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Incidence, morbidity and mortality of patients with achalasia in England: findings from a study of nationwide hospital and primary care data

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ABSTRACT

Background

Achalasia is an uncommon condition characterised by failed lower oesophageal sphincter relaxation. Data regarding its incidence, prevalence, disease associations and long term outcomes are very limited.

Methods

Hospital Episode Statistics (HES) include demographic and diagnostic data for all English hospital attendances. The Health Improvement Network (THIN) includes the primary care records of 4.5 million UK subjects, representative of national demographics. Both were searched for incident cases between 2006 and 2016 and THIN for prevalent cases. Achalasia subjects in THIN were compared with age, sex, deprivation and smoking status matched controls, for important co-morbidities and mortality.

Results

There were 10,509 and 711 new achalasia diagnoses identified in HES and THIN respectively. The mean incidence per 100,000 people in HES was 1.99(95% CI 1.87-2.11) and 1.53(1.42-1.64) per 100,000 person years in THIN. The prevalence in THIN was 27.1(25.4-28.9) per 100,000 population. Incidence Rate Ratios (IRR) were significantly higher in achalasia subjects (n=2,369) compared to controls (n=3,865) for: oesophageal cancer (IRR 5.22(95%CI: 1.88-14.45),p<0.001), aspiration pneumonia (13.38(1.66-107.79),p=0.015), lower respiratory tract infection (1.33(1.05-1.70),p=0.02) and mortality (1.33(1.17-1.51),p<0.001). The median time from achalasia diagnosis to oesophageal cancer diagnosis was 15.5(IQR 20.4) years.

Conclusion

The incidence of achalasia is 1.99 per 100,000 population in secondary care data and 1.53 per 100,000 person years in primary care data. Subjects with achalasia have an increased incidence of oesophageal cancer, aspiration pneumonia, lower respiratory tract infections and higher mortality. Clinicians treating patients with achalasia should be made aware of these associated morbidities and its increased mortality.

What is already known on this subject?

- Achalasia is uncommon, but data on its incidence and prevalence are unclear.
- An association to oesophageal cancer has been reported.

What are the new findings?

- Incidence of achalasia is 1.99 per 100,000 population and 1.53 per 100,000 person years based on secondary care and primary care data respectively.
- Achalasia prevalence is 27.1 per 100,000 people.
- Oesophageal cancer is over 5 times more likely in achalasia patients, presenting on average 15 years after diagnosis.
- Achalasia is associated with increased mortality and an increased risk of respiratory tract infections.

How might these findings impact on clinical practice in the foreseeable future?

- Incidence and prevalence data should inform service planning for therapy for this condition.
- The time to diagnosis of oesophageal cancer should be taken into account when considering screening for this patient group.

INTRODUCTION

Achalasia is characterised by a lack of relaxation of the lower oesophageal sphincter. Symptom onset is typically insidious, with several years of dysphagia, regurgitation and progressive weight loss until a diagnosis is made. It has a substantial impact on quality of life through making meal times miserable.

Only limited data exist to describe the epidemiology of achalasia. The reported incidence of achalasia varies between 0.03 per 100,000 in a Zimbabwean population(1), 1.07 per 100,000 in Chicago in the United States of America(2), and 1.63 per 100,000 in Canada(3). However these studies included small cohorts of only 25, 379 and 463 subjects with achalasia respectively. The largest UK study, in 1987, reported an incidence of 0.9 per 100,000 people but was derived only from hospital data(4). Estimates of achalasia prevalence have similar limitations.

Left untreated the clinical progress of achalasia subjects includes gradual dilatation of the oesophagus and eventual mega-oesophagus. However, there is little data available to describe the long term impact of achalasia following diagnosis and therapy. Life expectancy in patients with achalasia has been previously reported to be similar to background population but these estimates were derived from cases series rather than population based data(5). Several studies have suggested an association between achalasia and oesophageal cancer(6, 7), leading to debate regarding the potential value of endoscopic screening for this patient group.

We have therefore examined the incidence, prevalence, associated morbidity and mortality of subjects with achalasia in two national patient databases.

MATERIALS AND METHODS

Data Sources

Hospital Episode Statistics

Hospital Episode Statistics (HES) are recorded to deliver administrative functions such as payment to secondary care providers in England. HES has also been made available for secondary research purposes. Unique identification codes link each admission episode to individual patients enabling longitudinal analysis. Available data includes diagnostic codes (International classification of diseases 10 (ICD-10)), demographic and administrative data. HES includes procedures performed as an outpatient in secondary care such as endoscopy.

The Health Improvement Network

The Health Improvement Network (THIN) represents a group of General Practices (primary care) covering 6% of the UK population, which is representative of the UK population structure(8). Diagnosis and clinical presentations are recorded as Read codes, a hierarchical coding system(9). Additional information includes demographic, laboratory and prescription data. Individual practices were eligible for inclusion in the study from the later of the following two dates to ensure that the practice was making full use of the Electronic Medical Record (EMR): one year after the date their EMR was installed; and after the practice's acceptable mortality recording date. To ensure there was sufficient time to record baseline co-morbidities data, individual subjects were eligible for inclusion from the date their practice became eligible for inclusion in the study or one year after registration with their practice if this date was later.

Validation

HES data were validated by interrogation of local endoscopy reporting software, an oesophageal manometry database and surgical operation logs during the study period at Sandwell and West Birmingham Hospitals NHS Trust. All subjects with achalasia listed as a reported finding, prior diagnosis or indication were collated and electronic records were then hand searched to ensure suitability for inclusion in the study. This figure was then compared to the equivalent data generated from HES. There is no current mechanism to validate THIN data, however the data integrity is supported by the stringent minimum data quality standards described above.

Incidence and Prevalence Data

HES were searched for any subject with a diagnostic code in the primary position for achalasia (appendix A) from 1st of January 2006 to 31st Dec 2015. The code may be associated with any

hospital attendance including outpatient consultation, endoscopy or other diagnostic test, or for treatment and complications of achalasia. Subjects were considered to have an existing diagnosis if a diagnostic code for achalasia was present in HES at any time prior to this period. Sex, Index of Multiple Deprivations and Ethnicity were extracted for this group. Incidence was calculated using annual mid-year England population figures provided by the Office for National Statistics and reported per 100,000 population with 95% Confidence Intervals. HES data only includes subjects in England, rather than the whole UK, and the incidence was calculated on the basis of the source population (approximately 50 million persons).

THIN was searched using the READ code for achalasia for both new and previously diagnosed cases of achalasia (appendix B) as communicated from secondary care. Incidence is reported annually per 100,000 person years with 95% confidence intervals and prevalence as on 1st of January each year per 100,000 populations with 95% confidence intervals.

Retrospective Cohort Study of morbidity and mortality outcomes in the THIN database

For outcome analysis only THIN database was utilised because it is possible to generate controls from the source population to compare outcomes. The index date of the achalasia subjects in THIN were defined as the date they were eligible to take part in the study if they already had a diagnosis of achalasia, or the date they were diagnosed with achalasia if they were incident cases. Achalasia subjects in THIN were matched for age at index date (within 2 years), sex, deprivation (Townsend deprivation score) and smoking status to two control subjects without a diagnosis of achalasia. The controls were selected from the same general practice as the matched case. Group demographics and incidence rates for pre-specified outcomes of interest were calculated for achalasia and control groups during the study period from 1st January 1996 to the 1st September 2015. New outcome codes were sought in matched groups from the index date until the first of the following outcomes occurred (exit date); subject died, subject left practice, last data collection from practice, study end date or subject diagnosed with the outcome of interest. Subjects were excluded if there was a diagnosis of the outcome of interest prior to achalasia diagnosis. Subjects were also excluded from the study if they had a diagnosis of oesophageal cancer within one year of achalasia diagnosis, or if they had a diagnosis of Chagas' disease.

Prospectively determined new outcomes included: any cardiovascular disease (including ischaemic heart disease, stroke or TIA, and heart failure), oesophageal cancer, any cancer (excluding

oesophageal), peripheral vascular disease, aspiration pneumonia, lower respiratory tract infection (LRTI), dementia and all-cause mortality (Appendix B).

Statistical Analysis

The matched groups baseline characteristics in THIN are described in proportions for categorical variables (sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus, and use of lipid lowering medications) and with mean (standard deviation) for normally distributed continuous variables (age and BMI) and Mann-Whitney U test for skewed continuous variables (person years).

An estimated incidence rate ratio (IRR) was calculated for each outcome within the achalasia and control groups. Then adjusted IRRs were calculated using the Poisson regression for individual patient covariates (age, sex, Townsend deprivation score, smoking status, hypertension, diabetes mellitus and the use of lipid lowering medications) as appropriate. “Any cardiovascular disease”, stroke or TIA, heart failure and peripheral vascular disease were further adjusted for diabetes, lipid lowering drug use and hypertension. The median and interquartlie range (IQR) of time from achalasia diagnosis to oesophageal cancer, LRTI and death is also reported. In control subjects, start time was considered to be the time of study entry. Cumulative incidence plots were constructed for time to oesophageal cancer, LRTI and all cause mortality. BMI was treated as a categorical variable to address missing values. Mortality was adjusted for Charlson Score in addition to the factors listed above. The Charlson score is based on a list of co-morbidities, each with an assigned score. The sum of a patient’s individual co-morbidity scores is the final score(10). Incidence rate ratios were calculated with 95% confidence and a statistical significance threshold of $p<0.05$.

All analysis was conducted using Stata v14.0 software(11). The THIN data collection scheme received multi-centre research ethics committee (MREC) approval in 2003 with scientific committee approval of this particular study in March 2017 (SRC17THIN133) from ‘IMSHealth’ (data provider). Pseudonymised HES data has been shared by NHS Digital under a data sharing agreement for the purpose of service evaluation including estimation of disease burden. Ethical approval is not required for HES studies.

RESULTS

Validation

At Sandwell and West Birmingham Hospital NHS Trust there were 56 subjects with a new diagnosis of achalasia within the study period. This correlates strongly (96%) with the 54 coded for within the HES database for Sandwell and West Birmingham Hospitals NHS Trust during the study period.

Subject demographics

The HES subjects included 10,509 incident cases of achalasia in England over a 10 year period. The median age was 59 (IQR 43-75) years and the cohort was split evenly with respect to sex (49.7% male, 50.3% female). The THIN subjects included 711 incident achalasia diagnoses in the UK. The median age was 62 (IQR 45-75) years and the cohort was split evenly with respect to sex (47.1% male, 52.9% female). Full cohort demographics are shown in table 1.

Incidence and prevalence of achalasia

The overall incidence per 100,000 population over the study period in HES was 1.99 (95% CI 1.87-2.11) and 1.53 (1.42-1.64) per 100,000 person years in THIN. The mean prevalence measured in THIN was 27.1 (25.4-28.9) per 100,000 population. The incidence seen in HES increased over the study period from 1.73(1.62-1.85) in 2006 to 2.24(2.11-2.36) per 100,000 population in 2015. A similar increase was not observed in achalasia subjects in THIN. The annual incidence and prevalence from each database is presented in table 2.

Demographics and co-morbidity in the matched achalasia and control groups

There were 2,369 achalasia cases matched to 3,865 controls within THIN. There was a mean of 6.1 (SD 5.4) and 6.4 (5.4) person years follow-up for achalasia subjects and controls respectively. Achalasia subjects were slightly older as they were matched to within 2 years (56.7 vs. 55.5 years, p=0.03), however there was no difference in sex, BMI or deprivation index quintile. The incidence of hypertension(506(21%) vs. 928(24%), p=0.016), diabetes(126(5.3%) vs. 278(7.2%), p=0.004) and lipid lowering medication use(342(14.4%) vs. 635(16.4%), p=0.04) was lower in the achalasia cohort compared to the matched controls(table 3).

Morbidity outcomes in the matched achalasia and control groups

Following adjustment for potential confounding factors, oesophageal cancer was more common in the achalasia group compared to the control group; adjusted IRR 5.22 (95% CI 1.88-14.45), p=0.001. Also more common in the achalasia group were aspiration pneumonia 13.4(1.7-107.8), p=0.015 and

lower respiratory tract infection (LRTI) 1.3(1.1-1.7), p=0.02 (table 4). The incidence of ischeamic heart disease, peripheral vascular disease, heart failure, dementia and cancer (excluding oesophageal cancer) did not differ between the groups. The median time from achalasia diagnosis to oesophageal cancer and LRTI was 15.5 (IQR 5.8-26.2) and 7.5 (1.5–13.6) years respectively. Cumulative incidence plots of the time from achalasia diagnosis to oesophageal cancer and LRTI are displayed in figures 1 and 2 respectively.

Mortality in achalasia subjects

There were 441 deaths in 14,321 person years in the achalasia group compared to 553 deaths in 24,594 person years in the control group. The incidence rate ratio was 1.37 (1.21-1.55). Mortality remained significantly higher in the achalasia group despite adjusting for Charlson score, BMI, age, sex, smoking status, diabetes, lipid lowering drug use and hypertension; adjusted IRR 1.33(95% CI 1.2-1.5, p<0.001)(table 5). The median time to death was 6.8 (IQR 0.6-12.9) years. The cumulative incidence plot of time from achalasia diagnosis to death is displayed in figure 3.

DISCUSSION

The incidence of achalasia in England was between 1.42 and 2.11 per 100,000 between 2006 and 2016 and its prevalence 27.1 per 100,000. Both the incidence and prevalence are higher than previously thought in the UK population. A previously unrecognised increased mortality in achalasia subjects has been demonstrated, as has an association between achalasia and aspiration pneumonia and lower respiratory tract infections. Furthermore this study confirms a significant association between oesophageal cancer and achalasia with a fivefold higher incidence in achalasia.

There are limited recent data on the incidence and prevalence of achalasia. Although significantly higher than the incidence reported in the largest English study (0.9 per 100,000)(4), the results reported here are in keeping with the incidence reported in a more recent Canadian study, which reported an incidence of 1.63(95% CI 1.2-2.1) per 100,000(3). However the prevalence reported in the current study is significantly higher than that reported in Canada (10.8(9.7-11.9)). A potential reason for this discrepancy is due to case finding, as any achalasia subject was included in the present study, whereas the Canadian study only included subjects attending for treatment by pneumatic dilatation or surgical myotomy. Therefore any subject in the Canadian study that did not present for treatment would not be included. Although the authors have validated their data showing excellent sensitivity and specificity, the validation population were those attending for treatment. This important source of bias was not addressed in the prevalence analysis.

High resolution manometry diagnoses achalasia more accurately and provides information on subtypes that is relevant to response to therapy(12). The widespread use of high resolution manometry might be expected to marginally increase the incidence of achalasia and such a rise in incidence over time was seen in the HES database but not the THIN database.

An association with oesophageal cancer has been previously reported in achalasia. The mechanism is not understood, but, it has been postulated that poor oesophageal emptying leads to stasis and inflammation and subsequently dysplasia and eventually to neoplasia(13). Estimates of the magnitude of the increased risk vary. In a Swedish cohort study a 16-fold increase (SIR 16.6(8.8-28.3))(7) has been reported. However a more recent Swedish study described a 10-fold increase (SIR 10.5(7.0-15.9)) in risk of oesophageal cancer(6). The higher background UK oesophageal cancer incidence compared to Sweden is likely to have reduced the relative increase in risk in achalasia subjects in the present study. The median time from achalasia diagnosis to oesophageal cancer was

15.5 (IQR 5.8-26.2)years. This estimate is imprecise due to the small number of observed events, as oesophageal cancer remains a rare event even in this population. It is therefore not possible to discern a discrete period of increased risk following achalasia diagnosis, however cancers within 5 years of diagnosis appear uncommon. Unfortunately, a limitation of the present study is the inability to distinguish between oesophageal squamous cell carcinoma and oesophageal adenocarcinoma, as neither database is linked to a cancer registry.

Several case reports describe recurrent respiratory tract infections in the presence of recently or undiagnosed achalasia(14-16). There are no population based studies that have previously demonstrated an association between achalasia and aspiration pneumonia or lower respiratory tract infection (LRTI). The peak incidence of LRTI was 7.5 years following diagnosis, however, the cumulative incidence plot (figure 2) suggests this event occurs regularly in the years following diagnosis. 75% of these episodes occurred at least 18 months after diagnosis but a small proportion of LRTIs may be related to initial achalasia treatment (surgery or pneumatic dilatation). However it seems likely that generally this association represents the same process as may contribute to oesophageal cancer, i.e. incomplete emptying of the oesophagus with consequent risk of aspiration of oesophageal contents.

More subjects died in the achalasia group compared to the matched controls when adjusted for a number of risk factors. The median time to death was 6.8 (IQR 0.6-12.9) years, potentially coinciding with both any peri-procedural mortality from treatment (17) and excess LRTI in this group. However, these factors alone may be insufficient to explain the increased mortality. The increased incidence of oesophageal cancer is also likely to contribute, but this cause of increased mortality is later in the natural history and uncommon. Unfortunately the cause of death as stated on the death certificates was not available in this study. Although mortality in achalasia has been investigated previously in a tertiary centre case series, in that study, no increase in mortality was reported(5).

This analysis is dependent upon accurate coding of achalasia and associated diagnoses. The data provided by HES has been validated, demonstrating high levels of agreement in an individual provider. Data completeness can also supported by comparison of the median age to other studies including Samo (median age 56)(2) and Enestvedt (mean age 62)(18) compared to 59 in HES and 62 in THIN. Unfortunately oesophageal manometry data were not available within HES or THIN to support the coded diagnosis of achalasia. THIN data is centrally quality controlled, therefore providing reassurance that coding is accurate. However as the diagnosis is established in secondary

care, the primary care Read codes are dependent on accurate communication. Therefore ascertainment bias may lead to under-estimation of the incidence and prevalence of achalasia in THIN data. This potentially explains the variation in incidence between the two datasets, although this is small with the peak discrepancy between 95% CI 0.38 per 100,000. However, the similarity seen between data from THIN and HES is reassuring. A diagnosis of achalasia will be made in a hospital setting and recorded on HES, and then coded in THIN once the diagnosis is communicated to primary care. The similarity in incidence figures between the datasets supports the accuracy of coding and subsequent case ascertainment.

Several risk factors for oesophageal cancer were not available for this analysis. The prevalence of acid reflux, alcohol and dietary information were not available, therefore they could not be included in the matching or corrected for in the analysis. However groups were matched by age, sex, smoking status and deprivation. In addition mortality was also corrected for Charlson score. The use of two national databases to address the same question increases confidence in the accuracy of the incidence of achalasia reported here. THIN and HES are independent of each other, utilising different coding systems and different sources of clinical data. Therefore it is reassuring that the variation in reported incidence is small. This is also the largest epidemiological description of achalasia ever reported, including over 11,000 cases with no study since Mayberry et al in 1987 having reported more than 1000 cases (4).

This is the first study to report from population based data on increased mortality and key morbidities associated with achalasia. Our findings are crucial to the prevention of LRTI in achalasia through, for example, encouraging smoking cessation, and to the consideration of screening and risk factor modification (smoking and alcohol intake) for oesophageal cancer in subjects with achalasia. Clinical guidelines should consider highlighting identified complications of achalasia and urge vigilance among the clinicians to detect and manage them early. Future studies should aim to replicate our findings in other nations.

COMPETING INTERESTS

None declared.

FUNDING

Internal funding only.

CONTRIBUTORSHIP

PH, TT, NT and KN conceived of the study design. All authors participated in data collection and analysis. All authors contributed to the drafting of the final manuscript.

Table 1: The demographics of the Hospital Episode Statistics and The Health Improvement Network achalasia subjects

		HES	THIN
Sex	Male	5226 (49.7)	335 (47.1)
	Female	5283 (50.3)	376 (52.9)
Age (median, IQR)		59 (43-75)	62 (45-75)
Deprivation Quintile*	Most deprived quintile	1848 (17.6)	80 (11.3)
	2nd most deprived quintile	2094 (19.9)	124 (17.4)
	Middle quintile	2176 (20.7)	161 (22.6)
	2nd least deprived quintile	2199 (20.9)	148 (20.8)
	Least deprived quintile	2173 (20.7)	176 (24.8)
	Unknown	19 (0.0)	22 (3.1)
Ethnic Group**	White	9117 (86.8)	301 (42.3)
	Asian or Asian British	79 (0.8)	17 (2.4)
	Black or Black British	480 (4.6)	9 (1.3)
	Mixed	282 (2.7)	-
	Any other ethnic group	176 (1.7)	-
	Unknown	375 (3.6%)	384 (54.0)

*HES uses Index of multiple deprivations (2010), quintile 1 is the most deprived. THIN uses Townsend index, quintile 5 is the most deprived. Therefore this is displayed from most to least deprived quintiles.

** THIN was found to include multiple ethnicities per subject depending on the scale applied. Therefore when there was ambiguity subjects were listed as unknown.

Table 2 The incidence and prevalence of achalasia reported in Hospital Episode Statistics and The Health Improvement Network by year

Year	Incidence rate HES	95% CI	Incidence rate THIN	95% CI	Prevalence rate THIN	95% CI
2006	1.73	1.62-1.85	1.41	1.01-1.74	21.14	19.79-22.56
2007	1.80	1.69-1.92	1.66	1.08-1.81	21.72	20.37-23.14
2008	1.80	1.68-1.91	1.55	1.30-2.08	22.49	21.12-23.91
2009	1.85	1.74-1.97	1.70	1.21-1.96	23.16	21.79-24.6
2010	2.02	1.90-2.14	1.66	1.34-2.12	23.66	22.27-25.12
2011	1.78	1.67-1.90	1.42	1.31-2.09	24.62	23.19-26.12
2012	2.03	1.91-2.16	1.55	1.20-1.96	25.23	23.77-26.76
2013	2.18	2.06-2.31	1.62	1.26-2.05	26.06	24.56-27.62
2014	2.42	2.29-2.56	1.48	1.11-1.91	26.34	24.78-27.97
2015	2.24	2.11-2.36	1.34	0.96-1.80	27.10	25.44-28.85

HES – Hospital Episode Statistics

THIN – The Health Improvement Network

Table 3 The Health Improvement Network achalasia and matched control groups characteristics

	Achalasia Cases	Control Cases	P value
Number of subjects	2,369	3,865	-
Person years of follow-up (SD)	6.1 (5.4)	6.4 (5.4)	0.02
Age (SD)	56.6 (19.8)	55.5 (19.3)	0.03
Male Sex	1166 (49.2%)	1902 (49.2%)	0.995
Body mass index (SD)	25.62 (5.3)	25.37 (4.1)	0.07
Current smoking	379 (16%)	573 (14.8%)	0.211
Hypertension	506 (21%)	928 (24%)	0.016
Lipid regulating medications	342 (14.4%)	635 (16.4%)	0.04
Diabetes mellitus	126 (5.3%)	278 (7.2%)	0.004
Charlson Co-morbidity score: 0	1468 (62.0%)	2550 (66.0%)	0.001
1	496 (20.9%)	797 (20.6%)	
2	220 (9.3%)	285 (7.4%)	
3	110 (4.6%)	129 (3.3%)	
>3	75 (3.2%)	104 (2.7%)	
Townsend index*: 1	1026 (27%)	592 (25%)	0.377
2	890 (23%)	525 (22%)	
3	776 (20%)	482 (21%)	
4	612 (16%)	390 (17%)	
5	400 (10%)	267 (11%)	
Not available	108 (3%)	81 (3%)	

*1 is the least deprived group for Townsend deprivation index

Table 4 Comparison of disease outcomes between achalasia cases and matched controls in The Health Improvement Network

	All Cardiovascular Disease		Ischaemic Heart Disease		Stroke/TIA		Heart Failure		Peripheral Vascular Disease		Oesophageal Cancer		Any Cancer		Aspiration Pneumonia		LRTI		Dementia	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
No. Subjects	2,033	3,369	2,147	3,520	2,262	3,706	2,289	3,776	2,303	3,801	2,366	3,863	2,226	3,699	2,359	3,864	2,263	3,744	2,338	3,824
No. of Outcomes	278	451	128	242	113	182	97	120	63	73	16	6	150	224	9	1	135	170	86	127
Person-years	15,379	26,027	15,985	26,818	16,218	27,503	16,306	27,841	16,379	27,925	16632	28229	16,071	27,420	16,617	28,235	16,207	27,630	16,468	27,981
Incidence Rate (per 1000 person-years)	18.1	17.3	8.0	9.0	7.0	6.6	5.9	4.3	3.8	2.6	1.0	0. 2	9.3	8.2	0. 5	0.04	8.3	6.2	5.2	4.5
Incidence Rate Ratio (95% CI)	1.01 (0.83-1.21)		0.97 (0.74 - 1.26)		1.02 (0.79-1.31)		1.27 (0.94-1.72)		1.21 (0.82-1.78)		5.09 (1.85-14.01)		1.12 (0.89-1.40)		13.62 (1.70-108.87)		1.34 (1.05-1.70)		1.11 (0.82-1.49)	
***p*-value**	0.958		0.802		0.892		0.118		0.331		0.002		0.3333		0.014		0.018		0.507	
Adjusted Incidence Rate Ratio (95% CI)	1.04 (0.86-1.26)		1.00 (0.76-1.31)		0.99 (0.77-1.28)		1.32 (0.97-1.80)		1.31 (0.88-1.94)		5.22 (1.88-14.45)		1.10 (0.88-1.38)		13.38 (1.66-107.79)		1.33 (1.05-1.70)		1.10 (0.82-1.50)	
***p*-value**	0.714		0.993		0.953		0.077		0.186		**0.001**		0.413		**0.015**		**0.02**		0.521	

Table 5 Mortality in achalasia subjects and controls in The Health Improvement Network

	Achalasia	Control
Number of Subjects	2,369	3,865
Numbers of deaths	441	553
Person-years	14321	24594
Incidence Rate (per 100 person-years)	3.08	2.25
Incidence Rate Ratio (95% Confidence intervals)	1.37 (1.21-1.55)	
***p*-value**	<0.001	
Incidence Rate Ratio (95% Confidence intervals) adjusted*	1.33 (1.17-1.51)	
***p*-value**	<0.001	

***** Adjusted for Charlson Score, Body mass index, age, sex, smoker, diabetes, lipid lowering drugs and hypertension

Figure 1: The cumulative incidence plot of time from achalasia diagnosis to oesophageal cancer

Figure 2: The cumulative incidence plot of time from achalasia diagnosis to lower respiratory tract infection

Figure 3: Cumulative incidence plot of time from achalasia diagnosis to death

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