2.2.2 Cancer of the oesophagus

There are two main histological subtypes of cancer of the oesophagus: adenocarcinoma and squamous cell carcinoma. Oesophageal squamous cell carcinoma arises from epithelial cells that line the oesophagus and typically occurs in the upper and middle parts of the oesophagus. Oesophageal adenocarcinoma originates from glandular cells; it occurs in the lower portion of the oesophagus and can spread into the gastric cardia.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for oesophageal adenocarcinoma. Although recent pathological classification recognizes the histological similarity between oesophageal adenocarcinoma and gastric cardia cancer, most epidemiological studies classify gastric cardia cancer with stomach cancer, and therefore these studies are considered in Section 2.2.3. Also, because evidence to date strongly suggests differences in etiological factors between oesophageal adenocarcinoma and squamous cell carcinoma, the results are presented separately for each histological subtype, and no results are presented for oesophageal cancer overall.

(a) Cohort studies

See Table 2.2.2a.

(i) Adenocarcinoma of the oesophagus

Several cohort studies (with at least 75 incident cases) have been published since the previous IARC evaluation (IARC, 2002). In all of those studies, BMI and/or weight were positively associated with risk (Engeland et al., 2004; Lindblad et al., 2005; Samanic et al., 2006; Merry et al., 2007; Reeves et al., 2007; Abnet et al., 2008; Corley et al., 2008; O'Doherty et al., 2012; Lindkvist et al., 2014; Steffen et al., 2015). Associations were similar across follow-up periods in one study (Engeland et al., 2004) and in another study that excluded the first 5 years of follow-up (Abnet et al., 2008). There did not appear to be any meaningful differences in associations when stratifying by smoking status (O'Doherty et al., 2012; Lindkvist et al., 2014) or when limiting results to non-smokers or never-smokers only (Reeves et al., 2007; Abnet et al., 2008).

In a meta-analysis including five prospective studies (Renehan et al., 2008), a relative risk of 1.5 for a 5 kg/m^2 increase in BMI at baseline was reported, with similar values in men and in women.

Few studies have examined the association between BMI measured at younger ages and subsequent risk of oesophageal adenocarcinoma. In the Netherlands Cohort Study, there was evidence of a positive association between high BMI at age 20 years and risk, although the relative risk estimate was not statistically significant (Merry et al., 2007).

The association between BMI change and incidence of oesophageal adenocarcinoma was examined in two prospective studies (Samanic et al., 2006; Merry et al., 2007). The first study, which considered BMI change during a period of 6 years, did not find evidence for a positive association [the analysis was based on only 28 incident cases] (Samanic et al., 2006). The second study, which included 113 cases, found that a 1 kg/m^2 increase in BMI from age 20 years to baseline was significantly associated with a 14% higher risk (95% CI, 1.06–1.23) (Merry et al., 2007).

There have been few prospective studies of abdominal fatness in relation to risk of oesophageal adenocarcinoma. A study nested within the Multiphasic Health Check-up cohort of Kaiser Permanente Northern California members observed a positive association between sagittal abdominal diameter [distance from the anterior to the posterior of the abdomen] and incidence

of oesophageal adenocarcinoma (Corley et al., 2008). Similarly, strong positive associations were reported of both waist circumference and waist-to-hip ratio with incidence of oesophageal adenocarcinoma in the National Institutes of Health–AARP Diet and Health Study (NIH-AARP) cohort ($P_{trend} \leq 0.01$ for both) (O'Doherty et al., 2012) and with oesophageal adenocarcinoma incidence/mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC) study ($P_{trend} \leq 0.0001$) (Steffen et al., 2015).

(ii) Squamous cell carcinoma of the oesophagus

Since 2001, the association between BMI and/or weight assessed at baseline and the incidence and/or mortality of oesophageal squamous cell carcinoma has been examined in at least nine individual prospective studies (Engeland et al., 2004; Lindblad et al., 2005; Tran et al., 2005; Samanic et al., 2006; Merry et al., 2007; Reeves et al., 2007; Corley et al., 2008; Steffen et al., 2009; Lindkvist et al., 2014) and in one meta-analysis (Renehan et al., 2008). In all of the studies, BMI and/or weight were inversely associated with risk. Notably, higher risks were found in the lowest BMI categories (i.e. BMI < 20 kg/m^2) compared with categories within the normal range of BMI, whereas lower risks were observed in the overweight and obese categories. Although most studies adjusted for tobacco use, not all studies included alcohol consumption, another strong risk factor for oesophageal squamous cell carcinoma in their model. Furthermore, in two studies that stratified by smoking status, there was an inverse association in current smokers but no association in non-smokers [supporting a possible confounding effect of tobacco smoking] (Steffen et al., 2009; Lindkvist et al., 2014). In contrast, in the Million Women Study, an inverse association with both incidence and mortality of oesophageal squamous cell carcinoma was noted even in the never-smokers group (Reeves et al., 2007). An inverse association was also observed in the only study in Asia, which included 1958 incident cases in China (Tran et al., 2005). There was no evidence of differences in associations based on follow-up time (Engeland et al., 2004).

A meta-analysis of five prospective studies by Renehan et al. (2008) reported a relative risk per 5 kg/m^2 increase in BMI of 0.71 (95% CI, 0.60–0.85) in men and 0.57 (95% CI, 0.47–0.69) in women.

The association between BMI measured at age 20 years and risk of oesophageal squamous cell carcinoma was examined in the Netherlands Cohort Study (Merry et al., 2007). The relative risk for BMI ≥ 25 kg/m^2 compared with BMI 20–21.4 kg/m^2 was 2.49 (95% CI, 1.15–5.40), but there was no evidence of dose–response [$P_{trend} = 0.58$]. In that study, weight loss from age 20 years to baseline was associated with a statistically significant increased risk, with a relative risk of 2.57, but there was no evidence that weight gain was associated with risk.

Only two prospective studies examined measures of abdominal fatness in relation to risk of oesophageal squamous cell carcinoma. In the Kaiser Permanente Multiphasic Health Check-up nested case–control study, there was no association between sagittal abdominal diameter and risk (Corley et al., 2008), whereas in the EPIC study, there was some evidence of a weak inverse trend of waist circumference with incidence/mortality ($P_{trend} = 0.08$) (Steffen et al., 2009).

(b) Case–control studies

See Table 2.2.2b.

(i) Adenocarcinoma of the oesophagus

Of the case–control studies reporting on oesophageal adenocarcinoma, most studies showed increases of 2.5-fold and higher in risk of oesophageal adenocarcinoma when comparing the highest and lowest BMI categories, although in a few studies these associations were not statistically significant. When assessed, adjustments

for self-reported frequency or severity, or stratification by presence or absence of gastric reflux symptoms did not substantially alter the relative risk estimates (Chow et al., 1998; Lagergren et al., 1999; de Jonge et al., 2006; Anderson et al., 2007; Löfdahl et al., 2008; Whiteman et al., 2008; Olsen et al., 2011).

A pooled analysis of data from 10 case–control studies and 2 cohort studies (Hoyo et al., 2012), including a total of 3719 adenocarcinoma cases and 10 481 controls, showed significant trends of increasing adenocarcinoma risk with increasing BMI, up to odds ratios of 4.76 (95% CI, 2.96–7.66) for oesophageal adenocarcinoma and 3.07 (95% CI, 1.89–4.99) for oesophagogastric junction adenocarcinoma when comparing BMI ≥ 40 kg/m^2 with BMI < 25 kg/m^2. Subset analyses showed similar increases in risk of adenocarcinoma when stratifying by symptoms of gastro-oesophageal reflux disease. No differences in associations were observed by sex.

(ii) Squamous cell carcinoma of the oesophagus

For oesophageal squamous cell carcinoma, several case–control studies reported an inverse association between risk and recent BMI (Vaughan et al., 1995; Chow et al., 1998; Lahmann et al., 2012), and this inverse association was observed within both smokers and never-smokers (Lahmann et al., 2012). Of the two studies that investigated the association of risk of oesophageal squamous cell carcinoma with recalled BMI at age 20 years, one found a non-significant decrease in risk in relation to higher BMI (Lahmann et al., 2012), whereas the other study, based on a total of 167 cases in Sweden, showed an increase in risk with higher BMI (Lagergren et al., 1999).

(c) Mendelian randomization studies

See Table 2.2.2c.

One Mendelian randomization study estimated the causal association between BMI and risk of oesophageal adenocarcinoma (Thrift et al., 2014). Using a genetic risk score based on 29 SNPs previously shown to be associated with BMI (Speliotes et al., 2010), this Mendelian randomization study showed that each 1 kg/m^2 increase in BMI was associated with a 23% increase in risk (95% CI, 6–43%; P = 0.01), compared with a 6% increase in risk (95% CI, 5–8%; P < 0.001) observed in the same sample by conventional epidemiological analyses.

Table 2.2.2a Cohort studies of measures of body fatness and cancer of the oesophagus

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adenocarcinoma							
Engeland et al. (2004) Population-based Norwegian cohort Norway 1963–2002	Men: 963 709 Women: 1 038 010 Incidence	Oesophageal adenocarcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	448 total	Men: – 1.00 1.80 (1.48–2.19) 2.58 (1.81–3.68) [< 0.001]	Age at measurement, height, birth cohort	
			BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	127 total	Women: 4.07 (1.44–11) 1.00 1.64 (1.08–2.49) 2.06 (1.25–3.39) [0.002]		
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 287 Men and women Incidence	Oesophageal adenocarcinoma	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	8 49 94 36	1.44 (0.67–3.10) 1.00 1.68 (1.18–2.40) 1.93 (1.24–3.01) [0.005]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Oesophageal adenocarcinoma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	34 38 10	1.00 1.58 (0.98–2.53) 2.72 (1.33–5.55) [< 0.01]	Attained age (10-yr interval), calendar year, smoking	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2006) (cont.)			BMI, 6-yr change				
			−4% to +4.9%	19	1.00		
			5–9.9%	3	0.44 (0.13–1.49)		
			10–14.9%	5	2.24 (0.81–6.21)		
			> 15%	1	1.21 (0.16–9.45)		
			[P_{trend}]		[> 0.5]		
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 (case–cohort sample from 120 852 main cohort) Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline			Age, sex For BMI change only: adjustment for BMI at age 20 yr	First year of follow-up excluded from the analyses
			< 20	3	1.29 (0.40–4.16)		
			20–24.9	51	1.00		
			25–29.9	60	1.40 (0.95–2.04)		
			≥ 30	19	3.96 (2.27–6.88)		
			[P_{trend}]		[0.001]		
			per 1 kg/m²		1.14 (1.08–1.21)		
			BMI at age 20 yr				
			< 20	21	1.07 (0.59–1.94)		
			20–21.4	24	1.00		
			21.5–22.9	37	1.61 (0.95–2.72)		
			23.0–24.9	18	1.02 (0.55–1.90)		
			≥ 25	13	1.97 (0.99–3.94)		
			[P_{trend}]		[0.17]		
			per 1 kg/m²		1.04 (0.95–1.14)		
			BMI change, age 20 yr to baseline				
			< 0	8	0.75 (0.34–1.64)		
			0–3.9	51	1.00		
			4–7.9	37	1.34 (0.86–2.08)		
			≥ 8	17	3.41 (1.88–6.18)		
			[P_{trend}]		[0.001]		
			per 1 kg/m²		1.14 (1.06–1.23)		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Oesophageal adenocarcinoma ICD-10: C15	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity	Results remained significant after excluding never-smokers and excluding the first 2 yr of follow-up
			< 22.5	22	1.06 (0.70–1.62)		
			22.5–24.9	27	1.00 (0.68–1.46)		
			25–27.4	30	1.28 (0.90–1.83)		
			27.5–29.9	23	1.57 (1.04–2.36)		
			≥ 30	48	2.54 (1.89–3.41)		
			per 10 kg/m²		2.38 (1.59–3.56)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) (cont.)			BMI	Mortality:			
			< 22.5	20	1.35 (0.87–2.11)		
			22.5–24.9	19	1.00 (0.64–1.57)		
			25–27.4	20	1.21 (0.78–1.87)		
			27.5–29.9	15	1.44 (0.87–2.39)		
			≥ 30	37	2.75 (1.97–3.85)		
			per 10 kg/m²		2.24 (1.40–3.58)		
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: "adenocarcinoma"	BMI			Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	Results were stable after excluding the first 5 yr of follow-up
			< 18.5	2	1.61 (0.39–6.55)		
			18.5–24.9	71	1.00		
			25–29.9	194	1.65 (1.26–2.18)		
			30–34.9	77	1.91 (1.38–2.66)		
			≥ 35	27	2.27 (1.44–3.59)		
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: 8140–8573	BMI			Age, sex, year of health check-up BMI results also adjusted for ethnicity	
			< 18.5	1	1.36 (0.12–15.52)		
			18.5–24.9	28	1.00		
			25–29.9	51	2.20 (1.31–3.67)		
			≥ 30	14	3.17 (1.43–7.04)		
			per 1 kg/m² increase		1.10 (1.04–1.17)		
			Sagittal abdominal diameter (cm)				
			< 20	8	1.00		
			20–22.4	13	0.92 (0.31–2.74)		
			22.5–25	12	2.35 (0.78–7.12)		
			≥ 25	22	3.47 (1.29–9.33)		
			per 1 cm increase		1.10 (1.03–1.17)		
Renehan et al. (2008) Meta-analysis 1966–2007	4 673 213 Men and women Incidence	Oesophageal adenocarcinoma	BMI	Men:		Geographical region, age (all studies), and other factors (not in all studies) such as Western diet, alcohol consumption, medical conditions (e.g. type 2 diabetes, acromegaly), or physical activity	
			per 5 kg/m² increase	1315 total	1.52 (1.33–1.74)		
			BMI	Women:			
			per 5 kg/m² increase	735 total	1.51 (1.31–1.74)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: "adenocarcinoma"	BMI			Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, intake of red and white meat, intake of fruits and vegetables; for weight, also adjusted for height	Waist-to-hip ratio also significantly associated with risk (Q3 and Q4)
			< 18.5	0	–		
			18.5–24.9	59	1.00		
			25–29.9	119	1.30 (0.94–1.78)		
			30–34.9	64	2.28 (1.57–3.30)		
			≥ 35	11	2.11 (1.09–4.09)		
			[P_{trend}]		[< 0.01]		
			Weight, quartiles (sex-specific)				
			Q1	41	1.00		
			Q2	58	1.49 (0.99–2.23)		
			Q3	53	1.37 (0.89–2.10)		
			Q4	101	2.66 (1.76–4.02)		
			[P_{trend}]		[< 0.01]		
			WC, quartiles (sex-specific)				
			Q1	37	1.00		
			Q2	49	1.36 (0.89–2.09)		
			Q3	79	1.51 (1.02–2.25)		
			Q4	88	2.01 (1.35–3.00)		
			[P_{trend}]		[< 0.01]		
Lindkvist et al. (2014) Me-Can cohort (prospective cohorts) Austria, Norway, and Sweden 1972–2006	587 700 Men and women Incidence	Oesophageal adenocarcinoma ICD-7: 150	BMI, quintiles			Sex, age, study cohort, smoking status	
			Q1	5	1.00		
			Q2	18	3.37 (1.25–9.10)		
			Q3	18	3.17 (1.17–8.57)		
			Q4	31	5.19 (2.00–13.42)		
			Q5	42	7.34 (2.88–18.68)		
			[P_{trend}]		[< 0.0001]		
			per 5 kg/m^2		1.78 (1.45–2.17)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/ mortality	Oesophageal adenocarcinoma ICD-10: C15	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 15 22 24 30 33 17 25 23 26 33 7 22 20 26 39 	 1.00 1.30 (0.67–2.52) 1.36 (0.71–2.62) 1.76 (0.93–3.31) 2.15 (1.14–4.05) [0.004] 1.00 1.54 (0.82–2.88) 1.41 (0.74–2.70) 1.57 (0.82–3.01) 2.19 (1.14–4.21) [0.03] 1.00 2.78 (1.18–6.54) 2.47 (1.03–5.92) 3.19 (1.36–7.49) 5.08 (2.21–11.7) [< 0.0001]	Age at recruitment, centre, sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each Positive associations with waist-to-hip ratio (Q4 and Q5)
Squamous cell carcinoma							
Engeland et al. (2004) Population-based Norwegian cohort Norway 1963–2002	Men: 963 709 Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	1023 total 	 2.80 (1.73–4.54) 1.00 0.72 (0.63–0.82) 0.68 (0.50–0.93) [< 0.001]	Age at measurement, height, birth cohort	
	Women: 1 038 010 Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	472 total 	 2.11 (1.23–3.62) 1.00 0.52 (0.42–0.65) 0.43 (0.32–0.59) [< 0.001]	Age at measurement, height, birth cohort	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 140 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 9 34 39 4	 1.93 (0.90–4.11) 1.00 1.13 (0.71–1.80) 0.28 (0.10–0.79) [0.01]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	1958 total	 1.00 0.96 (0.85–1.08) 0.80 (0.71–0.91) 0.81 (0.72–0.92) [< 0.001]	Age, sex	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Oesophageal squamous cell carcinoma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 134 57 13	 1.00 0.53 (0.39–0.72) 0.77 (0.43–1.36) [< 0.01]	Attained age, calendar year, smoking	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 (case–cohort sample from 120 852 main cohort) Men and women Incidence	Oesophageal squamous cell carcinoma ICD-10: C15 Histology: 8050–8076	BMI at baseline			Age, sex, current smoking, cigarettes per day, number of years of smoking For BMI change only: adjustment for BMI at age 20 yr	
			< 20	9	2.21 (0.99–4.92)		
			20–24.9	51	1.00		
			25–29.9	26	0.63 (0.39–1.02)		
			≥ 30	6	0.93 (0.38–2.26)		
			[P_{trend}]		[0.04]		
			per 1 kg/m^2		0.90 (0.82–0.98)		
			BMI at age 20 yr				
			< 20	22	1.35 (0.70–2.62)		
			20–21.4	16	1.00		
			21.5–22.9	11	0.72 (0.33–1.57)		
			23.0–24.9	13	1.03 (0.48–2.21)		
			≥ 25	12	2.49 (1.15–5.40)		
			[P_{trend}]		[0.58]		
			per 1 kg/m^2		1.07 (0.96–1.20)		
			BMI change, age 20 yr to baseline				
			< 0	18	2.57 (1.40–4.72)		
			0–3.9	32	1.00		
			4–7.9	16	0.73 (0.39–1.36)		
			≥ 8	8	1.39 (0.62–3.15)		
			[P_{trend}]		[0.10]		
			per 1 kg/m^2		0.90 (0.81–1.00)		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Oesophageal squamous cell carcinoma ICD-10: C15	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity	Negative associations remained stable in non-smokers and excluding the first 2 yr of follow-up
			< 22.5	106	2.04 (1.67–2.48)		
			22.5–24.9	63	1.00 (0.78–1.28)		
			25–27.4	52	0.96 (0.73–1.26)		
			27.5–29.9	21	0.61 (0.40–0.94)		
			≥ 30	21	0.47 (0.31–0.73)		
			per 10 kg/m^2		0.26 (0.18–0.38)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) (cont.)			BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	Mortality: 75 44 39 11 13	 2.10 (1.66–2.65) 1.00 (0.74–1.35) 1.02 (0.75–1.40) 0.45 (0.25–0.82) 0.42 (0.24–0.73) 0.22 (0.14–0.35)		
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Oesophageal squamous cell carcinoma ICD-10: C15.0–15.9 Histology 8050–8082	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m² increase Sagittal abdominal diameter (cm) < 20 20–22.4 22.5–25 ≥ 25 per 1 cm increase	 3 78 46 9 19 24 14 15	 0.91 (0.19–4.29) 1.00 0.66 (0.44–1.00) 0.30 (0.13–0.72) 0.89 (0.84–0.94) 1.00 0.91 (0.43–1.94) 0.89 (0.35–2.24) 0.78 (0.32–1.92) 1.00 (0.94–1.06)	Matched for age, sex, year of health check-up BMI results also adjusted for ethnicity	
Renehan et al. (2008) Meta-analysis 1966–2007	4 673 213 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI per 5 kg/m² increase BMI per 5 kg/m² increase	Men: 6201 total Women: 1114 total	0.71 (0.60–0.85) 0.57 (0.47–0.69)	Geographical region, age (all studies), and other factors (not in all studies) such as Western diet, alcohol consumption, medical conditions (e.g. type 2 diabetes, acromegaly), or physical activity	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2009) EPIC cohort 10 European countries 1992–2007	346 554 Men and women Incidence/ mortality	Oesophageal squamous cell carcinoma ICD-10: C15	BMI, quintiles (sex-specific) Men: Women: < 23.4 < 21.7 23.4–25.2 21.7–23.6 25.2–26.9 23.6–25.6 26.9–29.1 25.6–28.7 ≥ 29.2 ≥ 28.8 [P_{trend}]	 42 22 15 14 17	 1.00 0.47 (0.27–0.79) 0.31 (0.17–0.57) 0.27 (0.14–0.51) 0.26 (0.14–0.51) [< 0.0001]	Age, study centre, education level, smoking, alcohol consumption, physical activity, consumption of fruits/vegetables/meat	BMI and WC were significantly inversely related to oesophageal squamous cell carcinoma only in smokers
			Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 41 28 14 10 17	 1.00 0.61 (0.37–1.01) 0.30 (0.16–0.57) 0.19 (0.09–0.40) 0.33 (0.18–0.60) [< 0.0001]		
			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 23 19 23 16 22	 1.00 0.76 (0.41–1.43) 0.78 (0.43–1.43) 0.51 (0.26–1.00) 0.62 (0.32–1.20) [0.08]		
Lindkvist et al. (2014) Me-Can cohort (prospective cohorts) Austria, Norway, and Sweden 1972–2006	587 700 Men and women Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] per 5 kg/m^2	 55 29 46 30 24	 1.00 0.50 (0.32–0.79) 0.76 (0.51–1.12) 0.46 (0.30–0.72) 0.38 (0.23–0.62) [< 0.0001] 0.62 (0.50–0.79)	Sex, age, study cohort, smoking status	

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.2b Case–control studies of measures of body fatness and cancer of the oesophagus

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Vaughan et al. (1995) USA (13 counties of Western Washington State) 1993–1990	EAC: Men and women: 133 Population	BMI, percentiles 1–10% 10–49% 50–89% 90–100%	 12 43 50 26	 1.6 (0.7–3.6) 1.0 1.2 (0.7–2.1) 2.5 (1.2–5.0)	Age, sex, education level, race, cigarette use, alcohol consumption	BMI percentiles based on sex-specific distribution in controls (1 yr before diagnosis in cases, 1 yr before interview in controls)
	ESCC: Men and women: 106 Population	BMI, percentiles 1–10% 10–49% 50–89% 90–100%	 34 41 24 6	 3.2 (1.4–7.1) 1.0 0.7 (0.3–1.4) 0.2 (0.1–1.0)		
Chow et al. (1998) USA 1993–1995	EAC: Men and women: 292 Population	BMI up to 1 yr before diagnosis (sex-specific) Men: / Women: < 23.12 / < 21.95 23.12–25.08 / 21.95–24.12 25.09–27.31 / 24.13–27.43 ≥ 27.32 / ≥ 27.44 [P_{trend}]	 45 63 85 99	 1.0 1.3 (0.8–2.2) 2.0 (1.3–3.3) 2.9 (1.8–4.7) [< 0.0001]	Geographical location, age, sex, race, cigarette smoking, respondent status	No effect modification was observed by history of gastro-oesophageal reflux disease
	ESCC: Men and women: 220 Population	BMI up to 1 yr before diagnosis (sex-specific) Men: / Women: < 23.12 / < 21.95 23.12–25.08 / 21.95–24.12 25.09–27.31 / 24.13–27.43 ≥ 27.32 / ≥ 27.44 [P_{trend}]	 79 50 53 38	 1.0 0.5 (0.3–0.9) 0.8 (0.5–1.3) 0.6 (0.3–1.0) [< 0.11]		
Lagergren et al. (1999) Sweden 1995–1997	EAC: Men and women: 189 Population	BMI 20 yr before interview < 22 22–24.9 25–30 > 30 [P_{trend}]	 10 68 89 22	 1.0 3.2 (1.6–6.7) 6.9 (3.3–14.4) 16.2 (6.3–41.4) [< 0.001]	Age, sex, tobacco smoking, alcohol consumption, SES, reflux symptoms, intake of fruits and vegetables, energy intake, physical activity	No differences were observed in the associations for both cancer types when stratifying by presence of reflux symptoms

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories		Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lagergren et al. (1999) (cont.)		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:				
		< 20.7	< 19.3	28	1.0		
		20.7–22.1	19.3–20.4	29	0.9 (0.5–1.6)		
		22.2–23.7	20.5–22.1	51	1.6 (0.9–2.8)		
		> 23.7	> 22.1	81	2.7 (1.6–4.6)		
		[P_{trend}]			[< 0.001]		
	ESCC: Men and women: 820 Population	BMI 20 yr before interview					
		< 22		48	1.0		
		22–24.9		67	1.0 (0.6–1.7)		
		25–30		42	1.3 (0.8–2.3)		
		> 30		10	2.0 (0.8–4.9)		
		[P_{trend}]			[0.12]		
		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:				
		< 20.7	< 19.3	36	1.0		
		20.7–22.1	19.3–20.4	38	1.2 (0.7–2.1)		
		22.2–23.7	20.5–22.1	40	1.4 (0.8–2.4)		
		> 23.7	> 22.1	53	1.8 (1.1–3.1)		
		[P_{trend}]			[0.03]		
Wu et al. (2001) USA 1992–1997	EAC: Men and women: 222 Population (proxy control)	BMI at age 40 yr, quartiles (sex-specific)				Smoking, sex, race, birthplace, education level	
		Men:	Women:	202 total			
		≤ 22	≤ 21		1.00		
		> 22–25	> 21–23		1.13 (0.7–1.7)		
		> 25– ≤ 27	> 23– ≤ 25		1.76 (1.1–2.9)		
		> 27	> 25		2.78 (1.7–4.4)		
		[P_{trend}]			[< 0.0001]		
		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:	207 total			
		≤ 20	≤ 18		1.00		
		> 20–22	> 18–20		1.23 (0.8–1.9)		
		> 22– ≤ 24	> 20– ≤ 22		1.34 (0.9–2.1)		
		> 24	> 22		1.77 (1.1–2.7)		
		[P_{trend}]			[0.011]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
de Jonge et al. (2006) The Netherlands 2003–2005	EAC: Men and women: 91 Hospital	BMI 10 yr before questionnaire			Age, sex, education level, smoking status, alcohol consumption, reflux symptoms	Controls were patients with Barrett oesophagus
		< 25	29	1.0		
		> 25	58	1.8 (1.1–3.3)		
		BMI at age 20 yr				
		< 25	63	1.0		
		> 25	20	2.6 (1.2–5.5)		
Anderson et al. (2007) Ireland 2002–2004	EAC: 227 (192 men and 35 women) Population	Current BMI, tertiles			Sex, age at interview date, smoking status, alcohol consumption, years of full-time education, job type, gastro-oesophageal reflux	
		< 25.8	115	1.00		
		25.8–29.0	54	0.35 (0.21–0.58)		
		> 29.0	50	0.33 (0.20–0.56)		
		BMI 5 yr before, tertiles				
		< 25.0	51	1.00		
		25.0–28.1	55	1.74 (0.66–1.97)		
		> 28.1	120	2.69 (1.62–4.46)		
		BMI at age 21 yr				
		< 22.1	55	1.00		
		22.1–24.1	64	1.10 (0.65–1.25)		
		> 24.1	96	1.81 (1.08–3.02)		
Löfdahl et al. (2008) Sweden 1995–1997	EAC + EJAC: Men: 388 Women: 63 Population	BMI 20 yr before interview			Age, education level, alcohol consumption, cigarette smoking, intake of fruits and vegetables, *Helicobacter pylori* infection Maximum and minimum adult BMI, also adjusted for gastro-oesophageal reflux	The associations for maximum adult BMI and for minimum adult BMI were weaker, but also showed a stronger association in women than in men
			Men:			
		< 22	45	1.0		
		22–24.9	143	1.5 (1.0–2.3)		
		25–29.9	164	2.7 (1.8–4.1)		
		≥ 30	36	5.4 (2.6–10.8)		
			Women:			
		< 22	12	1.0		
		22–24.9	25	2.4 (0.9–6.0)		
		25–29.9	16	4.3 (1.4–13.1)		
		≥ 30	10	10.3 (2.6–42.3)		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Whiteman et al. (2008) Australia 2001–2005	EAC: Men and women: 367 Population	BMI in the last year			Age, sex, state, household income, cumulative smoking history, mean alcohol consumption, frequency of aspirin use in the 5 yr before diagnosis	Results did not significantly change when additionally adjusted for gastro-oesophageal reflux; significantly higher risk in men than in women; no significant associations or trend between change in BMI and risk of EAC or EJAC
		< 18.5	1	0.3 (0.0–2.6)		
		18.5–24.9	71	1.0		
		25.0–29.9	150	1.4 (1.0–1.9)		
		30.0–34.9	89	2.7 (1.8–3.9)		
		35.0–39.9	25	3.1 (1.8–5.5)		
		≥ 40	16	7.0 (3.3–15.0)		
		[P_{trend}]		[< 0.001]		
		Maximum BMI				
		< 18.5	1	0.9 (0.1–8.7)		
		18.5–24.9	39	1.0		
		25.0–29.9	136	1.4 (0.9–2.0)		
		30.0–34.9	114	2.5 (1.6–3.7)		
		35.0–39.9	43	4.1 (2.4–6.8)		
		≥ 40	24	5.2 (2.7–9.9)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 18.5	14	0.8 (0.4–1.4)		
		18.5–24.9	227	1.0		
		25.0–29.9	81	1.7 (1.2–2.3)		
		30.0–34.9	13	2.6 (1.3–5.2)		
		35.0–39.9	5	3.6 (1.0–13.0)		
		[P_{trend}]		[< 0.001]		
	EJAC: Men and women: 426 Population	BMI in the last year				
		< 18.5	1	0.2 (0.0–1.7)		
		18.5–24.9	107	1.0		
		25.0–29.9	168	1.1 (0.8–1.4)		
		30.0–34.9	98	1.9 (1.3–2.6)		
		35.0–39.9	27	2.0 (1.2–3.4)		
		≥ 40	9	2.6 (1.1–6.2)		
		[P_{trend}]		[< 0.001]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Whiteman et al. (2008) (cont.)		Maximum BMI				
		< 18.5	0	–		
		18.5–24.9	55	1.0		
		25.0–29.9	178	1.3 (0.9–1.8)		
		30.0–34.9	122	1.9 (1.3–2.7)		
		35.0–39.9	47	2.9 (1.8–4.6)		
		≥ 40	13	2.1 (1.1–4.2)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 18.5	9	0.4 (0.2–0.8)		
		18.5–24.9	282	1.0		
		25.0–29.9	97	1.6 (1.2–2.1)		
		30.0–34.9	13	2.1 (1.0–4.1)		
		≥ 35.0	2	1.1 (0.2–5.9)		
		[P_{trend}]		[< 0.001]		
Olsen et al. (2011) Australia 2002–2005	EAC: Men and women: 364 Population	BMI 1 yr before			Age, sex, education level, NSAID use, smoking status, heartburn/acid reflux in the past 10 yr	
		18–24.9	71	1.0		
		25–29.9	149	1.4 (1.0–2.0)		
		30–34.9	89	2.5 (1.7–3.6)		
		≥ 35	40	3.7 (2.2–6.2)		
		Overweight or obese		1.8 (1.3–2.5)		
	EJAC: Men and women: 425 Population	BMI 1 yr before				
		18–24.9	107	1.0		
		25–29.9	168	1.1 (0.8–1.5)		
		30–34.9	98	2.0 (1.4–2.9)		
		≥ 35	36	2.5 (1.5–4.1)		
		Overweight or obese		1.8 (1.3–2.5)		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hoyo et al. (2012) International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) Pooled analysis of 10 case–control and 2 cohort studies from Australia, Europe, and USA	EAC: Men and women: 1997 Population	BMI			Age, sex, smoking, education level, and other study-specific adjustment variables (e.g. study centre)	In stratified analyses, results were independent of the presence of symptoms of gastro-oesophageal reflux No differences in associations by sex
		< 25	577	1.00		
		25.0–29.9	862	1.54 (1.26–1.88)		
		30.0–34.9	331	2.39 (1.86–3.06)		
		35.0–39.9	86	2.79 (1.89–4.12)		
		≥ 40	41	4.76 (2.96–7.66)		
		continuous	1897	1.09 (1.06–1.12)		
	EJAC: Men and women: 1900 Population	BMI				
		< 25	663	1.00		
		25.0–29.9	742	1.28 (1.13–1.45)		
		30.0–34.9	304	2.08 (1.75–2.47)		
		35.0–39.9	85	2.36 (1.75–3.17)		
		≥ 40	28	3.07 (1.89–4.99)		
		continuous	1822	1.07 (1.05–1.09)		
Lahmann et al. (2012) Australia 2002–2005	ESCC: Men and women: 287 Population	BMI in the last year, quintiles (sex-specific)			Age, sex, education level, alcohol consumption, smoking status, NSAID/aspirin use, physical activity BMI at age 20 yr (only for BMI in the last year)	
		Men: / Women:				
		< 22.1 / < 23.7	108	1.00		
		22.1– ≤ 24.6 / 23.7– < 25.6	65	0.61 (0.42–0.90)		
		24.6– ≤ 27.0 / 25.6– ≤ 27.2	35	0.32 (0.20–0.50)		
		27.0– ≤ 31.9 / 27.2– ≤ 29.7	41	0.40 (0.26–0.61)		
		> 31.9 / > 29.7	38	0.36 (0.23–0.57)		
		[P_{trend}]		[< 0.001]		
		Maximum BMI, quintiles (sex-specific)				
		Men: / Women:				
		≤ 23.5 / < 25.1	90	1.00		
		23.5– ≤ 26.0 / 25.1– ≤ 27.0	73	0.78 (0.53–1.15)		
		26.0– ≤ 28.7 / 27.0– ≤ 28.9	42	0.49 (0.32–0.76)		
		28.7– ≤ 33.9 / 28.9– ≤ 31.7	43	0.45 (0.29–0.69)		
		> 33.9 / > 31.7	39	0.44 (0.28–0.69)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 25	233	1.00		
		≥ 25	42	0.85 (0.57–1.25)		
		[P_{trend}]		[< 0.40]		

BMI, body mass index (in kg/m²); CI, confidence interval; EAC, oesophageal adenocarcinoma; EJAC, oesophagogastric junction adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; GCAC, gastric cardia adenocarcinoma; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; yr, year or years

Table 2.2.2c Mendelian randomization studies of measures of body fatness and cancer of the oesophagus

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI)	Adjustment for confounding	Comments
Thrift et al. (2014) Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study (BEAGESS)	Subset of ethnically homogenous individuals from 14 studies in Australia, North America, and western Europe	5229 (999 EAC cases and 2169 controls)	1 kg/m^2 increase based on a genetic risk score of 29 SNPs	1.23 (1.06–1.43)	NR	Similar associations in men and women. Associations with the genetic instrument were stronger than those of conventional epidemiological analyses in the same sample

CI, confidence interval; EAC, oesophageal adenocarcinoma; NR, not reported; SNP, single nucleotide polymorphism

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