ORIGINAL ARTICLE

What Happens to the Worried Well? Follow-Up of Subjective Cognitive Impairment

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ABSTRACT: ***Background:*** Increasing concern around perceived neurocognitive decline is increasing the number of referrals to specialists and anxiety for patients. We aimed to explore the likelihood of the "worried well" experiencing neurocognitive decline and developing a neurological diagnosis. ***Methods:*** A total of 166 "worried well" patients who attended the Rural and Remote Memory Clinic (RRMC) between 2004 and 2019 were included in this study. Demographic, health, social, and behavioral factors were measured at the initial visit. Mini-Mental State Examination (MMSE), Center for Epidemiologic Studies Depression Scale (CESD), and Functional Activities Questionnaire (FAQ) scores were measured and compared at initial assessment and at 1-year follow-up. MMSE scores over time were assessed with a mean follow-up of 2.95 years (SD 2.87). ***Results:*** No statistically significant difference was seen in MMSE, CESD, or FAQ scores when comparing clinic day to 1-year follow-up, and no consistent pattern of MMSE score over time was seen. Of the 166 patients with subjective cognitive impairment (SCI) on initial assessment, 5 were diagnosed with Alzheimer's disease (AD) at 8.5, 3.5, 5, 3, and 1.75 years; 2 were diagnosed with MCI at 1 and 2 years; 1 was diagnosed with vascular cognitive impairment at 5 years; and 1 was diagnosed with frontotemporal dementia (FTD) at 0.5 years. ***Conclusion:*** The likelihood of a patient with SCI developing a neurological diagnosis is reassuringly low (9/166), but not irrelevant. This, along with the benefits of early diagnosis and treatment for dementia, leads us to believe that patients with SCI should still be seen in follow-up at least at the 1-year mark.

RÉSUMÉ : Que se passe-t-il vraiment avec les « inquiets asymptomatiques » ? Un suivi d'individus atteints de troubles cognitifs subjectifs. ***Contexte :*** Au sein de la population, la préoccupation croissante des individus quant à un certain déclin neurocognitif a pour effet d'augmenter le nombre d'orientations vers des spécialistes ainsi que leur niveau d'anxiété. Nous avons donc voulu explorer la probabilité que des « inquiets asymptomatiques » (*worried well*) fassent l'expérience d'un déclin neurocognitif et qu'on établisse chez eux un diagnostic de trouble neurologique. ***Méthodes :*** Au total, nous avons inclus dans cette étude 166 patients dits « inquiets asymptomatiques » ayant fréquenté entre 2004 et 2019 une clinique de la mémoire en région rurale ou éloignée. Des facteurs démographiques, sanitaires, sociaux et comportementaux ont été mesurés à l'occasion de leurs premières visites. Leurs scores au *Mini Mental Status Examination* (MMSE), à l'échelle du *Center for Epidemiologic Studies Depression* (CESD) et au *Functional Assessment Questionnaire* (FAQ) ont été mesurés lors d'une première évaluation. On les a ensuite comparés à ceux obtenus au moment d'un suivi 12 mois plus tard. À noter que les scores au MMSE ont été évalués au fil du temps en fonction d'un suivi moyen de 2,95 ans (écart type = 2,87). ***Résultats :*** Si on compare les scores initiaux à ceux obtenus à l'occasion d'un suivi 12 mois plus tard, aucune différence notable sur le plan statistique n'a été observée en ce qui concerne le MMSE, l'échelle du CESD et le FAQ. De plus, aucune tendance constante n'a émergé au fil du temps en ce qui regarde les scores au MMSE. Parmi tous les patients atteints de troubles cognitifs subjectifs (TCS) lors d'une évaluation initiale, on a fini par en diagnostiquer 5 avec la maladie d'Alzheimer (MA) au bout de 8,5, 3,5, 5, 3 et 1,75 ans. Précisons que 2 autres patients ont reçu un diagnostic de trouble cognitif léger au bout d'un an et deux ans tandis qu'un patient a reçu un diagnostic de trouble vasculaire cognitif au bout de 5 ans et un autre un diagnostic de démence frontotemporale au sixième mois. ***Conclusion :*** La probabilité que des patients atteints de TCS reçoivent un diagnostic de trouble neurologique est à la fois faible et rassurante (9/166) mais pas sans importance. Cette constatation, tout comme les bénéfices d'un diagnostic précoce et d'un traitement destiné à la démence, nous amènent à penser que ces patients devraient encore être rencontrés lors d'un suivi effectué au moins après 12 mois.

Keywords: Dementia, Worried well, Subjective cognitive impairment

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Introduction

The prevalence of dementia and of subjective cognitive impairment (SCI) is increasing.[1] This indicates a laudable increase in awareness of dementia's presentation and its impact on patients, but also an increased burden on the healthcare system and healthcare providers.[1] Alzheimer's disease (AD) is predicted to increase in incidence in the coming decades due to more accurate diagnosis and aging of the population.[2] Contrastingly,

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some population-based studies demonstrate a trend of decreasing incidence of dementia.[3,4] Nonetheless, public awareness of AD along with its burdens and its symptoms is increasing. AD is quickly emerging as a particularly feared condition, creating anxiety and concern in the general population.[5] These concerns are especially common among middle-aged and older adults with first-degree relatives who have been diagnosed with AD.[6] In addition to the impact on the general population, this disease and its increasing prevalence has a significant impact on primary care providers and specialists. The number of referrals to specialists for memory complaints has become disproportionate to dementia diagnoses.[1] Additionally, epidemiological studies have shown that many people with dementia do not have a diagnosis.[7] This is known as the diagnosis gap, and indicates a need for improved detection of dementia.[1,7] In the majority of cases, the diagnosis is largely based on clinical evaluation.[1] Due to this, factors increasing patients' risk need to be identified to narrow the number of patients referred, and to ensure that those with dementia are diagnosed and receive prompt treatment.

Some factors that have already been associated with AD risk include older age and lower Mini-Mental State Examination (MMSE) score. Higher levels of education and working at least part time may be associated with an increased chance of presenting with cognitive complaints. This may be due to increased awareness of the impact of dementia and memory changes becoming more apparent due to consistent routines and tasks, respectively.[1] Depression and other psychiatric illnesses may also be risk factors for dementia. Depression can be both an early symptom of dementia, and a contributor to memory concerns.[1] There are also similarities between patients with dementia and patients with depression, as apathy often develops in both.[1] Depression is an important factor to consider when studying patients with suspected cognitive decline, as up to 50% of patients with AD also have depression.[8] This comorbidity impacts the patient's quality of life and clinical presentation, and worsens the caregiver burden.[8] A study of cognitive decline in rural and remote populations found that a history of hypertension and decreased ability to perform daily activities predicted greater cognitive decline 1 year later.[9]

SCI has increasingly been investigated as a potential risk factor for the development of dementia. The "worried well", a term used to describe individuals with SCI, refers to people who are concerned that they may have dementia, but are neurologically normal relative to others in their demographic upon examination and testing.[1] Psychological and environmental factors may play a role in these concerns, as this group is more likely to have relatives with dementia, or other personal relationships with dementia patients.[1] SCI has been identified as a risk factor for mild cognitive impairment.[1] It is important to note that the pathologic changes that occur in AD patients often take place years before symptoms develop.[10] Biomarker and imaging studies support the idea that pathological processes may begin more than a decade before a diagnosis of dementia is made.[11]

Based on the information gathered to date, psychiatric illness and psychological factors may be predictors of SCI, or may independently lead to memory concerns.[1] Psychiatric symptoms may also overlap with behaviors present in the early stages of dementia.[1] It has been established that long-term, severe worries surrounding dementia are associated with decreased psychological well-being, as well as poorer physical health.[12] Patients with dementia also clearly benefit from early assessment and diagnosis.[8] It is crucial that the association between SCI and objective cognitive impairment be established, to better understand SCI as a potential predictor of dementia diagnosis to both improve care for patients in need and to decrease the burden on the healthcare system. We aimed to explore measures of cognitive function, function in general, and depressive symptoms through comparing the MMSE, FAQ, and Center for Epidemiologic Studies Depression (CESD) scores, respectively, at clinic day and at 1-year follow-up. In addition, we aimed to explore the MMSE scores over time for those who were followed up long term, as well as the diagnoses given to some of these patients.

Methods

A total of 672 consecutive patients were seen for the initial assessment at the Rural and Remote Memory Clinic (RRMC) between March 2004 and June 2019, 166 of whom were neurologically and neuropsychologically normal at clinic day and, therefore, included in this analysis. 54.8% of patients returned for follow-up. Patients were followed for between 1 and 15.25 years, with a mean follow-up of 2.95 years (SD 2.87). Follow-up appointments occurred between May 2004 up to and including May 2020. Data collection occurred simultaneously. The eligibility criteria for participation in this study were patients presenting to the RRMC within the timeframe of data collection deemed to have SCI at initial assessment and no other neurological diagnosis. The University of Saskatchewan's RRMC provides an interdisciplinary assessment for rural patients with memory concerns from across Saskatchewan.[1] The team involved at the initial visit consists of a neurologist, a physiotherapist, a dietician, a nurse, and a neuropsychology team. The patient undergoes neuropsychological testing and a standard workup for reversible causes of memory concerns.[1] This workup includes a complete blood count (CBC), electrolytes including calcium, thyroid-stimulating hormone (TSH), vitamin B12, neuroimaging, and other investigations when indicated.[1] The neuropsychological battery includes measures of premorbid ability, attention, speeded mental processing, receptive and expressive language, visuospatial abilities, executive function, and verbal and visual memory.[1] The RRMC began operating in 2004 and is located in the University of Saskatchewan in Saskatoon. The multidisciplinary staff at the RRMC assess and provide care to rural patients with cognitive impairments. The assessments take one full clinic day and follow-up assessments are conducted at 6 weeks, 12 weeks, 6 months, 1 year, and then annually, with added appointments in between as clinically needed. Clinical and evaluation data are centrally managed to enhance data quality and accessibility, and to facilitate interdisciplinary analyses.[13] The neuropsychological testing battery is approximately 2 h. More detailed information regarding the RRMC can be found in previous publications.[13–16]

Data collection at initial visit includes age, sex, years of formal education, MMSE score, CESD score, FAQ score, Self-Rating of Memory Scale, alcohol consumption, marital status, hours per week of work, past medical history, sleep concerns, possession of a driver's license, and information regarding a family history of memory concerns.[1] The assessment team agrees on a diagnosis, which is delivered to the patient at the end of the clinic day.[1]

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A diagnosis of SCI is given if the following criteria are met: no clinical evidence of neurologic disease; normal neuroimaging; and normal performance on neuropsychological testing relative to normative comparison standards that are adjusted for demographic variables, which include age, sex, and education.[1] The patients with a diagnosis of SCI at initial assessment were included in this study, as they were cognitively normal at clinic day. We then compared MMSE, FAQ, and CESD scores at clinic day to those at the 1-year follow-up and examined all of the MMSE scores collected at follow-up appointments at various times for each patient to determine if there was a pattern present. Statistical analyses were conducted using SPSS version 27.[17]

The MMSE has been shown to be a reasonable screening tool for assessing possible dementia in the community and primary care.[18] The neurological examination conducted at clinic day also includes relevant features of a motor exam, which has been demonstrated to be relevant to SCI.[19] Ability to perform daily activities can be measured by many scales, one of which is the Functional Activities Questionnaire (FAQ).[20] The FAQ has been shown to have internal consistency, reliability, and diagnostic validity.[20] Other scales, such as the Scale of Instrumental Activities of Daily Living have similar characteristics, but the FAQ is superior in terms of specificity and sensitivity. The FAQ is also less influenced by sex and age.[20] Studies have shown that using the CESD is an accurate and valid way to screen for depression in the general population.[21]

The outcomes assessed include a significant change in MMSE, CESD, and FAQ scores or lack thereof, and subsequent neurological diagnosis at follow-up or continued SCI designation. Lifestyle and overall health-related variables are outlined in Table 1. Information on these variables was collected by surveying the patients on clinic day. Age may be a potential confounding variable. Potential bias was avoided by analyzing the information without any patient identifiers. Additionally, those that administered the testing of the patients did not analyze the data.

Descriptive analyses were completed using frequencies, measures of central tendency, and variability. The two times (clinic day and 1-year follow-up) were compared using paired sample *t*-tests for continuous variables. Case summaries were used to build the profiles of the nine patients who developed a neurologic diagnosis. Ethics approval was obtained from the University of Saskatchewan Biomedical Research Ethics Board.

Results

The population of 166 patients with SCI had a higher proportion of females than males. The education level of the patient population was predominantly a high school diploma or more/postsecondary education. Most patients were married or common law, owned their house, had a valid driver's license, and did not experience problems due to drug use. The number of times per week that the patients exercised varied, but most exercised one or more times per week. Most of the patients had been smokers at some point, but a small portion of the patients were current smokers. The number of patients with a family history of dementia was similar to those without.

The majority of the 166 SCI patients had been diagnosed with arthritis. Conversely, only a small portion of the population had been diagnosed with diabetes, heart disease, kidney trouble, or stroke. The proportion of the population diagnosed with hyperlipidemia, hypertension, poor hearing, poor vision, chronic respiratory problems, head injury, stomach problems, and psychiatric problems was relatively similar to the number of those who were not diagnosed with these conditions. The average number of drinks of alcohol per week for the population assessed was 3.8 (SD 3.7), which is well under the recommended maximum for both males and females. The average age at clinic day, years of formal education, and number of times engaged in exercise per week are all included in Table 1. All variables, aside from age at clinic day, have missing values due to the data being primarily self-reported in questionnaires.

Eighty-one of the 166 cases with SCI were followed up to year 1. The results of the analysis of the scores for MMSE, FAQ, and CESD at clinic day and at 1-year follow-up showed no significant difference, as seen in Table 2. Ninety-one of the 166 patients' MMSE scores over time were examined in the second analysis, as these patients had initial clinic day MMSE scores as well as follow-up MMSE scores at various times after clinic day. No consistent pattern in MMSE scores over time was demonstrated, as seen in Figure 1.

Nine of the 166 patients developed a neurological diagnosis. These diagnoses were made between 0.5 and 8.5 years after the initial assessment. Of these, five were diagnosed with AD; two with MCI; one with vascular cognitive impairment; and one with frontotemporal dementia (FTD). One of the patients with MCI had mild vascular cognitive impairment specifically. Of the patients diagnosed with AD, three were previously diagnosed with MCI. One of the patients with AD had previously undergone chemotherapy prior to and following the clinic day. The patient with vascular cognitive impairment had a history of cardiovascular events leading up to the diagnosis that occurred after the initial clinic visit. The patient with FTD was very slow progressing, and was temporarily suspected to have FTD phenocopy syndrome due to this. These cases are detailed in Table 3.

Discussion

SCI often leads to referral to a neurologist or other specialist, and further testing to rule out a neurological diagnosis. This can put a strain on the healthcare system due to the influx of specialist consults and can cause a great degree of stress for these patients and their families. It is, therefore, important to determine whether or not these patients truly benefit from referral. Through our exploration of this topic, we were able to gain insight into the progression of the "worried well" following their initial visit to the RRMC, and whether or not they progress to having a neurological diagnosis.

Deficits related to attention that are associated with brain activation changes in early AD progression may be associated with SCI. One study showed that patients in the SCI group had increased activation in the anatomical areas in which decreased activation normally occurs during divided attention in AD patients.[9] This indicates that compensatory changes may occur in patients with SCI.[9] Patients with SCI have been shown to have a significant increase in the risk of conversion to AD compared to people without SCI.[9,22] One study found that those with SCI and those with MCI have the same risk of progression to AD.[23] This information collectively supports the suggestion that SCI may be

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Table 1: Characteristics of normal SCI patients at baseline including those who remained normal and those who received a diagnosis

	Normal at baseline ($n = 166$)	Remained normal ($n = 157$)	Received diagnosis ($n = 9$)	
Variable	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**P-value**
Age at clinic day, years	60.9 ± 12.0	60.3 ± 12.0	70.5 ± 7.9	0.01
Years of formal education	12.7 ± 3.2	12.6 ± 3.2	13. 2 ± 3.4	0.64
Number of times engage in physical activity or exercise per week	3.8 ± 3.7	3.7 ± 3.8	4.6 ± 3.3	0.57
Drinks of alcohol per week	3.0 ± 5.4	3.1 ± 5.5	1.4 ± 1.3	0.39
CESD (Depression Score)	16.9 ± 10.5	17.0 ± 10.3	15.2 ± 13.5	0.64
Functional Activities Questionnaire (FAQ) scale	4.7 ± 5.4	4.8 ± 5.5	4.1 ± 4.0	0.77
MMSE, total score/30	27.5 ± 2.8	27.5 ± 2.8	28.5 ± 1.6	0.38
Sex				
Male	75 (45.2)	72 (45.9)	3 (33.3)	0.52*
Female	91 (54.8)	85 (54.1)	6 (66.7)	
Education level				
< high school	46 (29.9)	43 (29.5)	3 (37.5)	0.69*
≥ high school	108 (70.1)	103 (70.5)	5 (62.5)	
Marital status				
Married/Common law	127 (83.6)	121 (84.0)	6 (75.0)	0.62*
Other (single, divorced, separated, widowed)	25 (16.4)	23 (16.0)	2 (25.0)	
Current housing				
Own house	132 (86.3)	126 (86.9)	6 (75.0)	0.30*
Rented house/apartment	10 (6.5)	9 (6.2)	1 (12.5)	
Other (special care, senior's high rises, group home)	11 (7.1)	10 (6.9)	1 (12.5)	
Valid driver's license				
No	10 (6.5)	10 (6.8)	0 (0.0)	1.00*
Yes	144 (93.5)	136 (93.2)	8 (100.0)	
Number of times engage in physical activity or exercise per week – grouped				
Not at all	33 (25.3)	31 (25.2)	2 (28.6)	0.32*
One–three times per week	34 (26.2)	34 (27.6)	0 (0.0)	
>3 times per week	64 (48.5)	58 (47.2)	5 (71.4)	
Ever experienced problems due to drug use				
No	142 (97.3)	134 (97.1)	8 (100.0)	1.00*
Yes	4 (2.7)	4 (2.9)	0 (0.0)	
Smoking status				
Current smoker	32 (21.3)	29 (20.4)	3 (37.5)	0.22*
Ex-smoker	58 (38.7)	57 (40.1)	1 (12.5)	
Never smoker	60 (40.0)	56 (39.5)	4 (50.0)	
Family history of dementia				
No	78 (48.8)	75 (49.7)	3 (33.3)	0.49*
Yes	82 (51.2)	76 (50.3)	6 (66.7)	
Diagnosed with arthritis				
No	28 (28.9)	27 (28.7)	1 (33.3)	1.00*
Yes	69 (71.1)	67 (71.3)	2 (66.7)	

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Table 1: *(Continued)*

Variable	Normal at baseline ($n = 166$) Mean ± SD	Remained normal ($n = 157$) Mean ± SD	Received diagnosis ($n = 9$) Mean ± SD	P-value
Diagnosed with diabetes				
No	65 (77.4)	62 (76.5)	3 (100.0)	1.00*
Yes	19 (22.6)	19 (23.5)	0 (0.0)	
Diagnosed with hyperlipidemia				
No	46 (54.1)	45 (55.6)	1 (25.0)	0.33*
Yes	39 (45.9)	36 (44.4)	3 (75.0)	
Diagnosed with heart disease/any other heart problems				
No	57 (63.3)	55 (63.2)	2 (66.7)	1.00*
Yes	33 (36.7)	32 (36.8)	1 (33.3)	
Diagnosed with hypertension				
No	48 (49.0)	45 (47.4)	3 (100.0)	0.11*
Yes	50 (51.0)	50 (52.6)	0 (0.0)	
Diagnosed with kidney trouble				
No	70 (88.6)	68 (89.5)	2 (66.7)	0.31*
Yes	9 (11.4)	8 (10.5)	1 (33.3)	
Diagnosed with poor hearing				
No	44 (51.2)	43 (51.8)	1 (33.3)	0.61*
Yes	42 (48.8)	40 (48.2)	2 (66.7)	
Diagnosed with poor vision				
No	57 (59.4)	54 (58.1)	3 (100.0)	0.27*
Yes	39 (40.6)	39 (41.9)	0 (0.0)	
Diagnosed with chronic respiratory problems				
No	46 (56.8)	44 (56.4)	2 (66.7)	1.00*
Yes	35 (43.2)	34 (43.6)	1 (33.3)	
Diagnosed with stroke				
No	67 (90.5)	64 (90.1)	3 (100.0)	1.00*
Yes	7 (9.5)	7 (9.9)	0 (0.0)	
Diagnosed with head injury				
No	50 (55.6)	48 (55.8)	2 (50.0)	1.00*
Yes	40 (44.4)	38 (44.2)	2 (50.0)	
Diagnosed with stomach problems				
No	49 (54.4)	48 (55.8)	1 (25.0)	0.33*
Yes	41 (45.6)	38 (44.2)	3 (75.0)	
Diagnosed with psychiatric/psychological problem and depression				
No	42 (51.9)	41 (52.6)	1 (33.3)	0.61*
Yes	39 (48.1)	37 (47.4)	2 (66.7)	

*Fisher's Exact Test P-values were reported due to small cell counts.

an early stage of AD occurring prior to clinical detection or diagnosis. However, other studies suggest that SCI is associated with psychological factors including health anxiety and dementia worry rather than objective cognitive impairment.[24] These studies suggest that dementia worry acts as a confounding factor in the relationship between objective memory impairment and SCI.[24] It may well be that there are two groups of patients with SCI: those who are noticing subtle changes presaging dementia and those who are not at risk for dementia, but are concerned about normal changes with age.

Biomarkers such as serum neurofilament light (NfL) have also been shown to be altered in patients with mutations prior to

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Table 2: Comparison of MMSE, CESD and FAQ Scores at Clinic Day and Year 1 for patients with SCI at initial assessment using paired *t*-test

Variable	Mean ± SD	n	Mean difference (clinic day – year 1)	t-statistic	df	P-value
MMSE clinic day	27.35 ± 2.98	81	−0.062	−0.268	80	0.790
MMSE 1 year	27.41 ± 3.08	81				
CESD clinic day	13.46 ± 7.36	63	0.381	0.347	62	0.729
CESD 1 year	13.08 ± 9.12	63				
FAQ clinic day	4.33 ± 4.47	55	0.600	0.910	54	0.367
FAQ 1 year	3.73 ± 5.63	55				

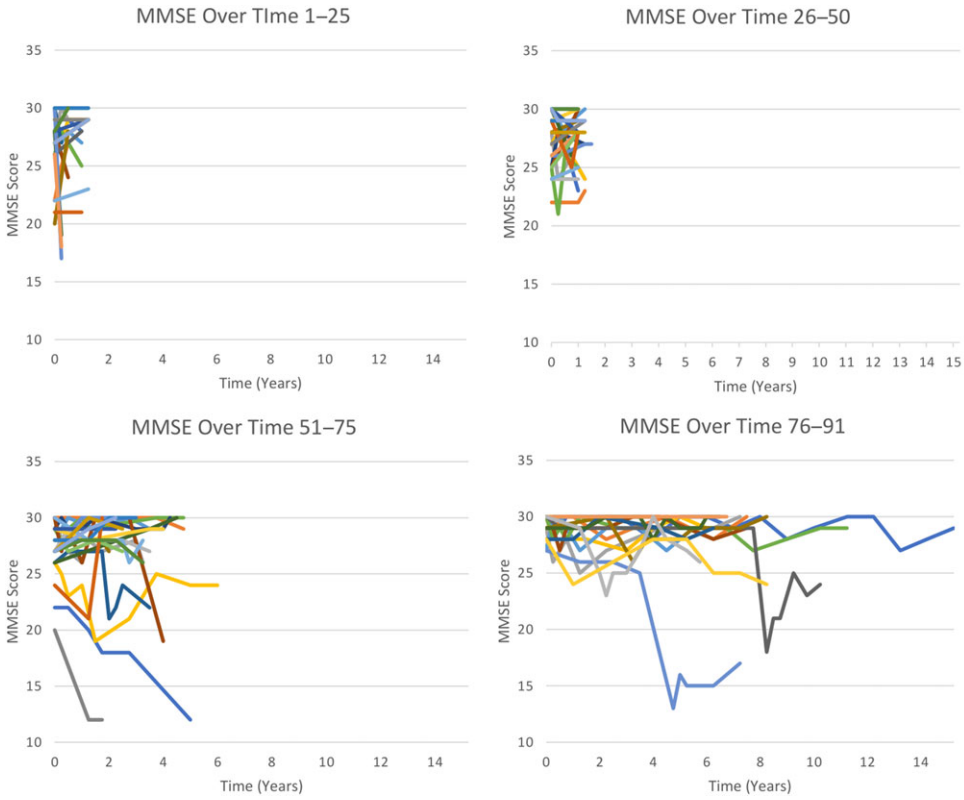

Figure 1: *MMSE scores over time of 91individual normal SCI patients separated into four groups based on length of follow-up.*

symptom onset.[25] One study demonstrated that patients with a mutation associated with familial AD, but without symptoms, have metabolic changes years before the expected onset of the disease.[10] The proteinopathies that have the most evidence supporting their role in AD biomarker changes are tau and amyloid beta.[26]

The characteristics of the patient population outlined in Table 1 likely have more to do with the age range of the patients, with a mean age of 61, rather than the SCI. However, the family history of dementia in 51.2% of patients, and the predominant high school or higher educated characteristic (70.1%) may be relevant. A family history of dementia often means that patients are more aware of the signs of cognitive decline, as well as its effects.[1] Higher levels of education are also associated with the "worried well", as their education often gives them insight into medical conditions, and they are often well-versed in utilizing critical thinking.[1]

The data we collected showed no significant overall change in MMSE, CESD, or FAQ over 1 year in patients with SCI at initial assessment, and showed no consistent pattern in MMSE scores throughout long-term follow-up. It is important to note that follow-up did not occur in all patients. Ninety-one out of the 166 patients returned for follow-up assessments, making the follow-up rate 54.8%. Patients usually informed us that they

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Table 3: MMSE scores and important events of patients with neurological diagnoses

Patient ID	MMSE scores	Other events following initial visit
Patient A	Clinic day: 30 6 months: 29 1 year: 29 2 years: 29 3 years: 29 4 years 3 months: 29 5 years 3 months: 29 7 years 9 months: 29 8 years 3 months: 19 8 years 6 months: 21 8 years 9 months: 21 9 years 3 months: 25 9 years 9 months: 23 10 years 3 months: 24	• Stopped chemotherapy for lymphoma 1 year 9 months after clinic day • MCI diagnosis 8 years 3 months after clinic day • Alzheimer's disease diagnosis 8 years 6 months after clinic day
Patient B	Clinic day: 29 2 years 3 months: 30 2 years 9 months: 28 3 years 3 months: 26 3 years 9 months: 28 4 years 3 months: 28 5 years: 28 5 years 6 months: 29 6 years 3 months: 29 7 years 3 months: 29 8 years 3 months: 30	• Mild stroke 2 years 3 months after clinic day • Myocardial infarction 2 years 4 months after clinic day • Mild vascular cognitive impairment diagnosis 3 years 3 months after clinic day • Vascular cognitive impairment diagnosis 5 years after clinic day
Patient C	Clinic day: 30 6 months: 30 1 year: 30 3 years: 30 3 years 3 months: 29 3 years 6 months: 30 3 years 9 months: 26 4 months: 28 5 years 6 months: 28 6 years: 28	• Mild vascular cognitive impairment diagnosis 1 year after clinic day
Patient D	Clinic day: 27 1 year 3 months: 26 2 years 6 months: 26 3 years 6 months: 25 4 years 9 months: 13 5 years: 16 5 years 3 months: 15 6 years 3 months: 15 7 years 3 months: 17	• Alzheimer's disease diagnosis 3 years 6 months after clinic day
Patient E	Clinic day: 29 6 months: 29 9 months: 29 1 year: 29 1 year 6 months: 29 2 years 3 months: 30 2 years 9 months: 30 3 years 6 months: 30 4 years: 28 4 years 6 months: 30 5 years: 29 5 years 9 months: 29 6 years: 30 6 years 6 months: 30	• Major depressive disorder diagnosis 3 months after clinic day • Frontal variant frontotemporal dementia diagnosis 6 months after clinic day • FTD phenocopy syndrome suspected instead of FTD 6 years after clinic day • Very slow progressing FTD diagnosis confirmed 6 years 5 months after clinic day
Patient F	Clinic day: 30 1 year 6 months: 30 3 years 6 months: 30 3 years 9 months: 22 4 years: 23 4 years 6 months: 22 5 years: 21	• Alzheimer's disease diagnosis 5 years after clinic day
Patient G	Clinic day: 29 2 years: 29 2 years 6 months: 30 3 years 6 months: 27	• MCI diagnosis 2 years after clinic day
Patient H	Clinic day: 29 6 months: 28 1 year: 30 1 year 6 months: 27 2 years: 27 2 years 9 months: 26 3 years: 22	• MCI diagnosis 1 year after clinic day • Alzheimer's disease diagnosis 3 years after clinic day
Patient I	Clinic day: 26 6 months: 27 1 year: 27 1 year 6 months: 27 1 year 9 months: 21 2 years: 22 2 years 3 months: 24 2 years 9 months: 23 3 years 3 months: 22	• MCI diagnosis 1 year 6 months after clinic day • Alzheimer's disease diagnosis 1 year 9 months after clinic day

did not wish to attend follow-up because they did not have progressing or concerning symptoms, and presumably stayed neurologically normal.

In a study comparing cognitively normal patients to patients with SCI over time, a significantly larger proportion of the SCI group developed a neurological diagnosis.[27] This supports the theory that patients with SCI, or the "worried well", are more at risk for neurological decline than the general population. We observed a subsequent neurological diagnosis in 9/166, or 5.4%, of the SCI patients analyzed. This suggests that, for the most part, those with SCI could be reassured at their initial visit, not following up or being referred further. Though this would be sufficient for most of the patients in this analysis, as the vast majority did not receive a neurological diagnosis throughout follow-up, early detection and treatment of disease would be important for those few who did receive a later diagnosis. The trouble, of course, is how to tell the difference between patients likely to remain stable and those likely to show deterioration.

As aforementioned, the pathology of AD is present long before a diagnosis can be made.[10] The early detection and treatment of AD are associated with better outcomes for patients.[8] With this being taken into account, it can be said that the optimal course of action for the "worried well" is to reassure and educate them on the low probability of their progression to a neurological diagnosis, but to nonetheless follow-up with them to ensure that they receive adequate and early care and intervention if they require it. MCI has been described as being a precursor to AD in some cases.[28] It may, therefore, be worthwhile to increase the frequency of follow-ups following an MCI diagnosis, so as to ensure early detection of AD. Though our sample size of patients who developed AD was too small to be significant, the majority of them did have a previous diagnosis of MCI, supporting this idea. The only variable found to have a significant difference between the population of patients who remained cognitively normal and those who developed a neurological diagnosis is age, as seen in Table 1. Most of the patients who received a diagnosis

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were older than those who did not. Additional studies surrounding the variables summarized in Table 1 should also be conducted to investigate who is at greater risk with respect to potentially modifiable risk factors such as exercise per week, general health, education level, living situation, and degree of hearing loss. Previous studies suggest that moderate exercise, balanced diet, and educational activities may decrease the likelihood of one developing dementia, but further inspection is required.[29]

Limitations

As previously discussed, not all of the patients attended follow-ups. We were usually informed that their lack of attendance was due to improvement or stability of their condition, but we cannot know for certain in all cases. Another feature of the cohort that should be noted is the average age of 60.9 (SD 12.0). This relatively young age for a study on cognitive decline and dementia, which are strongly associated with older age, does create limitations. The data in Tables 1 and 3 highlighting features of those who received a neurological diagnosis may also suggest some possible risks for developing a neurological diagnosis, but the sample size is too small to be significant. Follow-up studies exploring this with a larger patient population may be useful.

Additionally, the setting of data collection needs to be considered. In a study comparing SCI in the patient presenting to memory clinics and those in the general population, assessed through a population study, it was found that SCI is more likely to progress to MCI in the group that attended the memory clinic.[30] As we do not have a comparison in this study, we cannot know for certain that the attendance at the RRMC was not a factor in the presence of later diagnoses of MCI in the population we studied.[8] Other techniques, such as neuroimaging to assess biomarkers or CSF analysis are also used for diagnosing AD.[31,32] Amyloid-beta imaging techniques are also useful in early diagnosis of AD, and potential monitoring of AD progression.[33] We did not have access to these modalities, which could be useful for prognostication, during the conduct of our study.

Conclusion

Overall, we did not observe a significant change in MMSE, FAQ, or CESD score at 1-year follow-up compared to clinic day, nor did we observe a consistent pattern of MMSE score decline over long-term follow-up. This supports the course of action of being optimistic regarding the "worried well", as measurable neurological decline is unlikely. A small proportion of patients analyzed developed a diagnosis. The pathology of AD occurs before diagnosis, meaning that the disease process was likely underway in these patients at initial assessment, despite normal neurological test results.[8] This, along with the fact that AD has better outcomes with early recognition, demonstrates the need for follow-up, despite the low probability of progression.[10]

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Conflicts of Interest

There are no conflicts of interest.

Statement of Authorship

All authors contributed in the preparation and editing of the final manuscript. MS wrote the manuscript under the guidance of AK. AK and MS developed the study design and oversaw the data collection. CK conducted the statistical analysis. DM was a member of the team that conceived the clinic model and managed data entry. MEO and AK oversaw the clinical assessments and performed the diagnosis. MEO administered and oversaw neuropsychological testing, depression testing, and function testing.

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