The Natural History of Health and Symptoms in Narcolepsy: a 10 year Longitudinal Study

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Australian Journal of Primary Health, 2003, 9(1),59-67

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KEYWORDS: narcolepsy symptoms, longitudinal, health, life impact, sleep propensity

Abstract

The aim of the study was to compare, over a 10 year period (1991/2001), reported changes in people with narcolepsy in terms of (1) life impact of symptoms (2) sleep propensity (3) body mass index, and (4) concomitant illnesses. Also, to document, using retrospective report, (5) environmental factors influencing narcolepsy severity, and (6) reported time of worst symptom severity following narcolepsy onset.

In 1991 127 people with diagnosed narcolepsy and cataplexy completed a wide ranging questionnaire. In 2001 attempts were made to recontact these participants and 67 were traceable. Of these, 47 people, (18 males, 29 females; mean age 61.76 years, age range 31-86 years) returned a revised questionnaire. The reported impact of excessive daytime sleepiness (EDS) on the ability to carry out day to day activities showed minor increases in severity over the 10 year period in this older narcolepsy sample, and this could not be attributed to major changes in medication status. It is argued that the underlying severity of EDS does not increase with time, but rather that the interaction of EDS with the aging process increases its detrimental impact. There was no evidence that any narcolepsy symptom became substantially worse with time for most people with the disorder. The influence of environmental factors on symptoms was inconsistent within the group. In terms of other health issues, the elevated BMI, stable over time, suggested that excess weight may be a trait often associated with narcolepsy, possibly linked to hypocretin deficiency. A high prevalence rate of diabetes was noted in the sample.

The need for longitudinal studies of how narcolepsy progresses across the lifespan has long been recognised [1]. To our knowledge only one published study [2] presents data which follows the same people with narcolepsy over a number of years. Three 36 hour polygraphic recordings were conducted at up to 15 year intervals for 8 patients. They reported a worsening of excessive daytime sleepiness (EDS) in three patients and an improvement in three.

The early literature contains some general statements on the course of the disorder with several clinicians saying narcolepsy remains essentially unchanged once the symptoms emerge [3,4,5,6]. Occasionally anecdotal information is cited, such as reports of a worsening of symptoms with age [7].

More frequently age is investigated as an independent variable within a study. One investigation [8] reported no significant differences between the under and over 40 year age groups in terms of life disruption due to symptoms during the day or night, medication effectiveness and side effects, or overall psychosocial adjustment. As in people without narcolepsy, nocturnal sleep quality in those with narcolepsy appears to decline with age. Time awake during the night increases with age in narcolepsy and also REM episode length declines [2,9]. Nocturnal sleep efficiency has been shown to have a more rapid decline in narcolepsy than in the general population [9]. A recent study [10] compared age related changes in symptoms in patients older and younger than 65 years of age. They reported no significant differences in EDS between the groups but reduced cataplexy in the aged group.

The course of narcolepsy and fluctuations in symptoms have been investigated using retrospective report [2]. Forty four percent indicated a peak in EDS across the course of their disorder and fluctuations were attributed most to climatic conditions. Furthermore they reported falling asleep more readily when they were in a state of inner tension than with mental / emotional steadiness.

In terms of health, people with narcolepsy have an increased association with being overweight or obese [11,12] but no studies have considered how their weight may vary longitudinally. There are reports of people with narcolepsy being more prone to also having other physical illnesses, in particular diabetes mellitus [13] and other sleep disorders [14] and it is expected that the incidence of concomitant illnesses would increase with advancing age. There are numerous reports of a higher incidence of depressed mood and depressive symptomatology in people with narcolepsy [15,16,17] but the degree of association with major clinical depression is controversial, as is the association between narcolepsy and psychiatric disorders [18,19,20].

This study set out to investigate the natural history of narcolepsy symptoms and other selected health variables. The main way this was achieved was through a comparison of responses, as provided in 1991 and 2001, by a group of participants with narcolepsy. The specific issues addressed include comparisons over the 10 year period of;

- reported life impact of six narcolepsy symptoms
- sleep propensity

- body mass index
- concomitant illnesses

In 2001 additional questions were posed that relied on retrospective report and these related to

- environmental factors which altered symptom severity
- the time of worst symptom severity

Method

Participants, Procedure and Demographics

In 1991 127 people with diagnosed narcolepsy and cataplexy completed a wide ranging questionnaire, the data from which was published [8]. The clinical criteria for inclusion in this sample was (a) diagnosis of narcolepsy by a medical specialist and (b) a reported clinical history of cataplexy (from minor to severe). All participants were recruited and followed up through the Australian narcolepsy support group (NODSS). In 2001 it was ascertained that of the original 127, no current addresses were available for 50 and 10 had died. Thus 67 potential participants received the revised questionnaire package and, of these, 42 returned the completed package immediately and a further five returned the questionnaire after a follow up phone call (70% response rate).

The sample thus consisted of 47 people, 18 males and 29 females with an age range (in 2001) of 31 to 86 years (mean age = 61.766 years, SD = 15.16). Three quarters of the 2001 sample had been diagnosed for at least 15 years. The age of diagnosis of the

sample was as follows: 0-20 years of age = 25%; 21-50 yrs = 66%; 50-70 yrs = 19%. The mean age of onset of six different symptoms, as reported by the participants in 1991 are shown in Table 1.

Table 1: Mean onset age and age range for each narcolepsy symptom

Symptom	**Mean Age(years)**	**Age Range(years)**
EDS	22	9-52
Cataplexy	30	2-57
Sleep Paralysis	29	14-53
Hallucinations	26	3-61
Nocturnal Disruption	31	16-59
Automatic Behaviour	34	14-73

* EDS = excessive daytime sleepiness

Comparison of the percentage of participants in different categories of marital and employment status in 1991 and 2001 are shown in Table 2.

Table 2: Frequency statistics for demographic data in 1991 and 2001

	1991	***2001***
Marital Status:		
-married	31	30
-divorced	5	7
-never married	8	6
-widowed	3	4
Employment Status:		
-retired	12	17
-full-time	13	11
-part-time	7	6
-home duties	6	6
-sickness pension	5	3
-Other	4	4

Questionnaires:

The questionnaire packages that were distributed in 1991 and 2001 consisted of several different sections that covered a range of variables. In most cases participants simply responded to closed or open ended questions. Five point Likert scales were used to measure the reported life impact of symptoms where subjects were asked "To what extent does (..symptom) affect you ability to carry out day to day activities?" with

response possibilities from “not at all” to “completely”. Sleep propensity was measured using the Epworth Sleepiness Scale [21].

Additional information that was also sought in both years, and will be described in a subsequent article on longitudinal changes, included psychosocial adjustment (measured using the Psychosocial Adjustment to Illness Scale, PAIS); vocational impact, income security, acceptance of the disorder, medication issues and behavioural control of symptoms.

The Victoria University Human Experimentation Ethics Committee approved the study.

Data Analysis

Data was analysed using the SPSS package and where comparisons between 1991 and 2001 mean values were sought, paired t-tests were used with alpha at 0.05.

Results

Life impact of symptoms

In both 1991 and 2001 each person was asked to assess on a 5 point Likert scale the extent to which a particular symptom had affected their ability to carry out day-to-day activities during the previous two week period. This was scored such that a higher score indicated greater impact. Comparing results across the 10 year period showed that a significant difference was found for the impact of excessive daytime sleepiness (EDS), with a greater impact in 2001 than 1991 (see Table 3). In contrast the life impact of sleep paralysis, hallucinations and automatic behaviour were reduced across the 10 year period. There were no significant changes in impact for cataplexy or nocturnal sleep disturbance.

Table 3: The means, SD and t-test results of the difference between the impact of symptoms on the lives of sufferers (last two weeks) in 1991 and 2001.

	1991		2001		t	df	p	Change over time
	Mean	**SD**	**Mean**	**SD**				
EDS	1.28	0.89	1.73	0.76	3.96	1,41	.000	worsens
Cataplexy	2.18	2.01	1.72	1.85	-1.43	1,43	.158	stable
Sleep paralysis	2.66	2.23	1.66	1.94	-3.17	1,44	.003	improves
Hallucinations	2.47	2.27	1.45	1.73	-3.17	1,43	.003	improves
Nocturnal disruption	2.43	1.66	2.02	1.30	-1.37	1,43	.216	stable
Automatic behaviour	2.27	1.89	1.40	1.40	-3.19	1,43	.003	improves

In order to explore the extent of individual differences within these mean comparisons the 1991 and 2001 ratings of life impact were compared for each individual. Two types frequencies were collated (1) differences of one point (on the 5 point Likert scale) indicating a *minor* change in symptom impact over time, and (2) differences of two or more points , suggesting a more *major* shift in symptom impact. These frequencies are shown in Figure 1.

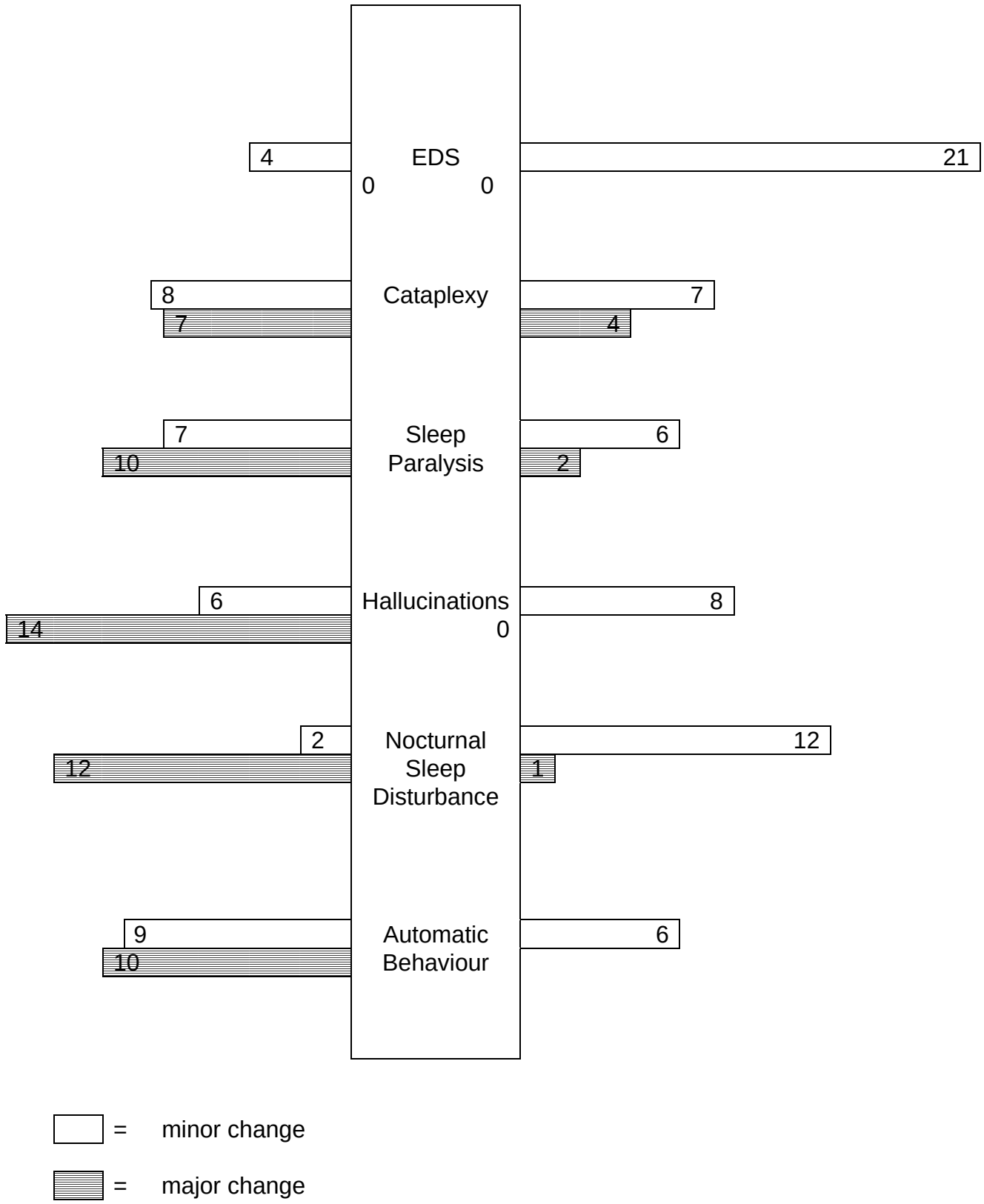
Improved Symptom Impact
Worse Symptom Impact
4
EDS
21
0
0
8
Cataplexy
7
7
4
7
Sleep
Paralysis
6
10
2
6
Hallucinations
8
14
0
2
Nocturnal
Sleep
Disturbance
12
12
1
9
Automatic
Behaviour
6
10
= minor change
= major change

Figure 1: Frequency with which minor and major changes (see text) in symptom impact were noted between 1991 and 2001 for 47 individuals with narcolepsy.

Figure 1 clearly shows that the significant 1991/2001 difference in EDS impact is largely a result of nearly half the group reporting minor worsening in the life impact of their EDS. This is in marked contrast to the other symptoms where more considerable numbers of people are reporting major improvements in the life impact of the symptoms. Thus the significant differences for sleep paralysis, hallucinations and automatic behaviour shown in Table 3 result primarily from major symptom impact improvements in 10-14 individuals within each symptom.

Post hoc analyses of the number of people who had changed their medication status found that this was not an important confounding factor in the significant EDS finding. Analyses showed that only 17% of the people who reported greater EDS impact in 2001 than 1991 had ceased taking stimulant medication between the years 1991 and 2001.

Environmental Factors influencing Narcolepsy Severity:

In 2001 all participants were asked about the influence of a series of factors on changes in the severity of their narcolepsy symptoms. All questions were prefaced with the statement, ”Over the past 10 years, which of the following events do you believe have contributed to any changes you have experienced in the severity of your narcolepsy symptoms?” Frequency data are presented in Table 4 below.

Table 4: Frequency of different environmental factors changing severity of narcolepsy symptoms.

	Worse	No change	Better	Not applicable
Medical condition (eg virus, infection, head injury, hospitalisation)	11	13	2	19
Stress due to life events (eg bereavement, war, exams, work)	16	17	3	8
Life cycle events (eg pregnancy, puberty, menopause)	11	12	0	21
Severe disruption to sleep patterns (eg shiftwork, stress, other environmental factors)	17	11	1	16
Hot/ humid weather	20	14	0	10

Where participants found an event applied to them, they were usually evenly divided on whether it made their narcolepsy worse or no different, although most people noted that severe sleep disruption and hot/humid weather made their symptoms worse. Interestingly, three people noted that stress made their symptoms better.

Worst symptom severity period

In both 1991 and 2001 participants were asked to nominate the year that each symptom was worst or whether the symptom severity had been constant over time. There was remarkable consistency in the responses provided in both questionnaires and the 2001 data is presented. Where a year was nominated as the worst year for a particular symptom, this was compared to the year nominated as the time of onset of

that symptom. Table 5 below shows the frequency of respondents in each category where '0-2 yrs" indicates the years since symptom onset when a symptom was the worst.

Table 5: Frequency of indicating particular years since symptom onset as the worst years

	0-2 yrs	3-10 yrs	10+ yrs	Last 2 yrs	Consistent	Never present	Can't remember
EDS	11	2	3	1	22	0	8
Cataplexy	10	2	1	5	25	0	4
Sleep paralysis	9	1	3	1	11	17	5
Hallucinations	9	1	5	3	0	24	5
Nocturnal disruption	12	0	4	8	12	6	5
Automatic behaviour	12	1	5	1	3	13	12

For the four classic symptoms of narcolepsy (EDS, cataplexy, sleep paralysis and hallucinations) approximately half the sample reported that the severity of the symptoms were consistent since their onset. About a fifth ((18-24%) reported that the worst period was within two years of symptom onset. While a smaller minority said that their nocturnal sleep disruption (17%) and cataplexy (11%) was worst in the last 2 years there was no overall pattern suggesting increased severity with time for most of the sample. However, these individual differences are considerable enough to suggest that

the course of narcolepsy is a heterogenous phenomenon across the sample with some people experiencing peaks in severity.

The raw data was further analysed to determine whether it was also the same group of people with narcolepsy who experienced the first two years as the worst for different symptoms and no such pattern was evident.

Body Mass Index

Body mass index was calculated from the reported height and weight measures provided in both 1991 and 2001 and then categorised as underweight, normal, overweight and obese [22]. The frequencies within each category did not change substantially between 1991 and 2001 (see Table 6) and a paired t-test confirmed no significant change in BMI values over the 10 year period (1991 mean = 3.18(SD=0.78); 2001 mean = 3.26(0.74), $t(1,43)=1.15$, $p>.05$).

Table 6: Frequency (and percentage) statistics for BMI categories in 2001 and 1991

Condition	**Frequency(%) 1991**	**Frequency(%) 2001**
Underweight	1 (2%)	1 (2%)
Normal	5 (11%)	7 (15%)
Overweight	19 (40%)	21 (45%)
Obese	22 (47%)	18 (38%)

Concomitant Illnesses

An open ended question invited documentation of other illnesses. It was found that the reported presence of concomitant illness was greater in 2001 than 1991. While one quarter had no other illness in 1991, after 10 years only one half of the group reported such health. Table 7 summarises the frequencies within the major reported illness groups. The high prevalence of diabetes is particularly noteworthy.

Table 7: Frequency statistics for the prevalence of concomitant illnesses in 1991 and 2001

Condition	1991	2001
No other illnesses	36	24
Cardiovascular	4	6
Diabetes	2	5
Musculoskeletal	2	4
Mental Illness	2	4
Other Sleep Disorders	0	2
Respiratory	2	1
Visual	0	1
Alcoholism	1	0

Discussion

Symptoms

Interestingly, EDS was found to have a greater short-term impact on life activities in 2001 than 1991, in this older aged sample of people with narcolepsy. This detrimental change in symptoms stands alone among the other data that indicated either reduced

symptom impact or no change over the 10 year period. There are several possible interpretations:

- That, taken as a group, there is no change in narcolepsy severity over the 10 year period and the worsening life impact of EDS can be attributed to age-related changes in sleep-wake patterns interacting with EDS. These changes lead to a reported greater impact of sleepiness on day to day activities when the person gets older. The assumption is that many older people (with or without narcolepsy) make more room for sleep/napping in their lives and that this is independent of an underlying increase in sleep propensity. In support of this assumption is the fact that there are no reports of ESS increasing with age in normal populations. A study of 528 adults aged from their 30s to late 60s found that age was not a predictor of Epworth Sleepiness Score (ESS score) [23]. A similar conclusion was drawn from an investigation of 1560 elderly WW2 veterans [24]. The employment data indicates that a minority of the group were in fulltime employment at both time points of the study (27% in 1991 and 23% in 2001), suggesting that most of the sample follow a lifestyle where they can choose the pace for most, if not all, the time. In these circumstances people may make more opportunities to sleep as they get older, even though their underlying propensity to doze while engaged in another activity (ESS) may not have increased. The finding that all the ratings of increased EDS impact with time were minor rather than major, further supports this interpretation.
- Alternatively, perhaps the greater impact of EDS in 2001 may result from the older sample ingesting less stimulant medication because their lifestyle is less demanding now than in 1991 or they have more difficulty with side effects. While the data

showed that only 17% of those people who reported more impact in 2001 than 1991 ceased their stimulant medication, what is not known is how many may have substantially reduced their daily stimulant intake. Medication issues may thus play a secondary role in the EDS finding.

- A different interpretation of the data may be that the narcolepsy symptom of EDS has worsened over the 10 year period and the measure of sleep propensity (ESS) is not sufficiently sensitive in these circumstances to document this. Some support for this interpretation is provided by the study [25] comparing the Maintenance of Wakefulness Test (MWT) with the ESS. Using modelling techniques on the data sample of 522 people with narcolepsy, they found that as the MWT level of severe sleepiness increased, the ESS remained stable. Arguing against this explanation of the present data are the retrospective reports which found no suggestion that any symptom of narcolepsy gets worse for most people. In fact only one person in the sample felt their EDS was at its worst during the last two years. For the EDS symptom, as for the other narcolepsy symptoms, the worst period was either when the symptoms first appeared or, more typically, were consistent over time.

Consideration of all the available information, leads most strongly to the interpretation that the reported increase of EDS impact on daily activities is a consequence of the narcolepsy EDS interacting with age-related changes in sleep wake behaviour and that the underlying severity of any symptom of narcolepsy does not increase over time. Reduction in medication may have partially contributed to increased EDS impact.

It would appear that the main trend within the sample is that if symptom impact becomes worse with time it does so in a fairly minor way, whereas if a symptom improves for a person, the improvement is usually quite substantial. This is consistent with the major patterns evident in people's self report of the worst year for a symptom since symptom onset, with very few citing the most recent years as the worst. However, clearly individual differences are important in the course of narcolepsy.

The influence of the different environment factors was quite variable across the sample with numbers typically evenly divided between factors making their symptoms worse or no change with a minority reporting improvement with some events. The question arises as to whether this variability in the sample is due to

- the differences in the nature of the factors experienced – for example four options are listed under **"**Stress due to life events - bereavement, war, exams, work", and each of these may affect people differently and created ambiguity in the responses;
- people's individual differences; or
- the possibility that narcolepsy itself is not homogenous but represents a heterogenous syndrome encompassing a series of etiologically different disorders.

Health

An increased body mass index (BMI) was found in this sample of people with narcolepsy and this is consistent with many other reports [11,12]. While the present study found 86% were overweight or obese (in 2001), the percentage across the

Australian population for these BMI categories is 51.8% for females and 67.3% for males [26]. No major increase in the proportion of overweight or obese people across the 10 year period was noted. This supports the case that elevated BMIs in narcolepsy are not secondary to behavioural consequences of the disorder but may be a trait characteristic, possibly associated with hypocretin deficiency [27]. An increased appetite in narcolepsy is supported by a study of dietary intake which reported an increased frequency of snacking and sweet consumption, and a higher overall food intake in people with narcolepsy compared to age matched controls. Results also suggested that it was not simply the case that the more overweight people ate more snacks but that narcolepsy itself was the critical factor [11].

Advancing age was associated with an increase in the prevalence of concomitant illnesses in the sample. The reported prevalence rate of cardiovascular disorders in 2001 of 13% is in line with the Australian rate of 16% [28]. However, a rate of 11% for diabetes (type not specified) in 2001 for the people with narcolepsy is higher than the prevalence rate of diabetes in Australia which is 7.2% of the population over 25 (this rate includes people previously undiagnosed) [26]. As epidemiologists estimate that approximately one half of the people with diabetes are currently undiagnosed, the true rate of diabetes among the narcolepsy sample may be higher than 11%. Comparison of prevalence rates must be done with caution as the most predominant type of diabetes (type 2) is an illness that expresses itself more in later life and this narcolepsy cohort is predominately older. However, the current finding is consistent with the conclusion of Honda and colleagues [13] that there is had an increased association between

narcolepsy and diabetes mellitus. While they concluded that the diabetes was independent of obesity in their narcolepsy patients, the close association between diabetes and excess weight [29] in the normal population suggests this association warrants further investigation in narcolepsy.

The low reported frequencies of both mental illness and other sleep disorders is surprising and at variance with reports in the literature, where higher rates of mental illness and other sleep disorders among people with narcolepsy are documented [14,18,19,20]. Perhaps the open-ended nature of the responses in this section on illnesses led to some under reporting. With regard to mental illnesses, those with problems in this area may be less likely to return the lengthy questionnaire or have traceable home addresses after 10 years.

Conclusions: The reported impact of EDS on the ability to carry out day to day activities was greater in 2001 than 1991 in this older narcolepsy sample, and this could not be attributed to major changes in medication status. While nearly half the group reported increased impact, in all these individuals this change was reported as minor. Interestingly, sleep propensity did not change over time. While various explanations of the EDS finding are possible it is argued that the underlying severity of the narcolepsy symptom has not increased with time, but rather that the interaction of EDS with the aging process increases the detrimental impact of EDS.

In contrast, the life impact of sleep paralysis, hallucinations and automatic behaviour was reduced over the 10 year period. Both longitudinal evaluations and retrospective reports provided no evidence that narcolepsy symptoms became substantially worse with time and for many people the impact of the non-EDS symptoms of narcolepsy was associated with major improvements. The influence of environmental factors on symptoms was inconsistent within the group.

In terms of other health issues, the elevated BMI, stable over time, was felt to suggest that excess weight may be a trait often associated with narcolepsy. A high prevalence rate of diabetes was noted and warrants further investigation in narcolepsy populations.

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