Prediagnostic body fat and risk of death from amyotrophic lateral sclerosis

The EPIC cohort

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ABSTRACT

Objectives: The aim of this study was to investigate for the first time the association between body fat and risk of amyotrophic lateral sclerosis (ALS) with an appropriate prospective study design.

Methods: The EPIC (European Prospective Investigation into Cancer and Nutrition) study included 518,108 individuals recruited from the general population across 10 Western European countries. At recruitment, information on lifestyle was collected and anthropometric characteristics were measured. Cox hazard models were fitted to investigate the associations between anthropometric measures and ALS mortality.

Results: Two hundred twenty-two ALS deaths (79 men and 143 women) occurred during the follow-up period (mean follow-up = 13 years). There was a statistically significant interaction between categories of body mass index and sex regarding ALS risk ($p = 0.009$): in men, a significant linear decrease of risk per unit of body mass index was observed (hazard ratio = 0.93, 95% confidence interval 0.86–0.99 per kg/m^2); among women, the risk was more than 3-fold increased for underweight compared with normal-weight women. Among women, a significant risk reduction increasing the waist/hip ratio was also evident: women in the top quartile had less than half the risk of ALS compared with those in the bottom quartile (hazard ratio = 0.48, 95% confidence interval 0.25–0.93) with a borderline significant p value for trend across quartiles ($p = 0.056$).

Conclusion: Increased prediagnostic body fat is associated with a decreased risk of ALS mortality.

Neurology® 2013;80:829–838

GLOSSARY

ALS = amyotrophic lateral sclerosis; **BMI** = body mass index; **CI** = confidence interval; **EPIC** = European Prospective Investigation into Cancer and Nutrition; **HR** = hazard ratio; ***ICD-10*** = *International Statistical Classification of Diseases*, 10th revision; **WHR** = waist/hip ratio.

Amyotrophic lateral sclerosis (ALS) is a progressive motor disease characterized by degeneration of the upper and lower motor neurons, rapidly leading to death (with a median survival of 3 years).[1] Cigarette smoking is the only environmental or lifestyle factor that has been consistently shown to increase the risk of this disease in women,[2,3] although there is less conclusive evidence for smoking in men, and a number of other factors including heavy metals[4] and some occupational exposures.[5,6]

Clinical observations consistently report that patients with ALS are generally lean with a normal or low body mass index (BMI).[7–9] They typically lose muscle mass, bone density, and body fat, and consequently weight, as the disease progresses,[8,10–12] and although neurogenic muscle wasting is the main pathophysiologic mechanism explaining this, their energy stores are also decreased.[13] Several lines of evidence have indicated that patients with ALS have an increased metabolism with higher energy expenditure than energy intake.[13] In a case-control study, patients with motor neuron diseases were more likely than controls to report that they had always been slim (odds ratio = 2.21, 95% confidence interval [CI] 1.40–3.47).[14] However, what is not known is the extent to which lean body mass (and the associated increase in metabolism) is a cause of ALS, a noncausal indicator of the very early stages of the disease itself, or a consequence of the disease. In other words, is ALS a disease that develops preferentially in people with given anthropometric characteristics, or are these the early consequences of the preclinical onset of the disease itself?

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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To gain more insight into these questions, we evaluated the associations between prediagnostic anthropometric characteristics and risk of mortality from ALS in the European Prospective Investigation into Cancer and Nutrition (EPIC),[15] a large, prospective European cohort.

METHODS

Participants. The vast majority of the 152,368 men and 366,040 women aged 35 to 70 years were recruited from the general population residing in defined geographical areas between 1992 and 2002, in 23 centers across 10 Western European countries (Norway, Sweden, Denmark, United Kingdom, Netherlands, Germany, France, Spain, Italy, and Greece).[15] Exceptions were the French cohort (based on women members of the health insurance for state school), the Ragusa (Italy) cohort (based on blood donors and their spouses), the Utrecht (Netherlands) and Florence (Italy) cohorts (based on breast cancer screening participants), and part of the Oxford (UK) cohort (based on vegetarians and vegans).[15] The Norway, France, Naples (Italy), and Utrecht cohorts were restricted to women, whereas all other cohorts involved both sexes.

At recruitment, information on lifestyle and dietary habits was collected through standardized questionnaires. Anthropometric characteristics were measured following standardized protocols with participants in light underwear (Spain, Germany, Denmark, and Florence, Varese, Ragusa, and Naples), in light clothing (Greece, Bilthoven [Netherlands], and Malmö [Sweden]), or normally dressed without shoes (Turin [Italy], Utrecht, and Umeå [Sweden]), or this information was self-reported (France, UK, and Norway). All measures were corrected for clothing type to minimize systematic error arising from differences across centers.[15] Follow-up for mortality and specific causes of death is conducted actively or through linkage with mortality registries at regional and national levels.[15] To date, follow-up is 98.5% complete.[15] The Norwegian EPIC subcohort (n = 37,185) was excluded from the present analysis because it did not contribute any ALS cases, given its younger age composition.

Information on subject vital status is collected independently from the causes of death of those deceased: this implies that there is a certain proportion of deaths accrued over the last months of follow-up for which the causes of death are not yet known. To avoid a high proportion of missing data for causes of death, follow-up time was censored according to the proportion of reported causes of death: during each 6-month period, follow-up was censored by center when the cause of death was considered complete. This resulted in censoring follow-up time between June 2005 and June 2009 generating a total of 5,252,239 person-years.

Standard protocol analysis, registrations, and patient consents. The EPIC study was approved by the ethical committee of the International Agency for Research on Cancer and by the ethics committees of each participating center; all participants signed an informed consent.

Measured anthropometric characteristics. Details on the standardized procedures for taking anthropometric measurements in the EPIC study centers were previously described in detail,[16] and will only be summarized here. Weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1, 0.5, or 1.0 cm depending on the study center. Height was measured for 421,067 individuals (87.5%); weight for 420,355 individuals (87.4%). Height and weight of each participant were used to calculate the BMI as a measure of body fatness, and this was grouped into the standard categories of underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 to <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Waist circumference was measured for 392,490 individuals (81.6%) either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest. Hip circumference was measured for 389,744 individuals (81.0%) at the widest circumference or over the buttocks. Weight, waist, and hip measurements were corrected to account for protocol differences among centers in clothing worn by participants during body measurements.[16] The waist and hip circumferences of each participant were used to estimate waist/hip ratio (WHR) as an additional measure of fat distribution.

Self-reported anthropometric characteristics. Self-reported anthropometric measures from the Oxford health-conscious cohort were corrected for expected reporting errors using age- and sex-specific prediction equations. Measured or self-reported height was available for 478,349 individuals (99.4%); BMI was available for 475,201 individuals (99.0%). Similarly, waist circumference was available for 396,440 individuals (82.4%), and hip circumference for 392,921 individuals (81.7%).

In some centers (Varese and Naples, UK, Greece, Potsdam [Germany], Denmark, and Malmö), participants were asked to self-report their weight when they were aged 20 years: BMI at age 20 was therefore available for 112,428 individuals (44.1%). Using this self-reported weight, a measure of average annual weight change was also calculated using the following formula: (weight at recruitment − weight at age 20)/(age at recruitment − 20).

Case ascertainment. ALS cases were defined as those subjects for whom "motor neuron disease" (G12.2 according *ICD-10*) was reported as an immediate, antecedent, or underlying cause of death (for more details, see reference 17). A total of 222 deaths caused by ALS were recorded during follow-up.

Statistical analysis. Demographic and anthropometric characteristics of the cohort and of the subjects who died of ALS were analyzed. A subgroup analysis excluding centers recruiting women only was conducted; these yielded similar results to those analyses including all centers and therefore we present the latter analyses.

Potential confounders for which we had information included age at recruitment, highest level of education attained (none/primary, technical, secondary, university, undetermined), and a composite smoking variable (never smoker, former smoker $\geq$10 years; former smoker $<$10 years, current smoker 1–4 cigarettes/d; 5–14 cigarettes/d, 15–24 cigarettes/d, $\geq$25 cigarettes/d, undetermined).

Cox hazard models, with age as main time variable were fitted to investigate the associations between anthropometric measures and ALS mortality. Hazard ratio (HR) estimates were derived for the entire sample, and for men and women separately if the p value for the cross-product term of sex with the categorical exposure variable was suggestive of an interaction ($p < 0.100$), stratified by 1-year categories of age and center of recruitment. The exposure variables considered for this analysis included height, BMI (both in categories and in quartiles of distribution), waist circumference, hip circumference, and WHR. All models were adjusted for potential confounders: highest level of education attained and the composite smoking variable. For each Cox regression analysis, a p value for trend across sex-specific quartiles (or categories) is reported, together with an HR for the continuous measure (in appropriate units).

Two sensitivity analyses were conducted: first, an analysis on measured anthropometry—after excluding the self-reported ones—was conducted; Cox regression models were fitted using date of measurement as entry. Second, models excluding ALS cases arising during the first 3 years of follow-up were run in order to minimize the potential for reverse causation (i.e., anthropometric measures being modified as a consequence of preclinical onset of the disease). The latter was performed for all measures except height, given its stability from adolescence onward.

Supplemental data at www.neurology.org

The shape of the dose-response relationships was investigated by fitting restricted spline regression models with 3 knots placed at the 5th, 50th, and 95th percentiles of the anthropometric measurement followed by corresponding likelihood ratio tests comparing the goodness-of-fit of the models with and without the spline terms.[18,19]

RESULTS Characteristics of the cohort participants by BMI categories are described in table 1. A total of 222 ALS deaths (79 men and 143 women) occurred during a mean 13-year (SD 3 years) follow-up period. Underweight men and women were more likely to be current smokers, and more educated individuals had a lower BMI (table 1).

Overall, the inclusion of smoking and highest level of education attained in Cox regression models did not substantially change the risk estimates; therefore, only the adjusted models are shown. In the Cox regression analyses, height was not significantly associated with ALS (table 2); when restricting the analysis to measured height only, results did not change (table 3).

The p value for heterogeneity of the association of categories of BMI by sex was statistically significant ($p = 0.009$). Overall, underweight subjects were at a significantly increased risk of ALS (HR = 2.79, 95% CI 1.35–5.77) (table 2). Overweight and obese men were at a nonsignificant reduced risk compared with normal-weight men (p value for trend across categories 0.053), with a significant risk reduction increasing BMI

Table 1 Demographic and anthropometric characteristics of the cohort according to sex

	Body mass index (kg/m^2)							
	Men				Women			
	Underweight (<18.5)	Normal weight (18.5–24.9)	Overweight (25–29.9)	Obese (30+)	Underweight (<18.5)	Normal weight (18.5–24.9)	Overweight (25–29.9)	Obese (30+)
No. of participants (%)	647 (0.4)	53,007 (35.6)	72,124 (48.5)	23,028 (15.5)	4,964 (1.8)	140,610 (51.9)	84,662 (31.2)	40,849 (15.1)
Age at recruitment, y, mean (SD)	49.8 (15.3)	50.7 (11.3)	53.2 (9.5)	53.8 (8.9)	46.0 (13.2)	49.1 (11.0)	53.2 (9.8)	54.1 (9.4)
Height, cm, mean (SD)	176.1 (8.1)	176.1 (7.2)	174.3 (7.2)	172.6 (7.6)	164.0 (6.7)	163.1 (6.4)	160.9 (6.7)	158.9 (7.1)
Weight, kg, mean (SD)	54.8 (5.6)	71.5 (7.1)	82.7 (7.7)	97.4 (11.5)	47.6 (4.4)	59.4 (6.1)	70.3 (6.6)	85.3 (11.4)
Waist circumference, cm, mean (SD)	74.4 (5.8)	86.0 (6.1)	96.2 (6.2)	109.1 (8.2)	64.6 (4.5)	73.2 (6.2)	84.1 (7.0)	97.8 (9.8)
Hip circumference, cm, mean (SD)	87.9 (4.7)	95.7 (4.6)	101.6 (4.7)	109.7 (6.6)	87.1 (4.4)	95.5 (5.2)	103.9 (5.3)	115.4 (8.6)
Waist/hip ratio, mean (SD)	0.84 (0.06)	0.90 (0.06)	0.95 (0.05)	1.00 (0.06)	0.74 (0.06)	0.77 (0.06)	0.81 (0.06)	0.85 (0.07)
Smoking status, n (%)								
Never	220 (34.0)	19,849 (37.5)	22,205 (30.8)	6,242 (27.1)	2,674 (53.9)	74,682 (53.1)	48,318 (57.1)	2,674 (53.9)
Former 10 y+	101 (15.6)	11,227 (21.2)	18,944 (26.3)	6,009 (26.1)	584 (11.8)	21,509 (15.3)	12,430 (14.7)	5,057 (12.4)
Former <10 y	34 (5.3)	4,733 (8.9)	9,379 (13.0)	3,738 (16.2)	286 (5.8)	11,483 (8.2)	6,759 (8.0)	2,981 (7.3)
Current 1–4 cigarettes/d	15 (2.3)	1,413 (2.7)	1,785 (2.5)	503 (2.2)	151 (3.0)	4,305 (3.1)	2,031 (2.4)	763 (1.9)
Current 5–14 cigarettes/d	81 (12.5)	4,107 (7.8)	4,601 (6.4)	1,236 (5.5)	557 (11.2)	12,547 (8.9)	6,040 (7.1)	2,201 (5.4)
Current 15–24 cigarettes/d	114 (17.6)	5,669 (10.7)	6,854 (9.5)	2,096 (9.1)	516 (10.4)	10,604 (7.5)	6,073 (7.2)	2,213 (5.4)
Current 25+ cigarettes/d	73 (11.3)	5,154 (9.7)	2,078 (9.8)	2,773 (12.0)	137 (2.8)	3,409 (2.4)	1,827 (2.2)	864 (2.1)
Education level, n (%)								
None/primary	157 (24.3)	12,955 (24.4)	26,045 (36.1)	11,172 (48.5)	651 (13.1)	29,292 (20.8)	34,513 (40.8)	22,992 (56.3)
Technical	147 (22.7)	12,732 (24.0)	17,821 (24.7)	5,083 (22.1)	1,056 (21.3)	34,774 (24.7)	20,134 (23.8)	7,946 (19.5)
Secondary	121 (18.7)	8,278 (15.6)	8,572 (11.9)	2,202 (9.6)	1,187 (23.9)	29,666 (21.1)	12,746 (15.1)	4,258 (10.4)
University	190 (29.4)	17,197 (32.4)	17,568 (24.4)	3,957 (17.2)	1,822 (36.7)	40,058 (28.5)	13,263 (15.7)	3,931 (9.6)

Table 2 HR of dying of ALS according to anthropometric characteristics stratified for age at recruitment and center, and adjusted for sex, highest educational level attained, and smoking, including *p* values for interaction with sex

	Range in men	Range in women	Cases	Adjusted HR (95% CI)
Height				
First quartile	<170	<157	55	1.00 (ref.)
Second quartile	170–174.9	157.2–161.9	62	1.18 (0.82–1.71)
Third quartile	175–179.9	162–165.9	55	1.19 (0.80–1.76)
Fourth quartile	180+	166+	49	1.12 (0.74–1.69)
p Trend				0.603
Continuous (per 5 cm)				1.00 (0.98–1.02)
BMI				
Underweight			8	2.79 (1.35–5.77)
Normal			103	1.00 (ref.)
Overweight			77	0.83 (0.61–1.14)
Obese			32	0.92 (0.60–1.40)
p Trend				0.145
BMI (men only)				
Underweight			0	—
Normal			32	1.00 (ref.)
Overweight			39	0.78 (0.48–1.27)
Obese			7	0.44 (0.19–1.02)
p Trend				0.053
Continuous (per kg/m^2)				0.93 (0.86–0.99)
BMI (women only)				
Underweight			8	3.36 (1.61–7.04)
Normal			71	1.00 (ref.)
Overweight			38	0.81 (0.54–1.21)
Obese			25	1.24 (0.75–2.04)
p Trend				0.506
Continuous (per kg/m^2)				0.99 (0.95–1.03)
BMI				
First quartile	<24	<21.8	60	1.00 (ref.)
Second quartile	24–26.1	21.8–24.1	54	0.76 (0.52–1.10)
Third quartile	26.2–28.6	24.2–27.3	50	0.62 (0.42–0.92)
Fourth quartile	28.7+	27.4+	56	0.70 (0.47–1.04)
p Trend				0.052
Continuous (per kg/m^2)				0.97 (0.94–1.01)
Waist circumference				
First quartile	<87.8	<71.9	46	1.00 (ref.)
Second quartile	87.8–93.9	71.9–77.9	40	0.72 (0.47–1.11)
Third quartile	94.0–100.9	78.0–86.9	39	0.55 (0.36–0.86)
Fourth quartile	101+	87+	57	0.80 (0.52–1.22)
p Trend				0.248
Continuous (per cm)				0.99 (0.97–1.00)
Hip circumference				
First quartile	<96.1	<94.9	51	1.00 (ref.)
Second quartile	96.1–100.1	94.9–99.9	39	0.71 (0.47–1.08)

Continued

Table 2 Continued

	Range in men	Range in women	Cases	Adjusted HR (95% CI)
Third quartile	100.2–104.9	100.0–105.9	44	0.72 (0.48–1.09)
Fourth quartile	105.0+	106.0+	47	0.74 (0.49–1.13)
p Trend				0.189
Continuous (per cm)				1.00 (0.98–1.01)
Waist/hip ratio				
First quartile	<0.897	<0.743	41	1.00 (ref.)
Second quartile	0.897–0.938	0.744–0.785	40	0.73 (0.47–1.13)
Third quartile	0.939–0.979	0.786–0.833	53	0.87 (0.57–1.33)
Fourth quartile	0.980+	0.834+	47	0.72 (0.46–1.12)
p Trend				0.295
Waist/hip ratio (men only)				
First quartile			18	1.00 (ref.)
Second quartile			12	0.50 (0.24–1.05)
Third quartile			17	0.65 (0.33–1.29)
Fourth quartile			25	0.90 (0.47–1.70)
p Trend				0.898
Waist/hip ratio (women only)				
First quartile			23	1.00 (ref.)
Second quartile			28	0.87 (0.50–1.52)
Third quartile			36	1.00 (0.58–1.73)
Fourth quartile			22	0.59 (0.30–1.04)
p Trend				0.110

Abbreviations: ALS = amyotrophic lateral sclerosis; BMI = body mass index; CI = confidence interval; HR = hazard ratio; ref. = reference.

units (HR = 0.93, 95% CI 0.86–0.99 per kg/m^2). These results were confirmed when the analysis was repeated after excluding self-reported measures (model 1, table 3) and after excluding ALS cases accruing during the first 3 years of follow-up (model 2, table 3). The same pattern was not evident in women among whom the risk significantly increased more than 3-fold for underweight compared with normal-weight women (table 2). This finding remained significant in both sensitivity analyses. When BMI was analyzed in sex-specific quartiles of distribution, a borderline significant trend across quartiles of reduced risk increasing BMI was evident; this is also reflected in the significant—or borderline significant—reduced risk among subjects in the third and fourth quartile compared with the first. This pattern was replicated in the sensitivity analyses, although it fell short of statistical significance after excluding cases accruing during the first 3 years of follow-up (table 3). Overall, the spline regression supports the possibility of an increased risk at low BMI comparable in effect across sex (i.e., the effect below 22 kg/m^2, in figures 1 and 2), which reaches statistical significance in women only, given the higher proportion of women in this category.

The association between waist circumference and ALS was not modified by sex. Overall, a borderline significant reduced risk of ALS per centimeter of waist circumference was observed (HR = 0.99, 95% CI 0.97–1.00), with subjects in the third quartile at a significant reduced risk compared with those in the first one (table 2). These findings were replicated in sensitivity analyses (table 3). No significant association with hip circumference was observed (tables 2 and 3).

The analysis of WHR suggests a possible nonsignificant reduction of risk of ALS increasing the WHR, not modified by sex (table 2). However, in the sensitivity analysis of measured anthropometric characteristics, an interaction with sex was suggested ($p = 0.075$) and results were described separately. Among men, no trend or association was observed (tables 2 and 3, figure 2). Among women, a significant risk reduction increasing the WHR was evident: women in the fourth quartile had a more than halved significant risk of ALS compared with those in the first quartile with a borderline significant *p* value for trend across quartiles. Analogous results were observed in sensitivity analyses (table 3). These results are also supported by the spline regression

Table 3 Sensitivity analysis after excluding individuals with self-reported anthropometric measurements (model 1), and after excluding the first 3 years of follow-up (model 2)

	Model 1 ALS cases	Adjusted HR (95% CI)	Model 2 ALS cases	Adjusted HR (95% CI)
Height				
First quartile	44	1.00 (ref.)		
Second quartile	57	1.15 (0.75–1.74)		
Third quartile	49	1.01 (0.64–1.59)		
Fourth quartile	41	1.11 (0.69–1.81)		
p Trend		0.827		
Continuous (per 5 cm)		1.00 (0.98–1.03)		
BMI (men only)				
Underweight	0	—	0	—
Normal weight	32	1.00 (ref.)	26	1.00 (ref.)
Overweight	39	0.84 (0.51–1.38)	35	0.87 (0.52–1.46)
Obese	7	0.48 (0.20–1.13)	6	0.47 (0.19–1.18)
p Trend		0.124		0.156
Continuous (kg/m^2)		0.94 (0.87–1.01)		0.94 (0.87–1.01)
BMI (women only)				
Underweight	7	4.27 (1.78–10.2)	8	3.74 (1.78–7.87)
Normal weight	51	1.00 (ref.)	63	1.00 (ref.)
Overweight	32	0.75 (0.46–1.22)	35	0.84 (0.55–1.28)
Obese	23	1.23 (0.71–2.14)	23	1.30 (0.77–2.19)
p Trend		0.510		0.579
Continuous (kg/m^2)		0.99 (0.94–1.04)		0.99 (0.95–1.04)
BMI				
First quartile	51	1.00 (ref.)	50	1.00 (ref.)
Second quartile	49	0.85 (0.56–1.29)	50	0.84 (0.57–1.25)
Third quartile	44	0.62 (0.40–0.97)	45	0.67 (0.45–1.02)
Fourth quartile	47	0.71 (0.45–1.10)	51	0.78 (0.51–1.18)
p Trend		0.065		0.162
Waist circumference				
First quartile	41	1.00 (ref.)	42	1.00 (ref.)
Second quartile	29	0.62 (0.38–1.01)	35	0.69 (0.44–1.08)
Third quartile	32	0.54 (0.33–0.86)	35	0.54 (0.34–0.86)
Fourth quartile	53	0.88 (0.57–1.36)	50	0.78 (0.50–1.21)
p Trend		0.629		0.236
Continuous (per cm)		0.99 (0.97–1.00)		0.99 (0.97–1.01)
Hip circumference				
First quartile	51	1.00 (ref.)	44	1.00 (ref.)
Second quartile	39	0.73 (0.47–1.14)	34	0.71 (0.45–1.20)
Third quartile	43	0.75 (0.48–1.16)	39	0.74 (0.48–1.16)
Fourth quartile	47	0.79 (0.51–1.23)	44	0.81 (0.52–1.27)
p Trend		0.349		0.426
Continuous (per cm)		1.00 (0.98–1.02)		1.00 (0.98–1.02)
Waist/hip ratio (men only)				
First quartile	17	1.00 (ref.)	14	1.00 (ref.)
Second quartile	12	0.59 (0.27–1.26)	11	0.58 (0.26–1.29)

Continued

Table 3 Continued

	Model 1 ALS cases	Adjusted HR (95% CI)	Model 2 ALS cases	Adjusted HR (95% CI)
Third quartile	17	0.71 (0.35–1.47)	16	0.76 (0.36–1.58)
Fourth quartile	25	1.04 (0.53–2.04)	20	0.87 (0.43–1.78)
p Trend		0.578		0.996
Waist/hip ratio (women only)				
First quartile	23	1.00 (ref.)	22	1.00 (ref.)
Second quartile	28	0.81 (0.45–1.47)	27	0.89 (0.50–1.58)
Third quartile	36	0.96 (0.54–1.69)	33	1.00 (0.57–1.75)
Fourth quartile	22	0.48 (0.25–0.93)	18	0.51 (0.26–0.98)
p Trend		0.056		0.074

Abbreviations: ALS = amyotrophic lateral sclerosis; BMI = body mass index; CI = confidence interval; HR = hazard ratio; ref. = reference.

analysis, which showed a linear inverse association between WHR and risk of ALS in women (figure 2).

BMI at age 20 years seems to not be associated with ALS. The analysis of weight change suggests that having gained some weight over follow-up time is inversely associated with risk of ALS: those individuals who lost weight between age 20 years and the recruitment in the study were at a nonsignificant increased risk of ALS, whereas those in the second and third tertile of distribution of weight gain showed a nonsignificant decreased risk (table e-1 on the *Neurology*® Web site at www.neurology.org).

The potential for reverse causality, i.e., loss of weight as consequence of a prediagnostic phase of the disease, was explored by plotting the age-adjusted means of BMI and WHR among cases and controls according to the number of years of follow-up (figures e-1 and e-2). This showed no clear trend for BMI, but for WHR, if anything, the trend showed a lower WHR in subjects followed up for a longer time (thus whose anthropometric measurements were taken longer before disease onset and mortality).

DISCUSSION The present study suggests the presence of a decreased subsequent risk of dying of ALS with increasing measures of body fatness taken at enrollment, in both men and women. Underweight women were at significantly higher risk of dying of ALS compared with those of normal weight, although a decreasing risk with increasing BMI was not found. However, an increasing WHR was associated with a decreasing risk of dying of ALS in women. Although there were not enough underweight men to draw a conclusion on this category, increasing BMI seemed to be associated with a reduced risk of dying of ALS for men. The direction, and often also the significance level, of these results were maintained in sensitivity analyses reducing the potential for misclassification error after excluding individuals with self-reported body measurements, and for reverse causality after excluding cases accrued during the first

Figure 1 Spline regression curves of body mass index in relation to amyotrophic lateral sclerosis mortality in men (A) and women (B)

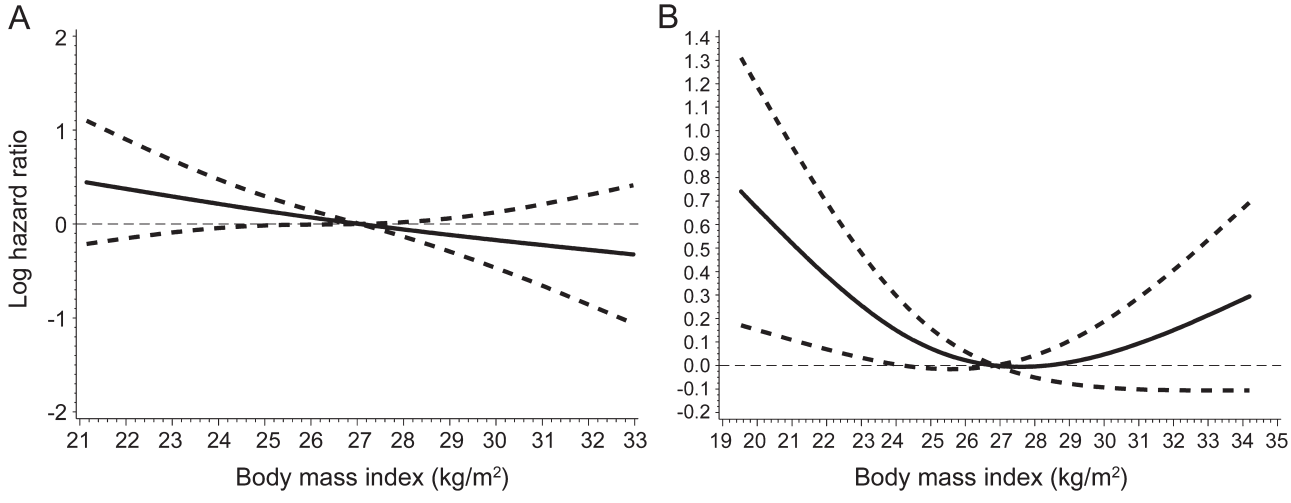
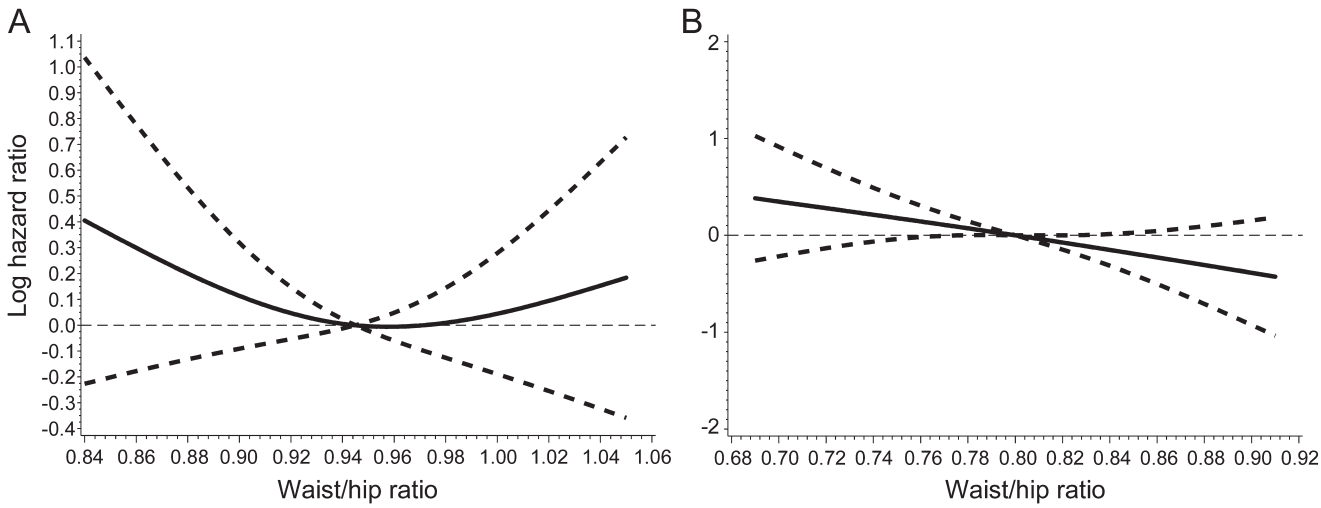


Figure 2 Spline regression curves of waist/hip ratio in relation to amyotrophic lateral sclerosis mortality in men (A) and women (B)



3 years of follow-up. Although BMI in early adulthood seems not to be strongly associated with ALS, we found a nonsignificant trend of decreasing ALS mortality with increasing weight gain.

The clinical and pathophysiologic meaning of each measurement of adiposity for assessing the risk of disease is currently a matter of debate.[20] BMI has been criticized given its relative high specificity (~97%) but low sensitivity (~42%) in detecting body fat.[21] Conversely, waist circumference and WHR have been proposed as better indicators of abdominal adiposity,[21–23] which is more closely associated with disease risk and mortality.[24] A previous analysis of the EPIC cohort found that 3 indicators (BMI, waist circumference, and WHR) were all independently associated with mortality from any cause.[25]

The association of decreasing risk of ALS with increasing body fat could also be explained by a preclinical alteration of the metabolism not related to smoking. An alteration of energy metabolism has already been observed in patients with ALS leading to weight and body fat loss as disease progresses.[13] This has been attributed to hypermetabolism with increased energy expenditure throughout disease progression.[26–28] ALS-associated hypermetabolism may be genetically driven because it is higher in patients with genetic forms of the disease.[28] A high metabolism and low body weight have also been observed in SOD1 mice compared with wild type weeks before disease onset.[29] In these mice, the correction of the energy deficit with a high-fat diet delayed disease onset and increased lifespan.[29,30] Moreover, a few environmental factors, known to modulate disease course, affect metabolism: environmental neurotoxins, strenuous exercise, response to hypoxia, and statins.[30] In a recent report, body weight at 18 years was borderline significantly lower in men who subsequently developed ALS compared with controls, but there are no data reported on BMI.[31]

The findings of the present study, the first on anthropometric measures taken before disease onset, are consistent with previous observations from case-control studies[14,32] and with other studies reporting a longer ALS survival with increasing BMI.[33] Inconsistencies in the findings across sexes remain to be explained. Possible explanations are limited power, or a true effect, possibly mediated by sex hormones, or the inconsistencies could reflect the different abilities of anthropometric indices (BMI, WHR) to measure body fat across sexes.

This study has the major advantage of prospectively using anthropometric measures in relation to the subsequent risk of developing ALS, thus ruling out recall bias. However, considering that mortality is used as proxy for incidence, and that underlying pathologic mechanisms might have a role well before disease onset, it might be argued that these findings describe a presymptomatic phase, more than a risk factor for the disease. If this was the case, one would expect, on average, BMI and WHR to decrease with decreasing the numbers of years of follow-up (i.e., decreasing the time lag between anthropometric measurements and ALS death) among ALS cases; however, this could not be observed (figures e-1 and e-2). Also, although underpowered, the analysis of weight change does not support this interpretation, suggesting the presence of a protective role for weight increase (thus, the notion that it is increasing body fat that would confer protection toward ALS, not the other way around). Another drawback of using ALS mortality as proxy for incidence is that at least some of the association observed could be attributable to differential survival across BMI or WHR categories. In fact, a high BMI was shown to significantly increase survival in patients with ALS.[33] However, given that overall the relationship between BMI and ALS survival was described as an inverse U

shape and that the survival increase was calculated on a period of approximately 12 months, it is unlikely that this substantially biased the reported estimates. Moreover, a sensitivity analysis conducted after removing 85 cases ascertained over the last 3 years of follow-up shows comparable results (data not shown).

Finally, ALS incidence has been approximated with mortality; however, death records have been demonstrated to be a reliable proxy for ascertaining ALS in large population studies.[18,34]

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Dr. Gallo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: V. Gallo, M. Jenab, G. Hallmans, R. Kaaks, H.B. Bueno-de-Mesquita, P.H. Peeters, A. Tjønneland, A. Trichopoulou, K. Overvad, D. Palli, R. Tumino, K.-T. Khaw, A. Barricante-Gurrea, F. Clavel-Chapelon, H. Boeing, E. Riboli, P. Vineis. Analysis and interpretation of data: V. Gallo, P. Wark, M. Jenab, N. Pearce, C. Brayne, R. Vermeulen, P. Andersen, A. Kyrozis, N. Vanacore, M. Vahdaninia, V. Grote, P. Vineis. Drafting of the manuscript: V. Gallo, M. Jenab, P. Wark. Data collection: G. Hallmans, R. Kaaks, A. Mattiello, H.B. Bueno-de-Mesquita, P.H. Peeters, R.C. Travis, J. Petersson, O. Hansson, L. Arriola, J.-M. Jimenez-Martin, A. Tjønneland, J. Halkjær, C. Agnoli, C. Sacerdote, C. Bonet, A. Trichopoulou, D. Gavrila, K. Overvad, E. Weiderpass, D. Palli, J.R. Quirós, R. Tumino, K.-T. Khaw, N. Werham, A. Barricante-Gurrea, V. Fedirko, P. Ferrari, F. Clavel-Chapelon, M.-C. Boutron, H. Boeing, M. Vigl, L. Middleton, E. Riboli, P. Vineis. Critical revision of the manuscript for important intellectual content: P. Wark, M. Jenab, N. Pearce, C. Brayne, R. Vermeulen, P. Andersen, A. Kyrozis, N. Vanacore, M. Vahdaninia, V. Grote, G. Hallmans, R. Kaaks, A. Mattiello, H.B. Bueno-de-Mesquita, P.H. Peeters, R.C. Travis, J. Petersson, O. Hansson, L. Arriola, J.-M. Jimenez-Martin, A. Tjønneland, J. Halkjær, C. Agnoli, C. Sacerdote, C. Bonet, A. Trichopoulou, D. Gavrila, K. Overvad, E. Weiderpass, D. Palli, J.R. Quirós, R. Tumino, K.-T. Khaw, N. Werham, A. Barricante-Gurrea, V. Fedirko, P. Ferrari, F. Clavel-Chapelon, M.-C. Boutron, H. Boeing, M. Vigl, L. Middleton, E. Riboli, P. Vineis.

STUDY FUNDING

This research has been made possible thanks to a grant of the European Community (Fifth Framework Programme) to Prof. Paolo Vineis (grant QLK4CT199900927), and a grant of the Compagnia di San Paolo to the HuGeF. All authors are independent form founders. Mortality data from the Netherlands are obtained from "Statistics Netherlands." In addition, the authors thank the following for their financial support: Europe Against Cancer Program of the European Commission (SANCO); ISCIII, Red de Centros RCESP, C03/09; Deutsche Krebshilfe; Deutsches Krebsforschungszentrum; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health; Spanish Regional Governments of Andalucia, Asturias, Basque Country, Murcia and Navarra; Cancer Research UK; Medical Research Council, United Kingdom; Stroke Association, United Kingdom; British Heart Foundation; Department of Health, United Kingdom; Food Standards Agency, United Kingdom; Wellcome Trust, United Kingdom Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer (AIRC); Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports (VWS); Netherlands Cancer Registry (NKR); LK Research Funds; Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); Statistics Netherlands (the Netherlands); Swedish Cancer; Swedish Scientific Council; Regional Government of Skåne and Västerbotten, Sweden; Norwegian Cancer Society; Research Council of Norway; French League Against Cancer, INSERM, Mutuelle Generale l'Education National, and IGR.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received May 22, 2012. Accepted in final form October 24, 2012.

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