Implications of Hyperactivity in Anorexia Nervosa

From Redefinition to Clinical Research

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Abstract

Anorexia nervosa is a serious and complex psychiatric pathology included in eating disorders. Its symptoms include physical hyperactivity, which has been associated by many with a worse clinical and therapeutic outcome. Much remains to be known and understood about physical activity, which is problematic in eating disorders, especially in anorexia nervosa.

The aims of this thesis are to: 1) critically and exhaustively examine the literature published during the past 40 years (1975-2015). This is done in order to clarify the landscape and give general clinical and research perspectives for future studies. 2) Investigate the impact of different definitions of problematic physical activity, found in the literature, on its prevalence in a large sample of patients suffering from acute anorexia nervosa. We will examine the associations between these different definitions and core eating disorders symptoms, emotional profile and quality of life. 3) Investigate the impact of problematic physical activity on nutritional status (body mass index and body composition) of patients. This is done by taking into account clinical features. These features include anorexia nervosa subtypes (restricting or binge-eating/purging type), age at onset, illness duration, premenarchal anorexia nervosa, and presence of amenorrhea.

Finally, we propose a comprehensive model of the development of problematic physical activity in anorexia nervosa. We highlight the fact that physical activity could be positively taken into account in global treatment programs. It could be integrated in these programs, in addition to their psychological, somatic and social dimensions.

Problematic physical activity in anorexia nervosa is in need of immediate attention from clinicians and researchers.

Keywords: Eating disorders; Anorexia nervosa; Physical activity; Problematic; Excessive; Nutritional status; Clinical; Research.
Résumé

L’anorexie mentale est une pathologie psychiatrique grave et complexe, faisant partie des troubles du comportement alimentaire. L’un de ses symptômes est l’hyperactivité physique, généralement associée à un pronostic clinique et thérapeutique défavorable. La connaissance et la compréhension de l’activité physique, qui s’avère être problématique dans les troubles du comportement alimentaire, restent à éclaircir, en particulier dans l’anorexie mentale.

Cette thèse a pour objectifs : 1) d’examiner exhaustivement la littérature publiée au cours des 40 dernières années (1975-2015). Cela permettra de mieux comprendre ce phénomène et de donner des recommandations générales, clinique et de recherche, pour les futures études. 2) D’étudier l’impact des différentes définitions de l’activité physique problématique, retrouvées dans la littérature, sur la prévalence de celle-ci au sein d’un large échantillon de patientes souffrant d’anorexie mentale aigue. Nous examinons aussi les associations entre ces différentes définitions et les principaux symptômes alimentaires, le profil émotionnel et la qualité de vie. 3) D’étudier l’impact de l’activité physique problématique sur le statut nutritionnel (indice de masse corporelle et composition corporelle) de ces patientes. Cela est réalisé en prenant en compte les manifestations cliniques de la maladie, incluant les types d’anorexie mentale (restrictif ou avec crises de boulimie/vomissements ou prise de purgatifs), l’âge à la découverte et la durée de la maladie, le diagnostic de l’anorexie mentale avant la ménarche et la présence d’aménorrhée.

Finalement, nous proposons un modèle compréhensif du développement de l’activité physique problématique dans l’anorexie mentale. En outre, ce travail met en relief le fait que l’activité physique pourrait être positivement ciblée dans les programmes thérapeutiques. Sa prise en charge pourrait être intégrée dans la modalité thérapeutique conjointement aux différentes dimensions psychologiques, somatiques et sociales.

L’activité physique problématique dans l’anorexie mentale doit urgemment solliciter l’attention des cliniciens et des chercheurs.

Mots-clés: Troubles du comportement alimentaire; Anorexie mentale; Activité physique; Problématique; Excessive; Etat nutritionnel; Clinique; Recherche.
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<th>Description</th>
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<tbody>
<tr>
<td>ABA</td>
<td>Activity-based Anorexia</td>
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<tr>
<td>AN</td>
<td>Anorexia Nervosa</td>
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<tr>
<td>AN-R</td>
<td>Restrictive subtype of Anorexia Nervosa</td>
</tr>
<tr>
<td>AN-BP</td>
<td>Binge-eating/purge subtype of Anorexia Nervosa</td>
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<td>APA</td>
<td>American psychiatric association</td>
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<tr>
<td>BC</td>
<td>Body composition</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BN</td>
<td>Bulimia Nervosa</td>
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<tr>
<td>BSQ</td>
<td>Body shape questionnaire</td>
</tr>
<tr>
<td>BVAQ-B</td>
<td>Bermond–Vorst Alexithymia Questionnaire-Form B</td>
</tr>
<tr>
<td>CNIL</td>
<td>Commission nationale de l’informatique et des libertés</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
</tr>
<tr>
<td>EAT-26</td>
<td>26-item Eating Attitudes Test</td>
</tr>
<tr>
<td>ED</td>
<td>Eating disorders</td>
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<tr>
<td>EDE-Q</td>
<td>Eating Disorder Examination Questionnaire</td>
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<tr>
<td>EDNOS</td>
<td>Eating Disorders Not Otherwise Specified</td>
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<tr>
<td>EDQOL</td>
<td>Eating Disorders Quality of Life scale</td>
</tr>
<tr>
<td>EVHAN</td>
<td>Evaluation of Hospitalization for Anorexia Nervosa</td>
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<tr>
<td>FM</td>
<td>Fat mass</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat-free mass</td>
</tr>
<tr>
<td>FMI</td>
<td>Fat mass index</td>
</tr>
<tr>
<td>FFMI</td>
<td>Fat-free mass index</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression scale</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases, 10th edition</td>
</tr>
<tr>
<td>INSERM</td>
<td>Institut nationale de la santé et de la recherche médicale</td>
</tr>
<tr>
<td>MET</td>
<td>Metabolic equivalent</td>
</tr>
<tr>
<td>MOCI</td>
<td>Maudsley Obsessive Compulsive Inventory</td>
</tr>
<tr>
<td>ORQ</td>
<td>Obligatory Running Questionnaire</td>
</tr>
<tr>
<td>PPA</td>
<td>Problematic physical activity</td>
</tr>
<tr>
<td>R</td>
<td>Programming language and statistical software</td>
</tr>
<tr>
<td>RSES</td>
<td>Rosenberg Self-esteem Scale</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Initially,

“Even when all is known, the care of a man is not yet complete, because eating alone will not keep a man well; he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health.”

- Hippocrates, 460 – 370 BC.

However,

“Both excessive and defective exercise destroys the strength, and similarly drink or food which is above or below a certain amount destroys the health.”

- Aristotle, 384-322 BC.

And,

“Never sit if you can stand, never stand if you can walk, never walk if you can run”.

Anorexia Nervosa (AN) is a serious and complex psychiatric pathology included in eating disorders (ED). Ranking among the deadliest psychiatric illnesses, with considerably high morbidity, comorbidity (Roux et al., 2013) and mortality (Keshaviah et al., 2014), it is usually diagnosed in adolescent and young women and less common in prepubertal children and older individuals (Chapter 29, Beumont, 2002). It is mainly characterized by self-engendered weight loss, a low body mass index (BMI) and pathological concerns with weight and body shape. The clinical presentations of AN also include many symptoms that are not part of the diagnostic criteria but that are linked to the severity and complexity of the disorder. These symptoms include severe obsessional symptoms usually related to food and eating behaviors, voluntary exposure to cold and voluntary or involuntary (due to insomnia) decrease of sleeping time. Others symptoms include as excessive physical activity (Hebebrand et al., 2003) and a scholar or professional hyper-investment motivated by great perfectionism. In addition, other features linked to AN include feelings of ineffectiveness, worries about eating in public, rigid thinking, limited social spontaneity, a strong desire to control the surrounding environment and restrained emotional expression (Godart et al., 2009).

With a chronicity frequency of 21% (Roux et al., 2013), it seems that despite the best available treatment, many patients remain chronically ill (Strober, 2004). Incontestably, the mechanisms triggering and maintaining this behavior remain insufficiently understood (Treasure and Schmidt, 2013). Therefore, the need to identify and understand the pathophysiology of the mechanisms behind the development and persistence of AN is indispensable.

One of the mechanisms that has been associated by many with a worse clinical and therapeutic outcome and that could be a hallmark feature of AN is physical activity. It is linked with a longer length of hospitalization (Solenberger, 2001), poor treatment outcome (Taranis
and Meyer, 2011), interference with refeeding strategies and body weight stabilization (Ng et al., 2013) and an increased risk of relapse and chronicity (Strober et al., 1997). It has been identified as complex, paradoxical and multifaceted feature commonly present in AN since its early clinical description (Gull, 1874). Wallier et al. (1940) talk about an “internal urge toward increased physical activity”. We can also go back to the Middle Ages when there were reported cases of women and girls, mostly Catholics, starving themselves in association with physical hyperactivity, sometimes to the point of death, in the name of God (Pearce, 2004). This phenomenon was known by the name of “Anorexia mirabilis”, literally meaning “miraculous lack of appetite” and also by “inedia prodigiosa” meaning “prodigious fasting” (Grey, 2011).

Despite this early recognition and with more than 400 articles and six partial reviews published (Davis, 1997; Hebebrand et al., 2003; Kohl et al., 2004; Meyer and Taranis, 2011; Meyer et al., 2011; Young et al., 2013) on the subject in the past three decades, the main problem remains in the lack of an international consensus on how to define, conceptualize or treat these observed high levels of physical activity in AN. Much remains to be known and understood about physical activity which is problematic in ED, especially in AN. We decided to focus my PhD thesis on this question.
Part 1: Background and presentation of anorexia nervosa

Chapter 1: Clinical presentation

Clinical description

1. International classifications of anorexia nervosa

ED are severe psychiatric disorders, which involve disturbances in eating behaviors. Its main diagnosis are AN, BN and EDNOS. Starting in 1969, operational criteria for AN emphasizing symptoms and signs have been developed (Russell, 1970). AN was initially defined according to the 3A in French: “Anorexie, Amenorrhée, Amigrissement” (translated in English respectively into: anorexia, amenorrhea and weight loss) (Jeammet, 1984). These criteria varied widely with time, leading to the currently used criteria in research: the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5) (American Psychiatric Association, 2013) and the Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization, 2010 Edition).

The diagnostic criteria for AN, as defined precisely by the DSM-IV-TR (the most used in my research), and the DSM-5 and the ICD-10 (most recent ones) are presented in appendices 1, 2 and 3 respectively.

2. Hyperactivity or excessive exercise

Considered as a restricting behavior and as a feature that supports diagnosis in the DSM-5 and ICD-10 respectively, excessive exercise has not been frequently clinically described in
the literature. We found only three clinical papers (Kron et al., 1978; Casper, 1998; Kohl et al., 2004;) and one book (Beumont, 2002) that tried to give a full qualitative description of the complexity of the clinical manifestations of excessive exercise in AN. Kron et al. (1978) reported a qualitative description of hyperactivity by AN patients who revealed certain consistent features in their pre- and post-weight loss phases and during the excessive dieting-weight loss phase. According to these authors, during the pre- and post-weight loss phases, activity was described as “goal-directed, organized and planned”. However, during the acute phase of the disorder, activity was “more intense and driven, but also more disorganized and aimless than it has been previously”. Patients even declared not being able to literally sit still and experiencing a diffuse restlessness (Kron et al., 1978, p.435). Casper (1998) also mentioned the disproportionality of physical activity level opposite to the emaciation observed in very ill patients. In addition, Kohl et al. (2004) lingered on this clinical aspect of excessive exercise in AN and proposed four distinct forms: 1) The restless form of physical activity; where the patient cannot literally stand still, even for a short period of time. Physical activity in this case is considered aimless, stereotyped and inefficient. 2) A form of excessive physical activity with which patients tend to maximize their daily energy expenditure. For example, they stand up when they normally should be sitting down or walk instead of standing still. 3) A form of excessive physical activity in which activity is always practiced alone and in a routine way. This latter type is initially practiced for fitness or competitive aims but progressively loses its entertainment side and eventually gets to a point when it’s practiced for the sole purpose of losing weight. 4) When the physical activity’s intensity is modeled by the amount of food ingested, depending on the moment when the physical activity is practiced compared to a meal. Thus, if practiced before a meal, it allows the patient to eat more at that particular meal. If
practiced after a meal, it allows him/her to compensate for what he/she ate (Kohl et al., 2004, p.493).

In his book on ED and obesity, Beumont (2002) reports a quote from his patients that describes very well their feeling: “Never sit if you can stand, never stand if you can walk, never walk if you can run”. He considers that there are two kinds of presentation of excessive exercise: 1) voluntary exercise to increase calories burned and weight loss. 2) Involuntary persistent restlessness that occurs late in the illness and which is associated with sleep disturbance and is similar to hyperactivity found in animal models (Beumont, 2002).

In fact, when it comes to voluntary increase of exercise, some authors questioned the links between AN and sports: different manifestations of the same disorder, common risk factors or same underlying mechanisms? (Afflelou et al., 2004). Afflelou et al. (2004) seem to think that excessive physical activity could be a cause as well as consequence of ED, when it is developed in a socially accepted and even valued framework such as athletes’ trainings. In fact, one out of five athletes have been found to have excessive food and weight preoccupations during a period of their lives (Venisse and Grall-Bronnec, 2012). Investigating ED in athletic populations would have been extremely interesting; however, time limits did not allow further analysis of this point.

Voluntarily exercising to lose weight has been commonly used by healthy individuals and AN patients. The latter will use exercise to increase energy expenditure and accelerate loss of fat mass (Houssaim, 2010; Poudevigne et al., 2003).

As physical activity is problematic in ED, in terms of clinical and therapeutic outcomes, we will call it problematic physical activity (PPA) in the following thesis.
Epidemiology

AN is primarily a female disorder, with young girls being 10 times more likely to be affected than boys (APA, 2013). It commonly starts at adolescences, between ages of 12 and 19 years old, especially at 14 and 18 years old (Hudson et al., 2007). Puberty seems to be very critical period that could lead to body dissatisfaction, damaging one’s self-esteem. In fact, in subjects with delicate identity foundations, adolescence, which is normally a time of big physical and psychological rearrangements, could open the doors for the development of an ED (Jeammet, 2004; Fornari and Dancyger, 2003). In his book, Philippe Jeammet claimed that “[the eating disorder] becomes an alternate identity [the young girl] will hold on to not to lose herself. The interrogation becomes the following: If I am not anorexic, who am I?” (Jeammet, 2004, p.35). Other precipitating factoring during this period could be combined to stressful life events, such as grieving or separation, and thus, the start of a food diet could serve here as a possible gateway into AN (Godart and Duclos, Chapter “Etiopathogénie des troubles des conduites alimentaires” (Guelfi and Rouillon, 2011)).

AN prevalence varies widely due to measurements difficulties (Hoek and van Hoeken, 2003). In non-clinical population, it varies from 0.4% to 2.2% in women aged between 11 and 65 years old; as mentioned, it is far less common in men for whom lifetime prevalence is around 0.3% (Roux, 2013).

The heritability of AN is estimated between 50 and 70% (Gorwood et al., 2003; Bulik et al., 2010).
Complications and comorbidities

AN is a serious clinical disorder that has detrimental somatic and psychological effects on the sufferer. It is complex, with a high prevalence of associated medical complications that affect most major organ systems (see appendix 4) (Mehler and Brown, 2015). This is essentially due to the degree of weight loss, malnutrition, and the chronicity of the disorder (Miller et al., 2005). Many of these complications, irrespective of the cause, are known to be common to the semi-starvation state (Fairburn and Brownell, 2001). Encouragingly, the vast majority of them are reversible with weight gain and nutritional rehabilitation. Unfortunately, it can in some cases cause death.

AN is also linked to pre-morbid and comorbid psychiatric disorders (Fairburn et al., 1999). It is mainly associated to: 1) depressive signs and symptoms, including social withdrawal, insomnia, depressed mood, irritability and diminished sex interest. Lifetime incidence of depression varies from 15% to 60% (Godart et al., 2002). 2) Anxiety and obsessive-compulsive features (related and/or unrelated to food), with lifetime prevalence varying from 20% to 60% (Godart et al., 2002). 3) Substance abuse, in 13.7% to 23.9% of patients (Root et al., 2010), with higher rates of alcohol and other drugs abuse for the binge-eating/purging type (DSM-5). 5) Personality disorders, in 20% to 80% of patients (Halmi et al., 1991).

Treatment

The development and effectiveness of AN treatment is critical, especially that its medical complications account for more than half of all deaths of patients (Mehler and Brown, 2015). It is one of the hardest psychiatric disorders to treat, essentially due to the denial of the illness, the ambivalence of patients concerning health care, and the high rate of treatment dropout.
(Halmi et al., 2005). The treatment of AN is generally multidisciplinary with three main objectives: psychological, physical and pharmacological (English guidelines (NICE, 2004); American guidelines (APA, 2009); Australian guidelines (Beumont, 2004); French guidelines (HAS, 2010)).

1. Psychological interventions

The objectives of the psychological treatment are to decrease risk and other symptoms related to an ED, to encourage weight gain and healthy eating, and to promote psychological and physical recovery. Generally, therapies to be considered include cognitive behavior or analytic therapies, focal psychodynamic therapy, and interpersonal psychotherapy. Family interventions are also very important and strongly recommended for children and adolescents suffering from AN. In their case, the therapeutic involvements of siblings and other family members should be considered (Godart et al., 2012). There are three periods in which psychological treatment is provided: (1) outpatient care in first and last episodes; (2) inpatient care; (3) post-hospitalization care.

All care should be provided by a competent healthcare professional in the ED field, and should always be associated to physical monitoring. It should last at least for 12 months after recovery. Dietary and nutritional counselling should be provided in parallel to outpatient care. In case of:

- A significant physical deterioration of the patient with or without risk of suicide or severe self-harm, and/or
- Inconsequential improvement, and/or
- Family difficulties to cope with patients,
a more intensive form of treatment should be considered (i.e. day-care or hospitalization).

Inpatient psychological care should focus on emotional state (anxiety, depression), on eating behaviors, and on attitudes towards weight and shape. With expectations of weight gain, a structured symptom-based treatment system should be provided in parallel of careful monitoring of the patients’ physical state during refeeding.

Post-hospitalization outpatient psychological care should be provided after inpatient weight restoration. Similarly, to inpatient care, it includes eating behaviors, attitudes to weight and shape and on wider psychological issues. It should be supplemented with constant monitoring of psychological and physical risk, and typically lasts a minimum of 12 months.

2. Physical management

With significant risk of serious physical morbidity, physical management and nutritional rehabilitation should mainly focus on:

(1) The short run:

- Resuming a stable nutritional state by restoring weight,
- Normalizing eating patterns,
- Achieving normal perception of hunger and satiety,
- Normalizing psychological and somatic consequences of malnutrition.

(2) The long run:

- Achieving and maintaining a healthy weight and nutritional state for adults or a normal growth velocity for children and adolescents,
- Establishing regular eating patterns with adequate food choices and appropriate behaviors,
- Demonstrating a relaxed and flexible attitude to food, with normal responses to hunger and satiety feelings.

Regular physical monitoring and occasionally oral supplements (multi-vitamins or multi-mineral) are recommended during weight restoration periods. The frequency of the monitoring and the nature of the investigations depend on patient’s physical risk. It is recommended for the carers of children and adolescent suffering from AN to be included in the dietary education and meal planning. During weight gain, treatment should aim at an average weekly weight gain of 0.5 to 1 kg for inpatients and 0.5 kg for outpatients. This requires around 3500 to 7000 extra calories per week.

Feeding against the will of the patient should always be of last resort in the management of AN and is a highly specialized procedure that should be done in a legal medical context. Nasogastric feeding may be required in some cases, however oral feeding is the best approach to weight restoration (Sylvester and Forman, 2008). Regular pre-prepared meals are usually proposed in French facilities. However, severe cases (i.e. no food intake, bradycardia < 50, hypotension, hypothermia, apathy, etc.) could require enteral feeding (Godart et al., 2005).

Independently of the nutritional strategy adopted (oral or enteral), extreme caution should be taken while patients receive nutritional treatment to avoid the refeeding syndrome (American Academy of Pediatrics. Committee on Adolescence, 2003). Being the consequence of a very rapid nutritional replenishment in severely malnourished individuals, the refeeding syndrome can have important cardiovascular, neurologic, and hematologic complications. Reason why regular monitoring of heart rate, orthostatic vital signs, glucose and phosphorus should be done (Sylvester and Forman, 2008), in parallel of very slow renutrition, especially during the first week of care.
3. Pharmacological interventions

Pharmacotherapy does not have a well-established place in the treatment of AN and provides relatively little benefit for these patients (Crow et al., 2009). It should never be used as the primary or sole treatment for AN. Some drugs could be used with extreme cautions to treat comorbid conditions such as depression or obsessive-compulsive features. The side effects of these drugs, especially cardiac side effects, should be carefully considered.
Chapter 2: Research context

Questions

When it comes to hyperactivity in AN, several questions arise:

- What is hyperactivity in AN? What is it called and how is it defined in the literature?
- Why does the prevalence range of hyperactivity in AN vary widely from 31% to 80% in the literature (Hebebrand et al., 2003)?
- Is hyperactivity higher in individuals suffering from AN than the general population?
- Is hyperactivity higher in AN than in BN? Does it differ according to AN subtypes?
- Are there links between hyperactivity and psychological factors in ED?
- Are there links between hyperactivity and ED symptomatology?
- Are there links between hyperactivity and ambient temperature?
- Are there any links between hyperactive animal models and hyperactivity in AN?
- Are there links between hyperactivity and nutritional status of AN?
- Are there any available treatments for hyperactivity in AN?

In order to try answering the questions above, I initially had to contextualize what is general human physical activity and then realize an exhaustive systematic critical review of everything that has been done before when it comes to hyperactivity in ED.
Objectives of thesis

In order to clarify what is PPA in AN, the following work was designed to:

1. Critically examine all the clinical literature published during the past 40 years (1975-2015). Investigate definitions given to PPA, methodology difficulties and finally, categorize all past definitions given to PPA in order to analysis studies’ results according to new criteria (allowing us to better analyze published data in terms of prevalence and linked factors). Give general clinical and research perspectives for future studies on the matter.

2. To test the hypotheses developed in our literature review on a large sample of severely ill AN patients:

   2.1. To investigate the impact of the different PPA definitions found in the literature on its prevalence and explicative factors. To examine how core ED symptoms, emotional profile and quality of life scores are associated with these different definitions.

   2.2. To investigate the impact of exercise on nutritional status (BMI and body composition), conjointly taking into account clinical features including AN subtypes (restricting or binge-eating/purging type), age at AN onset and illness duration, premenarchal AN, and presence of amenorrhea.

3. In conclusion, propose a comprehensive model of the development of PPA in AN, and therapeutic and research perspectives.
Part 2: Problematic Physical Activity in Anorexia Nervosa

Chapter 1: Critical review of the literature: Methodology

(Review article submitted to Eating and Weight Disorders.
Currently under review)

Introduction

A display of abnormally high levels of physical activity (PA) has been observed from the earliest clinical description of eating disorders (ED) (Gull, 1874). It has been considered to affect 31% to 80% of patients suffering from anorexia nervosa (AN) (Hebebrand et al., 2003). It also has been associated with worse clinical and therapeutic outcomes (El Ghoch et al., 2013; Ng, Ng, & Wong, 2013; Solenberger, 2001; Strober, Freeman, & Morrell, 1997; Taranis & Meyer, 2011). There are more than 400 articles and seven reviews published (Davis, 1997; Gümmer et al., 2015; Hebebrand et al., 2003; Kohl, Foulon, & Guelfi, 2004; Meyer & Taranis, 2011; Meyer, Taranis, Goodwin, & Haycraft, 2011; Young, Rhodes, Touyz, & Hay, 2013) on the subject in the past three decades. These reviews pulled studies using heterogeneous definitions, instruments and methodology, did not include all published studies, and/or focused only on one aspect of the topic. For example, the latest review only focused on studies that used accelerometers to measure PA in AN (Gümmer et al., 2015). Consequently, it omitted more than 62% of the literature by excluding studies that measured PA using a subjective method. Despite all these important publications, there is still no consensus on a clear and valid definition and treatment for these observed high levels of PA in AN.
We designed the following review in order to provide an overview of all the definitions proposed so far in the literature and to suggest recommendations for future research. Since this topic is extremely large and includes substantial information, the review will be divided into two parts. The first part will provide an exhaustive critical analysis of the methodology of all studies evaluating PA in AN samples. The second part will focus on their results. Considering all previous literature on what we will call problematic physical activity (PPA) in AN., the aims of this chapter (first part) are to: 1) Critically analyse the methodology of reviewed studies, hypothesized to have impacted their results. 2) Review all terms and definitions given to PPA and instruments used to assess it. 3) After clarifying the landscape, propose a categorization of PPA based on the quantitative and qualitative dimensions of PA assessed in studies.
Methods

The systematic literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) (Figure 1).

Data sources and search strategies

Searches were done in online databases, namely MEDLINE and Web of Science. The following search strategy was conducted (adapted for each database): (“Eating disorders” OR “anorexia nervosa”) AND (“Exercise” OR “activity” OR “physical”) AND (“Excessive” OR “dependence” OR “addiction” OR “compulsive” OR “driven” OR “abuse” OR “over” OR “restless” OR “obligatory” OR “urge” OR “energy”). Only articles in English or French, published between 1970 and September 2015 were reviewed. This search was complemented by a manual search: reference lists of articles were manually investigated to identify studies potentially relevant for inclusion and that were not detected by electronic search. When data were missing in the paper, additional information from authors was systematically sought.

Study selection and quality assessment

Eligible studies in the empirical literature should have aimed to evaluate the prevalence, the frequency, the nature and/or the clinical associated features (psychological or somatic) of PA in AN. Our inclusion criteria limited our review to human studies that recruited all participants, or at least part of them, diagnosed with AN (with or without the mention of the restrictive or binge-eating/purging types). All studies including healthy individuals, athletes or animals were excluded. Studies exclusively including other disorders such as Bulimia Nervosa, Binge Eating Disorder or
Attention Deficit Hyperactivity Disorder and case reports were excluded. All studies that did not match the aim of our review (for example, papers on the treatment and/or management of PA in ED) were not considered.

We carefully analysed studies that included more than one ED type. Many have previously found that patients suffering from AN had more PPA than the ones suffering from bulimia nervosa (Brewerton, Stellefson, Hibbs, Hodges, & Cochrane, 1995; Dalle Grave, Calugi, & Marchesini, 2008; Davis et al., 1997; Pirke, Trimborn, Platte, & Fichter, 1991; Shroff et al., 2006; Solenberger, 2001). Consequently, we chose to exclude studies that mixed more than one ED type without reporting separate results for each type. Despite mixing patients with AN and patients suffering from eating disorders not otherwise specified (EDNOS), the studies of Carrera et al. (Carrera et al., 2012), Kostrzewa et al. (Kostrzewa et al., 2013), Pinkston et al. (Pinkston et al., 2001) and Mond and Calogero (Mond & Calogero, 2009) were not excluded. The only difference between patients was that patients with EDNOS did not meet the DSM-IV weight criterion. However, they had a weight that was “clearly below that which expected from their own growth curves” (p.2) (Kostrzewa et al., 2013). This converges with the new DMS-5 weight criteria (APA, 2013). Mond and Calogero (Mond & Calogero, 2009) excluded the EDNOS group from the statistical analyses.

It should be noted that some studies included totally or partially the same study samples (studies of Carrera et al. (Carrera et al., 2012) and Kostrzewa et al. (Kostrzewa et al., 2013) and of El Ghoch et al. (El Ghoch, Alberti, Capelli, Calugi, & Dalle Grave, 2012) and Alberti et al. (Alberti et al., 2013)). They were not excluded because they had different objectives and/or used different instruments to measure PA. In addition, for efficient comparison purposes, we chose to exclude the only study that exclusively included men (Murray et al., 2012).

A quality checklist was developed for this review based on items widely used when assessing epidemiological studies (Pocock et al., 2004; Zaccai, 2004). It allowed us to identify potential
sources of selection and/or information bias (figure 1). The first author extracted the necessary data (information on eligibility criteria, study designs, baseline characteristics and methodological quality) from included studies and the last author checked this data. Disagreements between reviewers were resolved by consensus, mainly concerning studies that matched or not the purpose of the review.

It was not possible to conduct a meta-analysis due to the high variability and heterogeneity in the study populations and methodologies. Thus, the following is a descriptive and critical systematic review of 37 retained articles (figure 1).

Physical activity in the general population

What is physical activity in the general population?

Physical activity is considered to be any body movement produced by the contraction of skeletal muscles, resulting in a substantial increase of energy expenditure relatively to basal metabolism (Caspersen et al., 1985). In this thesis, the term physical activity includes exercise and sports. Generally, there are three main characteristics of physical activity: 1) frequency, referring to the number of physical activity sessions per day, week, or month; 2) volume or duration, described respectively as the number of physical activity minutes in each physical activity session and as the total time of physical activity session; 3) intensity, described as energy expenditure (light, moderate or vigorous) associated with certain physical activity (Vanhees et al., 2012).
What is considered as a healthy /unhealthy physical activity in the general population?

General recommendations for adults aged between 18 and 64 years old are to “do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity” (WHO, 2010, p.26). Moreover, the practice of physical activity can be described along a continuum from inactivity to excessive physical activity. Nowadays, physical activity has been widely recognized to increase health and functional capacity (Booth et al., 2012). It seems that only individuals with a moderate to regular practice benefit from the positive effects of physical activity (United States Department of Health and Human Services [USDHHS], 1996). Defining when a physical activity is considered problematic is not easy and is too often a subjective data. A PPA is one that has relatively high levels of physical activity intensity, frequency and/or volume. Hausenblas and Downs (2002) talk about dependence to exercise in the general population. It includes seven major criteria: withdrawal, continuity, tolerance, loss of control, decrease in other activities, time and intention (appendix 8). There are two types of exercise dependence (Ogden et al., 1997; Bamber et al., 2003): primary and secondary. The primary dependence is reported in individuals without eating disorders and its prevalence is generally low (around 4%, INSERM 2005). However, it is the second type that is associated with ED.

In other words, PPA is identified by the physical activity’s characteristics and by the relation that links a person with his physical activity. Thus, we can talk about a PPA in general when a physical activity becomes increasingly intrusive, repetitive, and/or uncontrolled; when its withdrawal results in the person's suffering while its continuation causes the people around this person to suffer; when it causes physical damages (chronic or stress injuries) and/or has psychological consequences (overtraining syndrome, burnout, depression) (Cook et al., 2013).
PPA in the general population has been strongly associated with eating disorders (Bratland-Sanda et al., 2011).

**Results**

**Study designs**

Studies were cross-sectional (18/37), prospective (15/37), retrospective (2/37) or follow-ups (1/37) (table 1, column 2). One study had a prospective design and included a short-term follow-up at one year (Kostrzewa et al., 2013).

About half the studies were case-controls (14/37) (table 1, column 3). Controls generally consisted of healthy individuals except for two studies that included healthy exercisers (Davis et al., 1995) or an anxiety group (Keyes et al., 2015) which was based on a moderate severity score at the 7-item General Anxiety Disorder scale.

**Sample characteristics**

Out of 37 studies, 14 included less than 30 patients suffering from ED (table 1, column 3). All studies reported the diagnostic criteria used for AN (table 1, column 4). Current age of participants was reported in all studies except one (Brewerton et al., 1995) (table 1, column 5). Illness duration was mentioned in 16 studies (table 1, column 6); it varied widely, from 11 months to 28 years. Age at onset of ED was only reported in seven studies (table 1, column 7). The majority of studies (33/37) included participants suffering from a current ED (table 1, column 8); inpatients (19/37), outpatients (6/37) or a mix of both (8/37) (table 1, column 9). Two studies evaluated women recovered from AN (Dellava, Hamer, Kanodia, Reyes-Rodriguez, & Bulik, 2011; Kaye, Gwirtsman, George, Ebert, & Petersen, 1986). Shroff et al. (Shroff et al., 2006) had the biggest
study sample that consisted of 1857 individuals suffering from lifetime ED. However, they included a particular sample of female proband and affected female relatives from three different genetic studies. Thornton et al. (Thornton, Dellava, Root, Lichtenstein, & Bulik, 2011) included a population of twins. The statistical analyses (multivariate and univariate) produced in each study are presented in table 1 (column 10).

**Terms and definitions of problematic physical activity**

As mentioned earlier by Meyer and Taranis (Meyer & Taranis, 2011), researchers have given a plethora of terms and definitions to describe PPA in ED patients. Terms included “motor activity”, “hyperactivity”, “compulsive exercise”, “excessive exercise”, “motor restlessness”, “exercise dependence”, “inner-restlessness”, “drive for activity”, and “drive to exercise” (table 2, column 2). Since this PA is problematic in AN, we proposed to call it PPA in the following paper. This terminology comprehensively covers both problematic dimensions of PA in AN, in terms of quantity and quality.

In healthy individuals, independently of ED, PA is generally defined by three characteristics: frequency (number of PA sessions per day, week, or month), duration (total time of PA session) and intensity (light, moderate or vigorous energy expenditure associated with a particular PA) (Vanhees et al., 2012).

After reviewing all the definitions of PPA proposed in the AN literature, we found that these definitions generally included two dimensions: 1) a quantitative dimension, including frequency and/or duration and/or intensity of PA. Cut-offs varied widely, ranging from a “minimum of 5 hours per week” (Davis et al., 1995) to “more than two hours per day” (Thornton et al., 2011) (table 2, column 3). 2) A qualitative dimension, including motivation to exercise (i.e. “to control weight and shape” (Mond & Calogero, 2009)), a description of a feeling associated with PA (i.e. “feeling
distress if unable to exercise” (Shroff et al., 2006)) or a description of PA itself (i.e. “exercise described as "obsessive," "driven," and "out of control" (Davis et al., 1997)) (table 2, column 3). Some authors combined both dimensions in their definitions and this led to many possible combinations. The definition of PPA that was used the most in the literature (7/37) was exercising at least 5 hours a week (Davis & Fox, 1993).

**Evaluation of physical activity**

There is an important variety in instruments used to assess PA. PA was measured: 1) objectively (14/37) (using an accelerometer (8/14) and/or the doubly labelled water method (4/14), or an actimeter (3/14)); 2) subjectively retrospectively (29/37) (with a self-report (17/29), an interview (16/29), or from clinical charts (2/29)) or prospectively (3/37) (with reports or diaries) (table 2, column 4). We only identified three studies that used a validated subjective method: two studies (Alberti et al., 2013; Keyes et al., 2015) used the International Physical Activity Questionnaire and one (Pinkston et al., 2001) used the Seven-day Physical Activity Recall. The rest used non-validated subjective methods (table 2, column 4).

**Discussion**

This review highlights a considerable heterogeneity of definitions and methods used in studies, which undeniably contributed to highly variable and even contradictory results.

**Evaluation of physical activity**

The quantitative dimension of PPA was measured using objective and/or subjective methods and both have advantages and inconveniences. Most studies (23/37) based their PA
measure exclusively on a subjective method, mainly with self-reports (21/37). Collecting valid data through self-reports depends on the reliability of the interviewee in reporting accurately his/her practice of PA over a determined period. Unfortunately, denial is a common process in AN. Patients are known to give unreliable answers and/or deliberately omit to talk about their symptoms (Couturier & Lock, 2006; Vandereycken & Vanderlinden, 1983). These methods were found to underestimate (Alberti et al., 2013; van Elburg, Hoek, Kas, & van Engeland, 2007; Vandereycken & Vanderlinden, 1983) or overestimate (Keyes et al., 2015) PA. Many studies (8/37) used accelerometers. Gümmer et al. (Gümmer et al., 2015) underlined that these instruments are a valid objective method in AN, however, could be difficult to implement, especially in an inpatient setting, leading to problems of refusal or compliance. Consequently, if we consider all these elements, it would be more practical for studies that include large samples to use self-reports to assess PA (Davis, Kennedy, Ravelski, & Dionne, 1994). Studies that include smaller samples could benefit from precise measures of PA assessed using accelerometers or the doubly-labelled water method. In an inpatient setting, the nurses’ observations of PA levels of patients may be an easy and informative evaluation (van Elburg et al., 2007). It should be seriously considered in future research.

One of the most frequent qualitative dimension of PPA evaluated in studies was compulsion to exercise. Compulsion in psychopathology is generally defined as a trait leading to “actions inappropriate to the situation which persist, have no obvious relationship to the overall goal and which often result in undesirable consequences” (p. 680) (Dalley, Everitt, & Robbins, 2011). Compulsion to exercise has not been consensually defined yet. Historically, it was initially assessed, in the studies included in this review, using instruments not associated to ED such as the Obligatory Running Questionnaire (Blumenthal, O'Toole, & Chang, 1984). However, other questionnaires (the Eating Disorders Examination (Fairburn & Beglin, 1994), the Eating Disorders
Examination-Questionnaire (Cooper, Cooper, & Fairburn, 1989), Diagnostic Survey of the Eating Disorders (Johnson, 1987) and the Compulsive Exercise Test (Taranis, Touyz, & Meyer, 2011)) assessed compulsion to exercise associated with eating pathology. Unfortunately, this could create large discrepancies between published results: attempts at interpreting the results as confirmation of the links between ED symptoms and compulsion to exercise is bound to lead to a certain circularity.

**Other methodological problems**

There is a particular lack of longitudinal studies which limits interpretations of causality in the associations identified. Most studies were cross-sectional (18/37) and only half of them included controls. The choice of controls is very critical when it comes to studies that aim to determine various aspects of PPA in an ED population (Eisler & Le Grange, 1990). The control group should be chosen in adequacy with the study purpose.

Furthermore, around 40% of studies included less than 30 participants. If this is justifiable for studies that used a complicated technique (i.e. the doubly labelled water method), such a small number of participants is less than what is classically required to serve as an acceptable proxy for the population it represents (Bauer, 2009).

Samples are frequently heterogeneous in terms of diagnostic criteria, age at illness onset and illness duration. Illness duration and age at onset were mentioned in less than half the studies. Few studies controlled their sample for factors impacting PA in the general population such as age (PA prevalence is found to be higher during childhood and adolescence than among young adults and older age groups (Owen, Leslie, Salmon, & Fotheringham, 2000).
Terms and definitions of problematic physical activity

The lack of an official valid terminology for PPA in AN has translated into a plethora of terms and definitions. This phenomenon has been described in social psychology as the “déjà-vu” phenomenon. It’s “the feeling that one has seen a variable with the same definition and content before only referred to by a different term” (Hagger, 2014). Unfortunately, this phenomenon misleads reviewers into concluding that findings are inconsistent or contradictory, when in fact it is the definitions that are inconsistent and contradictory (Hagger, 2014). In addition, the same term used in different studies would not automatically have the same definition (i.e. “compulsive exercise” (Brewerton et al., 1995; Dalle Grave et al., 2008)) (table 2 column 2).

Some authors preferred certain terms over others. For example, in their review on terms and definitions, Meyer and Taranis (Meyer & Taranis, 2011) suggest “compulsive exercise” as a consistent term. We do not agree with this position since the use of the word “compulsive” only highlights the qualitative aspect of PA in AN. Gümmer et al. (Gümmer et al., 2015) suggested the use of “high levels of physical activity” as an understandable term, which only highlights the quantitative aspect of PA. Nonetheless, clinical descriptions of PA in AN show that there PA is problematic in quantitative and qualitative aspects (Adkins & Keel, 2005). The term PPA, which we suggested, embraces both aspects of PA which are problematic in terms of quantity (frequency, intensity and/or duration) and/or quality (compulsion to exercise, psychopathological motivations to exercise, dependence and addiction).

Furthermore, some authors used the term “PA” when in fact they were assessing exercise (Solenberger, 2001). It should be noted that exercise is a subgroup of physical activity: it is a physical activity that is planned, structured, repetitive, and purposeful. General physical activity includes any body movement that contracts the muscles to burn more calories than the body
would normally do at rest (Caspersen, Powell, & Christenson, 1985). These terms should be used accurately in future research.

**Neglected clinical aspect of problematic physical activity in anorexia nervosa**

There is no definition of what is considered a “normal” PA in AN. In the general adult population (18 to 64 years old), a healthy PA is characterized by “at least 150 minutes of moderate-intensity aerobic physical activity throughout the week” (Organization, 2010). In their study on PPA in AN, Davis et al. (Davis et al., 1997) acknowledged that six hours a week of PA is not excessive for healthy normal-weight women. However, it is excessive for emaciated women such as those with AN. Thus, it seems that the determination of “normal” levels of PA and of PPA in AN should be done according to the degree of emaciation of patients. No study, except for Bouten et al. (Bouten, van Marken Lichtenbelt, & Westerterp, 1996), considered using thresholds of body mass index when assessing PPA. Clinically, it seems that quantitative PA varies along a continuum from total inactivity to PPA. We noticed the lack of research devoted to patients with extreme levels of PA. On the one hand, there are patients with low to no PA and on the other hand, there are patients who feel an increasingly strong compulsion to be physically active despite pain, severe injuries (i.e. broken ankle), very low weight and exhaustion (Davis, 1997).

We only found three papers on the clinical description of PPA in AN (Casper, 1998; Kohl et al., 2004; Kron, Katz, Gorzynski, & Weiner, 1978). Kron et al. (Kron et al., 1978) reported some consistent features in patients during the different phases of AN. During the pre- and post-weight loss phases, PA was described by patients as “goal-directed, organized and planned”. During the acute phase, PA was “more intense and driven, but also more disorganized and aimless” (p. 435). Casper (Casper, 1998) mentioned the disproportionality of PA levels in contrast to the emaciation
observed in very ill patients. Kohl et al. (Kohl et al., 2004) proposed four distinct forms of PPA in AN: 1) A restless form of PA (when patients cannot literally stand still, even for a short period of time. PA is considered aimless, stereotyped and inefficient). 2) PA practiced to maximize daily energy expenditure (i.e. stand up when normally should be sitting down or walk instead of standing still). 3) Exercise practiced alone and in a routine way, without pleasure. This exercise could initially have started as a hobby but will gradually lose its notion of pleasure and will only be practiced in efforts to lose weight. 4) PA practiced according to the amount of food ingested. PA will allow the patient to eat more before a meal or to compensate what he/she ate after a meal. Beumont (Beumont, 2002) described two manifestations of PPA: voluntary exercise to increase calories burned and weight loss and involuntary persistent restlessness that occurs late in the illness and that is associated with sleep disturbance (similar to hyperactivity found in animal models). He reported that his patients never sat when they could stand, never stood when they could walk and never walked when they could run. Research on the clinical description of PPA in AN is strongly needed.

In our clinical practice, we can identify three manifestations of PPA in patients: conscious and voluntary PPA, unconscious and involuntary PPA and conscious and involuntary PPA. Voluntary/conscious PPA includes an increase of PA. This PA could consist of conditioning exercises such as sit-ups (hundreds of sit-ups in daily rigid routines that could be performed in a secret and compulsive way). It could also involve a voluntary increase of exercise in terms of duration and/or intensity (exercising for longer periods, practising high intensity physical activities such as running or rock climbing). This voluntary increase of PA could also be observed in daily activities: some patients will voluntarily walk instead of using public transportation, or use the stairs instead of the elevator. Involuntary/unconscious PPA includes the constant need to maintain movement (restlessness, aimless wandering or inability to sit still). Even when obliged to sit, there
is a constant need to maintain movement in the form of leg swinging or constant jiggling of a part of the body. It could also take the form of static muscle pressure (keeping abdominal muscles tensed when seated or standing on one leg to increase pressure on the other). This PA often increases with the evolution of AN and loses its initial function of well-being. If limited, it could create withdrawal-like symptoms along with feelings of anxiety and discomfort. Involuntary/unconscious PPA could become, with the evolution of the treatment, conscious PPA. PPA will however stay involuntary because despite acknowledging this symptom, patients will not be able to control it.

Finally, it seems that considerations of PA as a dependence or addiction is also neglected in AN. Few studies have mentioned this aspect of PA (Bratland-Sanda et al., 2011; Bratland-Sanda et al., 2010; Keyes et al., 2015; Klein et al., 2004; Long & Smith, 1993). This is not the case in the general population where exercise dependence has been very well defined and identified (Hausenblas & Downs, 2002).
Conclusion: proposition of categorization of PPA

We propose to differentiate studies according to the nature of PA considered (quantitative or qualitative dimension), in line with Adkins and Keel (Adkins & Keel, 2005). We defined two groups: Group 1 and Group 2. Group 1 (PPA-qT) includes all the results of studies only evaluating the quantitative dimension of PA in terms of frequency, duration and/or intensity. Group 2 (PPA-qL) includes the results of all studies evaluating the qualitative dimension of PA (the relationship an individual has with his/her PA and/or its links with ED behaviours, pathological motivation(s) for exercise, compulsion to exercise, exercise dependence or addiction).

The results of 30 studies were exclusively included in Group 1 (15) or Group 2 (15), and the results of seven studies were included in both groups (table 3).

If a study measured both quantitatively and qualitatively dimensions of PA, the results would be included in the appropriate group. Consequently, the same study could belong to both groups. Davis et al. (Davis, Kaptein, Kaplan, Olmsted, & Woodside, 1998) defined PPA over two assessment periods: “current” (in the previous month) and “lifetime” (in the previous year) (table 2, column 3). Lifetime definition included a quantitative criterion (duration of PA) and a qualitative criterion (exercise described as “obsessive,” “driven,” and “out of control”). Results emerging from this definition were included in Group 2. However, current definition only included a quantitative criterion. Results emerging from this definition were included in Group 1. This is applicable for all studies that used the “current” and “lifetime” definitions of PPA developed by Davis et al. (Davis et al., 1998). Nonetheless, in the latest study of the same research team, Davis and Kaptein (Davis & Kaptein, 2006), the “current” definition included a qualitative criterion of PPA (“out of control” or “excessive”). Only the results of this particular study were included in Group 2. See part two of this review for the results.
Figures

Figure 1. Flow diagram of study selection for review

- Literature search
  Databases: MEDLINE and Web of Science
  Limits: English- or French-language articles only

- Search results combined (n= 414)

- Articles screened on basis of title and abstract (n= 262)
  Excluded (n= 149)
    General population: 73
    Animal models: 23
    Duplicates: 22
    Athletes: 20
    Binge eating disorder: 4
    Bulimia Nervosa: 3
    Case studies: 5
    Attention deficit hyperactivity disorder: 1

- Included (n= 113)

- Manuscript review and application of inclusion criteria
  Excluded (n= 55):
    Do not match purpose of review: 29
    Treatment/management programs: 19
    Other reviews: 7

- Included (n= 58)

- Articles screened on basis of quality checklist
  1. Sufficient response or attrition rate achieved (≥ 60%)
  2. Report of the characteristics of drop-outs or non-responders
  3. Sufficient description of the study population (gender, age, etc.)
  4. Use of research diagnostic criteria for eating disorders
  5. Replicable definition given for problematic physical activity
  6. Distinction in the study sample between eating disorders types
  7. Pulled study groups for results

- Excluded* (n=21)
  No distinction between eating disorders types
  (and/or no comparison between types) : 11
  No replicable definition of physical activity : 6
  No use of research diagnostic criteria for eating disorders : 3
  Only included men: 1

- Included in review (n=37)

*Studies excluded for one or more reasons.
<table>
<thead>
<tr>
<th>References Country</th>
<th>Study design</th>
<th>Sample composition</th>
<th>Diagnostic criteria</th>
<th>Age (years) Mean ± SD (range)</th>
<th>Duration of illness (years) Mean ± SD (range)</th>
<th>Age of onset of ED (years) Mean ± SD (range)</th>
<th>Prevalence period of ED</th>
<th>Type of treatment</th>
<th>Statistical analyses nature</th>
</tr>
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<td>Falk et al. (1985) USA</td>
<td>Prospective</td>
<td>20 AN</td>
<td>DSM-III</td>
<td>21.1±5.6</td>
<td>-</td>
<td>-</td>
<td>Current</td>
<td>In</td>
<td>Univariate</td>
</tr>
<tr>
<td>Kaye et al. (1986) USA</td>
<td>Prospective</td>
<td>22 AN; 11 HC</td>
<td>DSM-III</td>
<td>RW-R=25.0±1.1 LtW-R=24.9±1.7</td>
<td>RW-R=7.0±1.1 LtW-R=8.3±1.2</td>
<td>RW-R=17.6±0.9 LtW-R=16.5±1.4</td>
<td>Lifetime</td>
<td>Recovered</td>
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<tr>
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<td>6 AN; 6 HC</td>
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<td>24.5±0.8</td>
<td>1.9±0.9</td>
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<td>Out</td>
<td>Univariate</td>
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<tr>
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<td>Prospective</td>
<td>8 AN; 8 BN; 11 HC</td>
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<td>AN= 27.8±5.2 BN= 24.3±4.7</td>
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<td>Current</td>
<td>In</td>
<td>Univariate</td>
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<tr>
<td>Long et al. (1993) Canada</td>
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<td>21 AN; 62 HC</td>
<td>DSM-III-R</td>
<td>25.0±9.7</td>
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<td>-</td>
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<td>In</td>
<td>Univariate</td>
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<td>Cross-sectional</td>
<td>18 AN; 71 BN; 21 EDNOS</td>
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<td>-</td>
<td>Ces: 12.1±3.0 Non-Ces: 16.3±1.8</td>
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<td>In</td>
<td>Univariate</td>
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<td>46 AN; 88 regular exercisers; 40 high-level exercisers</td>
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<td>Multivariate</td>
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<td>73 AN</td>
<td>Feighner criteria</td>
<td>Early adolescent onset: 16.2±3.3 Late adolescent onset: 19.7±3.3 Adult onset: 25.2±3.7</td>
<td>2.9</td>
<td>Early adolescent onset: 13.9±1.1 Late adolescent onset: 17.3±0.8 Adult onset: 22.2±2.6</td>
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<td>“5 to 28”</td>
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<td>DSM-IV</td>
<td>Sample 1: 27.7±7.8</td>
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<td>In and out</td>
<td>Univariate</td>
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<td>Sample 2</td>
<td>Methods</td>
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<td>34 AN; 49 BN</td>
<td>DSM-III-R</td>
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<td>In and out</td>
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<td>15.4±1.4</td>
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<td>Multivariate</td>
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<td>Current</td>
<td>Out</td>
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<td>Current</td>
<td>-</td>
<td>Multivariate</td>
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<td>In</td>
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<td>Current</td>
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<td>DSM-IV</td>
<td>23.4±4.8</td>
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<td><strong>Shroff et al. (2006)</strong></td>
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<td>521 RAN; 336 PAN; 182 BAN; 296 PBN; 25 NPBN; 400 ANBN</td>
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<td>15.6±1.9</td>
<td>Current</td>
<td>In</td>
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<td>DSM-IV</td>
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<td>USA</td>
<td>14 AN-R; 22 AN-BP</td>
<td>DSM-IV</td>
<td>26.3±5.9</td>
<td>Current</td>
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<td>Prospective</td>
<td>Italy</td>
<td>35 AN-R; 30 AN-BP; 28 BN-P; 72 EDNOS</td>
<td>DSM-IV</td>
<td>26.0±7.8</td>
<td>Current</td>
<td>In</td>
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<td>Mond and Calogero (2009)</td>
<td>Cross-sectional</td>
<td>Australia</td>
<td>15 AN-R; 13 AN-BP; 41 BN; 33 EDNOS; 184 HC</td>
<td>DSM-IV</td>
<td>AN-R: 21.0±8.3; AN-BP: 23.6±8.3; BN: 23.8±6.2; EDNOS: 20.5±7.8</td>
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<td>Out</td>
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<td>Bewell-Weiss and Carter (2010)</td>
<td>Cross-sectional</td>
<td>Canada</td>
<td>98 AN-R; 61 AN-BP</td>
<td>DSM-IV</td>
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<td>6.4±8.0</td>
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<td>Thornton et al. (2011)</td>
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<td>Sweden &amp; USA</td>
<td>32 AN; 22 AN+GAD; 5424 HC</td>
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<td>AN:34.8±6; AN+GAD: 30.1±6.5</td>
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<td>Lifetime</td>
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<td>Dellava et al. (2011)</td>
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<td>Lifetime</td>
<td>Recovered</td>
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<td>Carrera et al. (2012)</td>
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<td>The Netherlands</td>
<td>25 AN-R; 9 AN-BP; 3 EDNOS*</td>
<td>DSM-IV</td>
<td>15.3±1.25</td>
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<td>El Ghoch et al. (2013)</td>
<td>Prospective</td>
<td>Italy</td>
<td>32 AN-R; 21 AN-BP; 53 HC</td>
<td>DSM-IV</td>
<td>24.5±8.8</td>
<td>-</td>
<td>Current</td>
<td>In</td>
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<tr>
<td>Alberti et al. (2013)</td>
<td>Prospective</td>
<td>Italy</td>
<td>52 AN</td>
<td>DSM-IV</td>
<td>24.4±8.4</td>
<td>5.0±9.0</td>
<td>Current</td>
<td>In</td>
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<tr>
<td>Kostrzewa et al. (2013)</td>
<td>Prospective and follow-up</td>
<td>The Netherlands</td>
<td>25 AN-R; 9 AN-BP; 3 EDNOS*</td>
<td>DSM-IV</td>
<td>15.2±1.2</td>
<td>-</td>
<td>Current</td>
<td>23 In; 14 Out</td>
<td>Univariate</td>
</tr>
<tr>
<td>Zipfel et al. (2013)</td>
<td>Prospective</td>
<td>Australia</td>
<td>8 AN-R; 4 AN-BP; 12 HC</td>
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<td>21.9±6.2</td>
<td>4.3±3.9</td>
<td>Current</td>
<td>In</td>
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(Note: AN = Anorexia Nervosa, BN = Bulimia Nervosa, EDNOS = Eating Disorder Not Otherwise Specified, GAD = Generalized Anxiety Disorder, HC = Healthy Control, * = includes patients with other eating disorders)
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<th>Study</th>
<th>Design</th>
<th>Sample Description</th>
<th>DSM-5</th>
<th>DSM-IV</th>
<th>Outcomes</th>
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<td>Keyes et al. (2015) United Kingdom</td>
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<td>29.0</td>
<td>-</td>
<td>Current 18 In; 37 Out</td>
<td>Multivariate</td>
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Table 2. Terms, definitions and cut-offs of problematic physical activity (PPA) and instruments used to assess physical activity (PA) (columns 1 to 4)

<table>
<thead>
<tr>
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<tr>
<td>References</td>
<td>Terms used by authors</td>
<td>Definitions and cut-offs of PPA</td>
<td>Assessment instrument of PA</td>
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<td>Falk et al. (1985)</td>
<td>Motor activity</td>
<td>Frequency - Duration - Intensity -</td>
<td>Actimetry -</td>
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<td>Kaye et al. (1986)</td>
<td>PA</td>
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<td>Accelerometry -</td>
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<td>Casper et al. (1991)</td>
<td>PA</td>
<td>- - -</td>
<td>DLW -</td>
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<tr>
<td>Pirke et al. (1991)</td>
<td>Hyperactivity</td>
<td>- - -</td>
<td>DLW Diary</td>
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<td>Long et al. (1993)</td>
<td>Hyperactivity</td>
<td>- - -</td>
<td>ORQ; Modified CRQ</td>
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<tr>
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<td>Compulsive exercise</td>
<td>&gt; once a day ≥ 60 min -</td>
<td>Exercise to control weight -</td>
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<td>Caetano et al. (1996)</td>
<td>Excessive exercise</td>
<td>- ≥5 h per week -</td>
<td>-</td>
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<td>Casper and Jabine (1996)</td>
<td>Excessive exercise</td>
<td>- &gt; 4 h per week -</td>
<td>- Interview</td>
</tr>
<tr>
<td>Bouten et al. (1996)</td>
<td>PA</td>
<td>- - Low, moderate or high</td>
<td>Accelometer; DLW -</td>
</tr>
<tr>
<td>Davis et al. (1997)</td>
<td>Excessive exercise</td>
<td>&gt; 6 days per week &gt; 1 h per day -</td>
<td>Exercise described as &quot;obsessive,&quot; &quot;driven,&quot; and &quot;out of control&quot;. -</td>
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<td>Davis and Claridge (1998)</td>
<td>Excessive exercise</td>
<td>&gt; 6 days per week &gt; 1 h per day -</td>
<td>Exercise described as &quot;obsessive,&quot; &quot;driven,&quot; and &quot;out of control&quot;. -</td>
</tr>
<tr>
<td>Davis et al. (1999)</td>
<td>Excessive exercise</td>
<td>&gt; 6 days per week &gt; 1 h per day -</td>
<td>- Interview; CES</td>
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<td>Excessive exercise</td>
<td>- &gt; 1 h per day Intensive -</td>
<td>- Interview</td>
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<tr>
<td>Pinkston et al. (2001)</td>
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<td>- - Moderate, hard or very hard</td>
<td>- 7d PAR; CES</td>
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<td>Solenberger (2001)</td>
<td>PA</td>
<td>- &gt; 6.7 h per week -</td>
<td>- Clinical charts</td>
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<tr>
<td>Penas-Lledo et al. (2002)</td>
<td>Excessive exercise</td>
<td>- ≥1 h without stopping -</td>
<td>Aim of burning calories -</td>
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<td>Davis and Woodside (2002)</td>
<td>Excessive exercise</td>
<td>- ≥ 6 h a week -</td>
<td>- Clinical charts</td>
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<tr>
<td>Holtkamp et al. (2003)</td>
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<td>Exercising despite physical weakness and pain -</td>
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<td>Exercising despite physical weakness and pain -</td>
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<td>Shroff et al. (2006)</td>
<td>Excessive exercise</td>
<td>-</td>
<td>-</td>
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<td>Holtkamp et al. (2006)</td>
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<td>&gt; 1.5 h</td>
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<td>Bewell-Weiss and Carter (2010)</td>
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<td>≥ 1 h per day</td>
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Table 3. Categorization of 37 reviewed studies in Group 1 and Group 2.

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Chapter 2: Critical review of the literature: Results

Introduction

A display of abnormally high levels of physical activity (PA) has been observed from the earliest clinical descriptions of eating disorders (ED) (Gull, 1874). The prevalence of problematic physical activity (PPA) in patients with anorexia nervosa (AN) varies considerably in the literature, with wide ranges from 31% to 80% (Hebebrand et al., 2003). It was very difficult to compare and analyse the results of all studies investigating this matter, essentially because each author gave this “hyperactivity” a particular name, defined it and measured it in its own way. To overcome this difficulty, we proposed a categorization of studies into two groups (Group 1 and Group 2), taking into account methodological discrepancies (see part one for details). In this Group 1, PPA will be referred to as PPA-qT and in Group 2, PPA will be referred to as PPA-qL. We hypothesized that this categorization will make comparison between studies possible and consequently harmonize their results.

The aims of this second part are: 1) to give an overview of the prevalence of PPA in patients suffering from AN. We will also present links found between PPA and potential explanatory factors. 2) To discuss the results of studies, in line with animal models. 3) To propose a comprehensive model of the development of PPA in AN and suggest recommendations for future research.
Methods

The methodology of this review was described in details in the first part of this review (chapter 1, p.27). The categorization of the 37 reviewed articles in two groups is presented in table 4. Comparisons across studies were made according to methodological factors possibly impacting their results. These factors, identified in the first part of this review, include sample size, illness duration and age at onset (when reported), body mass index (severity of malnutrition), status of patients (in vs outpatients), current age, statistical analyses (univariate vs multivariate), assessment periods of ED and PA, instruments used to measure PA and to assess a given factor (ED symptomatology or a psychological factor). We will mention them in our analyses if they potentially impacted results.

Results

Prevalence of problematic physical activity

In Group 1, current prevalence of PPA-qT varied from 30% to 75%. The study with the lowest duration cut-off (more than four hours per week) had the highest prevalence (Casper & Jabine, 1996). The one with the highest duration cut-off (at least one hour per day) had the lowest prevalence (Favaro, Caregaro, Burlina, & Santonastaso, 2000) (table 4, column 3).

In Group 2, there were two assessment periods of PPA-qL: current and lifetime. Current prevalence varied in smaller ranges, from 34% to 58%. Lifetime prevalence was very high, around 80%, and homogeneous throughout the studies that measured it (Davis & Kaptein, 2006; Davis, Kaptein, Kaplan, Olmsted, & Woodside, 1998; Davis et al., 1997) (table 4, column 3).
Prevalence of problematic physical activity according to anorexia nervosa subtypes

In Group 1, no difference in the prevalence of PPA-qT was found between patients with AN-R and AN-BP (El Ghoch et al., 2013; Klein, Mayer, Schebendach, & Walsh, 2007; Kostrzewa et al., 2013) (table 4, column 3).

In Group 2, the two studies with the largest samples (n=165 (Dalle Grave, Calugi, & Marchesini, 2008) and n=159 (Bewell-Weiss & Carter, 2010)) were both in favour of higher prevalence of PPA-qL in patients with AN-R compared to AN-BP. However, in a very small sample (n=23), Klein et al. (Klein et al., 2004) did not find this difference between subtypes. Shroff et al. (Shroff et al., 2006) found that patients with purging behaviour and no bingeing behaviour (PAN) had a significantly higher prevalence of PPA-qL than restrictive patients (RAN) (table 4, column 3). However, they used a unique form of classification for their ED types that does not follow any international research criteria (cf. legend of table 4).

Problematic physical activity in women with current AN vs healthy controls.

All control samples were matched by age or very close in age to the AN samples.

Prevalence of problematic physical activity

In group 1, the prevalence of PPA-qT was higher in patients compared to healthy controls (C. Davis, E. Blackmore, D. K. Katzman, & J. Fox, 2005) (table 4, column 3).

Duration of physical activity

In Group 1, two studies (El Ghoch et al., 2013; Pirke, Trimborn, Platte, & Fichter, 1991) reported an increased duration of PA in AN patients compared to healthy controls. Davis et al. (Davis et al., 1995) compared AN patients to two control groups: individuals who exercised
moderately or at high levels and did not find a difference in time spent exercising per day, independently of the physical activity’s intensity.

Furthermore, there was no difference in the duration of PA between inpatients and healthy controls (Keyes et al., 2015; Zipfel et al., 2013). However, outpatients had a longer total duration of PA per week than controls (Keyes et al., 2015).

**Intensity of physical activity**

In Group 1 (PPA-qT), AN patients exercised more at low or high levels than healthy controls while controls exercised more at moderate activity levels (Bouten, van Marken Lichtenbelt, & Westerterp, 1996). Energy expenditure was assessed in six studies (Casper, Schoeller, Kushner, Hnilicka, & Gold, 1991; El Ghoch et al., 2013; Keyes et al., 2015; Pinkston et al., 2001; Pirke et al., 1991; Zipfel et al., 2013). When measured objectively, energy expenditure was significantly higher in patients compared to controls in two studies (Casper et al., 1991; El Ghoch et al., 2013) out of six, notably in the one with a big study sample (n=106 (El Ghoch et al., 2013)). The remaining four studies did not find a significant group effect. When measured subjectively, energy expenditure was not correlated to the duration of PPA-qT in neither patients nor controls (Pinkston et al., 2001).

**Motivations and commitment to exercise**

In Group 2 (PPA-qL), Keyes et al. (Keyes et al., 2015) found that exercising for fitness and health reasons, for enjoyment and to improve physical attractiveness was more important to healthy controls than outpatients.

Commitment to exercise (the degree to which feelings of well-being are influenced by exercising, the degree to which adherence to exercise is maintained in the face of various adverse conditions,
and the extent to which exercise regimens interfere with social commitments) was assessed in five studies (Caroline Davis, Elizabeth Blackmore, Debra K. Katzman, & John Fox, 2005; Davis et al., 1995; Keyes et al., 2015; Long & Smith, 1993; Pinkston et al., 2001). All these studies used the same instrument (the Commitment to Exercise Scale (CES)). Patients had significantly higher commitment to exercise scores than healthy controls (C. Davis et al., 2005) (Keyes et al., 2015) (Pinkston et al., 2001), moderate exercisers (Davis et al., 1995) and anxiety controls (Keyes et al., 2015). Long et al. (Long & Smith, 1993) didn’t find significant differences in a small sample of older patients (n=21) with surprisingly low scores of CES compared to the two other studies. However, they found that patients spent more time thinking about their PA than controls.

**Type of physical activity**

In Group 2 (PPA-qL), AN patients varied more their type of PA per week compared to healthy controls. They were also more likely to exercise in a secret or solitary manner (Long & Smith, 1993). Patients preferred walking as a sport (Keyes et al., 2015), followed by aerobics and gymnastic routines. Healthy controls preferred cycling or swimming (Long & Smith, 1993).

**Problematic physical activity in women recovered from AN and comparison with healthy controls**

In Group 1 (PPA-qT), one study (Kaye, Gwirtsman, George, Ebert, & Petersen, 1986) found that recently weight-recovered patients (range 14 to 40 days) had greater total daily activity counts than both long-term weight-recovered patients (range 6 to 84 months) and healthy controls. This difference was not found between long-term weight-recovered patients and controls (Dellava, Hamer, Kanodia, Reyes-Rodriguez, & Bulik, 2011; Kaye et al., 1986).
In Group 2 (PPA-qL), there was no difference in reasons for exercising between recovered patients and healthy controls (Dellava et al., 2011).

Links between problematic physical activity and psychological factors

Instruments used to measure psychological factors are presented in table 5.

Depression

In Group 1 (PPA-qT), the majority of studies (4/5) did not find any association between PPA-qT and depression (Carrera et al., 2012; Keyes et al., 2015; Klein et al., 2007; Kostrzewa et al., 2013). An association was found in one study (Falk, Halmi, & Tryon, 1985) with the less active patients at admission being the more depressed. This link however disappeared after 14 days of hospitalization.

In Group 2 (PPA-qL), four studies (Bewell-Weiss & Carter, 2010; Keyes et al., 2015; Penas-Lledo, Vaz Leal, & Waller, 2002; Zipfel et al., 2013) out of seven (Holtkamp, Hebebrand, & Herpertz-Dahlmann, 2004; Klein et al., 2004; Long & Smith, 1993) reported patients exercised more when depressed (on both categorical and dimensional approaches). The two studies with the smallest samples (n=30 (Holtkamp et al., 2004); n=21 (Klein et al., 2004)) did not find this association. Long et al. (Long & Smith, 1993) found that depression in patients was associated with a greater tendency for secret and solitary exercising.

Anxiety

In Group 1 (PPA-qT), all studies (Carrera et al., 2012; Keyes et al., 2015; Klein et al., 2007; Kostrzewa et al., 2013) did not find links between anxiety and: a) sedentary and light PA levels (Carrera et al., 2012); b) intensity of PA (in counts per day) (Carrera et al., 2012; Keyes et al.,
2015); c) problematic vs non-problematic exercisers (Klein et al., 2007; Kostrzewa et al., 2013). However, Carrera et al. (Carrera et al., 2012) noticed that the more time patients spent in the moderate to vigorous PA level, the less they reported to be anxious.

In Group 2, five studies (Holtkamp et al., 2004; Keyes et al., 2015; Klein et al., 2004; Penas-Lledo et al., 2002; Sternheim, Danner, Adan, & van Elburg, 2015) out six (Bewell-Weiss & Carter, 2010) found a significant increase in PPA-qL in case of elevated anxiety levels. In addition, patients who exercised had significantly greater levels of somatization than the ones who did not (Penas-Lledo et al., 2002). Long et al. (Long & Smith, 1993) found that patients were more likely to cope with negative emotional states (feelings of anxiety, anger, low mood/depression) by using exercise than healthy controls and that anxiety levels and phobic anxiety, similarly to depression, were associated with a greater tendency for solitary and secret exercising in AN.

Thornton et al. (Thornton, Dellava, Root, Lichtenstein, & Bulik, 2011) found that women with AN, with or without generalized anxiety disorder (GAD), reported more PPA-qL than healthy controls and women with GAD only.

**Obsession and compulsion**

In Group 1, PPA-qT was not associated with obsession and compulsion (Kostrzewa et al., 2013).

In Group 2, three studies (Davis & Kaptein, 2006; Davis, Katzman, & Kirsh, 1999; Davis et al., 1995) out of six (Bewell-Weiss & Carter, 2010; Holtkamp et al., 2004; Penas-Lledo et al., 2002) found that more PPA-qL was associated with obsessive-compulsive personality characteristics and higher obsessive-compulsive disorder symptoms. There were no associations between PPA-qL and obsessive-compulsiveness (Holtkamp et al., 2004) or obsessive-compulsive symptoms (Penas-Lledo et al., 2002). Only one study found that PPA-qL was associated with lower obsessive-compulsive-
compulsive symptomatology (Bewell-Weiss & Carter, 2010). This was also the only study to use the Padua Inventory (Van Oppen, Hoekstra, & Emmelkamp, 1995) to assess these symptoms.

**Stress**

In Group 1 (PPA-qT), problematic exercisers tended to have higher levels of stress linked to life-events than non-problematic exercisers (Casper & Jabine, 1996). In Group 2, stress contributed significantly to 11.7% of the variance of PPA-qL in outpatients (Keyes et al., 2015).

**Self-esteem**

In Group 2 (PPA-qL), a higher self-esteem was associated with PPA-qL (Bewell-Weiss & Carter, 2010).

**Addictive personality**

In Group 2 (PPA-qL), addictive personality was linked to more obligatory attitudes towards exercising (Davis et al., 1999).

**Links between problematic physical activity and eating disorders symptomatology**

ED symptomatology was studied either globally or focused on one aspect. Instruments used to assess these symptoms are presented in table 2.

In Group 1 (PPA-qT), general ED pathology was not associated with locomotor activity (Klein et al., 2007), actimetry counts (Keyes et al., 2015) or levels of PA (Kostrzewa et al., 2013). However, when core ED symptoms were studied separately, higher weight preoccupation was
linked to a higher level of PA (Davis et al., 1995). This was not the case for body dissatisfaction (Carrera et al., 2012).

Davis et al. (Davis et al., 1997) found that significantly more patients started exercising regularly before dieting than dieting before exercising.

Of an important note, PPA-qT was associated with greater body dissatisfaction and drive for thinness in patients with AN than healthy controls (Casper et al., 1991; El Ghoch et al., 2013). In Group 2, PPA-qL was correlated to higher levels of general eating symptoms (Keyes et al., 2015; Penas-Lledo et al., 2002; Sternheim et al., 2015), bulimic scores (Penas-Lledo et al., 2002), weight preoccupation (C. Davis et al., 2005), drive for thinness (Zipfel et al., 2013) and quantitative food restriction (Holtkamp et al., 2004). In addition, ED symptomatology, along with exercising to improve mood, contributed the most to the variance of PPA-qL (25.3% and 26.5% respectively) (Keyes et al., 2015).

**Links between problematic physical activity, age, onset, illness duration and lifetime activity status**

In Group 1 (PPA-qT), the current age of inpatients was not associated with their current levels of locomotor activity (Klein et al., 2007) or levels of PA (Carrera et al., 2012; Kostrzewa et al., 2013) as usually observed in general population. PPA-qT significantly increased one year prior to the onset of AN (C. Davis et al., 2005). Furthermore, a longer illness duration, an earlier age at onset of AN, was associated with more PPA-qT at admission to treatment (Kostrzewa et al., 2013). In Group 2 (PPA-qL), patients that were the most physically active during their illness were also very active during their childhood (ages of 10 and 12) (Davis et al., 1997; Davis et al., 1999).
Links between problematic physical activity and physical activity of patients’ parents

In Group 2 (PPA-qL), mothers of patients reported twice as often than mothers of healthy controls (49% and 26% respectively) that their spouse was physically very active (C. Davis et al., 2005).

Links between problematic physical activity and ambient temperature

In Group 1 (PPA-qT), patients treated during the “cold” season (between October and April) were significantly more physically active than the ones treated during the “warm” season (between April and October) (Carrera et al., 2012).

Discussion

We hypothesized that categorizing studies in two groups, Group 1 (PPA-qT) and Group 2 (PPA-qL) would harmonize results and facilitate comparison between studies. This was only partially verified. The categorization we proposed slightly decreased the wide prevalence range of PPA found in the AN literature to 30% to 75% for PPA-qT and 34% to 58% for PPA-qL. PPA-qL (and not PPA-qT) was associated with higher psychopathology in terms of general ED symptoms, weight preoccupation, drive for thinness, quantitative food restriction, depression, anxiety, obsession and compulsion, addictive personality, and higher self-esteem. Furthermore, we were able to confirm that patients suffering from AN had more PPA than healthy controls.

Prevalence of problematic physical activity

When considering published studies, the wide ranges of prevalence of both dimensions of PPA are inarguably dependent on: 1) the duration cut-off used by authors to define PPA; the lowest
duration cut-off showed the highest prevalence and vice versa. 2) The status of patients (inpatients vs outpatients); current prevalence was considered during hospitalization, which could have directly or indirectly limited PPA (Ng, Ng, & Wong, 2013). 3) Instruments used to measure PA (subjective vs objective); methods of self-evaluation are very critical among AN patients who are known to hide/underestimate their symptoms (Couturier & Lock, 2006; Vandereycken & Vanderlinden, 1983). 4) Assessment period of PA (current vs lifetime); lifetime prevalence of PPA-qL was nearly twice as high as current prevalence (80% vs 46%).

Problematic physical activity and psychological factors

Since depression, anxiety and obsessive–compulsive disorder frequently co-occur with AN, it was not surprising to find that they were the most studied psychological factors to be associated with PPA. We can see here all the interest of using our categorization to re-analyse inconclusive results, found in previous reviews, since results from Group 1 were frequently the opposite of results from Group 2.

PPA-qT was negatively correlated to depression (Falk et al., 1985) or completely not associated with it. Similarly, in the general population, greater amounts of occupational and leisure time activities as well as all PA intensity levels were associated with reduced symptoms of depression (Byrne & Byrne, 1993; Dunn, Trivedi, & O'Neal, 2001), anxiety and stress (Fox, 1999). Conversely, more PPA-qL was associated with higher psychopathology (depression (or depressive disorder), anxiety, obsessive-compulsiveness, addictiveness) and higher self-esteem. We hypothesized that the links between PPA and psychopathological dimensions studied could be established via the qualitative dimension of PPA (the relationship an individual has with his/her PA and/or its links with ED behaviours, pathological motivation(s) for exercise, compulsion to exercise, exercise dependence or addiction). Many authors have hypothesized that patients who are
physically active could be trying to improve their mood and emotional state (Davis et al., 1997; Keyes et al., 2015; Long & Smith, 1993; Penas-Lledo et al., 2002), and are not only concerned by their weight and shape (Meyer, Taranis, Goodwin, & Haycraft, 2011). Thus, PPA could be considered as a way of coping with chronically negative affect (Vansteelandt, Rijmen, Pieters, Probst, & Vanderlinden, 2007) by pursuing the boosting effect of endogenous opioids (Kohl, Foulon, & Guelfi, 2004).

Problematic physical activity and eating disorder symptomatology

ED pathology was one of the most important predictors (with mood improvement) of the variance of PPA-qL in AN outpatients (Keyes et al., 2015). PPA (both quantitatively and qualitatively) increases when patients are highly preoccupied about their weight and are motivated by their drive for thinness. Thus, PPA could be, at least partially, a conscious attempt to work off calories (Vansteelandt et al., 2007). It could accelerate the process of obtaining their desired thinness ideal. This makes drive for thinness an important motive to engage in PPA in AN. In fact, this is also the case in the general population where people commonly exercise to control weight and shape (Goncalves & Gomes, 2012).

Problematic physical activity and age, onset, illness duration and lifetime activity status

PPA-qT was associated with an earlier age at illness onset (Davis et al., 1997; Kostrzewa et al., 2013) and could appear before AN (Davis et al., 1997). This is in accordance with results from the general population where PA tends to decrease with age (Wall, Carlson, Stein, Lee, & Fulton, 2011). In addition, it seems that at younger ages, exercise behaviours as a weight control mechanism are easier to access than other purging behaviours such as laxatives and purgatives (Shroff et al., 2006).
PPA-qL was related to PA during childhood: highly active patients during their illness were also very active during their childhood (Davis et al., 1997; Davis et al., 1999). This goes in agreement with findings from the general population implying that sport participation during childhood and adolescence is particularly predictive of being more physically active later in life (Wall et al., 2011).

**Problematic physical activity and ambient temperature**

Carrera et al. (Carrera et al., 2012) found that high PA levels in patients with AN have been reported in the cold months and low levels in the warm months. These findings support the hypothesis of PA as a thermoregulatory behaviour to cope with hypothermia and the approach of heat supply as a useful complementary component for the treatment of AN (Bergh, Brodin, Lindberg, & Sodersten, 2002; Cerrato, Carrera, Vazquez, Echevarria, & Gutierrez, 2012).

**Problematic physical activity and compulsivity: suggested animal models**

Some patients feel an increasingly strong compulsion to be physically active despite weight loss, pain and exhaustion (Davis et al., 1997). These findings are in accordance with results from the general population where compulsive exercise was positively associated with eating-disordered cognitions and behaviours (Meyer et al., 2011; Taranis & Meyer, 2011). In fact, maintaining high levels of PA despite emaciation is an exclusive specificity of patients with AN. This is not the case in situations of starvation due to other illnesses (i.e. increase in circulating inflammatory cytokines (Braun & Marks, 2010)). This phenomenon is also observed in animal models where reductions in food intake and body weight have paradoxically accompanied a progressive increase in PA. The most described animal model combining food restriction and elevated PA is the “activity-based
anorexia” model (ABA model) (Adan et al., 2011). This model shows that rodents who have free access to a running wheel will develop hyperactivity in response to a limited food supply (one to two hours of food access per day). These behaviours, occurring two to three days after the start of the protocol, led to feedback inhibition of food intake (or self-starvation). This eventually caused a negative energy balance and finally led to death (Adan et al., 2011). Animals would literally run and starve themselves to death (Spatz & Jones, 1971). Similar hyperactivity has been described in patients with AN (Scheurink, Boersma, Nergårdh, & Södersten, 2010).

In animal models, four main explanations have been provided. Firstly, the hyperactivity noted as food anticipatory activity has been associated with reward addiction or reward-seeking behavior, involving principally disturbances in the non-homeostatic neuronal circuit involved in food intake, namely the meso-cortico-limbic system that comprises the dopaminergic cells of the ventral tegmental area targeting the nucleus accumbens, located in the ventral striatum. According to this hypothesis, increased physical activity along with food restriction could activate brain reward circuits and induce an addiction to this behavior (Fladung et al., 2010), by activating common neural pathways between hyperactivity and anorexia that involve the serotonin receptor 5-HTR4 (Jean et al., 2012) via the CART peptide in the nucleus accumbens. Besides these noticeable variations in the nucleus accumbens, a second remarkable possibility is related to the alteration in the activity of the dopaminergic system involving two major eating behavior related hormones: leptin and ghrelin (Adan et al., 2011; Mequinion et al., 2013). Indeed, Adan et al. (2011) have hypothesized that the increase of ghrelin and decrease of leptin plasma levels observed in the ABA model (as well as in AN patients) alter the activity of the dopaminergic system which could be involved in the hyperactivity as well as the aberrant cognitive processing related to food that is found in some patients suffering from AN (Adan et al., 2011). A third hypothesis is the “fleeing-famine” or “foraging behavior” hypothesis (Duclos et al., 2013) which is interpreted as an increased
running wheel activity of rodents to metaphorically move away/migrate from a location lacking food towards new habitats, thus increasing the odds of survival. They also demonstrate the fundamental role of corticosterone in the maintenance of the food anticipatory activity, which levels are elevated similarly to what is observed in AN patients. Moreover, such behavior involves chronic elevations in the satiety-producing biochemical signalers including cholecystokinin, dopamine and serotonin, associated with lowered levels of appetite-promoting galanin and norepinephrine (Guisinger, 2003). Finally, a fourth hypothesis concerned a thermoregulatory behavior to avoid hypothermia (Cerrato et al., 2012). In fact, wheel running will cause an increase in body temperature in order to counterattack the decrease in the basal metabolic rate usually associated with starvation and thus prevent hypothermia (Hebebrand et al., 2003).

Until this day, neuroendocrine and physiological findings emerging from animal models have showed similarities in the occurrence of symptoms known to be specific to AN. However, the true role of PA in the maintenance of self-starvation in patients with AN remains unresolved. Nonetheless, when taking into account findings on animal models, it seems that PPA could be considered as a consequence of food restriction (Adan et al., 2011; Exner et al., 2000; Pirke, Broocks, Wilckens, Marquard, & Schweiger, 1993) in parallel to a voluntary compensatory behaviour.
Conclusion

Implications for clinical practice and future perspectives

This review underlines the complex and multifaceted nature of PA in patients suffering from AN. PA should not be viewed in a unidirectional fashion in this population. We need research in order to define a consensual definition of PPA in AN that takes into account its evolving aspects and its different clinical manifestations (voluntary/conscious and involuntary/unconscious) and dimensions (qualitative and quantitative). Such research would strongly benefit from the recommendations presented in table 6. The development of common research protocols between fundamental and clinical research teams as well as specialized professionals in adapted physical activity is needed to establish effective translation research for the treatment of PPA.
### Tables

Table 4. Group categorization of 37 reviewed studies and prevalence of problematic physical activity (columns 1 to 3).

<table>
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<td>Holtkamp et al. (2003)</td>
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<td>X</td>
<td>48</td>
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<tr>
<td>Davis et al. (2005)</td>
<td>X</td>
<td>AN: 64; HC: 2.1</td>
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<tr>
<td>Shroff et al. (2006)*</td>
<td>X</td>
<td>RAN: 40.3; PAN: 54.5; BAN: 37.4; ANBN: 43.5</td>
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<td>AN-R: 80; AN-BP: 43.3</td>
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<tr>
<td>Zipfel et al. (2013)</td>
<td>X</td>
<td>AN: 58.3; HC: 16.7</td>
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<td>Sternheim et al. (2015)</td>
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<td>Keyes et al. (2015)</td>
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*Uses a unique form of categorization of lifetime eating disorder types: “RAN: AN with restrictive eating and no purging or bingeing behavior; PAN: AN with purging behavior and no bingeing behavior; BAN: AN with bingeing with or without compensatory behaviors; ANBN: lifetime diagnosis of both full syndromal AN and BN” (Shroff et al., 2006, p.457).
Table 5. Instruments used to assess psychological factors and eating disorder symptomatology (columns 1 to 3).

<table>
<thead>
<tr>
<th>References</th>
<th>1</th>
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<td>STAI</td>
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Kostrzewa et al. (2013) | CPRS-S-A | CPRS-S-A | CPRS-S-A | - | - | - | EDI-2; MROAS
Zipfel et al. (2013) | BDI | - | - | - | - | - | EAT; EDI-2
Sternheim et al. (2015) | - | STAI | - | - | - | - | EDE
Keyes et al. (2015) | DASS | DASS | - | DASS | - | - | EDE-Q

( ): Results evaluated but not reported to be linked to PPA in study.
*Inventory designed to assess the "obsessional" or "anal" personality type derived from psychoanalytic theory (Lazare et al., 1966; Lazare et al., 1970).
Table 6. Recommendations for future research concerning physical activity in anorexia nervosa.

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Use a consensual terminology that includes the quantitative and qualitative dimensions of PA found in AN. It should include exercise and daily activities, which are both problematic in AN. We propose the term “problematic” physical activity.</th>
</tr>
</thead>
</table>
| Definition of PPA |  - Consider all physical activity subgroups including daily activities and exercise.  
  - According to a patient’s degree of emaciation, define quantitative cut-offs for duration, frequency and intensity of PA.  
  - Include a qualitative dimension, independently of the quantitative aspects of PPA and of ED symptoms. Consider, for example:  
    ✓ Compulsion to exercise: need to precisely define what compulsion to exercise is.  
    ✓ Dependence to exercise: need to test dependence to exercise criteria in AN (7 criteria in the general population assessed by the Exercise Dependence Questionnaire: withdrawal, continuity, tolerance, loss of control, decrease in other activities, time and intention). |
| Evaluation |  - Use instruments that are validated in the general population to assess the:  
    ✓ Quantitative dimension of PPA, such as the International Physical Activity Questionnaire.  
    ✓ Qualitative dimension of PPA, such as the Obligatory Exercise Questionnaire, the Exercise Addiction Inventory, the Commitment to Exercise Scale and the Reasons for Exercise Inventory.  
  - Determine the most suitable instrument according to study protocol: small sample sizes would benefit more from objective methods to measure PA while big sample sizes would benefit more from validated questionnaires to assess PA.  
  - Evaluate all clinical manifestations of PPA and their characteristics: voluntary, involuntary, conscious and unconscious. To do so, develop instruments (on the basis of clinical observations and patients’ interviews) to evaluate specific clinical manifestations of PPA in AN such as restlessness, aimless wandering or inability to sit still, keeping abdominal muscles tensed when seated or standing on one leg to increase pressure on the other.  
  - Include criteria on the motivation(s) and reason(s) behind being physically active. |
| Study methodology |  - Research protocol should evaluate together all aspects of the quantitative (frequency, duration, intensity) and qualitative (the relationship an individual has with his/her PA and/or its links with ED behaviours, pathological motivation(s) for exercise, compulsion to exercise, exercise dependence or addiction) dimensions of PA. It should also investigate the associations between these dimensions.  
  - If more than one ED type is included in the study sample, give separate results for each type.  
  - If more than one AN subtype is included in the study sample, give separate results for each subtype.  
  - Clearly differentiate status of patients (in vs outpatients) and assessment period of ED (current vs lifetime).  
  - Report illness duration and age at illness onset. When possible, include these factors in multivariate analyses as confounding factors. |
| Long-term outcome |  - Need for more follow-up studies and longitudinal study designs in order to understand if PA is globally a pejorative factor on the outcome or if some of its aspects have pejorative impacts and others positive ones. |
| Therapeutic guidelines and treatment of PPA |  - Develop therapeutic guidelines on how to manage/treat PPA in AN and/or introduce PA in AN treatment.  
  - Guidelines should: 1) consider different management programs for each dimension (quantitative and qualitative) and clinical manifestations (voluntary and involuntary) of PPA. 2) Should take into consideration the different phases of evolution of AN and the patient’s degree of emaciation |

Part 3: Problematic physical activity and psychological and somatic factors

Chapter 1: Testing potential risk factors against different definitions of problematic physical activity in anorexia nervosa

(Research article published in PLoS ONE)

Introduction

Anorexia Nervosa (AN) is a severely debilitating eating disorder (ED) with considerable morbidity (Roux, Chapelon, & Godart, 2013) and mortality (Keshaviah et al., 2014). With a chronicity incidence of 21% (Steinhausen, 2009), it seems that, despite the best available treatment, many patients remain chronically ill (Strober, 2004). Undoubtedly, the mechanisms triggering and maintaining this behavior are still insufficiently understood (Treasure & Schmidt, 2013). Patients suffering from ED have been found to have the highest frequency of physical activity and participation in sports compared to all other psychiatric disorders (Mangerud, Bjerkeset, Lydersen, & Indredavik, 2014). This “hyperactivity”, affecting 31% to 80% of AN patients (Hebebrand et al., 2003), has been identified as a complex and multifaceted feature commonly present in AN. This wide range in prevalence range could be partly due to the plethora of definitions provided by researchers for patients with AN. Different terms, such as “hyperactivity” and “excessive exercise” have been used in the literature (Meyer & Taranis, 2011). However, there is no international
consensus on a clear and valid definition in AN. As the exercise involved is problematic, both in quantity (frequency, duration and intensity) and quality (compulsion to exercise), we will use the term “problematic exercise” (PE) in this paper and will carefully examine several ways of defining it. It should be noted that exercise is a subgroup of physical activity: it is a physical activity that is planned, structured, repetitive, and purposeful. General physical activity includes any body movement that contracts the muscles to burn more calories than the body would normally do at rest (Caspersen et al., 1985).

In a systematic review including 37 papers assessing physical activity in AN, PE was mainly evaluated using subjective methods centered on exercise (self-reports, semi-structured questionnaires, interviews, clinical charts or diaries (29 out of 37 studies)). It was less frequently evaluated using objective instruments that measure physical activity, and not solely exercise (14 out of 37 studies). Each of these methods has its own limitations. On the one hand, objective methods are based on complex methodologies and are therefore only used in small samples (on average 31 patients included in studies using accelerometers (Gümmer et al., 2015). In addition, they can be difficult to implement, especially in an inpatient setting, leading to problems of refusal or compliance (Gümmer et al., 2015). Subjective methods on the other hand, are mainly limited by the fact that they rely on patient recall. Patients, especially in AN, might give unreliable answers and/or deliberately omit to talk about PE as a symptom (Couturier & Lock, 2006; Vandereycken and Vanderlinden, 1983). Despite the fact they may underestimate physical activity (Alberti et al., 2013; Vandereycken and Vanderlinden, 1983; van Elburg et al., 2007), subjective methods seem easier to implement than an objective method in research that includes a large sample. Recently, Keyes et al. (2015) found a significantly positive correlation between a subjective (international physical activity questionnaire) and an objective (actimetry) measure of physical activity in their AN sample.
Many studies have investigated factors that could explain PE in AN, with conflicting results. During the acute phase of AN, patients have been found to use physical activity as a coping strategy to compensate for, remove, and/or alleviate both negative affective states (anxiety (Holtkamp et al., 2004; Penas-Lledo et al., 2002), depression (Penas-Lledo et al., 2002) and stress (Casper & Jabine, 1996; Keyes et al., 2015) and ED symptoms (Keyes et al., 2015) (including weight preoccupation (Davis et al., 1995; Keyes et al., 2015), drive for thinness (Casper et al., 1991; Favaro et al., 2000; Zipfel et al., 2013), body dissatisfaction (Casper et al., 1991) and restrictive profile (Bewell-Weiss & Carter, 2010; Dalle Grave et al., 2008). Past research has mainly studied these elements separately or using different definitions of PE. Some authors have found links between PE and an early age at AN onset (Shroff et al., 2006). Quality of life also seems negatively impacted by the effect of PE interacting with ED severity (Cook et al., 2014). In addition, alexithymia appears to have an important role in maintaining AN (Courty et al., 2015) by affecting the patient’s well-being (Taylor et al., 1997). To our knowledge, very few studies have simultaneously investigated all these factors and their implication in PE in AN. Furthermore, no study has taken into account the various qualitative characteristics (compulsive exercise) and/or the quantitative characteristics of exercise (frequency, duration and intensity) to investigate their association with the different predictive factors identified.

The purpose of this study was two-fold: 1) to assess the variance of prevalence rates of PE based on seven different definitions found in the literature. 2) To examine how ED symptoms, emotional profile and quality of life scores are associated with PE according to these different definitions.
Methods

Procedures and ethics

This study was part of a larger longitudinal multi-centered study named EVHAN (Evaluation of Hospitalization for AN, Eudract number: 2007-A01110-53, registered in Clinical trials). The study protocol was approved by the Ile-de-France III Ethics Committee and the CNIL (Commission nationale de l’informatique et des libertés). In accordance with the Helsinki declaration, written informed consent was obtained from each patient before inclusion, and from the parents of those who were under 18 years old. Both patients (either adults or children and their parents) gave a written consent.

Prior to inclusion in the study, all participants were hospitalized in an inpatient care unit for life-threatening physical and/or mental states (including a body mass index (BMI) below 14 and/or rapid weight loss and/or compromised vital functions, severe depression, high suicide risk, chronic under-nutrition with low weight, and/or failure of out-patient care). The EVHAN inclusion criteria were patients aged 8 to 65 years old referred for an acute anorexia nervosa episode to one of the 11 French specialized inpatient treatment facilities participating in the EVHAN study. Individuals were excluded if they: 1) refused to participate in the research; 2) had insufficient knowledge of the French language; 3) were suffering, in addition to their ED, from potentially confounding somatic pathologies (diabetes, Crohn’s disease, or metabolic disorders); 4) had already been included in the protocol during a previous hospitalization.
Participants

A total sample of 233 patients was included in the EVHAN study between April 2009 and July 2012. Current AN diagnosis was based on the DSM-IV-TR criteria (APA, 2000) and assessed using the CIDI 3.0 (WHO, 1997). The following BMI criteria were applied: BMI < 10th percentile up to 17 years of age, and BMI < 17.5 for 17 years of age and older. Purging symptoms were evaluated using the Eating Disorder Examination Questionnaire (EDE-Q v. 5.2) (Cooper et al., 1989). At inclusion: (1) seven patients did not meet DSM-IV-TR criterion A. However, two of them had shifted from a BMI above the 97th percentile to a BMI on the 10th percentile relative to their age in the three months preceding hospitalization. The remaining five had had a BMI < 17.5 in the previous three months but had been initially admitted to a medical ward. They had gained weight just before their transfer to a psychiatry unit and inclusion in the study; (2) 39 patients did not meet DSM-IV-TR criterion B; (3) 16 patients did not meet DSM-IV-TR criterion C; (4) 10 patients did not meet DSM-IV-TR criterion D. We considered all the patients (AN full syndrome and sub-threshold) in our analyses.

The exclusion criteria for the present analyses were male gender (n=10) and age younger than 13 years (n=11) (age from which all patients had the same versions of the questionnaires of interest). Participants who had significant missing data for the variables of interest (n=32) were also excluded.

Measures

All data were collected during the first 2 weeks of inpatient admission.
Anthropometry

Body weight and height were measured using standard beam balance scales (Omega-SECA, Germany) and a stadiometer (wall mounted model 222-SECA, Germany) respectively. BMI was derived from weight (kg) divided by the square of height (meters) (WHO, 2009).

Emotional profile

Anxiety and depressive symptoms were evaluated using the Hospital Anxiety and Depression scale (HADS) (Zigmond & Snaith, 1983). In the present analyses, a summed scale score for anxiety and depression (ranging from 0 to 42 points) was calculated. The higher this composite score, the higher the level of anxiety and depressive symptoms reported by the subject. Difficulties in emotional introspection and regulation were measured using the Bermond–Vorst Alexithymia Questionnaire-Form B (BVAQ-B) (Deborde et al., 2004). This is a 20-item questionnaire that includes five subscales: verbalizing emotional experiences (B1), daydreaming and fantasies (B2), identifying emotions (B3), proneness to being aroused by emotion inducing events (B4), and analyzing one’s own emotional states and reactions (B5). We used the BVAQ-B total score; a higher score indicates a higher level of alexithymia.

Self-esteem was measured using the 10-item version of the Rosenberg Self-Esteem Scale (RSES) (Dorard et al., 2014). A higher score indicates better self-esteem.

Obsessive-compulsive symptoms

Obsessive-compulsive symptoms were assessed using the Maudsley Obsessive Compulsive Inventory (MOCI) (Hodgson & Rachman, 1977). It includes 30 items and four subscales: Checking compulsions, Washing/cleaning compulsions, Slowness, and Doubting. The MOCI total score was
used in the present analyses. A higher score indicates higher levels of obsessive-compulsive symptoms.

**Body shape concerns**

The body shape questionnaire (BSQ) (Rousseau et al., 2007) is a 34-item questionnaire used to evaluate worries and concerns about body shape. The BSQ total score was used in the present analyses. A higher score indicates marked worries and concerns about body shape.

**Eating disorder symptomatology**

ED symptoms were assessed using two subscales from the 26-item Eating Attitudes Test (EAT-26): the dieting and bulimia and the food preoccupation subscales (Garner et al., 1982). The present analyses included these two subscales because they were the only ones associated with PE in the literature (Bewell-Weiss & Carter, 2010; Dalle Grave et al., 2008).

**Quality of life**

Quality of life was evaluated with the Eating Disorders Quality of Life (EDQOL) scale. It includes 25 items and four subscales: Psychological, Physical/Cognitive, Work/School and Financial (Engel et al., 2006). A higher score indicates poorer quality of life.

**Exercise: duration, intensity and type**

Participants were interviewed by trained evaluators, using a semi-structured questionnaire. This questionnaire was designed to ascertain at what level patients were engaging in a given type of exercise in the month preceding hospitalization. It was intended to evaluate the type of exercise (walking, running, swimming, cycling and household activities), frequency and duration (in hours
per week). At the end of the questionnaire, in an open question, patients were asked to specify any other activity they were practicing. Each exercise pattern was then matched with its intensity in metabolic equivalents (METs) using the compendium of physical activity proposed by Ainsworth et al. (2011). The MET value of each physical activity represents the ratio of the energy expended per kilogram of body weight per hour during the activity compared to the energy expended when sitting quietly. The number of hours spent per day on each activity was multiplied by its MET score. The daily amount of exercise was then obtained by summing the MET-hours for all activities. Mean intensities of exercise were categorized under light-intensity (1.1 to 2.9 METs), moderate-intensity (3.0 to 5.9 METs) and vigorous-intensity (6.0 to 10 METs) (appendix 1 (UDHHS, 2008). These cut-offs have been frequently used in other studies (Alberti et al., 2013; Bratland-Sanda et al., 2010; Bratland-Sanda et al., 2011; El Ghoch et al., 2013). Exercises were also classified into two types: individual and team sports (Holmen et al., 2002). Individual sports included walking, jogging, cycling, swimming, long-distance running, body-building, esthetics-oriented sports, martial arts, and technical or adrenaline sports.

**Problematic exercise**

We identified seven definitions of PE based on the quantitative (duration and intensity of physical activity) or qualitative (compulsion to exercise) dimensions implemented by studies in the literature and the instruments they used to evaluate these (Table 7). The first three definitions were based on a single quantitative or qualitative criterion. The fourth, fifth and sixth definitions included combinations of two of the first three definitions. The seventh definition combined all three (Fig. 1):
- The first definition, labeled “PE-duration”, was based on the duration of exercise per week. In this case, a patient was considered a problematic exerciser if she exercised for at least six hours a week before admission. This duration criterion is the most commonly used in the literature to assess excessive exercise in AN (Table 7).

- The second definition, labeled “PE-compulsion”, was based on compulsion to exercise. In this case, the frequency of compulsion to exercise for reasons of weight or shape was assessed from item 18 in the EDE-Q (Fairburn & Beglin, 1994). Specifically, episodes of compulsion to exercise were calculated on the basis of the participants’ answer to the question: “over the past 28 days, how many times have you exercised in a restraining or compulsive way in order to control your weight or the shape of your body, to eliminate fat or to burn calories?” (Mond et al., 2006). In this case, patients were considered problematic exercisers if they exercised for reasons of weight or shape more than five times a week in the 28 days prior to assessment (Luce et al., 2008; Mond et al., 2006; Mond et al., 2004).

- The third definition, labeled “PE-intensity”, was based on the intensity of exercise. In this case, a patient was considered a problematic exerciser if she exercised at a vigorous intensity level (≥ 6.0 METs).

- The fourth definition, labeled “PE-duration+compulsion”, was a combination of a quantitative criterion (duration) and a qualitative criterion (compulsion): in this case, patients were considered problematic exercisers if they exercised for more than 6 hours a week and exercised for reasons of weight or shape more than five times a week in the 28 days prior to assessment.

- The fifth definition, labeled “PE-duration+intensity”, was a combination of two quantitative criteria: here, patients were considered problematic exercisers if they exercised for more than 6 hours a week and at a vigorous intensity level.
- The sixth definition, labeled “PE-compulsion+intensity”, was a combination of a quantitative criterion (intensity) and a qualitative criterion (compulsion): in this case, patients were considered problematic exercisers if they exercised at a vigorous intensity level and exercised for reasons of weight or shape more than five times a week in the 28 days prior to assessment.

- The seventh definition, labeled “PE-duration+compulsion+intensity”, was a combination of two quantitative criteria (duration and intensity) and one qualitative criterion (compulsion): in this case, patients were considered problematic exercisers if they exercised for more than 6 hours a week and at a vigorous intensity level and exercised for weight or shape reasons more than five times a week in the 28 days prior to assessment.

Statistics

A statistical analysis was performed using SPSS software (SPSS Statistics, version 21.0; Chicago) and R 3.1.2 (R statistical programing language version 3.2.1). Numerical variables were summarized as mean and standard deviation, while counts and frequencies were used for categorical variables. Group differences were tested using the appropriate univariate analyses (the Student t-test for independent samples, the Wilcoxon signed rank test for paired samples and the Welch t-test for continuous outcomes). A fixed Type I error of 5% was considered.

A series of multivariate logistic regressions was used to further explain the seven definitions of PE (mentioned above) in relation to our potential explanatory variables of interest. The following explanatory variables were considered in each model: Age, BMI, Illness duration, AN subtype, EAT dieting and bulimia subscale scores (ED symptomatology), BSQ score (body image), MOCI total score (obsession and compulsion), HADS Anxiety and Depressive symptoms summed as a single score, Rosenberg score (self-esteem), and BVAQ-B total score (alexithymia).
The seventh definition was excluded from our statistical analysis on account of the very small number of patients involved (n=5). The outcomes considered in the remaining six multivariate models were respectively: 1) PE-duration for model 1; 2) PE-compulsion for model 2, 3) PE-intensity for model 3; 4) PE duration + compulsion for model 4, which is a combination of models 1 and 2; 5) PE duration + intensity for model 5, which is a combination of models 1 and 3. 6) PE compulsion + intensity for model 6, which is a combination of models 2 and 3. Because of the large number of predictors in relation to the number of positive cases in each model, two approaches were undertaken to select relevant markers in the set of predictors. First, a Lasso (L1 norm or Lasso) penalization was applied to the parameters of the logistic regression models in order to provide sparse solutions by zeroing low-contributing variables. A tuning of model hyper-parameters (penalty) was performed using repeated 10-fold cross-validations (25 repetitions). The final solution chosen was the one that most minimized the cross-validated log-likelihood on the optimal penalty parameter using a hybrid algorithm. It combined Newton’s method and a gradient descent, implemented in the penalized R package (Goeman, 2010). To assess the stability of this Lasso solution, bootstrap resampling (1000 samples) was used to estimate the 2.5 and 97.5 quantiles of the empirical distribution of regression coefficients for all selected variables. These solutions were then compared with those obtained from a simple stepwise backward model selection using the AIC criterion. This was enhanced by a bootstrap procedure (200 samples) to assess the variability of the final set of selected covariates. Finally, the number of times each covariate was retained in the final model and the frequency with which their regression coefficient was found statistically significant at a 5% level were computed on all bootstrap models.
Results

Participants’ characteristics

Our final sample consisted of 180 inpatients. There were no statistically significant differences between excluded patients and patients retained for further analyses for age (p=0.745), BMI (p=0.817), illness duration (p=0.296), AN subtype (p=0.314), EDE-Q scores (item 18, p=0.206), total hours of exercise per week (p=0.982), and HADS anxiety (p=0.236) or depression (p=0.211).

At admission to inpatient treatment, the mean age of patients was 20.7 years (SD=5.9), their mean BMI was 14.3 (SD=1.5) and the mean illness duration was 4.3 years (SD=4.4). Regarding AN subtypes, 85 (47.2%) were restrictive AN (AN-R) and 95 (52.8%) were binge-eating/purging AN (AN-BP). Characteristics at inclusion and global scores on psychological scales are presented in Table 8. Compared to AN-BP patients, AN-R patients had a lower BMI (13.9±1.3 vs 14.7± 1.6, p<0.001), lower scores of EAT-26 dieting (17.6±10.9 vs 22.0±9.9, p<0.1), EAT- 26 bulimia (6.0±3.4 vs 8.7±4.6, p<0.001) and BSQ (107.1±37.2 vs 123.3±37.2, p<0.01).

Type of exercise

Walking was the most frequently reported exercise for both AN-R (72.9%) and AN-BP (66.3%). For AN-R, it was followed by cycling (27%), swimming (18.8%) and running (16.5%). For AN-BP, walking was followed by running (26.3%), cycling (22.1%) and swimming (17.9%). Patients mostly preferred individual sports (97.9%) to team sports (2.1%).
Prevalence of PE

Fifty-four percent (n=97), 30.4% (n=55), 13.3% (n=24), 21.7% (n=39), 5.5% (n=10) and 5% (n=9) of participants were classified as problematic exercisers in model 1, 2, 3, 4, 5 and 6 respectively (Fig. 1).

Associations between definitions of PE and ED symptoms, emotional profile and quality of life

Univariate analyses

When PE was defined using PE-duration, PE-compulsion and PE-duration+compulsion, compared to non-problematic exercisers, problematic exercisers had significantly higher MOCI, BSQ and EAT-26 dieting scores. They also had significantly higher EAT-26 bulimia scores when PE was defined using PE-compulsion (Table 9). When PE was defined using PE-duration and PE-duration+compulsion, problematic exercisers had significantly lower RSES scores than non-problematic exercisers. No between-group differences were observed for HADS and BVAQ-B scores for any of the PE definitions.

Concerning quality of life, problematic exercisers defined by PE-duration, PE-compulsion and PE-duration+compulsion had significantly lower EDQOL total scores than non-problematic exercisers (Table 9). Problematic exercisers had significantly lower scores on the psychological and financial subscales compared to non-problematic exercisers when PE was defined by PE-duration, PE-compulsion and PE-duration+compulsion. They also had significantly lower scores on the physical/cognitive subscale when PE was defined by PE-duration and PE-compulsion.
**Multivariate analyses**

The results of the series of multivariate regressions are presented in Table 10. This table only includes significant variables. Age and BMI were retained in all models as adjustment variables.

In model 1 (PE-duration), problematic exercisers were significantly older, and had higher EAT-dieting scores and MOCI total scores than non-problematic exercisers. However, they had lower EAT-bulimia scores. In models 2 (PE-compulsion) and 4 (PE-duration+compulsion), problematic exercisers also had significantly higher EAT-dieting scores and lower EAT-bulimia scores than non-problematic exercisers. This difference in EAT-dieting scores was also found in model 6 (PE-compulsion+intensity). There was a trend for problematic exercisers to have higher MOCI total scores in model 2 (PE-compulsion). In model 3 (PE-intensity), besides a tendency for higher EAT-dieting scores, problematic exercisers were younger and had lower BSQ total scores compared to non-problematic exercisers.

No significant differences were found between problematic and non-problematic exercisers concerning illness duration, AN subtype, RSES, BVAQ-B, HADS and EDQOL scores in any of the models studied.
Discussion

On the basis of a literature review of all the definitions previously given for PE in AN, our study was conducted for the following purposes: 1) to determine the prevalence of PE in AN according to seven different definitions: three definitions implementing a single dimension of PE (duration, compulsion or intensity) and four definitions combining these dimensions (three combining two and one combining the three dimensions); 2) to study simultaneously, across six different PE definitions, the impact of different factors that have been linked to PE in the literature, something that has never been done before.

During the acute phase of AN, almost all our patients indulged in an individual sport rather than a team sport (97.9% vs 2.1% respectively). Adolescents with ED have previously been found to participate more in individual sports than adolescents suffering from any other psychiatric disorder (even after adjusting for gender, age and socioeconomic status) (Mangerud et al., 2014). In addition, social avoidance seems to be common in AN, and difficulties in social adaptation have been observed particularly in leisure activities (Courty et al., 2015). Patients suffering from AN tend to avoid other people’s gaze and feel they are constantly judged on their physical appearance. In addition, taking part in team sports (i.e. football and basket) is highly dependent on others, which is not the case for individual sports. Walking was the most popular sport in our sample. This concurs with the few studies that assessed the types of exercise in their AN samples (Keyes et al., 2015; Long & Smith, 1993). Walking seems to be an accessible and practical way to exercise even when patients are severely emaciated and/or hospitalized (despite the direct and/or indirect restrictions of exercising imposed by a hospital environment (Ng et al., 2013).

One of our main results was that the prevalence of PE varied considerably, as expected, from 5% to 54%, according to the definition used. This variation therefore results from the
criteria used to define PE. The most stringent definition, combining two quantitative criteria (duration and intensity) and one qualitative criterion (compulsion), identified the smallest proportion of problematic exercisers (n=5). Conversely, the least stringent definition, entailing only a duration cut-off, identified the largest number of problematic exercisers (n=97). This approach clearly highlights a considerable overlap of patients assigned to two or more definitions of PE (Fig. 1). We notice, for example, that PE-duration and PE-compulsion have a huge overlap of participants of 40.2% (n=39/97) and 70.9% (n=39/55) respectively. Thus, including one or more criteria in PE definitions has major consequences on prevalence results. This could considerably affect the conclusions of studies assessing PE but using different definitions. To our knowledge, no one has previously studied the impact of different PE definitions on the same study sample. This is a very important result, since it could contribute to understanding why previous studies on PE in AN are not comparable: the problematic exercisers included in the different samples were partially or completely different. Without a valid common definition of PE, each author subjectively defined PE in the way he/she thought was appropriate for his/her study sample.

Interestingly, we found that patients exercising for more than 6 hours a week (PE-duration) generally scored higher on the compulsion item of the EDE-Q (12.0±10.5) compared to other patients (6.3±9.1). To evaluate the duration of a 6-hour a week physical activity as an efficient cut-off value for PE in AN, a Spearman rank correlation between scores for this item and the total number of hours of physical activity was estimated at 0.324 (p < 0.001). Then, a ROC analysis suggested that this cut-off value (the most widely used in the literature following the work of Davis and Fox (1993) seemed the best compromise in terms of sensitivity (0.672) and specificity (0.597) when one considers compulsion to exercise status derived from response to item 18 on the EDE-Q. The area under the curve (0.674) was comparable after adjusting for illness duration, BMI, and AN subtype (0.687).
When all potentially linked factors described in the literature were considered simultaneously, the various definitions of PE were significantly associated with different combinations of factors. The type and level of ED symptomatology (high restriction and/or low bulimia) were associated with the majority of our six models, except for model 5 (PE-duration+intensity) where the sample was very small. It is worth noting that AN subtypes were not linked to any PE definition. Thus, problematic exercisers tend to have considerable food restrictions and/or little bulimic behavior, regardless of PE definition and AN subtype. This result is in accordance with the study by Holtkamp et al. (2004) study who found that food restriction was positively related to higher levels of exercise in their AN sample, significantly contributing to its variance (along with anxiety). Furthermore, Brewerton et al. (1995) found that problematic exercisers suffering from AN or from bulimia nervosa (and defining PE as “exercise to control weight at least once a day and for at least 60 minutes”) were significantly less likely to show bulimic behaviors, such as binge eating, vomiting or using laxatives, than non-problematic exercisers. One hypothesis is that PE could be a consequence of food restriction. In findings on animal models, a reduction in food intake was also followed by a progressive increase in physical activity (Pirke et al., 1993; Exner et al., 2000; Adan et al., 2011). On the other hand, PE could be considered as a voluntary compensatory behavior. Patients with AN seem to prefer PE as a compensatory behavior rather than purging.

Problematic exercisers had higher MOCI total scores compared to non-problematic exercisers in 2 of the 6 models (significantly for PE-duration and tendency for PE-compulsion; noting that these two dimensions have a huge overlap of problematic exercisers). Davis et al. (1999) proposed a model in which obsessive-compulsive personality factors have a direct influence on levels of exercise in AN (Davis et al., 1995; Davis & Kaptein, 2006; Davis et al., 1999; Davis et al., 1998). They also suggested a positive link between obsessive-compulsive disorders and PE in
patients with AN. Davis and Kaptein (2006) also found that patients with AN exercising excessively had pronounced obsessive-compulsive disorder symptoms. They used the same duration cut-off (6 hours a week) for their definition of excessive exercise and the same instrument (MOCI) as we did to assess obsessive-compulsive symptomatology. When taking a closer look at the patient’s exercising, it appeared that some patients exercised in a very repetitive and stereotyped manner (Kohl et al., 2004). Given that exercising for psychological motives (including stress management) is one of the most frequently endorsed motivations for exercise, we could be tempted to hypothesize that this particular aspect of physical activity supports an anxiolytic effect of exercise (Markland & Ingledew, 1997).

Problematic exercisers tended to have lower BSQ scores (reflecting fewer worries about body shape) than non-problematic exercisers when considering PE-intensity. Exercising to control weight and shape is very common in the general population (Goncalves & Gomes, 2012) and in eating disorders (Mond & Calogero, 2009). It therefore seems that patients found relief for their concerns about body shape when exercising at high intensity levels. Unfortunately, we did not find any previous studies investigating associations between PE (only defined by high intensity) and body image concerns in ED.

Problematic exercisers were found to be significantly older in model 1 (PE-duration) and tended to be younger in model 3 (PE-intensity) than non-problematic exercisers. It seems that older patients preferred exercising for longer periods, while younger patients favored more intensive physical activities. The only study we found that included a large sample of participants (n= 1856) suffering from lifetime ED (including AN, bulimia nervosa and eating disorders not otherwise specified) (Shroff et al., 2006) also found that younger age at study inclusion was associated with PE. In this study, participants were considered problematic exercisers if they reported: 1) that their exercise interfered severely with important activities; 2) exercising for more than 3 hours per day
and feeling distressed if unable to exercise; 3) frequently exercising at inappropriate times and places with little or no attempt to overcome this behavior; and 4) exercising despite serious injury, illness or medical complication.

Surprisingly, problematic exercisers had better self-reported quality of life compared to non-problematic exercisers in studies using PE-duration, PE-compulsion and PE-duration+compulsion. Generally, EDs are associated with reduced quality of life compared to healthy controls (Sy et al., 2013). To our knowledge, Cook et al. (2014) were the only authors to determine the associations between exercise dependence, ED symptomatology and quality of life in healthy individuals (Cook et al., 2014). They found that dependence on exercise combined with ED symptoms had a negative impact on quality of life compared to ED symptoms alone. It seems that PE, defined by duration and/or compulsion, could mainly reflect the feeling of a positive impact of exercising on the quality of life reported by our patients.

There were no significant between-group differences in HADS anxiety and depression scores in any of our models. This is in accordance with studies where physical activity was only defined by its characteristics (intensity, duration and/or frequency (Keyes et al., 2015; Klein et al., 2007; Carrera et al., 2012; Kostrzewa et al., 2013). This however contrasts with studies that added a notion of compulsion or motivation to exercise in their PE definitions: (1) four studies (Bewell-Weiss & Carter, 2010; Keyes et al., 2015; Penas-Lledo et al., 2002; Zipfel et al., 2013) out of seven (Holtkamp et al., 2004; Long & Smith, 1993; Klein et al., 2004) found a positive association between PE and depression. (2) Five studies (Holtkamp et al., 2004; Keyes et al., 2015; Penas-Lledo et al., 2002; Klein et al., 2004; Sternheim et al., 2015) out of six (Bewell-Weiss & Carter, 2010) found a positive association between PE and anxiety. In fact, previous studies have suggested that PE is a coping strategy to compensate for, remove, and/or alleviate anxiety (Holtkamp et al., 2004; Penas-Lledo et al., 2002) and depression (Penas-Lledo et al., 2002). Furthermore, it seems
that tailored physical activity could reduce anxiety symptoms in the general population (Hale & Raglin, 2002) and significantly lower scores for depressive symptoms in AN (Vancampfort et al., 2014). Further research on this matter is needed.

One of the main strengths of our study was that it identified a large number of definition criteria for PE in the ED literature. Nonetheless, there is a lack of research concerning one criterion that should be taken into consideration when defining PE: dependence on or addiction to exercise. There is growing evidence that exercise should be considered as a dependence or addiction, both in the general population and in animal models. In fact, some authors have hypothesized that changes in the meso-cortico-limbic system (Fladung et al., 2010) and alterations in the dopaminergic system (Adan et al., 2011) (found in hyperactive animal models mimicking AN) seem to activate brain reward circuits. They could induce addiction to high levels of physical activity. Davis et al. (1999) pointed to PE as a type of addictive behavior in AN more than 15 years ago. In spite of this, very little attention has been given to exercise as a potential behavioral addiction in AN. This area has been neglected despite the startling similarities between PE and drug seeking (in substance addiction disorders) or between PE and addictive drugs (on brain reward pathways) (Davis & Kaptein, 2006).
Strength and limitations

We investigated conjointly psychological and ED-related symptoms linked to exercise in the largest homogeneous clinical sample of inpatients with severe AN studied to date. However, there are three main limitations to take into account: 1) Exercise was assessed using a retrospective semi-structured questionnaire. It is worth noting that this was also the case in more than 75% of the studies in the literature that evaluated physical activity in their AN sample. Since we wanted to investigate associations between PE and a number of explicative factors, we initially intended to recruit a large study sample from 11 treatment units. Using objective measures, such as accelerometers, in such a large cohort would have been extremely hard to monitor and very expensive. Furthermore, we were focusing on inpatients, for whom the use of an objective method to assess physical activity has been associated with problems of refusal or compliance (Gümmer et al., 2015). This is why we chose to use a semi-structured questionnaire to evaluate exercise in our sample. In this case, collecting valid data depended solely on patient recall and accurate report of exercising over a fixed period. The use of this subjective method therefore seemed more appropriate in our sample (Davis et al., 1994). 2) The frequency of compulsion to exercise was assessed using a reliable and widely used instrument of ED symptomatology (the EDE-Q). Assessing frequency with a single item (question 18) is a limitation of this study, as mentioned by other authors who performed the same assessment (Keyes et al., 2015). However, this method has been commonly used in the literature to assess the frequency of hard exercise for weight or shape reasons (Bewell-Weiss & Carter, 2010; Dalle Grave et al., 2008; Mond & Calogero, 2009; Smith et al., 2013; Brownstone et al., 2013), which is widely known as a compulsion to exercise in the ED literature (Table 7). 3) The cross-sectional design of our study investigates associations rather than causality.
Conclusion

A display of abnormally high levels of physical activity has been observed from the earliest clinical descriptions of ED (Gull, 1974). Since then, researchers have come up with many different terms, definitions and explanatory factors for this phenomenon. As a result, this lack of consistency in terminology and definition has strongly limited all attempts to examine the complex links between physical activity and AN. It has also partly led to the wide prevalence range for PE found in the AN literature. The differing prevalence rates according to the definition of PE implemented should prompt research to determine a valid consensus definition of PE in AN. This could be done, for example, by clearly distinguishing two dimensions of exercise: a quantitative dimension (in terms of frequency, duration and intensity) and a qualitative dimension (the relationship an individual maintains with his/her exercise, and/or its links with ED behaviors, pathological motivation(s) for exercise, compulsion to exercise, exercise dependence or addiction). These two dimensions: 1) do not strictly concern the same patients; 2) probably do not have the same explanatory factors. Concerning instruments: for the quantitative dimension, it is important to use instruments validated in the general population such as the IPAQ (Craig et al., 2003). For the qualitative dimension, many instruments previously used to assess compulsion to exercise are linked to ED symptomatology. In future research, it seems necessary to assess different aspects of the qualitative dimension of PE conjointly (obligatory exercise, exercise addiction, commitment to exercise and reasons for exercise) using the appropriate instruments (used in the general population) (i.e. using the obligatory exercise questionnaire, the exercise addiction inventory, the commitment to exercise scale and the reasons for exercise inventory) (Keyes et al., 2015). Further research on PE as an addiction in AN should be considered (Klein et al., 2004). It could be the
missing piece of a large jigsaw puzzle entitled “How much exercise is too much in AN?” and help to develop optimal therapeutic approaches.
Figures

Figure 3. Seven problematic exercise (PE) definitions and the number of problematic exercisers included in each definition and subgroup. (n) Number of patients included in each subgroup.
## Tables

Table 7. Definitions of problematic exercise found in the literature and instruments used for assessment.

<table>
<thead>
<tr>
<th>References</th>
<th>Definitions of problematic exercise</th>
<th>Instruments used to assess exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al. (1995)</td>
<td>Exercise on average, at least 5 hours a week in the year prior to assessment</td>
<td>Interview and physical activity diaries</td>
</tr>
<tr>
<td>Davis et al. (1997)</td>
<td>The level of physical activity is considerably higher than what is typical for someone of the similar age. If time spent exercising exceeded 1 hour a day for at least 6 days a week for a period of no less than 1 month, and if the participant described the exercising as &quot;obsessive,&quot; &quot;driven,&quot; and &quot;out of control&quot; during the excessive phase.</td>
<td>Interview</td>
</tr>
</tbody>
</table>
| Davis and Claridge (1998)   | -Lifetime exercise status: If time spent exercising exceeded 1 hour a day for at least 6 days a week for a period of no less than 1 month, and if the participant described the exercising as "obsessive," "driven," and "out of control" during the excessive phase.  
-Current exercise status: exercise activity at least 6 hours a week averaged over the 12 months prior to assessment. | Interview                                         |
| Davis et al. (1998)         | Exercise activity at least 6 hours a week averaged over the 12 months prior to assessment.          | Interview                                         |
| Davis et al. (1999)         | Exercise activity at least 6 hours a week averaged over 1 month prior to assessment.                | Interview                                         |
| Carruth and Skinner. (2000) | Two physical activity levels: ≤ 7 hours/week of physical activity or >7 hours/week of physical activity | Actimeter                                         |
| Solenberger (2001)          | “Patients were categorized into high- or low-level exercise groups by a median split of total exercise. The high-level exercise group spent greater than 6.7h/week exercising”. | Clinical charts                                   |
| Penas-Lledo et al. (2002)   | Physical exercise at least 5 times a week, for at least 1h without stopping, and with the aim of burning calories. | Clinical charts                                   |
| Davis and Woodside (2002)   | Exercise activity for a minimum of 6 hours a week averaged over 1 month prior to assessment.        | Interview                                         |
| Davis and Kaptein (2006)    | -Lifetime exercise status: If time spent exercising exceeded 1 hour a day for at least 6 days a week for a period of no less than 1 month, and if the participant described the exercising as "obsessive," "driven," and "out of control" during the excessive phase.  
-Current exercise status: exercise activity at least 6 hours a week averaged over the 12 months prior to assessment. | Interview                                         |
<p>| Klein et al. (2007)         | Exercising at least 6 hours a week, on average.                                                   | Accelerometer and interview                       |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Dietary Intake</th>
<th>Other Intake</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalle Grave et al. (2008)</td>
<td>Compulsive exerciser in case of a positive answer to the first question below and to any of the remaining: “(1) Over the past 4 weeks, have you exercised with the aim of burning up calories to control your shape or weight? (2) Have you felt compelled or obliged to exercise? (3) Have you exercised even when it caused severe interference with important activities? (4) Have you exercised to a level that might be harmful for you? (5) Have you felt distressed if you were unable to exercise?”</td>
<td>Eating disorder examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mond and Calogero (2009)</td>
<td>“Hard [exercising] as a means of controlling their shape or weight during the preceding 4 weeks”</td>
<td>Eating disorder examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bratland-Sanda et al. (2010)</td>
<td>Three criteria: (1) moderate- to-vigorous physical activity if exercising for at least 6 hours a week at admission; (2) persistence of this amount for at least 1 month before admission; (3) classification as exercise dependent symptomatic.</td>
<td>Accelerometer and exercise dependence scale – Revised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bewell-Weiss and Carter (2010)</td>
<td>Minimum of one hour of obligatory exercise aimed at controlling shape and weight, 6 days a week in the month preceding admission.</td>
<td>Eating disorder examination</td>
<td></td>
<td></td>
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<tr>
<td>Stiles-Shields et al. (2011)</td>
<td>“Over the past four weeks have you exercised as a means of controlling your weight, altering your shape or amount of fat, or burning off calories? Have you felt driven or compelled to exercise?”</td>
<td>Eating disorder examination</td>
<td></td>
<td></td>
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<tr>
<td>Smith et al. (2013)</td>
<td>“Hard [exercising] as a means of controlling their shape or weight during the preceding 4 weeks”.</td>
<td>Eating disorder examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brownstone et al. (2013)</td>
<td>“Hard [exercising] as a means of controlling their shape or weight during the preceding 4 weeks”.</td>
<td>Eating disorder examination</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Patient characteristics (n=180) at inclusion and global scores on psychological scales.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>14.3</td>
<td>1.5</td>
<td>10.3</td>
<td>18.9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.7</td>
<td>5.9</td>
<td>13.4</td>
<td>43.8</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>4.3</td>
<td>4.4</td>
<td>.22</td>
<td>24.4</td>
</tr>
<tr>
<td>MOCI</td>
<td>11.9</td>
<td>5.3</td>
<td>2.0</td>
<td>26.0</td>
</tr>
<tr>
<td>BSQ</td>
<td>115.8</td>
<td>37.9</td>
<td>34.0</td>
<td>194.0</td>
</tr>
<tr>
<td>RSES</td>
<td>11.0</td>
<td>5.0</td>
<td>3.0</td>
<td>24.0</td>
</tr>
<tr>
<td>EAT-26 dieting</td>
<td>19.9</td>
<td>10.5</td>
<td>0</td>
<td>39.0</td>
</tr>
<tr>
<td>EAT-26 bulimia</td>
<td>7.4</td>
<td>4.2</td>
<td>0</td>
<td>17.0</td>
</tr>
<tr>
<td>HAD anx.dep</td>
<td>22.1</td>
<td>7.4</td>
<td>17.0</td>
<td>27.5</td>
</tr>
<tr>
<td>BVAQ-B</td>
<td>56.4</td>
<td>9.0</td>
<td>34.0</td>
<td>80.0</td>
</tr>
<tr>
<td>EDE-Q compulsive</td>
<td>16.1</td>
<td>41.8</td>
<td>0</td>
<td>497</td>
</tr>
<tr>
<td>Duration PA (hours/week)</td>
<td>9.0</td>
<td>10.2</td>
<td>0</td>
<td>60.0</td>
</tr>
<tr>
<td>Intensity PA (METs)</td>
<td>3.6</td>
<td>2.3</td>
<td>0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

BMI: Body mass index. BSQ: Body Shape Questionnaire score. BVAQ-B: Bermond–Vorst alexithymia questionnaire-form B. Duration PA: Total duration of physical activity. EAT-26 bulimia: 26-item Eating Attitudes Test bulimia and food preoccupation subscale score. EAT-26 dieting: 26-item Eating Attitudes Test dieting subscale score. EDE-Q compulsive: Item 18 of the EDE-Q. HAD anx.dep: Hospital anxiety and depression scale composite score. Intensity PA: Mean intensity of physical activities. MOCI: Maudsley obsessive-compulsive inventory total score. RSES: Rosenberg self-esteem scale score.
Table 9. Associations between problematic and non-problematic exercisers and ED symptoms, emotional profile and quality of life according to definition of problematic exercise.

<table>
<thead>
<tr>
<th></th>
<th>PE-duration</th>
<th>PE-compulsion</th>
<th>PE-intensity</th>
<th>PE-duration+compulsion</th>
<th>PE-duration+intensity</th>
<th>PE-compulsion+intensity</th>
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<tbody>
<tr>
<td>MOCI</td>
<td>t=3.2*</td>
<td>t=3.3**</td>
<td>NS</td>
<td>t=3.0*</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>BSQ</td>
<td>t=3.6†</td>
<td>t=4.3†</td>
<td>NS</td>
<td>t=3.5**</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>RSES</td>
<td>t=-2.1*</td>
<td>NS</td>
<td>NS</td>
<td>t=-2.0*</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>EAT-26 dieting</td>
<td>t=3.9†</td>
<td>t=5.4†</td>
<td>NS</td>
<td>t=4.4†</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>EAT-26 bulimia</td>
<td>NS</td>
<td>t=2.5*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HAD anx.dep</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BVAQ-B</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td><strong>EDQOL subscales:</strong></td>
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<td>Psychological</td>
<td>t=-3.0*</td>
<td>t=-3.5**</td>
<td>NS</td>
<td>t=-2.4*</td>
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<td>NS</td>
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<tr>
<td>Physical/cognitive</td>
<td>t=-2.2*</td>
<td>t=-2.7*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Financial</td>
<td>t=-3.2*</td>
<td>t=-2.7*</td>
<td>NS</td>
<td>t=-2.9*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Work/School</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total score</td>
<td>t=-3.3**</td>
<td>t=-3.4**</td>
<td>NS</td>
<td>t=-2.6*</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

t: t values determined using the t-test for independent samples.
* p ≤ 0.05; **p ≤ 0.01; † p ≤ 0.001.
BSQ: Body Shape Questionnaire score. BVAQ-B: Bermond–Vorst alexithymia questionnaire-form B. EAT-26 bulimia: 26-item Eating Attitudes Test bulimia and food preoccupation subscale score. EAT-26 dieting: 26-item Eating Attitudes Test dieting subscale score. EDQOL: Eating Disorders Quality of Life score. HAD anx.dep: Hospital anxiety and depression scale composite score. MOCI: Maudsley obsessive-compulsive inventory total score. NS: Not significant. RSES: Rosenberg self-esteem scale score.
### Table 10. Series of multivariate regressions for each definition of problematic exercise (PE): significant predictive factors.

<table>
<thead>
<tr>
<th></th>
<th>PE-duration (n=97)</th>
<th>PE-compulsion (n=55)</th>
<th>PE-intensity (n=24)</th>
<th>PE-duration + compulsion (n=39)</th>
<th>PE-duration + intensity (n=10)</th>
<th>PE-compulsion + intensity (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intercept</strong></td>
<td>-3.37 (1.72)</td>
<td>-4.73 (1.88)</td>
<td>-0.14 (2.45)</td>
<td>-6.22 (1.23)</td>
<td>-6.40 (3.55)</td>
<td>-1.28 (3.89)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.06* (0.03)</td>
<td>0.02 (0.03)</td>
<td>-0.09* (0.05)</td>
<td>0.04 (0.03)</td>
<td>0.04 (0.07)</td>
<td>0.05 (0.08)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>0.06 (0.11)</td>
<td>0.11 (0.12)</td>
<td>-0.10 (0.15)</td>
<td>0.16 (0.13)</td>
<td>0.17 (0.21)</td>
<td>0.21 (0.25)</td>
</tr>
<tr>
<td><strong>EAT diet.</strong></td>
<td>0.08*** (0.02)</td>
<td>0.10*** (0.03)</td>
<td>0.07 (0.04)</td>
<td>0.11*** (0.03)</td>
<td>0.12 (0.04)</td>
<td>0.11* (0.05)</td>
</tr>
<tr>
<td><strong>EAT bulim.</strong></td>
<td>-0.14* (0.06)</td>
<td>-0.12* (0.06)</td>
<td>-0.16* (0.07)</td>
<td>-0.00 (0.07)</td>
<td>0.85 (0.74)</td>
<td>1.12 (1.25)</td>
</tr>
<tr>
<td><strong>HAD anx.dep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07 (0.05)</td>
<td>1.08 (0.98)</td>
</tr>
<tr>
<td><strong>MOCl</strong></td>
<td>0.07* (0.03)</td>
<td>0.07* (0.04)</td>
<td>-0.07 (0.05)</td>
<td>0.08 (0.04)</td>
<td>0.08 (0.01)</td>
<td>-0.03 (0.01)</td>
</tr>
<tr>
<td><strong>BSQ</strong></td>
<td>235.5</td>
<td>203.8</td>
<td>-1.11.7</td>
<td>135.0</td>
<td>170.6</td>
<td>519.7</td>
</tr>
</tbody>
</table>

† p < .10, * p < .05, ** p < .01, *** p < .001.
Illness duration, anorexia nervosa subtypes, self-esteem and alexithymia were not significant in any of our six models.
AIC: Akaike Information Criterion; BMI: Body Mass Index; BSQ: Body Shape Questionnaire score; CI: Confidence Interval; EAT diet.: 26-item Eating Attitudes Test bulimia and food preoccupation subscale scores. EAT diet.: 26-item Eating Attitudes Test dieting subscale score. HAD anx.dep: Hospital anxiety and depression scale composite score; LL: log-likelihood; MOCl: Maudsley obsessive-compulsive inventory total score; OR: Odds ratio; Pen. c.: Penalized coefficient; SE: Standard error; Unp. c.: Unpenalized coefficient
Chapter 2: Impact of exercise on body composition in acute anorexia nervosa.

(Research article under review in European Eating Disorders Review)

Introduction

Anorexia nervosa (AN) is a potentially life-threatening eating disorder with several somatic and psychiatric comorbidities (Roux, Chapelon, & Godart, 2013; Woodside & Staab, 2006). These complications are essentially due to the degree of weight loss, malnutrition, and chronicity of the disorder (Miller et al., 2005). AN has a severe impact on nutritional status which is reflected by a marked decrease in body mass index (BMI) and changes in body fat (Probst, Goris, Vandereycken, & Van Coppenolle, 1996), impacting long-term outcome. A lower BMI at admission to AN inpatient unit is associated with a worst prognosis (Hebebrand et al., 1997; Huas et al., 2011).

Excessive exercise is a core symptom of AN and a restrictive behaviour used by patients to lose weight (APA, 2013). It also interferes with nutrition rehabilitation and increases the risk of short-term somatic complications such as fractures and bruises (Rizk, Kern, Godart, & Melchior, 2014). It is associated with worse clinical and therapeutic outcomes (El Ghoch et al., 2013; Ng, Ng, & Wong, 2013; Solenberger, 2001). Data concerning the link between excessive exercise and nutritional status in AN are scarce and contradictory. It has been associated with either lower (Hechler et al., 2008) or higher (Casper, Schoeller, Kushner, Hnilicka, & Gold, 1991) BMI in AN.

Historically, exercise in AN was mainly considered in the literature as a problematic activity that should be limited or even completed banned, especially during the acute phase of the
disorder (Rizk, 2015). However, there is a recent growing interest in the place exercise could have as a component in the treatment of several mental disorders (Zschucke, Gaudlitz, & Strohle, 2013), including eating disorders (Hausenblas, Cook, & Chittester, 2008; Vancampfort et al., 2014) and AN (Ng et al., 2013; Zunker, Mitchell, & Wonderlich, 2011).

In addition, recent findings in animal models suggest elements in favour of a protective effect of exercise in case of food restriction. Mequinion et al. (2015) evaluated the impact of voluntary physical activity on two groups of mice that were both food restricted. The first group had access to a running wheel while the second group didn’t. On the short run, the first group of mice adapted faster to food restriction compared to the second one. Despite reaching a crucial point of body weight faster, the first group also stabilized their weight faster compared to the second group. Long term results showed that the first group had a better use of ingested glucose and less fat oxidation. They finally concluded that physical activity could have positive effects on the global adaptation to severe condition of food restriction found in patients with AN.

In the general population, associations between physical activity and body composition seem to be mainly influenced by gender: in men, high physical activity is associated with lower percent of body fat, which was not the case in women (Westerterp & Goran, 1997). However, the magnitude of changes in BMI and body composition is highly dependent on the characteristics of the exercise program (in terms of duration, frequency, and intensity) practiced by healthy individuals (Wilmore, 1996); for example, greater increase in fat-free mass and decrease in fat-mass are generally observed in individuals that indulge in resistance training rather than standard forms of aerobic training such as cycling or running (Gwinup, 1987).

We question the possible links between exercise, and not excessive exercise, as usually done, and the nutritional status of patients with AN (in terms of BMI and body composition indexes). We wonder if exercise in acute AN could be a protective factor, as suggested by animal
models (Mequinion et al., 2015) and by results of adapted physical activity programs. To our knowledge, no research to date has investigated this question.

The purpose of this study is to investigate the links between exercise, in terms of duration and intensity, and nutritional status (BMI, Fat-Free Mass Index (FFMI) and Fat-Mass Index (FMI)) while considering potential confounders related to body composition (identified in the literature, see method) in 191 hospitalized patients with acute AN.
Methods

Procedures and ethics

This chapter used the same procedures and ethics of the chapter 1 of part 3 (see page 74).

Participants

Two-hundred and thirty-three patients were included in the EVHAN study between April 2009 and July 2012. Current AN diagnosis was based on the DSM-IV-TR criteria (APA, 2000) and assessed using the CIDI 3.0 (WHO, 1997) with the following BMI criteria: BMI < 10th percentile up to 17 years of age, and BMI < 17.5 for 17 years of age and above. Purging symptoms were evaluated using the Eating Disorder Examination Questionnaire (Cooper, Cooper, & Fairburn, 1989). At inclusion: (1) seven patients did not meet DSM-IV-TR criterion A. However, two of them had shifted from a BMI above the 97th percentile to a BMI on the 10th percentile relative to their age in the three months preceding hospitalization. The remaining five had had a BMI<17.5 in the previous three months but had been initially admitted to a medical ward. They had gained weight just before their transfer to a psychiatry unit and inclusion in the study; (2) 39 patients did not meet DSM-IV-TR criterion B; (3) 16 patients did not meet DSM-IV-TR criterion C; (4) 10 patients did not meet DSM-IV-TR criterion D. We considered all the patients (AN full syndrome and sub-threshold) in our analyses. The exclusion criteria for the present study were men (n=10), age younger than 13 years (n=11) (age from which all patients had the same versions of the questionnaires of interest) and patients with negative values of FMI (n=4). These values were observed in patients with very low BMI values (10.34, 11.55, 12.57 and 13.34). They reflect the inadequacy of the bioelectrical impedance formula to calculate body fat in case of extreme emaciation associated with massive body water expansion. In addition, due to
technical problems (inadequate electrodes), FFMI and FMI were not measured in 17 patients.

Finally, 191 patients were included in the present analyses.

Measures

**Nutritional status: Body Mass Index, Fat-Free Mass Index and Fat Mass Index**

Three markers of the nutritional status were considered: BMI, FFMI and FMI. Body weight was measured to the nearest 0.1 kg using standard beam balance scales (Omega-SECA, Germany). Height was measured to the nearest 0.1 cm using a stadiometer (wall mounted model 222-SECA, Germany). BMI was derived from weight (kg) divided by the square of height (meters). Body composition (fat mass and fat-free mass) was assessed in the first two weeks of admission to the inpatient unit. This allowed the stabilization of the patients’ fluid and electrolytes status by sustaining from compensatory behaviours (purging, vomiting or laxative/diuretic abuse) (Probst et al., 2001; Piccoli et al., 2005). It was measured using the Bioelectrical Analyzer (FORANA, Helios, Frankfurt, Germany) with an alternating electric current at 50 kHz and 800 mAmp, 4 skin electrodes (BIANOSTIC, DataInput, Darmstadt, Germany) and using the Deurenberg equation. Complete methods to assess fat-mass and fat-free mass are described in Mattar et al. (Mattar, Huas, group, & Godart, 2012). FMI and FFMI were calculated to evaluate fat mass and fat-free mass independently of height (Kyle, Schutz, Dupertuis, & Pichard, 2003). FMI and FFMI are the equivalent of fat mass (in kg) and fat-free mass (in kg) divided by squared height (in m) respectively.

**Why the use of FFMI and FMI instead of percentages of lean and fat masses?**

The nutritional status of our patients was evaluated using three components: BMI, FFMI and FMI. As mentioned earlier, AN has a significant impact on body composition and will have...
different effects on total body water, FFM and FM. Efficiently assessing the nutritional status of
patients is crucial in order to determine the severity of their condition and the appropriate treatment.
Using either BMI or percentages of FFM and FM for height alone could be inaccurate. On the one
hand, the use of percentages of FFM and FM alone is limited by their fluctuations with age and sex
(Molarius and Seidell, 1998). On the other, BMI and body weight are not sensitive instruments to
solely determine nutritional status (Moreno et al., 2008; Trocki et al., 1998). Thus, nutritional status
should be assessed using FFMI, FMI and BMI. FFMI and FMI will allow a normalization of FFM
and FM for height, making comparisons between AN patients possible by allowing independent
evaluations of FFM and FM according to body size (Pichard et al., 2004; Kyle et al., 2003; Wells,
2001; VanItallie et al., 1990)(L54; L55, L56, L59). FFMI and FMI can be categorized in low,
normal or high (Deurenberg et al., 1991) (appendix 11).

Exercise: Duration and intensity

Participants were interviewed by trained evaluators, using a semi-structured questionnaire.
This questionnaire was designed to ascertain at what level patients were engaging in a given type
of exercise in the month preceding hospitalization. It was intended to evaluate the type of
exercise (walking, running, swimming, cycling and household activities), frequency and duration
(in hours per week). At the end of the questionnaire, in an open question, patients were asked to
specify any other activity they were practicing. Each exercise pattern was then matched with its
intensity in metabolic equivalents (METs) using the compendium of physical activity proposed
by Ainsworth et al.(2011). The MET value of each physical activity represents the ratio of the
energy expended per kilogram of body weight per hour during the activity compared to the
energy expended when sitting quietly. The number of hours spent per day on each activity was
multiplied by its MET score. The daily amount of exercise was then obtained by summing the MET-hours for all activities.

Confounding factors

The body composition of patients with AN is affected by factors that could either be specifically linked to their disorder (AN subtype (Probst et al., 1996), age at illness onset (Mattar, Huas, et al., 2012), illness duration (Mattar, Huas, et al., 2012), premenarchal AN (Demerath et al., 2004) and presence of amenorrhea (Pitts, Blood, Divasta, & Gordon, 2014)) or by factors found in the general population (age (Zamboni et al., 1997) and birth weight (Mattar, Pichard, Godart, & Melchior, 2012)).

These elements were evaluated by the CIDI 3.0 (WHO, 1997) for AN characteristics, and by the study questionnaire for other elements.
Statistical Analyses

A statistical analysis was performed using SPSS software (SPSS Statistics, version 21.0; Chicago). First descriptive statistics were produced. Numerical variables were summarized as mean and standard deviation (SD), while counts and frequencies were used for categorical variables. Associations between nutritional status markers (BMI, FFMI and FMI), exercise duration and exercise intensity, and other confounding variables (age, age at AN onset, illness duration, birth weight, premenarchal AN status and AN subtypes) were tested using the appropriate univariate analysis (the Chi-squared test and the Student t-test). If assumptions of parametric counterparts (normality and homoscedasticity) were not met and if two-group comparisons had highly imbalanced sample size, non-parametric tests were used (the Mann-Whitney U test). A fixed Type I error of 5% was considered. Finally, linear multiple regression analyses were carried out using BMI, FFMI and FMI as dependent variables and including exercise duration, exercise intensity, and variables that were significantly associated with each dependent variable in univariate tests (p<0.1).
Results

Patients characteristics

Characteristics of patients at inclusion to inpatient treatment are presented in table 1. Our sample consisted of very emaciated patients, with mean values of BMI, FFMI, FMI and percentage of body fat far below the normal values for healthy adult women (BMI < 18.5, FFMI < 15, FMI < 4.8, and percentage of body fat < 14) (Kyle et al., 2003).

Ninety-seven participants (50.8%) met criteria for AN restrictive type (AN-R), and 94 participants (49.2%) met criteria for the binge-eating/purging type (AN-BP). At admission to the inpatient program, 95.8% (183/191) of participants had premenarchal AN and 12% (23/191) had amenorrhea.

Links between BMI, body composition variables and variables of interest

Results of univariate tests between BMI, FFMI, FMI, clinical characteristics (age, age at AN onset, illness duration, birth weight, AN subtypes, premenarchal AN status, and presence of amenorrhea) and exercise (duration and intensity) are presented in table 12. BMI was significantly correlated to FFMI (r =0.663, p<0.001) and FMI (r =0.823, p<0.001). Age was negatively linked to FFMI and positively to FMI. Birth weight was only positively correlated to FFMI (p<0.05). Exercise intensity was positively correlated to BMI (p<0.05) and FFMI (p<0.001) but not to FMI. Both amenorrhea and premenarchal AN were linked to lower BMI and FFMI (p<0.05). There was a tendency for a lower FMI in patients with amenorrhea (p=0.054).
Multiple regression using BMI, FFMI or FMI as dependent variable

The results of the multivariate regressions are presented in table 13. These analyses were performed to explore the extent to which exercise (in terms of duration and intensity) and other variables of interest, significantly identified in univariate analysis, predicted BMI, FFMI and FMI. Current age was highly correlated to illness duration (r =0.722, p<0.001) and age at AN onset (r=0.687, p<0.001). Premenarchal AN status was linked to age at AN onset (p<0.001). Thus, only age and premenarchal AN status were included in our analyses.

A lower BMI was independently and significantly linked to a lower intensity of exercise, AN-R, and presence of amenorrhea (table 13). The total variance accounted for by the model was 14.2% (F (5,185) =7.31, p< 0.001).

A lower FFMI was independently and significantly linked to lower intensity of exercise, an older age, AN-R, and premenarchal AN (table 13). The total variance accounted for by the model was 19.2% (F (6,184) =8.53, p< 0.001).

We also tested a model including the same variables but excluding birth weight because it was only available for 131 patients. The total variance accounted for by this model was 21.2% (F (7,123) =5.99, p< 0.001). Higher birth weight, in addition to higher exercise intensity, younger age, AN-R and premenarchal AN, were independently and significantly associated with higher FFMI (p=0.004).

A lower FMI was independently and significantly linked to AN-R, a younger age and presence of amenorrhea (table 13). The total variance accounted for by the model was 11.3% (F (5,185) =5.82, p< 0.001).
Discussion

To our knowledge, this is the first study to examine the links between exercise (in term of duration and intensity and not excessive exercise) and nutritional status (BMI, FFMI and FMI) of patients with acute AN, while taking into account both factors specific to AN (AN subtype, age at AN onset, illness duration, premenarchal AN and presence of amenorrhea) and factors found in healthy individuals (age and birth weight).

Exercise intensity significantly predicted variations in BMI and FFMI values. Higher exercise intensity was linked to higher BMI and FFMI. On the one hand, it seems that patients with higher BMI had the strength and energy to exercise at higher intensities, which is in accordance with the results of Falk et al. (1985) and Hechler et al. (2008). Since the most exhausted patients are generally the ones with the lowest BMI values, it was not surprising to find that these patients also had the lowest exercise intensity. This is most probably the consequence of their malnutrition and declining energy and physical capacities. On the other hand, it seems that exercise could play a protective role in keeping a patient’s BMI from further decreasing during the acute phase of the disorder. Individuals who exercise at high intensities could “allow” themselves to eat more and consequently, have a higher BMI. This was initially proposed by Garner and Garfinkel (1997). In fact, physical activity has been found to play an enhancing role in patients’ weight recovery, especially in recovering body fat (Kostrzewa et al., 2013). This hypothesis is also in accordance with animal models; as mentioned in the introduction, Mequinion et al. (2015) reported that case of food restriction, the mice who exercise stabilized their weight faster in comparison with those who didn’t. Consequently, this positive association between exercising at high intensity and a better nutritional status (higher BMI and FFMI values) could be a substantial argument in favour of including adapted physical activity sessions in AN.
treatment. In fact, the introduction of a graduated exercise program adjusted to the patient’s somatic status (if clinically safe), after admission to inpatient treatment, has been suggested more than 15 years ago (Garner & Garfinkel, 1997). Moderated under the appropriate conditions (adapted to the food intake and energy expenditure of the patient and taking into account bone mineral density and cardiac function (Association, 2006)), supervised exercise interventions integrated in AN inpatient treatment appeared to be safe (Hausenblas et al., 2008; Ng et al., 2013; Vancampfort et al., 2014; Zunker et al., 2011) and were associated with a positive outcome (Zunker et al., 2011) and a significant decrease in patients’ concerns about body weight and shape (Ng et al., 2013). After summarizing the evidence of eight randomized controlled trials, Vancampfort et al. (2014) concluded that adapted exercise sessions significantly increased BMI, percentage of body fat and muscular strength of patients with AN and that aerobic exercises, yoga and massages significantly decreased eating disorder symptomatology and depressive symptoms in these patients.

Exercise duration (in terms of hours per week) was not linked to any of the three markers of nutritional status, which is in accordance with previous studies (Kostrzewa et al., 2013; Pirke, Trimborn, Platte, & Fichter, 1991).

The subtype of AN contributed to explain all three markers of the nutritional status, which has been previously found in patients with AN for BMI (Godart et al., 2006) and FMI (Probst et al., 1996). FFMI was positively linked to birth weight, which is in accordance with results from the general population (Singhal, Wells, Cole, Fewtrell, & Lucas, 2003).

The presence of amenorrhea was significantly linked to lower BMI and FMI. This is in accordance with previous studies in the general population (Abraham, Pettigrew, Boyd, & Russell, 2006; Ahima, 2004) and in AN (Abraham et al., 2006). Pitts et al. (2014) found that
patients who recovered their menses had significantly higher percentages of body fat than the ones who didn’t. They did not find a difference in BMI.

Finally, age was significantly linked to FFMI and FMI in opposite directions. An older age was associated with lower FFMI and higher FMI. To our knowledge, this has not been previously investigated in AN. However, these results are in accordance with results from the general population; in healthy individuals, BMI and percentage of body fat increase significantly with age (up to middle age) (Shimokata et al., 1991).

**Strength and limitations**

The main strengths of this study were: 1) the use of a valid bioelectrical impedance analysis equation in AN (Mattar et al., 2011) to assess body composition in a very large sample of inpatients; 2) the focus on exercise and not excessive exercise; 3) simultaneous consideration of several factors associated with the nutritional status of patients. To our knowledge, this has not been done before.

The main limitation of this study was the lack of information concerning the food intake and energy expenditure of patients. Both these factors have been reported to significantly predict the nutritional status of patients with AN (Mitchell & Truswell, 1987) and healthy individuals (Thibault, Genton, & Pichard, 2012). Taking into account energy intake and energy expenditure would have brought more insights to understanding our patients’ nutritional statuses. Future research should investigate these parameters in addition to the factors investigated in this study. Another limitation was the use of a subjective method to assess the duration and intensity of exercise. Using an objective method, such as accelerometers, in our huge cohort would have been very difficult to implement and expensive. The use of a semi-structured questionnaire seemed more appropriate (Davis, Kennedy, Ravelski, & Dionne, 1994). Future studies could benefit more from
including an objective instrument in their protocols to assess both physical activity and energy expenditure.

**Conclusion**

Exercising at higher intensity in acute AN is associated with a better nutritional status. This is a substantial argument in favour of including physical activity sessions to AN treatment, as suggested by the growing evidence of the positive effects of adapted physical activity in the treatment of AN. This physical activity should be carefully adapted in terms of exercise intensity, according to a patient’s clinical state. New research on this topic is needed. Furthermore, when required to handle undernourished patients suffering from AN, clinicians should be aware that current AN restrictive type is associated with a worse nutritional status compared to current AN binge-eating/purging type.
## Tables

**Table 11. Patients characteristics of 191 patients with acute anorexia nervosa (AN).**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.0</td>
<td>6.9</td>
<td>13.2</td>
<td>52.3</td>
</tr>
<tr>
<td>Age at AN onset (years)</td>
<td>16.4</td>
<td>4.2</td>
<td>6.0</td>
<td>33.0</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>4.4</td>
<td>4.4</td>
<td>0.2</td>
<td>24.2</td>
</tr>
<tr>
<td>Birth weight* (kg)</td>
<td>3.2</td>
<td>0.4</td>
<td>1.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Body mass index</td>
<td>14.6</td>
<td>1.5</td>
<td>11.2</td>
<td>18.6</td>
</tr>
<tr>
<td>Fat-free mass index</td>
<td>12.6</td>
<td>0.8</td>
<td>10.4</td>
<td>15.4</td>
</tr>
<tr>
<td>Fat mass index</td>
<td>2.0</td>
<td>1.1</td>
<td>0.1</td>
<td>5.1</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>13.4</td>
<td>6.3</td>
<td>.94</td>
<td>28.0</td>
</tr>
<tr>
<td>Exercise duration (h/week)</td>
<td>9.0</td>
<td>10.2</td>
<td>0</td>
<td>60.0</td>
</tr>
<tr>
<td>Exercise intensity (METs)</td>
<td>3.7</td>
<td>2.2</td>
<td>0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

* Birth weight is obtained for 131 patients.
Table 12. Results of univariate analyses between BMI, FFMI, FMI and variables of interest.

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>FFMI</th>
<th>FMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>r=-.00</td>
<td>r=-.26***</td>
<td>r= .20**</td>
</tr>
<tr>
<td>Age at AN onset</td>
<td>r=.08</td>
<td>r=.04</td>
<td>r=.08</td>
</tr>
<tr>
<td>Illness duration</td>
<td>r=-.02</td>
<td>r=-.28***</td>
<td>r=.20*</td>
</tr>
<tr>
<td>Birth weight</td>
<td>r=.13</td>
<td>r=.18*</td>
<td>r=.03</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>r=-.01</td>
<td>r=-.01</td>
<td>r=.00</td>
</tr>
<tr>
<td>Exercise intensity</td>
<td>r=.15*</td>
<td>r=.25***</td>
<td>r=.01</td>
</tr>
<tr>
<td>AN subtype†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AN-R†</td>
<td>14.2 ± 1.3 ***</td>
<td>12.4 ± .86**</td>
<td>1.8 ± 1.06**</td>
</tr>
<tr>
<td>AN-BP†</td>
<td>15.0 ± 1.5</td>
<td>12.7 ± 1.0</td>
<td>2.3 ± 1.2</td>
</tr>
<tr>
<td>Premenarchal AN †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes†</td>
<td>14.1 ± 1.0*</td>
<td>12.2 ± .6*</td>
<td>1.9 ± .8</td>
</tr>
<tr>
<td>No†</td>
<td>14.6 ± 1.5</td>
<td>12.6 ± .8</td>
<td>2.0 ± 1.1</td>
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<tr>
<td>Amenorrhea §</td>
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<tr>
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<td>14.5 ± 1.4*</td>
<td>12.5 ± .8*</td>
<td>2.0 ± 1.1</td>
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<tr>
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<td>13.2 ± .8</td>
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r: Pearson’s correlation coefficients.

†: t-test for independent samples.

§: Mann-Whitney test for independent samples.

‡: Mean ± SD.

* p ≤ 0.05; **p ≤ 0.01; ***≤ 0.001.

AN: anorexia nervosa. AN-R: anorexia nervosa restrictive type. AN-BP: anorexia nervosa binge-eating/purging type.

FFMI: Fat-free mass index. FMI: Fat mass index.
Table 13. Relationship among nutritional status markers and significant variables of interest.

<table>
<thead>
<tr>
<th>Outcome variable</th>
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<th>Model Summary</th>
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Chapter 1: Findings, results and proposed model of problematic physical activity.

Findings and results

Physical activity in AN is a problematic component of its clinical presentation. Mainly, it aggravates the outcome, interferes with nutrition rehabilitation and increases the risk of short-term somatic complications such as fractures, bruises and skin necrosis and of global long term worse outcome. The aim of my thesis was to better understand the nature, the determinants, and the link with nutritional status of PPA in AN in order to open new perspectives for treatment.

In what is physical activity problematic in AN? How frequent is it?

In the interest of fully answering this question, we critically reviewed 57 studies and showed that considerable heterogeneity in many aspects, such as terms and definitions used for PPA, instruments used to measure physical activity, time of assessment, characteristics of study samples considered, could impact observed results. We proposed and developed a synthesizing classification of PPA in two groups: PPA-qT (qT for quanTitative) and PPA-qL (qL for quaLitative). This was in accordance with Meyer and Taranis’ (2011) and Adkin and Keel’s (2005) reviews, mentioning that “the terms used to describe excessive exercise in ED tended to fall on one of two related dimensions: a quantitative dimension defined in terms of duration, frequency and/or intensity; and a qualitative dimension defined in terms of compulsivity” (p.169).
These groups, defined by us, distinguish the quantitative (evaluating the frequency, duration and/or intensity of physical activity) and the qualitative (evaluating, in addition to physical activity characteristics, the relation an individual has with her/his physical activity and/or its links to ED behaviors, motives for exercise, compulsivity and exercise dependence/addiction). After analyzing studies using our proposed classification, we found that the prevalence of PPA observed varied considerably depending on the cut-off used in each study, based on the duration of physical activity: the highest prevalence corresponding to the lowest cut off. Furthermore, a high level of PPA-qL was associated with more anxiety, obsessive-compulsiveness and addictiveness, and surprisingly higher self-esteem. This was not the case when PPA was measured in a quantitative way. Thus, it seems that the link between PPA and psychopathological dimensions mentioned above is established via the relation the patient has with his/her physical activity.

While working on this review, we found no precise clinical description on the evaluation of PPA in AN, starting by initially defining what is “normal” physical activity in AN.

We conclude that there is a need to develop a more precise evaluation of PPA that distinguishes the different dimensions of PPA in AN that includes different aspects. In clinical practice, when observing patients or listening to them, one can distinguish conscious and unconscious physical activity, who are generally voluntary and involuntary respectively.

Clinicians can observe two components of PPA in AN:

1) Voluntary/conscious PPA:

- Constant need to maintain movement, i.e. restlessness, aimless wandering or inability to sit still. Even when obliged to sit, there is a constant need to maintain movement in the form of leg swinging or constantly jiggling a part of the body.
- Static muscle pressure, i.e., keeping abdominal muscles tensed when seated, standing on one leg to increase pressure on the other, or keeping back and head in very straight, vertical (rectilinear) position.

2) Involuntary/unconscious PPA:

- Increase of conditioning exercises such as sit-ups and pushups, i.e., including hundreds of sit-ups in daily rigid and generally covert routines and rituals. These exercises could also include a compulsive component.

- Voluntary increase physical activity in terms of duration and/or intensity, i.e. exercising for a longer period, preferring high intensity physical activity such as running, or rock climbing. This voluntary increase of physical activity could be observed in daily activities; some patients will voluntarily walk instead of using public transportation, or use the stairs instead of the elevator.

Both these clinical descriptions led us to develop a comprehensive model of development and maintenance of PPA in AN (see below).

**How does the definition of PPA impact prevalence and linked factors?**

Based on the results of our critical systematic review, we hypothesized that the different definitions of PPA could seemingly explain the wide prevalence generally reported in the literature. Thus, we tested in a study the impact of seven different definitions of PPA in the same sample, on its prevalence. We also examined how core ED symptoms and emotional profile scores are associated with these different definitions and their impact on quality of life. We found that PPA varied considerably from 5% to 54% in the same study sample, depending on the number of criterion used for its definition, as we hypothesized earlier. In addition, the type of ED symptomatology (i.e.: high restriction and/or low bulimia) was found to be associated to the
majority of our definitions of PPA, independently of the criteria of the definition. A better self-reported quality of life was found among problematic exercisers compared to non-problematic exercisers in three definitions. PPA was also associated to more obsessions and compulsions in two definitions (PPA-duration and PPA-compulsion) and more worries towards body shape in one definition (PPA-intensity).

These results highlight again the need to clearly clinically define the different dimensions of PPA that can be explained or linked to very different factors. Only then, we will be able to optimally study the links between these dimensions (separately and/or conjointly) and the psychological factors we chose to assess.

**How does PPA impact the nutritional status of acute AN patients at admission?**

Also following our critical review, we wanted to determine the possible impact of PPA on the nutritional status of acute AN patients at admission. To do so, we decided to take into account factors that were previously described to be linked to AN or that could impact nutritional status (age at illness onset, illness duration, anorexia nervosa subtype, and premenarchal status) and those found in the general population (birth weight, age and presence of amenorrhea).

The three components of nutritional status (BMI, fat-free mass and fat mass indexes) were explained by both factors that are linked to AN characteristics and factors described in the general population, with number and type of factors varying for each component. Restricting type of AN was the only factor linked to a worse nutritional status in all three components. Mean intensity of all physical activities was associated with higher body mass and fat mass indexes independently of other factors considered. As usually explained in the literature this could be due to the fact AN patients with higher BMI had more strength and energy to exercise at high intensities than the ones
with lower BMI. This is most probably the consequence of the latters’ declining physical capacity and energy and malnutrition.

However, in line with some authors, and in contrast to commonly beliefs, we highlighted a positive perspective for physical activity in AN. Physical activity could play a protective role in keeping a patient’s BMI from further decreasing during the acute phase of the disorder. Individuals who exercise could “allow” themselves to eat more, hence keep a higher BMI, than the ones who don’t. This was proposed by Garner and Garfinkel (1997). They cite Keys et al. (1950, p. 828) when talking about the fact that some men, involved in the Minnesota starvation experiment (designed to determine the effects of severe and prolonged food restriction and the effectiveness of nutrition rehabilitation strategies), excessively increased their energy expenditure despite their starvation state. They did this in order to be allowed to eat more bread. This is opposite to the majority of other men who responded to semi starvation by reducing physical activity. Furthermore, physical activity has been found to play an enhancing role for weight recovery in AN patients, especially in recovering body fat (Kostrzewa et al., 2013).

Lately, Méquinion et al. (2015) evaluated the impact of voluntary physical activity on two groups of mice that were both food restricted. The first group had access to a running wheel while the second group didn’t. The consequences were: 1) on the short run, the first group of mice adapted faster to food restriction compared to the second one. Despite reaching a crucial point of body weight faster, the first group also stabilized their weight faster compared to the second group. 2) Long term results showed that the first group had a better use of ingested glucose and less fat oxidation. They finally concluded that “physical activity could have positive effects on the global adaptation to the severe condition of food restriction” (p.2, Méquinion et al., 2015).
Proposed model of problematic physical activity

As Beumont (2002) stated, two opposite components of PPA can be identified in AN:

1) PPA that is voluntarily increased in AN for the soul purpose of burning-off more calories and thus viewed as a conscious strategy of AN patients to optimize weight loss;

2) PPA that is involuntarily increased simultaneously with weight-loss, indicating that exercise might not be under voluntary cognitive control of the patient, with a subconscious biological drive (in accordance with results of studies on animal models and on subjective reports of patients’ experiences), a part of this activity becoming totally automatic.

At this point, we can propose a comprehensive model of the development of PPA in AN (Figure 5). This model takes into account all the plausible and empirically-supported findings suggested by the reviewed articles. It is divided into five periods depending on the evolution of AN. In parallel, these periods evolve in three clinical phases (1, 2 and 3). Voluntary/conscious and involuntary/unconscious clinical manifestations (Beumont, 2002) could vary with time and within the same individual. Voluntary manifestations are observed early in the evaluation of the disorder, in parallel to weight loss and ED symptoms. With time and with increasing weight-loss, there seems to be an increase in PPA that is involuntarily and unconscious. It could occur in parallel to voluntary PPA. The respective proportions of voluntary vs involuntary PPA vary in a given subject according to patients themselves and to time. A part or all of this activity can become totally automatic in a compulsive way.

Clinical observations suggest that a subgroup of patients can be hyperactive despite the negative consequences of PPA. In this case, PPA could have a subconscious biological drive (in accordance with results of studies on animal models and on subjective reports of patients’ experiences) and could be an addictive behaviour, as it has been well defined and identified in the general population
Klein et al. (Klein et al., 2004) were the only ones to investigate PPA as an “addiction” in AN, assessing it using a version of the “Substance Dependence Severity Scale” (SDSS) that was modified to specifically measure symptoms of exercise dependence. They found that the exercise addiction criteria were positively correlated to anxiety scores. Further research on exercise as an addiction in AN is needed.

Chapter 2: Future perspectives

How to treat problematic physical activity in anorexia nervosa

Despite noticing and describing the problematic aspect of physical activity since early clinical description of AN (Gull, 1974), the approaches required to take care of this phenomena are poorly described in the literature. No clear guidelines truly exist. Full withdrawal of physical activity was privileged for a long time (Rizk et al., 2014), since it has been mainly associated with interference of refeeding strategies and body weight stabilization (Ng et al., 2013; Strober et al., 1991) and a longer length of hospitalization (Solenberger, 2001).

Relatively recent guidelines of this treatment introduced the idea of progressive increase of physical activity but they remained very vague and general. No one proposed to include a program at the acute phase of AN. During this critical phase of the disorder, limiting physical activity is the most important idea developed. Nothing is mentioned about preventing complication of physical activity by psychoeducation. On one hand, the American Psychiatric Association (2006) recommends that “physical activity should be adapted to the food intake and energy expenditure of the patient, taking into account bone mineral density and cardiac function. For the severely underweight patient, exercise should be restricted and always carefully supervised and monitored.
Once a safe weight is achieved, the focus of an exercise program should be on physical fitness as opposed to expending calories. The focus on fitness should be balanced with restoring patients’ positive relationship with their bodies—helping them to take back control and get pleasure from physical activities rather than being compulsively enslaved to them. An exercise program should involve exercises that are not solitary, are enjoyable, and have endpoints that are not determined by time spent expending calories or changing weight and shape. Sports such as soccer, basketball, volleyball, or tennis are examples” (p.42). On the other hand, the Haute Autorité de Santé (2010) recommends raising the awareness of AN patients on their hyperactivity and its direct link to anorexic functioning in order to reduce their level of physical activity (p.23). NICE (2004) does not mention treatment of PPA at all.

Nevertheless, as early as 1997, based on clinical practice, Garner and Garfinkel (1997) suggested the introduction of a graduated exercise program adjusted to the patient’s somatic status, after admission to inpatient treatment, if clinically safe. Lask and Bryant-Waugh (2007) mention the fact physiotherapy is often ignored while it could be a major approach in better outcome. There is limited literature on clear therapeutic approaches to manage PPA in both the general population (Adams, 2009; Landolfi, 2013) and ED patients (Zunker et al., 2011), there is a growing interest in the place physical activity could take in AN treatment. Landolfi (2013) suggested some type of a cognitive-behavioral intervention that would focus on assisting patients in changing their attitudes towards PA, while returning to “healthy levels” of PA, thus becoming physically active in a health enhancing way (Adams, 2009; Landolfi, 2013). To go back to healthy levels of PA, Freimuth et al. (2011) suggest that in some cases the practice of a new type of exercise might be recommended while in others, the person may continue to do the same type of exercise but in a more moderate and controlled manner (Freimuth et al., 2011).
1. Adapted physical activity in eating disorders

According to all elements developed in this thesis, the inclusion of an adapted and monitored physical activity in ED treatment could optimize refeeding strategies. Garner and Garfinkel (1997) found that a “graduated exercise program” during inpatient treatment will allow a better distribution of the restored weight (p.343). If patients are allowed to exercise, they could accept more easily to eat, thus regaining weight and restoring muscles faster. In addition, physical activity could increase body satisfaction. These elements led some authors to study the impact of physical activity in programs designed for these patients called adapted physical activity or physiotherapy.

1.1. Literature data

Hausenblas et al. (2008), Zunker et al. (2011), Ng et al. (2013), and Vancampfort et al. (2014) studied and/or reviewed the effects of physiotherapy and adapted physical activity in the treatment of AN. They concluded that, moderated under the appropriate conditions, supervised exercise interventions integrated in AN inpatient treatment appeared to be safe, since it did not have significant detrimental effect on anthropometry (body weight, BMI, percentage of body fat and lean body mass).

In her review on six studies, Hausenblas et al. (2008) suggested adapted exercise programs as a treatment for patients with excessive exercise concerns and suffering from ED. Furthermore, these programs have been associated with a positive outcome (Zunker et al., 2011), with a significant decrease in concerns about body weight, shape, depression as well as perception of exercise (Ng et al., 2013). In the most recent review on the matter, Vancampfort et al. (2014) summarized the evidence of eight randomized controlled trials and concluded that physiotherapy significantly increases BMI, percentage of body fat and muscular strength in AN patients and that
aerobic exercises, yoga and massages significantly decrease ED symptomatology and depressive symptoms in both AN and BN patients.

In this direction, a typical treatment goal would be to return to a moderate and healthy level of exercise, with growing evidence that it could be effective in improving mental as well as physical well-being. Interestingly, Zschucke et al. (2013), in their review about the effect of exercise and physical activity as an adjunct treatment in several mental disorders including anxiety, obsessive-compulsive, affective, substance use and eating disorders, have suggested that exercise can be a promising and cost-effective intervention (especially as a treatment for clinical depression and anxiety).

1.2. Practical application during my thesis

All the findings mentioned above suggest the importance of integrating proper care of physical activity in AN, both in quantity and quality, depending on the patient’s physical and nutritional status. Thus, we integrated, in association with Dr. Kern, sessions of adapted physical activity in the treatment of AN inpatients at the Institut Mutualiste Montsouris in Paris (Rizk et al., communications 2014 and 2015).

These sessions were given one time per week, for 1h30, over a period of six weeks. Their main objectives were to:

1) Regain the notion of pleasure in physical activity.

2) Promote a physical activity that is safe and adapted to each person: respectful of the body (progressive increase, work of agonist and antagonist muscles, recuperation, learn how to listen to your body, its pain and its limits).

3) Decrease uncontrolled physical activity in terms of intensity and duration.
4) Practice of low-to-moderate intensity physical activities with muscles reinforcement (strengthening of body parts completely neglected).

5) Psychoeducation on physical activity: what is dangerous (i.e. development of bruises, skin irritation due to exercising on hard grounds, abdominal enlargement with risk of urinary leakage, spinal friction due to excessive sit-ups on solid grounds, sores, ulcerations (increasing risks of infections), risk of stress fractures and/or damage of joints).

Sessions also included corporal expressions sessions, in order for the patient to get in effective contact with his/her body, and collective games. They ended with stretching exercises. All the exercises suggested in these sessions were ideally proposed in pair to prevent the patient from repeating them alone in his room.

Sessions usually ended up with a discussion during which we pointed out the dangerous effects of high levels of physical activity without judgement.

During the first and last sessions, patients filled a series of self-reports assessing:

- Dependence to physical exercise with the Exercise Dependence Scale-Revised (EDS-R) (Kern, 2007).
- Motivation to exercise with the Exercise Dependence Questionnaire (EDQ) (Kern and Baudin, 2011).
- Physical activity with the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (Godin and Shephard, 1985).
- Health-related quality of life with the DUKE Health Profile (Guillemin et al., 1997).
- ED symptomatology with the Eating Disorders Examination-Questionnaire (EDE-Q v.5.2) (Cooper et al., 1989).
Subjective physical condition with the International Fitness Scale (IFIS) (Ortega et al., 2011).

Objective physical condition with the BOUGE-fitness test battery (Vanhelst et al., 2014).

We only have preliminary results showing a significant decrease in the total score of EDS-R and in its tolerance subscale score, between the first and last sessions of adapted physical activity. These results are promising and we hope to continue this fruitful collaboration in order to efficiently introduce adapted physical activity sessions in the treatment of AN inpatients.

2. Heat therapy

Treatment based on heating the ambient temperature have arisen from the hypothesis that hyperactivity in AN could be, at least partially, a thermoregulatory behavior to avoid hypothermia was developed (Cerrato et al., 2012). In their randomized controlled trial including AN and BN inpatients, Bergh et al. (2002) found that restricting physical activity to a minimum (i.e. using wheelchairs instead of walking, or walking very slowly) and settling patients in warm rooms (room temperature up to 40°C) for 1 h after each meal had a decrease in their time to remission compared to patients without treatment. Cerrato et al. (2012) found, in ABA animals, that warming the ambient temperature (up to 32°C) decreased the wheel activity of rats while preserving their food intake compared to rats that were kept at constant ambient temperature of 21°C.

3. Other suggested treatments

Some have found that high-caloric meals indirectly reduced physical activity by producing a positive energy balance and inducing weight gain (Exner et al., 2000; Falk et al., 1985). Others
recommended a period (mainly an hour) of supervised bed rest after each meal to prevent PPA or other purging behaviors such as vomiting (Epling and Pierce, 1985; Beumont et al., 1994). However, prescribed bed rest seems to have many disadvantages: 1) it is difficult to ensure by staff as it is time-consuming and may need a 24-hour supervision (Lask and Bryant-Waugh, 2007). Periods during which the patient is kept alone could turn into sessions of PPA. 2) It also puts the nursing staff in a particularly difficult position: they have to ensure the patient remains in bed, which could result in an entailed battle of wills, while they have to try building a supportive general relationship.

Research perspectives

There is so much that still needs to be done when it comes to PPA in ED. There is an urgently growing need of an international consensus of the definition and diagnostic criteria of PPA in ED. In the light of the findings in this thesis, we could recommend:

1. That the definition of PPA:
   1.1. Includes specific criteria for the characteristics of the physical activity in terms of:
      - Duration: determining the optimal cut-off of hours of physical activity per week. Six hours per week seems to be the best compromise.
      - Intensity: Low-intensity physical activity would decrease risk of injuries compared to vigorous-intensity activities.
      - Static muscular tension
      - Differentiation between voluntary vs involuntary features of PPA
      - Differentiation between conscious and unconscious dimensions of PPA.

    1.2. Takes into account the severity of the patient’s nutritional status (i.e. malnutrition).

2. To define (or develop) instrument of evaluation for this PPA definition.
3. That research for the evaluation of PPA (in terms of frequency, determinants, evolution and impact on short term (at discharge) and long term (at one year and more) AN outcome) takes into consideration the following points:

3.1. Separate types of ED.

3.2. Implement the use of universal subjective and objective instruments to assess physical activity, while using questionnaires that assess compulsion to exercise separately from eating pathologies.

4. To develop evaluation of physical activity program in different phases of AN treatment. This will help determine a better program in terms of intensity, frequency and duration.

5. To develop clear therapeutic guidelines on how to manage PPA, taking into account all previous suggested treatments (adapted physical activity, heat therapy, etc.).
Strength and limitations of thesis

A key strength of this thesis was the execution of the largest critical review of the literature, to date, while developing a new classification in order to compare findings on the matter. It allowed us to better understand the complexity of defining PPA in ED, with varied mechanisms underlying each PPA component in ED.

Another important strength is the fact we studied our questions on one of the largest sample of AN inpatients considered in the current literature.

Concerning limitations, there is a detailed section at the end of each chapter. However, the main limitation of our study was the instruments used to assess PPA in AN (using solely self-reports instead of adding objective instruments such as accelerometers).

Last but not the least, I must mention the sudden discontinuation of my thesis’ funding. This strongly influenced the time I was able to devote to my thesis, while having to finance my studies by a part-time job. It was a big restraint to the initial research protocol in which adapted physical activity was projected to be tested as potential treatment of PPA in AN (which was one of the initial objectives of my thesis). Furthermore, the findings of this research are valid mainly for women suffering from acute severe AN and should be evaluated in a more heterogeneous sample. The mechanisms underlying PPA in ED might be different in men. Unfortunately, men have a rare ED presentation, making them harder to recruit than women.
Figures

Figure 4. Vicious circle between problematic physical activity, weight loss and food restriction in Anorexia Nervosa

Adapted from Rizk et al., 2014.
Figure 5. Proposed comprehensive model of the development of problematic physical activity (PPA) in anorexia nervosa (AN): integration of empirically-supported findings and clinical aspects.

Voluntary PPA

- Increased PPA majored by early age at onset of AN.
- Strategy to optimize weight loss.
- Popular sport: walking.

Automation of the behavior

PPA: coping strategy to compensate for, remove, and/or alleviate both negative affective states (anxiety, depression and stress) and eating disorder symptoms (weight preoccupation, drive for thinness, body dissatisfaction and restrictive profile).

± Voluntary PPA

Composite nature of PPA: involuntary (compulsive component not under voluntary cognitive control) ± voluntary (motivated by body dissatisfaction and weight preoccupation related to possible weight increase during treatment).

± Involuntary PPA

Biological findings on animal models

Effect of ambient temperature

Period 0:
Factors preceding AN

High physical activity during childhood
- Physically active fathers
- Participation in esthetic or weight-oriented sports or running
- Increase in physical activity one year prior to onset of AN

Period 1:
Onset of AN

Voluntary PPA

Period 2:
Evolution of AN

Period 3:
Acute phase of AN

Period 4:
Long-term outcome

Clinical phase 1

Physical activity progressively increases in duration and/or intensity. It is described by patients as “goal-directed, organized and planned”.

Clinical phase 2

Daily conditioning exercises routines that could become rigid and secret with time (becoming rituals).

Physical activity becomes an increasingly autonomous process, with automation of the behavior with time. PPA associated with a diffuse restlessness and constant need to maintain movement or static muscle pressure. Continual need to increase physical activity in daily activities.

Clinical phase 3

This phase associates clinical manifestations of phases 1 and 2, in varying proportions.

Physical activity described by patients as “more intense, driven, and disorganized” and as “aimless, stereotyped and inefficient”.

Three observable profiles of patients: 1) Patients with low to normal physical activity. 2) Patients with PPA that they can control. 3) Patients with PPA that they can’t control.

Physical activity similar to healthy controls in long-term weight recovered individuals.


Conclusion

We hope that this thesis contributed to understanding PPA in AN, and could serve for future researches on the matter.

This work allowed me to grow as a scientist, as a researcher, as a student and as a person. I have been lucky enough to have integrated a specialized clinical and research unit, which allowed me to learn and grow. It strongly improved my statistical and analytic skills. I also had the great opportunity to work on a thesis that fully included both my dietetic and nutrition license and my sports’ nutrition and physiology masters degree. Furthermore, I was able to work on a huge database of a multicentric and multidisciplinary study including more than 275 variables for more than 230 patients. I learned how to establish and develop a research protocol (a workshop of adapted physical activity for AN patients at Institut Mutualiste Montsouris) from A to Z. From writing the whole protocol from scratch, asking the permission from national ethical institutions such as the CNIL (Comission Nationale de l’Information et des Libertés) and coordinating between many collaborators on the project, to establishing practical measures on the ground (finding the appropriate participants, setting a time frame convenient to all participants, etc.) and following the evolution of the workshop during 6 weeks, for 2 years in a row.

It should be noted that during these 3 years, I have been surrounded with psychiatrists and psychologists, while I was the only nutritionist in the research team. This greatly enriched my scientific and medical knowledge. I was able to attend many doctoral formations (see list in appendix 12) offered by the Institute of Doctoral Formations of Paris Sorbonne Universities. I took a total of 97 hours of doctoral formations. These formations were extremely helpful on all levels,
including academic, professional and self-development. I was also able to attend more than 50 hours of seminars (see appendix 12), including seminars on the psychopathology of ED, given at the Institut Mutualiste Montsouris. Since I love writing articles and analyzing data, I took a University Diploma in Statistics and Life Sciences (option: Epidemiological Research) to further develop my statistical skills. This, in addition to the continuous help and encouragements of my advisor, allowed me to submit parts of my thesis in national and international journals for publication.

The fact PPA had a serious negative influence on AN patients during the whole evaluation of the disorder was uncontested. PPA plays a crucial role in the lives of many ED patients, interferes in their treatment outcome and in the efficiency of their nutritional rehabilitation. It also seems to affect quality of life, but not always in a negative way. In fact, our work highlights the fact physical activity should perhaps not only be viewed in a negative way as previously described. It could actually be targeted in global treatment programs in addition to the psychological, somatic and social dimensions of treatment. PPA in AN is in need of immediate attention from clinicians and researchers. Research on introducing physical activity in the treatment of AN are needed. In fact, with the help of fundamental research on animal models, including pharmacological and clinical researches, a clear clinical consensual definition of PPA and its different dimensions can hopefully open the path to new and developed treatment perspectives.
## Appendix 1: DSM-IV-TR Diagnostic Criteria for Anorexia Nervosa

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<th>Description</th>
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<tr>
<td>A</td>
<td>Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).</td>
</tr>
<tr>
<td>B</td>
<td>Intense fear of gaining weight or of becoming fat, even though underweight.</td>
</tr>
<tr>
<td>C</td>
<td>Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.</td>
</tr>
<tr>
<td>D</td>
<td>In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., oestrogen, administration).</td>
</tr>
</tbody>
</table>

**Specific type:**

**Restricting type:** During the current episode of anorexia nervosa, the person has not regularly engaged in the binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enema).

**Binge-eating/purging type:** During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

---

# Appendix 2: DSM-5 Diagnostic Criteria for Anorexia Nervosa

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly, low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.</td>
</tr>
<tr>
<td>B</td>
<td>Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.</td>
</tr>
<tr>
<td>C</td>
<td>Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.</td>
</tr>
</tbody>
</table>

**Specific type:**
- **Restricting type:** During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enema). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.
- **Binge-eating/purging type:** During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

**Specific current severity:**
The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

- **Mild:** $\text{BMI} \geq 17 \text{ kg/m}^2$
- **Moderate:** $16-16.99 \text{ kg/m}^2$
- **Severe:** $15-15.99 \text{ kg/m}^2$
- **Extreme:** $\text{BMI} < 15 \text{ kg/m}^2$

Appendix 3: ICD-10 Diagnostic Criteria for Anorexia Nervosa

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Weight loss, or in children a lack of weight gain, leading to a body weight of at least 15% below the normal or expected weight for age and height.</td>
</tr>
<tr>
<td>B</td>
<td>The weight loss is self-induced by avoidance of “fattening foods”</td>
</tr>
<tr>
<td>C</td>
<td>A self-perception of being too fat, with an intrusive dread of fatness, which leads to a self-imposed low weight threshold.</td>
</tr>
<tr>
<td>D</td>
<td>A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis, manifest in the female amenorrhoea, and in the male as a loss of sexual interest and potency (an apparent exception is the persistence of vaginal bleeds in anorexic women who are on replacement hormonal therapy, most commonly taken as a contraceptive pill).</td>
</tr>
<tr>
<td>E</td>
<td>Does not meet criteria A and B of Bulimia nervosa*</td>
</tr>
</tbody>
</table>

Comments:
The following features support the diagnosis, but are not necessary elements: self-induced vomiting; self-induced purging; excessive exercise; use of appetite suppressants and/or diuretics

* Criterion A for Bulimia nervosa: Recurrent episodes of overeating (at least two times per week over a period of three months) in which large amounts of food are consumed in short periods of time. Criterion B for Bulimia nervosa: Persistent preoccupation with eating and a strong desire of a sense of compulsion to eat (craving).

# Appendix 4: Medical complications of Anorexia Nervosa

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Endocrine and Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia and hypotension</td>
<td>Amenorrhea</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>Infertility</td>
</tr>
<tr>
<td>Sudden death – arrhythmia</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Refeeding syndrome</td>
<td>Thyroid Abnormalities</td>
</tr>
<tr>
<td>Echo changes</td>
<td>Hypercortisolemia</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td>Hyperamylasemia</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Lanugo hair</td>
<td>Hypozincemia</td>
</tr>
<tr>
<td>Starvation-associated pruritus</td>
<td>Hypophosphatemia</td>
</tr>
<tr>
<td></td>
<td>Hypochloremia</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Pancytopenia due to starvation</td>
<td>Neurogenic diabetes insipidus</td>
</tr>
<tr>
<td>Decreased sedimentation rate</td>
<td>Arrested growth</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Metabolic alkalosis</td>
</tr>
<tr>
<td>Mild anemia</td>
<td>Mild metabolic acidosis</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Lagophthalmos</td>
</tr>
<tr>
<td>Refeeding pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Acute gastric dilatation</td>
<td></td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td><strong>Bone metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Low bone mineral density</td>
<td></td>
</tr>
<tr>
<td>Increased risk of fracture</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine and Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
</tr>
<tr>
<td>Thyroid Abnormalities</td>
<td></td>
</tr>
<tr>
<td>Hypercortisolemia</td>
<td></td>
</tr>
<tr>
<td>Hyperamylasemia</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>Hypozincemia</td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td></td>
</tr>
<tr>
<td>Hypochloremia</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Neurogenic diabetes insipidus</td>
<td></td>
</tr>
<tr>
<td>Arrested growth</td>
<td></td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td></td>
</tr>
<tr>
<td>Mild metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td>Lagophthalmos</td>
<td></td>
</tr>
<tr>
<td>Lagophthalmos</td>
<td></td>
</tr>
<tr>
<td>Cerebral atrophy</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td></td>
</tr>
<tr>
<td>Spontaneous pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Mehler and Brown (2015) and the DSM-5 (2013).
## Appendix 5: PRISMA checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>Title page</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>Abstract</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>4</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>NA</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>4</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>4</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>Appendix 1</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>5</td>
</tr>
<tr>
<td>Component</td>
<td>Step</td>
<td>Description</td>
<td>Page(s)</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>5</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>Table 1</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>5</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>NA</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I² for each meta-analysis).</td>
<td>NA</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>NA</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>NA</td>
</tr>
</tbody>
</table>

**RESULTS**

<table>
<thead>
<tr>
<th>Component</th>
<th>Step</th>
<th>Description</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td>Page 5 and figure 1</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>6</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>Table 1</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>Review part 2</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>Review part 2</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>NA</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>NA</td>
</tr>
</tbody>
</table>
**DISCUSSION**

<table>
<thead>
<tr>
<th>SECTION</th>
<th>PAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
</tr>
</tbody>
</table>

**FUNDING**

<table>
<thead>
<tr>
<th>SECTION</th>
<th>PAGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
</tr>
</tbody>
</table>

*Reference of review: Rizk et al. (2015).*

**Justification of missing items in the PRISMA checklist:**

- Item #5 (protocol and registration): When we requested a registration number, the team of the Centre for Reviews and Dissemination told us that our review had progressed to a point beyond completion of data extraction and thus, could not be registered anymore in PROPSERO.
- Item #13 (summary measures), item #14 (Synthesis of results), Item #15 (risk of bias across studies), Item #16 (additional analyses), Item #22 (risk of bias across studies) and Item #23 (additional analysis): Items concerning systematic reviews of reports of randomized trials and meta-analysis and not for systematic reviews of other types of research, like our systematic review of epidemiological studies.
- Item #27 (funding): This review was not funded by any organism
Appendix 6: Search strategy in MEDLINE

Search strategy: MEDLINE (OVID)
01. eating/
02. disorder$.tw.
03. activity.tw.
04. 1 or 2 or 3
05. anorexia/
06. anorexia.tw.
07. anorexia nervosa/
08. anorexia nervosa.tw.
09. physical/
10. physical.tw.
11. physical activity/
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 4 and 12
14. exercise/
15. physical exercise.pt.
16. bulimia/
17. bulimia.tw.
18. bulimia nervosa/
19. 14 or 15 or 16 or 17 or 18
20. exercise/
21. ((excessive or compulsive or driven or over or obligatory) adj (exercise$)).ti,ab.
22. abuse.tw
23. urge. tw
24. restless. Tw
25. energy. tw
26. dependence$
27. addiction$
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 4 or 12 or 21
30. 4 and 28
Appendix 7: Data items

Variables for which data were sought

Information was extracted from each included study on: (1) terms and definitions given to physical activity, (2) instruments used to measure physical activity (including time of assessment), (3) prevalence of physical activity, when measured, (4) study design (including case vs controls studies), (5) characteristics of study samples and participants (including inclusion and exclusion criteria, size of sample, method of diagnosis of eating disorder, eating disorder types and subtypes, age, gender, body mass index, type of eating disorder treatment, illness duration, age at onset and characteristics of control sample if existent), (6) factors associated with physical activity measures (psychological factors (including depression, anxiety, obsessive-compulsiveness or stress), eating disorder symptomatology, weight, body composition, treatment outcome, etc.).
Appendix 8: Proposed diagnostic criteria for Exercise Dependence

Exercise dependence is manifested by three or more of the following criteria

1. **Withdrawal**: characteristics withdrawal symptoms for exercise (i.e. anxiety, fatigue) or exercise taken to relieve or avoid symptoms.

2. **Continuity**: exercise is continued despite knowledge of having a persisting/recurring physical or psychological problem that is likely to have been cause or exacerbated by the exercise (i.e. continued running despite injury).

3. **Tolerance**: need for increase amounts of exercise to achieve desired effect: diminished effect with continued use of same amount of exercise.

4. **Loss of control**: a persistent desire or unsuccessful effort to cut down or control exercise.

5. **Decrease in other activities**: social, occupational, or recreational activities are given up or reduced because of exercise.

6. **Time**: a great deal of time is spent in activities necessary to obtain exercise.

7. **Intention**: exercise is often taken in larger amounts or over a longer period than was intended.

*Adapted from Hausenblas and Downs, 2002.*
Appendix 9: Questionnaire on physical activity

« En ce qui concerne vos activités physiques, pratiquez-vous :

Marche (extérieure ou intérieure) : Non = 0. Oui= 1

Si Oui, Combien d’heures par semaine ? |__| |__| |__| heure(s)
Sur quelle distance approximativement en Km ? /__/__/__/ km

Course à pied (extérieure ou intérieure) : Non = 0. Oui= 1

Si Oui, Combien d’heures par semaine ? |__| |__| |__| heure(s)
Sur quelle distance approximativement en Km ? /__/__/__/ km

Natation : Non = 0. Oui= 1

Si Oui, Combien d’heures par semaine ? |__| |__| |__| heure(s)
Sur quelle distance approximativement en Km ? /__/__/__/ km

Vélo (d’extérieur ou d’intérieur) : Non = 0. Oui= 1

Si Oui, Combien d’heures par semaine ? |__| |__| |__| heure(s)
Sur quelle distance approximativement en Km ? /__/__/__/ km

Ménage : Non = 0. Oui= 1

Si Oui, Combien d’heures par semaine ? |__| |__| |__| heure(s)

Autres activités sportives : Non = 0. Oui= 1

Si Oui, Lesquelles, précisez : [champs de texte assez long]
Combien d’heures par semaine ? |__| |__| |__| heure(s)
Appendix 10: Examples of MET values and intensity classification

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Energy demands (MET)</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking, 3.0 mph, moderate speed, not carrying anything.</td>
<td>3.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Jogging, general</td>
<td>7</td>
<td>Vigorous</td>
</tr>
<tr>
<td>Swimming, leisurely, not lap swimming, general</td>
<td>6</td>
<td>Vigorous</td>
</tr>
<tr>
<td>Bicycling, general</td>
<td>7.5</td>
<td>Vigorous</td>
</tr>
<tr>
<td>Health club exercise, general</td>
<td>5.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cleaning, house or cabin, general</td>
<td>3.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Standing, light</td>
<td>2.5</td>
<td>Light</td>
</tr>
</tbody>
</table>


Adapted from Ainsworth et al., 1993 and 2011.

Appendix 11: FFMI and FMI values according to three categories

<table>
<thead>
<tr>
<th>Low</th>
<th>Normal</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFMI</td>
<td>FMI</td>
<td>FFMI</td>
</tr>
<tr>
<td>FFMI</td>
<td>FMI</td>
<td>FFMI</td>
</tr>
<tr>
<td>FFMI</td>
<td>FMI</td>
<td>FFMI</td>
</tr>
</tbody>
</table>

Women
- < 15.0
- 15.1 - 16.6
- 17.5 - 19.7
- > 18.0

Men
- < 17.4
- 17.5 - 19.7
- > 19.8

Adapted from Deurenberg et al., 1991.
Appendix 12: Formations during thesis

1. **Doctoral formations**

1.1. Cycle «Maitriser l’information scientifique»

- Séminaire S-Info Sc Maitriser l’information scientifique.

1.2. Cycle «Communication»

- Séminaire S-Comm Découvrez les principes d’efficacité de la communication écrite et orale.
- Atelier «Entrainez-vous à la prise de parole en public».

1.3. Cycle «Pratiques managériales»

- Séminaire S-PM : Découvrez les grands principes du management.

1.4. Cycle «Avenir professionnel»

- Séminaire S-AvProD : «Poser les bases de son avenir professionnel».
- C-PP : Conseil personnalisé en projet professionnel.

1.5. Cycle «La thèse électronique»

- Séminaire S-ThElec : Séminaire «La thèse électronique : structure, dépôt et diffusion».
- Atelier A-ThElec1 : «La thèse électronique en pratique : utiliser une feuille de style».
- Atelier A-ThElec2 : «Gérer sa bibliographie et ses PDF avec Zotero ».
1.6. Cycle « Innovation et Valorisation »

➢ Séminaire S-Entrlno : Entreprenariat innovant.

2. **Seminars**

I attended more than 50 hours of seminars that I benefitted from, directly and indirectly throughout my thesis. Below is the list of the seminars I attended:


2.2. Symposium on the mental health of students and young adults (CLIPSY, Research Center D. Anzieu (EA4430), Nanterre, France).


2.4. Symposium on digital health of diabetics, first *matinale* of “Doctors 2.0 and you” (Paris, France).

3. **University Diploma**

During my last year of thesis, I took a University Diploma in Statistics and Life Sciences (option: Epidemiological Research) at Sorbonne Paris XI. It is a specialization in planning & analyzing experimental and observational studies in the fields of epidemiology and public health. It strongly helped my statistical and analytical capacities, which was extremely beneficial for my publications.
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