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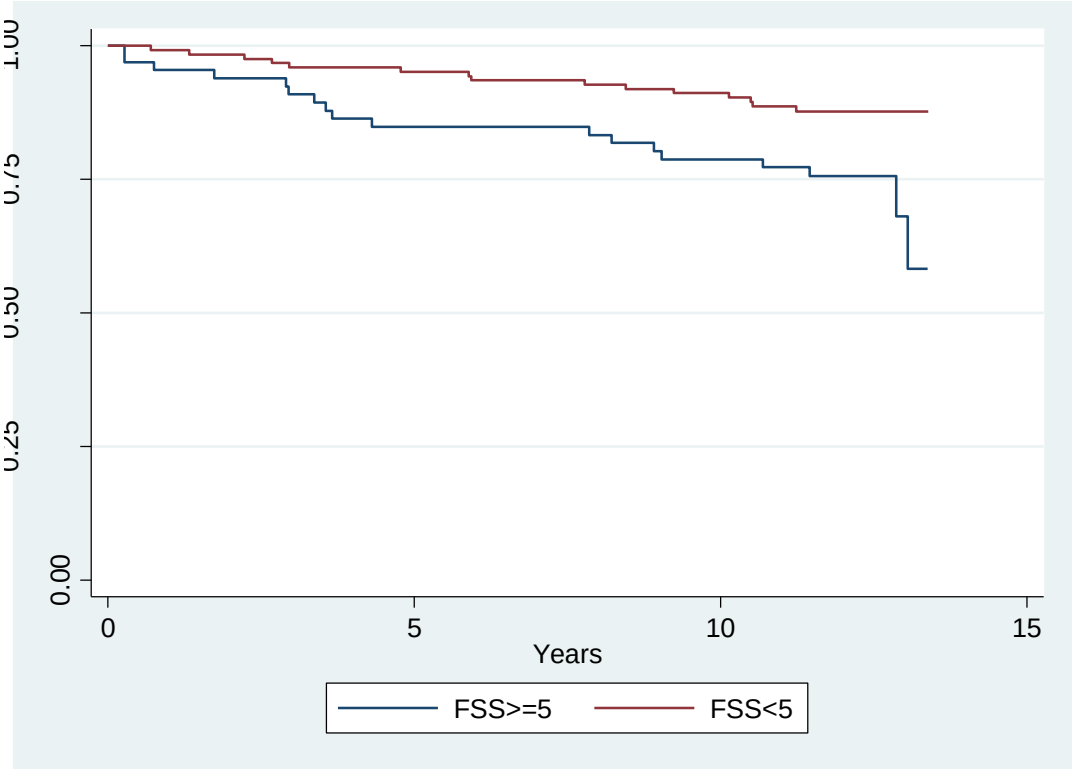
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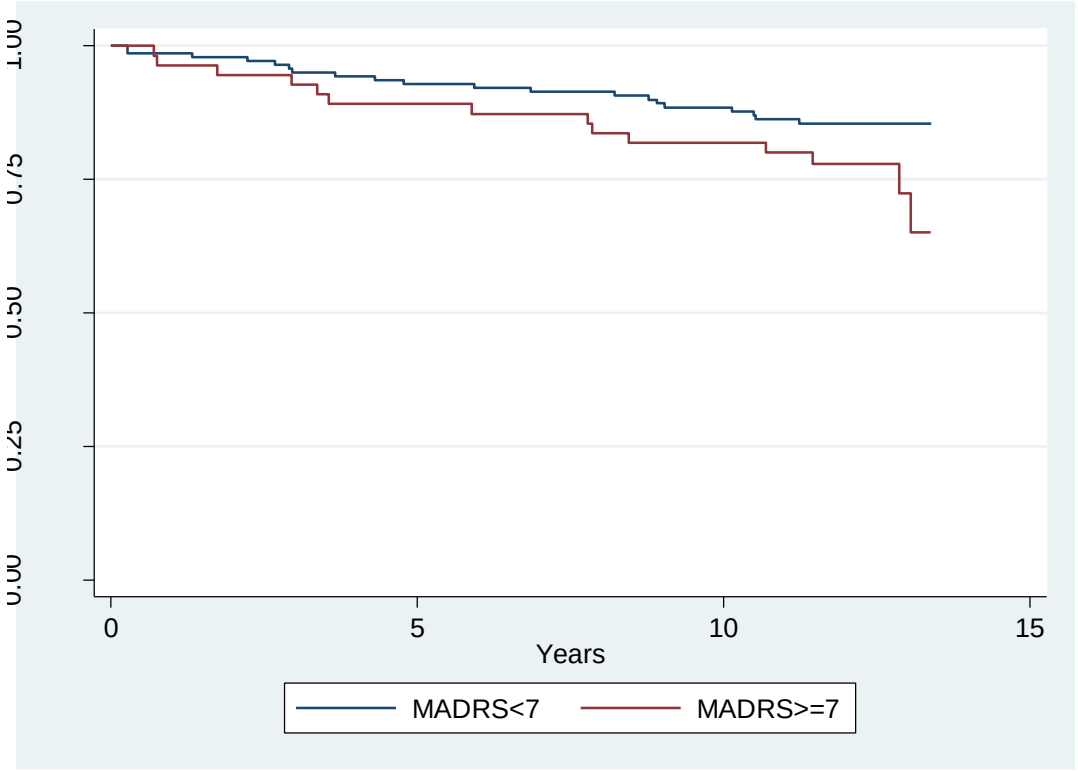

Post-stroke fatigue and depression are related to mortality in young adults

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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.

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

Young stroke patients need information on prognosis, including factors related to fatigue or depression, to make informed choices about vocation and employment. Among old stroke patients it has been shown that both fatigue[4] and depression[5] are associated with mortality. However, little is known about the effect of fatigue or depression on survival in young adults with ischemic stroke.

Here we present data on the effect of fatigue and depression measured on average 6 years after the index stroke and subsequent mortality. We hypothesized that fatigue and depression are associated with increased mortality in young adults with ischemic stroke irrespective of stroke severity.

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.[6] 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.[7]

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).[8 9] 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 ≥5.[10]

Depressive symptoms were quantified using Montgomery-Åsberg Depression Rating Scale (MADRS) at the follow-up.[11] PSD was defined as MADRS score ≥ 7. [12 13]

Subsequent survival state was registered by examining the official population registry by the first of August 2011. The study was approved by the local Ethics committee.

Statistics

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

Results

A total of 232 patients had first-ever ischemic stroke. At the time of invitation 209 patients were alive and the present study includes 190 patients; 81 (43%) females and 109 (57%) males. Mean age on follow-up was 48 years. During a subsequent mean follow-up time of 12.4 years 32 (16.8%) patients had died. (The mean total follow-up time since the index stroke was 18 years).

Univariate analyses showed that mortality was associated with being unmarried, unemployed, alcoholism, diabetes mellitus, myocardical 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 <5and ≥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 ≥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.[14 15] Likewise others have reported depression to be associated with mortality in older stroke patients.[5 16]

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. A study including older stroke patients reported post-stroke fatigue to be associated with diabetes mellitus, and myocardial infarction.[14] Both diabetes mellitus and myocardial infarction are diseases associated with mortality in young adults with ischemic stroke.[1] 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.[5 14] It is possible that there is a more direct link between depression and mortality than between fatigue and mortality. Possible mechanisms include suicide, alcoholism and less focus on healthy lifestyle. The weak correlation between smoking and depression among our patients hints to the presence unhealthy lifestyle among depressed patients.

On univariate analyses, we found that depression was mostly linked to psychosocial factors whereas fatigue was linked to a wider set of factors including both psychosocial factors and specific diseases such as diabetes mellitus and myocardial infarction. Similar findings have been disclosed among older stroke patients.[5 14] This shows that there is a multifactorial basis for post-stroke fatigue. Careful investigations are needed to determine the

cause of fatigue and target treatment both to improve general health and survival. Depression seems mostly confined to psychosocial factors. Alcoholic abuse should be considered as should unhealthy lifestyle which may need particular attention in depressed patients with ischemic stroke.

The strengths of this study are the population-based approach and the long-term follow-up period. A weakness is that patient finding was done retrospectively which may have affected both case finding and case ascertainment. Another weakness is that we have no data on the cause of death.

In 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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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
	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[1] 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

[1] 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
Introduction			
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
Methods			
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
Results			

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	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	na
		(c) Summarise follow-up time (eg, average and total amount)	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	5-6
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
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
Other information			
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.

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Abstract

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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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The study of stroke among young people is important for several reasons. The etiology of stroke is much more diverse and risk factors for stroke differ between young and old patients and may indicate separate approaches as to treatment. Stroke in young adults provides an opportunity to study stroke in general because of less comorbidity than in old patients. Fatigue has been recognized as a disabling symptom in non-depressed stroke patients.[4] Young stroke patients need information on prognosis, including factors related to fatigue or depression, to make informed choices about vocation and employment. Among old stroke patients it has been shown that both fatigue[5] and depression[6] are associated with mortality. However, little is known about the effect of fatigue or depression on survival in young adults with ischemic stroke.

Here we present data on the effect of fatigue and depression measured on average 6 years after the index stroke and subsequent mortality. We hypothesized that fatigue and depression are associated with increased mortality in young adults with ischemic stroke irrespective of stroke severity.

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.[7] 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.[8]

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

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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).

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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.[15 16] Likewise others have reported depression to be associated with mortality in older stroke patients.[6 17 18 19]

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. Studies including older stroke patients reported post-stroke fatigue to be associated with diabetes mellitus, and myocardial infarction.[15 20] Both diabetes mellitus and myocardial infarction are diseases associated with mortality in young adults with ischemic stroke.[1] 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.[6 15] It is possible that there is a more direct link between depression and mortality than between fatigue and mortality. Possible mechanisms include suicide, alcoholism and less focus on healthy lifestyle. The weak correlation between smoking and depression among our patients hints to the presence unhealthy lifestyle among depressed patients.

On univariate analyses, we found that depression was mostly linked to psychosocial factors whereas fatigue was linked to a wider set of factors including both psychosocial factors and specific diseases such as diabetes mellitus and myocardial infarction. Similar findings have been disclosed among older stroke patients.[6 15] This shows that there is a multifactorial basis for post-stroke fatigue. Careful investigations are needed to determine the cause of fatigue and target treatment both to improve general health and survival. Depression seems mostly confined to psychosocial factors. Alcoholic abuse should be considered as should unhealthy lifestyle which may need particular attention in depressed patients with ischemic stroke.

We found age to be associated with increased mortality on univariate analysis, but this association disappeared on Cox regression analyses. Others have found increasing age to be associated with higher mortality among young ischemic stroke patients.[2 3]

The strengths of this study are the population-based approach and the long-term follow-up period. A weakness is that patient finding was done retrospectively which may have affected both case finding and case ascertainment. Another weakness is that we have no data on the cause of death or the use of antidepressive medication. Risk factor profile and stroke treatment have changed since 1988 to 1997, and this should be taken into account when interpreting the results.

In 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.

Acknowledgements: none

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
	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[1] 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

[1] 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
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Post-stroke fatigue and depression are related to mortality in 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.

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

The study of stroke among young people is important for several reasons. The etiology of stroke is much more diverse and risk factors for stroke differ between young and old patients and may indicate separate approaches as to treatment. Stroke in young adults provides an opportunity to study stroke in general because of less comorbidity than in old patients. Fatigue has been recognized as a disabling symptom in non-depressed stroke patients.[4] Young stroke patients need information on prognosis, including factors related to fatigue or depression, to make informed choices about vocation and employment. Among old stroke patients it has been shown that both fatigue[5] and depression[6] are associated with mortality. However, little is known about the effect of fatigue or depression on survival in young adults with ischemic stroke.

Here we present data on the effect of fatigue and depression measured on average 6 years after the index stroke and subsequent mortality. We hypothesized that fatigue and depression are associated with increased mortality in young adults with ischemic stroke irrespective of stroke severity.

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.[7] 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.[8]

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).[9 10] 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 ≥5.[11]

Depressive symptoms were quantified using Montgomery-Åsberg Depression Rating Scale (MADRS) at the follow-up.[12] PSD was defined as MADRS score ≥ 7. [13 14]

Subsequent survival state was registered by examining the official population registry by the first of August 2011. The study was approved by the local Ethics committee.

Statistics

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

Results

A total of 232 patients had first-ever ischemic stroke. At the time of invitation 209 patients were alive and the present study includes 190 patients; 81 (43%) females and 109 (57%) males. Mean age on follow-up was 48 years. During a subsequent mean follow-up time of 12.4 years 32 (16.8%) patients had died. (The mean total follow-up time since the index stroke was 18 years).

Univariate analyses showed that mortality was associated with being unmarried, unemployed, alcoholism, diabetes mellitus, myocardical 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 <5and ≥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 ≥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.[15 16] Likewise others have reported depression to be associated with mortality in older stroke patients.[6 17 18 19]

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 ~~s~~tudies~~y~~ including older stroke patients reported post-stroke fatigue to be associated with diabetes mellitus, and myocardial infarction.[15 20] Both diabetes mellitus and myocardial infarction are diseases associated with mortality in young adults with ischemic stroke.[1] 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.

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Competing interests: none

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	Mean (SD*)	Mean (SD)	

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* SD: standard deviation

[1] Montgomery-Åsberg Depression Rating Scale

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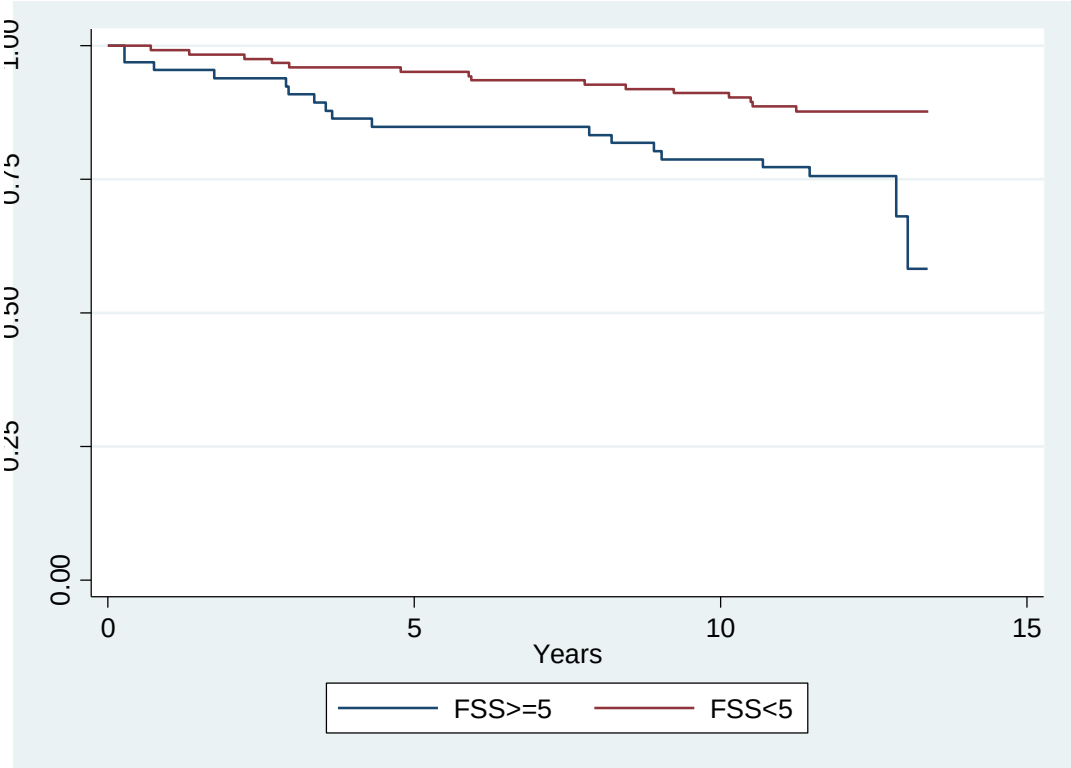

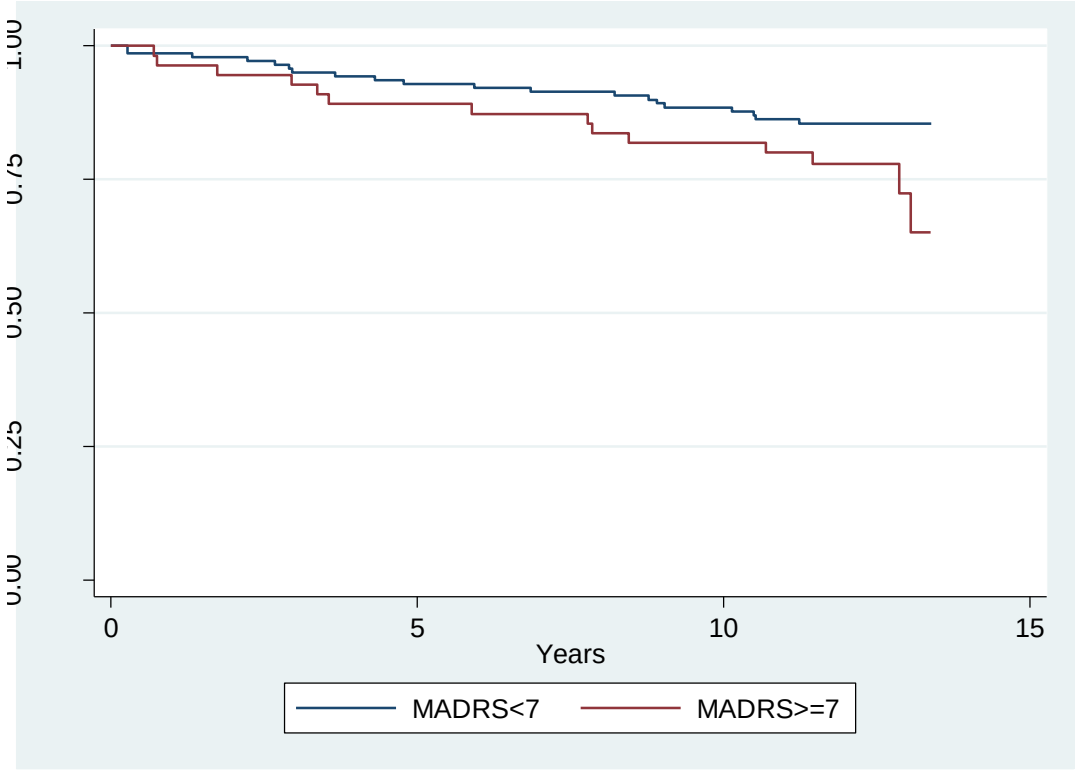
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

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
Introduction			
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
Methods			
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
Results			

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	5
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	na
		(c) Summarise follow-up time (eg, average and total amount)	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	5-6
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	na
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
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
Other information			
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.