

The vegetative state/unresponsive wakefulness syndrome: a systematic review of prevalence studies

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One of the worst outcomes of acquired brain injury is the vegetative state, recently renamed ‘unresponsive wakefulness syndrome’ (VS/UWS). A patient in VS/UWS shows reflexive behaviour such as spontaneous eye opening and breathing, but no signs of awareness of the self or the environment. We performed a systematic review of VS/UWS prevalence studies and assessed their reliability. Medline, Embase, the Cochrane Library, CINAHL and PsycINFO were searched in April 2013 for cross-sectional point or period prevalence studies explicitly stating the prevalence of VS/UWS due to acute causes within the general population. We additionally checked bibliographies and consulted experts in the field to obtain ‘grey data’ like government reports. Relevant publications underwent quality assessment and data-extraction. We retrieved 1032 papers out of which 14 met the inclusion criteria. Prevalence figures varied from 0.2 to 6.1 VS/UWS patients per 100 000 members of the population. However, the publications’ methodological quality differed substantially, in particular with regards to inclusion criteria and diagnosis verification. The reliability of VS/UWS prevalence figures is poor. Methodological flaws in available prevalence studies, the fact that 5/14 of the studies predate the identification of the minimally conscious state (MCS) as a distinct entity in 2002, and insufficient verification of included cases may lead to both overestimation and underestimation of the actual number of patients in VS/UWS.

Introduction

For patients surviving severe brain damage of either traumatic or non-traumatic origin, one of the worst possible outcome is the vegetative state, recently renamed ‘unresponsive wakefulness syndrome’ (VS/UWS) [1]. A patient in VS/UWS shows reflexive behaviour such as spontaneous eye opening and breathing, but no signs of awareness of the self or the environment [2,3].

While science is steadily unravelling the physiological basis of disorders of consciousness [4], the number of patients in VS/UWS remains unclear; the most commonly cited prevalence figures are based on estimates [5,6]. This is partly due to diagnostic difficulties, reflected in a high misdiagnosis rate: up

to 43% of patients presumed to be in VS/UWS turn out to be at least in a minimally conscious state (MCS)[7] when examined by means of a structured assessment scale [8,9]. The difference between MCS and VS/UWS is of considerable clinical relevance: patients in MCS appear to have a better prognosis [10–12] and to process emotional, auditory and noxious stimuli in a way very similar to that of healthy individuals [13,14].

Epidemiological data form the basis of insight in every clinical condition. In order to apprehend the impact of a disease or syndrome, the number of patients it affects is one of the first things clinicians, scientists and policy makers need to know. The prevalence of VS/UWS, a condition often referred to as ‘a fate worse than death’ [15], is therefore relevant to epidemiologists, neurologists, primary care physicians, psychiatrists, ethicists and policy makers. This paper gives an extensive overview of VS/UWS prevalence figures and their reliability by means of a systematic review.

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Methods

A literature search of Medline, Embase, the Cochrane Library, CINAHL and PsycINFO was carried out in April 2013, using complete timescales and no language restrictions or other limits. We used the following search terms: 'vegetative state', 'unresponsive wakefulness syndrome', 'apallic syndrome' and 'akinetic mutism', combined with search terms for epidemiology (Appendix S1). Experts in the field were asked for so-called grey data, e.g. governmental reports or personal communications possibly containing VS/UWS prevalence figures.

Titles and abstracts were scanned for relevance by two researchers (WvE, JL) independently. Whenever at least one of the researchers considered a paper relevant or possibly relevant, it was read full text. Publications were included provided they were original cross-sectional point or period prevalence studies, explicitly stating the number of VS/UWS patients within the general population. We excluded studies that concerned only VS/UWS due to degenerative and other non-acute causes, outcome studies within populations with specific medical characteristics (e.g. out-of-hospital cardiac arrest, subarachnoid hemorrhage), and papers post-dating 1994 not using the Multi-Society Task Force on PVS-criteria [3]. The latter criterion, however, was dropped as it soon turned out to exclude nearly all otherwise eligible publications.

Upon inclusion, both researchers independently assessed study quality in a structured manner (Appendix S2), based on an earlier systematic review of prevalence studies [16] and two methodological papers [17,18]. In short, we looked at study design, whether a point or period prevalence was obtained, response rates in case of questionnaires, the way estimates were constructed and the manner of diagnosis verification in included cases. Although no gold standard for the diagnosis of VS/UWS exists, expert opinions agree that a validated assessment tool for the level of consciousness after the acute phase should be used, preferably the Coma Recovery Scale- revised [19–21]. Repeated assessments and the involvement of proxies and professionals familiar with the patient are recommended [22–24]. Complementary diagnostics like fMRI and EEG could be considered as well [24,25]. Next to these items, we checked whether authors mentioned the presence of consensus about the diagnosis in included cases.

When needed in the process of quality assessment, agreement was reached through discussion. As one researcher (JL) was the author of one of the publications [26], a third, independent researcher (FvL) carried out quality assessment in this case. We

recalculated absolute patient numbers to prevalence per 100 000 people if demographic data from the period concerned were available on www.oecd.org.

Results

The search strategy and consultation of three experts in the field produced 1001 unique records. Of every publication considered relevant or possibly relevant by one or both authors ($n = 107$), including 31 additional titles from bibliographies, full text was evaluated for eligibility. In four out of 107 cases we were unable to obtain the original publication [27–30], despite attempts to contact the authors. A further 89 papers were discarded as their full texts did not meet inclusion criteria. Finally, 14 studies were included. A flow chart of the selection procedure is shown in Figure 1 and study characteristics can be found in Table 1.

Over the past 40 years, 14 prevalence studies on VS/UWS were found to have been published, originating from Japan, the Netherlands, France, the USA, Denmark, Austria and Italy. The average year of publication was 1996 (range 1976–2011). We will discuss the studies' methodological characteristics and the prevalence figures they led to.

Researchers used various strategies to identify patients, from questionnaires to the members of the Child Neurology Society [31] to insurance registries [32] and phone interviews with nursing homes' medical directors [26]. In prevalence studies based on questionnaires, response rates turned out fairly high (78–100%) with the exception of a 26% response in a survey amongst members of the Child Neurology Society [31]. Information about non-responders was lacking in all cases. Three papers based on surveys did not mention response rates [33–35]. Sampling frames (i.e. the populations in which the prevalence was investigated) were countries or smaller geographical regions. It should be noted that 2 papers based their prevalence on the nursing home population exclusively [26,36], and that none of the studies included patients being cared for at home. Demographic and socioeconomic variables possibly affecting the samples were described in none of the studies. The two papers in which results from a smaller sample were extrapolated to a nationwide prevalence figure gave no indication of corrections for sample bias [37,38]. Estimates in these and other studies came without confidence intervals [31,32,37–40].

Eight studies [26,35–37,40–43] were carried out after the publication of internationally accepted diagnostic criteria for VS/UWS [3]; three of them also used these as their inclusion criteria [26,36,44]. Nine prevalence studies [31,33,34,37,39,41,42,45,46] took place before

Table 1 Characteristics of studies included (*italic figures calculated by authors*)

First author, year of publication	Study year	Population	Diagnostic criteria; inclusion of Degen. causes	Point/period prevalence; method	Response rate	Validation	Result	Remarks
Kodama (1976) [38]	1972	All neurosurgical clinics in Japan	Local criteria; Degen. causes included	Unclear Questionnaire to clinics	90% of clinics	None	646 (abs) 'approx. 2000 in Japan' <i>0.6/100 000</i>	Inclusion criteria cover MCS
Higashi (1977) [32]	1973	All hospitals in Yamaguchi (Japanese prefecture)	Local criteria; Degen. causes included	Point; Questionnaire to hospitals	Unclear	100%; unvalidated assessment by researcher within unknown timeframe	2.5/100 000	Inclusion criteria cover MCS; Terms 'prevalence' and 'incidence' used erroneously
Sato (1978) [31]	Unclear (<1978)	All hospitals with registered VS/UWS pts in Tohoku (Japanese district)	Local criteria; Degen. causes included	Unclear; Pts identified through insurance system, then questionnaire to hospitals	78%	None	1.88/100 000 Authors estimate actual prevalence to be 2–3/100 000	Inclusion criteria cover MCS; Terms 'prevalence' and 'incidence' used erroneously
Minderhoud (1985) [51]	1983	Hospitals, nursing homes, Netherlands (unclear whether nationwide or regional)	Unclear; Only acute causes	Unclear; Questionnaire to hospitals and nursing homes	79.6%	None	53 (abs) <i>0.37/100 000</i>	
Tasseau (1991) [33]	1987	Unclear; 18/23 regions in France	Unclear; Unclear	Unclear; Unclear	Unclear	Unclear	2.0/100 000 ('all VS patients) 1.4/100 000 ('patients in VS > 3 months') 1600 children (abs), 6000 (abs) <i>0.63/100 000</i>	Personal communication cited in book, limited information. Extrapolation. Authors hypothesize that the actual number may be higher
Ashwal (1992) [30]	1991	Patient populations of Child Neurology Society-members, USA	Unclear; definition was subject to discussion within the questionnaire	Unclear; Questionnaire sent to all members of CNS (presumably covering the country)	250/960 26%	None		
Engberg (2004) [36]	1997	Brain injury registry, 4 Danish regions	Unclear; traumatic causes, surviving > 5 years after injury	Point; From the outcomes of patients with TBI in 1982, 1987 and 1992 the prevalence of VS/UWS is calculated	Does not apply	None	<0.13/100 000 (figure follows from the fact that sample contained no VS/UWS)	Possibility of sampling error not discussed. Terms 'prevalence' and 'incidence' used erroneously

(continued)

Table 1 (Continued)

First author, year of publication	Study year	Population	Diagnostic criteria; inclusion of Degen. causes	Point/period prevalence; method	Response rate	Validation	Result	Remarks
Plexus Medical Group (1998) [37]	1997	Sample, no information except indirectly; 2 academic hospitals, 10 general hospitals, 18 nursing homes in 6 cities in the Netherlands	*Coma patients', GCS < 7, >4 weeks; Unclear	Period; Questionnaire to hospitals and nursing homes	29/30 96.7%	None	1.045/100.000	National prevalence calculated as the mean of city prevalence figures Possibility of sampling error not discussed 1 patient excluded for not being from the region
Stepan (2004) [41]	2001	All hospitals and nursing homes in Vienna, Austria	Local criteria, patients in VS/UWS > 14 days; Unclear	Point; Inventory of potential cases 1 month before study date, then validation	96%	88%; assessment by researcher within 3 days after study date; Glasgow coma scale, Glasgow outcome scale, Edinburgh 2 coma scale, Barthel score	1.9/100 000	1 patient excluded for not being from the region
Lavrijsen (2005) [25]	2003	All nursing homes in the Netherlands	>1 month after acute injury [3]	Unclear; Announcement with diagnostic criteria, then interview by phone with all institutions	100%	3/32 9.4%; WNSSP	0.2/100 000	Validation only when doubt about diagnosis
Stepan (2006) [42]	2003	All hospitals and nursing homes in Vienna, Austria	Local criteria, patients in VS/UWS > 14 days; Unclear	Point; Inventory of potential cases 1 month before study date, then validation of reported cases	98%	100%; assessment by researcher within 3 days after study date; Glasgow coma scale, Glasgow outcome scale	1.7/100 000	1 patient excluded for not being from the region
Saoût (2010) [34]	Unclear (<2010)	All nursing homes, hospitals and rehabilitation centres in Maine-et-Loire county, France	Unclear; Unclear	Unclear; Questionnaire to all institutions	Unclear	100%; assessment by researcher within unknown timeframe, WHIM	2.8/100 000 4 VS/UWS + 9 MCS 0.86/100 000	No prevalence given for VS/UWS separately
Pistarini (2010) [39]	2002–2006	All hospitals, Italy	Unclear; Unclear	Unclear; National registry of hospital discharge diagnoses checked for VS/UWS	Does not apply	None	6.1/100 000 'crude estimate', possibly a mean value for all years. 3.36/100 000	Only calculated for Lombardia region Conference abstract, limited information
Donis (2011) [35]	2007–2009	All nursing homes, Austria	Unclear [3]	Period; Inventory of potential cases, then interview by phone for reported cases	100%	None		

Degen., degenerative; MCS, minimally conscious state; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

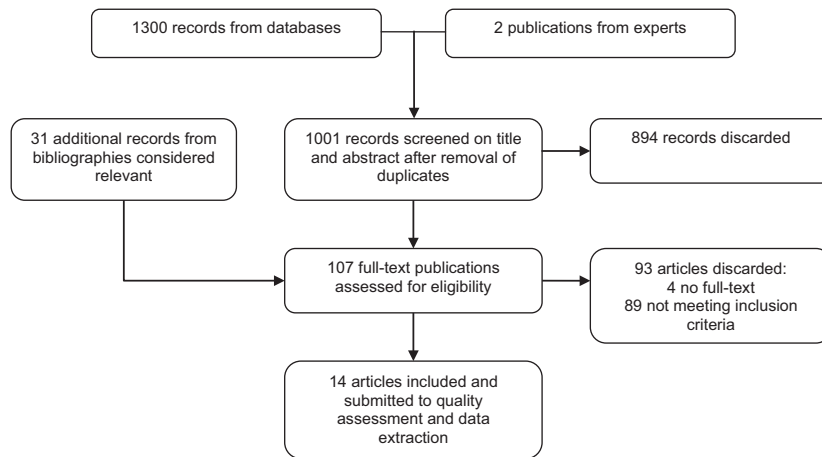


Figure 1 Study selection. Selection process for identification of published prevalence studies on VS/UWS prevalence, according to the PRISMA Statement.

the identification of the minimally conscious state (MCS) as a distinct entity in 2002 [7] and three of these publications explicitly stated inclusion criteria which also cover MCS (e.g. visual fixation, inconsistent command following) [33,39,45]. Diagnoses of included patients were verified by researchers in 5/14 studies [26,33,35,42,43]. Two groups [26,35] deployed scales specifically designed for level of consciousness determination in the post-acute setting: the Western Neuro Sensory Stimulation Profile [47] and the Wessex Head Injury Matrix [48], respectively. In the remaining three studies [33,42,43], researchers used unvalidated assessment methods, descriptive scales (e.g. the Glasgow Outcome Scale [49]) and/or scales unsuitable for level of consciousness assessment in the post-acute and long-term setting, such as the Glasgow Coma Scale [50]. Case verification was carried out within 3 days in two studies [42,43], while the time lapse between study date and assessment remained unclear in the other 3. One study involved caregivers' and/or proxies' observations and whether consensus about the patient's diagnosis existed between those two parties, but only verified cases in which there were doubts about the diagnosis [26]. In none of the studies, repeated assessments or complementary diagnostics, such as functional magnetic resonance imaging, seem to have been used.

Four papers discussed point prevalence [33,37,42,43] and two studies reported period prevalence figures [36,41]. From 8/14 studies, it remained unclear whether a point or a period prevalence had been the objective [26,31,32,35,38–40,51]. The terms 'prevalence' and 'incidence' were used erroneously in three papers [32,33,37]. As the number of patients at a certain time point was clearly mentioned in these texts, we remained able to extract the prevalence figures.

Keeping aforementioned methodological differences in mind, the prevalence figures showed a broad variety from publication to publication. Authors of one study concluded that the prevalence in their population had to be less than 0.13/100 000 as there were no VS/UWS patients in a sample of 389 individuals [37]. This figure set aside because of the small sample it arose from, according to literature the prevalence of VS/UWS varies from 0.2/100 000 (the Netherlands, 2003)[26] to 6.1/100 000 inhabitants (Lombardia, Italy 2009–10) [40].

Discussion

This systematic review of prevalence studies on VS/UWS shows a wide range in available prevalence figures, from 0.2/100 000 to 6.1/100 000 inhabitants [26,40]. Interestingly, no publications were found from the African continent, Latin-America or Asia outside of Japan, while this last country accounted for 3/14 of the publications (as did Austria and the Netherlands). The broad distribution of VS/UWS prevalence figures themselves may be attributable to various factors.

First of all, the prevalence of VS/UWS is expected to vary between and maybe even within countries due to quality and availability of emergency and intensive care services [52]. Secondly, end-of-life decisions in the intensive care unit, on hospital wards, and in post-acute and long-term care settings are strongly influenced by a country's political, professional, judicial and cultural profile [53]. The Netherlands, for example, allows for withholding life-sustaining medical treatment and withdrawal of artificial nutrition and hydration (ANH) in VS/UWS once prognostic boundaries of recovery of consciousness have passed [54,55]. Between 2000 and 2003, 9 out of 43 deaths of VS/

UWS patients were preceded by cessation of ANH and 24 by a decision not to treat complications [26]. The low Dutch VS/UWS prevalence, 30 times smaller than what was found in the Italian study, might be partially attributable to this.

However, we believe that the considerable different ways in which the prevalence studies were carried out render it impossible to draw legitimate conclusions on this sensitive subject. This brings us to a third explanation of the differences in VS/UWS prevalence. What the assessment of the included studies' methodological quality reflects, is the challenge of shedding light on a relatively small, silent group of patients who mostly live in long-term care facilities. Those being cared for at home form an even more difficult population to reach. The absence of a gold standard for the diagnosis of VS/UWS is another complicating factor. In this context, it is understandable that only 5/14 prevalence figures were (partly) based on verified cases, none according to current expert recommendations. This fact, combined with the possibility that the 9/14 studies pre-dating the definition of the minimally conscious state (MCS) in 2002 [7] may have resulted in a combined prevalence of MCS and VS/UWS together, undermines the reliability of available prevalence figures on VS/UWS. Both inclusion of MCS and failure to identify signs of consciousness might lead to a substantial overestimation of the actual number of VS/UWS patients in reported publications, while incomplete coverage of the various care settings may also cause underestimation.

To our knowledge, only one systematic review has evaluated the prevalence of the VS/UWS before [56]. It showed heterogeneity in both methodology and outcomes, which our study confirms. However, in contrast, we found 14 instead of five eligible prevalence studies and were able to assess the methodological quality of studies and their context as well. These differences can be attributed to a more extensive literature search and the use of established quality criteria for prevalence studies in our study.

A limitation to our study is that four possibly relevant papers [27–30] could not be retrieved, despite attempts to contact the authors and publishers. One of these records is an early Japanese study, in which authors of two studies we did include, were involved [27]. The abstracts nor contents of the other three have been clarified.

In conclusion, the VS/UWS prevalence figures which keep appearing in public debate, influencing health care policy and the public picture, are an unreliable representation of the actual patient population. This calls for new, nationwide point prevalence studies in which patients could be identified by addressing medical professionals in hospitals, rehabilitation cen-

tres, nursing homes, facilities for people with intellectual disability and general practitioners. Inclusion criteria should cover VS/UWS due to acute brain injury at least 1 month prior to the study date, as by this time the incidence of complications related to the causative trauma or illness is expected to drop. With regards to diagnosis verification, the value of repeated measurements, which is strongly recommended in clinical practice [57,58], should be weighed against the methodological challenges of visiting patients as soon as possible after the point prevalence date. A single CRS-r assessment, for example, could be enhanced by the active involvement of proxies and caregivers who observe the patient on a daily basis. When it comes to VS/UWS, one of the most dramatic conditions we face in modern medicine, it is time to get the epidemiological facts straight.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategies.

Appendix S2. Method of quality assessment and data extraction.

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