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Eighteen-month Course and Outcome of Adolescent Restrictive Eating Disorders: Persistence, Crossover, and Recovery

Lauren Breithaupt^{a,b,*}, Danielle L. Kahn^{c*}, Meghan Slattery^c, Franziska Plessow^{b,c}, Christopher Mancuso^c, Alyssa Izquierdo^c, Melissa J. Dreier^a, Kendra Becker^{a,b}, Debra L. Franko^d, Jennifer J. Thomas^{b,a,b}, Laura Holsen^{b,e}, Elizabeth A. Lawson^{b,c,**}, Madhusmita Misra^{b,c,f,**}, and Kamryn T. Eddy^{b,a,b,**}

^aEating Disorders Clinical and Research Program, Massachusetts General Hospital; ^bDepartment of Psychiatry, Harvard Medical School; ^cNeuroendocrine Unit, Massachusetts General Hospital; ^dDepartment of Psychology, Northeastern University; ^eDivision of Women's Health, Brigham and Women's Hospital; ^fDivision of Pediatric Endocrinology, Massachusetts General Hospital

ABSTRACT

Objective: In adults, low-weight restrictive eating disorders, including anorexia nervosa (AN), are marked by chronicity and diagnostic crossover from restricting to binge-eating/purging. Less is known about the naturalistic course of these eating disorders in adolescents, particularly atypical AN (atyp-AN) and avoidant/restrictive food intake disorder (ARFID). To inform nosology of low-weight restrictive eating disorders in adolescents, we examined outcomes including persistence, crossover, and recovery in an 18-month observational study.

Method: We assessed 82 women (ages 10–23 years) with low-weight eating disorders including AN ($n = 40$; 29 restricting, 11 binge-eating/purging), atyp-AN ($n = 26$; 19 restricting, seven binge-eating/purging), and ARFID ($n = 16$) at baseline, nine months (9 M; 75% retention), and 18 months (18 M; 73% retention) via semi-structured interviews. First-order Markov modeling was used to determine diagnostic persistence, crossover, and recovery occurring at 9 M or 18 M.

Results: Among all diagnoses, the likelihood of remaining stable within a given diagnosis was greater than that of transitioning, with the greatest probability among ARFID (0.84) and AN-R (0.62). Persistence of BP and atypical presentations at follow-up periods was less stable (AN-BP probability 0.40; atyp-AN-R probability 0.48; atyp-AN-BP probability, 0.50). Crossover from binge-eating/purging to restricting occurred 72% of the time; crossover from restricting to binge-eating/purging occurred 23% of the time. The likelihood of stable recovery (e.g., recovery at both 9 M and 18 M) was between 0.00 and 0.36.

Conclusion: Across groups, intake diagnosis persisted in about two-thirds, and recovery was infrequent, underscoring the urgent need for innovative treatment approaches to these illnesses. Frequent crossover between AN and atyp-AN supports continuity between typical and atypical presentations, whereas no crossover to ARFID supports its distinction.

Introduction

Eating disorders marked by weight loss and restrictive eating, punctuated in some by binge-eating episodes and compensatory purging, modally onset in adolescence and often persist into adulthood (Galmiche et al., 2019; Mitchison et al., 2020). The adult eating disorders literature demonstrates that low-weight eating disorders are severe, with longitudinal data highlighting illness chronicity and protracted time to recovery, particularly in anorexia nervosa (AN; Eddy et al., 2017; Steinhausen, 2002, 2009). Few evidence-based treatments for low-weight eating disorders exist, although randomized controlled clinical trials of AN demonstrate that a subset of adolescents can have favorable outcomes in family based

treatment, with up to half achieving full recovery at 12-month follow-up (Lock et al., 2010). In practice, access to family based treatment in the community is limited (Lock & Le Grange, 2019) and little is known about the naturalistic course of adolescent AN. Among the few studies that report the naturalistic course of adolescent AN (e.g., Andrés-Pepiñá et al., 2020), single follow-up assessment occurs after decades, rather than years, reducing sensitivity to detect early course and outcomes. Furthermore, data describing the course and outcomes of the broader spectrum of low-weight eating disorders, including atypical AN (atyp-AN; Strand et al., 2020) and avoidant/restrictive food intake disorder (ARFID), are

CONTACT Lauren Breithaupt  lbreithaupt@mgm.harvard.edu  Eating Disorders Clinical and Research Program, Massachusetts General Hospital, 2 Longfellow Place, Suite 200, Boston, MA 02114

*Denotes shared first authorship

**Denotes shared senior authorship

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scarce, although these illnesses are as equally or more common than AN (Hay et al., 2017) and associated with similar restrictive eating-related sequelae (Aulinas et al., 2020).

The National Institute of Mental Health Research Domain Criteria (RDoC) initiative calls for transdiagnostic study of these illnesses to investigate cross-cutting candidate neurobiological mechanisms, which may underlie shared clinical features. In turn, findings may be used to inform treatment innovations and improve outcomes (Insel, 2010). DSM-5 (American Psychiatric Association [APA], 2013) defines AN by low weight and restrictive eating that is motivated by fear of weight gain; in approximately half of individuals with AN, restriction is accompanied by binge-eating and/or purging. Atyp-AN resembles AN, with similar clinical phenotypes and medical severity (i.e., Garber et al., 2019) but weight remains at or above the underweight category compared with the general population. Demarcation between AN and atyp-AN, and recognition of subtypes in atyp-AN have been identified as research priority areas (Strand et al., 2020). ARFID is defined by a restrictive and/or avoidant eating pattern, with or without low weight, but motivated instead by sensory sensitivity, fear of aversive consequences, or lack of interest in eating or food rather than fat phobia or body image disturbance. Boundaries between these eating disorders, which all share the common core feature of restrictive eating, are not clear (Becker et al., 2020).

Supporting transdiagnostic study, our own longitudinal data (Eddy, Swanson, et al., 2010; Eddy et al., 2002, 2008; Eddy, Le Grange, et al., 2010) and those of others (Milos et al., 2005; Schaumberg et al., 2019; Tozzi et al., 2005) have demonstrated the diagnostic instability of AN in adults – with frequent bidirectional crossover between the restricting and binge-eating/purging types – and crossover to bulimia nervosa. We have also demonstrated that weight fluctuates in adults with AN such that longitudinally, individuals can move in and out of meeting the low-weight AN criterion over time (Eddy, Swanson, et al., 2010). Fewer studies have described the course of atyp-AN in adolescents, but suggest that diagnostic instability and symptom fluctuation are especially common in those with subthreshold eating disorders (Andrés-Pepiñá et al., 2020; Garber et al., 2019; Nagl et al., 2016). Furthermore, as ARFID is a relatively new diagnosis, little is known about its naturalistic course and no published studies have examined illness course in adolescence. One study of children with ARFID found that the majority had a chronic course by age 11 (Lucarelli et al., 2018). Epidemiological studies suggest that childhood picky eating, which can overlap with ARFID, can give way AN over time (Herle et al., 2020; Jacobi et al., 2008; Marchi &

Cohen, 1990), and symptom overlap between ARFID and atyp-AN has been described in case reports (Becker et al., 2020). Still, the marked clinical differences in the motivation for restriction in AN and atyp-AN, relative to ARFID, challenge the ready acceptance of a common underlying process or development of a universal treatment for these illnesses. Longitudinal description of course and outcomes could support application of the RDoC initiative to low-weight eating disorders or help to delineate boundaries between these diagnoses.

To inform the nosological conceptualization of low-weight eating disorders, we examined the naturalistic course of AN, atyp-AN, and ARFID in adolescence. We described outcomes including: (1) persistence of initial diagnosis; (2) diagnostic crossover; and (3) eating disorder recovery over 18-months of follow-up (measured at nine months and 18 months). To capture the dynamic and fluctuating course of adolescent eating disorders, we allowed multiple outcomes within an individual, such that individuals could demonstrate both crossover and recovery within the study period. We build on previous research by our group (Eddy et al., 2008; Eddy, Swanson, et al., 2010) that demonstrates that adults with eating disorders will, at times, remain symptomatic but no longer meet full criteria by characterizing specific presentations considered to be subthreshold for AN-R and AN-BP (atypical AN restricting subtype [atyp-AN-R] and binge/purge subtype [atyp-AN-BP]) in adolescents. We hypothesized that (1) eating disorders would be persistent, as evident by sustained presentation of eating disorder diagnosis; (2) subthreshold presentations experienced would be symptomatically similar to the initial diagnosis (e.g., AN-R and atyp-AN-R); and (3) that fewer than one-half of participants would recover during follow-up. If our hypotheses were borne out, these data would support transdiagnostic study of low-weight eating disorders, guiding research into cross-cutting mechanisms underlying restrictive eating and consequent low weight.

Method

Participants

Eighty-two adolescent and young adult women (ages 10–23 years; mean age 18.3 years $\pm$ 3.2 years) with low-weight eating disorders were recruited from New England through advertisements, flyers, and health-care providers, outpatient practices, and higher level of care programs to participate in a longitudinal observational study of the neurobiology of low-weight eating disorders (R01MH103402). Most of the sample identified as white (83%; $n = 68$) and

were non-Hispanic (93%; $n = 76$). Participants were cisgender females at study entry; one identified as transgender at nine-month follow-up. Eligibility criteria included: (1) current low-weight defined as $\leq 90\%$ of median expected body weight (50th percentile body mass index [BMI: $\text{weight (kg)}/\text{height(m)}^2$] for age and gender); and (2) a DSM-5 diagnosis of AN, atyp-AN, or ARFID. Exclusion criteria included use of systemic hormones, pregnancy or breastfeeding within eight weeks, history of psychosis, active substance abuse, active suicidal ideation, hematocrit less than 30%, potassium level less than 3 mmol/L, history of gastrointestinal tract surgery or other conditions that could lead to low weight (e.g., neoplasia, diabetes mellitus).

Table 1 depicts baseline characteristics of the sample, including treatment status and level of care. Baseline clinical characteristics for a subset of participants were previously reported (Aulinas et al., 2020; Aulinas, Plessow et al., 2019; Aulinas, Pulumo et al., 2019; Becker et al., 2021; Breithaupt et al., 2020), but no data for longitudinal course or outcomes of this sample have been published.

Procedures

This study was approved by the Mass General Brigham (MGB) Human Research Committee. Following informed consent/assent, participants were screened for study inclusion, followed by baseline, nine- and 18-month (9 M, 18 M) visits. The following were completed at study visits: (1) medical history and physical examination with a research nurse practitioner or MD, including height (measured on a wall-mounted stadiometer in triplicate) and weight (measured on an electronic scale) to calculate BMI; and (2) Eating Disorder Examination 17.0 (EDE; Fairburn et al., 2008) and the longitudinal interval follow-up evaluation, third edition eating disorders version (LIFE-EAT-3) to assess eating disorder symptom diagnostic presentations. Note that for a subset of participants who declined to complete longitudinal interview measures, their eating disorder diagnosis, behaviors (including type and frequency), and clinician reported height/weight, were extracted via medical record review ($n = 3$ at 9 M and $n = 8$ at 18 M).

Measures

Height and weight measurements were used to calculate BMI, percent median BMI, and percent expected body weight for age and height. Percent median BMI and percent of expected body weight were determined using the growth charts available from the Centers for

Disease Control and Prevention (CDC) and 20 years was used as the reference age for any participant older than 20 years (as the CDC charts only go to 20 years).

The EDE (Fairburn et al., 2008) was used to assess the severity of eating disorder psychopathology and frequency of eating disorder behaviors including binge eating, purging, and other compensatory behaviors. Inter-rater reliability for a random subset of the sample was excellent ($\kappa = 1.0$ (Wang et al., 2019)).

The LIFE-EAT-3 was used to assess eating disorder course and psychosocial functioning on a weekly basis over time administered at baseline and throughout the follow-up period. The LIFE-EAT-3 was modified from the LIFE II (Keller et al., 1987) to include assessment of ARFID. The core measurement, the psychiatric status rating (PSR), assessed the course of eating disorder symptoms on a weekly basis on a scale from “1” to “6” where “1” and “2” indicate no/minimal symptoms, “3” or “4” indicate moderate symptoms, and “5” or “6” indicate severe symptoms (Spitzer et al., 1978). Inter-rater reliability for PSR scores ranged from adequate to excellent ($\kappa = 0.64\text{--}0.91$).

Treatment status was self-reported by subjects, and organized by level, of care using the American Psychiatric Association Level of Care Guidelines for Patients with eating disorders, which included: outpatient, intensive outpatient, partial hospitalization/full-day program, or residential treatment (Kaufman et al., 2013). Of note, we allowed outpatient treatment to be defined by the subject and included a variety of therapy modalities (i.e., CBT-E, FBT, hypnotherapy, psychodynamic therapy, group therapy, vital/weight checks by a medical provider), delivered by a variety of providers (i.e., Ph.D. level psychologists, masters level therapists, dietitians, psychiatrists, school counselors), with varying frequencies (i.e., once per week, bi-weekly, monthly).

Diagnoses: Symptom Presentation Profiles

Diagnostic criteria were evaluated at baseline, 9 M, and 18 M using height and weight, and relevant information gathered during EDE and LIFE-EAT-3 interviews to create the five presentation types listed in Table 2. At baseline, participants were classified with the following presentation profiles: 40 with AN (restricting type [AN-R], $n = 29$; binge-eating/purging type [AN-BP], $n = 11$), 26 with atyp-AN (restricting presentation [atyp-AN-R], $n = 19$; binge-eating/purge type presentation [atyp-AN-BP], $n = 7$), and 16 with ARFID. Diagnoses were reevaluated at 9 M and 18 M based on symptom presentations over the preceding three months, consistent with DSM-5 criteria. (Note that by study entry criteria, all of these

Table 1. Baseline characteristics of the full sample by diagnostic group.

	AN-R (N = 29)	AN-BP (N = 11)	atyp-AN-R (N = 19)	atyp-AN-BP (N = 7)	ARFID (N = 16)
Age	19.5 (2.3)	21.6 (1.3)	19.9 (3.0)	20.1 (1.3)	15.3 (4.9)
Mean (SD)	11.9–22.3	18.8–22.5	11.8–22.1	15.7–21.9	10.1–21.8
Range					
Race	3 (10%)	4 (36%)	0	2 (29%)	2 (13%)
Asian	1 (3%)	0	0	0	1 (6%)
Other	25 (86%)	7 (64%)	19 (100%)	5 (71%)	13 (81%)
White					
Ethnicity	2 (7%)	2 (29%)	0	0	2 (2%)
Hispanic/Latino	27 (93%)	9 (82%)	0	0	14 (17%)
Non-Hispanic/Latino					
BMI Percentile	4.2 (4.4)		16.4 (8.2)	23.9 (8.9)	8.8 (5.9)
(for <18 y)	10.3		25.4	12.6	19.7
Mean (SD)	0.1–10.4		11.7–37.1	17.6–30.2	0.1–19.8
Range					
BMI (for >18 years)	16.62 (1.3)	17.27 (1.5)	18.89 (0.3)	19.11 (0.7)	15.63 (3.7)
Mean (SD)	14.3–18.4	16.23–18.3	16.1–20.9	18.0–19.7	13.0–18.3
Range					
Duration of Illness (years)	5.6 (5.2)	9.1 (0.6)	5.4 (6.5)	7.6 (9.1)	1.3 (0.7)
Mean (SD)	0.8–13.3	0.5–9.5	0.8–10.0	0.9–14.1	0.7–12.5
Range (self-report)					
Psychiatric Medication Use at Baseline, N (%)	16 (55%)	6 (55%)	11 (58%)	5 (71%)	12 (75%)
Antianxiety	3 (10%)	2 (18%)	6 (32%)	3 (43%)	4 (25%)
Antidepressants	12 (41%)	5 (45%)	5 (26%)	3 (43%)	5 (31%)
Antiobsessive	1 (3%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Stimulants	2 (7%)	1 (9%)	0 (0%)	0 (0%)	2 (13%)
Mood Stabilizers	0 (0%)	1 (9%)	0 (0%)	1 (14%)	0 (0%)
Other	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (6%)
Level of Care of Treatment at Baseline, N (%)					
Outpatient	17 (59%)	3 (27%)	11 (58%)	1 (14%)	10 (63%)
Intensive Outpatient	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (6%)
Partial Hospitalization (Full-day Outpatient care)	1 (3%)	0 (0%)	2 (11%)	0 (0%)	0 (0%)
Residential Treatment	5 (17%)	3 (27%)	5 (26%)	3 (43%)	0 (0%)
No treatment	6 (21%)	5 (45%)	0 (0%)	3 (43%)	5 (31%)

individuals were $\leq 90\%$ of expected body weight and thus even when binge-eating/purging was present it was in the context of restrictive eating.)

Defining Recovery, Illness, Persistence, or Crossover

We examined the following outcomes: (i) illness persistence, maintenance of baseline diagnosis at one or two follow-up assessment visits; (ii) crossover, meeting criteria for an eating disorder at 9 M or 18 M follow-up that differed from the baseline diagnosis; and (iii) recovery, defined as a LIFE-EAT-3 PSR score of 1 or 2, indicating absent or minimal/residual symptoms and no functional impairment due to eating disorder cognitions and/or behaviors.

Statistical Analyses

Statistical analyses of the outcomes (presentation persistence, presentation crossover, and recovery) were completed in R (R Development Core Team, 2021) with all participants with follow-up data available at 9-M and/or 18-M follow-up. Frequencies of outcomes were compared to baseline diagnosis. Follow-up data at one or both time points were available for 85% (70/82) of the

sample, thus this represented the full sample denominator; follow-up data were available for 75% of the sample at 9 M and 73% of the sample at 18 M. By baseline diagnosis, follow-up data at one or both time points were available for 90% (36/40) of those with AN (AN-R, 93% [27/29]; AN-BP, 82% [9/11]), 77% (20/26) of those with atyp-AN (atyp-AN-R, 79% [15/19]; atyp-AN-BP, 71% [5/7]), and 87.5% (14/16) of those with ARFID. These frequencies are supplemented by figures depicting the patterns of diagnosis in the sample to aid in the interpretation of transitions. As individuals could contribute data at multiple timepoints (i.e., 9 M and 18 M), multiple outcomes per person could be reported (e.g., crossover at 9 M and recovery at 18 M) to describe the fluctuating and dynamic course of each participant.

We used first-order Markov modeling to estimate the persistence, crossover, and recovery probability between outcomes for any follow-up (9 M and/or 18 M) by intake diagnosis. This modeling assumes that the probability of transitioning is a stationary process and has been used in prior work to model persistence, crossover, and recovery in eating disorder populations (e.g., Eddy et al., 2007; Peterson et al., 2012). Markov modeling allows individuals to change between states over time, while holding the necessary information from the prior history (Wohlin

Table 2. Symptom presentation profiles.

Presentation	Criteria
AN	• AN criterion by EDE/LIFE-EAT-3 • BMI percentile of ≤ 10 for adolescents or BMI was ≤ 18.5 for adults • LIFE-EAT PSR score ≥ 3 (indicating moderate symptoms) for the previous three months
AN-R	Binge eating and/or purging occurred < 3 times per month for the preceding three months
AN-BP	Binge eating and/or purging occurred ≥ 3 times per month over the previous three months
atyp-AN	• AN criterion by EDE/LIFE-EAT-3 • BMI percentile > 10 if < 18 years old, or had BMI > 18.5 if ≥ 18 years old • LIFE-EAT-3 PSR score ≥ 3 for the previous three months
atyp-AN-R	Binge eating and/or purging occurred < 3 times per month for the preceding three months
atyp-AN-BP	Binge eating and/or purging occurred ≥ 3 times per month over the previous three months
ARFID	• ARFID criteria by EDE/LIFE-EAT-3 • Restricting intake due to sensory sensitivity, fear of aversive consequences, or lack of interest in eating or food and not for weight and shape reasons • Denied binge eating and/or purging • LIFE-EAT PSR score ≥ 3 for the previous three months

AN, anorexia nervosa; AN-R, anorexia nervosa restricting subtype; AN-BP, anorexia nervosa binge/purge subtype; atyp-AN, atypical anorexia nervosa; atyp-AN-R, atypical anorexia nervosa restricting subtype; atyp-AN-BP, atypical anorexia nervosa binge/purge subtype; ARFID, avoidant restrictive food intake disorder

et al., 2003). Probabilities are assigned to the transitions and represent the expected outcomes (i.e., diagnostic category or recovery) in terms of relative frequencies. The benefit of Markov models, for this particular aim, is that the model is completely general and the generated sequences look like a sample of the real outcomes because it captures the past and future behaviors.

Results

Figure 1 depicts the longitudinal diagnostic descriptive outcomes and recovery from baseline to 9-M and 18-M follow-up in the full sample by intake diagnosis. Each row represents the course of a single individual participant at each timepoint. At study entry, 51% of participants were receiving outpatient care (ranges from 14%–63%). Twenty-three percent of the sample reported no treatment involvement, with individuals reporting binge/purge symptoms reporting the highest rates of no treatment (AN-BP: 45%; atyp-AN-BP: 43%).

Persistence of Baseline Diagnosis

Transition analyses demonstrated that, during any nine-month period of follow-up (e.g., baseline to 9 M or 9 M to 18 M), the likelihood of remaining stable within a given diagnosis was greater than that of transitioning (Table 3). This was particularly true for individuals with ARFID and AN-R. The probability of continuing to meet ARFID diagnostic criteria at all follow-up periods was 0.84. The probability of continuing to meet AN-R diagnostic criteria at all follow-up periods was 0.62. The persistence of BP and atypical presentations at all follow-up periods was less stable (AN-BP probability 0.40; atyp-AN-R probability 0.48; atyp-AN-BP probability, 0.50).

Symptom Crossover

Transitions from typical to atypical presentations were more likely to occur among restricting subtypes (Table 3). The likelihood of crossover from baseline binge-eating/purging (AN-BP/atyp-AN-BP) presentations to restricting presentations (AN-R/atyp-AN-R) at 9 M or 18 M was more probable than the transition from restricting presentations (AN-R/atyp-AN-R) to binge-eating/purging (AN-BP/atyp-AN-BP) presentations. Crossover from binge-eating/purging to restricting occurred 72% of the time; crossover from restricting to binge-eating/purging occurred 23% of the time.

Recovery

Transition analyses demonstrated that, during any nine-month period of follow-up, recovery was unlikely (Table 3). A fluctuating course (e.g., transition from recovery at 9 M to eating disorder symptoms at 18 M) was most likely among individuals with a baseline diagnosis of atyp-AN-BP and atyp-AN-R symptoms at 18 M (0.50) or atyp-AN-BP symptoms at 18 M (0.50). Persistence in recovery was unlikely across all individuals (AN-R, 0.08; AN-BP, 0.00; atyp-AN-R, 0.24; atyp-AN-BP, 0.33; ARFID, 0.36). Of the 11 individuals who recovered during any nine-month period of follow-up, 81% were in outpatient treatment (AN-R, $n = 3$; atyp-AN-R, $n = 3$; ARFID, $n = 3$). One individual with a baseline diagnosis of AN-BP recovered without any treatment during the study period.

Conclusion

The 18-month naturalistic course of adolescent and young adult restrictive low-weight eating disorders is grim. In this heterogeneous sample of individuals recruited through

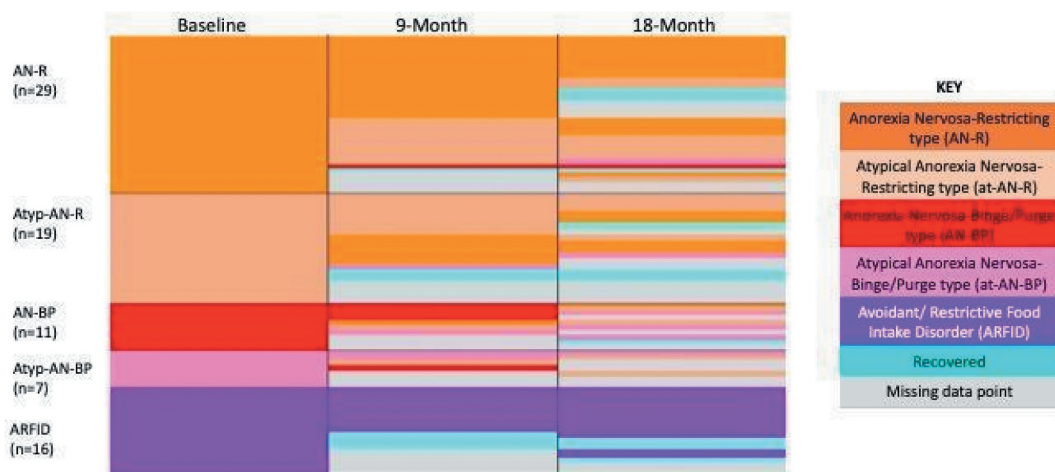


Figure 1. Longitudinal course at nine- and 18-month follow-up by intake diagnosis.

Table 3. Transition matrix: probability of transitioning during any nine-month interval for initial diagnosis AN-R, AN-BP, atyp-AN-R, atyp-AN-BP, ARFID.

Time 2 (18 M)						
Time 1 (9 M)	AN-R	AN-BP	atyp-AN-R	atyp-AN-BP	ARFID	REC
AN-R	0.62 /0.13/0.37/0.00/ 0.00	0.41/0.13/0.26/0.00/ 0.00	0.46/0.25/0.32/0.00/ 0.00	0.41/0.13/0.32/0.00/ 0.00	0.41/0.13/0.26/0.00/ 0.00	0.46/0.13/0.26/0.00/ 0.00
AN-BP	0.04/0.50/0.13/0.25/ 0.00	0.08/ 0.40 /0.00/0.25/ 0.00	0.04/0.50/0.00/0.25/ 0.00	0.04/0.50/0.00/0.25/ 0.00	0.04/0.40/0.00/0.25/ 0.00	0.04/0.40/0.00/0.25/ 0.00
atyp-AN-R	0.33/0.13/0.43/0.25/ 0.00	0.24/0.13/0.33/0.25/ 0.00	0.36/0.13/ 0.48 /0.25/ 0.00	0.27/0.25/0.33/0.25/ 0.00	0.24/0.13/0.33/0.25/ 0.00	0.24/0.13/0.38/0.25/ 0.00
atyp-AN-BP	0.00/0.14/0.07/0.33/ 0.00	0.00/0.14/0.07/0.33/ 0.00	0.00/0.00/0.07/0.50/ 0.00	0.00/0.14/0.07/ 0.50 / 0.00	0.00/0.14/0.07/0.33/ 0.00	0.00/0.14/0.07/0.33/ 0.00
ARFID	0.00/0.00/0.00/0.00/ 0.42	0.00/0.00/0.00/0.00/ 0.42	0.00/0.00/0.00/0.00/ 0.42	0.00/0.00/0.00/0.00/ 0.42	0.00/0.00/0.00/0.00/ 0.84	0.00/0.00/0.00/0.00/ 0.42
REC	0.04/0.00/0.12/0.33/ 0.21	0.04/0.00/0.12/0.33/ 0.21	0.04/0.00/0.12/0.50/ 0.21	0.04/0.00/0.12/0.50/ 0.21	0.04/0.00/0.12/0.33/ 0.29	0.08/0.00/0.24/0.33/ 0.36

Cell entries represent the estimated probability of transitioning from Time 1 diagnosis to Time 2 diagnosis within any interval for patients with an initial diagnosis of AN-R/AN-BP/atyp-AN-R/atyp-AN-BP/ARFID, respectively. Persistence of diagnosis is represented in bold.

AN-R, anorexia nervosa (AN) restricting (R) type; AN-BP, AN binge/purge (BP) type; atyp-AN-R, atypical AN-R; atyp-AN-BP, atypical AN-BP; ARFID, avoidant restrictive food intake disorder; 9 M, 9 months; 18 M, 18 months.

clinical and community-based streams, persistence of an eating disorder was the norm, whereas progression to full recovery was uncommon. The likelihood of stable recovery (i.e., recovery at both 9 M and 18 M) of the entire sample was between 0.00 and 0.36. Our data demonstrate that the 18-month course of adolescent AN and atyp-AN differs from that of ARFID. While persistent illness occurred across the three conditions, in line with our hypothesis, adolescents with AN or atyp-AN experienced fluctuating or changing symptoms such that they met criteria for AN or atyp-AN over time. By contrast, there was no movement to or from ARFID over the follow-up period. While our baseline ARFID sample was smaller than the other eating disorders, the longitudinal separation of ARFID from AN or atyp-AN in this low-weight adolescent sample supports its diagnostic distinction and suggests that unique mechanisms may drive persistent restriction in AN and atyp-AN relative to ARFID.

Similar to the adult literature in AN (e.g., Eddy et al., 2017; Steinhausen, 2002, 2009), these naturalistic data underscore the severity of low-weight restrictive eating disorders in adolescents and young adults. Very little research has been conducted on the naturalistic course of atyp-AN and ARFID. Our results suggest that both individuals with atyp-AN and those with ARFID have a protracted course of illness over 18 months that is similar to that of AN. The reported rates of recovery across the sample was higher than treatment-seeking adults with AN in that window (Herzog et al., 1999) and lower than that observed in adolescent randomized controlled treatment trials of AN (e.g., Lock et al., 2010). In AN and atyp-AN, the low rates of recovery in our study may be related to the duration of illness prior to study entry and heterogeneity of treatment status (e.g., some individuals were in treatment while others were not). Of note, 51% of our sample were engaged in outpatient

treatment at study entry, which could have included evidence-based treatments (i.e., FBT, CBT-E, CBT-AR) and team approaches (i.e., therapist and dietitian); 23% of our sample were not receiving any type of treatment at study entry. Individuals with AN and atyp-AN reported a duration of illness of over five years prior to the start of the study, which is longer than the duration of illness seen in most adolescent randomized controlled clinical trials of AN (e.g., Lock et al., 2010). This discrepancy may highlight the illness severity in our sample and contextualize the relatively poor outcomes, but also serves as a frank mirror of the naturalistic course of illness in a mixed sample. While the argument for early intervention in adolescence is frequently made, our data suggest that intervention may need to be even earlier, as for many, the illness will already be entrenched by adolescence. For ARFID, we were struck by a relatively short reported duration of illness (1.3 years) which may reflect either the recent formal inclusion of ARFID in DSM-5 or the difficulties inherent in recognizing an eating disorder in the context of an often long-standing low weight in this patient group (e.g., Nicely et al., 2014).

As hypothesized, our data demonstrated frequent bidirectional diagnostic crossover between AN and atyp-AN, reflecting weight gain or loss. As we and others have suggested previously (e.g., Agras et al., 2009; Eddy, Swanson, et al., 2010), these longitudinal fluctuations are suggestive of a single disorder with a course that can include longitudinal symptom variation, rather than separate illnesses. Notably, we did not find that transition to recovery in AN was preceded by an atyp-AN presentation, belying the notion that atyp-AN represents an intermediate or less severe presentation. While it is possible that for some with AN, an atyp-AN presentation is an improved state – marked by weight gain, for example – the eating disorder cognitions persist in atyp-AN and these are often associated with equally intense impairment and distress (Thomas et al., 2009). Crossover between the restricting and binge-eating/purging subtypes of AN and atyp-AN was common for those with initial binge-eating/purging presentations, but occurred less frequently from the restricting to binge-eating/purging subtypes of AN or atyp-AN than we have observed in adults with AN-R (e.g., Eddy et al., 2008). It may be that our follow-up window was too short to observe restricting to binge-eating/purging type crossover in adolescence.

To our knowledge, this is the first naturalistic longitudinal study examining the course and outcome of ARFID in comparison with AN and atyp-AN. While recovery outcomes were similar, crossover between ARFID and AN or atyp-AN was absent over follow-up, in contrast to our hypothesis. Although longitudinal

epidemiological studies have suggested that picky eating in young children may lead to AN in adolescents (Herle et al., 2020), this crossover may not occur in adolescents with ARFID, or perhaps a longer follow-up and larger sample size is needed to observe such trajectories. Becker et al., (2020) have suggested that weight and shape concerns or fear of weight gain can emerge in individuals with ARFID during the process of weight gain. Although some individuals with ARFID may not have identified a fear of weight gain at initial clinical intake, as weight restoration occurs over treatment (Becker et al., 2020), some characterized this physical change as challenging their identity (e.g., as a thin person) which may promote emergence of fat phobia. Further research – particularly including larger longitudinal clinical cohorts – may be helpful to inform when and in whom crossover among those with ARFID is most likely to occur, if at all.

Study strengths include the longitudinal naturalistic examination of a heterogeneous adolescent sample over multiple timepoints with a range of low-weight eating disorders and the use of well-validated semi-structured clinical interviews. Use of comprehensive interviews yielded rich phenotyping data allowed us to set a strict threshold for full recovery, encompassing both physical and psychological symptom resolution. Our definition of recovery is consistent with expert recommendations (e.g., Bardone-Cone et al., 2018; Richmond et al., 2020) and reflects our clinical expectation that individuals with eating disorders can fully recover, albeit over a longer period of time. We elected to present the data descriptively to take full advantage of the rich data available, multiple points of assessment, and to capture the dynamic and fluctuating course of illness. Limitations also warrant acknowledgment. Although every effort was made to retain participants over time, a subset of participants in each group declined to complete follow-up interviews. Furthermore, the majority of the sample was receiving treatment at study entry, which, while increasing external validity with regard to application to clinical samples, may also represent a more ill sample (e.g., Berkson's bias) that differs from community-based cohorts (Ziobrowski et al., 2019). Additional limitations included the small overall sample size, with few individuals reporting binge-eating/purging; the small ARFID sample; and the exclusively female sample. Furthermore, as these participants were recruited through an NIH-funded study of low-weight eating disorders, our findings cannot generalize to the full weight spectrum of individuals with atyp-AN or ARFID. The sample size did not permit inclusion of clinical characteristics that may influence diagnostic crossover (i.e., duration of illness) or recovery (i.e., type of treatment) and thus, we

have presented these findings descriptively. Finally, the majority of our sample identified as non-Hispanic white, limiting the generalizability of these findings. Eating disorders are prevalent among people who come from marginalized racial, ethnic, and socioeconomic backgrounds, and evidence shows that unique risk factors may be at play for these populations (Distel et al., n.d.; Egbert et al., 2020; Goel et al., 2020; Gordon et al., 2010; Monterubio et al., 2020).

Taken together, our findings highlight the severity of low-weight eating disorders and the likelihood that even in adolescents these illnesses can be protracted in course. Data from clinical trials demonstrate that a subset of individuals with low-weight eating disorders do well in treatment (e.g., Lock et al., 2010), and the longitudinal outcomes across decades likewise demonstrate that favorable outcomes occur in the long-term (e.g., Eddy et al., 2017). Nonetheless, the relatively low rates of recovery across these low-weight eating disorders should be used to compel the innovative study of trans-diagnostic – as well as unique – mechanisms that can be targeted in order to improve (and expedite favorable) outcomes. AN and atyp-AN have an often-overlapping course suggestive of a shared underlying illness, while no crossover with ARFID prompts questions about non-shared underpinnings. While recent data support the use of elements such as the promotion of regularized eating, focus on early weight gain, and family involvement in treatment as active ingredients for all psychological treatments across the low-weight eating disorders (Lock et al., 2019; Thomas & Eddy, 2018), more research is needed to clarify for whom these interventions do and do not work, and why. Neurobiological study of shared and divergent mechanisms of illness course across low-weight eating disorders may hold clues as we move forward.

Disclosure Statement

Dr. Breithaupt is currently a consultant for HealthiVibe. Dr. Misra is a consultant for Sanofi and Abbvie, and has served on the scientific advisory board of Abbvie and Ipsen. Dr. Lawson is on the scientific advisory board and has a financial interest in OXT Therapeutics, a company developing oxytocin-based therapeutics for treatment of obesity and metabolic disease. Drs. Lawson and Misra received royalties from UpToDate. Drs. Thomas, Eddy, and Becker receive royalties from Cambridge University Press for the sale of their books. The interests of all authors employed at Massachusetts General Hospital were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict-of-interest policies.

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Presentation Information

Preliminary findings from this study were presented as a virtual poster presentation at the MGH Clinical Research Day (October 2020) and Eating Disorders Research Society annual meeting (October 2020).

ORCID

Lauren Breithaupt  <http://orcid.org/0000-0002-2439-6519>
Jennifer J. Thomas  <http://orcid.org/0000-0003-2601-581X>
Laura Holsen  <http://orcid.org/0000-0003-1292-7789>
Elizabeth A. Lawson  <http://orcid.org/0000-0001-8619-3349>
Kamryn T. Eddy  <http://orcid.org/0000-0002-1586-0930>

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