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Elina Sihvola, Anna Keski-Rahkonen, Danielle M. Dick, Hans W. Hoek, Anu Raevuori, Richard J. Rose, Lea Pulkkinen, Mauri Marttunen, and Jaakko Kaprio

Department of Public Health, University of Helsinki, Finland
Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland
Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, United States
Department of Psychiatry, Groningen University, The Netherlands
Department of Psychological and Brain Sciences, Indiana University, Indiana, United States
Department of Psychology, University of Jyväskylä, Jyväskylä, Finland
Department of Mental Health, National Public Health Institute, Helsinki, Finland
Department of Adolescent Psychiatry, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Abstract

Objective—To study the developmental relationships of adolescent-onset Axis I mental disorders and eating disorders.

Method—1318 adolescent twins born 1983-87 completed a professionally administered semi-structured psychiatric interview at age 14 and a questionnaire follow-up at age 17.5.

Results—Eating disorders at age 17.5 were significantly predicted by major depressive disorder (MDD, odds ratio [OR] 5.9, 95% confidence interval [CI] 2.6-15.3), and generalized anxiety disorders (GAD, OR 4.7, 95% CI 1.8-15.6) at age 14, when baseline eating disorders were excluded. Early-onset MDD in combination with GAD increased the likelihood of developing eating disorders compared to either mood or anxiety disorders alone. Similar risks and trends were evident in within-family analyses of twin pairs discordant for baseline predictors and eating disorder outcome.

Conclusions—Depressive and generalized anxiety disorders manifest at age 14 predict future eating disorders. Analysis of discordant twins suggested that early-onset depressive and generalized anxiety disorders prospectively relate to eating disorders in adolescence, even after familial factors are taken into account.

Keywords
major depression; generalized anxiety; eating disorders; adolescence; familial factors

Introduction
The developmental relationships of juvenile eating disorders and other mental disorders are poorly understood. To date, only few studies have examined the longitudinal relationships of
eating disorders and other psychopathology in adolescence. In general, these studies are suggestive of the existence of longitudinal relationships between depression, ADHD, substance use and eating disorders, but the sequence in the development of these disorders remains unknown because of inconclusive and mixed results. In some studies, eating disorders have preceded other forms of psychopathology [1,2], while in others, eating disorders have followed the same disorders [3-6].

Once comorbidity is established, several etiologic mechanisms are possible; one disorder may affect the expression of another, a third mediating factor may exist or, comorbidity may be caused by a common underlying factor, such as common genes. Studying twins discordant for a particular disorder offers an elegant way to control familial background [7,8]. In fact, if the within-twin-pair analyses replicate the association found among twins as individuals, it rules out the confounding effects associated with shared family background, i.e. family structure or family history of disorder. The importance of these tests is highlighted, since most of the prospective associations in clinical patients and population rests in individuals.

Thus, using a large prospective adolescent sample, we addressed the predictive value of Axis I disorders for the development of eating disorders. To control for familial factors, we studied the associations among twins discordant for predictive baseline disorders and later eating disorders.

**Methods**

**FinnTwin12 Study Design**

FinnTwin12 (FT12) is an ongoing longitudinal twin study launched in 1994 to investigate developmental genetic epidemiology of health-related behaviors [9]. From 1994 to 1998, all Finnish families with twins born in 1983-87 were identified from Finland's Population Register Centre and included in the Finnish Twin Cohort [10]. The FT12 study has a two-stage sampling design. The first-stage study included questionnaire assessments of all twins and parents at baseline, starting with the initial family questionnaire (87% participation rate, 2,724 families) conducted during autumn of the year in which each twin cohort reached 11 years, with follow-up of all twins at age 14 and 17½. Nested in this epidemiological, population representative study was an intensive assessment of a subsample of 1035 families, comprising about 40% of all twins, most (72%, 748 families) selected at random. A modest part of the subsample (28%, 287 families) was enriched with twins assumed to be at elevated familial risk for alcoholism, based on one or both parents’ elevated scores on the 11-item lifetime version of the Malmö-modified Michigan Alcoholism Screening Test [11]. Details about the sub-sample have been described earlier [9]. However, we have performed a series of model-fitting analyses to diverse phenotypes to test for potential bias introduced by the sample enrichment, and we find no evidence that model-fitting results were systematically affected [12].

In this subsample, both twins and parents were interviewed using the adolescent version of SSAGA (Semi-Structured Assessment for the Genetics of Alcoholism) [13], a highly reliable instrument providing lifetime diagnoses for alcohol dependence, major depressive disorder, anxiety disorders, conduct disorder, oppositional defiant disorder (ODD), attention-deficit-hyperactivity disorder (ADHD) and eating disorders. Assessments of non-responders at each stage revealed no evidence of selection for family type, parental age, area of residence, zygosity, sex of the twin or other systematic bias. All the interviewers had previous interview experience and were professionals. Masters of Psychology and Health Care or registered nurses trained at Indiana University Medical School using standard COGA-interview training procedures (The Collaborative Study on the Genetics of Alcoholism) [14]. The interviews were highly age-standardized; the mean age at interviews was 14.19 years, with 75% of interviews completed between 14 years and 14.3 months of age, and all interviews completed before age...
15. The final sample consisted of 1852 interviewed boys (N=945, 51%) and girls (N=907, 49%). The participation rate was 90%.

Later, during 2000 - 2005 at the average age of 17½ years, the participants from all five birth cohorts were approached again. All twins received a follow-up questionnaire including eating disorder assessments. A total of 1545 interviewed adolescents (83% participation rate) born 1983-87 replied at age 17 (mean age 17.6; 754 females, 49% and 791 males, 51%). The complete eating disorder status data at follow-up was available for 1318 adolescents (671 females, 49%, 641 males, 51%) Non-respondents did not significantly differ from respondents in baseline disorder status, sex or age. Zygosity of twins was determined from well-validated questionnaire method supplemented by information from parents, photographs and genotyping [15,16]. Data collection was approved by the ethics committee of Helsinki University and the Institutional Review Board of Indiana University.

**Baseline Assessments**

The Finnish translation of the adolescent SSAGA (C-SSAGA-A) collected full information on major depressive disorder (MDD) generalized anxiety disorder (GAD), attention-deficit hyperactivity disorder (ADHD), oppositional-defiant disorder (ODD) and conduct disorder (CD), as well as alcohol abuse and dependence diagnoses. All disorders were assessed according to DSM-IV criteria [17] without considering impairment.

Eating Disorders were analyzed in the same interview using both full DSM-IV criteria and broader ad-hoc definition (meeting at least 2/4 of current diagnostic criteria).

**Eating disorders at follow-up**

At follow-up, the adolescents were asked: Do you have or do you think that you have ever had an eating disorder? 6 alternatives were given: 1) yes, anorexia nervosa, 2) yes, bulimia nervosa, 3) yes, both anorexia and bulimia nervosa, 4) yes, an other type of an eating disorder, 5) I have not had an eating disorder and 6) I don't know. The reliability of questionnaire assessments have been studied by authors in Finnish population previously and despite their simplicity, they showed satisfactory and more specific and sensitive detection of lifetime eating disorders compared to the longer and more elaborate EDI subscales [18].

**Statistical Analysis**

Logistic regression analyses were conducted to test the predictive value of Axis-I disorders for the development of eating disorders. Conditional logistic regression war performed among twins discordant for significant predictors at baseline and also discordant for eating disorder outcome.

First, a univariate logistic regression model to study the association with eating disorder and another Axis-I disorder was examined. Second, other Axis I mental disorders were added to the model. Finally, to investigate whether Axis I disorders also predicted eating disorders among those without eating disorders at baseline, the adolescents with baseline eating disorders were excluded from the analysis.

As the subjects of the study were individual twins sampled on the bases belonging to families with twins, we adjusted p-values and confidence intervals in individual analyses using standard procedures for complex survey data [19] to correct for the non-independence of observations within twin pairs. All analyses were conducted using the statistical software Stata 9.2.
Results

Lifetime prevalences of adolescent-onset eating disorders

Baseline interview assessments demonstrated the rarity of full DSM-syndromes among adolescents at age 14 years; the prevalences for DSM-IV anorexia and bulimia nervosa were 0.32% (95% CI 0.06-0.58) and 0.05% (95% CI 0.00-0.10), respectively. Broad syndromes, defined ad-hoc as the presence of at least 2/4 current DSM-IV diagnostic criteria, were considerably more common (N=73, 3.9%). At the age of 14, binge-eating, body image concerns and fear of gaining weight while being underweight (BMI equivalent to adult BMI<17.5) were the most frequent eating disorder symptoms among adolescents (Table 1).

At follow up, the lifetime prevalence for any lifetime eating disorder was 4.3%. Among responders at follow-up, the prevalences for self-reported anorexia and bulimia nervosa were 1.4% (95% CI 0.74-1.99) and 0.7% (95% CI 0.23-1.13), respectively. Eating disorder symptomatology, such as eating pathology and body image preoccupation were not assessed at follow-up.

Cross-sectional and longitudinal analysis of comorbidity with DSM mental disorders

We then conducted cross-sectional analysis simultaneously assessing the impact of baseline axis-I psychiatric disorders for eating disorders adjusted for sex. Results were that the participants with depressive disorders had over four-fold risks of concurrent comorbidity with broadly defined eating disorders and participants with generalized anxiety exhibited over fivefold-risk. Externalizing disorders showed significant comorbidity with eating disorders in cross-sectional analysis as well. (Table 2)

In longitudinal analysis, major depressive disorders and generalized anxiety disorders at age 14 were strongly associated with eating disorders at follow-up at age 17½. These relationships between generalized anxiety and EDs and depressive disorders and EDs were statistically significant also among those without baseline eating disorders and eating disorder symptomatology (Table 2). Because of high comorbidity of these two disorders, we also stratified the sample based on lifetime diagnoses of major depressive disorders and generalized anxiety into four groups; those with neither baseline diagnosis, those with both, those with major depressive disorders alone and those with generalized anxiety alone. The presence of major depressive disorder in combination with generalized anxiety disorder increased the likelihood of future disorders compared to mood or anxiety disorders alone (adjusted odds ratio, 11.3). The results remained significant after adjustment of other mental disorders at baseline and excluding baseline eating disorders (Table 3).

Major depressive and generalized anxiety disorders in twins discordant for eating disorders

Among participants, 42 pairs discordant for eating disorders at follow-up were identified. A pair was not included if the unaffected co-twin at age 17½ had reported any eating disorders symptoms in baseline interview at the age of 14 but had not developed an eating disorder. Among these 42 pairs we then identified twins also discordant for predictors at baseline, yielding 10 sister-sister pairs (two monozygotic, eight dizygotic pairs), discordant for major depressive disorder at age 14 and future eating disorders at age 17½ and 5 pairs (all girls, one monozygotic, four dizygotic pairs) discordant for generalized anxiety and later eating disorder outcome (no pairs were discordant for all three disorders). In 8 out of 10 pairs, it was the depressed twin who developed an eating disorder (while the twin sister did not) and in 4 out of 5 pairs it was the twin sister with generalized anxiety who went on to develop an eating disorder. Thus, the results show that within a twin pair with shared family background, the twin affected with depressive or generalized anxiety disorder was 4 times more likely to develop an eating disorder. In conditional logistic regression models adjusted for sex and all

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other Axis-I disorders this translated to increased risks of co-twin with MDD (OR 1.29, 95% CI 1.02-1.64) and similar, but statistically nonsignificant trend of co-twin with GAD (OR 1.60, 95% CI 0.75-3.43) for later eating disorders.

Discussion

This large prospective study demonstrates that depressive and generalized anxiety disorders manifest at age 14 predict eating disorders in later adolescence. Despite the low-rates of these disorders, our results showed that adolescents meeting criteria for both major depressive and generalized anxiety are at even higher risk for future eating disorders compared to those with either major depressive of generalized anxiety disorder alone. Further, exploratory analyses of discordant twin pairs suggest that a causal link independent of shared familial background may exist between these disorders.

Recent evidence supports high comorbidity between depressive and anxiety disorders both in community and clinical settings [20]. Interestingly, comorbid generalized anxiety plus depression has been described as a significant risk factor also for suicidality in adolescents [21]. In addition to comorbid state of both conditions, the co-existence of depression and general anxiety might be related to a distinct condition of mixed depression-anxiety (MAD) suggested previously as a viable diagnostic category among youth [22]. Thus, our results further imply that this category also might have clinical significance in eating disorder subjects and suggest it be evaluated among adolescents with eating disorders. It is possible, that the elevated risk associated with combination of these disorders may reflect general psychological stress or a broader phenotype associated with eating disorders.

This current study assessed eating disorder symptoms; refusal of maintaining body weight, intense fear of becoming fat or gaining weight even though underweight, binge-eating, compensatory behaviors and self-evaluation influenced by body weight or shape using a structured interview at the age of 14. The study establishes important relationships of eating disorder symptoms below diagnostic threshold to concurrent comorbidity in adolescence, thereby supporting the conclusions about the importance of partial syndromes in adolescence [23,24]. It also highlights generalized anxiety and depressive disorders as vulnerability factors with temporal precedence in line with the previous longitudinal studies of eating disorders in adolescence [3-5,25]. Further, overanxious disorders similar to classification of current classification of generalized anxiety disorders, although based on retrospective recall, may have an effect on severity of eating disorders, especially anorexia nervosa in adult females [26]. Together, these findings support the clinically meaningful predictive value of early-onset depressive and anxiety disorders for future eating disorders. However, a recent study of Marmorstein et al [27] examining eating pathology among adolescent girls found that eating pathology predicted depressive symptoms but not vice versa. One explanation to these different results could be that different definitions of depression may not be fully comparable in adolescence thus influencing the associating prognosis. Further, the study of Marmorstein et al. did not assessed comorbidity.

At this early developmental phase, very few studies have assessed the causes underlying the association of depression, anxiety and eating disorders among adolescents. In 2005, Silberg et al [5] found a pervasive genetic effect influencing the development of these disorders. Our discordant twin model does not quantify, how much the association is attributable to genes or environment, but it suggests, interestingly, that these associations remain after shared familial factors, such as socioeconomic status or childhood environment, are taken into account. These analyses also partially control for shared genetic effects (the discordant twins included DZ twins, who share 50% of their genetic variation). Together with temporal precedence of generalized anxiety and eating disorders [28-30], our analyses suggest that early depression
and generalized anxiety may be important factors in a causal pathway in developing eating disorders in adolescence.

The generalizability of current results must be evaluated in the context of the following limitations. The baseline assessments were defined by interviews by experienced health-care professionals and confirmed by an experienced clinician, but the follow-up assessments were analyzed by questionnaire and were vulnerable to self-report bias. Further, because of limited number of twins with eating disorders, we were unable to assess anorexia and bulimia as separate diagnostic categories at follow-up. It would have also been preferable to assess boys and girls separately, rather than via sex-adjustment in statistical analysis. The sample limitations also prohibited quantitative assessments of specific genetic and environmental influences using formal twin model fitting analysis and the nature of pairwise analysis was mainly exploratory. Further, with longer follow-up, it’s possible that some of the unaffected co-twins may later develop an eating disorder.

Overall, the study shows that of other Axis I disorders, depressive and generalized anxiety disorders stood out as antecedents of eating disorders. In particular, the mixed state of these two syndromes, a symptom presentation common in adolescents, seems to increase the risk for developing eating disorders and further challenges the diagnostic boundaries between these disorders in adolescence. Interpreted as exploratory results, the data also suggested that these relationships may be independent of familial confounds and warrant further studies considering risk factors other than family environments, for example, the influence of peers or dispositional personality traits which may be of importance in these developmental associations. Clinical implications are suggested: the professionals in adolescent health care should acknowledge that adolescents with generalized anxiety and depression (which are often episodic and short by nature), are at significantly elevated risk for developing future eating disorders. Thus, potential emerging eating disorder symptoms; signs of bingeing, intentional weight loss and preoccupation with food, body weight and shape should be carefully assessed. Longitudinal studies are also warranted to evaluate, whether interventions for early depressive and anxiety conditions could have an effect on terminating the pathway to developing eating disorders in vulnerable adolescents. As other pathways may also exist for developing eating disorders, depressive and generalized anxiety disorders may be comprehensible and easy to conceptualize especially in primary health care, where the majority of partial eating disorders and mood disorders are seen today. Further, increasing knowledge on these important developmental associations could be utilized for educational purposes among young people.

Acknowledgements

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References


Table 1
The distribution of eating disorders (ED) and diagnostic symptom presentation at age 14 and 17 among Finnish boys and girls born 1983-1987.

<table>
<thead>
<tr>
<th>Baseline assessments (age 14)</th>
<th>N(%) Girls N=907</th>
<th>N(%) Boys N=945</th>
<th>N(%) All N=1852</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia Nervosa (DSM-IV)</td>
<td>6(.66)</td>
<td>-</td>
<td>6 (.32)</td>
</tr>
<tr>
<td>Bulimia Nervosa (DSM-IV)</td>
<td>1(.11)</td>
<td>-</td>
<td>1 (.05)</td>
</tr>
<tr>
<td>Broadly defined eating disorders **</td>
<td>65(7.2)</td>
<td>8(.85)</td>
<td>73(3.9)</td>
</tr>
<tr>
<td>Lifetime dieting</td>
<td>173(19.2)</td>
<td>66(7.0)</td>
<td>239(13.0)</td>
</tr>
<tr>
<td>Underweight ^</td>
<td>20(2.21)</td>
<td>2(0.21)</td>
<td>22 (1.19)</td>
</tr>
<tr>
<td>Recurrent binge eating</td>
<td>50(5.51)</td>
<td>26(2.75)</td>
<td>76(4.0)</td>
</tr>
<tr>
<td>Distorted body image</td>
<td>28(3.09)</td>
<td>6(.63)</td>
<td>34(1.84)</td>
</tr>
<tr>
<td>Intense fear of gaining weight/fat ^</td>
<td>18(2.0)</td>
<td>-</td>
<td>22(1.25)</td>
</tr>
<tr>
<td>Compensatory behaviors</td>
<td>5(.55)</td>
<td>-</td>
<td>5(.77)</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>7(.77)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Assessments (age 17.5)</th>
<th>Girls N=671</th>
<th>Boys N=647</th>
<th>All N=1318</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia Nervosa</td>
<td>17(2.53)</td>
<td>1(.15)</td>
<td>18(1.37)</td>
</tr>
<tr>
<td>Bulimia Nervosa</td>
<td>9(1.34)</td>
<td>-</td>
<td>9(.68)</td>
</tr>
<tr>
<td>Both AN&amp;BN</td>
<td>4(.6)</td>
<td>-</td>
<td>4(.3)</td>
</tr>
<tr>
<td>Any eating disorder</td>
<td>19(2.83)</td>
<td>3(.46)</td>
<td>22(1.67)</td>
</tr>
<tr>
<td>Lifetime dieting</td>
<td>250(37.26)</td>
<td>114(17.62)</td>
<td>364 (27.62)</td>
</tr>
<tr>
<td>Dissatisfaction of weight/shape</td>
<td>328(48.88)</td>
<td>125(19.32)</td>
<td>453 (34.37)</td>
</tr>
</tbody>
</table>

- = no observations

^ BMI≤17.5

** = Participants fulfilling 2/4 DSM-IV criteria for anorexia or bulimia nervosa

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Table 2
Cross-sectional and longitudinal analysis of adolescent-onset eating disorders and mood, generalized anxiety, externalizing disorders and alcohol use disorders.

<table>
<thead>
<tr>
<th></th>
<th>Cross-Sectional Univariate</th>
<th></th>
<th>Multivariate</th>
<th>Multivariate, 95% CI</th>
<th></th>
<th>Longitudinal Multivariate, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>OR†</td>
<td>95% CI</td>
<td>AOR‡</td>
<td>95% CI</td>
</tr>
<tr>
<td>No Disorder</td>
<td>41</td>
<td>2.7</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>15</td>
<td>17.6</td>
<td>4.41</td>
<td>2.22-8.75</td>
<td>2.41</td>
<td>1.06-5.47</td>
</tr>
<tr>
<td>GAD</td>
<td>12</td>
<td>16.4</td>
<td>5.48</td>
<td>2.62-11.46</td>
<td>3.41</td>
<td>1.56-7.43</td>
</tr>
<tr>
<td>CD</td>
<td>20</td>
<td>9.1</td>
<td>4.29</td>
<td>2.35-7.82</td>
<td>2.67</td>
<td>1.35-5.30</td>
</tr>
<tr>
<td>ODD</td>
<td>5</td>
<td>29.4</td>
<td>7.97</td>
<td>2.41-26.35</td>
<td>2.14</td>
<td>.50-9.12</td>
</tr>
<tr>
<td>ADHD</td>
<td>1</td>
<td>12.5</td>
<td>2.48</td>
<td>.30-20.36</td>
<td>.50</td>
<td>.09-2.72</td>
</tr>
<tr>
<td>AUD</td>
<td>5</td>
<td>8.8</td>
<td>2.23</td>
<td>.84-5.95</td>
<td>1.45</td>
<td>.47-4.43</td>
</tr>
</tbody>
</table>

N, % = No. and prevalence of eating disorders among participants affected with other baseline disorder. AOR=adjusted for sex, clustered sampling and other adolescent-onset disorders. ††Participants with baseline eating disorders excluded. MDD=Major depressive Disorder, GAD=generalized anxiety disorder, CD=conduct disorder, ADHD=attention-defiant-hyperactivity disorder, ODD=oppositional defiant disorder, AUD=alcohol use disorders; abuse/dependence.
Table 3
Eating disorders in middle and late adolescence in relation to baseline major depressive and generalized anxiety disorders.

<table>
<thead>
<tr>
<th>Baseline Disorders</th>
<th>Eating Disorders at baseline (age 14.2)</th>
<th>Eating Disorders at follow-up (age 17 1/2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ED N=1779</td>
<td>ED N=73</td>
</tr>
<tr>
<td>No GAD/MDD</td>
<td>1708(92.2)</td>
<td>50 (2.9)</td>
</tr>
<tr>
<td>MDD only</td>
<td>60 (84.5)</td>
<td>11 (15.5)</td>
</tr>
<tr>
<td>GAD only</td>
<td>51(86.4)</td>
<td>8(13.5)</td>
</tr>
<tr>
<td>MDD and GAD</td>
<td>10 (71.4)</td>
<td>4 (28.5)</td>
</tr>
</tbody>
</table>

*Baseline Eating disorders excluded

* Adjusted for sex and other mental disorders at baseline (conduct, attention-deficit hyperactivity, oppositional defiant and alcohol abuse/dependence disorders)

Abbreviations: MDD=Major Depressive Disorder, GAD=Generalized Anxiety Disorder