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CLINICAL RESEARCH

Overweight and obesity are associated with improved survival, functional outcome, and stroke recurrence after acute stroke or transient ischaemic attack: observations from the TEMPiS trial

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Aims The aim of the study was to evaluate the association of the body mass index (BMI) with mortality and with non-fatal functional outcome in patients with acute stroke or transient ischaemic attack (TIA). Obesity is an established risk factors in *primary* cardiovascular disease prevention including stroke. The impact of overweight in patients with stroke or TIA on *secondary* fatal and non-fatal functional outcomes is less well established.

Methods and results Data from 4428 patients with acute stroke or transient ischaemic attack (TIA) from the Telemedical Project for Integrative Stroke Care (TEMPiS) were studied in this *post hoc* analysis. The body mass index was available in 1521 patients. Patients were categorized as underweight (BMI <18.5), normal (BMI 18.5 to <25) overweight (BMI 25 to <30), obesity (BMI 30 to <35), advanced obesity (BMI ≥ 35 all kg/m^2), and no body weight assessed. Outcome measures after 30 months were all-cause mortality and non-fatal outcomes: recurrent stroke, need for institutional care, and functional impairment (Barthel index <60, modified Rankin score >3). Mortality risk was lower in overweight patients [hazard ratio (HR): 0.69, 95% confidence interval (CI): 0.56–0.86) and lowest in obese (HR: 0.50, 95% CI: 0.35–0.71) and very obese patients (HR: 0.36, 95% CI: 0.20–0.66] compared with normal BMI. Functional, non-fatal outcomes, and recurrent stroke followed the same inverse pattern: underweight patients had the worst outcomes but obese patients had better outcomes than patients with normal BMI (all $P < 0.01$). After adjustment for multiple confounding factors, obese patients had a lower risk of the combined endpoints of death or institutional care (OR: 0.60, 95% CI: 0.38–0.92), death or high dependency (OR: 0.60, 95% CI: 0.39–0.91) and death or recurrent stroke (OR: 0.56, 95% CI: 0.37–0.86). Mortality was significantly lower in obese patients (all BMI >30 kg/m^2) than patients with normal weight (HR: 0.70; 95% CI: 0.50–0.98). Underweight patients had consistently the highest risks for all endpoints.

Conclusion Overweight and obese patients with stroke or TIA have better survival and better combined outcomes of survival and non-fatal functional status than patients with the BMI <25 kg/m^2.

Keywords Stroke • Overweight • Obesity • Mortality • Dependency • Outcome

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Introduction

Overweight and obesity are established risk factors for cardiovascular disease.[1–5] Accordingly, obesity is associated with an increased risk for stroke.[6,7] While these studies observed the primary risk of incident stroke in the general population, the interaction between body weight and the outcome *after* a stroke or TIA occurred is less well established. Few studies have investigated the impact of the nutritional status and body weight on the outcome after stroke. They found, however, an inverse relationship between body weight and mortality in patients after stroke: in the FOOD trial, the impact of the nutritional status on stroke mortality was investigated.[8] Undernourished patients had a 2.3-fold higher risk of dying within 6 months compared with patients with normal nutritional status, whereas overweight patients had no increased risk. In the Danish National Indicator Project (NIP) including data from 21 884 patients with stroke the highest mortality was, again, observed in underweight patients.[9] In turn, patients with overweight and obesity had significantly better survival than patients with normal body weight. In a recent Greek study including 2785 stroke patients, an inverse association between body weight and mortality was reported.[10] The impact of body weight on non-fatal outcome after stroke was not addressed in these studies.

These data may seem to be in contrast to common knowledge of obesity as a risk factor in *primary* disease prevention. They are, however, in line with increasing evidence that in patients with *established* cardiovascular disease a more differentiated perspective on body weight should be adopted. In fact, overweight and obesity are associated with better survival in a range of cardiovascular conditions including heart failure[11–13] acute myocardial infarction,[14] bypass surgery,[15] valvular surgery,[16] and coronary artery disease.[17,18] The debate is ongoing whether the inverse relation with body weight may also be applicable to stroke patients. Stroke is the most important cause of physical disability and dependency in adult life. We hypothesized that the body weight may inversely relate to mortality as well as to functional outcome after stroke. So far, no studies have investigated the association of body weight with functional outcome and dependency after stroke or TIA. The aim of the present study is to evaluate the impact of body weight on outcomes of mortality, functional disability, need for institutional care, and stroke recurrence.

Methods

Patients and study protocol

The Telemedical Project for integrative Stroke Care (TEMPiS) study was a prospective, multi-centre, non-randomized intervention study comparing acute stroke treatment in hospitals with TeleStroke Units and hospitals without specialized stroke care. The study was described in detail previously.[19] In summary, patients who were admitted to hospital within 3 days from onset of acute neurological deficits and suspected cerebrovascular stroke were included in the study. Discharge diagnoses were used to conform the diagnosis and for the allocation to stroke or transient ischaemic attack (TIA). Consecutive enrolment in 10 general hospitals started in July 2003 and ended in March 2005.

Documented baseline parameters included demographic characteristics, cardiovascular risk factors and vascular co-morbidities, TIA or subtype of stroke, and stroke severity. Stroke severity was assessed as the cumulative number of stroke-related neurological deficits including limb weakness or paresis, dysphasia, dysarthria, and disturbance of consciousness. Patients were classified for stroke severity as mild (no or 1 deficit), moderate (2 symptoms), severe (3 symptoms), and very severe (4 symptoms present). This index has previously been proved to be a strong predictor of short-term mortality[20] and has been validated against the National Institutes of Health stroke scale.[21] The body mass index at hospital admission was calculated as the ratio of body weight and squared height, given as kg/m^2 in all patients with available weight and height assessment. The study complies with the Declaration of Helsinki and was approved by the local Ethics Committee and patients or their representatives gave informed consent.

Follow-up and endpoints

Patient follow-up at 30 months was managed centrally and performed by specially trained interviewers using a structured telephone interview or by mailed questionnaires. The interviewers were trained using the training DVD 'Modified Rankin Scale. A Training & Certification Resource' (University of Glasgow). Follow-up information about death, institutional care, self dependency (Barthel index and modified Rankin scale), and stroke recurrence were obtained.

The endpoints were all-cause mortality at 30 months, recurrent stroke, and the composite outcomes of all-cause mortality or institutional care and all-cause mortality or high dependency (including institutional care or severe functional disability) at 30 months. Institutional care was defined as patients living in residential/nursing homes and patients in acute and rehabilitation hospitals at the time of the follow-up. Severe functional disability was defined as modified Rankin scale >3 or Barthel index <60.[22]

Statistical analyses

For this *post hoc* analysis from the TEMPiS database, a detailed analysis plan was set out on the basis of available clinical and outcome variables[23] with *a priori* defined endpoints (see above) and analyses steps. Clinical characteristics are displayed as means ($\pm$ standard deviation) or median (inter-quartile range) for continuous variables and by frequency (percentage) for categorical variables as appropriate. For comparison between groups, the Mann–Whitney *U* test, Kruskal–Wallis test, and Chi-square test were used for continuous and for dichotomous variables as appropriate.

The patient population was subgrouped for BMI categories as defined by the World Health Organization[24] as underweight (<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), mild obesity (BMI 30 to <35 kg/m^2), and advanced obesity (BMI ≥ 35 kg/m^2). The subgroup with BMI from 18.5 to 25 kg/m^2 (normal weight) was used as a reference group. Mortality was the only outcome parameter with assessed time of event. This outcome is therefore presented with Kaplan–Meyer event rates and survival curves. Mortality was assessed by Cox proportional hazard analysis and hazard ratios (HR) and 95% confidence intervals (CI) are presented. In addition to the *a priori* defined analyses, we combined all patients with the BMI >30 for an add-on analysis of the association of obesity with mortality. For functional outcomes, odds ratios and corresponding 95% CIs are reported. Univariable and multivariable logistic regression was performed to adjust for effects of potential confounders. In the multivariable analyses, all relevant variables as identified in the primary analysis of the TEMPiS study were included.[19] Thus, multivariable analyses included age, sex, living in partnership

prior to the event, co-morbidities (all listed in the Tables), stroke severity, classification of the cerebral event (TIA vs. ischaemic stroke vs. intracerebral haemorrhage), and also assignment to the Telestroke Unit or conventional treatment arm of the TEMPiS study protocol. A probability value of <0.05 was considered statistically significant. The software package SPSS 14.1 (SPSS, Inc.) was used for statistical analyses.

Results

A total of 4428 patients were included in the analysis. Of those, 3101 patients (70%) had ischaemic cerebral infarcts, 373 (8%) had intracranial haemorrhage, and 954 patients (22%) had a TIA. The body mass index (range 13 to 69 kg/m^2) was assessed on hospital admission in 1521 patients (34%), whereas 2907 patients had no BMI assessment. Normal body weight was observed in 599 patients (39%), overweight was observed in 588 patients (39%), obesity and advanced obesity in 208 patients (14%), and 87 patients (6%), respectively. Underweight was present in 39 patients (3%). Epidemiologic characteristics, comorbidities, and stroke severity between BMI subgroups are shown in *Table 1*. Obese patients were on average younger but had more often a metabolic risk profile including hypertension, diabetes, and hyperlipoproteinaemia, but had less often atrial fibrillation. Stroke severity and classification of the cerebral event (ischaemic, haemorrhage, and TIA) was not different between BMI groups.

Comparison of patients with available BMI assessment vs. those without available BMI are shown in Supplementary material online, *Table S1*: no differences for the presence of co-morbidities were found including hypertension, diabetes, atrial fibrillation, or previous stroke. Patients without BMI available were on average older, more often female and living in institutional care, and had more severe symptoms of strokes and more haemorrhagic events. Survival and non-fatal functional outcomes were worse in

Table 1 Epidemiologic characteristics, co-morbidities, and stroke severity by body mass index subgroup

	Underweight <18.5 (*n* = 39)	Normal weight 18.5 to <25 (*n* = 599)	Overweight 25 to <30 (*n* = 588)	Obese 30 to <35 (*n* = 208)	Very obese ≥35 kg/m^2 (*n* = 87)	*P*-value
Age in years						
Mean ± SD	78 ± 13	76 ± 12	73 ± 11	69 ± 11	65 ± 12	
Median (IQR)	81 (74–83)	78 (69–84)	74 (66–81)	71 (62–77)	65 (59–73)	<0.001
Female (%)	84.6	54.8	44.7	40.4	50.6	<0.001
Living with partner at home (%)	12.8	38.2	47.8	55.8	46.0	<0.001
Living in institution	12.8	6.8	4.9	3.8	6.9	0.13
Hypertension (%)	61.5	73.5	76.0	79.8	83.9	0.027
Diabetes (%)	25.6	20.9	26.4	35.6	43.7	<0.001
Hyperlipoproteinaemia (%)	20.5	27.9	35.4	38.9	36.8	0.004
Atrial fibrillation (%)	25.6	27.5	22.3	16.3	11.5	0.001
Previous stroke (%)	12.8	22.4	20.4	19.7	10.3	0.081
Other previous vascular disease (%)	25.6	27.7	27.4	28.4	18.4	0.45
Severity of event (%)						
No symptoms	12.8	25	26.2	31.7	26.6	
Mild	38.5	31.7	34.0	34.1	28.7	
Moderate	38.5	29.9	27.2	26.0	37.9	0.116
Severe	7.7	11.4	11.7	8.2	5.7	
Very severe	2.6	2.0	0.9	0.0	1.1	
Classification (%)						
Transient ischaemic attack	20.5	23.7	24.3	22.6	25.3	
Cerebral infarct	79.5	69.6	71.1	72.1	64.4	
Intracerebral haemorrhage	0	6.7	4.6	5.3	10.3	0.31[a]
Treatment in TeleStroke Unit	69.2	72.8	66.8	67.3	62.1	0.11

Numbers indicate percentage within the respective BMI group.
[a]vs. all ischaemic events.

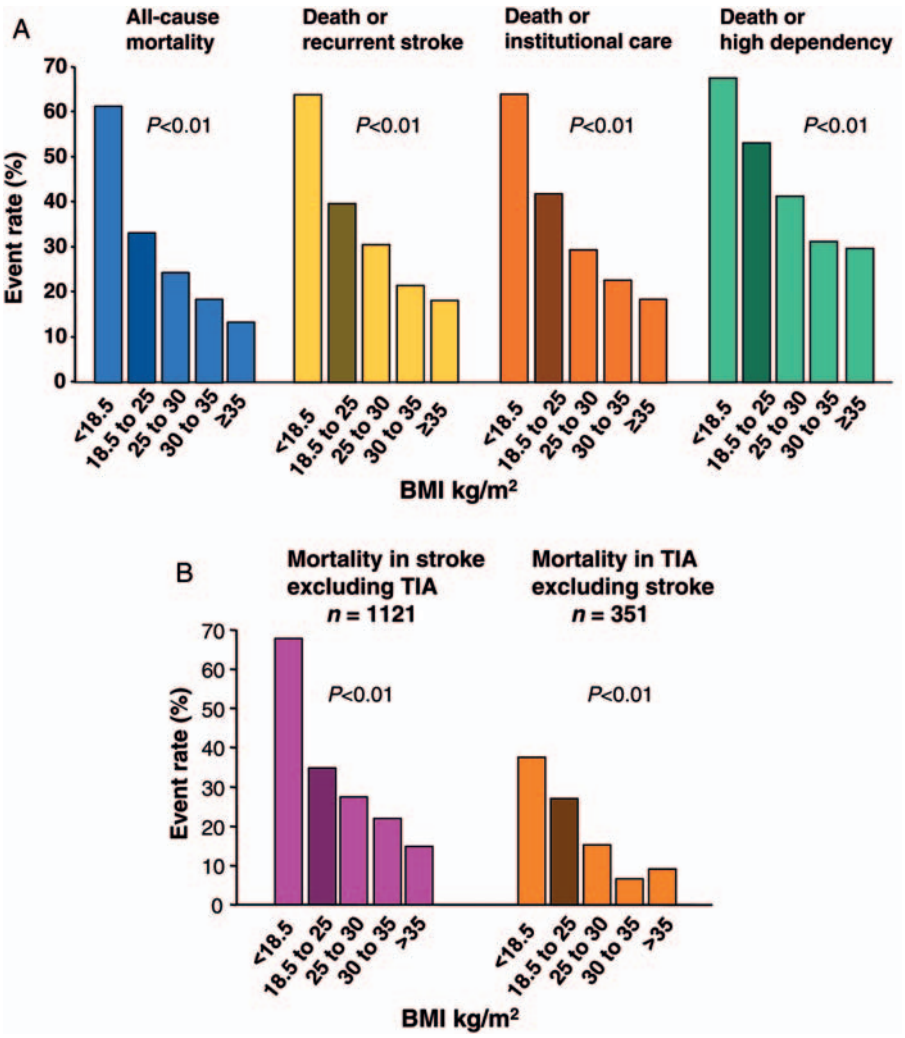

Figure 1 Event rates of outcome variables in patients with stroke or transient ischaemic attack in body mass index subgroups (*A*) and mortality separated for patients with stroke and with transient ischaemic attack (*B*). Normal body mass index range: 18.5–25 kg/m^2, dark colour.

patients with no BMI measurement than in patients with normal weight or any overweight (*Table S1* and *Figure 2*).

Outcome data on survival status at 30 months of follow-up were available in 97% of patients. Patient numbers for individual outcome variables are presented in Supplementary material online, *Figure S1*, and are shown in the respective tables.

Outcome analyses and body mass index

Outcomes at 30 months for all pre-defined endpoints in BMI subgroups are shown in *Figure 1* and *Table 2*. Mortality was highest in underweight patients (Kaplan–Meier event rate 61%) and declined stepwise to 35, 25, 19, and 13% with increasing BMI (groups 18.5 to <25, 25 to <30, 30 to <35, and ≥35 kg/m^2, respectively; $P <$ 0.01). The composite endpoints, including death and non-fatal outcomes of institutional care, high dependency, or recurrent stroke, showed similar patterns: patients with underweight had the worst outcomes and obese and very obese patients had the lowest event rates (all $P < 0.01$). The same pattern was observed when non-fatal outcomes were assessed in the surviving population alone: event rates were significantly lower in the overweight and obese patients compared with normal BMI. Recurrent strokes were non-significantly lower in the obese patients (*Table 2*).

A similar pattern on mortality was observed when patients with stroke and patients with TIA were studied separately (*Table 2*, lower part). Mortality rates were highest (68%) in underweight patients and decreased stepwise to 35, 27, 11, and 15%, with increasing BMI (stroke patients) and from 38 to 27, 15, 7, 9% in patients with TIA (both $P < 0.01$).

Survival curves during the follow-up for BMI subgroups are shown in *Figure 2*. Mortality risk (unadjusted) was highest in underweight patients (HR: 2.42, 95% CI: 1.55–3.76, $P < 0.001$) compared with patients with normal BMI (reference group). In contrast, mortality risk stepwise decreased in patients with overweight (HR: 0.69, 95% CI: 0.56–0.86) and obesity (HR: 0.50,

Table 2 Outcome event rates at 30 months in body mass index subgroups (upper panel) and mortality separated for patients with stroke and with transient ischaemic attack (lower panel)

	Under-weight	Normal weight	Overweight	Obese	Very obese	*P*-value
Body mass index	<18.5	18.5 to <25	25 to <30	30 to <35	≥35 kg/m^2	
Death, $n = 1472$, *n* (%)	22 (61.1)	191 (34.7)	140 (24.5)	37 (18.6)	11 (13.3)	<0.01
Death or institutional care, $n = 1377$, *n* (%)	20 (64.5)	226 (42.2)	161 (29.7)	44 (22.8)	14 (18.4)	<0.01
Death or high dependency, $n = 1374$, *n* (%)	21 (67.7)	284 (53.3)	224 (41.4)	60 (31.3)	23 (29.9)	<0.01
Death or recurrent stroke $n = 1462$ (%)	23 (63.9)	228 (39.8)	174 (30.5)	43 (21.5)	15 (18.1)	<0.01
Institutional care in surviving patients, $n = 1031$, *n* (%)	2 (15)	61 (16.5)	40 (9.5)	11 (6.5)	5 (7.5)	<0.01
High dependency in surviving patients, $n = 1028$, *n* (%)	3 (23)	119 (32.3)	103 (24.5)	27 (17.0)	14 (20.6)	<0.01
Recurrent stroke in surviving patients, $n = 1061$, *n* (%)	1 (7)	37 (9.7)	34 (7.9)	6 (3.7)	4 (5.6)	0.178
Mortality in stroke patients (excluding TIA) $n = 1121$, *n* (%)	19 (67.9)	154 (34.8)	119 (27.4)	34 (21.9)	9 (14.8)	$P < 0.01$
Mortality in TIA patients (excluding stroke) $n = 351$, *n* (%)	3 (37.5)	37 (27.0)	21 (15.2)	3 (6.5)	2 (9.1)	$P < 0.01$

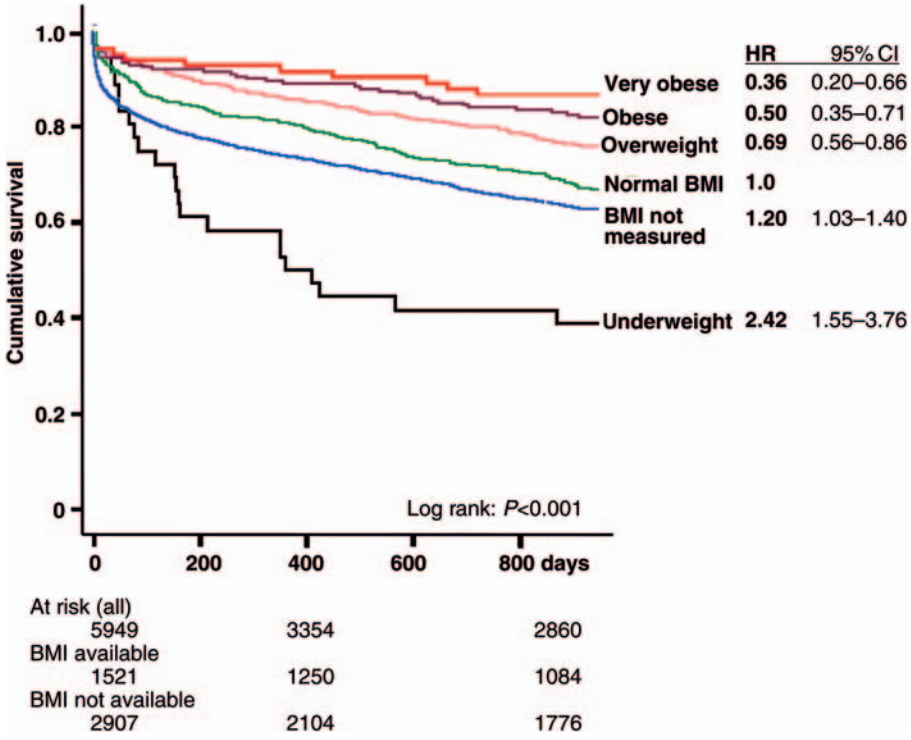

Figure 2 Survival probability over time since stroke for body mass index subgroups (univariable analysis). The Kaplan–Meyer survival plot and odds ratios with 95% CI are presented.

95% CI: 0.35–0.71) and was lowest in advanced obesity (HR: 0.36, 95% CI: 0.20–0.66, all $P \leq 0.001$). Patients without BMI assessment had increased mortality (HR: 1.20, 95% CI: 1.03–1.40; $P = 0.020$).

Multivariable adjustment confirmed the inverse relationship between BMI and outcome variables (*Tables 3* and *4*): underweight patients had the highest risk for mortality, for death or recurrent stroke, and for death or high dependency. Risks decreased with an increasing BMI and were constantly lowest in obese and very obese patients independent of age, sex, living situation, stroke severity, stroke aetiology, co-morbidities, and allocation to treatment

Table 3 Outcome at 30 months for death (left) and for death or recurrent stroke (right) in stroke patients stratified for body mass index subgroups, multivariable analysis including all covariables

	Death at 30 months (n = 1472)		Recurrent stroke or death within 30 months (n = 1462)	
	HR (95% CI)	*P* value	OR (95% CI)	*P* value
Variable				
Underweight (BMI <18.5)	2.76 (1.75–4.36)	<0.001	2.74 (1.23–6.03)	0.012
Normal weight (18.5 to <25)	1.0 (reference)		1.0 (reference)	
Overweight (25 to <30)	0.86 (0.69–1.08)	0.19	0.79 (0.60–1.03)	0.085
Obese (30 to <35)	0.76 (0.53–1.10)	0.15	0.56 (0.37–0.86)	<0.01
Very obese (≥35)	0.55 (0.29–1.02)	0.059	0.51 (0.27–0.97)	0.039
Co-variables				
Age group, year				
<65	1.0 (reference)		1.0 (reference)	
65–74	1.81 (1.19–2.74)	<0.01	1.65 (1.09–2.50)	0.017
75–84	2.67 (1.80–3.95)	<0.01	2.74 (1.84–4.08)	<0.01
>84	4.75 (3.11–7.25)	<0.01	6.23 (3.85–10.07)	<0.01
Sex				
Male	1.0 (reference)		1.0 (reference)	
Female	0.77 (0.61–0.96)	0.022	0.75 (0.57–0.99)	0.041
Partnership				
Living alone	1.0 (reference)		1.0 (reference)	
Living with partner	0.80 (0.63–1.02)	0.076	0.67 (0.50–0.88)	<0.01
Residential situation				
Living at home	1.0 (reference)		1.0 (reference)	
Living in institution	1.93 (1.41–2.62)	<0.01	2.63 (1.56–4.43)	<0.01
Stroke severity				
No symptoms	1.0 (reference)		1.0 (reference)	
Mild symptoms	1.22 (0.87–1.71)	0.25	1.16 (0.80–1.60)	0.47
Moderate	1.89 (1.37–2.61)	<0.01	1.82 (1.29–2.57)	<0.01
Severe or very severe symptoms	3.70 (2.62–5.23)	<0.01	3.62 (2.36–10.07)	<0.01
Co-morbidities[b]				
Diabetes mellitus	1.60 (1.29–2.00)	<0.01	1.43 (1.08–1.89)	0.013
Hypertension	1.18 (0.89–1.55)	0.25[a]	1.34 (0.97–1.84)	0.077[a]
Hyperlipoproteinaemia	0.70 (0.55–0.88)	<0.01	0.79 (0.60–1.04)	0.089[a]
Previous stroke	1.03 (0.81–1.30)	0.83[a]	0.99 (0.73–1.35)	0.97[a]
Atrial fibrillation	1.63 (1.32–2.02)	<0.01	1.66 (1.24–2.21)	<0.01
Other vascular disease	1.41 (1.14–1.75)	<0.01	1.75 (1.33–2.29)	<0.01
Subtype				
Ischaemic	1.0 (reference)		1.0 (reference)	
Intracerebral haemorrhage	2.73 (1.95–3.82)	<0.01	2.57 (1.56–4.24)	<0.01
Treatment in TeleStroke Unit	1.07 (0.86–1.34)	0.54[a]	0.98 (0.75–1.29)	0.90[a]

HR, hazard ratio; OR, odds ratio; CI, confidence interval.
[a]Variable not statistically significant in multivariate analyses; non-significant variables were removed from the equation at a α-level of 0.05; HR and ORs, CI, and *P*-values were given just before removal.
[b]Reference categories for respective variables were patients without the respective co-morbidity.

Table 4 Outcome at 30 months for death or institutional care (left) and for death or institutional car or dependency (right) in stroke patients stratified for body mass index subgroups; multivariable analysis including all covariables

	Death or institutional care at 30 months (n = 1377)		Death or high dependency at 30 months (n = 1374)	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Variable				
Underweight (BMI <18.5)	2.18 (0.90–5.28)	0.083	1.28 (0.50–3.25)	0.61
Normal weight (18.5 to <25)	1.0 (reference)		1.0 (reference)	
Overweight (25 to <30)	0.68 (0.51–0.91)	0.01	0.74 (0.50–1.00)	0.048
Obese (30 to <35)	0.60 (0.38–0.92)	0.02	0.60 (0.39–0.91)	0.018
Very obese (≥35)	0.49 (0.25–0.99)	0.045	0.68 (0.37–1.25)	0.21
Co-variables				
Age-group, year				
<65	1.0 (reference)		1.0 (reference)	
65–74	1.46 (0.94–2.26)	0.089	1.69 (1.14–2.51)	<0.01
75–84	3.48 (2.32–5.22)	<0.01	4.69 (3.23–6.82)	<0.01
>84	9.27 (5.57–15.43)	<0.01	14.08 (8.25–24–05)	<0.01
Sex				
Male	1.0 (reference)		1.0 (reference)	
Female	1.23 (0.84–1.51)	0.43[a]	1.19 (0.89–1.58)	0.24[a]
Living situation				
Living at home alone	1.0 (reference)		1.0 (reference)	
Living at home with partner	0.72 (0.53–0.98)	0.035	0.63 (0.48–0.82)	<0.01
Stroke severity				
No symptoms	1.0 (reference)		1.0 (reference)	
Mild symptoms	1.56 (1.08–2.26)	0.018	2.16 (1.52–3.06)	<0.01
Moderate	2.79 (1.92–4.05)	<0.01	4.29 (2.99–6.15)	<0.01
Severe or very severe symptoms	7.63 (4.72–12.33)	<0.01	14.44 (8.42–24.75)	<0.01
Co-morbidities[b]				
Diabetes mellitus	1.60 (1.19–2.16)	<0.01	1.72 (1.27–2.31)	<0.01
Hypertension	1.21 (0.86–1.70)	0.28[a]	1.04 (0.75–1.44)	0.83[a]
Hyperlipoproteinaemia	0.88 (0.66–1.17)	0.36[a]	0.64 (0.48–0.85)	<0.01
Previous stroke	1.12 (0.81–1.56)	0.49[a]	0.99 (0.73–1.35)	0.97[a]
Atrial fibrillation	1.59 (1.17–2.17)	<0.01	1.23 (0.90–1.70)	0.20[a]
Other vascular disease	1.70 (1.28–2.27)	<0.01	1.72 (1.28–2.31)	<0.01
Subtype				
Ischaemic	1.0 (reference)		1.0 (reference)	
Intracerebral haemorrhage	3.07 (1.80–5.23)	<0.01	2.87 (1.62–5.09)	<0.01
Treatment in TeleStroke Unit	0.92 (0.69–1.23)	0.58[a]	0.94 (0.70–1.25)	0.65[a]

OR, odds ratio; CI, confidence interval.
[a]Variable not statistically significant in multivariate analyses; non-significant variables were removed from the equation at a α-level of 0.05; OR, CI, and *P*-value were given just before removal.
[b]Reference categories for respective variables were patients without the respective co-morbidity.

arms within the TEMPiS protocol. For the endpoint 'death at 30 month', the statistical significance was lost after adjustment for multiple co-variables. When all obese and very obese patients (BMI >30 kg/m^2) were analysed in a combined BMI subgroup, however, these patients had a significantly lower mortality than patients with normal weight (HR: 0.70; 95% CI: 0.50–0.98).

Discussion

The main finding of this study is that patients hospitalized for acute stroke or TIA who are overweight and obese have better survival *and* non-fatal functional outcomes when compared with patients with normal weight. In contrast, underweight patients constantly show the worst mortality, morbidity, and functional outcome. It is noteworthy, that the risk of recurrent stroke was not higher in overweight or obese patients. The inverse associations of body weight and outcome measures remained after adjustment for confounding factors including age, gender, prior living situation, stroke subtype and severity, co-morbidities, and stroke treatment facility. The inverse association between body weight and mortality was observed in all patients admitted with suspected cerebral event including patients with stroke and those with TIA.

Our data confirm and extend previous studies reporting an inverse relation between body weight and post stroke mortality.[8–10] Vemmos *et al.*[10] observed reduced mortality in overweight (−18%) and obese patients (−29%) when compared with the reference group. The latter, however, included *all* patients with the BMI <25 kg/m^2 (i.e. normal weight plus underweight patients), which may distort the comparison given the higher event rates seen in underweight patients. Similarly, the Danish NIP showed highest mortality rates in underweight patients (BMI <18.5 kg/m^2) and best survival in overweight and obese patients (BMI 25–35 kg/m^2).[9]

The novel findings from our study are that not only mortality, but also *non-fatal morbidity* and *functional outcomes* followed the same inverse pattern of association with body weight. Non-fatal and functional outcomes were worst in underweight patients but improved with higher body weight. Overweight and obese patients had a lower risk of institutional care and dependency than patients with normal weight or underweight. Also the risk for recurrent stroke was lowest in obese patients. Moreover, this inverse association applied to all patients admitted with suspected cerebral event including stroke and TIA. When looked at patients with stroke and with TIA separately, the same inverse association of body weight and the outcome was observed in both groups.

The current study extends the ongoing debate on the scope of the so-called obesity paradox and puts strokes on a level with a range of other cardiovascular diseases. Data in chronic heart failure from a large range of studies (ELITE II, SOLVD, Copernicus, V-HeFT II, CIBIS II, COMET, CHARM, Val-HeFT, and others) have shown that overweight does not carry a survival disadvantage in these patients.[25] Recently, we have reported a similar inverse epidemiology for patients with type 2 diabetes mellitus plus cardiovascular co-morbidity.[26] In the population of the INVEST study with >22 500 patients, overweight and obese patients had lower mortality and morbidity risks than normal weight patients.[17] The cardiovascular risk profile of the INVEST population (hypertension plus documented coronary artery disease) may be very similar to the risk profile in the stroke patients of the present study.

Our data further support the concept that indeed a patient specific perspective on body weight management should be pursued that may be different from the primary prevention approach for healthy subjects. Notably, current treatment guidelines (US and European) for patients with stroke pursue the weight management recommendation to reduce body weight.[27,28] This recommendation has explicitly derived from primary prevention data,[27] whereas no study has ever reported on a benefit of weight reduction in patients after stroke. Indeed, a systematic review revealed that no prospective study has shown that weight reduction improved stroke outcome in overweight and obese people.[29]

As an explanation for the advantage of higher body weight, an overall catabolic imbalance has been hypothesized as a result from the underlying disease.[30] Indeed, progressing weight loss of as little as 3 kg or more after stroke has been observed as an independent predictor of an adverse outcome.[31] Particular skeletal muscle tissue wasting is an described yet under-appreciated aspect of impaired post-stroke recovery.[32] Emerging evidence suggests a specific stroke-related muscle wasting (i.e. sarcopenia) as a result from combined effects of denervation/re-innervation, immobilization, spasticity, inflammation, and others.[33]

The body mass index was assessed only in about one-third of the TEMPiS population, whereas in two-thirds, no body composition data were available. This lack of data is remarkable and needs to be discussed. Body weight and BMI may seem relevant measurements to assess the risk profile of patients with cardiovascular disease such as stroke or TIA. In contrast, the record of the BMI was not monitored for completeness in the data documentation of the TEMPIS efficacy evaluation as it had not been expected to be a contributing factor for stroke prognosis when the TEMPiS study was designed.[19] Notably, it is a general observation, that body weight is poorly assessed in stroke patients: in the Danish (NIP) national stroke registry for instance, height and weight were explicitly stated to be routine clinical assessment but were available in only 55% of patients.[9] This was despite the indication in the protocol to use chair scales and height measurement in lying position if required. Further, the prospective FOOD trial aimed particularly for the evaluation of the nutritional status in stroke patients. However, only 20% of patients had their weight measured or BMI calculated.[8] This lack of data indicates a surprising disregard of this basic clinical measurement in stroke patients. Given the emerging impact of body weight and body composition on post-stroke fatal and non-fatal outcome, regular assessment of these measurements in stroke trials as in clinical settings should be recommended.

Measuring body weight and height may be more difficult in patients with severe neurological deficits or more fragile persons due to incapability to stand up. Accordingly, in the TEMPIS cohort, patients without available BMI assessment had more severe strokes, were older, and had a higher mortality than those with available BMI assessment. The numbers of patients with underweight or advanced obesity were small in our study resulting in wide CIs. As a consequence, the association of high bodyweight with better survival was confirmed in multivariable adjusted analysis only when the groups of obese and very obese patients were combined for comparison against normal weight patients. Apart from these characteristics, we cannot see a systematic bias that would otherwise challenge our conclusions. The co-morbidity profile was not different between patients with and without BMI. Patients who died before hospital arrival were not included in the analysis and it cannot be excluded that this may account for a survival bias in the present analysis. This is,

however, a very small proportion (<1%) of the patient population with acute stroke in Germany.[34]

Follow-up for outcome variables was performed by telephone interviews and questionnaires rather than by face-to-face contact which may be seen as a limitation of the study. To minimize the impact of this factor on our results, the follow-up was managed centrally and performed by specially trained interviewers using a structured interview protocol. It has been demonstrated previously, that the use of structured interviews can improve the validity of the results[35] and a centrally managed interviewing procedure may reduce bias and inter-rater variability.[36] Moreover, studies on the reliability of structured telephone interviews have confirmed a high agreement with face-to-face assessments.[36,37]

Our study is a *post hoc* analysis that suffers from typical limitations of such studies. Several variables of interest were not recorded and were, therefore, not accessible for analysis. We cannot compare the results of BMI with the waist-to-hip ratio. Also data on weight change (repeated weight measurements) and nutritional behaviour during the follow-up were not recorded, which would allow for the evaluation of dynamic weight change in relation to outcome. We adjusted the outcome analyses for a range of identified confounding variables; however, effects from other potential confounders (such as smoking, alcohol intake, cancer co-morbidity) cannot be excluded. Differences between BMI subgroups may to some degree contribute to the different outcome results: obese patients were younger and lived more often at home within a partnership. Obese patients, in turn, had a worse comorbidity profile regarding components of the metabolic syndrome. Indeed, hypertension, diabetes, and hyperlipoproteinaemia were more common in obese patients. Notably, stroke severity and classification of the cerebral event were not different between BMI groups. Ageing has clearly a differential effect on the relationship between obesity and mortality in stroke patients as in the general population with the inverse association particularly among the elderly.[38] The mean age in the Danish stroke registry and in our study was 72 and 74 years, respectively. The body mass index remained, however, a significant factor associated with outcome after adjustment for age and further confounding variables including sex, living situation, stroke severity, risk-relevant comorbidities, or stroke subtype.

Conclusion

The present study shows that patients with acute stroke or TIA who are overweight or obese have a better prognosis and better non-fatal functional outcomes when compared with patients with normal body weight or underweight. Underweight is associated with highest mortality and dependency. A better outcome after stroke or TIA in obese patients is in contrast to primary prevention data but concurs with similar evidence in other cardiovascular diseases. Body weight management recommendations in patients after stroke should not be based on mere projection from primary prevention. The assessment of body weight seems often undervalued but should become compulsory in stroke settings. Prospective studies are needed to confirm the observational data and to investigate the effect of weight change during the follow-up.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: H.J.A. received consultancy honoraria by Lundbeck Pharma, Pfizer and Bayer Vital as well as speaker honoraria by Takeda Pharma, Boehringer Ingelheim, Lundbeck, Bayer Vital, UCB Pharma and Sanofi-Syntelabo. W.D. received research support and speaker honoraria from Nutricia, Vifor Pharma, BRAHMS, Bristol Myers-Squibb, and Sanofi. J.S., S.D.A. and J.S. declare no conflict of interest.

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