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A scientific review addressing delayed onset posttraumatic stress disorder and posttraumatic depression

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Dansk resume

Posttraumatisk stresslidelse (PTSD) er en psykisk lidelse, der er karakteriseret ved stadigt tilbagevendende genoplevelse og mareridt (flashbacks), undvigende adfærd, følelsesmæssig affladning og "hyperarousal" (irritabilitet, tendens til sammenfaren, søvn- / koncentrationsbesvær og humørsvingninger). Disse symptomer er relateret til en tidligere udsættelse eller overværelse af traumatiske begivenheder af katastrofelignende karakter, der vil forventes at fremkalde rædsel hos næsten enhver. I litteraturen er det fortsat omdiskuteret, om disse symptomer kan opstå mere end 6 måneder efter den traumatiske begivenhed og om der kan være en symptomfri periode mellem traume og tilstandens opståen. PTSD der opstår mere end 6 måneder efter traumet benævnes forsinket PTSD (delayed onset PTSD).

Udvikling af depression kan muligvis også være relateret til tidligere traumatisk begivenhed og det er påvist, at der er en stærk sammenhæng mellem PTSD og depression.

Formål:

Formålet med rapporten, der er bestilt at Arbejdsmiljøforskningsfonden, er at beskrive og diskutere forekomsten af forsinket PTSD (hvis dette overhovedet forekommer), samt at foretage en kritisk vurdering af den tilgængelige viden om risikoen for udvikling af depressiv lidelse efter udsættelse for traumatiske hændelser.

Definition:

PTSD er defineret i "The Diagnostic and Statistical Manual for Mental Disease"(DSM), som er udstedt af: "The American Psychiatric Assosiation" og I "International Classification of Diseases" (ICD), udstedt af WHO.

Symptomer skal være til stede gennem minimum 1 mdr. og inkludere:

1) Genoplevelse af traumatisk begivenhed

2) Undvigende adfærd overfor situationer og hændelser der minder om begivenheden, samt følelsesmæssig affladning

3) "hyper arousal" (irritabilitet, tendens til sammenfaren, søvn- og koncentrationsbesvær og humørsvingninger).

Herudover inkluderer DSM-IV også et fjerde symptom i form af hæmmet socialt og/eller arbejdsmæssigt funktionsniveau.

Den udløsende årsag til disse symptomer er en traumatisk og belastende begivenhed, der ligger udover hvad et menneske normalt vil forventes at opleve. Det antages, at stort set alle mennesker vil opleve hændelsen som traumatisk og belastende. I DSM kriterierne er det endvidere en betingelse at den/de involverede reagerer med udtalt frygt og hjælpeløshed i relation til den traumatiske påvirkning.

Der er gennem tiden udviklet adskillige spørgeskemaer vedr. screening for PTSD. Disse er valideret på baggrund af kliniske vurderinger af samme patienter.

Forekomst:

Undersøgelser har vist at prævalensen af PTSD i den amerikanske baggrundsbefolkning er omkring 8 % og 1-års prævalensen er omkring 3-4 %. Der findes flere velkendte risikofaktorer for udvikling af PTSD. Alvorligheden og intensiteten af det udløsende traume har betydning. Ligeledes findes andre veldefinerede risikofaktorer som: Initial panikreaktion, forudgående psykisk sygdom, belastninger i barndommen, samt demografiske forhold som lav alder, kvinde og lav socialklasse.

Antallet af PTSD tilfælde efter en traumatisk begivenhed topper efter nogen få måneder og begynder herefter at falde. De fleste tilfælde af PTSD er forbigående, men en andel persisterer og kan udvikles til en kronisk tilstand. Adskillige studier har vist en stærk kobling mellem PTSD, angstlidelser, depression og misbrugsproblematik.

Mekanismer:

I løbet af de sidste cirka 30 år har der været en stor stigning i antallet af eksperimentale og biologiske studier vedrørende PTSD. Det er blevet påvist, at PTSD patienter har et øget ubevidst respons på udefrakommende stimuli, nedsat volumen af et bestemt center i hjernen (Hippocampus), samt et muligt reduceret niveau af stresshormonet kortisol. Oprindeligt har man troet, at disse forandringer har været element i en psykopatologisk proces, men nyere studier indikerer at de nærmere repræsenterer en øget psykisk modtagelighed/følsomhed og ikke en direkte effekt af den traumatiske eksponering.

Forsinket PTSD:

I de senere år er der publiceret to systematiske gennemgange med fokus på forsinket PTSD, hvilket vil sige PTSD med debut senere end 6 måneder efter en formodet udløsende traumatisk begivenhed. På baggrund af en analyse af 29 både tilbageskuende (retroperspektive) og fremadrettede (prospektive) studier konkluderede Andrews et al, at forsinket PTSD er sjældent forekommende, hvis ikke der har været subkliniske symptomer indenfor de første måneder. Når der initialt fandtes subkliniske symptomer, udgjorde forsinket PTSD knap 40 % af alle PTSD tilfældene i militære studier og godt 15 % i civile studier. Smid et al konkluderede på baggrund af en metaanalyse af 24 prospektive opfølgningsstudier, at omkring 25 % af alle PTSD tilfælde udgjordes af forsinket PTSD, mens kun få ikke rapporterede symptomer de første 6 måneder. Ingen af disse 2 studier forholder sig til de metodemæssige udfordringer, der findes i denne type studier i form af systematisk forvrængning af resultaterne (bias og confounding).

Metode:

Litteratursøgning:

Rapporten er baseret på offentlig tilgængelig videnskabelig litteratur på området. Litteratursøgningen blev udført med 2 parallelle søgestrenge i MEDLINE med det formål at identificere relevante artikler vedrørende dels forsinket PTSD og dels risiko for udvikling af depressiv lidelse. Vi inkluderede originale artikler på engelsk fra perioden 1980-2013 på baggrund af 2 forskellige inklusionskriterier. 1) Artikler vedr. forsinket PTSD blev inkluderet, hvis de indeholdt data om antal ny diagnosticerede tilfælde af PTSD minimum 6 måneder efter formodet udløsende årsag og på baggrund af minimum 2 undersøgelser for PTSD. Artikler baseret på retrorspektive erindringer om PTSD symptomer blev ekskluderet. 2) Artikler vedr. risiko for udvikling af depression blev inkluderet, hvis de indeholdt riskoestimater for udvikling af depression som følge af eksponering for en traumatisk begivenhed, sammenlignet med risikoen i en sammenlignelig ikke-eksponeret kontrolgruppe. Kohorte-, case-reference og tværsnitsstudier blev inkluderet.

Eksponering:

Eksponeringen blev defineret som en traumatisk, katastrofeagtig begivenhed inkluderende naturkatastrofer (jordskælv, oversvømmelse, orkan, tsunami, skovbrand mv.), store ulykker (flystyrt, fyrværkerieksplosioner, skibsforlis, togulykker mv.), terrorhandlinger og militære kamphandlinger. I undersøgelsen vedr. forsinket PTSD blev der desuden inkluderet studier, hvor

eksponeringen omhandler traumatiske begivenheder på individniveau, såsom trafikuheld og alvorlig sygdom. Almindeligt forekommende "livsbelastninger" såsom tab af pårørende, skilsmisse, arbejdsløshed, fattigdom og andre sociale belastninger blev ikke inkluderet.

Diagnostik:

PTSD blev defineret i overensstemmelse med DSM-III, DSM-IV eller ICD-10 kriterierne. PTSD blev defineret som sandsynlig PTSD, hvis symptomerne var selvrapporterede i et spørgeskema (eksempelvis: Posttraumatic stress checklist, PCL). Hvis diagnosen blev stillet ved et klinisk interview af en trænet interviewer, psykolog eller psykiater blev det defineret som klinisk PTSD. Subklinisk PTSD blev defineret som forekomst af nogle PTSD symptomer men ikke i det omfang der forudsættes for at stille den kliniske diagnose PTSD..

Depression blev defineret i overensstemmelse med DSM-III og DSM-IV kriterierne og diagnosen blev stillet enten ved spørgeskema (depressive symptomer) eller ved klinisk interview (klinisk depression).

Kvalitetsvurdering:

To af forfatterne vurderede uafhængigt inklusionskriterierne for hver artikel. Uoverensstemmelse blev afklaret ved en fælles gennemgang og vurdering af artiklen.

Den videnskabelige kvalitet af de inkluderede artikler blev vurderet på baggrund af "completeness of reporting", der inkluderer syv forskellige kvalitetsparametre (studiedesign, undersøgelsesgruppe, in- og eksklusions kriterier, responsrate, kriterier for eksponering og diagnoser samt statistiske forhold). Herudover blev det vurderet om der var potentiale for systematisk skævvridning af resultaterne (confounding og/eller bias).

Dataanalyse:

I analysen vedr. forsinket PTSD var det primære resultat antal tilfælde af forsinket PTSD som andel af alle tilfælde af PTSD i løbet af den undersøgte periode. Estimaterne blev vægtet i forhold til den inverse variation i de enkelte studier. Effekten af andre studiekarakteristika, såsom type af traumatisk begivenhed, population og diagnostisk metode blev vurderet på baggrund af en såkaldt random effect meta-regressions model.

Risikoen for depression blev vurderet på baggrund af en vægtet relativ risiko for depression efterfølgende en traumatisk begivenhed på tværs af alle inkluderede studier.

Resultater:

Forsinket PTSD:

Forsinket PTSD blev rapporteret i 38 ud af de 39 inkluderede studier, med en gennemsnitlig forekomst (prævalens) på 5 % (95 % CI 3-7 %). Andelen af forsinket PTSD i forhold til alle PTSD tilfælde i de respektive perioder var i gennemsnit 26.6 % (95 % CI 21-32 %), med stor variation. I 5 studier med relevant data var forsinket PTSD i de fleste tilfælde en forværring af subkliniske brosymptomer, der var til stede indenfor de første 6 måneder efter traumet. I et stort amerikansk studie af militærpersonale blev der fundet høje niveauer af forsinket PTSD, der ikke var forud gået af brosymptomer. Der blev fundet en betydeligt højere andel af forsinket PTSD blandt militærpersonale og professionelle end blandt civile.

Depression:

Den vægtede relative risiko for depression efterfølgende traumatiske begivenheder på tværs af alle 25 studier med 43 risikoestimater var 1.77 (95 % 1.50-2.09). Risikoen var signifikant forhøjet i alle undergrupper af diverse eksponeringer. Studierne indikerer ikke at udsendelse som militært personel i sig selv var en risikofaktor, men enkelte studier viser konsistent at der var en øget risiko i forbindelse med deltagelse i kamphandlinger. Den højeste risiko blev fundet blandt en stor gruppe soldater, der blev hospitaliseret efter skader fra kamp.

Konklusion:

De deskriptive opfølgningsstudier der er inkluderet i dette arbejde, indikerer kraftigt at PTSD kan udvikles i sin fulminante form mere end 6 måneder efter udsættelse for en traumatisk begivenhed. Forsinket PTSD er oftest forud gået af subkliniske brosymptomer inden for de første måneder. Forsinket PTSD forekommer hyppigere blandt professionelle faggrupper end i den civile baggrundsbefolkning. Der er således et behov for at udføre opfølgningsstudier, med relevante referencegrupper, for at få yderligere informationer om denne uafklarede sammenhæng med forsinket PTSD blandt professionelle.

Adskillige epidemiologiske studier, inklusiv prospektive opfølgningsstudier af høj kvalitet rapporterer samstemmende en moderat forhøjet risiko for depressiv lidelse blandt personer, der

har været udsat for en traumatisk begivenhed. Tilfældige fund eller skævvridning af risikoen (confounding og bias) ser ikke ud til at kunne forklare denne forhøjede risiko, men der er ikke tilstrækkelige data til at vurdere, hvordan risikoen er relateret til traumets omgang (eksponering-respons sammenhæng) eller den tidsmæssige relation mellem traume of depressionsrisiko.

Evaluering:

Den epidemiologiske evidens er baseret på de systematiske litteraturgennemgange med statistiske metaanalyser, der er præsenteret i denne rapport. Disse er vurderet i overensstemmelse med kriterierne, som defineret i Dansk Selskab for Miljø- og Arbejdsmedicins retningslinjer (DSAM, appendiks VI). Nedenstående tabel giver overblik over evidensgraden vedr. en række centrale problemstillinger, som er undersøgt i denne rapport:

Punkt	Påstand	Vurdering af evidensniveau ifølge DSAM´s retningslinjer[1]
I	Eksponering for en traumatisk begivenhed er kausalt forbundet med udvikling af PTSD symptomer, som defineret i DSM-IV eller ICD-10 kriterierne, med debut senere end 6 måneder efter begivenheden (forsinket PTSD)	++
II	Forsinket PTSD er forud gået af subkliniske PTSD symptomer indenfor de første 6 måneder efter begivenheden	(++)
III	Forsinket PTSD kan udvikles efter en latent periode uden symptomer (mere end 6 måneder efter eksponering) der adskiller sig fra baggrundsbefolkningens	(+)
IV	En traumatisk, pludselig og uventet psykisk eksponering er kausalt forbundet med en øget risiko for udvikling af depressiv lidelse, som defineret i DSM-IV eller ICD-10 kriterierne	+++

1) +++ stærk evidens; ++ moderat evidens; + begrænset evidens; 0 utilstrækkelig evidens; - evidens for at der ikke er kausal sammenhæng. Definitionerne fremgår af Appendix VI. (++) indikerer evidens mellem + og ++

Kommentarer:

Punkt I: Adskillige epidemiologiske opfølgningsstudier med prospektiv dataindsamling rapporterer samstemmende om forsinket PTSD over baggrundsniveau. Tilfældige fund kan udelukkes med stor sikkerhed, men bias og confounding er sandsynlig grundet den

ukontrollerede, deskriptive natur, der præger størstedelen af disse studier. Ydermere er der alvorlig risiko for at spøregeskema rapportering i denne type studier påvirkes af kontekstuelle og sociale forhold. Der er begrænset evidens for eksponerings-responsforhold og høj forekomst af forsinket PTSD bland US veteraner sammenlignet med UK-veteraner kan sandsynligvis ikke forklares af forskelle i krigstraumer.

Punkt II: Få epidemiologiske studier rapporterer samstemmende om øget risiko for forsinket PTSD blandt eksponerede individer med subkliniske symptomer, men skævvredne resultater forårsaget af bias og confounding er ikke usandsynlig i disse studier.

Punkt III: Evidens fra case studier og deskriptive studier er ikke blevet fuldt op af kontrollerede opfølgningsstudier med tilstrækkelig kontrol for eksterne faktorer. Resultaterne i forskellige undersøgelser er modstridende og studie design og omstændigheder omkring studiernes gennemførelse medføre sandsynligvis for høje skøn over den faktiske forekomst i studier, hvor dett er påvist.

Punkt IV: Adskillige epidemiologiske studier, inklusiv prospektive opfølgningsstudier af høj kvalitet, med klinisk verificering af depressiv lidelse, rapporterer om en moderat øget risiko for depressiv lidelse efter eksponering for traumatiske begivenheder. Tilfældige fund, confounding og bias kan udelukkes med rimelig sikkerhed. Der er begrænset evidens for sammenhængen mellem eksponering og respons. Opmærksomheden henledes på, at dette er den første systematiske gennemgang af epidemiologiske studier af sammenhængen mellem traumatiske begivenheder af katastrofekarakter og depression, der foreligger internatinalt. Resultater og konklusion har ikke været udfordret gennem et sædvanligt uafhængigt peer-review som led I publikationsprocessen. Uafhængig bekræftelse af resultater og fortolkning er ønskelig.

English summary

Posttraumatic Stress Disorder (PTSD) is a mental disorder defined by intrusive recollections, avoidant behaviour, numbing and hyperarousal caused by exposure to or witnessing a natural or technological disaster, terroristic incidences or similar traumatic events (labelled trauma in the following). It has become a controversial issue whether the disorder may occur detached in time from the assumed causal event. Depressive disorders may also be related to traumatic events and have shown strong comorbidity with PTSD.

Objective: The objective of this report commissioned by The Danish Working Environment Fund is to describe and discuss the occurrence of delayed onset PTSD, to identify risk factors for delayed onset PTSD (if any) and to critically evaluate the evidence addressing the risk of depressive disorder following exposure to traumatic events.

Definition: PTSD is defined by the Diagnostic and Statistical Manual for Mental Disease issued by the American Psychiatric Association and by the International Classification of Diseases issued by WHO. The characteristic symptoms must persist through at least one month and includes 1) re-experiencing of the traumatic event, 2) avoidance of stimuli associated with a trauma and numbing of general responsiveness and 3) symptoms of increased arousal. The DSM-IV criteria, but not the ICD-10 criteria include as a fourth symptom cluster, namely impairment in social or occupational functioning. The triggering cause is defined as a traumatic stressor outside the range of usual human experience that would markedly be distressing to almost everybody. The DSM-criteria also requests that the subject reacts with intense fear and helplessness in relation to the terrifying experience. Several screening questionnaires have been developed and validated against clinical ascertainment of the diagnosis.

Occurrence: The lifetime prevalence of PTSD in the general adult American population is about 8% and the one-year prevalence is 3-4%. Well established risk factors are in addition to the severity and intensity of the traumatic event initial panic symptoms, a history of psychiatric disease and childhood adversity and demographic determinants as low age, female gender, and social disadvantaged position.

The incidence of PTSD reaches a peak within the first few months, before it starts to decline. Although a large fraction of PTSD cases are transient some cases are persistent and associated with chronic morbidity. Numerous studies have shown strong comorbidity between PTSD and anxiety, depression and substance abuse.

Mechanisms: During the past 3 decades there has been an explosive growth in experimental and biological research into PTSD. It has been demonstrated that PTSD patients have increased autonomic activity to external stimuli, reduced volume of the brain structure hippocampus and possibly reduced levels of the stress hormone cortisol. Although originally believed to be steps in pathophysiological processes, new research indicates that these outcomes more likely represent increased susceptibility and not effects of exposure.

Delayed onset PTSD: Two recent systematic reviews have addressed delayed onset PTSD occurring more than 6 months after the supposed triggering event. Based upon an evaluation of retrospective and prospective studies Andrews et al concluded that onset of full syndromal PTSD rarely is delayed by several months, unless symptoms at a subthreshold level has been present during the initial phase. According to Andrews delayed onset PTSD account for some 40% of PTSD in military personnel and some 15% in civilian populations. Smid et al concluded based on a meta-analysis of 24 prospective follow-up studies that about 25% of all PTSD cases across highly different trauma experiences and populations were delayed onset, but only some 4% without symptoms during the first 6 months. None of the authors discuss methodological issues related to bias, confounding and common methods variance.

METHODS

Literature search: This report is based upon the public scientific literature and no original data is included. We performed in parallel 2 MEDLINE searches to identify papers addressing delayed onset PTSD and risk of depressive disorder, respectively. We included original papers in English published 1980-2013 by two sets of criteria: For purposes of the evaluation of delayed onset PTSD we included papers that provided rates of newly onset PTSD diagnosed more than 6 months after the event of interest based upon one baseline assessment and at least one follow-up examination. Retrospective recall of earlier PTSD symptoms was not accepted. For purposes of the evaluation of risk of depression we included papers that provided risk estimates for depressive disorder for adult populations exposed to a traumatic event relative to an appropriate reference group. We included cohort, case-reference as well as cross-sectional studies.

Exposure definition: A traumatic event was defined as mass-scale events including natural disasters (earth quake, flooding, hurricane, tsunami, and bushfire), technological disasters (firework, air plane crash, shipwrecking, and transport accident), terroristic acts and military combat. The delayed onset PTSD review but not the review of depression also included

individual events such as motor vehicle accidents, serious disease and assaults. Life events such as loss of close relatives, divorce, property loss, unemployment, poverty and other social calamities did not qualify for inclusion in the analysis of either PTSD or depression.

Outcome definition: PTSD was defined according to the DSM-III, DSM-IV or ICD-10 criteria, and categorised as 'probable PTSD' if the diagnosis was based upon self-reports in questionnaires (such as the posttraumatic stress check list PCL), and as clinical PTSD when the PTSD diagnosis was ascertained by clinical interviews by trained interviewers, psychiatrists or psychologists. Subthreshold PTSD was defined as symptom scores above average background levels, but below cut-off levels qualifying a PTSD diagnosis.

Major depression was defined according to DSM-III and -IV criteria and was ascertained either by self-report questionnaire (depressive symptoms) or by clinical interview (major depression).

Quality assessment: Two of the authors independently assessed the inclusion criteria for each paper and disagreements were resolved by consensus. The scientific quality of the studies was rated according to completeness of reporting of seven essential study characteristics, and the potential for bias and confounding.

Data analyses: For delayed onset PTSD analysis the primary outcome was the proportion of delayed onset PTSD relative to all identified cases of PTSD. Point estimates were weighted by the inverse variance of each study, and the effects of other study characteristics including type of traumatic event, population and diagnostic methods were evaluated in random effects meta-analysis with subgroup models.

The risk of depression was evaluated by computing the weighted relative risk (or equivalent) for depressive disorder following a traumatic event across all studies.

RESULTS

Delayed onset PTSD: Delayed onset PTSD was reported in all studies except one with an average prevalence of 5% (95% CI 3-7%). The weighted proportion of delayed onset PTSD relative to all identified cases of PTSD was in average 26.6% (95% CI 21-32%) with large variation. In five studies with appropriate data delayed onset PTSD were in most cases an aggravation of symptoms already present during the first 6 months, but one large study of military personnel found high rates of newly onset PTSD without symptoms bridging the event

and onset of full syndromal PTSD. Delayed onset PTSD was compromising a substantially higher proportion of PTSD cases in military personnel and professionals than in populations of civilians.

Depression: The weighted relative risk for depressive disorder following a traumatic event across all 24 studies with 42 risk estimates was 1.77 (95% 1.50-2.09). The risk was significantly elevated in all subgroups of exposure categories except deployed military personnel. Although studies did not indicate that deployment in it-self is a risk factor few studies consistently indicated increased risk in relation to combat experience and the risk was highest in a large group of soldiers hospitalized following battle injuries.

CONCLUSION

Descriptive follow-up data suggests that PTSD may become manifest more than 6 months after a traumatic event, that delayed onset PTSD most often is preceded by sub-threshold PTSD symptoms during the first months after the trauma and that a higher proportion of PTSD cases are delayed among professional groups than in civilian populations. There is insufficient evidence to evaluate whether PTSD that develops years after a specified traumatic event primarily is caused by that event (the ticking bomb hypothesis). There is a need to perform follow-up studies with appropriate external reference groups to get insight regarding the unexplained high proportion of delayed onset PTSD among professionals.

Several epidemiological studies including high quality prospective follow-up studies consistently report moderately increased risk of depressive disorder in subjects exposed to traumatic events. Chance, bias and confounding can be ruled out with reasonable confidence, but the evidence database is too limited to resolve issues relating to exposure-response relationships and timing of exposure and outcome.

EVALUATION

The epidemiological evidence is based upon the systematic reviews and meta-analyses presented in this report and rated according to the criteria defined by The Danish Society of Occupational and Environmental Medicine (DASAM, Appendix VI)

Issue	Statement	Rating of evidence according to DASAM criteria[1]
I	Exposure to traumatic events is causally linked to development of PTSD symptom clusters defined by DMS-IV or ICD-10 criteria with onset later than 6 months after the event (delayed onset)	++
II	Delayed onset PTSD is preceded by subthreshold PTSD symptoms during the initial six months after the trauma	(++)
III	Delayed onset PTSD may develop after a latent period without above background level of PTSD symptoms	(+)
IV	A terrifying sudden and unexpected psychological exposure is causally linked to risk of depressive disorder as defined by DMS-IV-R or ICD-10 criteria	+++

1) +++ strong evidence; ++ moderate evidence; + limited evidence; 0 insufficient evidence;
2) - evidence of no causal association, for definitions se Appendix VI . (++) indicates evidence between '++' and '+';

Comments:

Issue I: Numerous epidemiological follow-up surveys with prospective data collection consistently report PTSD above background levels with delayed onset. Chance findings can be ruled out with high confidence, but bias and confounding are likely because of the uncontrolled descriptive nature of the majority of studies and the likely high impact of contextual and social factors inherent in descriptive questionnaire studies . There is limited evidence for exposure-response relationships and high rates of delayed PTSD in US veterans compared to UK-veterans are most likely explained by factors, that are not related to combat exposure.

Issue II: Few epidemiological studies consistently report substantially increased risk of delayed onset PTSD among exposed subjects with subthreshold PTSD symptoms, but confounding is not unlikely.

Issue III: Evidence from case stories and descriptive studies has not been corroborated by controlled follow-up studies with adequate control for extraneous factors. Findings are conflicting and study design and settings are likely inflating the estiamates of occurrence.

Issue IV: Numerous epidemiological studies including high quality prospective follow-up studies with clinical ascertainment of major depression consistently report moderately increased

risk of depressive disorder in subjects exposed to traumatic events. Chance findings, bias and confounding can be ruled out with reasonable confidence. There is limited evidence for exposure-response relationships. This is the first review med meta-analysis in the field and results has not been challenged by the the formal scientific review process related to publishing od scientific papers. Independent approval is warranted.

FOREWORD

Following an international open call issued by the Danish Work Environment Fund in December 2012 with application deadline January 2 2013, the authors received a research grant, which financed the present work. The draft report was prepared from February 1 through April 31 and revised during May 2013 by a working group including

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   Reiner Rugulies, professor, PhD in Psychology, MPH

The report is based upon two original reviews and meta-analyses. The manuscripts are confidential working papers intended for publication in medical journals and these are provide separately and not intended for public access before further peer-review and publication.

The draft report including manuscripts was April 31th 2013 submitted to Professor Sir Simon Wessely, Kings College, London, UK, and Dr Geerd Smid, MD, PhD, Diemen, The Netherlands, who performed independent external reviews. A closed workshop including the working group, the reviewers and invited guests convened at Bispebjerg Hospital on May 31th in order to discuss the evidence addressing delayed onset PTSD and depressive disorders. The report and included papers are entirely the responsibility of the working group and do not necessarily express the views of the external reviewers or the funding agency. The working group is indebted to research secretary Hanne Tulinius who supported the work throughout.

Bispebjerg June 1 2013, the Authors

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a mental disorder defined by intrusive recollections, avoidant behaviour, numbing and hyper-arousal following the experience of or witnessing of a horrifying traumatic event. Symptoms as we know them today was first described among soldiers in Europe at the end of the ninetieth century, but it was not until the aftermath of the War in Vietnam that the disorder was formally recognised as a diagnostic entity in US (1). PTSD was in 1980 included in the third edition of the American Diagnostic and Statistical Manual of Mental Disorders [DSM III (2)] and became applicable to all sorts of unusual horrifying events whether in relation to combat or technical or natural disaster. WHO recognised the disorder by slightly different criteria in 1992 [ICD-10 1992 (3)]. A fourth disease criterion, social or occupational disability (impaired functioning), was added to the latest DSM-IV-TR edition in 1994 (4), but is not included in ICD-10 (3).

Numerous papers published during past 30 years describe occurrence, risk factors and clinical course of PTSD. We will in the following background chapter briefly summarize this evidence based upon review literature. One notable difference between the American diagnostic criteria and the WHO criteria is that the former distinguish PTSD with delayed onset more than 6 months after the traumatic event. It seems obvious that it becomes increasingly uncertain to attribute mental symptoms (some of which are unspecific and common) to a specific event as time from the event to onset of symptoms increases. This may be one of the reasons that the existence of delayed onset PTSD has been debated since the introduction of the concept in the1980 American diagnostic Manual (5). There are other reasons as well. In particular it is not clear whether delayed onset PTSD is defined by a completely symptom-free interval of at least 6 months duration before symptoms develop or whether disorders with a slow development starting shortly after the event but only reaching a full syndromal disorder with delay is included (6). This issue has also become prominent in Denmark in relation to delayed development of symptoms among deployed soldiers returning home from service in Iraq and Afghanistan (SFI report 6 (in Danish): Hjemvendte danske soldater, 2012). On this background the main objective of the present report is to describe and evaluate the prevalence of delayed onset PTSD and identify risk factors, if any.

OBJECTIVES

The objective of this report is

(1) to describe and discuss the prevalence of delayed onset PTSD

(2) to identify risk factors for delayed onset PTSD related to

- the nature of the traumatic event (type, intensity and duration)
- affected populations (military, professionals, residents)
- presence of PTSD subthreshold symptoms during the initial 1-5 months
- individual and environmental pre- and post-event characteristics

Considering the descriptive nature of the PTSD literature and the strong comorbidity between PTSD and depressive disorder an additional aim of our documentation is

(3) to critically evaluate the evidence addressing the risk of depressive disorder following exposure to traumatic events

GENERAL STATE OF THE ART

Definition of PTSD according to DSM-IV and ICD-10 criteria

According to the American Psychiatric Association the essential feature of the posttraumatic stress disorder is development of characteristic symptoms following exposure to an extreme traumatic stressor that creates intense fear, helplessness or horror. The characteristic symptoms must be persistent during at least one month and includes (1) re-experiencing of the traumatic event, (2) avoidance of stimuli associated with the event and numbing of general responsiveness, (3) symptoms of increased arousal and (4) impairment of social or occupational functioning (2,7). The criteria are specified in Appendix I. Although remaining largely consistent, the criteria have changed across succeeding versions of the Diagnostic and Statistical Manual for Mental Disorders (DSM) from the third version in 1980 to the fourth version in 2000. Of particular importance is the impairment criterion introduced in the DSM-IV edition in 1994.

To be diagnosed as having PTSD according to the DSM criteria, a subject must - in addition to being exposed to a traumatic event outside the range of usual human experience that would be markedly distressing to almost anyone - present with at least one of the symptoms from the intrusive and re-experience category, have at least three symptoms from the avoidance and numbing category, and at least two of the symptoms from the hyperarousal category.

The WHO criteria issued in the ICD-10 classification from 1992 differ slightly from the American Psychiatry Association criteria in that the WHO criteria do not request a subjective feeling of fear, helplessness or horror in relation to the event and do not include social or occupational impaired functioning. Moreover, the international guidelines do not explicitly classify delayed onset PTSD as a disorder that starts more than six months after the event. The WHO criteria are detailed in Appendix II.

Measurement of PTSD

The most common instrument used to measure PTSD in large scale epidemiological surveys at present is the PTSD check-list (PCL, Appendix III), which is a 17-item questionnaire existing in two versions – civil (PCL-C) and military (PCL-M). The questionnaire in its generic form is not referencing any specific event, but earlier traumatic experience in general. Thus the PTSD

diagnostic criterion requesting exposure to a traumatic event is not part of the questionnaire and neither is the fourth impairment criterion. The first eight items is referencing symptoms relating to one or more traumatic events (intrusive re-experience and avoidance), while the last nine are psychiatric symptoms (anhodenia, hyperarousal, sleep disorders, cognitive difficulties, irritability and anger). Respondents indicate how much they have been bothered during the past month on a 5-point scale from 1 (not at all) to 5 (extremely). Points are summed and a score above 50 (range 17-85) combined with an average score of at least 3 for each of the three clusters of symptoms has a sensitivity around 85% and a specificity above 75% to diagnose PTSD using the clinician administered PTSD scale (CAPS) psychiatric interview as golden standard (8,9). The comprehensive CAPS interview is lasting 2-4 hours. Several other tools to identify probable or clinical PTSD in epidemiological surveys have been developed and applied and diagnostic sensitivity and specificity varies between tests and study populations (10) . A comprehensive outline of screening instruments for adults at risk for PTSD is given by Brewin (11).

A follow-up study of 113 directly exposed survivors of the Oklahoma City bombing used the Diagnostic Interview Schedule/Disaster supplement to diagnose PTSD. The relative prevalence of symptoms belonging to the three PTSD symptom clusters is given in Figure 1 in order to illustrate the item response profile (12).

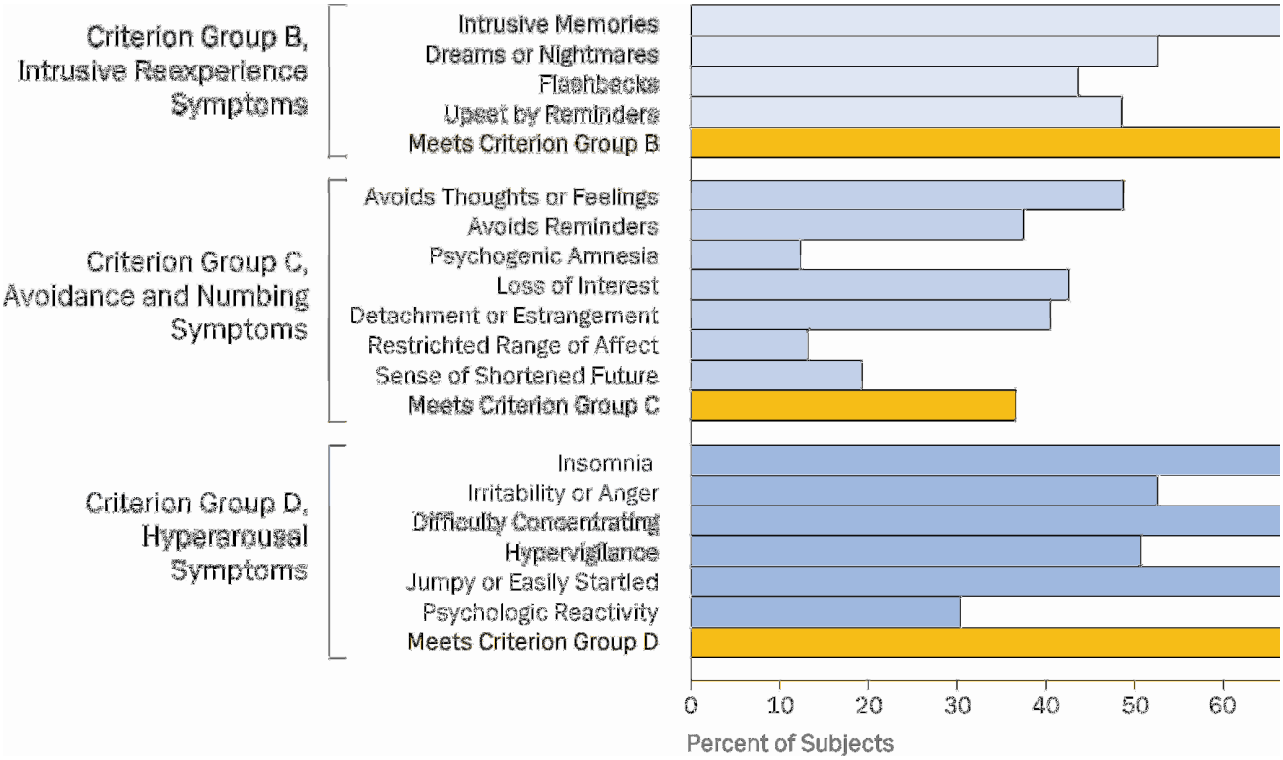


Figure 1. Prevalence of symptoms among directly exposed survivors of the Oklahoma City bombing according to the DSM-IV symptom clusters B-D. An example of an item response profile. Reproduced from (12)

Advanced latent class analysis of symptom clusters in prospective studies with repeated follow-up examinations indicate that the numbing cluster strongly distinguish subjects at risk for developing PTSD with social impairment from those less severely affected (13).

Prevalence

The lifetime prevalence of PTSD in the general adult American population (15 through 54 years of age) is about 8% according to the US National Comorbidity Survey (14). Motor vehicle accidents account for 20% of cases. The one-year prevalence is as expected considerably lower – about 3-4% according to both US and UK community samples (14,15). Similar one-year prevalence rates have been reported in non-deployed military personnel (15). Most studies of directly exposed adult survivors of natural, man-made and technological disasters report a prevalence of PTSD within the first 3 months in the range of 30-60% with an extreme of 75% PTSD cases among survivors of the Piper Alpha oil rig disaster in 1988, where a gas leak caused an explosion killing more than 150 men (10). Among rescue workers the prevalence of PTSD during the first months following a disaster is overlapping the prevalence among direct survivors, but one study directly comparing rates among victims and rescue workers involved in the same disaster, report lower values in rescue workers than among survivors (16). The prevalence of PTSD in the general population during the first year after a disaster is even lower in the range of 1-10%. For example, the prevalence of PTSD in the general New York City population 1-2 months after the 9/11 terror attack was 8% in random telephone based samples and 11% in a world wide web based sample [cited from (10)]. A comprehensive reporting of PTSD prevalence following disasters is available on the Epidemiologic Reviews website (http://epirev.oupjournals.org), se also (10).

Risk factors and modifiers

PTSD is by definition caused by the experience of an unusual and horrifying event but as is true for all exposure-outcome relations the risk varies across individuals reflecting different types and levels of exposure (risk factors) and individual and social characteristics (susceptibility and/or modifying factors). Numerous studies have examined event-related and demographic,

environmental and personal characteristics that predict (event-related factors) or modify (other factors) the risk of PTSD. Findings across studies are rather consistent (17-19).

First, the severity of the traumatic event has in numerous studies been associated with the risk of PTSD. Magnitude of the immediate threat to life, the amount of perceived control in the situation, the degree of mutilation and physical injury, the amount of destruction and the number of fatalities are major determinants of PTSD risk. Thus the prevalence is higher among victims and survivors with direct exposure than among rescue workers, witnesses and the general population. And the prevalence of PTSD is higher among persons closer to a disaster than among those in more distant areas (18). However, in spite of an exposure-response relationship between severity of the traumatic event and the risk of PTSD, indirectly exposed people who were not at the epicentre of a disaster but who suffered loss of relatives or were displaced may be at higher risk than professionals as fire-fighters, other rescue workers or policemen (18,20). But within firefighters and rescue workers the risk of both PTSD and delayed onset PTSD is related to the intensity of the traumatising exposure according to a least one large US study [Figure 2, (21)]. In this study firefighters arriving first after the WTC tower collapses during 9/11 were at higher risk of developing PTSD than those arriving later.

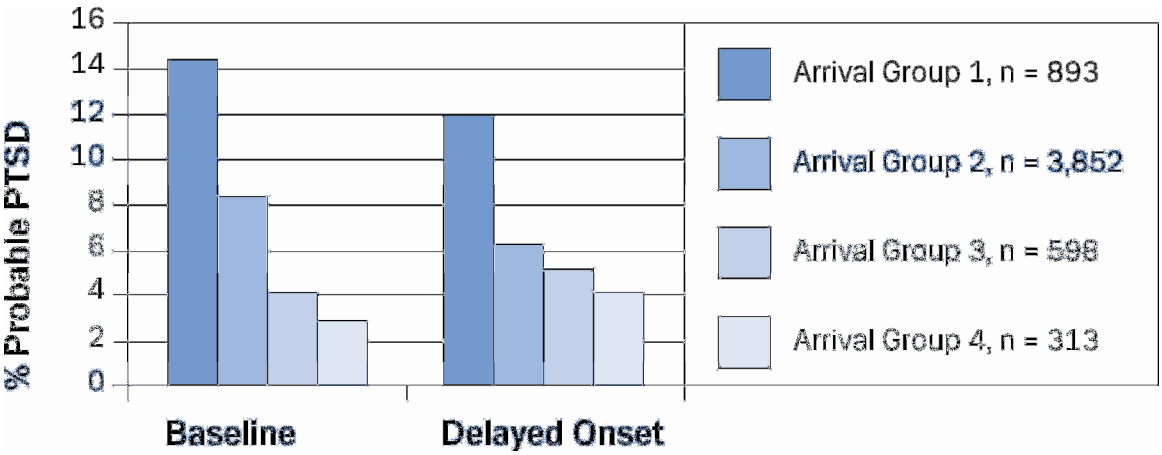


Figure 2. Prevalence of probable PTSD and delayed onset probable PTSD by day of arrival at the WTC building site after the 9/11 terroristic attack. Adapted from Berninger et al 2010

Whether indirect exposure through television broadcasting as happened in relation to the 9/11 attack in New York City is a relevant risk factor for PTSD remains to be established.

Second, although virtually all persons are at risk of developing PTSD if the terrifying exposure is strong enough, there is consistent evidence that occurrence of psychiatric disease in the family and a history of earlier psychiatric disease and childhood adversity are strong modifiers of the exposure-outcome relation and these personal susceptibility factors increase the risk substantially (17).

Third, there is cross-sectional evidence of an association between initial panic symptoms and subsequent development of PTSD (20), which has been corroborated in a prospective study (22). In this some two thirds of motor vehicle accident survivors with initial acute stress disorder (13% of all victims) and subsyndromal acute stress disorder (21% of all victims) were diagnosed with PTSD two years after the accident.

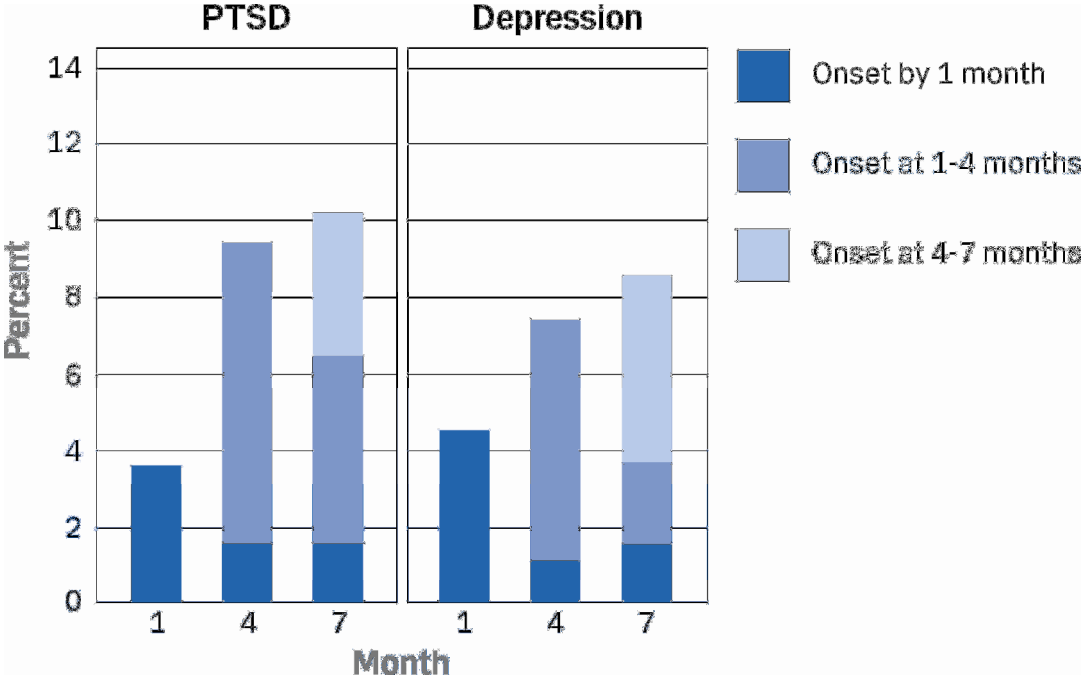
Fourth, demographic determinants include ethnicity (minority), age (young), gender (women), education (disadvantaged) and military rank (low). However, some of these determinants such as low social class and low military rank may be associated with increased risk because of higher risk of exposure. Psychiatric history and childhood adversity are among the strongest and most consistent risk factors (17).

Risk factors for normal-onset PTSD are not necessarily risk factors for delayed onset PTSD and vice versa. Goodwin et al performed a two-wave study of a large subset of UK armed forces with the first survey 6-60 months after return from deployment and the second some 40 months later without military deployment taking place in-between (23). In this study common mental disorder and multiple physical symptoms at the baseline survey predicted delayed onset PTSD. These findings are in line with a report, which based on retrospective interviews with 142 UK veterans receiving war pension for PTSD or physical injury, concludes that compared to immediate onset PTSD delayed onsets involve a more general stress sensitivity and a progressive failure to adapt to continued stress exposure (24). It may be that immediate and delayed onset PTSD reflects to different phenotypes of the same underlying disorder.

Onset and course of PTSD following traumatic events

Only few longitudinal studies provide data on timing of the onset of PTSD during the first weeks and months after traumatic events. One example is given in Figure 3, which outlines the development of PTSD and depressive disorder in severely injured US combat soldiers (25). The prevalence was almost 40% already after the first month with additional 15% new cases after 4 and 7 months, respectively. This study indicates an increasing prevalence with time during the first 7 months and possibly delayed onset of both PTSD and major depression. Other studies of military personnel relate development of PTSD to the time of return after deployment and therefore the potentially traumatic event may have taken place many months earlier depending on the length of deployment.

Figure 3. Prevalence of PTSD and depression among injured US soldiers according to time after the traumatic event. Reproduced from (25).

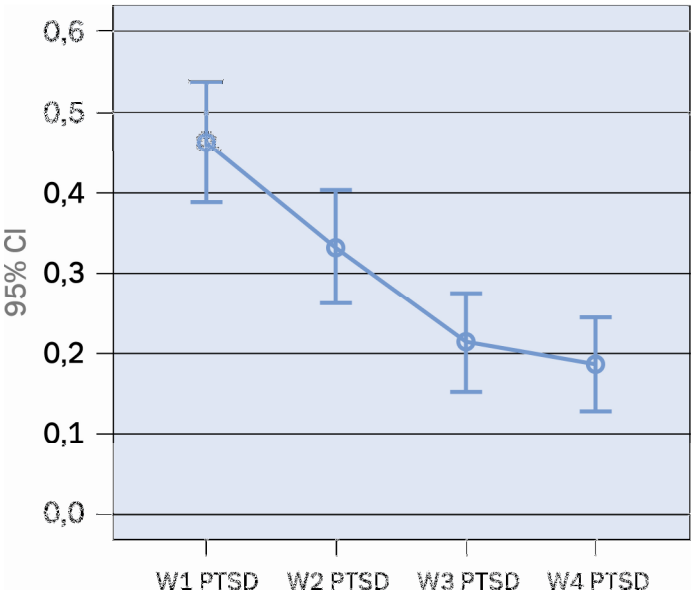


Delayed onset PTSD with start more than 6 months after the traumatic event has been addressed in two recent systematic reviews. Based upon an evaluation of retrospective and prospective studies Andrews et al concluded that the onset of full syndromal PTSD rarely is delayed by several months unless symptoms at a subthreshold level have been present during the initial phase (6). However, delayed onset PTSD with symptoms at the subthreshold level during the initial phase may be common and account for some 40% of PTSD in military men and some 15% among civilians of both genders. Smid et al identified 24 prospective follow-up studies with

a PTSD screening within the first 1-5 months after the traumatic event and again after 12 months and concluded that about 25% (95% CI 23% -27%) of all PTSD cases were delayed onset, but only few were without symptoms during the first 6 months (26). During the past five years a number of additional large prospective studies with identification of newly-onset cases at various follow-up times have been performed. Moreover, several studies with very long follow-up have been published.

The course of PTSD with immediate or early onset following natural or technological disasters has been described in several longitudinal studies referenced in (10) and show a rapidly declining prevalence during the first 3-6 months (as an indication of fast recovery) – often from high initial rates as 50% during the first month to some 10-15% after one year. This has been described mong aircraft passengers surviving a crash landing, among rescue workers involved in serious accidents and in the general population following the 9/11 attack in New York City (10). On the other hand, a follow-up study of PTSD and serious mental illness after the hurricane Katrina in the New Orleans region showed contrary to the usual pattern an increasing prevalence during the first year after the disaster, which was attributable to continued unresolved problems as housing and loss of property after the disaster rather than terrifying experience related to the disaster in itself (27). Also very severe life threatening exposure as seen among survivors of disasters seems associated with a chronic course of the disease. Thus a slow rate of recovery and a high rate of persistence of symptoms has been described among persons directly exposed to the Oklahoma City Bombing (12) and in a population struck by mud flood in Mexico 1999 (Figure 4, (28)] .

Figure 4. Course of PTSD over time (6, 12, 18 and 24 months post disaster) in a population struck by mud flood in Mexico, 1999 (reproduced from (28))



McFarlane investigated in a longitudinal design the onset of post-traumatic stress disorders in a group of firefighters, who had an intense exposure to a bushfire disaster. In this study the intensity of exposure, the perceived threat, and the losses sustained in the disaster were not predictors of post-traumatic stress disorder. By contrast, introversion, neuroticism, and a past history and family history of psychiatric disorder were premorbid factors significantly associated with the development of chronic post-traumatic stress disorders (29).

A detailed account of The Danish report on Afghanistan veteran's mental health 2013

The prospective study includes data collected from the seventh team of Royal Danish Army soldiers (ISAF 7) deployed in Afghanistan from February 2009 to August 2009. A total of 6 assessments on various health issues were conducted using different validated tests among the 749 persons in question. The tests were performed before, during and immediately after deployment, 2-3 month post deployment, 7-8 month post deployment and 3 years post deployment (time 1-6). The sample is mainly young males (95.1%) with an average age of 26 years. The response rate between various rounds varies significantly. At time 4 and 5 the response rate is about 50% and at 3 years 78%s.

PTSD symptom scoring was performed using the self-report PTSD scoring tool, *the PTSD-checklist*. This ranges from 17-85 and a cut-off point of 44 and above was selected for probable

PTSD. As mentioned in the report other veteran studies have used cut-off points of 50 and above.

Assessment of depression used *Becks Depression Inventory 2* (BDI - II). A score of 20-28 was equal to moderate depression and 29-63 to severe depression.

Before deployment 3.3% had symptoms in accordance with probable PTSD and 2.3% with symptoms suggesting moderate to severe depression. During deployment these numbers declined to 1.9% and 1.8% respectively. Immediately after deployment 2.4% reported PTSD and 2.3% depression. At time 4 and time 5 PTSD ascended to 2.7% and 5.1% and depression ascended to 3.7% and 5.9% respectively. At the 3 year follow-up 9.7% reported PTSD. Approximately 6.5% showed symptoms of PTSD later than 6 month post deployment, which adjusted for following deployments was about 4%. The study defines PTSD found at the 7-8 month assessment as being diagnosed within the first 6 month and thereby not delayed onset. Moderate to severe depression was found in 9.2% at the 3 year follow-up. It is noted that many individuals reported both PTSD and depression at the same time. 74.2% were resilient to PTSD at all time-points.

Predictors of PTSD were: Prior traumatic events, low educational level and higher depression scoring before deployment. Self-reported mission related danger and injury during deployment were also predictors of PTSD, but this information was not corroborated by independent objective measures of exposure and the role of possible earlier traumatic events are not adjusted for. Number of traumatic events after deployment was also found to be associated with PTSD.

Predictors of delayed onset PTSD were: Being part of the Army's reaction force education program, which means that employment is limited by a short term contract with the Army and recruitment of personnel after normal conscription. This increased the risk about 3 times. Similar results have been obtained in US reservists (30). Prior traumatic events at baseline and traumatic events after deployment also increased the risk of delayed onset PTSD with 32% and 38% respectively.

Of the 32 cases with delayed onset PTSD, 19 had a PCL-score of 17-29 within the first 6 month and 13 had subclinical PTSD with scores from 30-43.

At 3 years 429 of the included persons were also screened for PTSD using SCID (Structured Clinical Interview for DSM IV). 27.7% of those with PTSD according to SCID did not meet the PCL cut-off point for PTSD of 44. As shown in our included paper on PTSD, clinical interviews

normally reports a lower prevalence of PTSD than self-reported cases found by questionnaires. This however does not seem to be the case here. The authors of the report suggest further statistical analysis of the relationship between PCL and SCID in future publications. This fact suggests that the chosen cut-off point at 44 does not cover report cases of probable PTSD.

We conclude that there is a significant increase in PTSD cases at the 3 years follow-up compared to the 7-8 month assessment suggesting occurrence of delayed onset PTSD. This accounts for more than half of all PTSD cases. Depression shows the same trend rising from 5.9% at 7-8 month to 9.2% at 3 years. Three quarters of the 749 deployed soldiers never shows significant symptoms of psychological illness during the follow-up period. The main limitation of the study is lack of appropriate control groups.

Long-term prognosis and vocational outcomes

Data suggest that if recovery from PTSD has not occurred within 18 months it is likely to become persistent and several studies indicate that persistent symptoms occur in one third of patients with newly onset PTSD (14,28,31). A large US national and representative study of functional outcomes after hospitalisation for traumatic injury provides evidence that PTSD as well as major depression one year after the trauma was strongly associated with low prevalence of return to work (32). See also (25).

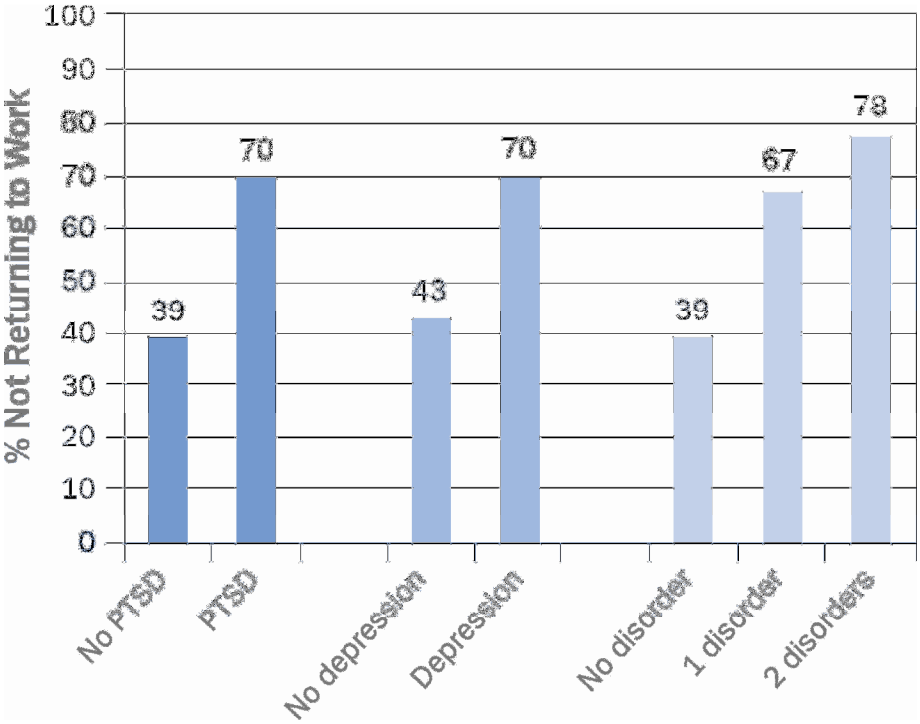


Figure 5. Percentage of persons hospitalized for traumatic injury that had not returned to work 12 months after the injury by psychiatric diagnosis (reproduced from (32))

Comorbidity

Numerous studies have shown strong comorbidity between PTSD, anxiety, mood disorders and alcoholic drinking disorders. Figure 6 provides an example in a population severely affected by a mud flood in 1999 (28). The prevalence of major depression among PTSD cases was 20-25% at all times compared to about 5% among persons without PTSD

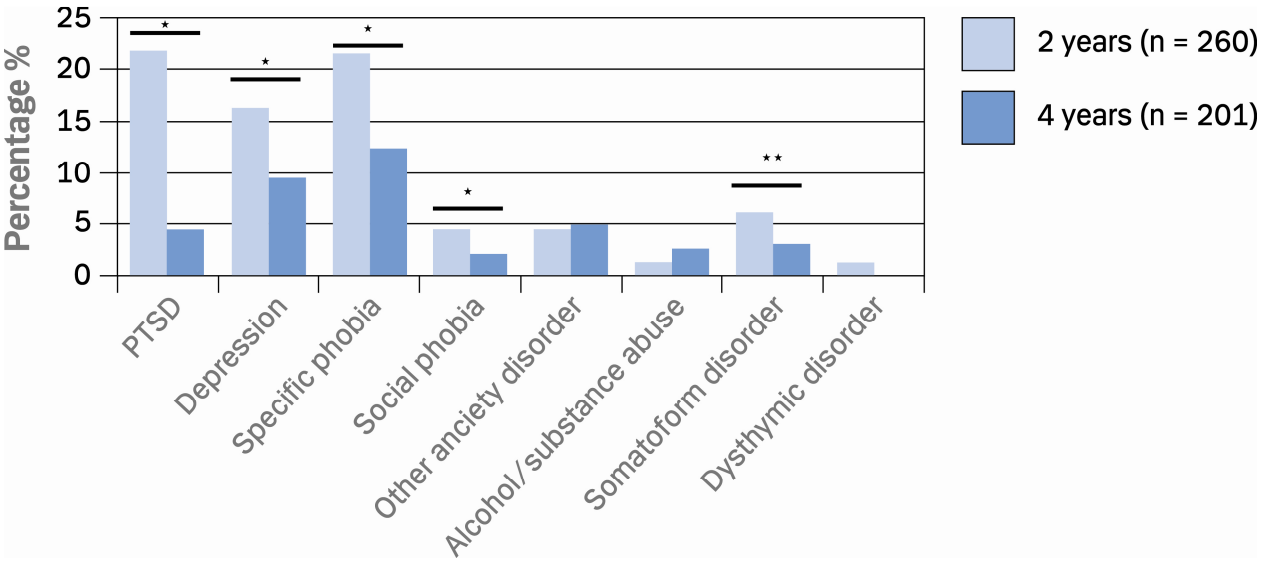


Figure 6. The prevalence of PTSD, major depression and several other mental disorders in the most severely affected region 2 and 4 years after a mud flood in Mexico (28).

An analysis of Israeli victims with three follow-up examinations at 2, 4 and 6 weeks after the traumatic event indicates that depressive disorders contribute to development of PTSD rather than the opposite (7).

Mechanisms and pathophysiology

During the past three decades there has been an explosive growth in experimental and biological research into PTSD (33). A behavioural and physiological PTSD animal model has been developed using stressors such as exposure to predators or scents of these. In humans research addressing psycho-physiological reactions, genetic and endocrinological markers and using neuroimaging techniques has provided a wealth of new insights into the biology of PTSD. For a recent comprehensive and critical review the reader is referred to an excellent overview by Pitman et al (33).

In short, increased autonomic reactivity to external stimuli such as increased heart rate and skin conductance has been demonstrated repeatedly among PTSD patients. The magnitude of increased reactivity is related to the severity of the disorder. However, it is still unknown whether the heightened autonomic activity is reflecting a pre-existing condition or is developed in parallel with the disorder. Autonomic reactivity is far too unspecific and insensitive to be used as a biomarker of PTSD.

The most replicated structural anomaly observed in PTSD is reduced volume of hippocampus. Early results have been corroborated in a meta-analysis by Bremner and co-workers (34). First believed to represent trauma-induced effects of hypersecretion of cortisol, twin studies based upon combat discordant twin brothers clearly indicate that small hippocampal volume more likely represents increased susceptibility to develop PTSD after traumatic events than effects of the exposure (35). Moreover, numerous studies have shown that, if anything, circulating levels of cortisol are reduced rather than increased in PTSD patients. And challenge tests using dexamethasone in small doses have shown increased suppression of plasma cortisol in PTSD patients – factors that are thought to present pre-trauma characteristics and not effects of exposure (36,37).

Other seminal results include the observation that low expression of the serotonin transporter gene increases the risk of PTSD among hurricane-exposed adults and that a traumatic event may induce downstream alterations in immune function by reducing methylation levels of immune-related genes.

In spite of remarkable progress in biological PTSD research studies have still not resulted in development of biomarkers with sufficient sensitivity and specificity to be used in clinical practise.

METHODS

This report is based upon the published scientific literature and no original data are included.

The Literature Search

We performed in parallel two electronic searches in the National Library of Medicine (PubMed) to identify papers addressing delayed onset PTSD (objectives 1 and 2) and the risk of depressive disorder (objective 3), respectively. We included original papers published in English during the period 1980 to 1.4.2013, if

1. PTSD (objectives 1 and 2): The paper provided rates of newly onset PTSD diagnosed more than 6 months after the event of interest. In order for the newly onset criterion to be fulfilled a baseline line assessment indicating no full syndromal PTSD was inquired. Retrospective recall of earlier PTSD symptoms as basis for diagnosing newly onset PTSD was not accepted. Only a diagnosis based upon the DSM III-IV or ICD-10 criteria qualified.

2. Depressive disorder (objective 3): The paper provided risk estimates for depressive disorder for adult populations exposed to a traumatic event relative to an appropriate reference group. We included cohort, case-control and cross-sectional studies. Only papers diagnosing depressive disorder according to the DSM III-IV or ICD-10 criteria qualified for inclusion. In addition to major depression we accepted depressive symptoms identified by validated screening questionnaires.

Exposure definition. The scientific literature has not arrived at a universally accepted definition of a relevant traumatic event (10). For purposes of this report a traumatic event was defined by mass-scale events such as natural disasters (earth quake, flooding, hurricane, tsunamis, bushfire), technological disasters (firework, air plane crash, train accidents, shipwrecking), terroristic incidences (bombing, shooting) and military combat and by traumatic events at the individual level such as motor vehicle accidents, serious disease and assaults. Life events such as loss of close relatives, divorce, loss of property, bankruptcy, unemployment, poverty, and other social calamities did not qualify for inclusion because these exposures are not considered traumatic events according to the DSM and ICD-10 guidelines (3,7).

The systematic Medline search was supplemented by searches in EMBASE and PSYCHINFO during the same time period. Moreover, we performed hand searches and included relevant references identified by reviews and reference lists.

Altogether we identified 39 articles addressing the risk of delayed onset PTSD, and 24 original articles reporting relative risk of depressive disorder following exposure to traumatic events in comparison with appropriate reference groups.

Quality Assessment and Data Extraction

Two of the authors (Nicolai Utzon-Frank and Jens Peter Bonde) independently assessed the inclusion criteria for each paper and extracted the relevant information according to a scheme with variables defined a priori. We recorded type of the traumatic event and type of the population according to predefined categories, population size, age-, gender-, and minority distribution, number and timing of follow-up surveys, response rates at baseline and loss to follow-up, diagnostic tools, and number of PTSD cases and delayed onset PTSD cases at each follow-up round. Disagreements were resolved by consensus.

Quality Assessment

For both PTSD and depression reviews we graded the quality of the studies according to description of study design, sampling procedure, in- and exclusion criteria, response rate, ascertainment of exposure and outcome, and statistical analysis. Giving equal weight to each of the seven study characteristics we considered quality sufficient if the sum of the 0/1 scores was >5. For the studies examining delayed onset PTSD we examined the risk of selection bias due to asymmetry in sampling (recruitment not independent of symptoms) and for studies addressing depression we evaluated both bias and confounding according to criteria specified in the review manuscript.

Data Analyses

Delayed onset PTSD: Delayed onset PTSD was defined as newly onset PTSD identified more than 6 months after the traumatic event in prospective studies. Persons with subthreshold PTSD symptoms at the initial baseline examination 1-5 months after the event were accepted as delayed PTSD-cases. The primary outcome was the proportion of delayed onset PTSD relative to

all identified cases of PTSD. We first analysed the crude prevalence of delayed onset PTSD not taking loss to follow-up into account. In sensitivity analyses we adjusted the prevalence of PTSD according to attrition during follow-up assuming that this was independent of PTSD symptoms. The average proportion of delayed onset PTSD relative to total occurrence of PTSD was computed in random-effects models using the inverse variance as weights. Hereby the mean prevalence is primarily reflecting the large studies.

Depressive Disorder: The primary outcome was the relative risk of depressive disorder diagnosed by the DSM III-IV or ICD10-criteria in a population exposed to traumatic events in comparison with an unexposed population in terms of an odds ratio, a relative risk ratio or a hazard ratio. We computed a common risk estimate across all 24 studies by weighing the relative risk or equivalent by the inverse variance using random effects models because the true risk (if any) is expected to vary with trauma and study population. Analyses were performed using the STATA macro METAN (38).

To create an overview of studies we produced forest plots (39). Furthermore, we inspected plots for all papers and for subsets of papers to evaluate publication bias.

RESULTS

Delayed onset PTSD

We identified 39 longitudinal studies that provided 2 or more point prevalences of PTSD after exposure to a traumatic event or following discontinuation of military deployment. These studies addressed in total 30.099 persons that in average were surveyed 2.5 times after the traumatic event. Most studies addressed technological disasters and accidents (n=15) followed by terroristic acts (n=9) and military combat and deployment (n=6), while disease and natural disasters were more rarely studied (n=5 and 4, respectively).

The weighted average crude proportion of delayed onset PTSD relative to all identified cases was 26.6 (95% CI 21.2-32.0) with values spanning 0 and 71%. In meta-regression analyses it was shown that the weighted relative prevalence of delayed onset PTSD was significantly higher among military personnel and other professionals (firefighters, rescue workers, police officers) than in other exposed populations.

There was no difference in proportion of delayed onset PTSD in studies with early baseline assessments compared to studies with later baseline assessments.

Only 7 studies provided information about threshold symptoms during the initial posttraumatic period. In all of these, the majority of delayed onset PTSD cases were preceded by increased level of PTSD symptoms during the initial 6 months after the traumatic event or end of deployment, but in one large study of UK military personnel almost 3 out of 4 did not have subthreshold symptoms at the baseline examination. Similar results were obtained in a survey of Danish soldiers after deployment in Afghanistan.

Five studies provided data on the risk of delayed onset PTSD relative to indicators of the severity of the traumatic event. All these reported increased risk of PTSD (but not necessarily delayed onset PTSD) with increasing exposure intensity defined by different criteria.

Depressive Disorders

We identified 24 controlled epidemiological studies with 42 risk estimates with at least one estimate of the relative risk of depression in relation to a traumatic event. The 24 studies addressed a little less than 1.9 million subjects with an equal number addressing natural

disasters, terroristic acts, and military combat and deployment, and fewer addressing technological accidents.

The weighted relative risk for depression following the traumatic event across all 24 studies and 42 risk estimates was 1.7 (95% CI 1.50 - 2.09). The risk was significantly elevated in all types of traumatic events except among deployed military personnel. However, combat exposure was related to an increased risk of depression.

DISCUSSION

PTSD became acknowledged by the American Psychiatry Association in 1980 in the wake of the Vietnam war and the high prevalence of mental health disorders among war veterans (5). Still the new disease was controversial the first years, but now it seems to have become generally accepted in the international scientific community that extreme and terrifying exposure may cause transient and sometimes persistent psychiatric disorders and that the DSM criteria for PTSD delineates one of these mental disorders.

It is remarkable that the PTSD diagnostic entity - as a mental disorder defined by its cause - has not been identified by carefully controlled epidemiological studies that consistently demonstrate higher rates among exposed than unexposed. There may in particular be two reasons that the usual epidemiological criteria for causal inference (40) largely have been ignored in the PTSD literature. The first reason is that the disorder develops in close time relation to an event that is clearly defined in time and space. PTSD is to some extent comparable to an accidental injury. The second reason is that two of the four symptom clusters that define the disease are specifically pointing to the traumatic event (intrusive memories and avoidant behaviour). But this also explains why it raises scepticism when it is hypothesized that the disorder may develop with delayed onset several months and even years after the traumatic event(s) took place (1,15). This question is at the core of this report. Do we have evidence that PTSD may become manifest later than 6 months after the traumatic exposure as (arbitrarily) defined by consensus among experts in the DSM-IV criteria? If so, how much delayed, how often and how come? Are specific characteristics related to the traumatic event or the exposed populations explaining delayed onset PTSD?

Updating and extending two earlier systematic reviews addressing the evidence for delayed onset PTSD we identified 39 epidemiological studies which through repeated follow-up surveys enabled diagnosis of new cases of PTSD in persons that did not have the disorder at an earlier survey. These base-line examinations were performed 1-6 month after the traumatic event in 29 studies (in average 4 months after the event) and later than 6 months in 10 studies (in average 16 months after the event). The number of studied persons was increased more than five-fold in comparison with the latest review and meta-analysis by Smid et al (26). Since these studies with few exceptions are descriptive and uncontrolled surveys we also - and to the best of our knowledge for the first time – identified 24 controlled epidemiological studies that examined the risk of depressive disorder after exposure to traumatic events. Although these studies did not

offer data on the post-event time-specific incidence of depression (which would allow an evaluation of 'delayed posttraumatic depression'), we believe that knowledge on the risk of a comorbid mental disease not defined by its cause would support the evaluation of delayed onset PTSD. An example of the strong comorbidity of physician diagnosed PTSD, depression and anxiety among police responders to the 9/11 terrorist attack is given in Figure 7 (41).

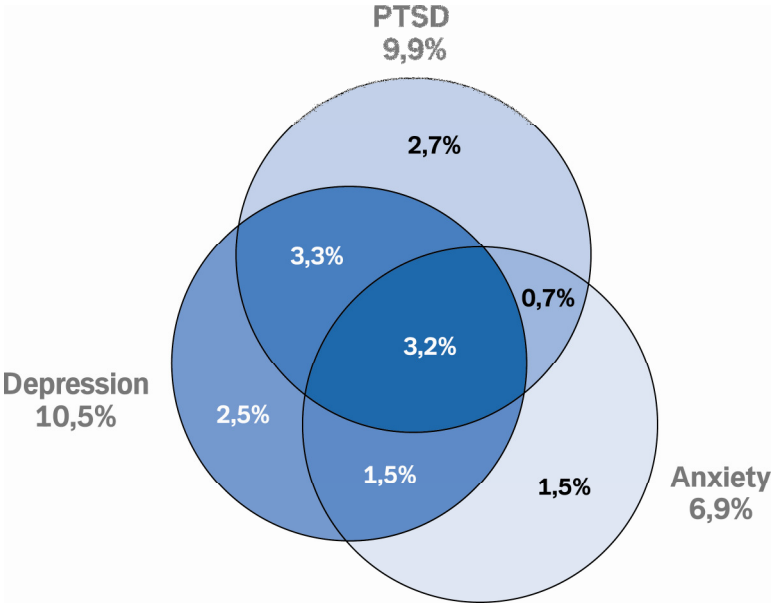


Figure 7. Physician diagnosed mental health disorders among police responders to the 9/11 terroristic attacks. Modified after Bowler et al 2012.

Results seem convincing: 38 of 39 prospective studies report newly onset PTSD-cases among subjects that did not have the disorder at an earlier baseline examination taking place after the traumatic event. This holds true for all types of populations (citizens, rescue workers, firefighters, police and military personnel) and all types of events (man-made disasters, technological disasters, natural disasters and no large-scale accidents). Biased recall of the onset of symptoms is not an issue because of the prospective data collection with repeated follow-up. The high variation of the PTSD prevalence across studies may be explained by heterogeneity with respect to type and severity of the traumatic events, study populations, sampling frames, duration of follow-up, screening instruments and diagnostic criteria. As expected prevalence rates were higher in studies using self-report questionnaires than clinical appraisal of the diagnosis (42) and lower in studies using the DMS-IV criteria including social disability than studies based upon the DSM III criteria without this criterion (even differences were not

statistically different). We accounted for the large differences in prevalence of normal onset PTSD by computing the proportion of delayed onset PTSD relative to all identified PTSD cases. In spite of this 'standardisation', the variation in delayed onset PTSD proportions was high reflecting strong heterogeneity across studies.

An important inherent limitation of the identified PTSD studies is that appropriate reference groups are seldom included. The fact that all studies with one single exception (43) report cases of delayed- onset PTSD can be taken as evidence for the existence of this condition. On the other hand, such an unusual consistency across observational studies may also raise concern that some strong bias is operating – for instance that contextual factors related to the announcement and conduct of the study play a role and the fact that questions and interviews to ascertain the outcome at the same time explicitly are addressing the supposed cause. This is in psychosocial epidemiology named common method variance (44-46). That contextual factors are important has for instance been shown in studies of indoor climate complaints (47) and in veteran studies addressing the effect of priming (48). The question is not whether the PTSD diagnoses to some extend are misclassified but whether the described conditions are causally linked with the traumatic event, which implicitly is part of the PTSD concept. Since studies are uncontrolled and falsely positive PTSD cases are inevitable the latter question must be answered with caution.

In spite of these caveats the authors argue that the reviewed literature provide some evidence that delayed onset PTSD is a common disorder for the following reasons. First, reported prevalences of delayed onset PTSD are high constituting in the range of 25% of all identified cases of PTSD. It should be acknowledged, however, that this is not a strong argument because systematic bias might also produce strong and consistent associations. Second, delayed onset PTSD is reported following all types of severe traumatic events and in diverse populations which indicate that factors related to for example professional groups are not the only explanation. Third, all studies with adequate data observe a substantially increased risk of delayed onset PTSD by subthreshold PTSD symptoms during the initial 1 - 6 months after the traumatic event. This evidence links the event with the subsequent development of full syndromal PTSD and is corroborated in 7 studies that - at the individual level - observe that delayed onset PTSD is preceded by elevated levels of subthreshold PTSD in the initial phase after the trauma. Fourth, our supplementary review provides evidence that traumatic events increase the risk of depression and depression is highly comorbid with delayed PTSD (41). Finally, five of the 39 studies included in our review reported the risk of delayed onset PTSD in relation to the severity or intensity of the traumatic event and

all observed increasing risk with increasing intensity of exposure. This supports that the observed associations between the event and delayed onset PTSD are indeed of a causal nature.

If it is agreed that there overall is reliable evidence that PTSD may take more than 6 months to develop from subthreshold symptoms into the full syndromal disorder, the next question is how long? A study of former American prisoners of war (World War II and the Korean War) found that long-delayed onset of PTSD was rare but support a PTSD symptom pattern of immediate onset, gradual decline followed by increasing PTSD levels among older survivors (49). A retrospective study of 15 elderly Australian war veterans identified PTSD cases with supposed significantly delayed onset but this small retrospective study of a highly selected group does not delineate the role of the primary war trauma (49). Unfortunately it is not possible to arrive at any evidence based limits, but it seems obvious that the longer the period between exposure and disorder onset, the more likely it becomes that other determinants are involved (50-52) and the more significant is the lack of properly controlled studies. Only few studies examine stressors occurring after the supposed triggering traumatic event(s), but so far the limited evidence among UK military personnel does not indicate that leaving the military or breakdown of relationships are explaining late onset PSTD (23). Although the data at present indicate that six months is too short a time period it is not possible to set evidence based upper limits.

It has been hypothesized that a traumatic event may become a ticking bomb that only after a symptom free latency period of many months or even years elicit delayed onset PTSD without symptoms bridging the event with the disorder (53,54). This hypothesis can only be corroborated or refuted by controlled cohort studies which unfortunately are not available at present. Thus there is insufficient evidence to evaluate this hypothesis.

The meta-analyses of subgroups did not unravel significant determinants of delayed onset PTSD except that military and other professional personnel are at higher risk than other groups (55). It is well known that the perceived stigma of having a mental disorder acts as a barrier to report mental health problems. In a study of randomly selected groups of UK military personnel it was shown that PTSD and subthreshold PTSD (but not common mental disorders) was reported 2-3 times as often in anonymous self-reports compared to identifiable questionnaires (56). Moreover, those completing the anonymous questionnaire were more concerned about leaders that discourage use of mental health services, about been seen as weak and to be embarrassed by

reporting PTSD symptoms. It seems possible that military personnel and other groups that are exposed traumatic events in relation to their job are more reluctant to report symptoms and seek help than other groups because it may have career consequences. Soldiers, firefighters, rescue workers and other professional groups are requested to have a good mental health, which may delay reporting and help seeking. Others have suggested that less access to medical care, less support from union peers and stress reintegrating with civilian society are other possible explanations of delayed PTSD among soldiers returning back after deployment (57). However, longitudinal data do not indicate any 'ticking bomb' phenomenon even in the group of UK reservist that seem more vulnerable to develop PTSD than regular troops (58).

CONCLUSION

Descriptive follow-up data indicate that PTSD may become manifest more than 6 months after a traumatic event, most often with sub-threshold PTSD symptoms bridging the traumatic event and disease onset. The proportion of delayed onset PTSD seems substantially higher among military personnel and other professionals. A likely reason is that the stigma of having a mental disorder is a stronger barrier to report PTSD symptoms in professional groups than among civilian victims of traumatic events. The length of the time interval from a traumatic event to development of the full PTSD symptom clusters may be in the range of 1-2 years or more but there are no controlled data to indicate that a traumatic event may act a ticking bomb becoming manifest years after the event.

These findings in descriptive studies of PTSD are reinforced by several high quality prospective follow-up studies that consistently report moderately increased risk of depressive disorder in subjects exposed to traumatic events. Chance, bias and confounding can be ruled out with reasonable confidence, but the evidence database is too limited to resolve issues relating to exposure-response relation-ships and timing of exposure and depression.

EVALUATION

The epidemiological evidence is based upon the systematic reviews and meta-analyses presented in this report and rated according to the criteria defined by The Danish Society of Occupational and Environmental Medicine (DASAM, Appendix VI)

Issue	Statement	Rating of evidence according to DASAM criteria[1]
I	Exposure to traumatic events is causally linked to development of PTSD symptom clusters defined by DMS-IV or ICD-10 criteria with onset later than 6 months after the event (delayed onset)	++
II	Delayed onset PTSD is preceded by subthreshold PTSD symptoms during the initial six months after the trauma	(++)
III	Delayed onset PTSD may develop after a latent period without above background level of PTSD symptoms	(+)
IV	A terrifying sudden and unexpected psychological exposure is causally linked to risk of depressive disorder as defined by DMS-IV or ICD-10 criteria	+++

1) +++ strong evidence; ++ moderate evidence; + limited evidence; 0 insufficient evidence; - evidence of no causal association, for definitions se Appendix VI . (++) indicates evidence between '++' and '+';

Comments:

Issue I: Numerous epidemiological follow-up surveys with prospective data collection consistently report PTSD above background levels with delayed onset. Chance findings can be ruled out with high confidence, but bias and confounding are likely because of the uncontrolled descriptive nature of the majority of studies and the likely high impact of contextual and social factors inherent in descriptive questionnaire studies . There is limited evidence for exposure-response relationships and high rates of delayed PTSD in US veterans compared to UK-veterans are most likely explained by factors, that are not related to combat exposure.

Issue II: Few epidemiological studies consistently report substantially increased risk of delayed onset PTSD among exposed subjects with subthreshold PTSD symptoms, but confounding is not unlikely.

Issue III: Evidence from case stories and descriptive studies has not been corroborated by controlled follow-up studies with adequate control for extraneous factors. Findings are conflicting and study design and settings arer likely inflating the estiamates of occurrence.

Issue IV: Numerous epidemiological studies including high quality prospective follow-up studies with clinical ascertainment of major depression consistently report moderately increased risk of depressive disorder in subjects exposed to traumatic events. Chance findings, bias and confounding can be ruled out with reasonable confidence. There is limited evidence for

exposure-response relationships. This is the first review med meta-analysis in the field and results has not been challenged by the the formal scientific review process related to publishing od scientific papers. Independent approval is warranted.

APPENDIX I: DSM IV TR diagnostic criteria for 309.81 PTSD (7)

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others

(2) the person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently re-experienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.

(2) recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.

(3) acting or feeling as if the traumatic event were recurring (includes a sense of Reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). Note:
In young children, trauma-specific re-enactment may occur.

(4) intense psychological dirtress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general Responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, fee lings, or conversations associated with the trauma

(2) efforts to avoid activities, places, or people that a rouse recollections of the trauma

(3) inability to recall an important aspect of the trauma

(4) markedly diminished interest or participation in significant activities

(5) feeling of detachment or ertrangement from others

(6) restricted range of affect (e.g., unable to have loving feelings)

(7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep

(2) irritability or outbursts of anger

(3) difficulty concentrating

(4) hypervigilance

(5) exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed onset: if onset of symptoms is at least 6 months after the stressor

APPENDIX II: ICD-10 diagnostic criteria for F43.1 Post-traumatic stress disorder (59)

This arises as a delayed and/or protracted response to a stressful event or situation (either short- or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone (e.g. natural or man-made disaster, combat, serious accident, witnessing the violent death of others, or being the victim of torture, terrorism, rape, or other crime).

Predisposing factors such as personality traits (e.g. compulsive, asthenic) or previous history of neurotic illness may lower the threshold for the development of the syndrome or aggravate its course, but they are neither necessary nor sufficient to explain its occurrence.

Typical symptoms include episodes of repeated reliving of the trauma in intrusive memories ("flashbacks") or dreams, occurring against the persisting background of a sense of "numbness" and emotional blunting, detachment from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities and situations reminiscent of the trauma. Commonly there is fear and avoidance of cues that remind the sufferer of the original trauma. Rarely, there may be dramatic, acute bursts of fear, panic or aggression, triggered by stimuli arousing a sudden recollection and/or re-enactment of the trauma or of the original reaction to it. There is usually a state of autonomic hyperarousal with hypervigilance, an enhanced startle reaction, and insomnia. Anxiety and depression are commonly associated with the above symptoms and signs, and suicidal ideation is not infrequent. Excessive use of alcohol or drugs may be a complicating factor.

The onset follows the trauma with a latency period which may range from a few weeks to months (but rarely exceeds 6 months). The course is fluctuating but recovery can be expected in the majority of cases. In a small proportion of patients the condition may show a chronic course over many years and a transition to an enduring personality change (see F62.0).

Diagnostic guidelines

The disorder should not generally be diagnosed unless there is evidence that it arose within 6 months of a traumatic event of exceptional severity. A "probable" diagnosis might still be possible if the delay between the event and the onset was longer than 6 months, provided that the clinical manifestations are typical and no alternative identification of the disorder (e.g. as an anxiety or obsessive-compulsive disorder or depressive episode) is plausible. In addition to evidence of trauma, there must be a repetitive, intrusive recollection or re-enactment of the event in memories, daytime imagery, or dreams. Conspicuous emotional detachment, numbing of feelings and avoidance of stimuli that might arouse recollection of the trauma are often present but are not essential for the diagnosis. The autonomic disturbances, mood disorder, and behavioural abnormalities all contribute to the diagnosis but are not of prime importance. The late chronic sequelae of devastating stress, i.e. those manifest decades after the stressful experience, should be classified under F62.0.

Includes: traumatic neurosis

APPENDIX III: The PTSD checklist, the civil form (PCL-C).

In the military version (PCL-M) 'stressfull experience' is substituted by 'military stressfull experience' throughout.

PTSD CheckList – Civilian Version (PCL-C)

Client's Name: _____

Instruction to patient: Below is a list of problems and complaints that veterans sometimes have in response to stressful life experiences. Please read each one carefully, put an "X" in the box to indicate how much you have been bothered by that problem *in the last month*.

No.	Response	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1.	Repeated, disturbing *memories, thoughts, or images* of a stressful experience from the past?					
2.	Repeated, disturbing *dreams* of a stressful experience from the past?					
3.	Suddenly *acting* or *feeling* as if a stressful experience *were happening* again (as if you were reliving it)?					
4.	Feeling *very upset* when *something reminded* you of a stressful experience from the past?					
5.	Having *physical reactions* (e.g., heart pounding, trouble breathing, or sweating) when *something reminded* you of a stressful experience from the past?					
6.	Avoid *thinking about* or *talking about* a stressful experience from the past or avoid *having feelings* related to it?					
7.	Avoid *activities* or *situations* because they *remind you* of a stressful experience from the past?					
8.	Trouble *remembering important parts* of a stressful experience from the past?					
9.	Loss of *interest in things that you used to enjoy?*					
10.	Feeling *distant* or *cut* off from other people?					
11.	Feeling *emotionally numb* or being unable to have loving feelings for those close to you?					
12.	Feeling as if your *future* will somehow be *cut short*?					
13.	Trouble *falling* or *staying asleep*?					
14.	Feeling *irritable* or having *angry outbursts*?					
15.	Having *difficulty concentrating*?					
16.	Being *"super alert"* or watchful on guard?					
17.	Feeling *jumpy* or easily startled?					

PCL-M for DSM-IV (11/1/94) Weathers, Litz, Huska, & Keane National Center for PTSD - Behavioral Science Division

This is a Government document in the public domain.

PTSD CheckList – Civilian Version (PCL-C)

The PCL is a standardized self-report rating scale for PTSD comprising 17 items that correspond to the key symptoms of PTSD. Two versions of the PCL exist: 1) PCL-M is specific to PTSD caused by military experiences and 2) PCL-C is applied generally to any traumatic event.

The PCL can be easily modified to fit specific time frames or events. For example, instead of asking about "the past month," questions may ask about "the past week" or be modified to focus on events specific to a deployment.

How is the PCL completed?

- The PCL is self-administered
- Respondents indicate how much they have been bothered by a symptom over the past month using a 5-point (1–5) scale, circling their responses. Responses range from **1** *Not at All* – **5** *Extremely*

How is the PCL Scored?

1) Add up all items for a total severity score
or
2) Treat response categories **3–5** (*Moderately* or above) as symptomatic and responses **1–2** (below *Moderately*) as non-symptomatic, then use the following DSM criteria for a diagnosis:
- Symptomatic response to at least 1 "B" item (Questions 1–5),
- Symptomatic response to at least 3 "C" items (Questions 6–12), and
- Symptomatic response to at least 2 "D" items (Questions 13–17)

Are Results Valid and Reliable?

- Two studies of both Vietnam and Persian Gulf theater veterans show that the PCL is both valid and reliable (Additional references are available from the DHCC)

What Additional Follow-up is Available?

- All military health system beneficiaries with health concerns they believe are deployment-related are encouraged to seek medical care
- Patients should be asked, **"Is your health concern today related to a deployment?"** during all primary care visits.

• If the patient replies "**yes**," the provider should follow the Post-Deployment Health Clinical Practice Guideline (PDH-CPG) and supporting guidelines available through the DHCC and www.PDHealth.mil

DHCC Clinicians Helpline: 1 (866) 559-1627 DSN: 662-6563 www.PDHealth.mil
PDH-CPG Tool Kit Pocket Cards Version 1.0 December 2003

APPENDIX IV : Working paper, not provided. (Working title: Occurrence of delayed onset posttraumatic stress disorder: a systematic review with meta-analysis of prospective studies.

APPENDIX V: Working paper, not provided. (Working title: Risk of depressive disorder following exposure to traumatic events: a systematic review with meta-analysis of controlled studies.

Appendix VI: Criteria for rating Epidemiological Evidence for Causal Inference proposed by the Danish Society of Occupational and Environmental Medicine.

Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome

The following categories are used:

+++ strong evidence of a causal association
++ moderate evidence of a causal association
+ limited evidence of a causal association
0 insufficient evidence of a causal association
- evidence suggesting lack of a causal association

Description of categories:
Strong evidence of a causal association (+++):
A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):
A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association (+):
A causal relationship is possible. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):
The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):
Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments:
The classification does not include a category for which a causal relation is considered as established beyond any doubt. The key criterion is the epidemiological evidence.
The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc.

Biological plausibility and contributory information may add to the evidence of a causal association.

APPENDIX VII: Reviewer comments and author responses

The draft report was in May 2013 reviewed by two independent reviewers, Dr Geert Smid, Amsterdam University and Professor Sir Simon Wessely, Kings College, London.

Geert Smid, MD PhD, is a Dutch Psychiatrist and researcher focusing on trauma and PTSD. In 2011 he completed his PhD project entitled *Deconstructing Delayed Posttraumatic Stress Disorder* addressing epidemiological, clinical, and conceptual aspects of delayed PTSD. He is acknowledged for major scientific contributions to the understanding of PTSD and in particular the onset of course of this disorder.

Sir Simon Wessely is a British psychiatrist, professor of Psychological Medicine at the Institute of Psychiatry, King's College London and Head of its department of psychological medicine. He is Vice Dean for Academic Psychiatry, Teaching and Training at the Institute of Psychiatry, as well as Director of the King's Centre for Military Health Research. He is also honorary Consultant Psychiatrist at King's College Hospital and the Maudsley Hospital, as well as Civilian Consultant Advisor in Psychiatry to the British Army. He was knighted in the 2013 New Year Honours for services to military healthcare and to psychological medicine.

In the following we provide the review comments and the author responses to the criticism.

Dr Geert Smid, Diemen, The Netherlands	**Author response**
Thank you for giving me the opportunity to comment on your important work. I read the report and the two scientific papers with much pleasure and interest.	
English summary	
P. 5: "Smid et al concluded …that about 25% … but only some 4%..." Two percentages with different denominators are being juxtaposed (25% and 4%). To avoid confusion, I would prefer: "Smid et al concluded based on a meta-analysis of 24 prospective follow-up studies that about 25% of all PTSD cases across highly different trauma experiences and populations were delayed-onset, and that participants with initial subthreshold PTSD were at increased risk of developing delayed PTSD."	We agree. Text corrected as suggested
P. 5: Exposure definition. The term	This has been the subject of major discussions

"terrifying event" seems to me an understatement. In addition, this term has not been used comparably in the existing literature. Therefore, alternative terms such as "large-scale potentially traumatic event" or "disaster or military combat exposure" should be considered.	in working group. There is no agreed single term that captures all type of events that according to DSM III and IV and ICD-10 are assumed to cause PTSD. We have now throughout report and papers used the term *traumatic event* (rather than terrifying event) defined this as event of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in almost anyone and examples include natural or man-made disaster, terroristic acts, combat, serious accidents, witnessing the violent death of others, or being the victim of torture, terrorism, rape, or other crime
P. 7: "… that delayed onset PTSD most often if not always is preceded by sub-threshold PTSD symptoms". The qualification "if not always" seems not in line with the results summary ("but two large studies of military personnel and non-rescue workers found high rates of newly onset PTSD without symptoms bridging the event and onset of fulblown PTSD") and may therefore be removed.	Agree. Corrected (sentence removed)
Introduction 4.P. 10: The impaired functioning criterion for PTSD was already added to the DSM-IV edition that was published in 1994.	Corrected
General state f the art P. 17: "Smid et al identified …that about 25% … but only some 4%..." Two percentages with different denominators are being juxtaposed (25% and 4%). To avoid confusion, I would suggest: "Smid et al identified… and that participants with initial subthreshold PTSD were at increased risk of developing delayed-onset PTSD (with 26% of participants reporting subthreshold PTSD symptoms developing delayed-onset PTSD, against only 4% of those not reporting these symptoms)."	Corrected
P. 20: "short term contract with the Army": cf. similar findings of heightened PTSD risk in US reservists (Milliken, Auchterlonie, & Hoge, 2007)	This paper does not fulfil the inclusion criteria for the meta-analysis (assessments were performed immediately on return and 3-6 months later), but we agree that this is a large high quality study highlighting mental health problems among reservists during the first half year after return form service. It is now

	referenced in the general state of the art.
Discussion P. 33: "As expected prevalence rates … than studies based upon the DSM III criteria without this criterion." Please replace "DSM III" by "DSM-III or DSM-III-R".	Corrected
P. 35: "If it is agreed … the next question is how long?" Although the evidence about the possible duration of the delay from retrospective studies and case reports may be considered less strong from an epidemiological point of view, the authors may still refer to it (e.g., Port, Engdahl, & Frazier, 2001; Ruzich, Looi, & Robertson, 2005). Cases of PTSD with onset several decades after the trauma have been described (e.g., Herrmann & Eryavec, 1994; Pomerantz, 1991; Ramchandani, 1990).	We acknowledge that several reports have described the occurrence of PTSD several years after the assumed primary cause but have throughout report and papers pinpointed the methodological flaws related to retrospective studies and case-studies. Moreover – there are also studies that do not report PTSD with very delayed onset (for instance the Port et al study of prisoners of war). The discussion in the PTSD report has been extended to accommodate this important issue.
Conclusion P. 37: "… that delayed onset PTSD most often if not always is preceded by sub-threshold PTSD symptoms". The qualification "if not always" appears not in line with the results reported on p. 29 ("but in one large study of UK military personnel almost 3 out of 4 did not have subthreshold symptoms at the baseline examination. Similar results were obtained in a survey of Danish soldiers after deployment in Afghanistan") and may therefore be removed.	We agree and have corrected as suggested. Nevertheless we consider the evidence of 'the ticking bomb' hypothesis for insufficient
Minor comments: p. 4: "as a fourth symptom cluster" should read "as a fourth criterion"; p. 9: "Geerd" should read "Geert"	Corrected
Comments on: Occurrence of delayed onset posttraumatic stress disorder: a systematic review and meta-analysis of prospective studies (Bonde JP et al.)	
Overall: The authors use the term "terrifying event" interchangeably with "(potentially) traumatic event" or "trauma". The latter terms may be preferred because they are commonly used in the existing literature.	We have corrected and use the term *traumatic event* throughout, cf above.
Abstract P3: "… that delayed onset PTSD most often if not always is preceded by sub-threshold PTSD symptoms". The qualification "if not always"	We agree, corrected

seems not in line with the results summary ("but two large studies of military personnel and non-rescue workers found high rates of newly onset PTSD without symptoms bridging the event and onset of fulblown PTSD") and may therefore be removed	
Introduction P. 4: The impaired functioning criterion for PTSD was initially added to the DSM-IV that was published in 1994.	Corrected
P. 6: "determinants of delayed PTSD": please specify which determinants are being examined	We have specified the examined determinants in the objective
Methods P. 6: "determinants of delayed PTSD": please specify which determinants are being examined P. 7: "Five studies included in the Smid et al review were not included in the present study (three addressing children and adolescents, one with less than 25 participants and one in Polish), while four other studies published before 2008 were added (20,23,26,51)" should read (corrections underlined): "Five studies included in the Smid et al review were not included in the present study (two addressing children and adolescents, two with less than 25 participants and one in Polish), while three other studies published before 2008 were added (19,23,43)."	Corrected as suggested
P. 7: Reference 51 duplicates reference 19.	Reference list updated
P. 9: A publication bias analysis appears to be lacking and may be added (for the primary outcome).	We have performed a funnel plot (attached) which, however, is not very informative about possible publication bias. Large studies do not systematically report lower proportion of delayed onset PTSD as demonstrated in Table 2.
Results Overall: the results sections contains a number of analyses that may be more explicitly anticipated in the Introduction and/or Methods sections.	We agree. The method section has been updated
The authors may omit crude averaged prevalence rates, as inverse variance weighted prevalences are more representative.	Crude prevalence rates omitted where weighted means are more appropriate
P. 10: "bias towards too high prevalences was likely in 20 studies – mostly because of assignment of exposure status was not independent of PTSD symptoms" – please	The assigned criteria for bias are given in the methods section. The papers with likely bias has been explicitly indicated in the revised text (Carty, 2006;Cukor, 2011;Curran, 1990;Eytan,

clarify. Which studies does this refer to?	2011 ;Gray, 2004;Hauff, 1994;Hepp, 2008;Johnson, 2002;Karamustafalioglu, 2006;Mayou, 1997 ;North, 1997;Solomon, 2006;Southwick, 1995; Su, 2010;Tjemsland, 1998;Andersen, 2013;Bowler, 2012;Wadsworth, 2009;Scott, 1995)
P. 11: "The proportion of delayed onset PTSD was lower in studies applying clinical ascertainment of the PTSD diagnosis". The difference appears statistically insignificant, given overlapping confidence intervals. Otherwise, please report the between-group Q heterogeneity statistic.	Yes, we think the confidence clearly demonstrates that findings are not significantly different but the direction is as expected.
P. 11: "In the subset of 10 studies with baseline examination more than 6 months after the traumatic event… the proportion of all identified PTSD cases with delayed onset PTSD naturally increased with time." This finding appears to represent an artifact, since apparent delayed-onset PTSD may reflect a fluctuating course in cases who had a time-limited first episode of PTSD that had remitted prior to the baseline assessment. Indeed, the likelihood of such missed cases increases with the length of time between traumatic event and baseline PTSD assessment. The authors should preferably reconsider their study inclusion criteria or otherwise acknowledge this limitation in the Discussion section.	We agree that some cases of delayed PTSD identified in the 10 studies with baseline assessment after 6 (9) months may not be truly delayed but represent reoccurrence of PTSD that primarily developed before 6 months but subsequently then subsided before the baseline assessment. However, a similar problem is related to studies with baseline assessment before 6 months. In these cases the full syndromal PTSD disorder may have developed after the baseline assessment but before 6 months. In both designs the direction of bias is towards inflated delayed onset PTSD prevalence. Although the magnitude of the proportion of delayed PTSD for these reasons may be inflated there are also mechanism operating in the other direction: PTSD with delayed onset may have developed after the baseline examination but subsided before the follow-up examination. These limitations are acknowledged in an update of the discussion
P. 12: Extended exposure and bereavement. The division of studies according to likelihood of extended exposure and/or bereavement appears arguable. Secondary and/or distal stressors are likely to occur after most potentially traumatic events. This paragraph may therefore be omitted from the manuscript.	We agree that secondary stressors are likely following any type of traumatic event but refrain to omit the paragraph on bereavement. It seems reasonable to distinguish between traumatic event with and without severe personal loss. Bereavement seems to be a core issue in the ongoing discussions related to the revision of the ICD-10 criteria (Maercker A, et al. Proposals for mental disorders specifically associated with stress in the International Classification of Diseases. Lancet. 2013;381:1683-5)
Discussion P. 17: "Soldiers and other professional groups	We agree. *In part* has been added

may be reluctant to report symptoms until they become severe because of fear loosing job (…). For the same reason professionals with early symptoms might be less likely to participate in surveys. Thus both reporting and selection bias may explain delayed PTSD without apparent initial symptoms." Although this may hold true for some cases without apparent initial symptoms, it certainly needs not pertain to all such cases. Thus, reporting and selection bias may ¬in part explain delayed PTSD without apparent initial symptoms.	
P. 18: "previous systematic review (66)" should read: "previous meta-analysis (15)"	Corrected
Conclusion P. 20: "… most often if not always with sub-threshold PTSD symptoms bridging the traumatic event and disease onset". The qualification "if not always" seems not in line with the results and may therefore be removed.	Agree, corrected
Tables	
Table 4. Column 2: the number of studies adds up to 42 or 41, but the Table title mentions 39 studies. Please explain.	Errors in numbers have corrected. The reason for the confusion is that three studies provide 2 risk estimates (more or less exposed or different types of exposures).
Table 5. The table title "… with late follow-up (> 9 months)" should read "with late baseline assessment (> 9 months)".	Corrected throughout
Comments on: Risk of depressive disorder following exposure to terrifying events: a systematic review with meta-analysis (Bonde JP et al.)	
Abstract P. 2: The term "terrifying event" seems to me an understatement. In addition, this term has not been used comparably in the existing literature. Therefore, alternative terms such as "large-scale potentially traumatic event" or "disaster or military combat exposure" should be considered.	We changed the generic term *terrifying event* to *traumatic event* throughout, see comments above.
Introduction P. 3: "Since there is strong evidence that life-events of this sort increase the risk of depression is seems plausible that also terrifying events could be an important risk factor for depression." Evidence from twin	We have included the paper by Kendler in the introduction and updated the introductory text

studies suggests a substantial causal relationship between stressful life events and depression (Kendler, Karkowski, & Prescott, 1999). Therefore, stressful life events may more appropriately be termed "an important causal risk factor for depression".	
Methods P. 4: "Articles were identified through a systematic search in The National Library of Medicine database Medline from January 1st, 1980 through March, 24th, 2013." The meta-analysis would be strengthened by searching additional databases besides Medline, including Embase and PsycInfo. Thus, additional evidence regarding dose-response relationships and time course patterns may be obtained.	We agree that a more comprehensive and formal literature is warranted. So far we checked various ways that important studies have not been left out. This includes preliminary searches in EMBASE and Psych-info. A formal supplementary search has been planned but results will hardly be available before 1.6.2013. We are aware of prospective studies of symptom cluster trajectories but these studies are uncontrolled and do not fulfil our inclusion criteria.
Results P. 11: "Among civilians…" Please refer the reader again to Table 3 in this paragraph.	Done
Discussion In their discussion of the risk of depression over time, the authors may refer to studies of depression trajectories following potentially traumatic events using Latent Class Growth Analysis (LCGA) (Kaptein, de Jonge, van den Brink, & Korf, 2006; Nandi, Tracy, Beard, Vlahov, & Galea, 2009).	Agree that these papers provide valuable information. Now referenced in an updated discussion.
Figures Figure 1: Study names and subgroups are hard to read.	Figures have been reformatted using STATA software (the METAN macro). Moreover results are presented by type of traumatic exposure.
Overall evaluation	
Are conclusions sound and supported by the data: Conclusions concerning the prevalence of delayed-onset PTSD and associated risk factors (i.e. profession-related exposure) appear sound and firmly supported by the data. I suggest reformulating the conclusion "delayed onset PTSD is most often if not always preceded by sub-threshold PTSD symptoms", thereby omitting "if not always", because this formulation is somewhat ambiguous, and the conclusion appears not in line with the author's own findings. The authors may consider additional evidence	'If not always' has been omitted. An extended literature search will be performed. The discussion has been updated and includes studies of symptom trajectories. The authors note that reviewers have not indicated studies fulfilling the inclusion criteria that have not been included.

pertaining to a causal relationship between stressful or traumatic events and depression based on an extended literature search and/or additional single references.	
Are applied methods appropriate and adequate: (1) For the delayed-onset PTSD meta-analysis, study inclusion and exclusion criteria may need to be reconsidered. Specifically, a study selection time frame specifying the time of the first assessment relative to the traumatic event appears to be missing. Apparent delayed-onset PTSD may reflect a fluctuating course in cases who had a time-limited first episode of PTSD that had remitted prior to the baseline assessment and that was reactivated prior to a follow-up assessment. The goal of a study selection time frame would be to reduce the potential number of missed cases who had a time-limited episode of PTSD that had remitted prior to the first assessment. The likelihood of such missed cases increases with the length of time between traumatic event and baseline PTSD assessment. (2) For the delayed-onset PTSD meta-analysis, a publication bias analysis may be added for the primary outcome. (3) The depression meta-analysis would be strengthened by searching additional databases besides Medline, including Embase and PsycInfo.	We have explained the time frames in more detail and discuss implications of limitations with respect to timing of the baseline and follow-up examinations: some factors causing inflated point estimates and others deflated point estimates. It is not possible to quantify the magnitude of bias in any of these directions and at best the bias operating in opposite directions may cancel out the respective effects. We have performed funnel plots but these are not informative with respect to possible publication bias. Extended literature searches will be performed.
Major flaws in data or reasoning: None	
Is the discussion sensible and balanced: Yes (see specific remarks above).	
Is important literature missing: The authors may cite evidence of a substantial causal relationship between stressful life events (of which potentially traumatic events are a subcategory) and depression (Kendler et al., 1999).	Done
Are important arguments or view-points missing: Evidence on PTSD and depression course may need to be considered from (1) case-reports and retrospective studies (Herrmann & Eryavec, 1994; Pomerantz, 1991; Port et al., 2001; Ramchandani, 1990; Ruzich et al., 2005); (2) life charting studies (Johnson, Westermeyer, Kattar, & Thuras, 2002; Osuch et al., 2001); (3) trajectory	Case-reports and uncontrolled retrospective studies were not included because of methodological limitations – but in the updated discussion we acknowledge, comment upon and reference this literature

approaches using Latent Class Growth Analysis (LCGA) or Latent Growth Mixture Modeling (LGMM) for PTSD symptoms, depressive symptoms, or both (e.g., DeRoon-Cassini, Mancini, Rusch, & Bonanno, 2010; Dickstein, Suvak, Litz, & Amy, 2010; Dolgin, 2007; Hobfoll, Mancini, Hall, Canetti, & Bonanno, 2011; Kaptein et al., 2006; Le Brocque, Hendrikz, & Kenardy, 2010; Nandi et al., 2009; Norris, Tracy, & Galea, 2009).	
	We thank Geert Smid for a very systematic and comprehensive review that has been very useful when revising the first version of the report. Geert Smid has not had the opportunity to approve our response.

Professor Sir Simon Wessely, Kings College, London	**Author response**
Introduction PTSD is a mental disorder, not disease	We fully agree. Corrected throughout.
Shell shock is most definitely not the same as PTSD - see Jones, E., Vermaas, R., McCartney, H. Beech, C., Palmer, I., Hyams, K. Wessely, S. Flashbacks and post-traumatic stress disorder: the genesis of a 20th-century diagnosis. British Journal of Psychiatry 2003, 182, 158-163.	Agree. Text updated and reference provided
You might to look at the ICD-11 proposal - Maercker A, Brewin C, Bryant R, Cloitre M, Reed G, van Ommeren M, Humayun A, Jones L, Kagee A, Llosa A, Rousseau C, Somasundaram D, Souza R, Suzuki Y, Weissbecker I, Wessely S, First M, Saxena S. Proposals for mental disorders specifically associated with stress in the ICD-11. Lancet 2013: 381: 1683-1685	We included this commentary in the introduction
Whether or not PTSD is or is not delayed doesn't mean it should be included in the ICD or DSM as a category – any more than cancers should be classified by latency periods.	We agree on this. The objective of this report is to provide evidence which may be useful for authorities in issues related to follow-up programs and management of litigation issues
29 out of the 39 studies don't have the first assessment until at least 6 months after the traumatic event so the onset could really have been before 6 months – in other words in the majority of studies there might be a misclassification of true delay as not delayed.	In 10 studies the first assessment is after 6 months or more. We think this may cause inflated point estimates (truly not delayed onset misclassified as delayed) – not the opposite. The discussion has been extended and also considers bias operating in the opposite

	direction. See also response to Geert Smid's remarks.
The latter assumes that loss to follow-up is independent of PTSD status. Is that valid? Especially when you later say "Completeness of reporting was considered high in 28 studies (sum score 7/7 in 12 studies and 6/7 in 16 studies), but bias towards too high prevalences was likely in 20 studies – mostly because of assignment of exposure status was not independent of PTSD symptoms".	Loss to follow-up is probably not independent of PTSD status, but the direction of bias may be in either direction. Nevertheless the follow-up response rate was high: The average loss to follow-up from one round to the next was 11.4% (0-44%). We consider selection bias related to recruitment of participants a more important source of bias.
One comment that is often made is that delayed onset might really be related to time of leaving the forces and hence the ending of free access to health care (or to be strict, two years after leaving for US until very recently) in the US. I would be interested in an analysis of country – comparing those with universal health care to those in which access to health care for veterans depends on having a service related disability (ie US) in the military samples.	We agree and reconsidered options for analysis of this aspect but unfortunately the number of studies are too sparse to allow further analyses.
Methods The method was not to require two follow up assessments (ie 3 assessments), but a minimum of one assessment and one follow up.	Yes, we have clarified the terminology as suggested (baseline assessment and at least one follow-up)
Discussion "It has been shown that the aim and setting of a study may strongly influence reporting and attribution of subjective symptoms and descriptive studies of PTSD inherently point to the assumed causes." I agree, but am wondering what evidence you have for this? I am thinking off LaGuardia, R. L., G. Smith, et al. (1983). "Incidence of delayed stress disorder among Vietnam era veterans: the effect of priming on response set." American Journal of Orthopsychiatry 53(1): 18-26.	We are referencing a Danish study showing how reporting and beliefs of symptoms related to the indoor climate is influenced by the study aim and set-up (Brauer C, Mikkelsen S. The context of a study influences the reporting of symptoms. Int.Arch.Occup.Environ Health 2003;76:621-4). We did not know about the LaGuardia paper on priming which is most interesting. This has been added an extended discussion of the subject. Contextual factors and 'wish-bias' is indeed a major issue.
"Findings have implications for diagnosis and compensation of disaster victims" . Hmmm, I wish I knew what these were!	Danish legal praxis has so far strongly adhered to the 6 months criterion as described by the ICD-10
Missing studies You really must include the classic Lee, K., G. Vaillant, et al. (1995). "A 50-year Prospective Study of the Psychological Sequelae of World War II Combat." American Journal of	Agree, we have included this and other studies in an extended discussion although we note that the paper does not fulfil our inclusion criteria. We cannot identify the Weisath 2001

Psychiatry 152: 516-522., with a remarkable length of follow up, and in which despite high levels of combat exposure they did not find delayed onset, albeit small sample size, but still a classic study there is also a fairly large literature of World war 2 studies that lack a prospective design, but also don't find delay – Weisath 2001 study of survivors of the Battle of Narvik for example	study in Pub Med.
What about? Disaster Survivors in Their Third Decade: Trajectories of Initial Stress Responses and Long-Term Course of Mental Health Author(s): Holgersen, KH (Holgersen, Katrine Hoyer)[1] ; Klockner, CA (Klockner, Christian A.)[2] ; Boe, HJ (Boe, Hans Jakob)[1] ; Weisaeth, L (Weisaeth, Lars)[3] ; Holen, A (Holen, Are)[1] JOURNAL OF TRAUMATIC STRESS Volume: 24 Issue: 3 Pages: 334-341 DOI: 10.1002/jts.20636 Published: JUN 2011	We comments on studies of symptom trajectories but do not consider this literature as core evidence given the objective of the report. We reference this report but since only symptom scores and not diagnostic entities are reported it is not fulfilling the inclusion criteria .included
Style Your English is excellent (far better than my Danish), but it does need an edit in places. I would have done that, but can't edit the PDF File.	Thanks (we have later received numerous edits to the PTSD review paper draft not provided here).
	We thank Sir Simon Wessely for thoughtful comments and references to seminal papers that we did not know about. This has been useful when revising the first version of the report. Simon Wessely has not had the opportunity to approve our comments.

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