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Sex Differences in the Associations of Specific Adverse Childhood Experiences (ACEs) with Comorbid Psychiatric Disorders

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Abstract

Using nationally representative data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), we examined associations of specific Adverse Childhood Experiences (ACEs) on the comorbid combinations of Depression (DEP), Anxiety (ANX) and Post-Traumatic Stress Disorder (PTSD). The measures of ACEs were derived from the CDC-Kaiser ACE Study. Unlike prior research focusing on the number of ACEs, we hypothesize that there are specific types of ACEs strongly associated with psychiatric comorbidity (i.e., high-risk ACEs) and that these associations differ by sex.

The results demonstrated that emotional, physical, and sexual abuse was strongly associated with all combinations of these three disorders. Mental illness in household was also strongly associated with DEP+ANX as well as DEP+PTSD but not DEP+ANX+PTSD.

Among females, the odds ratios for the combination of DEP+ANX given 1 or 2 or more high-risk ACEs were 2.07 (95% CI: 1.50-2.85, p<0.0001) and 4.17 (95% CI: 2.90-6.01, p<0.0001); the odds ratios for the combination of DEP+PTSD given 1 or 2 or two or more high-risk ACEs were 2.53 (95% CI: 0.84-7.64, p=0.10) and 16.01 (95% CI: 5.41-47.39, p<0.0001); the odds ratios for the combination of DEP+ANX+PTSD given 1 or 2or more high-risk ACEs were 6.53 (95% CI: 3.22-13.22, p<0.0001) and 18.91 (9.20-38.88, p<0.0001). Similar graded relationships were not found among males.

The results reveal that exposure to two or more of the specific high-risk ACEs in females increased their odds of DEP+PTSD by 16 and the odds of DEP+ANX+PTSD by 19 when compared to females with zero high-risk ACE exposure. These findings were not observed in males.

Keywords: Sex difference; Comorbidity; Adverse Childhood Experiences (ACEs); Early trauma; Childhood; Young adulthood

Introduction

It is widely accepted in contemporary psychiatry that stressful situations may give rise to depressive and anxiety disorders even though these disorders may occur on their own without preceding stressors [1]. However, the development of PTSD requires exposure to a traumatic event (or its occurrence in a close friend or family) beyond the usual stressors of life [1]. Consequently, traumatic events could provide a shared environmental trigger for all three psychiatric disorders. Thus, disorders seen in individuals with a trauma history may be trajectories from a common etiology. Various psychiatric studies have shown that individuals with history of abuse and trauma may have multiple overlapping or comorbid psychiatric disorders depending on their underlying vulnerability [2-8]. The severity of one disorder may worsen prognosis for another disorder or may interact in such a manner that quality of life is negatively affected [7,8]. Traumatic experiences confer a large burden of disease and impact including psychiatric and medical impact on individuals and communities [9-12].

Epidemiological research suggests that women have higher community rates of both major depression and anxiety disorders, as well as comorbid psychiatric disorders [13-15]. The causal relationship between trauma and these disorders as single entities or comorbid entities in women remains unclear. However, data from the National Comorbidity Survey Replication indicates that about half of all women in the U.S. will be exposed to at least one traumatic event in their lifetime [16]. Although women are somewhat less likely to experience traumatic events overall [3,4,17], research findings indicate that they are more vulnerable to sexual assault and childhood sexual abuse than men[18]. Furthermore, there is some evidence that women with PTSD are more likely to have comorbid mood and anxiety disorders compared with men [19]. Less is known about any differential impact of childhood stress and adversity on adult psychopathy in women and men.

The 1998 CDC-Kaiser Foundation Adverse Childhood Experience (ACE) Study demonstrated a graded relationship between the breadth of exposure to abuse, neglect, and household dysfunction during childhood and multiple risk factors for several of the

leading causes of negative physical and mental health outcomes for adults and adolescents [20]. Childhood trauma has been shown to be associated with increased risk of psychopathology including mood disorders, psychosis as well as having long term effects on neurocognitive functioning [21-23]. The number of ACEs experienced has a relationship to both recent and lifetime depressive disorders suggesting that the exposure to four or more ACEs is associated with an increased risk for depressive disorders up to decades after the ACE occurrence [24].

In this exploratory study, we examine any sex-differences in the associations between ACEs and young adult reports of comorbid Depression (DEP), Anxiety (ANX), and Post-Traumatic Stress Disorder (PTSD) employing nationally representative data from the National Longitudinal Study of Adolescent to Adult Health (Add Health). Our goal is to not only examine the relationship between number of ACEs exposed and comorbid conditions differentially among men and women, but also to examine the identity of the most impactful adverse childhood experiences. We posit that by identifying these specific ACEs it may allow for more efficient resource allocation towards prevention and treatment of ACE-associated morbidities and comorbidities.

Methods

Study sample and design

We conducted a secondary analysis of data from Add Health, a nationally representative prospective U.S. survey that started during the 1994-95 school year at Wave I [25]. This cohort was followed into young adulthood with four in-home interviews. Wave 4 was collected in 2008, when the subjects were young adults aged 24-32. Comorbidity outcomes are based on this Wave 4 cohort. Systemic sampling and implicit stratification into the Add Health study design guaranteed that the sample was representative with respect to region of the country, school size/type, and ethnicity [25].

Informed consent

Prior to participation, all add health participants provided written informed consent in accordance with the University of North Carolina School of Public Health Institutional Review Board guidelines, which are based on the Code of Federal Regulations on the Protection of Human Subjects 45CFR46: http://www.hhs.gov/ohrp/humansubjects/guidance45cfr46.html. These secondary data analyses from add health restricted use dataset was approved by the University of California, Riverside Institutional Review Board.

Inclusion and exclusion criteria

There was a total of 9421 subjects (4276 males and 5177 females) available for analysis in the Add Health longitudinal study across Waves 1 to 4 consistent with the official Add Health documentation [26]. Of these available subjects, 1470 endorsed the statement that they responded to survey questions: "1: Not honestly at all" or "2: Somewhat honestly". Consequently, these subjects were excluded from the analyses to enhance validity. In a separate sensitivity analysis (not shown), we found that including such subjects would result in lower response endorsements to ACE questions. In addition, 483 subjects who endorsed homeless or responded "did not know" or "refused" to ACE or diagnostic items were also excluded to avoid demographic confounds and missing data. Of these, 86 of the subjects were already excluded based on "honesty responding: criteria". As a result, a total of 7554 young adults were eligible for analysis in the present study.

Measures

Socio-demographic variables: The identification of male or female sex was based upon self-report. Ethnicity was determined based upon interview responses to specific questions such as "Are you of Hispanic or Latino origin" and "What is your race- White, African American or Black, Indian or Native American, or Asian or Pacific Islander?" In this study, due to small sample sizes of Indian, Native Americans, Asians and Pacific Islanders, the ethnicity variable was compressed in classifications of non-Hispanic White; non-Hispanic African American, Hispanic, and Other. Other was defined as Indian, Native American, Asian or Pacific Islander. Economic distress was indexed based upon responses to the inquiry: "At any time during a given year, even for one month, did you receive any public assistance or welfare payments from a state or local welfare office other than food stamps?" These responses were scaled as never (0), occurring only once (1) or having occurred multiple times (2). Educational attainment was based upon an inquiry as to whether the respondent has attended a college, university, or vocational/technical school to take courses for academic credit after high school.

Adverse Childhood Experiences (ACEs): ACE scores were assessed from Add Health items derived from those employed in the CDC-Kaiser study as a template [20]. Nine individual ACE items were constructed (Supplementary Table 1). One item from the CDC-Kaiser study could not be reconstructed from Add Health items and was therefore eliminated from these analyses. As a result, there were 9 ACEs found in Add Health data rather than the original 10 from the CDC-Kaiser study. In previous research, the summation of the number of ACEs provided an overall measure of the individual burden of childhood adversity.

Psychiatric disorders: A history of DEP was determined from the following question asked at Wave IV: "Has a doctor, nurse or other health care provider ever told you that you have or had: Depression?" A history of ANX was determined from the following question asked at Wave IV: "Has a doctor, nurse or other health care provider ever told you that you have or had: Anxiety?" A history of PTSD was determined from the following question asked at Wave IV: "Has a doctor, nurse or other health care provider ever told you that you have or had: post-traumatic stress disorder or PTSD?"

Statistical analyses

National prevalence rates of ACEs and differences across sociodemographic groups: National prevalence was estimated by sample weighted frequency function, which was conducted by PROC SURVEYFREQ in SAS 9.4. Within this function, contingency tables built to calculate the prevalence rates for sociodemographic groups, the underlying associations between the prevalence rates and sociodemographic groups were examined by Chi-Square test. In addition, these estimations used regions (i.e., Northeast, Midwest, South, and West in the US.) as strata variable and the sample unit school ID as a cluster factor.

Associations of comorbidity with specific ACEs: Using survey based logistic regression in SAS 9.4, association between each ACE and each comorbid combination of the three psychiatric disorders was examined after the logistic regression was adjusted by demographics, including sex. In general, any strong association was defined as OR>1 and p<=0.05 with a two-tailed test, and thus the specific ACEs were treated as high-risk ACEs for the psychiatric conditions under study in this model. In addition, we also considered the association to be a high-risk ACE when the magnitude of relative risk of a specific ACE associated with comorbidities was at least moderately defined as odds

ratio between 2.00-3.00 and p<=0.10 due to clinical and interventional consideration [26].

Relative risk of specific ACE scores: These relative risks were assessed as odds ratios using survey based logistic regression models. In the models, each of the defined comorbidity was a dependent variable. Specific ACE scores were the main effect. These models were adjusted by demographics, including sex, ethnicity, education level, and economic distress. Whenever multiple comparisons appeared, p values were adjusted by the Dunnett's method, or the SAS-based simulation procedure if the former method was not feasible. Interaction between sex and ACE score was specifically tested to determine if the effects of ACE scores were different based on sex, and the significance of the interaction term was evaluated by its p-value. For each comorbidity, the model outcome was reported as ORs, and 95% CIs of ORs, and p-values for males and females, respectively.

Results

Prevalence of individual and comorbid psychiatric disorders across demographics

Overall, the population prevalence estimates derived from the nationally representative Add Health data for DEP, PTSD, and ANX were 16.14%, 2.71%, and 13.39%, respectively (Table 1).

The estimated prevalence rates for the comorbid conditions of DEP+ANX, DEP+PTSD, DEP+ANX+PTSD were 6.88%, 0.47%, and 1.38%, respectively. Due to the low rate and small sample size of ANX+PTSD (0.23%), this combination was excluded from the risk analysis.

As noted in table 1, the prevalence rates of psychiatric disorders were strongly correlated with the demographics such that ethnicity, education, economic distress, and sex, all affected prevalence of these disorders. These sociodemographic factors were associated with the prevalence rates for the comorbid combinations of DEP+ANX and DEP+ANX+PTSD but not DEP+PTSD.

Associations between specific ACEs and comorbid combinations of DEP, ANX, and PTSD

All nine ACEs were examined for their associations with comorbidities of DEP+ANX, DEP+PTSD and DEP+ANX+PTSD (Table 2). The presence of DEP+ANX was strongly associated with emotional abuse (OR=3.12, 95% CI: 2.34-4.16), physical abuse (OR=2.18, 95% CI: 1.42-3.36), sexual abuse (OR=2.21, 1.66-2.93) and mental illness in household (OR=1.94, 95% CI: 1.30-2.89). In addition, living in a household with an incarcerated member was also considered as a specific ACE for DEP+ANX, due to a moderate OR (i.e., 2.11) with a p-value of 0.09. Parental separation/divorce was not a high-risk ACE, due to OR<1, with p-value of 0.05. DEP+PTSD was significantly associated with emotional abuse (OR=7.75, 95% CI: 3.08-19.54), physical abuse (OR=5.29, 95% CI: 2.12-13.20), sexual abuse (OR=3.98, 95% CI: 1.83-8.67), and mental illness in household (OR=2.72, 95% CI: 1.00-7.41). DEP+ANX+PTSD was strongly associated with emotional abuse (OR=7.32, 95% CI: 4.11-13.04), physical abuse (OR=4.50, 95% CI: 2.29-8.87), and sexual abuse (OR=6.77, 95% CI: 3.61-12.68).

As a result, there were five high-risk ACEs that were summed for the comorbidity of DEP+ANX; four high-risk ACEs summed for the comorbidity of DEP+PTSD, and three ACEs for the comorbidity of DEP+ANX+PTSD. The presence of any of these specific high-risk ACEs was scored as 1 if it occurred, otherwise as 0. These specific ACEs were summed as 0, 1, 2 or more (i.e., 0, 1,2+).

Table 1: Demographics and risk factors of DEP, ANX, PTSD and their comorbid combinations.

Demographics and risk factors		Prevalence rate of psychiatric disorders					
		Individual disorders			Comorbid disorders		
Factors	levels	DEP	ANX	PTSD	DEP+ANX	DEP +PTSD	DEP+ANX+PTSD
Overall		16.14	13.39	2.71	6.88	0.47	1.38
Sex	Male	9.75	8.01	1.93	3.70	0.31	0.66
	Female	21.85	18.19	3.40	9.71	0.62	2.02
	P value	<0.0001	<0.0001	0.002	<0.0001	0.16	0.0002
Ethnicity	White	18.61	15.73	3.10	8.12	0.58	1.67
	AA	7.85	5.45	0.68	3.19	0.13	0.44
	Hispanic	11.41	9.72	2.54	4.03	0.27	0.69
	Others	15.72	11.69	3.01	6.46	0.42	1.44
	P value	<0.0001	<0.0001	0.004	<0.0001	0.27	0.02
Education	HS+	14.85	12.36	2.25	6.03	0.46	1.07
	HS and below	17.83	14.73	3.31	7.98	0.48	1.79
	P value	<0.0001	0.04	0.001	0.02	0.92	0.05
Social support	0	14.77	12.69	2.55	6.39	0.43	1.15
	1	19.61	15.20	4.32	7.74	0.40	2.36
	2	28.34	19.45	5.57	11.78	1.08	2.75
	P value	<0.0001	0.007	0.0007	0.005	0.21	0.01

AA: African American/HS+ with more than high school education/HS for high school and below population prevalence estimates derived from the nationally representative Add Health data for DEP, PTSD, and ANX were 16.14%, 2.71%, and 13.39%, respectively. Ethnicity, education, economic distress, and sex affect prevalence of these disorders.

Relative risks of comorbid combinations of DEP, ANX, and PTSD associated with ACE scores by sex

Risk assessment was conducted with a survey based logistic regression model adjusted by demographics. The model also tested if sex strongly modified effects of ACE scores on the comorbid combinations. For each comorbid combination, a strong interaction between specific high-risk ACE scores and sex was noted, implying that sex modified the effects of specific ACE scores on each comorbid combination.

Table 3 showed how the risk estimations (presented as OR) of each specific ACE score on each comorbid combination of disorder differed between males and females. For DEP+ANX, high-risk ACE sums of 1 and 2+ had OR 2.07 (95% CI: 1.50-2.85) and 4.17 (95% CI: 2.90-6.01), respectively compared to score 0 among females; while for males, specific ACE sums of 1 and 2+ had OR 2.72 (95% CI: 1.58-4.66) and 3.43 (95% CI: 1.70-6.84) respectively. For those subjects with a single specific high-risk ACE, the risk for females was somewhat lower than the risk for male peers. However, for those with specific scores of 2 or more, the risk for the females was higher than the risk for male peers. Therefore, for males the scores 1 and 2+ were within the same range of error, but for females, the risk of score 2+ doubled that risk. For females endorsing DEP+PTSD, specific high-risk ACE sums of 1 and 2+ had OR 2.53 (95% CI: 0.84-7.64) and 16.01 (95%

Table 2: Associations between specific ACES and comorbid combinations of DEP, ANX, and PTSD.

	DEP+ANX		DEP+PTSD		DEP+ANX+PTSD	
Emotional abuse	3.12 (2.34-4.16)	<0.0001	7.75 (3.08-19.54)	<0.0001	7.32 (4.11-13.04)	<0.0001
Physical abuse	2.18 (1.42-3.36)	0.0005	5.29 (2.12-13.20)	0.0004	4.50 (2.29-8.87)	<0.0001
Sexual abuse	2.21 (1.66-2.93)	<0.0001	3.98 (1.83-8.67)	0.0006	6.77 (3.61-12.68)	<0.0001
Substance abuse in household	1.11 (0.76-1.63)	0.59	0.83 (0.28-2.43)	0.73	0.89 (0.43-1.86)	0.76
Mental illness in household	1.94 (1.30-2.89)	0.001	2.72 (1.00-7.41)	0.05	1.66 (0.75-3.65)	0.21
Parental separation or divorce	0.72 (0.51-1.00)	0.05	1.37 (0.50-3.74)	0.54	0.49 (0.21-1.11)	0.09
Incarcerated household	2.11 (0.90-4.97)	0.09	3.07 (0.36-26.23)	0.30	2.55 (0.58-11.11)	0.21
Emotional neglect	1.53 (0.96-2.43)	0.07	0.60 (0.13-2.81)	0.51	1.63 (0.77-3.43)	0.20
Physical neglect	1.03 (0.49-2.17)	0.94	--	-	0.60 (0.12-2.99)	0.53

DEP+ANX was associated with emotional abuse, physical abuse, sexual abuse, mental illness in household (and living in a household with an incarcerated member; not statistically significant).
DEP+PTSD were associated with emotional abuse, physical abuse, sexual abuse, and mental illness in household. DEP+ANX+PTSD were associated with emotional abuse, physical abuse, and sexual abuse.

Table 3: Relative risks of comorbid combinations of DEP, ANX, and PTSD associated with ACE scores by sex.

ACE scores	Males			Females		
	OR	95% CI	P value	OR	95% CI	P value
DEP+ANX						
1 *vs.* 0	2.72	1.58-4.66	0.0004	2.07	1.50-2.85	<0.0001
2+ *vs.* 0	3.43	1.70-6.84	0.0007	4.17	2.90-6.01	<0.0001
DEP+PTSD						
1 *vs.* 0	5.16	0.66-40.51	0.12	2.53	0.84-7.64	0.10
2 + *vs.* 0	5.62	0.67-47.48	0.11	16.01	5.41-47.39	<0.0001
DEP+ANX+PTSD						
1 *vs.* 0	1.96	0.44-8.80	0.38	6.53	3.22-13.22	<0.0001
2+ *vs.* 0	5.87	1.16-29.82	0.03	18.91	9.20-38.88	<0.0001

Among females with DEP+ANX+PTSD, specific high-risk ACE scores of both 1 and 2+ had significant associations at ORs of 6.53 (95% CI: 3.22-13.22) and 18.91 (95% CI: 9.20-38.88) respectively, compared to score 0.

Supplementary Table 1: Derivation of adverse childhood experiences items employed based on CDC-Kaiser permanent study using add health measures.

	CDC-Kaiser Permanente Study ACE Item	ACE Item Derived from Add Health Survey
ACE 1: Emotional Abuse	"[Before your 18th birthday] A parent, stepparent, or adult living in your home swore at you, insulted you, put you down, or acted in a way that made you afraid that you might be physically hurt."	"Before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?"
ACE 2: Physical Abuse	"[Before your 18th birthday] A parent, stepparent, or adult living in your home pushed, grabbed, slapped, threw something at you, or hit you so hard that you had marks or were injured."	"[Before your 18th birthday] A parent, stepparent, or adult living in your home pushed, grabbed, slapped, threw something at you, or hit you so hard that you had marks or were injured."
ACE 3: Sexual Abuse	"[Before your 18th birthday] An adult, relative, family friend, or stranger who was at least 5 years older than you ever touched or fondled your body in a sexual way, made you touch his/her body in a sexual way, attempted to have any type of sexual intercourse with you."	Any endorsed: "How old were you the first or only time this happened? [been forced, in a non-physical way, to have any type of sexual activity against your will]"-"How old were you the first or only time this happened? [Been forced, in a physical way, to have any type of sexual activity against your will. "How old were you the first time one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?"
***ACE 4: Viewing Domestic Violence (*Not Employed in these analyses)**	"[Before your 18th birthday] Your mother or stepmother was pushed, grabbed, slapped, had something thrown at her, kicked, bitten, hit with a fist, hit with something hard, repeatedly hit for over at least a few minutes, or ever threatened or hurt by a knife or gun by your father (or stepfather) or mother's boyfriend."	No Equivalent Item found in Add Health
ACE 5: Household Substance Abuse	"[Before your 18th birthday] A household member was a problem drinker or alcoholic or a household member used street drugs."	Any endorsed: "Does biological mother currently have the following health problem: Alcoholism" "Does biological father currently have the following health problem: Alcoholism"
ACE 6: Mental illness or suicide in household	"[Before your 18th birthday] A household member was depressed or mentally ill or a household member attempted suicide"	Any endorsed: "Have any of your family members tried to kill themselves during the past 12 months?" "Have any of your family members tried to kill themselves during the past 12 months?"
ACE 7: Parental separation, divorce or death.	"[Before your 18th birthday] Your parents were ever separated or divorced."	This was broadened in our analysis to also include the death of a parent. "Mother interview: What is your current marital status?" "How did it end?" "How old were you when she (biological mother) died?" "How old were you when he [biological father] died?"
ACE 8: Criminality and Incarceration in household	"[Before your 18th birthday] A household member went to prison?"	Any endorsed: How old were you when your [mother figure] went to jail or prison (the first time)? How old were you when your [father figure] went to jail or prison (the first time)?
ACE 9: Emotional Neglect	"[Before your 18th birthday] Someone in your family helped you feel important or special, you felt loved, people in your family looked out for each other and felt close to each other, and your family was a source of strength and support."	"How much do you feel that your family pays attention to you?"
ACE 10: Physical Neglect	"[Before your 18th birthday] There was someone to take care of you, protect you, and take you to the doctor if you needed it, you didn't have enough to eat, your parents were too drunk or too high to take care of you, and you had to wear dirty clothes."	"[Before your 18th birthday] How often had your parents or other adult caregivers not taken care of your basic needs, such as keeping you clean or providing food or clothing?"

CI: 5.41-47.39) respectively, compared to score 0, while for males the specific ACE sum of 1 and 2+ had OR 5.16 (95% CI: 0.66-40.51) and 5.62 (95% CI: 0.67-47.48) respectively. The risk for males did not reach statistical significance and the ORs for both scores 1 and 2+ were within the same range of error. In females, specific score 2+ had a large risk with OR as 16.01 (95% CI: 5.41-47.39), compared to score 0. Thus, among females with DEP+PTSD, the specific ACE score demonstrated a strong dose-response pattern. Among males endorsing DEP+ANX+PTSD, only the summary high-risk ACE score of 2+ had a significant association (OR of 5.87 (95% CI: 1.16-29.82). Among females with DEP+ANX+PTSD, specific high-risk ACE scores of both 1 and 2+ had significant associations at ORs of 6.53 (95% CI: 3.22-13.22) and 18.91 (95% CI: 9.20-38.88) respectively, compared to score 0. Among females, the specific ACE score demonstrated a strong dose response pattern for those who had DEP+ANX+PTSD.

Overall, there was a strong dose-response pattern among females, but not males for all three psychiatric comorbidities in this study such that an increasing number of specific ACEs were associated with an increase in risk of having psychiatric disorders. Of note, among females with two or more specific ACEs, the relative risk for the comorbidity of DEP+ANX+PTSD had an OR of 18.91, that was over three times that of the males (OR of 5.87).

Discussion

Our exploratory study demonstrated that when females had specific high-risk ACEs summed as scores from 0 to 2+, the risk for the comorbidity of these psychiatric comorbid combinations understudy increased such that associations with DEP+ANX, DEP+PTSD, DEP+ANX+PTSD increased in a strong dose-response fashion. This pattern was not observed in males. It is noteworthy that females with an ACE score of 2+ were about 19 times more likely to develop DEP+ANX+PTSD when compared to those without an ACE and were about 16 times more likely to develop DEP+PTSD when compared to those who did not endorse a specific high-risk ACE. Among females with 2+ high-risk ACE scores, the relative risk for DEP+ANX+PTSD in females (OR of 18.91), was more than 3 times that of the males (OR of 5.87).

Given these findings, one might argue that these psychiatric comorbid combinations under study represent a severe form of psychopathology resulting from the exposure to the specific ACEs that manifest differentially in males and females. It is unclear if biological or social factors drive the severity and susceptibility to the comorbid disorders noted in females. One might expect that these predisposing or causative factors will be multifactorial in nature as is typical with other psychopathological disorders. Research has demonstrated that women are diagnosed with DEP twice as often as men [13]. One could argue that the diagnostic criteria utilized in clinical practice are more sensitive to traditional female symptoms of DEP (sadness, crying spells) leaving men less likely to endorse these symptoms. This may relate to the acceptable gender roles in our society, or males' alternative expression of symptoms of DEP such as anger, irritability or other externalizing behaviors not accounted for in the current diagnostic criteria. However, research has also shown that women have a two-fold higher prevalence of PTSD than men [14] and women are twice as likely to suffer from any anxiety disorder when compared to men [15]. Prior research indicates that the risk for individual psychiatric disorders of DEP, ANX and PTSD in women is twice that of the risk in men. Findings from our study reveal that among females the risk for a comorbid combination of all three disorders in the presence of two or more specific high-risk ACEs is over three times the risk for men with similar ACE exposure. Certain cultural schemas may explain the mental health presentation of individuals according to their sex and gender roles. Self-salience schemas that put others' needs above one's own increase the risk of internalizing problems, while those that put one's own interests first facilitate externalizing problems. Overall, some research suggest that women may have lower self-salience than men which may explain women's excess of internalizing problems and men's predominance of externalizing problems [27,28]. Sex and gender also shape the meaning of stressors for women and men, which has implications for their mental health. Studies have shown that environmental and sociocultural factors contribute to sex differences in health including mental health. Coping styles, personality traits, sex roles, demographic groups (e.g., age, marital status, educational status, and income), social support, social isolation, childhood adversity, societal change, and cultural norms may differ by sex and produce varying experiences [29].

While the underlying mechanisms for the sex differences remain under investigation, a recent study suggests sex-dependent role for the glucocorticoid receptor in depression such that variants of Glucocorticoid Receptor (GR)-related genes have a strong association with the development of pathophysiology of depression in women but not in men [30]. In addition, involvement of the Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)/Pituitary Adenylate Cyclase (PAC) 1 receptor pathway in the regulation of the psychological and physiological responses to traumatic stress as well as fear- and estrogen-dependent regulation of PACAP systems have been documented [31]. These findings suggest sex-specific differences in PTSD diagnosis, symptoms, and fear physiology [31].

There is an increased risk of morbidity and disability among those suffering with individual psychiatric disorders. Depression and Anxiety contribute significantly to the global burden of disease with depression reported as the second largest contributor to years lived with disability in individuals aged 15 to 44 [32]. The severity of disability increases exponentially when there is psychiatric comorbidity [33,34]. The comorbid psychiatric disorders are associated with greater symptom severity, treatment resistance, lost productivity, greater healthcare cost, increased substance use, and suicidal risk [33]. Patients presenting with comorbid psychiatric disorders in the psychiatric clinic are usually the more severe cases and tend to make up the bulk of the utilization of psychiatric services and overall healthcare cost [35]. Severity of comorbidity influences treatment outcomes such that fewer symptoms are associated with better prognosis [36]. In this study, the comorbidity of DEP +ANX was strongly associated with the specific ACEs of emotional abuse, physical abuse, sexual abuse, and mental illness in the household while the comorbidity of DEP+PTSD was strongly associated with emotional abuse, physical abuse, and sexual abuse. Mental illness in household was considered an important ACE due to the large magnitude of association noted even though this did not reach statistical significance. The comorbidity of DEP+ANX+PTSD was strongly associated with emotional abuse, physical abuse, and sexual abuse. It is noteworthy that all the comorbidities in this study have strong associations with the specific ACEs of emotional abuse, physical abuse, and sexual abuse. These ACEs seem to be the most consistently potent traumatic stresses in childhood affecting later mental health. Future prospective research addressing the role of sex in the impact of these specific ACEs on comorbidities will replicate and extend these associations more clearly.

Limitations

There are several limitations to the interpretation of secondary analyses of existing data sets as described herein. For example, the variables employed in this study are those chosen by others to address

different goals, and the timing of ascertainment was in the hands of the researchers who developed the survey. In our case, we constructed variables to mirror the types of ACEs measured in the CDC-Kaiser study. We based our use of the variable for DEP, ANX and PTSD on the interviewer asking participants about 'being diagnosed with Depression, Anxiety and PTSD' and this question was asked at age 24-32 during wave IV. Thus, no formal psychiatric diagnosis was performed nor was diagnoses confirmed by a clinician. Hence one is unable to make any inference of specific DSM diagnoses or disorders. Among those with more than one disorder, the developmental sequence of these conditions cannot be determined here due to the absence of survey questions inquiring about temporal issues. Additionally, it is noteworthy that until recently, the diagnosis of PTSD was considered under the broader umbrella of anxiety disorders, and this may introduce some confounds in survey responses. Greater precision in defining the sociodemographic measures such as economic distress might result in more accurate assessments of their contribution to prevalence rates. Another concerning issue is the small sample size of males in the study, in that it is not representative of the national population.

Conclusions/Implications

Our exploratory study revealed an association between differential dose-dependent/cumulative effects of specific high-risk ACEs (physical abuse, emotional abuse, sexual abuse) and specific combinations of comorbid psychiatric disorders in females. Should our results be replicated by prospective research, it may have important impact upon the structure of prevention and early interventional programs, as well as having a potential impact on mental health policy.

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Disclosures

The authors of this study declare no conflicts of interest.

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