Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

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To cite this article: Éilis J. O'Reilly, Molin Wang, Hans-Olov Adami, Alvaro Alonso, Leslie Bernstein, Piet van den Brandt, Julie Buring, Sarah Daugherty, Dennis Deapen, D. Michal Freedman, Dallas R. English, Graham G. Giles, Niclas Håkansson, Tobias Kurth, Catherine Schairer, Elisabete Weiderpass, Alicja Wolk & Stephanie A. Smith-Warner (2018) Prediagnostic body size and risk of amyotrophic lateral sclerosis death in 10 studies, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 19:5-6, 396-406, DOI: 10.1080/21678421.2018.1452944

To link to this article: https://doi.org/10.1080/21678421.2018.1452944

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2018; 19: 396–406

RESEARCH ARTICLE

Prediagnostic body size and risk of amyotrophic lateral sclerosis death in 10 studies

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Abstract

Objectives and Methods: Using pooled multivariable-adjusted rate ratios (RR), we explored relationships between prediagnostic body-mass-index (BMI), waist-to-hip-ratio (WHR), and weight-gain during adulthood, and ALS in 419,894 women and 148,166 men from 10 community-based cohorts in USA, Europe, and Australia; 428 ALS deaths were documented in women and 204 in men. *Results*: Higher mid-to-later adulthood BMI was associated with lower ALS mortality. For 5 kg/m^2 increased BMI, the rate was 15% lower (95% confidence interval [CI]: 4–24%; $p = 0.005$). Although a clear linear trend was not evident for WHR at enrollment ($p = 0.099$) individuals in the highest cohort-specific quartile had 27% (95% CI: 0–47%; $p = 0.053$) lower ALS compared to those in the lowest. BMI in early adulthood did not predict ALS; fewer than 10% of participants had early adulthood BMI >25 kg/m^2, limiting power. Weight-gain during adulthood was strongly associated with lower ALS; for an additional 1kg gain in weight/year, the RR = 0.43 (95% CI: 0.28–0.65; $p < 0.001$). Associations persisted when adjusted for diabetes at enrollment, restricted to never-smokers, and ALS deaths in the 5 years after enrollment were excluded (accounting for recent weight loss). *Conclusions*: These findings confirm somewhat conflicting, underpowered evidence that adiposity is inversely associated with ALS. We newly demonstrate that weight-gain during adulthood is strongly predictive of lower ALS risk.

Keywords: Amyotrophic lateral sclerosis, body mass index, waist-to-hip ratio, weight gain

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(Received 5 December 2017; revised 27 February 2018; accepted 5 March 2018)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2018.1452944

Introduction

ALS, a neurodegenerative disease affecting 1.5–3 in 100,000 people per year, is characterized by progressive wasting and death within 2–3 years of diagnosis (1). While the main pathological basis of ALS is degeneration of motor neurons, other systemic changes occur. In particular, patient's exhibit increased energy metabolism (2–7) contrary to expectation based on continued muscle-wasting. *SOD1* mutant mice similarly exhibit hypermetabolism and leanness, even several weeks before symptom onset and high-energy diets delayed onset, and improved motor neuron survival (6). Whether leanness or hypermetabolism is part of the disease pathology, is a risk factor for ALS (in other words, could obesity be a protective factor or hypermetabolism detrimental), or whether leanness or hypermetabolism and ALS are independently triggered by other factor(s) remains to be fully elucidated. Prior prospective studies suggest mid-life BMI is related to ALS risk, but findings are somewhat inconsistent (8–10). It remains unclear whether early-adulthood BMI or weight gain in adulthood predicts ALS, and data on prediagnostic waist and hip circumference and waist-to-hip ratio (WHR) are limited. Some previous studies have not completely adjusted for smoking (10), a very strong predictor of BMI and risk factor for ALS.

We aim to further clarify the relation between body size in early- and mid-life and ALS death in a larger study of 419,894 women and 148,166 men, 632 of whom died from ALS, and almost all of whom were recruited from the general population in the USA, Europe, and Australia. Specifically, we will evaluate the hypermetabolism hypothesis further by exploring propensity to gain weight since age 18 which may be more indicative of life-long leanness/hypermetabolism than either BMI at age 18 or BMI at the particular age the participant was recruited (generally, middle-age). We have adequate power to consider these anthropometric predictors of ALS among never smokers and excluding ALS deaths during the 7 years after enrollment (accounting for recent weight loss).

Methods

Participants

The Pooling Project of Prospective Studies of Diet and Cancer (DCPP) is an ongoing collaboration with the primary goals of assembling sufficient data to examine nutrition and cancer associations with standardized analyses of primary data across cohorts. We invited all cohorts participating in DCPP to extend their collaboration to include ALS; many of these cohorts had insufficient cases to independently investigate ALS epidemiology with precision. Five cohorts that participate in DCPP are already in an established ALS collaboration (9,11,12). In addition, the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort has sufficient numbers for independent analyses (8,13); excluding these six DCPP cohorts from the current project facilitated the establishment of an independent data set that could validate results from the other two prospective projects (EPIC and 5-cohort ALS study). Ten prospective cohorts with 568,060 participants from Europe, USA, and Australia are included in our analyses (Table 1).

Cohort participant descriptions

The DCCP studies are prospective cohorts or randomized trials analyzed as prospective cohorts. The main disadvantage of this study design is the possibility that the self-selecting subjects who chose to enroll in each study do not represent the population base. While this may affect external generalizability, it will not affect internal validity. Each study has been described previously and is briefly outlined.

Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP) during 1973–1981 recruited over a quarter of a million women at 29 US centers who participated in a mammography screening program. In 1987–1989 a subset completed a FFQ and was followed for subsequent outcomes (14).

California Teachers Study (CTS) is a cohort of female public-school teachers and administrators that began enrollment in 1995. Over 130,000 teachers answered a questionnaire on risk factors for breast cancer including anthropometrics and diet (15).

Cohort of Swedish Men (COSM) is a population-based cohort comprising 48,850 men aged 45–79 years who were residents in central Sweden. In 1997, they completed a comprehensive questionnaire on lifestyle factors, diet, and medical history (16).

Iowa Women's Health Study (IWHS) is a population-based prospective cohort that enrolled 41,836 women age 55–69 years in 1986. Women were invited to complete a 16-page mailed questionnaire if they held an Iowa driver's license in 1985 (17).

Melbourne Collaborative Cohort Study (MCCS) is a cohort study of 24,479 women and 17,049 men mostly aged 40–69, with oversampling of Southern European migrants (30%), in Melbourne between 1990 and 1994. Detailed information on lifestyle factors as well as blood samples and direct physical measurements was collected in face-to-face interviews (18).

The Netherlands Cohort Study (NLCS) comprises 58,279 and 62,573 Dutch men and women aged 55–69 years old. Baseline questionnaires were self-administered in 1986. Follow-up is ongoing. NLCS uses a case-cohort design where all cases of interest and

Table 1. Enrollment characteristics of men and women in ten cohorts worldwide followed for death due to ALS.

Cohort (follow-up years)	Sex	Baseline cohort size	Age at enrollment range (years)	Number of ALS deaths	Age at ALS death (years)	BMI at enrollment (kg/m^2)	BMI at age 18/20 (kg/m^2)	Waist circumference at enrollment (cm)	Hip Circumference at enrollment (cm)	Height (m)
					Median (10th and 90th percentile)					
BCDDP (1987–2005)	F	38,950	40–93	52	73 (65–82)	23.8 (20.0–30.4)	/	81.3 (68.6–96.5)	101.6 (91.4–114.3)	1.63 (1.55–1.70)
CTS (1995–2009)	F	102,607	22–104	63	73 (54–84)	23.6 (19.8–31.4)	20.8 (18.3–25.0)	78.7 (67.3–100.3)	99.1 (90.2–115.6)	1.65 (1.57–1.73)
COSM (1997–2010)	M	43,010	45–79	70	70 (58–84)	25.4 (22.0–30.0)	21.8 (19.2–24.6)	95.0 (85.0–108.0)	101.0 (94.0–110.0)	1.77 (1.69–1.86)
IWHS (1986–2009)	F	34,540	55–69	91	75 (67–84)	25.2 (20.8–32.4)	20.5 (17.8–24.4)	86.1 (71.1–106.7)	102.9 (92.7–119.1)	1.63 (1.55–1.70)
MCCS (1990–2006)	F	22,803	31–75	15	70 (56–79)	25.8 (21.3–32.9)	21.1 (18.2–25.0)	78.0 (66.0–95.0)	100.0 (90.1–114.0)	1.60 (1.51–1.69)
	M	14,895	27–72	15	65 (55–78)	26.8 (22.9–31.5)	22.4 (19.4–26.0)	92.5 (81.0–105.5)	100.5 (92.5–109.5)	1.73 (1.63–1.82)
NLCS (1986–2003)	F	62,573	55–69	61	73 (64–80)	24.6 (21.1–29.7)	21.3 (18.0–24.6)	/	/	1.65 (1.58–1.73)
(# in the subcohort)		(2,367)								
	M	58,279	55–69	81	71 (63–77)	24.8 (21.8–28.1)	21.7 (18.9–24.5)			1.76 (1.68–1.85)
		(2,244)								
PLCO (1992–2009)	F	28,115	55–74	27	71 (58–85)	25.9 (21.3–34.1)	20.8 (18.3–24.3)	/	/	1.63 (1.55–1.70)
	M	29,310	55–74	32	71 (58–80)	27.0 (23.1–32.8)	22.9 (19.4–26.6)			1.78 (1.70–1.85)
SMC (1997–2010)	F	35,944	48–83	51	75 (63–84)	24.5 (20.6–30.1)	20.3 (17.6–23.6)	82.0 (71.0–98.0)	102.0 (92.0–115.0)	1.64 (1.57–1.72)
WHS (1992–2009)	F	37,570	45–89	40	65 (57–80)	24.9 (20.8–32.6)	/	87.6 (72.4–109.2)	105.4 (94.0–122.6)	1.65 (1.57–1.73)
WLHS (1991–2009)	F	45,739	30–49	18	60 (52–65)	22.8 (19.8–28.0)	20.2 (17.6–23.7)	75.0 (67.0–89.0)	98.0 (90.0–108.0)	1.66 (1.59–1.73)
Total women		408,841		418						
Total men		145,494		198						

Cohort size is determined after applying cohort-specific exclusion criteria and further excluding participants with energy intakes beyond 3 SDs of their $\log_e$-transformed cohort-specific mean energy intake and BMI below 14 and above 50 kg/m^2.

The NLCS was analyzed as case–cohort study; above exclusions were applied to the analysis data set, and not applied to the baseline cohort size presented in the table.

F: female; M: male; BCDDP: Breast Cancer Detection Demonstration Project Follow-up Study; CTS: California Teachers Study; COSM: Cohort of Swedish Men; IWHS: Iowa Women's Health Study; MCCS: Melbourne Collaborative Cohort Study; NLCS: The Netherlands Cohort Study; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC: the Swedish Mammography Cohort; WHS: the Women's Health Study; WLHS: the Women's Lifestyle and Health Study

deaths are enumerated while the non-case experience is estimated using a sub-cohort (19).

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) is a two-armed trial set in multiple centers across the USA that was designed to evaluate whether a screening test reduces risk of death from the named cancers. Over 150,000 men and women aged 55–74 participated between 1992 and 2001 (20). Only the screened arm participants, who completed a diet history questionnaire, are included in the DCPP.

Swedish Mammography Cohort (SMC) comprises 66,651 women born between 1914 and 1948 who returned a completed 6-page questionnaire between 1987 and 1990 in response to an invitation to participate in mammography screening (21).

The Women's Health Study (WHS) is a $2 \times 2 \times 2$ randomized double-blind, placebo-controlled clinical trial of aspirin, beta-carotene, and/or vitamin E that enrolled almost 40,000 US women over 45 years old during 1992–1995. Enrollees completed questionnaires prior to randomization-phase (22).

Women's Lifestyle and Health Study (WLHS) in 1991 recruited 50,000 premenopausal (30–49 years old) women who returned comprehensive questionnaires on lifestyle, diet, and reproductive factors (23).

Exposure and covariate assessment

Each cohort collected information on height and current weight by self-report on baseline questionnaires, except MCCS in which they were directly measured. Weight during early adulthood (asked on the questionnaires as weight at age 18 or at 20) was also collected at enrollment in eight cohorts. Baseline BMI (mid-to-late adulthood) and BMI during early adulthood were calculated using weight at baseline and recalled weight from early adulthood, respectively, divided by height reported at baseline squared (kg/m^2). In a US national health survey, correlations between current self-reported and technician measured BMI values were very high (0.90–0.95 across groups) (24). Weight is reasonably well-remembered over time: correlation was 0.80 for middle-aged men who recalled weight at age 25 compared to weight recorded on military records, and 0.87 for middle-aged women who recalled weight at age 18 compared to weight recorded at entry to nursing school (25,26). In men and women over 70 years old, the correlations for recalled BMI and measured BMI in adolescence were 0.63 and 0.82, respectively (27). WHR was available in eight cohorts and was calculated using self-assessed waist and hip tape measurements at baseline. Self-measured WHR has moderate validity; for example in one study correlations between self-reported waist circumferences and the average of two technician-measured waist circumferences were 0.95 for men and 0.89 for women, hip measurements were 0.88 for men and 0.84 for women, and WHR were 0.69 for men and 0.70 for women (28). The yearly rate of change in weight was calculated comparing weight in early adulthood and weight at time of enrollment, divided by age at enrollment less 18 or 20 years. Information on dietary and other factors, including smoking and education attained, was also collected on baseline questionnaires.

Exclusions

Individuals with missing or implausible BMI (<14 or >50 kg/m^2) were excluded from all analyses shown here (3% of the overall study population; ranging from none in MCCS to 8% in BCDDP). When we analyzed other parameters of adiposity, individuals were excluded when that parameter was missing.

Outcome

A participant was considered to have died from ALS if his or her death certificate recorded motor neuron disease (International Classification for Disease version 9 (ICD-9) 335.2 or ICD-10 G12.2; World Health Organization, Geneva, Switzerland) as an intermediate, underlying, or other cause of death.

Statistical analysis

Anthropometric measures were modeled continuously, as predefined categories, or as study- and gender-specific quartiles. Baseline BMI was classified as follows: <18.5, 18.5–<23, 23–<25, 25–<30, and 30 + kg/m^2 following the World Health Organization's (WHO) definitions of underweight, low-normal weight, high-normal weight, overweight, and obese. BMI in early adulthood was classified into the following categories: <18.5, 18.5–<21, 21–<23, 23–<25, and 25 + kg/m^2 reflecting leaner body mass at this age. WHR, height, and rate of weight change during adulthood were categorized as quartiles.

Relative rates (RR) and their 95% confidence intervals (95% CI) were calculated using Cox proportional hazards models for each gender within each cohort. The model included stratification by baseline age (years) and year the baseline questionnaire was returned; follow-up time (months) was the timescale, resulting in a time metric that simultaneously accounted for age, calendar time, and time since entry into the study. Multivariable RRs were further adjusted for smoking status (ever smoking, smoking pack-years <10, 10–<20, 20–<30, 30–<40, 40+), education attained (<high-school, high-school, >high-school), physical activity (low, moderate, high), and race (if appropriate to the cohort: overall >90% of participants were Caucasian). In the analyses of waist and hip circumferences, WHR, and BMI in early adulthood, the effect of adjustment for baseline BMI was examined. The missing indicator method (assigning the same value to all missings within a covariate, and

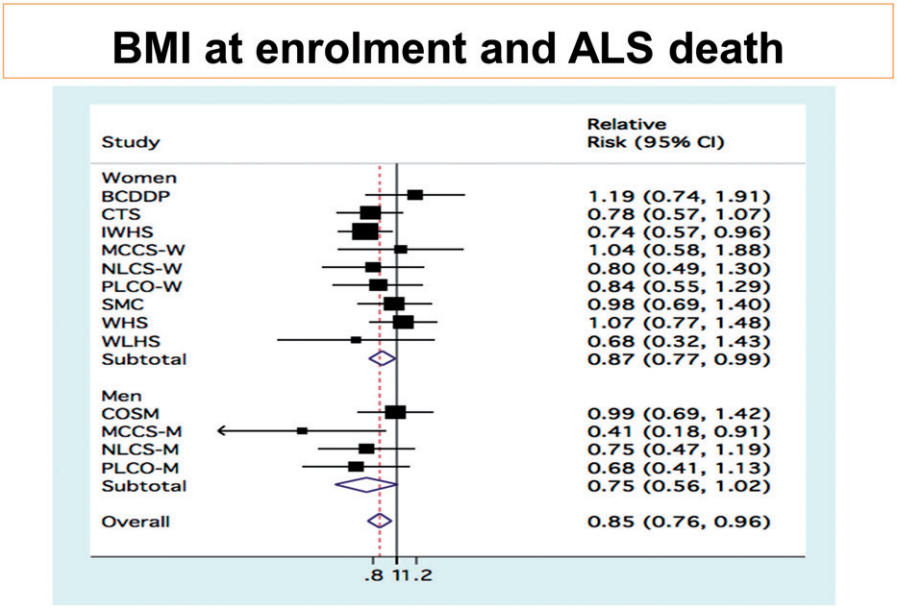

Figure 1. Pooled results for 5 kg/m^2 increase in BMI at enrollment. Pooled RR = 0.85 (95% CI: 0.76–0.96; $p = 0.005$). Among women, pooled RR = 0.87 (95% CI: 0.77–0.99; $p = 0.036$). Among men, pooled RR = 0.75 (95% CI: 0.56–1.02; $p = 0.062$).

adding a further stratification (dummy) variable indicating the value was originally missing = yes/no to the model) was used within a cohort, if needed. In general, data on covariates were missing for <10% of each study population (29). NLCS was analyzed as a case-cohort study (30) because questionnaires were processed for only a random sample of the cohort in addition to all ALS deaths (19). Cohort-specific results were pooled using a random-effects model (31), weighted by the inverse of their variance. Between-studies heterogeneity was investigated using the Q test statistic (31).

Results

Ten participating cohorts comprised 419,894 women and 148,166 men, 428 and 204 of whom, respectively, had ALS listed as their cause of death. After excluding participants with missing or implausible baseline BMI, 408,841 women (418 ALS deaths) and 145,494 men (198 ALS deaths) remained for the main analyses. The cohort-specific follow-up ranged from 13 to 23 years. Median baseline BMI ranged from 22.8 to 27.0 kg/m^2 across studies; average baseline BMI was at least 2.5 kg/m^2 higher than BMI in early adulthood (Table 1).

BMI at enrollment: Overall individuals with higher BMI at the time of enrollment had lower rates of ALS mortality compared to individuals with lower BMI. For each 5 kg/m^2 higher increment in baseline BMI the pooled age-adjusted rate of ALS mortality was 13% lower (95% CI: 2–22%; $p = 0.023$; p-for-heterogeneity = 0.344) and the multivariable-adjusted rate was 15% lower (95% CI: 4–24%; $p = 0.005$; p-for-heterogeneity = 0.486) for men and women combined (Figure 1); among women, the multivariable-adjusted rate was 13% (95% CI: 1–23%; $p = 0.036$) lower for each 5 kg/m^2 higher baseline BMI while there was a borderline statistically significant lower rate among men (25% [95% CI: −2–44%; $p = 0.062$] for the same increment; p-for-heterogeneity due to gender >0.9). Tests for deviation from linearity were not statistically significant (p-for-nonlinearity >0.05; data not shown).

BMI at enrollment categorized according to WHO definitions of underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–<30 kg/m^2), and obesity (30 + kg/m^2): Compared to men and women in the low-normal weight range at baseline (18.5–<23 kg/m^2) the pooled multivariable-adjusted RR of ALS death was 2.56 (95% CI: 1.38–4.77; $p = 0.003$) for underweight individuals, RR = 0.74 (95% CI: 0.58–0.95; $p = 0.016$) for high-normal, RR = 0.75 (95% CI: 0.59–0.95; $p = 0.017$) for overweight, and 0.73 (95% CI: 0.53–1.00; $p = 0.053$) for obese individuals (Table 2).

Findings were similar for women (compared to low-normal weight, pooled multivariable-adjusted RR = 2.21 (95% CI: 1.13–4.34; $p = 0.021$) for underweight, RR = 0.83 (95% CI: 0.62–1.12; $p = 0.226$) for high-normal, RR = 0.84 (95% CI: 0.63–1.13; $p = 0.244$) for overweight and RR = 0.75 (95% CI: 0.52–1.08; $p = 0.120$) for those who were obese), and men (only one study could contribute to the multivariate categorical analysis of BMI <18.5 kg/m^2 due to small numbers; compared to low-normal, the RR = 0.59 (95% CI: 0.38–0.89; $p = 0.013$) for high-normal, RR = 0.61 (95% CI: 0.42–0.88; $p = 0.008$) for overweight and RR = 0.57 (95% CI: 0.23–1.41; $p = 0.225$) for obese). Five cohorts of women (CTS, IWHS, NLCS-w, PLCO-w, and WHS) had adequate

Table 2. Analyses of body mass index at enrollment and ALS death in men and women.

			World Health Organization categories of BMI (kg/m^2)				
		Continuous BMI per 5 kg/m^2 increment	14–<18.5[a]	18.5–<23 (reference)	23–<25	25–<30	30+
All	No. of cases	616	15	178	127	214	67
	RR (95% CI)	0.85 (0.76–0.96)	2.75 (1.49–5.08)	1.00	0.74 (0.58–0.95)	0.75 (0.59–0.95)	0.73 (0.53–1.00)
	p Value	0.005	0.001		0.016	0.017	0.053
	p-H between studies	0.486	0.402		0.533	0.294	0.368
	p-H due to sex	0.417	0.153		0.179	0.172	0.662
Three-year lag	No. of cases	556	8	161	112	196	64
	RR (95% CI)	0.90 (0.80–1.01)	1.81 (0.87–3.77)	1.00	0.74 (0.57–0.95)	0.79 (0.63–0.98)	0.79 (0.58–1.09)
	p Value	0.081	0.112		0.020	0.035	0.146
	p-H between studies	0.617	0.621		0.705	0.731	0.629
	p-H due to sex	0.978	0.566		0.201	0.336	0.965
Five-year lag	No. of cases	497	8	142	103	173	56
	RR (95% CI)	0.89 (0.79–1.01)	2.16 (1.03–4.52)	1.00	0.76 (0.58–1.00)	0.79 (0.62–1.00)	0.79 (0.56–1.11)
	p Value	0.060	0.042		0.047	0.050	0.176
	p-H between studies	0.680	0.616		0.645	0.689	0.504
	p-H due to sex	0.872	0.666		0.201	0.211	0.915
Seven-year lag	No. of cases	414	7	117	86	145	47
	RR (95% CI)	0.89 (0.78–1.02)	2.24 (1.02–4.93)	1.00	0.80 (0.58–1.10)	0.78 (0.60–1.02)	0.83 (0.57–1.20)
	p Value	0.091	0.045		0.168	0.070	0.320
	p-H between studies	0.872	0.700		0.393	0.662	0.608
	p-H due to sex	0.966	0.534		0.238	0.359	0.836
Non-smokers	No. of cases	501	11	140	96	177	62
	RR (95% CI)	0.87 (0.76–1.00)	2.91 (1.19–7.14)	1.00	0.69 (0.52–0.91)	0.73 (0.55–0.95)	0.74 (0.50–1.10)
	p Value	0.050	0.020		0.009	0.020	0.140
	p-H between studies	0.292	0.187		0.675	0.269	0.185
	p-H due to sex	0.327	0.091		0.111	0.069	0.478

Multivariable RRs were further adjusted for smoking status (ever smoking and smoking pack-years <10, 10–<20, 20–<30, 30–<40, 40+), level of education attained (<high-school, high-school, >high-school), physical activity (low, moderate, high), and race (if appropriate to the cohort); age in years and year of questionnaire return were included as stratification variables.

[a]MCCS-female are not part of the categorical analyses because no cases occurred among participants in the reference range of BMI 18.5–<23 kg/m^2. COSM, CTS, IWHS, NLCS-females, SMC, and WHS are included in the analyses of BMI <18.5 kg/m^2; no cases occurred in the remaining cohorts. Including the non-cases in these cohorts (1.5% of overall populations) with BMI <18.5 kg/m^2 in the reference category did not change the results.

p-H between studies: *p* value for the test for between-studies heterogeneity; *p*-H due to sex: *p* value for the test for between-studies heterogeneity due to sex

Table 3. Yearly rate of weight (kg) gain from early adulthood to enrollment by cohort and risk of ALS death.

Cohort	Continuous yearly weight gain per 1 kg increment	Quartile 1 median (10th–90th percentile) RR (95% CI)	Quartile 2 median (10th–90th percentile) RR (95% CI)	Quartile 3 median (10th—90th percentile) RR (95% CI)	Quartile 4 Median (10th-90th percentile) RR (95% CI)
Women					
CTS	RR = 0.71	−0.10 (−0.60, 0.04)	0.16 (0.08, 0.23)	0.35 (0.26, 0.46)	0.76 (0.54, 1.49)
	(95% CI: 0.29, 1.71), $p = 0.440$	Ref	RR = 1.00 (95% CI: 0.52, 1.89)	RR = 0.55 (95% CI: 0.25, 1.21)	RR = 0.86 (95% CI: 0.37, 1.96)
IWHS	RR = 0.29	0.03 (−0.17, 0.11)	0.21 (0.15, 0.27)	0.37 (0.30, 0.45)	0.63 (0.50, 0.96)
	(95% CI: 0.12, 0.71), $p = 0.007$	Ref	RR = 0.82 (95% CI: 0.49, 1.39)	RR = 0.51 (95% CI: 0.28, 0.93)	RR = 0.43 (95% CI: 0.21, 0.80)
MCCS	RR = 0.51	0.04 (−0.18, 0.13)	0.24 (0.17, 0.31)	0.42 (0.35, 0.51)	0.74 (0.57, 1.18)
	(95% CI: 0.06, 4.35), $p = 0.541$	Ref	RR = 1.69 (95% CI: 0.44, 6.47)	RR = 1.30 (95% CI: 0.29, 5.83)	RR = 0.47 (95% CI: 0.05, 4.68)
NLCS	RR = 0.36	0 (−0.21, 0.08)	0.16 (0.11, 0.21)	0.29 (0.24, 0.35)	0.49 (0.38, 0.73)
	(95% CI: 0.06, 2.11), $p = 0.260$	Ref	RR = 0.49 (95% CI: 0.22, 1.07)	RR = 0.29 (95% CI: 0.12, 0.70)	RR = 0.58 (95% CI: 0.25, 1.35)
PLCO	RR = 0.47	0.06 (−0.11, 0.14)	0.23 (0.17, 0.29)	0.40 (0.32, 0.48)	0.68 (0.53, 1.07)
	(95% CI: 0.10, 2.18), $p = 0.333$	Ref	RR = 1.32 (95% CI: 0.51, 3.41)	RR = 0.67 (95% CI: 0.21, 2.13)	RR = 0.64 (95% CI: 0.18, 2.25)
SMC	RR = 0.47	0.03 (−0.16, 0.11)	0.20 (0.14, 0.25)	0.34 (0.28, 0.42)	0.57 (0.45, 0.89)
	(95% CI: 0.10, 2.26), $p = 0.344$	Ref	RR = 1.21 (95% CI: 0.50, 2.92)	RR = 1.20 (95% CI: 0.47, 3.04)	RR = 0.70 (95% CI: 0.23, 2.19)
WLHS	RR = 0.55	0 (−0.38, 0.11)	0.23 (0.16, 0.31)	0.43 (0.35, 0.53)	0.78 (0.60, 1.33)
	(95% CI: 0.11, 2.77), $p = 0.467$	Ref	RR = 1.75 (95% CI: 0.42, 7.27)	RR = 1.95 (95% CI: 0.47, 8.04)	RR = 0.34 (95% CI: 0.03, 3.45)
Pooled	RR = 0.46	Ref	RR = 0.93 (95% CI: 0.69, 1.25),	RR = 0.66 (95% CI: 0.42, 1.02),	RR = 0.57 (95% CI: 0.39 − 0.83),
	(95% CI: 0.28, 0.75), $p = 0.002$		$p = 0.624$	$p = 0.059$	$p = 0.003$
	P heterogeneity = 0.915		P for heterogeneity = 0.532	P for heterogeneity = 0.189	P for heterogeneity = 0.898
Men					
COSM	RR = 0.65	0.04 (−0.12, 0.12)	0.20 (0.15, 0.26)	0.35 (0.29, 0.43)	0.60 (0.47, 0.92)
	(95% CI: 0.20, 2.18), $p = 0.487$	Ref	RR = 0.74 (95% CI: 0.37, 1.46)	RR = 0.53 (95% CI: 0.24, 1.17)	RR = 0.92 (95%CI: 0.44, 1.94)
MCCS	RR = 0.04	0.06 (−0.13, 0.15)	0.26 (0.19, 0.33)	0.44 (0.36, 0.53)	0.74 (0.58, 1.13)
	(95% CI: <0.001, 0.52), $p = 0.013$	Ref	RR = 1.11 (95% CI: 0.34, 3.66)	RR = 0.15 (95% CI: 0.02, 1.38)	RR = 0.17 (95% CI: 0.02, 1.71)
NLCS	RR = 0.43	0 (−0.15, 0.08)	0.16 (0.11, 0.21)	0.28 (0.23, 0.33)	0.49 (0.38, 0.71)
	(95% CI: 0.09, 2.12), $p = 0.303$	Ref	RR = 0.67 (95% CI: 0.32, 1.43)	RR = 0.74 (95% CI: 0.33, 1.66)	RR = 0.66 (95% CI: 0.25, 1.74)
PLCO	RR = 0.23	0.05 (−0.13, 0.13)	0.22 (0.16, 0.28)	0.38 (0.31, 0.45)	0.63 (0.50, 0.97)
	(95% CI: 0.05, 1.13), $p = 0.070$	Ref	RR = 0.86 (95% CI: 0.36, 2.03)	RR = 0.49 (95% CI: 0.18, 1.39)	RR = 0.35 (95% CI: 0.10, 1.17)
Pooled	RR = 0.32	Ref	RR = 0.78 (95% CI: 0.52, 1.18),	RR = 0.56 (95% CI: 0.34, 0.90),	RR = 0.63 (95% CI: 0.37, 1.09),
	(95% CI: 0.13, 0.83), $p = 0.018$		$p = 0.236$	$p = 0.017$	$p = 0.097$
	P heterogeneity = 0.251		P for heterogeneity = 0.907	P for heterogeneity = 0.594	P for heterogeneity = 0.368
All pooled	RR = 0.43	Ref	RR = 0.87 (95% CI: 0.69, 1.11),	RR = 0.60 (95% CI: 0.45, 0.81),	RR = 0.59 (95% CI: 0.44, 0.81),
	(95% CI: 0.28, 0.65), $p < 0.001$		$p = 0.273$	$p = 0.001$	$p = 0.001$
	P heterogeneity = 0.773		P for heterogeneity = 0.808	P for heterogeneity = 0.375	P for heterogeneity = 0.853

Multivariable RRs were adjusted for smoking status (ever smoking and smoking pack years <10, 10–<20, 20–<30, 30–<40, 40+), level of education attained (<high-school, high-school, >high-school), physical activity (low, moderate, high), BMI at age 18/21 (continuous), and race (if appropriate to the cohort); age in years and year of questionnaire return were included as stratification variables.

California Teachers Study (CTS); Cohort of Swedish Men (COSM); Iowa Women's Health Study (IWHS); Melbourne Collaborative Cohort Study (MCCS); The Netherlands Cohort Study (NLCS); Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO); the Swedish Mammography Cohort (SMC); the Women's Health Study (WHS); and the Women's Lifestyle and Health Study (WLHS). RR: relative rate; CI: confidence interval.

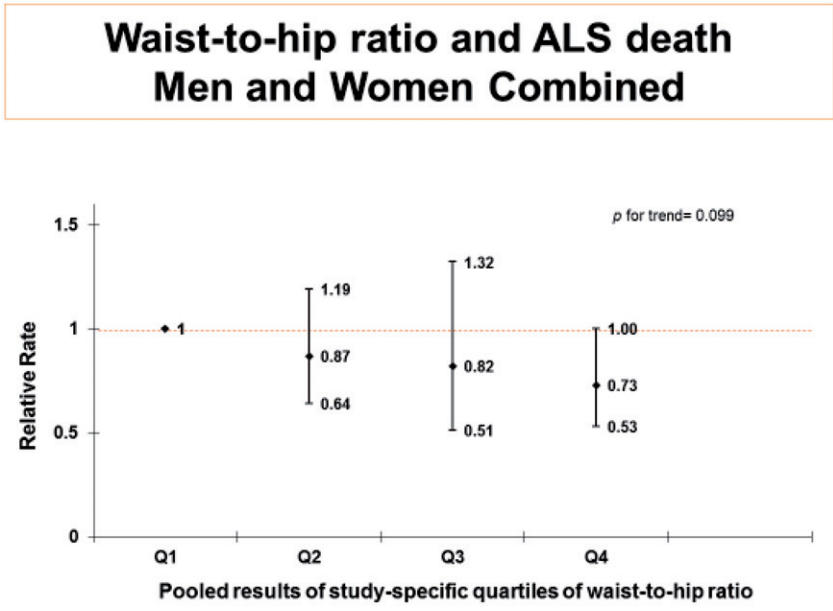

Figure 2. BCDDP (w), CTS (w), SMC (w), WHS (w), IWHS (w), MCCS (w & m), WLHS (w) and COSM (m) had waist and hip measurements, however, WLHS was not included in the analyses because of small case numbers. Quartiles results are cohort-specific (and gender specific in MCCS), then pooled. All tests of heterogeneity had p-values >0.05. Analyses are adjusted for age, education, race, smoking, and physical activity. Further adjustment for BMI at baseline changed effect sizes minimally.

case numbers for analyses in individuals with baseline BMI of 35 + kg/m^2; compared to women with low-normal BMI, the pooled multivariable-adjusted RR = 0.63 (95% CI: 0.29–1.37; $p = 0.247$).

In sensitivity analyses excluding ALS deaths occurring 3, 5, and 7 years after baseline to exclude weight loss from pre-clinical disease, findings were only very slightly attenuated: for a 5 kg/m^2 higher increment in baseline BMI, RRs were 0.90 (95% CI: 0.80–1.01; $p = 0.081$), 0.89 (95% CI: 0.79–1.01; $p = 0.06$), and 0.89 (95% CI: 0.78–1.02; $p = 0.091$) for 3, 5, and 7 year lags, respectively. Because smokers weigh less than nonsmokers on average and smoking may be a risk factor for ALS, analyses were repeated in nonsmokers at baseline; findings were not materially changed (Table 2). In addition, the associations persisted when adjusted for self-reported diabetes at enrollment (for a 5 kg/m^2 higher increment in baseline BMI, RR = 0.85 (95% CI: 0.76–0.95; $p = 0.006$; p-for-heterogeneity = 0.51).

BMI in early adulthood: Weight in early adulthood was collected in eight cohorts (145,494 men and 332,321 women [198 and 326 cases, respectively]; Table 1). BMI in early adulthood was not associated with ALS mortality (pooled multivariable-adjusted RR = 1.04 [95% CI: 0.88–1.22; $p < 0.001$] per 5 kg/m^2 increase). However, within each cohort fewer than 10% of participants were overweight or obese in early adulthood, except 23% of the men in PLCO, and 17% of the men in MCCS.

Weight gain during adulthood: The median weight gained from early adulthood to baseline was 12.0 kg for men and 9.5 kg for women. For every additional 1 kg gain in yearly weight gain, the pooled multivariable-adjusted RR were 0.43 (95% CI: 0.28–0.65; $p < 0.001$) overall, 0.32 (95% CI: 0.13–0.83; $p = 0.018$) among men, and 0.46 (95% CI: 0.28–0.75; $p = 0.002$) among women (Table 3). Tests for deviation from linearity were not statistically significant (not shown). Risk estimates were similar when analyses were *not* adjusted for BMI in early adulthood (RR = 0.49 [95% CI: 0.34–0.71; $p < 0.001$]) for men and women combined for every additional 1 kg yearly weight gain. Excluding the first 5 years of follow-up (to reduce misclassification of yearly weight gain by recent weight loss) slightly attenuated the association (RR = 0.48 [95% CI: 0.31–0.75; $p = 0.001$]) for each additional 1 kg increase yearly weight gain). When restricted to never-smokers to exclude those who did not gain weight due to smoking at any time during adulthood the RR = 0.52 (95% CI: 0.25–1.09; $p = 0.082$) for each additional 1 kg increase yearly weight gain.

Waist, hip, and WHR at enrollment: Eight cohorts collected baseline waist and hip circumference (57,905 men and 318,513 women [85 and 330 cases, respectively]; Table 1). Among men and women in the fourth quartile of WHR, there was a 27% (95% CI: 0–47%; $p = 0.053$) reduction in ALS mortality compared to those in the first (Figure 2). Findings were virtually unchanged when adjusted for baseline BMI. Among women, rates were similarly lowered comparing the fourth to the first quartile, but were borderline statistically significant (28% [95% CI: −5%–51%]; $p = 0.085$]). In the two male cohorts with WHR, there was no relationship with ALS, perhaps due to inadequate power. Results were similar when WHR was categorized as WHO sex-specific cut-points: among women, RR = 0.76

(95% CI: 0.55–1.05; $p = 0.096$) for WHR above 0.85 compared to 0.85 or below; among men, RR = 0.57 (95% CI: 0.25–1.33; $p = 0.195$) for WHR above 0.90 compared to 0.90 or below. Height was not associated with ALS (RR = 1.09; 95% CI: 0.82–1.44; $p = 0.557$ comparing men and women in the top quartile to the bottom).

No statistically significant heterogeneity across studies or gender was observed in any of the results above.

Discussion

In ten existing cohorts, BMI and WHR at enrollment were inversely associated with ALS mortality during follow-up. There was no association with BMI in early adulthood; this may be partly explained by the low prevalence of overweight and obesity in the decades the participants reached adulthood. Among these mostly lean young adults, those with a propensity to gain weight during adulthood had substantially lower ALS death in later life.

Our findings extend observations of two prospective analyses. In a pan-European prospective cohort (8) (EPIC) of 152,368 men and 366,040 women with 222 ALS deaths during a 13-year follow-up findings were suggestive of an association between anthropometrics and subsequent ALS death. Briefly, while a clear pattern did not emerge, perhaps due to low case numbers across categories in analyses stratified on sex, there was evidence that ALS rates were lower among men with higher enrollment BMI. Among women, those who were underweight had higher ALS but rates among normal weight, overweight, and obese individuals did not differ. All findings in the European study were materially unchanged when ALS deaths during the first 3 years of follow-up were excluded. In a prospective project of five US cohorts with a total of 1153 ALS deaths during 14–28 years of follow-up among 537,968 women and 562,942 men, higher BMI was associated with lower risk of ALS (9). Compared to individuals with a BMI of 18.5–$<25\,kg/m^2$, ALS rates were significantly lower among overweight and obese men and women. Finer categorization of the obese category revealed that rates were further lowered as the degree of excess weight increased. These findings persisted among nonsmokers and when up-to the first 7 years of follow-up were excluded. The apparent inconsistent findings for BMI at enrollment among women in EPIC compared to the five-cohort US study would appear to be due to low power given that in our study, with 410 ALS deaths among women, the association was manifest. Further, there was no significant heterogeneity between studies in our results, which included four European studies, one Australian study, and several US studies.

The association between baseline BMI and ALS in this report was not attenuated when adjusted for diabetes in contrast to a finding among Danish nationals (odds ratio [OR] = 0.72 [95% CI: 0.50–1.02] versus OR = 0.81 [95% CI: 0.57–1.16]). While ascertainment of incident ALS using the national registries was excellent, obesity was defined as a hospital admission listed as *ICD-8* code 277.99 and *ICD-10* codes E65.0–E66.9 because BMI was unknown, and COPD was used in place of smoking status (10). The question of whether BMI or diabetes, or both, are predicting lower ALS rates cannot be fully addressed by the current (diabetes only at baseline) or the Danish study (the definition of obesity used means that many individuals with BMI 25–$<30\,kg/m^2$ or $30+\,kg/m^2$ were considered non-obese, and smoking was not fully adjusted for) but could be explored in a prospective cohort study with routinely updated diabetes ascertainment and confounder assessment.

ALS patients exhibit hypermetabolism at diagnosis with a resting energy expenditure that is higher than expected (2–7). If hypermetabolism is an early symptom of ALS, then it is unclear when in the preclinical disease stage it begins. In an animal model of ALS, hypermetabolism and subsequent lower body mass were observed during the asymptomatic phase (6). The finding of this study that weight gain was perhaps less rapid in those who subsequently developed ALS does not contradict the notion that hypermetabolism begins early in the disease process. Alternatively, additional weight or body-fat itself could be protective of ALS. A higher BMI at diagnosis (up to $35\,kg/m^2$) predicts better survival (32). A third explanation for the observed association is confounding by a factor related to both adiposity/weight maintenance and ALS. Thus far a common genetic cause has not been identified. Strenuous physical activity, either as sport or occupation, is a potential environmental factor (33–37), although a considerable number of studies do not find an increased risk with physical activity (38–40). There were insufficient data to fully address this hypothesis in this study, with few cohorts with adequate case numbers in the high (according to the cohort-specific questionnaire) physical activity category. The interplay between cardiometabolic health, obesity, type-2 diabetes, and physical activity remains to be untangled in relation to ALS.

This study takes advantage of a pre-existing database of 10 cohorts worldwide, individually underpowered to examine the epidemiology of ALS. In each cohort adiposity parameters were measured at baseline, and, therefore, bias from differential recall in individuals with ALS compared to those without was minimized. Further, with the closed cohort study design, the non-case participants are representative of the ALS case population reducing internal selection bias. This study was well powered for sensitivity analyses including lagged analyses and restriction to nonsmokers.

A potential disadvantage of this study is the use of ALS on death certificates to approximate incident disease. Underreporting of ALS on death certificates would bias findings only if the probability of ALS diagnosis and of the report in death certificates were related to BMI. For example ALS may be less likely to be recorded on death certificates of those overweight with weight-related comorbidities. Strong bias from this source seems unlikely because the factors associated with BMI that would be expected to affect the accuracy of death certificates (age, smoking, and education) were included in the models. With evidence of improved survival with higher BMI at diagnosis, it could be argued that using ALS death will underrepresent incidence where there is longer survival (32). This scenario is unlikely to fully explain our findings given the long follow-up in each cohort and their persistence in lagged analyses. Using death certificates may increase the likelihood that the baseline BMI measurement has been affected by as of yet undiagnosed ALS. Materially unchanged associations in lagged analyses suggest that these findings cannot be fully attributed to reverse causation. Another possibility is overreporting of bulbar and/or pyramidal ALS as follow-up progresses and the participant's age when symptoms are due to non-diagnosed cerebrovascular disorders. Were this to occur then the true association of BMI and ALS in this study would be attenuated because higher BMI is a risk factor for cerebrovascular events (41).

In summary, this study confirms previously somewhat conflicting and underpowered evidence for an inverse relation between adiposity and future ALS risk. In particular, we newly demonstrate that the rate of weight gain during adulthood is strongly statistically correlated with ALS risk.

Declaration of interest

There are no other conflicts to report.

This work was supported by NIH grant [R01-NS072494-01A1] awarded to EOR and NCI grant [CA55075] awarded to SSW. The COSM and SMC cohorts are supported by the Swedish Research Council and by Strategic funds at Karolinska Institutet, Stockholm, Sweden. TK has received within the last 2 years investigator-initiated research funding from the French National Research Agency, the US National Institutes of Health, and the Parkinson's Research Foundation. Further, he has received honoraria from the American Academy of Neurology and Allergan for educational lectures and from the BMJ and Cephalalgia for editorial services.

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