VARIATIONS IN THE CO-OCCURRENCE OF MENTAL HEALTH PROBLEMS IN ADOLESCENTS WITH PRENATAL DRUG EXPOSURE

by

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Dedication

To my mother, Sunghee Lee, for your love, encouragement, and prayers

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Variations in the Co-occurrence of Mental Health Problems in Adolescents with Prenatal Drug Exposure

Abstract

by

JUNE-YUNG KIM

Prenatally drug exposed adolescents are at heightened risk of developing mental health problems due to biologic insults. However, little is known about the nature of mental health condition in this at-risk population. Informed by the general and specific liability to psychopathology model and Research Domain Criteria (RDoC) framework, this study examined variations in the co-occurrence of mental health problems among at-risk adolescents and assessed potential roles of childhood impulsivity, irritability, and social disinhibition corresponding to the cognitive, affective, and social RDoC risk factors of varied symptom patterns. This study further evaluated predictive validity of the empirically observed symptom co-occurrence patterns by examining how adolescent symptom patterns were associated with emerging adulthood outcomes.

Participants were 365 adolescents from a 21-year prospective study of the effects of prenatal drug exposure in the Midwestern United States. Latent class modeling was conducted to identify distinct variations of mental health problems. Multinomial logistic regression was used to examine childhood impulsivity, irritability, and social disinhibition as the RDoC risk factors of latent class group membership. Logistic regression was used to validate the identified latent classes by associating them with emerging adulthood outcomes.

Four subgroups with distinct patterns of co-occurrence of mental health problems were identified: *no problem group* (57%), *drug-using group* (24%), *mental health problem group* (11%), and *multimorbid group* (7%). Irritability and social disinhibition predicted membership in the multimorbid group. Irritability specifically predicted membership in the mental health problem group whereas social disinhibition predicted membership in the drug-using group. Adolescents in high-risk groups were more likely to have problematic drug use and mental health problems and less likely to have completed high school education at age 21.

The multimorbid group represents the general liability to psychopathology as their responses on all measured symptoms were consistently high. Conversely, the mental health group and drug using group capture the specific liability to psychopathology due to unique covariances on the symptoms. Both irritability and social disinhibition translated to broad-transdiagnostic risks leading to a multimorbid pattern. These affective and social RDoC constructs should be further investigated to prevent adolescent mental health problems, which have implications for emerging adulthood adjustment.

Chapter 1: Introduction

Background

Mental health comorbidity presents significant public health problems and has raised clinical and research debate on the conceptualization of psychopathology. The co-occurrence of mental health syndromes that share substantial common variances and exist on liability continuums (Achenbach & Edelbrock, 1984; Caspi et al., 2014) is prevalent across all age groups and diverse populations (Angold, Costello, & Erkanli, 1999; Angst, 1996; Kendler, Prescott, Myers, & Neale, 2003). One in every three adolescents meets diagnostic criteria for psychopathology. Among this group, up to 40% also meet diagnostic criteria for another syndrome (Merikangas et al., 2010 for the National Comorbidity Survey Adolescent Supplement data). Approximately 50% of adults meet diagnostic criteria for lifetime psychopathology. Among these individuals, about half meet diagnostic criteria for additional syndromes (Kessler et al., 2012).

In mental health research and clinical settings, comorbidity of psychopathology refers to the simultaneous manifestation of two or more mental health syndromes in an individual (Angold & Costello, 1993; Beuachaine & McNulty, 2013; de Graaf et al., 2002; Stein et al., 2001). These syndromes are construed as constellations of related behavioral or cognitive symptoms. Grounded in this definition, the current study interchangeably uses co-occurrence of mental health symptoms or symptom co-occurrence to refer to comorbidity. This study adopts a conceptual definition of mental health disorder that is consistent with the American Psychological Association (APA). Mental health disorder is defined as:

> "Any condition characterized by cognitive and emotional disturbances, abnormal behaviors, impaired functioning, or any combination of these. (APA, 2020)."

The APA indicates that the term psychopathology is considered synonymous with mental health disorders/syndromes (APA, 2020). The current study, in this sense, refers to mental health disorders, including substance use disorders, as psychopathology, and both terms are interchangeably used. Using a lifespan approach to mental health, this study refrains from the use of the word 'disorders' when mental health syndromes are discussed in relation to individuals who are at developmental stages prior to adulthood when clinical diagnoses are made (American Psychiatric Association, 2013). Instead, mental health problems or conditions are used to refer to mental health syndromes that emerge in infancy, childhood, and adolescence.

Comorbidity is associated with adverse correlates and sequelae, including poor treatment responses (Cummings, Caporino, & Kendall, 2014; Drabick & Kendall, 2010). This pattern is clearly illustrated by findings in both epidemiological (e.g., Connor, Steeber, & McBurnett, 2010) and clinical samples (e.g., Goldstein & Levitt, 2008). To illustrate, individuals with comorbidity were found to have more functional impairment, including greater symptom severity (Connor et al., 2010; Goldstein & Levitt, 2008), more frequent days of disability (Newman, Moffitt, Caspi, & Silva, 1998), less social competence (Renouf, Kovacs, & Mukerji, 1997), greater life dissatisfaction (Newman et al., 1998), more suicide attempts (Lewinsohn, Rohde, & Seeley, 1995; Rohde, Clarke, Lewinsohn, Seeley, & Kaufman, 2001), additional treatment challenges, and greater unmet needs for treatment (Connor et al., 2010; Goldstein & Levitt, 2008), when compared with single-diagnosed counterparts. Given the prevalence of comorbidity and

the severe impairment and cost incurred by the phenomenon, consideration of comorbidity is crucial to inform mental health research relevant to etiology, nosology, and intervention (Angold et al., 1999; Bubier & Drabick, 2009; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017).

Accumulating evidence indicates that individuals with prenatal exposure to drugs are at greater risk of adverse neurobehavioral outcomes across later development stages (e.g., Lester & Lagasse, 2015; Minnes et al., 2017; Richardson, Larkby, Goldschmidt, & Day, 2013). Each year in the United States, 15 % of newborns are prenatally exposed to alcohol or illicit drugs (National Center on Substance Abuse and Child Welfare [NCSACW], 2019). Biologic insults due to prenatal substance exposure, particularly the immaturity of monoaminergically regulated arousal systems, combined with epigenetic factors and negative postnatal environmental contexts (e.g., ongoing parental substance use and psychological distress, exposure to child maltreatment and intimate partner violence, and adoptive/foster care placements) may increase vulnerability to developmental impairment (Minnes, Lang, & Singer, 2011), including the sequelae of psychopathology. However, no known neurobehavioral teratology research (i.e., the study of abnormal development of the nervous system and behavior as a consequence of prenatal exposure to toxic agents) has focused on the complexity of psychopathology and the nuance of comorbidity evidenced among individuals with prenatal drug exposure. A better understanding of the nature and ontogenic processes of comorbid psychopathology in this vulnerable population is needed to inform social work research, and public health policy, as well as for prevention and treatment efforts.

Problem Statement

Prevalence of comorbidity in psychopathology has been a serious concern in clinical science. A substantial body of mental health literature has documented the extensive degree of comorbid psychopathology in childhood and adolescence (e.g., Kessler et al., 2012; Merikangas et al., 2010), and its associations with reduced functioning and quality of life, as well as adverse long-term outcomes including societal costs (Andrews, Slade, & Issakidis, 2002; Pirkola et al., 2009; Weich et al., 2011). In this context, the underlying structure of comorbidity in youth has been investigated mostly with variable-centered approaches that organize the structure of symptom indicators assessed. Such transdiagnostic factor analytic approaches aim to understand its nature, etiological mechanisms, and persistence of syndromes over time (Blanco et al., 2015; Carragher et al., 2016; Caspi & Moffitt, 2018; Kessler et al., 2012; Lahey et al., 2008; Patalay et al., 2015).

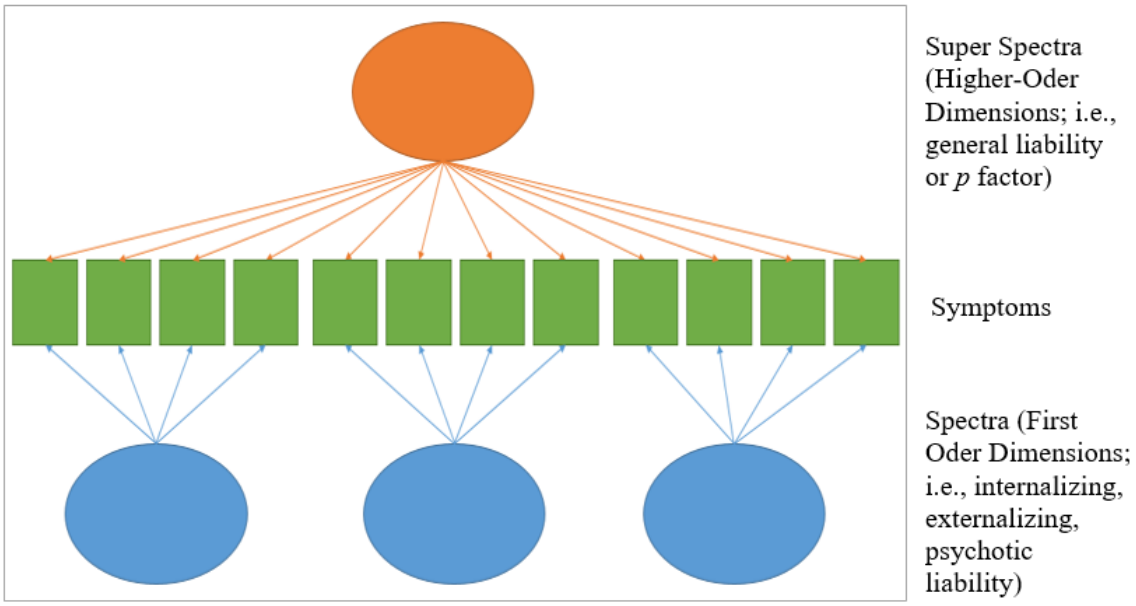
Variable-centered comorbidity research has focused on the interrelationships among psychopathology symptom variables to identify their common sources of variance, such as associations among symptom/syndrome variables within the same boundaries (e.g. internalizing, externalizing[1], or psychotic domains; mental health or substance dependence) and/or symptom/syndrome variables that transcend diagnostic domains (Olino, Klein, Farmer, Seeley, & Lewinsohn, 2012). Namely, such variable-centered work has demonstrated that the organization of psychopathology can be

[1] Internalizing here refers to thoughts or actions directed toward the self, ranging from depression, anxiety, to social withdrawal (Achenbach, Edelbrock, & Howell, 1987; Salkind, 2005). Externalizing, on the other hand, refers to uncontrolled non-self-directed actions. These can take the form of aggression and disruption (Achenbach et al., 1987; Salkind, 2005).

accounted for by a few underlying latent factors (Blanco et al., 2015; Laceulle, Vollebergh, & Ormel, 2015) that are hypothesized to reflect adolescents' liability to develop any or all forms of common psychopathology (Kendler et al., 2003; Krueger & Silva, 1998).

Likewise, recent comorbidity research (e.g., Caspi et al., 2014; Deutz et al., 2019; Lahey et al., 2012; Laceulle et al., 2015; Olino et al., 2014) has provided evidence of a general dimension of psychopathology—the *p* factor, which points to a fundamental liability to experience any or all forms of psychopathology. For example, Lahey et al. (2012) found that the general and specific liability to psychopathology model (*see* Figure 1) that conceptualizes the psychopathology structure as being composed of general and specific liability dimensions best fits the data from a U.S. epidemiologic sample (ages 18-64 years). Caspi et al. (2014) demonstrated the robustness of the general and specific liability to psychopathology model using the lifetime psychopathology data from a large, community-based New Zealand sample covering adolescence through adulthood. Other independent research replicated this structure using community-based Dutch (Laceulle et al., 2015) and UK (Patalay et al., 2015) adolescent data. Liu et al. (2017) further found that the general and specific liability model best fits minority adolescent psychopathology data using a 15-year-old African American youth sample from urban neighborhoods. There have been additional replications of the organization of psychopathology that involve the general and specific liability dimensions in cross-sectional studies across samples of children and adolescents (Hankin et al. 2017; Pataly et al., 2015) and adults (Kim & Eaton, 2015; Murray, Eisner, & Ribeaud, 2016; Pettersson, Larsson, & Lichtenstein, 2016; Stochl et al., 2015).

Figure 1
Example of General and Specific Liability (Bifactor) Model



Note. Adapted from "All for One and One for All: Mental Disorders in One Dimension" by Caspi and Moffitt (2017).

Emerging research has employed person-centered perspectives as a complementary way of understanding the structural organization of comorbid psychopathology (e.g., Kim & Eaton, 2017; Deutz et al., 2019; Vaidyanatahn, Patrick, & Iacono, 2011). Person-centered approaches investigate how adolescents (rather than psychopathology symptom/syndrome variables) group together and thus identify meaningful, homogenous subgroups among them with shared patterns of co-occurring mental health symptoms. This is how person-centered approaches examine latent group structures of psychopathology.

Prior studies of at-risk samples with prenatal drug exposure have so far demonstrated high prevalence of adverse neurobehavioral developmental outcomes, specifically externalizing symptomatology and substance use problems, likely due to

prenatal insults altering the developing fetal brain. These prenatal insults particularly influence the monoamine neurotransmitter system affecting emotion dysregulation and executive function (Mayes, 2002; Min, Minnes, Yoon, & Singer, 2017; Minnes et al., 2011; Thompson et al., 2009). Beyond such heightened risks of developing mental health problems, however, little is known about the actual structure of mental health condition in this at-risk population. Currently, there is a limited understanding of the nature of the co-occurrence of mental health problems among prenatally drug exposed adolescents and how various symptom co-occurrence patterns may be influenced by childhood etiological factors across the cognitive, affective, and social domains. It is essential to generate advanced knowledge regarding variations in symptom expression that allows for the planning and development of targeted intervention and prevention strategies. These strategies can effectively address the mental health service needs dependent on symptom severity or combinations. There is also a lack of knowledge about differential prognoses of adolescents with distinct comorbidity patterns as they enter emerging adulthood. The assessment of the clinical significance and validity of adolescent symptom co-occurrence patterns by linking those patterns with emerging adulthood adjustment will contribute to our knowledge of earlier childhood interventions targeting adolescent mental health, further providing implications for strategies in emerging adulthood.

Overview and Aims of the Study

This study examined variations in the co-occurrence of mental health problems in a sample of prenatally drug exposed adolescents at age 15 who were born and raised in low socioeconomic status, urban neighborhoods of a Midwestern region in the United States.

This study also identified childhood etiological factors at age 12 as potential correlates of heterogeneity in the symptom co-occurrence patterns. This study focused on impulsivity, irritability, and social disinhibition as the three early risk factors that are relevant to prenatally drug exposed individuals' cognitive and behavioral development. Doing so, this study examined the unique effects of these etiological factors in determining various comorbidity patterns in adolescence. Adolescents' and their caregivers' information that might confound and obscure the effects of childhood etiological constructs were considered. Included were *adolescents' potential confounding factors* assessed at their birth (i.e. gender, race, gestational age, birth weight and height, and prenatal drug exposures) and in childhood (i.e., IQ, parental monitoring, violence exposure, and always in birth parents' care by age 12), as well as *biologic mothers' potential confounders* assessed at child delivery (i.e. maternal age at child delivery, education, marital status, vocabulary ability, psychological distress, and socioeconomic status) and *current caregiver-level confounders* (i.e. education, vocabulary ability, psychological distress, quality of home environment, and caregiver substance use in the past 30 days).

Additionally, the clinical significance and validity of the empirically derived patterns of the co-occurrence of mental health problems during adolescence were examined. Such validity test was carried out by associating the identified symptom co-occurrence patterns with emerging adulthood outcomes at age 21 (i.e., problematic substance use, mental health symptoms, and educational attainment), while considering important covariates of the outcomes (i.e., gender, child maltreatment, sexual victimization, receipt of free lunch, and always in birth parents' care by age 15).

Age 15 is critical for prenatally drug exposed adolescents' developmental course and etiology of comorbid mental health problems. During adolescence, particularly, at 15-16 years of age, disparities in behavioral health such as substance use can begin to get exacerbated (Kessler et al., 2005a; Vallejo-Torres, Hale, Morris, & Viner, 2014). Moreover, mental health syndromes manifested in this significant life stage further risk functional adjustment in adulthood (Bongers et al., 2008; Englund et al., 2013; Hawkins et al., 2015). Adolescence is an important transition period marked as a developmental era where health trajectories of individuals are likely to be laid out (Hutchison, 2015). In this context, ages 12 or 13, pre-adolescent years, have been suggested as an optimal timing for evaluating future risks of developing mental health problems (Santucci, 2012; Ridenour et al., 2015). Such preventive screening interventions in this peripubertal stage are beneficial and cost effective in promoting overall psychological wellbeing. As such, the use of the 15-year mental health data along with 12-year etiological factor data in the current study were informed by these conceptual discussions traditionally agreed and practiced in clinical settings.

The major aims of this dissertation research are as follows.

Aim 1. To identify distinct variations in the empirically observed patterns of the co-occurrence of mental health problems among prenatally drug exposed adolescents at age 15.

Aim 2. To examine how childhood etiological factors (i.e., impulsivity, irritability, and social disinhibition) assessed at age 12 are associated with empirically observed patterns of the co-occurrence of mental health problems in adolescence, while controlling for adolescent-level confounders (assessed at birth: gender, race, gestational

age, birth weight and height, and prenatal drug exposure; assessed in childhood: IQ, parental monitoring, violence exposure, and always in birth parents' care by age 12) and caregiver-level confounders (assessed at child delivery: maternal age at child delivery, education, marital status, vocabulary ability, psychological distress, and socioeconomic status; assessed when children are at age 12: education, vocabulary ability, psychological distress, quality of home environment, and caregiver substance use in the past 30 days).

Aim 3. To assess how patterns of the co-occurrence of mental health problems in adolescence are associated with emerging adulthood outcomes assessed at age 21 (i.e., problematic drug use, mental health symptoms, and completion of high school education), while controlling for important covariates (i.e., gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15).

Significance of the Study in Social Welfare Policy and Practice

Individuals who were exposed to drugs in utero are at heightened risks of developing mental health problems across postnatal developmental stages (Min et al., 2017; Minnes et al., 2011, 2017). However, social work policy initiatives and practice interventions to date have not been successful in engaging in strategies that can promote healthy growth of the at-risk population. Especially given multiple associated environmental risk factors in their developmental contexts, rigorous research endeavors exploring the variation in the (co)occurrence of mental health symptoms and earlier etiological factors underlying severe forms of symptom co-occurrence are key to the design of effective preventive interventions and mental health policy initiatives. Such

investigations could enhance the psychological wellbeing of vulnerable populations and have lasting protective benefits for individuals and communities.

Social workers have the obligation “to enhance human well-being and help meet the basic human needs of all people, particularly those who are vulnerable, oppressed, and living in poverty” (National Association of Social Workers, 2017). To fulfil this calling, social workers must work to address the needs of infants with prenatal drug exposure by offering various intervention and preventive public health programs to the dyads of these high-risk children and their caregivers across the lifespan. In this vein, social work policy makers should foremost increase public and academic awareness of the higher prevalence of prenatal drug exposure than is generally assumed. Every year, in the United States, one or two out of every 10 newborns is prenatally exposed to alcohol or illegal drugs (NCSACW, 2019). Social workers could alleviate this problem by allocating resources in ways to prioritize policy planning and to develop new social service programs for such population at high risk but traditionally underserved.

Further, evidence-based policymaking can be informed by research demonstrating heterogeneity in the manifestation of mental health symptoms among prenatally drug exposed adolescents and identifying earlier, childhood etiological factors that distinguish more vulnerable subgroups from resilient individuals within this at-risk population. Evidence-inspired policy decision making will facilitate more effective allocation of financial resources and advancement of mental health services that support healthy lives of the high-risk population. To illustrate, new knowledge could direct the creation of novel early screening tools. These preventive methods will generate advantages in the long run by targeting childhood dysfunctional process underlying mental health problems

in adolescents with prenatal drug exposure. The provision of intervention services that are developmentally on target may prevent the manifestation of mental health problems and help the at-risk adolescents lead resilient lives.

It is critical that social welfare practitioners not assume that the manifestation of mental symptoms is uniform among prenatally drug exposed adolescents when designing and delivering specific interventions that prevent mental health problems. To be more effectively informed, an investigation of variations in the (co)occurrence of mental health problems of prenatally drug exposed adolescents needs to be established first. Knowledge of heterogeneous patterns of symptom co-occurrence and varied prognoses that are observed when adolescents with distinct comorbidity patterns develop into emerging adults will significantly improve these at-risk individuals' psychological well-being during a critical transition period of their development. Our expanded knowledge about childhood indicators that identify a more vulnerable subgroup with severe combinations of co-occurring symptoms may help social welfare practitioners to develop and implement preventive screening tools as well as aiding these high-risk adolescents.

Chapter 2: Theoretical Framework

This chapter first reviews the main theoretical lines of thoughts guiding the development of the current study. These theoretical models are the general and specific liability to psychopathology model and the Research Domain Criteria (RDoC) framework. This chapter then introduces the resulting conceptual model as derived from the literature.

General and Specific Liability to Psychopathology Model

Widespread comorbidity has given rise to models that perceive psychopathology as consisting of various broad dimensions. According to one model, psychopathology is "psychological continua that reflect individual differences in maladaptive characteristics across the entire population" (Kotov et al., 2017, p. 456). In that model, broad dimensions reflect underlying liabilities that are argued to contribute to experiencing diverse and comorbid phenotypic behavioral symptoms (e.g., Krueger 1999; Krueger, Caspi, Moffitt, & Silva. 1998; Krueger & Markon 2006; McElroy, Belsky, Carragher, Fearon, & Patalay, 2018; Slade & Watson, 2006; Tackett et al., 2013). Currently, the most widely discussed model is the general and specific liability for psychopathology model (Caspi et al., 2014; Kotov et al., 2017; Lahey et al., 2017). This novel model conceptualizes psychopathology in a hierarchical form that organizes "dimensions of psychopathology from specific symptoms to first-order domains of those symptoms to broader, higher-order domains that are defined by associations among first-order domains and their inferred causes" (Kotov et al., 2017; Krueger & Piasecki, 2002; Lahey et al., 2017; *see* Figure 1 in Chapter 1). These phenotypic associations (i.e., shared variance) among both first- and

higher-order dimensions of psychopathology reflect a general liability to psychopathology (Kotov et al. 2017; Lahey et al., 2017).

This general liability to psychopathology, labeled the *p* factor, is best represented with a bifactor model (Caspi et al., 2014; Lahey et al., 2012; *see* Figure 1 in Chapter 1). As such, *p* captures the common variance shared across all measured mental health symptoms (Caspi et al., 2014; Lahey et al., 2012). Unique covariances observed among the mental health symptoms are then explained by particular liability dimensions. Such additional and specific dimensions can be internalizing and externalizing, with further domains based on the symptoms assessed such as thought disorders, or attention problems.

In the general and specific liability to psychopathology model, the shared etiological influence on psychopathology is hypothesized to operate through a number of psychobiological mechanisms in a pleiotropic way. The pleiotropic principle suggests that causal factors (e.g., broad-acting environmental exposures and genetic effects) nonspecifically increase risks for all or multiple phenotypic mental health symptoms to varying degrees (Carragher et al., 2016; Castellanos-Ryan et al., 2016; Lahey et al., 2017; Tackett et al., 2013).

The phenomenon of pleiotropy is in line with the developmental psychopathology concept of "multifinality," which posits that shared, similar adverse experiences may lead to different symptoms (Nolen-Hoeksema & Watkins, 2011). According to this conceptualization, individuals who have been exposed to drugs in utero may manifest distinct patterns and severity of mental health problems in adolescence. For instance, it is possible that a subgroup of this population develops combinations of a broad spectrum of

mental health symptoms that are inter-related. This theoretical premise of variations in the symptom manifestation has been supported by recent empirical studies that found different, broad latent dimensions of symptom covariations (e.g., Caspi et al., 2014; Castellanos-Ryan et al., 2017; Tackett et al., 2017) or patterns of symptom co-occurrence (e.g., Kim & Eaton, 2019; Olino et al., 2014) that represent general and specific liabilities to psychopathology among general or community samples of youth.

The general and specific liability to psychopathology model is a powerful comorbidity research framework as it can guide advanced investigations that determine specific adolescent subgroups characterized by shared patterns of mental health problems (Beauchaine & McNulty, 2013; Kotov et al., 2017). This framework allows researchers to transcend solely investigating pairwise comparisons of diagnoses and questions regarding prevalence. Through replications and validation across diverse samples in childhood, adolescence, and adulthood, the general and specific liability to psychopathology model has demonstrated its theoretical usefulness in informing investigations of variations in the co-occurrence of mental health problems. This framework is also beneficial in helping researchers and clinicians create and deliver mental health services that are empirically supported and developmentally on target (Ruggero et al., 2019). When we gain an understanding regarding nuanced, accurate patterns of symptom co-occurrence that are derived from research, the prevention of the emergence or progression of mental health problems would be more effective. This can be possible particularly by targeting and aiding subgroups of individuals at higher risks with severe patterns of combinations of mental health symptoms.

Research Domain Criteria (RDoC) Framework: The Role of Impulsivity, Irritability, and Social Disinhibition

Constructed by the National Institute of Mental Health (NIMH), the Research Domain Criteria (RDoC) framework (NIMH, 2008; NIMH, 2020) details the selection of multiple risk factors. These factors, which are thought to underlie the etiology of mental health problems in various syndrome domains and levels of severity, range from cognitive, and affective, to social processes (Cuthbert, 2014; Insel, 2014). The main task of RDoC, a framework to link internalizing, externalizing, and psychotic symptoms to biological and psychosocial mechanisms that underlie psychopathology (Insel et al., 2010), is to grasp the neurobehavioral-developmental origins of mental health problems (Morris & Cuthbert, 2012). What the RDoC focuses on is the full range of functioning from normal to abnormal by utilizing a developmental perspective to comprehend mental health on a continuum from typical to pathological functioning. According to the RDoC framework, unearthing links between neurobiological and behavioral constructs and phenotypic symptoms could help with the creation and implementation of new intervention and prevention strategies by eradicating atypical, dysfunctional processes underlying psychopathology (Insel, 2014).

As a framework to link etiological factors to mental health symptoms, the RDoC is being continuously developed and validated. To date, the RDoC has identified five major functioning domains with certain neurobiological correlates which are considered to be linked to various forms of psychopathology. These are positive valence systems that respond to rewards, negative valence systems that respond to aversive situations, cognitive systems, systems for social processes, as well as arousal/regulatory systems

(NIMH, 2020). According to the RDoC framework, these domains can be evaluated with respect to the specific units of analysis to understand psychopathological processes (Franklin, Jamieson, Gleen, & Nock, 2015). Such analysis can be in the form of molecular, genetic, neural circuitry, and behavioral. Nevertheless, the RDoC framework is claimed to have a stronger focus on neurobiology than on alternative units of analysis when it comes to research application (Franklin et al., 2015).

It has been pointed out that to establish preventive interventions to ameliorate dysfunctional processes which underlie psychopathology, it is of utmost importance to initially pinpoint and develop behavioral constructs from various functional domains (Ip, Jester, Sameroff, & Olson, 2019). Researchers and clinicians can then have a sense of which particular behavioral risk constructs to take into consideration via early intervention, once these behavioral constructs are categorized to make a distinction between typical versus atypical development of psychopathology.

To identify the RDoC behavioral constructs central to mental health of prenatally drug exposed adolescents, it is crucial to understand them in the context of the neurobehavioral teratology perspective (Mayes, 2002; Vorhees, 1986, 1989). According to the neurobehavioral teratology model, when the central nervous system is damaged before birth, that can have significant effects in later periods of development. These effects may show variation depending on the effect of postnatal, as well as ongoing developmental contexts. To illustrate, the influence of prenatal drug exposure has been identified in neural systems, specifically in monoamine neurotransmitter functions, such as cognitive control, emotional arousal, and inhibitory control/attention (Kosofsky, Wilkins, Gressens, & Evrard, 1994; McCarthy, Kabir, Bhide, & Dosofsky, 2014;

Thompson et al., 2009). These are regarded to be neurobehavioral features associated with etiology of mental health symptoms. This dissertation focuses on the following behavioral RDoC constructs across cognitive, affective, and social domains related to monoaminergically regulated arousal systems. These constructs are impulsivity, irritability, and social disinhibition that are central to prenatally drug exposed individuals' mental health development.

Cognitive systems: Impulsivity. Impulsivity refers to a tendency to act without thinking about ramifications (Meda et al., 2009; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). The inability to regulate attention or resist certain desires, postponing gratification, haphazard decision making, and premature behavior are the main characteristics of impulsivity (Berlin & Hollander, 2016). Such impulsive behavior can lead to immediate rewards yet risking long-term objectives. Temporal circumstances such as the distance of a reward versus the acquisition of short-term pleasure can influence the manifestation of impulsivity. Another variable that affects impulsivity is how it relates to motor behaviors and higher-order cognitive factors.

In the RDoC framework, the definition of impulsivity specifically involves the attention and cognitive control constructs within the Cognitive Systems (Berlin & Hollander, 2016). The RDoC Cognitive Systems is made up of various constructs "that are responsible for cognitive processes, including attention, perception, declarative memory, and language" (NIMH, 2020). Attention refers specifically to the processes involved in regulating access to capacity-limited systems. These systems consist of awareness, higher perceptual processes, and motor action. Cognitive control is conceptualized as a system regulating how other cognitive and emotional systems

function in cases of goal-directed behavior, when prepotent response modes are insufficient to meet the demands of the current condition. What is more, control processes work in new contexts where appropriate responses get selected out of competing alternatives (NIMH, 2020).

Negative valence system: Irritability. Irritability refers to a propensity toward anger (Stringaris & Taylor, 2015), characterized as irritable mood, temper outburst and low tolerance of frustration (Leibenluft, 2011). Irritability is regarded as an expression of the frustrative nonreward construct in the RDoC domain of Negative Valence (Deveney et al., 2013; Glenn, Cha, Kleiman, & Nock, 2017; Leibenluft, 2011; Vidal-Ribas, Brotman, Validivieso, Leibenluft, & Stringaris, 2016). The RDoC Negative Valence Systems consist of five constructs related to the responses to aversive situations or contexts. These include acute threat, potential threat, sustained threat, loss, and frustrative nonreward (NIMH, 2020). Frustrative nonreward particularly describes negative emotional reactions that occur in a situation where a reward is withdrawn or prevented. An example would be a situation where an individual is unable to obtain positive rewards after a series of trials or continued endeavor. The irritable emotional reaction to blocked goal attainment is conceptualized as a subconstruct under frustrative nonreward.

Social process systems: Social disinhibition. Social disinhibition refers to a lack of respect for social norms (Russo et al., 1993). It can manifest itself in actions that disregard social conventions. Some concrete examples of such behavior demonstrating social disinhibition are impolite behavior or violating laws (Iacono et al. 2008; Weafer & Fillmore 2012). Social disinhibition could be classified in the Social Communication construct that composes the RDoC domain of systems for social processes, as systems for

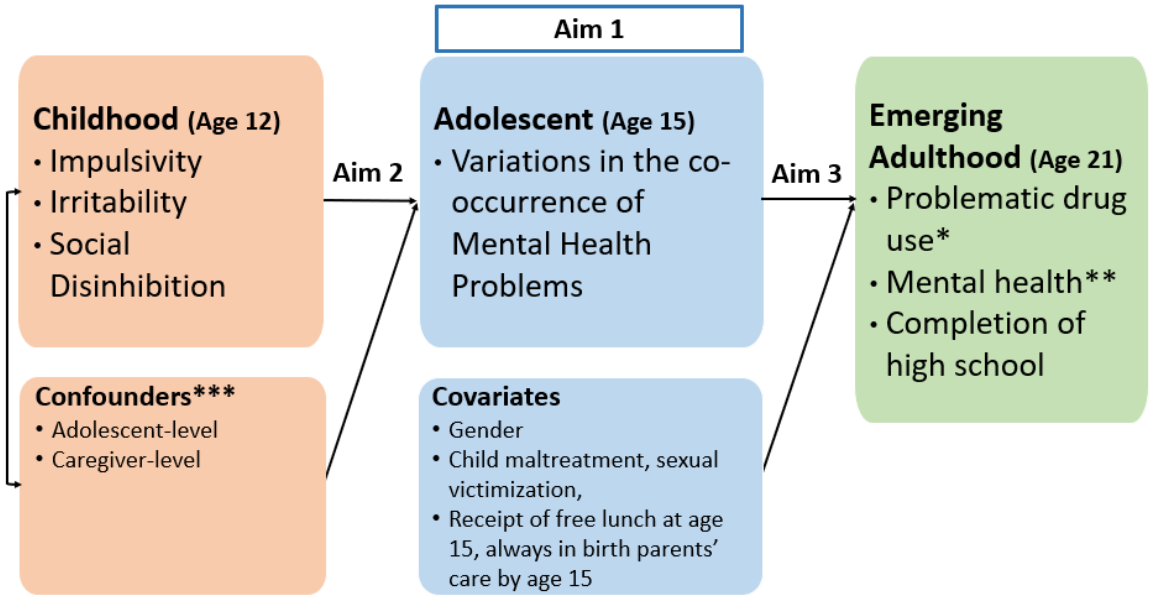
social processes in the RDoC framework involve constructs that regulate responses to interpersonal situations of various types (Glenn et al., 2017). The social communication construct specifically refers to a dynamic process used for the exchange of socially relevant information (NIMH, 2020). The RDoC framework postulates that social communication is crucial for the integration and maintenance of the individual in the social environment. Social communication is distinct from other cognitive systems, such as cognitive control and attention, in that social communication encompasses interactions with other cognitive systems (NIMH, 2020).

As such, using the RDoC framework, impulsivity, irritability, and social disinhibition are proposed as the cognitive, affective, and social constructs that may have utility as a risk marker of later psychopathology for explaining patterns of associations between different mental health symptoms among prenatally drug exposed adolescents.

Conceptual Framework of the Current Study

Figure 2 below presents the conceptual framework of the current study. It is posited that there would be variations in mental health outcomes among prenatally drug exposed adolescents (Aim 1). It is also posited that childhood impulsivity, irritability, and social disinhibition are differentially associated with these various patterns of symptom co-occurrence (Aim 2), which may in turn lead to diverse emerging adulthood outcomes (Aim 3).

Figure 2
Conceptual model: Variations in the co-occurrence of mental health problems in prenatally drug exposed adolescents



Note. Single-arrowed lines represent regression coefficients whereas a double-arrowed line represents a correlation.
* Problematic use of alcohol, tobacco, and marijuana defined by the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5)
** Mental health symptoms in the clinically at-risk range defined by the Adult Self-Report (ASR)
***Adolescent-level confounders assessed at birth include gender, race, gestational age, and birth weight and height, and prenatal drug exposure. Adolescent-level confounders assessed in childhood include IQ at age 11, parental monitoring at age 12, violence exposure at age 12, and always in birth parents' care by age 12. Caregiver-level confounders assessed at child delivery include maternal age at child delivery, education, marital status, vocabulary ability, psychological distress, and socioeconomic status. Caregiver-level confounders assessed when children are at age 12 include caregivers' education levels, vocabulary ability, psychological distress, quality of home environment, and caregiver substance use in the past 30 days.

The fundamental premises of the general and specific liability to psychopathology model and Research Domain Criteria (RDoC) framework motivate this dissertation's investigations. Currently, both the general and specific liability to psychopathology

model and RDoC framework have been getting increased academic and clinical attention in the area of mental health as well as being widely discussed and employed as conceptual bases to guide comorbidity research. Through such recent research endeavors and applications to diverse populations across different developmental stages, these models have been expanded. In addition, their explanatory power in understanding the structure of comorbidity and its etiological factors across cognitive, affective, and social domains has increased.

In this respect, it would prove more fruitful to adopt an integrated approach combining these two models. The general and specific liability to psychopathology model is beneficial with respect to identifying the existence of heterogeneity in the co-occurrence of mental health problems, guiding our interpretations of such patterns observed in prenatally drug exposed adolescents to reflect the general and specific liabilities to psychopathology. The RDoC framework works well with the general and specific liability to psychopathology model and systematically informs the selection of etiological constructs across cognitive, affective, and social domains that determine the variations of mental health symptom co-occurrence in prenatally drug exposed adolescents. Here, neurobehavioral teratology perspective plays an important role in identifying etiological factors central to prenatally drug exposed adolescents by providing a foundation for understanding the neurobehavioral development of this at-risk population. The foundational knowledge is relevant to altered brain function of this population due to biologic insults to developing fetal brain, particularly immaturity of monoaminergically regulated arousal systems.

It should be noted that the proposed conceptual model (Figure 2) includes potential confounders adjusted for when associating the childhood predictors with adolescent symptom co-occurrence patterns (Aim 2), as well as covariates controlled for when associating the symptom co-occurrence patterns with emerging adulthood outcomes (Aim 3). They were informed by prior theories and empirical literature. However, whether those potential confounders and covariates should be entered into the analysis models was determined based on the results of *ad hoc bivariate* correlation analyses. The relevant extant research that provides evidence for specific confounders and covariates used in this dissertation is described in detail in the following chapter (*see* literature gaps 2-1 for confounders of the childhood etiological constructs, and 3-1 for covariates related to the emerging adulthood outcomes). Also, selection processes of confounder and covariates are detailed in Chapter 4 (*see* Data Analysis Plan).

Chapter 3: Literature Review

Comorbidity Patterns Identified in General Populations

Emerging studies have investigated the latent group structures of comorbidity in different developmental stages, such as childhood (Olino et al., 2012), adolescence (Althoff, Rettew, Ayer, & Hudziak, 2010; Basten et al., 2013; Bonadio, Dynes, Lackey, Tompsett, & Amrhein, 2016; Gomez & Vance, 2014; Hammer & Toland, 2017), and adulthood (El-Gabalawy et al., 2013; Kessler et al., 2005a, 2005b; Rosellini, Coffey, Tracy, & Galea, 2014; Kim & Eaton, 2017; Urbanoski, Kenaszchuk, Veldhuizen, & Rush, 2015), as well as across the life span (Vaidyanathan et al., 2011; Weich et al., 2011). Such investigations identifying the latent group structure of comorbidity focus on how participants relate to one another with respect to similar patterns of symptom manifestation and empirically determine distinct subgroups.

There have been a plethora of studies on general youth that empirically investigated patterns of the co-occurrence of mental health problems (e.g., Althoff et al., 2010; Basten et al., 2013; El-Gabalawy et al., 2013; Olino et al., 2012; Vaidyanathan et al., 2011, 2012; Weich et al., 2011). In these studies, researchers identified variations in symptom co-occurrence. There were broadly two groups of individuals identified in these studies. These were a resilient group having a lower probability of all mental health syndromes and another group having a higher probability in the same domains. These clusters of individuals represent the general psychopathology liability factor that demonstrates the common variance across all mental health syndromes. These researchers also identified various other patterns that characterize unique covariations among the mental health syndromes. These patterns included internalizing and

externalizing groups, as well as additional groups based on the syndromes assessed (e.g., attention problem group), all reflecting specific psychopathology liabilities.

Variation in the distinctive comorbidity patterns and in the ratio of children displaying different patterns across these studies may stem from differences in the demographics of the participants, operationalization of psychopathology (e.g., symptoms *vs*. diagnoses; breaths/inclusiveness of symptoms assessed), measurement levels (e.g., symptom level *vs*. syndrome/disorder level), and analytical approaches (latent class *vs*. latent profile). A significant contribution of these studies was pinpointing a parsimonious collection of patterns to describe the latent group structure of adolescent psychopathology.

Gaps in the Literature

There are important literature gaps that need to be addressed to advance this line of research investigating the nature of variations in patterns of adolescent comorbid psychopathology particularly. The current dissertation extends this work in three major ways.

Gap 1: Symptom co-occurrence and its variations in prenatally drug exposed adolescents.

Prior studies examining the latent group structure of comorbidity tend to employ community-based general samples (e.g., Althoff et al., 2010; Basten et al., 2013; Olino et al., 2012; Weich et al., 2011), identifying subgroups that are more vulnerable or more resilient with respect to mental health adjustment among all participants in a given sample. Although informative, these findings may not be generalizable to under-researched, at-risk samples, such as adolescents with prenatal drug exposure in urban

settings. Prior neurobehavioral teratology research has documented that externalizing problems, including aggression and delinquency (e.g., Bada et al., 2011; Min et al., 2014a, 2014b; Richardson et al., 2011), as well as attention problems (e.g., Singer et al., 2015; Min et al., 2014b; Noland et al., 2005), and substance use (e.g., Delaney-Black et al., 2011; Glantz & Chambers, 2006; Minnes et al., 2014a, 2017; Richardson et al., 2013) are more prevalent among adolescents with prenatal drug exposures. These studies, however, have been conducted on the premise that all these prenatally drug exposed individuals would manifest a common pattern of mostly heightened levels of such symptoms, estimating an averaged, single trend of all participants. More importantly, despite the consistent observations of the co-occurrence of mental health problems in clinical settings, no known studies involving prenatally drug exposed samples have focused on the comorbidity phenomenon. Given that these adolescents are at heightened risk of developing diverse mental health problems, it is important to understand the nature of the heterogeneity of the symptom co-occurrence. Beyond the high prevalence of such forms of psychopathology, however, little is known about more nuanced and complex patterns of the co-occurrence of mental health problems in this at-risk sample.

In the only known investigation of patterns of psychopathology among predominantly minority children from urban poor neighborhoods, Tolan and Henry (1996) performed a latent class analysis in 4,125 school-aged children (i.e., grades 1-6), using the seven syndrome scales (i.e., aggression, thought, attention, anxious/depressed, somatic complaints, withdrawn, and social problems) from the Teacher Report Form (TRF) of the Child Behavior Checklist (CBCL; Achenbach, 1991). They provided intriguing evidence, indicating aggression to be a central aspect of all emergent patterns

of comorbid psychopathology (i.e., high degree of psychopathology with highest aggression; aggression/thought problems without internalizing syndromes; low aggression but moderate on other syndromes) in urban minority children. As a result, further research is required to understand whether the discrete accounts of general and specific liabilities to psychopathology, consistently observed in general adolescent samples, best characterize patterns of comorbid psychopathology among underserved at-risk youth with prenatal drug exposure. The current study is among the first to examine the heterogeneity in the patterns of symptom co-occurrence in the at-risk, predominantly African American adolescents with prenatal drug exposure living in urban areas.

In a similar vein, it is crucial to incorporate prevalent mental health syndromes into comorbidity research so as to examine the accurate structure of psychopathology in an at-risk sample and scrutinize the emergence of nuanced symptom co-occurrence patterns. Despite the increasing number of comorbidity research that include adolescent samples (e.g., Althoff et al., 2010; Basten et al., 2013; Bonadio, Dynes, Lackey, Tompsett, & Amrhein, 2016; Gomez & Vance, 2014; Hammer & Toland, 2017), there have been only a handful of such studies that dwelled on substance use problems (e.g., Castellanos-Ryan et al., 2016). This is a serious drawback as the peak of onset for many mental health problems is observed during adolescence. One concrete example is the emergence of substance use that usually starts in this period (Kessler et al., 2005a; Vallejo-Torres et al., 2014). To illustrate, it has been reported in multiple prospective birth cohort research that there is increased substance use among prenatally drug exposed adolescents (e.g., Delaney-Black et al., 2011; Glantz & Chambers, 2006; Minnes et al.,

2014a, 2017; Richardson et al., 2013). This potentially translates to unique variations in the symptom co-occurrence that can be identified in this at-risk sample.

In addition, many studies used lifetime diagnoses (Burstein et al., 2012; Neuman et al., 2001; Olino et al., 2012; Volk et al., 2005) in their identification of relatively homogenous subgroups of adolescents with similar patterns of symptom co-occurrence. Although informative, that approach does not guarantee that mental health symptoms were co-occurring. This study contributed to previous research on latent group structure through investigating the patterns of the co-occurrence of mental health problems. The particular novelty of the current study is including substance use problems in adolescents with prenatal drug exposure, as well as focusing on the concurrent symptoms assessed in the past year.

Gap 2: Behavioral constructs across RDoC domains as correlates of symptom co-occurrence in prenatally drug exposed adolescents.

Identifying behavioral risk constructs can advance our understanding of how adolescents may develop distinctive mental health comorbidity patterns (Basten et al., 2013; Olino et al., 2012; Urbanoski et al., 2015; Vaidyanathan et al., 2011). However, because heterogeneity in mental health adjustment among prenatally drug-exposed adolescents remains unexamined, not much is known regarding the etiological correlates of such differences in their mental health development. Motivated by the National Institute of Mental Health Research Domain Criteria (NIMH RDoC) framework, this study identified three specific constructs across cognitive, affective, and social domains that are central to prenatally drug exposed adolescents' mental health development. These constructs are impulsivity, irritability, and social disinhibition.

Impulsivity. Impulsivity refers to the inability to regulate attention or resist urges (Goldenberg et al., 2013; Khurana et al., 2012). High levels of impulsivity, an RDoC cognitive construct, may be critical to mental health of prenatally drug exposed adolescents, especially in terms of aggressive and disruptive behaviors (Eiden, Colder, Edwards, & Leonard, 2009; Eisenberg et al., 2009, 2010). Research on the general population has demonstrated that impulsivity is linked to the development of various mental health symptoms, ranging from pathological gambling to attention deficit hyperactivity disorder (ADHD; Dalley, Everitt, & Robbins, 2011). Similarly, there is a negative association between attentional regulation and problematic drug use among youth (Eiden et al., 2009).

Recent dimensional psychopathology modeling work that has successfully identified general and specific psychopathology liabilities in general adolescent populations (e.g., Castellanos-Ryan et al., 2016; Tackett et al., 2013) demonstrated high impulsivity as a significant correlate of general psychopathology liability (Carragher et al., 2016; Castellanos-Ryan et al., 2016). Consistently, adolescents with heightened levels of all spectrum of mental health symptoms were characterized with poor regulation of impulses in a community sample of teenagers (Olino et al., 2012).

Irritability. Irritability refers to adolescents' inability to modulate their emotion in times of frustration (Cole, Martin, & Dennis, 2004). This construct can be classified in the RDoC domain of Negative Valence. Higher levels of irritability are associated with a propensity to have increased mental health problems (Deveney et al., 2013; Glenn et al., 2017; Leibenluft, 2011; Vidal-Ribas et al., 2016). Negative emotionality, specifically the inclination towards anger and frustration, has usually been positively correlated with

internalizing and externalizing problems in investigations on the general population (Ip et al., 2019; Olino et al., 2012). To give an example, in a variable-centered comorbidity study with a sample of 1,709 teenagers (ages 14-18 years; mean age, 16.6 years; SD, 1.2), high emotionality was associated with multimorbid patterns that have both internalizing and externalizing problems (Olino et al., 2012).

High levels of irritability in youth may lead to negative consequences, such as risk for suicidal thoughts (Pickles et al., 2010; Vidal-Ribas et al., 2016) and impaired functioning (Copeland, Brotman, & Costello., 2013). These consequences may lead to the development of mental health symptoms (Ip et al., 2019; Vidal-Ribas et al., 2016). Certain adolescent mental health problems may be triggered partly due to difficulties to modulate anger and frustration. To illustrate, research has indicated that regulation of negative emotion due to frustration distinguished girls with clinical symptoms from the ones who showed chronic behavioral problems in childhood (Hill, Degnan, Calkins, & Keane, 2006).

Social Disinhibition. Social disinhibition, defined as disregard for social norms (Iacono et al., 2008), may be an RDoC social construct that enhances risks of developing mental health problems among prenatally drug exposed adolescents. Social disinhibition has a critical role in social competence in general youth (Lahat, Walker, Lamm, Degnan, Henderson, & Fox, 2014; Ridenour, in preparation; Russo et al., 1991, 1993). To give an example, children with higher levels of social disinhibition tend to demonstrate lower school success compared to their peers (Ridenour, in preparation). Moreover, children with higher levels of social disinhibition are observed to be less socially competent during stressful social situations (Lahat et al., 2014). Russo and colleagues (1991, 1993)

showed that children with higher social disinhibition were more likely to develop less favorable attitudes toward social norms.

Similarly, in community samples, children who manifested social disinhibition were more likely to have symptoms of conduct disorder and attention deficit disorders (Ridenour, in preparation; Russo et al., 1991; 1993). What is more, individuals with higher social disinhibition levels were more likely to have used alcohol and tobacco in adolescence (Cable & Sacker, 2007; Ridenour, Minnes, Maldonado-Molina, Reynolds, Tarter, & Clark, 2011). The role of social disinhibition has also been observed in the emergence of children's self-rated internalizing and externalizing problems in prenatally drug exposed children at age 9 (Ridenour et al., 2011; Ridenour, in preparation). Additionally, in studies of dimensional psychopathology structures that captured general and specific liabilities to psychopathology, high social disinhibition was associated with both general and specific externalizing liabilities of adolescents (Castellanos-Ryan et al., 2016; Tackett et al., 2013).

It remains unclear whether childhood etiological factors across cognitive, affective, and social domains are uniquely and specifically associated with variations in the co-occurrence of mental health problems among prenatally drug exposed individuals, particularly during adolescence. Determining the roles of impulsivity, irritability, and social disinhibition in at-risk adolescents' mental health outcomes, while adjusting for meaningful individual and environmental confounders, has significant practice and policy implications. It is important to note that these factors across the different RDoC domains have been targeted for major public health policy and intervention (NIMH, 2020). To

illustrate, there have been transdiagnostic approaches to intervention and prevention (Ip et al., 2019).

Gap 2-1. Confounders of the RDoC constructs predicting mental health problems among prenatally drug exposed adolescents.

The following biological and environmental elements affecting substance use and mental health problems among prenatally drug exposed adolescents are discussed here as potential confounders that were suggested by previous literature to obscure the effects of childhood impulsivity, irritability, and social disinhibition.

Adolescent-level factors.

Children with prenatal cocaine exposure have higher levels of prenatal exposure to other drugs, including opiates, tobacco (Maughan et al., 2004), and alcohol (Larkby et al., 2011). These prenatal drug exposures have been associated with heightened levels of mental health symptoms, including internalizing (Minnes et al., 2010, 2017; Min et al., 2017) and externalizing problems (Bada et al., 2011; Min et al., 2014a, 2014b; Richardson et al., 2011) as well as attention (Singer et al., 2015; Min et al., 2014b; Noland et al., 2005) and psychotic problems (McLaughlin et al., 2011; Minnes et al., 2017) along with increased risk of substance use in adolescence (Delaney-Black et al., 2011; Glantz & Chambers, 2006; Richardson et al., 2013). Simultaneously, children with prenatal drug exposure have shown higher levels of neurobehavioral and emotional regulatory problems (Eyler et al., 2009; Minnes et al., 2014b, 2016a; Rose-Jacobs et al., 2009; Singer et al., 2008). Prenatal exposure to cocaine, alcohol, tobacco, and marijuana constitute potential confounders, while this study examines the effects of childhood

etiological constructs that predict distinct patterns of the co-occurrence of mental health problems among prenatally drug exposed adolescents.

In addition, children's general cognitive functioning has been associated with their mental health outcomes (Buelow, Austin, Dunn, & Fastenau, 2003; Caspi & Moffit, 2018). Particularly among samples with prenatal drug exposure, cognitive functions are associated with higher rates of children's own drug use and externalizing problems (Singer et al., 2018).

Violence exposure is associated with early initiation of alcohol use (Taylor & Kliewer, 2006; Bossarte & Swahn, 2008), cocaine use (Delaney-Black et al., 2011), and marijuana use (Mason & Mennis, 2010; Richardson et al., 2013) among adolescents. Continuous exposure to violence is related to higher rates of substance abuse and other mental and physical health problems later in life (Moffitt, 2013). Evidence has also shown that violence exposure is linked with mental health problems including substance abuse after accounting for prenatal drug exposure (Frank et al., 2014; Minnes et al., 2010, 2014, 2016b, 2017).

Further, suboptimal developmental environments, including instability in placement (Singer et al., 2004; Linares et al., 2005), and inadequate parental monitoring (Min et al., 2014a, 2014b), have been reported to increase drug use and mental health problems in prenatally drug exposed adolescents, possibly obscuring the effects of the childhood etiological constructs predicting varied patterns of mental health comorbidity in this sample.

Caregiver-level factors

Maternal history of psychological distress from birth and throughout childhood has been associated with offsprings' own mental and behavioral health symptoms, including the use of drugs (Minnes et al., 2017, 2018). Maternal psychological distress has implications for genetic transmission of mental health symptoms as well as introducing negative early parenting behaviors that can influence child behavior and emotional regulation (Hannigan et al., 2018).

Other caregiver characteristics which are known to influence mental health outcomes include quality of the home environment and caregiver vocabulary ability (Bennett et al., 2008; Singer et al., 2008, 2015). In addition, low socioeconomic conditions are often prevalent among women using drugs during pregnancy and are an important factor to consider while evaluating the mental and behavioral health outcomes in their children.

Caregiver current substance use is argued to contribute to the development of mental health symptoms in adolescence (Min et al., 2017; Minnes et al., 2016b). It can also lead to a nearly six-fold increase in risk of problematic substance use among adolescents (Delaney-Black et al., 2011; Frank et al., 2014).

Gap 3: Validation of the variations in the symptom co-occurrence.

With few exceptions (e.g., Olino et al., 2012; Urbanoski et al., 2014), latent group structures of psychopathology have rarely been validated. External validity can be achieved if distinct comorbidity patterns are indicated by differential associations with variables other than the LCA indicators (Lenzenweger, 2004). Particularly, our understanding of functional outcomes of adolescents with different comorbidity patterns

can be further improved with the investigations of adolescents' real-world life outcomes (Basten et al., 2013; Urbanoski et al., 2015; Vaidyanathan et al., 2011).

Studies have demonstrated that differences in functioning and well-being usually emerge as expected across symptom co-occurrence patterns. Most of the times, the more highly comorbid groups display greater impairment and poorer outcomes (Olino et al., 2012; Urbanoski et al., 2015; Weich et al., 2011). However, we have a limited understanding of the course and developmental outcomes of comorbid psychopathology across groups with different symptomatology patterns in this at-risk population with prenatal drug exposure. It is likely that these at-risk adolescents might show different, unique functional outcomes compared to the general population, considering continued, cumulative exposures to environmental risk factors that might affect their adjustment as adolescents transition into adulthood. Likewise, further research is needed to determine whether and how the symptom co-occurrence patterns during adolescence are prospectively associated with outcomes during emerging adulthood in this at-risk population.

Gap 3-1: Covariates related to emerging adulthood outcomes.

Among prior latent group studies that validated the patterns of comorbid psychopathology, no known studies have adjusted for important factors that might affect subsequent outcomes, when testing the predictive validity of the latent group structure of comorbidity. Prior studies conducted within the neurobehavioral teratology model have identified various covariates that might affect mental health outcomes among prenatally drug exposed adolescents. Because the gender differences in levels of externalizing symptoms as well as substance use have been consistently reported (e.g., Keenan et al.,

2011; Zahn-Waxler et al., 2008), gender was included as a covariate of emerging adulthood outcomes. Environmental risk factors, such as child maltreatment and sexual victimization (Buckingham & Daniolos, 2013; Keyes et al., 2011; Min et al., 2007; 2016) have been consistently associated with the increased risk for mental health and substance use diagnoses in the literature regarding individuals with prenatal drug exposure. Ecological support and resources, such as receipt of free lunch, and stability in placement (e.g., always birth parents' care by age 15), have been shown to affect individuals' adaptive adjustment in this population (Min et al., 2017; 2018; 2019). Thus, such developmental environment elements that have the potential to affect emerging adulthood outcomes were considered when associating the symptom co-occurrence patterns identified with problematic substance use (alcohol, tobacco, and marijuana), which is defined by the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), clinically-relevant mental health problems, and high school completion in emerging adulthood.

Research Questions and Hypotheses

This dissertation research examined the latent grouping structure of psychopathology by identifying the variations in the comorbidity of psychopathology among adolescents with prenatal drug exposure. Specifically, this research uncovered distinct subgroups of these at-risk adolescents based on patterns of the co-occurrence of mental health syndromes, including substance use problems. Then, roles of childhood impulsivity, irritability, and social disinhibition corresponding to the RDoC cognitive, affective, and social risk factors were tested to predict varied comorbidity patterns. Lastly, the clinical significance and validity of the emerged patterns were evaluated by

associating the identified patterns with emerging adulthood outcomes. The specific research questions (RQ) and corresponding hypotheses (H) for this study are as follows.

RQ 1. Are there distinct variations in the empirically observed patterns of co-occurrence of mental health problems among prenatally drug exposed adolescents?

H 1. Heterogeneous patterns of mental health problems will manifest in adolescents with prenatal drug exposure, based on which distinct subgroups will be identified.

RQ 2. How are childhood etiological factors (i.e., impulsivity, irritability, and social disinhibition) associated with empirically observed patterns of the co-occurrence of mental health problems in adolescence?

H 2a. Higher levels of impulsivity in childhood will predict membership in groups with adolescents exhibiting more problematic symptom co-occurrence patterns.

H 2b. Higher levels of irritability in childhood will predict membership in groups with adolescents exhibiting more problematic symptom co-occurrence patterns.

H 2c. Higher levels of social disinhibition in childhood will predict membership in groups with adolescents exhibiting more problematic symptom co-occurrence patterns.

RQ 3. How are patterns of the co-occurrence of mental health problems in adolescence associated with emerging adulthood outcomes?

H 3a. More problematic symptom co-occurrence patterns in adolescence will be related to subsequent problematic substance use (alcohol, tobacco, marijuana) in emerging adulthood.

H 3b. More problematic symptom co-occurrence patterns in adolescence will be related to subsequent mental health symptoms in the clinically at-risk range in emerging adulthood.

H 3c. More problematic symptom co-occurrence patterns in adolescence will be related to incompletion of high school education.

Chapter 4: Methodology

This dissertation is a secondary data analysis derived from selected portions of the de-identified datasets from Project Newborn (PI: Sonia Minnes, RO1 DA07957). Project Newborn is a National Institute on Drug Abuse (NIDA) funded, 21-year prospective cohort study of prenatally drug exposed children and their caregivers, designed to examine the effects of prenatal exposure to cocaine and other substances (alcohol, tobacco, marijuana) on developmental outcomes across multiple pertinent neurobehavioral and psychosocial domains.

This chapter describes the study methodology. The sampling and research procedures of the parent study—Project Newborn—are first reviewed, followed by descriptions of the current dissertation study's sample, measures, and analysis plan.

Parent Study: Project Newborn

Sample.

The participants of the parent study and their birth mother were recruited at infant birth (September 1994 to June 1996) from an urban county hospital for a longitudinal study on the effects of prenatal exposure to cocaine and other drugs (Singer et al., 2002). Six hundred and forty-seven infants and their mothers, identified to be at high risk of prenatal drug exposure, were administered urine drug toxicology screens at child delivery. Specific clinical criteria were used to identify pregnant women who were suspected of substance use. The selection criteria included lack of prenatal care, self-admitted drug use, maternal behavior showing intoxication, or a history of encounters with the Department of Human Services. To detect metabolites of cocaine and other illegal drugs, ranging from opiates, cannabinoids, phencyclidine, amphetamines, to

benzodiazepines, urine specimens from the infants and the mothers were collected immediately after delivery. The Syva Emit method (Syva Company, Palo Alto, California) was utilized to analyze the urine samples. In addition, gas chromatography was conducted to confirm presumptive positive test results (Singer et al., 2002). Upon agreement to participate in the study, infant meconium was further collected and assessed for metabolites of cocaine (cocaethylene, meta-hydroxybenzoylecgonine, and benzoylecgonine) and other drugs (marijuana, tobacco and opiates). Positive results of biologic indicators such as infant meconium or maternal and infant urine, or maternal self-report of cocaine use during pregnancy indicated the status of prenatal cocaine exposure (PCE). Participants whose screening measures on cocaine were all negative were assigned to the Non-cocaine-exposed (NCE) status. The NCE group, which formed the original comparison group, might have been exposed to other drugs (alcohol, tobacco, and/or marijuana).

Fifty-four mother-infant pairs were excluded from the study due to confounding conditions observed either in the infant or the mother during the screening procedure for eligibility. These extraneous conditions, which might have obscured the effects of PCE, included fetal alcohol syndrome (1), infant Down syndrome (2), infant illness (3), lack of meconium (15), maternal age less than 19 years (2), maternal chronic illness (4), maternal psychiatric history of schizophrenia, severe depression, or bipolar disorder (16), primary heroin use (2), maternal low intellectual functioning (1), HIV positive status (5), and other (3). Out of the 593 eligible mothers, 415 (218 PCE, 197 NCE) gave consent to participate in the study, while 155 mothers (49 PCE, 106 NCE) declined to take part in the study. Twenty-three mothers (9 PCE, 14 NCE) were absent for the post-partum

enrollment interviews. Since enrollment, 12 children (9 PCE *vs*. 3 NCE, $\chi^2 = 2.50$, $p = .11$) died because of accidental asphyxia (1 PCE), cardiopulmonary arrest (1 PCE), pneumonia (1 PCE), respiratory distress syndrome (1 PCE, 1 NCE), sudden infant death syndrome (4 PCE, 2 NCE), and unknown illness (1 PCE).

Procedure.

The Institutional Review Board (IRB) of the hospital that took part in the study reviewed and approved all the procedures of the parent study. The initial screenings and enrollment were performed in the participating hospital. The subsequent longitudinal follow-up assessments were carried out at the university-based developmental research lab when the subjects were < 1, 6, and 12, months and 2, 4, 6, 9, 10, 11, 12, 15, 17, and 21 years. For each visit, written informed consent was obtained from the parents, while the child assent started at age 9. With a view to protect the release of drug-related information from forced disclosure, a Certificate of Confidentiality (DA-09-146) was acquired from the U.S. Department of Health and Human Services. A trained research assistant, blind to cocaine exposure status, was responsible for administering the cognitive and behavioral assessment protocol to the children, while a different research assistant performed private caregiver interviews at each follow up visit. As part of the 15-, 17- and 21-year assessments, participants who agreed to such a procedure, were referred to the affiliated hospital's National Institute of Health (NIH) supported Clinical Research Unit so that their biologic specimens (i.e., urine, hair, and/or bloodspots) could be collected by trained research nurses. Compensation for taking part in the study included monetary stipend, lunch, and transportation costs.

Current Study Sample

The sample for this dissertation study consisted of 358 individuals (165 boys, 193 girls) who provided mental health data at age 15, representing an 89% retention of the 403 active, living participants in the original study. There was an attrition of 45 participants because 44 participants dropped out and 1 had missing drug use data. Comparison of the 358 adolescents who provided the mental health data with the 45 that did not provide data indicated no group difference in all assessed variables.

The majority of participating adolescents were African American (82%) with a mean age of 15.5 years (*SD* = 0.27). Eighty-seven percent of the sample were prenatally exposed to at least one substance while two thirds were prenatally exposed to two or more substances. Half of the sample were prenatally exposed to cocaine, 76% to alcohol, 64% to tobacco, and 31% to marijuana. Their gestation age was 38.09 (*SD* = 2.88). The birth weight and length were relatively small with 2900.205 grams (*SD* = 679.29) and 48.16 cm (*SD* = 3.875), respectively. About half of the adolescents (54%) had always been in birth parents' care by age 12.

A majority of the adolescents were recipients of free lunch (83%) and Medicaid (80%) at the 15-year assessment. Forty percent of their mothers had not finished high school, with a mean of 11.7 years of education (SD = 1.52). The biologic mothers were 27.61 years old (*SD* = 9.73) at child delivery. About 12% were married and 98% had low socioeconomic status at child birth. The Institutional Review Board (IRB) at Case Western Reserve University determined on June 15, 2019 that the current dissertation study does not require IRB approval since this dissertation, a secondary data analysis of the Project Newborn, is not research involving human subjects.

Measures

There are different sets of measures corresponding to their function in the analysis plan. These are: (1) measures assessing mental health symptom co-occurrence, (2) measures assessing childhood etiological constructs, (3) confounders of childhood etiological constructs, (4) measures assessing emerging adulthood outcomes, and (5) covariates related to emerging adulthood outcomes. Table 1 shows an overview of all measures.

Table 1

Constructs and Measures

Constructs	Measures
Adolescents' symptom co-occurrence	
Mental health symptoms	Youth Self-Report (YSR; Achenbach & Rescorla, 2001)
Drug use	Biologic assays (urine, hair, and/or bloodspots) and Youth Risk Behavior Surveillance System (YRBSS; Centers for Disease Control and Prevention, 2009)
Childhood etiological factors	
Impulsivity	Assessment of Liability and Exposure to Substance Use and Antisocial Behavior (ALEXSA; Ridenour, Clark, & Cottler, 2009)
Irritability	
Social disinhibition	
Confounders of childhood etiological factors	
Adolescent-level confounders	
At birth	
Gender assigned at birth (1 = Male)	Hospital birth records
Race	
Gestational age	
Birth weight	
Birth height	
Prenatal exposure to cocaine, tobacco, marijuana, and alcohol	Maternal or infant urine assay, infant meconium assay, or maternal self-report of drug use
Postnatal	
IQ at age 11	WISC-IV (Wechsler, 2003)

Constructs	Measures
Parental monitoring	ALEXSA
Violence exposure	
Placement (1 = Always in birth parents' care by age 12)	Self-report survey system
Maternal/caregiver-level confounders	
At birth	
Biologic mother's age	Hospital medical record
Marital status	Hospital interview
Years of education	
Socioeconomic status	Hollingshead score of IV or V (Hollingshead, 1957)
Maternal vocabulary ability	Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn., 1981)
Maternal psychological distress	Global Severity Index (GSI), a summary measure on the Brief Symptom Inventory (BSI; Derogatis, 1992)
Postnatal	
Current caregivers' education	Self-report survey system
Current caregivers' vocabulary ability	PPVT-R
Current caregivers' psychological distress	BSI GSI
Quality of caregiving environment	Environment-Early Adolescent version (EA-HOME; Caldwell & Bradley, 2003)
Current caregivers' use of cocaine, tobacco, marijuana, and alcohol	Self-report survey system
Emerging adulthood outcomes	
High school education	Self-report survey system
Problematic use of alcohol, tobacco, and marijuana	SAM-5 modules of Composite International Diagnostic Interview (CIDI; Cottler, 2000)
Mental health symptoms	Adult Self-Report (ASR; Aschebach & Rescorla, 2003)
Covariates of emerging adulthood outcomes	
Placement (1 = Always in birth parents' care by age 15)	Self-report survey system
Receipt of free lunch at school	Self-report survey system
Child maltreatment	Juvenile Victimization Questionnaire (JVQ) – Adult Retrospective Version (Hamby et al., 2004)
Sexual victimization	
Adolescent gender (1 = Male)	Self-report survey system

Adolescent symptom co-occurrence.

Mental health symptoms at age 15. This study utilized seven mental health syndrome scales from the Youth Self-Report (YSR; Achenbach & Rescorla, 2001) assessed at age 15. These were: Anxious/Depressed (α = .86), Withdrawn/Depressed (Cronbach's α = .86), Somatic Complaints (Cronbach's α = .82), Attention Problems (Cronbach's α = .74), Thought Problems (Cronbach's α = .72), Aggression (Cronbach's α = .87), and Delinquency (Cronbach's α = .87). The YSR is a widely used, 105-item adolescent self-rating of symptoms in the last 6 months on a scale from 0 (not at all true) to 2 (very true). The syndrome scores were calculated by summing the responses of the items in the respective scales and converting the raw scores for gender and age normed *t*-scores. *T*-scores were dichotomized to classify adolescents as being clearly in the clinically at-risk range (≥ 65; coded as '1') versus the normal range (< 65; coded as '0') following the YSR manual (Achenbach & Rescorla, 2001). These dichotomized *t*-score syndrome variables were used in latent class analysis.

Substance use at age 15. Using self-report and biologic samples, adolescent substance use was assessed at age 15. Self-reported alcohol, tobacco, and marijuana use were assessed utilizing the Youth Risk Behavior Surveillance System (YRBSS; Centers for Disease Control and Prevention, 2009). Samples of adolescents' urine, hair, and/or bloodspots were collected by research nurses from the university's NIH-funded Clinical Research Unit. Then, they were sent to the United States Drug Testing Laboratory for analysis (*see* Minnes et al., 2014b for a complete description of drug use assessment). Adolescents who tested positive on either self-report or biologic assays for a particular drug were coded 1 (yes) for that drug.

Childhood etiological constructs.

Children's impulsivity, irritability, and social disinhibition were self-reported at age 12 using the Assessment of Liability and Exposure to Substance Use and Antisocial Behavior (ALEXSA; Ridenour et al., 2009). ALEXSA is an illustration-based, audio, and computer-assisted self-report of antisocial behavior, as well as substance involvement and associated risk factors for children between ages 9–12. The ALEXSA subscales that measured impulsivity, irritability, and social disinhibition use the same structure interview format and the same response scale, from 0 (*never/no way*) to 3 (*always/yes, definitely*). Each construct score consists of the mean of its items and these mean scores were used in analyses. Higher mean scores indicate greater levels of respective childhood constructs. The *impulsivity* subscale is composed of 6 items, assessing volatility and regulations of emotional and behavioral impulses (e.g., how often do you get into trouble because you do things without thinking?; Cronbach's $\alpha = .82$). The *irritability* subscale is composed of 10 items, assessing valence of agitation (e.g., how easily do you fly off the handle with people who do not want to listen or understand you?; Cronbach's $\alpha = .84$). The *social disinhibition* subscale is composed of 5 items, assessing the level of disregard for social norms (e.g., how much do you like to be with kids who are wild and crazy, even at serious times?; Cronbach's $\alpha = .80$).

Confounders of the effects of childhood etiological constructs.

Child-level confounders. ***<u>At birth</u>***. Infants' ***gender*** (female = 0, male = 1), ***race*** (others = 0, African American = 1), ***gestational age***, *and* ***birth weight and height*** were obtained from hospital birth records. Positive results of maternal or infant urine assay, infant meconium assay, or maternal self-report of drug use during pregnancy at the

newborn visit determined the status of **p*renatal exposures to cocaine, tobacco, marijuana, and alcohol*** (coded as '1'). Infants were assigned to a non-exposed group of each drug if their biologic and self-report indicators were all negative (Singer et al., 2004). At the newborn visit, the researchers asked birth mothers to recall the frequency and amount of drug use for the month prior to the pregnancy as well as for each trimester of the pregnancy. To determine the approximate intake of cocaine, researchers collected information regarding the number of "rocks" valued at $20 on the street market as well as the amount of money that the mothers spent per day on cocaine. The $20 rock was calculated as one standard unit of cocaine. For alcohol, researchers collected information with respect to the number of drinks of beer, wine, or hard liquor consumed. Each drink was calculated as being equal to 0.5 oz. of absolute alcohol. Finally, the researchers gathered data on the number of tobacco cigarettes and marijuana joints the mothers smoked per day. Based on the data from cocaine, alcohol, tobacco, and marijuana use, a Likert-type scale ranging from 0 (not at all) to 7 (daily use) was created to indicate the frequency of each drug use. This frequency scale included information regarding the average number of days per week the given drug was used, except for cigarettes, collected as the number smoked per day (*see* Singer et al., 2004 for a complete description of maternal drug use assessment during pregnancy).

Postnatal. ***Adolescent IQ*** was assessed at the 11-year visit based on the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) Full Scale IQ scores (Wechsler, 2003). Parental monitoring and violence exposure were assessed at age 12 via the Assessment of Liability and Exposure to Substance Use and Antisocial Behavior (ALEXSA; Ridenour et al., 2009). The ***parental monitoring scale*** (Cronbach's $\alpha = .74$),

using five items on a four-point Likert scale, assesses the youths' perceptions of whether their parent(s) usually is (are) aware of the youths' whereabouts and activities. Higher scores indicate a greater degree of parental monitoring. The ***violence exposure scale*** (Cronbach's $\alpha = .75$), using eight items on a five-point Likert scale, assesses experiences of violence inflicted on the respondent as well as violence the respondent has witnessed (beaten, robbed or mugged, stabbed or shot). Higher scores showing greater exposure. At each visit, the child's ***placement*** (with either biological mother/ relative or adoptive/foster caregiver) and changes (defined by a change in both primary caregiver and physical setting lasting greater than one month) were recorded. Using such placement and changes information, a variable that indicates the status of always in birth parents' care by age 12 was created to be adjusted for as a confounder of childhood etiological constructs.

Maternal/Caregiver-level confounders. <u>At birth.</u> Biologic mothers' age at child delivery, marital status (married = 1), and ***years of education*** were extracted from hospital medical records. ***Low socioeconomic status*** (low SES = 1) was measured by the Hollingshead score of IV or V (Hollingshead, 1957) through post-partum research interviews. Hollingshead scores were computed based on information regarding maternal occupation, years of education, and the number of members in the family. At infant birth, ***maternal vocabulary*** was assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn &Dunn., 1981). ***Maternal psychological distress*** was assessed at birth using the Global Severity Index (GSI), a summary measure on the Brief Symptom Inventory (BSI; Derogatis, 1992).

Postnatal. At the 12-year visit, ***current caregivers' education levels*** were assessed. PPVT-R and GSI BSI were administered to current caregivers to measure their levels of ***vocabulary ability*** and ***psychological distress***, respectively. ***The quality of the caregiving environment*** was assessed using the Home Observation for Measurement of the Environment-Early Adolescent version (EA-HOME; Cronbach's α = .83; Caldwell & Bradley, 2003). The drug assessment was updated with the adolescents' current caregivers at each follow-up visit to assess ***recent (prior 30-day period) postpartum, caregiver use of cocaine, tobacco, marijuana, and alcohol*** (*see* Singer et al., 2004 for a complete description of postnatal assessment for caregiver drug use).

Emerging adulthood outcomes.

Problematic use of alcohol, tobacco, and marijuana during the past 12 months was assessed at age 21 using the SAM-5 modules, a self-report, detailed version of the substance use section of the Composite International Diagnostic Interview (CIDI; Cottler, 2000). The SAM-5 modules consist of the items pertaining to the DSM-5 diagnostic criteria for substance use disorders (i.e., greater/longer use than intended, out of control, time lost due to substance use, craving, recurrent and continued use, adverse consequences, use despite physical or psychological problems, tolerance, and withdrawal symptoms). A symptom count was generated, and problematic substance use (1 = yes; 0 = no) was defined as having any two or more DSM-5 diagnostic criteria of substance use disorder in the last year.

Emerging adulthood mental health symptoms were assessed at age 21 using the Adult Self-Report (ASR; Achenbach & Rescorla, 2003), a 126 item self-rating of a participant's own emotional symptoms and social problems in the last 6 months on a

scale from 0 (not at all true) to 2 (very true). Scores were standardized for gender and age, with higher *t*-scores indicating greater symptoms. Due to the high correlation (*r* of .80) between internalizing (Cronbach's α = .90) and externalizing symptom scale scores (Cronbach's α = .88), total scale scores (Cronbach's α = .91) were determined to be used in the current study. The gender and age normed *t*-scores of the total scale scores were dichotomized to classify emerging adults as being in the clinically at-risk range ($\geq$ 60; coded '1') *versus* the normal range (< 60; coded '0') in accordance with the ASR manual (Achenbach & Rescorla, 2003). These dichotomized *t*-scores of the total scale scores were used in the validation analyses

Completion of high school education. During the age 21 follow-up visit, research participants reported on their highest level of education completed, and such information was dichotomized to indicate high school completion (1 = yes).

Covariates related to emerging adulthood outcomes.

Adolescent gender (0 = female, 1 = male) was employed as a covariate of the emerging adulthood outcomes. At age 17, using the Juvenile Victimization Questionnaire (JVQ) – Adult Retrospective Version (Hamby, Finkelhor, Ormrod, & Turner., 2004), ***child maltreatment*** and ***sexual victimization*** were assessed (1= yes; 0= no) retrospectively. Information about the ***receipt of free lunch*** at school at age 15 (1 = yes) was also obtained. At each follow-up interview, the ***child's placement*** (with either biological mother/relative or adoptive/foster caregiver) and shifts, if any, in placement, determined by a change in both primary caregiver and physical setting lasting more than one month, were recorded. Based on such information, always in birth parents' care by age 15 (1 = yes) was created and used for the analysis.

Data Analysis Plan

Analysis was performed in three phases, reflecting the three aims of this dissertation research.

Analysis for Research Question 1 ***(Variations in the co-occurrence of mental health problems).*** Latent class analysis (LCA) was conducted to identify underlying subgroups with similar patterns of the co-occurrence of mental health problems in Mplus v. 8. As a type of person-centered approach, LCA identifies subgroups (i.e., classes) of characteristics in a defined sample. Empirical identification of subgroups is carried out on the basis of similar patterns of response to observed categorical indicators. Individuals can be assigned to subgroups on the basis of their patterns of these characteristics. The dichotomized *t*-scores of the seven YSR syndrome scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Attention Problems, Thought Problems, Aggression, and Delinquency) and the measures of alcohol, tobacco, and marijuana use were used as LCA indicators.

To determine the number of latent classes, a series of unconditional LCA were conducted. Initially, a single latent group model was specified. Until a stable, best fitting solution was achieved, the number of latent classes (e.g., 2-, 3-, …, 5-classes) were increased subsequently. The best fitting model was determined by evaluating the following model fit statistics: Aikaike information criterion (AIC), Bayesian information criterion (BIC), Adjusted BIC (ABIC), bootstrap likelihood ratio test (BLRT), and Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-LRT). For the ACI, BIC, and ABIC, lower absolute values represent better fit to data (Nylund, Asparouhov, & Muthén, 2007). The BLRT and LMR-LRT test whether the addition of a class leads to a significant

improvement in model fit. These tests are carried out by calculating *p*-value for improved fit of the current solution to the solution with one less class (Nylund et al., 2007).

For models with more than one class, entropy (i.e., a measure of how well the adolescents are classified) was employed to assess classification quality. Entropy values approaching 1.0 represent precise group classification (Collins & Lanza, 2010). Entropy values ≥ .80 indicate that study participants were precisely classified into latent classes at least 90% of the time (Lubke & Muthen, 2007). The likelihood of correct membership classification was assessed by posterior probabilities (i.e., average latent class probabilities for each class; avePP). AvePP values approaching 1.0 indicate complete certainty of classification. AvePP values ≥ .70 are considered good (Warner, 2013).

In addition, the substantive relevance (i.e., interpretation) of each latent class was considered to identify distinct and meaningful groups to determine the number of classes (Collins & Lanza, 2010). Such interpretability of latent classes was examined based on graphic outputs (i.e., conditional item probability profile plots for best-fitting model). The proportions of participants assigned to classes were also assessed. Adequate class size was defined as a class with more than 5 % of the total sample (Collins & Lanza, 2010). All criteria were evaluated as a whole along with model identification and interpretability for final model selection (Collins & Lanza, 2010).

After determining the best-fitting model, the latent classes of symptom co-occurrence were interpreted and named, through which meaning of the pattern was assigned to each class. Each adolescent was then assigned to the subgroup for which the adolescent has the highest probability of membership based on estimated posterior probabilities of class membership obtained from LCA.

Using these class assignments, ANOVA (for continuous covariates) and Chi-square analyses (for categorical covariates) with Tukey or Bonferroni post-hoc adjustment were conducted to compare adolescent symptom co-occurrence groups in terms of multiple adolescent and caregiver characteristics.

Analysis for Research Question 2 (*Childhood etiological constructs and symptom co-occurrence groups*). After the identification of the best–fitting model and the optimal number of latent classes, multinomial logistic regression modeling was conducted to examine how childhood etiological constructs (impulsivity, irritability, social disinhibition) were associated with distinctive symptom co-occurrence patterns, while controlling for confounders (*see* Figure 2).

Confounders were entered into a multinomial logistic regression models when they were correlated with overall group membership at $p < .20$. ANOVA (for continuous covariates) or Chi-square analyses (for categorical covariates) were used to assess the bivariate association between each potential confounders and the comorbidity group membership. Confounders were retained in the final multivariate model, if, on entry, they were significant at $p < .10$ or caused substantial change in the coefficients of childhood etiological constructs (> 10%). Such procedures were taken to avoid multicollinearity and saturation of the multivariate modeling (Micky & Greenland, 1989).

Comorbidity group membership was first regressed on childhood etiological constructs, followed by adolescents' socio-demographic confounders, and maternal and current caregiver confounders. Prenatal cocaine exposure status was adjusted for, even if it was not significantly correlated with the comorbidity group membership at the bivariate level. This approach was determined by acknowledging the design of the parent study

Project Newborn where the current research data come from. Project Newborn was designed to prospectively examine the developmental effects of prenatal cocaine exposure. Multinomial logical regression modeling was performed using SPSS v. 24.

Analysis for Research Question 3 (*Symptom co-occurrence groups and emerging adulthood outcomes*). To evaluate the clinical significance and validity of the empirically observed patterns of the co-occurrence of mental health problems, hierarchical logistic regression modeling was performed to examine how different symptom co-occurrence patterns were associated with emerging adulthood problematic drug use, mental health symptoms indicating the clinically at-risk range, and completion of high school education.

Among potential covariates (gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, always in birth parents' care by age 15), the ones that correlated with outcomes at $p < .20$ were included in the logistic regression models. For the consistency of the modeling and comparable interpretability, potential covariates that met the selection criterion for at least one outcome were added as covariates in the multivariate models.

Three separate logistic regression models were tested for each outcome using SPSS v. 24. When symptom co-occurrence grouping variables indicated an overall significant effect, all pairwise group differences were probed. Adjusted percentages of each class on the emerging adulthood outcomes were calculated from the estimated models.

Chapter 5: Results

Research Question 1: Variations in the Co-occurrence of Mental Health Problems

Table 2 presents the descriptive statistics for indicators used in latent class analysis (LCA) identifying patterns of the co-occurrence of mental health problems among prenatally drug exposed adolescents. About one fifth of the adolescents met clinical criteria of having attention problems (22.1%) and being withdrawn/depressed (20.1%). About 16.5% were in the clinically at-risk range of somatization symptoms, 15.6% had thought problems, and 12.3% displayed anxious/depressed symptoms. About one tenth had aggression (10.9%) and delinquency problems (9.8%). The most commonly used drug was alcohol (38.3%). About 31.3% of the sample used tobacco and similar number of the participants used marijuana (30.2%).

Table 2
Descriptive Statistics of LCA Indicators in Overall Sample (N = 358)

Symptoms	%	*(n)*
Mental health problems [a]		
Anxious/Depressed	12.3	(44)
Withdrawn/Depressed	20.1	(72)
Somatic complaints	16.5	(59)
Attention problems	22.1	(79)
Thought problems	15.6	(56)
Aggression	10.9	(39)
Delinquency	9.8	(35)
Substance use [b]		
Tobacco use	31.3	(112)
Marijuana use	30.2	(108)
Alcohol use	38.3	(137)

[a] YSR clinical *t*-scores ≥ 65.
[b] Positive on either self-report YRBSS (past 30 days) or biologic samples (urine specimens, hair, and/or bloodspots) at age 15.

Optimal latent class solution selected. Using the ten items presented in Table 2, one- through five-latent class models were estimated. Table 3 summarizes model fit indices for each LCA model with different numbers of latent classes.

Table 3
Fit Information for 1- Through 5-Latent Class Models

No. of Classes	1-class	2-classes	3-classes	4-classes	5-classes
No. of Free Parameters	10	21	32	43	54
Log-Likelihood	-1735.246	-1564.736	-1475.170	-1436.350	-1427.164
AIC	3490.493	3171.472	3014.339	2958.700[a]	2962.328
BIC	3529.298	3252.963	3138.516	3125.563[a]	3171.877
Adj. BIC	3497.573	3186.341	3036.997	2989.146[a]	3000.563
BLRT	N/A[b]	$p < .001$	$p < .001$	$p < .001$	1.0000
LMR-LRT	N/A[b]	$p < .001$	$p < .001$	*0.0007*	0.3463
Entropy	N/A[b]	0.877	0.831	0.834	0.785
Smallest Class Size *n* (%)	358 (100)	55 (15.3)	48 (13.4)	25 (6.9)	25 (6.9)

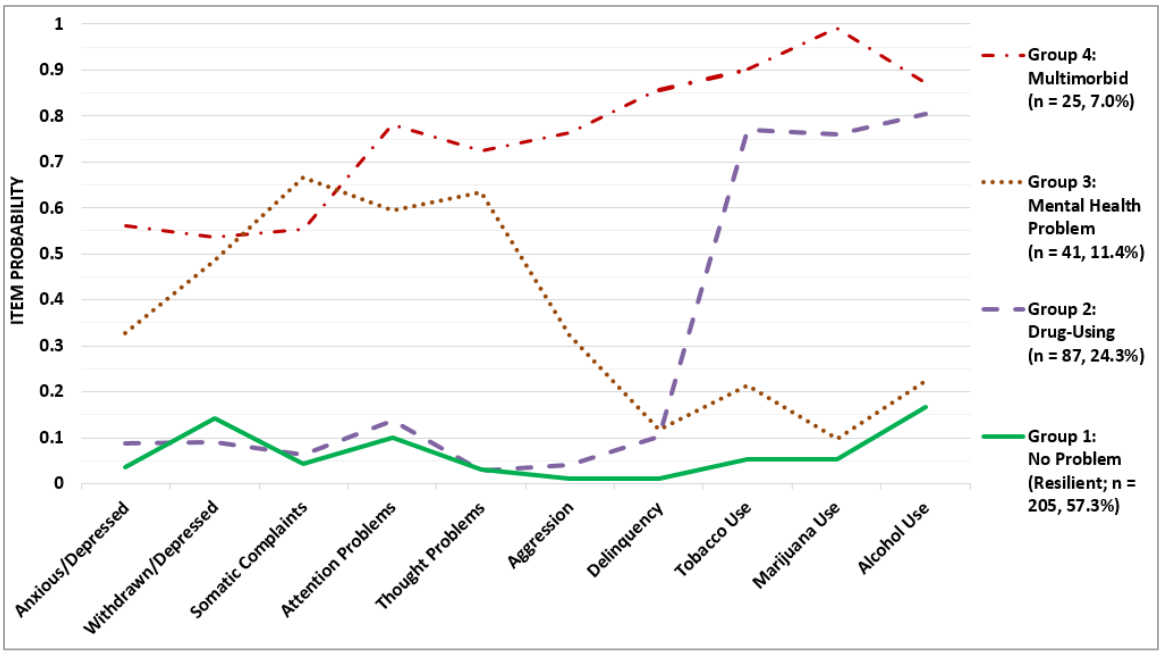
Note. Adj. BIC = adjusted Bayesian Information Criterion; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BLRT = Bootstrap Likelihood Ratio Test; LMR-LRT = Lo-Mendell-Rubin likelihood ratio test.
[a] Best-fitting model according to that index.
[b] BLRT, LMR-LRT and entropy not available for the one-class model.

Entropy values for models with 2-, 3-, and 4 classes were higher than .80, indicating that the classification quality and precision were acceptable for these models. AIC, BIC, and adjusted BIC were lowest for the model with four classes. The addition of a fifth class, however, resulted in an increase in AIC, BIC, and adjusted BIC. The BLRT and LMR-LRT for the 5-class solution were not statistically significant, indicating that the 4-class model is preferable. Comparison of the 4-latent class model with 5-latent

classes in plots of the estimated latent classes further confirms that the 4-class model is an optimal model. In the 4-calss model, distinctive and meaningful comorbidity patterns were indicated with each latent class whereas, in the 5-class model, one class in the 4-class model (i.e., later named as 'drug-using group') was separated into two latent classes that were not meaningfully distinct from each other. Considering theoretical value and multiple fit statistics, the 4-class solution was selected as the best fitting model.

Latent classes of co-occurrence of mental health problems identified. Figure 3 shows the latent classes of the co-occurrence of mental health problems identified in prenatally drug exposed adolescents.

Figure 3
Latent Classes of the Co-occurrence of Mental Health Problems in Prenatally Drug Exposed Adolescents at Age 15



Each of the four classes in the model was substantively meaningful, identified as distinct subgroups. These groups are 1) no problem, 2) drug-using, 3) mental health problem, and 4) multimorbid groups. The average latent class probabilities for most likely latent class membership ranged from .92 (mental health problem group) to .93 (multimorbid group). Moreover, the average posterior probabilities for all subgroups were higher than the cutoff value of .70, showing that participating adolescents were correctly assigned into the four latent classes identified. Each latent class had an adequate size with greater than 5% of the sample.

The first group (G1) was largest with 57% of the sample. Group 1 termed *no problem group* (57%) had clear emotional and behavioral adjustment as reflected in lower likelihood of meeting clinical criteria for being anxious and depressed, being withdrawn and depressed, having somatic complaints, attention problems, thought problems, aggression, and exhibiting delinquency as well as having lower rates of tobacco, marijuana, and alcohol use. The second group (G2), *drug-using group* (24%), demonstrated elevated rates of tobacco, marijuana, and alcohol use but lower likelihood of being anxious and depressed, being withdrawn and depressed, having somatic complaints, attention problems, thought problems, aggression, and delinquency. The third group (G3), *mental health problem group* (11%), exhibited elevated likelihood of meeting clinical criteria for being anxious and depressed, being withdrawn and depressed, having somatic complaints, attention problems, thought problems, and aggression, although there was decreased likelihood of delinquency. Taken together, this group largely displays elevated rates of mental health problems, while showing lower rates of tobacco, marijuana, and alcohol use. Finally, the fourth group (G4) was named

multimorbid group (7%) as it was characterized by heightened levels of all LCA indicators involving every mental health and substance use symptom assessed. Despite those heightened levels of LCA indicators, the multimorbid group displayed moderate elevations on internalizing symptoms, which were being anxious/depressed, being withdrawn/depressed, and having somatization.

Comparison of characteristics by latent class. Table 4 compares the members of each latent class for the 4-class solution by adolescent- and caregiver-level characteristics assessed at birth and postnatally. Bivariate group comparison showed that prenatally drug exposed adolescents in the no problem group (G1) had significantly lower levels of irritability and social disinhibition when compared to those in the high-risk groups (G2, G3, G4). A significant group difference was not observed with respect to levels of impulsivity ($p = 45$).

Significantly more number of adolescents in the no problem group (G1) than the high-risk groups (G2, G3, G4) had always been in birth parents' care by age 12. Among the three high-risk groups, however, levels of irritability, levels of social disinhibition, and the percentage of adolescents always being in birth parents' care by age 12 did not statistically differ from each other.

Higher levels of maternal psychological distress at child birth and higher rates of current caregivers' marijuana use were observed in the multimorbid group (G4) when compared to the other groups (G1, G2, G3). The drug-using group (G2) had significantly more males than other groups (G1, G3, G4). No other adolescent and caregiver characteristics had significant bivariate associations with the symptom co-occurrence groups.

Table 4
Sample Characteristics by Groups (N = 358)

	G1: No Problem (*n* = 205)	**G2: Drug-Using** (*n* = 87)	**G3: Mental Health Problem** (*n* = 41)	**G4: Multi-morbid** (*n* = 25)	***p***
Adolescents at birth					
Male, %	41[a]	58[b]	51[a]	32[a]	.02
African-American, %	85	77	80	76	.29
Gestational age, weeks	38.3 (2.7)	38.1 (2.5)	37.1 (4.2)	37.9 (3.4)	.09
Birth weight, g[§]	2925.7 (673.5)	2929.8 (652.2)	2702.8 (912.6)	2848.0 (769.5)	.29
Birth length, cm[§]	48.3 (3.6)	48.4 (3.8)	47.1 (5.5)	47.9 (4.5)	.29
Prenatal drug exposure, %					
Alcohol	68	58	64	64	.41
Tobacco	71	74	73	72	.96
Marijuana	27	28	27	40	.58
Cocaine	47	56	54	64	.24
Adolescents at postnatal ages					
Full Scale IQ at age 11	85.5 (13.5)	86.9 (10.9)	80.8 (16.7)	82.8 (10.4)	.09
Always in birth parents' care by age 12, %	65[a]	48[b]	43[b]	38[b]	.002
Parental monitoring at age 12	2.5 (0.6)	2.4 (0.6)	2.3 (0.7)	2.2 (0.8)	.10
Violence exposure by age 12	2.6 (2.4)	3.0 (2.5)	3.7 (2.7)	3.5 (2.9)	.08
RDoC constructs at age 12					
Impulsivity	1.8 (2.4)	2.2 (2.4)	1.9 (1.7)	2.1 (1.8)	.45
Irritability	0.9 (0.5)[a]	1.3 (0.5)[b]	1.3 (0.5)[b]	1.4 (0.6)[b]	<.001
Disinhibition	0.8 (0.6)[a]	1.3 (0.7)[b]	1.0 (0.5)[ab]	1.1 (0.8)[ab]	<.001
Biologic mothers at child birth					
Age at child delivery	27.9 (5.3)	27.2 (5.1)	28.5 (5.5)	26.1 (5.4)	.24
Education, years	11.8 (1.5)	11.7 (1.5)	11.7 (1.6)	11.2 (1.8)	.23
Married, %	9	17	7	20	.10
Vocabulary ability	75.2 (15.3)	75.9 (13.3)	75.8 (14.7)	72.2 (11.9)	.72
Psychological distress	0.6 (0.6)[a]	0.6 (0.7)[a]	0.7 (0.5)[ab]	1.2 (1.0)[b]	<.001
Low SES, %	97	100	100	92	.67
Current caregivers at age 12					
Education, years	12.5 (2.0)	12.3 (2.0)	12.0 (3.1)	12.3 (2.3)	.54
Vocabulary ability	78.8 (15.2)	78.6 (14.0)	82.3 (17.1)	82.2 (12.5)	.49
Psychological distress	0.3 (0.4)	0.3 (0.4)	0.4 (0.4)	0.4 (0.4)	.67
Home quality	46.8 (11.4)	44.4 (14.7)	45.1 (14.3)	44.2 (12.0)	.31

	G1: No Problem (*n* = 205)	**G2: Drug-Using** (*n* = 87)	**G3: Mental Health Problem** (*n* = 41)	**G4: Multi-morbid** (*n* = 25)	***p***
Caregiver substance use in the past 30 days					
Alcohol	1.9 (5.2)	0.8 (1.8)	2.1 (7.3)	0.4 (0.9)	.20
Tobacco	4.1 (6.6)	4.6 (6.4)	4.9 (7.7)	6.5 (10.1)	.44
Marijuana	0.4 (3.3)[a]	0.1 (0.3)[a]	0.0 (0.1)[a]	3.6 (17.5)[b]	.02

Note. RDoC = Research Domain Criteria; SES = socioeconomic status.
Different superscript indicates significant (p <.05) post-hoc pair-wise difference using Tukey (for continuous variable) or Bonferroni (for categorical variable) correction.

Research Question 2: Childhood Impulsivity, Irritability, and Social Disinhibition as Correlates of the Comorbidity Group Membership

Multinomial logistic regression was performed to assess whether childhood etiological constructs were associated with patterns of the co-occurrence of mental health problems in prenatally drug exposed adolescents, while controlling for confounders. In multivariate models, the effects of irritability and social disinhibition in predicting the adjusted odds of the comorbidity group membership were tested. At the bivariate level, impulsivity was not significantly correlated with the comorbidity group membership at p = .45 (*see* Table 4).

Among multiple potential confounders (*see* Table 1), six adolescent characteristics (gender, head circumference, always in birth parents' care by age 12, parental monitoring at age 12, violence exposure by age 12, IQ at age 11) and two maternal/caregiver characteristics (biologic mothers' psychological distress at child delivery, current caregivers' marijuana use) were correlated with the comorbidity group membership at p < .20 (*see* Table 4). In the final multivariate models, five confounders (gender, always in birth parents' care by age 12, parental monitoring at age 12, violence

exposure by age 12, IQ at age 11) were retained, since, on entry into the models, they were significant at $p < .10$ or caused > 10% change in the coefficients of either irritability or social disinhibition (Micky & Greenland, 1989). In addition, prenatal cocaine exposure status was also adjusted for in the final multivariate models, although it was not correlated with adolescent comorbidity group membership at $p = .24$. This decision was made due to the research design of the parent study Project Newborn, the prospective investigation of the effects of prenatal cocaine exposure on children's developmental outcomes.

In the final multivariate models featuring irritability, social disinhibition and all selected confounders, significant group differences ($p <. 05$) were found only when the no problem group (G1) was treated as a reference group. Table 5 summarizes the results.

Higher levels of irritability were related to increased odds of belonging to the mental health problem group (G3; OR = 3.27; 95% CI = 1.29, 8.28) compared to the no problem group (G1). Higher levels of social disinhibition were related to increased odds of belonging to the drug-using group (G2; OR = 2.57; 95% CI = 11.49, 4.44) compared to the no problem group (G1). Higher levels of irritability (OR = 3.03; 95% CI = 1.16, 7.91) and social disinhibition (OR = 2.12; 95% CI = 0.97, 4.63) were respectively related to increased odds of belonging to the multimorbid group (G4) compared to the no problem group (G1).

Table 5

Multivariate Multinomial Logistic Regression of Childhood Etiological Constructs Predicting Adolescents' Comorbidity Group Membership

Reference group	G1: No Problem *vs.*		
	G2: Drug-Using	G3: Mental Health Problem	G4: Multimorbid
	OR [95% CI]	OR [95% CI]	OR [95% CI]
Prenatal cocaine exposure	1.17 [0.61, 2.27]	0.55 [0.20, 1.48]	0.84 [0.28, 2.52]
Gender, male	1.85 [1.00, 3.41]*	1.62 [0.65, 4.01]	0.63 [0.22, 1.79]
Always in birth parents' care by age 12	0.45 [0.23, 0.89]*	0.38 [0.14, 1.03]	0.28 [0.09, 0.87]*
Parental monitoring at age 12	1.33 [0.76, 2.32]	0.94 [0.48, 1.85]	1.05 [0.51, 2.16]
Violence exposure by age 12	1.18 [0.78, 1.79]	1.14 [0.66, 1.98]	1.11 [0.60, 2.03]
Full Scale IQ at age 11	1.02 [1.00, 1.05]	0.99 [0.96, 1.03]	0.99 [0.96, 1.03]
RDoC constructs at age 12			
Irritability	1.68 [0.86, 3.29]	3.27 [1.29, 8.28]**	3.03 [1.16, 7.91]*
Social disinhibition	2.57 [1.49, 4.44]***	1.42 [0.66, 3.05]	2.12 [0.97, 4.63]†

Note. CI = Confidence intervals; OR = Odds ratio; RDoC = Research Domain Criteria.
†$p < .10$, *$p < .05$, **$p < .01$, $p < .001$.

As for the confounders, being male than being female was related to increased odds of being in the drug-using group (G2; OR = 1.85; 95% CI = 1.00, 3.41) compared to the no problem group (G1). Fewer adolescents in the drug-using group (G2; OR = 0.45; 95% CI = 0.23, 0.89) and the multimorbid group (G4; OR = 0.28; 95% CI = 0.09, 0.87) were always in birth parents' care by age 12 than adolescents in the no problem group (G1). However, prenatal cocaine exposure, violence exposure by age 12, parental monitoring at age 12, and IQ at age 11 did not distinguish adolescents in high-risk groups

(G2, G3, G4) from those in the no problem group (G1). No correlates were identified that distinguished the risk groups (i.e., G2, G3, G4) from each other.

Research Question 3: Relation of Comorbidity Group Membership to Emerging Adulthood Outcomes

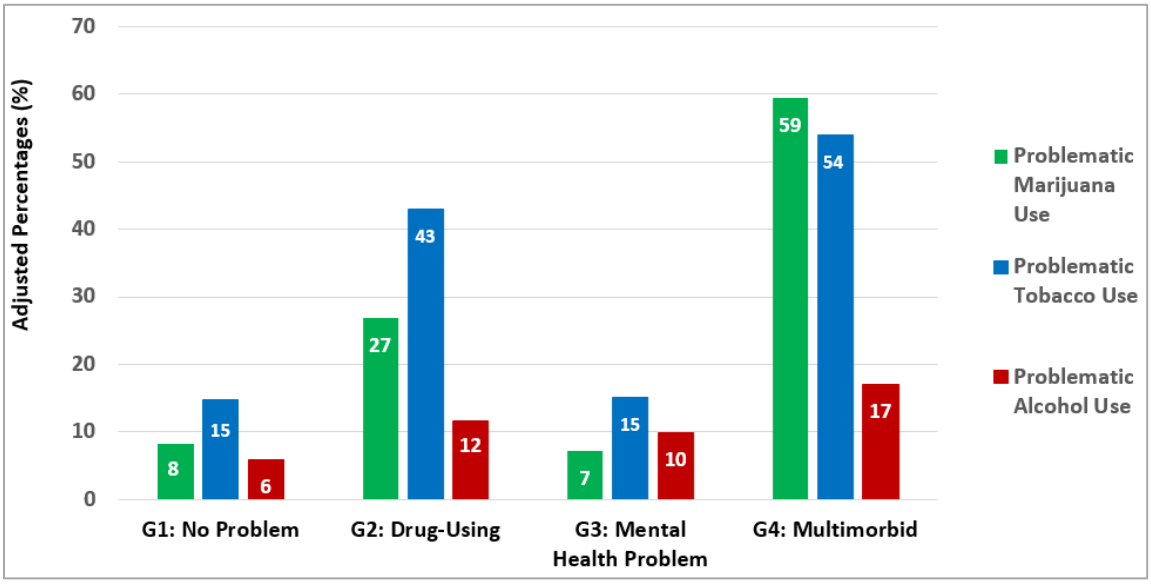
Figure 4 summarizes the results of logistic regression analysis examining adolescents' symptom co-occurrence latent classes as predictors of emerging adulthood outcomes (i.e., problematic use of marijuana, tobacco, and alcohol defined by the DSM-5 diagnostic criteria at age 21, mental health symptoms in the clinically at-risk range at age 21, and completion of high school education) adjusted for all covariates (i.e., gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15). Since the latent classes were not related to emerging adults' problematic use of alcohol, this section focuses on other four emerging adulthood outcomes.

Problematic use of marijuana. After controlling for gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15, more emerging adults in the drug-using group (G2; 27%) and in the multimorbid group (G4; 59%) had problematic marijuana use than those in the no problem group (G1; 8%). Compared to those in the mental health problem group (G3; 7%), more emerging adults in the drug-using group (G2; 27%) and in the multimorbid group (G4; 59%) had problematic marijuana use.

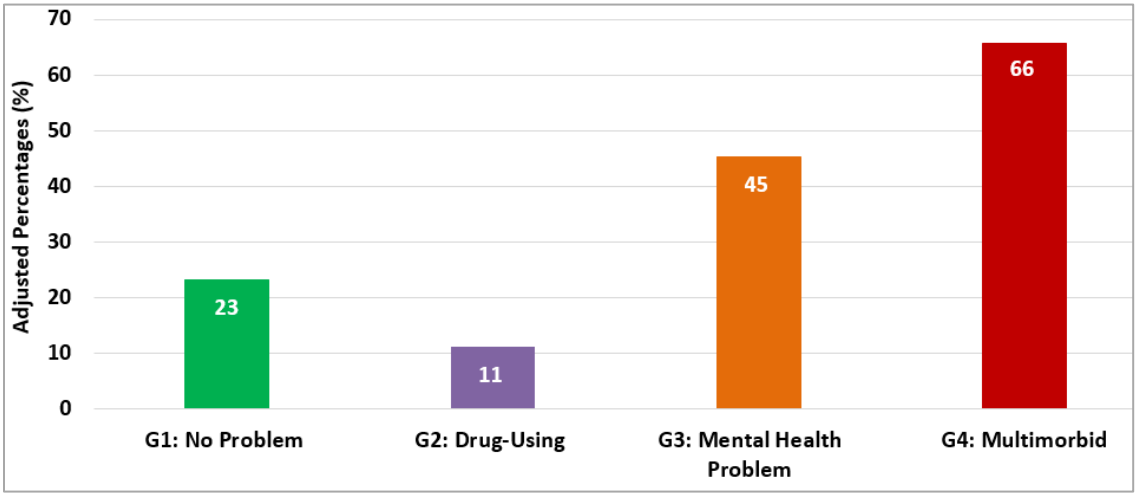
Figure 4

Emerging Adulthood Outcomes at Age 21 by Latent Classes

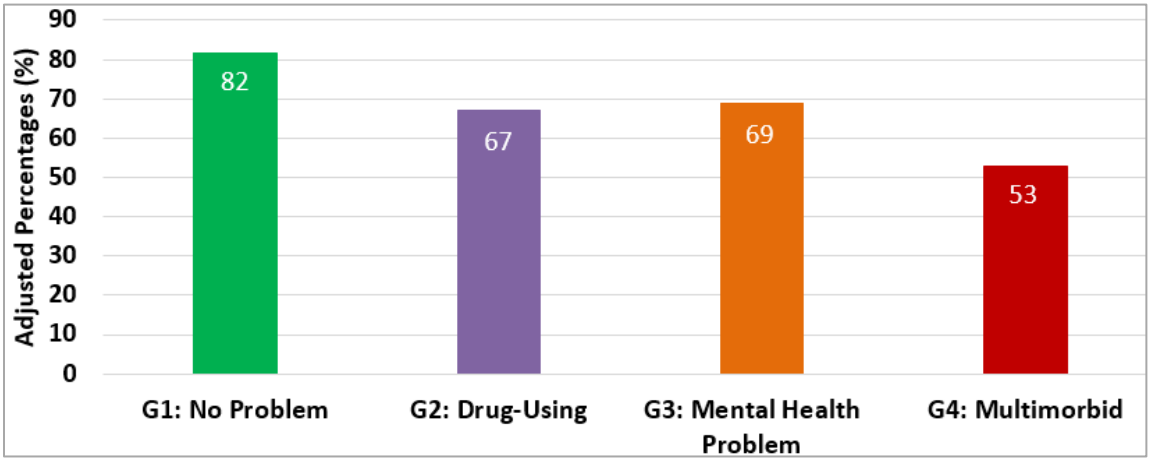
a. 21-Year Problematic Use of Marijuana, Tobacco, and Alcohol Defined by the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)



b. 21-Year Mental Health Symptoms in the Clinically At-risk Range Defined by the Adult Self-Report (ASR)



c. Completion of High School Education



Note. For problematic marijuana use and tobacco use (a), Group 1 differs from Groups 2 & 4; Group 3 differs from Groups 2 & 4. For mental health (b), Group 1 differs from Groups 3 & 4; Group 2 differs from Groups 3 & 4. For completion of high school education (c), Group 1 differs from Groups 4.

Being male than female was related to increased odds of problematic marijuana use at age 21 (OR = 2.39, 95% CI = 1.35, 4.25). Child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15 were not related to problematic marijuana use at age 21.

Problematic use of tobacco. After controlling for gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15, a greater number of emerging adults in the drug-using group (G2; 43%) and in the multimorbid group (G4; 54%) had problematic tobacco use than those in the no problem group (G1; 15%). Compared to those in the mental health problem group (G3; 15%), more emerging adults in the drug-using group (G2; 43%) and in the multimorbid group (G4; 54%) had problematic tobacco use.

Being male than female was related to increased odds of problematic tobacco use at age 21 (OR = 2.39, 95% CI = 1.35, 4.25). Always being in birth parents care by age 15 was related to decreased odds of problematic tobacco use at age 21 (OR = 0.03, 95% CI = 0.30, 0.95). Child maltreatment, sexual victimization, and receipt of free lunch at age 15 were not related to problematic tobacco use at age 21.

Mental health symptoms in the clinically at-risk range. After controlling for gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15, a higher percentage of emerging adults in the mental health problem group (G3; 45%) and in the multimorbid group (G4; 66%) reported being in clinically at-risk range of mental health problems at age 21 than those in the no problem group (G1; 23%). Compared to those in the drug-using group (G2; 11%), a higher number of emerging adults in the mental health problem (G3; 45%) and in the multimorbid group (G4; 66%) reported being in clinically at-risk range of mental health problems at age 21.

Child maltreatment was related to increased odds of having mental health symptoms in clinically at-risk range at age 21 (OR = 3.54, 95% CI = 1.62, 7.76). Gender, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15 were not related to having mental health symptoms in clinically at-risk range at age 21.

Completion of high school education. After controlling for gender, child maltreatment, sexual victimization, receipt of free lunch at age 15, and always in birth parents' care by age 15, fewer number of emerging adults in the multimorbid group (G4;

53%) had completed high school education by age 21 than those in the no problem group (G1; 82%).

Receipt of free lunch at age 15 was related to decreased odds of the completion of high school education (OR = 0.26, 95% CI = 0.07, 0.89). Gender, child maltreatment, sexual victimization, and always in birth parents' care by age 15 were not related to completion of high school education.

Chapter 6: Discussion

This chapter outlines the major findings of the current study, followed by the discussion of the findings within the context of a broader literature. Then, the chapter reviews the limitations and strengths of the study. The theoretical implications as well as the implications for social work practice and policy are discussed. This chapter concludes with the directions for future research.

Summary of Major Findings

Motivated by the general and specific liability to psychopathology model, this study investigated the variations in the co-occurrence of mental health problems among prenatally drug exposed adolescents. This study examined the roles of childhood impulsivity, irritability, and social disinhibition within the Research Domain Criteria (RDoC) framework to predict the distinctive symptom co-occurrence patterns in adolescence. This study further determined differential associations between the empirically observed comorbidity patterns and emerging adulthood outcomes to evaluate the clinical significance and validity of each pattern. The key findings of this study based on the three research questions are as follows:

Research Question 1. Variations were observed in the co-occurrence of mental health problems in 15-year adolescents with prenatal drug exposure. Three high-risk groups (multimorbid group 7%, mental health problem group 11.4%, and drug-using group, 24.3%) and one resilient group, named as ‘no problem group’ (57.3%) were identified.

Research Question 2. Twelve-year irritability and social disinhibition distinguished the three high-risk groups from the resilient group with no mental health and substance use problems (57%).

Research Question 3. Adolescents in the high-risk groups, particularly in the multimorbid group, were more likely than the resilient group to have problematic use of tobacco and marijuana as well as mental health symptoms in the clinically at-risk range at age 21. They were also less likely than the resilient group to have completed high school.

Research Question 1: Variations in the Co-occurrence of Mental Health Problems

Results from latent class analysis provided empirical evidence that not all prenatally drug exposed adolescents experience mental health symptoms, and that heterogeneous development is observed in this at-risk population. In support of Hypothesis 1, this study found four latent classes of symptom co-occurrence that differ in both degree of co-occurrence among symptoms and levels of symptoms in prenatally drug exposed adolescents at age 15. More than half of the adolescents (57%; no problem group, G1) appeared to show healthy development in the present study. Three high-risk groups were identified with the drug-using group (24%; G2), the mental health problem group (11%; G3), and the multimorbid group (7%; G4).

To my knowledge, the current study is one of the first studies to examine the variations in the co-occurrence of mental health problems in prenatally drug exposed adolescents. While the selection of the sample may have influenced the structure and prevalence of the latent classes in general (Basten et al., 2013; Lenzenweger, 2004), the identified patterns in this study are largely in line with the pattern of combinations that can be derived from the dimensions reported in variable-centered analytic studies from

other populations (e.g., Castellanos-Ryan et al., 2017; Tackett et al., 2013). These findings suggest that, regardless of whether a research employs a variable-centered or a person-centered approach, a structural organization of psychopathology may be constituted of a core set of fundamental transdiagnostic dimensions underlying phenotypic mental health symptoms. This core set represents a broad general liability construct with additional, more specific liability factors.

The multimorbid group (G4) corresponds to the conceptualization of general liability to psychopathology. This was the smallest group of the study sample (7%). They manifested heightened levels of all mental health problems, including substance use. This smallest but highest risk group shared the similar tendency observed in Tolan and Henry (1996)'s study which identified a subgroup of urban minority children who had high degrees of psychopathology overall with aggression being the highest. The findings of this study differ somewhat as the current study relied on a broader spectrum of symptoms by additionally including delinquency and alcohol, tobacco, and marijuana use. Along with aggression, these added symptoms were heightened in this highly problematic subgroup. Another uniqueness observed in this highest risk subgroup is similar to that of Tolan and Henry's work in that, while these children at highest risk manifest highest levels of problems across all symptoms than other groups, they have relatively lower or moderate elevations on internalizing symptoms (i.e., being anxious/depressed, being withdrawn/depressed, and having somatization).

Both the drug-using group (G2) and the mental health group (G3) reflect specific liabilities to develop symptoms within the same boundaries. Identification of these two specific liability groups that uniquely exist in this high-risk population is the main

contribution presented in previous studies. Person-centered studies of community or representative samples have shown that patterns of distinct comorbidity profiles are generally characterized by particularly elevated levels of the internalizing and externalizing symptoms (e.g., El-Gabalawy et al., 2013; Olino et al., 2012; Vaidyanathan et al., 2011; Weich et al., 2011). These differences in findings may stem from the difference in the breadth of the considered symptoms. As discussed above in the gaps in the literature, the current study included more dimensions of psychopathology than prior studies that examined adolescent psychopathology structure. Previous studies on adolescence comorbidity research usually investigated mental health symptom measures, involving internalizing and externalizing symptoms, psychotic, and thought problems. The current study added drug use measures in addition to the ones covered in previous literature. This measurement approach might have contributed to a difference in the symptom co-occurrence patterns empirically observed.

Another possibility might lie in the sample characteristics. Unlike prior LCA comorbidity studies that focused on general adolescent populations (e.g., El-Gabalawy et al., 2013; Kim & Eaton, 2017; Olino et al., 2012; Vaidyanathan et al., 2011; Weich et al., 2011), the current study may have provided a unique latent structure of psychopathology specific to adolescents with prenatal drug exposure. Future person-centered studies might be able to confirm whether these two specific patterns of symptom co-occurrence are substantially distinctive dimensions that reflect specific liabilities to develop symptoms within the same boundaries (i.e., mental health spectrum and drug use spectrum) in this at-risk sample. Overall, findings of this study augmented previous comorbidity research by revealing distinct patterns of symptom co-occurrence characterized by either

particularly elevated levels of the mental health symptoms, the drug use symptoms, and a combination of the two (multimorbid) in an adolescent sample with prenatal drug exposure, highlighting the generalizability of the general and specific liability to psychopathology model.

Research Question 2: Childhood Impulsivity, Irritability, and Social Disinhibition as Correlates of the Comorbidity Group Membership

Research question 2 was an inquiry as to how childhood etiological factors across cognitive, affective, and social RDoC domains, identified as impulsivity, irritability, and social disinhibition, are significantly related to distinctive patterns of mental health problems among prenatally drug exposed adolescents, while accounting for adolescent-level and caregiver-level confounders.

In support of Hypothesis 2b and 2c, irritability and social disinhibition constituted both broad and specific risk factors. Higher irritability and higher social disinhibition increased the odds of being in the multimorbid group (G4), relative to a normative, resilient group (G1). The current study confirms the results of the previous research in that irritability and social disinhibition play critical roles in the etiology of a broad range of mental health problems (Olino et al., 2012). It has also been found, in line with previous research, that the inability to regulate anger and tolerate frustrations is associated with a broad spectrum of mental health problems, ranging from internalizing, externalizing, thought, and psychotic problems to substance use problems (Ip et al., 2019; Vidal-Ribas et al., 2016). The findings also contribute to the previous literature by indicating that the irritability component of the RDoC negative valence domain and the social disinhibition component of the RDoC systems of social processes predicted the

multimorbid pattern in this prenatally drug exposed sample. These findings were demonstrated even after controlling for important confounders, suggesting the robustness of the study. In this sense, high irritability and social disinhibition translate to broad-transdiagnostic risks that lead to a multimorbid pattern. This pattern is characterized by the manifestation of all symptoms assessed in prenatally drug exposed adolescents.

Additionally, in multinomial logistic regression modeling where the no problem group was taken as a reference group and important confounders were adjusted for, higher levels of social disinhibition were specifically associated with the drug-using group (G2). However, the higher levels of irritability were specifically associated with the mental health group (G3). Conversely, social disinhibition was not associated with the mental health group (G3) and irritability was not associated with the drug-using group (G2), which further provide evidence of discriminant validity.

These findings are in accord with prior research on other adolescent samples since they indicate that the social disinhibition scale specifically predicts substance use problems in adolescence (Cable & Sacker, 2007, Ridenour et al., 2011; Ridenour, in preparation). The fact that irritability is linked to internalizing and externalizing problems to the exclusion of substance use problems is consistent with previous literature (Castellanos-Ryan et al., 2016; Olino et al., 2012; Vidal-Ribas et al., 2016). The present results are significant since they clarify the unique links between particular etiological constructs corresponding to the RDoC affective and social domains and specific symptom co-occurrence patterns in prenatally drug exposed adolescents.

It should be noted that childhood irritability and social disinhibition did not distinguish the three high-risk classes from each other. In future investigations, it will be

essential to validate these classes with other types of etiological constructs across different RDoC domains. In contrast to the mental health problem group and the drug using group, the multimorbid class exhibited notably heightened delinquency symptoms, possibly indicating different neural correlates.

Contrary to Hypothesis 2a, 12-year impulsivity did not distinguish the mental health comorbidity groups identified at age 15 in this at-risk sample of prenatally drug exposed adolescents. The lack of association between childhood impulsivity and the symptoms co-occurrence patterns may be because this sample with prenatal drug exposure has heightened levels of impulsivity regardless of the comorbidity patterns. Indeed, corresponding percentile scores form the ALEXSA standardization sample indicate that all subgroups are very high on the impulsivity subscale. Their respective ALEXSA impulsivity scale scores put the no problem group (G1) at the 84th percentile, the drug-using group (G2) at the 92th percentile, the mental health problem group (G3) at the 88th percentile, and the multimorbid group (G4) at the 91th percentile. Such limited variability in the levels of impulsivity may have reduced its discriminant validity.

Research Question 3: Relation of Comorbidity Group Membership to Emerging Adulthood Outcomes

The clinical significance and validity of the four symptom co-occurrence patterns were evaluated based on problematic substance use, mental health symptoms in the clinically at-risk range, and completion of high school education. In support of all three hypotheses for Research Question 3, poorer outcomes were noted among the three high-risk groups (G2, G3, G4), particularly in the multimorbid group (G4), compared to the no problem group (G1). The findings of this study are likely robust since important

covariates (i.e., gender, child maltreatment, sexual victimization, receipt of free lunch, and placement stability) were adjusted, when the associations between 15-year symptom co-occurrence patterns and each of the 21-year outcomes were tested.

The group comparison using the 21-year outcomes revealed that significant differences were indicated among the high-risk groups, demonstrating the predictive validity of the different high-risk patterns of symptom co-occurrence. Namely, when compared to the mental health problem group (G3), more emerging adults in the drug-using group (G2) and the multimorbid group (G4) had problematic use of marijuana and tobacco. Moreover, when compared to the drug-using group (G2), more emerging adults in the mental health problem group (G3) and the multimorbid group (G4) reported mental health symptoms that put them in the clinically at-risk range at age 21. The findings of the current study suggest that, among prenatally drug expose individuals, the trends of the symptom co-occurrence might be consistent from adolescence to adulthood. These findings are in line with previous research of general population demonstrating the strong stability of latent psychopathology liabilities over time in youth (Murray et al., 2016; Snyder et al., 2016) and adults (Greene & Eaton, 2017).

This study also indicated that patterns of the co-occurrence of mental health problems in adolescence were related to the completion of high school. However, significant differences were observed only for the multimorbid group (G4) when compared to the no problem group (G1) in terms of high school completion. Significantly fewer number of adolescents in the multimorbid group (53% of this group) had completed high school education by age 21 than those in the no problem group (82% of this group). These findings are consistent with previous studies reporting poorer

prognosis in adulthood in individuals with dual diagnoses (i.e., having both mental health and drug use disorders) than in individuals having no symptoms (e.g., Drabick & Kendall, 2010). This finding suggests that adolescents in the multimorbid group reporting both mental health and drug use problems (G4) should be a primary concern for preventive intervention. According to the results of the group comparison on developmental environment characteristics (*see* Table 4 in Chapter 5), interventions that capitalize on the enhancement of placement stability seem promising in serving this highest risk group.

Although more research is needed to replicate and further validate the maintenance of consistency in comorbidity patterns among prenatally drug exposed individuals, the early identification of individual differences in irritability and social disinhibition in childhood has importance in understanding processes that can contribute to the development and stability of mental health problems over time across adolescence to emerging adulthood. In the present study, adolescents' comorbidity patterns at age 15 were not significantly associated with problematic use of alcohol age 21. This insignificance across different adolescent comorbidity patterns may be due to overall reduced rates of alcohol consumption in adulthood regardless of different subgroups. African American adults are less likely to use alcohol than other types of drugs (National Center for Health Statistics. 2019).

Limitations and Strengths

Limitations. The limitations of the present study should be noted. First, the sample composition of this study limits the generalizability of the findings solely to low income, urban, and primarily African-American adolescents with a history of prenatal

substance exposure. Nonetheless, this study is among the first to provide an accurate evidence of variations in the co-occurrence of mental health problems in the neurobehavioral teratology literature. To this end, replications are needed to improve the generalizability of the findings to different at-risk samples, such as those with prenatal opioid exposure, given the recently increased concern regarding this population (National Institute on Drug Abuse, 2020).

Second, this study focused on irritability, social disinhibition, and impulsivity when linking childhood behavioral measures at age 12 to the variations in the co-occurrence of mental health problems at age 15. The findings suggest that more comprehensive sets of etiological factors (e.g., sleep and calming) and further elaboration of particular characteristics of each factor might be needed to identify effective intervention strategies to foster resilience in this vulnerable population. Such investigations can be carried out by examining mediating roles of etiological factors between the effects of prenatal drug exposure and the symptom co-occurrence, and by exploring their moderating roles in relation to postnatal environmental conditions. Nonetheless, no other studies to date have evaluated these pre-adolescent characteristics as etiological factors. While self-report measures can be efficiently applied to children in their own assessment of risk factors, it would be important to cross-validate those measures with parental, teacher, and/or clinician observations.

Third, through latent class analysis (LCA), group classification was produced as a latent variable that take into account possible uncertainty about the class membership. However, both multinomial logistic regression (to examine the associations between childhood RDoC constructs and the adolescent symptom co-occurrence patterns; Aim 2)

and binary logistic regression (to link with emerging adulthood outcomes; Aim 3), treated group membership as a known variable. Both logistic approaches disregard such uncertainty about the group classification when estimating regression coefficients. However, excellent classification accuracy was indicated with the entropy value of .834 of the 4-class solution that was determined to optimally fit the study data. The validity of the empirically observed patterns was also demonstrated as the four symptom co-occurrence patterns were differentially related to subsequent emerging adulthood outcomes. To further assess stability of the findings, however, an alternative analytic approach that employs the pseudo-class method can be utilized. This method, also known as the Mplus AUXILIARY(r) function (Clark & Muthen, 2009), allows for uncertainty in the class classification. Using each adolescent's posterior probability distribution, this method also generates several random draws. Based on such pseudo-class draws, the Mplus AUXILIARY(r) function estimates regression coefficients.

Strengths. Despite these limitations, this study has important strengths and contributions to the existing mental health literature. First, there has been no known study applying advanced and comprehensive approaches to assessing the co-occurring mental health symptoms among adolescents with prenatal drug exposure. The present study addressed this gap by taking a person-centered approach, assessing a broad spectrum of mental health symptoms, including substance use problems, to accurately examine the complexity of prenatally drug exposed adolescents' comorbidity patterns. These empirically observed patterns were validated by various external variables from earlier (childhood) and later (emerging adulthood) developmental stages.

Second, the data for this study came from a prospective longitudinal birth cohort study and well characterized sample with a good retention rate, thereby increasing the validity of the findings. The consideration of important confounders and covariates strengthened the current findings that support differential associations that the symptom co-occurrence patterns have with childhood etiological factors and with emerging adulthood outcomes.

Further, the use of multiple assessment methods, including biological indicators of prenatal drug exposure (maternal and infant urine or infant meconium) and adolescent substance use (urine, hair, and/or bloodspots) in addition to standardized substance use questionnaires, ensured the most precise way to assess biologic mothers' drug use during pregnancy and adolescents' drug use.

Implications

Findings of the current study have implications for comorbidity theories as well as social work practice and policy. This study underscores the importance of identifying and targeting subgroups of prenatally drug exposed adolescents based on person-specific profiles of the co-occurrence of mental health problems, rather than population-based comparisons.

Implication for the Conceptualization of Comorbidity. Concepts of general and specific liabilities to psychopathology were supported by this study, as distinct patterns of mental health comorbidity were identified. These patterns were characterized as multimorbid, mental health problem, and drug-using. Particularly, the identification of the multimorbid class, which was characterized by increased endorsement probability of all symptoms assessed, supports that there is considerable variance among these

symptoms which can be accounted for by a general psychopathology factor. These empirically supported latent classes of general and specific psychopathology liabilities are aligned with prior comorbidity research. The current research also indicates that the co-occurrence of mental health problems cannot be explained by pure chance (e.g., Kessler et al, 2005b). This implies that these mental health syndromes should not solely be conceived as discrete categories as posited in widely current classification systems, such as DSM–5 (American Psychiatric Association, 2013). This study contributed to the general and specific liability to psychopathology model by extending its power to explain comorbidity phenomenon in prenatally drug exposed adolescents, by providing more nuanced, accurate understanding of this high-risk cohort's mental health problems.

Importance for Social Work Practice and Policy. In the light of the findings of the study, the following policy and practice strategies are recommended to preclude the co-occurrence of mental health problems and to promote psychological well-being among at-risk adolescents with prenatal drug exposure.

The current study highlights the significance of acknowledging and addressing distinct patterns of the co-occurrence of mental health problems through a person-centered methodology among adolescents with prenatal drug exposure. Latent class analysis, which is the person-centered approach utilized in this study, identified the complexity of interrelationships among the diverse mental health symptoms, known to affect prognosis and intervention outcomes (e.g., Larsen, Nylund-Gibson, & Cosden, 2014). Identification of such heterogeneity is critical to develop individualized, targeted directions for intervention and prevention planning and service provision. This is because the prognosis and nature of treatment outcomes are usually not constant across levels and

combinations of symptom co-occurrence (Urbanoski et al., 2015). The results of this study illustrated that prenatally drug exposed adolescents are not homogeneous. They are heterogeneous subgroups that display distinctive sets of symptom co-occurrence and these subgroups are differentially related to subsequent emerging adulthood outcomes. Thus, it would be wrong to assume that all adolescents with prenatal drug exposure develop a common, homogeneous pattern of mental health problems. More importantly, consideration of variations in the symptom co-occurrence, while making clinical and policy decisions, may make it easier and more effective to assign adolescents to suitable treatment groups (Ferdinand et al., 2005; Geronazzo-Alman et al., 2017).

In this respect, the results of the current dissertation may help mental health practitioners and policy makers identify adolescents at heightened risk for co-occurrence of mental health problems. Latent class analysis offers a precise method of empirically identifying a homogenous group of adolescents, employing multiple mental health indicators simultaneously. That allows for better assignment of subgroups into effective treatments (Lanza & Rhoades, 2013; Spilt, Koot, & Lier, 2013). Although further research is needed to explicate the developmental mechanisms and prognosis of such complex presentations, it seems reasonable that remedial and preventive treatments prioritize adolescents manifesting multimorbid symptoms involving a wide range of mental health symptoms including substance use problems.

Second, behavioral measures of the RDoC systems of negative valence and social processes may serve as transdiagnostic screening tools to identify adolescents at higher risk for later adverse mental health outcomes. The current study is among the first to integrate RDoC constructs into the general and specific liabilities to psychopathology

framework by pinpointing potential etiological factors in pre-adolescence that underlie co-occurring mental health problems.

Since validated, applicable, and standardized behavioral assessment tools to investigate RDoC domains in these at-risk adolescents are absent, the real-life application of the RDoC criteria for mental health research has been limited (Ip et al., 2019). The results of the current study indicated that higher irritability and social disinhibition distinguished high-risk subgroups from those who are resilient within a prenatally drug exposed sample. These findings indicate that we should have intervention strategies for behavioral training, particularly with respect to children's negative emotion and social competencies. Such preventive efforts could reduce the risk of the (co-)occurrence of mental health problems including drug use problems in adolescence before the onset of clinically significant symptoms. Targeted interventions have been shown to be efficacious in recent randomized controlled trials as they can treat and prevent diverse mental health syndromes including substance misuse (e.g., Conrod et al., 2013; O'Leary-Barrett et al., 2013; Olthuis, Watt, Mackinnon, & Stewart, 2014, 2015). Such interventions could be applied to high risk adolescent populations to ease their mental health symptoms and promote their emotional and social competencies. These interventions can take the form of school-based group interventions, as well as face-to-face and web-based individual interventions (e.g., telephone, Zoom video communications).

Direction for Future Research

This study found distinctive and meaningful patterns of mental health problems, providing evidence of heterogeneity in symptom co-occurrence among prenatally drug

exposed adolescent. However, the findings need to be replicated with other at-risk samples (e.g., youth with prenatal exposure to opioids) and further verified in future research. Moreover, future research should demonstrate the validity of latent classes that represent general and specific liabilities to psychopathology across multiple methodologies. The identified patterns of the co-occurrence of mental health problems should be cross-validated by using a complementary statistical approach (Deutz et al., 2019; Olino et al., 2012; Kim & Eaton, 2017) in the current sample or a multi-informant approach to assessing youth mental health (Kircanski et al., 2017; De Los Reyes & Kazdin, 2005). For example, the structure of psychopathology may be tested by using confirmatory factor analysis, or factor mixture model methods. As informant agreement is relatively low in youth psychopathology research (De Los Reyes & Kazdin, 2005), the stability of symptom co-occurrence patterns can be simulated and validated by involving youth, parents, teachers, and clinicians (e.g., Althoff et al., 2010, Kircanski et al., 2017; Bonadio et al., 2016)

In the current study, no childhood etiological factors significantly distinguished memberships among the high-risk groups (i.e., multimorbid group *vs.* drug-using group *vs*. mental health problem group). This may be due to the failure of the inclusion of comprehensive sets of RDoC factors. It should be noted that the current dissertation did not intend to develop new constructs. Instead, this study identified RDoC constructs central to prenatally drug exposed individuals' development in childhood guided by past neurobehavioral teratology literature. Doing so, this study provided solid behavioral evidence for future mental health investigations regarding affective and social RDoC constructs. In this context, future studies may benefit from identifying and incorporating

various RDoC factors across cognitive, affective, and social domains in earlier childhood, and further examining their influence on the emergence and development of varied mental health conditions. The RDoC perspective will allow researchers to view mental health on a continuum rather than construing it solely as an abnormal construct. The Youth Risk Index (YRI; Ridenour et al., 2015) that taps the ALEXSA measures utilized in the current study may be incorporated into such an investigation.

This study focused on adolescent mental health (age 15 years) linked with childhood etiological factors (age 12 years) and emerging adulthood outcomes (age 21 years), leaving typical versus atypical symptom trajectories across developmental stages untested. Investigating the heterogeneity in developmental trajectories of the co-occurrence of mental health problems would inform well-timed and targeted interventions by providing knowledge regarding the developmental continuity/discontinuity of symptom co-occurrence among this at-risk sample. Treatment approaches that take into account optimal timing of intervention in specific cohorts may be particularly effective in preventing or delaying the progression to more severe and long-lasting mental health symptoms (Berstein et al., 2012). In addition, investigating mental health symptoms in conjunction with of physical health may be another important area for future investigations, generating integrated health implications for vulnerable populations at high risk but the ones who are traditionally underserved (SAMHSA-HRSA, 2020).

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