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Characteristics and Stability of Empirically Derived Anorexia Nervosa Subtypes: Towards the Identification of Homogeneous Low-Weight Eating Disorder Phenotypes

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Abstract

Anorexia nervosa (AN) is characterized by within-group heterogeneity in symptom presentation, which poses problems for research on etiology and treatment. This study sought to identify homogeneous subtypes of AN, and examine their short-term stability, using empirical methods. A treatment-seeking sample with AN ($N = 194$) was assessed at baseline and six- and 12-month follow-ups. Latent class analysis was used to identify homogeneous AN subgroups, and latent transition analysis was used to examine the stability of latent classes. Three low-weight eating disorder classes were identified: 1) fat-phobic restricting (AN-R-FP); 2) fat-phobic binge-eating/purging (AN-BP-FP); and 3) non-fat-phobic restricting (AN-R-NFP). Subtype membership was stable over follow-up, with .68 to .88 probabilities of remaining in the same class from baseline to six months, and .87 to 1.00 from six months to 12 months. The most common transition pattern was between AN-R-FP and AN-R-NFP (56.8% of transitions); the majority of these participants transitioned *from* AN-R-FP *to* AN-R-NFP ($n = 20/21$). Predictors of latent class membership included lifetime mood and substance use disorder comorbidities, negative temperament, illness duration, and body mass index at treatment presentation. Disinhibition (vs. constraint), history of overweight or obesity, and illness duration decreased the probability of latent transition. Findings support the presence of three low-weight eating disorder phenotypes that are highly stable over short-term follow-up. Identification of a stable non-fat-phobic AN phenotype is intriguing, and highlights the importance of studying mechanisms that differentiate fat-phobic and non-fat-phobic eating disorders.

Keywords

anorexia nervosa; eating disorder; latent transition analysis; non-fat-phobic

With the recent publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (*DSM-5*; American Psychiatric Association, 2013), issues of nosology are at the forefront of the psychopathology literature. Interest in the development of a more valid diagnostic system has been particularly pronounced for the eating disorders (EDs) (for

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review, see Keel, Brown, Holland, & Bodell, 2012). Although there is evidence that the *DSM-5* ED categories represent an improvement over previous nosological schemes, particularly in decreasing the frequency of ED not otherwise specified diagnoses (Birgegard, Norring, & Clinton, 2012; Keel, Brown, Holm-Denoma, & Bodell, 2011; Machado, Goncalves, & Hoek, 2013), a number of potential limitations remain (Birgegard et al., 2012; Fairburn & Cooper, 2011). *DSM-5* is intended to be a “living document with a permanent revision infrastructure” (Regier, Narrow, Kuhl, & Kupfer, 2009, p. 649); thus ongoing efforts to inform ED classification are critical. Moreover, in light of the growing interest in alternative approaches to classifying mental disorders on the basis of underlying mechanisms— as exemplified by the Research Domain Criteria (RDoC) initiative from the National Institute of Mental Health (Sanislow et al., 2010), the elucidation of ED phenotypes that may be linked to distinct etiologic processes could have important implications for research and clinical practice.

There are few mental disorders for which novel conceptualizations are needed more than anorexia nervosa (AN). AN is a serious ED associated with substantial morbidity and mortality (Arcelus, Mitchell, Wales, & Nielsen, 2011; Attia, 2010). Yet, little is known about mechanisms that underlie the expression and maintenance of AN symptoms (Attia, 2010), and evidence-based treatments are scarce, especially for older adolescent and adults, who comprise the majority of AN patients (Bulik, Berkman, Brownley, Sedway, & Lohr, 2007).

One challenge in designing studies of AN relates to the substantial within-group heterogeneity in symptom presentation that characterizes the illness. Although individuals with AN, by definition, share the symptom of extremely low body weight, they may differ with respect to other ED features such as binge eating, compensatory behaviors, and fear of fatness. This symptomatic heterogeneity poses problems for research on etiology and treatment. For example, biological components like those included in the RDoC matrices are far more likely to be linked to specific behaviors or symptoms than to diagnostic categories (Der-Avakian & Markou, 2012). Likewise, efforts to develop novel treatments may show limited promise if a “one-size-fits-all” approach is applied to a group of individuals characterized by variable symptoms and underlying mechanisms. Thus, the overall goal of the current study was to identify homogeneous subtypes of AN, and examine their short-term stability using empirical methods. A secondary aim was to document predictors of class membership and transition to generate hypotheses about characteristics that might be linked to particular AN phenotypes.

Existing Approaches to Subtyping AN

Restricting and binge-eating/purging subtypes

A large literature has focused on the delineation of AN subtypes, but empirical support for existing methods has been mixed. The best-studied approach, and the only ED subtyping scheme included in *DSM-5*, emphasizes differences between AN patients who have and have not engaged in recurrent episodes of binge eating or purging (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas) during the last three months. In general, studies comparing binge-eating/purging (AN-BP) and restricting (AN-R) subtypes have documented differences in clinical correlates and outcome, supporting the validity of this approach (Peat, Mitchell, Hoek, & Wonderlich, 2009).

Nevertheless, several questions about AN-R and AN-BP remain. For example, the criteria for AN-BP suggest that this subgroup may be highly heterogeneous, as individuals with AN-BP can exhibit binge eating, purging, or both behaviors. Empirical studies utilizing samples with broadly-defined EDs (i.e., AN, bulimia nervosa, and ED not otherwise specified) have

provided support for classification schemes that group binge eating and purging (Crow et al., 2012; Keel et al., 2004; Peterson et al., 2011); however, no study has used empirical methodology to evaluate whether underweight individuals who binge and purge are best classified with those who engage in only one of these behaviors. There also may be variability within AN-BP in the size of binge eating episodes (i.e., objective versus subjective binge eating). Data from other EDs suggest that loss of control over eating rather than the amount of food consumed constitutes the cardinal feature of binge eating (Wolfe, Baker, Smith, & Kelly-Weeder, 2009), and thus objective and subjective binge episodes may co-aggregate in AN patients. Yet, few studies have characterized binge eating in AN (for a notable exception, see Dalle Grave, Calugi, & Marchesini, 2012). Finally, prospective longitudinal data indicate that membership in the AN-R and AN-BP subtypes is unstable, with crossover rates ranging from 18%-64% (Peat et al., 2009). Although there is some evidence that a stable, homogeneous AN-R subtype exists, and may be etiologically distinct from AN-BP (Anderluh, Tchanturia, Rabe-Hesketh, Collier, & Treasure, 2009; Gordon, Holm-Denoma, Smith, Fink, & Joiner, 2007), little is known about factors that predict stability and change in the presentation of AN symptoms. Several predictors of crossover from AN to bulimia nervosa have been identified (e.g., older age, longer duration of illness, and higher maximum lifetime body mass index), but few of these variables have been replicated across samples, and the extent to which factors that predict the onset of BN also predict transitions between AN-R and AN-BP is unknown (Castellini et al., 2011; Monteleone, Di Genio, Monteleone, Di Filippo, & Maj, 2011; Tozzi et al., 2005).

Fat phobic versus non-fat phobic AN

Another subtyping scheme that was considered for inclusion in *DSM-5*, but ultimately not adopted, focuses on distinguishing underweight individuals with and without “intense fear of weight gain or becoming fat” (p. 544), which was a required symptom for a *DSM-IV* diagnosis of AN (American Psychiatric Association, 1994). Initial interest in “non-fat-phobic AN” (Becker, Thomas, & Pike, 2009, p. 620) derived from the clinical observation that patients presenting for treatment of low-weight EDs in non-Western contexts (primarily Hong Kong) often denied weight phobia, ascribing their underweight status to other causes (Lee, Ho, & Hsu, 1993; Lee, Lee, Ngai, Lee, & Wing, 2001). Subsequent studies using descriptive (e.g., Carter & Bewell-Weiss, 2011; Dalle Grave, Calugi, & Marchesini, 2008; Santonastaso et al., 2009) and empirical (e.g., Crow et al., 2012; Dechartres et al., 2011; Keel et al., 2004) methods to classify individuals with EDs have provided further support for the presence of a non-fat-phobic subgroup in Western, as well as non-Western, environments.

However, several questions regarding the validity of non-fat-phobic AN need to be resolved to determine whether this subgroup should be considered for inclusion in future ED classification schemes. Of particular importance is the issue of diagnostic stability. Individuals who deny fear of fatness or weight gain while they are underweight may begin to exhibit these symptoms after they enter treatment and weight gain is initiated, which would argue against the presence of an etiologically distinct non-fat-phobic subtype. Although a few studies have shown that non-fat-phobic AN is stable during treatment (Carter & Bewell-Weiss, 2011; Dalle Grave et al., 2008), others have not (Soomro, Crisp, Lynch, Tran, & Joughin, 1995), and little is known about the longer-term stability or clinical correlates of non-fat-phobic EDs.

The Current Study

In summary, AN is characterized by within-group heterogeneity in ED behaviors and cognitions, which may hinder efforts to elucidate etiologic mechanisms and develop effective treatments. However, research focusing on the validity of clinically-defined AN

subgroups has produced inconsistent findings. Of particular concern, there is evidence that membership in clinically-defined AN subgroups is unstable (Peat et al., 2009; Soomro et al., 1995), but little is known about predictors of AN class membership over time that might help to elucidate stable, homogeneous phenotypes for future research. Thus, the overall aim of the current study was to characterize homogeneous subgroups of AN, and examine their stability over one-year follow-up. Based on previous research, we hypothesized that there would be at least three empirically-derived AN subgroups at baseline, namely, AN-R with fat phobia, AN-BP with fat phobia, and non-fat phobic AN. Because this is the first study to examine the longitudinal stability of empirically-derived AN subgroups, we did not have specific hypotheses about patterns of change in AN symptoms or predictors of latent transition.

Method

Participants

Participants were recruited from consecutive unique admissions ($N = 256$) to the inpatient and day hospital ED programs at an academic medical center between April 2008 and April 2011. Study inclusion criteria were: 1) age ≥ 16 years, 2) body mass index (BMI) < 18.5 or BMI percentile < 10 (patients aged 16–19 years) at admission, and 3) medical stability. Patients were excluded from the study if they were psychotic or had a chart diagnosis of mental retardation ($n = 4$). Additional details regarding study recruitment and inclusion/exclusion criteria have been reported (Wildes & Marcus, 2012; Wildes et al., 2011). After the study was described, 194 individuals (75.8%) signed consent forms approved by the local Institutional Review Board (assent for individuals under 18 years) and completed baseline study assessments.

Participants ($N = 194$) had a mean age of 26.5 years ($SD = 10.1$) and a mean BMI of 15.7 ($SD = 1.8$) at treatment admission. The sample was primarily female ($n = 185$; 95.4%) and non-Hispanic Caucasian ($n = 185$; 95.4%). One participant self-identified as African American (0.5%), two were Asian (1.0%), two were Hispanic (1.0%), and four were multiracial (2.1%). The majority of participants were employed ($n = 49$; 25.3%) or in school ($n = 84$; 43.3%).

As described previously (Wildes et al., 2011), ED diagnoses were made using *DSM-IV* criteria with two exceptions: 1) amenorrhea was not required for a diagnosis of AN and 2) individuals with a BMI < 17.5 who denied fear of fatness were included, consistent with descriptions of non-fat-phobic AN. Using these criteria, 84 participants (43.3%) were diagnosed with AN-R and 110 (56.7%) were diagnosed with AN-BP at baseline. Self-reported duration of ED symptoms ranged from less than one year to 45 years ($M = 8.6$, $SD = 9.0$); nearly half the sample ($n = 92$; 47.4%) had at least one previous hospitalization for ED.

Procedure

Assessments were conducted within approximately two weeks of admission for intensive treatment ($M [SD] = 12.9 [10.0]$ days after admission), at discharge, and at three, six, and 12 months post-discharge. Baseline assessments were delayed for two weeks after admission to mitigate the effects of acute starvation on cognitive function (Wildes et al., 2011). To maximize participant retention, follow-up assessments were conducted in-person or by phone and mail. Telephone interviews are equivalent to in-person interviews in terms of validity, reliability, precision of estimates, and response rates (Keel, Crow, Davis, & Mitchell, 2002; Rohde, Lewinsohn, & Seeley, 1997). Interviewers were bachelor's-, master's-, or doctoral-level research clinicians who were trained and supervised by two

experienced psychologists during weekly consensus meetings. Interviews were audiotaped, and a randomly selected 10% of the tapes were re-rated by independent clinicians to establish reliability.

Measures

Demographics and treatment history—At baseline, participants self-reported demographic information and prior treatment using an investigator-designed questionnaire. Participants also self-reported their highest and lowest non-pregnancy weights (with corresponding heights and ages) between the ages of 12 and 18 years and over 18 years. The validity of recalled past weights has been supported in previous research (Tamakoshi et al., 2003). Weight history was used to calculate two variables that were examined as predictors of AN subtype membership: 1) weight suppression, defined as *highest weight at current height – weight at admission to treatment* (Wildes & Marcus, 2012); and 2) history of overweight or obesity, defined as BMI ≥ 25.0 (weights that occurred when participants were 20 years old) or BMI $\geq 85^{\text{th}}$ percentile for age and sex (weights that occurred between the ages of 12 and 19).

Psychiatric diagnoses—The Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2007) was administered at baseline to diagnose current and lifetime eating, mood, anxiety, and substance use disorders. Inter-rater reliabilities in the current study were good to excellent ($\kappa = 0.64$ to $\kappa = 1.00$).

ED symptoms—The Eating Disorder Examination, 16th edition (EDE; Fairburn, Cooper, & O'Connor, 2008) was administered at baseline, discharge, and three, six and, 12 months post-discharge to evaluate ED symptoms. The EDE is a clinician-rated interview that measures *DSM-IV* criteria for EDs and the cognitive correlates of disordered eating on four subscales (Restraint, Eating Concern, Shape Concern, and Weight Concern) and a Global scale calculated as the mean of the four subscales. The EDE also assesses the frequency of ED behaviors (e.g., objective binge episodes, subjective binge episodes, self-induced vomiting, laxative misuse, diuretic misuse) and the severity of psychological ED symptoms (e.g., overvaluation of shape and weight, fear of fatness) during the past three months. The psychometric properties of the EDE are well-documented (for review, see Berg, Peterson, Frazier, & Crow, 2012). In the current study, internal consistencies of EDE scales ranged from .65 to .94, and intra-class correlation coefficients were between .94 and .99. Inter-rater reliabilities for number of objective binge episodes, number of subjective binge episodes, and number of purging episodes were 1.0, 0.99, and 0.99, respectively.

Height and weight—Height and weight were measured at each assessment to calculate BMI (weight in kg/height in meters squared). At the baseline and discharge assessments, information about height and weight was collected by medical chart review. Participants were weighed on a digital scale in a hospital gown without shoes; height was measured using a stationary stature board.

At in-person follow-up assessments, research staff measured height and weight using the methods described above. If a participant completed a follow-up assessment by phone and mail, a release of information was obtained to collect data about current height and weight from a physician, therapist, or other treatment professional (e.g., dietician). Using these procedures, we were able to obtain in-person or verified heights and weights from 87.8% ($n = 144$) of participants who completed the 3-month follow-up, 91.7% ($n = 143$) of participants who completed the 6-month follow-up, and 91.8% ($n = 135$) of participants who completed the 12-month follow-up. As a last resort if verified height and weight data could not be obtained, participants' self-reported heights and weights were used.¹

Personality traits—At baseline, participants completed the Schedule for Nonadaptive and Adaptive Personality, 2nd edition (SNAP-2; Clark, Simms, Wu, & Casillas, in press), a factor-analytically derived, 390-item self-report questionnaire. SNAP-2 items are rated using a true-false format and summed to produce 12 trait and three temperament scales, namely, 1) Negative Affect, 2) Positive Affect and 3) Disinhibition (i.e., the tendency to act spontaneously with little regard for the consequences of one's behavior to self or others) versus Constraint (i.e., a behavioral style that emphasizes order, rules, and taking action only after consideration of the broad consequences for oneself and others). The SNAP-2 scales have demonstrated good to excellent internal consistency (median $\alpha = 0.85$) and adequate test-retest reliability (median $r = 0.68$) in individuals seeking treatment for mental disorders (Clark et al., in press). Internal consistencies for the SNAP-2 scales in the current sample ranged from $\alpha = 0.79$ to $\alpha = 0.89$ (median $\alpha = 0.85$).

Current treatment—Participants' medical records were reviewed at discharge to obtain information about: 1) length of current treatment episode, 2) type of treatment (inpatient, day hospital, both) and 3) discharge type (planned, against medical advice).

Treatment after discharge—The McKnight Follow-up of Eating Disorders (M-FED), a clinician-rated measure that has been used in several multicenter and treatment studies to document service utilization (e.g., Agras, Crow, Mitchell, Halmi, & Bryson, 2009), was administered at the three-, six- and, 12-month follow-up assessments. Participants were queried about admission(s) to intensive treatment (i.e., inpatient, day hospital, or residential) and the receipt of outpatient psychotherapy and psychotropic medications since their last interview. There was excellent inter-rater agreement (κ 's = 1.00) for categorical ratings of any intensive treatment admission, any psychotherapy and any pharmacotherapy at the follow-up assessments.

Statistical Analyses

Data were analyzed using SAS/STAT© software version 9.2 (SAS Institute Inc., 2011) and Mplus version 6 (Muthén & Muthén, 2007). Missing data were imputed using maximum-likelihood multiple imputation - averaged over 11 imputations - if participants completed at least one post-discharge assessment.²

Latent class analysis (LCA)—LCA was used to identify homogeneous sub-groups of AN separately at baseline and six- and 12-month follow-ups as a preliminary step in model selection for latent transition analysis.³ LCA models account for associations between observed indicators in terms of mutually exclusive groups of individuals (i.e., mutually exclusive latent classes) when group memberships are unknown. We tested the fit of one-through five-class models to the observed data. The best-fitting LCA model was determined through a comparison of standard fit indices, including the Bayesian Information Criterion

¹Self-reported height and weight were obtained for a portion of the sample at baseline ($n = 40$; 20.3%) and discharge ($n = 32$; 16.2%). Correlations between self-reported and objective BMI were .81 at intake and .94 at discharge, indicating high correspondence.

²For latent transition analysis models, missing data were handled using the default option in Mplus version 6, which estimates models under missing data theory using all available data.

³In many contexts it is preferable to use latent profile analysis (LPA), instead of LCA, to identify latent classes because LPA can be applied to continuous and ordinal outcomes, which have more variance than categorical outcomes. However, within the context of LTA, the issue of whether to choose continuous or categorical outcomes is impacted by the complexity of the analysis. For a three class LCA model with three assessment times (baseline, 6- and 12-month follow-ups), the number of transition patterns is 3 to the 3rd power or 27 (Collins & Lanza, 2010). Modeling additional assessment times or using ordinal indicators further increases model complexity, which results in several empty cells for certain transitions. This is particularly problematic when the sample size is modest (e.g., less than 300 or 400 participants). For these reasons, we chose to use categorical data (LCA) in order to minimize model complexity relative to our sample size. Nevertheless, we also ran individual LPA models at each assessment time point to see if the overall results would be replicated using ordinal indicators. Importantly, we identified the same three-profile model at each time point using ordinal indicators.

(BIC), sample-size adjusted Bayesian Information Criterion (aBIC), and Akaike Information Criterion (AIC). We also examined the mean posterior probability of each latent class (which provides a class-specific measure of how well the observed variables predict latent class membership) and entropy (N.B: Although entropy is a frequently reported statistic for LCA in the ED literature, it is associated with increasing assignment error as a function of increasing numbers of latent classes (Collins & Lanza, 2010); therefore, we placed greater emphasis on fit indices and mean posterior probabilities).

Latent transition analysis (LTA)—LTA was used to examine the stability of latent classes over time. LTA consists of a measurement model for the latent classes at each time point and a structural model that describes the relations among latent class variables. LTA models estimate three parameters: 1) item-response probabilities, which reflect the probability of endorsing an item conditional on latent class membership, with values close to zero or one indicating the item is a strong indicator of the latent variable; 2) probability of membership in each latent class at each time point; and 3) transition probabilities (i.e., the probability of transitioning among latent classes over time).

To avoid ‘sparseness’ – which is a function of the total sample size (N) to the size of the contingency table of all indicators of the latent class variable (W) or N/W – we did not include the three-month assessment in LTA because the inclusion of this time point made the average expected cell count too small for model convergence (N.B.: we did examine a LCA model at the three-month time point; data are available upon request). Examining outcomes at the six- and 12-month follow-ups is consistent with timeframes used in clinical trials for AN (e.g., Lock et al., 2010) and previous research using LTA in ED patients (Peterson et al., 2011).

To account for the possibility that participants were recovered at follow-up assessments, we created a “zero-class” at six- and 12-month follow-ups (see, e.g., Peterson et al., 2011). Participants in the zero-class were required to meet the following criteria: 1) BMI ≥ 18.5 ; 2) no objective or subjective binge episodes in the past three months; 3) no purging episodes in the past three months; 4) EDE score < 4 on the fear of weight gain item for the past three months; and 5) EDE scores < 4 on the overvaluation of weight and shape items for the past three months. We tested the fit of one- through four-class LTA models (and additional zero-class models at the six- and 12-month follow-ups) to the observed data using three time points. The BIC, aBIC, AIC, mean posterior probabilities, and entropy were used to determine the best fitting model.

Predictors of class membership and transition—Although covariates can be added to the best-fitting LTA model to identify characteristics that predict membership in different latent classes at each time point and to predict transitions between latent classes across time, this approach becomes problematic when the sample sizes in individual rows of the transition probability matrix are small, and can lead to unstable parameter estimates (Collins & Lanza, 2010). For this reason, binomial or multinomial logistic regression was used to identify predictors of class membership and latent transition (see Collins & Lanza, 2010 for additional description of this approach).

Results

Participant Retention

Retention rates at the three-, six-, and 12-month follow-ups were 84.0% ($n = 163$), 82.5% ($n = 160$), and 79.4% ($n = 154$), respectively. More than 90% of the sample ($n = 177$; 91.2%) completed at least one post-discharge assessment.

LCA

LCA was carried out separately at baseline, six-month, and 12-month follow-ups using the following indicators from the EDE: overvaluation of weight and shape (score = 4), fear of 'fatness' (score = 4), presence of purging, presence of objective binge episodes, and presence of subjective binge episodes. Correlations among indicators were small to moderate (r 's ranged from -.09 for overvaluation of weight and shape at discharge with objective binge episodes at six-month follow-up to .44 for overvaluation of weight and shape at six-month follow-up with fear of 'fatness' at 12-month follow-up), indicating that the assumption of conditional independence was unlikely to have been violated.

As shown in Table 1, fit indices supported a three-class model at baseline and 12-month follow-up, and a four-class model at six-month follow-up. Posterior probabilities of class membership were used to assign participants into classes, which were compared on model indicator variables to characterize the groups. Class 1 was a highly fat-phobic restricting class (AN-R-FP); Class 2 was a fat-phobic binge-eating/purging class (AN-BP-FP); and Class 3 was a non-fat-phobic restricting class (AN-R-NFP) (see Figure 1). The four-class model at six-month follow-up included the AN-R-FP and AN-R-NFP groups; however, the AN-BP class split into non-fat-phobic and fat-phobic groups. Entropy for the best-fitting LCA models ranged from .71 (at 12-month follow-up) to .79 (at six-month follow-up), and mean posterior probabilities of class membership were good to excellent at each time point (Mean P 's ranged from .87 to .95 at baseline, .82 to .92 at six months, and .81 to .96 at 12 months).

LTA

Next, we ran one- through four-class LTA models, with transition probabilities constrained to be equal across time. Based on the BIC, aBIC, and AIC, the three-class model demonstrated the best fit to the data (see Table 2). Because entropy was somewhat low for the constrained model, we re-ran the three-class model allowing the latent transition probabilities to vary freely across time points, which demonstrated a better fit to the data and improved entropy (see unconstrained model in Table 2). Posterior probabilities of class membership were used to assign participants into latent classes, which were then compared on the indicator variables. Notably, the same three-class model identified in the LCA (i.e., AN-R-FP, AN-BP-FP, and AN-R-NFP) was replicated using LTA (see Figure 1).⁴

Table 3 presents latent class transition probabilities from baseline to six-month follow-up, and from six-month to 12-month follow-up. Results indicate that there was relatively little change in the three-class structure over brief intervals. The majority of participants ($n = 157$; 80.9%) remained in the same latent class across all time points. Of the participants who transitioned among latent classes at follow-up ($n = 37$; 19.1%), the majority moved between AN-R-FP and AN-R-NFP (see Table 4). Notably, nearly all of these of these individuals ($n = 20$; 95.2%) transitioned *from* AN-R-FP *to* AN-R-NFP. The second most common transition pattern occurred between AN-R-NFP and the recovery class (see Table 4).

Predictors of Class Membership

To predict membership in the latent classes at each time point, we used multinomial logistic regression with AN-R-NFP as the referent group (see Table 5). At baseline, lifetime history of a mood disorder, higher scores on Negative Temperament, longer duration of current treatment episode, and higher baseline BMI were associated with significantly greater odds

⁴We re-ran the one- through four-class LTA models including BMI as an indicator, and using data only from individuals who had their weight verified at six or 12-month follow-up ($n = 164$). Results from both sets of analyses replicated findings reported in the manuscript and indicated that the three-class latent transition model provided the best fit to the data.

of being in the AN-R-FP class relative to the AN-R-NFP class, whereas only lifetime history of a mood disorder was associated with significantly greater odds of membership in the AN-BP-FP class relative to the AN-R-NFP class. At six-month follow-up, longer duration of illness and receipt of intensive treatment post-discharge were associated with significantly increased odds of membership in AN-R-FP relative to AN-R-NFP, while lifetime histories of mood and substance use disorders were associated with increased odds of membership in AN-BP-FP. No significant predictors of latent class membership emerged for AN-R-FP at 12-month follow-up. However, individuals with a lifetime mood disorder had significantly increased odds of membership in AN-BP-FP relative to AN-R-NFP at 12-month follow-up.

Predictors of Latent Transition

Logistic regression was used to identify predictors of latent class stability and change in the current sample. Participants who transitioned among the latent classes were coded as “movers” ($n = 37$), and the rest of the sample were coded as “stayers” ($n = 157$). This dichotomously coded variable then was used as the dependent variable in binomial logistic regression. As shown in Table 6, high scores on Disinhibition versus Constraint – indicating a behavioral style characterized by impulsive action with little regard for the consequences of one’s behavior to self or others (Clark et al., in press), history of overweight or obesity, and longer duration of illness were associated with significantly lower odds of latent transition over time. No significant positive predictors of latent transition emerged in these analyses.

Discussion

Phenotypic heterogeneity poses serious challenges for research on the etiology and treatment of low-weight EDs. This study is important as the first effort to document homogeneous subtypes of AN on the basis of ED symptoms, and examine their short-term stability using empirical methods. By applying LTA in a sample of nearly 200 AN patients, we found evidence for three low-weight ED phenotypes that were highly stable over short-term follow-up. The first two phenotypes – AN-R-FP and AN-BP-FP – conformed closely to the restricting and binge-eating/purging subtypes of AN included in *DSM-5*. The third phenotype – AN-R-NFP – bears a strong resemblance to clinical descriptions of non-fat phobic AN. Most importantly, subtype membership was stable over one year follow-up, with probabilities of remaining in the same class ranging from .68 to .88 from baseline to six months, and .87 to 1.0 from six months to 12 months. These findings converge with previous research documenting the short-term stability of empirically-derived ED classes (Peterson et al., 2011), and provide insight into the latent structure of disordered eating symptoms in underweight individuals.

The identification of a stable non-fat-phobic low-weight phenotype (i.e., AN-R-NFP) in a Western cultural setting is a novel finding of this study. Although two reports have shown that non-fat-phobic AN is stable during ED treatment (Carter & Bewell-Weiss, 2011; Dalle Grave et al., 2008), we are aware of no research that has examined the longer-term course of non-fat-phobic AN in a Western context. Notably, the current data suggest that membership in a non-fat-phobic underweight ED class is at least as stable over 12-month follow-up as membership in fat-phobic classes. Limited information about diagnostic stability was noted as one of the reasons that non-fat-phobic AN was excluded from *DSM-5* (Becker et al., 2009). Although our findings require replication, they provide initial evidence that non-fat-phobic AN is a stable phenotype and thus may have a place in future ED classification schemes.

An interesting pattern emerged with respect to the longitudinal association between the fat-phobic and non-fat-phobic AN-R classes. Of the participants who transitioned from one

latent class to another during follow-up ($n = 37$), more than half ($n = 20$) moved *from* AN-R-FP *to* AN-R-NFP. In contrast, only one participant transitioned from AN-R-NFP to AN-R-FP. One possible explanation for these findings is that for some underweight patients, non-fat-phobic AN represents an early stage in the remission of ED symptoms rather than a distinct subtype. This idea is intriguing in light of evidence that non-fat-phobic AN is associated with a more benign course and better outcome than fat-phobic AN (Lee, Chan, & Hsu, 2003; Strober, Freeman, & Morrell, 1999). Moreover, in the current study, the second most common pattern of latent transition was from AN-R-NFP to the zero class.

Alternatively, because fat phobia was assessed using a structured clinical interview that relies on participant self-report, it is possible that transition from AN-R-FP to AN-R-NFP is a demand characteristic of the treatment milieu. The idea that low-weight individuals who deny fat phobia may be lying or lack insight about fear of fatness (e.g., due to limited capacity for abstract reasoning or self-awareness) has been raised repeatedly in the EDs field (for review, see Thomas, Hartmann, & Killgore, 2013). Although this explanation may fit for some individuals, it is not consistent with historical accounts of AN (e.g., “holy anorexia;” Bell, 1985), and data from non-Western environments, which indicate that a low-weight ED phenotype exists even in cultures that do not emphasize a thin ideal (for review, see Keel & Klump, 2003). One promising direction for future research will be to incorporate more objective measures of fat phobia into ED assessments, in addition to self-reports. For example, Thomas et al. suggest the use of performance-based tasks (e.g., implicit association test, eye tracking) and neuroimaging to examine covert aspects of body image disturbance. Finally, it is important to emphasize that the majority of participants assigned empirically to the AN-R-NFP class at baseline remained in this group at six- and 12-month follow-ups, suggesting that a low-weight phenotype characterized by the absence of fat phobia has strong short-term stability. Additional work is needed to elucidate whether low-weight individuals who transition from fat-phobic to non-fat-phobic EDs differ from those with no history of fat phobia with respect to underlying mechanisms or clinical outcomes.

This study also contributes to knowledge about the characteristics of binge eating in underweight ED patients. Consistent with a recent descriptive study (Dalle Grave et al., 2012), we found strong support for the co-aggregation of objective and subjective binge episodes in individuals with AN. Moreover, both forms of binge eating distinguished the AN-BP-FP class from the AN-R-FP and AN-R-NFP groups. These findings converge with studies in normal-weight and overweight EDs, which have supported the validity of loss of control over eating, rather than amount of food consumed, as the core feature of binge eating (Wolfe et al., 2009). Finally, our results lend further support to the nosological distinction between ED patients who binge and/or purge and those who do not engage in these behaviors. Importantly, the current data suggest that there is little crossover between empirically-derived restricting and binge-eating/purging underweight classes over 12-month follow-up.

As a secondary aim, we examined predictors of latent class membership and transition to generate hypotheses about characteristics that might be linked to particular low-weight phenotypes. Several factors emerged as predictors of latent class membership, including lifetime mood and substance use disorder comorbidities, negative temperament, illness duration, and BMI at treatment presentation. Of note, although comorbid mood disorders, negative temperament, and longer duration of illness were associated with increased odds of membership in the AN-R-FP class relative to AN-R-NFP at various time points, lower baseline BMI was associated with increased odds of membership in the AN-R-NFP class versus AN-R-FP. Thus, AN-R-NFP was not merely a less severe manifestation of restricting AN. Indeed, the mean BMI in the AN-R-NFP group at baseline was 15.14 ($SD = 2.03$), which corresponds to “Severe” AN as defined by *DSM-5* (in comparison, the mean BMI in

the AN-R-FP group at baseline was 15.84 [SD = 1.72], and the mean BMI in the AN-BP-FP group at baseline was 15.80 [SD = 1.80]). Finally, lifetime mood disorder comorbidity was associated with an increased likelihood of membership in the AN-BP-FP class relative to AN-R-NFP at each time point, suggesting that mood disturbance may be a particularly important factor in distinguishing a fat-phobic low-weight phenotype characterized by binge eating and purging from non-fat-phobic EDs.

We identified three negative predictors of latent transition, namely, increased disinhibition (i.e., recklessness, impulsivity), history of overweight or obesity, and illness duration. The negative association between illness duration and latent transition is unsurprising given that diagnostic crossover typically occurs within the first seven years after AN onset (Anderluh et al., 2009). Thus, underweight ED patients with a longer duration of illness would be expected to exhibit greater phenotypic stability than those early in the course of the disorder. Similarly, the association between disinhibition and class stability is consistent with evidence that impulsive personality traits are related to symptom chronicity in AN (Fichter, Quadflieg, & Hedlund, 2006). Finally, underweight ED patients with a history of overweight or obesity may be less likely to experience symptom remission or transition to a non-fat-phobic class due to fear of returning to their premorbid weight.

Strengths of this study include the large sample of AN patients, prospective longitudinal design, use of well-studied assessment measures, and application of LTA to document the presence and stability of homogeneous low-weight phenotypes. Nevertheless, certain limitations should be considered when interpreting the findings. First, although the sample represents one of the largest studies to identify AN phenotypes empirically, it is somewhat smaller than recommended for LTA. Smaller sample sizes for LTA may engender sparseness, which can be associated estimation and convergence problems for complex models. To circumvent these issues, we reduced model complexity using standard procedures, e.g., by including only three time points and using logistic regression to identify predictors of class membership and transition (Collins & Lanza, 2010). Second, in an effort to facilitate comparison with previous research on non-fat-phobic EDs (Carter & Bewell-Weiss, 2011; Dalle Grave et al., 2008), we used an EDE score ≥ 4 as the threshold for clinically significant fear of fatness and overvaluation of shape or weight. However, we acknowledge that this cutoff is somewhat arbitrary and that individuals with subthreshold fat phobia may differ from those with no fat-phobia on important outcomes (Becker et al., 2009). Third, participants were recruited from inpatient and day hospital ED programs; thus, findings may not generalize to underweight individuals with less severe forms of eating disturbance, or those who do not seek treatment. Likewise, because the sample was primarily female and Caucasian, and inclusion criteria required that participants be aged ≥ 16 years, results may not apply to ethnic minorities, males, or younger adolescents with low-weight EDs. Finally, research over longer time intervals would be useful for further characterizing the long-term course and stability of identified AN phenotypes.

The current findings suggest several directions for future research that could inform models of AN etiology and maintenance, and efforts to develop novel systems of psychiatric classification. First, the identification of a stable non-fat-phobic low-weight phenotype lends support to recent calls for research focusing on mechanisms that differentiate fat-phobic and non-fat-phobic EDs (Thomas et al., 2013). Moreover, the current data suggest a need to elucidate processes involved in the expression of stable versus unstable non-fat-phobic ED phenotypes. Second, the present findings underscore the importance of studying mechanisms that are shared by (and distinguish) ED phenotypes characterized primarily by dietary restriction and those that involve binge eating and purging. For example, data from one study suggest that adolescents with AN-R differ from those with AN-BP and bulimia nervosa in neural correlates of inhibitory control (Lock, Garrett, Beenhakker, & Reiss,

2011). Similarly, we hypothesize that variations in the salience of two neurobiologically distinct facets of cognitive inflexibility – attentional set-shifting and reversal learning (Hampshire & Owen, 2006) – might help to explain phenotypic heterogeneity across AN-R, AN-BP, and bulimia nervosa (Wildes, Forbes, & Marcus, under review). Ultimately, research focusing on mechanisms associated with the expression of homogeneous low-weight phenotypes could inform efforts to group psychiatric disorders on the basis of shared biology, as exemplified by the RDoC initiative, and might lead to the identification of novel treatment targets for the development of subtype-specific interventions.

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Figure 1.

Mean item responses for best-fitting latent transition analysis model.

OBE=Objective binge episodes, SBE=Subjective binge episodes, Purge=Purging behavior, Fatphob=Fear of gaining weight or becoming 'fat,' and Overval=Overvaluation of weight or shape. LC1=Fat-phobic restricting; LC2=Fatphobic binge-eating/purging; LC3=Non-fat-phobic restricting; LC4="Zero" class.

Table 1

Latent Class Analysis Models

Model	Baseline	Six Month					12 Month					
	LL	AIC	BIC	aBIC	LL	AIC	BIC	aBIC	LL	AIC	BIC	aBIC
1c	-564.41	1138.81	1155.15	1139.31	-516.44	1042.89	1058.74	1042.90	-528.54	1067.07	1082.93	1067.09
2c	-532.80	1087.59	1123.54	1088.70	-463.38	948.75	983.63	948.79	-480.97	1001.95	1036.82	1001.99
3c	-518.39	1070.79	1126.34	1072.49	-453.90	941.81	995.71	941.87	-479.01	992.01	1045.91	992.07
4c	-515.31	1076.62	1151.78	1078.92	-446.74	939.48	1012.40	939.57	-473.39	992.79	1065.71	992.87
5c	-509.79	1077.58	1172.35	1080.48	-443.48	944.95	1036.90	945.06	-472.64	1003.29	1095.23	1003.40

Note. Bold font indicates lowest (best fitting) fit index. LL=log likelihood; AIC=Akaike's Information Criterion; BIC=Bayesian Information Criterion. aBIC=Sample Size Adjusted Bayesian Information Criterion.

All models were significant at $p<.001$.

Table 2

Latent Transition Analysis Models

Model	Constrained transition probabilities					Unconstrained transition probabilities				
	-LL	AIC	BIC	aBIC	Entropy	-LL	AIC	BIC	aBIC	Entropy
1c	-1621.24	3266.48	3305.70	3267.68	.966	--	--	--	--	--
2c	-1523.86	3087.73	3153.08	3089.73	.709	--	--	--	--	--
3c	-1492.75	3041.50	3133.00	3044.30	.651	-1356.37	2798.736	2939.254	2803.039	.878
4c	-1570.63	3213.27	3330.91	3216.87	.869	--	--	--	--	--

Note. Bold font indicates lowest (best fitting) fit index. LL=log likelihood; AIC=Akaike's Information Criterion; BIC=Bayesian Information Criterion. aBIC=Sample Size Adjusted Bayesian Information Criterion. Initial models constrained the transition probabilities between time points to be equal. After identifying the best-fitting constrained model, we compared this to an unconstrained latent transition analysis model that allowed transition probabilities to vary across time points. Models 2c–4c include an additional “zero-class” of recovered individuals who did not display current eating disorder psychopathology. Dashed lines are used to indicate models that were not applicable (not run).

Best fitting latent transition analysis model is in bold.

All models were significant at $p<.001$.

Table 3

Latent Class Transition Probability and Odds

<i>Transition probabilities</i>				
	AN-R-FP	AN-BP-FP	AN-R-NFP	Zero-Class
Transition from Baseline* (rows) to 6-month follow-up (columns)				
AN-R-FP	.677	.000	.253	.069
AN-BP-FP	.049	.876	.000	.072
AN-R-NFP	.042	.000	.855	.103
Transition from 6-month follow-up (rows) to 12-month follow-up (columns)				
AN-R-FP	.973	.000	.027	.000
AN-BP-FP	.000	1.00	.000	.000
AN-R-NFP	.054	.000	.872	.073

Note. Item-response probabilities are free to vary across time points. Bolded values indicate transition probabilities for membership in the same latent class at both time points (i.e., stability). AN-R-FP= fat-phobic restricting class (latent class 1); AN-BP-FP=fat-phobic binge-eating/purging class (latent class 2); AN-R-NFP =non-fat-phobic restricting class (latent class 3).

* The zero-class of recovered participants was not included at baseline, because all participants met criteria for anorexia nervosa at baseline.

Table 4

Patterns of Latent Transition for “Movers”

Transition Pattern	Frequency (<i>n</i>)	Percent
AN-R-FP and AN-BP-FP ^a	2	5.4
AN-R-FP and AN-R-NFP ^{a,b}	21	56.8
AN-BP-FP and AN-R-NFP ^a	2	5.4
AN-R-FP and Zero-Class	3	8.1
AN-R-NFP and Zero-Class	5	13.5
AN-R-FP, Zero-Class, and AN-R-NFP	3	8.1
AN-BP-FP, AN-R-NFP, and Zero-Class	1	2.7

Note. *N*=37 participants transitioned from one latent class to another from baseline to follow-up. Participants that remained in classes across all three follow-ups (*N*=157) are not reported in this table. AN-R-FP= fat-phobic restricting class (latent class 1); AN-BP-FP=fat-phobic binge-eating/purging class (latent class 2); AN-R-NFP =non-fat-phobic restricting class (latent class 3).

^a Participants transitioned from one class to another (e.g., from AN-R-FP to AN-BP-FP or from AN-BP-FP to AN-R-FP); other transition patterns are in the order listed in the table (e.g., from AN-R-FP to Zero-Class and from Zero-Class to AN-R-NFP).

^b The majority of participants transitioned from AN-R-FP into AN-R-NFP (*n*=20), with one participant transitioning from AN-R-NFP into AN-R-FP.

Table 5

Predictors of Membership in Baseline, 6-month, and 12-month Latent Class Analyses

Variables	Baseline			6-mo.			12 mo.		
	AN-R- FP	AN-BP- FP	AN-R- FP	AN-R- FP	AN-BP- FP	AN-R- FP	AN-R- FP	AN-BP- FP	AN-R- FP
<i>Lifetime mood disorder</i>									
β	1.36**	1.76**	.93	1.50*	1.39*	1.00	1.00	1.39*	
OR	3.91	5.84	2.54	4.50	4.00	2.68	2.68	4.00	
<i>Lifetime anxiety disorder</i>									
β	-.43	-.75	-.63	-1.00	-.75	-.28	-.28	-.75	
OR	.65	.48	.54	.37	.47	.76	.76	.47	
<i>Lifetime substance use disorder</i>									
β	.02	1.20	.30	1.42*	1.07	.02	.02	1.07	
OR	1.02	3.33	1.35	4.13	2.92	1.02	1.02	2.92	
<i>Negative Temperament</i>									
B	.08*	.06	.04	.06	.04	.03	.03	.04	
OR	1.08	1.06	1.04	1.06	1.04	1.03	1.03	1.04	
<i>Positive Temperament</i>									
B	.03	.01	.02	.00	-.01	.01	.01	-.01	
OR	1.03	1.01	1.02	1.00	.99	1.01	1.01	.99	
<i>Disinhibition vs. Constraint</i>									
β	-.01	.03	.01	.04	.05	.01	.01	.05	
OR	.99	1.03	1.01	1.04	1.05	1.01	1.01	1.05	
<i>History of overweight/obesity</i>									
β	.07	.20	-.37	-.14	-.49	-.65	-.65	-.49	
OR	1.08	1.23	.69	.87	.61	.52	.52	.61	
<i>Weight suppression</i>									
β	.08	.07	.04	.03	.02	.02	.02	.02	
OR	1.08	1.07	1.04	1.03	1.02	1.02	1.02	1.02	
<i>Duration of illness</i>									
β	.02	-.01	.08*	.04	.03	.06	.06	.03	

Variables	Baseline			6-mo.			12 mo.		
	AN-R-FP	AN-BP-FP	AN-R-FP	AN-R-FP	AN-BP-FP	AN-R-FP	AN-R-FP	AN-BP-FP	AN-R-FP
OR	1.02	.99	1.08	1.04	1.06	1.03			
<i>Length of current treatment</i>									
β	.02*	-.01	.01	-.02	.00	-.02			
OR	1.02	1.00	1.01	1.00	1.00	.98			
<i>Baseline body mass index</i>									
β	.38*	.31	.23	.33	.13	.23			
OR	1.46	1.36	1.26	1.40	1.14	1.26			
<i>Discharge at low body mass index</i>									
β	.38	.99	-.04	.79	-.18	.69			
OR	1.46	2.69	.96	2.20	.84	2.00			
<i>Any intensive treatment post-discharge</i>									
β	-.--	-.--	.91*	.29	.77	.25			
OR	-.--	-.--	2.50	1.33	2.15	1.28			

Note. AN-R-FP= fat-phobic restricting class (latent class 1); AN-BP-FP=fat-phobic binge-eating/purging class (latent class 2); AN-R-NFP =non-fat-phobic restricting class (latent class 3). AN-R-NFP was the reference class and is not reported.

* Significant at $p<.05$.

** Significant at $p<.01$. Post-discharge treatment was not included as a predictor of baseline class membership.

Table 6

Predictors of Latent Transition ("Movers")

Variable	β	S.E.	Wald	p-value	OR
Lifetime mood disorder	-.14	.55	.06	.80	.87
Lifetime anxiety disorder	.12	.51	.06	.81	1.13
Lifetime substance use disorder	-.09	.57	.03	.87	.91
Negative Temperament	-.01	.03	.15	.70	.99
Positive Temperament	.03	.02	1.73	.19	1.03
Disinhibition vs. Constraint	-.07	.03	5.84	.02	.93
History of overweight/obesity	-1.34	.65	4.26	.04	.26
Weight suppression	-.01	.03	.17	.70	.99
Duration of illness	-.09	.04	5.53	.02	.91
Length of current treatment	.00	.01	.11	.75	1.00
Baseline body mass index	.00	.15	.00	.98	1.00
Discharge at low body mass index	-.15	.53	.08	.78	.86
Any intensive treatment post-discharge	.73	.48	2.32	.13	2.07

Note. ORs associated with significant Wald tests ($p < .05$) are in bold face. The interpretation of results did not change when individuals who recovered at either 6- or 12-month follow-up were excluded from regression analyses.