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Kellye D. Sliger Date

THE EFFECTS OF STRESS, ANXIETY, AND DEPRESSION ON THE DEVELOPMENT OF CARDIOVASCULAR DISEASE AND INFLAMMATORY DISORDERS IN THE U.S. DEPARTMENT OF ENERGY WORK FORCE

BY

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Career MPH

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Kellye D. Sliger
M.P.H., Emory University, 2011
B.S., University of Tennessee, 2008

Thesis Committee Chair: Bradley Pearce, Ph.D.

An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master of Public Health in the Career MPH Program
2011

Abstract

THE EFFECTS OF STRESS, ANXIETY, AND DEPRESSION ON THE DEVELOPMENT OF CARDIOVASCULAR DISEASE AND INFLAMMATORY DISORDERS IN THE U.S. DEPARTMENT OF ENERGY WORK FORCE

BY
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For decades, research has shown an association between having a cardiovascular event (CVD) and the development of stress, anxiety, or depression (SAD). These studies indicate a strong association between individuals reporting a CVD event and later reporting SAD. As well, many years of research have shown a strong association between inflammatory disorders (INF) and SAD. As expected, individuals with active inflammatory disease are more likely to experience SAD. This analysis examines the temporal relationship between reporting SAD prior to a CVD event or an INF. Logistic regresion models were conducted with variables considered to be non-modifiable risk factors.

The data analyzed for this study support the temporal association between SAD and CVD events or INF. A fully adjusted model, controlling for demographic variables, for the SAD-CVD association indicated a positive association between reporting a prior SAD diagnosis and reporting a subsequent CVD diagnosis, OR: 1.68; CI: 1.45, 1.94; *P<.0001*. For the SAD-INF association, a fully adjusted model indicated a positive association between reporting a prior anxiety and a subsequent INF diagnosis, OR: 2.87; CI: 2.19, 3.78; *P<.0001*.

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ACKNOWLEDGEMENTS

I would like to graciously thank Dr. Bradley Pearce for his support during the development and completion of this thesis. He spent a tremendous amount of hours and provided a wealth of knowledge for this project.

I would also like to thank my mentor, Dr. Elizabeth Ellis. She has provided many hours of assistance and understanding during completion of my degree at Emory University. If it were not for her support, I would not have been able to complete this program.

Finally, I would like to thank my husband, Jim. If not for his unwavering love and support, I would not have been able to successfully balance my work, education, and home life.

TABLE OF CONTENTS

INTRODUCTION

Chronic diseases, such as cardiovascular disease or inflammatory disorders, are the leading causes of death and morbidity in the United States. The Centers for Disease Control and Prevention reports that "chronic diseases account for 70% of all deaths in the United States (U.S.)" (1). These illnesses contribute to a reduced quality of life, considerable health care costs, and shorten the lives of those who suffer from them. The Milken Institute estimates a projected annual cost of $217.6 billion in treatment and $905.1 billion in lost productivity due to chronic diseases by 2023 (2).

It is reported that 50% of U.S. adults will develop at least one mental illness during their lifetime (3). Mental health expenditures were over $100 billion in 2003 in the U.S. (4). In 2007, there were over 600,000 deaths attributed to heart disease (4). Estimated costs of cardiovascular disease in the U.S. in 2010 were estimated at $444 billion (1). Many chronic inflammatory conditions are caused by autoimmune disorders. Over 23.5 million Americans are affected by autoimmune disorders alone (5).

Previous research has shown a direct relationship between having a cardiovascular (CVD) event and the development of psychological stress, prolonged anxiety, or depression (SAD) (6-9). These studies indicate a strong association between individuals reporting a CVD event and later reporting SAD (10,11) . Some research indicates that this may be caused by the medication used to treat cardiovascular conditions or by nutritional levels (12,13). One could reasonably presume that this could also be caused by the psychological trauma that an individual faces when coping with such a life-altering event. An adverse emotional response to a major life stressor that is transient is typically categorized under the rubric of an adjustment disorder. Life stress chronic stress can lead to or exacerbate an anxiety disorder or depression.

There are many known risk factors for CVD, which include both modifiable and non-modifiable behaviors. Tobacco use, alcohol use, hypertension, high cholesterol, obesity, physical inactivity, and unhealthy diets are all modifiable behaviors (14). Non-modifiable risk factors are age, family history, gender, and ethnicity. Age and gender will be explored during this analysis as potential effect modifiers.

Research has also shown a strong association between inflammatory disorders (INF) and SAD. Individuals with active inflammatory disease are more likely to experience SAD (15). Current research indicates that this may be related to immune cytokines that activate the immune function and also trigger central stress-responsive neurotransmitter systems to regulate the immune response and behaviors which may be adaptive in inflammation. These cytokines signal corticotropin-releasing hormone neurons to activate pituitary-adrenal counter-regulation of the response through glucocorticoids. The corticotropin-releasing hormones also trigger behavioral and physiological responses (16).

Unlike CVD, most risk factors for INF are non-modifiable. Non-modifiable risk factors for INF include genetics, environment, age, race, and family history. In theory, environment can be modified, as is often difficult to achieve a practice. Modifiable risk factors are smoking, use of NSAIDs, and dietary habits (17). NSAIDs block two key enzymes which regulate the digestive system, cyclooxygenase-1, and the inflammatory process, cyclooxygenase-2 (18). Age and gender will be explored in this analysis as a potential effect modifier.

New research has shown that a temporal relationship exists between having SAD and developing a CVD or an INF (19-22). The purpose of this analysis is to examine this temporal relationship between SAD and the development of CVD or INF in a population of working adults. Findings from this analysis may provide a basis for future wellness and educational programs.

MATERIALS AND METHODS

Study Population

Data were collected through the U.S. Department of Energy (DOE) Illness and Injury Surveillance Program (IISP) for the period of 1996-2010. The IISP was established by DOE to collect, maintain, analyze, and interpret return-to-work data on illness and injury prevalence in the DOE contractor work force. The IISP data is maintained by the Oak Ridge Institute for Science and Education (ORISE) Occupational Exposure and Worker Health (OEWH) Program. There were 16 sites participating in the IISP during the analysis period (Table 1).

Roster data are collected at least annually for each worker employed at the site during active participation years. The roster file contains basic demographic information on the worker: age, gender, job category, and year on roster. These variables will be explored for potential effect modifiers on the SAD-CVD and SAD-INF relationships.

Table 1. DOE sites included in analysis

		Active Participation Years
ANL	Argonne National Laboratory, Argonne, IL	2009- present
BNL	Brookhaven National Laboratory, Upton, NY	1993- present
ETTP	East Tennessee Technology Park, Oak Ridge, TN	1999- present
FMP	Fernald Facility, Fernald, OH	1993-2004
HAN	Hanford Site, Richland, WA	1993-present
INL	Idaho National Laboratory, Idaho Falls, ID	1993- present
KCP	Kansas City Plant, Kansas City, MO	2002- present
LANL	Los Alamos National Laboratory, Los Alamos, NM	2003-2008
LLNL	Lawrence Livermore National Laboratory, Livermore, CA	2002- present
NNSS	Nevada National Security Site, Las Vegas, NV	2002- present
ORNL	Oak Ridge National Laboratory, Oak Ridge, TN	1999- present
PTX	Pantex Plant, Amarillo, TX	1994- present
RF	Rocky Flats Plant, Golden, CO	1993-2000
SNL	Sandia National Laboratories-Albuquerque, Albuquerque, NM	1993- present
SRS	Savannah River Site, Aiken, SC	1993- present
Y-12 NSC	Y-12 National Security Complex, Oak Ridge, TN	1998- present

Return-to-work data are recorded when a worker returns after a qualifying absence. The definition for a qualifying absence varies from site to site and depends on the current contractor at that site. Contractors generally require that a worker return through their occupational medicine office after a specified number of missed workdays or after surgery. This reporting variability impacts the ability to compare the number of absences across sites.

There were no restrictions placed on the length of absence used in this analysis. The workers self-report their diagnosis which is then recorded by the occupational medicine office. The diagnoses are coded by certified nosologists at the site or at the IISP data center. All diagnoses are coded using International Classification of Diseases (ICD-9-CM) 2010 codes (23). Return-to-work information may also be supplied by industrial hygiene and safety organizations or human resource departments. This information is then submitted to the IISP data center at ORISE.

In both the roster and return-to-work data, all data are de-identified to protect worker confidentiality. Any personal identifiers are removed at the site and not stored in the IISP database. However, a unique pseudo-identifier is assigned to each worker by the site so that the worker's data can be linked together over time.

Data collected at the IISP data center are checked for syntax and logical errors upon receipt. Any errors are sent back to the site for correction. In addition to the first check, there are many checks along each step to ensure that the data are accurate, internally consistent, and free from errors.

Classification as a SAD diagnosis was determined by an algorithm used by the Agency for HealthCare Research and Quality's Mental Health and Substance Abuse Clinical Classification Software (CCS-MHSA) (24). This algorithm has the disadvantage of being over inclusive, for example, recurrent depression is categorized together with transient adjustment disorders. Therefore, we have used the term SAD, recognizing the lack of refinement the term implies with respect to psychological diagnostic categories. However, this broad category which was used in our initial analysis based on a distribution of IISP mental health diagnoses. IISP mental health codes were divided into three subsets: alcohol and substance abuse, stress, anxiety, and depression, and all other. The AHRQ algorithm for stress, anxiety, and depression most closely fit the IISP diagnosis distribution and is a nationally recognized source for health care information.

Cardiovascular diagnoses were classified as any diagnosis from the ICD-9-CM grouping, Diseases of the Circulatory System, 390-459. Inflammatory disorders were selected based on literature review that specified illnesses as inflammatory conditions (Appendix B).

Analyses were conducted using these groupings to explore the SAD-CVD and SAD-INF relationships. Additional analyses were conducted using a subset of the CVD diagnosis classification. This subset narrows the CVD grouping into CVD events more commonly attributed to SAD (Appendix B). For simplification, this group will be referred to as CVD2. Anxiety and depression were explored separately to determine if these diagnosis groups indicated different results from the SAD grouping (Appendix B).

Other variables from the IISP worker data were explored to determine potential effect modification or confounding: gender, age first on roster, birth decade, socioeconomic status (SES), region, and length on roster. Age first on roster and birth decade were calculated from the first appearance of the worker on the roster. Age first on roster and length on roster are used as a continuous variable. Birth decade, used as a categorical variable, was divided into five groups depending on the workers decade of birth: 1940 or earlier, 1950, 1960, 1970, and 1980 or later. The age of the individual when they first reported the work loss illness was also considered. Socioeconomic status, a categorical variable, was determined from classification of IISP job categories into three levels: low, medium, and high (Appendix C). When the IISP was first created, each site used its own job categories and titles. In order to standardize the job categories to allow for comparative analysis, ORISE developed 10 job categories that were associated with the nature of the work and amount of exposure a worker may experience. Job category was recorded as the job category reported the first time the worker appeared on the roster. Regions, a categorical variable, were created by grouping the sites into five major geographical regions: West, Northeast, Midwest, Southwest, and Southeast (Appendix C). Length on roster was recorded as the number of years that the worker appeared on the roster. Birth decade and age first on roster are used jointly as an indicator of worker age.

Statistical Methods

SAS 9.2 frequency and logistic regression procedures were used to calculate odds ratio (OR) and 95% confidence intervals (CI) for all associations. A full logistic regression model was conducted with all variables of interest: gender, birth decade, age first on roster, SES, and region. These variables were chosen as non-modifiable risk factors for the disease outcome. The final adjusted model was determined using the Breslow-Day Test of homogeneity of odds ratios to test for effect modification and the 10% rule to test for confounding. Variables that had a Breslow-Day test p-value of <.05 were considered statistically significant effect modifiers while those that were equal to or greater than .05 were tested for confounding. Confounding was determined by comparing adjusted odds ratio to crude odds ratios. If the adjusted odds ratio fell outside of a 10% boundary, the variable was considered a confounder. All significance levels are reported at alpha=0.05.

All computations were at 95% or greater power.

RESULTS

There were 161,109 workers considered for analysis. These workers were employed at one of the participating DOE sites some time during the analysis period, 1996-2010. Out of these individuals, 53,553 reported at least one absence during the analysis period while 107,556 did not report any absences.

From the 53,553 workers reporting an absence, 2,121 reported a SAD diagnosis but did not report a CVD diagnosis. There were 7,680 workers who reported a CVD diagnosis but never reported a SAD diagnosis. Additionally, 2,406 workers reported a SAD diagnosis but did not report an INF diagnosis. Contrarily, there were 2,216 workers who reported an INF diagnosis but never reported a SAD diagnosis.

Overall, there were 2,746 workers who reported a SAD diagnosis. Women made up the largest percentage of those workers, 51.1%. The majority were born in the decade of 1950, 41.9%. Most workers reporting SAD were from the medium SES, 39.7%, and were from the Southeast region of the United States, 33.6%. The median age first on roster was 40.47 years, median 41. Mean length of time on roster was 9.34 years, median 9, and mean calendar days absent per absence was 18.57 days, median 6 days (Table 2). There were 4,784 SAD diagnoses reported by the 2,746 workers that reported a SAD diagnosis (Table 3).

There were 8,305 workers who reported a CVD diagnosis. The largest majority of those were men, 77.2%. Most workers reporting CVD were born in the decade of 1940 or earlier, 41.9%. The majority of workers who reported CVD was from the high SES group, 35.1% and was from the Southeast region, 43.1%. The mean age at first appearance on the roster was 45.36 years, median 46 and mean time on roster was 10.52 years, median 11. Mean calendar days absent, per absence, was 15, median 5 (Table 2). There were 15,553 diagnoses from those 8,305 workers who reported a CVD diagnosis (Table 3).

For workers reporting INF, 2,556, the majority were women, 51.9%. Most workers were born in the 1950 decade, 39.0%. The medium SES represented the majority of workers reporting INF, 44.7%. The majority were from the Southwest region, 41.0%. Mean age first on roster was 41.64 years, median 42, and mean time on roster was 10.26 years, median 10. The mean calendar days absent, per absence, was 22.74 days, median 9 (Table 2). There were 6,212 diagnoses from the 2,556 workers who reported an INF diagnosis (Table 3).

Table 2. Characteristics of U.S. Department of Energy, Illness and Injury Surveillance Program workers who reported a SAD, CVD, or INF event and those who did not, 1996-2010.

Characteristic	SAD		No SAD		X^2 (d.f.)	CVD		No CVD		X^2 (d.f.)	INF		No INF		X^2 (d.f.)
	n=2,746	%	n=158,363	%	*p-value*	n=8,305	%	n=152,804	%	*p-value*	n=2,556	%	n=158,553	%	*p-value*
Gender															
Women	1,343	*48.9%*	44,048	*27.8%*		1,890	*22.8%*	43,501	*28.5%*		1,229	*48.1%*	44,162	*27.9%*	
Men	1,403	*51.1%*	114,315	*72.2%*		6,415	*77.2%*	109,303	*71.5%*		1,327	*51.9%*	114,391	*72.2%*	
					593.44 (1)					126.96 (1)					508.71 (1)
					<.0001					*<.0001*					*<.0001*
Birth decade															
1940	609	*22.2%*	39,652	*25.0%*		3,481	*41.9%*	36,780	*24.1%*		730	*28.6%*	39,531	*24.9%*	
1950	1,151	*41.9%*	48,426	*30.6%*		3,370	*40.6%*	46,207	*30.2%*		997	*39.0%*	48,580	*30.6%*	
1960	709	*25.8%*	36,372	*23.0%*		1,190	*14.3%*	35,891	*23.5%*		528	*20.7%*	36,553	*23.1%*	
1970	227	*8.3%*	21,704	*13.7%*		229	*2.8%*	21,702	*14.2%*		242	*9.5%*	21,689	*13.7%*	
1980	50	*1.8%*	12,209	*7.7%*	312.77 (4)	35	*0.4%*	12,224	*8.0%*	2916.91 (4)	59	*2.3%*	12,200	*7.7%*	205.43 (4)
					<.0001					*<.0001*					*<.0001*
Socioeconomic Status															
Low	880	*32.1%*	31,701	*20.0%*		2,626	*31.6%*	29,955	*19.6%*		781	*30.6%*	31,800	*20.1%*	
Medium	1,090	*39.7%*	53,199	*33.6%*		2,766	*33.3%*	51,523	*33.7%*		1,142	*44.7%*	53,147	*33.5%*	
High	776	*28.3%*	73,463	*46.4%*	415.47 (2)	2,913	*35.1%*	71,326	*46.7%*	792.90 (2)	633	*24.8%*	73,606	*46.4%*	486.14 (2)
					<.0001					*<.0001*					*<.0001*
Region															
West	859	*31.3%*	69,648	*44.0%*		2,116	*25.5%*	68,391	*44.8%*		411	*16.1%*	70,096	*44.2%*	
Northeast	100	*3.6%*	6,342	*4.0%*		358	*4.3%*	6,084	*4.0%*		98	*3.8%*	6,344	*4.0%*	
Southwest	574	*20.9%*	32,314	*20.4%*		1,780	*21.4%*	31,108	*20.4%*		1,049	*41.0%*	31,839	*20.1%*	
Midwest	291	*10.6%*	9,901	*6.3%*		468	*5.6%*	9,724	*6.4%*		153	*6.0%*	10,039	*6.3%*	
Southeast	922	*33.6%*	40,158	*25.4%*	252.71 (4)	3,583	*43.1%*	37,497	*24.5%*	1751.28 (4)	845	*33.1%*	40,235	*25.4%*	1055.05 (4)
					<.0001					*<.0001*					*<.0001*
	Mean	Med	Mean	Med		Mean	Med	Mean	Med		Mean	Med	Mean	Med	
First Age (age first on roster)	40.47	41	41.26	42		45.36	46	41.02	41		41.64	42	41.24	42	
Roster Years (years on roster)	9.34	9	6.52	5		10.52	11	6.36	5		10.26	10	6.51	5	
Calendar Days Absent per Absence	18.57	6	20.40	8		15	5	22.63	9		22.74	9	9.75	2	

Abbreviations: X^2, Chi-square test; d.f., degrees of freedom; med, median
For ICD-9-CM codes for SAD and CVD diagnoses, see Appendix B.

Table 3. Distribution of diagnoses among U.S. Department of Energy, Illness and Injury Surveillance Program workers, 1996-2010.

SAD Diagnoses

ICD-9-CM Code	Description	Women	Men	Total
293.83	Mood disorder in conditions classified elsewhere	1	1	2
239.84	Anxiety disorder in conditions classied elsewhere	2	3	5
296.2	Major depressive disorder, single episode	219	229	448
296.3	Major depressive disorder, recurrent episode	145	117	262
300	Anxiety, dissociative and somatoform disorders	644	772	1,416
308	Acute reaction to stress	317	305	622
309	Adjustment reaction	301	273	574
311	Depressive disorder	740	715	1,455
	Total	2,369	2,415	4,784

CVD Diagnoses

ICD-9-CM Code	Description	Women	Men	Total
390-392	Acute Rheumatic Fever	3	6	9
393-398	Chronic Rheumatic Heart Disease	17	37	54
401-405	Hypertensive Disease	1,441	3,163	4,604
410-414	Ischemic Heart Disease	466	4,022	4,488
415-417	Diseases of Pulmonary Circulation	71	85	156
420-429	Other Forms of Heart Disease	570	1,882	2,452
430-438	Cerebrovascular Disease	195	547	742
440-449	Diseases of Arteries, Arterioles, and Capillaries	138	501	639
451-459	Diseases of Veins, Lymphatics, Other	665	1,724	2,389
	Total	3,566	11,967	15,533

INF Diagnoses

ICD-9-CM Code	Description	Women	Men	Total
780.71	Chronic fatigue syndrome	91	27	118
493	Asthma	1,012	802	1,814
496	COPD	93	200	293
714	Rheumatoid arthritis and other inflammatory polyarthropathies	280	283	563
695.4	Lupus erythematosus	8	2	10
710.0	Systemic lupus erythematosus	184	22	206
710.2	Sicca syndrome	36	5	41
710.4	Polymyositis	2	3	5
696	Psoriasis and similar disorders	40	76	116
729.1	Fibromyalgia	592	323	915
555-558	Noninfectious enteritis and colitis (IBD)	655	983	1,638
564.1	Irritable bowel syndrome	260	233	493
	Total	3,253	2,959	6,212

SAD and CVD Association

To explore the temporal association of a prior SAD diagnosis, workers who reported missing work with a SAD at the same time as missing work with a CVD and those absences reporting a SAD after reporting a CVD were excluded from the final analysis (Figure 1). The term "temporal" as it is used here refers to an absence for one type of illness that precedes an absence for another type of illness during the course of employment.

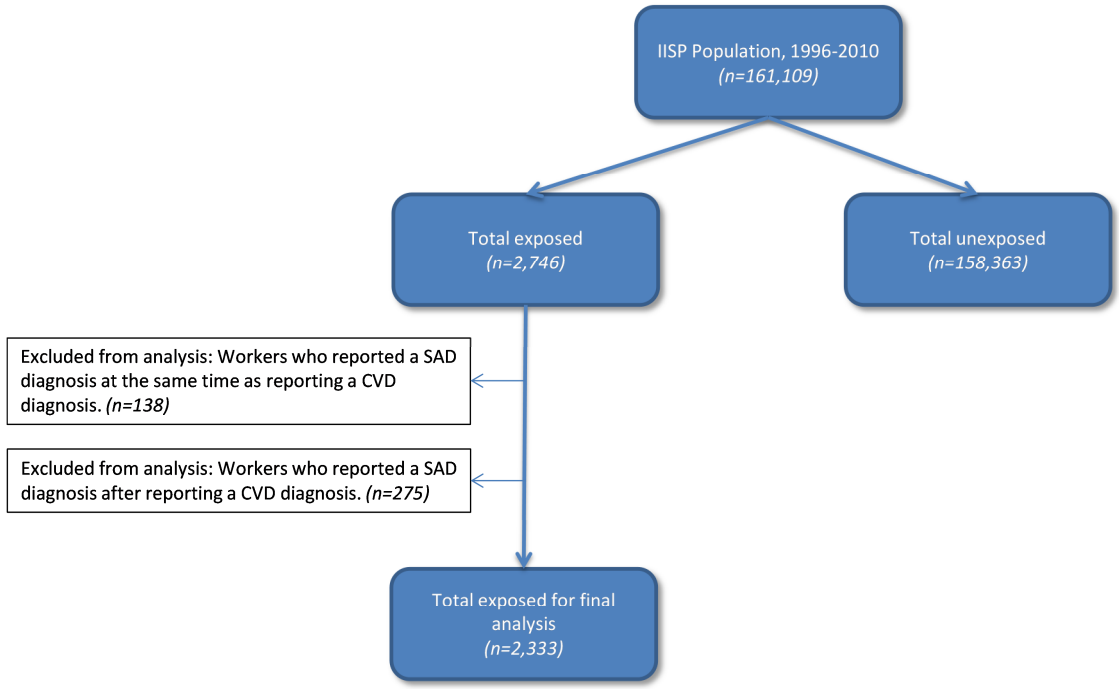

Figure 1. Flow chart of the population used in the SAD-CVD analysis.

There were 625 workers who reported a SAD diagnosis and a CVD diagnosis at some time during their employment. The majority of workers with a CVD did not report a SAD, 92.5%. Of those workers reporting a SAD and a CVD, most reported a SAD after reporting the CVD, 44.0% (Table 4). Workers who reported a SAD prior to reporting a CVD were used in the

analysis as the group of interest to determine the temporal association of reporting SAD and the development of CVD.

Using the smaller subset of CVD codes, the analysis indicated 428 workers who reported a SAD diagnosis and a CVD2 diagnosis at some time during their employment. Most workers who reported a CVD2 did not report a SAD, 90%. Of those workers reporting a SAD and a CVD2, the majority reported a CVD2 diagnosis prior to reporting a SAD diagnosis, 39.7% (Table 4).

In analysis of the association between anxiety (ANX) and CVD2, 185 workers reported an ANX diagnosis and a CVD2 diagnosis at some time during their employment. The majority of these workers reported a CVD2 diagnosis prior to reporting an ANX diagnosis, 43.8% (Table 4).

In the depression (DEP) to CVD2 analysis, 252 workers reported a DEP diagnosis and a CVD2 diagnosis at some time during their employment. Most workers never reported a DEP diagnosis, 94.1%. Workers reporting a CVD2 diagnosis prior to reporting a DEP were the largest majority, 40.9%, although the percentage of workers reporting a DEP prior to reporting a CVD2 was close, 38.9% (Table 4).

Table 4. Characteristics of U.S. Department of Energy, Illness and Injury Surveillance Program workers who reported SAD and CVD, 1996-2010.

Characteristic	CVD		No CVD			
	n=8,305	%	n=152,804	%	X^2 (d.f.)	*p-value*
Stress, anxiety, and depression (SAD) diagnosis reported						
No SAD diagnosis reported	7,680	*92.5%*	150,683	*98.6%*		
SAD diagnosis reported	625	*7.5%*	2,121	*1.4%*	1771.03 (1)	*<.0001*
SAD reported prior to CVD	212	*33.9%*	2,121	*100.0%*		
SAD reported at the same time as CVD	138	*22.1%*	0	*0.0%*		
SAD reported after CVD	275	*44.0%*	0	*0.0%*		

	CVD2		No CVD2			
	n=4,263	%	n=156,846	%	X^2 (d.f.)	*p-value*
Stress, anxiety, and depression (SAD) diagnosis reported						
No SAD diagnosis reported	3,835	*90.0%*	154,528	*98.5%*		
SAD diagnosis reported	428	*10.0%*	2,318	*1.5%*	1815.95 (1)	*<.0001*
SAD reported prior to CVD2	140	*32.7%*	2,318	*100.0%*		
SAD reported at the same time as CVD2	118	*27.6%*	0	*0.0%*		
SAD reported after CVD2	170	*39.7%*	0	*0.0%*		

	CVD2		No CVD2			
	n=4,263	%	n=156,846	%	X^2 (d.f.)	*p-value*
Anxiety (ANX) diagnosis reported						
No ANX diagnosis reported	4,078	*95.7%*	156,001	*99.5%*		
ANX diagnosis reported	185	*4.3%*	845	*54.0%*	943.88 (1)	*<.0001*
ANX reported prior to CVD2	49	*26.5%*	845	*100.0%*		
ANX reported at the same time as CVD2	55	*29.7%*	0	*0.0%*		
ANX reported after CVD2	81	*43.8%*	0	*0.0%*		

	CVD2		No CVD2			
	n=4,263	%	n=156,846	%	X^2 (d.f.)	*p-value*
Depression (DEP) diagnosis reported						
No DEP diagnosis reported	4,011	*94.1%*	155,411	*99.1%*		
DEP diagnosis reported	252	*5.9%*	1,435	*0.9%*	999.92 (1)	*<.0001*
DEP reported prior to CVD2	98	*38.9%*	1,435	*100.0%*		
DEP reported at the same time as CVD2	51	*20.2%*	0	*0.0%*		
DEP reported after CVD2	103	*40.9%*	0	*0.0%*		

Abbreviations: X^2, Chi-square test; d.f., degrees of freedom
For ICD-9-CM codes for SAD, CVD, CVD2, ANX, and DEP diagnoses, see Appendix B.

Crude and adjusted odds ratios were computed on the association of SAD with CVD on the full population with no consideration for temporality. The crude OR indicated a strong positive association between SAD and CVD in the IISP population, OR: 5.78; CI: 5.27, 6.34. Odds ratios for other variables are similarly high, with length on roster having the lowest odds ratio, OR: 3.89; CI: 3.54, 4.28. All odds ratios had very narrow confidence intervals ranging from 0.74 to 1.36, indicating good precision. The Breslow-Day Test for homogeneity of odds ratios indicated that gender and SES were not significant effect modifiers of this association. Neither of these variables was found to be a confounder using the 10% rule for confounding (Table 5).

To explore the temporal association of prior SAD-CVD, crude and adjusted odds ratios were computed excluding those workers who reported a SAD and CVD at the same time and those reporting a SAD after reporting a CVD (Figure 1). The crude OR indicated a positive association between reporting a SAD diagnosis prior to reporting a CVD diagnosis, OR: 1.96; CI: 1.70, 2.26. Odds ratios adjusting for the other variables one at a time were similar to the unadjusted odds ratio with gender being the highest, OR: 2.13; CI: 1.84, 2.46. Confidence intervals were very narrow, ranging from 0.38 to 0.62, indicating very good precision. The Breslow-Day Test indicated that gender and SES were not significant effect modifiers of this association. Neither variable was a confounder in this relationship (Table 5).

Table 5. Association of stress, anxiety, and depression (SAD) diagnosis with cardiovascular disease (CVD) diagnosis, unadjusted and adjusted for other characteristics of U.S. Department of Energy, Illness and Injury Surveillance Program workers, 1996-2010.

Adjusted For	SAD	No Temporality[a]			Temporality[b]		
		Odds Ratio	*95% C.I.*	*B-D Test p-value*	Odds Ratio	*95% C.I.*	*B-D Test p-value*
Nothing (crude)	SAD diagnosis reported	5.78	*5.27, 6.34*		1.96	*1.70, 2.26*	
	No SAD diagnosis reported (reference)	1	---		1	---	
Gender	SAD diagnosis reported	6.27	*5.72, 6.89*	0.7893	2.13	*1.84, 2.46*	0.5878
	No SAD diagnosis reported (reference)	1	---		1	---	
Birth Decade	SAD diagnosis reported	5.37	*4.89, 5.90*	<.0001	1.82	*1.58, 2.11*	<.0001
	No SAD diagnosis reported (reference)	1	---		1	---	
Age First on Roster	SAD diagnosis reported	5.63	*5.12, 6.18*	0.0040	1.91	*1.65, 2.21*	0.0221
	No SAD diagnosis reported (reference)	1	---		1	---	
Socioeconomic Status	SAD diagnosis reported	5.26	*4.79, 5.77*	0.0951	1.78	*1.54, 2.06*	0.7612
	No SAD diagnosis reported (reference)	1	---		1	---	
Region	SAD diagnosis reported	5.31	*4.84, 5.83*	0.0003	1.81	*1.57, 2.09*	<.0001
	No SAD diagnosis reported (reference)	1	---		1	---	
Length on Roster	SAD diagnosis reported	3.89	*3.54, 4.28*	<.0001	1.30	*1.13, 1.51*	0.0165
	No SAD diagnosis reported (reference)	1	---		1	---	

Abbreviations: C.I., confidence interval; B-D Test, Breslow-Day test for homogeneity of odds ratios
For ICD-9-CM codes for SAD and CVD diagnoses, see Appendix B.

[a] Straight SAD to CVD relationship with no consideration for temporality

[b] Temporal association for prior SAD to CVD, excludes workers who reported a SAD diagnosis at the same time as a CVD diagnosis AND workers who reported a SAD diagnosis after they reported a CVD diagnosis

Logistic regression models were computed using all variables as potential effect modifiers to explore the temporal relationship of reporting SAD prior to reporting a CVD, excluding those workers who reported a SAD and CVD at the same time and those reporting a SAD after reporting a CVD (Figure 1).

The fully adjusted model for the prior SAD to CVD relationship indicated a positive association that is statistically significant, OR: 1.36; CI: 1.17, 1.58; Wald p-value: <.0001. The final adjusted model excluded gender and SES since neither were effect modifiers or confounders on this association (Table 6). Birth decade, age first on roster, region, and length on roster were effect modifiers of this association.

The odds ratio for the fully adjusted model of prior SAD to CVD2 is slightly higher than the odds ratio for the prior SAD to CVD association, OR: 1.59; CI: 1.33, 1.90; Wald p-value: <.0001; and is statistically significant. In the final model, length on roster was excluded since it was neither an effect modifier nor confounder (Table 6). Birth decade, age first on roster, and region were significant effect modifiers while gender and SES were confounders for this association.

In the fully adjusted model for the prior ANX to CVD2 association, the odds ratio was similar to that of the prior SAD to CVD association and statistically significant, OR: 1.37; CI: 1.02, 1.85; Wald p-value: <.0001. The final model excluded length on roster because it was not an effect modifier or a confounder (Table 6). Age first on roster and region were significant effect modifiers while gender, birth decade, and SES were confounders.

The fully adjusted model for the prior DEP to CVD2 association indicated a positive association, OR: 1.68; CI: 1.35, 2.08; Wald p-value: <.0001; and was statistically significant. As with ANX to CVD2, this model excluded the length on roster because it was neither an effect

modifier nor a confounder (Table 6). Birth decade, age first on roster, and region were significant effect modifiers, while gender and SES were confounders. This association was the highest odds ratio out of the prior SAD to CVD, prior SAD to CVD2, prior ANX to CVD2, and prior DEP to CVD2 analyses.

Table 6. Fully Adjusted and Final Logistic Regression Models for the Temporal SAD to CVD Association Using Data from the U.S. Department of Energy, Illness and Injury Surveillance Program workers, 1996-2010.

Association	Fully Adjusted Model[b]			Final Model		
	Odds Ratio	*95% C.I.*	*Wald p-value*	Odds Ratio	*95% C.I.*	*Wald p-value*
SAD to CVD[a]	1.36	1.17, 1.58	<.0001	1.43[c]	1.24, 1.66	<.0001
SAD to CVD2[a]	1.59	1.33, 1.90	<.0001	1.71[d]	1.43, 2.05	<.0001
Anxiety to CVD2[a]	1.37	1.02, 1.85	<.0001	1.53[d]	1.14, 2.05	<.0001
Depression to CVD2[a]	1.68	1.35, 2.08	<.0001	1.76[d]	1.43, 2.18	<.0001

Abbreviations: C.I., confidence interval

For ICD-9-CM codes for SAD, CVD, CVD2, ANX, and DEP diagnoses, see Appendix B.

[a] Temporal association for prior SAD to CVD, excludes workers who reported a SAD diagnosis at the same time as a CVD diagnosis AND workers who reported a SAD diagnosis after they reported a CVD diagnosis

[b] Fully adjusted models are adjusted for gender, birth decade, age first on roster, socioeconomic status, region, and length on roster

[c] Adjusted for birth decade, age first on roster, region, and length on roster

[d] Adjusted for gender, birth decade, age first on roster, socioeconomic status, and region

SAD and INF Association

To explore the temporal association of a prior SAD diagnosis, workers who reported a SAD at the same time as a INF and those workers reporting a SAD after reporting a INF were excluded from the final analysis (Figure 2).

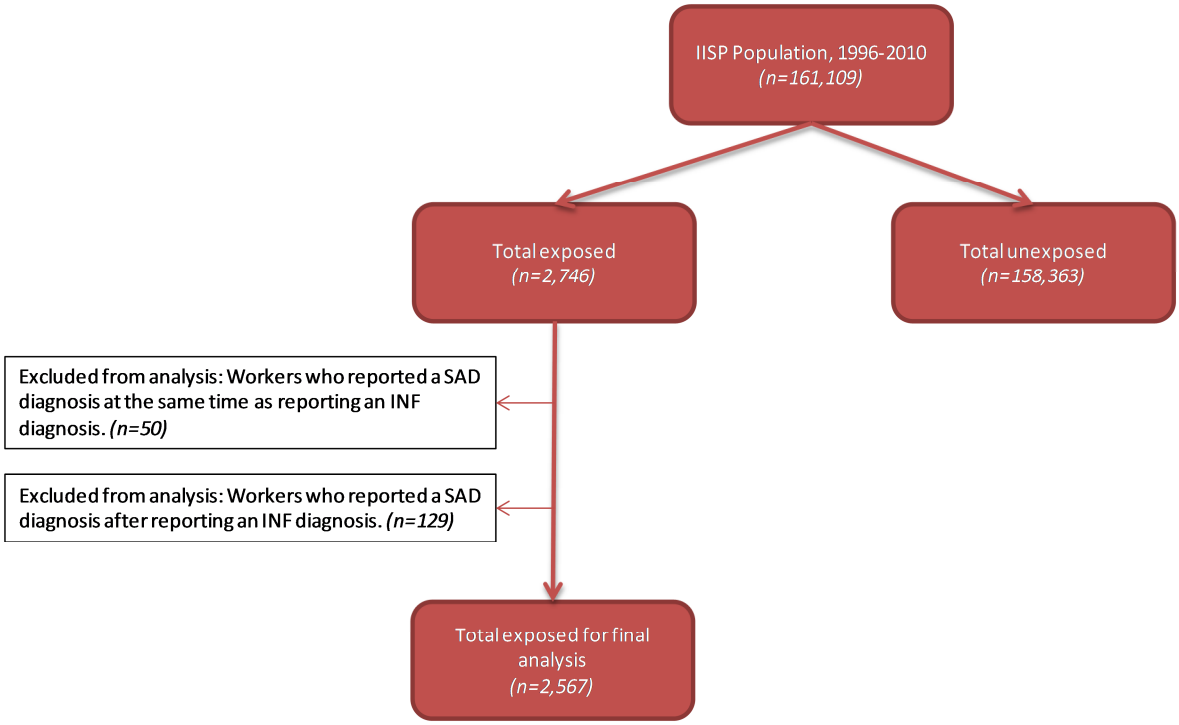

Figure 2. Flow chart of the population used in the SAD-INF analysis.

There were 340 workers who reported a SAD diagnosis and an INF diagnosis at some time during their employment. The majority of workers with an INF did not report a SAD, 86.7%. Of those workers reporting a SAD and an INF, most reported a SAD prior to reporting the INF, 47.4% (Table 7). Workers who reported a SAD prior to reporting an INF were used in the analysis as the group of interest to determine the temporal association of reporting SAD and the development of INF.

In analysis of the association between anxiety (ANX) and INF, 124 workers reported an ANX diagnosis and an INF diagnosis at some time during their employment. The majority of these workers reported an INF diagnosis after reporting an ANX diagnosis, 46.0% (Table 7).

In the depression to INF analysis, 240 workers reported a depression diagnosis and an INF diagnosis at some time during their employment. Most workers never reported a DEP diagnosis, 90.6%. Workers reporting a DEP prior to reporting an INF diagnosis were the largest majority, 47.1% (Table 7).

Table 7. Characteristics of U.S. Department of Energy, Illness and Injury Surveillance Program workers who reported SAD and INF 1996-2010.

Characteristic	INF		No INF			
	n=2,556	%	n=158,553	%	X^2 (d.f.)	*p-value*
Stress, anxiety, and depression (SAD) diagnosis reported						
No SAD diagnosis reported	2,216	*86.7%*	156,147	*98.5%*		
SAD diagnosis reported	340	*13.3%*	2,406	*1.5%*	2085.10 (1)	*<.0001*
SAD reported prior to INF	161	*47.4%*	2,406	*100.0%*		
SAD reported at the same time as INF	50	*14.7%*	0	*0.0%*		
SAD reported after INF	129	*37.9%*	0	*0.0%*		
Anxiety (ANX) diagnosis reported						
No ANX diagnosis reported	2,435	*95.2%*	157,647	*99.4%*		
ANX diagnosis reported	124	*4.9%*	906	*57.0%*	725.36 (1)	*<.0001*
ANX reported prior to INF	57	*46.0%*	906	*100.0%*		
ANX reported at the same time as INF	20	*16.0%*	0	*0.0%*		
ANX reported after INF	47	*37.9%*	0	*0.0%*		
Depression (DEP) diagnosis reported						
No DEP diagnosis reported	2,316	*90.6%*	157,106	*99.1%*		
DEP diagnosis reported	240	*9.4%*	1,447	*91.0%*	1744.54 (1)	*<.0001*
DEP reported prior to INF	113	*47.1%*	1,447	*100.0%*		
DEP reported at the same time as INF	35	*14.6%*	0	*0.0%*		
DEP reported after INF	92	*38.3%*	0	*0.0%*		

Abbreviations: X^2, Chi-square test; d.f., degrees of freedom
For ICD-9-CM codes for SAD, INF, ANX, and DEP diagnoses, see Appendix B.

Crude and adjusted odds ratios were computed on the association of SAD with INF on the full population with no consideration for temporality. The crude OR indicated a very strong positive association between SAD and INF in the IISP population, OR: 9.96; CI: 8.82, 11.24. Odds ratios adjusting for the other variables one at a time are similarly high with length on roster having the lowest odds ratio, OR: 6.82; CI: 6.04, 7.72. The Breslow-Day Test for homogeneity of odds ratios indicated that birth decade and age first on roster were not significant effect modifiers of this association. Gender and length on roster were found to be confounders (Table 8).

To explore the temporal association of prior SAD-INF, crude and adjusted odds ratios were computed excluding those workers who reported a SAD and INF at the same time and those reporting a SAD after reporting an INF (Figure 2). The crude OR indicated a strong positive association between reporting a SAD diagnosis prior to reporting an INF diagnosis, OR: 4.72; CI: 4.00, 5.56. Odds ratios adjusting for the other variables one at a time were similar to the unadjusted odds ratio with birth decade and region being the highest, OR: 4.41. The Breslow-Day Test indicated that region was the only significant effect modifiers of this association. Gender, age first on roster, and length on roster were confounders (Table 8).

Table 8. Association of stress, anxiety, and depression (SAD) diagnosis with inflammatory disorders (INF), unadjusted and adjusted for other characteristics of U.S. Department of Energy, Illness and Injury Surveillance Program workers, 1996-2010.

Adjusted For	SAD	No Temporality[a]			Temporality[b]		
		Odds Ratio	*95% C.I.*	*B-D Test p-value*	Odds Ratio	*95% C.I.*	*B-D Test p-value*
Nothing (crude)	SAD diagnosis reported	9.96	*8.82, 11.24*		4.72	*4.00, 5.56*	
	No SAD diagnosis reported (reference)	1	---		1	---	
Gender	SAD diagnosis reported	8.50	*7.52, 9.62*	0.8066	4.02	*3.41, 4.75*	0.6153
	No SAD diagnosis reported (reference)	1	---		1	---	
Birth Decade	SAD diagnosis reported	9.30	*8.24, 10.51*	0.4418	4.41	*3.73, 5.20*	0.4233
	No SAD diagnosis reported (reference)	1	---		1	---	
Age First on Roster	SAD diagnosis reported	9.27	*8.20, 10.47*	0.6249	4.39	*3.72, 5.18*	0.8103
	No SAD diagnosis reported (reference)	1	---		1	---	
Socioeconomic Status	SAD diagnosis reported	8.63	*7.64, 9.76*	0.0100	4.09	*3.46, 4.82*	0.2722
	No SAD diagnosis reported (reference)	1	---		1	---	
Region	SAD diagnosis reported	9.31	*8.23, 10.54*	0.0116	4.41	*3.73, 5.21*	0.0012
	No SAD diagnosis reported (reference)	1	---		1	---	
Length on Roster	SAD diagnosis reported	6.82	*6.04, 7.72*	0.0718	3.23	*2.73, 3.81*	0.8026
	No SAD diagnosis reported (reference)	1	---		1	---	

Abbreviations: C.I., confidence interval; B-D Test, Breslow-Day test for homogeneity of odds ratios
For ICD-9-CM codes for SAD and INF diagnoses, see Appendix B.

[a] Straight SAD to INF relationship with no consideration for temporality

[b] Temporal association for prior SAD to INF excludes workers who reported a SAD diagnosis at the same time as an INF diagnosis AND workers who reported a SAD diagnosis after they reported an INF diagnosis

Logistic regression models were computed using all variables as potential effect modifiers to explore the temporal relationship of reporting SAD prior to reporting an INF, excluding those workers who reported a SAD and INF at the same time and those reporting a SAD after reporting an INF (Figure 2).

The fully adjusted model for the prior SAD to INF relationship indicated a positive association that is statistically significant, OR: 2.31; CI: 1.95, 2.75; Wald p-value: <.0001. The final adjusted model excluded birth decade and SES since neither were effect modifiers or confounders on this association (Table 9). This association was the highest odds ratio out of the prior SAD to INF, prior ANX to INF, and prior DEP to INF analyses.

In the fully adjusted model for the prior ANX to INF association, the odds ratio was slightly lower to that of the prior SAD to INF association and statistically significant, OR: 1.93; CI: 1.46, 2.56; Wald p-value: <.0001. The final model included all variables (Table 9). Gender, age first on roster, birth decade, region, and length on roster were confounders while SES was the only significant effect modifier.

The fully adjusted model for the prior DEP to INF association indicated a positive association, OR: 2.4; CI: 1.95, 2.94; Wald p-value: <.0001; and was statistically significant. As with ANX to INF, this model included all variables (Table 9). Region was the only significant effect modifier while gender, birth decade, age first on roster, SES, and length on roster were all confounders.

Table 9. Fully Adjusted and Final Logistic Regression Models for the Temporal SAD to INF Association Using Data from the U.S. Department of Energy, Illness and Injury Surveillance Program workers, 1996-2010.

Association	Fully Adjusted Model[b]			Final Model		
	Odds Ratio	*95% C.I.*	*Wald p-value*	Odds Ratio	*95% C.I.*	*Wald p-value*
SAD to INF[a]	2.31	1.95, 2.75	<.0001	2.77[c]	2.33, 3.29	<.0001
Anxiety to INF[a]	1.93	1.46, 2.56	<.0001	1.93[b]	1.46, 2.56	<.0001
Depression to INF[a]	2.4	1.95, 2.94	<.0001	2.4[b]	1.95, 2.94	<.0001

Abbreviations: C.I., confidence interval

For ICD-9-CM codes for SAD, INF, ANX, and DEP diagnoses, see Appendix B.

[a] Temporal association for prior SAD to INF excludes workers who reported a SAD diagnosis at the same time as an INF diagnosis AND workers who reported a SAD diagnosis after they reported an INF diagnosis

[b] Fully adjusted models are adjusted for gender, birth decade, age first on roster, socioeconomic status, region, and length on roster

[c] Adjusted for gender, age first on roster, region, and length on roster

DISCUSSION

The findings from this analysis indicate a positive association between reporting a work absence for SAD and a CVD. Another goal of this study was to ask if a worker reports an absence for a SAD are the more likely to subsequently have an absence for a CVD. Indeed, the data indicate an association between a SAD and a subsequent CVD-related work absence. Gender and SES did not have an impact on this association which simply means that there was no difference across strata for the association. Secondary analysis indicated a positive association between prior SAD and CVD2. Length on roster did not have an impact on this association. There was a positive association between prior ANX and CVD2--length on roster did not impact this association. Finally, there was a positive association between DEP and CVD2, with length on roster not having an impact on this association. All associations were statistically significant.

In the SAD to INF analysis, there was a positive association between reporting a prior SAD and INF with birth decade and SES having no impact on the association. Anxiety and INF also indicated a positive association with all variables either having an effect or confounding the association. Depression and INF had a similar effect.

These findings are similar to current research which indicates a positive association between a prior SAD diagnosis and the development of a cardiovascular event or an inflammatory disorder (24).

Methodological Considerations

As with any study, there are strengths and weaknesses. A strength of this analysis is the longevity of the population. This population is relatively stable, allowing the cohort to be followed for a 15 year period. Worker demographics are varied and contributed from sites all over the United States. The study population provided a large sample size--there were over 1 million records in the roster file with over 161,000 workers. Because IISP workers are generally covered under their contractor's health insurance policy and may have access to health care, more diagnoses are reported allowing for a better record of what is actually happening at the site.

Some possible limitations to the data include self-reporting. Self-reporting may lead to bias due to memory, stigma or embarrassment with reporting actual diagnosis, or miscommunication.

A key limitation to this analysis is the absence of baseline data on conditions. Most cohort studies are conducted with a previously unexposed population. With this analysis, it had to be assumed that a worker was unexposed if he did not report the condition while employed. Some workers may have had a condition for years but did not report it while they were employed

and would get classified as unexposed. This baseline information would provide better information on time of exposure to time of outcome. With this analysis, it was assumed that time of exposure was the date at first reported absence for the diagnosis of interest.

Reporting variability between contractors limits the ability compare absences across sites. If one contractor requires reporting after one day but another only requires reporting after three days, diagnosed illnesses are going to be lost. Some sites report only one diagnosis code so bias can be introduced depending on which code the contractor submits to the IISP data center. It would have been helpful to have diagnostic information on workers who were receiving treatment but did not actually miss work. Comparative analysis could be done on workers who had intermittent versus chronic disorders, disorders which did not cause absences, or even treatment strategies.

The data collected does not contain information which may be useful for advanced analyses, such as BP, BMI, smoking, or dietary habits which are known risk factors for both CVD and INF. More refined diagnostic information would be helpful to indicate which workers had acute versus chronic illness.

The IISP population is working adults so any inference to the general population of working and non-working adults must be made with caution.

The IISP population workers are generally covered under their contractor's health insurance policy and may have increased access to health care when compared to the general population.

The results from this analysis show that the effect is similar in the working population as well as in the general population. Those who may not be healthy enough to work are not influencing the results seen in this worker population. Further study in a worker population for which additional information on known risk factors are available may refine the risk estimates.

REFERENCES

1. Chronic Disease. Centers for Disease Control and Prevention (CDC). (http://www.cdc.gov/chronicdisease/index.htm). (Accessed November 24 2011).
2. DeVol R, et al. An Unhealthy America: The Economic Burden of Chronic Disease. Milken Institute, 2007.
3. Reeves, WC, Strine, TW, Thompson, W, et al. Mental illness surveillance among adults in the United States. *MMWR Surveill Summ* 2011; Sep 2; 60 Suppl 3:1-29.
4. *Health, United States, 2010*. Centers for Disease Control and Prevention (CDC).
5. Autoimmune diseases fact sheet. U.S. Department of Health and Human Services Office on Women's Health. (http://womenshealth.gov/publications/our-publications/fact-sheet/autoimmune-diseases.cfm). (Accessed December 1, 2011).
6. Martens EJ, de Jonge P, Na B, et al. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease:The Heart and Soul Study. *Arch Gen Psychiatry* 2010;67(7):750-8.
7. Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA* 2008;300(20):2379-88.
8. Meyer T, Buss U, Herrmann-Lingen C. Role of cardiac disease severity in the predictive value of anxiety for all-cause mortality. *Psychosom Med* 2010;72(1):9-15.
9. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship? *J Affect Disord* 2004;79(1-3):81-95.
10. Glassman AH. Depression and cardiovascular comorbidity. *Dialogues Clin Neurosci* 2007;9(1):9-17.

11. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 2003;54(3):227-40.

12. Maggo S, Clark D, Ashton JC. The effect of statins on performance in the Morris water maze in guinea pig. *Eur J Pharmacol* 2011.

13. May HT, Bair TL, Lappe DL, et al. Association of vitamin D levels with incident depression among a general cardiovascular population. *Am Heart J* 2010;159(6):1037-43.

14. Cardiovascular disease risk factors. World Heart Federation. (http://www.world-heart-federation.org/cardiovascular-health/cardiovascular-disease-risk-factors). (Accessed November 24, 2011).

15. Kurina LM, Goldacre MJ, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. *J Epidemiol Community Health* 2001;55(10):716-20.

16. Sternberg EM, Chrousos GP, Wilder RL, et al. The stress response and the regulation of inflammatory disease. *Ann Intern Med* 1992;117(10):854-66.

17. Inflammatory Bowel Disease: Symptoms and Risk Factors. Physicians Committtee for Responsible Medicine. (http://www.tcolincampbell.org/courses-resources/article/inflammatory-bowel-disease-symptoms-and-risk-factors/category/gastrointestinal-disorders/?tx_ttnews%5BbackPid%5D=76&cHash=df19d3da3b). (Accessed November 24 2011).

18. Takeuchi, K, Tanaka, A, et al. Roles of COX inhibition in pathogenesis of NSAID-induced small intestinal damage. *Clin Chim Acta*. 2010 Apr 2;411(7-8):459-66.

18. Heller, M, Lee, E, Koo, J. Stress as an Influencing Factor in Psoriasis. *Skin Therapy Letter* 2011; 16(5).

19. Maes M, Kubera M, Obuchowiczwa E, et al. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. *Neuro Endocrinol Lett* 2011;32(1):7-24.

20. Albus C, Bjarnson-Wehrens B, Gysan DB, et al. The effects of multimodal intervention for the primary prevention of cardiovascular diseases on depression, anxiety, and Type-D pattern : Initial results of the randomized controlled PreFord trial. *Herz* 2011.

21. Stojanovich L, Marisavljevich D. Stress as a trigger of autoimmune disease. *Autoimmun Rev* 2008;7(3):209-13.

22. *ICD-9-CM: international classification of diseases, 9th revision; clinical modification, 6th edition, 2010*. Hospital Edition. Volumes 1, 2, and 3 ed.: Ingenix.

23. *Healthcare Cost & Utilization Project (HCUP) Care of Adults With Mental Health and Substance Abuse Disorders in U.S. Community Hospitals, 2004: Fact Book No. 10*. Agency for Healthcare Research and Quality.

24. Maes, M. Major depression and activation of the inflammatatory response system. *Adv Exp Med Biol* 1999; 461:25-46.

APPENDIX A. ABBREVIATIONS

ANX	Anxiety
CVD	Cardiovascular Disease
CVD2	Subset of cardiovascular disease
DEP	Depression
DOE	U.S. Department of Energy
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IISP	Illness Injury and Surveillance Program
INF	Inflammatory Disorder
OEWH	Occupational Exposure and Worker Health
ORISE	Oak Ridge Institute for Science and Education
SAD	Stress, Anxiety, and Depression
SES	Socioeconomic Status

APPENDIX B. ICD-9-CM CODES USED IN ANALYSIS

Stress, Anxiety, or Depression (SAD):

ICD-9 Code	Description
293.83	Mood disorder in conditions classified elsewhere
293.84	Anxiety disorder in conditions classified elsewhere
296.2	Major depressive disorder, single episode
296.3	Major depressive disorder, recurrent episode
300.0	Anxiety states
300.10	Hysteria, unspecified
300.2	Phobic disorders
300.3	Obsessive-compulsive disorders
300.4	Dysthymic disorder
300.5	Neurasthenia
300.89	Other somatoform disorders
300.9	Unspecified nonpsychotic mental disorder
308	Acute reaction to stress
309.0	Adjustment disorder with depressed mood
309.1	Prolonged depressive reaction
309.22	Emancipation disorder of adolescence and early adult life
309.23	Specific academic or work inhibition
309.24	Adjustment disorder with anxiety
309.28	Adjustment disorder with mixed anxiety and depressed mood
309.29	Other
309.3	Adjustment disorder with disturbance of conduct
309.4	Adjustment disorder with mixed disturbance of emotions and conduct
309.81	Posttraumatic stress disorder
309.82	Adjustment reaction with physical symptoms
309.83	Adjustment reaction with withdrawal
309.89	Other
309.9	Unspecified adjustment reaction
311	Depressive disorder, not elsewhere classified
313.0	Overanxious disorder
313.1	Misery and unhappiness disorder
313.21	Shyness disorder of childhood
313.22	Introverted disorder of childhood
313.3	Relationship problems
313.82	Identity disorder
313.83	Academic underachievement disorder

*SAD diagnoses were chosen based on algorithm used by the Agency for Healthcare Research and Quality's Mental Health and Substance Abuse Clinical Classification Software (CCS-MHSA).

Cardiovascular Disease (CVD):

ICD-9 Code	Description
390-459	**Diseases of the Circulatory System**
390-392	Acute Rheumatic Fever (occurs mainly in children, NLM)
393-398	Chronic Rheumatic Heart Disease (complication of rheumatic fever)
401-405	*Hypertensive disease*
410-414	*Ischemic heart disease*
415-417	Diseases of pulmonary circulation
420-429	Other forms of heart disease *428 Heart failure*
430-438	*Cerebrovascular disease*
440-449	Diseases of arteries, arterioles, and capillaries *440 Atherosclerosis*
451-459	Diseases of veins and lymphatics, and other diseases of the circulatory system

Italicized items are included in the subset of CVD diagnosis, CVD2

Inflammatory disorders (INF)*:

ICD-9 Code	Description
780.71	Chronic fatigue syndrome
493	Asthma
496	COPD
714	Rheumatoid arthritis and other inflammatory polyarthropathies
695.4	Lupus erythematosus
710.0	Systemic lupus erythematosus
710.2	Sicca syndrome
710.4	Polymyositis
696	Psoriasis and similar disorders
729.1	Fibromyalgia
555-558	Noninfectious enteritis and colitis (IBD)
564.1	Irritable bowel syndrome

*Select inflammatory disorders were chosen based on literature review.

Anxiety:

ICD-9 Code	Description
300.00	Anxiety state unsp
300.0	Anxiety states
300.02	Generalized anxiety disorder
300.09	Oth Anxiety States
300.29	Oth Isolated/Simple phobia
300.01	Panic disorder
300.20	Phobia unsp
308.0	Predominant disturbance emotio
309.81	Prolong posttraumatic stress
300.23	Social phobia
309.24	Adjustment disorder with anxiety

Depression:

ICD-9 Code	Description
309.1	Prolonged depressive reaction
309.0	Adjustment disorder with depressed mood
311	Depressive disorder, not elsewhere classified
296.33	Maj depress aff dis recurr sev
296.30	Maj depress aff dis recurr uns
296.21	Maj depress aff dis sing mild
296.32	Maj depress affect dis recurr
296.3	Major depressive disorder recu
296.23	Major depressive disorder seve
296.20	Major depressive disorder unsp
300.4	Neurotic depression
298.0	Depressive type psychosis

APPENDIX C. VARIABLE GROUPS

Birth Decades:

- 1940 or earlier
- 1950
- 1960
- 1970
- 1980 or later

Regions:

West:

- Hanford Site, Richland, WA
- Idaho National Laboratory, Idaho Falls, ID
- Lawrence Livermore National Laboratory, Livermore, CA
- Nevada National Security Site, Las Vegas, NV
- Rocky Flats, Golden, CO

Northeast:

- Brookhaven National Laboratory, Upton, NY

Southwest:

- Los Alamos National Laboratory, Los Alamos, NM
- Pantex Plant, Amarillo, TX
- Sandia National Laboratories – Albuquerque, Albuquerque, NM

Midwest:

- Argonne National Laboratory, Argonne, IL
- Fernald Facility, Fernald, OH
- Kansas City Plant, Kansas City, MO

Southeast:

- East Tennessee Technology Park, Oak Ridge, TN
- Oak Ridge National Laboratory, Oak Ridge, TN
- Savannah River Site, Aiken, SC
- Y-12 National Security Complex, Oak Ridge, TN

Socioeconomic Status:

Low:

- Service - Typically includes but is not limited to custodians, drivers, laborers, laundry workers, linemen, mail clerks, pilots, railroad engineers, records center workers, stationary engineers, utility workers, and water plant operators. These workers support and maintain the facility's infrastructure and have the potential for a broad range of exposures. Most work is not performed sitting at a desk.
- Crafts - Typically includes bargaining unit employees and laborers. They have the potential for a broad range of exposures.
- Line Operators - Typically workers who are directly involved in process operation, or line activities at the facility. Potential for chemical and/or radiation exposure on a regular basis.

Medium:

- Administrative Support - Predominately office work at a desk; heavy computer usage; anticipated risks primarily ergonomic. This category includes but is not limited to information technology, clerical, and secretarial staff.
- Technical Support - Workers who typically support the field professionals and have hands-on work situations. Potential for exposure to chemical or radiation hazards; the potential for exposure may be higher than for the field professionals.
- Security and Fire - Typically includes protective forces and firefighters.

High:

- Management – Predominately office work at a desk; first level supervisor and above; anticipated risks primarily ergonomic.
- In-House Professionals – Predominately office work at a desk typically without supervisory responsibilities. The risks are primarily ergonomic.
- Field Professionals – Frequently works outside of their office in areas such as but not limited to laboratories, testing areas, and construction areas. Potential for exposure to chemical or radiation hazards.
- Biohazard - Workers who have the potential for exposure to biological hazards. This includes medical technicians, nurses, laboratory staff, animal caretakers, physicians, and veterinarians.

*Guests and Unknowns are not included in this analysis.

APPENDIX D. IRB DOCUMENTATION

In accordance with IRB requirements, this study protocol was submitted to the Emory IRB and the Oak Ridge Site-wide IRB for approval. This study was exempted from IRB review at the Oak Ridge Site-wide IRB. The Emory IRB determined that the study did not require IRB review. Documentation attached.

Oak Ridge Site-wide Institutional Review Board (ORSIRB)
Telephone (865) 576-1725
Becky.Hawkins@orise.orau.gov

MEMORANDUM

DATE:	September 20, 2011
TO:	Kellye Sliger
FROM:	Oak Ridge Site-Wide IRB (FWA #00005031)
STUDY TITLE:	[271284-1] The Effects of Stress, Anxiety, and Depressive Disorders on the Development of Cardiovascular Disease or Inflammatory Disorders in the U.S. Department of Energy Work Force
IRB REFERENCE #:	ORAU EX(11)-18
SUBMISSION TYPE:	New Project
ACTION:	DETERMINATION OF EXEMPT STATUS
DECISION DATE:	September 20, 2011

Thank you for your submission of New Project materials for this research study. The Oak Ridge Site-Wide IRB has determined this project is EXEMPT FROM IRB REVIEW according to federal regulations.

We will put a copy of this correspondence on file in our office and contact you in approximately a year to determine if tihs project is still ongoing. Any revisions to this project must be reported to the IRB using the appropriate Amendment Request form prior to any changes being implemented.

If you have any questions, please contact Becky Hawkins at 865-576-1725 or becky.hawkins@orise.orau.gov. Please include your study title and reference number in all correspondence with this office.

EMORY UNIVERSITY

Institutional Review Board

September 20, 2011

RE: Determination: No IRB Review Required
Title: The Effects of Stress, Anxiety, and Depressive Disorders on the Development of Cardiovascular Disease or Inflammatory Disorders in the U.S. Department of Energy Work Force
PI: Kellye Sliger

Dear Ms. Sliger:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" involving "human subjects" or the definition of "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will be conducting a secondary analysis of non identifiable data.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Andrea Goosen, MPH
Research Protocol Analyst
This letter has been digitally signed

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu

Oak Ridge Site-wide Institutional Review Board (ORSIRB) **Human Subjects Research Application (FWA0005031)**	
The protocol must be submitted in typed form and all applicable items must be answered using non-technical language.	
Protocol Title:	The Effects of Stress, Anxiety, and Depressive Disorders on the Development of Cardiovascular Disease or Inflammatory Disorders in the U.S. Department of Energy Work Force
Principal Investigator:	Kellye D. Sliger
Institution/Address:	Oak Ridge Institute for Science and Education P.O. Box 117, MS 45 Oak Ridge, TN 37831-0117
Phone:	865-576-0145
E-mail:	Kellye.Sliger@orise.orau.gov
Co-Principal Investigator:	Dr. Elizabeth Ellis
Institution/Address:	Oak Ridge Institute for Science and Education P.O. Box 117, MS 45 Oak Ridge, TN 37831-0117
Phone:	865-576-3528
E-mail:	Betsy.Ellis@orau.org
Collaborating Institution(s):	Emory University
Funding Source (including office within agency):	Department of Energy, Office of Health and Safety
Funding Agreement Number:	
Estimated Annual Funding:	$0
Estimated Start Date:	September 16, 2011
Human Subjects Training. *Principal Investigators and co-Principal Investigators MUST take and pass a training course on*	

human subjects research prior to commencement of work on non-exempt research. CITI at www.citiprogram.org is preferred; however, the ORSIRB may accept proof of training from other approved human subjects training. Documentation of training must be included in your "User Profile" in IRBNet if this is your first submission. This documentation will continue to be flagged in future submissions. Refresher training is required every three years.

I. General Information

Summarize the proposed research using non-technical language that can be understood by members whose primary concerns are non-scientific. ***Please answer all questions in the unshaded areas. Answer N/A for questions that do not apply to your research project.***

(a) Objective(s) of the study: Provide a brief, non-technical statement of the purpose, background, and significance of the study.

The purpose of this study is to examine the relationship between stress, anxiety, and depression and the development of cardiovascular disease or inflammatory disorders in a population of working adults. For many years, research has shown a direct relationship between having a cardiovascular event or an inflammatory disorder and the development of stress, anxiety, or depression (SAD). New research is showing a temporal relationship between having a SAD diagnosis and developing a cardiovascular disease or an inflammatory disorder. I wish to expolore this relationship in the U.S. Department of Energy (DOE) contractor work force data.

(b) Methods of Procedure: Explain in non-technical language the experimental design and how the study is being conducted?

Data was collected through the Department of Energy Illness and Injury Surveillance Program (IISP). The IISP database is maintained by the Oak Ridge Institute for Science and Education (ORISE) Occupational Exposure and Worker Health (OEWH) Program. The IISP regularly and systematically collects, maintains, analyzes, and interprets return-to-work data on illness and injury prevalence in the DOE contractor work force. At present, there are 14 sites participating in the IISP.

Illness and Injury Surveillance Program data analyze return to work data from records maintained by occupational medicine clinics, and other data from industrial hygiene and safety organizations, and human resource departments. The data are de-identified to protect worker confidentiality. Each worker is assigned a unique, permanent identification number encrypted by the occupational medicine department at the participating DOE site. Personal identifying information is removed from the record at the site and is not included in the IISP data base.

Note: The principal investigator is responsible for taking all necessary steps to maintain confidentiality and protection. This includes coding and choosing an appropriate and secure storage mechanism that will prevent unauthorized access to the data, biological specimen/tissues, or information obtained through interviews, surveys, or questionnaires. Clear explanation regarding use, access, duration of maintenance/storage, and disposal must be provided in the Informed Consent.

Does this project involve collection of data (records review, testing data, etc.) or biological materials samples/tissues, cells/cell lines)

OR

Interview/Survey/Questionnaires? ☒ Yes ☐ No Complete section (c).

(c) Data, biological materials, or Interview/Survey/Questionnaire information to be collected

Examples of types of items which may be associated with human subjects research data include, but are not limited to:

- Images
- Questionnaire or survey responses
- Sensor data
- Video and/or audio recordings
- Large datasets which include PII information
- Medical records/Clinical data
- Cell/Tissue/Body Fluid/Other Bodily Products

1) Describe how and from whom data, biological materials, or interview/survey information will be collected and recorded?

Illness and Injury Surveillance Program data analyze return to work data from records maintained by occupational medicine clinics, and other data from industrial hygiene and safety organizations, and human resource departments. The data are de-identified to protect worker confidentiality. Each worker is assigned a unique, permanent identification number encrypted by the occupational medicine department at the participating DOE site. Personal identifying information is removed from the record at the site and is not included in the IISP data base.

2) Who will have access?

Only staff members working on the project will have access to the data.

3) How will confidentiality be maintained?

The data are de-identified. All study files are password-protected and only those working on the project will have access.

4) Number of subjects expected to be enrolled or number or samples to be obtained.	190,290

Click twice on the appropriate box; then select "checked" in the new window that opens; then click on "ok." Cursor must be ON the box. Text answers should be typed into the unshaded box below the question.

5) Will information will be associated with any personal identifiers? ☐ Yes ☒ No If yes, explain and describe the coding method.

6) Will identifiable data be released? ☐ Yes ☒ No ☐ N/A If yes, specify the person or agency to whom they will be released.

7) How long will data, biological materials, or survey/interview information be kept after the

project's completion?
The computer files will be kept indefinitely for future analysis as is customary for occupational epidemiologic studies.
8) What are the methods of disposal of hard copy and electronic information?
Hard copy data will be limited. Those that are necessary will be shredded using the services of a secure shredding contractor. After the study is completed the data will be placed in the DOE Comprehensive Epidemiologic Data Resource.
9) Are surveys, interviews and/or focus groups going to be audio/video taped? ☐ **Yes** ☒ **No If yes, please explain why and how these recordings are going to be used, how long these audio/video tapes will be kept, and how they will be destroyed?**
10) Will data, biological materials, or survey/interview information will be used for any purpose other than for this study? ☒ **Yes** ☐ **No If yes, please explain.**
The data are collected through the DOE Illness and Injury Surveillance Program and will be used indefinitely as is customary for occupational epidemiologic studies.
11) Do you intend to create a new data base using the information from this study? ☐ **Yes** ☒ **No If yes, please explain the rationale for this and whether identifying information will be included in the new data base.**
12) Do you plan to publish the results of this study? ☒ **Yes** ☐ **No If yes, please explain.**
Results from this study will be sent to an epidemiologic or occupational health journal for publication.
13) If the data subject to the DHHS Health Insurance and Portability Accounting Act (HIPAA), please confirm that the institutions involved in this research are in compliance with the requirements of 45 CFR Parts 160 and 164.
The data are de-identified.

II. Beneficence: Risk/Benefit Considerations

The protocol must describe all procedures (including safeguards for preservation of confidentiality) for: maximizing potential benefits to subjects or to society; protecting against or minimizing known or potential risks. The potential benefits must outweigh the risks.

(a) Potential benefits to subjects: Describe any benefits that individual subjects may receive as a result of their participation in this research.

There are no direct benefits to the study participants.

(b) Potential benefits to others: Describe any potential benefits to society that may be expected from this research.

The results of this study will be added to the body of literature concerning the health effects associated with stress, anxiety, and depression and cardiovascular disease or inflammatory disorders in the DOE IISP population.

(c) Potential or real risks to subjects: Describe the risk/benefit ratio of the research compared to that of available alternatives.

There is no risk to the subjects.

(d) Does participating in this protocol present any unusual risks to the confidentiality of subjects' medical information (for example, history of drug use; genetic testing)?

☐ **Yes** ☒ **No If yes, please explain what will be done to protect confidentiality.**

Deception. Investigators must not exclude information from a subject that a reasonable person would want to know in deciding whether to participate in a study.

(a) Will information about the research purpose and design be withheld from subjects?

☐ **Yes** ☒ **No If yes, please explain and justify.**

Adverse Events. All UNANTICIPATED PROBLEMS and SERIOUS and UNEXPECTED adverse events must be reported to this office.

(a) Explain how and who will handle unanticipated problems and adverse events.

There is no risk to the subjects.

(b) Explain what facilities/equipment are available to handle adverse events.

There is no risk to the subjects.

III. Autonomy: Respect for Persons, PHI & Informed Consent

With very few exceptions, the protocol must describe the procedure to be followed in obtaining an

informed and legally effective consent to participate in the research and to use and disclose protected health information.

(a) Explain how and by whom potential subjects will be identified or approached for purposes of recruitment. Attach a copy of any planned advertisements/notices and letters to potential subjects.

The data used for this study will come entirely from the IISP. The data contained in the IISP are return to work data from records maintained by occupational medicine clinics, and other data from industrial hygiene and safety organizations, and human resource departments.

(b) Are there are any inclusion/exclusion criteria based on age, gender, pregnancy, childbearing potential, or race/ethnic origin? ☐ Yes ☒ No If yes, please explain.

(c) Explain how and by whom informed consent will be obtained.

Requesting a waiver of informed consent.

Please note: You may request a waiver of informed consent (45 CFR 46.116(d)) or a waiver of DOCUMENTATION of informed consent (45 CFR 46.117(c)). Please read both (d) and (e) to understand these requirements.

(d) Waiver of Informed Consent: An IRB may waive the requirement to obtain informed consent (45 CFR 46.116(d)), provided it finds that:

- **The proposed research presents no more than minimal risk to the subjects,**
- **A waiver of informed consent does not adversely affect the rights and welfare of subjects,**
- **It is impracticable to carry out the research without a waiver or alteration of informed consent, AND**
- **Whenever appropriate, the subjects will be provided with additional pertinent information about participation (i.e. Fact Sheet).**

NOTE: Your project must meet all these criteria before a waiver of informed consent can be approved.

Are you requesting a waiver of consent as outlined in 45 CFR 46(d) described above?

☒ Yes ☐ No If yes, please explain your rationale for requesting a waiver of consent.

The research is minimal risk to the participants and the participants will not be required to waive any rights nor will their welfare be adversely affected by participation. There is no information available to contact the participants. The data are de-identified at the site before being submitted to the IISP.

OR

(e) Waiver of Documentation of Informed Consent: An IRB may waive the requirements for an investigator to obtain a SIGNED consent form (45 CFR 46.117(c)) for some or all subjects if it finds EITHER:

- **That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a break of confidentiality, OR**

- **That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.**
  NOTE: Your project must meet at least one of these criteria before a waiver of documentation of informed consent can be approved.

Are you requesting a waiver of documentation of informed consent as outlined in 45 CFR 46.117(c) described above? ☐ Yes ☐ No If yes, please explain your rationale for requesting a waiver of documentation (signed) of informed consent .

IV. Justice

Subject selection must be equitable: The potential risks of participation should be shared by those who might be expected to benefit from the results of the study. Care must be taken not to recruit from groups that might be especially vulnerable to coercion.

(a) Does the subject population include fetuses, pregnant women, children, the mentally disabled, prisoners, or any other subjects whose ability to give voluntary consent may be in question? ☒ Yes ☐ No ☐ N/A If yes, briefly discussion the rationale for utilizing this population.

The IISP may include pregnant women who were employed by a DOE contractor at their time of return to work event.

(b) Do any particular physiological, health, or sociological characteristics of the subject population pose special medical, ethical, or legal problems? ☐ Yes ☒ No ☐ N/A If yes, explain what steps have been taken to minimize these potential problems.

V. Financial Considerations and Conflict of Interest

(a) Will subjects incur financial obligations as a result of participating in this study? ☐ Yes ☒ No ☐ N/A If yes, please describe.

(b) Will subjects have to pay for any treatment(s) received or tests performed in the research? ☐ Yes ☒ No ☐ N/A If yes, please describe.

(c) Are there any additional costs to the subject that may result from participation in the protocol? ☐ Yes ☒ No ☐ N/A If yes, please describe.

(d) In the event of a research-related injury, under what conditions might the sponsor(s) pay for medical care and/or hospitalization?

There is no risk to the subjects.

(e) Will subjects receive any payment for participation in the protocol or reimbursement for personal expenses? ☐ Yes ☒ No ☐ N/A If yes, explain how much and how this amount is determined.

(f) Do you or any of the other investigators or co-investigators at this site or members of your immediate families have any financial relationship with any entity sponsoring this study, or is any entity providing a product that is central to the purpose of the study or under the IRB's jurisdiction? ☐ Yes ☒ No If yes, please explain.

The Principal Investigator shall follow the procedures of the Oak Ridge Site-wide Institutional Review Board (ORSIRB) in obtaining "informed consent" from the subjects under study. The investigator recognizes acceptance of primary responsibility for safeguarding the interests of the participants under study. If applicable by prior agreement, the investigator is responsible for immediately notifying the ORSIRB of any significant changes in methods of procedure or of the development of unexpected risks. Continuation of the Board's approval of the project is contingent upon its approval of any such changes and acceptance of a progress report.

I accept the following responsibilities:

I will obtain approval from the IRB prior to instituting any changes in project protocol.

I will bring to the attention of the IRB the developments of any unexpected risks.

I will submit a status report (or closure request that includes a status report) at 12 month intervals or as indicated attesting to current status of the project.

If applicable to my project, I have attached a copy of the informed consent form(s) and a copy of the test instrument(s) for my project.

IRBNet submissions must contain all e-signatures prior to submission of the project for review. Typed and/or printed names and dates must be included here. If managers choose to sign a paper copy of this submission, a scanned signature is acceptable when attached to the documents submitted in IRBNet.

Principal Investigator	Kellye D Sliger	**DATE**	9/15/2011

Co-Principal Investigator		**DATE**	
Department or Program Manager	Elizabeth D Ellis	**DATE**	9/15/2011

APPENDIX E. SAS DOCUMENTATION

This is from the SAS log file (annotated). While I used the log for some descriptive information, the list output was used for most analysis.

For descriptive numbers in the beginning of the paper, I created temporary datasets and read the observation count from the log. I've only listed one example below.

```
data aa;  *number of workers with no SAD or no CVD but other absence;
      set uniqrtwwrkrs;
      where SAD_1stDate=. and CVD_1stDate=.;
run;
```

Table 2 information

For table 2, I created a dataset where 0 values became 2 so that the proc freq layout would give the correct odds ratio. I used the proc freq with chisq option.

```
data uniqwrkrs2;
      set uniqwrkrs;
      if SAD=0 then SAD=2;
      if CVD=0 then CVD=2;
      if INF=0 then INF=2;
      if sex=0 then sex=2;
      if CVDrev=0 then CVDrev=2;
      if ANX=0 then ANX=2;
      if DEP=0 then DEP=2;
run;

proc freq data=uniqwrkrs2 order=formatted;
      tables (gender birthdecade ses region)*SAD / nopercent ChiSq;
      format CVD SAD yesno. gender $sexgrp. birthdecade birthdecade. ses ses.
region region.;
run;
```

This presented a SAS output in the following manner for each variable that I listed in the parentheses of the above SAS statement. I've only listed one example below.

Table of Gender by SAD

Gender(Gender) SAD

Frequency Row Pct Col Pct	1-Yes	2-No	Total
Men	1403 1.21 51.09	114315 98.79 72.19	115718
Women	1343 2.96 48.91	44048 97.04 27.81	45391
Total	2746	158363	161109

Statistics for Table of Gender by SAD

Statistic	DF	Value	Prob
Chi-Square	1	593.4402	<.0001
Likelihood Ratio Chi-Square	1	535.8004	<.0001
Continuity Adj. Chi-Square	1	592.3983	<.0001
Mantel-Haenszel Chi-Square	1	593.4365	<.0001
Phi Coefficient		-0.0607	
Contingency Coefficient		0.0606	
Cramer's V		-0.0607	

Fisher's Exact Test

Cell (1,1) Frequency (F)	1403
Left-sided Pr <= F	1.158E-118
Right-sided Pr >= F	1.0000
Table Probability (P)	6.927E-119
Two-sided Pr <= P	1.796E-118

Sample Size = 161109

To get mean and median for the continuous variables, I used proc univariate. First I sorted by the diagnosis of interest then ran the proc univariate.

```
proc sort data=uniqwrkrs2 out=uniqwrkrsSAD;
      by SAD;
run;

proc univariate data=uniqwrkrsSAD;
      var firstage rosteryrs;
      by SAD;
run;
```

The SAS output is listed on the following pages. I'm only presenting one example.

SAD=1

Variable: FirstAge (FirstAge)

Moments

N	2746	Sum Weights	2746
Mean	40.4683176	Sum Observations	111126
Std Deviation	8.75532091	Variance	76.6556443
Skewness	-0.0507465	Kurtosis	-0.4223474
Uncorrected SS	4707502	Corrected SS	210419.744
Coeff Variation	21.635001	Std Error Mean	0.16707898

Basic Statistical Measures

Location		Variability	
Mean	40.46832	Std Deviation	8.75532
Median	41.00000	Variance	76.65564
Mode	40.00000	Range	48.00000
		Interquartile Range	13.00000

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	242.2107	Pr > |t|	<.0001
Sign	M	1373	Pr >= |M|	<.0001
Signed Rank	S	1885816	Pr >= |S|	<.0001

Quantiles (Definition 5)

Quantile	Estimate
100% Max	65
99%	60
95%	55
90%	52
75% Q3	47
50% Median	41
25% Q1	34
10%	29
5%	25
1%	21
0% Min	17

SAD=1

Variable: FirstAge (FirstAge)

Extreme Observations

----Lowest----		----Highest---	
Value	Obs	Value	Obs
17	2201	63	1292
18	2005	64	820
18	258	64	1217
19	1514	64	2145
19	199	65	1245

Table 3 information

For the distributions, I used proc tabulate to create a table. I'm only listing an annotated version of the output here.

```
proc tabulate data=rtw f=comma15.;
      class sex diagnosis_code;
      table diagnosis_code='' all, sex='' all ;
      where diagnosis_code in
('29383','29384','2962','29620','29621','29622','29623','29624','29625','2963
','29630','29631','29632',

      '29633','29634','29635','29636','3000','30000','30001','30002','30009',
'30010','3002','30020','30021','30022','30029',

      '3003','3004','3005','30089','3009','308','3080','3081','3082','3083','
3084','3089','30890',

      '3090','3091','30922','30923','30924','30928','30929','3093','3094','30
981','30982','30983','30989','3099','311','3130',
            '3131','31321','31322','3133','31382','31383') and SAD=1;
      format diagnosis_code $diagnosis_code_txt. sex sex.;
      keylabel all="Total" N=' ';
run;
```

	Women	Men	Total
ADJUST DISORD W/DISTURB CONDUC 3093	2	0	2
ADJ DISORD W/DISTURB COND/EMOT 3094	1	1	2
PROLONG POSTTRAUMATIC STRESS 30981	84	51	135
ADJUST REACTION W/PHYSICAL SYM 30982	0	2	2
OTH ADJUST REACTION OTH 30989	1	7	8
UNSP ADJUST REACTION 3099	30	70	100
DEPRESSIVE DISORDER OTH 311	740	715	1,455
Total	2,369	2,415	4,784

Table 4 and 7 information

I used proc freq here to give me distributions of each category. I will present one sample here.

```
proc freq data=uniqwrkrs2 order=formatted;
      tables (gender birthdecade ses region SAD)*CVD / nopercent ChiSq;
      format CVD SAD yesno. gender $sexgrp. birthdecade birthdecade. ses ses.
region region.;
run;
```

Table of Gender by CVD

Gender(Gender) CVD

Frequency Row Pct Col Pct	1-Yes	2-No	Total
Men	6415 5.54 77.24	109303 94.46 71.53	115718
Women	1890 4.16 22.76	43501 95.84 28.47	45391
Total	8305	152804	161109

Statistics for Table of Gender by CVD

Statistic	DF	Value	Prob
Chi-Square	1	126.9598	<.0001
Likelihood Ratio Chi-Square	1	132.2702	<.0001
Continuity Adj. Chi-Square	1	126.6777	<.0001
Mantel-Haenszel Chi-Square	1	126.9590	<.0001
Phi Coefficient		0.0281	
Contingency Coefficient		0.0281	
Cramer's V		0.0281	

Fisher's Exact Test

Cell (1,1) Frequency (F)	6415
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	7.755E-31
Table Probability (P)	2.736E-31
Two-sided Pr <= P	1.518E-30

Sample Size = 161109

Table 5 and 8 information

I used proc freq with the cmh option to give me the Cochran-Mantel-Haenszel statistics for variables of interest. I'm only listing one example here.

```
proc freq data=uniqwrkrs2 order=formatted;
      tables SAD*CVD / norow nocol nopercent cmh;
      format CVD SAD yesno. ;
run;
```

Table of SAD by CVD

SAD CVD

Frequency	1-Yes	2-No	Total
1-Yes	625	2121	2746
2-No	7680	150683	158363
Total	8305	152804	161109

Summary Statistics for SAD by CVD

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)

Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	1771.0266	<.0001
2	Row Mean Scores Differ	1	1771.0266	<.0001
3	General Association	1	1771.0266	<.0001

Summary Statistics for SAD by CVD

Estimates of the Common Relative Risk (Row1/Row2)

Type of Study	Method	Value	95% Confidence Limits	
Case-Control (Odds Ratio)	Mantel-Haenszel	5.7815	5.2728	6.3393
	Logit	5.7815	5.2728	6.3393
Cohort (Col1 Risk)	Mantel-Haenszel	4.6932	4.3660	5.0450
	Logit	4.6932	4.3660	5.0450
Cohort (Col2 Risk)	Mantel-Haenszel	0.8118	0.7954	0.8284
	Logit	0.8118	0.7954	0.8284

Total Sample Size = 161109

Table 6 and 9 information

I used proc logistic regression here for statistics on a full model and the final adjusted model. The adjusted model was adjusted based on Breslow-Day Test of homogeneity of odds ratios and 10% confounding rule. The SAS output shown is for the full model.

Full model:

```
proc logistic data=uniqwrkrs3;

      class SAD (param=ref ref='2')
            sex (param=ref ref='2')
            birthdecade (param=ref ref='1')
            ses (param=ref ref='1')
            region (param=ref ref='1');
      model CVD (event='1') = SAD sex birthdecade firstage ses region
rosteryrs;
run;
```

Final adjusted model:

```
proc logistic data=uniqwrkrs3;
      class SAD (param=ref ref='2')
            sex (param=ref ref='2')
            birthdecade (param=ref ref='1')
            ses (param=ref ref='1')
            region (param=ref ref='1');
      model CVD (event='1') = SAD birthdecade firstage region rosteryrs;
run;
```

Model Information

Data Set	WORK.UNIQWRKRS3
Response Variable	CVD
Number of Response Levels	2
Model	binary logit
Optimization Technique	Fisher's scoring

Number of Observations Read	160696
Number of Observations Used	160696

Response Profile

Ordered Value	CVD	Total Frequency
1	1	7892
2	2	152804

Probability modeled is CVD=1.

Class Level Information

Class	Value	Design Variables			
SAD	1	1			
	2	0			
sex	1	1			
	2	0			
birthdecade	1	0	0	0	0
	2	1	0	0	0
	3	0	1	0	0
	4	0	0	1	0
	5	0	0	0	1
ses	1	0	0		
	2	1	0		
	3	0	1		
region	1	0	0	0	0
	2	1	0	0	0
	3	0	1	0	0
	4	0	0	1	0

Class Level Information

Class	Value	Design Variables			
	5	0	0	0	1

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	62959.593	53463.867
SC	62969.580	53613.676
-2 Log L	62957.593	53433.867

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	9523.7253	14	<.0001
Score	9237.4839	14	<.0001
Wald	7091.2901	14	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
SAD	1	16.2247	<.0001
sex	1	74.0315	<.0001
birthdecade	4	152.0868	<.0001
FirstAge	1	96.9216	<.0001
ses	2	748.0625	<.0001
region	4	898.3509	<.0001
RosterYrs	1	2702.3214	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-8.1326	0.1914	1805.3065	<.0001
SAD	1	1	0.3078	0.0764	16.2247	<.0001
sex	1	1	0.2571	0.0299	74.0315	<.0001
birthdecade	2	1	0.6191	0.1871	10.9545	0.0009
birthdecade	3	1	0.9508	0.1832	26.9439	<.0001
birthdecade	4	1	1.3242	0.1909	48.1096	<.0001
birthdecade	5	1	1.6940	0.2027	69.8627	<.0001
FirstAge		1	0.0300	0.00304	96.9216	<.0001
ses	2	1	0.4827	0.0294	269.2381	<.0001
ses	3	1	0.8062	0.0301	719.0444	<.0001
region	2	1	0.4314	0.0625	47.7180	<.0001
region	3	1	0.6661	0.0349	364.4440	<.0001
region	4	1	0.7026	0.0564	155.2658	<.0001
region	5	1	0.8785	0.0300	858.2139	<.0001
RosterYrs		1	0.1755	0.00338	2702.3214	<.0001

Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
SAD	1 vs 2	1.360	1.171	1.580
sex	1 vs 2	1.293	1.220	1.371
birthdecade	2 vs 1	1.857	1.287	2.680
birthdecade	3 vs 1	2.588	1.807	3.705
birthdecade	4 vs 1	3.759	2.586	5.465
birthdecade	5 vs 1	5.441	3.657	8.095
FirstAge		1.030	1.024	1.037
ses	2 vs 1	1.620	1.530	1.717
ses	3 vs 1	2.239	2.111	2.375
region	2 vs 1	1.539	1.362	1.740
region	3 vs 1	1.947	1.818	2.084
region	4 vs 1	2.019	1.808	2.255
region	5 vs 1	2.407	2.270	2.553
RosterYrs		1.192	1.184	1.200

Association of Predicted Probabilities and Observed Responses

Percent Concordant	79.9	Somers' D	0.607
Percent Discordant	19.2	Gamma	0.612
Percent Tied	0.8	Tau-a	0.057
Pairs	1205929168	c	0.804