High BMI is associated with low ALS risk – a population based study

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Search terms: All neurology, Amyotrophic lateral sclerosis, All epidemiology, Cohort studies

Submission Type: Article

Title Character count: 56

Number of references: 38

Number of Tables: 4

Number of Figures: 3

Word count of Abstract: 250

Word Count of Paper: 3314

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Abstract

Objectives To investigate the temporal relationship between prediagnostic body mass index (BMI), weight change and risk of amyotrophic lateral sclerosis (ALS).

Methods From the compulsory Norwegian tuberculosis screening program, we collected objectively measured BMI from 85% (near 1.5 million) of all citizens between 20 and 70 years living in 18 of 19 Norwegian counties between 1963 and 1975. For those who participated in later health surveys we collected further information on weight change, lifestyle and health. We identified ALS cases until September 2017 through national registries of diagnoses at death and at encounters with the specialist health service. Both Cox hazard models and flexible parametric survival models were fitted to address our research question.

Results We identified 2968 ALS cases during a mean of 33 (maximum 54) years follow up. High prediagnostic BMI was associated with low subsequent ALS risk across the typical ALS-ages in both genders. Overall, hazard ratio (HR) for ALS per 5-unit increase in prediagnostic BMI was 0.83 (95 % CI 0.79-0.88). After an initial increase during the first 10 years, it decreased almost linearly throughout the observation period and was 0.69 (95 % CI 0.62-0.77) after 50 years. Those in the quartile with highest weight gain had lower ALS risk than those in the lowest quartile (HR = 0.63, 95 % CI 0.44-0.89).

Conclusions High BMI and weight gain are associated with low ALS risk several decades later. The strength of the association between BMI and ALS risk increases up to 50 years after BMI measurement.

Introduction

Except high-risk gene variants, the primary determinants for disease threshold in amyotrophic lateral sclerosis (ALS) are largely unknown [1]. An increasing body of evidence shows that ALS-patients have raised energy expenditure [2], and that metabolic alterations appear before clinical manifestations [3, 4]. Several studies have shown that high body mass index (BMI) [3, 5-9], as well as weight gain earlier in life [10, 11] are associated with decreased ALS risk. The findings are however not entirely consistent, as one study rather reported higher BMI among ALS-patients throughout most of their disease-free lifetime [11]. Moreover, the biological timing of the relationship between BMI and ALS risk is not well established, as former studies are partially limited by either retrospective self-reported measurements [3, 7, 10, 11], power [6], age or gender distribution [5, 8] or length of follow up [6, 9]. Hence, it is not known whether any association between BMI and ALS risk reflects a causal relationship, or rather reflects prediagnostic weight loss.

The compulsory screening program for tuberculosis included objectively measured anthropometric data in the vast majority of all individuals 15 years or older in 18 of Norway's 19 counties between 1963 and 1975 [12]. Several of the partakers also participated in later health surveys including weight and lifestyle. We ascertained later occurrence of ALS through death certificates and a national patient registry, and designed a population-based cohort study of nearly 1.5 million citizens, followed for up to 54 years, to disentangle the temporal relationship between BMI and ALS risk.

Methods

Study population

During 1963-1975, a compulsory screening program for tuberculosis in the general population was performed by the National Mass Radiography Service for all individuals 15 years or older living in 18 of Norway's 19 counties [12]. The mean total population was 3,348,373, and the overall attendance rate among eligible individuals was ≈ 85%. Non-attendance was mainly due to "acceptable excuses", such as already under control or treatment for tuberculosis, in military service or in hospital. Anthropometric characteristics were measured following standardized protocols with participants undressed from waist up and without shoes. In addition, year and month of birth, age, gender, residence (county), as well as vaccination status, results of tuberculin skin test and x-ray findings were registered. In the present study, we excluded individuals either missing anthropometric measures, having implausible BMI, aged more than 70 years or less than 20 years at screening, or ultimately, based on vaccination-status and x-ray findings, individuals were tuberculosis could not be excluded. Out of total 1,910,815 individuals registered in the screening program, our primary cohort comprised 1,468,250 individuals after these exclusions (Figure 1).

We retrieved vital status and emigration from the National Registry of Vital Statistics. Several Norwegian population-based health surveys conducted between 1974 and 2003 were used for confounder, mediator and weight change analyses: The Oslo Study [13], Cohort of Norway (a collection of health data and blood samples from several Norwegian health surveys) [14], the first, second and third Cardiovascular Survey of Oppland, Finnmark and Sogn og Fjordane [15] and the 40-year Surveys [16]. Information obtained in the surveys varies according to their different purposes, but all encompassed a combination of questionnaires and physical examination including measures of height and weight in the same standardized manner as in the tuberculosis screening program. As opposed to the tuberculosis screening program, these health surveys were voluntary. Attendance rate ranged from 52 % to 95 %, but their representativeness has nevertheless been reported adequate [17]. Thus, females were somewhat

overrepresented, but the distribution of smoking, alcohol consumption and education were the same as for the total population. If an individual participated in more than one survey after the tuberculosis screening program, the first was selected. A minimum of one year separation between the tuberculosis screening and later health survey was required. We gathered information from these surveys in 190,500 individuals also found in our primary cohort.

Case ascertainment

ALS cases were ascertained through the Norwegian Cause of Death Registry and the Norwegian Patient Registry. The Norwegian Cause of Death Registry collects and processes all death certificates, and provides digitalized data for the direct, contributing and underlying cause of all deaths in Norway since 1951. Causes of death are coded according to different revisions of the International Classification of Diseases (ICD). We collected data on all ALS deaths from the first year of the tuberculosis screening program (1963) to January 2017. ALS was defined as ICD-codes corresponding to motor neuron disease at any level of cause of death. The following codes were used: ICD 7 (1963-1968): 360.0 and 360.1, ICD 8 (1969-1985): 348.0, 348.1 and 348.2, ICD 9 (1986-1995): 335.2, ICD10 (1996 onwards): G12.2. We have earlier validated ALS-codes registered in the death registry and found them to be reliable [18]. A total of 2792 deaths caused by ALS were recorded.

The Norwegian Patient Registry is an administrative health register for all in– and outpatient admissions to Norwegian hospitals and private practice specialists with public reimbursement. Data on individual patients are available from March 1st 2007. Dates and ICD 10 diagnoses are registered electronically for each admission/consultation. We collected data from January 2008 until September 2017, defining ALS cases as those having two or more G12.2 (ICD-10) entries in the registry. Date of incidence was set to first entry. We have previously found this method to be the reliable for ascertaining incident ALS in Norway [19]. A total of 617 ALS cases were retrieved from Norwegian Patient Registry. If found in both registries (n=441), the

death registry was selected, hence only 176 incident cases from the patient registry contributed to our main analysis.

All Norwegians have a unique personal identification number, making linkage between registers possible.

Data analysis

Prediagnostic BMI: Each participant contributed follow-up time from the date of tuberculosis screening to the date of ALS death (Norwegian Cause of Death Registry), ALS incidence (Norwegian Patient Registry), death from other causes, emigration or the end of study follow up (September 1st 2017), whichever came first. BMI (kg/m2) was used both continuously (five unit steps) and as categories defined as underweight (<18.5), low normal weight (18.5-<23), high normal weight (23-<25), overweight (25-<30) and obese (>30). Hazard ratios (HR) and their 95 % confidence intervals were calculated using Cox proportional hazard models with time since screening (years) as main time variable. To obtain better age adjustment, fitted Cox models were stratified by age at time of BMI screening. The models were further adjusted for sex as a model covariate. Between-sex heterogeneity was tested using a likelihood ratio test between the basic model and a model including an interaction term of BMI and sex.

For visually investigating the dose-response relationship, we fitted our Cox regression models with restricted cubic spines with 3 knots on the continuous BMI measurement. For further predictive and graphical purposes, we additionally fitted flexible parametric models using the stpm2 package in Stata [20]. Here, we allowed the effect of BMI to vary over analysis time, using a spline. We then calculated and plotted predicted hazard ratios, using either time since screening or attained age as analysis time.

We conducted two sensitivity analyses. First, to minimize the possibility of including participants in an early clinical phase, the first ten years of follow up were excluded. Second, cases ascertained through the two different registries where analyzed separately.

Prediagnostic weight change: Yearly rate of weight change was calculated by subtracting the weight (kg) at the second weight measurement from the weight at the tuberculosis screening, divided by number of years between measurements. We fitted Cox regression models with yearly rate of weight change as explanatory variable, both continuous and as quartiles of distribution. Timeline was years since the second measurement. Models were adjusted for sex and BMI at tuberculosis screening as covariates, and stratified by age and calendar year at the time of the second measurement. In additional analyses we included diabetes (any type, yes/no), triglycerides (mmol/L) and total-cholesterol (mmol/L) as possible mediators for weight change. Hazard ratios for weight change were calculated including adjustment for a composite, three-level smoking variable (never-smoker, former smoker and current smoker) and categories of physical activity (four levels), all covariates collected from the health surveys. For also investigating the role of these potential confounders on the effect of BMI, hazard ratios for BMI at tuberculosis screening were evaluated within this sub cohort, both including and excluding smoke and physical activity as model covariates.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the regional ethics committee (REC South East, ref. no 2016/1731), with informed consent waived in the current study.

Data availability statement

Pseudonomized data are not sharable according to Norwegian law. Further information about the dataset is available from the corresponding author on reasonable request.

Results

Prediagnostic BMI

A total of 1,468,250 individuals (47 % males) participated in the study, collectively contributing to 49,138,492 person-years of observation time. Mean age at recruitment was 44 (SD 14) years. During a mean 33 (SD 14) years of follow-up, 2968 ALS cases (52 % males) were registered.

Baseline characteristics of our primary cohort are given in Table 1. Overall, the HR for ALS per each 5-unit increase in BMI at the tuberculosis screening was 0.83 (95 % CI 0.79-0.88) (Table 2). Similarly, there was a difference across BMI categories (p for trend <0.001). As compared to those with low-normal BMI (18.5-22.9 kg/m2) at tuberculosis screening, both overweight and obese individuals were at lower ALS risk (HR = 0.82, 95 % CI 0.74-0.98 and HR = 0.66, 95 % CI 0.56-0.78, respectively). This pattern was evident from age groups 30-39 years and older (Table 2). There was no evidence of gender heterogeneity over BMI categories (p=0.82).

During the first years after BMI measurement the inverse association with ALS risk subsequently weakened (Figure 2A). However, after approximately 15 years it increased steadily during the rest of the 50 years observation period. HR for ALS per each 5-unit increase in BMI was 0.85 (95 % CI 0.80-0.91) after 25 years and 0.69 (95 % CI 0.62-0.77) after 50 years. Higher BMI at tuberculosis screening was associated with reduced ALS risk at attained age of approximately 60 – 85 years (Figure 2B).

With a possible exception of participants with underweight or low-normal BMI there was a near linear dose-response relationship between BMI and ALS risk (Figure 3).

To address the possibility of reverse causality, we performed a sensitivity analysis excluding the first ten years of follow up, leaving 1,363,141 participants and 2623 cases. The results did not change materially. Compared to those with low-normal weight, HR for ALS was 0.83 (95 % CI 0.76-0.92) in in the overweight group and 0.71 (95 % CI 0.70-0.85) in the obese group. HR for ALS per five units increase in BMI was 0.85 (95 % CI 0.80-0.90). Analyzing cases ascertained through the Cause of Death Registry and Patient Registry separately did not materially change the results (data not shown). Mean age at ALS death (death registry) was 71 (SD 9) years, at ALS incidence (Patient Registry) 74 (SD 7) years. This difference likely reflects a selection for individuals who had survived until The Norwegian Patient Registry became operative in 2008.

Weight change

At mean 18 (SD 7) years after the tuberculosis screening, 190,500 subjects (46 % males, mean age 47 (SD 11) years) participated in later health screenings. Mean yearly weight gain between the two screenings was 0.26 (SD 0.54) kg. Younger individuals and men generally gained most weight. Notably, there was no clear association between smoking-status and weight gain (Table 3).

During a mean 27 (SD 10) year follow-up after the second screening, 329 (52 % males) of this sub-cohort developed ALS. The risk of ALS was lower among those in the fourth compared to the first quartile of yearly weight change (HR = 0.63, 95 % CI 0.44-0.89). On the continuous scale, one kg increase in yearly weight change was associated with a decrease in risk of ALS (HR 0.82, 95 % CI 0.67-1.00). Models additionally adjusted for smoking and physical activity produced similar results (Table 4). There were no evidence for heterogeneity between genders (p = 0.43). Excluding the first 10 years of follow up after the second weight measurement yielded 284 ALS cases. Multivariable models were materially unchanged (HR for ALS was 0.65 (95 % CI 0.45-0.93) in the upper quartile group of weight change and 0.84

(95 % CI 0.68-1.04) on the continuous scale). The association between weight change and ALS was also materially unchanged after inclusion of diabetes, levels of cholesterol and levels of triglycerides in the model.

This sub cohort was considerably younger at tuberculosis screening (mean 30 (SD 9) years) than the rest of the primary cohort (mean 44 (SD 14) years). As expected from the negative finding among the youngest participants in the main cohort (Table 4), BMI at tuberculosis screening in this young sub cohort was not associated with altered ALS risk (HR per each 5-unit BMI increment was 1.06 (95 % CI 0.88-1.27)). This remained unchanged when adjusting for smoking and physical activity. Ultimately, we also evaluated smoking and physical activity as predictors of ALS disease in models both including and excluding BMI at tuberculosis screening. Compared to never smokers the HR for ex-smokers was 1.02 (95 % CI 0.76-1.37) and for current smokers 1.04 (95 % CI 0.79-1.36). No clear trend was found across levels of physical activity.

Discussion

In this population-based study, a high prediagnostic BMI was associated with low ALS risk throughout all typical ALS ages. During follow up the strength of this inverse association displayed an inverted J shape. After 15 years it increased almost linearly and was most marked at the end of the observation period, 50 years after BMI measurement. We also found an inverse association between weight gain and subsequent ALS development three decades later. Reverse causality can hardly explain these long term associations.

Our data demonstrate that long follow up is necessary when assessing the relationship between anthropometric measures and ALS risk. Underlying pathologic mechanisms probably begins long before clinical manifestation, calling for caution when studying cohorts with

limited follow up, especially when using mortality as a proxy for incidence. The finding that high premorbid BMI and weight gain is associated with lower ALS risk confirms previous cohort-based and case-control studies [6, 7, 10]. Our results confirm findings from two case-control studies reporting weight loss 5-10 years prior to diagnosis [11, 21], compatible with prediagnostic hyper-metabolism. They do however contradict that higher mid-adulthood BMI is associated with lower ALS mortality [11]. This discrepancy can be explained by methodological differences, as the previous case-control study applied self-reported retrospective estimates of height and weight [11]. The Swedish conscription study reported a weak but significant association between low BMI and subsequent ALS risk also in men below 25 years of age [8]. We did not find such an association in the youngest age group, although this age group contributed more observation years than any other age group (exceeding 13 million), and close to the number of ALS cases recorded in the Swedish conscription study (443 versus 526). Our youngest participants were mainly included in the 1960-ies when overweight and obesity was rather uncommon in Norway [22], whereas the Swedish cohort was included up until 2005. There were few overweight and obese subjects in our youngest age group. Hence, the "obesity epidemic" caused by increased access to high-calorie foods and more sedate lifestyle likely influenced our cohort, including young adults, to a lesser extent.

The low HR for ALS among individuals with high BMI during the first years of follow-up could reflect prediagnostic disease-induced weight loss [4]. However, disease-induced hyper-metabolism cannot explain that the protective association with high BMI thereafter increases almost linearly with time for more than 50 years, or that weight gain is associated with low ALS risk decades later. These results rather point to shared genetic or environmental risk factors between BMI and ALS. The equal protection of high prediagnostic BMI across all typical ages for ALS onset is compatible with the hypothesis of shared genetic predisposition

for low BMI and ALS [23] [24]. The genetic basis for this hypothesis remains to be explored. The observed associations could also be explained by environmental factors that might operate in concert with genetic factors. Some environmental factors such as smoking, physical activity and diet have been associated with both BMI and ALS [3, 25-27]. The association between physical activity and ALS susceptibility is however unclear [28, 29], and we did not find evidence for any substantial effect of smoking and physical activity in this study. Previous studies restricted to never-smokers have generated concordant results [5, 10]. There are limited data from prospective studies on diet and ALS risk [27]. Dietary lipids may offer neuroprotection and hyperlipidemia may extend survival in ALS [4, 30]. We found that the association between weight gain and low ALS risk was not mediated by circulating levels of triglycerides or cholesterol. It should be noted that BMI is a rather rough measure of body composition, and that it likely fluctuates over time. More detailed anthropometric measures could possibly shed more light onto the relationship between body composition and ALS risk [31].

The strength of this study is its prospective design with long follow up in a large cohort with a broad age distribution recruited through a compulsory, near nationwide screening program. The data are hence truly population based. Moreover, all anthropometric data were objectively measured in a standardized way. Except from the Swedish male conscription cohort [8] and in part the EPIC cohort [6], previous studies on prediagnostic BMI and weight change have been based on self-reported anthropometric measures. A key finding in validity studies is that biases in self-reported height and weight measurements are not randomly distributed and therefore cannot be easily corrected [32]. Thus, bias in self-reporting of body height and body weight has been associated with body composition, socio-economic status and lifestyles with a somewhat different pattern between genders [32-34]. To our knowledge, this is the first study reporting prediagnostic weight change measured objectively and prospectively, minimizing measurement errors and eradicating recall bias.

There are several limitations to this study. First, cases were ascertained through both death records (mortality) and an administrative patient registry (incidence). When using mortality as proxy for incidence, the association observed could in part be due to differential survival across BMI categories. Although underpowered, our sensitivity analysis using only cases identified in the patient registry gained comparable results, as did the analysis of ten year lagged entry. Thus, and because ALS mortality data has good accuracy for incidence rates [35], also in Norway [18], the use of mortality data has not likely confounded our results. Second, we were only able to adjust for smoking and physical activity in a subset of our primary cohort which was rather young at the time of tuberculosis screening and not necessarily representative of our primary cohort. Although the participants in the voluntary health surveys were representative for the general population on alcohol consumption, smoking and education, we do not know if this applies for weight gain. Third, military service has been suggested a risk factor for ALS [36], and could also be associated with BMI. However, whereas the vast majority of Norwegian men, and no women in the birth cohorts studied, served one year mandatory military service, the observed association with BMI was equal in both genders. It is therefore unlikely military service has biased our results. Fourth, the study population was a homogenous cohort of Caucasians, limiting the generalizability of our results. Fifth, we lack phenotypic and genetic data. The prevalence of C9orf72 and some SOD1 mutations could be high in Scandinavian countries [37, 38], and the effect of these on BMI is not known.

We conclude that high prediagnostic BMI and weight gain are associated with low ALS risk several decades later. Further studies are needed to unveil possible mechanisms and clinical consequences of this finding.

Acknowledgement

Author Appendix

Name	Location	Role	Contribution
Ola Nakken	Akershus University Hospital/University of Oslo, Norway	Author	drafting/revising the manuscript for content, analysis or interpretation of data, statistical analysis
Haakon E Meyer	Norwegian Institute of Public Health/University of Oslo, Norway	Author	study concept or design, drafting/revising the manuscript for content, analysis or interpretation of data
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Table 1 *Baseline characteristics at the tuberculosis screening according to later ALS status and gender*

	Cases		Non-cases	
	Males	Females	Males	Females
Subjects; n (%)	1,552 (52)	1,416 (48)	695,554 (47)	769,728 (53)
Mean age, years (SD)	43.9 (12.3)	44.4 (12.5)	44.5 (13.9)	44.2 (14.1)
BMI category, n (%)				
<18.5	9 (1)	26 (2)	4,883 (1)	16,096 (2)
18.5 – 22.9	509 (33)	493 (35)	208,359 (30)	258,490 (34)
23.0 – 24.9	465 (30)	339 (24)	188,728 (27)	154,535 (20)
25.0 – 29.9	520 (33)	425 (30)	258,158 (37)	237,239 (31)
≥30	49 (3)	133 (9)	35,426 (5)	103,368 (13)

Abbreviations: ALS= Amyotrophic Lateral Sclerosis, BMI=Body Mass Index (kg/m2)

Table 2 *Risk (hazard ratio) of ALS according to BMI category and age group at tuberculosis screening.*

Age category	BMI category	Cases	Subjects	Risktime (years)	Adjusted[a] HR (95% CI)
All	< 18.5	35	21,014	787,449	1.03 (0.73-1.44)
	18.5 – 22.9	1,002	467,851	17,477,807	1 (base)
	23.0 – 24.9	804	344,067	11,890,621	0.98 (0.89-1.07)
	25.0 – 29.9	945	496,342	15,252,934	0.82 (0.74-0.90)
	≥30	182	138,976	3,729,682	0.66 (0.56-0.78)
	Continuous[b]	2,968	1,468,250	49,138,492	0.83 (0.79-0.88)
20-29 Years	< 18.5	11	10,510	473,674	0.81 (0.44-1.49)
	18.5 – 22.9	245	157,903	7,189,528	1 (base)

	23.0 – 24.9	101	65,328	2,965,991	0.89 (0.71-1.13)
	25.0 – 29.9	76	48,119	2,162,447	0.91 (0.70-1.18)
	≥30	10	6,820	299,029	0.97 (0.52-1.82)
	Continuous	443	288,680	13,090,668	1.00 (0.85-1.18)
30-39 Years	< 18.5	9	3,681	152,,812	1.18 (0.60-2.30)
	18.5 – 22.9	264	107,515	4,591,340	1 (base)
	23.0 – 24.9	201	73,599	3,128,912	1.04 (0.86-1.25)
	25.0 – 29.9	167	79,247	3,302,614	0.82 (0.67-0.99)
	≥30	21	13,654	548,468	0.71 (0.45-1.11)
	Continuous	662	277,696	11,724,146	0.86 (0.75-0.97)
40-49 Years	< 18.5	10	2,459	79,161	1.79 (0.95-3.36)

	18.5 – 22.9	261	90,484	3,226,489	1 (base)
	23.0 – 24.9	242	85,754	3,065,847	0.94 (0.78-1.11)
	25.0 – 29.9	288	123,699	4,306,468	0.80 (0.67-0.94)
	≥30	37	29,091	969,374	0.51 (0.36-0.72)
	Continuous	838	331,487	11,647,338	0.74 (0.66-0.83)
50-59 Years	< 18.5	3	2,141	49,209	0.77 (0.24-2.41)
	18.5 – 22.9	150	64,804	1,673,449	1 (base)
	23.0 – 24.9	158	70,262	1,866,382	0.93 (0.75-1.17)
	25.0 – 29.9	263	135,029	3,544,799	0.84 (0.69-1.03)
	≥30	71	44,938	1,145,367	0.81 (0.60-1.07)
	Continuous	645	317,174	8,279,207	0.89 (0.80-0.99)

60-69 Years	< 18.5	2	2,223	32,593	0.61 (0.15-2.50)
	18.5 – 22.9	82	47,145	797,002	1 (base)
	23.0 – 24.9	102	49,124	863,489	1.15 (0.86-1.54)
	25.0 – 29.9	151	110,248	1,936,605	0.77 (0.59-1.01)
	≥30	43	44,473	767,444	0.58 (0.40-0.85)
	Continuous	380	253,213	4,397,134	0.78 (0.68-0.89)

Abbreviations: BMI = Body mass index (kg/m2), ALS= Amyotrophic Lateral Sclerosis, HR= Hazard Ratio

[a]Cox models are adjusted for sex and age at screening (one year intervals) [b]per 5 kg/m2 increase

Table 3 *Characteristics for weight change cohort according to quartiles of yearly rate of weight change*

	Mean yearly rate of weight change			
	First quartile[a]	Second quartile	Third quartile	Fourth quartile
Participants (n)	53,387	42,055	47,435	47,623
Never-smokers (%)	37	40	39	36
High activity level (%)	19	21	20	17
Diabetes (%)	3	2	1	2
Mean serum cholesterol[b] (SD)	6.1 (1.3)	6.0 (1.2)	6.1 (1.2)	6.2 (1.2)

Mean serum triglycerides[b] (SD)	1.6 (1.0)	1.6 (1.0)	1.8 (1.1)	2.2 (1.4)
Mean age[c], years (SD)	33 (9)	30 (9)	28 (8)	27 (7)
Mean BMI[c] (SD)	24.7 (3.5)	23.2 (3.0)	22.9 (3.0)	23.1 (3.2)
Males (%)	42	43	46	52

Abbreviations: BMI= Body Mass Index

[a]Quartiles of weight change, kg/years (SD): First: -0.31 (0.42), Second: 0.14 (0.07), Third: 0.38 (0.08), Fourth: 0.98 (0.41) [b]In mmol/L [c]At tuberculosis screening

Table 4 *Risk of ALS by rate of weight gain (kg/years) from tuberculosis screening to second*

weight measurement

Weight change[a]	Cases	Subjects	Mean (SD) kg/years	Model 1[b] HR (95% CI)	Model 2[c] HR (95% CI)
1.quartile	111	53,387	-0.31 (0.42)	Ref	Ref
2.quartile	74	42,055	0.14 (0.07)	0.90 (0.66-1.24)	0.88 (0.64-1.22)
3.quartile	85	47,435	0.38 (0.08)	0.95 (0.70-1.30)	0.95 (0.70-1.30)
4.quartile	59	47,623	0.98 (0.41)	0.63 (0.44-0.89)	0.62 (0.44-0.87)
Per 1 kg increment, all	329	190,500		0.82 (0.67-1.00)	0.82 (0.67-1.00)

Abbreviations: ALS= Amyotrophic Lateral Sclerosis, BMI= Body Mass Index, HR= Hazard Ratio

[a]From tuberculosis screening to second weight measurement [b]Both models are stratified by age and calendar year at time of second weight measurement. Model 1 is adjusted for gender and BMI at first weight measurement. [c]Model 2 is further adjusted for smoking and physical activity level

Figure 1 *Flowchart showing selection of participants*

Figure 2 *Risk (hazard ratio) of ALS according to 5 units increase (kg/m2) in BMI*

In the left panel, ALS risk is plotted against time since BMI measurement, adjusted for age. In the right panel, ALS risk is plotted against attained age at death or incidence, independently of time since BMI measurement. Vertical lines indicate the 5 and 95 percentile of the ALS case distribution. Grey areas represent 95 % confidence intervals.

Abbreviations: ALS= Amyotrophic Lateral Sclerosis, BMI= Body Mass Index

Figure 3 *Spline regression curve for ALS risk (hazard ratio) according to BMI*

Grey areas represent 95 % confidence intervals.

Abbreviations: ALS= Amyotrophic Lateral Sclerosis, BMI= Body Mass Index