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The Long-Term Consequences of Trauma and Stress Disorders: Evidence from the Danish Registries

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Preface

This dissertation would have been impossible without the support of the amazing and inspiring Dr. Henrik Toft Sørensen in the Department of Clinical Epidemiology at Aarhus University Hospital. I'm so grateful for Dr. Sørensen's support and belief in me over the last decade – it has helped me navigate this challenging profession in more ways than he will ever know. I am also truly grateful to all of the people at the Department of Clinical Epidemiology who helped complete the studies included in this dissertation, specifically Dr. Elisabeth Svensson, who was instrumental in managing the day to day operations of most of the studies included herein, and Hanne K. Schlosser and Helle Vester who have been great and helpful friends and colleagues in the Department of Clinical Epidemiology. Also thank you to Tina Christensen and Jens Christian Djurhuus who reviewed this dissertation.

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Table of Contents

List of Studies

This dissertation is based on the following 9 studies, which are referenced in the text by their Roman numerals (listed in chronological order). Studies I-IV were previously included in my Doctor of Science thesis, which was approved in May 2009 at Boston University, Boston, Massachusetts.

I. Gradus, J. L., Qin, P., Lincoln, A. K., Miller, M., Lawler, E., Sørensen, H. T., Lash, T. L. (2010). Acute stress reaction and completed suicide. International Journal of Epidemiology, 39(6), 1478-1484.

II. Gradus, J. L., Qin, P., Lincoln, A. K., Miller, M., Lawler, E., Sørensen, H. T., Lash, T. L. (2010). Posttraumatic stress disorder and completed suicide. American Journal of Epidemiology, 171(6), 721-727.

III. Gradus, J. L., Qin, P., Lincoln, A. K., Miller, M., Lawler, E., Lash, T. L. (2010). The association between adjustment disorder diagnosed at psychiatric treatment facilities and completed suicide. Clinical Epidemiology, 2, 23-28.

IV. Gradus, J. L., Qin, P., Lincoln, A. K., Miller, M., Lawler, E., Sørensen, H. T., Lash, T. L. (2012). Sexual victimization and completed suicide among female adults in Denmark. Violence Against Women, 18(5), 552-561.

V. Gradus, J. L., Bozi, I., Antonsen, S., Svensson, E., Lash, T. L., Resick, P. A., Hansen, J. G. (2014). Severe stress and adjustment disorder diagnoses in the population of Denmark. Journal of Traumatic Stress, 27(3), 370-374.

VI. Gradus, J. L., Antonsen, S., Svensson, E., Lash, T. L., Resick, P. A., Hansen, J. G. (2015). Trauma, comorbidity, and mortality following severe stress and adjustment disorder diagnoses: A nationwide cohort study. American Journal of Epidemiology, 182, 451-458.

VII. Gradus, J. L., Farkas, D. K., Svensson, E., Ehrenstein, V., Lash, T. L., Adler, N., Milstein, A., Sørensen, H. T. (2015). Posttraumatic stress disorder and cancer risk: A nationwide cohort study. European Journal of Epidemiology, 30(7),563-568.

VIII. Gradus, J. L., Farkas, D. K., Svensson, E., Ehrenstein, V., Lash, T. L., Adler, N., Milstein, A., Sørensen, H. T. (2015). Stress disorders and risk of cardiovascular disease events: A nationwide cohort study. BMJ Open, 5: e009334.

IX. Gradus, J. L., Farkas, D. K., Svensson, E., Ehrenstein, V., Lash, T. L., Sørensen, H. T. (in press). Posttraumatic stress disorder and gastrointestinal disorders in the Danish population. Epidemiology.

I. Summary

I. Background

Stressful and traumatic events, and the diagnoses that follow such events, are receiving attention due to recent increases in the number of traumatic events (*e.g.,* conflict, terrorism, natural disasters) occurring worldwide. Traumatic experiences are common in both Denmark and abroad; it is estimated that 50% of adults will experience a traumatic event in their lifetime. Given the ubiquity of traumatic events, it is not surprising that a common diagnosis given following one of these experiences – posttraumatic stress disorder or PTSD – is characterized as conferring a large burden for individuals and society. Yet, population-based longitudinal studies of people with these experiences or diagnoses are few. Although there is a wealth of literature on PTSD and its sequelae, other stress disorders (including acute stress reaction and adjustment disorder) receive less scientific attention, and it is unknown if our knowledge about the occurrence and sequelae of PTSD would generalize to other stress disorders. Further, there is debate in the literature regarding the role of stress disorders, including PTSD, in the etiology of somatic illness, with studies providing conflicting evidence on the strength of associations across many disease outcomes. This dissertation contributes to the literature on the longitudinal course of stress and trauma by examining associations of traumatic experiences and stress disorders with a variety of mental and physical health and mortality outcomes in a prospective, population-based cohort with complete follow-up. Understanding long-term consequences is critical to the field of public health and ultimately ameliorating their impact.

II. Objectives

The overall goal of this dissertation is to improve our understanding the long-term physical and mental health and mortality consequences of severe trauma among adults using longitudinal Danish national registry data (see Appendix 1 for a description) with complete follow-up.

In the first study, we describe the prevalence (*i.e.,* the proportion of people in the overall population with a given disorder at a specific time) and incidence (*i.e.,* the proportion of people who develop a disorder over a period of time among those without the disorder) of hospital-based stress diagnoses in the population of Denmark over 15 years, as well as differences across time and important demographic characteristics (e.g., age of onset and gender) and by year within the study period. At the time this study was conducted, no study had examined the incidence of stress disorders in a population

and within important subgroups over an extended follow-up period, which is critical to our understanding of prevention of these disorders as incidence is a dynamic measure which may change with time. In the next study, we examine the cumulative incidence of hospital-based depression, anxiety disorders, alcohol abuse and dependence and drug abuse and dependence diagnoses following stress disorder diagnoses as compared to a reference group without stress disorders. When this study was conducted, no study had examined the incidence of psychiatric complications following stress disorder diagnoses in a population-based sample with complete follow-up over 15 years, which has important implications for tertiary intervention and prevention efforts.

The next few studies presented in this dissertation contribute to our understanding of suicide outcomes among people who experience sexual victimization and people who are diagnosed with hospital-based stress disorders using two different study periods (1994 – 2006 and 1995 – 2011) and two different epidemiologic study designs (case-control and cohort; case-control studies were conducted because at the time of these studies work in Statistics Denmark with the whole population – which would have allowed for a cohort study – was not permitted. Also, case-control studies are a preferred design when examining multiple exposures of a rare outcome, such as suicide). As suicide death is a relatively rare event, the literature on the associations between sexual victimization, stress disorders and suicide was scant at the time these studies were conducted – data from a whole population with complete follow-up is required for a meaningful examination of this phenomena. Thus, this work was the first to examine these associations using population-based longitudinal data over an extended period of time.

Finally, the last series of studies presented in this dissertation examines the incidence of three categories of hospital-based physical health diagnoses – cancer, cardiovascular disease events, and gastrointestinal disorders among people with hospital-based PTSD and adjustment disorder over an extended time period, as well as the association between all hospital-based stress disorder diagnoses and all-cause mortality. At the time these studies were conducted, these disorders had yet to be examined in detail (*i.e.,* by diagnosis within physical health category category), and overall all-cause mortality had not been examined, in a large population-based sample with complete follow-up. This work was critical in moving the field forward with regard to placement of tertiary prevention efforts for somatic illness following stress diagnoses.

III. Material

This dissertation is based on a literature review and the findings of nine epidemiological studies on the long-term impact of stress and trauma. The literature review was initially conducted at the time of manuscript preparation for each study, with an update conducted for the purposes of preparing this dissertation. Both PubMed and Google Scholar were used for the literature search, with all individual and combined relevant search terms entered (*e.g.,* "stress disorders," "trauma," "posttraumatic stress disorder," "mortality"). All resulting articles were reviewed and are included and summarized as appropriate herein. The studies summarized within this dissertation are based on data from the nationwide Danish medical and social registers (see Appendix 1 for a description) and include studies that use both cohort and case-control design methodology. For the purposes of this dissertation, we present the work included in the List of Studies section in the following order. Study I examines the prevalence and incidence of stress disorders in Denmark overall and by important subgroups from 1995 – 2011 (Paper V in the List of Studies). Study II examines psychiatric comorbidity following stress disorder diagnoses, as well as all-cause mortality and suicide (Paper VI in the List of Studies). Studies III – VI report the association between sexual victimization, stress disorder diagnoses and death from suicide (Papers I – IV in the List of Studies). Finally, studies VII-IX include examinations of the physical health consequences of stress disorders (Papers VII – IX in the List of Studies).

IV. Results

In Study I, we found that hospital-based adjustment disorder was the most common stress diagnosis during the study period, with hospital-based unspecified reaction to severe stress the second most common. Consistent with the existing literature on gender differences in PTSD, women received stress diagnoses more frequently than men, and diagnoses were most likely to occur before age 40. We found a sudden and maintained increase in the frequency of disorders in 2007, highlighting the dynamic nature of prevalence and incidence. The results of Study II showed that hospital-based depression diagnoses, anxiety disorder diagnoses and substance abuse and dependence diagnoses were all more common among those with stress diagnoses than among a comparison cohort without stress diagnoses over a 15 year period. Depression was the most common comorbidity, with a sharp increase in incidence in the immediate aftermath of stress diagnoses. The series of studies on sexual victimization and hospital-based stress disorders as risk factors for death from suicide presents a comprehensive overview of these associations. These studies are the first to document moderate to strong associations between all of these predictors and death from suicide. With regard to the physical health

consequences of stress disorders, we found no evidence of an association between PTSD and cancer; however we found evidence of comparable modest associations between PTSD and adjustment disorder and cardiovascular disease events and similar modest evidence of associations between PTSD and gastrointestinal diseases as compared with the general population. Risk of all-cause mortality was also increased among those with a stress disorder diagnosis relative to a comparison group without stress diagnoses.

V. Conclusions

This dissertation, in combination with the existing literature, suggests that stress disorders are a prevalent public health problem. Further, traumatic events and associated disorders have potential negative long-term consequences spanning multiple domains including mental and physical health and mortality, although not all outcomes we examined were increased among people with stress disorder diagnoses. This research has important implications for tertiary intervention and prevention efforts, and our understanding of where to best place resources during treatment for persons who experience trauma or receive a stress disorder diagnosis. My work in this area has propelled forward this field of research through the documentation of the potentially deleterious course trauma and associated disorders using prospective data with complete follow-up from a large unselected (*i.e.,* all patients who received treatment are included) population that is not subject to the biases found in previous studies in this area (*e.g.,* recall bias, loss to follow-up). Further, the application of advanced epidemiological study designs to a large prospective population-based data source with the goal of understanding the long-term course of stress and trauma has been a necessary and novel contribution to the literature.

II. Introduction

Stressful and traumatic events, and the diagnoses that follow such events, are receiving increased attention due to recent increases in the number of traumatic events (*e.g.,* conflict, terrorism, natural disasters) occurring worldwide. According to the Diagnostic and Statistical Manual for Mental Disorders (DSM) 5th Edition, a trauma is defined as an event in which a person is exposed to actual or threatened death, serious injury or sexual violation.[1] Traumatic experiences are common in both Denmark and abroad. It is estimated that 50% of adults will experience a traumatic event in their lifetime.[2-5] Given the ubiquity of traumatic events, it is not surprising that a common diagnosis following one of these experiences – posttraumatic stress disorder or PTSD – is characterized as conferring a large burden for individuals and society.[6] In the largest population-based study of the prevalence of psychiatric illness in the United States to date (The National Comorbidity Survey), the prevalence of PTSD was estimated to be approximately 5% among men and 10% among women.[2] The literature on the prevalence of other stress disorders is scant; population-based longitudinal studies of people with these experiences or diagnoses are few. Accordingly, research on diagnoses given following a severe stress or traumatic event is limited, with the wealth of research on PTSD being an exception.[6,7] The lack of research on stress disorders other than PTSD is likely due to the difficulty in obtaining national population-based samples in psychiatric research. The population-based studies that do exist have greatly advanced the study of trauma and associated disorders at a population-level, but they are typically limited in the number of diagnoses that can be examined, can be subject to biases found in studies that utilize a subset of a population (*e.g.,* poor generalizability), and typically include little to no follow-up time. As a consequence of this lack of existing research on all stress disorders, it is unknown if findings to date regarding the sequelae of PTSD would generalize to other stress disorders. Further, there is still debate in the literature regarding the role of stress disorders, including PTSD, as it contributes to the etiology and prognosis of somatic illness. The work included in this dissertation advanced the existing literature by utilizing longitudinal population-based data to examine the prospective clinical course of disorders associated with stress and trauma and documenting associations between sexual victimization and stress disorders and a variety of major mental and physical health outcomes.

I. Objectives

The overall goal of this dissertation is to improve the scientific understanding of the long-term physical and mental health consequences of trauma and the disorders that result from trauma among adults over 15 years of follow-up. This dissertation is divided into four main sections.

The first section characterizes the prevalence and incidence of five ICD-10 hospital-based stress diagnoses in the population of Denmark from 1995 through 2011. We further present differences in incidence of these disorders over time, and differences within categories of important demographic characteristics such as gender and age of onset.

The second part of the dissertation focuses on the long-term psychiatric consequences of stress disorders. Specifically, we examine incident hospital-based depression, anxiety, and substance abuse and dependence diagnoses in the 15 years following incident hospital-based stress diagnoses as compared to a matched reference group without these diagnoses.

The third part of this dissertation focuses on an examination of death from suicide as an outcome of hospital-based stress disorders and sexual victimization trauma. The association between individual stress disorders and suicide was examined both in a case-control study that included 12 years of longitudinal data from 1994 through 2006 and in a cohort study that included 15 years of longitudinal data from 1995 through 2011. A case-control design was chosen for the first study because the overall goal of that study was to examine a variety of predictors of suicide death (a rare outcome) across demographic, social, psychiatric and physical health domains. The use of a case-control design allowed for the examination of predictors from all of these domains while only sampling patients once based on their suicide case or matched control status. Further, at the time these studies were conducted work in Statistics Denmark with the whole population (which would have allowed for a cohort study) was not permitted. The association between sexual victimization and suicide was examined among Danish women from 2001 through 2006 using a case-control study design.

The final part of this dissertation focuses on three potentially important major diseases that may be associated with stress disorders – cancer, cardiovascular disease and gastrointestinal disorders. Specifically, we compare the expected number of each of these outcomes from the general Danish population during the study period to the observed number of outcomes among those with stress

disorders from 1995 through 2011. The association between stress disorders and all-cause mortality over 15 years of follow-up is presented as well.

II. Outline

This dissertation consists of a literature review and 9 original studies on the long-term consequences of trauma and associated disorders. The rationale and objectives have been presented in this chapter. Chapter III provides a summary of the definition and history of stress disorders based on the ICD-10 criteria. Chapter IV summarizes incidence of these disorders in Denmark over a 15 year time period (Study I) both overall and within important demographic categories. Chapter V provides a summary of the literature on the mental health sequelae of stress disorders, and includes a presentation of the results from study II within this context. In Chapter VI, a summary of the existing literature on suicide death as an outcome of traumatic events and stress disorders is presented, with the results of Studies II-VI. Chapter VII summarizes the current literature on stress disorders and physical health outcomes, specifically cancer, cardiovascular disease and gastrointestinal diseases, and presents the results of the studies on this topic that are included in this dissertation (Studies VII – IX). An overview and summary of the existing literature with the results of this dissertation incorporated is presented in the Conclusions chapter (Chapter VIII). These chapters are followed by the Danish summary, and appendix which describes the Danish healthcare system and associated national medical and social registries and references.

III. Description of stress disorders

The evolution in diagnostic categories across ICD versions is reflective of the evolution of the field of psychiatry's thinking regarding stress diagnoses themselves over the last half century. Severe stress and trauma have always been a part of the human condition. But it was not until after the first and second World Wars that increased attention was paid to the psychiatric consequences of trauma.[8] Since then our understanding of post-trauma psychopathology has continually evolved into the diagnostic categorizations we use today.

There are five diagnoses Within the International Classification of Diseases, 10th Edition (ICD – 10) that can be given following a stressful or traumatic event from which one is not recovering.[9] These are: acute stress reaction (a diagnosis given in the immediate aftermath of the event); posttraumatic stress disorder or PTSD (a diagnosis given following a traumatic event and a timed period of non-recovery); adjustment disorder (a diagnosis given after a stressful event and a timed period of non-recovery) and two catch-all diagnoses, other reactions to severe stress and reactions to severe stress unspecified (given to people who are experiencing distress following a stressful or traumatic event, but who do not meet full diagnostic criteria for one of the other disorders). Currently, these diagnoses are among the most frequently assigned psychiatric diagnoses worldwide.[10]

Stress disorders were first introduced as a diagnostic category in ICD – 10, which was implemented in Denmark in 1994.[9,11] Prior to that, in the International Classification of Diseases 9th Edition (ICD – 9; not used in Denmark), only acute stress reaction and adjustment disorder were included as diagnoses and these were subsumed under a category of "other" adult onset diagnoses.[10] In Denmark, the International Classification of Diseases 8th Edition (ICD – 8) was used immediately prior to the implementation of ICD – 10. As the diagnosis of PTSD we know it today was not formulated until 1980, this diagnosis was not included in ICD – 8. Instead, a stress diagnoses of "transient situational disturbance" was included in ICD – 8, which encompassed all stress reactions including adjustment issues and stress and reactions to combat.[10]

Although the International Classification of Diseases is used throughout most of the world for diagnosis, for mental disorders another diagnostic guide is also used, primarily in the United States, called the Diagnostic and Statistical Manual for Mental Disorders, or DSM.[1] It is important to consider

differences in diagnostic classification between the ICD and DSM when thinking about the generalizability of our results to countries where the DSM is primarily used for diagnosis.

I. Acute stress reaction

Acute stress reaction (ICD – 10 code: F43.0) is a short-term diagnosis given when symptomatology appears within one hour of the occurrence of a severe stress or traumatic event (e.g., natural disaster, combat, severe accident, witnessing violent death, sexual assault), with symptoms beginning to abate within 48 hours.[9] Besides an experience of a traumatic event, diagnostic criteria for acute stress reaction include the possible experience of transient depression, anxiety, "daze"-like, anger, despair, over –activity and social withdrawal symptoms, with no one symptom being dominant. Patients who receive this diagnosis must have no other mental disorder that could account for this symptomatology.

II. Posttraumatic stress disorder (PTSD)

PTSD (ICD –10 code: F43.1) is a severe and chronic disorder that is diagnosed after the experience of a severe stress or traumatic event (e.g., natural disaster, combat, severe accident, witnessing violent death, sexual assault).[9] According to ICD –10 criteria, PTSD symptomatology must still be present 6 months after the traumatic experience for a diagnosis to be given and symptoms may last for decades. Possible symptoms of PTSD include persistent reliving of the event through nightmares or flashbacks, avoidance of reminders of the event, inability to recall part of the event, and a general state of hyperarousal (e.g., difficulty sleeping or concentrating, exaggerated startle response).

III. Adjustment disorder

Adjustment disorder (ICD –10 code: F43.2) is a diagnosis given following a major psychosocial stressor or life event (e.g., divorce, job loss, serious physical illness) with symptom onset within one month of the event and with symptoms generally abating by six months after the event. [9] Symptoms of adjustment disorder are similar to those of affective disorders (e.g., depression, anxiety, conduct or emotional disturbance) but a diagnosis of adjustment disorder can be given if an identifiable psychosocial stressor was experienced and the criteria for a diagnosis of a specific affective disorder are not met.

IV. Unspecified stress diagnoses

Two unspecified catch-all diagnoses can also be given following a severe stress or traumatic event, which are other reactions to severe stress (ICD –10 code: F43.8) and reactions to severe stress, unspecified (ICD –10 code: F43.9).[9] Diagnoses of this type are typically reserved for patients who have experienced a stressful or traumatic event and who are experiencing distressing symptomatology, but do demonstrate the diagnostic symptom criteria required to receive one of the stress diagnoses listed above (e.g., patients with sub-syndromal stress disorders).

Our study of the validity of these diagnoses in the Danish Psychiatric Central Research Register, which compared the registry diagnoses with medical record review from an independent assessor, found differing variability for each diagnosis. [12] Specifically, the validity was good for the more severe or chronic diagnoses (i.e., positive predictive value was 83% for PTSD and 94% for adjustment disorder). However, the more transient and/or unspecified diagnoses (e.g., acute stress reaction, other reactions to severe stress and reactions to severe stress, unspecified) showed poorer validity (i.e., positive predictive value of 58% for acute stress reaction, 71% for other reactions to severe stress, 68% for reactions to severe stress unspecified). It is important to note when interpreting these results however, that they are based on the comparison of the registry diagnosis with just one entry in the medical record, and clinicians may assign a diagnosis based on either clinical observations that are not explicitly documented, other knowledge of a patient from previous visits that would not appear in the record from one specific day or both. Therefore, the true positive predictive values of these diagnoses may be found to be higher if other forms of validation were used to confirm the registry diagnoses (e.g., interview with the diagnosing clinician).

IV. Frequency of stress disorders

I. Empirical evidence

The prevalence of stress disorders has previously been examined using cross-sectional data in national samples (such as the National Comorbidity Survey in the United States).[13] Almost all of this work has focused entirely on the prevalence of PTSD, at the exclusion of other stress disorders. Although PTSD is important to examine, it is unknown if findings regarding the disease frequency of PTSD overall and among specific subgroups would generalize to other stress disorders. For example, we know that PTSD is more common among women than men, but whether this is true of the other stress disorders as well remains an unanswered question. Further, given that any estimate of prevalence is a function of the place and time in which it is obtained, it is unknown whether cross-sectional prevalence estimates that have been obtained from previous national studies represent a consistent and accurate estimate of stress disorder disease frequency or an unobservable fluctuation. Finally, although prevalence studies are important with regard to provision of resources, previous studies have not examined incidence, which provides important information about disease occurrence without the influence of survival. An examination of the prevalence and incidence of stress disorders in a population sample is critical to public health awareness of these diagnoses.

The first study included in this dissertation (Study I) presents the incidence of the five hospital-based ICD –10 stress disorders in Denmark from 1995 through 2011 among people of all ages.[14] All results are based on prospective data from the Psychiatric Central Research Register (see Appendix 1 for a description) and primary and secondary diagnoses were used. The findings from this study are presented with more detail below, in addition to a review of the relevant literature.

II. Overall and annual frequency of stress disorders

Research on the prevalence and incidence of ICD –10 stress disorders in the general population is incredibly limited. Of the stress disorders, only the prevalence of PTSD has been estimated in more than one general population study. In the most widely –cited studies of the prevalence of PTSD, based on data from the National Comorbidity Survey study in the United States, the lifetime prevalence of PTSD (i.e., a PTSD diagnosis at any point prior to the study) was reported to be 7.8% among study

participants who were representative of the general United States population aged 15 to 54.[2] In the National Comorbidity Survey replication, a nationally-representative study of adults aged 18 and older in the United States, the lifetime prevalence was estimated to be 6.8%.[15] In a population-based survey study of young adults (aged 14 –24 years) in Munich, the prevalence of lifetime PTSD was estimated to be lower, 1.3% and a 12-month prevalence of 0.7%.[16] Similarly, a general population survey study in Australia found that the 12-month prevalence of PTSD to be 1.33%.[17] Any estimate of prevalence is a function of the place and time in which it is obtained; therefore, it is unknown if the disease frequency estimates for PTSD and adjustment disorder were obtained from one point in time in cross-sectional studies represent a true prevalence or a temporary unobservable fluctuation due to temporary changes in disease incidence or duration.

The only population-based survey that has examined adjustment disorder found a prevalence of less than 1% among five European countries, although this surprisingly low proportion was attributed to the limitations of the diagnostic tool used.[18,19] At the time this dissertation work was conducted the prevalence of other stress disorders (e.g., acute stress reaction, and the unspecified stress disorders) was unknown. In Study 1 we address this limitation by examining the frequency of all five hospital-based ICD –10 stress disorders in the population of Denmark overall and annually over a 15 year time period from 1995 through 2011. This work is critical to advancing the public health knowledge of stress-related disorders. It is only through understanding the prevalence and incidence of these disorders over time and within important subgroups that targeted intervention and prevention efforts can be successfully implemented.

In total, 101,663 adults and 10,181 children were diagnosed with a stress disorder between 1995 and 2011 in Denmark. Although PTSD is the most commonly studied stress disorder, adjustment disorder was most commonly diagnosed in this population (incidence rate in adults = 97/100,000 person-years; in children = 85/100,000 person-years). Table 1 displays the incidence rates for all disorders, stratified by adult or child status at age of onset.

Table 1. Incidence rate of ICD-10 stress disorders (per 100,000 person-years), Denmark, 1995 – 2011

	Adults	Children
Acute stress reaction	13	11

PTSD	5.5	4.7
Adjustment disorder	97	85
Other reactions to severe stress	2.5	2.5
Unspecified reactions to severe stress	29	26

Study I expands upon the previous cross-sectional prevalence studies in this area[13] by examining the annual frequency of the five hospital-based stress disorder diagnoses over a 15 year period. From 1995 through 2007 the annual number of stress diagnoses remained relatively constant for each disorder. Interestingly, in 2007 there was a relatively large increase in the frequency for all disorders, with some diagnoses doubling in number (see Figure 1). There were large changes in the frequency of acute stress reaction (348 –1024), adjustment disorder (3717 –5141) and unspecified reactions to severe stress (1248 –2520) from 2006 –2007. There were also more modest increased in PTSD (196 –256) and other reactions to severe stress (117 –180). These increases were generally maintained following 2007 across disorders. It is important to note that this change in frequency does not represent a comparable change in the size of the underlying Danish population during this same time period.

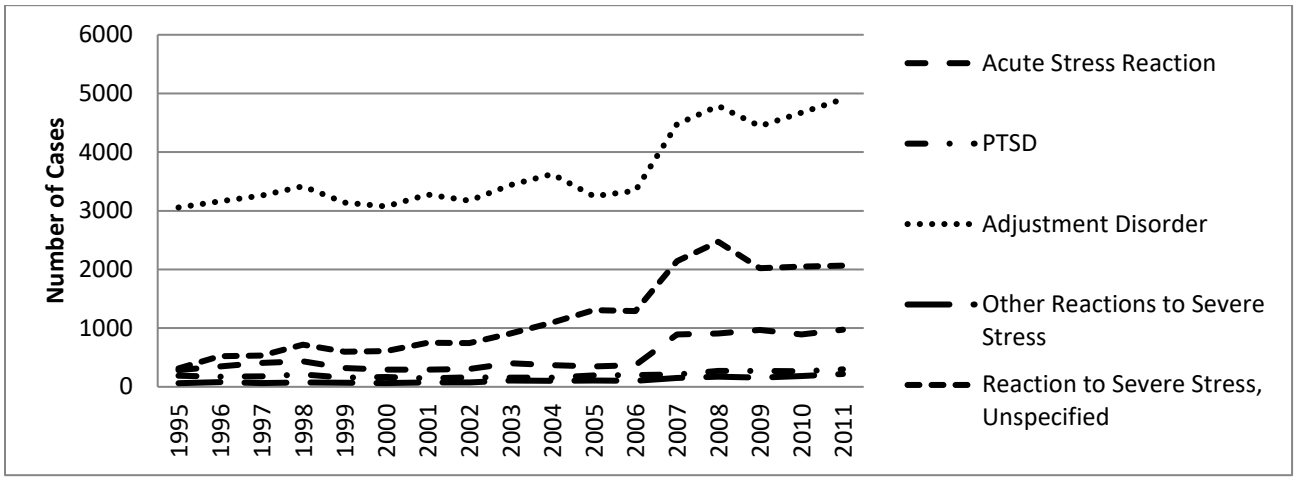

Figure 1. Number of Incident Severe Stress and Adjustment Disorder Diagnoses by Calendar Year, Denmark, 1995 to 2011

III. Prevalence and incidence of stress disorders in important subgroups

It is widely held that PTSD is more common among women than men in the general population.[2,20] Cross-sectional prevalence studies of the general population have consistently reported that PTSD is more prevalent among women than men.[2] In one of the first population-based studies to examine gender-specific PTSD prevalence, Resnick et al used random digit dialing to obtain a sample of women residing in the United States, and found an overall prevalence of 12.3%. [21] Subsequent studies confirmed an elevated prevalence among women. In the National Comorbidity Survey study the prevalence of PTSD was estimated to be 5% among men and 10.4% among women.[2] Other population-based studies using insurance data in the United States have provided evidence that the prevalence of PTSD is about two times higher among women than men.[20]

With regard to age of onset for PTSD, population-based research has consistently shown that the majority of cases occur before age 40. Utilizing data from the National Comorbidity Survey replication in the United States, Kessler et al found that 75% of PTSD cases in their sample occurred before age 40.[15] One study – a nationally representative sample of English-speaking residents of Ireland aged 18 and older – found a slightly different pattern with 75% of PTSD cases occurring before age 49.[22]

A limitation to the work summarized above is that the prevalence of stress disorders other than PTSD has not been examined within important demographic subgroups within a population-based sample. At the time our work was conducted, it was unknown if the gender and age distribution of these other stress disorders is comparable to what has been shown for PTSD. A lack of knowledge regarding the frequency of other stress disorders in large subsets of the population is a major limitation to the field of trauma public health, as we know that the events that lead to these diagnoses are increasing in occurrence and it is only through an awareness of the frequency of the diagnoses themselves that we can prepare for targeted intervention and prevention efforts. We addressed this limitation to the existing literature in Study I by examining the prevalence and incidence of all five hospital-based ICD – 10 stress disorders by gender and age of onset.

We found a consistent disorder distribution by gender, in that for all 5 diagnoses women made up approximately 60% of people with the diagnosis, with men only being 40%. This was also consistent across adults and children. Table 2 displays the distribution of each disorder by gender, as compared with the gender distribution of the general Danish population in the same time period.

Table 2. Gender Distribution of Stress Diagnoses, Denmark, 1995 to 2011

	Adults (N = 87,421)		Children (N = 9,315)	
	Males (N = 34,987; 40%)	Females (N = 52,434; 60%)	Males (N =3,745; 40%)	Females (N = 5,570; 60%)
Acute Stress Reaction (ICD – 10 code: F43.0)	3740 (45%)	4580 (55%)	184 (38%)	301 (62%)
Posttraumatic Stress Disorder (ICD – 10 code: F43.1)	1263 (39%)	1938 (61%)	100 (45%)	121 (55%)
Adjustment Disorder (ICD – 10 code: F43.2)	22,300 (39%)	34206 (61%)	2469 (41%)	3520 (59%)
Other Reactions to Severe Stress (ICD – 10 code: F43.8)	471 (33%)	954 (67%)	191 (43%)	251 (57%)
Reaction to Severe Stress, unspecified (ICD –10 code: F43.9)	7213 (40%)	10756 (60%)	801 (37%)	1377 (63%)
Weighted Average from the Danish General Population, 1995-2011	49%	51%	51.3%	48.7%

We also found age of onset to be consistent across disorders. The highest proportion of diagnoses occurred in the late teens to early twenties with subsequent declines and a second slight increase in diagnoses beginning in the late 20s, followed by a gradual decrease as age increased.

IV. Conclusions

The results from Study I suggest that hospital-based stress disorders, particularly adjustment disorder, are frequently assigned diagnoses in Denmark. The incidence of the various stress disorders over our 15 year study period is not comparable to the focus of research to date on stress disorders, which has concentrated primarily on PTSD – found to be a relatively infrequently occurring stress disorder in this study. This work is a call to action for research on all of the stress disorders that may have a large impact on individuals and society, in addition to the study of PTSD. The incidence of

unspecified stress diagnoses, particularly unspecified reactions to severe stress, was the second highest we observed. This indicates that there are many patients who present to their providers for care, but do not meet the criteria outlined in the ICD –10 for acute stress reaction, PTSD or adjustment disorder. This finding is particularly interesting, given recent efforts on the part of the National Institute of Health in the United States to direct research towards examination of symptomatology and domains of functioning that span across diagnoses rather than strict adherence to diagnostic criteria (e.g., Research Domain Criteria or RDoC).[23] The frequency of this diagnosis in the current work supports the move away from examinations of current diagnostic criteria towards examinations of trans-diagnostic constructs that include various forms of distress and psychopathology following stress and trauma.

We examined both the overall incidence of hospital-based stress disorders in Denmark over a 15 year period from 1995 through 2011, and also the frequency of stress disorders annually during this same time. One of our most interesting findings was the sudden, drastic, and then maintained increase in stress disorders starting in 2007. Changes in prevalence, such as what is shown here, could be due to many factors including changes in diagnostic practices or an increase in disease duration (*i.e.,* how long people live with the disease or disorder), or in this case a mass trauma which effected a large number of people simultaneously (although we know of no such event in Denmark in this time period). This work is important because it highlights that previous cross-sectional studies of the prevalence of PTSD specifically should be interpreted with caution. The prevalence estimates reported in those studies may have just captured a temporary fluctuation in prevalence, or may report a prevalence estimate that was accurate at the time, but has since changed drastically. This is a critical contribution to the public health literature as it demonstrates that previously reported prevalence estimates are subject to large changes over time due to changes in disorder incidence or duration, and it highlights the limitations of cross-sectional analyses of disease frequency.

With regard to gender and age of onset distribution of stress disorders, we found consistent patterns for PTSD and other stress disorders. For all stress disorders both the gender distribution, with diagnoses occurring more frequently among women than men, and the age of onset distribution, with the first occurrence of most diagnoses most commonly among people in their late teens through their early 30s, were consistent with the existing PTSD literature.

Despite the many contributions this work has made to our understanding of the prevalence and incidence of hospital-based stress disorders over a long period of time and in an unselected (*i.e.,* including all patients who are treated) population, this work is not without limitations. Specifically, data were obtained from only the Psychiatric Central Research Register and stress diagnoses contained in the National Patients Register were not included. We made this decision based on the belief that diagnoses contained only in the National Patients Register may represent stress disorders with different causes and prognosis than cases contained in the Psychiatric register, since these patients were not severe enough or chose not to seek psychiatric treatment. Due to this restriction, the disease frequency presented in this dissertation represents hospital-based stress disorder cases for which psychiatric treatment specifically was sought and may be an underestimate of the true population prevalence and incidence. In addition, the Psychiatric Central Research Register includes only hospital-based diagnoses (i.e., patients who have presented to a physician for diagnosis) there may be people in the general population of Denmark who are living with these disorders without seeking treatment, which may lead to our estimates being an underestimate of the true disease frequency. However, in our validation sub-study of stress diagnoses, we found that only a small proportion of people without a stress diagnosis in the Psychiatric Central Research Register were given this diagnosis from a General Practitioner but never sought psychiatric or psychological help, indicating that the effect of this bias is likely minimal.[12] Also, our validation of the stress diagnoses contained in the Psychiatric Central Research Register showed that the validity was variable for the stress diagnoses, with the more chronic/severe diagnoses (e.g., PTSD) demonstrating better validity than the more transient and less chronic diagnoses (e.g., acute stress reaction).[12] Therefore the true prevalence and incidence of these diagnoses may vary due to misdiagnosis, particularly for the more transient and less severe disorders.

V. Mental health sequelae of stress disorders

I. Empirical evidence

It is well known that psychiatric comorbidity, particularly depression, commonly occurs with PTSD, although this association has mostly been documented in population-based cross-sectional studies or clinical studies with small sample sizes. Further, at the time our studies we conducted, the incidence of psychiatric comorbidity following stress disorders other than PTSD had not been documented. Therefore it was unknown if the findings regarding comorbidity following other stress disorders will be comparable. Research on the incidence of psychiatric comorbidity following stress disorders makes an important contribution to the literature, particularly with regard to providing information about provision of resources and targeting of tertiary prevention and intervention efforts.

Study II of this dissertation presents the cumulative incidence of hospital-based depression, anxiety disorders, substance abuse and dependence and drug abuse and dependence among adults with one the five ICD –10 hospital-based stress disorders.[24] This study used a cohort study design which included Danes with stress disorder diagnoses of adults from 1995 through 2011 and a matched comparison group (matched to those with stress disorders at a ratio of 5 to 1 on date of birth, sex and calendar time) with complete follow-up. All results are based on prospective data from the Psychiatric Central Research Register (see Appendix 1 for a description) and primary and secondary diagnoses were used. The findings from this study are presented with more detail in addition to a review of the relevant literature below.

II. Incidence of depression following stress diagnoses

PTSD and depression symptoms so commonly co-occur that this combined symptomatology has been described as potentially one overarching post-traumatic symptom response which encompasses both disorders.[25] This co-occurrence of PTSD and depression has been consistently demonstrated in the literature. Among 211 trauma survivors in a United States emergency room, symptoms of both PTSD and depression were found to be present within one month of a traumatic event, although 48 participants experienced depression prior to the traumatic event as well.[26] In a sample of psychiatric outpatients in the United States, 69% of patients with a primary PTSD diagnosis also had a secondary depression diagnosis.[27] In the National Comorbidity Survey in the United States, men with PTSD had 6.9

times the odds of having a major depressive episode than men without PTSD (95% confidence interval: 4.4, 11) and women with PTSD had 4.1 times the odds of a major depressive episode than women without PTSD (95% confidence interval: 3.1, 5.4).[2] The National Epidemiologic Survey on Alcohol and Related Conditions – a nationally representative study of adults aged 18 and older in the United States – found that those with PTSD had 2.7 times the odds of major depression than those without PTSD using cross-sectional data.[28] A smaller epidemiologic study of young adults aged 21 –30 in Michigan found that those with PTSD had 2.8 times the rate of major depression using retrospective data reported during a baseline interview (95% confidence interval: 1.6, 5.0).[29] However, in a prospective 5-year follow-up to this study those with new-onset PTSD had 11.7 times the rate of major depression (95% confidence interval: 4.0, 35).[30]

At the time our study was conducted, only one study (summarized above) had used longitudinal data to examine the association between PTSD and depression,[30] limiting what is known about the incidence of psychiatric comorbidity following stress disorders over an extended period of time and the knowledge base on tertiary prevention of psychiatric disorders that are common complications of stress disorders. Further, although comorbidity between depression and PTSD has been frequently examined, at the time these studies were conducted, it was unknown if the cumulative incidence of depression diagnoses following other stress disorders would be comparable to that of PTSD. To propel forward the knowledge base of these associations, we examined the cumulative incidence of hospital-based depression diagnoses (ICD-10 codes: F32, F33, F34.1) among persons diagnosed with a stress disorder over 15 years of follow-up from 1995 through 2011. The cumulative incidence of depression in a comparison group without stress disorders over the same time period was plotted as well. The results of this analysis are included in Study II.

Depression diagnoses were frequent following stress diagnoses (Figure 2). All five stress diagnoses had a similar cumulative incidence pattern for subsequent depression diagnoses, with a sharp increase in incidence in the year after diagnoses and then a more gradual increase in the next 14 years, with the incidence of depression at the end of 15 years of follow-up between 20% and 25%. As also seen in Figure 1, the incidence of depression diagnoses among the comparison group during this same time period had a shallower increase compared with what was observed among those with stress diagnoses, never reaching 5%.

III. Incidence of anxiety disorders following stress diagnoses

Another common PTSD comorbidity is anxiety disorders,[2] which at the time of these studies had been examined less frequently than depression comorbidity in similar cross-sectional or clinical research. It has been estimated that approximately 13% of people with PTSD also have generalized anxiety disorder diagnoses.[31] In a sample of psychiatric outpatients in the United States, 62% of those with PTSD diagnoses also had a concurrent anxiety disorder diagnosis.[27] In the National Comorbidity Survey in the United States, men with PTSD had 5.9 times the odds of generalized anxiety disorder than men without PTSD (95% confidence interval: 2.6, 13). Women with PTSD have 2.8 times the odds of generalized anxiety disorder than women without PTSD (95% confidence interval: 3.1, 5.4). Cross-sectional data from the National Epidemiologic Survey on Alcohol and Related Conditions in the United States (described above) yielded similar results – those with PTSD had 4.3 times the odds of having any anxiety disorder than those without PTSD (95% confidence interval: 3.8, 4.8).[28]

A limitation of the studies that preceded the work included in this dissertation is that no studies have examined new-onset anxiety disorder diagnoses following stress diagnoses over an extended period of time in a population-based sample. Further, at the time this work was done it was unknown if the cumulative incidence of anxiety disorders diagnoses following other stress disorders other than PTSD would be comparable to that of PTSD. Both of these issues have important implications for intervention and prevention efforts following stress disorder diagnoses. To address these limitations, we examined the cumulative incidence of hospital-based anxiety disorder diagnoses (ICD-10 codes: F40, F41) among persons diagnosed with a stress disorder over 15 years of follow-up from 1995 through 2011 and present these results within Study II. The cumulative incidence of anxiety disorders were plotted for a comparison group without stress disorders over the same time period as well.

Results of this study show that the cumulative incidence of anxiety disorders following stress disorder diagnoses increased steadily over the 15 year follow-up period, ultimately reaching an incidence of 10% - 15% (Figure 2). This pattern was consistent across all five ICD-10 stress diagnoses. Among the comparison group, the incidence of anxiety disorders remained lower than among those with stress diagnoses over the study period, never increasing beyond 5%.

IV. Incidence of substance abuse and dependence following stress diagnoses

Substance abuse and dependence, encompassing both alcohol abuse and dependence and drug abuse and dependence is a third widely accepted comorbidity of PTSD.[2] In substance misusing clinical samples in the United States PTSD is common, with 39% of patients meeting current criteria for a PTSD diagnosis and 52% of patients meeting criteria for a PTSD diagnosis at any point in their lifetime.[32] This has been shown in other countries as well; in patients with alcohol dependence in Poland those with PTSD were more likely to have abuse of and dependence on psychoactive substances than those without PTSD.[33] Epidemiological studies have shown a similar significant level of comorbidity. In the National Comorbidity Survey, men with PTSD had 2.1 times the odds of alcohol abuse or dependence (95% confidence interval: 1.1, 3.7) and 2.9 times the odds of drug abuse and dependence (95% confidence interval: 1.5, 5.8) than men without PTSD. Among women, the odds of alcohol abuse or dependence for those with PTSD was 2.5 (95% confidence interval: 1.8, 3.5) and the odds of drug abuse and dependence was 4.5 (95% confidence interval: 3.1, 6.4) compared to those without PTSD.[2] In the National Epidemiologic Survey on Alcohol and Related Drugs those with PTSD had 1.8 times the odds of any alcohol or drug use disorder than those without PTSD (95% confidence interval: 1.7, 2.1).[28]

Although the literature summarized above is compelling, at the time of this dissertation work, no study had examined PTSD and substance abuse comorbidity over an extended period of time in a population-based sample. Further, the cumulative incidence of substance abuse and dependence diagnoses following stress disorders other than PTSD is unknown. As part of Study II we examined the cumulative incidence of hospital-based alcohol abuse and dependence diagnoses (ICD –10 codes: F10.1, F10.2, F10.3) and drug abuse and dependence diagnoses (ICD –10 codes: F11.2, F12.2, F13.1, F13.2, F14.2) among persons diagnosed with a stress disorder over 15 years of follow-up from 1995 through 2011 to address these limitations. As with depression and anxiety disorder, we further plotted the cumulative incidence of alcohol and drug abuse and dependence diagnoses among a comparison group without stress disorders over the same time period.

The cumulative incidence of alcohol abuse/dependence and drug abuse/dependence from Study II is also presented in Figure 2. The pattern of cumulative incidence was consistent for all five ICD

–10 stress disorders for both sets of diagnoses. For alcohol abuse and dependence, incidence increased steadily over the study period, ultimately reaching between 10% and 15% at the end of 15 years. For drug abuse and dependence, the overall incidence was lower with a shallow increase over the study period, reaching a cumulative incidence around 5% at the end of the study period. For both sets of diagnoses the cumulative incidence among the comparison group was lower than among those with stress diagnoses, reaching only 1% - 3% at the end of the study period.

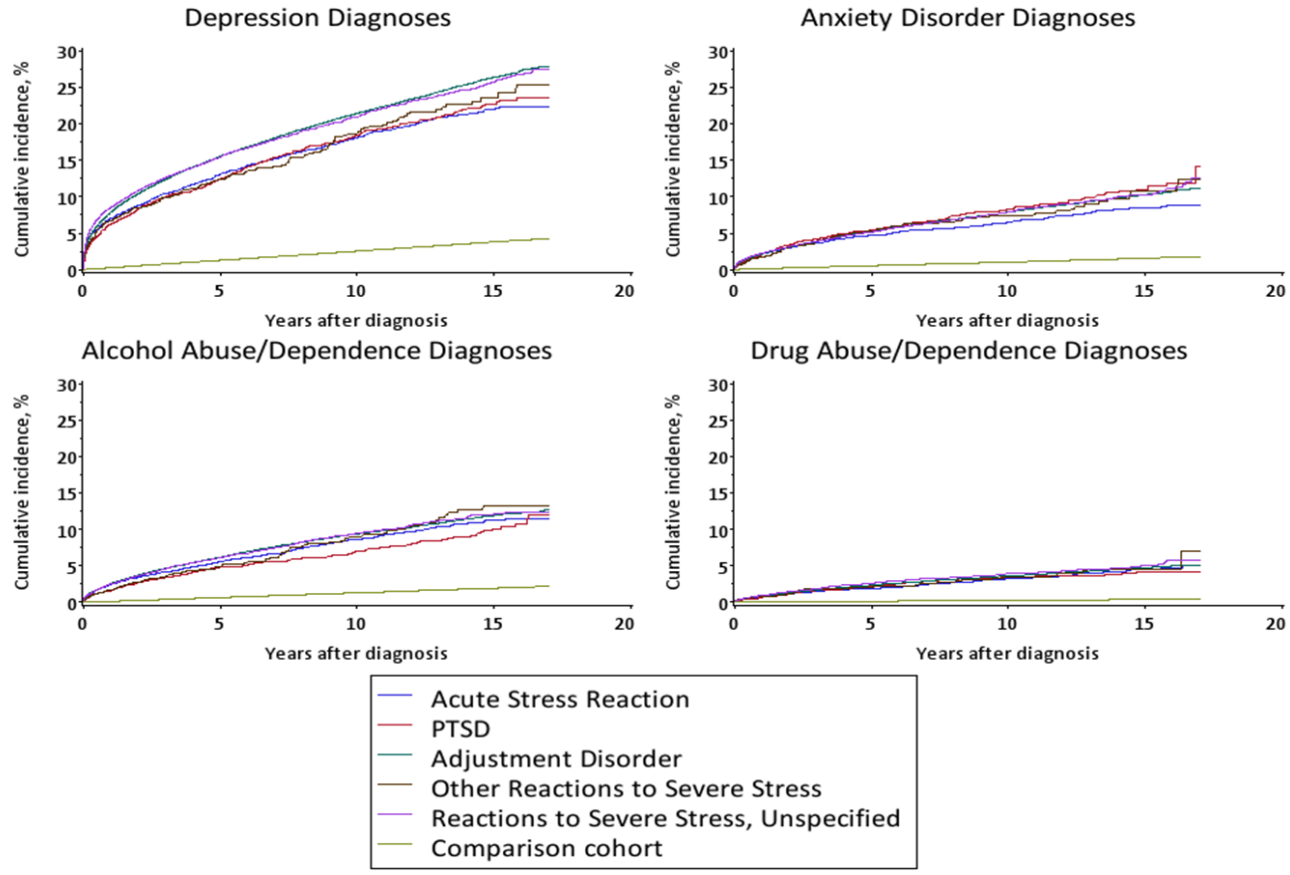

Figure 2. Cumulative Incidence Curves for Psychiatric Diagnoses following ICD-10 Stress Diagnoses, Denmark, 1995-2011

V. Conclusions

Results from Study II suggest that new-onset hospital-based depression, anxiety disorders and substance abuse/dependence are important complications following hospital-based stress diagnoses, which has critical implications for the understanding of the natural course of stress diagnoses and tertiary prevention efforts. The incidence of these disorders was higher among a cohort with stress diagnoses than among a comparison group without these diagnoses over the entire study period. As

has been noted in previous literature, depression was the most common psychiatric comorbidity of those examined across all five stress disorders, followed by anxiety disorders and then substance abuse/dependence. Drug abuse/dependence comorbidity had a lower incidence than alcohol abuse/dependence diagnoses.

The stress disorder psychiatric comorbidity literature has largely focused on PTSD to date, with very limited research conducted on the other stress disorders and most studies utilizing cross-sectional methodology. Our results are largely consistent with population-based cross-sectional studies of PTSD in the US in that depression, anxiety disorders, and substance abuse and dependence were frequently comorbid in our sample.[2] This study extends upon that work by providing evidence of this comorbidity over an extended time period of 15 years with complete follow-up and establishing a previously unexplored temporality between stress disorder diagnosis and new-onset psychiatric complications. This study is also the first to show that the pattern of psychiatric morbidity for stress disorders other than PTSD is similar to that of PTSD over an extended time period. Taken together, findings are important to the development of intervention and prevention efforts that target the sequelae of stress and trauma.

This study makes an important contribution to the literature as the first to document the cumulative incidence of psychiatric complications following all five hospital-based stress diagnoses over a longitudinal complete follow-up period; however it is not without limitations. Specifically, data were obtained from only the Psychiatric Central Research Register and stress diagnoses contained in the National Patients Register were not included. It is unknown how comorbidity patterns would differ if these less severe cases were included. Also, the diagnoses included in the Psychiatric Central Research Register are all hospital-based, therefore it is possible that there are persons in our sample who are incorrectly classified according to psychiatric diagnoses because they have not sought medical care for one of the examined psychiatric disorders.

VI. Suicide as an outcome of trauma and stress disorders

I. Empirical evidence

At the time this dissertation work was conducted research on death from suicide as an outcome of trauma or stress disorders was extremely limited. Suicide is a relatively rare event, and large population samples with complete follow-up are needed to generate valid and precise estimates of associations between risk factors and suicide outcomes. Although associations between trauma, stress disorders and suicidal behavior (e.g., suicide attempts) have been well-documented in the literature, documentation of associations with suicide death is not. The distinction between studies of suicidal behavior and suicide death is an important one because these suicide events are more distinct than one may realize. For example, only 15% of people who make a suicide attempt go on to die by suicide.[34] Therefore, research on the associations between trauma, stress disorders and death from suicide utilizing large general population-based samples make a critical and unique contribution to the existing literature.

Multiple studies included in this dissertation (Studies II – VI) present associations between sexual victimization, hospital-based stress disorder diagnoses and death from suicide among Danish adults. All results are based on prospective data with complete follow-up from the Danish national medical and social registers. Study II reports the results from a cohort study of all Danes at any age who received an ICD –10 hospital-based stress diagnosis between 1995 and 2011, and a comparison cohort (matched at a ratio of 5 to 1 on date of birth, sex and calendar time) of Danes who had not received a stress diagnosis at the time of their matched stress cohort members diagnosis. Data on death from suicide for this study were obtained in two ways. First, an ICD –10 code of X60-X84 in the Cause-of-Death register. As a second method of outcome ascertainment for this study, we used a record of suicide attempt in the Danish National Patient Registry with a death recorded in the Civil Registration System in the subsequent seven days.[35,36] Data on hospital-based stress disorders and psychiatric comorbidity diagnoses were obtained from the Psychiatric Central Research Register and both primary and secondary diagnoses were used. Confounders were selected for adjustment based on a review of the previous literature.

Studies III –VI present the results of a case-control study of suicide death in the base population of Denmark aged 15 – 90. As stated earlier, a case-control design was chosen for this study because the

goal was to examine a variety of predictors of suicide death across demographic, social, psychiatric and physical health domains. The use of a case-control design allowed for the examination of predictors from all of these domains while only sampling patients once based on their suicide case or matched control status. Cases had died by suicide between January 1, 1994 and December 3, 2006 (n = 9612). Controls were matched (up to 30 per case) on date of birth, sex and calendar time (n = 199,306). Data on suicide for this study were taken only from the Danish Register of Causes of Death (ICD-10 codes: X60-X84), and data on hospital-based stress diagnoses and psychiatric comorbidity diagnoses were obtained from the Psychiatric Central Research Register; only primary diagnoses were used (see Appendix 1 for a description of both registers). Confounders were selected for adjustment using change-in-estimate methods (which assess the impact of each potential confounder on the association of interest and then retain for adjustment all confounders that change this estimate by over 10%).[37]

We additionally examined interaction between hospital-based stress disorder diagnoses and psychiatric comorbidity in predicting suicide in these studies by calculating the relative excess risk due to interdependence (RERI).[38] RERI is a conceptualization of interaction in which an exposure and a third variable, or modifier, act at the same time to confer a greater rate (in the case of synergy) or lower rate (in the case of antagonism) of the outcome than would be expected based on the additive independent effects of the exposure and the modifier on the outcome. In a cohort study, in which actual rates can be calculated, this departure is referred to as an interaction contrast (IC).[38] The IC quantifies the actual excess or decreased rate of the outcome that occurs when both the exposure and modifier are present at the same time. Rates cannot be estimated directly in a case-control study; however the RERI can be calculated. This calculation is done by calculating the odds of the outcome in three groups: (a) the group who has experienced the exposure and modifier, (b) the group who has experienced the exposure alone, and (c) the group who has experienced the modifier alone. The comparison group for these calculations is those with neither the exposure nor the modifier. The following formula:

$$IC/R(E\text{-}M\text{-}) = OR(E+M+) - [OR(E+M-) - 1] - [OR(E-M+) - 1] - 1$$

is then used to calculate the RERI where E is the primary exposure and M is the modifier. The RERI provides an estimate of the direction and magnitude of the IC. In other words, a positive RERI indicates synergism between the exposure and the modifier and a greater rate of the outcome among those who are exposed to both compared with what is expected from the addition of the independent

effects. A negative RERI indicates antagonism between the exposure and the modifier and a decreased rate of the outcome among those exposed to both compared with what is expected from the addition of the independent effects. These interaction analyses can be thought of as a form of subgroup analyses, in which it is determined if the effect in the subgroup with both the exposure and modifier can be explained by the effects in the group with just the exposure, just the modifier and the group with neither exposure.

Results from these studies are presented below within the context of the relevant literature.

II. Sexual victimization

Sexual assault is associated with suicidal behavior including suicidal ideation and suicide attempt. [39,40 41] Given the low base-rates of sexual victimization and suicidal behavior, all research in this area at the time of this dissertation work had been population-based but cross-sectional. In an analysis of data from one site of the Epidemiological Catchment Area study at Duke University in the United States, the odds of suicide attempt among those who experienced sexual assault was 6.4 (95% confidence interval: 1.8, 22.3) even after adjustment for demographic and psychiatric confounders.[39] In a population-based study in Virginia, women aged 18 and older who experienced sexual assault had 4.5 times the odds of experiencing suicidal ideation than women who had not been sexually assaulted, after adjusting for relevant confounders (95% confidence interval: 3.2, 6.2).[40] A study based on data from the National Comorbidity Survey found that sexual assault history was associated with both suicidal ideation and suicide attempt in women age 15 to 54.[41]

Despite evidence of an association between sexual victimization and suicidal ideation or attempts, prior to our work no studies had examined the association between sexual victimization and death from suicide in a population-based sample with longitudinal data. Given that suicidal behavior and death from suicide are not entirely synonymous events, and that there are known risk factor differences between those who attempt suicide and those who die by suicide (e.g., males are more likely to complete suicide than females, but females are more likely to attempt suicide than males),[42] a study of sexual victimization and suicide death as an independent outcome fills an important gap in the existing literature.

In Study III, we present work that addresses this limitation in a study of the association between sexual victimization for which the perpetrator was convicted and death from suicide among Danish women from 2001 – 2006. This study used a case-control design as described above, within the base population of the overall female population of Denmark aged 15 to 54 years. Cases had died by suicide between 2001 and 2006 (n = 476) and up to 30 controls per case were matched based on date of birth and calendar time (n = 12,010). Data on sexual victimization were obtained from a registry of crimes reported to the Danish police and data on hospital-based psychiatric confounders were obtained from the Psychiatric Central Research Register. Suicide data were obtained from the Danish Register of Causes of Death (ICD – 10 codes: X60-X84). See Appendix 1 for a description of these registries. Among the suicide cases, seven had experienced sexual victimization using this definition (1.5%). The comparable number among the control participants was five (0.04%).

We found that those who experienced sexual victimization were 30 times more likely to die by suicide than those who did not have this experience in analyses that accounted only for the control to case matching (95% confidence interval: 9.4, 94). After adjusting for psychiatric confounders including depression diagnoses, anxiety disorder diagnoses and substance abuse and dependence diagnoses we found that those who experienced sexual victimization were 14 times more likely to die by suicide than those who had not (95% confidence interval: 3.4, 59).

This work represents the first study of the association between sexual victimization and death from suicide using prospective population-based data with complete follow-up. We found a strong association among Danish females aged 15 –54 even after adjustment for relevant confounders. In most Westernized countries, varying services are offered to victims of sexual assault following an attack. This study calls for particular assessment of potential for suicide in this population, regardless of psychiatric diagnostic status. Additional implications and limitations of this work are presented in the overall Conclusions section of this chapter.

III. Acute stress reaction

Prior to the studies presented herein, no study had examined the association between acute stress reaction diagnosis and suicide or suicidal behavior, despite evidence of associations between other ICD-10 stress diagnoses (i.e. PTSD and adjustment disorders) and suicide. In Studies II and IV, we

address this gap in the literature by presenting two studies in which the associations between hospital-based acute stress reaction and suicide were examined across two different time periods using two forms of study methodology.

Using the cohort study design methodology described above (Study II), we found a strong association between hospital-based acute stress reaction and death from suicide. In unadjusted analyses, those with acute stress reaction had 26 times the rate of suicide than those without this diagnosis (95% confidence interval: 14, 49). After adjusting for baseline hospital-based psychiatric confounders including depression diagnoses, anxiety diagnoses and substance abuse and dependence diagnoses, we found only a minimal attenuation in the acute stress reaction and suicide association. Those with acute stress reaction had 24 times the rate of suicide death than those without this diagnosis (95% confidence interval: 10, 53).

We also examined this association in a different time period using a case-control study design of all suicide deaths in Denmark from 1994 through 2006 (described above). We found that 99 of 9612 suicide cases had been diagnosed with hospital-based acute stress reaction, while 165 of 199,306 controls had received the diagnosis. In analyses adjusting for only the matched factors, we found that those with acute stress reaction had 14 times the rate of suicide than those without this diagnosis (95% confidence interval: 11, 18). After adjusting for hospital-based depression history and marital status, we found an association of 10 (95% confidence interval: 7.7, 14). Using these case-control data we additionally examined the interaction between adjustment disorder and depression and acute stress reaction and substance abuse in predicting suicide by calculated the RERI. Depression and substance abuse were chosen for examination because in stratified preliminary analyses these displayed the strongest effect modification. Synergy was in both analyses such that among those with acute stress reaction and depression the suicide rate was 15 times greater than the rate among those with neither acute stress reaction nor depression. For those with acute stress reaction and substance abuse the suicide rate was 16 times greater than among those with neither disorder.

This study is the first examination of these associations in the literature to date, so interpretation within the context of the prior literature is not possible. However, the knowledge that hospital-based acute stress reaction diagnoses have strong associations with suicide, particularly in conjunction with depression and substance abuse diagnoses, is a critical first step in this line of research

that will be built upon for many research generations to come. Further, it is important for clinicians who treat patients in post-trauma settings to know that even patients with short-term, transient negative adaptations to traumatic experiences who receive acute stress reaction diagnoses have an increased risk of suicide death. Additional implications and limitations of this work are presented in the overall Conclusions section of this chapter.

IV. PTSD

The vast majority of research on suicide outcomes following PTSD diagnoses has focused on suicidal ideation and suicide attempts, however much of this research has been population-based in contrast to the work done to date on the other stress disorders. In data from the National Comorbidity Survey, PTSD was associated with suicidal ideation and suicide attempts with odds ratios of 2.8 (95% confidence interval: 2.0, 3.8) and 2.7 (95% confidence interval: 1.8, 3.9), respectively.[43] In one wave of the National Epidemiologic Survey on Alcohol and Related Conditions in the United States, PTSD was associated with an 2.7 times increase in the odds of suicide attempt in adjusted analyses (95% confidence interval: 2.2, 3.2).[44] In a cross-sectional study of the Canadian general population, those with PTSD had 2.4 times the odds of suicide attempts compared to those without PTSD (95% confidence interval: 1.3, 4.3).[45] The same has been shown in a multi-country cross-sectional survey study in Europe, the European Study on the Epidemiology of Mental Disorders (ESEMED).[46] This study found that people with PTSD have 1.8 times the odds of lifetime suicidal ideation (95% confidence interval: 1.4, 2.4) and 1.9 times the odds of lifetime suicide attempts (95% confidence interval: 1.2, 2.9) compared to people without PTSD.[46]

Given the lack of research on PTSD and death from suicide, and the strong evidence of an association between PTSD and suicidal behavior, we examined this association using longitudinal data in a population-based cohort with complete follow-up. In Studies II and V, we add to this literature by presenting two studies in which the association between hospital-based PTSD and suicide were examined across two different time periods using two different study designs. Study II presents the association between PTSD and death from suicide. Study V includes the results of a case-control study examining PTSD as a predictor of suicide death. The methodology for both studies is described in detail above.

Within our cohort study of stress disorders (Study II), we found an unadjusted association of 19 for hospital-based PTSD and death from suicide (95% confidence interval: 7.6, 46). After adjustment for

hospital-based depression, anxiety and substance abuse diagnoses the association decreased modestly – those with PTSD had 13 times the rate of suicide death than those without PTSD diagnoses (95% confidence interval: 4.3, 42).

Study V reports the results of our case-control study of PTSD and suicide. Of 9,612 suicide cases, 38 (0.40%) had received a hospital-based PTSD diagnosis compared with 95 out of 199,306 controls (0.05%). Conditioning only on the case-control matched factors, the association between PTSD and suicide was 9.8 (95% confidence interval: 6.7, 15). After adjusting for the identified confounders of hospital-based depression diagnosis , marital status and income, those with PTSD had 5.3 times the rate of suicide than those without PTSD (95% confidence interval: 3.4, 8.1). In Study V we further examined the interaction between PTSD and depression diagnoses in predicting suicide by calculating the RERI. Depression was chosen for examination because in stratified preliminary analyses it displayed the strongest effect modification of this association. We found a synergistic interaction, such that those with both PTSD and depression had 10 times the rate of suicide compared with those who had neither PTSD nor depression.

These studies contribute to an existing literature on PTSD and suicidal behavior, and expand on this literature by examining death from suicide in a population-based sample with complete follow-up. At the time this study was conducted no study had examined the association between PTSD and suicide in a prospective population-based sample. We contributed to the existing literature by showing that hospital-based PTSD is strongly associated with death from suicide specifically over a long period of follow-up. This is a critical contribution to the literature as only 15% people who make a suicide attempt and do not die go on to eventually die by suicide.[47] Persons who attempt suicide and persons who die from suicide are distinct populations and research that contributes to our understanding of each outcome as a separate phenomenon is critical. This research highlights the importance of monitoring the possibility of suicide among patients with PTSD, and also with PTSD and comorbid depression, regardless of previous suicidal behavior. Additional implications and limitations of this work are presented in the overall Conclusions section of this chapter.

V. Adjustment disorder

Research conducted among clinical samples provides evidence that suicidal behavior is common among patients with adjustment disorder. Of 119 patients hospitalized in a psychiatric department in the United States with an adjustment disorder diagnosis, 60% had a history of suicide attempts and

almost 100% were suicidal while in the hospital.[48] In a chart-review study of 204 psychiatric emergency room patients, those who were admitted with an adjustment disorder diagnosis had a higher endorsement of suicidality as compared to those with other admission diagnoses.[49] These associations have been observed in other countries as well. In a study of psychiatric emergency room patients in Switzerland, those seeking care following a suicide attempt were more likely to have had an adjustment disorder diagnosis (48%) than those seeking care for other reasons (22%).[50] Among 370 psychiatric patients in Dublin, the proportion of adjustment disorder patients endorsing suicidal ideation or attempt (20%) was similar to the proportion of patients with depression – a widely held risk factor for suicidal behavior - who made this endorsement (25%).

While there is evidence of an association between adjustment disorders and suicidal ideation or suicide attempts, the association between adjustment disorders and death from suicide remains unexamined. Further, the research to date on the association between adjustment disorders and suicidal behaviors has largely been derived from small clinical samples – the associations in a population-based sample are unknown. Thus the goal of this line of research was to examine hospital-based adjustment disorder as a predictor of death from suicide in population-based samples using longitudinal data with complete follow-up. The results of this work are presented in Studies II and VI. Study II presents the association between adjustment disorder and death from suicide. Study V includes the results of a case-control study examining adjustment disorder as a predictor of suicide death. The methodology for both studies was described in detail above.

In Study II (cohort study; described above), we found a large association between hospital-based adjustment disorder and death from suicide. The crude association – unadjusted for any confounders – was 18 (95% confidence interval: 15, 21). After adjusting for baseline psychiatric confounders including hospital-based depression diagnoses, anxiety diagnoses and substance abuse and dependence diagnoses, we found a modest decrease in the observed association. Those with adjustment disorder had 12 times the rate of suicide compared to those without this diagnosis (95% confidence interval: 9.8, 15).

Within the case-control study described above (Study VI), 728 of 9,612 suicide cases (7.6%) had received a hospital-based adjustment disorder diagnosis, while among the 199,306 controls 1040 (0.52%) had received the diagnosis. The regression analysis revealed an association of 19 (95%

confidence interval: 17, 21) adjusting only for the case-control matched factors. After additional adjustment for depression diagnoses, marital status and income those with adjustment disorder diagnoses had 12 times the rate of suicide than those without these diagnoses (95% confidence interval: 11, 14).

At the time this study was conducted, only the association between adjustment disorder and suicidal behavior had been examined in small convenience samples. Of all the stress disorder diagnoses, adjustment disorder is the most commonly diagnosed.[14] Therefore, an understanding of deleterious long-term outcomes among people with this diagnosis has critical clinical and public health importance. The study of suicide death rather than suicidal behavior is a particularly important contribution to this literature as persons who engage in suicidal behavior and persons who die by suicide are distinct populations.[47] This study was the first to examine the association between hospital-based adjustment disorder and death from suicide in a large, prospective population-based sample with complete follow-up and we found evidence of a strong association across two study designs. As with PTSD, our study highlights the importance of monitoring the possibility of suicide among these patients regardless of psychiatric comorbidity and previous suicidal behavior. Additional implications and limitations of this work are presented in the overall Conclusions section of this chapter.

VI. Unspecified stress diagnoses

Similarly to acute stress reaction, no study has examined the association between unspecified reaction to severe stress and suicide or suicidal behavior. Hence the goal of this study was to report on the association between the two ICD-10 unspecified reaction to severe stress diagnoses (other reactions to severe stress and reactions to severe stress, unspecified) and death from suicide. Study II (cohort study described above) presents the association between the hospital-based unspecified stress diagnoses and death from suicide.

Table 3 displays the associations for both diagnoses with death from suicide. While adjusting for important hospital-based psychiatric confounders (including depression, anxiety and substance abuse and dependence diagnoses) we found that those with other reactions to severe stress had 29 times the rate of suicide and those with reactions to severe stress unspecified had 19 times the rate of suicide compared to those without these diagnoses.

Table 3. Associations between unspecified stress disorders and death from suicide, Denmark, 1995 – 2011

	Unadjusted rate ratio	95% CI	Adjusted rate ratio	95% CI
Other reactions to severe stress	25	5.4, 112	29	3.5, 244
Reactions to severe stress, unspecified	26	16, 41	19	12, 31

This work represents the first examinations of these associations, so interpretation within the context of the prior literature is not possible. As with acute stress reaction, however, the knowledge that these unspecified diagnoses have strong associations with suicide, even when controlling for comorbid psychiatric diagnosis, was a critical first step in this line of research. These unspecified hospital-based stress disorders might be expected by clinicians or researchers to have weaker associations with death from suicide as they likely represent sub-syndromal stress disorders. Our results show that patients with these diagnoses potentially experience a similar deleterious course to patients who meet symptom criteria for what may be perceived to be the more severe stress diagnoses (e.g., PTSD) and the knowledge that they warrant their own research and clinical attention is critical to mitigating the long-term public health impact of stress and trauma. This is also consistent with the initiative on the part of the National Institute of Health in the United States to move towards examinations of symptomatology (including sub-syndromal disorders) and away from strict examinations of diagnostic criteria-based disorders.[23] Additional implications and limitations of this work are presented in the overall Conclusions section of this chapter.

VII. Conclusions

At the time these studies were conducted, they represented the first population-based longitudinal studies of hospital-based stress disorders and death from suicide with complete follow-up. Taken together, the work summarized in this section provides a comprehensive overview of the strong associations between death from suicide and sexual victimization or hospital-based stress disorders in a population-based sample with complete longitudinal follow-up using two different study designs, which

bolsters confidence in the findings. Previous research has focused primarily on suicidal behavior as outcomes of trauma and stress disorders. The results of this dissertation suggest that death from suicide is also a significant negative consequence of sexual victimization and stress disorder diagnoses. This is an important contribution to the literature in that it will inform the development of intervention and prevention efforts that focus on the significant proportion of people who die by suicide without ever having made a previous suicide attempt.[34] Further, we found strong associations with death from suicide across all stress disorders – this is particularly important for the two catch-all diagnoses that had been previously unexamined: other reactions to severe stress and reactions to severe stress, unspecified. These diagnoses likely include patients with sub-syndromal stress disorders who may not be followed as closely for possible suicide as patients who meet full disorder criteria. This work serves to bring awareness to the clinicians and researchers alike regarding the potential for suicide among patients who may be considered less severe.

Although our study is the first population-based study of sexual victimization and suicide and a critical step for this field of research, there are limitations that should be kept in mind when interpreting our results. First, due to the nature of the data that were available to us, our definition of sexual victimization included only crimes for which a perpetrator was convicted, which no doubt excludes a significant proportion of events in which the victim did not come forward or in which there was no criminal conviction. In addition, sexual victimization in general is a notoriously underreported event. The result of this would be that our "unexposed" group (i.e., women who did not experience sexual victimization) likely included many women who had in fact had this experience. If this bias were non-differential with respect to suicide outcomes we would expect that our observed estimates represent a bias towards the null compared with an even stronger true association. However, it is also possible that assaults reported to the police may differ from unreported assaults in significant ways that could be associated with suicide risk (e.g., familiarity with the perpetrator). Therefore, it is possible that the association between a broader definition of sexual victimization and suicide could be stronger or weaker than what we have reported.

Regarding the stress diagnoses and suicide studies, research on the validity of the hospital-based stress diagnoses indicates that validity is very good for the more stringent diagnoses (e.g., PTSD) but less so for the more transient or less severe diagnoses (e.g., acute stress reaction). [12] Therefore it is possible that misclassification of true cases of stress disorders occurred due to misdiagnosis, which

could result in observed associations that are biased compared to the true underlying associations. Also, stress disorder and psychiatric confounder data were obtained from only the Psychiatric Central Research Register and data from the National Patients Register, which likely includes less severe psychiatric patients, were not included. It is unknown how associations with death from suicide would differ if these less severe cases of stress disorders or confounders were included. Also, all included diagnoses were hospital-based. It is possible that some people in the sample have psychiatric disorders but do not seek care. These people would be coded as not having a psychiatric diagnosis in our data and thus, there is potential for misclassification of stress disorders and residual confounding of psychiatric disorders in our association. However, given the strength of the observed associations this stress disorder misclassification or residual confounding is unlikely to explain our findings in entirety. In addition, with regard to confounder adjustment, we were unable to adjust for potentially important behavioral confounders (e.g., alcohol use) that are not included in the Danish registry data and may have had an impact on our associations of interest.

Interestingly, for acute stress reaction and PTSD we found associations with death from suicide that were different in magnitude in our case-control and cohort studies, with the results of the cohort study generally displaying stronger associations. There are a few differences in the study design and execution that may explain these disparate findings. In Study II (the cohort study), we used two methods for ascertaining death from suicide (e.g., suicide death data from the Cause-of-Death register and suicide attempt data from the National Patients Register combined with a death in the following seven days from the Civil Registration System), while in the case-control studies (Studies IV-VI) only data from the Cause-of-Death register was used, perhaps resulting in an under-ascertainment of suicide cases in the latter studies. Also, in Study II, we included both primary and secondary hospital-based diagnoses of stress disorders and psychiatric confounders, whereas in Studies IV-VI only primary psychiatric diagnoses were included, potentially resulting in an under-ascertainment of exposure or confounder data. Regarding confounders, in Study II we adjusted for all relevant confounders identified from a literature review, whereas in Studies IV-VI we used a model building strategy for confounder selection, resulting in slightly different sets of confounders used for adjustment across studies. This may have also had an impact on the magnitude of associations that were ultimately reported. Finally, Study II included a longer study period than Studies IV-VI, and we know the time period of Study II included a drastic increase in the number of stress disorders diagnoses in 2007 and beyond (see Study I),[14] which was not captured in Studies IV-VI with a study period that ended in 2006. Therefore Studies IV-VI may include an

under-ascertainment of stress disorder patients, if this 2007 and beyond increase represents a change in diagnosing patterns in which patients who were previously misdiagnosed with something other than a stress disorder were then accurately re-diagnosed. For adjustment disorder, the strength of associations with suicide death was consistent across the two studies potentially indicating that these issues did not have as big of an effect on the subgroup with that diagnosis. Despite these limitations, the work presented in this chapter had a strong and meaningful impact on the literature regarding death from suicide following trauma and stress disorders. For all disorders, our work was the first to examine these associations using high quality, prospective population-based data with complete follow-up that is necessary to study risk factors for rare, but incredibly deleterious events, such as suicide.

VII. Physical health sequelae of stress disorders

I. Empirical evidence

Stress disorders, PTSD in particular, have long has been implicated in the etiology of various somatic disorders.[6,51] Some somatic conditions, such as cancer, have been the subject of discussion in scientific publications during the past seven decades and even longer in historical literature.[52,53,54] Despite this, and plausible biological mechanisms for this association, research findings had been conflicting with some studies providing evidence of an association and other studies not. The same is true for gastrointestinal (GI) disorders. Even though GI disorders have been examined as a possible outcome of PTSD for over two decades,[55] evidence regarding the association has been mixed. Conversely, a stronger literature base for an association between PTSD and cardiovascular disease (CVD) has developed in recent years. PTSD has been consistently shown to be associated with CVD in predominantly male samples of United States Veterans[56-59] and in the general population.[60,61] However, this association has not been examined for other stress disorders and it is unknown if findings for PTSD would be consistent for adjustment disorder, which is more frequently diagnosed.[14] Further, at the time of these dissertation studies, studies of US veterans had documented an association between PTSD and all-cause mortality,[62-64] although one study found that this association was reduced to null when accounting for relevant confounders.[64] No study had examined all-cause mortality following other stress disorder diagnoses in a general population sample.

Multiple studies included in this dissertation (Studies VII-IX) present associations between hospital-based stress disorders and hospital-based somatic diagnoses including cancer, cardiovascular disease events and gastrointestinal disorders among Danish adults. All studies are based on prospective data from the Danish national medical and social registers and include complete follow-up. The stress disorder diagnosed cohorts in these studies included adults who received an ICD-10 hospital-based stress diagnosis between 1995 and 2011 in the Danish Psychiatric Central Research Register as well as all adults who received one of these diagnoses during this time period that was recorded only in the National Registry of Patients (see Appendix 1 for a description). Both primary and secondary diagnoses were used. For each somatic outcome, we calculated the expected number of incident cases after stress disorder diagnoses using national incidence rates according to sex, 5-year age groups, and 5-year calendar periods. Multiplying person-years of follow-up by incidence rates yielded the number of

somatic outcome cases that would be expected if persons with stress disorder diagnoses had the same risk of the somatic outcome as the general population.[65] We calculated standardized incidence ratios (SIRs) to measure the associations as the ratio of the observed to expected cancer cases. Confidence intervals (CIs) were calculated assuming that the observed number of cases for a specific somatic outcome follows a Poisson distribution. Exact confidence limits were calculated when there were fewer than 10 observed somatic outcome cases; otherwise Byar's approximation was used. Our presentation of results is limited to somatic outcomes for which there were 5 or more observed incident cases among persons diagnosed with a stress disorder during the study period. Stratified analyses were conducted to examine the impact of potentially important confounders and modifiers on associations of interest. The association between stress disorder diagnoses and all-cause mortality, as examined in Study II, is also presented. Results from these studies are presented below within the context of the relevant literature.

II. PTSD and cancer risk

As stated above, at the time of this dissertation work, cancer as a consequence of PTSD had been the subject of discussion in scientific publications during the past seven decades and even longer in historical literature.[52,53,54] The literature on this association has been conflicting, however, with some studies providing evidence of an association and others not, and many studies focusing on specific stressors rather than stress disorder diagnoses. Early small studies reported an association of stressful life events with breast cancer and gastric cancer. [66-69] In the Finnish Twin Study, acute stress events were associated with breast cancer.[70] In Denmark smoking-related malignancies among mothers to be weakly associated with loss of a child.[71] However, other studies found no evidence of an association,[54] including two population based studies of stress and cancer.[72-74] Most recently, a population-based study using registry data from Western Australia found no increased incidence of any type of cancer among persons diagnosed with stress or anxiety disorders, compared with the general population.[75] The focus on specific stressful events or selected cancer types in the literature may explain the inconsistent findings.

This study used the cohort design methodology described above to fill this important gap in the literature by examining the incidence of various forms of hospital-based cancer diagnoses in a nationwide cohort of patients with a prior hospital-based diagnosis of PTSD, which can serve as a marker for many experiences of extreme stress. Data on cancer outcomes were obtained from The Danish

Cancer Registry (see Appendix 1 for a description). Validation studies have found that 95% to 98% of records contained in this registry are valid.[76] Primary and secondary cancer diagnoses were included.

We identified 4,131 adults with a diagnosis of PTSD who had not had a cancer diagnosis one year after their PTSD diagnosis (60% female). Among PTSD patients, 159 cases of cancer were diagnosed one or more years after the PTSD diagnosis. An overall null association was found for PTSD and cancer diagnoses (SIR = 1.0, 95% CI = 0.88, 1.2). Near null associations (shown in Tables 1 and 2) were also found for PTSD and all immune-related cancers (SIR = 1.0, 95% CI = 0.77, 1.4); non-melanoma skin cancer (SIR = 1.2, 95% CI = 0.88, 1.6); all smoking and alcohol-related cancers (SIR = 0.99, 95% CI = 0.72, 1.3); lung, bronchial and tracheal cancers (SIR = 1.3, 95% CI = 0.73, 2.0); colon cancer including cancer of the rectosigmoid junction (SIR = 0.59, 95% CI = 0.19, 1.4); cancer at other common sites (SIR = 1.1, 95% CI = 0.87, 1.5); breast cancer (SIR = 1.2, 95% CI = 0.82, 1.7); and uterine cancer (SIR = 1.4, 95% CI = 0.46, 3.3). Stratified analyses revealed few differences in the pattern of these null results across subgroups.

This study was the largest to date to examine PTSD as a risk factor for a number of cancer outcomes in a unselected sample of patients who received PTSD treatment with complete follow-up. Observed associations between PTSD and cancer would have had a major public health impact, given the ubiquity of PTSD and cancer and their costs to individuals and society.[6,77] However, our results showed limited evidence of associations, thus making a major contribution to the literature in this area. This is consistent with some other population-based studies that reported that stressful life events are generally not associated with cancer incidence. In addition to corroborating results of other studies, our large population sample enabled us to conduct important stratified analyses, which also showed no evidence of specific potential associations among select subsamples. Additional conclusions and limitations are presented in the Conclusions section at the end of this chapter.

III. Stress disorders and cardiovascular disease events

In contrast to cancer outcomes among patients with PTSD, an association between PTSD and CVD has been well established in the literature. US veterans with PTSD have a 30–50% increased rate of incident myocardial infarction (MI) than veterans without PTSD.[56,57,59] Among twin Veterans, persons with PTSD have 2.2 the odds of CVD than persons without PTSD.[58] In the general population, people diagnosed with PTSD have 3.4 times the odds of heart failure than those without a PTSD diagnosis.[60]

Following the September 11, 2001 attacks, persons who developed PTSD had 1.7 times the risk of CVD than those without PTSD.[61]

Despite evidence of an association between PTSD and CVD, at the time that this dissertation work was conducted, no studies had examined associations between a stress disorder diagnosis other than PTSD and CVD. Adjustment disorder is particularly important – given the frequency of this diagnosis and CVD, a study that documents a meaningful association between these two diagnoses has critical public health impact.[14] At the time of this dissertation, the existing literature was also limited in assessing whether the association between stress disorders and CVD differs by gender.[78] Gender-based examinations of risk factors for CVD are important; CVD is less common at older ages and develops later among women than men but CVD prognosis among women is comparable to or worse than that of men once diagnosed.[79,80] No study had examined gender differences in the association between adjustment disorders and CVD at the time this dissertation work was conducted.

The goal of this study was to address the above gaps in the literature by examining hospital-based diagnoses of PTSD and adjustment disorders as risk factors for four hospital-based diagnoses of CVD events (*i.e.,* MI, stroke, ischemic stroke, and venous thromboembolism) using the cohort study methodology described above. We further examined gender differences in associations. Data on CVD events were obtained from the National Registry of Patients (see Appendix 1 for a description) and primary and secondary diagnoses were included. Validation studies of acute MI, stroke, and venous thromboembolism diagnoses contained in this register have shown moderate to high positive predictive value when compared with independent re-assessment of medical charts;[81-84] however, variability in the validity of venous thromboembolism diagnoses has been noted, with poorer validity of diagnoses received in emergency room settings.[84]

We identified 4,724 adults with a diagnosis of PTSD who had never been diagnosed with a CVD event (60% female) before the start of the study period. Among PTSD patients, 54 cases of MI, 95 cases of stroke, 50 cases of ischemic stroke and 78 cases of VTE were diagnosed during the follow-up period. We found moderate associations ranging from an SIR of 1.5 (95% CI: 1.1, 1.9) for MI, to 2.1 (95% CI: 1.7, 2.7) for VTE. Associations were generally consistent by sex, with the exception of ischemic stroke, which had a stronger association with PTSD among males than females. Stratified analyses further revealed

that associations between PTSD and all four CVD events exist in the absence of depression and alcohol abuse and dependence diagnoses.

We identified 64,855 adults with a diagnosis of adjustment disorder who had never been diagnosed with a CVD event (62% female) prior to the study period. Among adjustment disorder patients, 803 cases of MI, 1483 cases of stroke, 712 cases of ischemic stroke and 1006 cases of VTE were diagnosed during the follow-up period. Similar to our results for PTSD, we found moderate associations for adjustment disorder and the four CVD events ranging from an SIR of 1.5 (95% CI: 1.4, 1.6) for MI to 1.9 (95% CI: 1.8, 2.0) for VTE. Associations were generally consistent by sex across CVD events. Results were across strata of depression diagnosis, alcohol abuse and dependence diagnoses and comorbidity revealed associations among those with and without these potential confounders.

This is the first nationwide cohort study to examine hospital-based PTSD and adjustment disorder as risk factors for hospital-based diagnoses of four CVD events. Our results are consistent with the body of research that supports PTSD as a risk factor for CVD in various groups.[56-61,85] The current study propels forward the literature on cardiovascular sequelae of stress in two important ways. First, we examined adjustment disorder and found that its associations with CVD events that are similar in magnitude to those for PTSD. Second, we examined the associations between stress disorders and CVD events separately by gender.[78] Previous research has been limited by small numbers of women, and examinations of gender as a modifier of this association have been few.[61,86,87] We found that associations between events and either PTSD or adjustment disorder were relatively similar in magnitude across gender. In other stratified analyses, we found associations that were also consistent across levels of potential confounding variables.

This study makes an important contribution to the literature through the exploration of the association between adjustment disorder and CVD events, which has important public health and clinical intervention and prevention implications given the ubiquity of these diagnoses. Further, we documented limited gender differences in these associations, which has important implications for intervention as well, given that clinicians may monitor CVD risk differently in males and females. Additional conclusions and limitations are presented in the Conclusions section at the end of this chapter.

IV. PTSD and gastrointestinal disorders

Gastrointestinal (GI) disorders have been examined as a possible outcome of PTSD for over two decades.[55] Research examining the association between PTSD and GI disorders has yielded mixed evidence, however, owing in part to methodological differences across studies.[55] Some cross-sectional studies have documented an association,[45,88,89] and two prospective studies of US veterans have corroborated these findings. [90,91] Self-reported PTSD was associated with clinician-derived upper and lower GI disorders in male combat veterans.[90] In a recent study using clinical data, PTSD was associated with irritable bowel syndrome (IBS), GERD/reflux, and dyspepsia among veterans who served in Iraq and Afghanistan.[91] In contrast, other cross-sectional studies have not found evidence of these associations.[92,93] A larger prospective study of disaster survivors in The Netherlands found no association between self-reported PTSD and de-novo medically documented combined GI disorders.[94] In addition to inconsistency in results that may result from study methodology,[55] examining combined GI disorders or symptoms may potentially obscure differences in associations between PTSD and individual GI diagnoses.

At the time this dissertation work was conducted, no prospective population-based study had examined clinician-diagnosed PTSD as a risk factor for all major individual clinically-diagnosed GI disorders. The goal of this study was to fill this gap in the literature by comparing the incidence of all major individual non-malignant GI disorders in a nationwide cohort of patients with a prior diagnosis of PTSD using the cohort methodology described above. Data on hospital-based GI disorder diagnoses were obtained from the National Registry of Patients (see Appendix 1 for a description) and both primary and secondary diagnoses were used. Validation studies of GI diagnoses in this registry including pancreatitis, diverticulosis, liver cirrhosis, Crohn's disease, ulcerative colitis, and peptic ulcer have shown moderate to high validity.[95-99] In addition to the SIR calculations described above, we also calculated risk of overall and individual GI disorders among the PTSD cohort during the study period. We conducted additional analyses stratified by gender, age at PTSD diagnosis, substance abuse diagnosis status, somatic comorbidity and follow-up time to explore differences in associations across levels of these potentially important third variables.

We identified a nationwide cohort of 4,076 persons with an incident diagnosis of PTSD and no prior GI diagnosis from 1995 – 2011 and followed them for GI outcomes until December 31, 2013.

Cholelithiasis was the most common GI diagnosis during the study period (n = 130) followed by esophagitis (n = 119). Table 4 displays the risk and rate ratio estimates for PTSD and each outcome. Risk for any GI disorder among people with PTSD was 25% over the 18.9 year study period (95% CI= 21%, 29%). Risk estimates over the study period varied by GI disorder, with the lowest risk found for cirrhosis of the liver (0.44%, 95% CI = 0.18%, 0.96%) and the highest risk found for esophagitis (6.2%, 95% CI = 4.6%, 8.1%). The overall incidence rate of GI disorders was 1.8 times higher in the PTSD cohort than expected based on the rate in the general population (95% CI = 1.7, 2.0). No substantial association was found for PTSD and diverticula of the intestines (SIR = 1.1, 95% CI = 0.83, 1.5), and the magnitude of the remaining associations was variable. For example, there was more compelling evidence for a stronger association between PTSD and peptic ulcer, site unspecified (SIR = 3.3, 95% CI = 1.8, 5.5) and acute and subacute necrosis of the liver (SIR = 3.2, 95% CI = 2.5, 4.2), although the latter association may be due to uncontrolled confounding by excessive alcohol consumption or paracetamol poisoning.

Table 4. SIRs for incident gastrointestinal disorders among patients with PTSD, Denmark, 1995 – 2013

		Association with PTSD		
	Risk (95% CI)	Observed	Expected	SIR (95% CI)
All gastrointestinal disorders	25% (21%, 29%)	531	294.3	1.8 (1.7, 2.0)
Esophagitis	6.2% (4.6%, 8.1%)	119	52.9	2.3 (1.9, 2.7)
Stomach ulcer	2.7% (1.7%, 4.1%)	49	19.3	2.5 (1.9, 3.4)
Duodenal ulcer	0.67% (0.37%, 1.1%)	17	12.3	1.4 (0.80, 2.2)
Peptic ulcer, site unspecified	1.5% (0.32%, 4.7%)	14	4.3	3.3 (1.8, 5.5)
Gastritis and duodenitis	5.4% (4.1%, 7.0%)	103	39.9	2.6 (2.1, 3.1)
Acute appendicitis	3.4% (1.5%, 6.8%)	58	36.6	1.6 (1.2, 2.1)
Diverticula of the intestines	3.4% (2.0%, 5.4%)	44	38.4	1.1 (0.83, 1.5)
Chronic enteritis and ulcerative colitis	1.5% (1.0%, 2.2%)	37	22.5	1.6 (1.2, 2.3)
Irritable bowel syndrome	3.2% (1.9%, 4.9%)	57	31.8	1.8 (1.4, 2.3)
Acute and subacute necrosis of the liver	2.4% (1.7%, 3.1%)	57	17.6	3.2 (2.5, 4.2)
Cirrhosis of the liver	0.44% (0.18%, 0.96%)	7	4.4	1.6 (0.64, 3.3)
Cholelithiasis	5.8% (4.7%, 7.1%)	130	88.8	1.5 (1.2, 1.7)
Cholecystitis and cholangitis	0.98% (0.57%, 1.6%)	20	10.6	1.9 (1.2, 2.9)
Pancreatitis	1.9% (1.1%, 3.0%)	35	11.9	2.9 (2.1, 4.1)

In the stratified analyses, the pattern of associations between PTSD and the GI disorders was generally similar for males and females. Associations were mostly consistent across age group and marital status, with a few exceptions for which evidence of possible modification was found. For peptic ulcer site unspecified, those aged 16 –39 had an SIR of 7.4 (95% CI: 3.2, 15) while those aged 40 – 59 had an SIR of 2.3 (95% CI: 0.73, 5.3). Similarly, for married persons the SIR for this association was 2.5 (95% CI: 0.81, 5.9) but 7.2 (95% CI: 2.3, 17) for single persons. Evidence of possible modification by age was also found for acute appendicitis, among persons age 16 – 39 we found an SIR of 1.9 (95% CI: 1.4, 2.6) while among persons aged 40 – 59 the SIR was 0.93 (95% CI: 0.45, 1.7). We found evidence of effect modification by depression, alcohol abuse and drug abuse diagnosis for almost all associations, such that the associations between PTSD and individual GI disorders were stronger among persons with comorbid psychiatric diagnoses. This modification was particularly strong for the alcohol and drug abuse diagnoses. Further, associations among persons without psychiatric comorbidity were consistent with overall associations, indicating that diagnosed psychiatric comorbidity specific to these disorders does not account for observed associations. Some evidence of potential modification by CCI score was present for pancreatitis, where among those with a CCI score of 0 the SIR was 2.3 (95% CI: 1.5, 3.6) and among those with a CCI score of 1 or more the SIR was 5.1 (95% CI: 2.2, 10.1). Associations among those with a CCI score of 0 were generally comparable with overall associations. Finally, We found some evidence for increases in the associations between PTSD and stomach ulcer (SIR = 3.5, 95% CI = 1.8, 6.1), acute appendicitis (SIR = 2.5, 95% CI = 1.3, 4.5), and acute and subacute necrosis of the liver (SIR = 4.4, 95% CI = 1.8, 9.1) within the year following PTSD diagnosis.

This nationwide study makes a critical contribution to the existing literature on the association between hospital-based diagnoses of PTSD and GI disorders in that we explored associations between PTSD and all major individual non-malignant GI disorders, both overall, within important subgroups and at different lengths of follow-up. Our results are largely consistent with research documenting associations between PTSD and GI disorders in the general population and among US veterans which used varying study methodology and GI disorder definitions.[45,88-91,100] One previous study also used prospective population-based medical registry data to identify GI disorders and found no evidence of an association.[94] In that study GI disorders were grouped into one overall category for analysis, which may have obscured associations between PTSD and individual GI diagnoses, particularly if that sample

experienced mostly GI diagnoses that have a null or weak association with PTSD. Our work is a call for future examinations of individual GI diagnoses and not overall categories. Further, this study moved clinician practice forward through the findings of differential effects for individual GI disorders, thereby informing clinicians about which GI disorders their PTSD patients are the most likely to experience. Additional conclusions and limitations are presented in the Conclusions section at the end of this chapter.

V. All-cause mortality after stress disorders

As stated above, PTSD was associated with a higher rate of all-cause mortality in large cohort studies of US Veterans in both unadjusted and adjusted analyses, [62-64] although one study found that this association was null after adjustment for relevant confounders. [64] At the time the work of this dissertation was conducted no studies had examined all-cause mortality among people diagnosed with other stress disorders.

We contributed to the literature on mortality following stress diagnoses using a cohort study design as described in Study II. In brief, Study II included a cohort study of adults who received a hospital-based stress diagnosis in the Danish Psychiatric Central Register between 1995 and 2011 (using both primary and secondary diagnoses), and a comparison cohort (matched at a ratio of 5 to 1 on date of birth, sex and calendar time) of persons who had not received a stress diagnosis at the time of their matched stress cohort members diagnosis. Data on all-cause mortality were obtained from the Danish Register of Causes of Death. See Appendix 1 for a description of both registries. Given the previously documented strong associations between hospital-based stress disorder diagnoses and suicide mortality,[24] suicide death was excluded from all-cause mortality outcomes for the purposes of this study. Analyses were adjusted for confounders including hospital-based comorbid somatic diagnoses, baseline depression, anxiety, alcohol abuse/dependence, and drug abuse/dependence diagnoses.

Table 4 displays the associations between stress disorder diagnoses and all-cause mortality in this cohort. Unadjusted and adjusted associations that were similar in magnitude for all five stress diagnoses were found.

Table 4. *The Associations between Stress Diagnoses, All-cause Mortality, and Suicide, Denmark, 1995–2011*

	Acute Stress Reaction (N = 9,182)	PTSD (N = 3,786)	Adjustment Disorder (N = 66,823)	Other Reactions to Severe Stress (N = 1,692)	Reactions to Severe Stress, Unspecified (N = 20,180)	Comparison Cohort (N = 508,315)
All-cause mortality - unadjusted (95% CI)	2.9 (2.6, 3.2)	2.2 (1.9, 2.6)	2.6 (2.7, 2.9)	2.9 (2.3, 3.5)	2.6 (2.4, 2.8)	1
All-cause mortality - adjusted (95% CI)	2.2 (1.9, 2.4)	1.8 (1.5, 2.1)	1.9 (1.8, 2.0)	2.2 (1.7, 2.8)	2.0 (1.9, 2.2)	1

The results of this study show that hospital-based stress disorder diagnoses are associated with increased risk of all-cause mortality (excluding suicide), even after adjustment for somatic and psychiatric comorbidity. This finding is somewhat consistent with research in US Veterans that found an increased risk of all-cause mortality among those diagnosed with PTSD,[62,63] but contradicts one study that found that this association was null after adjustment for relevant confounders.[64] The difference in findings may be due to the examination of different populations, or the ability in the previous research to adjust for variables that we could not account for in the current study because they are not available in Danish registry data (i.e., smoking and exercise).

This study makes an important contribution to the literature on mortality following stress diagnoses, particularly with regard to the finding that risk of all-cause mortality is comparable among people who meet full criteria for stress diagnoses and among people with sub-syndromal diagnoses (e.g., the unspecific diagnoses). Additional conclusions and limitations are presented in the Conclusions section at the end of this chapter.

VI. Conclusions

At the time the work included is this dissertation was conducted, there were various gaps in the literature on the associations between stress disorders and cancer, CVD events and GI disorders. The work in this section provides an overview of the evidence we have complied with regard to these

associations. Previous research reported conflicting evidence with regard to the association between PTSD and cancer and examined mostly specific stressors and specific cancer diagnoses. The results of this dissertation suggest cancer is not an outcome of PTSD. This is a critical contribution to the public health literature on the consequences of stress disorder in that it will inform clinicians and researchers about where to place limited resources in an effort to ameliorate their long-term impact. In the next study presented within this dissertation we found that the rate of CVD outcomes is similar for persons with PTSD and adjustment disorder diagnoses. While this association had been previously documented in the PTSD literature, it had yet to be examined for adjustment disorder prior to our study. Given that adjustment disorder is the most frequently diagnosed stress disorder, an understanding of the CVD event risk in the population with this stress disorder diagnosis specifically has a great public health implications. We further examined the association between PTSD and all major non-malignant GI disorders, which demonstrated previous conflicting results, due in part to methodological differences across studies. We found associations of varying strength for PTSD and GI disorders, which may explain previous conflicting findings due to varying definitions of overall GI disorders across studies. This work also has important clinical implications because it highlights which GI disorders are the most likely following a PTSD diagnosis. Finally, we found that the rate of all-cause mortality was increased among persons diagnosed with any of the five stress disorders. This work has important clinical and research implications because it highlights the importance of prevention and intervention of negative sequelae among patients that meet sub-syndromal criteria for diagnoses, as their outcomes are just as severe as those that meet full diagnostic criteria.

Strengths of these studies include use of data from a large population-based cohort with complete follow-up resulting in little to no selection bias. As well, the large sample and long study period allowed us to examine associations that have not been studied previously. Despite these strengths, there are some limitations to be kept in mind when reviewing the results of this work. Even with the large size of the current study, it was too small to examine associations with rare cancers, particularly in the stratified analyses. Further, the diagnoses included in these studies were all hospital-based. Therefore there may be some misclassification of stress disorders or residual confounding of psychiatric confounders due to patients who have not sought care for their disorder that may have biased our findings. Other limitations included an inability to adjust for behavioral risk factors for the outcomes under study, such as smoking. Further, the data sources used for these studies did not include data on treatments, diagnostic activities, quality of care or adherence to therapy. Therefore it is unclear

how these potentially important variables may impact observed associations. With regard to CVD events specifically, data from the Danish National Patient Registry are frequently used for the study of CVD events;[79,101,102] however, validation studies comparing stroke and VTE diagnoses have found the positive predictive value of the diagnoses contained in the registry to be moderate and variable across diagnostic subgroups, treatment departments (*e.g.,* emergency room, specialty department), and type of diagnosis (primary versus secondary).[84,103] Despite these limitations, this work makes a critical contribution to the literature on somatic consequences of stress disorders. From a public health perspective, this work has propelled forward this field through the examination of where resources for intervention and prevention of the somatic consequences of stress disorders are best placed for three categories of highly prevalent somatic disorders.

VIII. Overall Conclusions

This dissertation advances our understanding of the longitudinal course of stress and trauma and associated diagnoses by examining sequelae spanning mental health, physical health and causes of mortality domains. Major strengths of the work summarized herein include the use of prospective population-based highly valid clinician diagnosis data with complete follow-up. These strengths directly address many of the limitations found in the existing literature at the time the work included in this dissertation was conducted. Specifically, the use of prospective rather than cross-sectional data allowed us to establish temporality of our associations. Knowing more about the natural course of diagnosis and the timing of outcomes has critical implications for the development of secondary and tertiary prevention and intervention efforts. Further, the use of prospective data obviated the recall bias issues that can be found in studies that require participants to report previous experiences and enhanced the validity of our estimates. Second, we have used highly valid data based on clinician diagnosis, which is subject to less biases than the self-report data used in many previous studies. Self-report data on both stress disorders and outcomes may be subject to dependent classification errors that are not a concern for our studies, again, enhancing the validity of our estimated associations. Finally, the studies presented in this dissertation have had the major advantage of complete follow-up data. In the few prospective studies of the sequelae of stress disorders that have relied on primary data collection, participant loss to follow-up is a major issue in that it is likely the people who experience the most distress and worst outcomes are also those who are no longer able or willing to participate in research. The complete longitudinal follow-up contained within our studies allows us to examine all outcomes among all participants in great detail, which eliminates biases due to an underascertainment of outcomes in primary data collection studies.

The studies in this dissertation contribute to the literature on occurrence and the negative sequelae of stress disorder in multiple domains. First, we explored the incidence and prevalence of these hospital-based diagnoses in the population of Denmark over a 15 year period and found important variability by both demographic characteristics and calendar time. This work has critical implications for intervention and prevention efforts, as well as the characterization of unexpected changes in the incidence of these disorders over a long time period. This characterization has enormous implications for public health as it relates to these disorders, and population intervention and prevention efforts. We also examined the cumulative incidence of common hospital-based psychiatric complications of stress

disorders in the 15 years following stress disorder diagnoses and found that these complications are common sequelae in this population.

We further examined the associations between hospital-based stress disorder diagnoses and death from suicide across multiple studies using two study designs over two different periods of time, and found that stress disorders are strongly associated with suicide death. The relatively consistent findings over the two study designs and two time periods can serve to bolster confidence in the associations we have uncovered. Stress disorder diagnoses are strongly associated with death from suicide, even when adjusted for other psychiatric comorbidities. Stress disorders had been previously documented as predictors of suicidal behavior; however, only a small minority of people who make a suicide attempt and do not die go on to die by suicide.[47] Therefore, persons who attempt suicide and who die by suicide are distinct populations. Our work is the first to document the important associations between hospital-based stress disorders and suicide death specifically. This work serves as a call for focused suicide intervention and prevention efforts among people with stress disorders, regardless of previous suicidal behavior.

Finally, we examined the somatic consequences of hospital-based stress disorders and found evidence of moderate associations for PTSD and most major GI disorders as well as PTSD, adjustment disorders and four CVD events. We found no evidence of an association between PTSD and various types of cancer. The somatic consequences of PTSD have been examined in the literature for decades, but at the time of these dissertation studies important gaps in this literature were present. We clarified the literature on the association between stress and cancer, by showing that cancer was not a consequence of PTSD in these data. Conversely, we showed that both PTSD and adjustment disorders are associated with CVD events, and that PTSD has varying associations with GI disorders – all disorders that are ubiquitous in any healthcare system. Given the limitations to both clinical and research resources, this line of research has important implications that call for tertiary prevention efforts with a focus on other somatic consequences of stress disorders.

Our studies were not able to examine the range of societal factors that may impact the clinical course of stress disorders. Social support and positive social networks are associated with decreased PTSD risk, and this relationship has been shown to be reciprocal in that increased PTSD symptomatology following trauma is also associated with social network deterioration.[104,105] PTSD has also been

associated with increased use of healthcare services and disability,[45,106-108] which may have varying implications for patients in different countries with different healthcare systems and disability benefits. Finally, there is a strong body of research conducted among US veterans that shows that PTSD is associated with decreased employment,[109-111] which may also have varying ramifications on stress disorder course depending on varying cross-national offerings and access of unemployment benefits, particularly in countries where healthcare benefits are closely tied to employment. All of these factors may play a role in the path from stress disorder diagnoses to deleterious outcomes, and serve as important contextual information to be mindful of when interpreting our findings. Further, the data sources used for these studies did not include data on treatment (e.g., diagnostic activity, quality of care or adherence to therapy); it is unclear how observed associations would differ if these potentially important variables were included in our analyses.

Another issue to consider when interpreting this work is that we used ICD diagnostic codes to categorize the majority of our predictors and outcomes of interest. These diagnoses are a valuable and commonly used tool in epidemiology. When diagnostic validity is high and registry-based data are available, they represent an incredibly cost-efficient and powerful method of classification. However, diagnostic criteria for psychiatric disorders in particular, including that outlined in the ICD, may not align perfectly with true underlying disorder biology, which may result in predictor and outcome misclassification. Although psychiatric diagnostic criteria at any given time represents the best the scientific community has to offer with regard to the observable representations of underlying etiology, psychiatry as a field lags behind other medical disciplines with regard to understanding the biology of many disorders. If we had a full understanding of the biology of all psychiatric disorders and were able to diagnose them accordingly, classifications may be different than what we could glean from the currently used diagnostic criteria, which are based entirely on symptom observation and report.

This line of work has significant public health and clinical implications. From a public health perspective, the documentation of the prevalence and incidence of stress disorders in the overall population of Denmark, as well as in important population subgroups, has critical implications for intervention and prevention planning. It is only through an awareness of the scope of the problem that appropriate resources can be allocated to prevention and treatment. From a clinical perspective, this line of work provides important information to clinicians worldwide about the etiology of the sequelae of stress disorders. This is critical to tertiary prevention efforts; as whole this work highlights the

negative sequelae of stress disorder diagnoses which warrant particular clinical attention among stress disorder patients. This is especially important when considering the treatment of patients with these complex disorders in health care systems with limited resources (e.g., large physician caseload, short appointment windows).

Taken together, this work contributes to the literature in these various areas through the use of high quality, population-based prospective data with complete follow-up. Due to our large sample size and extensive follow-up, we were able to clarify previous conflicting findings in many areas and explore previously unexamined associations, which have enormous implications for tertiary intervention and prevention efforts following stress disorders diagnoses, as well as laying a foundation for the best use of future research efforts in these areas.

IX. Dansk resume

I. Baggrund

Stressende og traumatiske hændelser og de diagnoser, der følger med sådanne oplevelser, får opmærksomhed på grund af den seneste tids stigning i antallet af traumatiske begivenheder (f.eks. konflikter, terrorisme, naturkatastrofer) over hele verden. Traumatiske oplevelser er udbredt i både Danmark og udlandet, og det anslås, at 50% af alle voksne vil opleve en traumatisk begivenhed i deres levetid. Den store udbredelse af traumatiske begivenheder taget i betragtning, er det ikke overraskende, at diagnosen posttraumatisk stresslidelse (PTSD), der ofte gives efter en sådan begivenhed, karakteriseres som værende en stor byrde for både enkeltpersoner og samfundet. Der findes dog kun få befolkningsbaserede longitudinelle studier af personer, der har været ude for sådanne oplevelser eller har fået diagnosen PTSD. Selv om der findes en større mængde litteratur om PTSD og dens følgevirkninger, får andre stresssygdomme (herunder akut stressreaktion og tilpasningsreaktion) mindre videnskabelig opmærksomhed, og det er uvist, om vores viden om forekomsten af og følgevirkningerne ved PTSD kan generaliseres til andre stresssygdomme. I litteraturen er der desuden debat om rollen af stresslidelser, herunder PTSD, i ætiologien af somatiske sygdomme, idet studier har vist modstridende evidens for styrken af associationer på tværs af forskellige sygdomme. Denne afhandling bidrager til litteraturen om længerevarende forløb af stress og traumer ved at undersøge sammenhænge mellem traumatiske oplevelser og stresslidelser og en række mentale og fysiske sundhedsmæssige udfald og dødelighed i en prospektiv, befolkningsbaseret kohorte med komplet opfølgning. At forstå de langsigtede konsekvenser af traumatiske begivenheder er afgørende for folkesundheden og for at kunne mildne deres påvirkninger.

II. Formål

Formålet med denne afhandling er at forbedre vores forståelse af de langsigtede fysiske og mentale sundhedsmæssige konsekvenser og dødelighed forbundet med alvorlige traumer blandt voksne ved brug af danske nationale registerdata (se appendix 1 for en beskrivelse) med komplet opfølgning.

I det første studie beskriver vi prævalensen (dvs. den del af befolkningen i den samlede population der har en given lidelse på et bestemt tidspunkt) og incidensen (dvs. andelen af mennesker, der over en periode udvikler en lidelse blandt dem uden denne lidelse) for hospitalsbaserede

stressdiagnoser i den danske befolkning over 15 år, såvel som forskelle på tværs af tid og vigtige demografiske karakteristika (f.eks. alder på tidspunktet for den traumatiske begivenhed og køn) og per år i studieperioden. På det tidspunkt denne undersøgelse blev gennemført, havde ingen studier undersøgt forekomsten af stresslidelser i en hel befolkning og inden for vigtige undergrupper over en længere follow-up periode, hvilket er afgørende for vores forståelse af hvordan disse lidelser kan forebygges, eftersom incidensen er en dynamisk måling, som kan ændre sig med tiden. I det næste studie undersøger vi den kumulative incidens af hospitalbaserede diagnoser for depression, angst, alkoholmisbrug og stofmisbrug stillet efter en diagnose for PTSD sammenlignet med en referencegruppe uden stresslidelser. Da dette studie blev gennemført havde ingen studier undersøgt forekomsten af psykiatriske komplikationer efter en diagnose for PTSD i en befolkningsbaseret undersøgelse med komplet opfølgning over 15 år, hvilket har stor betydning for tertiær intervention og en forebyggende indsats.

De næste undersøgelser i denne afhandling bidrager til vores forståelse af selvmord blandt mennesker, der har oplevet seksuelle overgreb, og mennesker, der har en hospitalsbaseret diagnose for stresslidelser. Der anvendes to forskellige studieperioder (1994-2006 og 1995-2011) og to forskellige epidemiologiske studiedesigns (case-kontrol og kohorte; case-kontrol studier blev anvendt, fordi det på tidspunktet for disse studier ikke var tilladt at arbejde med hele befolkningen ved Danmarks Statistik, hvilket ville have givet mulighed for en kohorteundersøgelse. Case-kontrol studier er også det foretrukne design ved undersøgelse af flere eksponeringer af et sjældent udfald, såsom selvmord). Da selvmord er en forholdsvis sjælden begivenhed, var litteratur om sammenhænge mellem seksuelle overgreb, stresslidelser og selvmord sparsomme, da disse studier blev gennemført. Data fra en hel befolkning med komplet follow-up er nødvendig for en meningsfuld undersøgelse af dette fænomen. Dette studie var således det første til at undersøge disse associationer ved brug af befolkningsbaserede data over en længere periode.

Endelig undersøger den sidste række studier i denne afhandling forekomsten af tre kategorier af hospitalbaserede diagnoser – kræft, hjerte-kar-sygdomme og gastrointestinale lidelser blandt mennesker med en hospitalsbaseret diagnose for PTSD og tilpasningsreaktion. Desuden ses på sammenhængen mellem alle hospitalsbaserede diagnoser for stresslidelser og dødelighed af alle årsager. På det tidspunkt disse undersøgelser blev gennemført, var disse lidelser endnu ikke blevet undersøgt i detaljer (dvs. baseret på en diagnose inden for kategorien fysisk sundhed), og generelt var dødelighed af alle årsager ikke blevet undersøgt i et stort befolkningsbaseret studie med komplet

follow-up. Dette arbejde var afgørende for at kunne gøre fremskridt med hensyn til placering af tertiær forebyggende indsats for somatisk sygdom efter en stressdiagnose.

III. Materiale

Denne afhandling er baseret på en litteraturgennemgang og resultaterne af ni epidemiologiske studier af de langsigtede virkninger af stress og traumer. En litteraturgennemgang blev oprindeligt udført samtidig med udarbejdelse af manuskript for hvert studie og blev efterfølgende opdateret i forbindelse med udarbejdelse af denne afhandling. Både PubMed og Google Scholar blev brugt til litteratursøgning med indtastning af alle individuelle og kombinerede relevante søgeord (f.eks. "stresslidelser," "traume", "PTSD", "dødelighed"). Alle fremkomne artikler blev gennemgået og er inkluderet og sammenfattet i relevant omfang i afhandlingen. De studier, der er opsummeret i denne afhandling, er baseret på data fra de landsdækkende danske medicinske og sociale registre (se appendiks 1 for en beskrivelse) og omfatter studier, der bruger både kohorte og case-kontrol design. I denne afhandling præsenterer vi arbejdet inkluderet i listen over studier i følgende rækkefølge. Studie I undersøger prævalensen og incidensen af stresslidelser i Danmark samlet set og i forhold til vigtige undergrupper fra 1995-2011 (artikel V på listen over studier). Studie II undersøger psykiatrisk komorbiditet efter en diagnose for PTSD samt dødelighed af alle årsager og selvmord (artikel VI på listen over studier). Studierne III–VI rapporterer om sammenhængen mellem seksuelle overgreb, diagnose for stresslidelser og dødsfald grundet selvmord (artiklerne I-IV på listen over studier). Endelig omfatter studierne VII-IX undersøgelser af de fysiske konsekvenser af stresslidelser (artiklerne VII-IX på listen over studier).

IV. Resultater

I studie I fandt vi, at en hospitalsbaseret diagnose for tilpasningsreaktion var den mest almindelige stressdiagnose i studieperioden, mens en hospitalsbaseret diagnose for uspecificeret reaktion på svær stress var den næstmest almindelige stressdiagnose. I overensstemmelse med den eksisterende litteratur om kønsforskelle i PTSD fik kvinder stillet en stressdiagnose oftere end mænd, og diagnoser var mest tilbøjelige til at forekomme før 40-årsalderen. Vi fandt en pludselig og vedvarende stigning i hyppigheden af lidelser i 2007, hvilket understreger den dynamiske karakter af prævalens og incidens. Resultater af studie II viste, at hospitalsbaserede diagnoser for depression, angstlidelser samt stofmisbrug og -afhængighed over en 15-årig periode var meget mere udbredt blandt personer med

stressdiagnoser end blandt personer i en sammenligningskohorte uden stressdiagnoser. Depression var den mest almindelige komorbiditet med en kraftig stigning i forekomsten umiddelbart efter en stressdiagnose. Rækken af studier om seksuelle overgreb og hospitalsbaserede diagnoser for stresslidelser som risikofaktorer for dødsfald grundet selvmord giver et samlet overblik over disse sammenhænge. Disse studier er de første til at dokumentere moderate til stærke associationer mellem alle disse prædiktorer og dødsfald grundet selvmord. Hvad angår stresslidelsers konsekvenser for det fysiske helbred fandt vi ingen beviser for en sammenhæng mellem PTSD og kræft, men vi fandt beviser på en moderat sammenhæng mellem PTSD og tilpasningsreaktion og hjerte-kar-sygdom og lignende beskedne beviser på en moderat sammenhæng mellem PTSD og gastrointestinale sygdomme sammenlignet med den generelle befolkning. Risikoen for dødelighed af alle årsager var også øget blandt dem med en diagnose for en stresslidelse i forhold til en sammenligningsgruppe uden stressdiagnoser.

V. Konklusion

Denne afhandling indikerer, i kombination med den eksisterende litteratur, at stresslidelser er et udbredt folkesundhedsproblem. Traumatiske hændelser og tilknyttede lidelser har desuden potentielt langsigtede negative konsekvenser, der blandt andet påvirker den mentale og den fysiske sundhed samt dødelighed, selv om der ikke var en øget forekomst blandt personer med stresslidelser af alle de faktorer, vi undersøgte. Denne forskning har stor betydning for tertiær intervention og den forebyggende indsats samt for vores forståelse af, hvordan man bedst anvender ressourcer i behandlingen af personer, der oplever traumer eller får stillet en diagnose for en stresslidelse. Mit arbejde på dette område har medført fremskridt inden for dette forskningsfelt gennem dokumentation af den potentielt skadelige virkning af traumer og tilknyttede lidelser ved hjælp af prospektive data med komplet opfølgning fra en stor uselekteret befolkning (dvs. alle patienter, der modtog behandling, er inkluderet), der ikke er omfattet af de bias, som findes i tidligere undersøgelser på dette område (f.eks. husker bias, tab til opfølgning). Endvidere har anvendelsen af avancerede epidemiologisk studiedesigns i forbindelse med en stor prospektiv befolkningsbaseret datakilde med det formål at forstå langsigtede forløb af stress og traumer været et nødvendigt, nyt bidrag til litteraturen.

X. Appendix 1: The Danish Healthcare System and Registries

I. The Danish Healthcare System

Universal medical coverage is provided to all persons registered as residents of Denmark through a tax-funded public health care system. This system covers all primary, specialist and hospital services (including mental health services), and care is almost entirely free for covered persons at the time of use. Public health care accounted for 85.3% of healthcare expenditures in Denmark in 2011.[35,112]

For the majority of the Danish population, general practitioners (GP) act as gatekeepers to further secondary and specialist care. Outpatient care is primarily provided through hospital-based clinics, with a smaller proportion provided through privately owned facilities. Almost all inpatient facilities are publicly owned (97%) and thus are covered by the tax-funded healthcare system. Mental health care is fully covered through the public system in Denmark; therefore there are few private outpatient facilities (and these cover mostly anxiety, affective, and personality disorders) and no private hospitals within psychiatry.[113,114]

More information about the Danish healthcare system is provided with regard to the specific data registries described below.

II. The Danish Registries

Receipt of healthcare among members of the Danish population is recorded in numerous medical and administrative registries at the national level.[115,116] The 10-digit Central Personal Register (CPR) number, a unique personal identifier assigned to all residents of Denmark, can be used as a key to retrieve and merge individual data from these national data sources. The first six digits of the CPR number are an individual's date of birth, and the next three digits are a serial number used to distinguish individuals with the same birthday. The numbers in the 5th, 6th, and 7th digits can be used as a century of birth indicator. The final digit indicates the sex of the individual (odd for males, even for females).[35,113]

The registries used in the studies that comprise this dissertation are described in more detail below.

1. The Danish Civil Registration System

History of the System

The Danish Civil Registration System (CRS) was established in 1968, primarily as a log of those alive and residing in Denmark for administrative purposes (*i.e*., tracking of addresses, tax collection). Prior to this, registration of residents had been done manually on index cards beginning in 1924, but with the establishment of the CRS came the use of an electronic registration system. The data contained in the CRS have been made available for research purposes through Danish legislation (The Danish Act on Processing of Personal Data), which also protects against the misuse of data and individual informed consent is not required for use.[35,113,117] Prior to 1988 the data contained in the CRS was updated weekly; from 1989 until today the data has been updated daily.[117]

The CRS is currently maintained by the Central Office of Civil Registration.[35] To access the data individuals must seek approval from the Data Protection Agency, which oversees data processing and sets deletion timelines (so data is not kept longer than is necessary to complete a project). The Research Service at the Danish Serum Institute releases the data, following the submission of the Data Protection Agency approval, a project protocol and a description of the requested data.[35] The CRS is considered a key tool in epidemiologic research in Denmark as it provides the ability to establish various comparison groups across study designs (*e.g.,* comparison cohorts in cohort studies, population-based controls in case-control studies).[35] Further, information contained in the CRS on vital status and emigration makes it possible to conduct long-term longitudinal studies with highly accurate censoring information.[35]

Description of Variables

The CRS contains data on CPR number, full name, sex, vital status, connections between parents, children, siblings and spouses, date of birth, place of birth, place of residence, citizenship, and death or emigration.[113,117]

Gender and date of birth are coded within CPR numbers and included as individual variables within the CRS. Following sex change procedures a new CPR number is assigned, but a link to the old CPR number is maintained. If more than one CPR number is present current gender can be derived from the most recent CPR number. [35,117]

Vital statistics for each individual are updated continuously and include information on mortality (living/dead; death only recorded if it occurs in Denmark or if the Danish authorities are notified), full address and residence (Denmark/Greenland), disappearance (according to Danish authorities), and emigration.[35] Dates are included for these events as appropriate. CRS contains data on residence for all individuals who were ever included in the register, from the time of first registration (all individuals registered in the CRS are required to notify the government of changes in address within 5 days under the National Registration Act).[35,117] Citizenship has been recorded since 1968, and recorded without deletion of previous data since 1991. If an individual has both Danish and other citizenship, only Danish citizenship is recorded; if there are multiple citizenships, none of which are Danish, the selection of recorded citizenship is random.[117]

Parent's CPR numbers are included for individuals in the CRS, beginning in 1968. At first this was recorded through residents at the same address, based on the previous system of manual registration on index cards maintained in the municipality where families resided.[117] From 1968 – 1978 the link between parents and children was deleted under a few circumstances: (1) the child moved, (2) the parent moved, (3) the child had their own children, or (4) the child reached 18 years of age. After 1978 the linkage between parents and children changed from being based on shared addresses to being based on legal relationships, and these links have been kept permanently until today. Further, links between parents and children from 1969 – 1978 was re-established through an extensive validation process using data from parish registers.[117] Due to data restrictions at the time of the establishment of the CRS (*i.e.,* in 1968 index card records maintained within individual municipalities were used to establish the CRS. These cards listed only children 15 years and younger who were living at the same address as their parents and thus not all children were captured with their mother's CPR number at this time) some information on family linkages prior to 1953 is incomplete. Information on siblings can be obtained by matching maternal or fraternal CPR numbers, or both for individuals whose mother was born after April 1935. From these data information on birth order, birth intervals, multiple births and number of siblings can be gleaned.[117] CRS further contains spouse's CPR number and date of marriage from 1968 onward. This information is continuously updated without the deletion of previous data.[113]

Beginning in 1978 place of birth was registered as maternal residence at the time of birth (*e.g.,* Danish or Greenlandic parish, municipality, country of birth if abroad).[117] In 1977 and earlier place of birth was registered as the physical location of the birth. Addresses and dates of moves are recorded

without the deletion of previous information and have been recorded from 1977 onward. For immigrants to Denmark, country of emigration as well as date of emigration is recorded from 1969 onward.

Data Completeness and Quality

Currently, the CRS includes all persons who were living, permanent residents of Denmark as of 2 April 1968 and living, permanent residents of Greenland as of 1 May 1972. Residents of the Faroe Islands are not included. At the end of 2006 the CRS included information for 8,284,477 persons.[113] As of 2006 those recorded in the register consisted of 65.8% living residents of Denmark, 0.7% living residents of Greenland, 26.6% deceased former residents, 0.3% disappeared former residents, and 6.7% emigrated former residents.[113]

With regard to specific family linkage variables included in the CRS, the percentage of linkages between children and parents has increased over time to almost 100% in 1970. The proportion has remained at that level since that time.[113] Further, 99.97% of children born in 1969 or later with a mother born in Denmark after 2 April 1935 have had their maternal link verified.[117]

A number of factors provide assurance of the data quality in the CRS and these data are widely accepted to be high quality.[35,113] First, the information in the register is continually utilized and thus mistakes are corrected through that process (*e.g.,* when Danish residents request a birth certificate the data contained therein is cross-checked with information in the parish registers and CRS is corrected if mistakes are found).[117] Also, residents receive a certificate with their CPR number and information and are encouraged to report errors. Relatedly, there is a positive attitude regarding the CRS among residents and registration in CRS is required by law, which bolsters reporting of corrections.

2. The Psychiatric Central Research Register

History of the Register

Systematic collection of data on patients admitted to eight psychiatric hospitals began in Denmark in 1938. Psychiatric departments in general hospitals began contributing data after their establishment in 1956 and in 1969 the electronic Psychiatric Central Register (PCRR) was established at the Department of Psychiatric Demography at Aarhus Psychiatric Hospital.[114] The non-electronic

register (spanning the years 1938 – 1969) is available for historical purposes only. Beginning in 1970, reporting to the PCRR was required of all psychiatric hospitals and departments and in 1995 the PCRR was expanded to include outpatient and emergency room treatment. The data contained in the register is updated monthly.[114]

The PCRR is currently maintained in the Centre for Psychiatric Research at Aarhus University Hospital, which is responsible for use of the data for research. Anonymous data can be released directly from the department for research purposes. If identifiable data is needed, approval must be received from the Danish Data Protection Agency, the National Board of Health and, if required, the Danish Ethical Committee.[114]

Description of Variables

CPR numbers are contained in the PCRR allowing for linkage with other Danish national registries, as well as admission and discharge dates and dates of treatment, all diagnoses for every encounter (registered as primary and secondary diagnoses), referral type, place of treatment, residence (municipality), and admission type (acute/planned).[114] Consistent with most national Danish registers, codes from the International Classification of Diseases, 8th Edition were used to log diagnoses in the registers prior to 1994; codes from the International Classification of Diseases 10th Edition have been used from 1994 onward.[118] For psychiatric diagnoses, the Danish National Board of Health and the Danish Psychiatric Association mandated that Danish diagnoses be consistent with the ICD-10-Diagnostic Criteria for Research beginning in January 1994 in an effort to increase reliability of diagnoses.[114]

Data Completeness and Quality

The PCRR contains data on the population of Denmark from 1969 onward, the population of the Faroe Islands from 1973 onward and the population of Greenland from 1973 onward, for a total of 747,176 individuals as of February 2010.[114] Data in the PCRR is kept for 50 years after an individual's death.[114] Private psychiatric hospitals do not exist in Denmark, therefore registration of more severe disorders is likely complete, however some cases of mild or moderate psychiatric disorders may be treated only by GPs and thus not registered in the PCRR. Our validation study of stress disorder diagnoses not covered by the PCRR found this proportion to be low.[12] Further, individuals who receive

private outpatient psychiatric treatment are also not registered in the PCRR (accounting for approximately 20% of individuals referred to psychiatric treatment in Denmark).[114]

An extensive validation process for PCRR data is in place, and has been for many decades. When data were still sent to the Department of Psychiatric Demography via paper (from 1969 – 1990), the data sheets were compared with written case summaries for validation purposes (cross-checked data included CPR numbers, admission and discharge dates, diagnostic codes, etc).[114] Electronic transfer of data began in 1990, and further in 1995 the National Board of Health took responsibility for obtaining data from psychiatric departments. Data validation still occurs, with electronic data compared to lists reported from departments at the Centre for Psychiatric Research.[114] Further, research studies examining the validity of some diagnoses (e.g., stress disorders, schizophrenia, depression) have documented high quality.[12,114]

3. The Danish National Patient Registry

History of the Registry

The Danish National Patient Registry (DNPR) was established in 1977 when the Danish National Board of Health asked Danish counties (which were responsible for the oversight of hospitals) to provide standardized patient data for the monitoring of health care use for planning purposes. Complete nationwide coverage was achieved in 1978.[119] Originally the DNPR included only somatic inpatient hospitalizations but has since been expanded (in 1995) to include outpatient somatic treatment as well as psychiatric inpatient and outpatient treatment and emergency room visits.[36] In 2003, reporting to the DNPR by private hospitals became mandatory as well, excluding private practice specialists and GPs.[119] Data included in the DNPR is updated continuously (weekly or daily), as required by law.[119]

As with the other registries, the Danish Act of Processing Personal Data provides legal authority for the use of health data for research purposes, while protecting against the misuse of these data. Further, permission for use of the data is required from the Danish Data Protection Agency and potentially the Danish Health and Medicines Authority. Data from the DNPR can be obtained through an application to the Research Service.[119]

Description of Variables

Data in the DNPR includes CPR numbers (allowing linkages with other registers), municipality/region of residence, hospital/department code, admission type (acute/not acute), contact type (inpatient/outpatient/emergency), date of treatment, information on accidents prior to treatment, and diagnostic and surgical procedure codes (registered as a primary and, if necessary, secondary diagnoses), and examination (*e.g.,* radiological procedures) codes.[36,119] Various changes in the classification of data in the DNPR over time are important to consider, all taking place after 1987. In that year, documentation of admissions, referral and discharge was simplified, while more detailed accident data was recorded.[36] In 2008, coding with the Nordic Classification of External Causes of Injury began for accident data. As with the other registries, codes from the International Classification of Diseases, 8th Edition were used to log diagnoses in the registers prior to 1994; codes from the International Classification of Diseases 10th Edition have been used from 1994 onward.[36] In 2006 the codes for surgical procedures were changed to be consistent with the Nordic Classification of Surgical Procedures. Classification codes for the DNPR can be found on the web-based Health Care Classification system.[36]

Data Completeness and Quality

From 1977 – 2012 the DNPR contained at least one contact for 8,085,603 individual persons, with 90% registered as an inpatient, 74% registered as an outpatient, and 63% registered as an emergency patient.[119] Although reporting from private hospitals and clinics is thought to be incomplete, this type of care accounted for only 2.2% of hospital treatment in Denmark in 2010.[119]

Data received from the hospitals is checked for missingness, errors and inconsistences (e.g., diagnoses and sex) before being entered into the DNPR.[119] Various studies have been conducted to examine the validity of the data contained within the DNPR, both by the Danish Health and Medicines Authority and by individual researchers.[119] The two national validation studies conducted by the Danish Health and Medicines Authority (using a random sample of data) have found high correlations between the data contained within the register and medical records.[119] With regard to validation studies of specific diagnoses, there has been a lot of variability in results with some studies documenting generally low validity (e.g., a positive predictive value of 15%) and others documenting perfect validity.[119] These results highlight the import of establishing validity of DNPR diagnoses before use for research purposes. Importantly, we have included validity information for all of the DNPR diagnoses used throughout this dissertation in the descriptions of the individual studies presented above.

4. The Danish Cancer Registry

History of the Registry

The Danish Cancer Registry was first established in 1942, with systematic data collection beginning in 1943.[120] Until 1996 the registry was maintained by the Danish Cancer Society with support from the Danish Board of Health; in 1997 and after the registry has been maintained by the Danish Board of Health. From 2004 – 2008 the registry underwent modernization (including electronic notifications, automated coding, conversion of old data) to ensure the ability to accommodate current and new electronic health record technologies. Paper notification to the registry was fully replaced by electronic data transfer in 2005.[120]

Description of Variables

The registry contains both personal characteristics and cancer characteristics. Personal characteristics include CPR numbers (allowing for linkage with other registers), birth date, sex, age at cancer diagnosis, municipality, and date of death or emigration (linked from the CRS once yearly).[120] With regard to cancer characteristics, International Classification of Diseases, 7th Edition, was used to code diagnoses from 1943 – 1978 and International Classification of Diseases, 10th Edition was used for diagnostic codes after 1978 (as both primary and secondary diagnoses as needed).[120] Additional variables contained in the register include tumor morphology, cancer stage, tumor topography, diagnosis date, and other tumor characteristics.

Data Completeness and Quality

The Danish Cancer Registry contains data on all malignant neoplasms that occur within the population of Denmark beginning in 1943 and in the population of Greenland beginning in 1953. Mandatory reporting to the registry has been in place since 1987.[120] Notification of cancer diagnoses from multiple sources (*e.g.,* the Danish Pathology Register) has increased completeness of the registry.[120]

Quality control procedures are in place which ensures validity of the data contained within the registry. There are multiple computerized checks for data validity which are consistently conducted including comparisons of multiple data sources, internal consistency checks (*e.g.,* cancer type by sex,

grade by stage by laterality for some cancers). [120] Individual validation studies of specific diagnoses have found that 95% to 98% of records contained in this registry are valid.[76]

5. The Danish Register of Causes of Death

History of the Register

Mandatory completion of death certificates has been required in Denmark since 1871. Shortly thereafter, in 1875, the National Board of Health established the registration of causes of death.[121] Paper records were used until 1970, and data was collected from death certificates; after this time the registry was computerized. From 1875 – 2007 all data contained in the register were coded at the National Board of Health. This coding was performed by specially trained physicians who reviewed death certificates and made a determination for cause of death according to WHO guidelines until the late 1990s.[121] Since this time there have been various changes in the coding of data within the register, including the use of automated classification of medical entities following scanning of data from 2002 – 2004, a brief period of delay in updating the register from 2004 – 2007, and finally in 2007 a move to electronic submission of death certificates with causes of death indicated by the medical doctor who verified the death.[121]

Description of Variables

Since 1994 the International Classification of Diseases, 10th Edition, has been used to code causes of death in the register.[121] Prior to this period, WHO classifications, Danish and Scandinavian and other international classifications have been used over various periods of time. All death certificates in Denmark contain information on underlying cause of death and other causes which contributed to the death. Data in the registry include CPR number (permitting linkage to other registers), municipality, marital status, age at death, manner of death (e.g., natural, accident, suicide, homicide, unknown), place of death, recent surgery, and autopsy results if conducted.

Data Completeness and Quality

The register includes data on all Danish residents who die in Denmark. Deaths occurring outside of Denmark are only available if they are reported back to Danish authorities. After 1983 the register was expanded to include individuals from Greenland or the Faroe Islands who died in Denmark or these other locations.[121] Every year there are approximately 200-400 deaths which are not fully

reported(0.3% - 0.6% of all deaths), according to the National Board of Health.[121] Additional information about these deaths is obtained from hospitals and GPs.

Since 2007, the time when individual physicians began coding causes of death and submitting these reports electronically, there is no longer a central validation of the cause of death classification at the National Board of Health.[121] This, in conjunction with other coding changes over time, may have an impact on the validity of cause of death codes in the register. To date no large-scale studies have been conducted to examine the validity of these codes.

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