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Comorbidity of Bipolar I Disorder and Conduct Disorder: A Familial Risk Analysis

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Abstract

Objective: To investigate the association between pediatric bipolar I (BP-I) disorder and conduct disorder (CD) using familial risk analysis.

Method: We compared diagnoses in relatives of youth in four proband groups defined by the presence or absence of BP-I and CD: 1) probands with neither CD nor BP-I (probands: N=550; relatives: N=1,656), 2) probands with CD and without BP-I (probands: N=40; relatives: N=127), 3) probands with BP-I and without CD (probands: N=197; relatives: N=579), and 4) probands with both CD and BP-I (probands: N=176; relatives: N=488). All subjects were evaluated with structured diagnostic interviews and diagnoses of relatives were made blind to the diagnoses of probands.

Results: Relatives of probands with BP-I disorder had high rates of BP-I and relatives of probands with CD had high rates of CD irrespective of the comorbidity with the other disorder. Relatives of probands with the combined condition of CD and BP-I had high rates of the combined condition.

Conclusion: The finding of co-segregation between BP-I disorder and CD is consistent with the hypothesis that the combined condition represents a distinct subtype of either disorder.

Keywords

Pediatric bipolar I disorder; conduct disorder; familial risk; comorbidity; structured diagnostic interview

Introduction

A robust and bidirectional association between pediatric bipolar I (BP-I) disorder and conduct disorder (CD) has been consistently reported in clinical, epidemiological, and research samples.¹⁻⁷ While BP-I and CD are distinct highly morbid disorders, their co-occurrence heralds a highly compromised clinical state.

Whether children with BP-I disorder comorbid with CD have BP-I, CD, or both disorders are questions of high scientific and public health concern. Because bipolar disorder at any age can bring about reckless activities, the question of whether individuals presenting with symptoms of both bipolar disorder and CD actually have one or the other or both creates a clinical dilemma. For example, if an individual with mania is irritable, overconfident/grandiose, and energized and goes on to lie, steal, or bully, does that represent CD or the reckless impulsivity of mania? If an individual is sociopathic and becomes moody when confronted, is that an indicator of mania or part of CD? When two disorders overlap clinically or with specific shared symptoms, familial risk analysis can assist in clarifying their relationship as it provides information that is external to the complex clinical picture of the individual patient. Considering that both BP-I⁸⁻¹² and CD disorder are familial conditions,¹³⁻¹⁷ one approach to gain insights as to the nature of the association between these two disorders is to examine the way they transmit in families through familial risk analysis.

In a report using data from a well-characterized longitudinal family study of boys with and without attention deficit hyperactivity disorder (ADHD), those with BP-I disorder comorbid with CD were found to have higher familial risk for mood disorders and antisocial disorders.¹⁸ Similar findings were reported in a small study of children with BP-I disorder that showed co-segregation between CD and BP-I disorder, suggesting that the combined condition of BP-I disorder comorbid with CD may represent a unique subtype of either CD or BP-I disorder.¹⁹ However, because these findings were reported in the context of a sample of boys with ADHD, and in a small sample of children with BP-I disorder, more work is needed to assess whether these findings generalize outside the context of ADHD and whether they extend to both sexes.

Further understanding of the nature of the association between BP-I disorder and CD has important implications. Such research can provide new insight on the etiologic and predictive validity of these disorders that can lead to better approaches for the management of children affected with these serious conditions. While there is no known pharmacological treatment for CD, BP-I disorder can be successfully treated and may mitigate symptoms of CD in children afflicted with both disorders.²⁰⁻²³

The main aim of this study was to further evaluate the nature of the association between BP-I disorder and CD. To this end we subjected 4 large datasets to familial risk analysis. Based on our previous work we hypothesized that BP-I disorder comorbid with CD will follow a pattern consistent with co-segregation in first-degree relatives.

Aims of the Study

Using familial risk analysis, the aims of this study were to examine the way BP-I disorder and CD transmit in families and to further evaluate the nature of the association between BP-I disorder and CD.

Methods

Sample

The sample was derived from four independent studies using identical assessment methodology: 1) and 2) were prospective controlled family studies of boys and girls 6 to 17 years of age with and without Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) ADHD and their first-degree relatives (Boys Study: N=140 ADHD probands with N=454 first-degree relatives and N=120 Control probands with N=368 first-degree relatives and Girls Study: N=140 ADHD probands with N=417 first-degree relatives and N=122 Control probands with N=369 first-degree relatives)^{24, 25}; 3) was a prospective controlled family study of youth 10 to 18 years of age with and without Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) pediatric BP-I disorder and their first degree relatives (N=105 BP-I probands with N=320 first-degree relatives and N=98 Control probands with N=288 first-degree relatives)²⁶; and 4) was a prospective family study of youth 6 to 17 years of age of both sexes with active symptoms of DSM-IV BP-I disorder and their first-degree relatives (N=239 BP-I probands with N=687 first-degree relatives).²⁷ The ADHD studies recruited subjects from pediatric and psychiatric clinics. The BP-I disorder studies recruited subjects from referrals to the Clinical and Research Programs in Pediatric Psychopharmacology at the Massachusetts General Hospital and through advertisements in the community. All studies excluded adopted subjects, subjects where the nuclear family was not available, and subjects with major sensorimotor handicaps, inadequate command of the English language, or Full Scale Intelligence Quotient (IQ) < 70 (< 80 for ADHD studies). Potential subjects were also excluded from the ADHD studies if they had psychosis and from the BP-I disorder studies if their BP-I disorder was due solely to a medication reaction. For all four studies parents provided written informed consent to participate. Children and adolescents provided written assent to participate. The Partners Human Research Committee approved these studies.

Assessment Procedures

In all four studies, psychiatric assessments of subjects were made with the Kiddie Schedule for Affective Disorders – Epidemiologic Version (KSADS-E).^{28, 29} Diagnoses were based on independent interviews with parents and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either reporter resulted in a positive diagnosis. Assessments of adult family members (siblings and parents) age 18 or older were made with the Structured Clinical Interview for DSM-IV (SCID)³⁰ supplemented with modules from the KSADS-E to cover the childhood diagnoses of ADHD, oppositional defiant disorder (ODD), and CD.

Extensively trained and supervised psychometricians with undergraduate degrees in psychology conducted all interviews. The 4 studies subjected to familial risk analysis,

although different in subject ascertainment, used identical diagnostic methodology. No subject could be enrolled in more than one study. We used the KSADS-E for pediatric patients and the SCID for all individuals ages 18 years and older. As the studies were done over many years, raters for the studies were not identical, however, all raters for the studies were trained in the same way in the use of these instruments and all used the same instruments for psychiatric assessment in all studies. All diagnoses were reviewed by a diagnostic sign-off committee chaired by the same service chief [JB] who reviewed both the items endorsed during the interview along with detailed notes taken by the interviewer. All diagnoses of BP-I and CD were presented for review and were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically concerning due to the nature of the symptoms, the associated impairment, and coherence of the clinical picture. For the ADHD studies and the controlled BP-I disorder study, raters were blind to the ascertainment status of the families. For the BP-I disorder family study, raters were blind to the study assignment and whether the subject was a proband or sibling.

To assess the reliability of our overall diagnostic procedures, we computed kappa coefficients of agreement by having experienced, blinded, board-certified child and adult psychiatrists and licensed experienced clinical psychologists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98 for the ADHD studies and the controlled BP-I disorder study, and 0.99 for the BP-I family study.

Socioeconomic status (SES) was measured using the 5-point Hollingshead scale.³¹

Statistical Analysis

For this study, we stratified the first-degree relatives of the probands into four groups based on the probands' CD and BP-I disorder diagnoses and created the following groups: 1) relatives of probands without CD and without BP-I disorder (No CD + No BP-I) (probands: N=550; relatives: N=1,656), 2) relatives of probands with CD and without BP-I disorder (CD + No BP-I) (probands: N=40; relatives: N=127), 3) relatives of probands with BP-I disorder without CD (BP-I + No CD) (probands: N=197; relatives: N=579), and 4) relatives of probands with both CD and BP-I disorder (CD + BP-I) (probands: N=176; relatives: N=488). One proband and 53 first-degree relatives were excluded from analysis because they were missing diagnoses for BP-I disorder, CD/antisocial personality disorder, or both.

First, we compared the four groups on demographic characteristics to identify any potentially confounding factors. We used linear, logistic, and ordered logistic regression models to make comparisons among the probands as well as the first-degree relatives. We controlled for any demographic characteristics that were significant at the 0.05 alpha level (proband age, proband sex, and family SES). We imputed family SES using the group means for three probands who were missing data points so we could include their family members in subsequent analyses.

Next, we separately assessed the rates of CD and BP-I disorder in first-degree relatives using logistic regression models that controlled for demographic confounders. Adult relatives

(parents and adult siblings) were evaluated using the SCID, which includes the diagnosis of antisocial personality disorder (ASPD). We used the combined category of either CD or ASPD or both (CD/ASPD) when analyzing adult first-degree relatives.

Lastly, we examined whether BP-I disorder plus CD represents a distinct familial subtype by testing for cosegregation (i.e. the co-occurrence of the two disorders in individual relatives). To do so, we stratified the first-degree relatives of probands with both BP-I disorder and CD by their BP-I diagnosis and examined the rate of CD within the two groups using logistic regression. If cosegregation is present, we would expect to see higher rates of CD in the first-degree relatives with BP-I disorder.

All regression models analyzing first-degree relatives used robust standard errors to account for the non-independence of family members. All tests were two-tailed and conducted at the 0.05 alpha level using Stata® (Version 15.1).

Results

Demographic Characteristics

As shown in Table 1, there were significant differences between the groups in proband age, proband sex, and family SES, although the results reported are similar. Our large sample size gives us high power to detect differences between groups. Our criteria for statistical significance was the standard $p < 0.05$. However, even if we made our criteria more stringent and considered statistical significance of $p < 0.001$, proband age and sex would still meet our criteria and family SES would be borderline. By controlling for these demographic characteristics in the main analysis, we remove potential confounding by these variables and are better able to examine the relationship between proband diagnosis and family history. Probands with CD alone were significantly older than the probands in the other three groups while probands with BP-I alone were significantly younger than probands in the other three groups. Compared to the No CD + No BP-I group, the other three groups had a significantly higher proportion of male probands. Furthermore, those in the two BP-I groups were of significantly worse SES compared to those in the No CD + No BP-I group. There were no differences between the groups in the age or sex of first-degree relatives. Given the differences among the probands, all subsequent analyses controlled for proband age, proband sex, and family SES.

Familial Risk Analysis

We first examined the rate of CD/ASPD in the first-degree relatives and found significant differences among the groups ($\chi^2_3 = 32.14$, $p < 0.001$) (Figure 1A). Relatives in the CD + BP-I group had significantly higher rates of CD/ASPD compared to those in the No CD + No BP-I group, while relatives in the CD + No BP-I group had higher rates of CD/ASPD compared to those in the No CD + No BP-I and BP-I + No CD groups.

We then examined the rate of BP-I in the first-degree relatives and found significant differences between the groups ($\chi^2_3 = 77.78$, $p < 0.001$) (Figure 1B). Both the BP-I groups (BP-I + No CD and CD + BP-I) had higher rates of BP-I in relatives compared to the CD + No BP-I and No CD + No BP-I groups.

When we restricted the sample to the first-degree relatives of probands with CD + BP-I and stratified the relatives by BP-I diagnosis (N=422 without BP-I and N=66 with BP-I), we found that the relatives with BP-I had a significantly higher rate of CD/ASPD compared to the relatives without BP-I ($\chi^2_3=37.51$, $p<0.001$) (Figure 1C). This finding of cosegregation between CD/ASPD and BP-I suggests that CD + BP-I is a distinct familial subtype.

Discussion

We examined the association between CD and BP-I in a large sample of youth with and without BP-I disorder of both sexes using familial risk analysis. Relatives of probands with BP-I disorder had high rates of BP-I and relatives of probands with CD had high rates of CD irrespective of the comorbidity with the other disorder. In addition, relatives of probands with the combined condition of CD and BP-I had high rates of the combined condition. These findings support and extend previous findings in smaller samples supporting the hypothesis that BP-I disorder comorbid with CD may represent a distinct familial subtype of either BP-I disorder or CD.^{18, 19}

The finding that both BP-I disorder and CD breeds true in families adds to the evidence that children with symptoms of BP-I and CD have both disorders which are truly comorbid with each other. These findings are not compatible with the hypothesis that one diagnosis is a misdiagnosis of the other condition.

Our findings are also consistent with a body of literature documenting that the comorbidity between BP-I disorder and CD is common. In our previous study of boys with ADHD, 55% of those with CD also had BP-I and 71% of the boys with BP-I also had CD.¹⁸ Similar findings were reported in a sample of consecutively referred youth showing that 40% of CD youth had comorbid BP-I and 41% of the youth with BP-I disorder had comorbid CD.³² These studies also documented that the clinical features of each disorder, patterns of comorbidity, and level of functional deficits were highly similar in children with BP-I disorder and those with CD, irrespective of the comorbidity with the other disorder.¹⁸

Our finding of familiarity and cosegregation between BP-I disorder and CD is consistent with our previous work. Pooling familiarity data from three small studies with identical methodology,¹⁹ we found elevated familiarity of BP-I in the relatives of probands with BP-I (irrespective of comorbidity with CD) and elevated familiarity of ASPD relatives of probands with CD (irrespective of comorbidity with BP-I).¹⁹ This study also found cosegregation between BP-I disorder and CD.

The finding that a sizeable subgroup of CD youth has comorbidity with BP-I disorder has important clinical implications. While pharmacological treatments are available and U.S. Food and Drug Administration (FDA) approved to treat BP-I disorder, no such options are available for CD, which remains a most difficult to treat disorder. As recently reported by our group,³³ remission of BP-I disorder was associated with remission of CD suggesting that the course of CD can be moderated by the treatment of BP-I disorder in comorbid cases. Additionally, adolescents with bipolar disorder and comorbid CD were recently reported to be at a significantly increased risk for later substance use disorders.^{34, 35} Thus, identifying

BP-I in youth with CD offers a tangible opportunity for treatment, which could mitigate the aggression, addiction potential, and antisocial behavior of a large subgroup of CD youth with comorbid BP-I disorder.

Strengths of this study include its large sample size, the sizeable representation of subjects of both sexes, the reliance on structured diagnostic interviews, the systematic direct assessment of all first-degree relatives, and the use of familial risk analysis.

However, our results need also to be viewed considering some methodological limitations. The retrospective nature of lifetime diagnoses especially of CD and ASPD in relatives is a limitation of this study. Future studies could benefit from following probands and relatives prospectively. Although this study included probands and relatives from four different data sets, each of the four studies utilized identical methodology, enabling the opportunity to pool the available samples to attain a very large sample size affording excellent statistical power to test the study hypotheses. The four data sets included one that only ascertained boys and another that ascertained only girls, but the methodology of those studies was identical and the number of probands in each study was identical, mitigating concerns regarding sex distribution. Although every effort was made to apply consistent criteria in the review of the diagnoses of BP-I and CD by the diagnostic sign-off committee, the fact that the studies did not occur concurrently provides a limitation to the findings. Lastly, because the subjects were referred for research, the findings of this study may not generalize to community samples.

Despite these limitations, our findings confirm and extend previous research supporting the notion that BP-I disorder and CD are frequently comorbid with each other and that both disorders breed true in first degree relatives. The finding of co-segregation between BP-I disorder and CD is consistent with the hypothesis that the combined condition represents a distinct subtype of either disorder.

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Declarations of Interest

In 2017–2018, Dr. Janet Wozniak received research support from PCORI. She is the author of the book, “Is Your Child Bipolar” published May 2008, Bantam Books. In 2015–2017, her spouse, Dr. John Winkelman, received an honorarium from Otsuka; royalties from Cambridge University Press and UpToDate; consultation fees from Advance Medical, FlexPharma and Merck; and research support from UCB Pharma, NeuroMetrix, and Luitpold.

In 2015–2018, Dr. Timothy Wilens receives or has received grant support from the following sources: NIH(NIDA). Dr. Wilens is or has been a consultant for Alcobra, Neurovance/Otsuka, and Ironshore. Dr. Wilens has published a book: *Straight Talk About Psychiatric Medications for Kids* (Guilford Press); and co/edited books: *ADHD in Adults and Children* (Cambridge University Press), *Massachusetts General Hospital Comprehensive Clinical Psychiatry*

(Elsevier) and *Massachusetts General Hospital Psychopharmacology and Neurotherapeutics* (Elsevier). Dr. Wilens is co/owner with MGH of a copyrighted diagnostic questionnaire (Before School Functioning Questionnaire) licensed to Ironshore (BSFQ Questionnaire). Dr. Wilens is Chief, Division of Child and Adolescent Psychiatry and (Co) Director of the Center for Addiction Medicine at Massachusetts General Hospital. He serves as a clinical consultant to the US National Football League (ERM Associates), U.S. Minor/Major League Baseball; Gavin/Phoenix and Bay Cove Human Services.

In the past year, Dr. Steven Faraone received income, potential income, travel expenses continuing education support and/or research support from Lundbeck, Rhodes, Arbor, KenPharm, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA, Sunovion, Genomind and Neurolifesciences. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received support from: Shire, Neurovance, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*, Oxford University Press: *Schizophrenia: The Facts* and Elsevier: *ADHD: Non-Pharmacologic Interventions*. He is principal investigator of www.adhdinadults.com.

Dr. Joseph Biederman is currently receiving research support from the following sources: AACAP, Feinstein Institute for Medical Research, Food & Drug Administration, Headspace Inc., Lundbeck AS, Neurocentria Inc., NIDA, Pfizer Pharmaceuticals, Roche TCRC Inc., Shire Pharmaceuticals Inc., Sunovion Pharmaceuticals Inc., and NIH. Dr. Biederman has a financial interest in Avekshan LLC, a company that develops treatments for attention deficit hyperactivity disorder (ADHD). His interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. Dr. Biederman's program has received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Ingenix, Prophase, Shire, Bracket Global, Sunovion, and Theravance; these royalties were paid to the Department of Psychiatry at MGH. In 2018, Dr. Biederman is on the scientific advisory board for Akili and Shire. Through MGH corporate licensing, he has a US Patent (#14/027,676) for a non-stimulant treatment for ADHD, and a patent pending (#61/233,686) on a method to prevent stimulant abuse. In 2017, Dr. Biederman received research support from the Department of Defense and PamLab. He was a consultant for Aevi Genomics, Akili, Guidepoint, Ironshore, Medgenics, and Piper Jaffray. He was on the scientific advisory board for Alcobra and Shire. He received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses. In 2016, Dr. Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses, and from Alcobra and APSARD. He was on the scientific advisory board for Arbor Pharmaceuticals. He was a consultant for Akili and Medgenics. He received research support from Merck and SPRITES. In 2015, Dr. Biederman received honoraria from the MGH Psychiatry Academy for tuition-funded CME courses, and from Avekshan. He received research support from Ironshore, Magceutics Inc., and Vaya Pharma/Enzymotec. In previous years, Dr. Biederman received research support, consultation fees, or speaker's fees for/from the following additional sources: AACAP, Abbott, Alcobra, Alza, APSARD, AstraZeneca, Boston University, Bristol Myers Squibb, Cambridge University Press, Celltech, Cephalon, The Children's Hospital of Southwest Florida/Lee Memorial Health System, Cipher Pharmaceuticals Inc., Eli Lilly and Co., Esai, ElMindA, Forest Research Institute, Fundacion Areces (Spain), Forest, Fundación Dr.Manuel Camelo A.C., Glaxo, Gliatech, Hastings Center, Janssen, Juste Pharmaceutical Spain, McNeil, Medice Pharmaceuticals (Germany), Merck, MGH Psychiatry Academy, MMC Pediatric, NARSAD, NIDA, New River, NICHD, NIMH, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Phase V Communications, Physicians Academy, The Prechter Foundation, Quantia Communications, Reed Exhibitions, Shionogi Pharma Inc, Shire, the Spanish Child Psychiatry Association, The Stanley Foundation, UCB Pharma Inc., Veritas, and Wyeth.

Maura DiSalvo, Abigail Farrell, and Rebecca Wolenski have nothing to disclose.

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Significant Outcomes

- The findings support the hypothesis that comorbid BP-I and CD may represent a distinct familial subtype of either BP-I disorder or CD. This information has high predictive value for future clinicians.
- The findings strongly suggest that children with symptoms of both BP-I and CD have both full disorders as opposed to previous hypotheses suggesting that one diagnosis is often a misdiagnosis of the other condition.
- Given that there is no medical intervention for CD as there is for BP-I, the identification of BP-I in youth with CD offers a tangible opportunity for treatment which could mitigate the impairing symptoms and potentially morbid outcomes within a large subgroup of CD youth with comorbid BP-I disorder.

Limitations

- This study included probands and relatives from four different data sets in order to obtain large sample size.
- Because the subjects were referred for research, the findings of this study may not generalize to community or clinical samples.
- The retrospective nature of lifetime diagnoses in relatives is a limitation of this study.
- Although every effort was made to apply consistent criteria in the review of the diagnoses of BP-I and CD by the diagnostic sign-off committee, the fact that the studies did not occur concurrently provides a limitation to the findings.

Figure 1.

Rates of (A) conduct disorder/antisocial personality disorder (CD/ASPD) and (B) bipolar-I disorder (BP-I) in first-degree relatives stratified by proband diagnosis of CD and BP-I. (C) Cosegregation of CD/ASPD and BP-I in first-degree relatives of probands with CD + BP-I.^a Compared to No CD + No BP-I, ^b Compared to CD + No BP-I; *P<0.05, **P<0.005, ***P<0.001

Table1.

Demographic characteristics of probands and their first-degree relatives. Data are presented as mean $\pm$ standard deviation or N (%).

	Proband Diagnosis				Test Statistic	P-Value
	No CD + No BP-I	CD + No BP-I	BP-I + No CD	CD + BP-I		
Probands	(N=550)	(N=40)	(N=197)	(N=176)		
Age	11.6 $\pm$ 3.2	13.4 $\pm$ 3.4 ^{a**}	11.0 $\pm$ 3.2 ^{a*b***}	12.2 $\pm$ 3.4 ^{b*c***}	F _(3, 959) =7.53	<0.001
Male	272(49)	32 (80) ^{a***}	134 (68) ^{a***}	127 (72) ^{a***}	χ^2_3 =45.57	<0.001
Family SES [†]	1.7 $\pm$ 0.9	2.0 $\pm$ 1.2	1.9 $\pm$ 1.0 ^{a*}	2.0 $\pm$ 1.0 ^{a***}	χ^2_3 =15.77	0.001
First-degreeRelatives	(N=1,656)	(N=127)	(N=579)	(N=488)		
Age	32.4 $\pm$ 15.2	32.0 $\pm$ 15.5	31.9 $\pm$ 15.7	31.4 $\pm$ 15.3	F _(3, 961) =0.87	0.45
Male	837(51)	61 (48)	275 (48)	230 (47)	χ^2_3 =6.59	0.09

^aCompared to No CD + No BP-I,

^bCompared to CD + No BP-I,

^cCompared to BP-I + No CD;

* P<0.05,

** P<0.005,

*** P<0.001

[†]Smaller sample sizes due to missing data. No CD + No BP-I: N=548, CD + No BP-I: N=40, BP-I + No CD: N=196, CD + BP-I: N=176