



Childhood anxiety associated with low BMI in women with Anorexia Nervosa

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ARTICLE INFO

Article history:

Received 12 June 2009

Received in revised form

20 September 2009

Accepted 22 September 2009

Keywords:

Anorexia Nervosa

Anxiety

Body mass index

ABSTRACT

Objective: Extremely low body mass index (BMI) values are associated with increased risk for death and poor long-term prognosis in individuals with anorexia nervosa (AN). The present study explores childhood personality characteristics that could be associated with the ability to attain an extremely low BMI. **Methods:** Participants were 326 women from the Genetics of Anorexia Nervosa (GAN) Study who completed the Structured Interview for Anorexia Nervosa and Bulimic Syndromes and whose mother completed the Child Behavioral Checklist and/or Revised Dimensions of Temperament Survey.

Results: Children who were described as having greater fear or anxiety by their mothers attained lower BMIs during AN ($p < 0.02$). Path analysis in the GAN and a validation sample, Price Foundation Anorexia Nervosa Trios Study, confirmed the relation between early childhood anxiety, caloric restriction, qualitative food item restriction, excessive exercise, and low BMI. Path analysis also confirmed a relation between childhood anxiety and caloric restriction, which mediated the relation between childhood anxiety and low BMI in the GAN sample only.

Conclusion: Fearful or anxious behavior as a child was associated with the attainment of low BMI in AN and childhood anxiety was associated with caloric restriction. Measures of anxiety and factors associated with anxiety-proneness in childhood may index children at risk for restrictive behaviors and extremely low BMIs in AN.

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Introduction

Anorexia nervosa (AN) is a debilitating and potentially lethal disorder (Berkman, Lohr, & Bulik, 2007; Fichter, Quadflieg, & Hedlund, 2006; Papadopoulos, Ekbom, Brandt, & Ekselius, 2009; Sullivan, 1995; Sullivan, Bulik, Fear, & Pickering, 1998) in which

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compulsive and unrelenting food avoidance results in dangerously low body mass index (BMI). Low BMI is associated with elevated mortality in the general population (Engeland, Borge, Selmer, & Tverdal, 2003; Kivimaki et al., 2008; Reis et al., 2009; Troiano, Frongillo, Sobal, & Levitsky, 1996; Whitlock et al., 2009) and individuals with AN are at significantly increased risk of sudden cardiac death (Lesinskiene, Barkus, Ranceva, & Dembinskas, 2008). Low BMI also has therapeutic and prognostic implications, has been associated with longer time to remission (Clausen, 2008), persistence of lower BMI following initiation of treatment (Pinter, Probst, Vandereycken, Pieters, & Goris, 2004), overall poorer prognosis (Steinhausen, Grigoriou-Serbanescu, Boyadjieva, Neumarker, & Metzke, 2009), increased risk of relapse in the year following hospital discharge (Walsh et al., 2006), and increased likelihood for re-hospitalization (Steinhausen, Grigoriou-Serbanescu, Boyadjieva, Neumarker, & Winkler Metzke, 2008).

Food intake in the weeks prior to treatment and shortly following treatment termination is also related to long-term prognosis. Caloric restriction and qualitative food item restriction, avoidance of certain food items or macronutrients (i.e., fat), are associated with a less favorable treatment outcome in those with eating disorders. Individuals with greater caloric restriction prior to treatment have higher rates of relapse following treatment (McFarlane, Olmsted, & Trotter, 2008). Following hospitalization for AN, women with limited dietary variety have a poorer prognosis than women who eat a wider range of food items (Schebendach et al., 2008).

As it is well known that anxiety is present in a substantial majority of individuals with AN prior to any signs of abnormal eating or distortions of body image (Godart, Flament, Lecrubier, & Jeammet, 2000; Raney et al., 2008; Salbach-Andrae et al., 2008), the identification of early developmental factors that confer risk of restrictive eating behaviors and attaining low BMI among those with AN has theoretical and clinical importance. One factor of potential significance is anxiety, which has been linked in cross-sectional studies of AN to elevations in resting energy expenditure (Van Wymelbeke, Brondel, Marcel Brun, & Rigaud, 2004), more extreme exercise (Penas-Lledo, Vaz Leal, & Waller, 2002; Shroff et al., 2006), and generally higher physical activity (Brewerton, Stelfox, Hibbs, Hodges, & Cochrane, 1995).

Given how often anxiety phenotypes are present in women with AN (Godart et al., 2000; Raney et al., 2008; Salbach-Andrae et al., 2008), and that anxiety disorders tend to predate the onset of AN (Godart et al., 2000; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004; Raney et al., 2008), and considering that persisting, morbid fear of weight gain and its avoidance is central to its descriptive psychopathology, an intuitive hypothesis is that caloric restriction is anxiolytic. This hypothesis is partially supported by neurobiological processes. Increased extracellular levels of serotonin in AN may lead to increased anxiety and decreased appetite; serotonin levels are reduced during starvation and could thereby reduce anxiety. Refeeding is associated with increased serotonin levels and increased anxiety (Kaye, Fudge, & Paulus, 2009). Reductions in dietary tryptophan, the dietary precursor to serotonin, has been shown to reduce anxiety in individuals with and recovered from AN (Kaye et al., 2003). This effect could account, at least in part, for the reinforcing nature of starvation in the ill state (Kaye, 2008; Kaye et al., 2003), accentuated further by the inherent, general anxiolytic properties of physical activity (Norris, Carroll, & Cochrane, 1992; Sexton, Maere, & Dahl, 1989). Thus, a biologically and psychologically plausible speculation is that more extreme anxiety indexes greater disease liability to AN and is associated with greater caloric restriction, consequent lower BMI, and perhaps a poorer long-term prognosis.

Other related personality and temperamental factors that may be associated with attainment of low BMI are timidity (Wilbur &

Colligan, 1981) and low self-esteem (Halvorsen & Heyerdahl, 2006; Wilksch & Wade, 2004). Personality and temperamental characteristics, such as timidity and low self-esteem are related to anxiety-proneness and captured by constructs such as harm avoidance (Cloninger, 1986; Cloninger & Svrakic, 1992; Joyce et al., 2003), often exhibited in individuals with AN (Fassino, Abbate-Daga et al., 2002; Fassino, Svrakic et al., 2002), and associated with chronic AN (Bulik, Sullivan, Fear, & Pickering, 2000). One study has identified neurotrophic tyrosine kinase receptor type 2 that may be associated with eating disorders, harm avoidance, and low BMI in those with eating disorders (Ribases et al., 2005).

An additional trait of interest in attainment of low BMI is early display of a rigid and unvarying schedule. Elevated rhythmicity could be associated with more severe eating disorder symptomatology. Teens with AN have less variation (greater rhythmicity) in their daily eating and sleep routines than teens with bulimia nervosa (BN) and adolescents with AN had less daily variation overall than adolescents with BN or depression (Shaw & Steiner, 1997). Childhood rhythmicity in those who develop AN needs to be explored to determine if early rhythmicity could serve as an early indication that a child may be prone to develop a low BMI. In children, high sleep activity (more restlessness during sleep) is associated with later development of anxiety disorders (Gregory et al., 2005). Childhood rhythmicity could be an early harbinger of later obsessiveness and sleep activity could index underlying anxious temperament.

Early identification of at risk individuals could allow for tailored, targeted prevention and early intervention for AN. In this study, we examined childhood measures of temperament that index anxiety-proneness to determine their association with lifetime lowest BMI (lowest BMI) in a cohort of individuals with AN. We further hypothesized that the relation between childhood anxiety and low BMI is mediated by illness related behavioral factors, specifically caloric restriction (Fig. 1).

Methods

Participants

Participants were from the Genetics of Anorexia Nervosa (GAN) Collaborative Study; a full description of the study is available in a separate publication (Kaye et al., 2008). The probands were age 16 or older, met criteria for a lifetime diagnosis of DSM-IV AN, with or without amenorrhea, at least 3 years prior to study entry and at or before age 45. All probands had at least one first, second, or third degree relative with AN (excluding parents and monozygotic twin) who was willing to participate in the study.

Exclusion criteria for probands included: (1) binge eating at least twice a week for at least three months [this criterion was implemented as the primary goal of the study was to attempt to replicate our previous linkage findings (Grice et al., 2002) so we ascertained a sample of probands who were predominantly of the restricting type, see (Kaye et al., 2008) for a more detailed discussion]; (2) a history of severe central nervous system trauma; (3) psychotic disorders or developmental disability; (4) medical, neurological, or substance use disorder that could confound the diagnosis of AN or interfere with the ability to complete assessments; (5) a maximum lifetime BMI exceeding 30 kg/m² (those with a maximum lifetime BMI of greater than 30 were excluded to insure sample homogeneity for genetic studies of AN, theoretically minimizing individuals with potentially obscuring obesity-related genotypes); or (6) did not speak either English or German. Affected relatives were required to meet the same inclusion criteria as probands, but could have regular binge eating and AN diagnostic criteria could have been met less than three years prior to the study. Relatives were required to have had a minimum BMI at or below

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