

IMPACTS OF EARLY CANNABIS USE AND CHILDHOOD ABUSE AND NEGLECT ON THE
OCCURRENCE OF SUB-CLINICAL PSYCHOTIC SYMPTOMS AND ADAPTIVE DISTRESS
IN A COHORT OF LOWER SES YOUNG ADULTS

by

Michael Todd Shearer

B.S. Slippery Rock University, 2001

Submitted to the Graduate Faculty of
the Department of Biostatistics of
the Graduate School of Public Health in partial fulfillment
of the requirements for the degree of
Master of Science

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

This thesis was presented

by

Michael Shearer

It was defended on

April 14, 2011

and approved by

Nancy Day, PhD, MPH, Professor, Department of Psychiatry, School of Medicine, University
of Pittsburgh

John Wilson, PhD, Assistant Professor, Department of Biostatistics, Graduate School of
Public Health, University of Pittsburgh

Thesis Director: Richard Day, PhD, Associate Professor, Department of Biostatistics,
Graduate School of Public Health, University of Pittsburgh

IMPACTS OF EARLY CANNABIS USE AND CHILDHOOD ABUSE AND NEGLECT
ON THE OCCURRENCE OF SUB-CLINICAL PSYCHOTIC SYMPTOMS AND
ADAPTIVE DISTRESS IN A COHORT OF LOWER SES YOUNG ADULTS

Michael Shearer, M.S.

University of Pittsburgh, 2011

It has been hypothesized that environmental stressors can exacerbate the onset of psychosis. We hypothesize that early marijuana use (EMU) and childhood abuse and neglect (CAN) are these types of environment stressors that could accelerate mental illness. Both EMU and CAN are significant concerns in public health because they are behaviors that are preventable and can cause a wide array of mental illness diagnoses. In addition, we hypothesize that even when given severe EMU and CAN exposures, an individual must have a genetic predisposition to developing psychosis.

A cohort of 608 subjects selected from the Maternal Health Practices and Child Development (MHPCD) project was selected for study. Subjects of a mother and a single child were selected from Magee-Womens Hospital in Pittsburgh, PA during their fourth month of pregnancy. Mothers were oversampled who engaged in potential teratogenic behaviors during pregnancy (i.e. substance use/abuse). Controls were randomly selected from those who agreed to participate in the study and who rarely or never used drugs and alcohol during pregnancy.

We tested two different models where the response variables were counts of psychotic experiences and an Adult Self Report (ASR) score that measured adaptive distress for the child at 22 years. Both models included race, sex, and the mother's use of marijuana during the first trimester, CAN, and EMU as covariates. Childhood Trauma Questionnaire (CTQ) score measured CAN, and

age of first use of marijuana measured EMU. ASR was modeled using OLS regression, and psychotic experiences were modeled using negative binomial regression.

Both models showed highly significant results for CTQ score or CAN. ($<.001$ p-value). This suggests an increasing risk for mean number of psychotic symptoms and increasing adaptive distress for higher exposures to CAN. Both models also showed an increasing dose-response relationship to EMU. However, the prevalence of schizophrenia or schizophrenia-like diagnosis (.5%) was less than that of an estimate the general population. CAN and EMU were also divided into four categories: no EMU and no CAN; EMU and no CAN, no EMU and CAN; EMU and CAN. All four categories showed an increasing, additive effect on adaptive distress, number of psychotic experiences, and other mental illnesses, respectively.

TABLE OF CONTENTS

1.0	INTRODUCTION.....	1
2.0	SUBJECTS AND METHODS	4
3.0	RESULTS	6
4.0	DISCUSSION	9
	APPENDIX A: TABLES.....	16
	APPENDIX B: FIGURES	21
	BIBLIOGRAPHY.....	24

LIST OF TABLES

Table A1: Disaggregate Data for Psychotic-Like Experiences on DIS	16
Table A2: Details of Continuous Variables for Figure 1 (n=591).....	17
Table A3: Negative Binomial Regression for Number of PLEs at 22-Years-Old on DIS	18
Table A4: Linear Regressions for ASR Mental Health Outcome Scales	19
Table A5: Logistic Regression Summaries: Diagnostic Categories by Exposure Groups n=591 controlling for sex, race, and PME	20

LIST OF FIGURES

Figure B1: Mean Frequency PLEs and ASR Total Scores by CAN and ECU Exposure Groups	21
Figure B2: 22 Year ASR Int. and Ext. Scores by CAN and ECU Exposure Gps.....	22
Figure B3: Percent 22 Year-Old MHPCD Subjects with Specific DIS Lifetime Diagnoses	23

1.0 INTRODUCTION

Cohort studies based on general population samples have shown that sub-clinical positive psychotic symptoms (i.e. delusions and hallucinations) may occur among a substantial proportion of otherwise healthy respondents. Van Os et al. (2009), in a review and meta-analysis of the literature, reported a median prevalence of 5.3% for these symptoms in the general population. They also report that these sub-clinical symptoms are for the most part brief in nature (i.e., non-persistent), of recent onset, and are not associated with severe levels of psychiatric distress (i.e., self-limiting and good outcome, van Os et al. 2009:190). They conclude that (Van Os et al. 2009:1) “75-90% of these developmental psychotic experiences are transitory and disappear over time.”

Van Os and his colleagues argue that the distribution these sub-clinical symptoms in general population samples suggests a “continuous phenotype” that is “measurable in both healthy and ill individuals” (2009:1). Kelleher and Cannon (2011) recently endorsed the idea of an “extended psychosis phenotype” and suggested that positive psychotic symptoms be termed “psychotic-like experiences” (PLE’s) in the absence of clinically diagnosable (schizophrenia-like) illness. Conceptually, van Os et al. (2009) put forward a “psychosis proneness-persistence-impairment” model to describe and explain the observed distribution of PLEs. This model hypothesizes an underlying genetic liability to psychosis which tends to become developmentally manifest in the form of PLE’s during adolescence. These sub-clinical developmental

experiences tend to be self-limiting and benign unless they are exacerbated by environmental exposures such as trauma, cannabis, urbanicity, and the like (i.e., environmental liability, see Figure 6 in van Os et al. 2009:189). Depending upon the severity of the exposure, these potentially benign developmental experiences (PLEs) may become increasingly persistent and severe, ultimately resulting in the emergence of clinically diagnosable forms of psychotic pathology (e.g., schizophrenia and/or schizophreniform psychoses).

This paper draws upon a longitudinal cohort of subjects who demonstrate a greater overall level of manifest environmental liability than is normally observed in general population samples. The Maternal Health Practices and Child Development (MHPCD) project comprises a large cohort of mothers and a single child that have been studied intensively from the first trimester of pregnancy through the offspring's young adulthood (22 years-old). This is a racially diverse, urban (Pittsburgh, PA) cohort drawn primarily from families from a lower socioeconomic setting. The MHPCD cohort over-sampled maternal subjects who engaged in potentially damaging forms of substance use behavior during pregnancy (i.e. tobacco, alcohol, and marijuana use). As a consequence of the sampling emphasizes on lower socioeconomic status and deviant prenatal behavior the MHPCD cohort necessarily includes a large number of environmentally at-risk subjects of a type are bound to be relatively rare in representative samples from the general population. This unique sample provides an opportunity to carry out an in depth investigation into the effects of certain environmental exposures on the hypothesized self-limiting and transient developmental experiences (PLEs) described by investigators like van Os et al. (2009) and Kelleher and Cannon (2011).

This paper focuses specifically on two environmental stressors -- early onset of cannabis use (ECU) and childhood abuse and neglect (CAN) – that previous investigators (references)

identified as being associated with the occurrence of PLEs. We will make the following general points:

1. PLEs are very frequent occurrences among the subjects in the MHPCD cohort – i.e. a high prevalence compared to general population;
2. The number of PLEs reported by MHPCD offspring are strongly associated with the number and severity of environmental stressors – i.e. ECU and CAN;
3. The numbers of reported PLEs are strongly associated with the severity of young adult psychopathology reported by the MHPCD offspring at 22 years-old – i.e. in this cohort PLEs are neither self-limiting, nor benign, and probably not transient either;
4. At the 22-year follow-up, the MHPCD offspring show a lower lifetime prevalence of schizophrenia-like diagnoses (schizophrenia or schizophreniform) than would be expected in light of items 1-3 above.

This final point leads us suggest some theoretical modifications to the psychosis proneness-persistence-impairment model (van Os et al. 2009), particularly with regard to the necessity of an underlying genetic liability for the production of an “extended psychosis phenotype” (Kelleher and Cannon 2011) in situations where unusually extreme child rearing conditions are observed.

2.0 SUBJECTS AND METHODS

Study participants were a consecutive sample of women who attended the prenatal clinic at Magee-Womens Hospital in Pittsburgh, Pennsylvania from 1983 through 1985. Women who were at least 18 years of age and English-speaking were approached during their fourth prenatal month visit. Eighty-five percent of the women agreed to participate in the study, resulting in an initial series of 1360 subjects. Two study cohorts were selected from the initial series based on their first trimester substance use. Women who used marijuana at the rate of two or more joints/month and a random sample of women who used marijuana less often or not at all were chosen for a study of the effects of marijuana use during pregnancy. Women who drank three or more drinks of alcohol per week and a random sample of women who drank less often or not at all were selected for a study of the long-term effects of prenatal alcohol exposure. There was overlap between cohorts. The two study cohorts were combined for this analysis for a total series of 829 women. Maternal follow-up examinations were carried out at seven months of pregnancy, and with their offspring at birth, 8, and 18 months, 3, 6, 10, 14, 16, and 22 years of age. Each examination assessed substance use, life style, current environment, medical history, and demographic status. Children were examined for growth, cognitive, and behavioral development at each phase. At delivery, the initial MHPCD sample of 829 mothers was reduced to 763 and their live-born singleton offspring. The 66 women who discontinued participation

included 21 who moved from the Pittsburgh area, 16 who were lost to follow-up, 8 who refused the delivery interview and newborn exam, 2 multiple births, 18 fetal deaths, and 1 adoption.

At 22 years.... (need description of 22-year old data). Total N at 22 years was 608 subjects

Mothers signed consent for their children to participate in this study and the Institutional Review Boards of the Magee-Womens Hospital and the University of Pittsburgh approved this study.

3.0 RESULTS

At the 22-year follow-up, 591 (97%) of the 608 participating offspring were examined using the Diagnostic Interview Schedule (DIS) and completed both the Adult Self-Report (ASR) and the Childhood Trauma Questionnaire (CTQ). The mean age of these subjects was 22.8 years (std. error: ± 0.03 , min. 21.2, max. 26.1); they were 53% female and 52% African-American. Forty-one percent (n=243) of these subjects were prenatally exposed to cannabis in their first trimester and 44% (n=257) were exposed at anytime during pregnancy. The mean level of first trimester maternal use amongst the exposed subjects was 0.92 joints/day (std. error: ± 0.08 , median=.40).

On the DIS, 280 (47%) of these 591 subjects reported experiencing at least a single positive psychotic-like experience (PLE). The mean number of symptoms among those reporting PLEs was 2.4 (std. error ± 0.12 , median 2.0, max. 16). Disaggregate data is presented on [Table A1](#). The greatest frequency of PLEs was among African-American males (55%) and females (49%), followed by Caucasian males (47%) and females (38%). In a simple logistic regression, Caucasian race was a significant protective factor (OR=0.67, p=.017) and male sex was a marginal risk factor (OR=1.35, p=.074).

Only a minority of the respondents (29%, n=81) were able to accurately recall their age at the first onset of these experiences. Amongst these subjects, the mean age at onset was 14.9 years (std. error: ± 0.51 , median 16 yrs., min. 5) and none of the respondents reported an onset of

symptoms occurring less than six months prior to the DIS interview. Subjects capable of recalling their age at initial onset of symptoms reported significantly higher numbers of PLEs than those who could not (mean \pm s.e: 3.9 \pm .31 vs 1.8 \pm .09, $p < .001$).

Adaptive functioning over the past 12 months was measured using the Young Adult Self-Report (Achenbach reference). The mean total ASR (standardized) for the preceding 12 months was 51.0 (std. error: \pm .42, min. 25, max. 81). Published normative standards for ASR total scores (Achenbach 19xx) indicate that approximately 9% ($n=52$) of our subjects reported borderline clinical levels of adaptive distress (ASR total of 60-63), while an additional 11% ($n=65$) reported levels of distress characteristic of individuals requiring clinical treatment (ASR total >63). The zero order correlation between total ASR and subjects' reported number of PLEs was .41 ($p < .001$).

With regard to our primary environmental stressors, by the time of the 22-year follow-up, 83% ($n=493$) of the respondent offspring had used cannabis on at least a single occasion. The median age at first cannabis use (Kaplan-Meier estimate) was 15.7 years (min. 8, max. 22). Twenty-nine percent ($n=174$) of the subjects reported childhood abuse and/or neglect at a moderate or more severe level in at least one of the five areas examined on the CTQ (sexual abuse, emotional abuse/neglect, physical abuse/neglect).

We initially configured our two primary environmental stressors as binary variables (onset of cannabis use <16 yrs, any CAN) and sorted each of the subjects into one of the four (2^2) resulting exposure groups. [Table A2](#) provides the mean numbers of positive psychotic symptoms reported on the DIS and short-term measures of adaptive distress from the standardized ASR summary scales for each exposure group. Much of these data are summarized on [Figure B1](#) and [Figure B2](#) which are bubble plots (group size proportionate to sample size)

with simultaneous 95% confidence intervals showing the mean performance of our exposure groups on key mental health outcome variables (i.e., PLEs, ASR total, internalizing, and externalizing).

Separate negative binomial and linear regression models for each one of our four mental health outcome variables, adjusted for age, sex, and PME are provided on [Table A3](#) and [Table A4](#). None of these regression models were able to detect a significant interaction effect between CAN and ECU.

[Figure B3](#) plots the proportion of subjects in each exposure group qualifying for specific lifetime diagnoses on the DIS. [Table A5](#) summarizes logistic regressions, controlling for sex, race, and PME, testing the increased risk of receiving a specific lifetime diagnosis amongst subjects exposed to different combinations of our primary environmental stressors. All of the two-way interaction effects between CAN and ECU were again non-significant.

4.0 DISCUSSION

The data summarized in this paper indicates that the prevalence of PLEs among respondents in the MHPCD cohort is significantly greater than that found in general population samples. Van Os et al. (2009) report an upper interquartile range for the prevalence of PLEs in the general population of approximately 14%, with the 90th percentile falling at 23%. The baseline exposure group in our study (no CAN, no ECU) has a prevalence of 34.5% (95%CI: 28.3-41.2%) and the other exposure groups are significantly higher. The precise reasons for this elevated prevalence of PLEs in our baseline exposure group are not completely apparent at this time. It may be the case that this excess prevalence is due to the fact that the MHPCD subjects have been exposed to a number of additional environmental risk factors over and above the ones investigated here. Drawing on the list of environmental factors provided by Kelleher and Cannon (2011:4), it is worth noting that all of our subjects reside in an urban setting (i.e., urbanicity), that approximately half of them are black (i.e., ethnic minority status), a majority were raised in a lower socioeconomic setting (i.e., lower SES), and a substantial proportion were reared in a single parent families characterized, at best, by a transient male presence. [Other factors might be included here like witnessed acts of violence, etc.]

Despite these elevated baseline rates, the MHPCD data lead to two clear conclusions. First, the frequency of PLEs in the MHPCD cohort is significantly associated with an exposure to childhood abuse or neglect (CAN), on the one hand, and/or the early onset of cannabis use

(ECU), on the other. And second, the number of reported PLEs is strongly associated with current levels of adaptive distress as measured by the Adult Self-Report (ASR) instrument and with the frequency and pattern of lifetime diagnoses on the DIS. In this cohort, PLEs are a potent at-risk marker for young adult psychopathology, rather than self-limiting developmental epiphenomena. We also suspect that they are persistent, rather than transient in nature, although our data remains somewhat equivocal on this point. These data speak directly to van Os et al.'s (2009:184) observation that few prior studies in the literature assessed the clinical significance of PLE's for current levels of psychological distress and/or help-seeking behavior.

The statistical analyses presented in this report suggest that CAN and ECU have a linear additive effect on the frequency of PLEs and current levels of adaptive distress. Moreover, differential exposure to each of these environmental stressors appears to be associated with contrasting patterns of lifetime diagnoses on the DIS. CAN is significantly associated with depression, PTSD, and panic disorder and unassociated with anti-social personality and substance-related disorders (dependence, abuse, and/or withdrawal). ECU, on the other hand, is significantly associated with diagnoses of anti-social personality and substance related disorders, and unassociated with depression, PTSD, and panic disorders. When both exposures are present, we observe a significant additive elevation in all of these diagnoses. Finally, the data appear to suggest that CAN is the more toxic of the two exposures, showing significantly greater effects on mean levels of young adult internalizing and externalizing problems than ECU.

What are the implications of these data for the “proneness-persistence-impairment” model proposed by Van Os et al. (2009) and the idea of an “extended” or “non-clinical psychosis phenotype” (Kelleher and Cannon 2011). One issue arises in connection with the elevated baseline rates of PLEs among the MHPCD subjects and the relatively frequent occurrence of

environmental stressors such as CAN and ECU. The proneness-persistence-impairment model as formulated by Van Os et al. (2009) would lead us to expect an increased prevalence of schizophrenia and/or schizophreniform disorders among the MHPCD subjects. This does not occur. Only three of the MHPCD subjects meet DSM-IV criteria for schizophrenia or schizophreniform disorder, an observed prevalence of one-half of one percent. NIH and the US Surgeon General (2011) estimate a US general population prevalence of 1.3% for schizophrenia and van Os et al. (2009:184) suggest about 3% for schizophrenia-like psychotic disorders. The same US government sources estimate a one-year general population prevalence of 21% for all psychiatric disorders combined. Our data indicate that at least 20% of the MHPCD cohort demonstrated borderline to clinical levels of adaptive distress (ASR total ≥ 60) at the time of the 22-year follow-up and 64% of the subjects qualified for at least a single lifetime psychiatric diagnosis on the DIS. Clearly, the MHPCD cohort, when compared to the US general population, is not lacking in psychopathology. At the same time, it is not exhibiting schizophrenia-like psychotic disorders at expected or predicted prevalence levels.

How is this apparent lack of schizophrenia-like psychotic disorders in the MHPCD cohort to be explained? One possible hypothesis is that the subjects in the MHPCD cohort do not manifest the same distribution of “psychosis-proneness” observed in general population samples. In the van Os et al. (2009) model, “psychosis-proneness” represents the underlying genetic component or loading for schizophrenia-like disorders in the “extended psychosis phenotype.” It is this underlying genetic vulnerability that explains the developmental appearance of PLEs during adolescence and which may be intensified and made persistent through the action of environmental stressors of the type observed in the MHPCD cohort. It is our hypothesis that the pattern of psychopathology observed among the MHPCD subjects emerges when you have

extreme environmental stressors impacting on subjects who lack a sufficient underlying genetic liability to produce fully formed schizophrenia-like psychotic disorders. In other words, we are suggesting that there may be at least two separate paths to the appearance of PLEs, each one having somewhat different potential outcomes with regard to clinical disorders. If a child is raised within the context of what Scarr (1992:5) classically termed “average expectable (environmental) conditions” they are not exposed to the types of “violent, abusive, and neglectful families” reported by a substantial proportion of our MHPCD respondents. (In passing, we would also suggest that a species-normal environment is unlikely involve the availability of potent psychoactive drugs to pre-adolescent children as young as seven or eight years of age.) It is our contention that children who are raised in this type of “good enough” environment must additionally have some type of underlying, genetically-based “psychosis proneness” in order to manifest PLEs during adolescence. These are the type of children that are routinely observed in general population studies and routinely produce the outcome prevalences described by van Os et al. (2009) and the US Surgeon General. However, there are also children who are regularly and systematically exposed to conditions that test the limits of what Scarr (1992) termed an “average expectable” or “species-normal” child rearing environment. These are the types of environments reported by a substantial proportion of our MHPCD subjects. In these types of settings, we still see the emergence of PLEs in adolescence and we can document the association of these developmental phenomena with certain varieties of young adult psychopathology (e.g., depression, PTSD, panic disorders, substance-use disorder), but what we do not see is their final conversion into elevated rates of schizophrenia-like disorders (e.g., schizophrenia or schizophreniform disorder). It is our belief that in this latter group children, we observe what amounts to an external, environmentally induced version of the “extended psychosis phenotype,”

one that is that is largely a product of extreme child-rearing conditions (both inside and outside the family) that “will not promote normal developmental patterns” (Scarr 1992:5). In a sense, these children are more genetically healthy than their environments can take advantage of. Although similar children are present in general population studies, they are difficult to identify due to their relatively small numbers when compared to subjects raised under “average expectable conditions.” Instead, a weighted or technically biased sampling procedure such as the one used in the MHPCD project is necessary in order to produce sufficient numbers of the latter sort of children to permit their specific identification and study.

In this connection, it is worthwhile recalling that a number of behavioral genetic studies (Scarr-Salapatek 1971, Scarr 1981, Fischbein 1980, Van den Oord and Rowe 1997, Rowe et al. 1999, Turkheimer 2003) have documented an inverse relationship between social class and the heritability of cognitive abilities (IQ, school achievement). With regard to clinical and behavioral outcomes, Raine (2002) has put forward a “social push” hypothesis which argues that the role of genetic factors in the development of anti-social and violent behavior in children is greater in socioeconomically advantaged, as opposed to socioeconomically deprived environments due to the relative paucity of external non-genetic predisposing factors (e.g., abuse, neglect, bullying, etc.) in the former. The Swedish longitudinal twin study (Tuvblad et al 2006) reports data on the heritability of adolescent anti-social behavior that further supports Raine’s (2002) hypothesis. Almost all of these investigators go on to suggest that social interventions carried out under the environment conditions that typify lower SES families are more likely to have more positive consequences than similar interventions carried in enriched environments.

A number of other authors have addressed the likelihood that CAN and ECU are primarily genetically mediated when they do occur. Jaffee, Caspi, Moffitt and their colleagues

(2004a,b) used a twin pair design to test the hypothesis that serious intra-familial physical maltreatment is a consequence of common genetic factors that explain both the parents' abusiveness and the child's tendency to stimulate the abuse. The authors' conclude that risk factors for serious physical maltreatment are less likely to reside in the common genetic background of the parents and children and more likely to reside in environmental (e.g., low education, single parenthood, neighborhood poverty, marital conflict, parental psychopathology, etc.) factors that differ between families. The evidence regarding the initiation of cannabis use and the progression to later abuse and dependence (Agrawal and Lynskey 2006) suggests a multi-stage model involving both environmental and genetic components at each phase. At the same time, Kendler et al. (2008) argue that earlier patterns of onset and use are more strongly influenced by external environmental factors (social and familial), whereas the later progression towards abuse and dependence is more strongly influenced by internal, genetic factors.

All of the above remarks are simply intended to reinforce the connection between two crucial observations: first, the types of non-genetic risk factors associated with an "extended psychosis phenotype" and the occurrence of psychotic-like experiences (e.g., urbanicity, abuse and neglect, bullying, minority status, unemployment, early cannabis use, and single parent families) are also strongly associated with a lower socioeconomic status; and, second, there is good evidence to suggest that within the context of a lower socioeconomic settings genetic factors play a reduced role in childhood developmental outcomes, generally, and in the appearance positive psychotic-like experiences, particularly. It is our belief that the greater prevalence in lower SES settings of child rearing conditions that approach the limits of the "species-normal" and "average expectable" (Scarr 1992) largely explains the connection between the above two observations. If we are correct, it would explain why in our data we see clearly

elevated rates of PLEs compared to general population studies, together with a less than expected frequency of schizophrenia-like outcomes. At the same time, this does not suggest that the PLEs occurring amongst our lower SES respondents are benign or self-limiting or have good developmental outcomes. To the contrary, it has been shown that the occurrence of positive psychotic-like symptoms in our MHPCD cohort are not only associated with unusually negative child rearing conditions, but tend to be relatively common in occurrence, persistent in nature, and significant predictors of both high levels of adaptive distress and a wide variety of diagnosable psychiatric conditions by the time of young adulthood. Our young adult psychiatric outcomes are not demonstrably better than the outcomes observed among the subjects of general population studies, only different in the final patterns that work themselves out.

APPENDIX A: TABLES

Table A1: Disaggregate Data for Psychotic-Like Experiences on DIS

PLE Group		Hallucinatio ns	Type of PLE Delusions	All PLEs
Hallucinations only				
	N	25	----	----
	Mean (SE)	1.28 (.11)		
	Median	1.0		
	Maximum	3		
Delusions only				
	N	---	181	----
	Mean (SE)		1.76 (.09)	
	Median		1.0	
	Maximum		8	
Delusions & Hallucinations				
	N	74	74	74
	Mean (SE)	1.73 (.16)	2.68 (.23)	2.72 (.32)
	Median	1.00	2.00	4.0
	Maximum	7	10	16
Overall				
	N	99	255	280
	Mean (SE)	1.60 (.12)	2.04 (.09)	2.42 (.12)
	Median	1.0	1	2.00
	Maximum	7	10	16

Table A2: Details of Continuous Variables for Figure 1 (n=591)

Continuous Variables	Exposure Groups (MJ Onset<16 yrs., CAN)				Statistical Significance	
	1 00 n=220 (37%)	2 10 n=197 (34%)	3 01 n=70 (12%)	4 11 n=104 (17%)	P-value	Pairwise Comparisons **
PLEs						
Mean (se)	0.59 (.08)	0.98 (.11)	1.54 (.21)	2.37 (.28)		
Median	0.0	0.0	1.0	2.0	>.001	1<2<3<4
%≥1	34.5	44.7	62.9	69.2		
ASR total						
Mean (se)	47.25 (.61)	49.87 (.67)	54.63 (1.18)	58.83 (.94)		
Median	47.0	49.0	52.5	59.0	>.001	1<2<3<4
%≥60	8.2	15.7	24.3	49.0		
ASR internal						
Mean (se)	47.30 (.68)	49.56 (.73)	56.00 (1.30)	60.52 (1.04)		
Median	46.0	50.0	54.0	61.0	>.001	1<2<3<4
%≥60	13.6	18.3	34.3	55.8		
ASR external						
Mean (se)	50.10 (.61)	53.36 (.70)	55.99 (1.01)	60.53 (.98)		
Median	50.0	50.0	56.0	61.0	>.001	1<2<3<4
%≥60	14.1	27.9	27.1	55.8		
PME						
Mean (se)	0.21 (.04)	0.41 (.07)	0.41 (.11)	.62 (.14)		
Median	0.0	0.0	0.03	0.0	>.003	1<2=3=4
%>0	33.6	44.2	50.0	42.3		
MJ Onset (yrs.)*						
Mean (se)	20.58 (.27)	13.78 (.09)	20.01 (.49)	13.38 (.15)		
Median	19.0	14.0	18.5	13.67	>.001	1=3<2=4
CTQ score						
Mean (se)	29.70 (.28)	31.22 (.38)	50.14 (1.53)	53.42 (1.30)		
Median	29.0	30.0	46.5	51.0	>.001	1<2<3<4

*Kaplan-Meier estimate **Adjusted for multiple comparisons (LSD)

Table A3: Negative Binomial Regression for Number PLEs at 22-Years-Old on DIS

Independent Variables	Number PLEs (0-16)		
	beta	s.e.	sig.
Race (white base)	-.269	.252	.030
Sex (male base)	.405	.124	.001
PME 1 st trimester	.060	.122	.337
Age Cannabis Onset			
<16	.623	.193	<.001
≥16	.426	.206	<.038
Never used (base)	---	---	---
Child Trauma Ques.	.033	.005	<.001

Table A4: Linear Regressions for ASR Mental Health Outcome Scales

Independent Variables	ASR total			Adult Self-Report Summary Scale					
	beta	s.e.	sig.	ASR internalizing			ASR externalizing		
	beta	s.e.	sig.	beta	s.e.	sig.	beta	s.e.	sig.
Race (white base)	-2.11	.76	.728	-1.73	.84	.038	-1.426	.78	.066
Sex (male base)	.26	.75	.005	1.79	.83	.030	-.89	.77	.246
PME 1 st trimester	.07	.41	.873	.048	.45	.914	.207	.42	.621
Age Cannabis Onset									
<16	-3.83	1.05	<.001	-2.82	1.16	.015	-4.25	1.08	<.001
≥16	-1.73	.85	.043	-2.14	.94	.023	-2.45	.87	.005
Never used (base)	----	----	----	----	----	----	----	----	----
Child Trauma Ques.	.33	.03	<.001	.396	.033	<.001	.256	.03	<.001

Table A5: Logistic Regression Summaries: Diagnostic Categories by Exposure Groups n=591 controlling for sex, race, and PME

Group No.	DIS Lifetime Diagnoses						
	Schiz. & Schizoaff	Depression	PTSD	Panic	Anxiety	Anti-Social	Substance-Related
Gp.1	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline	Baseline
Gp.2							
Risk Ratio	---*	1.92	1.01	1.46	8.67	3.55	2.53
P-Value	.995	.046	.983	.242	.045	.016	<.001
Gp.3							
Risk Ratio	1.08	4.43	5.68	2.72	12.97	2.04	1.24
P-Value	1.00	<.001	.001	.010	.023	.338	.581
Gp.4							
Risk Ratio	---*	8.19	7.46	3.55	29.58	10.25	4.65
P-Value	.995	<.001	<.001	<.001	.001	<.001	<.001

*=infinity or zero

APPENDIX B: FIGURES

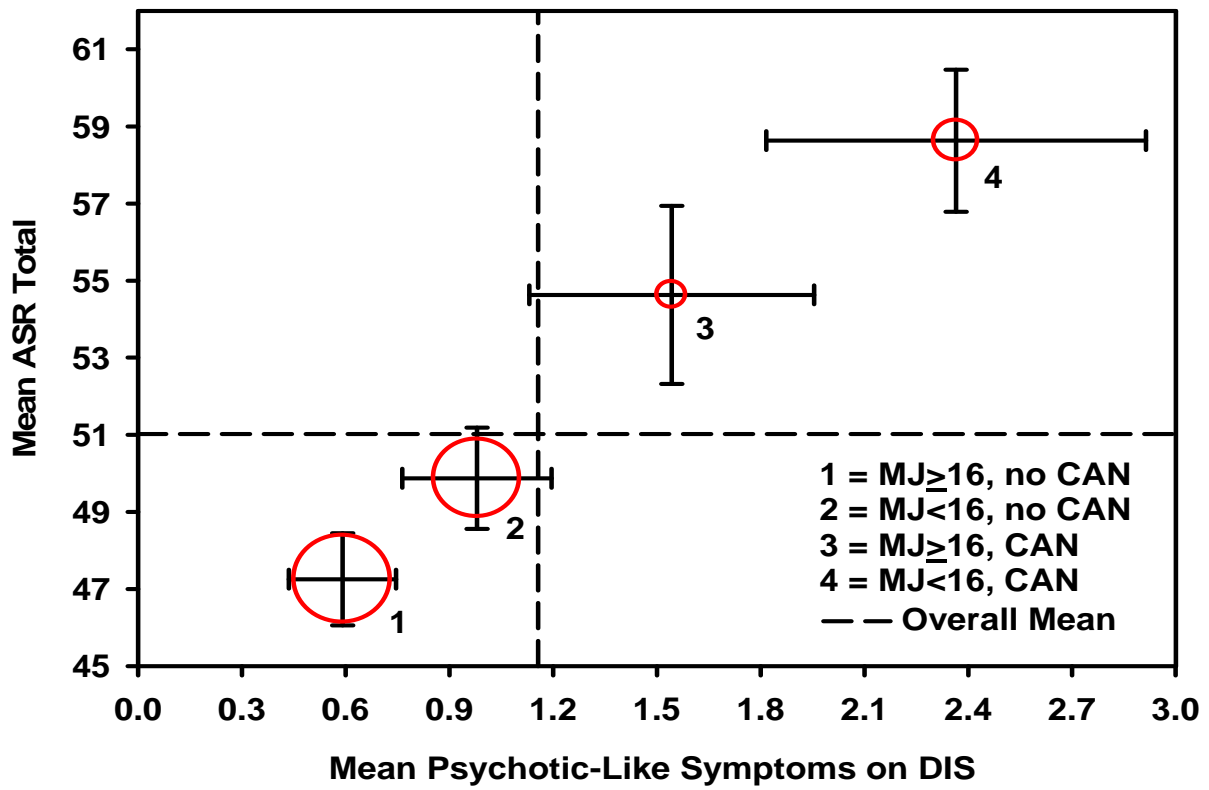


Figure B1: Mean Frequency PLE's and ASR Total Scores by CAN and ECU Exposure Groups.

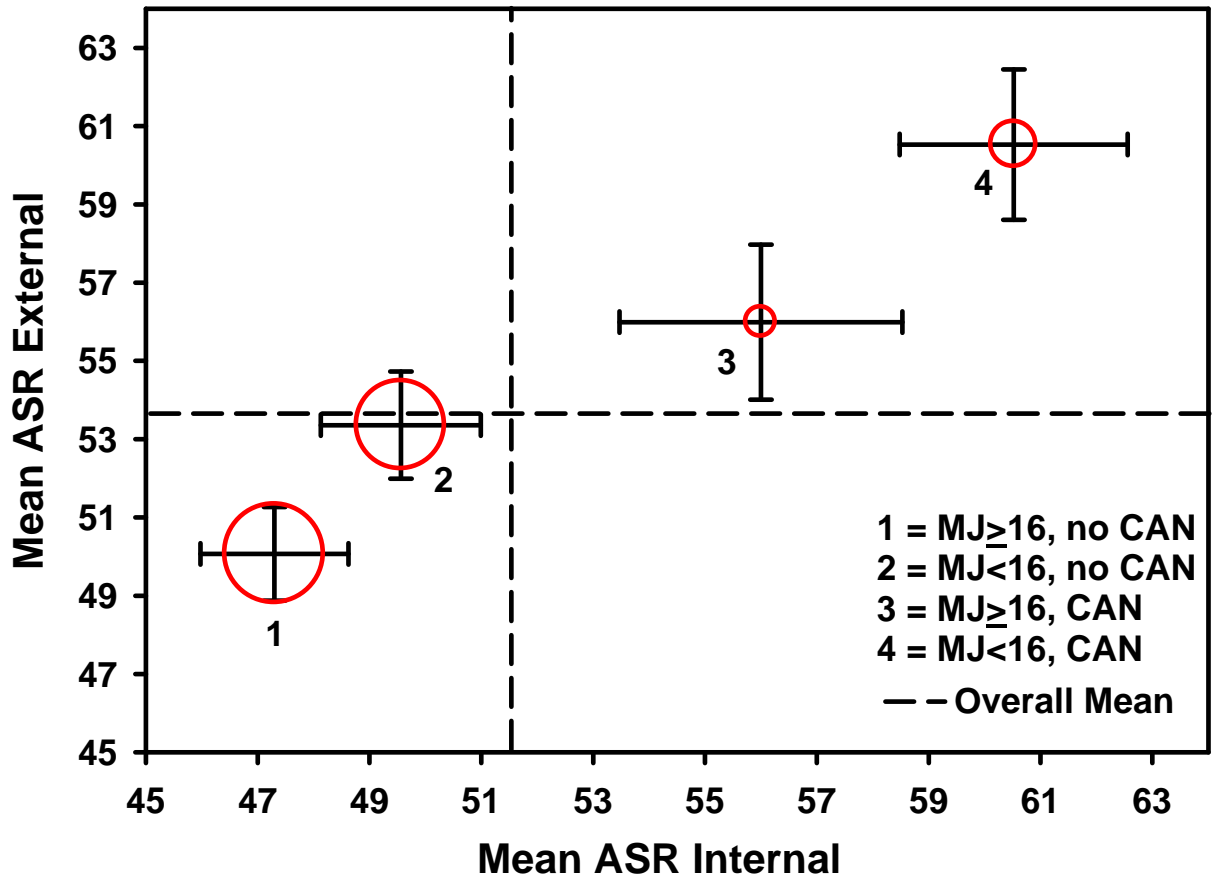


Figure B2: 22 Year ASR Internalizing and Externalizing Scores by CAN and ECU Exposure Groups

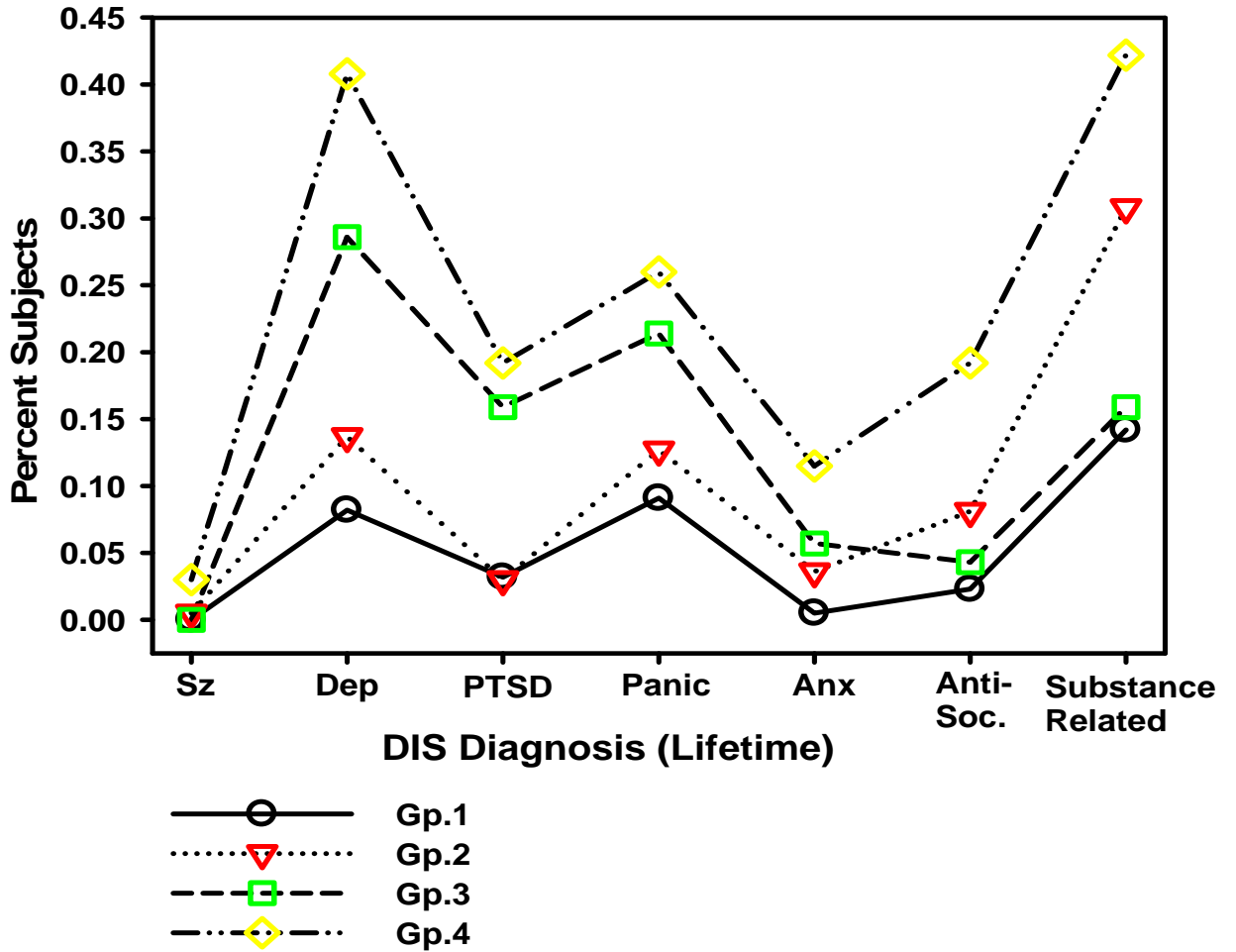


Figure B3: Percent 22 Year-Old MHPCD Subjects with Specific DIS Lifetime Diagnoses by Figure 1 Groups

BIBLIOGRAPHY

- Agrawal, A and Lynskey, M (2006). The Genetic Epidemiology of Cannabis Use, Abuse and Dependence. *Addiction*, 101: 801-812.
- Fischbein, S. (1980). IQ and Social Class. *Intelligence*, 4: 51-63.
- Jaffe, S; Caspi, A; Moffitt, T; et al (2004). Physical Maltreatment Victim to Antisocial Child: Evidence of an Environmentally Mediated Process. *Journal of Abnormal Psychology*, 113: 44-55.
- Kelleher, I. and Cannon, M. (2011) Psychotic-like Experiences in the General Population: Characterizing a High-risk Group for Psychosis. *Psychological Medicine*, 41: 1-6
- Kendler, KS et al (2008). Genetic and Environmental Influences on Alcohol, Caffeine, Cannabis, and Nicotine Use from Early Adolescence to Middle Adulthood. *Archives of General Psychiatry*, 65: 674-682.
- Mental Health: A Report of the Surgeon General, Accessed April 10, 2011.
<http://www.surgeongeneral.gov/library/mentalhealth/chapter4/sec4.html>
- Raine, A (2002). Biosocial Studies of Antisocial and Violent Behavior in Children and Adults: A Review. *Journal of Abnormal Child Psychology*, 30: 311-326.
- Rowe, D.C. et al (1999). Genetic and environmental influences on vocabulary IQ: parental education level as moderator. *Child Development*, 70:1151-62.
- Scarr, S. (1981). *Race Social Class, and Individual Differences in I.Q.: New Studies of Old Issues*. Hillsdale, NJ: Erlbaum
- Scarr, S. (1992). Developmental Theories for the 1990's: Development and Individual Differences. *Child Development*, 63: 1-19.
- Scarr-Salapatek, S (1971). Race, Social Class, and IQ. *Science*, 174: 1285-1295
- Turkheimer, E. et al (2003). Socioeconomic Status Modifies Heritability of IQ in Young Children. *Psychological Science*, 14: 623-628.

- Tuvblad, C et al (2006) Heritability for Adolescent Antisocial Behavior Differs with Socioeconomic Status: Gene-Environment Interaction. *The Journal of Child Psychology and Psychiatry*, 47: 734-743.
- Van den Oord, E., & Rowe, D.C. (1997). An Examination of Genotype-Environment Interactions for Academic Achievement in an U.S. Longitudinal Survey. *Intelligence*, 25: 205-219.
- Van Os et al (2009). A Systematic Review and Meta-analysis of the Psychosis Proneness-Persistence-Impairment Model of Psychotic Disorder. *Psychological Medicine*, 39: 179-195.