Post-Deployment Syndrome in Cambodia veterans

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Weemoed van jongvolwassenen bestaat uit
Niet kunnen wat ik wil, uit niet te willen wat ik kon, uit te verlangen naar wat ik niet heb en waar ik niet ben. En uit niet te begeren wat ik heb en niet te willen wezen waar ik ben, uit weemoed om het verleden dat voorbij ging en eerst daarna werd begrepen en wachten op wat komen zal en nooit komt.

Nescio, De Profundis, 1918. Uit: Verzameld Proza, pagina 548-551.Nijgh en Van Ditmar, Amsterdam: Van Oorschot, 1996.

Contents

Chapter I

Outline of this thesis

Introduction

After the ending of the civil war in Cambodia that had lasted two decades, the UN peace operation UNTAC (United Nations Transitional Authority for Cambodia) was established in March 1992. Between May 1992 and October 1993, 2616 Dutch servicemen were deployed in Cambodia, Southeast Asia, approximately 12.000 kilometres away from home. Three battalions were sent for a six-months term. The servicemen were confronted with a poverty-stricken and politically fragmented country strewn with millions of landmines.

UNTAC was a complex, multifaceted operation aimed to keep, make and build peace. Major tasks were supervising the administration of the country, disarming local factions, guiding free elections, guarding human rights, repatriating Cambodian refugees from camps in Thailand, mine clearance, and initiating the reconstruction of the country. Despite a tropical climate with accompanying diseases, a long history of extreme cruelty[1], and an armed civil population, the number of casualties was low. During hostilities, five Blue helmets got wounded. Two marines died in accidents and one marine lost his foot in a mine accident. Morbidity due to malaria was low, and all patients recovered.[2]

Although few people probably can recall the facts of this deployment, many will remember that previously fit servicemen returned home with ill health. Some months after return, reports of service-related health symptoms, such as severe fatigue, memory and concentration problems, headaches and co-ordination problems, started to emerge. The (ex-)servicemen perceived their symptoms to be service-related, especially to the malaria chemoprophylaxis mefloquine (Lariam®) or the vaccines they were exposed to. According to symptomatic Cambodia veterans, symptoms had started in Cambodia or just after return.

A number of symptomatic veterans reported their symptoms to the Ministry of Defence, but they had the perception that they fell on deaf ears. They did not encounter attention, recognition and respect, and conspiracy theories about Dutch UNTAC military personnel being used in medical experiments were unleashed. The level of distrust in the Ministry of Defence was intensified by an unlucky series of events such as the loss of pre-deployment blood samples, the absence of a written instruction supplied with mefloquine and a negligent vaccination registry system. The Ministry of Defence performed a limited somatic and psychological assessment on health symptoms in a subset of affected veterans. This revealed no homogenous description of symptoms or a single causative, service-related factor.[3,4] The affected Cambodia veterans were disappointed and made their problems public through the media. The

health symptoms became an issue of public and political interest. The Dutch press reported about "a mystery jungle disease" and a documentary on this topic was broadcasted in March 1996. That year, politicians decided to clear up the health claims and to request of an independent scientific study on symptoms in Cambodia veterans, guided by an independent committee of experts. Between December 1996 and December 2000, the Netherlands Fatigue Research Group of the University Medical Centre Nijmegen carried out an extensive two-phase study on symptoms in Cambodia veterans.

Contents of this thesis

This thesis, consisting of nine chapters, describes a part of the findings of the study on symptoms in Cambodia veterans. More somatically based studies can be found elsewhere.[5]

Chapter two starts with a historical overview of war syndromes. It is argued that symptoms in Cambodia veterans do not seem to be an unique syndrome or a single diagnostic category. Since the American Civil War, post-war illnesses have been described and the similarities among the so-called syndromes are striking. In the recent years, Gulf War related illness has been studied intensively and many parallels can be drawn with symptoms in Cambodia veterans.

Chapter three addresses the nature and prevalence of symptoms in Cambodia veterans and the way in which they are made operational for research purposes. The results of a large-scale cross-sectional postal survey among all Cambodia veterans and four relevant control groups are described.

Chapter four is concerned with a sequel to the previous chapter. It reports the results of a 18-months follow-up postal survey in a subset of Cambodia veterans with elevated levels of fatigue. The natural course of symptoms in Cambodia veterans is evaluated as well as factors associated with improvement.

Chapter five and six address the pathogenesis of symptoms in Cambodia veterans. Chapter five discusses the role of the anti-malaria drug mefloquine, vaccinations and illness caught during the peace operation. In chapter six it is questioned to what degree posttraumatic stress disorder can account for symptoms in Cambodia veterans.

Chapter seven and eight give more insight in the somatic and psychological assessment program which has been performed in a subset of symptomatic veterans and matched healthy controls. Since Cambodia veterans commonly complain about reduced activity levels, decreases in physical fitness and aggravation of symptoms after strenuous exercise, these symptoms were evaluated in a controlled study using actometers, diaries and a maximal exercise test. The results are described in chapter seven.

Chapter eight deals with neuropsychological complaints in Cambodia veterans. Self-reported neurocognitive problems are evaluated, standardised test results are shown and their concordance is discussed.

In chapter nine, the nomenclature "Post-Deployment Syndrome" is introduced for somatic symptoms after acts of war and peace operations. The importance of an

international standard is stressed, and limitations of international studies are discussed. This chapter also presents a hypothetical pathogenic model for Post-Deployment Syndrome that intends to answer the question why (ex-)servicemen become symptomatic. This thesis is concluded by a summary.

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Chapter 2

Somatic and psychological symptoms in (ex)-servicemen after acts of war and peace keeping operations

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Summary

After their return from the peace-keeping operation United Nations Transitional Authority for Cambodia (UNTAC), Dutch UN (ex-)servicemen are concerned about their health. They report physical and psychological complaints which are highly similar to those of Gulf War related illness.
The question is whether symptoms in Cambodia veterans, Gulf War related illness and other complaints related to military operations and peace-keeping missions represent unique syndromes or comparable complaints.
A historical review of war syndromes indicates that it is not likely that new and unique syndromes will develop with every war or peace-keeping mission. It is considered just as unlikely that all war syndromes can be reduced to one diagnostic category.
To explain symptoms in Cambodia veterans, four hypothetical models have been drawn up: the somatic start model, the psychotrauma start model, the pre-morbidity model and the non-Cambodia related complaints model. These models can probably, after validation, be generalised for application to other complaints that develop after military operations and peace-keeping missions. Furthermore, they could also serve as the starting point for prevention and treatment of complaints after future military operations and peace-keeping missions.

Introduction

Since the return of the peace-keeping mission United Nations Transitional Authority for Cambodia (UNTAC), Dutch UN (ex-)servicemen have expressed concern about the negative effects of this mission on their physical and mental health. They report complaints, known as "jungle disease" or "post-Cambodia complaints", which have been the subject of scientific research since 1996.[1,2] The complaints of the Cambodia veterans are similar to those of Gulf War related illness, a condition suffered by servicemen who served in the Persian Gulf War (1991-1992). In both cases the complaints consist of severe fatigue, loss of concentration, forgetfulness, aching muscles, and headaches. The cause of both was, in first instance, believed to be chemical factors: Gulf War related illness was attributed to prophylactic medication against chemical warfare (pyridostigmine tablets), vaccinations, and exposure to nerve gas, depleted uranium and oil well fires; post-Cambodia complaints were presumed to be due to multiple vaccinations and the anti-malarial Mefloquine.[1,3-5] In the recent past the importance of psychological factors, such as the feeling of being threatened and exposure to traumatic events, has been pointed out.[6,7] The many studies on Gulf War related illness have, with few exceptions, not been able to demonstrate somatic causes.[5,6,8,9] Similarly, posttraumatic stress disorder (PTSD) does not appear to be a uniform explanation for these complaints.[6] Estimates of the prevalence of PTSD among Gulf War veterans vary widely: from 3 to 50% whereby most studies report low percentages.[10]

The first phase of the Dutch study on symptoms in Cambodia veterans consisted of a cross-sectional postal survey administered to all Cambodia veterans and four control groups.[1,2] In addition, we carried out individual somatic and psychological investigations in a lobby group of Cambodia veterans with complaints and two control groups.[1]

Analysis of the postal survey indicated that 17% of the Cambodia veterans suffered severe complaints of fatigue five years after their posting. A somatic explanation could not be found. Depending upon the criteria chosen, the estimated prevalence of PTSD was 1-2%; 4-16% of them met at least one of the three criteria for PTSD.[1,2] In comparison: in a study of servicemen who have participated since 1975 in peace-keeping and crisis control operations, about 5% of the respondents met all criteria for PTSD and 16% at least one of these criteria.[11]

It was found that the complaints of the Cambodia veterans were not specific to this group: a surprising 29% of a small group of servicemen who participated in the period 1993-1996 in the United Nations Assistance Mission for Rwanda (UNAMIR) in Rwanda, Zaire and Burundi satisfied the criteria established for post-Cambodia complaints. In the absence of a set case definition, the fatigue severity subscale of the Checklist Individual Strength was used to produce an operational case definition. Respondents with CIS-fatigue severity scores equal to or greater than 37 were defined as cases.[1,12,13] In another study, similar complaints were reported by Dutch servicemen in the United Nations Protection Force (UNPROFOR) who were stationed in former Yugoslavia.[14]

Unexplained somatic and psychological complaints after military operations have been described since the American Civil War. Every war seems to be characterised by its

own symptoms and by new syndromes with their own unique names. Weerts and Weisaeth expect that new medical syndromes will also develop in the course of future armed conflicts and wars.[15]

In this connection, the question arises whether Gulf War related illness, symptoms in Cambodia veterans and complaints after military operations and peace-keeping missions are unique syndromes or comparable complaints. In this article we will try to answer this question by means of an historical review of somatic and psychological complaints after military operations and peace-keeping missions. The goal is to draw a comparison between various war syndromes, without attempting to achieve total historical accuracy. In conclusion, we will present four hypothetical models based on clinical experience which might explain symptoms in Cambodia veterans.

Wars and peace-keeping missions

In the following historical review, we will discuss somatic and psychological complaints after military operations and peace-keeping missions. In this respect we assume that there is no essential difference in the development of complaints between servicemen who participated in a war and those involved in a peace-keeping mission. In both cases they come into contact with war[16] and are confronted with situations which can induce such emotions as fear, anger, sorrow, helplessness and horror. Along this same line, O'Brien presumes that in war situations servicemen and civilians will experience similar psychological stressors and reactions, despite differences in position.[17] We do not mean to imply here that there are no differences between the veterans of war and those of a peace-keeping mission. They have different tasks and are involved in violence in different ways. Peace-keeping task forces are often bound by the rules of engagement, which means that they may only use their weapons when they themselves are in immediate danger and this danger cannot be averted by some other means.[18] As a result they cannot and may not intervene in many cases. In addition they are often required to perform non-military tasks such as the recovery of bodies of citizens or opening up mass graves.[17] Binneveld summarises the difference by describing the members of a peace-keeping mission as spectators of violence and misery who, in comparison with war veterans, are usually in less danger and suffer fewer hardships.[16]

Brief historical review of war syndromes

American Civil War

One of the first extensively documented war syndromes is the so-called "irritable heart", described by Da Costa.[19] During the American Civil War (1861-1865) he examined 300 servicemen with such complaints as chest pain, palpitations, shortness of breath, fatigue, headaches and dizziness. He found clear agreement between these complaints and those described earlier for British troops in India and the Crimean War and he assumed there was a somatic cause: excessive marching[19,20] The "irritable

heart" was later also observed among civilians, especially young women who performed strenuous work, who were highly emotional or who had to stand in a large crowd of people.[21] According to Da Costa, the complaints of this group were as a rule the result of a recent infectious disease. How many servicemen and civilians suffered an "irritable heart" is not clear, but according to English data it appears that 8-14% of all servicemen declared unfit for military service had a heart condition which was the direct cause of their discharge.[20]
Another disease pattern that was observed predominantly among young soldiers was described as nostalgia. The accompanying complaints such as anorexia, apathy, diarrhoea and fever were considered to be due to a severe form of homesickness.[22]

First World War

During the First World War (1914-1918) "effort syndrome" and "shell shock" were described as the most important war diseases. The complaints, which became worse upon exertion, were shortness of breath, sighing, palpitations, chest pain, fatigue, headaches, dizziness, confusion, lack of concentration and forgetfulness.
The effort syndrome was usually explained somatically: the straps of heavy backpacks and tight uniforms hampered breathing and circulation. This explanation, which had already been accepted by the British Army in the 19th century, was replaced in the course of time by other somatic explanations such as physical weakness and exhaustion due to infectious diseases, lack of sleep and exercise in the trenches and the effects of both poisonous gases and vaccinations.[20,22,23] During World War I the effort syndrome was the third most common reason for discharge from the army.[24] After the war more than 44,000 veterans in Great Britain alone received disability compensation for this condition.[22]
In the course of World War I, the term neurocirculatory asthenia became popular. "Neurasthenia" was a term introduced by Beard in 1869 to describe general nervous fragility. A hereditary predisposition for neurocirculatory asthenia was assumed. Servicemen with this predisposition were often recognised before combat due to their nervous complaints.[21] Aggravating factors such as exhaustion, undernourishment, or stress attributable to combat in trenches increased the chance of complaints.
In addition to the effort syndrome, considerable attention was also directed to another pattern of complaints: shell shock characterised by signs of paralysis, exhaustion, forgetfulness, irritation, anxiety, blindness, deafness and speech disorders.[16,22] At first, a somatic explanation for shell shock was given: brain damage due to exploding grenades. Since shell shock also occurred among servicemen who had not been exposed to grenades, it was then related to combat in trenches, danger and deprivation.[25] Synonyms for shell shock were trench neurosis, buried alive neurosis, gas neurosis and traumatic neurosis or war neurosis. Especially soldiers with a hereditary predisposition, a family history of psychiatric disorders, a weak constitution or a nervous personality structure were susceptible.
A number of physicians trained in psychiatry related shell shock and hysteria. This latter condition occurred predominantly in the lower social classes and among females of the upper social classes, whereas males from the high social class were more likely

to suffer from neurasthenia.[16,23] In the army this was also apparent: soldiers were said to have hysteria, officers had neurasthenia.[16]

Second World War

Immediately after the start of World War II (1940-1945) fatigue, palpitations, diarrhoea, headaches, loss of concentration, forgetfulness, sleeplessness, fear and nightmares were observed among American and British servicemen; 37% of the soldiers discharged from the American Army suffered such complaints as effort syndrome, war neurosis, psychoneurosis, combat neurosis or anxiety neurosis, battle fatigue, combat fatigue or operational fatigue and battle exhaustion or combat exhaustion.[26,27] Among German servicemen these complaints did not develop until after 1943. According to Binneveld, this can be explained by the attention directed to training, selection and prevention of these diseases in the German army.[16]

As the names of the complaints suggest, they were attributed mainly to psychological factors. About 94% of the servicemen who visited a centre specialised in war diseases during World War II were found to have a psychiatric condition.[28] It was presumed that complaints after military operations were caused by interaction between stress, the individual and the surroundings. Whether a soldier developed complaints depended on the nature, intensity and duration of the stress to which he was exposed, his pre-deployment mental health, character and styles of coping and finally the morale of and the support received from his military unit.[25] The roles of familial psychiatric burden and congenital personality structure were not considered as important as in World War I. Terms such as "the old sergeant syndrome" and "lone survivor syndrome" expressed the idea that each serviceman would suffer some form of complaint sooner or later.[16] The point was that the complaints would disappear on their own in the course of time. If this did not happen, then this was considered to be the result of character problems which had already existed for a long time.[29]

Vietnam War

At the beginning of the Vietnam War, it was presumed that combat exhaustion and stress could be prevented by directing considerable attention to the psychological preparation and mental resilience of groups of servicemen and by establishing the dates of departure, furlough and return ahead of time. During the Vietnam War the number of acute psychiatric cases, with the exception of those related to drug addiction, was indeed low.[16,25,30] The complaints that developed were called "acute battle stress reaction" or "combat stress". However after their return from Vietnam, depression, nightmares and alcohol and drug addiction became a major problem.[31] These complaints became known as the post-Vietnam syndrome.

Another problem that occurred after the war in Vietnam was the discussion about possible poisoning by Agent Orange, a chemical defoliant. Agent Orange was said to have caused complaints such as numbness, tingling of the extremities, rashes, fatigue, lack of interest in sex, changing moods, and general weakness and also to be responsible for cancer and congenital disorders among the children of Vietnam veterans.[22,32] The validity of this assertion is still today a subject of debate.[22]

Partly in reaction to the complaints of the Vietnam veterans, the diagnosis posttraumatic stress disorder (PTSD) was included in the Diagnostic and statistical manual of mental disorders (DSM-III) in 1980, thus establishing the fact that highly emotional events can in the long run have psychological effects.[33] By placing PTSD in the long term perspective and uncoupling it from existing character problems, there was more recognition of the problems of Vietnam veterans. According to the recent DSM IV, the diagnosis PTSD can be established whenever complaints of re-experience, avoidance, numbness and enhanced irritability develop after experiencing a traumatic event that induced subjective reactions of intense fear, helplessness or horror. The complaints must last a minimum of one month and cause severe suffering or limitation of daily functioning. When the complaints last more than three months, the condition is called chronic PTSD, less than three months is acute PTSD.[35,36]
Kulka and colleagues investigated the prevalence of PTSD among 1600 Vietnam veterans.[31] They found that 15% of men and 9% of women met the criteria for PTSD years after the Vietnam War. Among Vietnam veterans exposed to a high level of stress or permanently disabled as a result of the war, the prevalence of PTSD and other psychiatric conditions was even higher. That the symptoms of PTSD can develop years later was also demonstrated by the Dutch investigation of members of the Federation of Dutch War and Military Service Victims (BNMO) who were born between 1920 and 1929. The prevalence of PTSD in this group today is estimated to be 23%.[37]

Unique syndromes or comparable complaints

Weerts and Weisaeth find it striking that for every new war psychological symptoms and syndromes appear to be newly discovered or at least are provided with new names.[15] This finding is in agreement with the historical review presented above; every war seems to have its own specific somatic and psychological complaints. However, and now we have returned to the question posed at the beginning of this article, are there really unique syndromes or do the various names mask comparable symptoms? The first conclusion, based on the historical review, is that patterns of complaints of the various war syndromes appear at least superficially to exhibit similarities. Almost without exception, the complaints are non-specific such as fatigue, headaches, palpitations and anxiety.[5,22] In his commentary, Straus mentions the striking similarity between Gulf War related illness and the complaints registered during World War I.[38]
The question of whether the syndrome is unique can also be found in literature on Gulf War related illness. In several recently published articles, the general conclusion is that despite the fact that Gulf War veterans have more complaints and a lower psychological wellbeing than military control groups, there are no indications that an unique Gulf War syndrome exists.[6,8,38-40] In this connection is it suggested that the as yet unknown underlying cause of the complaints of the Gulf War veterans could also apply for servicemen stationed elsewhere.[40]
Data from our own investigation also contradict the existence of unique syndromes. Post-Cambodia complaints did not appear to be specific to Cambodia veterans. In a

control group of UNAMIR veterans, an even higher percentage of respondents satisfied the criteria than in the group of Cambodia veterans.[1]
In line with the assumption that war syndromes with different names are characterised by comparable symptoms, various authors state that these complaints today are called PTSD, panic disorder or chronic fatigue syndrome.[20,21,23,27,29,41] The question which follows is whether complaints after military operations and peace-keeping missions can indeed be reduced to a homogeneous disease pattern, in particular PTSD. In an investigation of 1000 Gulf War Veterans individual somatic and psychological studies were performed.[9] In total, 12% had PTSD and 39% reported one or more complaints which did not lead to a diagnosis. For 59% of the veterans studied, more than one somatic or psychiatric diagnosis was established. An investigation of Vietnam veterans also revealed that it was impossible to group the complaints into one diagnostic category: in addition to PTSD diverse other psychiatric diagnoses were established.[31] According to O'Brian one diagnosis is too simple, a misrepresentation of the situation. In his opinion war and PTSD are often considered incorrectly to be synonyms.[17]
In summary, on the basis of the similarities described by various authors between war syndromes and data from studies of Gulf War related illness and symptoms in Cambodia veterans, it appears barely plausible to assume that new and unique syndromes will become manifest with every war or peace-keeping mission. In fact, these complaints appear to be characterised by similarities. Furthermore various authors disagree with the assumption that complaints after military operations and peace-keeping missions can be reduced to a homogeneous disease pattern, for example PTSD.

Four models for post-Cambodia complaints

Finally, we would like to conclude this article with the presentation of four hypothetical models to explain post-Cambodia complaints. In view of the discussion above, these models might possibly be applied to other war syndromes. The models were developed as a result of clinical experience within the post-Cambodia complaints investigation.[1] In the first phase of this investigation, we performed somatic and psychological studies of each of the 21 symptomatic Cambodia veterans who were members of a lobby (the so-called Group of 27) and two control groups (21 Cambodia veterans without complaints and 15 healthy non-military neighbourhood controls). The studies consisted of physical and neurological examinations, perfusion single-proton emission computed tomography (perfusion SPECT) of the brain, microbiological, immunological and endocrinological tests; a bicycle ergometric test; interviews about service in Cambodia and the present state of health of the subject; screening for psychiatric conditions; neuropsychological studies and measurement of the activity level by means of an actometer[42], an apparatus the size of a matchbox which is attached to the ankle and measures the number of movements within each 5-minute period. In view of the limited size of the groups studied and the fact that generalisation of the data on the Group of 27 will probably be limited, the models are as yet

considered to be hypothetical in nature. At present we are carrying out a follow-up investigation to test their validity. We expect that the models will provide starting points for the treatment of symptomatic Cambodia veterans and for the prevention of physical and psychological complaints after future military operations and peace-keeping missions. In the first two models a differentiation is made between initiating and maintenance factors.

Somatic start model

In the somatic start model the complaints began during and shortly after the posting in Cambodia. A clear-cut somatic event can be indicated as cause of the complaints, such as an infection (e.g. dengue, malaria or amoebic dysentery). These initiating factors cannot however explain the persistence of the complaints. We assume that the complaints are maintained by cognitive and behavioural factors such as strong causal attributions, the degree of control over the complaint as experienced by the subject (self-efficacy), somatisation and inactivity. In other investigations it appeared that these are perpetuating factors for the chronic fatigue syndrome.[43]

Psychotrauma start model

In the psychotrauma start model the complaints developed after a severe incident that occurred during the posting to Cambodia. During, or after the posting the diagnosis PTSD was established with certainty or high probability. At the time of our examination the criteria for PTSD were no longer fulfilled, usually as a result of adequate treatment. Nevertheless some complaints persisted. Analogous to the first model, we assume that similar cognitive and behavioural factors contribute to the persistence of the complaints.

Premorbidity model

In the pre-morbidity model the actual complaints fit within the context of the physical and psychological disturbances which occurred in the years before the posting to Cambodia. Support for this model is found in literature: a psychiatric history is known to be an important predictive factor for the development of complaints after shocking events.[17,34]

Non-Cambodia related symptoms model

In the model of non-Cambodia related symptoms, the complaints develop long after return from Cambodia, for example after another war or posting. Logically speaking, a relationship with the posting to Cambodia cannot be demonstrated.

Of the 21 Cambodia veterans with complaints that we examined, six were assigned to the somatic start model, four to the psychotrauma start model, four to the premorbidity model and seven to the non-Cambodia related symptoms model.

Conclusion

Physical and psychological complaints occur after almost every war or peace-keeping mission. In general, practising physicians will seldom encounter this problem, since those in military service normally make use of the medical facilities provided by the Ministry of Defence. Physicians and specialists in civilian society are however often consulted by veterans who are still young and have left military service. According to Murphy, doctors should take the complaints of servicemen who have participated in a war or peace mission seriously; they should not attribute them directly to stress without supplementary somatic and laboratory examinations.[10]

As we have argued, it does not seem plausible that new and unique syndromes develop with every war or peace-keeping mission. In addition, it appears just as unlikely that the many war syndromes can be reduced to one diagnostic category. However, in a number of cases it is of course possible to deduce one diagnosis at the individual level, for instance PTSD. We have presented four models to explain the post-Cambodia complaints. The models require further validation, but then they could offer starting points for the prevention and treatment of complaints after future military operations and peace-keeping missions.

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Chapter 3

Fatigue in Cambodia veterans

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Summary

In 1992 and 1993 Dutch military personnel were deployed in the peace operation UNTAC in Cambodia. Since returning, Cambodia veterans have reported health complaints which they perceive to be related to their service. Their symptoms strikingly resemble health problems reported by Gulf War veterans. Four years post-return, a cross-sectional survey on health symptoms in Cambodia veterans was initiated. Questionnaires were sent to all Cambodia veterans and four comparison groups. Forgetfulness, difficulty concentrating and fatigue were the symptoms most commonly endorsed. An operational case definition was constructed using a validated fatigue severity questionnaire. Cases were not uniquely found in Cambodia veterans (17%). In Rwanda and Bosnia veterans, respectively, 27% and 11% also met our case definition. Fatigue severity level was predicted by pre-mission, during-mission and post-mission variables, of which retrospective recollection of side-effects of vaccines and causal attributions also have shown to be relevant in studies on Gulf War related illness.

Introduction

In the last few years there has been considerable public concern and medical interest in symptoms in veterans who have served in the Persian Gulf War, and veterans who have participated in other acts of war and peace operations. In the Netherlands, symptoms have been reported in (ex)-servicemen who were deployed in the peace operation United Nations Transitional Authority for Cambodia (UNTAC).
In 1992 and 1993, approximately 2616 Dutch servicemen were sent out to Cambodia in three battalions, each for a 6-month period. UNTAC was established in March 1992 after the ending of the civil war in Cambodia that had lasted two decades. Over 30 different nationalities, among which French, German and Australian military personnel have participated. The major tasks of UNTAC were supervising the administration of

the country, disarming local factions, guiding free elections, guarding human rights, repatriating Cambodian refugees from refugee camps in Thailand, and mine clearance. The majority of Dutch military personnel in Cambodia were blue helmets. They were stationed in the north-western province Bantey Meanchey.

Since returning, Cambodia veterans have reported health problems, which they attribute to their service in Cambodia. Their complaints, as voiced in the Dutch media, are severe fatigue, cognitive problems and headaches, which they perceive to be related to the malaria chemoprophylaxis mefloquine or the vaccines they were exposed to. According to symptomatic Cambodia veterans, symptoms had started in Cambodia or just after return.

On face of it, symptoms in Cambodia veterans strikingly resemble symptoms reported in military personnel with alleged Gulf War syndrome: the same main symptoms are reported, causal attributions to chemical factors also have been made, and the topic was discussed in the media.[1,2] Recent studies on Gulf War syndrome were not able to identify a unique Gulf related illness, or to prove dose-effect relationships between exposures and physical or psychological symptoms.[3-5] However, the nature and aetiology of Gulf War Syndrome remain controversial.

In 1997, we initiated a comprehensive, independent study on symptoms in Cambodia veterans. To our knowledge, no scientific studies have been conducted on Cambodia veterans in other countries. This article reports the first phase of our study in which we send a cross-sectional postal survey to all Cambodia veterans whose particulars were known to the Ministry of Defence. The findings of our study will be compared with recently published findings relating to Gulf War related illness. We investigated the prevalence of symptoms in Cambodia veterans, whether these symptoms were specific to Cambodia veterans, and what factors predicted symptoms in these Cambodia veterans.

Methods

Subjects

According to the latest figures of the Dutch Ministry of Defence, an entire sample of 2616 servicemen were deployed in Cambodia. Data were available for 2548 Cambodia veterans. Sixty-eight names and addresses (2.6%) could not be retrieved from the databases of the Ministry of Defence, probably because these files had been deleted after servicemen had left service. Thus, subjects were 2548 Cambodia veterans whose addresses were known to the Ministry of Defence. To control for symptoms in military who have been deployed elsewhere in tropical and non-tropical countries, servicemen who have not taken mefloquine but were administered vaccines, and military personnel who have never been deployed, four comparison groups were included: 120 (ex-) servicemen who were deployed in UNAMIR (United Nations Assistance Mission for Rwanda: 1994-1996; Rwanda group), 203 servicemen who were deployed in UNPROFOR (United Nations Protection Force in former Yugoslavia: 1993-1995; Bosnia group), 200 military personnel who were on stand-by for UNAMIR in 1994 (notice group), and 187 never-deployed marines (no-deployment group).

Material

The questionnaire collected information regarding:

Fatigue severity, using the Checklist Individual Strength (CIS).[6;7] The CIS measures different aspects of fatigue (fatigue severity, concentration problems, and physical activity level) over the last 14 days. Psychometric properties are excellent. Scores on the 8-item fatigue severity scale range from 8 to 56, higher scores indicate more fatigue and related problems. The CIS has been used in all studies of the Netherlands Fatigue Research Group, so data from different comparison groups as well as healthy controls are available.

Self-reported symptoms, using a questionnaire determining the presence of 33 symptoms which were selected on basis of literature on Gulf War related illness, chronic fatigue syndrome, side-effects of mefloquine and vaccinations, and tropical infectious diseases.

The period from notice until departure (pre-mission period) by including four questions on satisfaction with the preparation offered by the Ministry of Defence; attitude to the peace operation (3 items); length of time between notice and departure (1 item); side-effects of vaccines (1 item); and earlier experience in the tropics (1 item).

The time in Cambodia by including four questions on subjective experience of the peace operation; satisfaction with living conditions in Cambodia (3 items); problems at the home front (1 item); length of stay in Cambodia (1 item); repatriation (1 item); worries about one's health (1 item); and side-effects of mefloquine (1 item).

The period from return until the moment of study (post-mission period) by including a four-item self-efficacy questionnaire that measures perceived control over symptoms[5]; a 6-item questionnaire measuring consequences of the peace operation on relationships[8]; four questions measuring causal attributions (my complaints are related to mefloquine use; my complaints are related to traumatic events; my complaints are related to vaccines that were administered before departure; my complaints are related to disease caught in Cambodia); adaptation (5 items); problems at the home front (1 item); and satisfaction with military career (1 item).

The questionnaire was tested in a pilot study. Control groups received an adjusted version of the questionnaire to fit their personal situation.

Procedure

Given the independent nature of our study, we were bound by privacy regulations. The Ministry of Defence was not allowed to pass on their address database to the researchers, and vice versa. Thus, we did not possess the complete address database for all 2548 Cambodia veterans, and we were not allowed to inquire about the addresses of non-responders. Unfortunately, therefore, we were not able to investigate non-responders further.

The State Secretary for Defence announced our independent study in a letter directed to all Cambodia veterans. Two weeks later, the Ministry of Defence sent the questionnaires, including a postage paid return envelope addressed directly to the research group. A reminder was sent another 3 weeks later. Respondents who returned the questionnaire and wrote down their particulars were recorded in an

address database. All respondents were offered a gift voucher of 25 Dutch guilders, which they could donate to charity or which they could receive themselves. The ethics committee of our hospital approved the study.

Case definition

Based on news reports on Cambodia issues, literature on Gulf War syndrome and preliminary interviews with military personnel, fatigue, difficulty concentrating and forgetfulness were assumed to be frequent symptoms in Cambodia veterans. In the absence of a set case definition, the CIS-fatigue severity scale was used to produce an operational case definition. Respondents with CIS-fatigue severity ≥37 were defined as cases. The cut-off score of 37 was derived from the mean score of a group of healthy controls used in another study by adding two standard deviations (M=17.3±10.1) [95% C.I.: 14.5-20.2].[9]

Statistics

Data were entered twice in Dbase IV to check for errors in data entry. Data analysis was performed using SPSS (version 8.0). For reasons of homogeneity, only men were included. Univariate analyses were used to test differences between groups. The alpha level was set at p=0.05. We used exploratory factor analysis with varimax rotation to identify underlying factors in questions that collected information regarding the pre-mission period, the time in Cambodia, and the post-mission period. An eigenvalue >1.0 was chosen as the extraction criterion. Single factors were collected in a factor if Cronbach's alpha reliability coefficient was >0.60.

Prediction of outcome measures was done by linear regression analyses. The dependent variable was CIS-fatigue severity score. The independent variables were the factors and single items that related to the periods mentioned above. Factor and regression analyses could only be performed on Cambodia veterans who reported present symptoms or indicated that they had suffered symptoms during or after the peace operation, since the questions on perceived control over symptoms and causal attributions do not make sense to non-symptomatic respondents. This group of 672 respondents did not differ from the total group in age, marital status and service branch. The groups only differed in educational level, the former group being overall less educated (Chi^2, df=1, p<0.01). Respondents with missing values were not included in the analyses.

Results

A completed questionnaire was returned by 1721 male Cambodia veterans (68%). In the Rwanda, Bosnia, notice and no-deployment groups, the number of male respondents were 58 (48%), 75 (37%), 77 (39%), and 91 (49%), respectively. Biographical data are shown in table 1. Cambodia veterans and comparison groups differed significantly in age ($F(4,2003)=92.8$, p<0.001), marital status (Chi^2, df=4, p<0.001), educational level (Chi^2, df=4, p<0.001), and rank (Chi^2, df=4, p<0.05).

Symptoms

Cambodia veterans reported a mean of 3.0±3.9 current symptoms [95% C.I.: 2.8-3.2]. As expected, the main symptoms reported were forgetfulness (35%), difficulty concentrating (28%) and fatigue (24%), followed by feeling unrefreshed by sleep (21%), flatulence (20%), joint pain (15%), sight problems (14%), headache (14%), tension or nervousness (13%) and rashes (11%). Table 2 shows the respective percentages in comparison groups.

Between groups, significant differences were found on the total number of symptoms reported. Cambodia veterans reported more symptoms than the notice and no-deployment group ($F(4,2021)=9.8$, $p<0.001$). Results remained significant after correction for age, rank and education. No significant differences were found between Cambodia, Rwanda and Bosnia veterans.

Table 1 Biographical data

	Cambodia	Rwanda	Bosnia	Notice	No-deployment	*p*
Male respondents	*1721*	*58*	*75*	*77*	*91*	
Age						
M±SD	35.5 (8.1) [35.2-35.9]	37.2 (9.3) [34.8-39.7]	26.5 (2.5) [25.9-27.0]	25.3 (3.9) [24.4-26.2]	24.6 (5.2) [23.6-25.7]	<0.001
Marital status						
Married	55%	60%	4%	16%	9%	
Unmarried	45%	40%	96%	84%	91%	<0.001**
Educational level						
Lower	81%	72%	73%	80%	62%	
Higher	19%	28%	27%	20%	38%	<0.001**
Rank						
Lower	86%	80%	99%	91%	88%	
Higher	14%	20%	1%	9%	12%	0.05**
Service branch						
Marine Corps	54%	-	-	-	100%	
Navy	10%	-	-	-	-	
Army	7%	30%	98%	99%	-	
Air Force	5%	37%	-	1%	-	
Military Police	1%	3%	2%	-	-	
Left service	23%	30%	-	-	-	

ANOVA, *Chi^2-test, $p<0.05$; Lower educational level = elementary school, lower vocational & secondary education, intermediates; Higher educational level = school of higher general secondary education, higher vocational education, Royal Marine Academy, University

Table 2 Symptoms in Cambodia veterans and comparison group

	Cambodia	Rwanda	Bosnia	Notice	No-deployment
*Number of symptoms**					
M±SD	3.0 (3.9)	3.9 (5.4)	2.8 (3.8)	1.6 (2.8)	0.9 (1.6)
[95% C.I.]	[2.8–3.2]	[2.5–5.3]	[1.9-3.8]	[1.0-2.3]	[0.6-1.3]
Forgetfulness	596 (35%)	17 (30%)	11 (15%)	6 (8%)	4 (4%)
Difficulty concentrating	478 (28%)	15 (26%)	14 (19%)	8 (10%)	2 (2%)
Fatigue	408 (24%)	16 (28%)	17 (23%)	7 (9%)	4 (4%)
Unrefreshing sleep	356 (21%)	17 (30%)	19 (25%)	10 (13%)	5 (6%)
Flatulence	349 (20%)	10 (17%)	11 (15%)	3 (4%)	11 (12%)
Joint pain	265 (15%)	7 (12%)	15 (20%)	7 (9%)	9 (10%)
Sight problems	243 (14%)	9 (16%)	6 (8%)	3 (4%)	-
Headache	235 (14%)	10 (17%)	10 (13%)	5 (7%)	2 (2%)
Nervous / tense	228 (13%)	12 (21%)	8 (11%)	5 (7%)	4 (4%)
Skin rashes	180 (11%)	10 (17%)	10 (13%)	6 (8%)	4 (4%)

ANOVA, $p<0.05$

Cases and specificity

A total of 1716 Cambodia veterans completed the CIS-fatigue severity scale. Their mean score was 21.9±12.6). Elevated CIS-fatigue severity scores (≥37) were found in 288 respondents. Thus, 16.8% of Cambodia veterans were marked as cases (table 3). Between groups, significant differences were found on the CIS-fatigue severity scale ($F(4,2012)=19.2$, $p<0.01$). Cambodia veterans scored significantly higher than the notice and no-deployment group and significantly lower than Rwanda veterans (table 3). Results remained significant after correction for age, rank and education. Respondents in the comparison groups also met the case definition: 27.3% of Rwanda veterans, 10.8% of Bosnia veterans, 3.9% of the notice group and 2.2 % of the never deployed marines had a CIS-fatigue severity score ≥37 (table 3). Thus, cases were not found in Cambodia veterans exclusively.

Table 3 CIS-fatigue severity scores and number of cases

	Cambodia n=1716	Rwanda n=55	Bosnia n=74	Notice n=77	No-deployment n=91	*p*
CIS-fatigue severity						
M±SD	21.9 (12.6)	27.1 (14.3)	20.5 (10.4)	15.8 (8.7)	12.7 (6.8)	
[95% C.I.]	[21.3-22.5]	[23.2-30.9]	[18.1-22.9]	[13.8-17.8]	[11.3-14.1]	0.001*
CIS-fatigue severity ≥37	288 (16.8%)	15 (27.3%)	8 (10.8%)	3 (3.9%)	2 (2.2%)	

ANOVA, $p<0.05$

Factor analyses

For the pre-mission period, two factors (eigenvalue >1.0) were identified. Cronbach's alpha was >0.60 in only one factor, that we named "satisfaction with the preparation offered by the Ministry of Defence" (4 items, % of variance = 23, alpha=0.64).
For the time in Cambodia, four factors (eigenvalue >1.0) were identified. Again, Cronbach's alpha was >0.60 in only one factor: "subjective experience of the peace operation" (4 items, % of variance = 24, alpha=0.80).
Regarding the post-mission period, four factors (eigenvalue >1.0) were identified. Cronbach's alpha reliability coefficient was >0.60 in two factors: "adaptation after return" (4 items, % of variance = 22, alpha=0.61) and "causal attributions to medication" (2 items, % of variance = 14, alpha=0.68).
Table 4 gives an overview of all factors and single items that were entered as independent variables in regression analysis.

Predictors of severe fatigue and fatigue related problems

For the pre-mission period, higher current CIS-fatigue severity scores were predicted by less satisfaction with the preparation offered by the Ministry of Defence and more experienced side-effects of vaccines (table 5).
For the time in Cambodia, higher current CIS-fatigue severity scores were predicted by a greater impact of the mission, more problems at the home front and more worries about one's health (table 6).
For the post-mission period, higher current CIS-fatigue severity scores were predicted by lower self-efficacy, more problems in re-adjustment on return, less satisfaction with military career, stronger causal attributions to medication, more problems at the home front and a stronger causal attribution to disease caught in Cambodia (table 7). Taken the pre-mission, mission and post-mission predictors together, the same predictors come out as in the post-mission period.

Table 4 Independent variables in regression analysis

Pre-mission	
Factor	satisfaction with the preparation offered by the Ministry of Defence
Single items	voluntary or involuntary participation; own attitude and attitude of the home front to the peace operation; length of time between notice and departure; earlier experience in the tropics; experienced side-effects of vaccines
Time in Cambodia	
Factor	subjective experience of the peace operation
Single items	length of stay in Cambodia; did repatriation take place?; problems at the home front; worries about one's health; side-effects of mefloquine; quality of food; hygienic situation; satisfaction with means of communication
Post-mission	
Factors	adaptation after return from Cambodia; causal attributions to medication
Single items	self-efficacy questionnaire; consequences of the peace operation on relationships questionnaire; attribution to disease caught in Cambodia; satisfaction with military career; talking about emotional events; changes at the home front; problems at the home front

Table 5 Regression analysis regarding the pre-mission period

	Pre-mission period	T	*p*
CIS-fatigue severity:Multiple R= 0.159, delta R^2=0.023, F=8.7, p<0.001			
Satisfaction with preparation		3.0	0.003
Side-effects of vaccinations		2.5	0.012

Table 6 Results regression analysis regarding the mission period

	Mission period	T	*p*
CIS-fatigue severity: Multiple R= 0.199, delta R2=0.035, F=9.1, p<0.001			
Subjective experience of the mission		2.4	0.016
Problems at the home front during the mission		-3.1	0.002
Worries about one's health during the mission		2.3	0.023

Table 7 Results regression analysis regarding the post-mission period

	Post-mission period	T	*p*
CIS-fatigue: Multiple R= 0.389, delta R^2=0.144, F=19.7, p<0.001			
Self-efficacy		6.4	0.000
Adaptation after return		3.8	0.000
Satisfaction with military career		2.7	0.008
Attributions to medication		2.5	0.011
Problems at the home front after the mission		2.3	0.022
Attribution to disease caught in Cambodia		2.3	0.022

Discussion

Main conclusions

In the present study, the prevalence rate of health symptoms in Cambodia veterans was 17%. These symptoms were not specific to Cambodia veterans: in groups of Rwanda and Bosnia veterans, 27% and 10%, respectively, also met our case definition. Fatigue in Cambodia veterans is predicted by less satisfaction with the preparation offered by the Ministry of Defence in the pre-mission period and more side-effects of vaccines, as retrospectively recollected. Further, fatigue was predicted by a more poignant, threatening, aggravating and powerless subjective experience of the mission, more problems at the home front and more worries about one's health status during the mission. Finally, fatigue was predicted by less perceived control over symptoms, more adjustment problems after the mission, less satisfaction with military career, stronger causal attributions to mefloquine and vaccines, more problems at the home front after the mission and a stronger causal attribution to disease caught in Cambodia.

Limitations of the study

The present study has some limitations. Firstly, for reasons of privacy, data on non-responders are not available. Although the response rate among Cambodia veterans was quite high, information on non-responders would gain more inside in the representativeness of the results. Secondly, the sample sizes of the comparison groups are relatively small. Thirdly, and a major limitation of the study, is its retrospective nature. Since we relied on self-report of the Cambodia veterans, recall bias may have been induced, particularly in respondents with more health symptoms. Therefore, it can be questioned whether the factors found to be predictive of fatigue are initiating factors or mere attributions that contribute to the maintenance of the symptoms. Finally, no data are available on the pre-mission level of physical and psychological functioning of the Cambodia veterans. These data are considered important in establishing the onset of the symptoms. On basis of our survey, it can not

be ruled out that symptoms in some respondents already were present before the mission in Cambodia, or have started years after return.

Comparison with Gulf War syndrome

Symptoms in Cambodia veterans strikingly resemble Gulf War syndrome, seen in military personnel who were deployed in the Persian Gulf War. In various studies on American, British and Danish Gulf War veterans, using different designs and methods of selecting subjects, the same main symptoms are reported as in our study, namely fatigue, difficulty concentrating and forgetfulness.[3,10-14] However, it should be noted that the prevalences reported in US and British studies are higher than those in the Danish and our present study. This might be explained by the use of different case definitions. In the absence of a valid and agreed case definition, we used a validated fatigue severity scale to produce an operational case definition. A cut-off score of ≥37 was chosen. If we had used other cut-off scores that also lay beyond the scope of military personnel who have never been deployed or who have been on stand-by for UNAMIR, e.g. ≥33 (M+2SD for the stand-by group) and ≥26 (M+2SD for the no-deployedment group), these percentages would have been much higher, at 23% and 35%, respectively.

As in our study, Gulf War veterans report the same health problems as comparison groups, although at higher levels.[3] They further experience more psychological distress and they more often fulfil set case definitions such as CDC multisymptom syndrome criteria.[3,5]

In the present study, some of the Rwanda and Bosnia veterans also fulfilled our case-definition, in contrast with servicemen who have been on stand-by for Rwanda and never-deployed marines. However, Unwin et al. found that a comparison group of Bosnia veterans did not resemble Gulf War veterans, but rather resembled the non-deployed servicemen.[3] A first explanation for these conflicting results may be the large difference in sample size between the British and Dutch Bosnia groups (2620 and 75, respectively). Further, it could be suggested that the performance of the Dutch in Srebrenica could account for this difference. However, our data did not show an association between symptom reporting and deployment in Srebrenica. Seventeen percent (n=13) of the Bosnia veterans had been deployed in Srebrenica during the fall of the enclave. Fatigue severity scores did not differ between Srebrenica veterans and veterans who were deployed elsewhere in Bosnia during the period 1993-1995 (t=0.5, *p*=NS). Two Srebrenica and six other Bosnia veterans met our case definition.

In the present study, fatigue is predicted, among others, by more retrospectively recollected side-effects of vaccines, a stronger causal attribution to disease caught in Cambodia and a more poignant, threatening, aggravating and powerless subjective experience of the mission. Gulf War veterans also show a positive relationship between retrospective recollection of side-effects of vaccines and report of current symptoms.[3] Further, causal attributions are also considered important in Gulf War syndrome. Several studies have shown a relationship between more self-reported exposures or stronger opinions on being exposed to noxious agents and more health problems or lower health perception.[3,11]

Veterans syndromes

In literature, it is generally concluded that there is no new or discrete syndrome accounting for symptoms in Gulf War veterans.[3,11,14,15] A common factor in symptoms in veterans is further suggested by the resemblance to other symptoms after acts of war and peace operations, and the inability to find relations between specific exposures and specific symptoms.[1,2,14-16] In our opinion, findings on Gulf War syndrome are highly relevant to findings in Cambodia veterans and vice versa. Therefore we question specific names such as "Gulf War syndrome", and advocate a broader nomenclature, namely veterans syndromes. However, more research is needed to clarify exceptions. Further, to address problems on recall bias, cause and effect, initiating and maintaining factors, and baseline levels of functioning, prospective longitudinal studies are needed. This is especially so since participation in humanitarian operations is increasing, and symptoms in veterans are found a profound problem for military forces.

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Chapter 4

Unexplained somatic symptoms in Cambodia veterans: The role of mefloquine, multiple vaccinations and morbidity

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Abstract

During the 1992-3 peace operation United Nations Transitional Authority for Cambodia (UNTAC), 2616 Dutch servicemen were sent to Cambodia for 6 months. Since their return, some complained of persisting fatigue, concentration problems and memory loss; symptoms virtually identical to Gulf War-related illness. We investigated whether these symptoms were due to mefloquine, vaccinations or morbidity during UNTAC. Cambodia veterans who fulfilled our case definition for symptoms (n=292; symptomatic veterans) were compared with a-symptomatic Cambodia veterans and four relevant control groups. Of the former mefloquine users, 49.6% reported to have had side-effects during use. Those who attributed their current complaints to the peace mission to Cambodia, more frequently reported to have experienced side-effects of mefloquine than those who saw no link between their current symptoms and the peace mission and those without symptoms. In the group who attributed their complaints to the peace mission, side-effects of vaccinations were also reported more often. In the control group that participated in a peace mission in Rwanda and of whom a substantial part were symptomatic veterans, the incidence of side-effects of mefloquine was significantly lower than in the Cambodia group. In a regression analysis, self-reported side-effects of mefloquine and vaccinations predicted if veterans were symptomatic. We cannot rule out that mefloquine and/or vaccinations are a contributing factor to the onset of symptoms in veterans. However, because of the stronger causal attribution to mefloquine in the Cambodia group and because the number of mefloquine-users was similar between the different subgroups of symptomatic Cambodia veterans, we conclude that there is no support for a role of mefloquine use in the perpetuation of the complaints. Because a similar percentage of respondents of the Cambodia, Rwanda

and notice group reported side-effects of vaccinations, there is also no support for a role of multiple vaccinations in the perpetuation of the complaints. Prospective studies are needed to further address the role of these factors in initiating symptoms in veterans.

Introduction

In 1992-93, Dutch armed forces participated in UNTAC (United Nations Transitional Authority for Cambodia). Some 2616 troops were sent to Cambodia for 6 months. After return, veterans began to complain of persisting fatigue, concentration problems and memory loss,[1,2] similar to Gulf War-related illness.

Before departure to Cambodia, military personnel were vaccinated against hepatitis A and B, Japanese encephalitis, meningitis A/C, rabies, diphteria, tetanus, poliomyelitis and typhoid. Mefloquine was advised for malaria chemoprophylaxis because of chloroquine-resistant Plasmodium falciparum in Cambodia.

Many believed that the symptoms were due to mefloquine, vaccinations and morbidity in Cambodia. On request of the Minister of Defence, we initiated a comprehensive, independent study on symptoms in Cambodia veterans. This article reports the results of a cross-sectional postal survey sent to all Cambodia veterans and four relevant control groups. We investigated the prevalence of self-reported side-effects of antimalarials, compliance of antimalarials, side-effects of vaccinations, and morbidity during UNTAC as reported by the veterans. We compared the results of symptomatic veterans with a-symptomatic Cambodia veterans and four relevant control groups, i.e. Rwanda, Bosnia, notice and no-deployment group. Furthermore, we investigated which factors were associated with current symptoms.

Materials and methods

Study population

Data were available of 2548 of the 2616 deployed Cambodia veterans; 68 names and addresses could not be retrieved by the Department of Defence. This study population[1,2] included personnel from Navy/Marine Corps, Army, Air Force, and Military Police. A postal survey was announced in March 1997 by a letter of the State Secretary for Defence in which he assured confidentiality and independence of the study. 1733 (68%) Cambodia veterans returned the completed questionnaire (age: 35.5 ± 8.1 years; 12 females). At the same time, four relevant control groups were surveyed: 120 (ex-)servicemen who participated in UNAMIR (United Nations Assistance Mission for Rwanda, 1994-96, 6 weeks duration) and had used malaria prophylaxis and received multiple vaccinations; 203 (ex-)-servicemen who participated in UNPROFOR (United Nations Protection Force, 1993-95, 6 months duration) and who received no malaria prophylaxis or vaccinations; 200 military personnel who were on stand-by for UNAMIR in 1994 and who received multiple vaccinations; 187 never-deployed marines. These groups will be referred to as Rwanda, Bosnia, notice and no-deployment group. The response rates in the control groups were 54%, 40%, 41%,

and 49% respectively. Given the independent nature of our study, we were bound by privacy regulations. Thus, we were not allowed to inquire about the addresses of non-responders. Therefore we could not investigate non-responders further. The study was approved by the ethics committee of the hospital.

Case definition

In the group of 1733 Cambodia veterans, memory loss (35%), concentration problems (28%) and fatigue (24%) were most prominent.[1,2] Fatigue severity was measured by the validated questionnaire Checklist Individual Strength (CIS).[3] Seventeen percent (n=292) of the Cambodia veterans fulfilled our case definition for symptoms in Cambodia veterans (symptomatic veterans (SV); CIS-fatigue severity score ≥37).[1,2] The Cambodia and Rwanda veterans were asked whether they perceived their symptoms to be caused by their participation in the peace mission. The symptomatic veterans were divided into a group who saw a direct link between their symptoms and the peace mission (SV-link group) and into a group who did not (SV-no link group).

Postal survey

The survey included questions about malaria chemoprophylaxis, spontaneously reported side-effects of chemoprophylaxis, chemoprophylaxis compliance, reasons for non-compliance, side-effects of vaccinations, morbidity during and after the mission (with emphasis on amoebiasis, helminthiasis, dysentery, malaria, tuberculosis, and infectious mononucleosis). Mefloquine users were defined as those respondents who used only mefloquine or mefloquine in combination with other drugs.

Statistical analysis

Analyses were performed using SPSS (Statistical Package for the Social Sciences) for Windows 9.0. Results are given as mean ± SD or number (%) unless indicated otherwise. We assumed that respondents who did not fill in the question about side-effects of vaccinations did not have had such side-effects. Group analysis was performed using ANOVA for continuous variable or Chi^2-test for categorical variables. When significant differences were found the results were further analysed between two groups using Chi^2-test or Fisher's Exact Test (categorical variables) or unpaired Student's two-tailed t-test (continuous variable). Fisher's Exact Test was used when more than 20% of the cells had an expected count less than 5. A two-sided $p<0.01$ was taken as the level of significance to control for type I error.
To evaluate which factors predicted fulfilment of our case definition in male Cambodia veterans and which factors predicted high CIS-fatigue severity scores, regression analyses were performed. Because of the explorative character of regression analysis a two-sided $p<0.05$ was taken as the level of significance.

Results

Seventeen percent (n=292) of the Cambodia veterans fulfilled the case definition for symptoms in Cambodia veterans (SV); 223 respondents belonged to the SV-link group

and 69 to the SV-no link group. Symptomatic veterans were also found in the Rwanda (29%) and Bosnia group (11%). In the notice and no-deployment group these percentages were 4% and 2% respectively. An extensive description of the prevalence and nature of symptoms in Cambodia veterans and the controls is given elsewhere.[1,2] The general characteristics of the Cambodia veterans and the four relevant control groups are presented in Table 1. There were no significant differences in sex, age, service branch and rank between symptomatic Cambodia veterans (SV-link and SV-no link) and a-symptomatic Cambodia veterans.

Malaria chemoprophylaxis

According to the questionnaire, 95.6% (n=1638) of the Cambodia veterans had used mefloquine and 3% (n=57) doxycycline. The Air Force was advised to use doxycycline to avoid visual complaints and dizziness of mefloquine prophylaxis. Of the mefloquine users, 49.6% reported to have had side-effects compared to 12.5% of doxycycline users ($p<0.001$). The mean number of symptoms attributed to malaria chemoprophylaxis was significantly higher in mefloquine users (M=1.0 ± 1.2 symptoms) than in doxycycline users (M=0.2 ± 0.1; $p<0.001$).

The number of Cambodia veterans that had used either mefloquine or doxycline during the peace mission was similar in the symptomatic subgroups (SV-link group: 99.1% mefloquine, 0.4% doxycycline; SV-no link: 98.6% mefloquine, 1.4% doxycycline; a-symptomatic veterans: 94.8% mefloquine, 3.9% doxycycline). More respondents of the SV-link group reported to have had complaints due to mefloquine (63.7%) than those of the SV-no link group (23.3%; $p<0.001$) or those of the a-symptomatic group (7.9%; $p<0.001$). The total number of complaints was significantly higher for the SV-link groups (M=1.5±1.5) than for the a-symptomatic group (M=0.9 ±1.2; $p<0.001$) or for the SV-no link group (M=0.7±0.3; $p<0.001$).

Table 1 General characteristics of Cambodia veterans and four control groups

	Cambodia n=1733	Rwanda n=65	Bosnia n=75	Notice n=82	No-deployment n=91	*p*
Age (years)	*35.5 (8.1)*	*36.8 (9.1)*	*26.5 (2.5)*	*25.3 (3.9)*	*24.6 (5.2)*	*0.001**
Sex (male/female)	*1708/12*	*58/7*	*75/0*	*77/5*	*91/0*	-
Current service branch						-
Navy	167 (9.6%)	1 (1.5%)	-	-	-	
Marine Corps	920 (53.1%)	-	-	-	91 (100%)	
Army	122 (7.0%)	20 (30.8%)	56 (98%)	79 (98.8%)	-	
Air Force	98 (5.7%)	22 (33.8%)	-	1 (1.3%)	-	
Military Police	23 (1.3%)	2 (3.1%)	1 (2%)	-	-	
Left military service	403(23.3%)	20 (30.8%)	-	-	-	
Current rank						*NS*
below officer	1530(88.8%)	52 (82.5%)	74 (98.7%)	72 (88.9%)	80 (87.9%)	
officer and above	192 (11.1%)	11 (17.5%)	1 (1.3%)	9 (11.1%)	11 (12.1%)	
Malaria prophylaxis used						
Mefloquine	1638 (95.6%)	60 (92.3%)	-	-	-	-
Doxycycline	57 (3.3%)	1 (1.5%)	-	-	-	-
Other	19 (1.1%)	4 (6.2%)	-	-	-	-
Multiple vaccinations	*yes*	*yes*	*no*	*yes*	*no*	

Mean ± SD or number (%); *, significant difference between Cambodia and Bosnia group, between Cambodia and notice group, between Cambodia and no-deployment group, between Rwanda group and Bosnia group between Rwanda and notice group and between Rwanda and no-deployment group (p<0.01) and no significant difference between Cambodia and Rwanda group, between Bosnia and notice group and between notice and no-deployment group

The spontaneously self-reported side-effects of mefloquine are listed in table 2. These side-effects occurred during mefloquine use during the mission. Dizziness, visual complaints and fatigue are reported more often during mefloquine use by the SV-link group than by the a-symptomatic veterans. However, less than 25% of the SV-link group reported to have had these three side-effects together during mefloquine use. Of the Rwanda group, 93.6% used mefloquine and 1.6% doxycline. Significantly fewer Rwanda veterans (28.8%) than Cambodia veterans (49.6%) reported to have had side-effects of mefloquine (p=0.002). The number of side-effects was also less in the Rwanda (M=0.6 ± 1.0) than in the Cambodia group (M=1.0 ± 1.2; p=0.002). The kind of side-effects did not differ between the two groups. Within the Rwanda group, there was no significant difference in side-effects of mefloquine between respondents who did and did not fulfil our case definition for symptoms in veterans.

Table 2 Number (%) of Cambodia veterans who had used mefloquine during deployment and who reported retrospectively complaints attributed to mefloquine.

Symptom	SV-link group n=221	SV-no link group n=68	A-symptomatic group n=1344	*p*
Dizziness / vertigo	47 (21.3%)	3 (4.4%)	131 (9.7%)	<0.001[a,b]
Nausea / stomach complaints	33 (14.9%)	7 (10.3%)	121 (9.0%)	NS
Visual complaints	32 (14.5%)	3 (4.4%)	94 (7.0%)	<0.001[b]
Memory loss	28 (12.7%)	1 (1.5%)	133 (9.9%)	NS
Fatigue	27 (12.2%)	4 (5.9%)	74 (5.5%)	0.001[b]
Headache	26 (11.8%)	2 (2.9%)	120 (8.9%)	NS
Diarrhoea	15 (6.8%)	1 (1.5%)	76 (5.7%)	NS
Concentration problems	12 (5.4%)	1 (1.5%)	66 (4.9%)	NS
Sleep disturbances	4 (1.8%)	3 (4.4%)	18 (1.3%)	NS
Abdominal pain	2 (0.9%)	1 (1.5%)	9 (0.7%)	NS
Paraesthesia	2 (0.9%)	0 (0%)	4 (0.3%)	NS
Nightmares	1 (0.5%)	1 (1.5%)	4 (0.3%)	NS
Depressive feelings	1 (0.5%)	0 (0%)	5 (0.4%)	NS
Nervousness	0 (0%)	0 (0%)	7 (0.5%)	NS
Disturbed moving	0 (0%)	0 (0%)	1 (0.1%)	NS

a, SV-link significantly different from SV-no link, $p<0.01$; b, SV-link significantly different from no SV, $p<0.01$

Most Cambodia veterans using mefloquine and also those using doxycycline stated that they were fully compliant (78.0% versus 80.7%; *p*=NS). Reasons for non-compliance were: forgotten (19.2%), unnecessary (12.3%), harmful (27.3%), side-effects (29.8%), and other (32.0%). The compliance and the reasons for non-compliance were similar between the different symptomatic groups (SV-link, SV-no link, and a-symptomatic veterans). The mefloquine compliance did not differ between the Cambodia and the Rwanda group. The compliance was also similar between Rwanda veterans with and without symptoms.

Vaccinations

The number of respondents who reported to have had side-effects of vaccinations was similar between the Cambodia group, the Rwanda group, and the notice group. Significantly more Cambodia veterans of the SV-link group (81%) reported to have had side-effects of vaccinations than veterans of the SV-no link group (14.5%) ($p<0.001$) or a-symptomatic veterans (17.1%) ($p<0.001$). However, within the Rwanda group there was no significant difference in reporting side-effects of vaccinations between the group veterans who did or did not fulfil the case definition for symptoms.

Morbidity during UNTAC

The most frequently reported illness during UNTAC was amoebiasis (16.2% during and 4.4% after the peace mission). The other illnesses specifically asked for, were reported by less than 5% of the respondents. Between SV-link, SV-no link and a-symptomatic respondents, there was no significant difference in reported morbidity. Cambodia veterans reported significantly more often to have had amoebiasis than Rwanda veterans during the peace mission (16.2% vs. 3.1%; p=0.004), and reported less often to have had amoebiasis after the peace mission (4.4% vs. 16.9%; p<0.001). Dysentery was also less frequently diagnosed after the peace mission according to Cambodia veterans than to Rwanda veterans (0.9% vs. 12.3%; p<0.001).

Factors that predict symptoms in Cambodia veterans

By performing an enter logistic regression analysis we evaluated which factors predicted fulfilment of our case definition in male Cambodia veterans. After taking into account the influence of biographical variables (step 1), self-reported side-effects of mefloquine and self-reported side-effects of vaccinations were entered (step 2). Enter linear regression analysis was performed in order to evaluate what factors predicted CIS-fatigue severity. After taking into account the influence of biographical variables (step 1), self-reported side-effects of mefloquine and self-reported side-effects of vaccinations were entered (step 2). The factors that were entered in the regression analyses regarding male Cambodia veterans who used melfloquine during deployment are shown in table 3.

Table 3 Outcome measures and independent variables in regression analyses of male Cambodia veterans who had used mefloquine

Analysis	Outcome measure	Independent variables
Logistic regression	Fulfilment of case definition for symptoms	Step 1: age, service branch, rank Step 2: self-reported side-effects of mefloquine, self-reported side-effects of vaccinations
Linear regression	CIS-fatigue severity	Step 1: age, service branch, rank Step 2: self-reported side-effects of mefloquine, self-reported side-effects of vaccinations

Table 4 shows the results of the regression analyses regarding fulfilment of case definition for symptoms (logistic regression analysis) and regarding CIS-fatigue severity (linear regression analysis) in Cambodia veterans. Significant relations were found between the outcome measure ‘fulfilment of case definition for symptoms’ and the following variables: having self-reported side-effects of vaccinations, having self-

reported side-effects of mefloquine, serving in the Navy or Marine Corps. No significant relation was found between the outcome measure and age or rank. Higher CIS-fatigue severity scores were predicted by having self-reported side-effects of vaccinations, having self-reported side-effects of mefloquine, older age, serving in the Navy or Marine Corps, and lower rank.

Table 4 Logistic and linear regression analysis predicting fulfilment of case definition for symptoms and CIS-fatigue severity score in male Cambodia veterans who had used mefloquine

	Logistic regression analysis[1]	Linear regression analysis	
	Fulfilment of case definition for symptoms	CIS-fatigue severity	
	Beta	Beta	R^2 (adjusted)
Demographic variables			*0.014***
Age	0.015	0.122**	
Service branch	-0.365*	-2.760**	
Rank	-0.347	-2.274*	
Other independent variables			*0.041****
Reported attributed side-effects of mefloquine	0.309*	3.202***	
Reported attributed side-effects of vaccinations	0.662***	4.575***	
		Total R^2 (adjusted)	0.055***

1, Chi^2=37.8, p<0.0001. Correct of 'fulfilment of case definition'=100%, correct of 'no fulfilment of case definition'=0%; *, p<0.05; **, p<0.01, ***, p<0.001

Discussion

In this study, a high frequency of side-effects of mefloquine and vaccinations was reported by Cambodia veterans. Symptomatic Cambodia veterans who attributed their present complaints to the mission in Cambodia reported the highest frequency of side-effects of mefloquine and vaccinations, whereas lower frequencies were reported by those who did not and those without symptoms. A much lower frequency of side-effects of mefloquine was reported by veterans who participated in a peace keeping mission to Rwanda (UNAMIR). Self-reported side-effects of vaccinations were not significantly different between the Cambodia, Rwanda and notice group. It should be stressed that

these side-effects had occurred during the peace mission and were not part of current symptoms. There was no significant difference between symptomatic and a-symptomatic Cambodia veterans in morbidity during UNTAC. Furthermore, male Cambodia veterans who had served in the Navy or Marine Corps and who had used mefloquine, were more often a symptomatic veteran when they reported side-effects of mefloquine or vaccinations. The severity of complaints as measured by the CIS-fatigue severity score was greater in those of older age, those serving in the Navy or Marine Corps, those having a lower rank, and those reporting side-effects of mefloquine and vaccinations.

The first question to be discussed is how the frequencies of side-effects of mefloquine and vaccinations compare to the literature. When Cambodia marines were asked shortly after their return, 30% spontaneously reported possible mefloquine-related side-effects.[4] Similar frequencies were observed in Peace Corps volunteers in sub-Saharan Africa.[5] In previous studies, the reported frequency of side-effects of mefloquine varies from 1 to 47%.[5-8] Such a wide range may be due to study design, study populations (travellers vs. military personnel, age difference[4]), geographic conditions, duration of prophylaxis[5], and method of assessment.

In the logistic regression analysis, fulfilment of case definition of symptoms was not predicted by age in Cambodia veterans who had used mefloquine. However, a higher CIS-fatigue severity score was predicted by an older age according to linear regression analysis. Previous studies found that the frequency of mild side-effects declined with increasing duration of prophylaxis.[5] However, this could not be confirmed by studies in Cambodia veterans.[4,6]

Despite the use of open questions, we found a very high frequency of side-effects. This may have been due to a widespread distrust in mefloquine and vaccinations among Cambodia veterans. Denial of the role of mefloquine and vaccinations in initiating symptoms by the authorities probably strengthened their suspicion.

We found a significantly higher frequency of side-effects with use of mefloquine (almost 50%) than with doxycycline (12.5%). However, this might be explained by a large difference in sample size between mefloquine users and doxycycline users (n=1638 and n=57, respectively). According to some studies, side-effects during mefloquine prophylaxis occur in the same frequency with antimalarials such as doxycycline[9,10] and other antimalarials.[7,11,12]

In our study, the most important question was whether mefloquine contributed to symptoms in Cambodia veterans. In this respect it seems important - like in chronic fatigue syndrome[13] – to distinguish between pathogenetic factors that play a role at the start of symptoms vs. factors that sustain symptomatology.

One of the arguments for a role of mefloquine in initiating symptoms is the observation that side-effects from mefloquine were more frequent in the SV-link group than in the SV-no link and the a-symptomatic Cambodia group. Furthermore, according to regression analyses self-reported side-effects of mefloquine were related to fulfilment of case definition for symptoms.

Other findings do not support a role for mefloquine at the start of symptoms. In the first place, less veterans of the Rwanda group reported to have had side-effects of

mefloquine than those of the Cambodia group, despite the fact that a substantial part of Rwanda veterans fulfilled our case definition for symptoms.
Secondly, although a high proportion of the Cambodia respondents reported side-effects of mefloquine, mefloquine compliance remained high (78%). There was also no significant difference in compliance between mefloquine and doxycycline users and between mefloquine users with and without symptoms. High mefloquine compliance was also found by Hopperus-Buma and colleagues.[4]
Finally, symptomatic Cambodia veterans had a stronger attribution to mefloquine than a-symptomatic Cambodia veterans.[1,2,14] This could explain why symptomatic veterans reported more side-effects of mefloquine.
Although the symptomatic Cambodia veterans had a strong attribution to mefloquine, convincing arguments for a direct link between current symptoms and mefloquine were not found. First of all, the mefloquine attribution was much lower in Rwanda veterans.[2,14] Second, a similar proportion mefloquine users was found in the SV-link, SV-no link and a-symptomatic group of Cambodia veterans. Given the retrospective nature of our study and the five years delay between onset of symptoms and our survey, we cannot exclude that side-effects of mefloquine did not play a role at the start of symptoms.
The number of veterans with complaints due to vaccinations was similar in the Cambodia, Rwanda and notice group, although the number of respondents fulfilling the case definition for symptoms between these three groups was significantly different. Within the group of Cambodia veterans, the highest frequency of side-effects of vaccinations was reported by those who attributed their present complaints on the peace-mission in Cambodia (SV-link). There was no such difference between symptomatic and a-symptomatic Rwanda veterans. A direct relation between vaccinations and current symptoms in veterans could not be demonstrated. Based on the results of the regression analysis, a role of vaccinations in initiating symptoms cannot be excluded.
In Gulf War veterans, an association was found between vaccinations against biological warfare and the CDC multi-symptom syndrome.[15] Cambodia veterans did not receive biological warfare vaccinations. Unwin et al.[15] also found an association between multiple routine vaccinations and the CDC multi-symptom illness, but this association was only found in Gulf War veterans who did not use their vaccination records when they participated in this study, suggesting recall bias. Another interesting finding of these investigators was the fact that veterans who recalled experiencing side-effects of vaccinations were more likely to have current symptoms.[15] This is in agreement with our findings in the Cambodia group.
More recently, some investigators found a relation between multiple vaccinations given during deployment and later ill health in Gulf War veterans.[16] In this study, it is suggested that multiple vaccinations in themselves do not seem to be harmful, but combined with the ‘stress’of deployment they may be associated with adverse health outcomes. However, these findings demand cautious interpretation.[17] Firstly, only those responders with a vaccination record were included (28%). Although there were no significant differences between this group and the whole cohort, the findings in this

restricted sample might be biased. Secondly, the information obtained by participants might not have been reliable, because anthrax vaccination was reported much more frequently than pertussis vaccination, even though they were always given together. On the other hand, overreporting of received vaccinations might also have taken place, because it was suggested in the UK media that when an association between Gulf War related illness and vaccinations was found, veterans could get compensation. Finally, it is questionable if the registration of vaccinations given during a war is optimal. Cambodia and Rwanda veterans were vaccinated in advance and in principle not during deployment.

The present study has limitations. Firstly, information on non-responders was not available because of privacy issues. However, the response rate in the Cambodia group was high. Secondly, Dutch veterans were sent to Cambodia more than four years before this study. Therefore, it cannot be ruled out that recall bias has occurred, especially in those veterans with health complaints. The present study fully relied on self-report. McCauley and colleagues[18] found differences between self-reported symptoms on a postal survey and those confirmed by an assessment program three months later. According to these authors, there is a possibility of outcome misclassification in retrospective mail questionnaires, i.e. by overreporting. Prospective and well-documented studies on the relation between malaria chemoprophylaxis and vaccinations on the one hand and unexplained symptoms after a war or a peace mission on the other hand are warranted.

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Chapter 5

Natural course of symptoms in Cambodia veterans: a follow-up study

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Abstract

Dutch (ex-)servicemen were deployed in the 1992-1993-peace operation UNTAC in Cambodia. Since their return, they have voiced concerns about the health consequences of their service and they have reported symptoms such as fatigue and cognitive problems. The natural course of symptoms in Dutch Cambodia veterans was evaluated in a prospective study.

At 18-months follow-up, a questionnaire was sent to 354 veterans who met a set case definition for symptoms in Cambodia veterans or who had sub-threshold scores. Initial measurement of fatigue severity, psychological well-being, depression, post-traumatic stress disorder, trait-anxiety, self-efficacy and causal attributions, was used to evaluate predictors for self-reported improvement and low levels of fatigue at follow-up.

At follow-up, 19% of the respondents reported complete recovery, 20% felt much better, 57% had the same complaints and 4% had become worse compared with their initial assessment. Self-reported improvement and less severe fatigue at follow-up were predicted by less severe fatigue at initial assessment and more perceived control over symptoms.

In conclusion: Self-reported improvement was reported in a considerable percentage of Cambodia veterans, whereas another substantial percentage of Cambodia veterans continued to suffer with severe levels of fatigue and related symptoms.

Predictors of improvement in Cambodia veterans and patients with chronic fatigue syndrome show similarities, and also seem to bear importance for Gulf War veterans.

Introduction

During the last years, symptoms in veterans after acts of war and peace operations, especially in those involved in the Persian Gulf War, have been the subject of intensive scientific and public debate. In the Netherlands, symptoms were reported in veterans who were deployed in the peace operation UNTAC (United Nations Transitional Authority for Cambodia).

In 1992 and 1993, a total of 2616 Dutch military personnel were deployed for three periods of 6 months in Cambodia. Major tasks of UNTAC personnel were mine clearance, guiding free elections, disarming local factions, repatriating Cambodian refugees from Thailand, watching human rights and supervising the administration of the country. Since return, Cambodia veterans have reported various health complaints, which they attribute to the vaccines they were exposed to, and the prescribed malaria chemoprophylaxis mefloquine (Lariam®).

In 1997, we initiated a postal survey on symptoms in Dutch Cambodia veterans. In this study, the main symptoms reported were memory loss, difficulty concentrating and severe fatigue.[1] Health complaints voiced by Cambodia veterans strikingly resemble Gulf War related illness.[2,3] Firstly, Gulf War veterans also mainly report fatigue and cognitive problems.[4-7]

Secondly, Gulf War veterans also perceive their symptoms to be associated with service related causes such as exposure to chemical or biological warfare agents, pyridostigmine bromide, vaccines, oil well fires and depleted uranium.[8,9]

Thirdly, both Gulf War and Cambodia veterans have been subject of extensive news reports.

To our knowledge, no scientific studies have been conducted on Cambodia veterans in other countries. Health symptoms in Gulf War veterans have been subject of several retrospective and epidemiological studies. However, little research has been done on the course of the complaints and factors associated with chronicity. This is unfortunate since such studies could provide knowledge on both preventive and therapeutic measures.

In the present prospective study we focused on the natural course of symptoms in Cambodia veterans and evaluated factors associated with its persistence. A validated fatigue severity scale was used to produce an operational case definition for symptoms in Cambodia veterans at initial assessment. Eighteen months later, we sent a follow-up questionnaire to Cambodia veterans with problematical scores. Two central questions were dealt with: "Has improvement occurred according to self-report and a standardised questionnaire?"; and, if so "What factors predict improvement?".

Method

Design and subjects

At initial assessment, a postal questionnaire was sent to all Cambodia veterans whose personal particulars could be retrieved from the databases of the Ministry of Defence (n=2548, 97.4% of the entire sample). A total of 1721 male veterans responded (68%). Details of this study have been described elsewhere.[1] Eighteen months later, a follow-

up questionnaire was sent to 354 male veterans who had given permission for follow-up and who either met our case definition for symptoms in Cambodia veterans (score ≥37 on the fatigue severity subscale of the Checklist Individual Strength (CIS)[1], or who had sub-threshold scores (CIS-fatigue severity score ≥32 & <37).

Measures

The following instruments were used:

Checklist Individual Strength (CIS), subscales fatigue severity, concentration problems and physical activity.[10,11] The CIS is a standardised self-report 20-item questionnaire asking about different aspects of fatigue over the last 14 days. In the present study, three out of four subscales were used: CIS-fatigue severity (8 items, range 8-56), CIS-concentration (5 items, range 5-35) and CIS-physical activity (3 items, range 3-21).

Symptom Checklist 90 (SCL-90).[12] The SCL-90 is a 90-item indicator of psychological well-being. The total score was used (SCL-total: range 90-450).

Beck Depression Inventory (BDI).[13] The BDI is a standardised 21-item questionnaire that measures depression (range 0-63).

Self-rating Inventory for PTSD.[14] The Self-rating Inventory for PTSD is a standardised 52-item questionnaire (range 52 – 208), developed to measure symptoms of post-traumatic stress disorder in large populations.

Spielberger State Trait Anxiety Inventory (STAI).[15,16] The STAI is a 40-item self-report instrument measuring state and trait anxiety. In the present study, only trait-anxiety was measured (20 items, range 20-80).

Social Support List-Interactions (SSL-I).[17] The SSL-I is a standardised 41-item self-report questionnaire that measures the level of experienced positive and negative social support. The following subscales were used: daily emotional interactions (4 items, range 4-16), emotional support in problematical situations (8 items, range 8-32) and social companionship (5 items, range 4-20).

Self-efficacy. Perceived control over symptoms was measured by four items (range 5-20), e.g. "Do you think you can influence your symptoms?". This scale was used in previous studies and a Cronbach's reliability coefficient of .74 has been reported.[18]

Causal attributions. Respondents were asked to indicate on a 5-point scale to what extent they agreed on four causal attributions: my complaints are related to mefloquine use; my complaints are related to the vaccines that I have received before the mission; my complaints are related to traumatic events; my complaints are related to disease that I have caught in Cambodia.

Self-reported improvement. Respondents were asked to indicate whether they had completely recovered, felt much better, had the same complaints or had become worse compared to the previous measurement. "Self-reported improvement" has also been used in previous studies.[19-21]

Statistics

Data analysis was performed using SPSS (Statistical Package for the Social Sciences, release 8.0.0) (SPSS Inc., 1997). For reasons of homogeneity, only men were included in the analyses. Outcome measures were "Self-reported improvement" and fatigue

severity at follow-up, all independent variables were measured at initial assessment. Alpha level was set at p=0.05.
To evaluate biographical data, "Self-reported improvement" and fatigue severity at follow-up, descriptive statistics were used. For comparisons between respondents and non-respondents, Student's t test and Fisher's exact test were used.
To evaluate significant relations between the outcome measures and independent variables, Mann-Whitney U tests and Spearman rank correlation coefficients were used.
In order to evaluate what factors predicted "Self-reported improvement", a logistic regression analysis was performed. After taking into account the influence of biographical variables (step 1), all variables that were significantly related to either "Self-reported improvement" or CIS-fatigue severity at follow-up were entered (step 2).
In order to evaluate what factors predicted CIS-fatigue severity at follow-up, linear regression analyses were performed. After taking into account the influence of biographical variables (step 1), all variables that were significantly related to either CIS-fatigue severity at follow-up or "Self-reported improvement" were entered (step 2).
Before entering the variables self-efficacy and causal attributions in regression analyses, missing values were replaced. The linear trend at point method was used.

Results

At follow-up, the response rate was 68.6% (n=243), 227 respondents were included in the analyses. Sixteen respondents were excluded for reasons of missing values in variables other than self-efficacy and causal attributions.
At initial assessment, mean age was 37.4±8.1 years. A total of 23% had left military service. Of the respondents who were on active duty, 66% served in the Marine Corps, 13% in the Navy, 14% in the Army, 5% in the Air Force and 2% were military policemen. The majority of respondents were married (62%), 89% had finished elementary school, lower or intermediate vocational education or lower secondary education, and 90% hold a rank below officer.
Comparisons of follow-up respondents and non-respondents revealed that respondents were significantly older (M=37.4±8.1 vs. M=33.8±7.9; t=-3.9, p<0.001) and more often married (62% vs. 42%, p<0.001). Because of the inclusion procedure, baseline CIS-fatigue severity scores were elevated in both respondents (M=40.9±6.5) and non-respondents (M=39.2±6.0). However, respondents yielded significantly higher CIS-fatigue severity scores than non-respondents (t=-2.3, p<0.05). No significant differences were found in active duty status, service branch, rank and educational level.

"Self-reported improvement"
At follow up, 19% (n=42) indicated that they had completely recovered, 20% (n=46) reported that they felt much better, 57% (n=130) had the same complaints, and 4% (n=9) indicated that they had become worse.

In further analyses, respondents who had reported complete or partial recovery were combined into one group (39%), as well as respondents who indicated no change or decline in symptoms (61%). These groups will be referred to as the "improved" and the "non-improved" group.

Fatigue severity at follow-up

At follow-up, 44% (n=100) met the case definition for symptoms in Cambodia veterans (CIS-fatigue severity score ≥37), 20% (n=45) had sub-threshold scores (CIS-fatigue severity score ≥32 & <37) and 36% (n=82) had non-elevated levels of fatigue (CIS-fatigue severity score <32).

Table 1 Independent variables at initial assessment by groups

	Outcome measures at follow-up	
Variables at initial assessment	Self-reported improvement Mann-Whitney Z-statistic	Fatigue severity Spearman rank correlation
CIS-fatigue severity	-3.2 **	0.456 ***
CIS-physical activity level	-0.5	0.207 **
CIS-concentration problems	-1.7	0.180 **
SCL-total	-2.1 *	0.314 ***
STAI trait-anxiety	-1.0	0.234 ***
BDI	-0.9	0.285 ***
Self-rating Inventory for PTSD	-2.1 *	0.236 **
SSL-I-daily emotional interactions	-1.5	0.045
SSL-I emotional support in problematic situations	-0.6	0.061
SSL-I social companionship	-0.9	-0.012
Attribution on mefloquine (n=197)	-1.5	0.042
Attribution on trauma (n=195)	-0.5	-0.002
Attribution on vaccines (n=196)	-0.8	0.090
Attribution on disease (n=194)	-0.4	-0.074
Self-efficacy (n=195)	-2.1 *	0.158 *

* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Relations between outcome measures and variables at initial assessment

Significant relations were found between the outcome measure "Self-reported improvement" and the following variables at initial assessment: CIS-fatigue severity, psychological well-being (SCL-total), Self-rating Inventory for PTSD, and self-efficacy (table 1). No significant relations were found between "Self-reported improvement" and CIS-physical activity level, CIS-concentration problems, trait-anxiety (STAI), depression (BDI), social support (SSL-I subscales), causal attributions and biographical variables.

Significant correlations were found between the outcome measure CIS-fatigue severity at follow-up and the following variables at initial assessment: CIS-fatigue severity, CIS-physical activity level, CIS-concentration problems, psychological well-being (SCL-total), STAI trait-anxiety, depression (BDI), Self-rating Inventory for PTSD and self-efficacy. No significant correlations were found between CIS-fatigue severity at follow-up and social support (SSL-I subscales), causal attributions and biographical variables.

Table 2 Outcome measures and independent variables in regression analyses

		Variables at initial assessment
Analysis	*Outcome measure*	
1#	Self-reported	Step 1: Age, educational level, marital status, rank, branch of service
	improvement	Step 2: CIS-fatigue severity, CIS-physical activity level, CIS-concentration problems, SCL-total, STAI trait-anxiety, BDI, self-efficacy
2##	CIS-fatigue severity	Step 1: Age, educational level, marital status, rank, branch of service
		Step 2: CIS-fatigue severity, CIS-physical activity level, CIS-concentration problems, SCL-total, STAI trait-anxiety, BDI, self-efficacy
3##	CIS-fatigue severity	Step 1: Age, educational level, marital status, rank, ranch of service
		Step 2: SCL-total, STAI trait-anxiety, BDI, self-efficacy

logistic regression analysis; ## linear regression analysis

Table 3 Logistic and linear regression analysis predicting "Self-reported change" and CIS-fatigue severity score at follow-up

	Analysis 1#	Analysis2##		Analysis 3##	
	Self-reported improvement	CIS-fatigue severity at follow-up		CIS-fatigue severity at follow-up	
	Beta	Beta	R^2 (adj)	Beta	R^2 (adj)
			-0.001		*-0.001*
Demographic variables					
Age	-0.004	0.029		-0.031	
Educational level	-0.853	-2.927		-3.643	
Marital status	-0.159	-2.896		-2.863	
Rank	-0.096	2.019		4.270	
Service branch	-0.020	-0.240		-0.189	
Other independent variables			0.218**		0.111**
CIS-fatigue severity	0.072 *	0.675**			
CIS-concentration problems	-0.001	-0.044			
CIS-physical activity level	-0.033	0.109			
BDI	-0.043	0.148		0.128	
SCL-total	0.015	0.046		0.069	
STAI trait anxiety	-0.022	-0.082		0.055	
Self-efficacy	0.138 *	0.364		0.558*	
		Total R^2 (adjusted)	*0.217***		*0.110***

*p<0.05; **p<0.01, p<0.001

logistic regression analysis, Chi^2=25.1, p<0.05. Percent correct of improved group=47.7%, percent correct of non-improved group= 81.1%

linear regression analysis

Factors that predict improvement

The variables that were entered in the regression analyses are shown in table 2. Biographical variables were entered first (step 1), followed by variables that related significantly to at least one of the outcome measures. Since the Self-rating Inventory for PTSD highly correlated with psychological well-being (SCL-total) in our initial data sample, it was not included in the analyses (r=0.90, p<0.001).

Self-reported improvement was predicted by lower CIS-fatigue severity scores and higher self-efficacy scores at initial assessment (Chi^2=25.1, p<0.05; percent correct of improved group=47.7%, percent correct of non-improved group=81.1%). Thus, less

severe fatigue at initial assessment and more perceived control over symptoms predicted self-reported improvement (table 3).
Lower CIS-fatigue severity scores at follow-up were predicted by lower CIS-fatigue severity scores at initial assessment. Thus, less severe fatigue at initial assessment predicted less severe fatigue at follow-up (table 3).
Because fatigue severity at initial assessment had the largest contribution to the prediction of fatigue severity at follow-up, a linear regression analysis was also performed without the CIS subscales. Then, lower CIS-fatigue severity scores measured at follow-up were predicted by higher self-efficacy. Thus, more perceived control over symptoms predicted less severe fatigue at follow-up (table 3).

Discussion

This is one of the first prospective studies on the natural course of health symptoms in veterans after acts of war or peace operations. We have studied Dutch veterans who participated in the 1992-1993-peace operation UNTAC in Cambodia. Approximately five years post-return, 39% of the respondents reported full or partial recovery, whereas 61% did not report improvement. Compared with initial assessment, a decline in the number of veterans who met the set case definition for symptoms in Cambodia veterans (CIS-fatigue severity score ≥37) was also observed. At initial assessment, 288 veterans met the case definition (17% of the initial sample of 1721), whereas 100 veterans met the case definition at follow-up (6% of the initial sample of 1721). Thus, at follow-up, a considerable percentage of Cambodia veterans had recuperated, whereas another substantial percentage of Cambodia veterans continued to suffer with severe levels of fatigue and related symptoms. Fatigue severity scores at follow-up suited to self-reported improvement. Non-improved respondents still met our case definition for symptoms in Cambodia veterans. Respondents who reported that they felt much better, no longer met our case definition, but yielded sub-threshold scores (CIS-fatigue severity score ≥32 & <37). Fatigue severity scores of respondents who indicated that they had recovered completely, fell within the range of healthy civilians (M=17±10).[18]
Self-reported improvement was predicted by less severe fatigue at initial assessment and more perceived control over symptoms. Less severe fatigue at follow-up was predicted by less severe fatigue at initial assessment or high self-efficacy. No significant relations were found between the respective outcome measures and social support or causal attributions.
The present study has some limitations. First, it may be questioned whether response bias has occurred. Follow-up respondents were older, more often married and more severely fatigued than non-respondents were. However, no significant differences were found in perceived control over symptoms.
Secondly, the present study fully relied on self-report. In a study on Gulf War veterans, McCauley and colleagues found differences between self-reported symptoms on a postal survey and those confirmed in an assessment program three months later.[21] According to these authors, in mail questionnaires, there is a possibility of outcome

misclassification. However, one of the focuses of the present study was fatigue and its related symptoms. In the study of McCauley et al., fatigue showed the most persistent and unexplained symptom. Of self-reported unexplained fatigue, 79% was confirmed by clinical investigation.

In the present study, only 4% of the Cambodia veterans reported decline at 18-months follow-up. A percentage that could be expected just on statistical grounds. Wolfe and colleagues performed a prospective study in Gulf War veterans.[22] Measurements were taken immediately after return and at 18-24 months post-return. At follow-up, respondents were asked to indicate on a 5-point scale (much worse – much better) whether their physical and psychological health had changed since return. In this study, respectively, 30% and 27% of the respondents reported decline in physical and psychological health. At least three possible explanations can be given for the much higher percentage of Gulf War veterans who indicated decline. First, since duration of the period from return until the moment of the follow-up study differs (5 vs. 2 years), natural recovery may not have taken place at equivalent levels. Secondly, self-reported improvement in Gulf War veterans may have been influenced by the abundance of news reports on Gulf War related issues.[4] This is reflected by a study on enrolment in registry programmes, in which an increase in the number of Gulf War veterans seeking medical evaluation was found during periods of high media interest in Gulf War issues.[23] However, in another study, in which the relationship between media events and self-reported exposures was investigated, little or no effects were found.[24] Thirdly, in the present study, a case definition was used. Only respondents with severe fatigue at initial assessment were mailed for follow-up. In the study of Wolfe et al., follow-up respondents were not selected, and 79% of the original cohort completed the questionnaire. Therefore, it is assumed that respondents in the present study were more severely ill than in the Wolfe study. The differences in improvement rates partly might be explained by regression to the mean effects.

In literature, Gulf War related illness has been associated with chronic fatigue syndrome (CFS).[8,25] However, both in clinical investigation and self-report postal questionnaires, only a subset of Gulf War veterans were diagnosed CFS.[5,9,26] Although symptoms in veterans and CFS do not seem to be interchangeably, similarities can be observed. In the present study, self-reported improvement and lower levels of fatigue at follow-up were predicted by less severe fatigue at initial assessment and more perceived control over symptoms.

In a study on the natural course of CFS, self-reported improvement and lower levels of fatigue at follow-up were predicted by more sense of control over symptoms, less severe fatigue at initial assessment, shorter duration of complaints, weaker physical attributions and lower levels of functional impairment.[20] Other studies have also shown that physical attributions, in which complaints are ascribed to a somatic cause, are associated with poor prognosis in civilian populations with CFS.[27,28] In the present study, causal attributions were not found predictive of "Self-reported improvement" or less severe fatigue at follow-up. However, a significant relation was found between Self-reported recovery and attribution to mefloquine. At initial assessment, respondents who indicated that they had recovered completely yielded a significant weaker opinion

on mefloquine being related to the symptoms, as compared to respondents who reported that they felt much better, that they had the same complaints or that their symptoms had become worse (Mann-Whitney U test, z=-4.0, p<0.001).
As far as we know, perceived control over symptoms has not been investigated in Gulf War veterans.
From the present study, theoretical and practical implications can be derived. Given the similarities between symptoms in Cambodia veterans and Gulf War related illness, in our opinion these points may also bear importance to Gulf War veterans. First, since current fatigue is highly predictive of future fatigue, attention should be paid to fatigue and related symptoms in veterans after acts of war and peace operations. From our clinical experience with Cambodia veterans, we think that early recognition of symptoms by the Ministry of Defence might be beneficial to symptomatic veterans. Early attention and care might prevent them from seeking media attention and elaborating on their negative health status, its causes, consequences and the negligent role of their employer and it might enhance recovery. Secondly, enhancing self-efficacy should form a part of treatment.
To conclude, this is the first study to investigate the natural course of symptoms in Dutch Cambodia veterans. At 18-months follow-up, 39% of the respondents reported recuperation, whereas 61% reported continuation of symptoms. Self-reported improvement and lower fatigue at follow-up were predicted by less severe fatigue at initial assessment and more perceived control over symptoms.

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Chapter 6

The role of PTSD in symptoms in Cambodia veterans

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Abstract

Posttraumatic stress disorder is often put forward as an explanation for unexplained somatic symptoms in military who have been deployed in war or peace missions. Using a cross-sectional postal survey, it was investigated to what degree PTSD can account for symptoms in Dutch (ex-)servicemen who returned from the peace operation UNTAC in Cambodia and what features distinguish veterans with and without PTSD.

Elevated PTSD scores were found in 1.3% of 1698 veterans. There was no concordance between elevated PTSD scores and fatigue as defined in previous studies. Respondents with probable PTSD had more often left service, had more often been exposed to severe and potentially traumatic events, and they reported a greater impact of the mission. Furthermore, they reported more mental problems which they perceived to be service-related and they hold a stronger causal attribution to posttraumatic stress.

In conclusion, PTSD cannot offer an explanation for symptoms in Cambodia veterans.

Introduction

During the past four years, health concerns in Dutch (ex-)servicemen who were deployed in UNTAC (United Nations Transitional Authority for Cambodia), have been subject of extensive somatic and psychological investigation. Between 1992 and 1993, a total of 2616 Dutch servicemen were sent to Cambodia in three battalions. UNTAC was a complex, multifaceted operation aimed to keep, make and build peace. Major tasks were supervising the administration of the country, disarming local factions, guiding free elections, guarding human rights, repatriating Cambodian refugees from camps in Thailand, mine clearance, and initiating the reconstruction of the country.

Since returning, Dutch Cambodia veterans have reported unexplained health symptoms such as fatigue, forgetfulness and difficulty concentrating. An operational case definition for symptoms in Cambodia veterans was constructed using a validated fatigue severity questionnaire. Seventeen percent of the male respondents fulfilled the criteria.[1]

Unexplained somatic symptoms in Cambodia veterans do not seem to be a separate problem. Since the American Civil War, post-war illnesses have been described and in the past years, there has been increasing public and scientific interest on Gulf War related illness.[2-4] Various hypotheses have been put forward to explain the pathogenesis of symptoms after acts of war and peace operations. In 1980, posttraumatic stress disorder (PTSD) was introduced as a diagnostic entity in the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM).[5] Since then, problematic health status in military personnel has often been attributed to PTSD, not only by laymen. However, the tenability of this generally accepted relationship may be doubted by figures, such as the prevalence of PTSD in Gulf War veterans, which varies from 3% to 50%, with most studies in the lower range.[6]

This article reports the role of PTSD in Cambodia veterans as assigned in a cross-sectional postal survey. PTSD was measured using a validated self-rating scale. Although it is common practice to make use of quick and economic self-rating scales in survey research, they have the disadvantage of lacking clinical evaluation. Most screening-instruments assessing PTSD are formulated in a trauma-independent way. Therefore, clinical evaluation is a necessary tool to prevent PTSD diagnosis in subjects who do not meet the DSM-IV A-criterion of having experienced a severe event causing horror, helplessness or fear.[7] In the present study, scores above the cut-off are interpreted as an indication of PTSD, instead of a proof of PTSD. Two central questions are dealt with: To what degree can PTSD account for unexplained somatic symptoms in Cambodia veterans; and what features distinguish Cambodia veterans with and without elevated PTSD scores?

Methods

Design and subjects

A cross-sectional postal survey was conducted in all Cambodia veterans whose particulars were known to the Ministry of Defence (n=2548). The response rate was 68% (n=1721). In the present study, data of 1698 male veterans were used. Twenty-three respondents were excluded for reasons of missing values.

Two hundred and eighty-five respondents (17%) fulfilled our case definition for symptoms in Cambodia veterans (score ≥37 on the fatigue severity subscale of the Checklist Individual Strength, CIS), and were qualified as fatigued veterans. Details of the study and the operational case definition have been described elsewhere.[1]

Fatigued and non-fatigued veterans did not differ in age, marital status, educational level or rank. Significant differences were found in current branch of service (Chi^2=21.8, p<0.01) (fatigued vs. non-fatigued veterans: Marine Corps 50% vs. 55%;

Navy 8% vs. 10%; Army 12% vs. 6%; Military Police 0% vs. 1%; Left service 27% vs. 22%).

Materials

The following instruments were used:

Checklist Individual Strength (CIS)[8-10]: The CIS is a standardised self-report 20-items questionnaire measuring different aspects of fatigue over the last 14 days. In the present study, one out of four subscales was used: CIS-fatigue severity. Items are scored on 7-point Likert scales (1-7; range 8-56), higher scores indicate more fatigue.

Self rating Inventory for PTSD[11-13]: The Self-rating Inventory for PTSD is a Dutch-language instrument for diagnosing symptoms of PTSD in survey research. It consists of 22-items, reflecting the DSM-IV criteria for PTSD, which are shared over three subscales: re-experiencing (6 items); avoidance (9 items); and hyper-arousal (7 items). All items are written without special reference to trauma. Items are scored on 4-point Likert scales (1-4; range 22-88). The author proposes a cut-off score ≥52 for PTSD, with a specificity of 71% and a sensitivity of 86%. Psychometric properties are satisfactory: For the total scale, Cronbach´s alpha for internal consistency is >.90; Test-retest reliability is >.77; and concurrent validity seems adequate.

Severe events during the mission[14]: Respondents are asked to indicate whether or not they were confronted with 23 severe, potentially traumatic events during the mission in Cambodia.

Subjective experience of the peace operation[1]: Respondents are asked to rate on 5-point Likert scales (range 1-5; not at all – very much) to what degree they had perceived the mission as poignant, threatening and aggravating and to what degree they had felt powerless during the mission.

Causal attribution to posttraumatic stress[1]: Respondents are asked to indicate on a 5-point Likert scale (range 1-5; positively no – positively yes), whether they perceive their symptoms to be related to severe events that may have happened in Cambodia.

Physical and mental problems: Respondents are asked to indicate on 4-point Likert scales (range 1-4; not al all – very much) whether they currently experience physical or mental health problems which they perceive to be service-related.

General health status[15]: Respondents are asked to rate their general health status on a 5-point Likert scale (range 1-5; very good - bad).

Statistics

Data analysis was performed using SPSS [version 8.0.0] (SPSS Inc., 1997). For reasons of homogeneity, only men were included in the analyses. For all tests, the significance level was set at $p<0.05$. Differences between two groups, were tested using Student´s t-tests and Mann-Whitney U tests. Chi^2-tests and Fisher´s Exact tests were used for dichotomous variables. Differences between three groups were tested using Kruskal Wallis tests and Chi^2-tests. Concordance between elevated fatigue scores (CIS-fatigue severity score ≥37) and elevated PTSD scores (Self-rating Inventory for PTSD score ≥52) was evaluated by Cohen´s Kappa, which is a measure

of agreement between two dichotomous variables corrected for change. Values range from 0 (agreement no better than chance) to 1 (perfect agreement).

Results

Prevalence of PTSD

Fatigued veterans yielded significantly higher scores on the total Self-rating Inventory for PTSD and its three subscales than non-fatigued veterans (table 1). No agreement was found between elevated fatigue scores and elevated PTSD scores. Kappa was 0.049. Of the 1698 male respondents, 274 respondents (16.1%) were fatigued, 11 respondents (0.6%) had elevated PTSD scores, and 11 respondents (0.6%) were both fatigued and had elevated PTSD scores (table 2).

Table 1 Self-rating Inventory for PTSD scores of fatigued and non-fatigued Cambodia veterans

	Fatigued veterans (CIS-fatigue ≥37)	Non-fatigued veterans (CIS-fatigue <37)	p
PTSD_total (22 items)	32.8 (8.9)	25.9 (5.4)	<0.001*
PTSD_hyper-arousal	12.1 (3.7)	9.0 (2.4)	<0.001*
PTSD_re-experience	7.3 (2.2)	6.4 (1.1)	<0.001*
PTSD_avoidance	13.5 (4.2)	10.5 (2.7)	<0.001*

*Student´s t-test, $p<0.05$

Table 2 Number (%) of fatigued veterans and/or veterans who have probable PTSD

	Criteria	Cambodia veterans n=1698
Fatigue	CIS-fatigue severity ≥37 & PTSD score <52	274 (16.1%)
PTSD	CIS-fatigue severity <37 & PTSD score ≥52	11 (0.6%)
Fatigue and PTSD	CIS-fatigue severity ≥37 & PTSD score ≥52	11 (0.6%)
No-caseness	CIS-fatigue severity <37 & PTSD score <52	1402 (82.6%)

Distinct features

To evaluate what features distinguish respondents with and without presumptive PTSD, all respondents who had elevated PTSD scores (n=22) were combined into one group of PTSD cases, irrelevant of their fatigue severity score. Subsequently, the PTSD group was compared with respondents who only had elevated fatigue severity

scores (n=274; this group will further be referred to as "the fatigue group") and respondents without elevated PTSD or fatigue severity scores (n=1402; this group will further be referred to as "the no-caseness group"). Between groups, no significant differences were found in age, marital status, educational level and rank. The PTSD group had significantly more often left service than the fatigue and the no-caseness group (table 3).

Table 3 Biographical variables of the PTSD, fatigue and no-caseness group

Group	PTSD n=22	Fatigue n=274	No-caseness n=1402	*p*
Age				
Mean (SD)	35.2 (7.8)	36.4 (8.2)	35.4 (8.1)	NS*
Marital status				
Married	36%	59%	55%	
Unmarried	64%	41%	45%	NS**
Educational level				
Lower	81%	85%	80%	
Higher	19%	15%	20%	NS**
Rank				
Lower	91%	89%	86%	
Higher	9%	11%	14%	NS**
Service branch				
Marine Corps	32%	51%	55%	
Navy	14%	8%	10%	
Army	9%	12%	6%	<0.01**
Air Force	4%	3%	6%	
Military Police	0%	0%	2%	
Left service	41%	26%	21%	

* One-way ANOVA, $p<0.05$; ** Chi^2-test, $p<0.05$

Self-reported exposures

Compared with the fatigue and no-caseness group, the PTSD group reported significantly more often severe events related to threat (increase of threat while the cause is inside or outside view); personal severe events (hearing screaming of wounded persons, witnessing people being killed or getting severely wounded, frightening situations with local people at road blocks, being injured, and being battered or tortured); and severe events related to feelings of powerlessness (being unable to intervene, losing control of the situation, having the opinion that the mission was useless, and being rejected by local people) (table 4).

Subjective experience of the mission and self-reported health status

Compared with the fatigue and no-caseness group, the PTSD group had a significantly more poignant, threatening and aggravating subjective experience of the mission in Cambodia. They also reported significantly more feelings of powerlessness during the mission (table 5).

The PTSD group and the fatigue group did not differ in their rating of their general health status and current physical service-related problems. Both groups rated their health status significantly more negative and reported significantly more physical problems than the no-caseness group. Compared with the fatigue and no-caseness group, the PTSD group reported significantly more current service-related mental problems and had a significantly stronger causal attribution to posttraumatic stress (table 5).

Discussion

In the present study, a probable PTSD diagnosis was found in 1.3% (n=22) of all veterans who responded to a postal questionnaire. There was no concordance between elevated PTSD scores and elevated fatigue severity. Of the 285 veterans who fulfilled our case definition for symptoms in Cambodia veterans and were qualified as fatigued, only 11 (3.9%) had simultaneously elevated PTSD scores. It is concluded that Cambodia veterans who have elevated PTSD scores and fatigued Cambodia veterans are distinct groups. Thus, posttraumatic stress disorder (PTSD) cannot offer an explanation for unexplained somatic symptoms in Cambodia veterans.

Like the present study, investigations in Gulf War related illness have also been unable to attribute a substantial degree of symptoms to posttraumatic stress.[6,17] In a study on fatigued Gulf War veterans, symptoms could not be explained by PTSD or other psychiatric disorders as assessed by DSM-III-R criteria.[18] In another study, 1000 self-referred Gulf War veterans were examined in a medical assessment program. A total of 233 patients were routinely or on psychological grounds referred for psychological assessment. PTSD was diagnosed in 12% of the study population.[19] In another clinical evaluation program, in which 13161 self-referred Gulf War veterans were evaluated, PTSD occurred in less than 6%.[20] Finally, 1497 active-duty Seabees, of whom 527 had been deployed in the Gulf War, were studied with a questionnaire. Although Gulf War veterans were more likely than non-deployed veterans to report symptoms consistent with PTSD (15.2% vs. 9%), again PTSD could not cover Gulf War-related morbidity.[21]

In the present study, more proof for a distinction between Cambodia veterans who have presumptive PTSD and fatigued Cambodia veterans was found in distinguishing features. Cambodia veterans with elevated PTSD scores had more often left service, they had more often been exposed to severe and potentially traumatic events, and they reported a greater impact of the mission. Furthermore, they reported more mental problems which they perceived to be service-related and they hold a stronger causal attribution to posttraumatic stress. However, an equal general health status and a similar degree of self-reported service related physical complaints was observed in Cambodia veterans with presumptive PTSD and fatigued Cambodia veterans.

The present study has some limitations. Firstly, its retrospective nature. Since the postal survey was performed approximately four years post-return, we had to rely on self-report which may have been prone to recall-bias. Furthermore, we were only able to establish current health symptoms and current probable PTSD diagnosis. Unfortunately, we do not know how many Cambodia veterans have suffered from posttraumatic stress symptoms shortly after deployment, and in which subjects natural recovery or adequate treatment has taken place. In a study on servicemen who were deployed to the Persian Gulf, a survey was completed within five days of returning to the United States. Approximately 4% of the respondents had symptoms of PTSD.[22] No data are given on the number of servicemen in which the symptoms lasted for more than one month and who consequently met the DSM criteria for PTSD. Based on this study, we expect that the percentage of Cambodia veterans who have suffered from posttraumatic stress symptoms shortly after return, will be slightly higher than the observed 1.3% with current presumptive PTSD diagnosis. We further expect that posttraumatic stress symptoms in an early phase also cannot account for unexplained somatic symptoms in Cambodia veterans. To fully answer the question concerning the course of posttraumatic stress symptoms, longitudinal studies are needed.

The present study has another limitation. Since we used a postal questionnaire, and thus did not perform clinical assessment, we were only able to screen for probable PTSD diagnosis. In another study that we did two years later, we performed the Structured Clinical Interview for DSM-IV (SCID)[23] in a subset of 79 Cambodia veterans with chronic fatigue. Then, current diagnosis of PTSD was established in three (ex-) servicemen (3.8%).

To conclude, the present study implies that a great majority of Cambodia veterans who report ill health do not satisfy criteria for PTSD, and therefore will not benefit from specialized PTSD treatment. They should be treated otherwise. Based on our clinical experience with Cambodia veterans, we have the opinion that symptoms of PTSD are well recognized and treated by the health services of the Ministry of Defence, but that focussing just on PTSD is futile. Unexplained somatic symptoms after acts of war and peace operations are a profound current and future problem that demand a broader approach.

Table 5. Distinguishing features between respondents with probable PTSD diagnosis, the fatigue and the no-caseness group

	PTSD n=22	Fatigue n=274	No caseness n=1402	*p*
Subjective experience of the mission				
Poignant	3.7 (0.8)	3.0 (0.9)	2.7 (0.8)	<0.001*
Threatening	3.6 (0.9)	2.9 (0.9)	2.6 (0.8)	<0.001*
Aggravating	4.2 (0.9)	3.2 (1.1)	2.9 (1.1)	<0.001*
Feelings of powerlessness	3.5 (1.2)	2.8 (1.1)	2.3 (1.0)	<0.001*
Causal attribution to PTSD	3.3 (1.3)	2.0 (1.1)	1.9 (1.0)	<0.001*
General health status	2.8 (1.0)	3.0 (1.0)	1.7 (0.7)	<0.001**
Current physical problems	2.1 (1.1)	2.0 (0.8)	1.3 (0.5)	<0.001**
Current mental problems	2.0 (0.9)	1.4 (0.7)	1.1 (0.3)	<0.001*

Kruskal Wallis test, $p<0.05$ *All groups are significantly different from each other; ** No significant difference between PTSD and fatigue group, but both groups are significantly different from no-caseness group

Table 4 Self-reported exposure to stressful events during UNTAC of the PTSD, fatigue and no-caseness group

Group	PTSD n=22	Fatigue n=274	No-caseness n=1402	*p*
Presence of mines	96%	92%	93%	NS
Unaimed fire	96%	92%	92%	NS
Witnessing human suffering	100%	85%	89%	NS
Being exposed to dead or wounded bodies	100%	89%	88%	NS
Increase of threat: cause is outside view	100%	81%	79%	<0.05
Combination of being on patrol for a long time and constant watchfulness	73%	68%	66%	NS
Being ready for action, without actual action	73%	55%	59%	NS
Hearing screaming of wounded persons	96%	55%	56%	<0.01
Being unable to intervene	86%	63%	54%	<0.01
Increase of threat: cause is inside view	82%	57%	53%	<0.05
Being in danger caused by acts of war, accidents or threat	73%	56%	52%	NS
Witnessing people being killed or getting severely wounded	77%	48%	46%	<0.05
Frightening situations with local people at road blocks	64%	39%	38%	<0.05

Group	PTSD n=22	Fatigue n=274	No-caseness n=1402	p
Being held at gun point	41%	41%	34%	NS
Aimed fire	55%	39%	39%	NS
Dead or injured colleague	41%	27%	29%	NS
Losing control of the situation	68%	29%	27%	<0.001
Having the opinion that the mission was useless	68%	25%	25%	<0.001
Being rejected by local people	46%	22%	20%	<0.05
Colleagues were being taken hostage	14%	11%	8%	NS
Being taken hostage	5%	3%	1%	NS
Being injured	9%	2%	1%	<0.01
Being battered or tortured	14%	1%	1%	<0.001

Chi^2-test

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Chapter 7

Physical activity and exercise performance in symptomatic Cambodia veterans

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Summary

Dutch (ex-)servicemen who encounter health problems since return from the 1992-3 peace operation UNTAC, commonly complain about reduced activity levels, decreases in physical fitness and aggravation of symptoms after strenuous exercise. To evaluate these symptoms, an incremental maximal exercise test on a bicycle ergometer was performed in symptomatic and matched controls (healthy Cambodia veterans). Using an actometer and diaries, both groups were followed for a 12-day baseline period prior to an incremental maximal exercise test on a bicycle ergometer, followed by seven days of post-ergometer data.
During baseline, symptomatic Cambodia veterans reported more symptoms, had lower levels of physical activity and took longer periods of rest after high activity periods. Symptomatic veterans did not perceive the exercise test needing more exertion than healthy veterans did, although their physical fitness was decreased. Post-ergometer, daily observed symptoms did not aggravate in symptomatic veterans. Four days post-ergometer, actometer and daily observed activity scores were lowered in both groups. As compared to baseline, one day post-ergometer, levels of physical activity were changed in healthy veterans, but not in controls.
In conclusion, complaints about reduced activity levels and decreases in physical fitness in symptomatic Cambodia veterans were confirmed. Post-exertion malaise was not found. The observed post-exertion effects were traced back to weekday patterns.

Introduction

After return from the 1992-1993-peace operation UNTAC (United Nations Transitional Authority for Cambodia), Dutch Cambodia veterans have reported health symptoms, such as forgetfulness, difficulty concentrating and severe fatigue. In 1997, these symptoms became the subject of a number of studies. An operational case definition for symptoms in Cambodia veterans was constructed using a validated fatigue severity

questionnaire.[1] Cambodia veterans who yielded elevated fatigue severity scores on both an initial and a follow-up postal survey, were subsequently invited for extensive somatic and psychological assessment.

Clinical observations revealed that symptomatic Cambodia veterans commonly express complaints about reduced activity levels, decreases in physical fitness and aggravation of symptoms after strenuous exercise. Therefore, a controlled study on physical activity and exercise performance was performed. To our knowledge, such studies have not been done so far, but seem of interest for at least two reasons. First, to evaluate to what degree active-duty symptomatic veterans are able to meet military demands in terms of physical fitness, activity and ability to be prepared on request. Second, to contribute to the development of effective, evidence based, treatment of symptoms in veterans. In the U.S., specialised treatment programs for Gulf War veterans have been developed that incorporate gradual, paced physical activation.[2-4]

The aims of the present study were to evaluate physical activity, physical fitness and post-exertion malaise in symptomatic Cambodia veterans. To prevent inconsistencies stemming from the use of inappropriate control groups, great care was taken in the selection of well-matched military controls. To prevent bias by cognitions concerning illness and disability, physical activity was measured using both an actometer and self-report instruments.[5] The study consisted of three parts. Firstly, self-reported complaints and physical activity in symptomatic and healthy control Cambodia veterans were compared for a baseline period of 12 days (part 1). Secondly, a maximal incremental bicycle ergometer test was performed (part 2). We investigated whether symptomatic veterans had lower physical fitness and/or higher rates of perceived exertion during the exercise test. Thirdly, the exercise test was followed by 7 days of post-ergometer data (part 3). Self-report measurements and levels of physical activity were compared to baseline. We evaluated whether symptomatic veterans reported an increase in malaise and a decrease in physical activity following the exercise test. Furthermore, the impact of the exercise test in symptomatic veterans was compared with the impact in healthy veterans.

Methods

Subjects

Twenty-six symptomatic and 26 matched healthy control Cambodia veterans participated in the present study. Symptomatic veterans were randomly selected from a group of symptomatic veterans (n=82) who participated in our somatic and psychological assessment program. No significant differences were found in age, educational level, marital status, service branch during the mission, fatigue severity (CIS) and functional impairment (SIP) between the symptomatic veterans who participated in the present study (n=26) and those who did not (n=56), (Student's t-test, $p<0.05$ and Chi^2-test, $p<0.05$).

Healthy veterans were selected on the basis of low levels of fatigue (CIS-fatigue severity score <21) and low symptom reporting (<4 health symptoms) in the initial postal survey mentioned in the introduction.[1] Furthermore, they were matched for age,

service branch, rank during the mission in Cambodia and, as far as possible, geographical area, with the symptomatic veterans.
For reasons of homogeneity, only men were included. At the time of the study, symptomatic and healthy veterans were 42.1±7.6 and 41.3±6.5 years. It was not possible to match exactly for the variables "service branch" and "rank". During the mission, 58% of the symptomatic veterans were in the Marine Corps, 27% in the Navy and 15% in the Army. In healthy veterans, these percentages were 65%, 19% and 15%, respectively. Eighty percent of symptomatic veterans and 89% of healthy veterans hold a lower rank (below officer). No significant differences were found in marital status, educational level and active duty status between symptomatic and healthy veterans (table 1). At the time of the study, CIS-fatigue severity scores were 45.0±6.2 in symptomatic veterans and 12.3±5.5 in healthy veterans. The ethics committee of our hospital approved the study.

Table 1 Biographical data of symptomatic and healthy Cambodia veterans

	Symptomatic veterans n=26	Healthy veterans n=26	*p*
Educational level			
Lower	96%	92%	
Higher	4%	8%	1.000
Marital status			
Married	65%	62%	
Unmarried	35%	38%	1.000
Active duty status			
Active duty	81%	89%	
Left service	19%	11%	0.688

McNemar test, $p<0.05$
Lower educational level =elementary school, lower vocational and secondary education, intermediates. Higher educational level =school of higher general secondary education, higher vocational education, Royal Marine Academy, University.

Material

Fatigue severity and activity. The Checklist Individual Strength (CIS, subscales fatigue severity and activity) measures different aspects of fatigue over the last 14 days.[6-8] Scores on the 8-item fatigue severity scale range from 8 to 56, scores on the 3-item activity scale from 3-21. Higher scores indicate more fatigue and less activity experienced.

Functional impairment The total score of 8 subscales of the Sickness Impact Profile (SIP; subscales recreation and pastimes, home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions and work), was used to measure functional impairment.[9,10]

Actometer. An actometer is a motion-sensing device that can register and quantify the level of actual physical activity. The apparatus consists of a computerised piezo electric sensor, which is sensitive in three directions, and is attached to the ankle (size: 55*25*15mm; weight=26 grams). Accelerations of the sensor larger than a pre-defined threshold are considered as activity and are stored into an internal memory. Each second the counter of the actometer is read and reset by a micro-controller. This adds the value to an integration counter which is set at five minutes. Thus, every five minutes, an activity-score is produced. The actometer scores can be read out by a personal computer.[5,11] In the present study, subjects were instructed to wear the actometer day and night for 20 consecutive days, except for activities involving water (e.g. taking a bath) and rowdy sports (e.g. rugby, judo).

Activity patterns. Activity patterns were analysed using the following parameters. Baseline physical activity was quantified as the mean actometer score over the 12-day baseline period. In order to distinguish between relatively high (peak) and low (rest) activity periods the mean baseline physical activity score of the control group (table 2, mean score =92) was used as cut-off. The latter (5-minute) time periods above this cut-off were labelled as peaks and the periods below this cut-off as rest periods. The program identified the ten largest activity peaks by calculating the total energy of each peak (duration peak*D number of accelerations in each succeeding 5 minute period). Subsequently, both the average peak duration and average peak amplitude of these ten largest peaks were calculated.[11] Furthermore, the average duration of rest after peaks and the percentage activity reduction after peak were calculated.

Diaries. During the 20-day period that the actometer was worn, subjects completed a self-observation list[5] and the daily Profile of Mood States depression subscale (POMS).[12,13] On the self-observation list, daily observed fatigue, daily observed pain and daily observed activity were rated four times a day on 5-point Likert scales (0-4; range 0-16). On the daily POMS depression subscale, subjects indicated once a day, on 5-point Likert scales (range 0-4) how they had felt during the day.

Incremental maximal exercise test. Subjects performed a bicycle ergometer test with incremental load. Estimated maximal workload was calculated according to Folgering.[14] The steps varied from 10 to 30 W/min, aiming at completing the test in about 10 minutes. Subjects were strongly encouraged to carry on cycling, until they were too exhausted to continue.

Perceived rate of exertion. The modified Borg scale[15] was administered during the exercise test. Subjects were asked every 3 minutes and at point of maximum effort to indicate on a scale from 1 to 10 how exerted they were from pedalling.

Physical fitness. Fitness (W/bpm) was quantified as the slope of the heart-rate vs. external workload, calculated from the ratio of the observed maximal workload and the observed increase in heart rate, minus the ratio of the reference maximal workload and the reference increase in heart rate (220-age in years). The reference maximal workload is based on age, sex and height. Negative values indicate that fitness is worse than predicted, positive values indicate that fitness is better than predicted. In formula:

Fitness (Watt/bpm)= [Wmax/(HRmax-HRrest)] - [Wmax_pred / (HRmax_pred - HRrest)].
Predicted Maximal Workload: Wmax_pred (Watt) = (VO2max_pred – VO2rest_pred) / 10.29 mL/min/Watt.[16]
Predicted Maximal O2-uptake: VO2max_pred (male: L/min)=0.046*height - 0.021*age - 4.31.[17]

Procedure
Subjects and controls were recruited by telephone. Baseline measurements (part 1) were done on the first 12 days. On the 13th day, the maximal exercise test took place (part 2). This was deliberately on a Wednesday, in order not to confound possible post-exercise activity changes with weekend-effects. On the 14th until the 20th day, post-ergometer data were taken (part 3).

Statistics
Data analysis was performed using SPSS 8.0. Skewed variables were log-transformed.
In the matched case control design, biographical data and baseline measurements (part 1) were analysed by means of the paired samples t-test for continuous variables and the McNemar test for categorical variables. For these analyses, the alpha level was set at p=0.05.
Repeated measures data concerning the exercise test (parts 2 and 3) were analysed as follows. Firstly, to evaluate interaction effects (group*time), difference scores were calculated for physical activity and self-report measures at time points after the exercise test as compared to baseline, and difference scores were calculated for successive BORG scores. The difference scores of symptomatic and healthy veterans were compared using paired samples t-tests. Secondly, to evaluate main effects (time), time points were examined using paired samples t-tests. To prevent error resulting from multiple testing, in part two the alpha level was set at p=0.01.

Results

Part 1: Baseline measurements
Self-reporting
At baseline, significant differences were found on most self-report measures between symptomatic and healthy Cambodia veterans (table 2). Symptomatic Cambodia veterans reported significantly more fatigue and pain on the self-observation list. They were generally more impaired (higher SIP-total scores). They perceived themselves as less active than healthy Cambodia veterans did, as measured by CIS-activity. No significant differences were found in POMS-depression scores and daily observed activity scores.

Table 2. Baseline measurements of symptomatic and healthy Cambodia veterans

	Symptomatic veterans	Healthy veterans	*p*
Daily observed fatigue[1]	4.1 (1.9)	1.1 (1.1)	0.000
Daily observed pain[1]	2.2 (2.1)	0.4 (0.5)	0.000
Daily observed activity[1]	4.6 (1.8)	5.8 (2.4)	0.085
Daily POMS-depression[1]	0.1 (0.4)	0.02 (0.1)	0.100
SIP 8-total	860.2 (493.9)	74.0 (210.9)	0.000
CIS-activity	14.2 (4.6)	4.7 (2.9)	0.000
General physical activity[2]	81.6 (16.8)	92.0 (18.0)	0.016
Peak amplitude[2]	194.1 (21.4)	199.7 (20.9)	0.222
Peak duration[3]	129.6 (35.1)	135.4 (35.6)	0.560
Duration rest period after peak[3]	74.2 (31.6)	56.5 (19.3)	0.016
% Activity reduction after peak	56.4 (14.0)	54.6 (13.3)	0.614

Paired samples t-test, $p<0.05$
[1] Mean score baseline 12-day period
[2] Expressed in Number of accelerations per 5 minute period
[3] Expressed in Minutes

General physical activity and activity patterns

Symptomatic veterans had significantly lower actometer scores and thus a significantly lower baseline level of physical activity than healthy veterans (table 2). Furthermore, their rest periods after a peak took significantly longer. No significant differences were either found in peak amplitude, peak duration and percentage activity reduction after peak (table 2).

Part 2: Exercise test

All subjects and controls completed the maximal exercise test. A total of 23 symptomatic (88.5%) and 25 healthy Cambodia veterans (96.2%) achieved their maximal predicted workload [McNemar test, $p=0.625$]. Symptomatic veterans had significantly lower fitness than their matched healthy controls (figure 1, table 3). Since only 27% (n=7) of symptomatic and 69% (n=18) of healthy veterans performed the exercise test for 9 minutes (McNemar test, $p=0.007$), data on perceived rate of exertion were analysed for 3 and 6 minutes and point of maximum effort. No significant interaction effects (group*time) were found. Paired samples t-tests revealed significant main effects of time (t=-12.5, $p=0.000$ and t=-13.7, $p=0.000$), indicating that both symptomatic and healthy veterans perceived pedalling as significantly more tiring over time.

Table 3. Physical fitness of symptomatic and healthy Cambodia veterans

	Symptomatic veterans	Healthy veterans	*p*
Physical fitness (Watt/bpm)	-0.1 (0.7)	0.3 (0.5)	0.028
Wmax reached (Watt)	229.6 (38.9)	268.8 (32.4)	0.000
VO2 Max (L/min)	2.7 (0.5)	3.1 (0.5)	0.002

Paired samples t-test, $p<0.05$

Part 3: Post-ergometer data

On the first day after the exercise test, a significant group*time interaction effect in actometer score was found (t=3.9, p=0.001), indicating that, as compared to baseline, levels of physical activity were elevated one day post-ergometer in healthy veterans, but not in symptomatic veterans (figure 2a). As compared to baseline, on the fourth day after the exercise test, a significant decrease in physical activity was found in both groups. Paired samples t-test revealed a significant main effect of time (t=-3.2, p=0.002).

As compared to baseline, on the fourth day after the exercise test, a significant decrease in daily observed activity was found in both groups. Paired samples t-test revealed a significant main effect of time (t=4.8, p=0.000) (figure 2b).

The maximal exercise test did not induce any changes in daily observed fatigue, daily observed pain or depressive mood on the seven days after the exercise test as compared to baseline. No interaction or main effects were found.

Discussion

To our knowledge, this is the first controlled study on physical activity and exercise performance in (ex-)servicemen who encounter health problems after deployment. Symptomatic and healthy Dutch Cambodia veterans (of whom 85% were active-duty military personnel) were followed for a baseline period of 12 days prior to taking an incremental maximal exercise test on a bicycle ergometer, followed by seven days of post-ergometer data. During baseline, symptomatic Cambodia veterans reported higher levels of daily observed fatigue, pain and impairment. Self-reported and actual levels of physical activity were reduced in symptomatic Cambodia veterans, and duration of rest taken after peaks was consistently longer.

All participants were able to accomplish the strenuous exercise-test, 92% of all participants reached their predicted physiological maximum. Symptomatic veterans did not perceive pedalling as more tiring than healthy veterans did, although their physical fitness was lower.

After the maximal exercise test, we found no increase in daily observed complaints in symptomatic veterans. On the fourth day after the exercise test, a Sunday by definition, levels of physical activity and daily observed activity scores were decreased in both groups. However statistically significant, we question the relevance of this finding, since a baseline week-pattern was observed: at baseline, on Saturdays and

Sundays, levels of physical activity were lowered in both symptomatic and healthy veterans. Furthermore, in both symptomatic and healthy veterans, actometer and daily activity scores on the fourth post-ergometer day (Sunday) did not differ significantly from actometer and daily activity scores on the Sundays before the exercise test (10 and 3 days before the exercise test) (paired samples t-test, all tests p=NS). Likewise, in our opinion, the observed increase in actometer score in healthy veterans on the first day after the exercise test (Thursday) can also be traced back to weekday patterns. Again, no significant difference was found with the scores on the Thursday before the exercise test (paired samples t-test, all tests p=NS).

Two points can be brought up for discussion. Firstly, the level of physical activity was evaluated in both symptomatic and healthy veterans. Unexpectedly, the level of general physical activity in healthy control Cambodia veterans, of whom 85% hold an active duty status, was not significantly different from levels found in healthy male civilians (M=97±30).[11] This finding may cast doubt on the usefulness of an actometer for measuring physical activity in military personnel. Since in the present study physical fitness and physical activity were positively correlated (r=0.370, p<0.01) and previous studies have found better physical fitness in military personnel than in civilians[18,19], we had expected higher levels of physical activity in healthy Cambodia veterans as compared to healthy male civilians. It may be, we did not find this difference because healthy veterans had performed many rowdy sports and thus had, according to the instructions, more often removed the actometer from their ankles, leading to an underestimate of their actual level of physical activity. A total of 85% of healthy veterans performed sports on a regular basis, with an average of 6.4±8.4 h/week (in symptomatic veterans, 48% performed sports, with an average of 2.4±3.5 h/week). But, unfortunately, we do not possess detailed self-report data on periods that the actometer was removed. Nevertheless, the actometer was sensitive enough to demonstrate a difference in the level of physical activity in symptomatic vs. healthy Cambodia veterans.

Secondly, we did not monitor on the day of the exercise test, since most participants in the maximal exercise test had taken a day off from work and had to travel quite a distance to get to our hospital. Therefore, the day of the exercise test was not considered representative. Whether post-exertion effects have taken place on the day of the exercise test remains unanswered.

From the present study, it can be seen that symptomatic veterans may encounter serious problems in exercising their duty. In our view, it should be questioned whether servicemen who report health concerns and who are physically less active and less fit, are prepared for future deployment. Veterans who suffer from chronic symptoms, should be given an opportunity to recover, both by temporarily adjusting their tasks and by effective treatment. In previous studies we have elaborated on the role of fatigue, self-efficacy, causal attributions and other illness-related cognitions.[1;20] Physical activity and physical fitness could also form an essential part of therapy that integrates behavioural and cognitive aspects.

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Figure 1 Physical fitness (W/bpm)

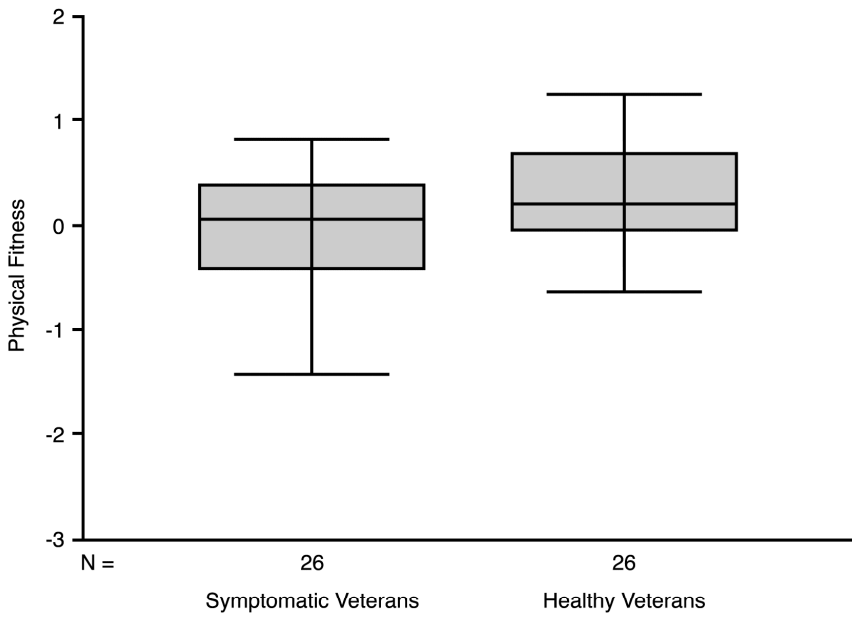
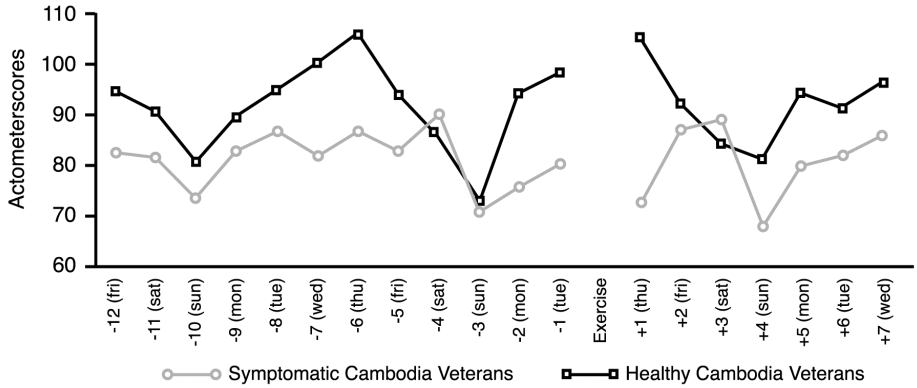
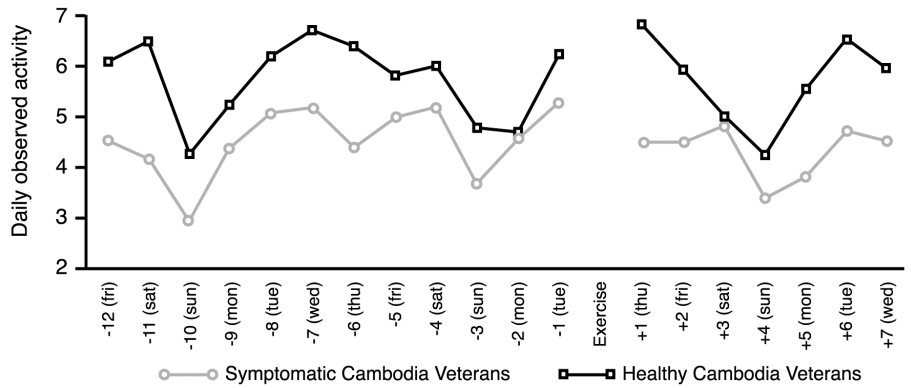


Figure 2 Actometer Scores, Daily observed activity





Chapter 8

Neuropsychological performance in symptomatic Cambodia veterans

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Abstract

Following the 1992-3 peace operation UNTAC, Dutch (ex-)servicemen have reported health complaints among which neuropsychological problems. The present study investigated self-reported neurocognitive problems, performance on standardized neuropsychological tests, and the tendency to underperform during neuropsychological testing in symptomatic Cambodia veterans as compared to matched healthy controls. Furthermore, the concordance between self-reported neuropsychological problems and performance on standardized neuropsychological tests was evaluated.
A neuropsychological battery was administered to 30 symptomatic and 30 matched control healthy Cambodia veterans.
Symptomatic veterans had higher levels of self-reported neuropsychological problems, but no different standardised test results. Symptomatic veterans did not have a stronger tendency to underperform, and no concordance was found between formal test results and self-reported complaints of memory and concentration.
In conclusion, symptomatic Cambodia veterans report cognitive difficulties in the absence of neuropsychological impairment in standardised testing. The subjective experience of memory and concentration problems, but not neuropsychological impairment is related to fatigue.

Introduction

Between 1992 and 1993, 2616 Dutch (ex-)servicemen were deployed in the peace operation United Nations Transitional Authority for Cambodia (UNTAC). After return, a

number of Cambodia veterans reported health symptoms of which forgetfulness, difficulty concentrating and fatigue were the primary complaints.[1]
Symptoms in Cambodia veterans do not seem to be a separate problem. Since the American Civil War, similar post-war illnesses have been described and in the past years there has been a broad public and scientific interest on Gulf War related illness.[2-5] The prominence of neurocognitive complaints in war related illness raises the question whether there is a neurological substrate or neuropsychological impairment that can explain the pathogenesis. Neurological examination in Cambodia veterans revealed no single neurological disease that can account for the symptoms.[6] To explain memory and concentration problems in the absence of a neurological diagnosis, poor motivation or malingering, are often put forward. Neuropsychological studies in Gulf War veterans have shown conflicting results, with some authors reporting modest to severe neurocognitive abnormalities[7-10] and others reporting no neurocognitive impairment.[11,12]
The present study reports the results of neuropsychological assessment in Cambodia veterans with chronic symptoms and healthy control Cambodia veterans. The following questions are investigated: do symptomatic veterans have more self-reported neurocognitive problems; do symptomatic veterans have worse performance on standardised tests; do symptomatic veterans have a stronger tendency to underperform during neuropsychological testing; and what is the concordance between self-reported neuropsychological problems and performance on standardised neuropsychological tests?

Method

Subjects

Sixty Cambodia veterans participated in the present study which was embedded in a broad somatic and psychological assessment program. One group consisted of 30 veterans who had elevated levels of fatigue as assessed in a previous postal survey[1] and who had met our case definition for symptoms (CIS fatigue severity score ≥37) in a 18-months follow-up survey (symptomatic veterans)[13]. The other group consisted of 30 veterans who had non-elevated levels of fatigue and who reported less than four symptoms in the previous postal survey (healthy veterans). Healthy veterans were matched for age, branch of service, rank during the mission in Cambodia and, as far as possible, geographical area, with the symptomatic veterans.
Between symptomatic and healthy Cambodia veterans, no significant differences were found in age, educational level, marital status, rank during the mission and branch of service. At the moment of study, mean CIS-fatigue severity scores were 44.5±6.1 in symptomatic veterans and 12.3±5.2 in healthy veterans. The ethics committee of our hospital approved the study.

Neurological status

Of symptomatic veterans, 97% (n=29) was seen by a senior-neurologist who performed a comprehensive neurological examination. Special attention was paid to the presence of possible vascular events and epileptic abnormalities in the history, and to the presence of signs of neuromuscular disorders. Details are described elsewhere.[6] None of the symptomatic veterans showed neurological abnormalities.

Instruments

The following concepts and neuropsychological functions were measured:

Fatigue severity. The Checklist Individual Strength (CIS)[14] is a standardised 20-item questionnaire asking about different aspects of fatigue over the last 14 days. In the present study, the fatigue severity subscale (8 items, range 8-56) was used to evaluate levels of fatigue.

Self-reported complaints of memory and concentration. The subscales concentration of the CIS (5 items, range 5-35) and alertness behaviour of the Sickness Impact Profile (SIP) (10 items, range 0-777)[15,16] were used to measure self-reported cognitive problems. Furthermore, the daily Self-observation List[17] was completed for a 12-day period. The presence or absence of concentration and memory problems was rated four times a day on four-point Likert scales. In the present study, mean daily observed scores were calculated (range 0-4).

Concentration. The Symbol Digit Test (SDT) of the Wechsler Adult Intelligence Scale (WAIS)[18] represents concentration problems. It is considered to be one of the most sensitive sub-tests of the WAIS for ageing and cognitive deterioration.[19]

Speed of information processing. The Complex Reaction Time Task (CRT)[20] is a measure of motor-related speed of information processing. Subjects are seated behind a response board which contains one start and five target buttons. In three consecutive tasks of 30 trials each, subjects are asked to react to stimulus lights. This test has been described in detail elsewehere.[20]

Information processing. The Paced Auditory Serial Addition Test (PASAT)[21,22] is a very sensitive test to evaluate deficits in information processing ability. Subjects are asked to add 60 pairs of randomised digits so that each is added to the digit immediately preceding it.[19] In the present study, the 2.0 and 2.8 second versions were used.

Verbal memory. The California Verbal Learning Test (CVLT)[23,24] consists of a 16-item shopping list, representing four semantic categories. The test measures short and long delay verbal memory. Included are the normscores on the short and long delay retrieval subtests as calculated by the Dutch version.

Malingering. The Amsterdam Short Term Memory Test (ASTMT)[25] is a 30-item forced choice verbal recognition task (range 0-90), developed to detect submaximal effort during neuropsychological testing. The test has been described in detail elsewhere.[26]

Statistics

Data analysis was performed using SPSS (Statistical Package for the Social Sciences, release 8.0.0). Alpha level was set at p=0.05. For reasons of homogeneity, only men were included. For comparisons between groups, Student's t-test, Mann Whitney U test, and Fisher's exact test were used. To evaluate significant relations between two variables, Spearman rank correlation coefficients were used.

Results

Self-reported neuropsychological problems

Symptomatic veterans reported more neuropsychological problems than non-symptomatic veterans. Symptomatic veterans had significantly higher CIS-concentration and SIP-intellectual functioning scores. On the self-observation list, symptomatic veterans reported significantly more daily observed concentration and memory problems (table 1).

Standardized neuropsychological testing

Symptomatic and healthy Cambodia veterans had equal neuro-psychological test results. No significant differences were found in any of the standardised tests (table 1). The percentage of veterans (0-7%) that scored below the mean of healthy veterans minus 2 standard deviations, did also not differ between symptomatic and healthy veterans in any of the tests (all tests Fisher's exact tests, p=NS).

Underperformance

Congruently with the previously mentioned standardised test results, no significant differences were found in mean ASTMT score (table 1) and in the percentage of both groups that scored below the cut-off of respectively 86 (13 vs 10%, Fisher´s exact test=NS). Thus, symptomatic Cambodia veterans did not underperform during neuropsychological testing as compared to healthy Cambodia veterans.

Relationship neuropsychological testing and self-report

Self-reported neuropsychological problems were not related to performance on standardised tests. No significant correlations were found between self-report (CIS-concentration, SIP-intellectual functioning scores, daily observed concentration and memory problems) and any of the formal tests measuring information processing (PASAT); speed of information processing and motor speed (CRT); concentration (SDT); and sub-maximal effort during neuropsychological testing (ASTMT) (All tests, Spearman´s rho = NS).

Table 1 Self-reported neuropsychological complaints and standardised neuropsychological test results (M±SD) in Cambodia veterans

	Symptomatic veterans n=30	Healthy veterans n=30	*p*
CIS-concentration	25.8 (7.2)	8.0 (3.5)	<0.001*
SIP-intellectual functioning	238.7 (204.7)	9.5 (26.8)	<0.001**
Daily observed concentration score	0.948 (1.27)	0.006 (0.03)	<0.001**
Daily observed memory score	0.960 (1.35)	0.003 (0.02)	<0.001**
PASAT 2.8 completed	100% (n=30)	100% (n=30)	NS**
PASAT 2.8 right answers	52.7 (5.5)	52.0 (9.6)	NS**
PASAT 2.0 completed	97% (n=29)	97% (n=29)	NS**
PASAT 2.0 right answers	43.7 (6.4)	43.2 (8.9)	NS**
Motor speed†			
Movement time task 1	0.19 (0.05)	0.19 (0.04)	NS*
Movement time task 2	0.18 (0.04)	0.19 (0.04)	NS*
Movement time task 3	0.20 (0.04)	0.21 (0.03)	NS*
Information processing†			
Baseline reaction time	0.3 (0.04)	0.3 (0.04)	NS*
Reaction time task 1-2	0.04 (0.04)	0.04 (0.03)	NS*
Reaction time task 2-3	0.09 (0.04)	0.09 (0.04)	NS*
SDT	57.5 (10.0)	57.5 (10.0)	NS*
CVLT			
Short delay retrieval	0.53 (2.90)	0.4 (2.37)	NS*
Long delay retrieval	-0.80 (2.25)	-0.77 (1.91)	NS*
ASTMT	88.0 (2.3)	88.4 (1.7)	NS**

Student´s t-test, *s*<0.05; ** Mann-Whitney U test, *p*<0.05
† measured in seconds

Discussion

In the present study, symptomatic Dutch Cambodia veterans exceeded their matched healthy controls in self-reported neuropsychological problems. However, standardised neuropsychological testing revealed equal results. No concordance was found between self-report and neuropsychological impairment. Since the standardised test results did not differ between groups, symptomatic veterans did not have a stronger tendency to underperform during neuropsychological testing. As expected, both groups had equal scores on a task originally designed to detect malingering.

Overlooking the present results, the question arises why symptomatic Cambodia veterans report cognitive difficulties while there is no relationship between these self-reported complaints on the one hand and neuropsychological testscores or neurological abnormalities on the other. Although there is no consensus on neurocognitive complaints in Gulf War veterans, several studies did not find

neuropsychological impairment in affected veterans. This led to the conclusion that self-reported neuropsychological symptoms are more indicative of emotional disruption than of neurocognitive impairment.[11] A similar conclusion that subjective neurocognitive complaints are more related to psychological variables, especially to fatigue, than to underlying physiological processes was drawn in studies on fatiguing illness in civil populations. In these studies, patients with Chronic Fatigue Syndrome (CFS) were compared to healthy controls and other clinical populations. Self-reported complaints were found to be most frequent and severe among CFS populations.[27]

In the present study, an operational case definition for symptoms in Cambodia veterans was constructed using a validated fatigue severity questionnaire. Since fatigue severity is positively related to self-reported complaints, it can be concluded that the subjective experience of memory and concentration problems, but not neuropsychological impairment is related to fatigue.

In our view, based on the present patient control study, symptomatic Cambodia veterans have a problematic experience of cognitive difficulties which is related to fatigue. Based on treatment outcome studies in CFS, we expect that these neuropsychological problems in symptomatic veterans would diminish if their level of fatigue would decrease, for example after appropriate treatment.

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Chapter 9

Post-Deployment Syndrome in Cambodia veterans

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Introduction

For ages, reporting of symptoms in (ex-)servicemen following deployment has been a common phenomenon. Since the American Civil War until recent military interventions in Kosovo, many examples of unexplained somatic symptoms are presented, all provided with their own names: e.g. effort syndrome, shell shock, combat fatigue, Agent Orange syndrome, Gulf War Syndrome, Bosnia syndrome, or symptoms in Cambodia veterans. On face of it, these separately described syndromes resemble each other: the same main (unexplained physical) symptoms are reported and an overlap in working mechanisms has been suggested. Recently, in Gulf War Syndrome and symptoms in Cambodia veterans, similar causal attributions to chemical factors have been made, and both have been an issue of great media interest. Many authors hold the view that the similarities between separately described syndromes outweigh the differences.[1-3] To shape the thought of a commonly shared functional somatic syndrome in veterans of war and peace operations, we propose the nomenclature "Post-Deployment Syndrome".*

In this final chapter, an attempt is made to answer the question why (ex-)servicemen become and remain symptomatic. Therefore, we developed a hypothetical pathogenic model for Post-Deployment Syndrome based on our studies in Dutch veterans who were deployed in the 1992-3 peace keeping operation UNTAC (United Nations Transitional Authority for Cambodia). The implications of the model will be discussed. In this context, limitations of previous studies in veterans will be reviewed.

* In earlier work of our study group[1, 27, 47] the nomenclature 'Veterans Syndrome' has been proposed. In the course of our investigation, 'Post Deployment Syndrome' seemed more appropriate.

International standard for Post-Deployment Syndrome

In their work on Gulf War veterans, several authors have tried to organise symptoms in a case definition or have sought for an operational working definition. However, none of the various case criteria have been adopted as a commonly shared golden standard for symptoms in Gulf War veterans. In the initial period of research on Gulf War related illness, the American Department of Defence has formulated diagnostic case criteria. Gulf War veterans who had at least 5 of the following 8 symptoms or signs: fatigue; joint pain or low back pain; headaches; intermittent diarrhoea without bloody stools; difficulty sleeping; low-grade fever; weight loss; neuropsychiatric symptoms (forgetfulness; difficulty concentrating; depression; memory loss; easy irritability), and whose symptoms could not be explained by medical or psychiatric illness, were diagnosed as having Gulf War Syndrome.[4] Using a clinical and statistical approach, Fukuda and colleagues have formulated a definition for Chronic Multisymptom Illness, which as its name suggests, distances from Gulf War Syndrome and also could be applied to military personnel who were not deployed in the Persian Gulf War. To meet the criteria for Chronic Multisymptom Illness, (ex-)servicemen should have one or more chronic symptoms (present for more than six months) from at least 2 of the following 3 categories: Fatigue; Mood-cognition (symptoms of feeling depressed; difficulty remembering or concentrating; feeling moody; feeling anxious; trouble finding words; difficulty sleeping); Musculoskeletal (symptoms of joint pain; joint stiffness; muscle pain).[5] Another operational research case criterion was formulated using conventional cut-off scores on the subscales subjective health perception and physical functioning of the SF-36.[6]

Some authors did not define whether or not veterans were cases of Gulf War related illness, they included self-referred Gulf War veterans in their clinical assessment program[7] or studied Gulf War veterans who fulfilled published case definitions for medically unexplained fatiguing illness, particularly Chronic Fatigue Syndrome and / or Multiple Chemical Sensitivity.[8]

Confronted with the lack of an international standard, we produced an operational case definition, using a standardised fatigue severity questionnaire.[9] In our view, research on Post-Deployment Syndrome would benefit from a valid and agreed case definition[10,11] since it would enhance international comparability and reproducibility of research on aetiology, treatment and prevention. It would further add to acknowledging the complaints and creating sympathy for affected (ex-)servicemen. Table 1 shows the diagnostic criteria which we propose for Post-Deployment Syndrome. International case criteria for Post-Deployment Syndrome should primarily reflect consensus and have a scientific foundation. Analogous to the 1994 CDC criteria for Chronic Fatigue Syndrome[12], such an international standard could include a time-criterion, a specification of core symptoms and exclusion criteria.

Table 1 Proposed diagnostic criteria for Post-Deployment Syndrome

	Proposal Diagnostic Criteria for Post-Deployment Syndrome
1. Deployment	The (ex-)servicemen has participated in a peace operation or war
2. Time criterion	Symptoms are of definite onset Symptoms have lasted for al least six months
3. Core symptoms	Fatigue Memory problems Concentration problems
4. Exclusions	Alcohol dependence Hospitalisation for mental disease in five years prior to deployment

Two important limitations of studies on symptoms in veterans

In the last decade, multiple studies have been performed on symptoms in Gulf War veterans and veterans who have participated in other wars and peace operations. In 1999, the Federal Government of the United States had already projected cumulative expenditures of over $130 million for research on Gulf War related illness.[13] In the Netherlands, studies were performed in UNTAC and UNPROFOR veterans.[14-17] A general limitation of studies on post-deployment health status is the delay in commissioning research. Both Gulf War research and our study in Cambodia veterans were started approximately four years post-return. As a consequence, the greatest part of the research had a retrospective character. Therefore, study results were based on (retrospective) self-report which may have induced recall-bias, especially in respondents with more health symptoms.[18,19] In the Dutch studies, for reasons of privacy, data on non-responders were not available. Although the response rates were quite high, information on non-responders would gain more insight into the representativeness of the results. This seems important since in a study on voluntary Gulf War health registries, significant differences were found between self-selected Gulf War veterans who enrolled in these registries as compared to all Gulf War veterans. Servicemen at highest risk of participating in a health registry had served in the Army or National Guard, were in the Gulf War theatre during fighting, were older and female, were enlisted personnel, and had been hospitalised during the 12-month period before the war.[20] For future studies on Post-Deployment Syndrome, we recommend prospective studies, in which pre-deployment psychological and somatic parameters can be compared with post-deployment variables. Furthermore, a long delay in performing research should be discouraged, not only to prevent recall-bias, but also to enhance trust in the military organisation and feelings of perceived attention, recognition and respect in (ex-)servicemen.

Descriptive hypothetical model

Based on the studies in Cambodia veterans and literature on Gulf War related illness, we developed a descriptive hypothetical model in order to gain more insight in factors that contribute to Post-Deployment Syndrome. As in many functional somatic syndromes, various factors that add to the onset and factors that add to the perpetuation of the symptoms are discerned. According to Hotopf and colleagues, initial symptoms (caused by initiating factors) could "sensitise" individuals to later symptoms or perhaps initial symptoms indicate differences in biological response.[18]

Onset of Post-Deployment Syndrome

In Post-Deployment Syndrome, symptoms have started during deployment or shortly following return. In our model (figure 1), we suppose service-related somatic events and service related traumatic experiences, to be initiating factors.

Somatic factors

There is a broad range of somatic factors that can give rise to complaints, e.g. medication, multiple vaccinations, infections, tropical disease, climate, or environmental factors. Since most diseases and side-effects of medication disappear over time, and studies on Gulf War and Cambodia veterans are limited by its retrospective character, the unique contribution of single initiating factors can only be estimated. Consequently, in our study in Cambodia veterans, we were not able to confirm or rule out that mefloquine or vaccinations had contributed to the onset of the symptoms.[21] Thus far, in literature on Gulf War related illness, no consensus has been reached in delineating whether the symptoms are caused by somatic factors such as vaccinations, nerve agent prophylaxis (pyridostimine bromide), neurotoxic exposures (e.g. pesticides), infectious diseases, or environmental hazards (e.g. oil well fire smoke, sand, depleted uranium).[22-25]

However, strong positive associations are found between self-reported exposures, self-reported side-effects of vaccinations and later ill health.[6,18,26] Whether recall bias, particularly in respondents with more health symptoms, can account for these findings remains unclear.

In our study on Cambodia veterans, 80 (ex-)servicemen were examined in an extensive clinical assessment program. In approximately 18% of Cambodia veterans, symptoms had started after a service-related somatic event. Previously, this has been described as the somatic start model.[14,15,27]

Although somatic events have started symptoms in a subset of Cambodia veterans, no somatic factors (e.g. infectious disease, neurological abnormalities, a shifted cytokine balance) were found that can be classified as perpetuating factors.[28-30]

Traumatic events

Traumatic or severe events that have happened during the period of deployment, are considered another initiating factor in Post-Deployment Syndrome. In the United States, a study was conducted in Gulf War veterans immediately after return.

Approximately 4% had symptoms of posttraumatic stress disorder.[31] Many studies in veterans and civilians have described a relationship between posttraumatic stress and physical health complaints. Posttraumatic stress disorder consistently diminishes the general health perception, it has a negative impact on psychological functioning and is linked to high symptom reporting.[32,33] Although traumatic events may have started symptoms in a subset of (ex-)servicemen, and many (ex-)servicemen may have experienced symptoms of posttraumatic stress shortly after deployment, both investigations in Gulf War related illness and Cambodia veterans have been unable to attribute a substantial degree of current symptoms to posttraumatic stress.[34-37] In Cambodia veterans, only 1.3% received a probable diagnosis of current posttraumatic stress disorder.[38] Therefore it is concluded that posttraumatic stress disorder cannot offer an explanation for Post-Deployment Syndrome. In our clinical assessment program, severe events causing horror, helplessness or fear had given rise to health symptoms in approximately 16%. Previously this has been described as the psycho-trauma start model.[14,15,27] In table 2, to demonstrate the variety between Post-Deployment Syndrome and Posttraumatic stress disorder, its main characteristics are summarised.

Table 2 Main characteristics of Post-Deployment Syndrome and Posttraumatic stress disorder

	Post-Deployment Syndrome	Post-traumatic stress disorder[39]
Onset	Deployment	Experience of a severe event causing horror, helplessness or fear
Core symptoms	Core symptoms: fatigue, memory and concentration problems	Three clusters of core symptoms: re-experiencing, avoidance, hyper-arousal
Duration	> 6 months	> 1 month

Continuation of Post-Deployment Syndrome

In our model, cognitions concerning symptoms and post-deployment features are considered factors that are held responsible for the perpetuation of the symptoms.

Cognitions

In literature there is a growing notion that psychological factors, especially cognitions, are important in maintaining symptoms in veterans.[23] In Cambodia veterans, negative self-efficacy, strong causal attributions on medication and disease, and worries about one's health were predictive of symptoms and negative prognosis.[19,40] In Gulf War research, causal attributions on environmental factors and toxicity are addressed.[23] In a

large-based study in UK military personnel and two comparison groups, potentially harmful exposures were most frequently reported by Gulf War veterans. All self-reported exposures, including the notion of exposure to a chemical attack, were associated with ill health and a low health perception.[6] According to Wessely, there is a vicious circle linking self-reported exposure, attributions and symptoms.[3] Mediated by causal attributions, increased fears and concerns, exposure to real or perceived environmental hazards leads to increased symptom reporting. In addition to this, in order to explain their symptoms, people may have strong causal attributions, which in its turn lead to more complaints.

Another psychological factor that is involved in the continuation of symptoms in Cambodia veterans is self-efficacy or perceived control over symptoms.[40] To our knowledge, self-efficacy has not been studied in Gulf War veterans. However, in studies on chronic fatigue syndrome, low self-efficacy has also shown to predict fatigue severity and chronicity.[41]

Post-deployment features

In reply to their health claims, Cambodia veterans had the perception that they did not encounter attention, recognition and respect from the military organisation. Like Gulf War veterans, they can be characterised as seriously distrusting the military authorities.[3] In Cambodia veterans, an explanation for this lack of trust can be found in the four-year delay in initiating research that could clear up the matter and unravel conspiracy theories, as well as an unlucky series of events such as the loss of pre-deployment blood samples, the absence of a written instruction supplied with mefloquine and a negligent vaccination registry system. Based on qualitative data gathered in more than 250 interviews with Cambodia veterans and literature on Gulf War syndrome, anger, disappointment and a sense of being used and not taken seriously are considered important perpetuating factors in Post-Deployment Syndrome. Other factors that contribute to the continuation of symptoms are problems at the home front during and after deployment; having a more poignant, threatening, aggravating and powerless subjective experience of the mission; more problems in re-adjustment on return; and less satisfaction with military career.[19] As far as we know, such factors have not been addressed in Gulf War research.

Facilitating factors

Based on our investigation in Cambodia veterans, physical and psychological disturbances (e.g. unexplained somatic, psychological or psychiatric complaints) which already occurred in the years before deployment are considered factors that facilitate the onset and continuation of symptoms. In literature on predictors of the development of complaints after stressful events, a psychiatric history is often mentioned.[42,43] Furthermore, in a study on Gulf War veterans, Fiedler and colleagues found personality and negative coping strategies predictive of current physical functioning. It is suggested that personality style is a significant factor in the illness of veterans.[44] Earlier research of the same study group revealed that post-deployment, veterans with

multiple pre-deployment psychiatric diagnoses often continue to show the same complicated history after deployment, and additionally develop medical or psychiatric morbidity.[8] In our clinical assessment program, in approximately 16% of Cambodia veterans, pre-deployment dysfunctioning was manifest. Previously this has been described as the pre-morbidity model.[14,15,27]

Another facilitating factor is dissatisfaction with the preparation offered by the Ministry of Defence. In our study, symptomatic Cambodia veterans were frustrated about the short period between notice and departure, which may give rise to feelings of distrust in the military organisation. Preparation is especially important in repeated deployment, since successive participation in acts of war or peace operations, with little time to recuperate or to get prepared in between, may sensitise veterans to develop symptoms after deployment.

Implications

The results of the studies on symptoms in Cambodia veterans have implications for the prevention and treatment of Post-Deployment Syndrome.

Prevention

Primary prevention of Post-Deployment Syndrome should start before deployment. As our study and the work of others suggest, a partial reduction of Post-Deployment Syndrome can be attained by screening out servicemen who are at risk because of pre-deployment malfunctioning, recent significant family affairs or successive deployment with little time to recuperate or to get prepared in between. In the Netherlands, before entering service, applicants undergo a strict selection procedure, but a pre-deployment screening is lacking.

In the period before the mission, clear risk communication and a unmistakable transfer of information about side-effects of medication and vaccinations will enhance a good and satisfactory preparation and it will prevent negative prognostic factors such as strong causal attributions, the development of conspiracy theories, and distrust in the military organisation.

Keeping trust is also of main importance after return. If post-deployment health complaints are being reported, the military authorities should take these claims seriously. Symptomatic veterans should be offered good prospects for recovery in the working situation and they should be enabled to be frank about symptoms and impairment. Finally, appropriate treatment should be offered if the symptoms last for more than six months.

Treatment

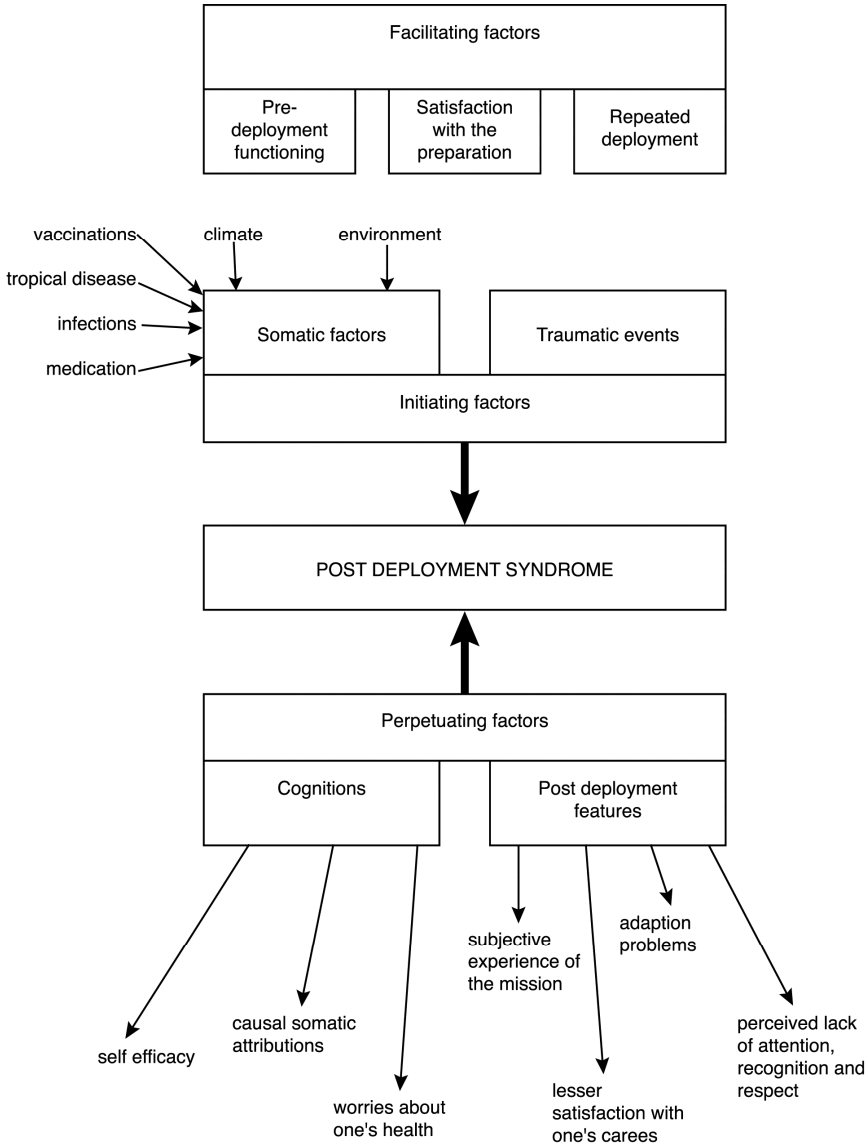
Based on our clinical experience with Cambodia veterans, we feel that symptoms of posttraumatic stress disorder are well recognised and treated by the health services of the Dutch Ministry of Defence, but that focussing just on posttraumatic stress disorder is futile. The majority of persisting symptoms cannot be explained by posttraumatic stress disorder, thus they should not be treated like post traumatic stress disorder. The

results of our investigation in Cambodia veterans have revealed a consistent picture of behaviour and cognitions which could serve as a starting point for cognitive behavioural therapy (CBT). Previously, CBT has proven to be effective for a wide range of physical and psychological disorders, among which chronic pain, depression and chronic fatigue syndrome. Recently, clinical randomised trials have started to evaluate CBT in treating (ex-)servicemen with Gulf War related illness.[23,45]

At the cognitive and emotional level, CBT should address perpetuating factors such as prognostically negative symptom-related cognitions (low self-efficacy, dysfunctional causal attributions, anger and suspicion toward the Ministry of Defence). Furthermore, CBT should address interventions at the behavioural level, such as graded exercise therapy aimed at increasing or adjusting physical, mental, and social activities, and improving physical fitness.

Post-Deployment has manifested itself through the years, and it is expected that new medical syndromes will also develop in the course of future armed conflicts and wars.[46] Five years of research on symptoms in Cambodia veterans have gained insight in symptoms in Cambodia veterans, and have smoothed the path for prevention, prospective studies and treatment of Post-Deployment Syndrome. In the next years, more study results on Gulf War related illness are coming. Hopefully, an international standard for Post-Deployment Syndrome will be constructed in the future, and military authorities will use the knowledge on their national war syndrome and those of other countries in enhancing prevention and treatment. It would be naive to suppose that Post-Deployment Syndrome can be stopped. In acts of war and peace keeping operations, servicemen will often be deployed overseas, under stressful conditions and on unknown ground. Despite preventive measures such as careful preparation, screening of servicemen and longitudinal studies, there will always be unexpected factors that can give rise to symptoms. Nevertheless, it is worth the effort to reduce the risk of ill health in men and women who serve their country and try to contribute to a more peaceful world.

Figure 1 Descriptive pathogenic model of Post-Deployment Syndrome



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Summary

After return from the 1992-93 peace keeping operation UNTAC (United Nations Transitional Authority for Cambodia), Dutch (ex-)servicemen have reported health complaints, among which severe fatigue, forgetfulness, concentration problems and decreased physical fitness. Between December 1996 and December 2000, an extensive independent investigation was performed on symptoms in Cambodia veterans. The aims of this study were to evaluate its nature and prevalence, specificity, etiological and risk factors and starting points for treatment. In this thesis, a large part of the results are presented.

At the start of our investigation, we reviewed literature concerning health symptoms following previous acts of war and peace operations. In Chapter 2 it is concluded that symptoms in Cambodia veterans do not seem to be a separate problem. Unexplained somatic and psychological complaints after military operations have been described since the American Civil War. Almost every war or peace operation is characterised by its own symptoms or syndromes with their own unique names.
Chapter 3 describes our initial study in Cambodia veterans. A cross-sectional postal survey was commissioned in all Cambodia veterans whose names were known to the Ministry of Defence, and four relevant comparison groups. Forgetfulness, difficulty concentrating and fatigue were the symptoms most commonly endorsed. In the absence of a set case definition, a validated fatigue questionnaire was used to produce an operational case definition. The prevalence rate of health symptoms in Cambodia veterans was 17%. Cases were not uniquely found in this group. In groups of UNAMIR and UNPROFOR veterans, 27% and 10%, respectively, also fulfilled the case definition.
Chapter 4 is a sequel to chapter 3. It describes a eighteen months follow-up study in all veterans who initially met the operational case definition or who had sub-threshold scores. At follow-up, a substantial 44% met the case-definition for symptoms in Cambodia veterans. For self-reported improvement, a majority of respondents reported continuation of the same complaints (57%) or worsening (4%). Complete or partial recovery was reported by 39%.
In Chapter 5 and 6, aetiological factors are evaluated. In Chapter 5, the role of mefloquine, multiple vaccinations and morbidity during UNTAC is addressed. Using the initial postal survey, no convincing arguments were found for a direct link between current symptoms on the one hand and mefloquine, multiple vaccinations, and morbidity on the other. Since the investigation on symptoms in Dutch Cambodia veterans was performed four years post-return, it is not hundred per cent sure that mefloquine or vaccinations did not play a general role in the onset of the symptoms. Disease caught in Cambodia may have initiated symptoms in a few symptomatic Cambodia veterans, but it cannot fully account for the onset of symptoms in Cambodia veterans.

Likewise, in Chapter 6 it is found that posttraumatic stress disorder (PTSD) cannot offer an explanation for symptoms in Cambodia veterans. Elevated PTSD scores were found in 1.3% of 1698 veterans only. There was no concordance between elevated PTSD scores and fatigue severity.

Chapter 7 describes a study in which in symptomatic and matched healthy control Cambodia veterans performed an incremental maximal exercise test on a bicycle ergometer in order to evaluate common complaints about reduced activity levels, decreases in physical fitness and aggravation of symptoms after strenuous exercise. Using an actometer and diaries, both groups were followed for a 12-day baseline period prior to taking the exercise test, followed by seven days of post-ergometer data. Lower levels of physical activity and lower physical fitness were found in symptomatic Cambodia veterans. However, post-exertion malaise was not found. The observed post-exertion effects were traced back to weekday patterns.

Chapter 8 describes a study in which a neuropsychological battery was administered to 30 symptomatic and 30 matched control healthy Cambodia veterans in order to evaluate neurocognitive problems. Symptomatic veterans had higher levels of self-reported neuropsychological problems, but no different standardized test results. It is concluded that the subjective experience of memory and concentration problems, but not neuropsychological impairment is related to fatigue.

In Chapter 9 the results of the studies presented in this thesis are placed into one perspective. A few limitations are discussed and a plea is made for an international standard for Post-Deployment Syndrome. Finally, a hypothetical explanatory model for Post-Deployment Syndrome is presented.

Samenvatting

In de periode 1992-1993 namen Nederlandse militairen deel aan de vredesmissie UNTAC (United Nations Transitional Authority for Cambodia) in Cambodja. Enkele maanden na terugkeer meldde een deel van de Cambodja-gangers dat zij gezondheidsklachten hadden, waaronder ernstige vermoeidheid, vergeetachtigheid, concentratieproblemen en een verslechterde lichamelijke conditie. Van december 1996 tot december 2000 waren de klachten van de Cambodja-gangers onderwerp van uitgebreid onafhankelijk onderzoek. Het doel hiervan was meer zicht te krijgen op de aard, omvang, specificiteit, en etiologie van de klachten, op de risicofactoren en op aangrijpingspunten voor behandeling. Dit proefschrift geeft een groot deel van de onderzoeksresultaten weer.

Bij aanvang van het onderzoek is in de literatuur gezocht naar wat bekend was over gezondheidsklachten na oorlogshandelingen en vredesmissies. In hoofdstuk 2 luidt de conclusie dat de klachten van de Cambodja-gangers geen op zichzelf staand probleem lijken te zijn. Al sinds de Amerikaanse burgeroorlog wordt melding gemaakt van omverklaarde lichamelijke en psychische klachten na militaire operaties. Vrijwel iedere oorlog of vredesmissie kent zijn eigen symptomen of syndromen. Deze worden telkens van een nieuwe naam voorzien.
In hoofdstuk 3 is de eerste studie beschreven die wij bij de Cambodja-gangers uitvoerden. Alle Cambodja-gangers van wie de naam bekend was bij het Ministerie van Defensie, werden benaderd in een cross-sectioneel vragenlijstonderzoek, evenals vier relevante controlegroepen. Vergeetachtigheid, concentratieproblemen en vermoeidheid vormden de top drie van meest gerapporteerde klachten. Om te onderzoeken hoeveel Cambodja-gangers klachten rapporteerden, werden operationele criteria opgesteld aan de hand van een gestandaardiseerde vragenlijst voor vermoeidheidsklachten. Zeventien procent van de Cambodja-gangers voldeed aan deze criteria. De klachten bleken echter niet specifiek te zijn. In een groep UNAMIR en een groep UNPROFOR militairen werden prevalentiecijfers van 27% en 10% gevonden.
Hoofdstuk 4 kan gezien worden als een vervolg op hoofdstuk 3. Hierin wordt de vervolgstudie beschreven die 18 maanden na het eerste vragenlijstonderzoek werd uitvoerd. Alle Cambodja-gangers die in het eerste vragenlijstonderzoek aan de operationele criteria voor klachten voldeden, evenals een groep met zogenaamde drempelwaarden, werden benaderd voor vervolgonderzoek. Op moment van het vervolg onderzoek, voldeed 44% van de respondenten aan de criteria voor klachten. Wat betreft zelf-gerapporteerde verbetering, zei een meerderheid van de respondenten nog steeds dezelfde klachten te hebben (57%) of zelfs verslechtering te hebben waargenomen (4%). Volledig of gedeeltelijk herstel werd door 38% van de respondenten gerapporteerd.
In hoofdstuk 5 en 6 komen ontstaansfactoren aan de orde. In hoofdstuk 5 wordt de rol van mefloquine, meervoudige vaccinaties en ziekte tijdens de uitzending belicht. Op

basis van het eerste vragenlijstonderzoek werden geen overtuigende argumenten gevonden ten gunste van een directe relatie met de huidige klachten. Het kan echter niet met zekerheid worden uitgesloten dat mefloquine of vaccinaties geen rol hebben gespeeld bij het ontstaan van de klachten, aangezien het Post-Cambodja Klachten Onderzoek ruim vier jaar na terugkeer uit Cambodja plaatsvond. Mogelijk heeft ziekte tijdens de uitzending bij een aantal Cambodja-gangers aanleiding gegeven tot het ontstaan van klachten, maar dit biedt geen volledig verklaring voor de grotere groep.
In hoofdstuk 6 wordt betoogd dat de diagnose post-traumatische stoornis (PTSD) eveneens geen verklaring biedt voor de klachten van de Cambodja-gangers. Slechts 1.3% van 1698 Cambodja-gangers heeft verhoogde PTSD-scores. Er werd verder geen samenhang gevonden tussen de hoogte van PTSD-scores en de ernst van vermoeidheidsklachten.
In hoofstuk 7 worden de resultaten beschreven van een fietsergometrie test met opklimmende belastbaarheid bij Cambodja-gangers met klachten en zorgvuldig gekozen gezonde militaire controles. Doel van deze proefopzet was veelvuldig genoemde klachten over afgenomen activiteit, een verminderde lichamelijke conditie en toename van klachten na forse inspanning, te onderzoeken. Met behulp van aktometers en dagboekregistratie werden beide groepen 12 dagen voor en 7 dagen na de inspanningstest gevolgd. Cambodja-gangers met klachten hadden een lager niveau van lichamelijke activiteit en een slechtere conditie dan hun controles. Voor zover er veranderingen van klachten werden waargenomen na de inspanningstest, konden deze aan normale fluctuaties gedurende de week worden toegeschreven. Er werd geen bewijs gevonden voor een verergering van klachten na flinke inspanning.
Hoofdstuk 8 beschrijft een studie waarbij bij 30 Cambodja-gangers met klachten en 30 zorgvuldig gekozen gezonde militaire controles een neuropsychologische testbatterij werd afgenomen met als doel neurocognitieve problemen te onderzoeken. De conclusie van dit onderzoek is dat Cambodja-gangers met klachten meer neurocognitieve problemen ervaren dan gezonde controles. De ervaren neurocognitieve problemen hangen eerder samen met de vermoeidheidsklachten dan met ernstig neuropsychologische gebreken.
In het afsluitende hoofdstuk 9 worden alle in dit proefschrift beschreven studies nog eenmaal in perspectief geplaatst. De beperkingen van het onderzoek worden besproken en er wordt gepleit voor een internationale standaard voor Post-Deployment Syndrome. Tot slot komt een hypothetisch verklarend model voor Post-Deployment Syndrome aan de orde.

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Curriculum Vitae

Maaike de Vries werd op 20 maart 1972 geboren in Enschede. De lagere school doorliep ze in Groningen en haar Atheneum diploma behaalde ze in Maastricht. Vervolgens studeerde ze Gezondheidswetenschappen aan de Universiteit Maastricht. Ze rondde haar studie cum laude af in 1996. Van december 1996 tot september 2001 was zij in het kader van het Post-Cambodja Klachten Onderzoek als onderzoeker verbonden aan de afdeling Medische Psychologie van het Universitair Medisch Centrum Nijmegen.
Maaike is gehuwd met Michiel Sweers. Met hun zoon Thijs wonen ze in Amsterdam.