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Large body size and sedentary lifestyle during childhood and early adulthood and esophageal squamous cell carcinoma in a high-risk population

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Background: Little is known about the association of obesity and physical activity at young ages with subsequent risk of esophageal squamous cell carcinoma (ESCC).

Patients and methods: Between 2003 and 2007, we conducted a case–control study in a high-risk population in northeastern Iran. Three hundred ESCC cases and 571 matched controls were recruited. Each individual was shown a standard pictogram, to report body size at ages 15 and 30. Demographic and health-related information, including physical activity at these ages was also collected.

Results: In the fully adjusted models, very obese body size (last two pictograms) at age 15 [odds ratio (OR) 3.2, 95% confidence interval (CI) 1.3–7.7] and age 30 (OR 3.1; 95% CI 1.1–8.5) were associated with ESCC in women, but not in men. Sedentary work at age 15 (OR 3.3, 95% CI 1.3–8.3) and 30 (OR 18.2, 95% CI 3.9–86.2) were also associated with ESCC risk in women only. The increased risk in women at age 15 remained high after later reduction in body size, while women who became very obese only at age 30 did not show a significantly increased risk.

Conclusion: These results highlight the importance of early lifestyle modifications in the context of cancer prevention, particularly in women.

Key words: esophagus, obesity, physical activity, squamous cell carcinoma

introduction

Since the 1970s, the incidence of esophageal adenocarcinoma (EAC) has increased in the United States, the UK and other developed countries, while the incidence of esophageal squamous cell carcinoma (ESCC) has remained stable or gradually decreased [1]. Studies of EAC in Western countries have consistently shown a significant association with obesity, and one of the reasons proposed for its increasing incidence is the obesity epidemic in these societies [2, 3]. ESCC, on the other hand, remains the more common type of esophageal cancer in most of the world, including Central Asian esophageal cancer belt (from the Caspian Sea to North Central China) [4]. While the predominant risk factors for ESCC in Western countries are tobacco smoking and heavy alcohol consumption, other risk factors must be important in these high-risk areas where the prevalence of smoking and alcohol consumption are low [5, 6].

Obesity is also rapidly becoming a major health problem in many developing countries of Asia [7], the Middle East and North Africa [8], especially among women. In Iran, as many as 24% of men and 42% of women have metabolic syndrome [9], and obesity rates in the predominantly rural northeast Iran are even higher than in many western societies, especially among women [10]. The age-adjusted prevalence of overweight and obesity in this area were reported to be 62.2% and 28.0%, respectively, and were higher in Iranian women compared with the American women [11].

Most studies have shown an inverse relationship between body mass index (BMI) and ESCC risk [2, 6]. Possible explanations for these findings include weight loss due to the presence of preclinical disease [12, 13] and confounding by factors such as tobacco smoking [14] or low socioeconomic status [12]. One recent study on the relationship between obesity and ESCC showed that after adjustment for BMI, larger waist circumference was associated with increased risk of ESCC [15], suggesting that abdominal obesity may be a better indicator of ESCC risk than BMI [3]. Studies in which obesity was measured at a younger age have reported both null [14] and positive associations with ESCC [16].

It is difficult to assess potential risk factors at younger ages in the context of epidemiologic studies. As such, very few studies have assessed the relationship between childhood or early adult

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original article

exposures and subsequent ESCC risk. In the current study, we used data from a case–control study of ESCC in northeast Iran to study the relationship of body size and physical activity during childhood and early adult life with ESCC risk later in life. We used the data from other exposures at different ages to adjust the analyses. This 'life course' approach [17] has the advantage that it is less likely to be confounded by the presence of early preclinical disease and thus is less likely to be due to reverse causation [18]. This is also, to our knowledge, the first study of the relationship between childhood and early adult physical activity and risk of later ESCC.

methods

study design

The Golestan Case–Control Study was performed between December 2003 and June 2007 in eastern Golestan Province, in northeastern Iran. Details of the study have been published previously [5]. Briefly, histologically proven cases of newly diagnosed ESCC were recruited from the only gastrointestinal specialty clinic in the region (Atrak Clinic). Two neighborhood controls, matched to the cases for age ($\pm$2 years) and sex, were recruited for each case. For $\sim$10% of the cases, only one control could be recruited.

The Golestan Case–Control Study was approved by the Institutional Review Boards of the Digestive Disease Research Center (DDRC), the USA National Cancer Institute (NCI), and World Health Organization International Agency for Research on Cancer (IARC), and all participants gave written informed consent before enrollment.

data collection

We collected demographic and health-related information from participants using structured questionnaires. The participants were asked to report where they had lived since birth and when they had changed their place of residence. Education was defined as the highest level of formal education attained and was divided into three groups: no education, primary school, and middle school or higher [19]. Tobacco smoking habits, opiate use, and alcohol consumption were questioned separately, including ever use (at least once a week for ≥6 months) and all dates of starting and quitting. Each person was asked about the diagnosis of cancer in family members, and a positive family history was defined as a prior diagnosis of esophageal cancer in a first-degree relative.

To estimate body size during earlier life, each individual was shown a standard pictogram (Figure 1), to report body size at ages 15 and 30, with pictures ranging from 1 to 7 in men and 1 to 9 in women. These pictograms have been previously validated for this population [20]. According to the validation study, pictogram 1 corresponded to a median BMI of 19.8 in men and 21.5 in women, pictogram 5 to 28.4 in men and 29.7 in women, and the last pictogram (7 in men and 9 in women) to 32.4 and 36.1, respectively.

Participants reported the type of work they did at different ages, and their corresponding level of physical activity at work, graded from 1 to 4. Level 1 was defined as sedentary work that mostly involved sitting (e.g. driving). Level 2 involved standing or occasional walking (e.g. teaching). Level 3 involved activities which caused mild increase in heart rate and sweating and were usually performed indoors (e.g. house keeping). Level 4 activities were defined as those causing significant elevation in heart rate and sweating and were usually performed outdoors (e.g. farming).

BMI was calculated as weight in kilograms divided by squared height in meters. We asked participants whether they had lost weight in the past year and if the weight loss was intentional (e.g. by diet or exercise). The amount of weight loss was recorded as reported by the individual. BMI before weight loss was calculated, based on the estimated pre-loss weight and using the same formula.

Use of piped water has been shown to decrease ESCC risk [6] and was used here for two purposes: first as a measure of socioeconomic status, since poorer families are less likely to have access to piped water, and second to adjust for exposure to a possible independent source of carcinogens in well or cistern water.

definition of life course risk factors

Childhood body size was defined as the picture chosen for age 15, and early adulthood body size was defined as the picture chosen for age 30. As described before [20], pictograms ≥5 (corresponding to a median BMI of 28.4 in men and 29.7 in women) were used to define obesity at both time points in both sexes. The last two pictograms in each sex were combined

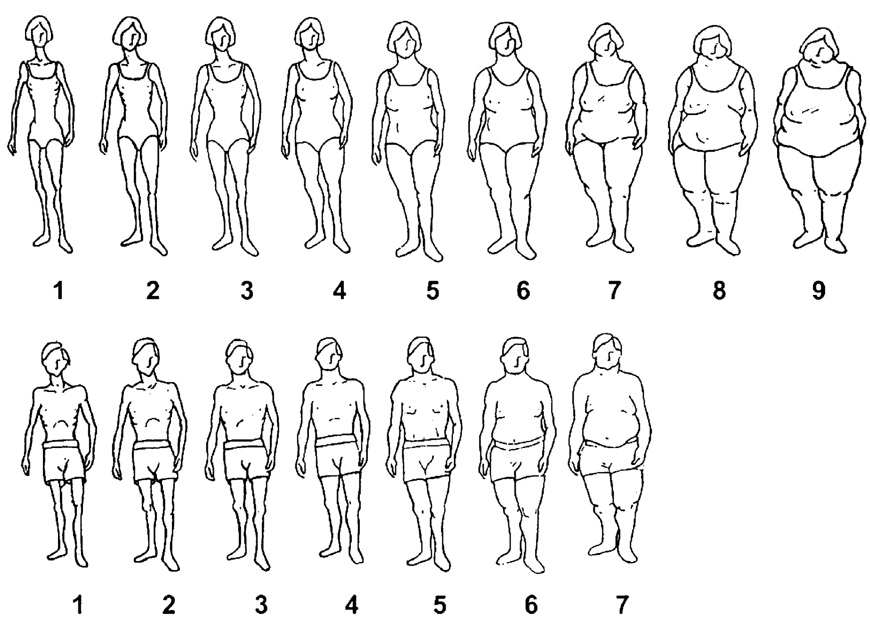

Figure 1. Body size pictograms used in Golestan Case–Control Study.

due to the relatively small number of individuals in each, and individuals choosing these two pictograms were considered very obese. Childhood work activity was defined as the level of activity with the longest duration before the age of 18, and work activity in early adulthood was defined as the level of activity with the longest duration between the ages of 18 and 30.

Childhood and early adulthood places of residence were defined as the longest presence in either a town or a village from birth to the age of 18 and from ages 18 to 30, respectively. Since in the past, oral opiates were sometimes used as pain-killing medications in children, the history of such exposure was defined as opiate use in childhood. After the age of 18, regular use of opiates was defined as the reported use of any form of opiate preparation at least once a week for ≥6 months.

Tobacco smoking history was categorized by the age when a person started smoking at least once a week for 6 months. Individuals were divided to three groups: never smokers, those who started regular smoking at or before 18, and those who started it after 18. Since there were very few people who reported alcohol consumption, the data were not used in this analysis. Oral health was assessed by the age of first adult tooth loss and categorized according to the results of a previous report [21] (<20, 20–25, 26–30, 31–39, or >40). The individuals' use of piped or well/cistern water was classified based on the reported year of first use of piped water in their households (never, before 18, or after 18).

statistical analysis

Categorical variables are presented as numbers and percentages. The chi-square test was used to test the associations between these variables, and odds ratios (ORs) and 95% confidence intervals (CIs) were reported as measures of effect size. Crude ORs were calculated separately in each sex and tested for homogeneity using the Breslow–Day statistic. When the homogeneity test was not significant (i.e. it was not in favor of effect modification by sex), the sex-specific ORs were combined and Mantel–Haenszel ORs (M–H OR) and CIs were calculated for men and women together. Continuous variables are reported as mean ± standard deviation (SD). The Student's *t*-test was used to compare the values of these variables between cases and controls.

Conditional logistic regression models (conditional on the matching factors) were used to calculate crude and adjusted ORs and 95% CIs for body size and physical activity at ages 15 and 30. The adjusted childhood model included body size at age 15 and childhood work activity and was further adjusted for education, family history of esophageal cancer, childhood place of residence, therapeutic opium use, smoking history, use of piped water, and age of first adult tooth loss. The early adulthood model included similar variables for early adulthood, as described earlier. A third model was created to assess variation in body size at ages 15 and 30 and included the following variables: four variables of pictogram data (not very obese at age 15 or 30, very obese at age 30 but not so at 15, very obese at age 15 but not so at 30, and very obese at both ages), three variables describing change in work activity level between ages 15 and 30 (decrease, no change, and increase), and the other adjustment variables described above. In all models, body size and activity level were once entered as categorical variables and then as ordinal variables to test for trend. We also included an interaction term for body size and work activity in the models, but since this did not show a significant result in any of the models, we did not include it in the final models, and only reported the main effects. For body size, 4 cases (1.3%) and 18 controls (3.2%) were unable to remember their previous body size and were excluded from the analyses using these data.

results

There were 300 cases and 571 age- and sex-matched controls. Table 1 summarizes selected demographic and other characteristics of the cases and controls. Emigration to town, family history of esophageal cancer, regular adult opium use, and unintentional weight loss in the past year were positively associated, and high school or more education, use of piped water, and higher BMI were inversely associated with ESCC.

At the age of 15, 104 cases (35%) and 147 controls (27%) had been obese (pictogram 5 and above); the ORs (compared with not being obese) in men and women were 1.5 (95% CI 0.9–2.6) and 1.6 (95% CI 1.0–2.4), respectively, and the M–H OR for men and women together was 1.6 (95% CI 1.1–2.1). At the age of 30, 145 cases (49%) and 233 controls (42%) had been obese; the OR was 1.5 (95% CI 0.9–2.2) in men and 1.6 (95% CI 1.0–2.4) in women, and the combined M–H OR was 1.3 (95% CI 1.0–1.8).

Tables 2 and 3 show the results of crude and adjusted logistic regression analyses in women and men separately. In the final adjusted model, women reporting the highest level of body size (pictograms 8 or 9, described as very obese) at age 15 (OR 3.2, 95% CI 1.3–7.7) and 30 (OR 3.1; 95% CI 1.1–8.5) had a significantly greater chance of developing ESCC, and the trend for increasing body size was also significant at both ages (Table 2). In men, significant associations between body size and ESCC risk were not found in the adjusted model (Table 3). In the model assessing variation in body size over time, women who were very obese at both ages or only at age 15 had significantly increased risk of ESCC, but women who were very obese only at age 30 did not (Table 2, Figure 2).

At age 15, 47 cases (16%) and 57 controls (10%) had low physical activity at work (level 1, described as sedentary); the ORs in men and women (compared with not being sedentary) were 1.3 (95% CI 0.8–2.3) and 2.5 (95% CI 1.2–5.4), respectively (M–H combined OR 1.7, 95% CI 1.1–2.5). At age 30, sedentary work was reported by 18 cases (6%) and 11 controls (2%); the ORs were 0.9 (95% CI 0.1–4.4) in men and 6.4 (95% CI 2.1–22.9) in women (M–H combined OR could not be calculated because the effect was heterogenous between men and women). At both ages, the adjusted model showed a significant association between sedentary work and ESCC risk in women, which was especially strong at age 30 (Table 2). There was also a significant trend for decreasing physical activity level in women at both ages. Over 75% of case and control men reported the highest level of work activity at both 15 and 30 years of age, and there were no significant associations between work activity level and ESCC (Table 3).

discussion

In this study, we saw a positive association between childhood and early adulthood obesity and risk of ESCC in women. We also observed that once this risk was increased at the age of 15, it remained high even after a later reduction in body size. On the other hand, women who had a very obese body size at 30, but not at age 15, did not show a significantly increased risk of ESCC.

Some studies reporting BMI long before the development of ESCC show similar results. Merry et al. [16] showed that a BMI >25 at age 20 was associated with increased risk of ESCC, even though later BMI did not show such an association with tumor occurrence. Lagergren et al. [22] also reported a weak

Table 1. Characteristics of cases and controls in Golestan Case–Control Study of esophageal squamous cell carcinoma (ESCC)

	ESCC cases (n = 300)	Controls (n = 571)	P value
Gender			0.9
Male	150 (50)	278 (49)	
Female	150 (50)	293 (51)	
Age	64.5 ± 10.1	64.3 ± 10.4	0.8
Ethnicity			
Turkman	171 (57)	312 (55)	
Non-Turkman	129 (43)	259 (45)	0.8
Rural residence			
During childhood	263 (88)	478 (84)	0.1
During adulthood	218 (73)	421 (74)	0.7
Emigrated to town	54 (19)	59 (10)	0.001
Education			0.05
No school	267 (89)	474 (83)	
Primary school	25 (8)	64 (11)	
High school or more	8 (3)	33 (6)	
Family history of esophageal cancer	78 (26)	41 (7)	0.001
Tobacco smoking start age			0.2
Never	230 (77)	467 (82)	
At age 18 or before	20 (7)	28 (5)	
After age 18	50 (17)	76 (13)	
Opium			
Childhood administration	23 (8)	37 (7)	0.5
Adult regular use	90 (30)	106 (19)	0.001
Age of first adult tooth loss			0.04
<20	42 (15)	85 (15)	
20–25	94 (33)	152 (27)	
26–30	67 (24)	115 (21)	
31–39	26 (9)	65 (12)	
≥40	54 (19)	143 (25)	
Age at start of piped water use			0.0001
Never	71 (24)	31 (5)	
At age 18 or before	13 (4)	26 (5)	
After age 18	216 (72)	514 (90)	
Unintentional weight loss in the past year	235 (79)	109 (19)	0.001
Body mass index			
At present	21.7 ± 5.0	26.3 ± 6.1	0.0001
Before past-year weight loss	24.0 ± 5.0	26.7 ± 6.2	0.0001

positive association between BMI at the age of 20 and ESCC risk in a Swedish population. And in a study by Gallus et al. [14], although an inverse relationship was found between current BMI and ESCC risk, this association disappeared when they studied BMI at the age of 30.

Body size during childhood and adolescence has been shown to affect the risk of breast [23] and ovarian cancers [24] and diabetes mellitus [25] in later life. Childhood body size has also been shown to affect the level of circulating insulin-like growth factors (IGFs) such as IGF-1 and IGF-binding protein-3 in adults [26]. Obesity during childhood may also be a sign of malnutrition, as families who cannot afford a diet rich in proteins may consume larger amounts of carbohydrates, leading to childhood obesity [27].

In this study, we also showed that sedentary work in childhood and early adult life may be a risk factor contributing to ESCC development in women. To our knowledge, this is the first observation of this association in the literature. We did not find an association between sedentary work and ESCC in men, but our ability to see such an association, if one exists, was probably reduced by the fact that in our study, 80% of men at age 15 and 90% at age 30 had a job that required our highest level of occupational physical activity, so there were low numbers of subjects in the other activity categories. Interestingly, the effect of sedentary lifestyle on ESCC risk was accentuated when adjusted for body size and other potential confounders, especially among women at age 30.

Almost all previous studies on the relationship between physical activity and esophageal cancer have included only adenocarcinoma [28, 29] or have made no distinction between histological subtypes [30, 31]. Leitzmann et al. [32] observed an inverse association between the level of recreational physical activity and the risk of EAC, but not ESCC, in a large prospective study. In their study, recreational physical activity

Table 2. Obesity, physical activity and risk of ESCC in women

	ESCC cases, *n* (%)	Matched controls, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	*P* for trend (adjusted model)
Body size at 15					
1 (very slim)	15 (10)	40 (15)	0.8 (0.4–1.7)	0.6 (0.2–1.5)	
2	26 (18)	60 (21)	Referent	Referent	
3	20 (13)	47 (17)	0.9 (0.5–1.9)	0.6 (0.2–1.5)	
4	16 (11)	31 (11)	1.3 (0.6–2.8)	0.9 (0.3–2.4)	
5	12 (8)	29 (10)	0.8 (0.3–1.8)	0.7 (0.3–2.2)	
6	12 (8)	27 (9)	1.0 (0.4–2.3)	1.4 (0.5–4.1)	
7	13 (9)	21 (7)	1.4 (0.6–3.3)	1.2 (0.4–3.4)	
≥8 (very obese)	34 (23)	27 (10)	2.9 (1.4–5.9)**	3.2 (1.3–7.7)**	
Per 1 level increase			1.1 (1.0–1.3)	1.2 (1.1–1.3)	0.004
Body size at 30					
1 (very slim)	5 (3)	12 (4)	1.0 (0.3–3.6)	1.5 (0.3–6.9)	
2	18 (12)	44 (16)	Referent	Referent	
3	15 (10)	45 (16)	0.8 (0.3–1.8)	0.5 (0.2–1.4)	
4	28 (19)	39 (14)	1.8 (0.8–3.9)	1.6 (0.6–4.5)	
5	19 (13)	40 (14)	1.1 (0.5–2.4)	0.8 (0.3–2.0)	
6	18 (12)	44 (16)	1.1 (0.5–2.4)	1.2 (0.4–3.3)	0.05
7	16 (11)	24 (8)	1.4 (0.6–3.4)	1.6 (0.5–4.6)	
≥8 (very obese)	29 (20)	33 (12)	2.4 (1.1–5.2)*	3.1 (1.1–8.5)*	
Per 1 level increase			1.1 (1.00–1.2)	1.1 (1.0–1.3)	
Being very obese at ages 15 and 30					
Neither	103 (70)	236 (84)	Referent	Referent	
Only at 30	11 (7)	19 (7)	1.4 (0.6–3.1)	1.5 (0.6–3.8)	
Only at 15	16 (11)	12 (4)	2.7 (1.2–6.0)*	3.3 (1.3–8.6)*	
Both	18 (12)	14 (5)	3.2 (1.4–7.4)**	3.6 (1.4–9.1)**	0.001
Level of work activity at 15					
1 (sedentary)	19 (13)	16 (5)	2.0 (1.0–4.2)*	3.3 (1.3–8.3)**	
2	12 (8)	8 (3)	2.5 (0.9–6.3)	2.5 (0.8–8.0)	
3	37 (25)	117 (40)	0.5 (0.3–0.8)*	0.5 (0.2–0.9)*	
4 (very active)	82 (54)	152 (52)	Referent	Referent	
Per 1 level decrease			1.2 (1.0–1.6)	1.4 (1.1–1.8)	0.02
Level of work activity at 30					
1 (sedentary)	15 (10)	5 (2)	4.8 (1.7–13.5)**	18.2 (3.9–86.2)**	
2	12 (8)	8 (3)	2.6 (1.0–6.7)*	1.7 (0.6–5.2)	
3	39 (26)	121 (41)	0.5 (0.3–0.9)**	0.6 (0.3–1.2)	
4 (very active)	84 (56)	159 (54)	Referent	Referent	
Per 1 level decrease			1.4 (1.1–1.8)	1.6 (1.2–2.1)	0.005

[a]All conditional logistic regression models adjusted for education, family history of esophageal cancer, smoking history, opium use, age of first adult tooth loss, and use of piped water, with models at 15 adjusted for childhood place of residence. Body size analyses also adjusted for physical activity at the same age and vice versa.

*$P < 0.05$, **$P < 0.01$.

ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

was measured at the start of the cohort, a maximum of 8 years before the end of follow-up. In the present study, we assessed occupational rather than recreational activity because in our population, physical activity comes mainly from work, and we estimated this activity at ages 15 and 30, a longer time before tumor development. Vigen et al. [29] also studied occupational activity and found a protective effect of high physical activity on the risk of adenocarcinoma. Low physical activity levels increase waist circumference and insulin resistance and have been shown to be a health risk [33].

It is not clear why all the effects in our study were seen only in women. Unlike some other parts of the world where ESCC has a clear male predominance, women in the Central Asian esophageal cancer belt have similar rates of ESCC as men [34]. Given the higher rates of obesity and overweight among women in this population [11], and their relative lack of physical activity, it is possible that the risks associated with these characteristics at least partially balance the risks of other exposures (such as cigarette smoking and opium use) that are present mostly in men.

We observed a lower BMI in patients compared with controls, a year before interview. It is possible that this association is due to reverse causation [13]. ESCC can cause rapid weight loss [35], both because of the direct effect of

Table 3. Obesity, physical activity and risk of ESCC in men

	ESCC cases, *n* (%)	Matched controls, *n* (%)	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	*P* for trend (adjusted model)
Body size at 15					
1 (very slim)	14 (9)	29 (11)	0.9 (0.4–2.0)	1.1 (0.4–3.2)	
2	32 (22)	67 (25)	Referent	Referent	
3	30 (20)	81 (30)	0.7 (0.4–1.3)	0.6 (0.3–1.3)	
4	39 (27)	52 (19)	1.5 (0.8–2.8)	1.6 (0.7–3.4)	
5	19 (13)	23 (8)	1.8 (0.9–3.9)	1.6 (0.6–4.0)	0.5
≥6 (very obese)	14 (9)	20 (7)	1.5 (0.7–3.4)	0.8 (0.3–2.2)	
Per 1 level increase			1.2 (1.0–1.4)	1.1 (0.9–1.3)	
Body size at 30					
1 (very slim)	1 (1)	5 (2)	0.5 (0.1–4.7)	0.1 (0.0–0.1)	
2	19 (13)	42 (15)	Referent	Referent	
3	27 (18)	51 (19)	1.4 (0.7–2.9)	0.6 (0.3–1.6)	
4	38 (26)	82 (30)	1.2 (0.6—2.2)	0.7 (0.3–1.5)	
5	37 (25)	44 (16)	2.1 (1.0–4.3)*	1.1 (0.5–2.6)	0.7
≥6 (very obese)	26 (17)	48 (18)	1.3 (0.6–2.7)	0.6 (0.3–1.6)	
Per 1 level increase			1.1 (1.0–1.3)	1.0 (0.9–1.3)	
Being very obese at ages 15 and 30					
Neither	113 (76)	218 (80)	Referent	Referent	
Only at 30	21 (14)	34 (13)	1.2 (0.6–2.2)	1.1 (0.5–2.2)	
Only at 15	9 (6)	6 (2)	2.7 (0.9–7.8)	1.5 (1.4–5.3)	
Both	5 (4)	14 (5)	0.6 (0.2–1.9)	0.5 (0.1–1.9)	0.7
Level of work activity at 15					
1 (sedentary)	28 (18)	41 (15)	1.3 (0.8–2.3)	1.9 (0.9–3.9)	
2	4 (3)	6 (2)	1.4 (0.4–4.9)	1.5 (0.3–7.0)	
3	4 (3)	4 (1)	1.9 (0.5–7.6)	4.0 (0.4–42.5)	
4 (very active)	114 (76)	227 (82)	Referent	Referent	
Per 1 level decrease			1.1 (0.9–1.3)	1.2 (1.0–1.5)	0.09
Level of work activity at 30					
1 (sedentary)	3 (2)	6 (2)	0.9 (0.2–3.7)	1.2 (0.2–8.4)	
2	5 (3)	16 (6)	0.4 (0.1–1.4)	0.6 (0.1–2.4)	
3	6 (4)	12 (4)	0.8 (0.3–2.4)	0.7 (0.1–3.3)	
4 (very active)	136 (90)	244 (88)	Referent	Referent	
Per 1 level decrease			0.8 (0.6–1.2)	0.9 (0.6–1.4)	0.6

[a]All conditional logistic regression models adjusted for education, family history of esophageal cancer, smoking history, opium use, age of first adult tooth loss, and use of piped water, with models at 15 adjusted for childhood place of residence. Body size analyses also adjusted for physical activity at the same age and vice versa.

*$P < 0.05$

ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

dysphagia and because of cancer-related cachexia. A more likely explanation for this inverse association is the presence of one or more confounders [36], such as low socioeconomic status [6, 12, 37] or smoking [2]; although studies in other populations that have adjusted for smoking did not show that this adjustment significantly altered their results [12, 14, 38]. Another possible explanation for the observed inverse association of BMI before recent weight loss and ESCC is that BMI is not a very good measure of abdominal obesity, which is the kind of obesity that may affect ESCC risk. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, BMI or waist circumference alone were inversely associated with ESCC in smokers, but waist circumference or waist-to-hip ratio adjusted for BMI showed a positive association with ESCC among both smokers and nonsmokers [15].

As in all case–control studies, we cannot rule out the possibility that recall bias influenced our results, but we think that it is unlikely that such bias had an important impact on the results of this study. First, obesity and lack of physical activity are not established risk factors for ESCC, so is it unlikely that cases would preferentially misreport their former body size or activity level at work. Second, studies have shown that the remote recall of childhood weight is not affected by current BMI, and lean and obese people have the same accuracy in remembering their childhood body size [39], so any misclassification of childhood body size would probably be non-differential with respect to this variable [25].

Obesity and sedentary lifestyle can be considered as component causes in a set of different factors (the 'sufficient cause') leading to many diseases [40]. So, depending on other genetic and environmental risks present in a population, the

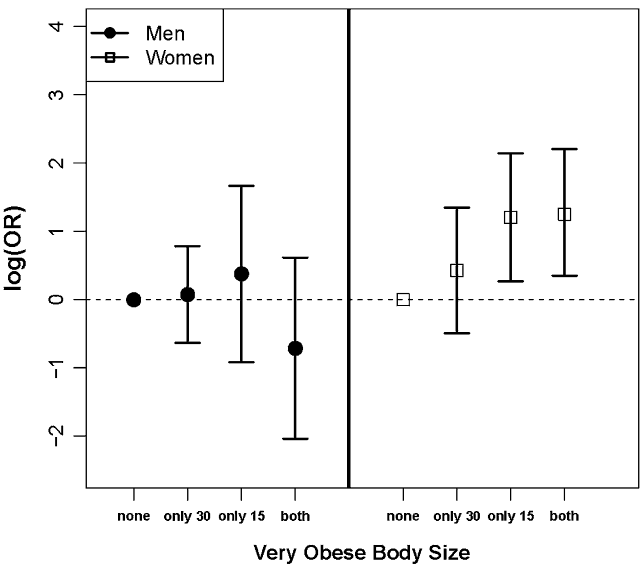

Figure 2. The adjusted log-odds ratios (log-OR) and 95% confidence intervals for esophageal squamous cell carcinoma in subjects with very obese body size (the last two pictograms) at ages 15 and/or 30, after adjustment for education, family history of esophageal cancer, opium use, smoking history, use of piped water, age of first adult tooth loss, and physical activity. Models at 15 years of age were also adjusted for childhood place of residence.

same common risk factors may contribute to the cause of different chronic diseases in different populations. According to this model, obesity and sedentary lifestyle are non-specific risk factors which modulate the effects of more disease-specific causes [5, 21, 41–44].

In summary, using a life course approach to the epidemiology of ESCC in a high-risk area, we found an association between obesity and sedentary work during childhood and early adult life with ESCC in women. Also striking is the finding that women with a very large body size in childhood retained the increased risk despite later slimming. These results underline the importance of lifestyle interventions early in life.

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disclosure

The authors declare no conflicts of interest.

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