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This is the accepted version of a paper published in *Scandinavian Journal of Public Health*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Lindner, H., Montgomery, S., Hiyoshi, A. (2020)

Risk of depression following traumatic limb amputation: a general population-based cohort study

Scandinavian Journal of Public Health, 48(3): 289-293

<https://doi.org/10.1177/1403494819868038>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

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Title: Risk of depression following traumatic limb amputation– a general population-based cohort study

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Word count: 1279 (excluding title page, abstract, references, figures and tables).

Abstract

Background Individuals with traumatic limb amputation (TLA) may be at risk of depression, but evidence for raised depression risk after TLA from longitudinal studies has been limited. It is also unknown whether physical function, cognitive function, employment prior to amputation affects depression risk. We aimed to examine longitudinal associations between TLA and depression in working age men and to explore the role of pre-amputation occupational and individual characteristics.

Methods A Swedish national register-based cohort of 189,220 Swedish men born between 1952 and 1956 and attended conscription assessments in adolescence followed from 1985 to 2009. Physical, cognitive and psychological characteristics were measured at the conscription examination and occupational information was obtained from the 1985 census.

Main outcome measures Hospital inpatient and outpatient admission for depression.

Results In total, 401 men underwent TLA and the mean age at amputation was 42.5 years (SD 7.4). Cox regression produced an unadjusted hazard ratio (and 95% confidence interval) of 2.61 (1.62-4.21) for risk of subsequent depression associated with TLA, compared with general population. Adjustment for occupational, physical, cognitive and psychological characteristics changed the association little, producing a hazard ratio of 2.53 (1.57-4.08).

Conclusion TLA was associated with an increased risk of depression in men over more than two decades of follow-up. Occupational and individual characteristics prior to amputation little changed the depression risk following amputation. We speculate that a coordinated combination of social

support and medical management may help to reduce persistent depression risk in men who experience amputation.

Keywords: amputation, traumatic, depression, cohort

Introduction

Depression after traumatic limb amputation (TLA) are often measured shortly after amputation and limited to cross-sectional studies [1,2]. Physical function and employment were reported as determinants for depression among amputees [2-5]. Low education appears to be associated with amputation and depression risk [1,6], cognitive function facilitates rehabilitation and independence [7,8] and resilience to facilitate positive emotions [5,9]. Evidence is limited whether these characteristics prior to amputation leads to a lower depression risk. Our objective was, first, to examine longitudinal association between TLA and depression, and second, to explore the role of pre-amputated occupational and individual characteristics on this association.

Methods

Study population

A cohort of men (n=284,257) who were born between 1952 and 1956 and underwent a compulsory conscription assessment between 1969 and 1976 were analysed. During this time, only those with severe illness or disability (4%) were exempted from the assessment [10]. Subjects were followed from 1st January 1985, when these men were between age 29 and 34 years until the date of depression, death, emigration or 31st December 2009, whichever occurred first.

Subjects were excluded due to: invalid data (n=2,623), emigration or death before the 1985 (n=8,397), conscription assessment ages not between 17 and 20 years (n=4,811), record of mental health conditions in conscription examination (International Classification of Diseases [ICD]-8 290-309),

hospital admission due to depression or amputation including causes other than trauma before 1985 (n=33,088), and missing data for relevant variables (n=46,118), resulting to 189,220 men with complete data. This study was approved by the Uppsala Regional Ethics Committee (Dnr 2014/324).

Measures

Traumatic amputation

The *Patient Register* holds records for all inpatient hospital discharge (from 1970 in our data) and outpatient assessment (from 2001). Incident date of all causes of TLA including all amputation levels, from digit level to complete loss, was identified using the record of primary and secondary diagnosis. ICD 8-10 codes are shown in Appendix. Separately, amputation including causes other than trauma before 1985 was identified using ICD as well as the procedure codes, and it was used to exclude individuals who had amputation before 1985.

Depression

Using the patient register, individuals with depression was identified using the record of primary diagnosis (ICD codes are shown in Appendix).

Other characteristics

Cognitive and physical function, and stress resilience in adolescence were assessed as part of the military conscription examination and described in detail in Appendix. Cognition function and stress resilience were assessed by psychologists and results were provided in the form of nine-level scores

[11]. Physical function was derived from a test using an electronically-braked bicycle ergometer.

These variables were recoded into high, moderate and low. Occupation was provided from the *Population and Housing Census* [FoB] in 1985, and it was grouped as non-manual, manual and farm workers.

Statistical analysis

Cox regression was used to calculate crude and adjusted hazard ratios and 95% confidence intervals [CI] for the association of amputation with depression. Hazard ratio is interpreted as a relative risk, which is the risk of exposed subjects compared to the subjects unexposed. Age was used as the underlying time scale, and the diagnosis of amputation was included as a time-dependent exposure status, with the value zero before amputation and one after the date of amputation. Residential region, occupation group in 1985, cognitive and physical function and stress resilience were considered as potential confounding characteristics and adjusted for in the analysis. Analyses were conducted using STATA V.14/SE (StataCorp LP, USA).

Results

In total 401 incidence of amputation was identified between 1985 and 2009 (Table 1), with the mean age of amputation was age 42.5 years (SD 7.4). In crude analysis, amputation was associated with 2.6 times risk of subsequent depression (Table2). Moderate and low cognitive function, physical fitness and stress resilience were associated with elevated risk of depression. Working for farms and manual

work was also associated with higher depression risk. When the analysis was adjusted for these characteristics, the risk of depression after amputation little changed.

Discussion

Using prospectively-recorded longitudinal data, TLA was associated with an increased risk of depression. The association was independent of the influence from occupational and individual characteristics prior to amputation.

The association of amputation with depression reported here are consistent with earlier reviews [1,2]. These reviews included both studies using diagnosis-based depression and self-reported depression. As suggested by both reviews, amputees might deny or overrate their self-reported depressive symptoms. Our result, which is diagnosis-based, may therefore serve as supportive evidence for preceding findings.

More than two-fold risk of depression after amputation remained after adjustment for the characteristics, indicating that the risk is substantial after removing the effects of physical fitness, cognitive function, stress resilience and employment. Trauma and changes in physical body are risk characteristics for depression [12] and TLA leads to permanent changes in physical appearance or functioning. Young traumatic amputees tend to get worse psychologically with increasing time since amputation as compared to older amputees [1,2,13]. Our finding therefore agrees that the risk of psychological consequences of TLA is substantial.

Physical function, cognitive function, stress resilience and employment were related to depression occurrence and rehabilitation outcomes in TLA patients [2-4,7,8,14] because physical and cognitive

function are important for prosthesis use, mobility and activity participation [14-16], and high stress resilience helps the amputees to develop new coping strategies to address their new role in society and in their employment [17]. However, in the preceding studies, these characteristics were measured after amputation and most studies focused on people with dysvascular amputation. Our study was the first to investigate the influences of pre-amputation characteristics and the depression risk following TLA was little confounded by these characteristics. This may suggest that physical, cognitive and psychological characteristics after amputation influence depression risk rather than the pre-existing characteristics. Long-term holistic care that meet physical, mental and social needs via peer support groups have shown to facilitate social support, and participation to such support groups has been reported to help to maintain cognition and stress resilience [7,18-22], which in turn may improve physical mobility in amputees [8] and reduce depression risk for amputees. Thus, interventions that may facilitate and maintenance of these factors may contribute to reduce depression risk among TLA patients.

A potential study limitation is that depression was based on diagnosis identified in- and outpatient hospital treatment, and untreated (or treated in primary care) depression was not included. As this may thus capture amputees with severe depression, the implication of our finding is substantial. Due to treatment for amputation, depression in amputees may be more likely to be identified than in general population. However, the use of primary diagnosis may have reduced the risk of bias. Although we adjusted for occupational group and residential region, we lacked information of some potential confounding factors such as living environment as well as more detailed socioeconomic characteristics [12]; thus residual confounding is possible, although the high effect size found in this study may be

unlikely to be explained entirely. As the sample was only men, our results may not be generalizable to women, but it is not implausible to expect the similar association in women.

Strengths of our study include the use of prospectively collected data and the long follow-up.

Completeness of the Patient Register is high [23]. Our study sample was at working-age and relevant characteristics have been measured prior to amputation.

In conclusion, this study provides more evidence that TLA was associated with an increased risk of depression over more than two decades of follow-up of men from age 29 to 57 years. Occupational and individual characteristics prior to amputation little changed the depression risk following amputation. We speculate that a coordinated combination of social support and medical management may help to reduce persistent depression risk in men who experience amputation.

Acknowledgment: This study received support from Örebro University Hospital Research Foundation (OLL- 488821, 429431) and the UK Economic and Social Research Council (ESRC) as grants to the International Centre for Life Course Studies (grants RES-596-28-0001 and ES/JO19119/1).

Table 1. Distribution of characteristics by amputation

	No amputation	Amputation*
	Frequency (%)	Frequency (%)
Number of amputation	188,819 (99.8)	401 (0.2)
Stress resilience		
High	50,343 (99.8)	85 (0.2)
Moderate	112,811 (99.8)	248 (0.2)
Low	25,665 (99.7)	68 (0.3)
		P = 0.017
Cognitive function		
High	52,748 (99.9)	71 (0.1)
Moderate	101,526 (99.8)	223 (0.2)
Low	34,545 (99.7)	107 (0.3)
		P < 0.001
Physical fitness		
High	89,284 (99.8)	197 (0.2)
Moderate	72,401 (99.8)	149 (0.2)
Low	27,134 (99.8)	55 (0.2)
		P = 0.758
Occupation in 1985		
Non-manual	94,330 (99.9)	115 (0.1)
Farm worker	9,647 (99.5)	46 (0.5)
Manual	84,842 (99.7)	240 (0.3)
		P < 0.001
Residential region in 1985		
Northern	29,487 (99.8)	68 (0.2)
Central	69,159 (99.8)	144 (0.2)
Southern	90,173 (99.8)	189 (0.2)
		P = 0.760
Birth year		
1952	37,611 (99.8)	71 (0.2)
1953	37,149 (99.8)	74 (0.2)
1954	36,389 (99.8)	90 (0.3)
1955	38,517 (99.8)	94 (0.2)
1956	39,153 (99.8)	72 (0.2)
		P = 0.154

n=189,220

*Individuals who had amputation at some point between 1985 and 2009 are presented in the group of amputation.

P-values are obtained from the chi-square test.

Table 2. Crude and adjusted hazard ratios for risk of depression after amputation between 1985 and 2009 for Swedish men

	Depression / n	Crude	Adjusted
Amputation			
No amputation	4,589 / 188,827	Reference	Reference
Amputation	17 / 393	2.61 (1.62, 4.21), <0.001	2.53 (1.57, 4.08), <0.001
Stress resilience			
High	1,007 / 50,428	Reference	Reference
Moderate	2,696 / 113,059	1.18 (1.10, 1.27), <0.001	1.12 (1.04, 1.21), 0.003
Low	903 / 25,733	1.77 (1.62, 1.94), <0.001	1.57 (1.42, 1.73), <0.001
Cognitive function			
High	1,027 / 52,819	Reference	Reference
Moderate	2,466 / 101,749	1.24 (1.15, 1.33), <0.001	1.22 (1.13, 1.31), <0.001
Low	1,113 / 34,652	1.65 (1.52, 1.80), <0.001	1.52 (1.39, 1.67), <0.001
Physical fitness			
High	2,011 / 89,481	Reference	Reference
Moderate	1,846 / 72,550	1.12 (1.05, 1.19), 0.001	1.03 (0.96, 1.10), 0.426
Low	749 / 27,189	1.21 (1.12, 1.32), <0.001	1.05 (0.97, 1.15), 0.247
Occupation			
Non-manual	2,182 / 94,445	Reference	Reference
Farm worker	261 / 9,693	1.15 (1.01, 1.31), 0.029	1.03 (0.91, 1.18), 0.629
Manual	2,163 / 85,082	1.10 (1.03, 1.16), 0.003	0.95 (0.89, 1.02), 0.139

n=189,220

The number of those with amputation is 393 because eight individuals had their follow-up ended the same date or before the date of amputation.

Crude and adjusted estimates are hazard ratios (95% confidence interval) and p-value.

Amputation was used as time-varying exposure status in Cox regressions. Adjusted model include all variables presented in the table and residential region in 1985.

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