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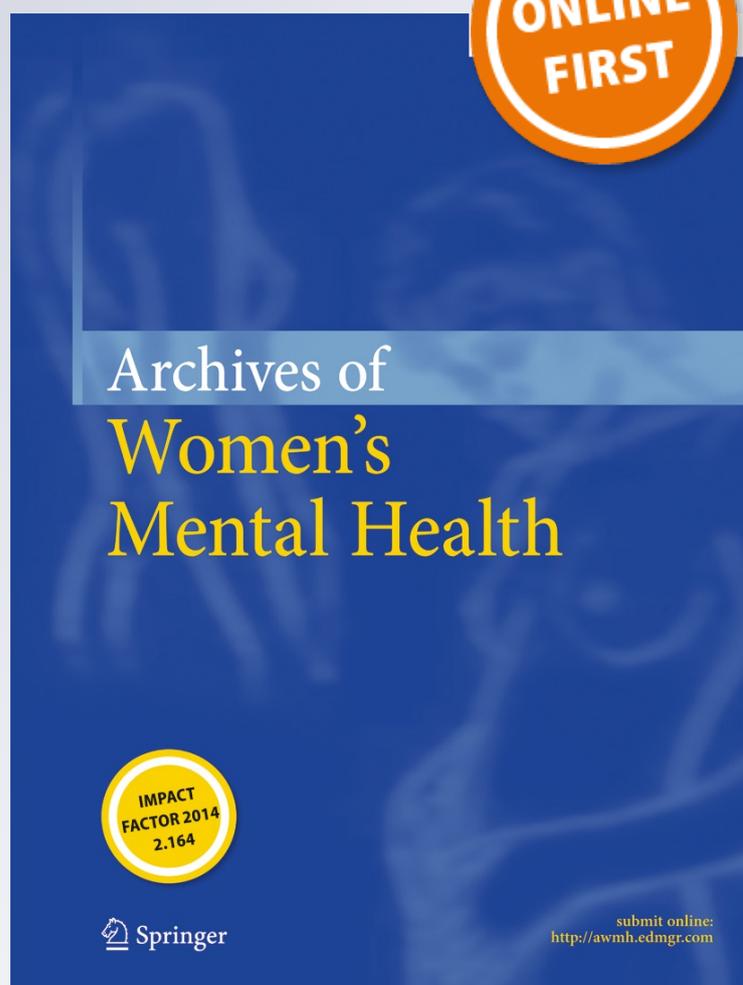
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Associations between eating disorder diagnoses, behaviors, and menstrual dysfunction in a clinical sample

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Abstract We explored associations between lifetime eating disorder (ED) diagnoses and behaviors and menstrual dysfunction using logistic regression models. Body mass index (BMI) fully explained differences in the odds of secondary amenorrhea (SA) across diagnoses. Women with dieting behaviors had borderline significantly higher odds of SA than those without after accounting for BMI. We suggest the presence of a strong association between BMI and SA and that dieting might represent a risk factor for SA regardless of BMI and ED diagnosis.

Keywords Eating disorders · Amenorrhea · Menstrual dysfunctions · Body mass index · Dieting

Menstrual dysfunction (MD) is frequent in women with eating disorders (ED) and particularly in women with anorexia

nervosa (AN) (Algars et al. 2014). Although no longer a diagnostic criterion for the latter in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM5), amenorrhea is one of its most common physical correlates (Algars et al. 2014). An increasing body of literature (Poyastro Pinheiro et al. 2007) has shown that amenorrhea and oligomenorrhea can also occur in women with bulimia nervosa (BN). In this group, however, evidence is inconsistent, with studies showing a prevalence of secondary amenorrhea in 7–40 % and of oligomenorrhea in 37–64 % of cases (Poyastro Pinheiro et al. 2007; Gendall et al. 2000). Although the literature suggests that malnutrition-related impairments in the hypothalamic-pituitary-ovarian axis and polycystic ovary syndrome (PCOS) could be risk factors for developing secondary amenorrhea in women with AN and BN, respectively (Vyver et al. 2008), evidence is still inconclusive with respect to both its prevalence across diagnoses and risk factors/mechanisms.

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ED behaviors such as binge eating, purging, dieting, and excessive exercising have also been associated with MD independent of ED diagnoses (Poyastro Pinheiro et al. 2007; Austin et al. 2008; Gendall et al. 2000). Energy intake fluctuations typical of binge eating could affect insulin resistance, whereas raised insulin secretion and opioid and dopamine release resulting from purging behaviors could cause impairments of menstrual function (Tortorella et al. 2014). Although impairments in gonadotropin secretion following weight loss, often associated with dieting and exercising (Montero et al. 1996; Mendelsohn and Warren 2010), have been implicated in the onset of MD, evidence on the role of low body mass index (BMI), often associated with these behaviors, in causing menstrual irregularities is contradicting (Vyver et al. 2008). Some studies suggest that low BMI is the only predictor of MD in women with ED (Dalle Grave et al. 2008). Others, however, have shown that amenorrhea often precedes weight loss and persists after weight recovery (Brambilla et al. 2003) or is independent from weight loss (Gendall et al. 2000) suggesting that other factors, such as neuroendocrine and psychological aspects (i.e., the persistence of anorexia-related symptoms such as body dissatisfaction), could be involved in the pathogenesis of amenorrhea (Brambilla et al. 2003).

Considering the scarcity of research in this area, we aimed to investigate the following: the association between MD (i.e., primary and secondary amenorrhea) and (a) AN [AN-restrictive (AN-R) and AN-binge purging (AN-BP)] and BN and (b) ED behaviors, such as dieting, binge eating, purging, and excessive exercising in a clinical ED sample (irrespective of diagnosis). Moreover, we explored the role of lowest ever BMI as a mediator of the association between ED and MD.

Methods

Sample

A total of 320 ED patients were recruited from secondary and tertiary services and self-help groups in four European countries (UK, Austria, Spain, Slovenia) as part of a multicenter study (Krug et al. 2012). Ethics committees of all participating organizations approved the study, and women gave their informed consent.

Measures

All variables were obtained through the EATATE diagnostic interview (Anderluh 2003), a purposely designed European adaptation of the Longitudinal Interval

Follow-up Evaluation (LIFE) (Keller 1987), as it elicits information on frequency and duration of ED behaviors (e.g., dieting, binge eating, and purging), cognitions (e.g., fear of fatness, preoccupation with food, and weight concerns), and menstrual function. We derived DSM-IV lifetime diagnoses of AN [restrictive (AN-R) or binge-purge type (AN-BP)] defined broadly as meeting all diagnostic criteria except amenorrhea, and BN, using a hierarchical approach. A diagnosis of AN-R “trumped” other diagnoses based on the assumption of a recognized association with MD (Brambilla et al. 2003). The AN-R group ($N=115$) thus also included women who had crossed over to AN-BP ($N=20$; 17.4 %) or BN ($N=16$; 13.9 %); AN-BP ($N=93$) women included those who had crossed over to BN ($N=30$; 32.3 %), but not AN-R; whereas BN included women who only ever had BN ($N=43$). Participants with an eating disorder not otherwise specified (EDNOS) ($N=12$) and binge-eating disorder (BED) ($N=13$) were excluded due to small numbers.

To investigate our second aim, we employed each of the following lifetime behaviors (i.e., yes/no) as predictors (not mutually exclusive): (i) binge eating ($n=145$), (ii) dieting ($n=220$), (iii) excessive exercise for weight loss ($n=169$), (iv) purging (self-induced vomiting, laxatives, or diuretics) ($n=169$), and (v) binge eating and purging ($n=135$).

Lifetime menstrual function was defined as follows: normal, primary amenorrhea (period never started or menarche after 16 years), and secondary amenorrhea (menstruation cycles ceased for ≥ 3 months after menarche).

Other covariates employed were as follows: age at interview, lifetime contraceptive use, age of onset of ED symptoms, and lifetime lowest BMI at final height.

Data analyses

The distribution of exposures, outcomes, and covariates in the sample was described using cross-tabulations with Fisher's exact test and ANOVAs.

We investigated the association between lifetime ED diagnoses, ED behaviors, and BMI and MD using crude and adjusted multinomial logistic and logistic regression models. A minimally adjusted model included the following: age, contraceptive use, and ED age of onset, as a priori confounders. Lowest lifetime BMI was subsequently included in a multivariate fully adjusted model to investigate its mediating role on the association between ED diagnosis, ED behaviors, and MD.

Only participants with complete data on predictors and outcomes were included in the analyses ($N=247$). A total of 5.6, 10.9, 6.6, and 1.6 % women had missing data, respectively, on age, age of ED onset, contraceptive use, and lowest BMI. These data were imputed using multiple

imputations with chained equations since the assumption of missing at random appeared plausible (Table S3). Analyses were run using Stata13.

Results

Sample

Our sample consisted of 247 ED participants (AN-R: $N=115$; BN: $N=39$; AN-BP: $N=93$). Lifetime lowest BMI differed across diagnoses and ED behaviors (Table S1).

ED diagnoses and MD

Both primary and secondary amenorrhea were more prevalent in women with AN-R (47.1 and 12.7 %, respectively) compared to women with other diagnoses (Table S2).

Women with BN had lower odds of lifetime secondary amenorrhea than women with AN-R in crude and minimally adjusted, but not in fully adjusted analyses (Table 1). Lifetime lowest BMI was associated with secondary amenorrhea both in crude and adjusted models $OR=0.7$ (95 % CI: 0.6–0.8).

ED behaviors and MD

Women with lifetime dieting behaviors and lifetime excessive exercising had higher odds of reporting secondary amenorrhea compared to those who did not in unadjusted and minimally adjusted models. In the fully adjusted models, dieting was weakly associated with MD ($P<0.08$), whilst excessive exercise was not. Women with lifetime binge-purge behaviors had lower odds of primary amenorrhea in crude and minimally adjusted, but not in fully adjusted models (Table 2).

Discussion

This study investigated the association between lifetime ED diagnoses and behaviors and MD. Women with BN had lower odds of secondary amenorrhea compared to those with AN, and this difference was explained by lifetime lowest BMI. We did not find associations between specific ED diagnoses and primary amenorrhea. Across the overall sample, lifetime dieting was associated with secondary amenorrhea, mostly due to low lifetime BMI.

In line with previous studies showing that secondary amenorrhea is highly prevalent in women with broadly defined AN (Poyastro Pinheiro et al. 2007), we found that women with AN (R and BP) had a higher prevalence and odds

Table 1 Crude and adjusted logistic regression for the associations between eating disorder (ED) diagnoses and menstrual dysfunction (MD) (secondary amenorrhea vs no MD): OR 95 % CI

Menstrual dysfunctions	N. Total	Diagnosis	N	Crude OR (95 % CI)	P (wald)	Adjusted ^a OR (95 % CI)	P (wald)	BMI-adjusted ^b OR (95 % CI)	P (wald)
Normal (Ref)	76								
Secondary	149	AN-R	72	1.0		1.0		1.0	
		AN-BP	64	1.4 (0.7–2.7)	0.3	1.4 (0.7–2.8)	0.3	1.4 (0.7–2.7)	0.3
		BN	13	0.2 (0.1–0.5)	<0.001	0.2 (0.1–0.5)	<0.001	0.6 (0.2–1.7)	0.4

AN-R anorexia-restrictive, AN-BP anorexia binge purging, BN bulimia nervosa, BMI body mass index

^a Minimally adjusted model by current age, contraceptive use, and age of onset

^b Fully adjusted model by current age, contraceptive use, age of onset, and lowest BMI ever

Statistical significance was defined as $P < 0.05$

Table 2 Crude and adjusted multinomial logistic regression for the associations between eating disorder (ED) behaviors and menstrual dysfunctions (MD) (primary/secondary amenorrhea vs no MD): OR 95 % CI

	Primary amenorrhea (vs none)			Secondary amenorrhea (vs none)		
	Crude OR (95 % CI)	Adjusted ^a OR (95 % CI)	BMI-adjusted ^b OR (95 % CI)	Crude OR (95 % CI)	Adjusted ^a OR (95 % CI)	BMI-Adjusted ^b OR (95 % CI)
Behaviors (N) 247						
Binge eating						
No (N=97)	1.0	1.0	1.0	1.0	1.0	1.0
Yes (N=145)	0.5 (0.2–0.9)	0.4 (0.2–1.2)	0.9 (0.3–2.5)	0.6 (0.4–1.2)	0.7 (0.4–1.2)	1.3 (0.7–2.6)
Binge eating and any purging						
No (N=112)	1.0	1.0	1.0	1.0	1.0	1.0
Yes (N=135)	0.4 (0.1–1.0)*	0.3 (0.1–0.9)**	0.6 (0.2–1.7)	0.8 (0.4–1.4)	0.7 (0.4–1.3)	1.4 (0.7–2.8)
Dieting						
No (N=23)	1.0	1.0	1.0	1.0	1.0	1.0
Yes (N=220)	0.8 (0.2–2.9)	1.2 (0.3–4.8)	0.8 (0.2–3.2)	3.8 (1.4–10.1)**	4.3 (1.6–11.9)**	2.7 (0.9–8.1)*
Exercising						
No (N=75)	1.0	1.0	1.0	1.0	1.0	1.0
Yes (N=169)	2.3 (0.8–7.0)	2.8 (0.9–8.8)*	2.4 (0.8–7.9)	1.9 (1.0–3.4)**	2.0 (1.1–3.6)**	1.7 (0.9–3.2)
Any purging						
No (N=75)	1.0	1.0	1.0	1.0	1.0	1.0
Yes (N=169)	0.8 (0.3–2.1)	0.7 (0.2–2.0)	1.0 (0.3–3.1)	0.7 (0.4–1.3)	0.7 (0.4–1.3)	1.0 (0.5–2.1)

BMI body mass index

^a Minimally adjusted model by current age, contraceptive use, and age of onset

^b Fully adjusted model by current age, contraceptive use, age of onset, and lowest BMI ever

** $P < 0.05$, * $0.1 > P > 0.05$

of secondary amenorrhea compared to BN. This difference was fully explained by lower BMI in this group. Although our study cannot provide evidence that factors other than BMI, such as ED-associated psychopathology (Brambilla et al. 2003) (i.e., anorexia-related symptoms such as drive of thinness) or comorbid behaviors (Gendall et al. 2000), could explain higher prevalence of amenorrhea in women with ED compared to healthy controls, it suggests that BMI is a strong discriminant across ED groups.

Evidence from ED samples suggests that ED behaviors (i.e., bingeing, purging, dieting, and excessive exercising) are associated with a higher prevalence of secondary amenorrhea (Poyastro Pinheiro et al. 2007). In this study, we only found dieting to be associated with secondary amenorrhea independent of BMI, an association seen also in non-ED populations, independent of BMI (Montero et al. 1996). Absolute weight loss and the decrease of fat mass secondary to dieting could contribute to ovarian dysfunction leading to MD (Vyver et al. 2008). More research is warranted to explore risk mechanisms as well as the associations across ED behaviors and a wider range of MD.

The main strength of this study was that ED diagnoses were obtained using a structured interview and included comprehensive lifetime data across a range of behaviors and cognitions. However, some limitations should be mentioned. We did not have a healthy control group; therefore, we could not compare the prevalence of MD in women with and without ED. The small size of index groups could have resulted in a type II error, especially in analyses for primary amenorrhea, due to low power. We could not control for PCOS, thought to increase the risk of MD in women with binge-eating behaviors (Vyver et al. 2008). We were unable to establish the temporality of occurrence of exposure and outcomes. Further detail on timing of diagnosis and MD could be useful especially in women with cross-over diagnoses. We assessed behaviors irrespective of frequency; thus, we could not investigate potential dose-response effects on outcomes.

In conclusion, in a clinical ED sample, we found that low BMI was the factor most strongly associated with secondary amenorrhea, although dieting behaviors were associated with the latter irrespective of ED diagnosis. More research is warranted to investigate risk factors for MD in population-based samples and to understand biological mechanisms. Our findings suggest that clinicians should screen women presenting with weight loss or dieting for adverse reproductive outcomes.

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