Depression as a predictor of occupational transition in a multiple sclerosis cohort

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Summary

In MS, transitions between working and not-working status may occur in association with depression. This can complicate patients' ability to promptly obtain disability support due to an expectation that their functioning will improve after the depression resolves, a viewpoint that sees depression assuming a role as a causal determinant of disability. In this study, prospective data were used to model the relationship between depressive symptoms and the transition out of employment. In unadjusted analyses, depression increased the risk of transition to non-working status, HR = 1.7 (95%CI 1.3-2.3). Adjustments for ambulation status, physical and mental quality of life composite scores and fatigue impact attenuated or eliminated the association. While depression commonly occurs around the time of occupational transitions in MS, it does not appear to be an independent or direct cause of such transitions.

KEY WORDS: depression, disability, functional status, multiple sclerosis, occupational status, prospective studies

Introduction

Major depression is a major comorbidity in multiple sclerosis (MS) due to its well-known association with poorer quality of life (Wang et al., 2000; Lobentanz et al., 2004; Janssens et al., 2003; Fruehwald et al., 2001; D'Alisa et al., 2006) and elevated suicide risk (Feinstein, 1997). Depressive symptoms are also correlated with workplace presenteeism (impairment while working) in people with MS (Glanz et al., 2012). Epidemiological studies indicate that the annual prevalence of major depression in MS is 16% (Patten et al., 2003) and that its lifetime prevalence may be as high as 50% (Minden et al., 1987; Sadovnick et al., 1996; Joffe et al., 1987). These prevalence estimates are approximately three times higher than those of the general population.

Depression may be a predictor of negative transitions during the disease course. However, most studies examining the association of major depression with employment status have been cross-sectional and therefore unable to fully clarify temporal relationships. The association of depression with occupational transitions is complicated by the possibility that loss, or threatened loss, of an occupational role (including elements associated with that role such as personal identity, social status, social support and income) may increase the risk of depression. Nevertheless, it is often assumed that depression makes an independent causal contribution to occupational disability in MS. This assumption can complicate patients' ability to obtain disability benefits, due to a belief on the part of claims assessors that functioning may improve once an episode of depression has been treated. We sought to evaluate whether depression is actually associated with occupational transitions using prospective data, with and without adjustment for other aspects of health status. An opportunity to evaluate these associations arose from the Canadian Impact of MS (CIMS) study.

Materials and methods

Between 2002 and 2006 registrants at the University of Calgary MS Clinic were invited to participate in the CIMS study. Invitations were mailed to all patients registered at the clinic. This MS clinic is a population-based service covering the southern part of the Canadian province of Alberta. CIMS participants provided written informed consent, and CIMS was approved by the University of Calgary Ethics Review Board. The data collection was broadly based and not specifically focused on depression, mental health or employment. However, relevant items were included. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Rating Scale (CES-D) (Radloff, 1997). This scale provides ratings on a scale of 0 (no symptoms) to 60 (highest possible rating on all 20 items). CES-D scores of 16 or higher are generally considered indicative of clinically

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significant depression (Radloff, 1997). The CIMS questionnaire also included a self-rated version of the Extended Disability Status Scale (EDSS), which is an MS-specific impairment/disability instrument (Kurtzke, 1983). Because of concerns about the validity of these self-ratings (EDSS ratings are normally assigned on the basis of a neurological assessment), we categorized respondents simply according to whether they reported current use of an ambulation aid. CIMS also included the MSQoL-54 (an expanded version of the widely used Medical Outcomes Study Short Form, or SF-36, that also includes a set of MS-specific items) (Vickery et al., 1995). The MSQoL-54, like the SF-36 can produce a variety of composite scales, including a physical and mental health composite subscale. All these subscales were incorporated into the modeling analysis, see below, as continuous variables. The CIMS data collection also included the Fatigue Impact Scale (FIS) (Fisk et al., 1994). This scale assesses fatigue by the extent to which it creates different types of functional limitations. Several different domains of fatigue impact are assessed by the FIS, which includes cognitive, physical and social subscales. In the modeling analysis, these subscales were also treated as continuous variables. Standard demographic items were also recorded by CIMS. Occupational status was assessed using an item that asked whether the respondent had worked in the previous eight weeks.

Between 2002 and 2006, CIMS respondents were asked to complete annual follow-up ratings. A maximum number of four ratings were therefore theoretically possible, but as the cohort was a dynamic one (with some new patients being enrolled near the end of the study), many of the respondents were involved only long enough to participate in two or three interviews, or in some cases only one interview (Table I).

We used longitudinal data analysis methods (proportional hazards modeling) to characterize the relationship between depression and occupational transitions with and without adjustment for other potential determinants of those transitions. The goal of the modeling was to determine whether depression was a possible causal determinant independent of the effects of other variables. Therefore, the unadjusted effect of depression was initially examined followed by model-based adjustments for other potential determinants.

Table I - Sample size in the Canadian Impact of MS Study (CIMS).

	Total number of questionnaires returned	Total number of participants returning questionnaires
Baseline	2,053	532*
Annual 1	1,521	349
Annual 2	1,172	572
Annual 3	600	331
Annual 4	274	269
Total	5,620	2,053

* This number returned only the baseline questionnaires and could not be included in the longitudinal analysis.

Disappearance of an effect of depression in association with an adjustment of this type was interpreted as a lack of an independent effect of depression. In principle, this could occur if the effect of depression was confounded with the other health status variables or because the variables all exist on the same causal chain. The CIMS database did not provide sufficient temporal resolution to distinguish between these two possibilities. A grouped time approach to proportional hazards modeling was used. These models were fitted as generalized linear models of the binomial family using the complementary log-log link function. The models were non-parametric in the sense that time (year of follow-up) was represented using an indicator variable, thereby requiring no assumptions about the shape of the hazard function. The proportional hazards assumption was evaluated by examining the statistical significance of time by depression interaction terms using a likelihood ratio test. All analyses were carried out using Stata software (Version 12.0, College Station, TX: Stata Corporation, 2012).

Results

Data were entered by CIMS project staff and examined at that time for data entry errors and missing data. The CIMS participants numbered 2,053 and they returned a total of 5,620 questionnaires. The first interview was considered a baseline time point. At this baseline time point 974 of the participants were employed and this group was taken to be “at risk” for transition to non-working status and therefore eligible for inclusion in the study. Of these participants, 759 returned more than one questionnaire and could therefore be included in the survival analysis. The working respondents had a higher level of education, a lower frequency of depression and were more likely to be fully ambulatory than the rest of the CIMS sample (Table II). The eligible subset (n=759) closely resembled the rest of the employed cohort at baseline (Table II).

Those who were working at baseline were slightly younger, with a mean age of 42.3 years (as compared to a mean age of 50.0 years among those not working at baseline). Table III details quality of life and fatigue ratings at baseline in the overall sample and in the subset eligible for the prospective analysis. The working subset had higher MSQoL-54 composite scores (both physical and mental) and lower fatigue impact across all domains than the overall CIMS cohort (Table III).

The respondents (n=257) providing four years of data showed baseline characteristics similar to those of the entire sample. Whereas 52.5% (95%CI 50.2-54.8) of the entire sample was working at baseline, the proportion in the subset providing four years of data was a comparable 49.2% (95%CI 43.1-55.3). In the full sample at baseline the median physical health composite score was 63 [inter-quartile range (IQR) 44.7-79.2], which was identical to that of the subset providing four years of data (median=63, IQR 47.9-80.8). Median values for the mental health composite in these groups

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were 76.4 (IQR 55.7-87.4) and 78.0 (IQR 57.8-87.4) respectively. The prevalence of depression in the entire sample at baseline was 29.4% (95%CI 27.4-31.5), whereas in the subset providing four years of data it was 27.8% (95%CI 22.3-33.4).

Of the 267 respondents recruited into the cohort in 2002 and who provided a valid CES-D rating at their baseline visit, 43 (16.1%) could not be included in the prospective analysis because they only participated in a single interview. Of the remaining respondents 120 (53.3%) were lost to follow-up in the subsequent year. While this attrition rate is high, loss to follow-up in CIMS was not associated with depression (Patten et al., 2010). In the current analysis the relative risk of attrition by depression status in the first two years was 0.93 (95%CI 0.74-1.16, p=0.50). Over time, the pro-

Table II - Description of the CIMS sample and of the subset included in the prospective analysis*.

		CIMS sample (%) (n=2,053)	Employed* (n=974)	Employed and eligible for the study** (n=759)
Sex	• male	484 (23.6)	231 (23.7)	171 (22.5)
	• female	1,569 (76.4)	743 (76.3)	588 (77.5)
Marital status	• married/common-law	1,450 (73.7)	714 (73.4)	549 (72.3)
	• single	223 (11.3)	120 (12.3)	92 (12.1)
	• widowed/separated/ divorced	295 (15.0)	139 (14.3)	118 (15.6)
Highest level of education	• <high school	152 (7.5)	42 (4.3)	28 (3.7)
	• high school	488 (24.1)	192 (19.8)	143 (18.9)
	• some post-secondary, certificate or diploma	906 (44.7)	441 (45.4)	352 (46.4)
	• ≥ bachelor's degree	479 (23.6)	297 (30.6)	235 (31.0)
Employment: ever worked?	• Yes	1,876 (97.7)	--	--
	• No	44 (2.3)	--	--
Recent employment	• worked in the past 8 weeks	978 (52.3)	--	--
	• did not work in the past 8 weeks	893 (47.7)	--	--
Living arrangements	• private home	1,993 (98.1)	967 (99.7)	755 (99.7)
	• institution	27 (1.3)	--	--
	• group home (supported living)	5 (0.3)	--	--
	• no permanent residence	6 (0.3)	3 (0.3)	2 (0.3)
Depression: CES-D>15	• depressed	552 (29.4)	216 (22.5)	160 (21.5)
	• not depressed	1,324 (70.6)	744 (77.5)	585 (78.5)
Self-rated EDSS***	• requires ambulation aid	585 (32.9)	85 (9.7)	71 (10.4)
	• does not require ambulation aid	1,191 (67.1)	794 (90.3)	614 (89.6)

* excluding 893 subjects who reported that they did not work in the eight weeks preceding their baseline interview.

** provided data from at least one follow-up assessment.

*** as the EDSS is not a self-rated instrument, the analog questionnaire included in CIMS was dichotomized at two levels depending on the need for an ambulation aid, which corresponds approximately to an EDSS score ≥ 6.

Table III - Additional characteristics of the CIMS sample and of the subset included in the prospective analysis*.

		CIMS sample (%) (n=2,053)	Employed* (n=974)	Employed and eligible for the study** (n=759)
Mean age in years (standard deviation)		46.2 (11.3)	42.3 (9.3)	42.5 (9.1)
Median MSQoL-54 (inter-quartile range)	• Physical health composite	63.0 (44.6-79.2)	74.1 (58.1-84.7)	74.3 (59.2-85.0)
	• Mental health composite	76.3 (55.5-87.4)	81.1 (65.1-89.5)	82.1 (67.1-89.9)
Fatigue Impact Scale (inter-quartile range)	• Cognitive subscale	9 (3-16)	6 (2-12)	6 (2-12)
	• Physical subscale	14 (7-23)	9 (4-17)	9 (4-17)
	• Social subscale	18 (7-33)	11 (4-23)	11 (4-23)

* excluding 893 subjects who reported that they did not work in the eight weeks preceding their baseline interview.

** provided data from at least one follow-up assessment.

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portion of the sample that was working diminished progressively (Fig. 1).

Median scores on the MSQol-54 physical and mental health composite subscales (Fig. 2) provided no convincing evidence of diminishing health status in the cohort over the follow-up interval. Nor was there any clear evidence of an overall increase in depressive symptoms (Fig. 3).

The hazard ratio (HR) quantifying the effect of depression at baseline on transition to non-working status was 1.7 (95%CI 1.3-2.3), a statistically significant association (Wald test p<0.001). Neither sex, age, marital status, nor level of education were associated with transition to non-working status. However, the use of an ambulation aid (HR 2.0, 95%CI 1.4-2.9) and all three of the fatigue-impact subscales predicted this transition in bivariate analyses. When the FIS subscales were included individually as continuous variables in proportional hazards models Wald tests for their effects all produced p-values ≤ 0.001.

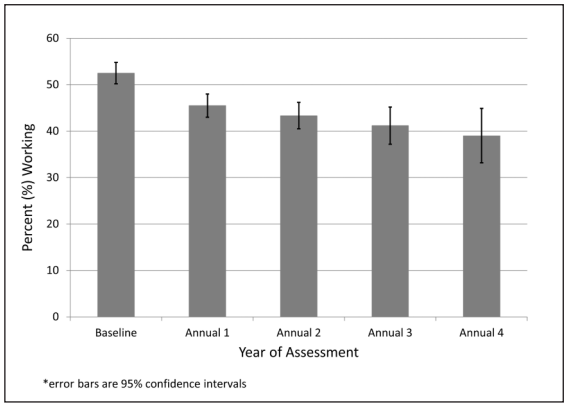

Figure 1 - Percent of CIMS cohort working, by year*.

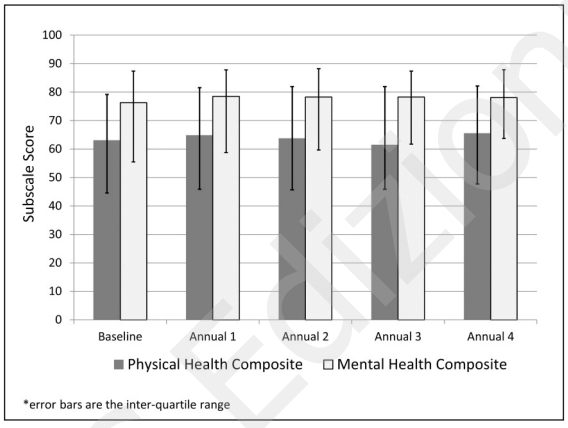

Figure 2 - Median MSQoL-54 composite scales, by year*.

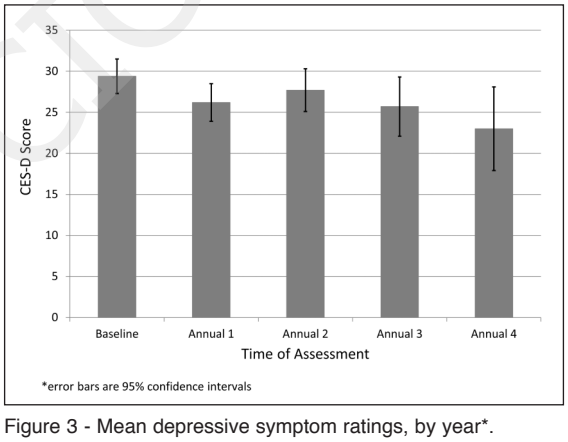

Figure 3 - Mean depressive symptom ratings, by year*.

There was significant collinearity between the various FIS subscales, such that p-values were unstable when multiple scale scores were included in a model. This was confirmed by a correlation analysis. For example, Spearman's rho for the physical and social fatigue impact subscales was 0.82. Similarly, the MSQoL-54 mental (Wald test, p=0.001) and physical (Wald test, p<0.001) composite scores predicted the occupational transition when examined in separate models. We sought to explore whether the association between depression and employment transition was confounded by demographic variables or the various fatigue and MSQoL-54 scores. This was accomplished by adding these variables one at a time to the proportional hazards models that included the depression indicator and then determining whether these adjustments altered the association between depression and the occupational transition.

Inclusion of demographic variables like age, sex, marital status and educational status did not change the HR of depression, which remained 1.7 after each of these adjustments. Similarly, inclusion of ambulation status and depression simultaneously did not change the HR for depression. Inclusion of FIS and MSQoL-54 subscale scores tended to weaken the effect of depression. For example, inclusion of the cognitive fatigue impact subscale reduced the HR for depression to 1.4 (95%CI 1.0-2.0, p=0.05). Inclusion of the physical fatigue impact subscale reduced it to 1.3 (95%CI 0.9-1.8, p=0.13) and the social fatigue impact subscale reduced it to 1.1 (95%CI 0.8-1.6, p=0.53). It is to be noted that the association of depression with the employment transition became non-significant after each adjustment. Simultaneous inclusion both of the MSQoL-54 composite scales (physical and mental health) reduced the depression HR to 1.2 (95%CI 0.8-1.9, p=0.39), and it remained non-significant. With adjustment for the mental health composite alone, the HR was 1.4 (95%CI 0.9-2.0, p=0.14) but with inclusion of the physical composite score alone the HR for depression became 1.0 (95%CI 0.7-1.4, p=0.85). Addition of sex and age to these models did not change the results. For example, with addition of age and sex to the model adjusting for the MSQoL-54 physical composite score, the HR remained 1.0.

In order to explore the impact of depression with simultaneous adjustment for multiple covariates, a model including the physical composite score, age and sex was fitted. In this model, depression was not significantly associated with the occupational transition (HR 1.3, 95%CI 0.8-2.0, p=0.34). The only variable attaining statistical significance was the MSQoL-

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54 physical composite score (p=0.01). The HR was 0.98, indicating a 2% increase in risk of the transition in association with each one-point (lower) rating on the scale.

Discussion

Depression is a major cause of disability in the general population. Major Depressive Disorders is ranked as the second leading cause of years lived with disability in the world (after back pain), according to the 2010 update of the Global Burden of Disease study (Vos et al., 2012). Clinically, it is also apparent that depression often occurs around the time of occupational transition in MS, an association confirmed by the elevated unadjusted HR observed in this study. It may therefore be tempting to assume that depression is a major causal contributor to these transitions. The results presented herein challenge this assumption, suggesting that depression is better conceptualized as an associated factor that does not necessarily have independent effects.

One of the most important factors in causal judgment in epidemiology is the temporal relationship between determinants and outcomes. Obviously, causes must precede effects (Rothman et al., 2008). This study was largely able to clarify the temporal relationship by the use of restriction. The study examined the predictive value of depressive symptoms at baseline when all of the subjects were working. Depressive symptoms predicted transition to non-working status in the absence of adjustment for other variables. However, after adjustment for other variables, both fatigue ratings and MSQoL-54 ratings, there was a substantial weakening or disappearance of the association. Adjustment for the physical composite score eliminated the association entirely. These results do not support the idea that the association of depression with transition to non-working status can be regarded as an independent causal association. Instead, the results suggest that the effects of depression on employment transitions are confounded or mediated by other manifestations of MS. A qualification is that all of the predictive variables (depression ratings, MSQoL-54 and FIS scores) were correlated with one another. At some level, these various measures may reflect overlapping dimensions of underlying disease-related changes.

These findings validate the idea that depression may be a marker, or indicator, of subsequent functional transitions, even if it cannot be regarded as an independent causal determinant. One may speculate that this is because the stress and uncertainty associated with struggling to maintain occupational functioning may begin to exact a toll on patients' emotional status before the actual transition occurs or because depression and fatigue are closely intertwined with other symptoms and impairments in MS. However, the analysis does not substantiate the idea that disability benefits should be withheld when depression is present in the hope that functional capacity will return once the depression resolves.

The strong effect of physical functioning and fatigue on one aspect of functioning (work) are consistent with a broader body of literature examining impairment in MS. For example, using data from the Lorraine MS Cohort, Debouverie et al. reported that SF-36 physical function and FIS physical fatigue ratings were associated with subsequent progression of EDSS scores (Debouverie et al., 2008), which replicated earlier reports also from prospective studies (Baumstarck et al., 2013; Visschedijk et al., 2004). A similar association was reported by Benito-León et al. (2013) using a disease-specific health-related quality of life scale, the Functional Assessment in Multiple Sclerosis (Cella et al., 1996).

Physical function scores and fatigue scores were found to be correlated in the CIMS data, as in previous studies (Lobentanz et al., 2004). These correlations may reflect complex interconnections between the various manifestations of MS. Drulovic et al. (2013) examined changes in fatigue scores during rehabilitation in a Serbian clinic and found that the physical health composite score and the cognitive functioning domains of the MSQoL-54 predicted less positive outcomes of a fatigue management intervention. These results are relevant to those reported in the CIMS because fatigue is regarded as one of the most disabling symptoms of MS (Fisk et al., 1994). Janssens et al. (2003), in a cross-sectional analysis, found evidence that depression and anxiety may modify the relationship between impairment and the physical health scale of the SF-36. This result suggests that a possible effect of depression on disability may be mediated through more negative perceptions of physical functioning among depressed persons at the same EDSS level. This possibility does not contradict the major finding of this study: the lack of an independent effect of depression on a functional transition, but it does raise the possibility that depression may have an indirect effect on functioning, by altering perceptions of physical functioning.

The extent to which these findings may be generalizable outside of the MS population is unclear. Holden and Isaac (2011) recently demonstrated that physical health composite scores from the SF-36 predicted depression in both MS and rheumatoid arthritis, but that the prevalence of depression was higher in MS despite this adjustment. The association between physical function scores and depression in rheumatoid arthritis suggests that perceived physical function may explain a component of the impact of depression on disability in this (and potentially other) populations. Additional studies are needed to examine these associations in various populations.

There are limitations associated with this study. One is that strong (i.e. neurologist-rated) information on disease activity or neurological impairment was not available. Also, although the CIMS collected data on working status, it did not collect detailed information on the types of jobs held by the respondents, their working hours or any specific difficulties they may have been having with their occupational functioning. The measure of depression employed in the study, the CES-D

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scale, is a self-report scale. It would have been preferable to have a more detailed assessment of mood status such as a fully or semi-structured psychiatric diagnostic interview. As the analysis was conducted using an existing database the study design did not include specialized procedures to ensure retention of subjects in the cohort. For this reason, the attrition rate was high, creating an inevitable vulnerability to bias. The survival analysis was able to include all subjects with at least one assessment during follow-up.

In spite of these limitations, this analysis suggests that depression is not an independent factor determining transitions to non-working status in people with MS. Depression is perhaps better viewed as a complex associated feature of this transition, itself likely having a complex etiology. It is likely that the occurrence of depression is related to stress and perceived threat and loss among those anticipating the transition or struggling to maintain their occupational engagements. It may also reflect interconnections between depression and aspects of neurological progression in people with MS.

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