Outcome in AN adult patients: A 13-year follow-up in 484 patients

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Abstract

Background. – To study the long-term prognosis of anorexia nervosa (AN), 484 adult AN patients were followed on a mean duration of 13 years.

Results. – The mortality rate was 1.2%. Eight factors were linked to the lack of recovery at 2 years: low BMI at discharge, low energy and fat intakes, high drive for excessive exercising, high score for perfectionism, for interpersonal distrust and for anxiety, use of tube-feeding and adhesion to treatment (P < 0.02). Four factors explained the risk of the binge/purging form at 2 years: having had binge-eating disorder and overweight before AN, having had purging episodes within the first 2 years of AN; having had very high energy intakes through meals and being not treated by tube-feeding. During the 13-year follow-up, very few binge/purging patients turned out to have the restrictive form. Two main factors explained 67% of the variance of menses recovery: having a BMI > 18.5 kg/m²; and having no physical hyperactivity. The recovery rate increased with the elapsing of relapse-free time (P = 0.02). After a 13.5-year follow-up, 292 out of the 484 patients were recovered (60.3%), 25.8% had a relatively good outcome and 6.4% a bad outcome and 6.4% a severe outcome. Very few factors were identified as predictors of a good outcome (binge-eating/purging subtype, personality disorder).

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Keywords: Anorexia nervosa; Outcome; Prognosis; Bulimia nervosa

Résumé

Devenir à 13 ans de 484 malades souffrant d’anorexie mentale.

Afin d’étudier le pronostic de l’anorexie mentale (AM), nous avons suivi régulièrement pendant 13 ans, 484 malades AM, ayant initialement soit la forme restrictive, soit la forme boulimique, après une première hospitalisation. La mortalité à terme fut de 1,2 %. Huit facteurs étaient associés à la rechute à deux ans : un IMC bas à la sortie, des apports énergétiques et lipidiques bas, une hyperactivité physique, un score de perfectionnisme, de méfiance à l’égard d’autrui et d’anxiété élevés, le refus de la nutrition entérale et le bas niveau d’adhésion au traitement. Quatre facteurs étaient associés à l’évolution vers la forme boulimique après deux ans : avoir été compulsive ou obèse avant l’AM, avoir eu quelques épisodes de vomissements ou de crises compulsives dans les deux premières années, avoir eu des apports énergétiques per os très élevés pendant l’hospitalisation et n’avoir pas eu de nutrition entérale. Le taux de guérison s’accroissait avec le temps passé sans rechute. Parmi les AM restrictives, 31 % devinrent AM boulimiques ou boulimiques à poids normal. À l’inverse, très peu d’AM boulimiques devinrent restrictives. Après 13,5 ans de suivi, 60,3 % des malades étaient guéris, 25,8 % avaient un pronostic plutôt bon, 6,4 % mauvais et 6,4 % très mauvais. Nous n’avons identifié que deux facteurs associés à un mauvais ou très mauvais pronostic : une forme boulimique et un trouble de la personnalité sévère.

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Mots clés : Anorexie mentale ; Pronostic ; Bulimie

1. Introduction

Anorexia nervosa (AN) is a chronic eating disorder with an increasing lifetime prevalence. AN begins generally during the late adolescence, but sometimes during adult life. In Burgundy, France, we found that 1.8% of 17- to 25-year-old girls and 1.4% of 25- to 45-year-old women (mean: 40.9 ± 4.9 years) quoted all the symptoms of AN [1]. AN is one of the most disabling of psychiatric diseases [2–5], and has a high mortality rate [6,7]. It is characterized by a fear of gaining weight and being obese, and a subsequent refusal to maintain minimal normal body weight for age and gender. There are two types of AN: the restricting...
Quadflieg [13] studied the 6-year course of 103 AN patients: 59% of 95 AN adult patients after 5 years, persistent AN in 21%, BMI < 13 kg/m²; several binge/purging episodes per week.

were unable to allow significant weight gain or when there were (TF). TF is prescribed for complementing meals when meals considerable practice in nutritional assistance and tube-feeding unit specialized in the treatment of eating disorders, with hospitalized. All these 484 adult patients were first hospitalized 2.1. Patients

The present cohort included only those patients needing to be hospitalized. All these 484 adult patients were first hospitalized between January 1985 and December 1995. Our team is a nutrition unit specialized in the treatment of eating disorders, with considerable practice in nutritional assistance and tube-feeding (TF). TF is prescribed for complementing meals when meals were unable to allow significant weight gain or when there were several binge/purging episodes per week.

The four main reasons to be hospitalized in our unit were:

- BMI < 13 kg/m²;
- malnutrition (BMI: 13–16 kg/m²) and no weight gain despite medical care;
- daily binge/purging episodes;
- severe somatic complications.

Our in-hospital treatment includes:

- diet counseling (2 h/week) and, if needed TF;
- interpersonal psychotherapy;
- cognitive behavioural therapy (CBT) [17].

This approach was scheduled both as individual and group sessions (3 h/week), and covered eating behaviour, emotions around meals, anxiety and self-esteem. Groups were managed by a recovered patient (HP) and by a nutritionist practitioner (DR) or a psychologist. There is no restriction for visits and permissions were encouraged. All of the patients (462 women, 22 men) fulfilled the DSM-IV diagnostic criteria for AN [18]. They were recruited from a total of 614 AN patients who were hospitalized in our unit during the same period (Table 1). Patients were not included if they were aged <18 years (42 patients), had no possibility of follow-up (geographical reason or refusal, 12 patients), had BMI > 18 kg/m² (n = 17), and there was doubt concerning the diagnosis of AN (restrictive form of EDNOS) – in other words, patients who said that their behaviour was not related to fear of gaining weight (n = 25). Of the 531 eligible patients, we did not obtain follow-up data in 47 patients (9.7%).

3. Methods

All AN patients were assessed at the first hospital admission, at discharge and at least every year during the 13 years. All data were collected by physicians who had at least 2 years of experience in eating disorders. The patients filled out an extensive 14-page questionnaire about symptoms and feelings, in part derived from Eating Disorder Examination Questionnaire (EDE) and the Eating Disorder Inventory (EDI) [19]. It included Beck’s Depression Inventory [20], the Hamilton Anxiety Score [21] and the Morgan–Russell outcome score [22]. According to this file, we classified the patients into the following categories: recovery; relatively good outcome; bad outcome; severe outcome; and death. For the patients who could not return for medical visits, contact was made by phone using the questionnaire. New inpatient treatment was decided based on the five reasons mentioned above. We recorded the onset of the disease, change from one subtype to another one, number of hospitalizations, body weight (BW) before AN, highest BW before AN, BW loss, lowest and highest BW during AN, medical complications and menstrual cycles. All patients were also contacted by phone or mail, and the questionnaire was sent every year. Treatment adhesion was defined as the ability to trust and act what it was explained by the medical staff (four classes) at the end of first hospitalization: No: no agreement; Immediate recall: agreement, but low ability to do anything; “anxious”, with low ability to take on body weight gain without a large increase in anxiety level; Fighting spirit: agreement and trust to do what was prescribed.
Table 1
Characteristics of the 484 adult patients with anorexia nervosa (AN).

<table>
<thead>
<tr>
<th>Patients with &gt; 10-year follow-up</th>
<th>Lost patients (no follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>484 (462 women, 22 men)</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>13.5 ± 2.8 (10–21)</td>
</tr>
<tr>
<td>Age at first admission (years)</td>
<td>22.8 ± 4.4 (16–43)</td>
</tr>
<tr>
<td>Age at first symptoms (years)</td>
<td>18.4 ± 2.7 (14–31)</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>3.3 ± 1.4 (1.4–25)</td>
</tr>
<tr>
<td>BMI at admission (kg/m²)</td>
<td>12.8 ± 1.6</td>
</tr>
<tr>
<td>BMI before AN (kg/m²)</td>
<td>22.4 ± 1.3</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>95.4% (22 males)</td>
</tr>
<tr>
<td>Restrictive type (inclusion rate)</td>
<td>347 (71.7%)</td>
</tr>
<tr>
<td>Bingeing/purging type (inclusion rate)</td>
<td>73 (15.1%)</td>
</tr>
<tr>
<td>Purging type (inclusion rate)</td>
<td>52 (10.7%)</td>
</tr>
<tr>
<td>Bingeing type (no purging) (n [%])</td>
<td>12 (2.5%)</td>
</tr>
<tr>
<td>Anxiety disorder before AN (n [%])</td>
<td>80 (16.5%)</td>
</tr>
<tr>
<td>Depressive disorder before AN (n [%])</td>
<td>63 (13%)</td>
</tr>
<tr>
<td>Personality disorder before AN (n [%])</td>
<td>29 (6%)</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD (range) unless otherwise specified.

BMI: body mass index.

3.1. Recovery and outcome

This involved three criteria:

- normal and stable body weight (BMI: 18.5–25 kg/m²);
- no excessive physical exercising;
- normal eating behaviour, with energy intake at the level of physiological energy needs [23], regular three or four meals/day, ability to eat face to face with other people and to eat out (restaurant, friends), no fear of fatty food or added fat, no weighing oneself every day and no obsession concerning body weight or food.

Other outcomes were:

- relatively good outcome: BMI 17.5–18.5 kg/m², energy and fat intakes near to energy needs, but restricting behaviour (restraint from eating, difficulty in eating with others) and/or no excessive physical hyperactivity (< 1 h, for weight loss);
- bad outcome: BMI 16.5–17.5 kg/m², abnormal eating behaviour (no added fat, no sugar, skipping meals, no meals with others); OR 3–6 binge/purging episodes/week and/or excessive exercising (> 1 h);
- severe outcome: more severe than a bad outcome, with BMI < 16.5 kg/m² and/or at least one binge-eating/purging episode/day or evolution to bulimia nervosa (DSM IV).

3.2. Statistical analyses

Statistical analyses were done with SPSS® software. The state of outcome constituted the dependent variables. Its association with independent variables (prognostic factors) was explored by analysis of variance (Anova), then multivariate regression analyses with 23 factors. We defined, before starting the analyses of data, six categories of BMI (> 18.5 kg/m²; 17.5–18.49 kg/m²; 16.0–17.49 kg/m²; 15.9–14.00 kg/m²; 13.9–12.00 kg/m²; and < 12.0 kg/m²). Also, we defined four classes of physical activity (normal, moderately hyperactive, clearly hyperactive, very hyperactive), four classes of treatment adhesion (see above), three classes of depression (Beck < 12, 12–20, 21–39) and of anxiety level (Hamilton < 15, 15–30, 31–56), three classes of eating disorder (RAN, BPAN, BN), three classes of AN duration (< 1 year, 1–3 years > 3 years) and three classes of previous hospitalization (never hospitalized before in a specialized unit, one time, more than once). Other factors were age, gender, age at onset, lowest BMI, and energy and fat intakes after 1 month of hospitalization. The dependent variable was the five classes of outcome (recovery, good outcome, bad outcome, severe outcome and death) at 3 and 13 years. Comparison between groups was performed by Student’s t test for quantitative data and the Chi² test for percentages.

4. Results

Between 1984 and 1995, we saw 42 to 58 new adult AN patients every year (Table 1). The AN patients were reassessed at 1.01 ± 0.05 year (n = 484), 2.1 ± 0.12 years (n = 469), at 4.0 ± 0.1 years (n = 467 out of 481 patients alive), 8.5 ± 0.2 years (n = 456/479) and 13.1 ± 0.3 years (n = 432). The median follow-up duration was 12.8 years (range: 10–21 years; mean: 13.5 ± 2.8 years). At inclusion, the mean age of the patients was 22.8 ± 4.4 years (16–43 years), their BMI was 12.8 ± 1.6 kg/m² and their median AN duration was 3.5 years (range: 1.4–25.1).

4.1. Mortality rate

Six patients (all women) died during the 12.8-year follow-up (1.24%); four during the first 10-year period (1984–1994), and the final two thereafter (0.4%). Four of the six had BPAN: suicide was the cause of their death (2.2% of all BPAN patients). The two other patients had RAN and died at home (they had refused TF). Of the 484 patients, 48 patients (9.9%) were hospitalized...
with a BMI < 10 kg/m². All were treated by TF; there was no death.

4.2. Relapse 2 years after discharge

During the 13-year follow-up, 230 patients were rehospitalized only once (47.5%), 73 patients twice (15.1%), 41 patients three times (8.4%), 22 patients four times (4.5%), 18 patients five times (3.7%) and six patients six times (1.2%); 94 patients were never rehospitalized (19.4%). Of the 22 male patients, 13 were rehospitalized thereafter only once (59%), four twice (18%), three patients three times (13%) and two never again. Defined as a 1.5-point BMI decrease (around 3 kg) and a high drive for thinness, we observed a 52.1% relapse rate at 1 year, and a further 16.4% at 2 years. The 2-year relapse rate was not explained (multivariate analysis) by gender, age, BMI before AN, AN duration or subtype, lowest BMI, severity of binge/purging episodes (number/week), excessive exercising, energy intake at inclusion or anxiety and depression levels. Twelve factors explained 51% of the variance of the 2-year relapse: low BMI at discharge ($P = 0.001$, Fig. 1), low energy intake (< 1700 kcal) after 1 month of hospitalization ($P = 0.001$), low (< 45 g) fat intake ($P = 0.018$), low BMI plus two previous hospitalizations for AN ($P = 0.001$), high drive for thinness ($P = 0.005$), high feelings of interpersonal distrust ($P = 0.008$), ineffectiveness ($P = 0.001$), body dissatisfaction ($P = 0.018$) and interoceptive awareness ($P = 0.05$), high drive for excessive exercising ($P = 0.027$), and high anxiety ($P = 0.021$) and depression levels ($P = 0.032$; Table 2). Only eight factors were independently associated with relapse: low BMI at discharge ($F = 11.6$; $P = 0.001$); low energy intake after 1 month of hospitalization ($F = 6.3$, $P = 0.035$); no TF ($F = 5.8$, $P = 0.05$); high drive for excessive exercising ($F = 6.4$, $P = 0.031$); high ineffectiveness ($F = 8.43$, $P = 0.008$); high interpersonal distrust ($F = 9.67$, $P = 0.002$); high anxiety ($F = 5.6$, $P = 0.03$); and low ability to trust and act ($F = 11.2$, $P = 0.001$). When patients were classified at the end of in-hospital treatment as agreeing and acting, their remission (or recovery) rate at 3 years was 85%; when they were classified as agreeing, but unable to act for more than a few days, or as suspicious, their remission rate was 54 and 29%, respectively ($F = 10.4$, $P < 0.001$). The relapse rate decreased with time: it was 52.1% after 1 year spent without relapse, 12.6% after 2 years and 3.8% after 3 years ($F = 16.3$, $P = 0.001$).

![Fig. 1. Rates of relapse during the first 2 years of follow-up, according to body mass index (BMI) at the time of hospital discharge, show a “BMI-at-discharge” effect (ANOVA, $F = 12.6$, $P < 0.0001$) and a “time” effect (lower rate of relapse during year 2 vs year 1).](image_url)

### Table 2

<table>
<thead>
<tr>
<th>At end of hospitalization</th>
<th>Recovered ($n = 271$; 58%)</th>
<th>Not recovered ($n = 199$; 42%)</th>
<th>Anova ($n = 470$), $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total EDI score</strong></td>
<td>31.4 ± 12</td>
<td>76.2 ± 14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Drive for thinness</td>
<td>5.2 ± 3.6</td>
<td>12.5 ± 3.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Interpersonal distrust</td>
<td>4.3 ± 2.4</td>
<td>13.4 ± 3.2</td>
<td>0.0008</td>
</tr>
<tr>
<td>Ineffectiveness</td>
<td>4.3 ± 3.5</td>
<td>15.8 ± 6.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body dissatisfaction</td>
<td>7.3 ± 2.4</td>
<td>12.4 ± 2.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>3.1 ± 1.7</td>
<td>4.9 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Perfectionism</td>
<td>7.6 ± 2.8</td>
<td>9.5 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Interoceptive awareness</td>
<td>8.5 ± 2.5</td>
<td>11.1 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Maturity fears</td>
<td>6.2 ± 2.1</td>
<td>7.5 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Treatment compliance</strong>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recallb</td>
<td>23 (8.5%)</td>
<td>42 (21.1%)</td>
<td></td>
</tr>
<tr>
<td>Eating-related anxietyd</td>
<td>38 (14.0%)</td>
<td>72 (36.2%)</td>
<td></td>
</tr>
<tr>
<td>Fighting spiritc</td>
<td>46 (17.0%)</td>
<td>50 (25.1%)</td>
<td></td>
</tr>
<tr>
<td>Patients tube-fed for &gt; 2 months</td>
<td>188 (69%)</td>
<td>74 (37%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD or as $n$ (%).

- **a** Ability to trust medical staff.
- **b** Not at all.
- **c** Agreement, but low ability to do anything.
- **d** Agreement, but low ability to gain body weight without increasing anxiety.
- **e** Agreement and action.
The majority of changes took place within the first 3 years of follow-up. To the bingeing/purging form (BPAN), or vice versa, observed over time. With

Fig. 2. Rates of changes in the form of AN from either the restrictive form (RAN) to the bingeing/purging form (BPAN), or vice versa, observed over time. With Anova, both “time” and “AN type” effects were observed (F = 6.3, p < 0.001).
The majority of changes took place within the first 3 years of follow-up.

4.3. Changing type of eating disorder

In 407 (84%) patients, AN was preceded by a slimming diet. In 69 patients, AN followed bulimia nervosa (14%). Considering only patients starting with RAN (n = 411, 86%), the conversion rate to BPAN changed with time (Fig. 2; time effect: F = 6.3; p < 0.01). During the 13-year follow-up, two-thirds of the non-recovered BPAN patients remained BPAN and one-third reached bulimia (with normal BMI). Of the RAN patients, 31% converted to BPAN or BN, 34% remained in RAN and 35% recovered. In those patients who had few binge-eating or purging episodes during the first 2 years, the probability for conversion to the BPAN subtype was 29% and, to bulimia nervosa, 16%. In contrast, when the patients remained in the RAN subtype for at least 3 years, the conversion to BPAN was 3% and, to BN, 5% (p < 0.0001). Only 8% of the BPAN patients shifted to RAN thereafter (p = 0.0001 vs RAN to BPAN). Of the 22 male patients, 20 had the restrictive form (91%) and two had the BPAN form (p = 0.02 vs women). We observed conversion to BPAN in two males and to BN in one (less than in women, p < 0.01).

Using a multivariate analysis, no relationship was found between the AN subtype and age at onset, lowest BMI, anxiety and depression levels, personality disorders and scores for EDI (drive for thinness, ineffectiveness, body dissatisfaction, perfectionism, interpersonal distrust, interoceptive awareness and maturity fears). Significant correlations were found with prior-to-AN binge-eating episodes (without purging) and overweight (F = 9.1; p = 0.0032), a very high per os energy intake during hospital stay (> 2600 kcal/day, F = 5.9; p = 0.024), and no use or refusal of TF (F = 7.4; p = 0.028).

4.4. Menstrual recovery

At the 13-year follow-up, 258 of the 463 AN women (53.3%) reached recovery of AN: 97% of them resumed their menses. Using multivariate analysis in those patients not taking estroprogestative therapies (61%), only four factors were linked with normal menses recovery: BMI > 18.5 kg/m²; no excessive exercising; energy intake ≥ energy needs; fat intake > 1.1 g/kg ideal weight/day (p < 0.02). In the patients reporting normal menses, 83% had a BMI > 18.5 kg/m² and normal energy intake. Another 9% had a BMI 17.5–18.5 kg/m², but normal fat and energy intakes. In 87% of those patients who reached a BMI > 18.5 kg/m², menses resumed; in a further 7% having reached a BMI > 18.5 kg/m², but no menses, normalization of fat and energy intakes restored menstrual cycles. In other 4% with normal BMI and normal energy intake, a major decrease in physical hyperactivity was associated with menses recovery. Of the patients who had normal menses for at least 3 months, 269 (96.7%) were classified as recovered within the same year, 82 patients (17%) reported irregular menses and 23 (4.8%) suffered from gynaecological diseases.

4.5. Patient’s recovery

At the 13-year follow-up, 292 patients (60.3%) were recovered, 125 patients (25.8%) had a relatively good outcome, 31 (6.4%) had a bad outcome and 31 (6.4%) had a severe outcome. In the 22 male patients, 14 (63.6%) were classified as recovered, six (27%) had a good outcome and two (9%) had a severe outcome. The probability of full recovery increased with the relapse-free time: after 1 year without relapse, the recovery rate was 52%; after 2 years, it was 88% (243/276 patients) and, after 3 years, 96%.

The prognosis was worse in the BPAN than in the RAN subtype (p < 0.01): at 13 years, 208 RAN had recovered (60%) compared with 67 BPAN patients (49%; F = 5.4; p = 0.01). A personality disorder was associated with a poor prognosis (F = 4.9; p < 0.05), but did not reach significance when BPAN subtype was included in the model. Neither gender, age, age at onset, AN duration, any BMI variables, EDI, anxiety and depression scores nor excessive exercising were able to explain recovery.

5. Discussion

In the present cohort of 484 adult patients followed for a mean of 13 years, the mortality rate was 1.2%. Four of the six deceased patients had the BPAN subtype. This mortality rate is lower than that published before 1995 [7,13], despite the severity of the disease and the fact that these were adult patients. No deaths were observed in a total of 151 AN adolescents during a 10-year follow-up [3,5,24]. Other authors observed a mortality rate of 1.2–2.7% in a total of 823 adolescent patients [25,26]. In contrast, the results observed in adults were not as good: in a 5-year survey of 258 patients, a 3.1–3.4% mortality rate was observed [11,27,28]. At 8 years, Pla and Toro observed a mortality of 2% [29]. With longer follow-ups, three recent studies including 229 adult patients found mortality rates of 11% [12,30] and 16% [6]. It is possible that our approach of systematically prescribing TF in severely malnourished AN patients (BMI < 13 kg/m²) might explain our low 13-year mortality rate. This needs to be proved by a randomized study. At the end of the 13-year follow-up, 60% of our 484 patients were totally recovered, and 12% had a bad or severe outcome.
Similar results have been found by others after 9–19 years of follow-up [5,6,8,11,12,28]. However, Strober et al. found a 76% recovery rate at 10–15 years [3], and Steinhauser (meta-analysis of adolescent cohorts) found a 73.2% recovery rate [7].

As with other authors [3–9,14,15,31–36], we were generally unable to identify, at the time of the first hospitalization, those patients who would have a poor prognosis 13 years later. We have previously published a report of 26 AN patients followed for 5–10 years that a bad outcome could be predicted by high perfectionism and high interpersonal distrust [35]. This was not the case at 13 years in the present larger study. This contrasts with the fact that we found eight prognostic factors at 2 years: low BMI at discharge; low energy and fat intakes after 1 month of hospitalization; high scores for excessive exercising; ineffectiveness; interpersonal distrust; anxiety; and a low ability to trust and act. Also, the role of BMI was found by others [9,10,32–34], as well as the role of BPAN [5,7], though not by all [3,4]. Greater social and psychological problems were identified as predictors of a poor outcome in AN [6]. It must also be noted that a high anxiety level could either disappear or be disconnected from eating behaviour 13 years later, although this needs to be confirmed. The lack of long-term prognostic factors could have several explanations: first, AN has a natural course, and its treatment is only conservative; second, the feeling that AN is bearable and that recovery is impossible take a long time to disappear; third, recovery is related to unknown factors, and hysteria may be one of them, as shown in a long-term study in 55 AN patients [36].

In conclusion, further studies including new hormonal, behavioural and psychological factors are needed to allow better prediction of recovery in AN. Nevertheless, it appears that nutritional factors play a role in the maintenance of the disease, at least in the short term (2–3 years).

Conflicts of interest statement

The authors declare no conflicts of interest.

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