] also associated with increased risk. While it is recognised that low individual socioeconomic status (SES) is associated with increased risk,[6] the components and pathways of this socioeconomic effect have had limited attention. Few studies examining the effect of socioeconomic factors on UADT cancer have adequately controlled for the known behavioural risk factors, and have simply adjusted for age.[6] Previous studies have identified independent effects of social factors having adjusted for smoking and alcohol drinking,[7,8] while others have found that the social effects are completely lost when adjusting for alcohol drinking and smoking.[9] One study found that the effects of low social class could be explained by co-existing occupational (toxic) exposures.[10]

It is almost unheard of to investigate the behavioural risk factors for UADT cancer without adjusting for socioeconomic status. However, for this analysis, in keeping with the classical methods in social epidemiology,[11] we flip this logic on its head, and take an alternative perspective a priori – aiming to assess socioeconomic factors both independently and through their influence on behavioural risk factors. Uniquely we aim to extensively adjust for the known behavioural risk factors of smoking, alcohol drinking and diet which would confound any relationship with social factors; and we have the opportunity to utilise one of the largest case–control studies undertaken for UADT cancer aetiology.[6,12] At a time of increased focus on genetic and lifestyle factors associated with cancer – we also feel this is a timely opportunity to take a step back and view a bigger picture of UADT cancer aetiology and the role of the social and economic context of risk.

2. Material and methods

The ARCAGE (Alcohol-Related Cancers and Genetic Susceptibility in Europe) multicentre case–control study was conducted in 14 centres in 10 European countries. Full details of study design have been described elsewhere[12] and will be only briefly summarised here. Following a common protocol (although slightly different in the Paris centre), cases were defined as those diagnosed with primary squamous cell tumours of the UADT between 2002 and 2005 (Paris: 1987–1992).

Diagnoses included malignant cancers of the oral cavity (ICD-O-3 topography: C00–C06), oropharynx (C09, C10), hypo-pharynx (C12, C13), larynx (C14, C32) or oesophagus (C15). Incident cases were ascertained through weekly monitoring of head and neck cancer clinics in hospital departments and confirmed by pathology department records.

In each centre, controls were frequency-matched to cases by sex and age (5-year groups). In the UK centres, population controls were randomly selected from the same community medical practice list as the corresponding cases. Specifically, for each case, a total of 10 controls were selected, matched by age and sex. Potential controls were approached in a random order one at a time until one agreed to participate. In all other centres, hospital controls were used. Only controls with a recently diagnosed disease were accepted and admission diagnoses related to alcohol, tobacco or diet were excluded. Eligible diagnoses included endocrine and metabolic; genito-urinary; skin, subcutaneous tissue and musculoskeletal; gastro-intestinal; circulatory; ear, eye and mastoid; nervous system diseases; trauma and plastic surgery patients. he proportion of controls within a specific diagnostic group could not exceed 33% of the total in any particular centre. In the Paris centre protocol never-smokers were not included among the cases or controls.

Data were collected from cases and controls, by trained interviewers conducting face-to-face interviews using a highly structured questionnaire including lifetime history information on socio-demographic characteristics, anthropometric measures, smoking and alcohol consumption, a brief medical and dental history, frequency of intake of selected foods and a detailed occupational history.

Measures of socioeconomic status used were education and occupational social class. Education variables recorded were level of educational attainment and number of years of full time education. These questions were asked separately (and are highly correlated). The Paris centre did not record level of education attainment and the Bremen centre recorded it in a slightly different way (to reflect their education system). This was recoded and standardised from the number of years of full time education – taking into account the education system of the country. Educational attainment levels were recorded in five categories: no education, primary, secondary, further/technical and university. (Further and technical education is education beyond secondary level and includes further and technical colleges.) For the detailed analysis this was further grouped into the three broad educational levels: primary (no education/primary); secondary and tertiary (further/technical/university).

Occupational social classification variables included the International Socio-Economic Index of Occupational Status (ISEI)[13] and the Registrar General's Social Class (RGSC).[14] The construct of the ISEI is based on the attributes of occupation that convert a person's education into income. The range of scores on the ISEI scale is 10–90 and the positions are derived from the average educational level and income related to that occupation. We stratified the ISEI into quartiles (as far as was possible given the categorical nature of the variable) – to provide a mechanism for ranking occupations related to both the level of education required and the income earned. The RGSC variable was divided into 'manual' (RGSC categories IIIM – skilled manual, IV – partly skilled manual and V – unskilled manual) and 'non-manual' (RGSC categories I – professional, II – intermediate and IIINM – skilled non-manual) codes.

The detailed life-time occupational history section collected data on every occupation, including start date, end date, job title, industry and nature of work. Each job title and associated industry was initially coded manually according to the International Standard Classifications for Occupation (ISCO).[15] All these ISCO job codes were allocated to the ISEI and RGSC using a combination of online conversion files[16] and manual coding by DIC. Occupational social class was explored in several recognised ways,[10] including ISEI/RGSC of the: (i) first job; (ii) last job; (iii) longest occupation and (iv) 'ever' lowest quartile of the ISEI and 'ever' manual codes of the RGSC. Lifetime experience of unemployment was also assessed.

Lifetime smoking history data on tobacco from cigarettes, cigars and pipes were used to calculate 'pack-years'. Lifetime alcohol consumption of beer, wine, hard liquor and aperitifs was converted into units of alcohol (approximately, 1 unit of alcohol = 8 g of ethanol). Alcohol variables computed cumulatively for all beverage categories, included lifetime duration of drinking; and average weekly alcohol consumption over lifetime (units/week). Food frequency diet histories were used to calculate total weekly consumption of fruits, and separately, of vegetables.

Odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) were computed by unconditional logistic regression adjusted for age, sex and centre. Forward stepwise logistic regression was used to determine the most significant behavioural risk factor variables ($p < 0.05$ level). This enabled the number of smoking and alcohol variables to be reduced to avoid problems of collinearity. The logistic regression model was repeated following adjustment for significant smoking, alcohol consumption and diet variables – to assess for potential independent effects of the range of socioeconomic variables. In addition the significant socioeconomic variables were explored with progressively more potential confounders to examine attenuation of the ORs. The key socioeconomic factors were analysed by sex in both univariate and multivariate models. Subgroup analyses were also performed for control source, centre and cancer subsite. Analyses were also conducted by sex and four defined geographical country groupings – United Kingdom/Ireland (British Isles); France/Germany/Norway (Central/Northern Europe); Greece/Italy/Spain (Southern Europe) and Croatia/Czech Republic (Eastern Europe). These groupings were broadly based on the research on inequalities in smoking.[17] All statistical analyses were performed on SAS version 9.1 (SAS Institute Inc.).

3. Results

Overall the ARCAGE study participation rates were 82% ($n = 2304$) cases and 68% ($n = 2227$) for controls. In this analysis 2198 cases and 2141 controls were included – 192 subjects were excluded as they had one or more key variables missing for education, smoking, alcohol or diet. The UADT cancer subsite distribution for cases was oral/oropharyngeal ($n = 1117$, 51%), hypopharynx/larynx ($n = 856$, 39%) and oesophageal cases ($n = 225$, 10%). The characteristics of the case and controls are shown in Table 1. There were four times more men than women who were cases, and women were slightly older than men.

UADT cancer increased with lower levels of educational attainment. Those with the lowest levels (no formal education) had an almost 3-fold increased risk when compared with those in the highest level (university education) (Table 2). This pattern was repeated when examining years of formal full-time education. When adjusting for behaviours (smoking, alcohol and diet), the risk associated with the lowest levels of education remained significant but showed some attenuation (Table 2) with the risk associated with the lowest educational attainment level reducing to OR = 1.68 (95% CI 1.08, 2.61) when compared to the highest education level.

Increased risk was also associated with low occupational social class (Table 2). When adjusting for age, sex and centre significantly elevated ORs were observed for those in the lowest ISEI socioeconomic quartile levels in their first, last or longest occupations when compared with those in the highest

Table 1 – Baseline characteristics relating to selected variables on age, education, occupational social class, smoking, alcohol consumption and fruit and vegetable consumption by sex.

Characteristic	Men		Women	
	Cases (*n* = 1785)	Controls (*n* = 1615)	Cases (*n* = 413)	Controls (*n* = 526)
	Numbers (%)		Numbers (%)	
Age (years)				
<50	302 (16.9)	293 (18.1)	70 (16.9)	109 (20.7)
50–59	658 (36.9)	539 (33.4)	123 (29.8)	148 (28.1)
⩾ 60	825 (46.2)	783 (48.5)	220 (53.3)	269 (51.2)
Education level				
University	108 (6.1)	191 (11.8)	21 (5.1)	41 (7.8)
Technical/further	219 (12.3)	265 (16.4)	56 (13.6)	84 (16.0)
Secondary	623 (34.9)	601 (37.2)	178 (43.1)	210 (39.9)
Primary	732 (41.0)	508 (31.5)	129 (31.2)	159 (30.2)
No education	103 (5.8)	50 (3.1)	29 (7.0)	32 (6.1)
Educations years				
>16	103 (5.8)	166 (10.3)	16 (3.9)	35 (6.7)
10–16	829 (46.4)	818 (50.7)	209 (50.6)	277 (52.7)
<10	853 (47.8)	631 (39.1)	188 (45.5)	214 (40.7)
ISEI – longest occupation				
1 highest quartile	193 (10.8)	240 (14.9)	34 (8.2)	41 (7.8)
2	246 (13.8)	280 (17.3)	79 (19.3)	135 (25.7)
3	599 (33.6)	507 (31.4)	60 (14.5)	81 (15.4)
4 lowest quartile	423 (23.7)	297 (18.4)	106 (25.7)	131 (24.9)
Missing	*324 (18.2)*	*291 (18.0)*	*134 (32.5)*	*138 (26.2)*
RGSC – longest occupation				
Non-manual	360 (20.2)	460 (28.5)	130 (31.5)	197 (37.5)
Manual	1174 (65.8)	934 (57.8)	166 (40.2)	220 (41.8)
Missing	*251 (14.1)*	*221 (13.7)*	117 (28.3)	109 (20.7)
Smoking (pack years)				
Never	92 (5.2)	407 (25.2)	121 (29.3)	296 (56.3)
<20	243 (13.6)	463 (28.7)	126 (30.5)	64 (12.2)
20–39	610 (34.2)	411 (25.5)	1223 (68.5)	581 (36.0)
⩾40	840 (47.0)	334 (20.7)	61 (14.8)	30 (5.7)
Alcohol (drinks/day)				
Never	51 (2.9)	110 (6.8)	86 (20.8)	151 (28.7)
<1	332 (18.6)	549 (34.0)	202 (48.9)	285 (54.2)
1–2	521 (29.2)	593 (36.7)	76 (18.4)	81 (15.4)
3–6	627 (35.1)	334 (18.3)	40 (9.7)	8 (1.5)
⩾7	254 (14.2)	68 (4.2)	9 (2.2)	1 (0.2)
Fruits (pieces/week)				
⩽1	745 (41.7)	594 (36.8)	173 (41.9)	184 (35.0)
2–6	448 (25.1)	463 (28.7)	129 (31.2)	169 (32.1)
⩾7	304 (17.0)	357 (22.1)	98 (23.7)	164 (31.2)
Missing	288 (16.1)	201 (12.5)	13 (3.2)	9 (1.7)
Vegetables (pieces/week)				
⩽1	145 (8.1)	83 (5.1)	13 (3.2)	16 (3.0)
2–6	694 (38.9)	495 (30.7)	149 (36.1)	132 (25.1)
7	538 (30.1)	520 (32.2)	135 (32.7)	204 (38.8)
>7	408 (22.9)	517 (32.0)	116 (28.1)	174 (33.1)

RGSC – Registrar General's Social Classification; ISEI – International Socio-Economic Index.

ISEI quartiles. This was replicated for manual compared with non-manual workers in the RGSC. In addition, ever lifetime experience of working in an occupation in the lowest ISEI quartile compared to the highest ISEI quartile was also associated with a significant increased risk. However, when taking into account smoking, alcohol and diet behaviours, the ORs decreased markedly and none of the occupational social class variables remained significant. Similarly, the experience of lifetime unemployment reported by our study subjects, although rather low – around only 6% for cases and 5% for

Table 2 – Associations of UADT cancer with socioeconomic factors.

Explanatory variable	Cases (n = 2198)	Controls (n = 2141)	Adjusted for age, sex and centre[a] OR (95% CI) (n = 4339)	Adjusted for age, sex, centre and significant behavioural factors[a,b] OR (95% CI) (n = 4339)
	Numbers (%)			
Education level				
University	129 (5.9)	232 (10.8)	1.00	1.00
Technical/further	275 (12.5)	349 (16.3)	1.58 (1.20, 2.08)*	1.19 (0.88, 1.62)
Secondary	801 (36.4)	811 (37.9)	1.94 (1.52, 2.47)**	1.22 (0.93, 1.59)
Primary	861 (39.2)	667 (31.2)	2.61 (2.04, 3.36)**	1.42 (1.07, 1.87)*
No education	132 (6.0)	82 (3.8)	3.00 (2.03, 4.43)**	1.68 (1.08, 2.61)*
Years				
>16	119 (5.4)	201 (9.4)	1.00	1.00
10–16	1038 (47.2)	1095 (51.1)	1.79 (1.39, 2.30)**	1.35 (1.02, 1.79)*
<10	1041 (47.4)	845 (39.5)	2.49 (1.92, 3.24)**	1.55 (1.15, 2.07)**
ISEI				
First occupation				
1 highest quartile	168 (7.6)	180 (8.4)	1.00	1.00
2	380 (17.3)	466 (21.8)	1.07 (0.82, 1.39)	0.93 (0.69, 1.25)
3	714 (32.5)	623 (29.1)	1.38 (1.07, 1.77)*	1.02 (0.77, 1.35)
4 lowest quartile	585 (26.6)	537 (25.1)	1.31 (1.01, 1.68)*	0.97 (0.73, 1.29)
Missing	*351 (16.0)*	*335 (15.7)*		
Last occupation				
1 highest quartile	196 (8.9)	239 (11.2)	1.00	1.00
2	211 (9.6)	253 (11.8)	1.17 (0.89, 1.54)	1.02 (0.75, 1.38)
3	444 (20.2)	361 (16.9)	1.57 (1.23, 2.01)**	1.03 (0.78, 1.37)
4 lowest quartile	404 (18.4)	353 (16.5)	1.49 (1.16, 1.92)**	1.09 (0.82, 1.44)
Missing	*943 (42.9)*	*935 (43.7)*		
Longest occupation				
1 highest quartile	227 (10.3)	281 (13.1)	1.00	1.00
2	325 (14.8)	415 (19.4)	1.07 (0.85, 1.36)	0.84 (0.64, 1.09)
3	659 (30.0)	588 (27.5)	1.42 (1.14, 1.76)**	0.96 (0.75, 1.23)
4 lowest quartile	529 (24.1)	428 (20.0)	1.60 (1.28, 2.00)**	0.84 (0.64, 1.09)
Missing	*458 (20.8)*	*429 (20.0)*		
Occupation				
Never lowest quartile	1177 (53.6)	1207 (56.4)	1.00	1.00
Ever lowest quartile	1021 (46.5)	934 (43.6)	1.19 (1.05, 1.36)*	0.99 (0.86, 1.14)
RGSC				
First occupation				
Non-manual	479 (21.8)	593 (27.7)	1.00	1.00
Manual	1439 (65.5)	1315 (61.4)	1.28 (1.10, 1.49)**	1.04 (0.87, 1.23)
Missing	*280 (12.7)*	*233 (10.9)*		
Last occupation				
Non-manual	401 (18.2)	478 (22.3)	1.00	1.00
Manual	1395 (63.5)	1331 (62.2)	1.26 (1.07, 1.49)**	0.90 (0.74, 1.08)
Missing	*402 (18.3)*	*332 (15.5)*		
Longest occupation				
Non-manual	490 (22.3)	657 (30.7)	1.00	1.00
Manual	1340 (61.0)	1154 (53.9)	1.51 (1.30, 1.75)**	1.16 (0.98, 1.37)
Missing	*368 (16.8)*	*330 (15.4)*		
Occupation				
Never manual	480 (21.8)	462 (21.6)	1.00	1.00
Ever manual	1718 (78.2)	1679 (78.4)	1.09 (0.91, 1.30)	0.77 (0.64, 1.02)
Unemployed				
Never	2055 (93.5)	2040 (95.3)	1.00	1.00
Ever	143 (6.5)	101 (4.7)	1.64 (1.24, 2.17)**	1.00 (0.73, 1.37)

OR – odds ratio; CI – confidence interval; RGSC – Registrar General's Social Classification; ISEI – International Socio-Economic Index.

* $p < 0.05$.

** $p < 0.01$.

[a] Unconditional logistic regression.

[b] Significant behavioural risk factors adjusted for: (1) alcohol drinking status (never, former and current) – for the former and current drinkers further control included, (2) frequency of alcohol consumption and (3) lifetime alcohol consumption; (4) smoking status (never, former and current) – for the former and current smokers further control included, (5) pack-years and (6) duration of smoking; (7) frequency of fresh fruit consumption and (8) frequency of fresh vegetable consumption.

Table 3 – Exploration of the relationship between low education attainment and UADT cancer risk by sequential models including behavioural risk factors (separately and in combination).

Education level	Adjusted for age, sex, and centre[d] OR (95% CI)	Adjusted for age, sex, centre and smoking[d,a] OR (95% CI)	Adjusted for age, sex, centre and alcohol[d,b] OR (95% CI)	Adjusted for age, sex, centre and diet[c,d] OR (95% CI)	Adjusted for age, sex, centre smoking[a] and alcohol[b,d] OR (95% CI)	Adjusted for age, sex, centre and all behaviours[a,b,c,d] OR (95% CI)
Tertiary	1.00	1.00	1.00	1.00	1.00	1.00
Secondary	1.46 (1.24, 1.71)**	1.17 (0.98, 1.41)	1.29 (1.09, 1.54)**	1.39 (1.17, 1.64)**	1.11 (0.92, 1.33)*	1.09 (0.90, 1.31)
Primary	1.98 (1.67, 2.36)**	1.52 (1.26, 1.84)**	1.57 (1.31, 1.89)**	1.85 (1.55, 2.20)**	1.33 (1.10, 1.62)**	1.29 (1.06, 1.57)**

OR – odds ratio; CI – confidence interval.
* $p < 0.05$.
** $p < 0.01$.
a Smoking variables: smoking status (never, former and current) – for the former and current smokers further control included pack-years and duration of smoking.
b Alcohol variables: drinking status (never, former and current) – for the former and current drinkers further control included frequency of alcohol consumption and lifetime alcohol consumption.
c Diet variables: frequency of fresh fruit consumption; and frequency of fresh vegetable consumption.
d Unconditional logistic regression.

controls – was not significantly associated with UADT cancer risk, when adjusted for these behaviours.

Table 3 presents the results of a series of models exploring the effects of behavioural adjustment on the risk associated with low education attainment (i.e. no or primary education only). The models successively show the contribution of smoking, alcohol and diet (and combinations of these factors) to the risk associated with low educational attainment. Individually, smoking and alcohol drinking attenuated the effect of low education similarly (45% and 40%, respectively), and when combined together by around 65%. Diets low in fresh fruits and vegetables only contributed under 10% of the risk associated with low educational attainment. Including all behaviours together around two-thirds (67%) of the excess risk for those with low education was explained. There was also a statistically significant interaction ($p = 0.016$) between education and sex. This was further explored in a subgroup analysis of the key variables by sex (Table 4). Significant in-

Table 4 – Stratification analysis of univariate and multivariate models of low versus high socioeconomic status by sex.

Socioeconomic factor	Men		Women	
	Adjusted for age, and centre[a] OR (95% CI) ($n = 3400$)	Adjusted for age, centre and significant behavioural factors[a,b] OR (95% CI) ($n = 939$)	Adjusted for age, and centre[a] OR (95% CI) ($n = 4339$)	Adjusted for age, centre and significant behavioural factors[a,b] OR (95% CI) ($n = 4339$)
Education level				
Tertiary	1.00	1.00	1.00	1.00
Secondary	1.47 (1.22, 1.77)**	1.07 (0.86, 1.32)	1.27 (0.85, 1.90)	0.93 (0.59, 1.46)
Primary	2.21 (1.82, 2.68)**	1.34 (1.07, 1.68)*	1.31 (0.91, 1.87)	1.06 (0.71, 1.58)
ISEI longest occupation				
1 highest quartile	1.00	1.00	1.00	1.00
2	1.05 (0.77, 1.44)	1.00 (0.70, 1.43)	1.33 (0.60, 2.94)	1.03 (0.42, 2.53)
3	1.61 (1.21, 2.13)**	1.08 (0.78, 1.49)	1.62 (0.70, 3.74)	1.10 (0.43, 2.82)
4 lowest quartile	1.75 (1.31, 2.34)**	1.18 (0.85, 1.65)	1.53 (0.69, 3.30)	1.18 (0.48, 2.88)
RGSC longest occupation				
Non-manual	1.00	1.00	1.00	1.00
Manual	1.66 (1.40, 1.96)**	1.16 (0.95, 1.40)	1.16 (0.84, 1.60)	1.02 (0.72, 1.46)
Unemployed				
Never	1.00	1.00	1.00	1.00
Ever	1.59 (1.18, 2.16)**	0.88 (0.63, 1.24)	2.00 (0.97, 4.16)	1.59 (0.69, 3.68)

OR – odds ratio; CI – confidence interval; RGSC – Registrar General's Social Classification; ISEI – International Socio-Economic Index.
* $p < 0.05$.
** $p < 0.01$
a Unconditional logistic regression.
b Significant behavioural risk factors adjusted for: (1) alcohol drinking status (never, former and current) — for the former and current drinkers further control included, (2) frequency of alcohol consumption and (3) lifetime alcohol consumption; (4) smoking status (never, former and current) – for the former and current smokers further control included; (5) pack-years and (6) duration of smoking; (7) frequency of fresh fruit consumption; and (8) frequency of fresh vegetable consumption.

Table 5 – Subgroup analyses of lowest versus tertiary level of educational attainment by source of controls, centre, and cancer subsite.

Subgroup	Tertiary education level		Primary education level [c]		Adjusted for age, sex, and centre[a] OR (95% CI)
	Cases	Controls	Cases	Controls	
	Numbers (%)		Numbers (%)		
Population controls	96 (29.8)	154 (40.0)	226 (70.2)	231 (60.0)	1.70 (1.23, 2.35)**
Hospital controls	308 (16.4)	427 (24.3)	991 (52.8)	748 (42.6)	1.84 (1.54, 2.20)**
Croatia – Zagreb	3 (5.6)	11 (23.9)	20 (37.0)	16 (34.8)	5.52 (1.22, 25.00)*
Czech Rep – Prague	38 (21.1)	77 (46.1)	106 (58.9)	64 (38.3)	3.41 (2.11, 5.52)*
France – Paris	33 (11.4)	40 (19.1)	110 (37.9)	65 (31.1)	2.04 (1.16, 3.58)*
Germany – Bremen	15 (5.5)	34 (10.5)	184 (67.4)	194 (60.1)	2.20 (1.15, 4.20)*
Greece – Athens	40 (16.7)	32 (16.5)	146 (60.8)	100 (51.6)	1.14 (0.66, 1.97)
Ireland – Dublin	10 (23.8)	6 (33.3)	16 (38.1)	3 (16.7)	1.31 (0.17, 10.17)
Italy – Aviano	33 (21.9)	33 (21.9)	85 (56.3)	75 (49.7)	1.30, (0.69, 2.44)
Italy – Padova	28 (20.9)	39 (30.0)	69 (51.5)	49 (37.7)	1.96 (1.01, 3.81)*
Italy – Turin	29 (18.3)	60 (30.6)	73 (46.2)	60 (30.6)	2.42 (1.35, 4.33)**
Norway – Oslo	47 (27.8)	74 (41.3)	59 (34.9)	39 (21.8)	2.32 (1.32, 4.06)*
Spain – Barcelona	32 (17.3)	21 (14.7)	123 (66.5)	83 (58.0)	1.07 (0.52, 2.19)
UK – Glasgow[b]	23 (26.1)	36 (40.5)	65 (73.9)	53 (59.6)	2.28 (1.13, 4.58)*
UK – Manchester[b]	49 (33.3)	82 (44.6)	98 (66.7)	102 (55.4)	1.75 (1.10, 2.79)*
UK – Newcastle[b]	24 (27.6)	36 (32.1)	63 (72.4)	75 (67.0)	1.33 (0.70, 2.53)
Oral and oropharyngeal	222 (19.9)	581 (27.1)	579 (52.0)	979 (45.7)	1.81 (1.46, 2.23)**
Larynx and hypopharynx	137 (16.0)	581 (27.1)	527 (61.6)	979 (45.7)	2.02 (1.59, 2.57)**
Oesophageal	45 (20.0)	581 (27.1)	111 (49.3)	979 (45.7)	2.23 (1.57, 3.43)**

OR – odds ratio; CI – confidence interval.
* $p < 0.05$.
** $p < 0.01$.
[a] Unconditional logistic regression (no centre adjustment in the analysis of centre subgroup).
[b] Population controls.
[c] Lowest education level is primary (or less) in all centres except UK where the lowest level recorded = secondary.

creased risks associated with low SES were only observed among men in univariate analyses, and following adjustment for behaviours only the risk associated with low educational attainment remained significant.

A further series of subgroup analyses were also performed (Table 5). These show that the risks associated with low educational attainment varied widely across the centres and this instability relates to the small numbers in each centre. Nevertheless the direction of effect was broadly consistent – with significant elevated risks observed for the source of controls, and the subsites of UADT cancer. Significant increased risks associated with low educational attainment were also only observed form men in the grouped country analyses (Table 6). Odds ratios were substantially lower in Southern European and Central/Northern European countries than in the British Isles and Eastern European countries. A similar pattern was observed for women (although not significantly).

4. Discussion

Our study demonstrates that wide socioeconomic inequalities in the risk of UADT cancer exist across Europe and they are not fully explained by the traditional recognised lifestyle behaviours of smoking, alcohol consumption and dietary factors. The lowest levels of educational attainment confer an almost doubling of risk associated with UADT cancer, remain

Table 6 – Subgroup analyses of lowest versus tertiary level of educational attainment by geographic region and sex.

European region	Education level*	Adjusted for age OR (95% CI)[a]	Adjusted for age OR (95% CI)[a]
		Men	Women
	Tertiary	1.00	1.00
British Isles	Lowest	19.88 (2.55, 154.94)**	3.07 (0.61, 15.42)
Central/Northern Europe	Lowest	1.89 (1.35, 2.65)**	1.32 (0.65, 2.68)
Southern Europe	Lowest	1.87 (1.39, 2.52)**	0.99 (0.55, 1.78)
Eastern Europe	Lowest	4.27 (2.57, 7.10)**	0.52 (0.12, 2.28)

OR – odds ratio; CI – confidence interval.
* $p < 0.05$.
** $p < 0.01$.
[a] Unconditional logistic regression.

significant when we adjust for behavioural factors, and were consistent across the subsites of UADT cancer. Adjustment for behaviours decreased the risk associated with low educational attainment by around two-thirds (67%) and the unexplained risk suggests that low socioeconomic status seems to be conferring risk through pathways other than through risk behaviours. These risks were confined to men and there were geographic differences.

There are a number of strengths to our study including (i) the study power and sample size – this is the largest case–control study to-date which has examined in detail the aetiology of UADT cancer associated with socioeconomic factors[6]; (ii) the strict inclusion criteria – which permitted only histologically confirmed incident cases; (iii) the multiple socioeconomic measures used – education, and detailed socioeconomic occupation history; and (iv) the considerable efforts to ensure that the confounding effects of risk factors were taken into account in our analyses – including the use of multiple variables thoroughly capturing smoking, alcohol consumption and dietary consumption of fresh fruits and vegetables.

All interview case–control studies have limitations imposed by study design.[18] Specifically, in relation to our study, several methodological issues need to be discussed. Both population and hospital sources of controls were used depending on the study centre. For socioeconomic analyses it would be preferable to have only population controls to permit full examination of socioeconomic differences – although low participation rates from population controls may also introduce socioeconomic bias. We previously explored these issues in the ARCAGE study Glasgow centre – where we investigated the effects of selection and participation bias and were able to demonstrate that the approach utilised to recruit population controls provided subjects socioeconomically representative of the population.[19] Hospital control recruitment has the advantage of better participation rates but introduces other problems of comparison. Where hospital controls were employed within the ARCAGE study efforts were made to exclude diagnoses related to smoking and drinking. However, in general, those in lower socioeconomic groups have a higher risk of hospital admission.[20] Thus the association between UADT cancer and low socioeconomic attainment could have been underestimated. We could not undertake a formal evaluation of this bias because we did not have socioeconomic data on the source population of the cases (and controls) from the hospital-based study centres. However, subgroup analysis showed similar findings independent on source of controls.

We measured socioeconomic status through education and occupational measures. Education is defined, in the context of socioeconomic status, as the aspect of 'formal education' related to the 'systematic instruction, schooling or training given to the young in preparation for the work of life'.[21] It relates to the 'status' domain of Weber's theory on social stratification[22] and it confers a broad set of resources including the ability to obtain knowledge and facts, learn concepts and ideas, obtain skills to access information, and gain the ability to critically evaluate information.[23] It can be measured as both a continuous variable – which gives greater importance to the length of time spent in education, and a categorical variable – where the levels capture achievements and elements of prestige.[23]

The advantages of education as a measure of SES include it is relatively easy to measure; it is not as loaded or controversial a question as other SES measures, e.g. income; it can capture SES in the early stages of the life course as it is strongly influenced by parental SES; it is broadly stable across the life course; and it usually predates and to some degree determines employment and the ability to earn income.[23] However, the disadvantages include it is generally fixed in adult life and generally shows little variance; it can be affected by broad cohort effects with secular changes to educational experiences being generational (e.g. the average level of education has increased markedly since the 1960s in Europe – particularly in women[24]); and it also only provides information on quantity rather than the quality of education received.[23] Pooling education data across different countries – with differing education systems is also a potential problem and inconsistencies in classification cannot be ruled out. Our analysis overcomes this to a degree, by standardising to recognised broad categories of education, and by undertaking subgroup analysis on the lowest and highest categories as recorded in each centre.

Occupational social class is basically a means of measuring SES based on employment. It measures 'prestige' and the 'status' domain of Weber's theory of social stratification.[22] We used both the RGSC which has a broad 'manual' and 'non-manual' stratification of jobs and the ISEI. The advantages of occupational social class include their wide use and the way in which they are the major way society is stratified which in turn influences the structure of individuals' lives. The disadvantages include the somewhat arbitrary and subjective method of coding and the heterogenous nature of each stratum.[23]

While we found an association with low educational attainment over and above behavioural risks, similar results were not observed for low occupational social class and unemployment experience. This difference between educational and occupational SES measures is an interesting, although not a unique finding in inequalities research – as the measures, while highly correlated, are not necessarily interchangeable and the results on the relative importance of SES measures on health are heterogenous.[25] Our findings – with the complete attenuation of risk (when adjusting for behaviours) associated with low occupational social class but not with education – are consistent with a Scottish study that shows that occupational social class was more strongly associated with smoking behaviour than with education.[26] However, this is not universally found – with other studies noting behavioural factors are more commonly associated with education than occupational SES measures.[27]

Investigating the specific occupational exposures was beyond the scope of our present analysis, however, no other study has explored the potential confounding effects of smoking, alcohol consumption and diet behaviours quite as thoroughly. Nevertheless residual confounding from the aspects of these behaviours not adequately captured by the variables could not be ruled out – although this is likely to be limited given the thorough lifetime lifestyle history and the use of multiple variables of smoking and alcohol consumption in our analysis. Occupational toxic exposures could play a relatively important role in particular for larynx cancer and may also help explain the greater inequalities observed in our study for this cancer site. Increased risk has previously been reported for occupations with exposure to asbestos, coal dust, formaldehyde, nickel,[10] as well as sulphuric or other strong acids.[28]

Our overall findings (independent of behaviours) are similar to a recent cohort study in Denmark of social inequality in oral, pharynx and larynx cancers which concluded that cancer risk increased with decreasing SES across a range of educational and occupational measures.[29] And our unadjusted overall risk estimate is comparable to a recent systematic review and meta-analysis of 37 case–control studies,[6] which found that compared to high SES, the risk associated with developing oral cancer was OR 1.85 (95% CI 1.60, 2.15) for those with low educational attainment. However, in our fully adjusted model the risk was reduced markedly when smoking, alcohol and diet behaviours were taken into account. This contrasts sharply to the earlier meta-analysis of the 17 studies which adjusted for smoking and alcohol consumption where the OR did not significantly reduce.[6] This could be explained by the thorough process and detailed models developed to adjust for behavioural confounding, and the benefits of individual-level analysis over the meta-analysis of published risk estimates.

The educational inequalities by sex and country grouping observed are somewhat consistent with the pervious studies – for men they mirror the inequalities in smoking and lung cancer incidence across Europe, but the reverse pattern for women was not seen.[30] Our data also relate to the evidence on inequalities in UADT cancer mortality which suggests differences between men and women across Europe – with no inequalities in UADT cancer observed among women, however, the pockets of wide inequalities among UADT cancer mortality previously noted among men (France and Spain) were not replicated here.[31] These mortality data have been described as corresponding weakly to the limited data available on alcohol consumption inequalities – which seems to show a north-south divide with high consumption among higher educated men in Northern Europe and among lower educated men in Southern Europe.[31]

Explanations for the association of low education attainment and poor health have yet to be fully 'unbundled'.[32] In terms of the association with UADT cancer risk, potential mechanisms could include low or lack of education: (i) acting across the life-course – as a potential direct causal effect – as it generally fixed in early life it may also reflect childhood experiences[33] – although the evidence in relation to cancer risk in general is quite limited[34]; (ii) influencing position in society and the inferred stresses – via a direct path[35] or through smoking and alcohol drinking[36]; (iii) influencing access to health care, health information[37] – e.g. access to dental services for a 'regular dental check-up' has been shown to be protective for UADT cancer risk[38]; (iv) influencing occupation and reflecting income[23]; (v) determining values for the future – and so 'risky' behaviours[39]; (vi) as a means of developing cognitive skills – and so decision-making[23,33]; (vii) affecting preferences – and so locus of control and (vii) determining social networks – including behaviours which can be 'culturally' patterned.[23,40] The potential explanations for socioeconomic inequalities of UADT cancer risk seem to broadly boil down to: (i) Rose's 'cause of the cause' hypothesis[41] – with the behavioural risk factors being the widely accepted intermediate pathway; or potentially (ii) more 'direct' roots from social factors – theorised as the: material, psychosocial, eco-social or life-course[42] models for social explanations of disease. In addition, the biological pathways between direct effects of socioeconomic circumstances and cancer development are not entirely clear, but emerging hypotheses include the 'biological ageing' effects resulting from poor socioeconomic circumstances[43] – with this process perhaps being mediated (or bio-marked) by shortened telomeres.[44]

Our study provides some evidence that socioeconomic inequalities in the risk associated with UADT cancer are not fully explained by the traditionally recognised risk factors of smoking, alcohol consumption and diets low in fruits and vegetables. However, a significant proportion (two-thirds) of cases could be prevented if we were able to address these risk behaviours – although to do this the socioeconomic context needs to be taken into account. Our data also demonstrate that the socioeconomic effect may operate through other mechanisms. Education is the most powerful socioeconomic factor. This unexplained residual risk association with low education warrants further investigation – perhaps through a lifecourse approach which focuses on early life experience, takes into account social mobility and includes the examination of biological processes.

Conflict of interest statement

None declared.

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