



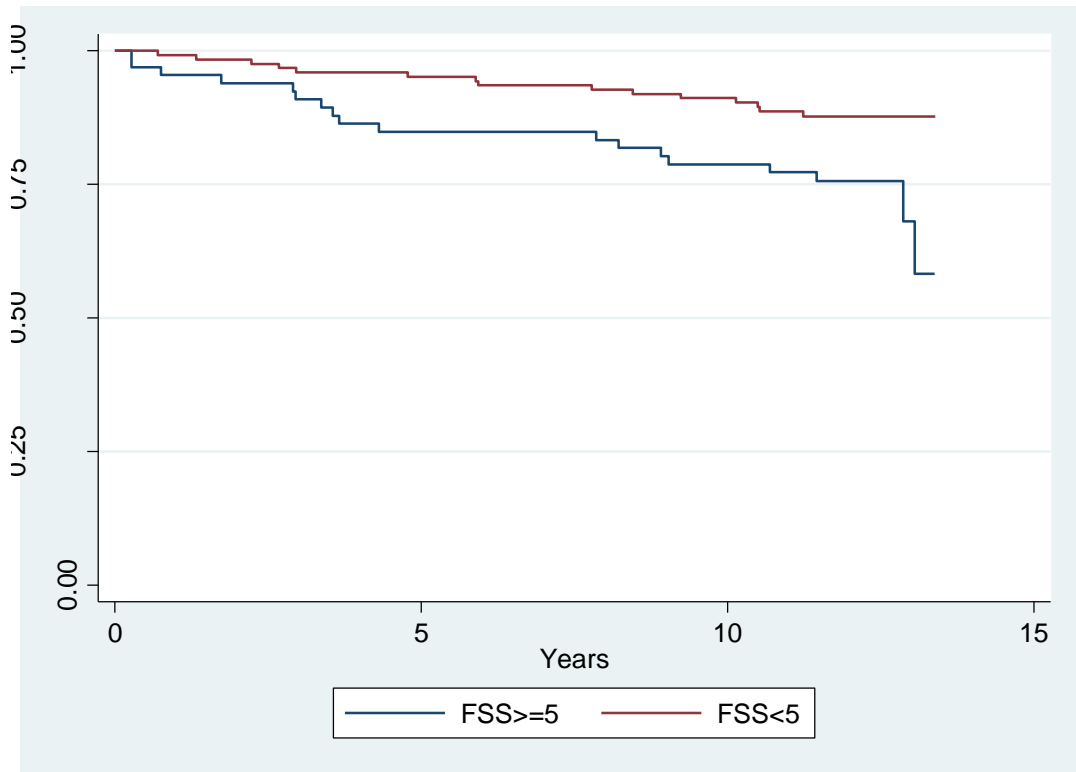
**Post-stroke fatigue and depression are related to mortality  
in young adults**

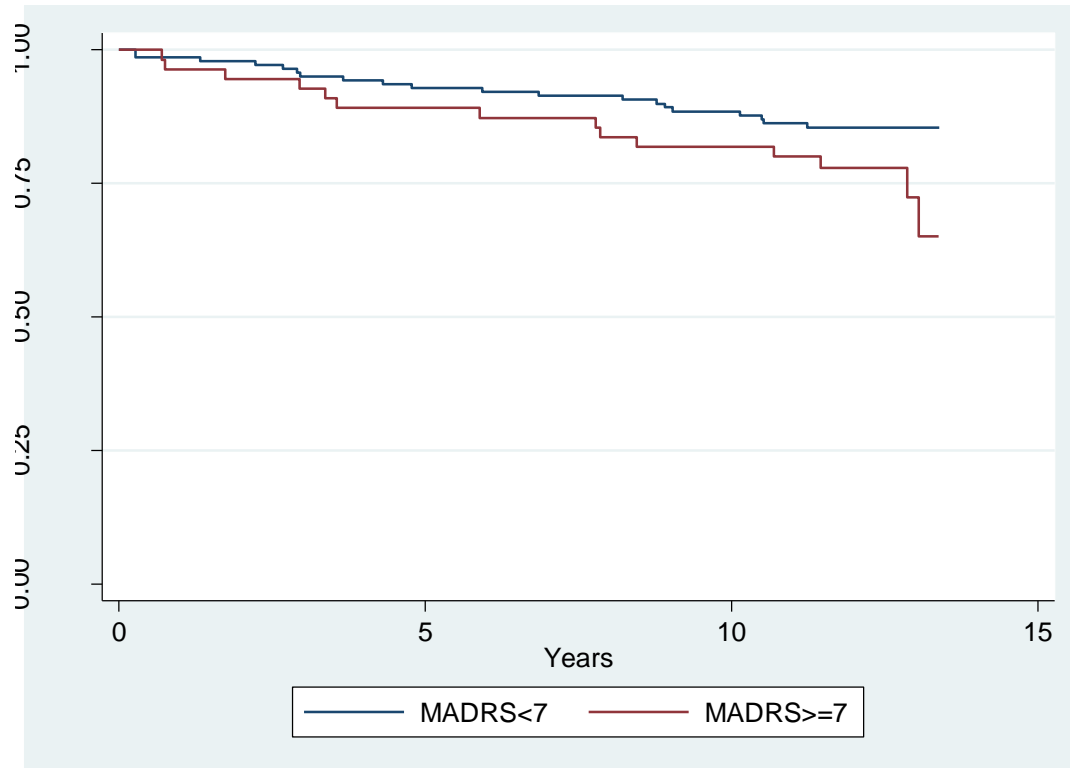
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3 Post-stroke fatigue and depression are related to mortality in  
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7 young adults  
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**Abstract**

*Objectives* –To investigate the relationship between post-stroke fatigue and depression and subsequent mortality in young ischemic stroke patients in a population-based study.

*Design* – Prospective cohort study.

*Setting* - All surviving young ischemic stroke patients living in Hordaland County.

*Participants* - Young ischemic stroke patients aged 15-50 years at the time of the stroke were invited to a follow-up on average 6 years after the index stroke. Psychosocial factors and risk factors were registered. Fatigue was self-assessed by the Fatigue Severity Scale (FSS). Depression was measured by Montgomery-Åsberg Depression Rating Scale (MADRS).

*Intervention* – No intervention was performed

*Primary and secondary outcome measure* – Mortality on follow-up.

*Results* – In total 190 patients were included. Mean age on follow-up was 48 years and subsequent follow-up period was 12 years. Cox regression analysis showed that mortality was associated with FSS score ( $P=.005$ ) after adjusting for age ( $P=.06$ ) and sex ( $P=.19$ ). Cox regression analysis showed that mortality was associated with MADRS score ( $P=.006$ ) after adjusting for age ( $P=.10$ ), and sex ( $P=.11$ ).

*Conclusion* - Both fatigue and depression are associated with long-term mortality in young adults with ischemic stroke. Depression may be linked to higher mortality because of psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality is broader including connection to diabetes mellitus, myocardial infarction and psychosocial factors.

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7 Outcome after ischemic stroke is better among young adults than older patients. However,  
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9 several studies have reported high long-term mortality in young adults with ischemic stroke as  
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11 compared to matched controls.<sup>1</sup> Factors such as hypertension, alcoholism, coronary heart  
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13 disease, severe stroke and age have been linked to mortality in young adults with ischemic  
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15 stroke.<sup>1-3</sup>  
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19 Young stroke patients need information on prognosis, including factors related to fatigue  
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21 or depression, to make informed choices about vocation and employment. Among old stroke  
22  
23 patients it has been shown that both fatigue<sup>4</sup> and depression<sup>5</sup> are associated with mortality.  
24  
25 However, little is known about the effect of fatigue or depression on survival in young adults  
26  
27 with ischemic stroke.  
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30 Here we present data on the effect of fatigue and depression measured on average 6  
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32 years after the index stroke and subsequent mortality. We hypothesized that fatigue and  
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34 depression are associated with increased mortality in young adults with ischemic stroke  
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36 irrespective of stroke severity.  
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## Method

All patients 15–49 years old with first-ever cerebral infarction from 1988 to 1997 living in Hordaland County were included in a database. Cerebral infarction was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings.<sup>6</sup> We excluded patients with cerebral infarction associated with other intracranial diseases such as subarachnoidal hemorrhage, sinus venous thrombosis, or severe head trauma. Case-finding was done retrospectively as described previously.<sup>7</sup>

Surviving patients were invited to a follow-up investigation on average 6 years after the index stroke. On follow-up data on employment, level of education, and marriage status were obtained. Risk factors including alcoholism, smoking, diabetes mellitus and myocardial infarction were registered. Stroke severity was determined by the modified Rankin Scale (mRS), Barthel Index (BI), and Scandinavian Stroke Scale (SSS) on follow-up. Cognitive function was assessed using the Mini-Mental State Examination (MMSE).

Fatigue was measured by the Fatigue Severity Scale (FSS).<sup>8,9</sup> FSS is a 9-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1, “completely disagree” to 7, “completely agree”. Examples of the items in the questionnaire are: “Fatigue is among my three most disabling symptoms”, “Exercise brings on my fatigue” and “I am easily fatigued”. The average score of the 9 items represents the FSS score (minimum score is 1 and maximum score is 7). Fatigue was defined as FSS score  $\geq 5$ .<sup>10</sup>

Depressive symptoms were quantified using Montgomery-Åsberg Depression Rating Scale (MADRS) at the follow-up.<sup>11</sup> PSD was defined as MADRS score  $\geq 7$ .<sup>12,13</sup>

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3 Subsequent survival state was registered by examining the official population registry  
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5 by the first of August 2011. The study was approved by the local Ethics committee.  
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### 8 9 *Statistics*

10 Fisher's exact test, Student's t-test, and pair-wise correlation test were used as appropriate.  
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12 Cox regression analyses were used for disclosing variable associated with mortality. Kaplan-  
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14 Meier survival curves grouped by dichotomized FSS scale and MADRS scores were obtained.  
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16 All tests were two-sided. Level of significance was set at  $P < 0.05$ . STATA 11.0 was used for  
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18 analyses.  
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### 25 **Results**

26  
27 A total of 232 patients had first-ever ischemic stroke. At the time of invitation 209 patients  
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29 were alive and the present study includes 190 patients; 81 (43%) females and 109 (57%)  
30  
31 males. Mean age on follow-up was 48 years. During a subsequent mean follow-up time of  
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33 12.4 years 32 (16.8%) patients had died. (The mean total follow-up time since the index  
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35 stroke was 18 years).  
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38 Univariate analyses showed that mortality was associated with being unmarried,  
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40 unemployed, alcoholism, diabetes mellitus, myocardical infarction, age, mRS, SSS, BI,  
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42 MMSE, FSS and MADRS scores (Table 1).  
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45 Cox regression analysis showed that mortality was associated with FFS score (hazard  
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47 ratio (HR) = 1.4, confidence interval (CI): 1.1 – 1.7,  $P = .005$ ) after adjusting for age ( $P = .06$ )  
48  
49 and sex ( $P = .19$ ). Including BI, mRS or SSS separately did not change these findings. Figure 1  
50  
51 shows Kaplan-Meier survival curves dichotomized for FFS  $< 5$  and  $\geq 5$ .  
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54 Cox regression analysis showed that mortality was associated with MADRS score  
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56 (HR = 1.06, CI: 1.02 – 1.11,  $P = .006$ ) after adjusting for age ( $P = .10$ ) and sex ( $P = .11$ ). Including  
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3 BI, mRS or SSS separately did not change these findings. Figure 2 shows Kaplan-Meier  
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5 survival curves dichotomized for MADRS<7 and  $\geq 7$ .  
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7 Step-wise Cox regression analyses based on all variables in Table 1 showed mortality to  
8  
9 be associated with alcoholism (HR=5.3, P=.001), myocardial infarction (HR=3.0, P=.011),  
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11 and unemployment (HR=2.9, P=.013) after adjusting for age (P=.29) and sex (P=.28).  
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13 Step-wise Cox regression analyses based on all variables in Table 1 excluding alcoholics  
14  
15 showed mortality to be associated with diabetes mellitus (HR=3.1, P=.023), myocardial  
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17 infarction (HR=4.1, P=.001), and MADRS score (HR=1.08, P=.002) after adjusting for age  
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19 (P=.32) and sex (P=.36).  
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22 Table 3 and 4 shows correlation analyses between MADRS and FSS scores and relevant  
23  
24 factors. MADRS was correlated with smoking, alcoholism, being unmarried, unemployment,  
25  
26 and stroke severity (all P<.05). FSS was correlated with diabetes mellitus, myocardial  
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28 infarction, alcoholism, unemployment, depression, and stroke severity (all P<.05). Correlation  
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30 was highest between MADRS scores and FSS scores ( $r=.60$ , P<.001). There was moderately  
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32 high correlation between FSS scores and unemployment ( $r=.31$ , P<.001).  
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## 38 Discussion

39 The main findings in the present study were that both fatigue and depression were associated  
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41 with subsequent long-term mortality irrespective of stroke severity. Consistent with these  
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43 findings other studies have disclosed that fatigue is associated with mortality in older stroke  
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45 patients.<sup>14 15</sup> Likewise others have reported depression to be associated with mortality in older  
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47 stroke patients.<sup>5 16</sup>  
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51 It is unlikely that fatigue causes death. It is more probable that fatigue is linked to other  
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53 factors that directly cause death. Consistent with this, fatigue disappeared in step-wise Cox  
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55 regression analyses including all variables associated with death on univariate analyses. We  
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3 found a strong correlation between fatigue and depression. Weaker correlations were found  
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5 between fatigue and mRS, unemployment, alcoholism, diabetes mellitus, and myocardial  
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7 infarction. A study including older stroke patients reported post-stroke fatigue to be associated  
8  
9 with diabetes mellitus, and myocardial infarction.<sup>14</sup> Both diabetes mellitus and myocardial  
10  
11 infarction are diseases associated with mortality in young adults with ischemic stroke.<sup>1</sup> It  
12  
13 seems likely that the link between fatigue and diseases such as diabetes mellitus and  
14  
15 myocardial infarction partially explains the association between fatigue and mortality in  
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17 young ischemic stroke patients. This probably also pertains to the link between fatigue and  
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19 alcoholism.  
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23 As with fatigue, we found that depression was weakly linked to other factors including  
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25 unemployment, being unmarried, alcoholism and mRS. However, unlike fatigue, depression  
26  
27 was not associated with diabetes mellitus and myocardial infarction. Consistent with our  
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29 findings another study including older stroke patients disclosed depression on follow-up to be  
30  
31 associated with being unmarried, but not with diabetes mellitus and myocardial infarction  
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33 whereas there was a correlation between fatigue and myocardial infarction and a trend  
34  
35 towards correlation between fatigue and diabetes mellitus.<sup>5 14</sup> It is possible that there is a more  
36  
37 direct link between depression and mortality than between fatigue and mortality. Possible  
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39 mechanisms include suicide, alcoholism and less focus on healthy lifestyle. The weak  
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41 correlation between smoking and depression among our patients hints to the presence  
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43 unhealthy lifestyle among depressed patients.  
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48 On univariate analyses, we found that depression was mostly linked to psychosocial  
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50 factors whereas fatigue was linked to a wider set of factors including both psychosocial  
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52 factors and specific diseases such as diabetes mellitus and myocardial infarction. Similar  
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54 findings have been disclosed among older stroke patients.<sup>5 14</sup> This shows that there is a  
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56 multifactorial basis for post-stroke fatigue. Careful investigations are needed to determine the  
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3 cause of fatigue and target treatment both to improve general health and survival. Depression  
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5 seems mostly confined to psychosocial factors. Alcoholic abuse should be considered as  
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7 should unhealthy lifestyle which may need particular attention in depressed patients with  
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9 ischemic stroke.  
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11 The strengths of this study are the population-based approach and the long-term follow-  
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13 up period. A weakness is that patient finding was done retrospectively which may have  
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15 affected both case finding and case ascertainment. Another weakness is that we have no data  
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17 on the cause of death.  
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20 In conclusion, both fatigue and depression are associated with long-term mortality in  
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22 young adults with ischemic stroke. Depression may be linked to higher mortality because of  
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24 psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality  
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26 is broader including connection to diabetes mellitus, myocardial infarction and psychosocial  
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28 factors.  
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41  
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44 The study was approved by the local ethics committee.  
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**Table 1 Characteristics of young ischemic stroke patients according to survival or not**

	Dead	Alive	P
	N (%)	N (%)	
Male	22 (20)	87 (80)	.17
Female	10 (12)	71 (88)	
Unmarried	13 (27)	36 (73)	.05
Higher education	8 (14)	48 (86)	.67
Unemployed	22 (29)	53 (71)	<.001
Alcoholism	6 (55)	5 (45)	.004
Smoking	17 (22)	60 (78)	.12
Diabetes mellitus	7 (35)	13 (65)	.05
Myocardial infarction	10 (53)	9 (47)	<.001
	Mean (SD*)	Mean (SD)	
Age on follow-up	51.2 (6.6)	47.2 (8.3)	.01
Modified Rankin Scale score	1.7 (1.1)	1.3 (1.0)	.03
Scandinavian Stroke Scale score	54 (8.4)	56 (4.5)	.08
Barthel Index	96 (13)	99 (5)	.04
Fatigue Severity Scale score	4.9 (1.6)	4.0 (1.6)	.003
MADRS <sup>1</sup> score	7.8 (7.3)	4.3 (5.9)	.004
Mini-Mental State Examination	26.8 (3.6)	28.2 (2.1)	.003

\* SD: standard deviation

<sup>1</sup> Montgomery-Åsberg Depression Rating Scale

**Table 2 Cox regression survival analysis among non-alcoholic young adults with ischemic stroke**

	Hazard ratio	Confidence interval	P
Age	1.04	.97 – 1.1	.32
Sex	1.5	.6 – 3.4	.36
Diabetes mellitus	3.1	1.2 – 8.3	.023
Myocardial infarction	4.1	1.8 – 9.4	.001
MADRS* score	1.08	1.03 – 1.13	.002

\* Montgomery-Åsberg Depression Rating Scale

**Table 3 MADRS\* and correlation analyses in young ischemic stroke patients**

	Correlation	P
Age	.05	.49
Females	.07	.31
Diabetes mellitus	.08	.27
Myocardial infarction	.01	.90
Smoking	.15	.04
Alcoholism	-.17	.02
Married	-.20	.007
Employed	-.31	<.001
Higher education	-.12	.11
Fatigue Severity Scale score	.60	<.001
Modified Rankin Scale score	.14	.05
Mini-Mental State Examination	-.08	.25

\* Montgomery-Åsberg Depression Rating Scale

**Table 4 Fatigue Severity Scale score and correlation analyses in young ischemic stroke patients**

	Correlation	P
Age	.05	.47
Females	.06	.41
Diabetes mellitus	.13	.007
Myocardial infarction	.16	.002
Smoking	.07	.36
Alcoholism	-.15	.003
Married	.13	.08
Employed	-.23	.002
Higher education	-.11	.13
MADRS*	.60	<.001
Modified Rankin Scale score	.24	.001
Mini-Mental State Examination	-.08	.25

\* Montgomery-Åsberg Depression Rating Scale

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	na
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	4
		(d) If applicable, explain how loss to follow-up was addressed	na
		(e) Describe any sensitivity analyses	na
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 na 4
Outcome data	15*	Report numbers of outcome events or summary measures over time	5-6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6 5-6 5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	8
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	na

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



**Post-stroke fatigue and depression are related to mortality  
in young adults**

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Secondary Subject Heading:	Mental health
Keywords:	Stroke < NEUROLOGY, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY

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**Abstract**

*Objectives* –To investigate the relationship between post-stroke fatigue and depression and subsequent mortality in young ischemic stroke patients in a population-based study.

*Design* – Prospective cohort study.

*Setting* - All surviving young ischemic stroke patients living in Hordaland County.

*Participants* - Young ischemic stroke patients aged 15-50 years at the time of the stroke were invited to a follow-up on average 6 years after the index stroke. Psychosocial factors and risk factors were registered. Fatigue was self-assessed by the Fatigue Severity Scale (FSS). Depression was measured by Montgomery-Åsberg Depression Rating Scale (MADRS).

*Intervention* – No intervention was performed

*Primary and secondary outcome measure* – Mortality on follow-up.

*Results* – In total 190 patients were included. Mean age on follow-up was 48 years and subsequent follow-up period was 12 years. Cox regression analysis showed that mortality was associated with FSS score (P=.005) after adjusting for age (P=.06) and sex (P=.19). Cox regression analysis showed that mortality was associated with MADRS score (P=.006) after adjusting for age (P=.10), and sex (P=.11).

*Conclusion* - Both fatigue and depression are associated with long-term mortality in young adults with ischemic stroke. Depression may be linked to higher mortality because of psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality is broader including connection to diabetes mellitus, myocardial infarction and psychosocial factors.

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7 Outcome after ischemic stroke is better among young adults than older patients. However,  
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18 The study of stroke among young people is important for several reasons. The etiology  
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26 patients. Fatigue has been recognized as a disabling symptom in non-depressed stroke  
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30 fatigue or depression, to make informed choices about vocation and employment. Among old  
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32 stroke patients it has been shown that both fatigue<sup>5</sup> and depression<sup>6</sup> are associated with  
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34 mortality. However, little is known about the effect of fatigue or depression on survival in  
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36 young adults with ischemic stroke.  
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40 Here we present data on the effect of fatigue and depression measured on average 6  
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42 years after the index stroke and subsequent mortality. We hypothesized that fatigue and  
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44 depression are associated with increased mortality in young adults with ischemic stroke  
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46 irrespective of stroke severity.  
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## Method

All patients 15–49 years old with first-ever cerebral infarction from 1988 to 1997 living in Hordaland County were included in a database. An upper limit of 49 years was chosen because these patients have low comorbidity compared to older patients and because they still have many years left in the work force. Cerebral infarction was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings.<sup>7</sup> We excluded patients with cerebral infarction associated with other intracranial diseases such as subarachnoidal hemorrhage, sinus venous thrombosis, or severe head trauma. Case-finding was done retrospectively as described previously.<sup>8</sup>

Surviving patients were invited to a follow-up investigation in person in our out-clinic department on average 6 years after the index stroke. On follow-up data on employment, level of education, and marriage status were obtained by the authors. Risk factors including alcoholism, smoking, diabetes mellitus and myocardial infarction were registered. Stroke severity was determined by the modified Rankin Scale (mRS), Barthel Index (BI), and Scandinavian Stroke Scale (SSS) on follow-up. Cognitive function was assessed using the Mini-Mental State Examination (MMSE).

Fatigue was measured by the Fatigue Severity Scale (FSS).<sup>9,10</sup> FSS is a 9-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1, “completely disagree” to 7, “completely agree”. Examples of the items in the questionnaire are: “Fatigue is among my three most disabling symptoms”, “Exercise brings on my fatigue” and “I am easily fatigued”. The average score of the 9 items represents the FSS score (minimum score is 1 and maximum score is 7). Fatigue was defined as FSS score  $\geq 5$ .<sup>11</sup>



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3 Depressive symptoms were quantified using Montgomery-Åsberg Depression Rating  
4 Scale (MADRS) at the follow-up.<sup>12</sup> PSD was defined as MADRS score  $\geq 7$ .<sup>13 14</sup>  
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10 Subsequent survival state was registered by examining the official population registry  
11 by the first of August 2011. The study was approved by the local Ethics committee.  
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### 14 15 16 *Statistics*

17  
18 Fisher's exact test (categorical variables), Student's t-test (continuous variables), and pair-  
19 wise correlation test were used as appropriate. Cox regression analyses were used for  
20 disclosing variable associated with mortality. Kaplan-Meier survival curves grouped by  
21 dichotomized FSS scale (FSS<5 versus FSS $\geq$ 5) and MADRS scores (MADRS<7 versus  
22 MADRS $\geq$ 7) were obtained. All tests were two-sided. Level of significance was set at P<0.05.  
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29 STATA 11.0 was used for analyses.  
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### 34 **Results**

35  
36 A total of 232 patients had first-ever ischemic stroke. At the time of invitation 209 patients  
37 were alive and the present study includes 190 patients; 81 (43%) females and 109 (57%)  
38 males. Mean age on follow-up was 48 years. During a subsequent mean follow-up time of  
39 12.4 years 32 (16.8%) patients had died. (The mean total follow-up time since the index  
40 stroke was 18 years).  
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47 Univariate analyses showed that mortality was associated with being unmarried,  
48 unemployed, alcoholism, diabetes mellitus, myocardial infarction, age, mRS, SSS, BI,  
49 MMSE, FSS and MADRS scores (Table 1).  
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54 Cox regression analysis showed that mortality was associated with FFS score (hazard  
55 ratio (HR) =1.4, confidence interval (CI): 1.1 – 1.7, P=.005) after adjusting for age (P=.06)  
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3 and sex ( $P=.19$ ). Including BI, mRS or SSS separately did not change these findings. Figure 1  
4  
5 shows Kaplan-Meier survival curves dichotomized for FFS  $<5$  and  $\geq 5$ .  
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7  
8 Cox regression analysis showed that mortality was associated with MADRS score  
9  
10 (HR=1.06, CI: 1.02 – 1.11,  $P=.006$ ) after adjusting for age ( $P=.10$ ) and sex ( $P=.11$ ). Including  
11  
12 BI, mRS or SSS separately did not change these findings. Figure 2 shows Kaplan-Meier  
13  
14 survival curves dichotomized for MADRS  $<7$  and  $\geq 7$ .  
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17 Step-wise Cox regression analyses based on all variables in Table 1 showed mortality to  
18  
19 be associated with alcoholism (HR=5.3,  $P=.001$ ), myocardial infarction (HR=3.0,  $P=.011$ ),  
20  
21 and unemployment (HR=2.9,  $P=.013$ ) after adjusting for age ( $P=.29$ ) and sex ( $P=.28$ ).  
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24 Step-wise Cox regression analyses based on all variables in Table 1 excluding alcoholics  
25  
26 showed mortality to be associated with diabetes mellitus (HR=3.1,  $P=.023$ ), myocardial  
27  
28 infarction (HR=4.1,  $P=.001$ ), and MADRS score (HR=1.08,  $P=.002$ ) after adjusting for age  
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30 ( $P=.32$ ) and sex ( $P=.36$ ).  
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33 Table 3 and 4 shows correlation analyses between MADRS and FSS scores and relevant  
34  
35 factors. MADRS was correlated with smoking, alcoholism, being unmarried, unemployment,  
36  
37 and stroke severity (all  $P<.05$ ). FSS was correlated with diabetes mellitus, myocardial  
38  
39 infarction, alcoholism, unemployment, depression, and stroke severity (all  $P<.05$ ). Correlation  
40  
41 was highest between MADRS scores and FSS scores ( $r=.60$ ,  $P<.001$ ). There was moderately  
42  
43 high correlation between FSS scores and unemployment ( $r=.31$ ,  $P<.001$ ).  
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## 46 47 **Discussion**

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49 The main findings in the present study were that both fatigue and depression were associated  
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51 with subsequent long-term mortality irrespective of stroke severity. Consistent with these  
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53 findings other studies have disclosed that fatigue is associated with mortality in older stroke  
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3 patients.<sup>15 16</sup> Likewise others have reported depression to be associated with mortality in older  
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5 stroke patients.<sup>6 17 18 19</sup>  
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8 It is unlikely that fatigue causes death. It is more probable that fatigue is linked to other  
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10 factors that directly cause death. Consistent with this, fatigue disappeared in step-wise Cox  
11  
12 regression analyses including all variables associated with death on univariate analyses. We  
13  
14 found a strong correlation between fatigue and depression. Weaker correlations were found  
15  
16 between fatigue and mRS, unemployment, alcoholism, diabetes mellitus, and myocardial  
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18 infarction. Studies including older stroke patients reported post-stroke fatigue to be associated  
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20 with diabetes mellitus, and myocardial infarction.<sup>15 20</sup> Both diabetes mellitus and myocardial  
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22 infarction are diseases associated with mortality in young adults with ischemic stroke.<sup>1</sup> It  
23  
24 seems likely that the link between fatigue and diseases such as diabetes mellitus and  
25  
26 myocardial infarction partially explains the association between fatigue and mortality in  
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28 young ischemic stroke patients. This probably also pertains to the link between fatigue and  
29  
30 alcoholism.  
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34 As with fatigue, we found that depression was weakly linked to other factors including  
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36 unemployment, being unmarried, alcoholism and mRS. However, unlike fatigue, depression  
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38 was not associated with diabetes mellitus and myocardial infarction. Consistent with our  
39  
40 findings another study including older stroke patients disclosed depression on follow-up to be  
41  
42 associated with being unmarried, but not with diabetes mellitus and myocardial infarction  
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44 whereas there was a correlation between fatigue and myocardial infarction and a trend  
45  
46 towards correlation between fatigue and diabetes mellitus.<sup>6 15</sup> It is possible that there is a more  
47  
48 direct link between depression and mortality than between fatigue and mortality. Possible  
49  
50 mechanisms include suicide, alcoholism and less focus on healthy lifestyle. The weak  
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52 correlation between smoking and depression among our patients hints to the presence  
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54 unhealthy lifestyle among depressed patients.  
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3 On univariate analyses, we found that depression was mostly linked to psychosocial  
4 factors whereas fatigue was linked to a wider set of factors including both psychosocial  
5 factors and specific diseases such as diabetes mellitus and myocardial infarction. Similar  
6 findings have been disclosed among older stroke patients.<sup>6 15</sup> This shows that there is a  
7 multifactorial basis for post-stroke fatigue. Careful investigations are needed to determine the  
8 cause of fatigue and target treatment both to improve general health and survival. Depression  
9 seems mostly confined to psychosocial factors. Alcoholic abuse should be considered as  
10 should unhealthy lifestyle which may need particular attention in depressed patients with  
11 ischemic stroke.  
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22 We found age to be associated with increased mortality on univariate analysis, but this  
23 association disappeared on Cox regression analyses. Others have found increasing age to be  
24 associated with higher mortality among young ischemic stroke patients.<sup>2 3</sup>  
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29 The strengths of this study are the population-based approach and the long-term follow-  
30 up period. A weakness is that patient finding was done retrospectively which may have  
31 affected both case finding and case ascertainment. Another weakness is that we have no data  
32 on the cause of death or the use of antidepressive medication. Risk factor profile and stroke  
33 treatment have changed since 1988 to 1997, and this should be taken into account when  
34 interpreting the results.  
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43 In conclusion, both fatigue and depression are associated with long-term mortality in  
44 young adults with ischemic stroke. Depression may be linked to higher mortality because of  
45 psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality  
46 is broader including connection to diabetes mellitus, myocardial infarction and psychosocial  
47 factors.  
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The study was approved by the local ethics committee.

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**Table 1 Characteristics of young ischemic stroke patients according to survival or not**

	Dead	Alive	P
	n (%)	n (%)	
Total	32 (17)	158 (83)	
Male	22 (20)	87 (80)	.17
Female	10 (12)	71 (88)	
Unmarried	13 (27)	36 (73)	.05
Higher education	8 (14)	48 (86)	.67
Unemployed	22 (29)	53 (71)	<.001
Alcoholism	6 (55)	5 (45)	.004
Smoking	17 (22)	60 (78)	.12
Diabetes mellitus	7 (35)	13 (65)	.05
Myocardial infarction	10 (53)	9 (47)	<.001
	Mean (SD*)	Mean (SD)	
Age on follow-up	51.2 (6.6)	47.2 (8.3)	.01
Modified Rankin Scale score	1.7 (1.1)	1.3 (1.0)	.03
Scandinavian Stroke Scale score	54 (8.4)	56 (4.5)	.08
Barthel Index	96 (13)	99 (5)	.04
Fatigue Severity Scale score	4.9 (1.6)	4.0 (1.6)	.003
MADRS <sup>1</sup> score	7.8 (7.3)	4.3 (5.9)	.004
Mini-Mental State Examination	26.8 (3.6)	28.2 (2.1)	.003

\* SD: standard deviation

<sup>1</sup> Montgomery-Åsberg Depression Rating Scale

**Table 2 Cox regression survival analysis among non-alcoholic young adults with ischemic stroke**

	Hazard ratio	Confidence interval	P
Age	1.04	.97 – 1.1	.32
Sex	1.5	.6 – 3.4	.36
Diabetes mellitus	3.1	1.2 – 8.3	.023
Myocardial infarction	4.1	1.8 – 9.4	.001
MADRS* score	1.08	1.03 – 1.13	.002

\* Montgomery-Åsberg Depression Rating Scale

**Table 3 MADRS\* and correlation analyses in young ischemic stroke patients**

	Correlation	P
Age	.05	.49
Females	.07	.31
Diabetes mellitus	.08	.27
Myocardial infarction	.01	.90
Smoking	.15	.04
Alcoholism	-.17	.02
Married	-.20	.007
Employed	-.31	<.001
Higher education	-.12	.11
Fatigue Severity Scale score	.60	<.001
Modified Rankin Scale score	.14	.05
Mini-Mental State Examination	-.08	.25

\* Montgomery-Åsberg Depression Rating Scale



**Table 4 Fatigue Severity Scale score and correlation analyses in young ischemic stroke patients**

	Correlation	P
Age	.05	.47
Females	.06	.41
Diabetes mellitus	.13	.007
Myocardial infarction	.16	.002
Smoking	.07	.36
Alcoholism	-.15	.003
Married	.13	.08
Employed	-.23	.002
Higher education	-.11	.13
MADRS*	.60	<.001
Modified Rankin Scale score	.24	.001
Mini-Mental State Examination	-.08	.25

\* Montgomery-Åsberg Depression Rating Scale

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7 Post-stroke fatigue and depression are related to mortality in  
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10 young adults

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31 Key words: cerebral infarction, young adults, mortality, depression, fatigue

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33 Word count: 1391

**Abstract**

*Objectives* –To investigate the relationship between post-stroke fatigue and depression and subsequent mortality in young ischemic stroke patients in a population-based study.

*Design* – Prospective cohort study.

*Setting* - All surviving young ischemic stroke patients living in Hordaland County.

*Participants* - Young ischemic stroke patients aged 15-50 years at the time of the stroke were invited to a follow-up on average 6 years after the index stroke. Psychosocial factors and risk factors were registered. Fatigue was self-assessed by the Fatigue Severity Scale (FSS).

Depression was measured by Montgomery-Åsberg Depression Rating Scale (MADRS).

*Intervention* – No intervention was performed

*Primary and secondary outcome measure* – Mortality on follow-up.

*Results* – In total 190 patients were included. Mean age on follow-up was 48 years and subsequent follow-up period was 12 years. Cox regression analysis showed that mortality was associated with FSS score ( $P=.005$ ) after adjusting for age ( $P=.06$ ) and sex ( $P=.19$ ). Cox regression analysis showed that mortality was associated with MADRS score ( $P=.006$ ) after adjusting for age ( $P=.10$ ), and sex ( $P=.11$ ).

*Conclusion* - Both fatigue and depression are associated with long-term mortality in young adults with ischemic stroke. Depression may be linked to higher mortality because of psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality is broader including connection to diabetes mellitus, myocardial infarction and psychosocial factors.

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10 Outcome after ischemic stroke is better among young adults than older patients. However,  
11 several studies have reported high long-term mortality in young adults with ischemic stroke as  
12 compared to matched controls.<sup>1</sup> Factors such as hypertension, alcoholism, coronary heart  
13 disease, severe stroke and age have been linked to mortality in young adults with ischemic  
14 stroke.<sup>1-3</sup>

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20 The study of stroke among young people is important for several reasons. The etiology  
21 of stroke is much more diverse and risk factors for stroke differ between young and old  
22 patients and may indicate separate approaches as to treatment. Stroke in young adults  
23 provides an opportunity to study stroke in general because of less comorbidity than in old  
24 patients. Fatigue has been recognized as a disabling symptom in non-depressed stroke  
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26 fatigue or depression, to make informed choices about vocation and employment. Among old  
27 stroke patients it has been shown that both fatigue<sup>5</sup> and depression<sup>6</sup> are associated with  
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29 young adults with ischemic stroke.  
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## Method

All patients 15–49 years old with first-ever cerebral infarction from 1988 to 1997 living in Hordaland County were included in a database. [An upper limit of 49 years was chosen because these patients have low comorbidity compared to older patients and because they still have many years left in the work force.](#) Cerebral infarction was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings.<sup>7</sup> We excluded patients with cerebral infarction associated with other intracranial diseases such as subarachnoidal hemorrhage, sinus venous thrombosis, or severe head trauma. Case-finding was done retrospectively as described previously.<sup>8</sup>

Surviving patients were invited to a follow-up investigation [in person in our out-clinic department](#) on average 6 years after the index stroke. On follow-up data on employment, level of education, and marriage status were obtained [by the authors](#). Risk factors including alcoholism, smoking, diabetes mellitus and myocardial infarction were registered. Stroke severity was determined by the modified Rankin Scale (mRS), Barthel Index (BI), and Scandinavian Stroke Scale (SSS) on follow-up. Cognitive function was assessed using the Mini-Mental State Examination (MMSE).

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9 Examples of the items in the questionnaire are: “Fatigue is among my three most disabling  
10 symptoms”, “Exercise brings on my fatigue” and “I am easily fatigued”. The average score of  
11 the 9 items represents the FSS score (minimum score is 1 and maximum score is 7). Fatigue  
12 was defined as FSS score  $\geq 5$ .<sup>11</sup>  
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23 by the first of August 2011. The study was approved by the local Ethics committee.  
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#### 26 27 28 *Statistics*

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32 disclosing variable associated with mortality. Kaplan-Meier survival curves grouped by  
33 dichotomized FSS scale (FSS<5 versus FSS $\geq$ 5) and MADRS scores (MADRS<7 versus  
34 MADRS $\geq$ 7) were obtained. All tests were two-sided. Level of significance was set at  $P<0.05$ .  
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39 STATA 11.0 was used for analyses.  
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#### 43 44 **Results**

45 A total of 232 patients had first-ever ischemic stroke. At the time of invitation 209 patients  
46 were alive and the present study includes 190 patients; 81 (43%) females and 109 (57%)  
47 males. Mean age on follow-up was 48 years. During a subsequent mean follow-up time of  
48 12.4 years 32 (16.8%) patients had died. (The mean total follow-up time since the index  
49 stroke was 18 years).  
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Univariate analyses showed that mortality was associated with being unmarried, unemployed, alcoholism, diabetes mellitus, myocardial infarction, age, mRS, SSS, BI, MMSE, FSS and MADRS scores (Table 1).

Cox regression analysis showed that mortality was associated with FFS score (hazard ratio (HR) =1.4, confidence interval (CI): 1.1 – 1.7, P=.005) after adjusting for age (P=.06) and sex (P=.19). Including BI, mRS or SSS separately did not change these findings. Figure 1 shows Kaplan-Meier survival curves dichotomized for FFS <5 and  $\geq$ 5.

Cox regression analysis showed that mortality was associated with MADRS score (HR=1.06, CI: 1.02 – 1.11, P=.006) after adjusting for age (P=.10) and sex (P=.11). Including BI, mRS or SSS separately did not change these findings. Figure 2 shows Kaplan-Meier survival curves dichotomized for MADRS <7 and  $\geq$ 7.

Step-wise Cox regression analyses based on all variables in Table 1 showed mortality to be associated with alcoholism (HR=5.3, P=.001), myocardial infarction (HR=3.0, P=.011), and unemployment (HR=2.9, P=.013) after adjusting for age (P=.29) and sex (P=.28).

Step-wise Cox regression analyses based on all variables in Table 1 excluding alcoholics showed mortality to be associated with diabetes mellitus (HR=3.1, P=.023), myocardial infarction (HR=4.1, P=.001), and MADRS score (HR=1.08, P=.002) after adjusting for age (P=.32) and sex (P=.36).

Table 3 and 4 shows correlation analyses between MADRS and FSS scores and relevant factors. MADRS was correlated with smoking, alcoholism, being unmarried, unemployment, and stroke severity (all P<.05). FSS was correlated with diabetes mellitus, myocardial infarction, alcoholism, unemployment, depression, and stroke severity (all P<.05). Correlation was highest between MADRS scores and FSS scores ( $r=.60$ , P<.001). There was moderately high correlation between FSS scores and unemployment ( $r=.31$ , P<.001).

## Discussion

The main findings in the present study were that both fatigue and depression were associated with subsequent long-term mortality irrespective of stroke severity. Consistent with these findings other studies have disclosed that fatigue is associated with mortality in older stroke patients.<sup>15 16</sup> Likewise others have reported depression to be associated with mortality in older stroke patients.<sup>6 17 18 19</sup>

It is unlikely that fatigue causes death. It is more probable that fatigue is linked to other factors that directly cause death. Consistent with this, fatigue disappeared in step-wise Cox regression analyses including all variables associated with death on univariate analyses. We found a strong correlation between fatigue and depression. Weaker correlations were found between fatigue and mRS, unemployment, alcoholism, diabetes mellitus, and myocardial infarction. SA-studiesy including older stroke patients reported post-stroke fatigue to be associated with diabetes mellitus, and myocardial infarction.<sup>15 20</sup> Both diabetes mellitus and myocardial infarction are diseases associated with mortality in young adults with ischemic stroke.<sup>1</sup> It seems likely that the link between fatigue and diseases such as diabetes mellitus and myocardial infarction partially explains the association between fatigue and mortality in young ischemic stroke patients. This probably also pertains to the link between fatigue and alcoholism.

As with fatigue, we found that depression was weakly linked to other factors including unemployment, being unmarried, alcoholism and mRS. However, unlike fatigue, depression was not associated with diabetes mellitus and myocardial infarction. Consistent with our findings another study including older stroke patients disclosed depression on follow-up to be associated with being unmarried, but not with diabetes mellitus and myocardial infarction whereas there was a correlation between fatigue and myocardial infarction and a trend towards correlation between fatigue and diabetes mellitus.<sup>6 15</sup> It is possible that there is a more

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7 direct link between depression and mortality than between fatigue and mortality. Possible  
8 mechanisms include suicide, alcoholism and less focus on healthy lifestyle. The weak  
9 correlation between smoking and depression among our patients hints to the presence  
10 unhealthy lifestyle among depressed patients.  
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14 On univariate analyses, we found that depression was mostly linked to psychosocial  
15 factors whereas fatigue was linked to a wider set of factors including both psychosocial  
16 factors and specific diseases such as diabetes mellitus and myocardial infarction. Similar  
17 findings have been disclosed among older stroke patients.<sup>6,15</sup> This shows that there is a  
18 multifactorial basis for post-stroke fatigue. Careful investigations are needed to determine the  
19 cause of fatigue and target treatment both to improve general health and survival. Depression  
20 seems mostly confined to psychosocial factors. Alcoholic abuse should be considered as  
21 should unhealthy lifestyle which may need particular attention in depressed patients with  
22 ischemic stroke.  
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31 We found age to be associated with increased mortality on univariate analysis, but this  
32 association disappeared on Cox regression analyses. Others have found increasing age to be  
33 associated with higher mortality among young ischemic stroke patients.<sup>2,3</sup>  
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37 The strengths of this study are the population-based approach and the long-term follow-  
38 up period. A weakness is that patient finding was done retrospectively which may have  
39 affected both case finding and case ascertainment. Another weakness is that we have no data  
40 on the cause of death or the use of antidepressive medication. Risk factor profile and stroke  
41 treatment have changed since 1988 to 1997, and this should be taken into account when  
42 interpreting the results.  
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49 In conclusion, both fatigue and depression are associated with long-term mortality in  
50 young adults with ischemic stroke. Depression may be linked to higher mortality because of  
51 psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality  
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is broader including connection to diabetes mellitus, myocardial infarction and psychosocial factors.

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Competing interests: none

Funding: none

The study was approved by the local ethics committee.

**Table 1 Characteristics of young ischemic stroke patients according to survival or not**

	Dead	Alive	P
	<u>n</u> (%)	<u>n</u> (%)	
<b>Total</b>	<b>32 (17)</b>	<b>158 (83)</b>	
Male	22 (20)	87 (80)	.17
Female	10 (12)	71 (88)	
Unmarried	13 (27)	36 (73)	.05
Higher education	8 (14)	48 (86)	.67
Unemployed	22 (29)	53 (71)	<.001
Alcoholism	6 (55)	5 (45)	.004
Smoking	17 (22)	60 (78)	.12
Diabetes mellitus	7 (35)	13 (65)	.05
Myocardial infarction	10 (53)	9 (47)	<.001
	Mean (SD*)	Mean (SD)	

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Age on follow-up	51.2 (6.6)	47.2 (8.3)	.01
Modified Rankin Scale score	1.7 (1.1)	1.3 (1.0)	.03
Scandinavian Stroke Scale score	54 (8.4)	56 (4.5)	.08
Barthel Index	96 (13)	99 (5)	.04
Fatigue Severity Scale score	4.9 (1.6)	4.0 (1.6)	.003
MADRS <sup>1</sup> score	7.8 (7.3)	4.3 (5.9)	.004
Mini-Mental State Examination	26.8 (3.6)	28.2 (2.1)	.003

\* SD: standard deviation

<sup>1</sup> Montgomery-Åsberg Depression Rating Scale

**Table 2 Cox regression survival analysis among non-alcoholic young adults with ischemic stroke**

	Hazard ratio	Confidence interval	P
Age	1.04	.97 – 1.1	.32
Sex	1.5	.6 – 3.4	.36
Diabetes mellitus	3.1	1.2 – 8.3	.023
Myocardial infarction	4.1	1.8 – 9.4	.001
MADRS* score	1.08	1.03 – 1.13	.002

\* Montgomery-Åsberg Depression Rating Scale

**Table 3 MADRS\* and correlation analyses in young ischemic stroke patients**

	Correlation	P
Age	.05	.49
Females	.07	.31
Diabetes mellitus	.08	.27
Myocardial infarction	.01	.90
Smoking	.15	.04
Alcoholism	-.17	.02
Married	-.20	.007
Employed	-.31	<.001
Higher education	-.12	.11
Fatigue Severity Scale score	.60	<.001

Modified Rankin Scale score	.14	.05
Mini-Mental State Examination	-.08	.25

\* Montgomery-Åsberg Depression Rating Scale

**Table 4 Fatigue Severity Scale score and correlation analyses in young ischemic stroke patients**

	Correlation	P
Age	.05	.47
Females	.06	.41
Diabetes mellitus	.13	.007
Myocardial infarction	.16	.002
Smoking	.07	.36
Alcoholism	-.15	.003
Married	.13	.08
Employed	-.23	.002
Higher education	-.11	.13

MADRS*	.60	<.001
Modified Rankin Scale score	.24	.001
Mini-Mental State Examination	-.08	.25

\* Montgomery-Åsberg Depression Rating Scale

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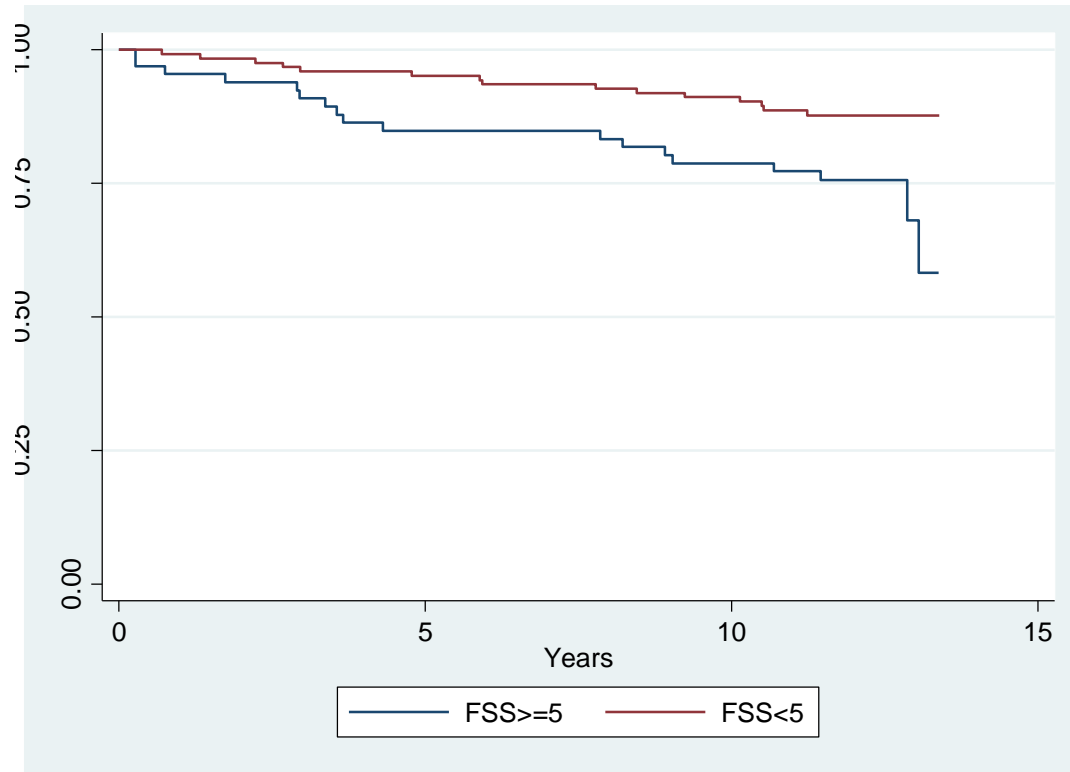
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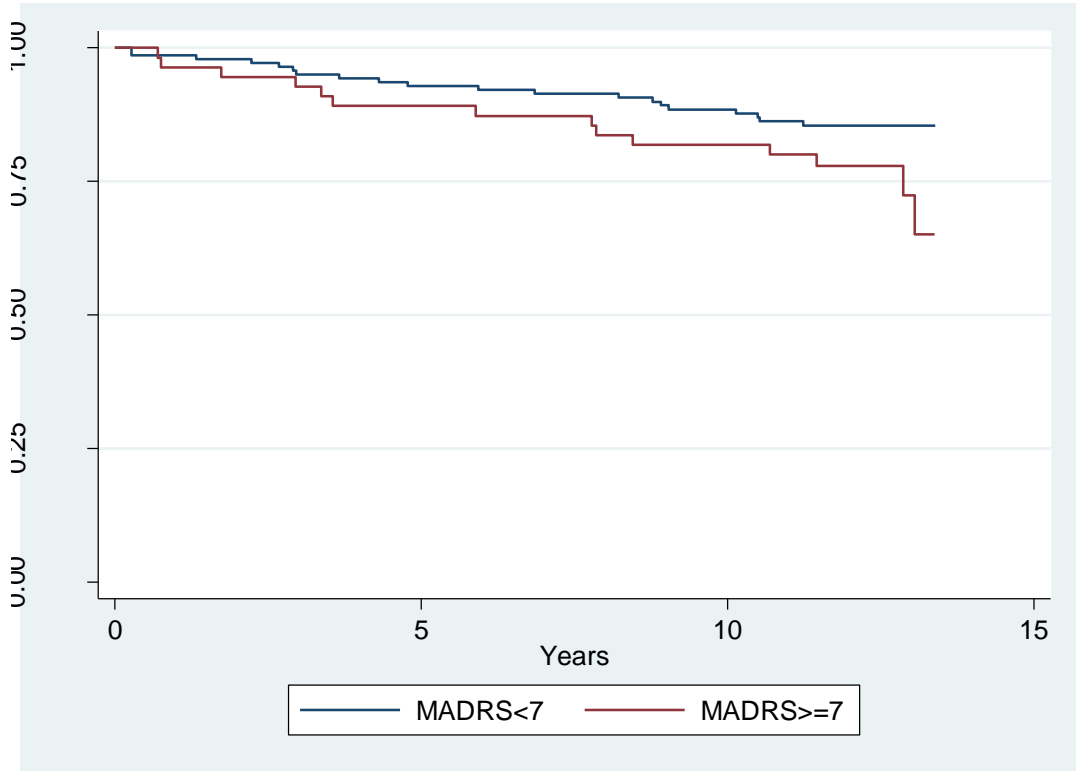
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	na
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	4
		(d) If applicable, explain how loss to follow-up was addressed	na
		(e) Describe any sensitivity analyses	na
<b>Results</b>			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9 na 4
Outcome data	15*	Report numbers of outcome events or summary measures over time	5-6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6 5-6 5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	8
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	na

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).