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Hypersexuality: the controversial mismatch of the psychiatric diagnosis
The role of psychopathology in modern psychiatry

Psychiatry has been significantly influenced by the social, economic and scientific changes that have occurred within the last few years. These influences have evolved psychiatry into a modern medical specialty that is increasingly knowledgeable about the structure and function of the brain, mind (thoughts, feelings, and consciousness), behaviors and social relationships. Nonetheless, this knowledge has not uniformly spread and, in many institutions, psychiatric education and practice remain largely based on knowledge developed over the last century. Over a century ago, the target of psychiatry was madness, and psychiatrists were called “alienists”. Along the years, the target has changed: for a number of years psychiatrists have been asked to treat mental disorders, and now the target has evolved to include the promotion of the mental health of the general population. In fact, some traditional illnesses have seemingly disappeared from clinical observation (e.g., organic brain disorder or involutional depression which were listed among the DSM-III diagnoses), while new forms of mental health problems have become of frequent observation by psychiatrists.

Body image is becoming more and more important in Western cultures, since it represents the link between the inner and outer world. Many new mental disorders arise from the need “to appear in order to be someone” rather than on the need “to be someone”. The pathological use of social media and the Internet, as well as the excessive importance attributed to body image (such as in orthorexia and vigorexia), are valid examples of this mismatch between being and appearing.

Excessive use of the Internet can have detrimental effects on mental health in vulnerable people, particularly younger persons. In fact, Internet Gaming Disorder has been recently included among the behavioral addictions in the ICD-11, following the cases of the Japanese hikikomori and the high rates of hospital admissions in emergency units after hours spent gaming online. Several pathological behaviors occurring in young people, such as excessive cannabis use, contribute to the increased suicide rates in this population, highlighting the need to better characterize the psychopathological characteristics of modern adolescents. Suicide is also increased in clinical populations, such as patients diagnosed with Traumatic Brain Injury (TBI) or Obsessive-Compulsive Disorder (OCD), but this relationship has too often been neglected by clinicians and needs to be deepened.

It is now clear that modern psychiatrists should balance the classical knowledge with new findings coming from research and evidence-based medicine. For example, OCD has been moved in both the DSM-5 and the ICD-11 from the chapter of anxiety disorders to a new stand-alone chapter, which also includes trichotillomania, hoarding disorder, body dysmorphic disorder, and excoriation disorder. This change is mainly due to a modern clinical and psychopathological characterization of OCD with relevant implications for clinical practice and treatment options. And yet, Post-Traumatic Stress Disorder (PTSD) and bipolar disorders have followed a similar course. Finally, research on schizophrenia is moving towards ultra-high risk and predictive models of psychoses. Schizophrenia is now conceptualized as a complex disorder with multiple genetic, environmental and psychosocial risk factors. The
polygenic risk score represents one good example of the complexity of schizophrenia. In order to achieve effective integration of the ever growing wealth of knowledge in mental health practice it is essential to redefine the clinical foundations of psychiatry, and to reconsider and reinterpret “old” concepts and approaches that are still valid (“back to fundamentals”). Psychiatrists will have to show a courageous openness towards innovation and experimentation. It is the time to update the training curricula by integrating the theoretical bases of psychiatry with recent evidence coming from scientific studies. In particular, from an educational perspective, it may be useful to identify a “common trunk” of knowledge and skills for all psychiatrists, and several different professional “ramifications” for differentiating skills and knowledge. This will characterize the professionalism of psychiatrists of the future, as it happens for other branches of medicine. Among the elements constituting the common trunk of the psychiatrist’s professionalism, psychopathology certainly plays a major role. Other elements of this common trunk are: 1) to care for the patient as a person. If the patient is not considered as a whole, with an attention on his/her life history, the clinical approach will fail, because patients will not trust psychiatrists who do not show a real interest toward them; 2) to differentiate mental health problems due to social difficulties from full-blown psychiatric syndromes. It is not the psychiatrist’s task to intervene in cases of social distress, but psychiatrists’ have the skills to recognize these situations and to propose psychological or social support; 3) to provide patients with evidence-based personalized treatments on the basis of the bio-psycho-social approach; 4) to organize and coordinate the community activities for promoting mental health.

The ramifications can include the application of the different psychotherapeutic techniques, the use of multiple diagnostic tools, the knowledge of the various rehabilitation methods, the specialization on specific population groups (e.g., adolescents or the elderly) or particular stressful conditions (e.g., the mental health of migrants or prisoners) or clinical situations (e.g., the pathologies due to excessive use of the new technologies or of the new drugs).

In this issue of the Journal, modern psychiatric psychopathological needs have been addressed in terms of clinical practice, training and research, bringing together epidemiological and clinical findings with psychopathological features of classical and new forms of mental disorders, in an integrated approach to psychiatry. We have read with the utmost interest the selected articles, which have been delivered by expert clinicians and researchers in their fields. We hope our readership will do the same.

References

Introduction

Polygenic Risk Scores (PRS), i.e. proxy values generated combining multiple genetic markers into a single score indicative of specific lifetime risk for a disease, are becoming increasingly popular as research and translational tools in somatic medicine and in psychiatry. Within psychiatry, PRS define cumulative risk profiles based on the identification of genetic variants related to psychiatric disorders, obtained through genome-wide association studies (GWAS). This approach has proven particularly promising in schizophrenia, although the etiopathogenetic complexity (and the multiple genotype-environment (GxE) interactions) involved in the development of its spectrum conditions remain largely unknown.

Most studies on schizophrenia-related PRS (s-PRS) mainly focused on testing and assessing possible associations between with overt (or emergent) clinical features in patients with already diagnosed schizophrenia spectrum disorders. In this perspective, a recent study reported that s-PRS was associated with general psychopathology at the Positive and Negative Syndrome Scale (PANSS) and with anxiety at the Hamilton Anxiety Rating Scale rather than with positive or negative symptoms in a sample of patients with first-episode of psychosis. Other studies focused on the association between s-PRS and psychopathological liability in the adult general population; in fact, another recent study reported that s-PRS was associated in youth (18-22 age range) with phenotypic expressions involving anxiety, depression, nicotine use, trauma and family history of psychological disorders.

Empirical evidence on the effects of s-PRS at different levels of analysis and in different populations (general vs. clinical) was recently reviewed,
and studies centered on s-PRS, published until March 2016 seem to converge on four main issues.

1. Pleiotropy between schizophrenia and other psychiatric disorders. Genetic risk for schizophrenia in the general population has a phenotypic effect at the psychopathological level not only related to schizophrenia spectrum disorder manifestations, but also to other non-schizophrenic manifestations, such as bipolar disorder, schizoaffective disorder and anxiety. Interestingly, s-PRS studies suggest possible relationships and overlaps between disorders 9; for example, in bipolar disorder s-PRS is associated with mood-incongruent psychotic symptoms 10 and is inversely associated with lithium response 11.

2. Less common-variant genetic overlap between schizophrenia and cognition with than other psychopathology. Available studies found an inverse relationship between s-PRS and global measures of cognition 12-14. No robust empirical data are available on the association between s-PRS and specific cognitive functions; interestingly, recent studies found effects of s-PRS on neural activations during specific cognitive tasks such as reward processing 15, working memory 16 and memory encoding 17. Considering the inverse association between s-PRS and cognition, an apparent counterfactual finding that needs replication regards the lack of association between s-PRS and primary school achievement 18; however, it could be hypothesized that the age of assessment could influence this possible relationship, therefore the effects of s-PRS on school achievement need to be evaluated along the academic course.

3. Small variance explained by currently available s-PRS for all phenotypes (presumably limited by the fact that PRS do not capture Copy Number Variants or rare Single Nucleotide Polymorphism contributions to variance).

4. Early phenotypic expression of genetic risk for schizophrenia in the general population through a broad range of soft (i.e. non-psychotic) neurocognitive and behavioral features during development. Vulnerability to schizophrenia spectrum conditions is manifested through a phenotypic cloud that incorporates cognitive-emotional, interpersonal and socio-functional features presumably more relevant for the emergence of negative symptoms and social impairments than for the onset of positive psychotic experiences 19-21. The latter point represents the specific focus of this review, that expands conclusions of the cited review 8 including recent additional empirical findings that might be useful to complete the phenotypic puzzle and enrich our understanding of the dynamic mosaic of early developmental expressions related to s-PRS in the general population.

s-PRS and vulnerability (endo)phenotypes

In the last two years, several empirical contributions investigated phenotypic effects in infancy and childhood of s-PRS in the general population. Jansen and colleagues 22 indicated a selective association of s-PRS with higher internalizing scores at Child Behavior Checklist at all ages, as well as with higher externalizing scores at age 3 and 6. Moreover, looking at the syndromic subscales, s-PRS was positively associated with higher emotional reactivity at age 3, all internalizing subscales (emotional reactivity, anxiety/depression, somatic complaints, withdrawal) at age 6, and Thought Problems (a proxy score for psychosis-proneness and soft positive symptoms) at age 10. Nivard et al. 23 reported a strong association of s-PRS with childhood (age 7 to 10) and adolescent (age 12 to 15) depression, a weaker association with Oppositional Defiant Disorder/Conduct Disorder (ODD/CD) at age 7, and a steeper increase in the association from childhood to adolescence for Attention Deficit/Hyperactivity Disorder and ODD/CD. Riglin et al. 24 reported an association of s-PRS with Performance IQ, speech intelligibility and fluency, and headstrong behavior at age 7-9, and with social difficulties and behavioural problems at age 4. In a subsequent study 25 of the same group, s-PRS was prospectively associated with broadly-defined emotional difficulties constantly from childhood (age 7) to mid-life adulthood (age 42) through six points of assessment, differently from depression-PRS that was associated with emotional difficulties only in the last assessment. Moreover, a higher s-PRS was associated with non-optimal overall infant neuromotor development between 2 and 5 months in a recent study by Serdarevic et al. 26.

Overall, despite contingent differences in experimental settings and designs, these recent empirical findings encourage an updated perspective on the neurodevelopmental antecedents of schizophrenia 19-21. From a developmental perspective, phenotypic effects of s-PRS are not only early and substantial, but they are also detectable at a behavioral level from the perinatal period (age 2-5 months) 26 through infancy (age 3-4) 22 24, childhood (age 7-9 years) 25 and adulthood 7 27. These findings on the phenotype cohere with preliminary findings on the endophenotypes, as suggested by the reported association between s-PRS and neurodevelopmental features. The effects of s-PRS on cortical gyration calculated at structural neuroimaging have been investigated in two independent and healthy general populations 28: a higher s-PRS was significantly associated with a lower local gyrification index in the
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bilateral inferior parietal lobes, where case-control differences have been reported in previous studies on schizophrenia. Similar findings were reported also by Neils et al. 29, who compared subjects at high familial risk of schizophrenia who remained well, with those who developed sub-diagnostic symptoms, or who developed schizophrenia with healthy controls. Authors tested whether individuals at high familial risk of schizophrenia carried an increased burden of trait-associated alleles using s-PRS, as well as the extent to which s-PRS was associated with gyral folding in the frontal and temporal lobes. Authors found that individuals at high familial risk of schizophrenia who developed the disorder carried a significantly higher s-PRS compared to those at high-risk who developed sub-diagnostic symptoms or remained well and to healthy controls; furthermore, within the high-risk cohort, there was a significant and positive association between s-PRS and bilateral frontal gyrification. These findings that S-PRS impacts on early neurodevelopment to confer greater gyral folding as detected in young adulthood are in line with early phenotypic effects.

Finally, a recent report 30 showed an interaction between the environment and genetics. In fact, parental behaviours can influence offspring developmental outcomes, supporting the hypothesis that PRS predict variation in characteristics beyond the target trait, including characteristics that are considered to be environmental. For example, the offspring genetic risk for schizophrenia is positively associated with paternal age: children whose father is over 45 at their birth have on average a genetic risk score for schizophrenia over one quarter standard deviation higher than children whose father is under the age of 26 at their birth. This finding may have implications for schizophrenia, in which several early environmental risk factors may play a trigger role for the atypical neurodevelopment.

Discussion: translational implication of s-PRS for early detection

The s-PRS approach applied in child-adolescent cohorts from the general population may provide an innovative opportunity to understand how the presumed genetic predisposition to schizophrenia is manifested in developmental time, attempting to disentangle the respective contribution of genetic and environmental risk factors along neurodevelopmental stages. This may be particularly helpful in the childhood premorbid period, in which neurobiological (schizotaxic 31 32) vulnerability expresses itself in a mixed bag of unspecific phenotypic features (e.g. motor, cognitive, behavioral and social impairments), that might be rather difficult to ponder in terms of potential for psychopathological progression and prognostic trajectory 20 21. Therefore, fine-grained empirical findings based on s-PRS, detailing the age-dependent stream of vulnerability phenotypes could have significant translational implications for the early detection of psychotic risk.

The construct of clinical high-risk state for psychosis (CHR) 33 – broadly conceived as a mental state at imminent risk of progressing into frank psychosis – has progressively evolved to capture the clinically subthreshold phase of psychosis, indexing people presenting with putatively prodromal symptoms. Early intervention mental health services for CHR may play a key role in preventing or delaying psychosis 34 35, but only a small proportion of those who develop psychosis is followed since prodromal stages in such services 36. Consequently, programs for the detection of a larger proportion of subjects at risk of psychosis should strive to intervene earlier in the longitudinal trajectory of psychosis development 37. Although the CHR/prodromal state and the subsequent risk of conversion to psychosis might appear, from a clinical and behavioral viewpoint, as early symptomatic stages, they nonetheless plausibly represent rather advanced/late stages from a neurodevelopmental perspective 38 39. According to the neurodevelopmental hypothesis of schizophrenia 39, as well as for the clinical staging model 40, psychosis conceivably represents the last long-term stages of an altered neurodevelopmental process. Such process, although usually manifested in late adolescence/early-adulthood, is often ante dated from the early years of life, by subtle expressions of biological vulnerability. Therefore, the goal of an early detection of psychotic risk in the premorbid period should be based on these subtle expressions of biological vulnerabilities, rather than on hypothetical early direct expressions of psychotic risks, as psychotic experiences, that has a modest and relative unspecific predictive power in youth 41. At the same time, this goal is hampered by the poor knowledge of those early phenotypic expressions of biological vulnerability that are more specific for a longitudinal psychotic risk: in this perspective, a developmental view, corroborated by s-PRS finding could further increase our understanding of specific age-dependent GxE interactive effects across neurodevelopment on both domain-general (e.g. cognitive and motor deficits) and domain-specific features of premorbid and prodromal stages (e.g. anomalies of subjective experiences, attenuated positive and negative symptoms) of psychosis. For example, motor functioning appears an intriguing specific domain of expression of the biological vulnerability to psychosis, as supported by distinct empirical paradigms, including the s-PRS paradigm 36, familial high-risk studies 42 43 and longitudinal birth-cohort studies 44 45. These studies globally show that motor manifestations: 1) emerge al-
ready in premorbid stages, in terms of later achievement of motor milestones and poor motor coordination (i.e., dyspraxia); 2) persist in prodromal stages in terms, for example, of neurological soft signs; 3) become more pronounced in psychotic clinical stages of schizophrenia (including drug-naïve individuals), due to distinct pathophysiological mechanisms, in terms of catatonia, chorea, dystonia, bradykinesia, tics, and stereotypes. Interestingly, impairments in basic neurophysiological mechanisms as corollary discharges may have a pathogenetic role both for early motor impairment and its maintenance as well as for specific longitudinal liability to psychosis in terms of potential triggers for abnormal self-experiences, representing trait-like non-psychotic anomalies of subjective experience that have been recursively corroborated as schizophrenia spectrum vulnerability phenotypes.

In conclusion, studies based on the s-PRS paradigm are in their infancy and appear to have currently a limited explanatory power, as exemplified by the small variance explained for all phenotypes; although findings of s-PRS studies may have significant clinical implications for the early detection paradigm if integrated with empirical findings derived from other empirical paradigms, such as familial-high risk studies and longitudinal birth cohort studies, investigating phenotypic manifestations along the neurodevelopmental trajectory/clinical staging of psychosis. In particular the PRS paradigm may corroborate the value of early non-psychotic vulnerability phenotypes, as they emerge along development, for an early detection of psychotic risk. This is particularly important for childhood and early-adolescence premorbid stages, in which the psychopathological trajectories towards positive psychotic symptoms (i.e. the current gold standard for clinical high-risk stratification) are still inchoate. At the same time, if psychosis prediction should be progressively antedated from prodromal stages, typically occurring in adolescence/young adulthood, to childhood premorbid stages, this has implications for the organization and the allocation of resources of mental health services, usually strictly distinct in Childhood and Adolescence Mental Health Services (CAMHS) and Adult Mental Health Services (AMHS) 52.

**Conflict of Interest**

The authors have no conflict of interests.

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The Adult Autism Subthreshold Spectrum (AdAS) model: a neurodevelopmental approach to mental disorders

Summary
A growing interest has been devoted to adult presentations of Autism Spectrum Disorders. This led to focus on comorbidity between ASD and other mental disorders, mainly (but not limited to) Borderline Personality Disorders, Post Traumatic Stress Disorders, Mood Disorders and Eating Disorders. The presence of any psychiatric comorbidity can mask ASD, in particular in subjects with no intellectual impairment. To address this psychopathological issue, studies adopting the AdAS questionnaire, an instrument with strong convergent validity with alternative dimensional measures of ASD and excellent internal consistency and test-retest reliability, able to detect subthreshold forms of ASD in adulthood, have been reviewed. Based on these evidences, the Subthreshold Autism Spectrum Model has been developed, which includes threshold-level manifestations but also mild/typical symptoms of the disorder, gender-specific features, behavioral manifestations and personality traits associated with ASD. This model encompasses, although not coinciding with, the Broad Autism Phenotype. This is a subthreshold form of autism described in the context of the neurodevelopmental trajectory that – starting from autistic traits – might lead to the broad range of mental disorders. Therefore, the Adult Autism Spectrum can be considered a transnosographic dimension. This approach should help to detect individual features for certain autistic cognitive and behavioral patterns that may predispose to other mental disorders.

Key words
Autism Spectrum Disorder • DSM-5 • AdAS spectrum • Subthreshold autism spectrum

Introduction
Autism Spectrum Disorder (ASD) defines a group of early-onset neurodevelopmental conditions characterized by alterations in brain connectivity with cascading effects on neuropsychological functions. Core symptoms include difficulties in communication and repetitive, stereotyped behaviors. While etiopathogenesis of ASD is still unknown, there is a good evidence for genetic correlates. In particular, specific genetic mutations can be identified in about 20% of ASD cases and twin studies estimate an heritability between 64-91%, suggesting the interaction between heritable and environmental factors. These data confirm the seminal findings by Kanner and Asperger, which observed that both first and second degree relatives of children with “autistic disturbances of affective contacts” shared some features with their offspring, such as late speech, mild obsessiveness and lack of interest in human interactions. Furthermore, Asperger found that parents of autistic-like children report characteristics of pedantry, aloofness, social withdrawal and eccentricity. Considering the early onset of these disorders, few studies have been described the adult courses of ASD. In particular, the mild subtype is likely to be underestimated since for a long-time only autism with pervasive intel-
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The AdAS questionnaire

The interest on a dimensional model for autism has considerably increased, since several authors highlighted the usefulness of such approach. Therefore, several psychometric instruments aiming to assess autistic symptoms as continuous dimensions have been developed. Manifestations of ASD may vary depending on different factors: severity of the autistic symptomatology, developmental level and age and this degree of intensity is reflected by the diagnostic category of Autism Spectrum Disorder. Moreover, the DSM-5 introduced the diagnosis of ASD with different levels of impairment. This radical change reflects the choice to classify psychopathology on the basis of both observable behavior and neurobiological measures, linking symptomatic manifestations with brain functioning.

The aim of this paper is to introduce a novel psychopathological model - the Subthreshold Autism Spectrum Model - broadening and redefining the dimensional approach introduced by the DSM-5. This model has been developed in the broader framework of an international Italy-USA research project (Spectrum Project), whose aim was to apply a Spectrum Model approach to mental disorders, giving relevance not only to proper criteria but also to subthreshold symptoms and signs, behavioral manifestations, atypical features, temperamental traits. This new approach has been proved to be quite accurate for understanding the clinical features, course and comorbidity of most mental disorders, and the continuity between general and clinical populations.

Available instruments mostly assess ASD in a quantitative way, such as the Autism Spectrum Quotient (AQ) developed by Baron-Cohen. “Restricted and repetitive interests and behaviors” have been recognized as a core feature of ASD, although this dimension has been poorly evaluated in the existing questionnaires. Moreover, available questionnaires have been tailored on male patients with ASD. As a result, the profile of female patients with ASD has disappeared from the current nosography and from the range of detection of most instruments.

In order to address such limitations, the Adult Autism Subthreshold Spectrum (AdAS Spectrum), a 160-items questionnaire for adult subjects with normal (or above normal) intelligence without language impairment, has been developed. In line with the Spectrum-Project approach to psychopathology, the AdAS Spectrum refers not only to the core manifestations of the disorder, but also to the attenuated and atypical symptoms, the personality traits, and the behavioral manifestations that may be associated with ASD but that may also be present in
subthreshold or partial forms. In developing the questionnaire, great attention was given to the female phenotypes of ASD as well as to the sensory reactivity area of symptoms. In the questionnaire, some gender-related manifestations have been included such as the tendency of female patients with ASD to mitigate social symptoms by imitation and by acting as someone socially successful. Another gender-related feature is the avoidance of social interactions and the preference in engaging in creative solitary activities, in spending time with pets, or enjoying fictional media. Moreover, female patients with ASD are usually able to recognize their own social difficulties, and consequently develop intense anxiety in social situations and avoidance behaviors, therefore, some social anxiety-like behavioral features have also been included in the questionnaire. The questionnaire includes 160 items, grouped into seven domains allowing the evaluation of a wider spectrum of manifestations of autism. Items’ responses are binary (yes/no) and domain scores correspond to the sum of positive answers. The “Childhood/adolescence” domain includes symptoms related to early developmental phases (such as, being very quiet or unable to speak at all, avoiding eating or playing with other children or being teased or bullied). The “verbal communication” domain covers features of the speaking behavior, the preference for media communication, difficulties in participating in a conversation. The “non-verbal communication” domain explores difficulties in eye-contact and in physical contact, the presence of anger outbursts. The “empathy” domain explores impairment in understanding and interpreting facial expressions, intentions or thoughts, but also the presence of intense attachment to pets or objects. The “inflexibility and adherence to routine” domain includes difficulty in understanding the subtle aspects of verbal communication, insistence on sameness and habits, unwillingness to eliminate useless objects, tendency to follow specific procedures. The “restricted interests and rumination” domain includes the tendency of talking about few preferred topics and being fascinated by numbers, the incapacity to be concise, and the tendency to waste time over details, to lose track of time and to take refuge in daydreaming. The “hyper/hypo-reactivity to sensory input” domain explores the tendency to over- or under-react to stimuli such as textures, smells, noises, temperature and pain. The AdAS Spectrum questionnaire – although evaluating the presence of features belonging to ASD psychopathology – it has not been developed as a diagnostic instrument. It aims to assess the presence/absence of a broad variety of clinical manifestations associated with ASD or that can be present in individuals not fulfilling the diagnostic threshold. The duration, the clustering and the severity of criterion symptoms, mandatory to make a diagnosis according to the DSM-5, cannot be defined using the AdAS Spectrum questionnaire. However, this assessment tool allows to define, assess and evaluate, together with the typical aspects of ASD, a wider area of clinical and non-clinical manifestations, with a specific focus to some gender-specific elements. In its validation study, the AdAS Spectrum questionnaire was administered to subjects endorsing at least one DSM-5 ASD symptom criterion, patients with Feeding and Eating Disorders (FED) and healthy controls. The AdAS Spectrum questionnaire has an excellent internal consistency, a good test–retest reliability, and a strong convergent validity. Although performing differently among the three groups, the questionnaire showed a good sensitivity in identifying subjects expressing either a full or a partial phenotype (i.e., only one symptom criterion) of ASD.

Toward the adult autism subthreshold spectrum: ASD, Borderline Personality Disorder and Post-Traumatic Stress Disorder

Several studies highlighted a certain degree of resemblances between ASD and Borderline Personality Disorder (BPD). Core symptoms of BPD do not seem to be closely related to those of ASD, being mainly characterized by impulsivity with a pattern of instability of interpersonal relationships, of self-image, and of affects. Stressful situations and difficulties in managing anger may elicit anticonservative behaviors, such as threat and self-injuring, suicidal thoughts and behaviors. However, ASD and BPD might show a significant overlap when considering patients with ASD and lack of cognitive impairment. In fact, impairments in social functioning, miscommunications, incorrectly assumed intentions and emotionally outbursts, which are core features of ASD, are frequently observed in patients with BPD as well. On the other hand, the focus on emotive actions and the establishment of intense relationships and superficial friendships, typical features of BPD, might also be observed in ASD presentations. The similarities between the two disorders also involve neuropsychological studies targeting the recognition of facial emotions and prosody have found that both subjects with ASD and BPD show similar difficulties in Theory of Mind tasks and in understanding emotions. The relationship between ASD and BPD addresses also the trauma and stress related psychopathology. Subjects with ASD suffering from chronic exposure to traumatic events may develop a peculiar post-traumatic phenotype known as Complex PTSD (cPTSD), characterized by emotional liability, long-term instability in in-
terpersonal relationships, unstable self-perception and maladaptive behaviors, substance abuse and self-injuring. Due to this peculiar clinical presentation, these subjects might be misdiagnosed as BPD patients. In this framework, it is noteworthy that the prevalence rate of BPD in patients with ASD is 10.6% while the prevalence rate of ASD in patients with BPD is about 15%. Moreover, a recent study showed a positive correlation between autistic spectrum symptoms and suicidality among BPD patients. Furthermore, not only full blown ASD, but also subthreshold autistic traits might enhance the overall suicidality, including both suicidal thoughts and attempts, in BPD subjects. Higher levels of autistic traits have been found in BPD subjects who report a history of abuse (physical or sexual) than in those without a history of trauma. Subjects with full-blown ASD are often bullied or suffer from violence and sexual abuse, and these experiences are also very frequently reported by BPD patients. Subjects with subthreshold ASD may both face a higher risk of exposure to trauma and have an increased vulnerability to the effects of the trauma, resulting in higher rates of PTSD and BPD-like symptoms. On the other hand, PTSD symptoms may include a feeling of detachment from others and a decreased interest in significant activities, which can be similar to autistic symptoms. The high level of autistic traits found among subjects with a history of physical/sexual abuse might be interpreted both as a risk factor for being target of certain behaviors and as a consequence of stress-related abuse.

It has been reported that patients with ASD may be often exposed to traumatic experiences and they may be likely to develop PTSD. Moreover, a growing body of data shows that individuals moderate forms of ASD, often come to clinical attention when other mental disorders arise. Takara et al. recently found a prevalence rate of ASD of 16% among first-visit depressed adult patients, while Kato et al. reported a 7.3% rate of previously unrecognized ASD among suicide attempters hospitalized. It has been shown that suicidal thoughts and behaviors seem to be common in young patients with ASD, and these are associated with the presence of depression and PTSD. It should be noted how individuals with ASD may represent a low-resilience group that could be prone to develop Trauma and Stress Related Disorders. Moreover, it has been reported that following the exposure to a natural disaster, the ability to cope with stressors decline faster over time in ASD than in healthy control subjects.

To explore the relationship between PTSD and ASD in the framework of the AdAS Spectrum model, the Trauma and Loss Spectrum Questionnaire (TALS-FS) and AdAS Spectrum have been administered to a sample of 134 parents of children diagnosed with epileptic syndrome. Higher PTSD rates were found in women compared to men, with a 10.4% of parents (mothers: 13.3%; fathers: 4.5%) presenting PTSD. Mothers reported higher scores of the TALS-SR compared to fathers in the reaction to loss or traumatic events domain. A significant correlation between the TALS-SR and the AdAS Spectrum domains was found in the subgroup of fathers. Similar findings have been found by Cernvall et al. in parents of children on cancer treatment, showing how avoidance behaviors and ruminations were positively correlated with PTSD and symptoms of depression. Ruminations represent a nuclear feature of PTSD, but they are a transversal symptom, present also in major depression, PTSD and ASD.

**Eating Disorders: the issue of phenotypes**

Several studies have been focused on the overlap between the clinical characteristics of ASD and Eating Disorders (ED). Since the early conceptualization proposed in the '80s by Gillberg, suggesting that Anorexia Nervosa (AN) should be conceptualized as an empathy disorder on the same spectrum of autism, research on the link between ASD and eating disorders has evolved. More recently, many studies confirmed the overlap in behavioral and cognitive features between AN and ASD. It has been noted that rigid attitudes and behaviors are typical features of AN, which can be seen as resembling the unusually narrow interests and repetitive behaviors in ASD. The main difference is that “insistence on sameness” in AN patients becomes mainly focused on food or weight. The overlap in cognitive features is quite extensive, as both ASD and AN show difficulties in advanced “Theory of Mind” tests, deficits in emotional intelligence, social anhedonia, poor performance on tests of set-shifting, and excellent skills on tests on attention to details. The behavioral and cognitive similarities are confirmed on a neurobiological level, as both ASD and AN are correlated with atypical structure and functioning of the fusiform face area, superior temporal sulcus, amygdala, and in the orbitofrontal cortex, which are involved in social processing. ED could share some traits of both ASD and Obsessive-Compulsive Disorder (OCD) in terms of obsession for proper nutrition, focus on weight loss, concern and rituals about food and food consumptions, rumination about eating. These patients are at risk for social isolation due to their sense of moral superiority and their intolerance to others’ food beliefs. These intrusive features and behaviors share some similarities with deficits in social-emotional reciprocity, restricted and repetitive patterns of behavior and interests, and inflexible adherence to routines, that are typical of patients with low levels of autistic spectrum disorder.
subjects with ASD an higher rate of eating problems has 
been reported since childhood, and the most frequent 
pattern appear related to food selection. The tendency 
to be over-selective or have an aversion to specific tex-
tures, colors, smells, and temperatures and to show ri-
gidity to specific foods is associated with an increased 
risk toward underweight condition. Recently, it has been 
conducted a study with 138 ED patients and 160 healthy 
control participants (HCs) assessed by the SCID-5, the 
Eating Disorders Inventory version 2 (EDI-2) and the 
AdAS Spectrum. ED patients showed significantly higher 
AdAS Spectrum total scores than HCs, confirming previous 
studies. Moreover, ED patients showed higher scores on 
all AdAS Spectrum domains with the exception of “non verbal 
communication” and “hyper/hypo-reactivity to sensory 
input” with binge eating/purging subtype of AN (AN-BP) 
participants, and of “childhood/adolescence” domain 
for AN-BP and with binge eating disorder participants. 
Subjects with restrictive AN scored significantly higher 
than subjects with binge-eating behaviors on the AdAS 
Spectrum total score, and on the “Inflexibility and ad-
herence to routine and Restricted interest/rumination” 
AdAS Spectrum domain scores. Significant correla-
tions emerged between the Interpersonal distrust EDI-2 
sub-scale and the “non verbal communication” and the 
“restricted interest and rumination” AdAS Spectrum do-
mains; as well as between the Social insecurity EDI-2 
sub-scale and the “Inflexibility and adherence to rou-
tine” and “restricted interest and rumination” domains. 
The results suggest the presence of a continuum 
across ED diagnostic groups, featuring also different 
degrees of severity. This discrete continuum confirms 
the strong psychopathological overlap between ED and 
ASD, corroborating the possible conceptualization of 
ED, and in particular of restrictive ED, as a part of the 
“female ASD phenotype”.

The Subthreshold Autism Spectrum Model

Based on these data, the Adult Autism Subthreshold 
Spectrum Model has been developed. This is a com-
prehensive psychopathological theory including the 
full-blown symptoms, mild and atypical manifestations, 
behavioral traits, and personality features associated 
with the ASD diagnostic category. These traits can be 
risk factors for other mental disorders, being distributed 
across a continuum from normality to pathology and 
including also positive aspects of neuroatypicality, such 
as originality, creativity, divergent thinking. ASD 
manifestations often overlap with other mental disorders 
leading the investigations on a possible link between 
the AdAS spectrum and the full-blown clinical manifest-
tations of mental disorders.

This model might have a huge impact in clinical prac-
tice, as AdAS instruments might help both to early de-
tection of high-risk subjects and to identify ASD in differ-
ent clinical presentations.

However, the AdAS Spectrum questionnaire – and its 
Model – allows investigations about the relationships 
between autism spectrum and other mental disorders, 
leading to a better understanding of psychopathology.

The Subthreshold Autism Spectrum Model and AdAS 
questionnaire could be also employed for investigate 
the genetic basis of autism. In fact, the DSM-5 still sepa-
rates what should be considered autism, and what should 
not and the DSM-5 criteria for ASD disregards atypi-
cal manifestations and more subtle phenomena such as 
the broad autism phenotype or the subthreshold autism 
spectrum. Although general population obviously do 
not generally meet ASD criteria, it should not be forgot-
ten that it does share genetic underpinnings with the 
clinical population. The AdAS Spectrum approach 
could allow to test a wider range of endophenotypes in 
order to better investigate the genetic basis of ASD.

The Subthreshold Autism Spectrum Model has the po-
tential to overcome the descriptive artifice of comorbid-
ity. Considering the shared genetic risk and overlapping 
clinical features of different mental disorders with ASD, 
it should be noted that a neurodevelopmental devia-
tion may represent a common vulnerability factor for the 
majority of mental disorders. The severity and the spe-
cific morphological features of the neurodevelopmental 
damage would lead to different grades of neuroatypi-
city, resulting in different psychiatric disorders. Such 
an hypothesis is consistent with the definition of 
psychiatric disorders as “globalopathies”, involving not 
only some specific brain networks, but the whole-brain 
organization, on the basis of a pathological neuro-
developmental trajectory with different outcomes.

According to this model, the AdAS Spectrum question-
naire might allow to assess some broad dimensions, 
which could predispose subjects to develop different 
kinds of clinical presentations. In this framework, some 
features associated with autistic psychopathology 
(such as ruminative thinking, social withdrawal, rigidity, 
perfectionism, social phobia, anhedonia, lack of empa-
thy) might be reconsidered as an autistic core shared 
by different kind of disorders, reflecting the high rates 
of comorbidity between ASD and other mental disor-
ders. The AdAS Spectrum Model can be consid-
ered a transnosographic dimension involved in different 
conditions. This should allow clinicians, by using the 
AdAS Spectrum assessment, to shed light on the phys-
opathology and clinical course, as well as on possible 
treatment response, of most mental disorders.

Conflict of Interest

The authors have no conflict of interests.
The Adult Autism Subthreshold Spectrum (AdAS) model: a neurodevelopmental approach to mental disorders

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The association between personality and eating psychopathology in inpatients with anorexia nervosa

Summary

Objectives
Anorexia nervosa is a severe mental illness with modest treatment outcomes, and hospitalizations are frequently required. AN is robustly associated with a constellation of personality traits, including perfectionism, harm avoidance and anxiety. Psychopathological and personality aspects can influence treatment response and outcome in the hospital setting potentially favoring a greater individualization of treatments. This study aims to analyze inpatients with AN to ascertain as to whether personality traits can be associated with the improvement of eating psychopathology. We expected that more adaptive personality traits upon admission could correlate with the improvement of eating psychopathology upon hospital discharge.

Methods
One-hundred and thirteen inpatients with AN were consecutively enrolled and asked to complete the following assessment instruments: Temperament and Character Inventory (TCI), State Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Eating disorders inventory-2 (EDI-2), and the Eating Disorders Examination Questionnaire (EDE-Q). Clinical parameters including Body Mass Index (BMI) were assessed at admission as well.

Results
When compared between admission and discharge, patients significantly improved in BMI, state anxiety and depression. As regards eating psychopathology, patients did not significantly improve on the EDI-2 core subscales (i.e., drive for thinness, bulimia, body dissatisfaction), with the exception of the bulimia subscale; in contrast, the EDE-Q total score showed a significant improvement upon discharge. According to their improvement (Improved Drive For Thinness, I-DT) versus worsening (Worsened Drive for Thinness, W-DT) of the DT subscale upon hospital discharge, 46 patients were classified as W-DT while 67 patients as I-DT. Only cooperativeness on the TCI was found to significantly differ between groups.

Conclusions
Increasingly effective and individualized treatments are needed for AN sufferers. We confirmed that hospitalizations are overall effective in improving eating symptoms; furthermore, higher cooperativeness upon admission, a character dimension of personality, resulted as associated with the improvement of drive for thinness upon discharge. A deeper psychopathological characterization of patients with AN could be helpful in planning treatments for AN patients.

Key words
Temperament • Drive for thinness • Cooperativeness • Hospitalization • Treatment outcome

Introduction
Anorexia nervosa (AN) is a severe psychiatric disorder for which the precise etiology remains elusive. Moreover, AN features severe medical sequelae, and demonstrates the highest rates of mortality among any psychiatric illness, and high psychiatric comorbidity with other psychiatric conditions. Importantly, AN is robustly associated with a particular
constellation of personality traits, which may provide clues to the elusive neurobiology of AN, since these traits are neurally encoded. Personality has been strongly linked to the development and maintenance of AN and personality traits ought to be taken into account as potentially impacting on outcome in AN. For example, neuroticism and perfectionism have been acknowledged as risk factors for eating disorders. With more detail, temperament in AN is typically characterized by heightened anxiety, marked cognitive inflexibility, high harm avoidance mirroring the alterations of the neural circuit functions found in AN. Moreover, such characteristics tend to persist after recovery and need to receive close attention when planning treatments. Treatment models focused on temperament and personality have been proposed, and personality traits also predict outcome in outpatient setting. Also, cognitive-behavioral and psychodynamic treatments positively modulate personality traits as well. However, it remains unclear as to whether changes in personality traits favor the improvement of symptoms or vice versa. Still, personality traits can impact on treatment compliance, possibly influencing those feelings of refusal and anger typical of a subgroup of patients with eating disorders.

The thorough explication of personality traits among patients with AN offers much promise, in both developing precision treatments, and discerning who may benefit from specific treatments. However, a key endeavor in expanding this body of evidence relates to the delineation of state-versus trait-level risk or maintaining factors in AN, as it relates to personality traits. Indeed, state-related neurocognitive effects of starvation are profound, portending both morphological and functional brain perturbations. As such, the careful delineation of state versus trait related personality variables in AN is of critical importance, since some evidence suggests a change in personality trait expression in those with AN upon recovery. While most studies of personality structure in those with AN have been conducted in outpatient settings, or those recovered from the illness, an important gap currently relates to the personality structure of AN patients in acute settings. Urgent hospitalizations are often required in the treatment of AN, given the propensity for rapid medical complications. Broadly speaking, these admissions can be effective over the short-term, and particularly in those patients whose life-threatening condition requires involuntary treatment. However, hospitalization admissions typically impact mostly on weight restoration and regularization of clinical parameters (i.e., blood tests), rather than on the cognitive symptoms of AN. In fact, it is well-known that about one-third of inpatients with AN significantly improve their weight but not their overall eating symptomatology, as measured by EDI-2 upon discharge. Therefore, it would be of clinical importance to identify early predictors of treatment response with respect to patients’ eating psychopathology, independently of patients’ clinical improvement. This would allow to sustain the improvement of both weight and clinical parameters over time.

A core feature of AN is encapsulated in the drive for thinness (DT), which refers to the ubiquitous and relentless pursuit of the thin ideal. An elevated drive for thinness is typical of those affected by both AN and bulimia nervosa (BN); in fact, sufferers report marked fear of weight gain with the strong tendency to restrictive eating. This core dimension of AN appears resistant to improvement during a brief and acute hospitalization, where a period of rapid weight gain is common. Earlier research showed that DT in individuals with AN or BN directly correlates with the degree of eating disorder-related psychopathology, suggesting that DT is a potential predictor of relapse. Additionally, DT is robustly associated with disordered eating and intentional weight loss as well. Interestingly, DT also significantly correlated with those structural brain changes (neuroanatomical signatures) that are early associated with AN in a machine learning approach model.

Psychopathological and personality aspects are considered factors influencing treatment response and outcome in programmed hospitalizations; notwithstanding, data on emergency hospitalizations are scarce. A better understanding of these variables could allow a greater individualization of treatments and therefore a more positive response to emergency admissions, mostly in regard to this core psychopathological element of the disorder.

The aim of this study is to analyze a group of inpatients with AN whose clinical severity required an emergency admission to an Eating Disorders Unit in order to ascertain as to whether personality traits can be associated with the improvement of eating psychopathology as measured by the DT subscale of the EDI-2. We expected that more adaptive personality traits upon admission could correlate with the improvement of eating psychopathology modulating patients’ fear of weight gain.

Materials and methods

Participants

We consecutively enrolled 113 adult and female inpatients diagnosed with AN both subtypes (79 with restricting AN [R-AN] and 34 with binge-purging AN [BP-AN]) according to DSM-5 criteria between March 2014 and November 2017 at the ward for Eating Disorders of the “Città della Salute e della Scienza” Hospital of the Uni-
The association between personality and eating psychopathology in inpatients with anorexia nervosa

University of Turin, Italy. Participants had to meet the following inclusion criteria: a) age > 18 and < 55 years old; b) female gender; c) no substance dependence; d) no psychosis or psychotic symptoms according to DSM-5 criteria.

Participants were all Caucasian. All participants completed the assessments within the first week of hospitalization to minimize confounders due to treatment interventions. All participants provided written informed consent.

The hospitalization intervention

All patients were hospitalized because of emergency reasons; therefore, the aims of this intervention were to achieve medical stabilization and re-feeding and to provide psychosocial interventions in order to motivating patients to the following treatment steps (i.e., partial hospitalization or outpatient services).

Therefore, during hospitalization, patients were provided with individualized treatment plans improving patients' overall motivation to treatment. The clinical team included psychiatrists, clinical psychologists, nurses, a registered dietician and an internal medicine physician.

Weight restoration (including parenteral and enteral re-feeding when needed) is intended as a first-step intervention in order to minimize the life-threatening risks due to severe malnutrition. Weight restoration is strictly monitored in order to avoid the refeeding syndrome. Five structured meals are provided (breakfast, half-morning snack, lunch, mid-afternoon snack and dinner) and more snacks can be administered according to individualized treatment plans. Blood tests and ECG were frequently performed per clinical evaluation.

Psychiatric visits are intended to assess the presence of psychiatric comorbidities and to investigate the medical issues related to psychopharmacology. Moreover, patients are provided with daily individual motivational sessions, daily individual psychotherapy and weekly psycho-educational and cognitive-behavioral groups in order to improve their compliance, motivation, therapeutic alliance and mobilize as much as possible patients' resources. Support to parents or significant others is offered to all patients.

Before discharge, all patients receive detailed clinical information about potential strategies to put in place at home in order to avoid relapses.

Measures

A trained nurse measured patients' height and weight upon admission (T0) and discharge (T1) to calculate Body Mass Index (BMI). Participants were asked to complete the following self-report assessments:

1. the Temperament and Character Inventory (TCI)

   The TCI is a 240-item self-administered questionnaire divided into 7 dimensions. Four of these dimensions assess temperament: novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P). The other three dimensions assess character: self-directedness (SD), cooperativeness (C), and self-transcendence (ST). The TCI showed sound psychometric properties.

2. State Trait Anxiety Inventory (STAI). The STAI is a well-established 20-item self-report instrument for the state and trait anxiety. All items are rated on a 4-point scale. The STAI measures two types of anxiety: state anxiety, a temporary condition experienced in specific situations, and trait anxiety, a general tendency to perceive situations as threatening. Total scores for state and trait sections separately range from 20 to 80, with higher scores indicating higher levels of anxiety.

3. Beck Depression Inventory (BDI). The BDI is a 13-item self-report questionnaire evaluating depressive symptoms. Scores from 0 to 4 represent minimal depressive symptoms, scores of 5-7 indicate mild depression, scores of 8-15 indicate moderate depression and scores of 16-39 indicate severe depression.

4. Eating Disorders Inventory-2 (EDI-2). The EDI-2 is a psychometrically sound self-report evaluation of disordered eating patterns, behaviors and personality traits shared by individuals affected by an eating disorder (ED). Ninety-one items and eleven subscales assess both symptoms and psychological correlates of EDs. Each item can be rated on a 6-point response scale; the higher the score, the more elevated eating psychopathology.

5. Eating Disorders Examination Questionnaire (EDE-Q) is a 28-item self-report questionnaire with high internal consistency that provides a measure of characteristics and severity of eating disorder features. Four subscales are available: Restrained, Eating Concern, Shape Concern, and Weight Concern but only the total score has been included in this study.

Statistical analysis

The SPSS 24.0 statistical software package (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) has been used for data analysis. Paired sample t-test has been used to verify any significant changes occurred between hospital admission and discharge. A repeated measures ANOVA has been conducted to assess DT changes between I-DT and W-DT groups.
Independent samples t-test have been applied to continuous variables (i.e., clinical data and questionnaires). Fisher’s exact test has been used for categorical variables to maximize reliability independently of cell counts. Statistical significance has been set at 0.05.

### Results

#### Socio-demographic and clinical characteristics of the sample

Twelve patients had to be excluded since males, 5 patients were discarded given their psychotic comorbidity and 9 patients failed to successfully complete the self-report battery of assessment. Therefore, the total sample was finally composed by 113 women affected by AN both subtypes: 79 with R-AN and 34 with BP-AN. Mean BMI was 14.27 ± 1.8, mean age was 24.5 ± 9.4 years, mean duration of illness was 6.8 ± 8.6 years, and mean duration of hospitalization 36.3 ± 17.1 days.

AN subtypes significantly differed only on duration of illness (R-AN: 5.43 ± 7.72 versus BP-AN 9.64 ± 9.72, t = -2.45, p = 0.016) but not with respect to age, BMI, duration of hospitalization and caloric intake upon admission (data not shown). With respect to general and eating psychopathology, R-AN and BP-AN groups differed in TCI self-directedness, trait-anxiety, and EDE-Q total score (data not shown).

#### Clinical outcomes for hospitalized patients with AN

Patients significantly improved in BMI, state anxiety and depression at discharge. Trait anxiety did not change in a statistically significant way (Tab. I).

As regards eating psychopathology, patients did not significantly improve on the EDI-2 core subscales (i.e., drive for thinness, bulimia, body dissatisfaction), with the exception of the bulimia subscale (Tab. I); in contrast, the EDE-Q total score showed a significant improvement upon discharge.

#### Relationship between personality and hospitalization outcome

According to the improvement versus worsening of the DT subscale upon hospital discharge, 46 patients were classified as W-DT (T0 11.89 ± 7.32, T1 14.87 ± 7.23, t = -6.774, p < 0.001) while 67 patients as I-DT (T0 12.95 ± 8.18, T1 10.02 ± 8.1, t = -5.398, p < 0.001). W-DT and I-DT groups had a significant impact on changes in DT (groups x time F 59,801; p < 0.001; see Figure 1).

Only the cooperativeness personality trait was found to significantly differ between W-DT and I-DT groups (see Table II). No other significant differences could be found either on clinical variables, diagnostic subtypes (Fisher’s exact test p = 1), or on the TCI and other questionnaires used (Tab. II).

#### Discussion

A psychopathological characterization of patients with AN is needed in order to provide increasingly effective and individualized treatments for those who suffer from such a severe disorder and tend to be hospitalized after an emergency admission. This study showed that hospitalizations are overall effective in improving eating symptoms; moreover, higher cooperativeness, a char-

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**TABLE I. Clinical changes between hospital admission and discharge of patients with anorexia nervosa.**

<table>
<thead>
<tr>
<th></th>
<th>AN patients (n = 113)</th>
<th></th>
<th>Test statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T1</td>
<td>t</td>
</tr>
<tr>
<td>Weight</td>
<td>37.23(5.69)</td>
<td>39.20(5.04)</td>
<td>-8.473</td>
</tr>
<tr>
<td>BMI</td>
<td>14.27(1.84)</td>
<td>15.05(1.59)</td>
<td>-7.606</td>
</tr>
<tr>
<td>Caloric intake</td>
<td>660.63(338.79)</td>
<td>1570.83(361.41)</td>
<td>-19.723</td>
</tr>
<tr>
<td>EDI-2 DT</td>
<td>12.54(7.83)</td>
<td>11.92(8.07)</td>
<td>1.307</td>
</tr>
<tr>
<td>DT</td>
<td>3.04(4.45)</td>
<td>1.58(2.86)</td>
<td>4.195</td>
</tr>
<tr>
<td>B</td>
<td>14.73(7.23)</td>
<td>14.41(7.37)</td>
<td>0.697</td>
</tr>
<tr>
<td>BD</td>
<td>55.65(14.31)</td>
<td>51.81(15.96)</td>
<td>3.087</td>
</tr>
<tr>
<td>STAI-State</td>
<td>57.59(12.94)</td>
<td>55.43(15.68)</td>
<td>1.842</td>
</tr>
<tr>
<td>STAI-Trait</td>
<td>15.78(8.04)</td>
<td>11.59(8.26)</td>
<td>6.024</td>
</tr>
<tr>
<td>EDE-Q-TOT</td>
<td>3.48(1.68)</td>
<td>2.76(1.68)</td>
<td>6.656</td>
</tr>
</tbody>
</table>

AN: anorexia nervosa; BMI: body mass index; EDI-2: Eating disorders inventory-2; DT: drive for thinness; B: bulimia; BD: body dissatisfaction; STAI: State Trait Anxiety Inventory; BDI: Beck Depression Inventory; EDE-Q-TOT: Eating Disorders Examination Questionnaire total score
The association between personality and eating psychopathology in inpatients with anorexia nervosa

Character dimension according to the TCI model of personality, resulted as associated with the improvement of DT after urgent hospital admission, a core psychopathological dimension of AN, as measured by the EDI-2. AN is plagued by marked mortality, with a standardized mortality ratio as high as 6 and 20% of deaths caused by suicide. Therefore, hospitalizations are frequently required for both psychiatric and medical acute stabilization. A main goal of hospitalization is weight restoration; since starvation-related medical complications are a leading cause of mortality in AN, and moreover, body weight is a well-known predictor of readmission and relapse.

Urgent hospitalization is common in clinical practice and entails treating patients with different degrees of compliance and motivation. Clinical trials usually include patients who seek treatment in order to restore

**FIGURE 1. Changes in drive for thinness at hospital admission (T0) and discharge (T1) of the groups with improved (I-DT) versus worsened (W-DT) drive for thinness.**

**TABLE II. Differences in baseline characteristics between patients with anorexia nervosa who improved versus worsened their scores of drive for thinness upon hospital discharge.**

<table>
<thead>
<tr>
<th></th>
<th>I-DT (n = 67)</th>
<th>W-DT (n = 46)</th>
<th>Test statistics</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of hospitalization</td>
<td>35.13(12.06)</td>
<td>38.29(20.80)</td>
<td>-0.847</td>
<td>0.399</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>13.86(1.8)</td>
<td>14.38(1.77)</td>
<td>0.839</td>
<td>0.404</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>23.97(9.1)</td>
<td>25.13(9.75)</td>
<td>0.599</td>
<td>0.551</td>
<td></td>
</tr>
<tr>
<td>Duration of illness, years</td>
<td>6.7(7.51)</td>
<td>7.53(10.52)</td>
<td>0.450</td>
<td>0.654</td>
<td></td>
</tr>
<tr>
<td>Caloric intake</td>
<td>662.50(345.01)</td>
<td>667.12(348.86)</td>
<td>-0.059</td>
<td>0.953</td>
<td></td>
</tr>
<tr>
<td>TCI NS</td>
<td>16.69(6.38)</td>
<td>15.61(6.62)</td>
<td>-0.809</td>
<td>0.421</td>
<td></td>
</tr>
<tr>
<td>TCI HA</td>
<td>20.94(7.69)</td>
<td>20.76(10.54)</td>
<td>-0.100</td>
<td>0.920</td>
<td></td>
</tr>
<tr>
<td>TCI RD</td>
<td>13.27(3.98)</td>
<td>11.84(5.01)</td>
<td>-1.556</td>
<td>0.123</td>
<td></td>
</tr>
<tr>
<td>TCI P</td>
<td>4.84(2)</td>
<td>4.47(2.69)</td>
<td>-0.781</td>
<td>0.437</td>
<td></td>
</tr>
<tr>
<td>TCI SD</td>
<td>23.28(9.24)</td>
<td>21.45(9.55)</td>
<td>-0.945</td>
<td>0.347</td>
<td></td>
</tr>
<tr>
<td>TCI C</td>
<td>29.74(9.27)</td>
<td>25.11(12.42)</td>
<td>-2.103</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>TCI ST</td>
<td>11.15(6.62)</td>
<td>9.13(7.32)</td>
<td>-1.407</td>
<td>0.163</td>
<td></td>
</tr>
<tr>
<td>EDI-2 DT</td>
<td>11.89(7.32)</td>
<td>12.95(8.18)</td>
<td>-0.645</td>
<td>0.520</td>
<td></td>
</tr>
<tr>
<td>EDI-2 B</td>
<td>2.95(4.23)</td>
<td>3.10(4.63)</td>
<td>-0.166</td>
<td>0.869</td>
<td></td>
</tr>
<tr>
<td>EDI-2 BD</td>
<td>15.24(6.39)</td>
<td>14.41(7.75)</td>
<td>0.550</td>
<td>0.584</td>
<td></td>
</tr>
<tr>
<td>EDI-2 STAI-State</td>
<td>53.89(14.05)</td>
<td>56.26(14.76)</td>
<td>-0.782</td>
<td>0.436</td>
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<tr>
<td>EDI-2 STAI-Trait</td>
<td>58.42(11.54)</td>
<td>56.97(13.78)</td>
<td>0.539</td>
<td>0.591</td>
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<tr>
<td>EDI-2 BDI</td>
<td>14.95(7.33)</td>
<td>16.49(8.42)</td>
<td>-0.921</td>
<td>0.359</td>
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<tr>
<td>EDI-2 EDE-Q-TOT</td>
<td>3.52(1.70)</td>
<td>3.49(1.69)</td>
<td>0.073</td>
<td>0.942</td>
<td></td>
</tr>
</tbody>
</table>

I-DT: improved drive for thinness; W-DT: worsened drive for thinness; BMI: body mass index; TCI: Temperament and Character Inventory; NS: novelty seeking; HA: harm avoidance; RD: reward dependence; P: persistence; SD: self-directedness; C: cooperativeness; ST: self-transcendence; EDI-2: Eating disorders inventory-2; DT: drive for thinness; B: bulimia; BD: body dissatisfaction; STAI: State Trait Anxiety Inventory; BDI: Beck Depression Inventory; EDE-Q-TOT: Eating Disorders Examination Questionnaire total score.
their weight and often motivational interviewing is delivered before hospitalization. Therefore, real-world studies (i.e., including patients who are poorly motivated to seek treatment, suddenly hospitalized) are scarce and needed. In this perspective, our study shows that an urgent hospital intervention lasting around 5 weeks is effective in improving weight, bulimic symptoms, caloric intake and eating symptomatology (i.e., EDE-Q total score). Nevertheless, some psychopathological core aspects, i.e., DT, do not improve in all patients. This finding is in line with previous literature showing similar results in both adults 23 and adolescents 26. Furthermore, this study illustrates the presence of two groups of patients: I-DT and W-DT, namely those patients whose drive for thinness improves or worsens during hospitalization as their weight stabilizes. These groups are largely comparable to one another on character traits measures, with the exception of cooperativeness, which is greater in those patients whose DT improves at discharge. Within Cloninger’s model of personality 35, cooperativeness is a character dimension that can be divided into five sub-dimensions: social acceptance vs intolerance (C1); empathy vs social disinterest (C2); helpfulness vs unhelpfulness (C3); compassion vs revengefulness (C4); principles vs. self-advantage (C5). Therefore, cooperativeness is a multifaceted and complex construct with multiple clinical implications. For example, it is relevant in the context of therapeutic alliance, which is centrally embedded in all therapeutic modalities in the clinical management of AN and bears much prognostic salience 42. Also, it can be crucial in intensive and urgent hospitalizations. In fact, patients with AN tend to refuse treatments and to be hardly engaged in the therapeutic relationship. Cooperativeness has been linked to dropout as well, which is characteristically elevated in patients with AN, alongside its closely correlated treatment-resistance 12. Earlier research showed that patients who dropout from psychotherapy report lower self-directedness and cooperativeness compared to patients who complete treatment 43. Further, findings from our group showed that patients with poor cognitive flexibility report also lower scores on cooperativeness and reward dependence than healthy controls 44. Finally, cooperativeness is linked to impulsive behaviors, including binge eating, with the mediation of anger in bulimia nervosa 16. Since AN is characterized by high treatment dropout, and poor outcomes 45, future research should investigate whether cooperativeness is correlated with more positive early life experiences; a crucial factor in determining both the extent to which patients trust their treatment 46 and long-term outcome 45. Our findings are only in part in line with previous research on severe inpatients with AN. For example, Bennett and collaborators 47 found that patients affected by restrictive type AN (R-AN) reported significantly higher cooperativeness than those with binge/purge type AN (BP-AN). The authors suggested that the R-AN group could be more prone than those with BP-AN to accept treatment in the very acute phase of AN 47. Although the authors focused on patients with BMI lower than 13, personality traits have been suggested to be independent of BMI scores 19; therefore, different sample sizes could be responsible for this contrasting finding but further research is needed relating to the personality and prognosis of those patients with AN requiring an emergency hospitalization.

Data on the stability of personality traits are mixed. On one hand, personality traits have been found to be stable after recovery 15 19, while other studies suggest a more state-related fluidity of personality 48. More specifically, cooperativeness is typically elevated in individuals who recovered from AN, as well as harm avoidance and self-directedness 19. Although longitudinal research is required to shed light on this issue, our findings provide support to this latter hypothesis, given the association found between higher cooperativeness scores and improvement in core eating psychopathology after hospitalization.

Drive for thinness is a core dimension of AN and a relevant maintaining factor; as a consequence, it would be of clinical interest to find eventual predictor of DT improvement. Recent prospective research found that fear of food could predict DT after an intensive ED treatment 49. In keeping with data on adult 23 and adolescent inpatients 46, no significant improvement could be found over the course of hospitalization although the vast majority of other clinical parameters did improve. From a psychopathological standpoint, this (non) datum further highlights DT as a key-element of AN.

In closing, some limitations can be acknowledged: participants’ severity (i.e., BMI and duration of illness) could jeopardize the generalizability of the results, data are limited to treatment seeking individuals, and no follow-up data are available. Nevertheless, these findings could have clinical implications. In fact, given the association between baseline personality and DT after hospitalization, cooperativeness could help patients being more prone to be engaged in treatment, helping patients overcome those eating-related anxiety and fears that substantially hinder recovery from AN 50. Also, in keeping with earlier literature 6 13, our findings confirm that personality should be taken carefully into account in defining treatment plans.

Conflict of Interest
The authors have no conflict of interests.
The association between personality and eating psychopathology in inpatients with anorexia nervosa

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The psychopathology of body image in orthorexia nervosa

Summary

The human body has a complex meaning and role in everybody’s life and experience. Body image has two main components: body percept (the internal visual image of body shape and size) and body concept (the level of satisfaction with one’s body), whose specific alterations may lead to different conditions, such as overestimation of one’s own body dimensions, negative feelings and thoughts towards the body, body avoidance and body checking behavior. Moreover, body dissatisfaction can be associated with a variety of other mental health and psychosocial conditions, but only a few studies have explored the body image construct in orthorexia nervosa (ON). ON is a condition characterized by concern and fixation about healthy eating, with mixed results available in the literature about the presence of body image disorders. The aim of this manuscript is to present the main findings from the literature about the psychopathology of body image in ON. Summarizing, while theoretically the presence of body image disturbances should help clinicians to differentiate ON from eating disorders, further research is needed to confirm this finding. It is not clear whether the body image disorder in ON depends on an altered body percept or body concept, and the relationship between the disordered eating behavior and body image disorder still needs to be disentangled. Further studies regarding the relationship between ON and body image could be helpful to better understand the relevance of body image as a transdiagnostic factor and its potential value as target for treatment interventions.

Key words
Orthorexia nervosa • Eating disorders • Body image

Introduction

The human body has a complex meaning and role in everybody’s life and experience. Our bodily being-in-the-world describes an existential position, where the body is both object and subject, and represents a subjective and intersubjective ground of and for experience. The complexity inherent the meaning and role of the human body mirrors itself in the complexity of defining constructs in this field. For instance, the term “body image” is and has been widely used, often in a rather unspecific manner, with a poor discrimination among different dimensions of embodiment, such as body schema, body image and lived body 1, with a consensus still lacking on terminology 2. Body image should be differentiated from body schema, which is an unconscious model or representation of one’s own body that constitutes a standard along which postures and body movements are judged, “a system of sensory-motor capacities that function without awareness or the necessity of perceptual monitoring” 2, 4. The lived body is a phenomenology-derived concept addressing the body experienced from within, the direct experience of one’s own body in the first-person perspective, as a spatio-temporal embodied agent in the world 4-8. According to Schilder, body image can be defined as “the picture of our own body which we form in our mind, that is to say, the way in which the body appears to ourselves” 3. Allamani and Allegranzi 9 refer to body image as “a complex psychological organization which develops through the
bodily experience of an individual and affects both the schema of behavior and a fundamental nucleus of self-image. Subsequently, Shontz integrated theory and data about cognitive and perceptual aspects of body experience (such as body size estimation) and was the first to consider the body experience as multidimensional. Afterwards, Cash and Pruzinsky defined body image as a multifaceted psychological experience of embodiment, a construct encompassing body-related self-perceptions and self-attitudes, including thoughts, beliefs, feelings, and behaviors. The same authors later conceptualized embodiment beyond body appearance and dissatisfaction, including in the construct body functionality and positive body image, as well. Interestingly, the terminological confusion described above can be found even within the body image research community, where the definition of the construct fluctuates depending on the aim of the researcher.

**Psychopathology of body image**

Body image can be defined as the internal representation of one's physical appearance; it is a multidimensional, socio-culturally dependent construct encompassing perceptual, cognitive, affective and behavioral issues. At a broad level, body image has two main components: body percept and body concept. The former is the internal visual image of body shape and size, while the latter refers to the level of satisfaction with one's body. The specific psychopathology of body image can thus span from disorders in body perception to the consequences of alterations in its cognitive-affective dimensions. Dysfunction in one or more of the body image components can lead to specific problems, such as: overestimation of one's own body dimensions, negative feelings and thoughts towards the body, body avoidance and body checking behavior. All these problems can be described with the definition of “body image distortion”, which means a disturbed pattern of individuals’ experience of their own body weight or shape. As body image, its distortion is a multifaceted construct including cognitive and affective components (concerns and feelings about the body), perception (estimation of body size) and body perception-related behaviors.

Experience of own body, together with body attitude, mirrors the individuals’ feelings about themselves as persons or social participants. Therefore, an altered body size perception may express people’s sense of self-worth; for instance, a sense of body smallness could express a sense of loss of worth and status. Moreover, body concept and the related construct of body dissatisfaction depend on the continuous comparison between one’s own body and an “ideal” body, as well as on vulnerability and sensitivity to judgment. Hence, the term “body dissatisfaction” refers to the negative emotions and thoughts elicited by the perceived discrepancy between ideal and current body shape and weight. Even though in the last years there has been such a steady increase of female body dissatisfaction that there seems to exist a “normative discontent”, body dissatisfaction is generally related to body shape and weight, possibly leading to eating disorders. Moreover, body dissatisfaction can be associated with a variety of other mental health and psychosocial conditions, including low self-esteem, emotional distress, depression, cosmetic surgery and steroid use, social anxiety, and sexual difficulties.

The specific abnormalities in lived corporeality described in patients with full-blown EDs, including anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED), have been linked to the individuals’ experience of their own body first and foremost as an object being looked at by other people, rather something lived and experienced from a first-person perspective. ED patients may feel alienated from their body, do not ‘feel’ themselves, and especially they do not feel their own body and emotions. Troubles in developing their personal identity may lead to the attempt of trying to define their own selves in terms of the way they are evaluated by others. From this viewpoint, EDs are considered a maladaptive “search for self-hood and a self-respecting identity”. The key role of feeding in the construction of the self, via the phenomenon of “affective attunement” with the caregiver, is an essential step toward the development of a narrative self and a sense of identity.

**Orthorexia**

In 1997, Steven Bratman introduced the term “orthorexia nervosa” (ON) and coined the phrase “health food junkies” to indicate individuals following strict dietary rules intended to promote health, but eventually leading to possible health-detrimental consequences. The term “orthorexia” is a neologism deriving from the Greek ὀρθός, right, and ὀρέξις, appetite; even though literally meaning “correct appetite”, it is used to designate an “obsession for healthy and proper nutrition”. Typically, individuals with orthorexic behaviors follow a very rigid diet and reject many foods, due to their composition or elaboration (including those containing significant amounts of fat, sugar, salt, or other undesired components). They may be vegetarians, vegans, frugivores (i.e., eat only fruit) or crudivores (i.e., eat only raw food), and usually refuse to eat away from home, due to lack of trust in food preparation procedures. Such a restrictive dieting attitude may lead to several nutritional deficits and medical complications (e.g. osteopenia, anaemia,
pancytopenia, hyponatraemia, metabolic acidosis and bradycardia), which closely resemble the qualitative and quantitative malnutrition status typical of AN 46. In addition, individuals with orthorexic behaviors may show feelings of moral superiority and self-righteousness related to their eating patterns and are at risk of social isolation 47.

The prevalence of ON is about 7% in the general population, while higher rates (up to 50%) have been found in "high-risk groups", including healthcare professionals, dietitians or artistic performers. 48,49, According to Dunn et al. 50, the variability in prevalence rates of ON is due to cultural issues or to diagnostic procedures (e.g., ORTO-15 test). Based on proxy categories for ON (seriousness of engagement about healthful eating and medical or social problems secondary to dieting), less than 1% of the US sample could be labeled as suffering from ON, and about 10% could be considered at risk for ON, even though the ORTO-15 scores suggest a prevalence rate of 71%.

It should be noted that despite having often been dubbed as "a disease disguised as a virtue", ON is currently not recognized as an "official" mental disorder 51. According to the DSM-5, ON would be most appropriately categorized as a distinct subtype of "avoidant/restrictive food intake disorder" (ARFID) 52. In ON it is not the healthy eating habit per se to be worrisome or pathological, but rather the excessive preoccupation about consuming healthy food, as well as an excessive amount of time spent on food thoughts 48. Mounting evidence shows that ON shares some clinical features with other mental disorders including AN, obsessive-compulsive disorder, obsessive-compulsive personality disorder, somatic symptom disorder, illness anxiety disorder and psychotic spectrum disorders 53.

Regarding the overlap between ON and EDs, shared features include lack of pleasure about food and eating, perfectionism, anxiety, and the displacement onto food of the sense of control one is not able to achieve with own life. Despite these shared features, ON individuals focus on quality and purity of food, while EDs patients focus on food quantity. The first strive for a pure body, while the latter strive for a body matching an "ideal" of extreme thinness; nonetheless, the literature suggests a much more complex relationship between ON and EDs. Segura-Garcia et al. 54 reported a common comorbidity between ON and EDs (including AN and BN), whose frequency increased over time during a 3-year follow-up study. Another study involving ED patients found that orthorexic behavior was negatively predicted by eating pathology, weight concern, health orientation and appearance orientation 55. Briefly, ON may precede the onset of a full-syndrome ED, coexist with it, or it may represent its evolution during remission and recovery phases 56.

From a psychopathological viewpoint, orthorexia has been also closely linked to obsessive-compulsive personality/disorder 56 (Fig. 1). Shared features with the obsessive-compulsive disorder spectrum include the presence of recurrent, intrusive thoughts about food and health, related to strong preoccupations with food contamination and purity, as well as the overwhelming need to investigate source, processing and packaging of foods and to arrange food and to eat in a ritualized manner. These behaviors are usually experienced as ego-syntonic in ON 57.

Whether ON is a unique disorder or just a variant of anorexia or obsessive-compulsive disorder is still open to debate 53. A more thorough understanding is needed about the motivations underlying the behaviors and body perception (e.g., pursuit of an ideal body shape vs. a healthy, pure body), ideation toward eating and food (e.g., worries about quantity vs. quality of food), insight/awareness (subjects with AN try to hide their habits whereas individuals with orthorexic tendencies allegedly show off their behavior) and socio-demographic characteristics (e.g., sex distribution, level of education, access to food-related information). This knowledge will help shedding light on the actual psychopathology at the root of ON 57.

**Body image in ON**

Due to similarities between ON and EDs, those factors which are widely acknowledged to play a role in the vulnerability, onset and maintenance of EDs (including body image, perfectionism, attachment style, self-esteem ecc.) 58,59, could be implicated also in ON.

A study investigating whether perfectionism, body image, attachment style and self-esteem predicted ON found that higher orthorexic tendencies significantly correlated with higher scores on perfectionism (self-oriented, others-oriented and socially prescribed), appearance orientation, overweight preoccupation, self-classified weight, fearful and dismissing attachment styles 60. As suggested above, perfectionism could be a potential risk factor for ON, just as it is for the development and maintenance of EDs 58,61. Interestingly, perfectionism may have an impact on adherence to strict food and dietary rules 45,58, which are shared key features of ON and EDs, but may also lead to a perfectionistic attitude towards one’s own body and appearance. Moreover, overweight preoccupation, appearance orientation and the presence of an ED history were identified as significant predictors of ON, with the last one being the strongest predictor. Previous research involving ED patients and healthy controls 54 found that the prevalence of ON is higher in the patients’ groups, and more recent studies do not yet allow to exclude that ON belongs to the same spectrum of AN and BN, with patients shifting between these conditions 52,63.
Considering the shared core similarities between AN and BN, an interesting perspective about ON is that the strenuous pursuit of a healthy diet may serve as a socially acceptable alternative for the unhealthy drive for thinness. Anyway, a discrepancy seems to exist between some preliminary clinical observations and the theoretical knowledge about ON. Regarding body image, ON individuals should not be concerned with weight loss, and they should not display the negative body image attitudes which are typical of AN and BN patients. Dunn and Bratman’s proposed diagnostic criteria identify ON as an independent pathological entity (Tab. I), and do not include features such as body uneasiness, general body/weight dissatisfaction, avoidance and compulsive body-checking behavior, feelings of disconnection from one’s own body and concerns about specific body parts. Even though ON may sometimes be associated with weight loss ensuing because of dietary choices, this is not likely the direct consequence of a desire to lose weight as the primary goal.
of the eating behavior, but rather seems the indirect one of an excessive preoccupation with eating healthy food. Even if the literature on orthorexia nervosa is until now mainly represented by descriptive and anecdotal data and focused primarily on measuring the prevalence of the condition in different countries and in at-risk groups, a few studies are available about ON and body image.

A study involving male and female university students and examining the predictive model of ORTO-15 in both groups found that in female students lower ORTO-15 scores (greater severity of orthorexic behaviors) were related to a less pathological body image discomfort, while in male students lower ORTO-15 scores were related to less pathological eating patterns. Another study reported that university students with ON were more likely to be engaged in regular physical exercise, more “health conscious”, trying to live a healthy routine, afraid of gaining weight and more likely to follow diets, compared to healthy controls. Moreover, they were more likely to monitor their body weight and over-estimate their body size. Regarding gender differences, females with orthorexic tendencies were less likely to pay attention to their appearance, while they were more likely to classify themselves as less fit and less healthy than males with orthorexia. Moreover, females with orthorexic preoccupations seemed to have higher body fat anxiety, to pay more attention to their body weight and to control their eating behavior more than males. Contrarily to what described above, a few studies are available suggesting body image concerns and disorders in ON. A positive relationship between ON and body image disturbance has been suggested: Varga and Máté reported that body image disturbances are more severe when more ON features are present. Similarly, an association between orthorexic tendencies and an increased preoccupation with appearance and fears of becoming overweight has been supported by the finding of a negative correlation between the ORTO-15 scores and appearance orientation and overweight preoccupation. Moreover, orthorexic behaviors are also associated with an unhealthy or negative body image among students, regardless of their concern about healthy and appropriate food choices.

A cross-sectional study investigating the prevalence of ON and EDs in dieticians found that about 50% is at risk for ON, and 12.9% for an ED. ON symptoms are associated with eating disturbances as well as with shape and weight concerns. Another study involving nutrition and dietetics students found orthorexic behaviors in 68.2% of them, who had an increased Body Mass Index (BMI), reduced saturated fatty acid intake, increased waist circumference and energy intake. Contrary to this study, Oberle and Lipschuetz found no significant relationship between BMI and ON symptoms among students, while a positive correlation was found between ON symptoms and perceived muscularity, and a negative one between ON symptoms and perceived body fat. In addition, Bundros et al. found a positive association between ON and body dysmorphic disorder among college students; this finding is consistent with a study involving fitness participants with orthorexic tendencies, who showed internalization of the thin ideal, social physique anxiety, body image dissatisfaction and disordered eating. According to Featherstone, a slim, muscular body can be regarded as an evidence
that the individual is adhering to an ideal lifestyle; therefore, the failure in matching this body ideal and expectation can give rise to appearance-related anxiety. This anxiety may lead individuals to exert greater control over their diets, to contrast the inner fear of becoming unattractive, being regarded as unhealthy, and losing the opportunity to enjoy an ideal life. Use of social media has negative effects on body image, depression, social comparison, and disordered eating. For example, a more frequent use of Instagram is associated with a greater tendency to develop ON 80. An analysis of the #fitspiration tag on Instagram, used to denote images intended to inspire people to become fit and healthy, found that most images of women showed thin and toned bodies with objectifying elements, with negative effects on body image and self-esteem 81.

Conclusions
According to the currently available diagnostic criteria 52 64, ON is an emergent condition that stands out from other EDs for lack of concern with body weight and shape. Further studies on the relationship between ON and nosographically recognized EDs are needed to better understand the correlation among healthy eating, pathologically healthful eating and EDs development. Currently, it cannot be excluded that, at least in some cases, an exaggerated focus on appearance and a fear of becoming overweight might be hidden behind the preoccupation with a healthy diet. Follow-up studies have suggested that ON symptoms may worsen following treatment for other EDs 54 55, suggesting that, for former ED patients, ON may be a compromise to continue controlling food and their body shape and weight, although to a lesser degree than in AN 61. Summarizing, while theoretically body image discomfort should be able to differentiate ON from other EDs, further research is needed to confirm this finding. At present, some studies 46-70 72-74 82-85 revealed a correlation between ON and body image concerns, in contrast to other studies 45 68 77 86 reporting the absence of body image or weight-related concerns in ON subjects. However, one of the limitations of available studies is the difficult assessment of the still unclassified construct of ON. Indeed, most studies in the field of ON have adopted the ORTO-15 questionnaire, whose possible limitations in detecting the severity of orthorexic behaviors and attitudes have been suggested 88, hence leading to the recommendation of being cautious when interpreting its results as a reliable measure of the prevalence of ON 89. The ORTO-15 40-points threshold value has a notable predictive capability concerning healthy eating behavior, while it seems less efficient in discriminating the other typical components of ON, that is the presence of obsessive traits 89, suggesting that the ORTO-15 is probably not likely to distinguish between healthy eating and pathologically healthful eating 90.

Future research could potentially benefit from investigations involving larger and more heterogeneous samples to gain more insight into the concept of body image and its association with ON 90. Some issues deserve to be deepened: from a psychopathological standpoint, it would be interesting to better understand whether the possible body image disorder in ON depends on an altered body percept or body concept; moreover, disentangling the relationship between disordered eating behavior and body image disorders would be helpful also from a clinical standpoint. Addressing these topics would improve knowledge about the relevance of body image as a transdiagnostic factor 91 and its potential value as target for treatment interventions.

Conflict of Interest
The authors have no conflict of interests.

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Is Internet gaming disorder really a new form of mental disorder? A critical overview

Summary
There is no doubt that the Internet has profoundly modified our daily life, in particular becoming an integral part of young people’s life and activities. It is a source for information, a new channel of communication and it is used for various leisure activities. On the other hand, it also carries a potential threat to people’s mental health, when people spend excessive amount of time on its use and when time spent gaming online tends to prevail when compared to other activities. The peak time spent on Internet gaming is increasing in young people, with near to 11 hours per day. Computer gaming has been conceptualized as continuum from an enjoyable activity to a pathological and an addictive use. In the new version of the International Classification of Diseases (ICD-11), Gaming Disorder (GD) has been included in the chapter of mental and behavioural disorders. Prevalence rates of Internet Gaming Disorder (IGD) range from 0.2% to 50%, but the true extent of the phenomenon is not yet known due to the lack of specific diagnostic criteria prior to the publication of ICD-11. The inclusion of this new disorder has generated keen debate and raised controversies in the scientific community. Like most behavioural disorders where pathology is identified by variation in norms, it would appear that there is a clear need to define an appropriate boundary between normal Internet gaming and IGD. We believe that considering IGD as proper mental disorder may generate a common ground for assessment, research and development of appropriate treatments. However, high-quality longitudinal multicenter studies are urgently needed in order to identify possible biomarkers of this new disorder and to understand the developmental trajectory of IGD.

Key words
Internet Gaming Disorder • Behavioural addiction • Technology • Impulsivity • Loneliness • Virtual reality

Introduction
There is no doubt that the advent and increased use of Internet around the globe has profoundly modified our daily living and functioning. This has become a major part of the millennial generation (the young people born between 1985 and 2000). The use of social media therefore has become not only a source of keeping in touch but also information and entertainment. The latter functions are likely to affect people’s mental health and well-being especially when young people spend excessive amount of time on its use to the detriment of other activities. In particular, effects of new technologies on mental health, especially the Internet, have profoundly modified our daily life, becoming an integral part of young people’s life. Internet provides information, it is a new way for communication, and also a leisure activity. Equally important, it also carries a number of problems and potential threats to mental health, especially when its use starts to dominate people’s lives as seen when time spent on gaming online becomes predominant over other daily activities and interferes with daily living. Use of the Internet and computer gaming is a frequent activity for children and adolescents. According to recent US data, adolescents spend more than 11 hours per day using mobile phones or computer, or searching web pages. Computer gaming has been recently
conceptualized as continuum from an enjoyable activity to pathological and addictive use. As a result of this over-activity and spending increasing amounts of time gaming online, there is a serious concern that vulnerable individuals will go on to develop a full-blown clinical disorder. This may lead to a neglect of “real-life” relationships, school or work-related duties, and even basic physical needs, with a detachment from reality and avoidance of social activities. Therefore, Internet gaming is becoming a serious public health concern in Asia where about 30 million internet gamers are recognized as addicted.

In the new version of the International Classification of Diseases (ICD-11) Gaming Disorder (GD) has been included in the chapter of mental and behavioural disorders. Therefore, there is the need to adapt training curricula and clinical practice to modern patients has been recently stated in the mental health field. In fact, many traditional mental disorders, such as catatonia, hysteria or hebephrenia, seem to have disappeared from clinical observation, while new forms of mental health problems emerge regularly. The question arises whether these are proper mental disorders or consequences of modern society, such as the ongoing economic downturn and crisis, the migration processes, the terrorist attacks, the use of novel psychoactive substances or response to development of new technologies.

The decision to include the GD in the ICD-11 has generated debates and caused controversies in the scientific community whether this should have been included or not. Criticisms mainly refer to the risk of overpathologizing and overtreating a common behavior of young people. On the contrary, the need for early detection and early treatment in young people, based on epidemiological and clinical data, remains the main argument in favour of the inclusion of GD among behavioural addictions and mental disorders. This paper is a critical overview of recent studies on Internet Gaming Disorder (IGD). The epidemiological, clinical and social characteristics of IGD will be described. The psychopathological characteristics of this disorder will also be highlighted.

Methodology

The databases MEDLINE, ISI Web of Knowledge – Web of Science Index, Cochrane Reviews Library and PsycINFO were searched for papers published in the past few years. The key word “Internet Gaming Disorder” has been matched with “prevalence”, “psychopathology”, “pharmacological treatments”, “psychosocial treatments”, and entered in PubMed. Only papers written in English and published in peer-reviewed journals have been included in our analysis. The reference lists of all papers selected in the primary search have been manually searched for other potential manuscripts. Papers have been grouped in four categories: 1) epidemiological studies; 2) papers related to IGD diagnostic characteristics; 3) psychopathological studies; 4) intervention studies.

Results

Epidemiological studies

The prevalence rates of IGD range from 0.2% in Germany to 50% in Korea. According to a large-scale study recently carried out in USA using the American Psychiatric Association (APA) criteria for GD, the prevalence rates are 1.0% in young and 0.5% in adult people. The majority of IGD population is between 15 and 20 years, but younger and older people can also be affected. IGD seems to be more frequent in male adolescents, especially among those who have a low level of education, living in Eastern Asian countries, or in those experiencing psychosocial adversities, such as familial difficulties, divorced parents, been bullied or having friends addicted to videogames.

Papers related to IGD diagnostic characteristics

In 2013, APA included the diagnosis of IGD in the appendix of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) manual under “Conditions warranting more clinical research before being classified as an official mental disorder”. King et al. claimed for the need to define a “gold standard” for the diagnosis of IGD since more than 18 different operational criteria were identified. In fact, several terms defined the same clinical condition, including problematic online gaming, pathological gaming, gaming addiction, excessive gaming, gaming use disorder, videogame addiction, videogame dependency, internet use disorder, pathological internet use, technology use disorder, pathological technology use, compulsive internet use. According to the DSM-5, in order to formulate a diagnosis of IGD, five (or more) of the following symptoms should be present in a 12-month period: 1) preoccupation with internet games; 2) withdrawal symptoms when internet gaming is stopped; 3) need to spend increasing amounts of time in internet games; 4) unsuccessful attempts to control the participation in internet games; 5) loss of interest in previous hobbies and entertainment as a result of internet games; 6) continued excessive use of internet games despite knowledge of psychological problems; 7) deceiving about time spent on internet gaming; 8) escaping negative moods through internet games; 9) loss of a significant relationship, job, or educational or career opportunity because of participation in internet games.
In the eleventh edition of the ICD for the first time a disorder related to the excessive use of videogames has been officially recognized by the medical community among the pathological conditions requiring clinical attention. This new edition of the ICD is published exactly 28 years after the ICD-10, which was published in 1990 and operationalized in 1994. It classified over 2000 diseases and related problems, including a specific chapter on mental disorders. The ICD system is more used by European psychiatrists, mainly because many national laws use this system for the reimbursement of benefits. The “Gaming Disorder” (GD) is included in the chapter of “Disorders due to addictive behaviours” and is defined as “a persistent or recurring pattern in gambling behaviour that occurs when videogames are prioritized to the point that they take precedence over other interests and daily activities, and continuation or escalation of video-gaming activity despite the occurrence of negative consequences”. For being considered a disorder, videogame addiction must result in “significant personal, family, social, educational and/or professional harm”.

Psychopathological studies
From a psychopathological viewpoint, the IGD includes two different subtypes: an online form, in which the subject must necessarily be connected to the Internet; and the offline subtype, where the player prefers to be alone. These two forms differ substantially; in fact, people with the online IGD subtype have narcissistic characteristics, are highly competitive with a severe risk of addiction. Moreover, they are exposed to social comparison and tend to consider virtual interactions as real ones. On the other hand, people affected by the offline form are usually covert, dependent, socially withdrawn and highly isolated. However, the differentiation between these two subtypes has not been officially recognized yet and their clinical utility is still debated. The online gaming has been better characterized in terms of physical and psychological consequences. Physical consequences include visual disturbances, postural problems, chronic back pain, weight gain, obesity and increased cardio-metabolic risk. Online gamers report negative consequences on their psychosocial functioning in terms of reduced social interactions, drop in academic or working performances, and reduced attention skills. Moreover, excessive gaming is also associated with poor sleep hygiene, low self-esteem, loneliness, increased aggression and hostility, and reduced verbal memory.

IGD symptoms frequently co-occur with those of other mental disorders especially with those with onset in children or adolescents, such as attention-deficit/hyperactivity disorder (ADHD), conduct disorders, depression, and anxiety. In particular, the relationship between depression and IGD has been deeply investigated, with a higher incidence of depressive symptoms in online gamers. A possible explanation could be that some young depressed patients cope with their negative emotional feelings by playing games on the Internet, while other patients with IGD may experience depressive symptoms as a consequence of social withdrawal from real-life relationships. Obviously, it can also be that depressive disorder and IGD share the same biological liability.

The development and expression of problematic gaming behaviors remains heterogeneous and dependent on multiple interacting factors. Individuals who are socially isolated or have poor interpersonal skills are particularly attracted to games that allow to develop online relationships and take on new personalities. Moreover, some personality factors, such as low levels of self-esteem, high impulsivity, negative affectivity, and perceived loneliness are associated with a higher risk of developing IGD. Brand et al. have highlighted the role of dysfunctional coping strategies as another risk factor for the development of IGD, suggesting that adolescents not able to cope with everyday life stressors may downregulate their negative emotions through online gaming.

Intervention studies
Only a few randomized controlled trials are available for evaluating the efficacy of pharmacological and non-pharmacological treatments in patients with IGD. As regards pharmacological treatment, available studies have investigated the efficacy of bupropion compared to placebo or to a no-treatment control condition. In a recent study by Bae et al., a 12-week bupropion treatment improved the severity of IGD as well as the associated clinical symptoms; moreover, a significant correlation between the changes in clinical scales and the changes in brain functional connectivity was found. In another study, bupropion was combined with cognitive-behavioural therapy (CBT) and the association was effective; however, it shall be noted that this study included patients presenting with depression in comorbidity with IGD. Therefore, the limited available data support the use of bupropion in patients with IGD, but these findings should be cautiously considered since samples are small and the follow-up periods are short.

Among psychological approaches, CBT has been proposed as a useful strategy for managing addictive behaviours. In particular, Young et al. tested the efficacy of a CBT-based approach specifically tailored on Internet addiction in 128 patients. At the end of the intervention, a majority of patients reported to be able to manage their symptoms both on short and long-term. In a study by Liu et al., the efficacy of a multi-family group
therapy was tested in patients with IGD and their relatives. At the end of the intervention, patients reported an improvement in addictive behaviours supporting the need to involve parents when adolescents are affected by this mental disorder. Other approaches have been tested more recently in patients with IGD, combining CBT and pharmacotherapy 55-57, or combining CBT with virtual reality 58 or with residential programmes 59. According to a recent systematic review 60, the extent of benefits of these approaches is not yet clear.

**Critical commentary**

IGD is a growing public health concern, and as such it should be detected and treated as soon as possible 61. 63. However, the clinical utility of this new diagnostic category in the international classification of mental
diseases is still debated, since it has been argued that
this disorder is not adequately supported by evidence-
based findings and that online gaming cannot be com-
pared with other behavioural addictions. DSM-5
includes the condition in the group requiring further
research, whereas the WHO has decided to include it
among the list of proper mental disorders. Therefore, a
lack of consensus for diagnostic criteria and the lack
of reliable assessment tools further limit the utility of
such diagnosis in routine clinical practice. Including
the GD in the international classification of diseases
can impact poorly on the public image of psychiatry,
already seen as unscientific and blamed for the over-
treatment of many normal conditions. On the other
hand, King et al. have highlighted the need to de-
fine an appropriate boundary between normal gaming
and GD, and recognizing that the new diagnosis of GD
does not have a negative impact on normal gaming.
Thus, refining criteria for GD diagnosis would benefit
from the collaboration of all stakeholders, including
gamers who could collaboratively discuss ideas and
share perspectives and experiences that may not be
immediately evident to researchers and clinicians.
As reported by Király and Demetrovics, considering
IGD as a proper mental disorder has several advantages
in terms of creating a common ground for assessment,
research and development of appropriate treatments.
The need to recognize this new diagnosis is confirmed
by the dangers associated with excessive gaming and
by the increasing number of people seeking for specific
treatments for their gaming-related problems.

The adoption of a formal diagnosis can reduce the
stigmatization on the problematic gaming, not consid-
ered anymore as a personal weakness. Recognizing
a disorder in a classification system represents the
first essential step for developing appropriate thera-
peutic strategies. Further high-quality longitudinal
multicenter studies will be helpful in order to identify
possible biomarkers of this new disorder and to fully
understand the developmental trajectory of such beha-
voural addiction. Markey et al. and Przybylski et al. emphasise that
videogame addiction represents a growing phenomenon, but its addictive potential is not directly compara-
able with that of gambling or alcohol, blaming the risk
of overtreating normal behaviors adopted by kids and
young adults. However, preventive strategies for reduc-
ing the maladaptive use of videogames and Internet
should be developed and implemented at family, school
and individual levels. At the family level, parents need
to reduce the time spent using smartphones and tablets
when they are at home with their children. It may be use-
ful to improve family communication, avoiding isolation
in a real world and seeking social access and links in
the virtual world. At school level, awareness campaigns
should be carried out in order to provide adolescents
with information on benefits and risks related to the use
of Internet and of other new technologies. At an indi-
vidual level, gamers should be made aware of the risk
of excessive time spent on gaming activities and should
be supported in engaging in real-world and in-persons
activities.

From a psychopathological viewpoint, this disorder
shares common elements with many mental disorders,
including personality disorders, major depression, psy-
choticism, autism, addictions. Therefore, a better char-
acterization of the psychopathological ground of IGD is
urgently needed, also in order to establish a treatment
plan.

As regards the efficacy of available interventions, the
only tested drug is bupropion, whose effects remain
unclear. CBT has been extensively studied, but trials
conducted so far are of poor quality and lack long-term
follow-ups. The quality of study design and consistency
of research in the area of behavioural addictions is im-
portant as these disorders lie on a continuum between
normal and pathological behaviours. Moreover, there is
a need to understand which aspects of CBT work better
in which patients with IGD, to define the optimal duration
of treatment, the format of the intervention (individual or
group therapy) and the long-term stability of treatment
responses.

Conclusions
IGD represents a new disorder for which mental health
professionals and psychiatrists are not yet equipped.
Epidemiological naturalistic follow-up studies should be
promoted in order to understand the exact incidence
rate, the long-term complications, the associated soci-
etal and personal burden. IGD has a significant impact
on a personal level, but also on a micro- and macro-
social level. For these reasons, the introduction of a new
diagnostic category in the ICD should be welcomed
by the scientific community, since it can represent the
basis for a common scientific ground in order to ade-
quately manage and treat these patients. Obviously,
implementing research protocols and developing clinici-
Cal guidelines for the management of this disorder are
needed. Finally, national and international associations
of stakeholders, scientific societies and policy-makers
should work together in order to effectively manage this
new disorder of the modern society.

Conflict of Interest
The authors have no conflict of interests.
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Socio-demographic and clinical characterization of patients with Obsessive-Compulsive Tic-related Disorder (OCTD): an Italian multicenter study

Summary
In the DSM-5 a new “tic-related” specifier for obsessive compulsive disorder (OCD) has been introduced, highlighting the importance of an accurate characterization of patients suffering from obsessive-compulsive tic-related disorder (“OCTD”). In order to characterize OCTD from a socio-demographic and clinical perspective, the present multicenter study was carried out. The sample consists of 266 patients, divided in two groups with lifetime diagnoses of OCD and OCTD, respectively. OCTD vs OCD patients showed a significant male prevalence (68.5% vs 48.5%; p < .001), a higher rate of psychiatric comorbidities (69.4 vs 50%; p < .001) – mainly with neurodevelopmental disorders (24 vs 0%; p < .001), a lower education level and professional status (middle school diploma: 25 vs 7.6%; full-time job 44.4 vs 58%; p < .001). Moreover, OCTD vs OCD patients showed significantly earlier age of OCD and psychiatric comorbidity onsets (16.1 ± 10.8 vs 22.1 ± 9.5 years; p < .001, and 18.3 ± 12.8 vs 25.6 ± 9.4; p < .001, respectively). Patients with OCTD patients were treated mainly with antipsychotic and with a low rate of benzodiazepine (74.2 vs 38.2% and 20.2 vs 31.3%, respectively; p < .001). Finally, OCTD vs OCD patients showed higher rates of partial treatment response (58.1 vs 38%; p < .001), lower rates of current remission (35.5 vs 54.8%; p < .001) and higher rates of suicidal ideation (63.2 vs 41.7%; p < .001) and attempts (20.9 vs 8.3%; p < .001).

Patients with OCTD report several unfavorable socio-demographic and clinical characteristics compared to OCD patients without a history of tic. Additional studies on larger sample are needed to further characterize OCTD patients from clinical and therapeutic perspectives.

Key words
Obsessive-Compulsive Disorder • Tic Disorder • Obsessive-Compulsive Tic Disorder

Introduction
Obsessive-Compulsive Disorder (OCD) and Tic Disorder (TD) represent disabling, comorbid, chronic and difficult-to-treat conditions, which may affect child and adult patients, associated with high levels of burden for patients and their relatives. Comorbidity between OCD and TD is frequent 1,2, although it can occur in different phases of patient’s lifespan (longitudinally) and not necessarily in the same period (cross-sectional). Moreover, comorbidity between OCD and TD may be at a subclinical level. It has been hypothesized that these disorders and their symptom-dimensions define a specific subtype of disorder, called Obsessive-Compulsive Tic Disorder (OCTD) 3,4. In the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) 5, OCD has been included in the new category of “OC and related disorders”, with the introduction of a new “tic-related” specifier. The introduction of this specifier encourages new investigations on the epidemiology, clinical presentation, disability and therapeutic approach of OCTD 6-10.

Tics and OCD share some phenomenological, autoimmune and neuro-
biological features and often co-occur in affected individuals and relatives. It has been recently highlighted that OCTD is more frequently associated with early onset, male gender, sensory phenomena and obsessions of symmetry, aggressiveness, hoarding, exactness and sounds, impulsive behaviors and ADHD comorbidity. Patients with OCD and comorbid TD accounted for approximately 15% of the primary OCD sample and they are smokers and have a higher rate of previous suicide attempts.

According to these features, it seems that patients with comorbid OCD and TD have a more severe phenotype of the disorder, in terms of treatment-resistance, reduced quality of life and levels of disability. Moreover, OCTD patients report a long delay to diagnosis, a high level of functional impairment caused by OC symptoms, a history of multiple treating clinicians and current polypharmacotherapy, with the use of deep brain stimulation in some cases.

In order to define socio-demographic and clinical characteristics of patients with OCTD, the present multicenter study has been conducted, including a sample of OCTD patients and a sample of OCD patients with no history of tic. We hypothesized that OCTD patients might exhibit different epidemiologic and clinical characteristics compared to OCD patients with no history of tic.

Methods
The recruitment is still ongoing, with a final target sample of more than 300 OCD patients. Patients affected by OCD or OCTD of any gender and age were assessed using a novel questionnaire, under validation, developed to better characterize OCTD patients. The questionnaire is composed of 35 questions assessing the following areas: 1) prevalence of OCTD; 2) patient’s main socio-demographic features (i.e., age, gender, occupation, level of education, marital status); 3) clinical history (i.e., age at OCD onset, age at TD onset, presence of other psychiatric comorbidities and age at comorbidities’ onset, family history, OCD duration of untreated illness - DUI); 4) perceived quality of life, course of illness, current psychotherapy and psychopharmacological therapies, treatment response, presence of past/current suicidal ideation or attempt.

Statistical analysis
In order to compare clinical and demographic features of OCD patients with and without comorbid TD, Pearson Chi-squared tests and Student’s t-test were used, as appropriate. All analyses were performed using SPSS for Windows software (Chicago, IL) with the level of statistical significance put at 0.05.

Results
The current sample includes 266 adult patients with OCD with and without comorbid TD of either gender and any age, afferent to different psychiatric departments across Italy, distributed as follows: 47 from Policlinico Hospital, Milan; 30 from Galeazzi Hospital, Milan; 16 from San Paolo Hospital, Milan; 60 from Istituto di Psicopatologia, Rome; 30 from Rita Levi Montalcini Department of Neuroscience, Turin; 24 from Department of Neuroscience, Florence; 26 from Teramo Hospital; 33 from Department of Biomedical and Neuro-motor Sciences, Alma Mater Studiorum University of Bologna.

Main demographic and clinical variables of the study sample are reported in Table I. In the OCD participating centers, the prevalence of OCD ranges between 5-25%, while in the Tic/Tourette Center the prevalence of OCD is more than 90%. The sample consists of 132 (51.5%) OCD patients without TD and 124 (48.5%) OCTD patients. OCTD patients are mainly male (OCTD: 68.5% vs OCD: 48.5%; p < .001), younger (OCTD: 30.7 ± 13.8 vs OCD: 37.4 ± 13.4; p < .001), with a low level of education and of professional status (OCTD: middle school diploma: 25 vs OCD: 7.6%; OCTD: full-time job 44.4 vs OCD: 58%; p < .001) compared to OCD patients (Figs. I-2).

OCTD patients report a significantly earlier age at OCD onset (OCTD: 16.1 ± 10.8 vs OCD: 22.1 ± 9.5 years; p < .001), a higher rate of comorbidities’ onset (OCTD: 18.3 ± 12.8 vs OCD: 25.6 ± 9.4; p < .001), a higher rate of psychiatric comorbidities (OCTD: 69.4 vs OCD: 50%; p < .001) mainly with neurodevelopmental disorders (e.g. ADHD), compared to OCD patients. As regards pharmacological treatment (Tab. II), OCTD patients are most frequently treated with D2 antagonist and/or D2, 5-HT2 antagonist treatment compared to OCD patients (p < .001). OCTD patients report lower rates of current remission of symptoms (35.5 vs 54.8%; p < .001), higher rates of suicidal ideation (63.2 vs 41.7%; p < .001) and suicide attempts (28.9 vs 8.3%; p < .001), and higher rates of partial treatment response (58.1 vs 38%; p < .001) compared to OCD patients.

Discussion
The first relevant finding of our study is the different prevalence of OCD and TD in primary OCD vs Tic/Tourette centers, indicating that Tic and Tic-related specifier is a consistent phenotype in primary OCD patients, but in primary TD/Tourette patients, comorbid OCD seems the rule rather than the exception. Our findings confirm that OCTD defines a more severe phenotype of OCD compared with OCD without Tic. We found a significantly higher male prevalence in the OCTD...
group, compared to the OCD without TD group. This finding seems to be consistent with most of the current literature indicating a male preponderance in tic-related OCD. As regards the onset of first OCD symptoms, we found an earlier onset in OCTD patients compared to OCD patients without tics. This finding is in line with Diniz et al., which found that patients with OCD and Tic Symptoms (TS) presented an earlier age at onset compared to OCD patients without tics. Moreover, we found that psychiatric comorbidity rate was significantly higher in OCTD patients compared to the group without TD. OCTD patients showed a significantly higher comorbidity with neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder and autism spectrum disorders. This finding is consistent with previous research from Coffey and colleagues and Lewin and coauthors, showing a higher prevalence of comorbid neurodevelopmental disorders both in children and adults with OCTD, when compared to OCD patients without TD.

Previous studies and ICOCS reports showed significant positive correlation between the number of comorbid DSM-IV-TR Axis I disorders and OCD severity and duration of illness. In the present study, the OCTD subgroup showed an overall higher severity of illness. This is the first study exploring socio-demographic features of OCTD patients; in particular, OCTD patients showed significantly lower rates of university/master education and full-time employment compared to OCD patients without TD. It should be that the burden of OCTD se-

### TABLE I. Socio-demographic and clinical features of OCD vs OCTD patients.

<table>
<thead>
<tr>
<th></th>
<th>OCD N = 132</th>
<th>OCTD N = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>64 (48.5%): 68 (51.5%)</td>
<td>85 (68.5%): 39 (31.5%)</td>
</tr>
<tr>
<td>Family history</td>
<td>74 (56.5%)</td>
<td>79 (63.7%)</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>66 (50%)</td>
<td>86 (69.4%)*</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>39 (37.9%)</td>
<td>27 (27%)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3 (2.9%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>11 (10.7%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Personality disorders</td>
<td>5 (4.9%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Neurodevelopmental disorders</td>
<td>0</td>
<td>24 (24%)*</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>2 (3.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Poly-comorbidity</td>
<td>4 (3.9%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Age</td>
<td>37.4 ± 13.4</td>
<td>30.7 ± 13.8*</td>
</tr>
<tr>
<td>Age at OCD onset</td>
<td>22.1 ± 9.5</td>
<td>16.1 ± 10.8*</td>
</tr>
<tr>
<td>Age at TIC onset</td>
<td>-</td>
<td>12 ± 9.5</td>
</tr>
<tr>
<td>Age at comorbidity onset</td>
<td>25.6 ± 9.4</td>
<td>18.3 ± 12.8*</td>
</tr>
<tr>
<td>DUI (months)</td>
<td>64.6.4 ± 88.6</td>
<td>60.8 ± 77.8</td>
</tr>
<tr>
<td>Married</td>
<td>49 (37.4%)</td>
<td>36 (29%)</td>
</tr>
<tr>
<td>Professional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>32 (24.4%)</td>
<td>22 (17.7%)</td>
</tr>
<tr>
<td>Full-time</td>
<td>76 (58%)*</td>
<td>55 (44.4%)</td>
</tr>
<tr>
<td>Part-time</td>
<td>2 (1.5%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Retired</td>
<td>6 (4.6%)</td>
<td>4 (3.2%)</td>
</tr>
<tr>
<td>Student</td>
<td>15 (11.5%)</td>
<td>40 (32.3%)*</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school diploma</td>
<td>10 (7.6%)</td>
<td>31 (25%)*</td>
</tr>
<tr>
<td>High school diploma</td>
<td>67 (51.1%)</td>
<td>62 (50%)</td>
</tr>
<tr>
<td>University degree/master degree</td>
<td>54 (41.2%)*</td>
<td>31 (25%)</td>
</tr>
</tbody>
</table>

Values for categorical and continuous variables are expressed as N (%) and mean ± SD, respectively.

* p < .001
FIGURE 1. Summary of categorical variables in OCD vs OCTD patients.

### TABLE II. Treatment related variables (prior and current) in OCD vs OCTD patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OCD</th>
<th>OCTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously treated in other medical centers</td>
<td>89 (67.9%)</td>
<td>84 (68.3%)</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>85 (64.9%)</td>
<td>76 (61.3%)</td>
</tr>
<tr>
<td>Psychopharmacological treatment (current)</td>
<td>126 (96.2%)</td>
<td>122 (98.4%)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>119 (90.8%)</td>
<td>112 (90.3%)</td>
</tr>
<tr>
<td>D2 antagonist and/or D2, 5-HT2 antagonist treatment</td>
<td>50 (38.2%)*</td>
<td>92 (74.2%)*</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>32 (24.4%)</td>
<td>29 (23.4%)</td>
</tr>
<tr>
<td>Gaba receptor agonist</td>
<td>41 (31.3%)*</td>
<td>25 (20.2%)</td>
</tr>
<tr>
<td>Family involvement</td>
<td>60 (46.2%)</td>
<td>44 (35.5%)</td>
</tr>
<tr>
<td>Worsened quality of life</td>
<td>65 (50%)</td>
<td>54 (43.5%)</td>
</tr>
<tr>
<td>Current treatment responders</td>
<td>70 (53.8%)*</td>
<td>45 (36.3%)</td>
</tr>
<tr>
<td>Current partial treatment responders</td>
<td>49 (38%)*</td>
<td>72 (58.1%)*</td>
</tr>
<tr>
<td>Residual tic symptoms</td>
<td>-</td>
<td>35 (26.5%)</td>
</tr>
<tr>
<td>Residual OCD symptoms</td>
<td>48 (82.8%)*</td>
<td>60 (65.5%)*</td>
</tr>
<tr>
<td>Residual OCD + tic</td>
<td>-</td>
<td>27 (27.8%)</td>
</tr>
<tr>
<td>Current remission</td>
<td>69 (54.8%)*</td>
<td>44 (35.5%)*</td>
</tr>
<tr>
<td>Past remission</td>
<td>43 (37.4%)*</td>
<td>72 (60%)*</td>
</tr>
<tr>
<td>Treatment resistance</td>
<td>17 (13.2%)</td>
<td>22 (17.9%)</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>20 (41.7%)*</td>
<td>24 (63.2%)*</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>4 (8.3%)*</td>
<td>11 (28.9%)*</td>
</tr>
</tbody>
</table>

Values for categorical variables are expressed as N (%)

* p < .001
In terms of clinical features, the administered questionnaire included a specific section investigating treatment response and symptoms’ remission. In this respect, a higher rate of OCTD patients was treated with an D2 antagonist and/or D2, 5-HT2 antagonist treatment, showing less favorable characteristics, such as lower current treatment response rate, higher current partial response rates, and lower current remission rates, compared to OCD patients without TD. This finding is consistent with previous literature reporting specific higher severity features for OCTD patients. Finally, another relevant novel finding of the present study concerns suicidality. OCTD patients showed significantly higher rates of lifetime suicidal ideation and attempts compared to OCD without TD subgroup. A previous ICOCS study on suicide attempts in OCD patients showed higher rates of suicide attempts in patients with psychiatric and medical comorbidities, who had TD and Tourette as more frequent comorbid conditions. The present study has some limitations, such as the lack of information on the severity of the disorder (measured with specific psychopathological scales) and the cross-sectional assessment design. Further follow-up studies are needed to better characterize long-term course of OCTD patients, their functional impairment and treatment response.

Conclusions
Based on the present findings, a tailored, personalized and multidisciplinary treatment seems a priority in the management of OCTD patients, given their early onset and long-term disabling course.

Conflicts of Interest
Bernardo Dell’Osso: speaker’s fee from Lundbeck, Angelini and FB Health.
Joseph Zohar: Grant/research support from Lundbeck, Brainsway, Servier and Pfizer; consultant or on advisory boards for Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca, Janssen and Roche; speakers’ bureaus for Lundbeck, Roch, Lilly Servier, Pfizer, Brainsway, Sunpharma and Abbott.
Orsola Gambini: took part in a European multicentre study sponsored by Medtronic about DBS in OCD. The study is concluded, results are under elaboration.
Domenico de Berardis: speaker’s fee from Lundbeck, Angelini, Janssen and Eli-Lilly
A. Carlo Altamura: Speaker’s fee from Lundbeck, Angelini and Janssen.
Beatrice Benatti, Eric Hollander, Liliana Dell’Osso, Naomi A. Fineberg, Matteo Marcattili, Sylvia Rigardetto, Matteo Briguglio, Donatella Marazziti, Federico Mucci, Antonio Tundo, Roberta Necci, Roberta Galentino, Sara De Michele, Claudio D’Addario, Domenico Servello, Umberto Albert, Giuseppe Maina, Diana de Ronchi, Mauro Porta: Nothing to Declare.

References
Factors associated with increased suicide risk in Obsessive-Compulsive Disorder

Summary

Objectives
Obsessive-Compulsive Disorder (OCD) is in itself at greater risk for suicide (suicidal ideation, suicide attempts and completed suicide) as compared to the general population. However, the majority of individuals with OCD do not have current or lifetime suicidal ideation nor did attempt suicide in their lifetime.

Methods
The present paper aims to provide an updated review on factors (socio-demographic and personal factors, OCD-related variables, comorbidities, emotion-cognitive factors, and biological variables) contributing to the increased suicide risk in patients with OCD.

Results
Several factors have been found to be strongly associated with suicide risk in patients with OCD, such as the severity of OCD, the unacceptable thoughts symptom dimension, having a comorbid Axis I disorder (Bipolar Disorder, Major Depressive Disorder, Substance Use Disorder), the severity of comorbid depressive and anxiety symptoms, a previous history of suicide attempts, having high levels of alexithymia and hopelessness.

Conclusions
Several contributing factors should be evaluated and identified in the clinical practice in order to improve early detection of suicide risk. Risk identification and stratification of risk remain essential components of suicide prevention and should guide the clinical approach to patients with OCD. Whether and how these risk factors for suicide in patients with OCD work together, and whether the specific factors act as moderators or mediators, remains to be fully clarified.

Key words
Obsessive-Compulsive Disorder (OCD) • Suicide • Risk factors

Introduction
Obsessive-Compulsive Disorder (OCD) has been considered for long time a disorder without a notable suicide risk. According to recent meta-analyses, patients with OCD may actually be considered at risk for suicidal ideation, suicide attempts and committed suicide. Harris et al. 1 found that patients with OCD has 10-times higher risk of suicide compared to the general population. Khan et al. 2 estimated the incidence of suicide attempts among subjects with anxiety disorders, and found a 4% incidence in the subset of patients with OCD. This is a notable result as these patients were enrolled in clinical trials and, since the risk of suicidal behaviors is often an exclusion criterion, it means they were likely not deemed at risk. In more recent years, two independent systematic reviews 3 4 confirmed a significant association between OCD, suicidal ideation and suicide attempts.

The concept that patients with OCD are not at risk of committing or attempting suicide, with the clinical consequence of underestimating and un-
Factors associated with increased suicide risk in Obsessive-Compulsive Disorder

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The present paper aims to provide an updated review of the contributing factors for suicide risk; other risk factors can interact with the diagnosis of OCD and determining the risk of suicide in each subject. The present paper aims to provide an updated review of the literature concerning the relationship between suicide risk and OCD. Specifically, we will focus our attention on factors (socio-demographic and personal factors, OCD-related variables, comorbidities, psychopathological and biological variables) contributing to the increased suicide risk in OCD (either in terms of suicidal ideation, suicidal attempts, or completed suicides).

**Methods**

We performed a systematic review of the literature by searching PubMed from the date of the first available article to January 8, 2018. The search terms [suicide] OR [suicidality] OR [suicide attempts] OR [suicidal ideation] OR [suicidal thoughts] were combined with [OCD] OR [obsessive*compulsive disorder] OR [obsessive*compulsive symptoms]. We included: 1) studies with appropriate definition of OCD (diagnosis made through specific structured interviews and/or established international criteria); 2) performed in adolescents and/or adults; 3) with a cross-sectional or prospective designs; 4) performed in clinical samples or in the general population (epidemiological studies); 5) which employed a quantitative measure of suicidality; and/or 6) reported an outcome measure of the association between suicidality and OCD (e.g. odds ratios) or examined factors associated with suicidality.

**Estimates of suicide risk in OCD**

A recent systematized review of the available literature investigated suicide risk in OCD patients in both clinical and epidemiological samples; estimates of suicidal ideation and suicide attempts rates in clinical samples were based on 37 studies while 14 epidemiological studies provided data on the association in the general population between a baseline diagnosis of OCD and suicidal ideation or suicide attempts.

**Suicidal ideation and suicide attempts in OCD: clinical samples**

The prevalence of current suicidal ideation ranges between 6.4% and 75% with an estimated mean of 25.9% (median: 15.6%)\(^4\), while the lifetime suicidal ideation is estimated to be 44.1% (median: 36.4%)\(^4\), varying from 26.3\(^7\) to 73.5%\(^8\). Lifetime suicide attempts rate is estimated at 14.2% (median 10.8%)\(^4\), ranging from 6\(^3\) to 51.7%\(^10\).

Concerning family history of suicide, the rates of suicide attempts range from 11.5\(^11\) to 27.1%\(^12\) (mean 17.9, median 18.2%)\(^4\) and rates of completed suicide among family members varying between 8.9\(^13\) and 16.1%\(^14\).

**Suicidal ideation, suicide attempt and suicide rates in OCD: epidemiological samples**

All epidemiological studies (among which three performed on national registers – the Swedish National Patient Register, the Danish Register and the British National Psychiatric Morbidity Survey)\(^1\) found that OCD increases significantly the odds of having a lifetime suicidal ideation as compared to the general population (OR ranging from 1.9 (CI 1.3-2.8) to 10.3 (CI 5.37-19.8)); the increased risk remains significant even after controlling for demographic variables and comorbid psychiatric disorders [Adjusted Odds Ratio ranging from 3.8 (CI 2.8-5.1) to 5.58 (CI 2.7-11.6)]\(^4\). Having a history of OCD is associated with an increased risk of lifetime suicide attempts [OR from 1.6 (CI 1.0-2.6) to 9.9 (CI 4.5-21.8)], although it is not clear whether this increased risk remains significant when controlling for comorbid psychiatric disorders.

The two prospective studies on national registers\(^15\) reported a higher risk of death by suicide in patients with OCD than expected [OR: 3.02 (CI 1.85-4.63) to 9.83 (CI 8.72-11.08)], and results remained significant even for pure OCD [OR: 13.18 (CI 10.76-16.16)].

Data coming from the analysis of prevalence rates and odds ratios show that, at least in part, suicide risk in OCD is influenced by several other psychiatric disorders, including unipolar and bipolar depression. Additionally, a substantial proportion of OCD patients never manifest suicidal ideation in their lifetime, even when the severity of the disorder is significant. This implies that a number of potential contributing factors to the increase of suicide risk are to be screened and identified. Risk identification and stratification of risk remain essential for suicide prevention and should guide the clinical approach to subjects with psychiatric disorders.

In the following paragraphs, we will present data concerning which factors are associated with a higher risk of suicidal ideation, attempting suicide or committing suicide in individuals with OCD. Socio-demographic and personal factors, OCD-related variables, comorbidities, psychopathological variables (emotion-cognitive and temperamental factors) as well as biological variables will be presented separately.

**Factors associated with increased risk of suicide**

**Socio-demographic and personal characteristics**

Table I shows the socio-demographic or personal factors associated with the increased suicide risk in pa-
patients with OCD. Being male is a risk factor for both suicidal ideation and for death by suicide \textsuperscript{15,18}, while being female is a risk factor for lifetime suicide attempts \textsuperscript{15}, confirming data from the general population \textsuperscript{19}. Having a low educational level, being older, having a low social economic status and not having children have been found to be significant risk factors for current and lifetime suicidal ideation \textsuperscript{14,18}.

As regards the impact on marital status of suicide risk, Torres et al. \textsuperscript{14} reported a significant correlation between being single and a higher risk of lifetime suicide attempts, contrasting with data by Maina et al. \textsuperscript{18}. An explanation may be that the family plays an important supportive role in OCD, tackling suicide-related sentiments when they emerge, urging patients to seek for professional help.

Another factor associated with increased risk of suicide (both suicidal ideation and suicide attempts) is a personal history of childhood trauma \textsuperscript{6,21}. In particular, childhood sexual abuse predicts later suicidal ideation and attempts among individual with OCD \textsuperscript{6,21}.

### OCD-related variables
The disorder-specific (OCD-related) variables associated with increased suicide risk in patients with OCD are reported in Table II.

Six studies investigated the relationship between OCD severity (in terms of Y-BOCS total score) and suicidal ideation/suicide attempts showing that higher levels of illness severity are associated with higher rates of lifetime suicide attempts \textsuperscript{12,25} and suicidal ideation \textsuperscript{18,24-26}. Whether or not the effect is mediated by the concomitant presence of comorbid depression, the chronicity of

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**TABLE I. Socio-demographic variables or personal factors found to be associated with increased suicide risk in OCD patients.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Suicidal ideation</th>
<th>Suicide attempts</th>
<th>Completed suicides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Maina et al., 2006 \textsuperscript{18}</td>
<td>Fernandez de la Cruz et al., 2017 \textsuperscript{15}</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>Fernandez de la Cruz et al., 2017 \textsuperscript{15}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older age</td>
<td>Maina et al., 2006 \textsuperscript{18}</td>
<td>Torres et al., 2011 \textsuperscript{14}</td>
<td>Alonso et al., 2010 \textsuperscript{27}</td>
</tr>
<tr>
<td>Marital status: single</td>
<td>Torres et al., 2011 \textsuperscript{14}</td>
<td>Alonso et al., 2010 \textsuperscript{27}</td>
<td></td>
</tr>
<tr>
<td>No children</td>
<td>Torres et al., 2011 \textsuperscript{14}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor educational level, lower social class</td>
<td>Maina et al., 2006 \textsuperscript{18}</td>
<td>Torres et al., 2011 \textsuperscript{14}</td>
<td></td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>Ay &amp; Erbay, 2018 \textsuperscript{21}</td>
<td>Khosravani et al., 2017 \textsuperscript{6}</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE II. Disorder-specific (OCD-related) variables found to be associated with increased suicide risk in OCD patients.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Suicidal ideation</th>
<th>Suicide attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of OCD: Y-BOCS total scores</td>
<td>Maina et al., 2006 \textsuperscript{18}</td>
<td>Velloso et al., 2016 \textsuperscript{12}</td>
</tr>
<tr>
<td></td>
<td>Balci &amp; Sevincok, 2010 \textsuperscript{26}</td>
<td>Dhyani et al., 2018 \textsuperscript{23}</td>
</tr>
<tr>
<td></td>
<td>Hung et al., 2010 \textsuperscript{24}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gupta et al., 2014 \textsuperscript{25}</td>
<td></td>
</tr>
<tr>
<td>Contamination/washing dimension</td>
<td>Gupta et al., 2014 \textsuperscript{25}</td>
<td>Alonso et al., 2010 \textsuperscript{27}</td>
</tr>
<tr>
<td>Symmetry/ordering dimension</td>
<td>De Berardis et al., 2014 \textsuperscript{13}</td>
<td>Alonso et al., 2010 \textsuperscript{27}</td>
</tr>
<tr>
<td></td>
<td>Gupta et al., 2014 \textsuperscript{25}</td>
<td></td>
</tr>
<tr>
<td>Unacceptable thoughts</td>
<td>Balci &amp; Sevincok, 2010 \textsuperscript{26}</td>
<td>Velloso et al., 2016 \textsuperscript{12}</td>
</tr>
<tr>
<td></td>
<td>Torres et al., 2011 \textsuperscript{14}</td>
<td>Khosravani et al., 2017 \textsuperscript{10}</td>
</tr>
<tr>
<td></td>
<td>Kim et al., 2016 \textsuperscript{30}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Velloso et al., 2016 \textsuperscript{12}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Khosravani et al., 2017 \textsuperscript{10}</td>
<td></td>
</tr>
<tr>
<td>Hoarding dimension</td>
<td>Torres et al., 2011 \textsuperscript{14}</td>
<td>Chakraborty et al., 2012 \textsuperscript{29}</td>
</tr>
<tr>
<td>Poor insight</td>
<td>Gupta et al., 2014 \textsuperscript{25}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>De Berardis et al., 2015 \textsuperscript{11}</td>
<td></td>
</tr>
<tr>
<td>Premenstrual worsening of OCD symptoms</td>
<td>Moreira et al., 2013 \textsuperscript{33}</td>
<td>Moreira et al., 2013 \textsuperscript{33}</td>
</tr>
</tbody>
</table>

\textit{OCD}: Obsessive-Compulsive Disorder; \textit{Y-BOCS}: Yale-Brown Obsessive-Compulsive Scale
the disorder/duration of untreated illness or other mediating factors is to be fully understood.

OCD is a heterogeneous disorder, with several symptom dimensions. Contrasting findings have been found on the role of obsessive thinking/compulsive behaviour and suicidal ideation. In particular, Gupta et al. 25 found a positive significant association between contamination obsessions/washing behaviors and lifetime suicidal ideation, while other studies identified the presence of symmetry as risk factor 13, 25, 27. Alonso et al. 27 found that symmetry obsessions/ordering symptoms are associated with lifetime suicide attempts. Chaudhary et al. 28 have observed that suicidality is most common in patients reporting obsessions on cleanliness and contamination (57%), religious obsessions (45%), sexual obsessions (33%) and repeated rituals (31%). Hoarding obsessions and compulsions predicted lifetime suicide attempts in one study 29. A clear association between unacceptable (aggressive, sexual, or religious obsessions) thoughts and suicidal behaviors has been found 10, 12, 14, 26, 30, both in terms of suicidal ideation and suicide attempts. Moreover, suicidal ideation was predicted by lack of insight 11, 25.

Moreira et al. 33 investigated the worsening of OCD symptoms in the premenstrual period as risk factor for suicidal ideation and suicide attempts. This relationship might be due to the hormonal changes preceding the menstrual period, which may heighten patients’ susceptibility to obsessions/compulsions cycle, causing an exacerbation of symptoms.

Comorbidities

The impact of psychiatric or medical comorbidities on suicide risk or suicidal behaviors in patients with OCD has been extensively investigated (Tab. III). Having at least one current or lifetime comorbid mental disorder impacts on suicidal behaviors 12, 15, 34, 35, in terms of higher number of suicide attempts and higher prevalence of suicidal thoughts 34. Several studies have analyzed the effects of specific comorbidities and suicidal behaviors. In particular, patients with OCD and comorbid bipolar disorder 36-38 or major depressive disorder (MDD) 14, 18, 26, 39-41 have an increased risk of suicidal attempts and suicidal ideation; moreover, patients with MDD and OCD have an increased risk of lifetime suicide attempts 14, 27, 39, 41. Furthermore, the severity of depressive symptoms is positively associated with suicidal ideation and lifetime suicide attempts in patients with OCD 10, 12, 14, 18, 24-26, 30.

As regards the impact of comorbidity with anxiety disorders on suicidal behaviors, having a PTSD or GAD increases the risk of suicidal ideation and lifetime suicide attempts 14, 42. On the other hand, the presence of comorbid anxiety disorders seems to be a protective factor for completed suicides 15. The severity of comorbid anxiety disorders is correlated with suicidal ideation 14, 18, 24-26, 43 and with suicide attempts 12, 14, although this has not been confirmed by Weingarden et al. 43. Patients with a comorbid substance and alcohol use disorders show a higher risk of suicidal ideation 7, 14, 36, suicide attempts 7, 15, 36 and death by suicide 15.

A significant correlation was found between cigarette smoking and suicide attempts in OCD patients by Dell’Osso et al. 44. In particular, the risk of suicide is higher in former cigarette smokers with OCD. A significant association between higher lifetime suicide attempts and comorbid eating disorders in OCD was found by Sallet et al. 50. The prevalence of lifetime suicide attempts was higher in bulimic-OCD patients (33%), followed by anorexic-OCD patients (19%), and then by binge eating disorder-OCD patients (16%). Personality disorders are correlated to a higher risk of both suicide attempts and completed suicide in patients with OCD, although it is unclear whether specific personality disorders account for this increased risk 15. Suicidal ideation increases the risk of attempting suicide 25-29 and a history of previous suicide attempts is strongly related to later suicidal ideation, suicide attempts and even death by suicide 15, 27, 39. Moreover, in the Swedish study that used a matched case-cohort design with a follow-up of 44 years, authors found that a previous suicide attempt increases the risk of 4.7 for death by suicide in patients with OCD 15. A positive family history for suicide attempts is also correlated with both suicidal ideation and suicide attempts in OCD patients 12.

Only one study 35 found that also comorbid medical disorders may be associated with increased risk of suicide; in fact, subjects who attempted suicide had more comorbid medical disorders than individuals who never attempted suicide.

Psychopathological variables

Several different psychopathological variables are associated with increased suicide risk in OCD patients (Tab. IV). De Berardis et al. 11 found a significant association between suicidal ideation and inflated responsibility in individuals with OCD and alexithymia, independently from depressive symptoms. Alexithymia is a multifaceted construct including difficulty in identifying and describing feelings, difficulty in distinguishing feelings from bodily sensations, reduction in fantasy, and concrete and minimally introspective thinking. Alexithymia itself is associated with suicidal ideation 11, 13, 30 and lifetime suicide attempts 30. Moreover, a study found that alexithymic individuals with OCD exhibit dysregulation of the cholesterol balance 13, which in turn is associated with suicidal ideation. Although the exact relationship between alexithymia, altered lipid profile and suicide in OCD is not clear, it is possible that the increased risk for suicide is mediated by the alterations of cholesterol levels associated with alexithymia.
### Table III. Comorbidities found to be associated with increased suicide risk in OCD patients.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Suicidal ideation</th>
<th>Suicide attempts</th>
<th>Completed suicides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current/lifetime comorbid psychiatric disorders</td>
<td>Torres et al., 2013 34 Torres et al., 2013 34 Velloso et al., 2016 12 Dell’Osso et al., 2017 35 Fernandez de la Cruz et al., 2017 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid Bipolar Disorder</td>
<td>Fineberg et al., 2013 36 Fineberg et al., 2013 36 Ozdemiroglu et al., 2015 37 Saraf et al., 2017 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid Mood Disorders/Comorbid Major Depressive Disorder</td>
<td>Maina et al., 2006 18 Kamath et al., 2007 39 Maina et al., 2007 40 Balci &amp; Sevincok, 2010 26 Torres et al., 2011 14 Viswanath et al., 2012 41 Kamath et al., 2007 39 Alonso et al., 2010 27 Torres et al., 2011 14 Viswanath et al., 2012 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of comorbid depressive symptoms</td>
<td>Maina et al., 2006 18 Kamath et al., 2007 39 Balci &amp; Sevincok, 2010 26 Hung et al., 2010 24 Torres et al., 2011 14 Gupta et al., 2014 25 Kim et al., 2016 30 Khosravani et al., 2017 10 Kamath et al., 2007 39 Alonso et al., 2010 27 Velloso et al., 2016 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid PTSD/GAD (and other anxiety disorders)</td>
<td>Torres et al., 2011 14 Fontenelle et al., 2012 42 Torres et al., 2011 14 Fontenelle et al., 2012 42 Fernandez de la Cruz et al., 2017 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of comorbid anxiety symptoms</td>
<td>Maina et al., 2006 18 Kamath et al., 2007 39 Balci &amp; Sevincok, 2010 26 Hung et al., 2010 24 Torres et al., 2011 14 Gupta et al., 2014 25 Weingarden et al., 2016 43 Torres et al., 2011 14 Velloso et al., 2016 12 Weingarden et al., 2016 43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance/alcohol use disorders</td>
<td>Gentil et al., 2009 7 Torres et al., 2011 14 Fineberg et al., 2013 36 Gentil et al., 2009 7 Fineberg et al., 2013 36 Fernandez de la Cruz et al., 2017 15</td>
<td></td>
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<tr>
<td>Cigarette smoking (former)</td>
<td>Dell’Osso et al., 2015 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid eating disorders</td>
<td>Sallet et al., 2010 50</td>
<td></td>
<td></td>
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<tr>
<td>Personality disorders</td>
<td>Fernandez de la Cruz et al., 2017 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime psychiatric hospitalizations</td>
<td>Dell’Osso et al., 2017 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Kamath et al., 2007 39 Dhyani et al., 2018 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous suicide attempts</td>
<td>Kamath et al., 2007 39 Alonso et al., 2010 27</td>
<td></td>
<td></td>
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<tr>
<td>Family history for suicide attempts</td>
<td>Velloso et al., 2016 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td>Dell’Osso et al., 2017 35</td>
<td></td>
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</tbody>
</table>

PTSD: Post-Traumatic Stress Disorder; GAD: Generalized Anxiety Disorder
Factors associated with increased suicide risk in Obsessive-Compulsive Disorder

Kim et al. found an association between suicidal behaviors and perfectionism, defined as a tendency to set extremely high personal standards and being critical of themselves in a perpetuating cycle of dissatisfaction. Weingarden et al. found a significant association between shame and suicidal ideation in OCD patients and hypothesized that shame may strengthen the destabilizing effects of egodystonic emotions and acts. Also hopelessness and hostility can impact on suicidal ideation and suicide attempts in patients with OCD. In particular, Gupta et al. found a correlation between hostility and suicidal ideation and found that the Beck Hopelessness Scale (BHS) predicts suicidal ideation in patients with OCD better than the Y-BOCS. Khosravani et al. found that the presence of early maladaptive schemas, such as mistrust/abuse schemas, is significantly correlated with an increased risk for suicidal ideation and suicide attempts in patients with OCD. Cyclothymic affective temperament represents a major risk factor for suicide in patients with OCD as in patients with MDD.

### Biological variables

In addition to the well documented serotonergic dysregulation in OCD, two recent studies reported a statistically significant correlation between lower HDL-Cholesterol levels and suicidality in OCD patients; De Berardis et al. found a statistically significant correlation between lower HDL-C levels, alexithymia, and higher suicidal ideation, while Aguglia et al. found a significant correlation between higher lifetime suicide attempts and lower HDL-C levels and higher blood levels of triglycerides. While the two studies investigated two different dimensions of suicidality, they agree on specific serum lipid alterations that seem to correlate with suicidal behavior. No other biological variables have been investigated concerning the risk for suicide in OCD.

### Discussion

Patients with OCD are at high risk for suicide, and not only due to the presence of other comorbid mental disorders. This new evidence is in contrast with the former assumption that patients with OCD are not exposed to suicidal risk. Therefore, clinicians should always evaluate the suicidal risk in patients with OCD in terms of suicidal ideation, past history of suicide attempts and family history of suicide (attempts and/or committed). Suicidality is a dynamic dimension, and the use of specific instruments, such as the Columbia Suicide Severity Rating Scale (C-SSRS) for evaluating the different dimension analysis of suicidal ideation and its severity, should be implemented in clinical practice. Clinicians dealing with OCD patients should keep in mind that most patients may not spontaneously report suicidal ideation, and a direct inquire is mandatory as it is generally considered to be when interviewing subjects with a major depressive episode.

The majority of patients with OCD do not have current or lifetime suicidal ideation nor did attempt suicide in their lifetime. This implies that identifying predictors of suicidal ideation and suicide attempts in OCD could result in improving our ability to screen subjects at greater risk needing intensive and careful monitoring. Of course, early recognition and diagnosis of OCD and effective pharmacological and psychological treatments of the disorder remain essential for the prevention of suicidality. We do not have pharmacological agents with an evidence-based demonstration of effectiveness in treating suicidality, apart from lithium in affective disorders and clozapine in schizophrenia. Therefore, the evaluation of risk factors remains crucial for suicide prevention.

Concerning sociodemographic factors, we found male gender, older age and poor socioeconomic status to be associated with suicide risk. The possible explanations for higher suicide mortality of males may be the more common use of alcohol and violent suicide method by

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**TABLE IV. Psychopathological variables found to be associated with increased suicide risk in OCD patients.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Suicidal ideation</th>
<th>Suicide attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflated responsibility</td>
<td>De Berardis et al., 2015</td>
<td>Kim et al., 2016</td>
</tr>
<tr>
<td>Ego-dystonic perfectionism</td>
<td>Kim et al., 2016</td>
<td>Kim et al., 2016</td>
</tr>
<tr>
<td>Alexithymia</td>
<td>Kim et al., 2016</td>
<td>De Berardis et al., 2014</td>
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<tr>
<td></td>
<td>De Berardis et al., 2015</td>
<td>De Berardis et al., 2015</td>
</tr>
<tr>
<td>Shame</td>
<td>Weingarden et al., 2016</td>
<td>Kim et al., 2016</td>
</tr>
<tr>
<td>Hopelessness</td>
<td>Kamath et al., 2007</td>
<td>Dhyani et al., 2018</td>
</tr>
<tr>
<td></td>
<td>Balci &amp; Sevincok, 2010</td>
<td>Gupta et al., 2014</td>
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<td></td>
<td>Gupta et al., 2014</td>
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</tbody>
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males and the higher prevalence of borderline personality disorder in women, which is more frequently correlated with attempted suicides than with completed ones. Some of the data taken in consideration may actually support this hypothesis, as Fernandez de la Cruz et al. actually found overlapping confidence intervals between genders in OR for suicide attempts after adjustments for personality disorders. Since no significant difference was found between age at diagnosis, suicidal ideation in older age may be considered a consequence of OCD which has not been resolved, and therefore which could have had a longstanding negative impact on quality of life. As of the poorer educational level as a risk factor, this specific group of subjects may lack the means or the knowledge to further understand their illness, or to recognize when to seek help in case of exacerbations, which may impact their quality of life and the course of the illness. When examining OCD-related variables, we found that severity of symptoms and the specific symptom dimension of aggressive obsessions are related to higher suicide risk. It is possible that other factors, such as hopelessness, could mediate the effect of specific symptom dimensions on suicide risk. It may be that individuals with a higher severity of symptoms, or higher severity of specific symptom dimensions (such as thoughts that are deemed unacceptable, or symptoms that severely impact a multitude of aspects of their day-to-day life, such as hoarding symptoms), are more likely to feel hopeless, and therefore may consider – or even act – against their own self in an attempt to regain control of their life. In this context, lack of insight may play a role as a risk factor as proper insight could promote a deeper knowledge and understanding of the illness, which could therefore lead to the better use of all the means available to patients to get help and appropriate treatment.

From our review of the literature we found that comorbid disorders (and, specifically, comorbid depression – both in major depressive disorder but also in bipolar disorder) are predictors of higher suicide risk. Clinicians should always inquire about suicidal ideation or previous suicide attempts in individuals with comorbid depression, keeping in mind that often these individuals are affected by bipolar disorder and that the pharmacological treatment for OCD (moderate-to-high doses of SSRIs) may worsen suicidal ideation, induce mixed states and expose the patient to a higher risk of committing suicide. Comorbid substance use disorders are also significant risk factors for suicidality. It may be that the development of an addiction to a substance and the distress caused by egodystonic obsessions and compulsions in OCD may work in synergy and amplify each other. Substance abuse may therefore be considered, in OCD patients who develop addiction, as a mean to escape from their obsessions and compulsions through the intoxication of the mind, which could cause an exacerbation of symptoms as soon as the effect of the substance wears off, thus reinforcing the cycle, eventually leading some patient to consider, attempt or even complete suicide. Comorbid cigarette smoking seems also to be a risk factor; it may be hypothesized that those who are at a higher risk for smoking are at a higher risk for impulsive behaviors; however, those who are no longer smoking may be those who are either determined enough to make long-term, definitive choices (both healthier choices, such as no longer smoking, but also harmful ones, such as attempting suicide), or they may be those who no longer feel that they have an easily accessible mean, such as a cigarette, to help coping with the stress of OCD symptoms and behaviors. Smoking could be not an important contributing factor for the elevated suicidality of OCD patients as, in spite of the fact that smoking is a risk factor for all forms of suicidal behavior both on clinical and on population level, it has been repeatedly shown that OCD patients smoke much less than other psychiatric patients and the general population. Further studies are needed to better understand the relationship between smoking and suicidality in OCD patients. Comorbid somatic diseases are also associated with suicidality in OCD. Since the presence of medical comorbidities is associated with an increased risk of suicide attempt, it is possible that the treatment of medical comorbidities could strongly affect the risk for suicide attempts in OCD patients, and should be a priority, although this assumption needs to be further confirmed. Concerning psychopathological variables, from our review of the literature we identified hopelessness and personality traits, such as alexithymia or ego-dystonic perfectionism, as emotion-cognitive factors increasing the risk of suicide in individuals with OCD. Regrettfully, it is not common in clinical practice to screen for the presence of these factors, nor is it routine clinical practice to distinguish between ego-dystonic perfectionism from OCD symptoms. Some clinicians with a cognitive-behavioral background may assess cognitive constructs such as inflated responsibility and evaluate its impact on the severity of the disorder (including suicide risk). Given that suicide risk is higher in people with these cognitive-emotional risk factors, we suggest adding their evaluation in the baseline assessment of individuals presenting with severe OCD. Early maladaptive schemas, such as mistrust/abuse schemas, are also predictors of suicidality. Mistrust/abuse schema refers to an attitude recognized by avoidance of relationships with others for fear of being betrayed or misled, which in turn may be related
to having suffered from physical and/or sexual abuse experiences, severe punishments or living in an emotionally or physically unsafe environment. This finding is particularly interesting and clinically useful if considered together with results concerning the role of childhood trauma and comorbid PTSD as two independent risk factors for suicide behaviors in OCD. Addressing adverse childhood experiences in patients at higher risk for suicide because of having suffered a childhood trauma could result in reduced suicide rates. Very few biological variables have been investigated concerning suicide risk and OCD; only low HDL-cholesterol levels have been found associated with an increase in suicidal ideation and suicide attempts. A possible explanation could be that altered cholesterol levels may impact vascular serotonin sensitivity, neuronal membrane balance and viscosity, and this may result in decreased serotonin activity, which could lead to more impulsive behaviors, such as suicidal ideation and attempts. Further studies are needed to better assess the cause and effect relationship between suicidality and altered serum lipid levels.

A few studies evaluated the relative weight of each risk factor in increasing risk suicide risk: family history for suicidality, previous suicide attempts and comorbid factor in increasing risk suicide risk: family history for suicidality, previous suicide attempts and comorbid factor in increasing risk suicide risk: family history for suicidality, previous suicide attempts and comorbid factor in increasing risk suicide risk: family history for suicidality, previous suicide attempts and comorbid factor in increasing risk suicide risk: family history for suicidality, previous suicide attempts and comorbid factor in increasing risk suicide risk. Addressing adverse childhood experiences in patients at higher risk for suicide because of having suffered a childhood trauma could result in reduced suicide rates.

Conclusions

Patients with obsessive-compulsive disorder have a greater risk for suicide (suicidal ideation, suicide attempts and completed suicide) as compared to the general population, and this increased risk is even greater in individuals who have specific characteristics, which we may assume are risk factors for suicidality in OCD. These factors should be routinely assessed in clinical practice: the severity of OCD, the symptom dimension of unacceptable (aggressive, sexual, religious obsessions) thoughts, having a comorbid Axis I disorder (especially bipolar disorder or major depressive disorder, but also substance use disorder), the severity of comorbid depressive and anxiety symptoms, a previous history of suicide attempts, and some psychopathological variables, such as alexithymia and hopelessness, all increase the risk of having suicidal ideation or attempting suicide. Whether and how these risk factors for suicide in OCD work together, and whether the specific factors act as moderators or mediators, remains to be elucidated. Nevertheless, identifying individuals who are at greater risk could result in improving our ability to prevent suicide in OCD.

Conflict of Interest

The authors have no conflict of interests.

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Factors associated with increased suicide risk in Obsessive-Compulsive Disorder


Traumatic brain injury and suicide risk

Summary
Among the various consequences of traumatic brain injury (TBI), evidence supports the notion that individuals exposed to such events may be at higher risk of suicide. We therefore aim at reviewing the literature by focusing on possible association between TBI and features of the suicidal spectrum, such as suicidal ideation, suicide attempts and completed suicides. We carried out a computerized search for reports of studies involving TBI and suicide risk. A total of 35 reports provide data with preliminary support of this association. Seven articles showed a direct correlation between TBI and completed suicides. Thirteen articles have shown a direct relationship between TBI and suicide attempts; five articles demonstrated a positive correlation with suicidal ideation and suicidality. We also found negative results failing to show a correlation between TBI and completed suicides (one article), suicide attempts (one article) and suicidality (one article). In addition, one article showed that patients who received psychological treatment (CBT therapy) after suffering a head injury showed a significant reduction in suicidal ideation.

These preliminary findings encourage further testing of the association between TBI and suicide risk regardless of the psychiatric history. Furthermore, those who have a history of psychiatric illness before the TBI present a greater risk of suicide than those who do not have psychiatric precedents.

Key words
Traumatic brain injury • Suicide risk • Psychiatric history • Prevention

Introduction
Traumatic brain injury (TBI) is defined as a change in neural functioning as a result of an external force which acts on the brain, either directly or indirectly. In Europe, the incidence of TBI is around 235 cases per 100,000 inhabitants per year. Head injuries, in terms of frequency and the use of medical resources, are one of the major health problems and the leading cause of death in people aged 15-44. In Italy, the hospitalization rate is about 250-300 cases per 100,000 inhabitants each year, which is in line with other European countries. The most frequent causes of head injuries in Europe are road accidents (10-56%), accidental falls (31-62%), interpersonal aggression (6-34%), suicide (12%), and other causes (9-15%).

After a TBI, most patients have a complete resolution within a few weeks or months, while about 10-25% will have persistent symptoms accompanied by social and occupational consequences based on the severity of the initial neurological trauma. These symptoms, defined as post-concussive syndrome (PCS), include somatic, cognitive and emotional disorders (such as headaches, increased fatigue, sleep disturbances, balance disorders, mood and behavioral changes). People with a history of head injury have a suicide risk ranging from 1.55 to 4.05 times higher than the general population.

The association between TBI and suicide has been evaluated in several studies. In particular, a higher rate of suicide among people with brain injuries has been found, although the sample sizes are small. TBI and
suicide share some risk factors, namely being male, with young age, living in unfavorable social conditions and having and abuse of alcohol and drugs. Therefore, it is of interest to understand the extent to which TBI itself is a risk factor for suicide.

The above-mentioned background encouraged the present overview of research pertaining to suicidal risk in relation to TBI. Given the relatively early state of this area of inquiry, we viewed our task as gathering and critically appraising the available research relevant to the topic, with the aim of formulating a hypothesis to be tested with further research.

By reviewing selected articles we identified some specific fields of interest. We also consulted a number of international experts in the field to determine whether the studies selected were relevant for discussing preventive measures for suicide risk in TBI. The authors and experts consulted performed a careful analysis of the literature data and agreed on a number of key subjects relevant to the aim of this paper.

We will therefore review studies dealing with the impact of TBI on completed suicide, attempted suicide, suicidal ideation and suicide risk as a whole. The aim of this paper is to evaluate the role of TBI as a risk factor for suicide and stimulate further discussion on the field of prevention of suicidal behaviour in TBI.

**Studies evaluating the impact of TBI on completed suicide**

The relationship between TBI and suicide has been confirmed in several studies. In a retrospective cohort study, it has been found that people with TBI had a 3-times higher risk of dying by suicide than people without a history of TBI (SMR: 2.95; CI 95%; 1.42-5.43).

In particular, Brenner et al. studied 7,850,472 veterans. Veterans with a previous TBI were 1.55 times more likely to die by suicide than those without TBI (p < 0.001): those with concussion or cranial fracture were 1.98 times more likely to die by suicide (p = 0.0002) and those with cerebral contusion or traumatic intracranial hemorrhage were 1.34 times more likely to die by suicide (p = 0.006) as compared to those without a TBI.

Richard et al. found that the association between TBI and death by suicide was higher if the trauma occurred in adulthood (HR = 2.53, 95% CI: 1.79-3.59) compared to adolescence (HR = 1.57, 95% CI: 1.09-2.26) or infancy (HR = 1.49, 95% CI: 1.04-2.14). The death by suicide was higher in subjects with male gender (HR: 4.69 vs 1.00), with the more serious injuries (HR = 2.77, 95% CI: 2.01-3.83), and with a mental disorder prior to the trauma. In a study conducted in Finland, it was found that the interval between the TBI and suicide was shorter if the individual had a prior psychiatric disorder. Patients with TBI had a higher risk of premature death in general and by suicide in the 6 months after a TBI compared to the general population. Death by suicide occurred significantly more often in TBI patients than in general population (OR = 3.3; CI 95%: 2.9-3.7).

In a 20-year follow-up study carried out in Canada, the authors found 667 suicide deaths after a median of 9.3 years since the TBI (a rate of 31 suicides per 100,000 patients annually).

In Denmark, Teasdale and Enberg found standardized mortality ratios for suicide that were higher in patients with concussion (3.02, 95% CI: 2.82-3.25), cranial fracture (2.7, 95% CI: 2.01-3.59) and brain lesions (4.1, 95% CI: 3.33-4.93) compared to the general population. Standardized mortality ratios for suicide were greater among females than male subjects in all groups. The suicide rate was higher in those aged 21-60, with substance abuse and with prolonged hospitalization (< 1 week (HR): 3.51, 95% CI: 2.08-5.92; > 3 months (HR): 4.85, 95% CI: 2.97-7.92).

Only one study by Shavelle et al. including 2,320 subjects with intellectual disability, found that TBI increased the overall mortality risk (SMR = 3.1; CI 95% 2.5-3.7), but not by suicide compared to the general population.

**Studies evaluating the impact of TBI on attempted suicide**

The association between having a TBI and suicide attempts have been evaluated in several longitudinal and cohort studies. In particular, Fonda et al. found, in a cohort study including 273,591 veterans (42,392 [16%] with TBI and 231,199 [84%] without TBI), a 4-times higher risk of attempted suicide for those with TBI (hazard ratio = 3.76, 95% CI: 3.15-4.49). Moreover, veterans with TBI more frequently had a psychiatric disorder than those without TBI. Comorbidity with psychiatric disorders explained 83% of the association between TBI and attempted suicide, with PTSD having the largest impact.

Brenner et al. studied 133 veterans and they found that veterans with a previous suicide attempt and TBI did not show any learning over the course of the Iowa Gambling Test (IGT) unlike all the other groups. No differences were found on other aspects of executive function.

Several studies have found a positive association between having a TBI and suicidal attempts after adjusting for any comorbid psychiatric disorder, demographic variables and quality of life.

In several longitudinal studies, it has been confirmed that rates of suicide attempts, suicidal ideation and of depressive symptoms were higher in patients with a TBI than in the general population.

Homafair et al. explored the relationship between TBI, executive dysfunction and suicide attempts, and found that patients attempting suicide had a higher level of perseveration than subjects without a previous suicide attempts (p = 0.04).
Illie et al. 61 found a statistically significant difference in psychological distress, suicidal ideation and suicide attempts in TBI patients compared to patients without TBI. However, in a study on the impact of PTSD and TBI on suicidal attempts, after adjusting for age and gender, the odds of a suicide attempt for subjects with PTSD were 2.8 (95% CI: 1.5, 5.1), while it was 1.03 if TBI was considered alone. When the impact of PTSD and TBI were evaluated together, only PTSD was significant 62.

Studies evaluating the impact of TBI on suicidal ideation
Several factors have been investigated as possible predictors of suicidal ideation in patients suffering from TBI. In particular, it was found that the trauma mode 63 and sleep quality 64 are significant factors.

In a study by Gunter et al. 65, having a TBI was found to be a risk factor for suicidal ideation or behaviour (p ≤ 0.007, OR = 2.63, 95% CI: 1.30-5.35), together with other factors such as Caucasian ethnicity (p ≤ 0.001, OR = 5.98, 95% CI: 2.38-14.97), depressive symptoms (p ≤ 0.003, OR = 1.13, 95% CI: 1.04-1.23), childhood trauma (p ≤ 0.008, OR = 2.70, 95% CI: 1.30-5.61) and avoidant personality (p ≤ 0.028, OR = 2.97, 95% CI: 1.12-7.87).

Wisco et al. 66 examined the association between TBI history and suicidal ideation and found that TBI was significantly associated with suicidal ideation only in male veterans (RR = 1.55). Moreover, multiple TBIs and TBI with loss of consciousness, depressive symptoms and PTSD were more strongly associated with suicidal ideation.

In a longitudinal study, it was reported that people with TBI are at higher risk to report suicidal ideation, even one year after the trauma 67.

Moreover, the mediating role of anger and depressive symptoms has been explored as an explanation for suicidal ideation in patients with TBI. It was found that TBI significantly predicted anger (B = 11.845, SE = 5.281, p = 0.026); anger significantly predicted depression (B = 0.020, SE = 0.002, p < 0.001) and depression significantly predicted suicide risk (B = 0.788, SE = 0.178, p < 0.001) 68.

An association between disinhibition and suicidal behavior was found 6 years after the TBI (p = 0.045, p = 0.033, respectively) 69. Bryan et al. 70 found that TBIs were significantly associated with increases in depression and PTSD symptom intensity. TBIs were also associated with a greater incidence of lifetime suicidal thoughts or behaviors. Greater suicide risk was related to the number of TBIs (β [SE] = 0.214 [0.098]; p = 0.03) after correcting for the influence of depression, PTSD, and TBI symptom intensity. Cumulative TBIs were also associated with a higher severity of depressive symptoms (β = 0.580 [0.283]; p = 0.04).

Studies evaluating the impact of TBI on suicide risk
The association between suicide risk and presence of TBI has been confirmed in several studies with veterans. In particular, Brenner et al. 71 found that veterans with TBI were 3.6 times more likely to report suicide risk, even after correcting for the number of psychiatric diagnoses (95% CI: 1.4, 9.0; p = 0.007). This finding has been confirmed in another study 72, showing that depressive and PTSD symptoms were significantly associated with increased suicide risk among patients with a diagnosis of TBI (p < 0.001). Moreover, veterans at greater risk of suicide exhibited post-TBI symptoms more frequently than those with no or low risk, including blurred vision, seizures, memory difficulties or problem-solving difficulties and difficulty in managing stress 73.

The association between suicide risk and TBI has been confirmed also in samples with college students 74, even after controlling for other well-known risk factors such as depression, perceived burdensomeness, thwarted belongingness, and acquired capability.

Only one study did not confirm the association between TBI and suicide risk 75. Simpson and Tate 76 found no relationship between injury severity and suicide risk.

Discussion
The present review aimed to investigate the relationship between TBI and suicide, in particular, the relationship between head injuries and suicidal ideation, suicide behaviors, suicide attempts and completed suicides. According to our findings, TBI is a risk factor for suicidal ideation, suicide attempts and deaths by suicide. In particular, the consequences of TBI can include psychological distress, depression and suicidal behavior. Furthermore, suicide and TBI share several common risk factors such as younger age, male sex, substance use and aggression. The present findings are consistent with previous reviews 78-81.

It is important to understand how TBI can indirectly increase the risk of suicidal ideation and behaviors, suicide attempts and complete suicide. Head injuries, especially mild ones, cause an indirect increase in suicide risk mediated by the worsening of depressive symptoms and aggressiveness 68.

Other factors can explain the increased risk of suicidal behaviours in patients with TBI, such as the increase in levels of TNF-α and the alteration of sleep quality. Moreover, the suicidal risk is even higher in patients with TBI and a history of mental and substance abuse disorders.

Therefore, in order to avoid the onset of suicidal ideation and suicide attempts, it is extremely important to detect and appropriately treat TBI and its consequences. In particular, in patients with TBI, it is the frequent development of post-traumatic amnesia and hopelessness,
which represent per se a relevant risk factor for suicide. It is necessary to promote screening programs for an early identification of patients at higher suicide risk, using the TBI-4 scale.

Several studies were conducted on war veterans. Veterans with a history of TBI and PTSD are at greater risk of suicide than those without a history of TBI. According to Barnes et al., PTSD and TBI are associated with a higher risk of suicide than PTSD alone, the added risk is attributable to the severity of the PTSD symptoms. A greater risk of dying by suicide has been shown in children, adolescents and adults with a history of TBI compared with those with no TBI. The risk of death by suicide is greater in subjects who suffered from TBI in adulthood compared to those experiencing TBI in childhood or adolescence.

Psychopathological implications

Traumatic brain injury is an alteration in brain function, or other evidence of brain pathology, caused by an external force. Neurotrauma can cause brain alterations that result in neuropsychiatric sequelae and functional deficits in those who experience such injuries. The brain regions most frequently affected by TBI damage are the frontal cortex and the subfrontal white matter, the basal ganglia and the diencephalon, the rostral cerebral trunk and temporal lobes including the hippocampus. In relation to the post-TBI brain damage, there is a consequent profile of neurobehavioural sequelae characterized by cognitive deficits (memory, attention, executive function, speed of information processing), personality changes (better characterized as dysexecutive syndromes involving social behavior, cognition and motivated behavior) and increased rates of psychiatric disorders, including mood disorders, sleep disorders, substance abuse, psychotic syndromes and post-traumatic stress disorder.

Limitations

This review has several limitations, which must be acknowledged. Firstly, it was not possible to carry out a meta-analysis due to the variety of methodologies adopted in the included studies. Second, only studies published in English and in peer-reviewed journals were considered. Furthermore, although our approach was comprehensive, we did not attempt a systematic analysis which may have left out of this review possible papers of interest. We chose to report those studies available in the literature that could support a broad analysis of the topic so as to offer a tutorial paper. After a careful and systematic search, we extrapolated from those studies with the aim of formulating a hypothesis to be tested with further research.

Conclusions

Although TBI represents a risk factor for suicidal ideation and suicide attempts, patients with a history of psychiatric illness prior to the TBI present a higher risk than those who do not have psychiatric precedents, and they die by suicide sooner after the initial evaluation than those who do not have psychiatric precedents. Indeed, it is important to note how subjects with a TBI, not only have an increased risk of developing suicidal behaviors, but they also die by suicide earlier than others regardless of the presence or absence of a psychiatric history.

Conflict of Interest

The authors have no conflict of interests.


34 Brenner LA, Ignacio RV, Blow FC. Suicide and traumatic brain injury among individuals seeking veterans health administration services. J Head Trauma Rehabil 2011;26:257-64.


38 Brenner LA, Ignacio RV, Blow FC. Suicide and traumatic brain injury among individuals seeking veterans health administration services. J Head Trauma Rehabil 2011;26:257-64.


Traumatic brain injury and suicide risk


# Positive Findings

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<th>Completed suicide studies</th>
<th>Study</th>
<th>Sample</th>
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<td>Teasdale &amp; Engberg, 2001</td>
<td>Population study</td>
<td>145,440 patients admitted for TBI between the years 1979 and 1993: patients with concussion (n = 126, 114), with a cranial fracture (n = 7,560), with a cerebral contusion or traumatic intracranial haemorrhage (n = 11,766)</td>
<td>To evaluate the suicide rate in a group of Danish patients with a history of TBI</td>
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<td>Mainio et al., 2007</td>
<td></td>
<td>1,877 suicide victims</td>
<td>To study the prevalence of TBI among suicides and to evaluate the association between suicide, TBI and psychiatric disorders</td>
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<td>Harrison-felix et al., 2009</td>
<td>Retrospective cohort study</td>
<td>1,678 TBI patients admitted to Craig Hospital within 1 year of injury (between 1961 to 2002)</td>
<td>To investigate mortality in patients with TBI</td>
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<td>Brenner et al., 2011</td>
<td>Observational retrospective study</td>
<td>81 veterans with a history of suicide attempts between October 2004 and February 2006</td>
<td>To examine the association between suicide attempt history among veterans with PTSD and/or TBI</td>
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<td>Fazel et al.; 2014</td>
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<td>218,300 patients with a previous TBI studied between 1969-2009 compared to 2,163,190 controls; and 150,513 TBI patients with siblings without TBI compared with 237,535 sibling controls without TBI</td>
<td>To evaluate premature mortality in TBI patients vs general population</td>
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<td>Richard et al., 2015</td>
<td></td>
<td>134,629 children aged 0-17 years</td>
<td>To evaluate the association between TBI and the subsequent risk of suicide deaths in a population of children</td>
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<tr>
<td>Fralick et al., 2016</td>
<td>Longitudinal cohort study</td>
<td>235,110 patients who received a diagnosis of concussion from 1st April 1992 to 31st March 2012 (weekend concussion n = 39,940; weekday concussion n = 195,170)</td>
<td>To evaluate if concussion could influence long-term risk of suicide</td>
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### Material and methods

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<td>14 years</td>
<td>0.62% (895) of TBI patients died from suicide. The standardized mortality ratios for suicide showed that the incidence was increased relative to the general population and was lower for patients injured before the age of 21 or after 60. There was a significantly higher risk of suicide among patients with cerebral contusions or traumatic intracranial haemorrhages than those with concussion or cranial fractures. In all diagnosis groups the ratios were higher for females than for males.</td>
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<td>16 years</td>
<td>Among all suicides, 103 (5.5%) had sustained a TBI. Patients with TBI died by suicide within 3 years after TBI (this time interval was shorter if the subject had a psychiatric disorder before TBI).</td>
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<td>40 years</td>
<td>130 deaths occurred after 1-year post injury (mortality rate: 7.7%). Standardized mortality ratio was 1.51 (95% CI: 1.25-1.78). 10 deaths caused by suicide. TBI patients are 3 times more likely to commit suicide than general population.</td>
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<td>21 years</td>
<td>The study found a higher risk of suicide for people who sustained a TBI during adulthood [(HR): 2.53] rather than during adolescence [(HR) = 1.57] and childhood [(HR) = 1.49]. Males who sustained a TBI were at a much higher risk for suicide than females [(HR): 4.69 vs 1.00]. More severe injuries were associated with a higher risk of suicide than low severity injuries [(HR): 2.77 vs 2.18]. Sustaining repeated injuries increased the risk of suicide for children [(HR) = 1.23], adolescents [(HR) = 1.41] and adults [(HR) = 1.61].</td>
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<td>20 years</td>
<td>667 patients committed suicide, with a median follow-up of 9.3 years (31 suicides/100,000 subjects annually). 519 suicides occurred after weekday concussion (29 suicides/100,000 subjects annually; ≥ 3-times the general population) and 148 after weekend concussion (39 suicides/100,000 subjects annually; ≥ 4 times the general population). Weekend concussion was associated with a greater risk of suicide than weekday concussion (RR = 1.36; CI 95% 1.14-1.64).</td>
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<td>Author, year</td>
<td>Study</td>
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<td>Jonathan et al., 2001</td>
<td>5,034 participants in the Epidemiologic Catchment Area Study</td>
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<td>Oquendo et al., 2004</td>
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<td>Gutierrez et al., 2008</td>
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<td>Homaifar et al., 2012</td>
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<td>assess levels of hopelessness and suicide ideation</td>
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<td>Attempts Rating Scale (LSARS) was used to characterize suicidal behaviors</td>
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<td>Ilie et al., 2014</td>
<td>Observational study</td>
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<tr>
<td>Brenner et al., 2015</td>
<td>Cohort study</td>
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<tr>
<td>Fonda et al., 2016</td>
<td>Cohort study</td>
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<tr>
<td>Schneider et al., 2016</td>
<td>Longitudinal study</td>
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<tr>
<td>Simpson et al., 2002</td>
<td>Longitudinal study</td>
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<td>Fisher et al., 2016</td>
<td>Longitudinal study</td>
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<tr>
<td>Kesinger et al., 2016</td>
<td>Longitudinal study</td>
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**Suicidal ideation**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample</th>
<th>Aims</th>
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<tbody>
<tr>
<td>Simpson et al., 2002</td>
<td>172 out-patients with TBI from the Liverpool Hospital Brain Injury Rehabilitation Unit (BIRU) in Sydney (Australia)</td>
<td>To evaluate the suicidal ideation, suicide attempts, hopelessness and other clinical correlates after TBI</td>
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<tr>
<td>Material and methods</td>
<td>Follow-up</td>
<td>Results</td>
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<td>Measures were: assessment of TBI; Mental/ emotional Health with General Health Questionnaire (GHQ12); suicide ideation and suicide attempts; asking help through a crisis help-line/ website; need to receive pharmacological treatment for anxiety, depression or both; evaluation of conduct behaviours</td>
<td>From April 2007 to September 2012</td>
<td>There was a significantly difference in suicide ideation and attempts between adolescents with and without TBI (suicide ideation: AOR = 1.93, CI = 95% 1.42-2.63, p value ≤ 0.001; suicide attempts: AOR = 3.39, CI 95% 2.15-5.35, p value ≤ 0.001)</td>
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<tr>
<td>Iowa Gambling Test (IGT), Immediate and Delayed Memory Test, State-Trait Anger Expression Inventory-2, Wisconsin Card Sorting Test</td>
<td>1 year</td>
<td>Veterans with a history of both SA and TBI demonstrated a lack of learning over the course of the IGT, unlike all the other groups. No significant differences were identified on other measures of executive functioning among the groups</td>
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<tr>
<td>TBI exposure: VA primary TBI screen and comprehensive TBI evaluation; Suicide attempt and outcome: ICD-9 injury E codes (E950–E959); Covariates: sex, race (white, black, other, unknown/missing), age, marital status (single, married, or divorced/separated/other), and psychiatric conditions (using ICD-9 diagnosis code)</td>
<td>545 attempted suicides, more frequently among veterans with TBI (n = 227, 0.54%) than those without TBI (n = 318, 0.14%). Veterans with TBI had higher proportion of each psychiatric condition than those without TBI (from 16% vs 5% for substance-use disorder to 63% vs 10% for PTSD). Co-occurring psychiatric conditions mediated 83% of the association between TBI and attempted suicide: PTSD had the largest impact (73% of the association)</td>
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<tr>
<td>The TBI-4 was administered to 1,097 veterans at the time of mental health intake. Follow-up data regarding suicide attempts for one year post-mental health intake were obtained from suicide behavior reports (SBRs) in Veteran electronic medical records (EMRs)</td>
<td>468 participants screened positive on Question 2 (Have you ever been knocked out or unconscious following an accident or injury?) of TBI-4. 7 (1.5%) of them made a suicide attempt 1-year post-assessment (vs 0% in those who did not endorse this item)</td>
<td>Suicidal ideation and depression rates were, respectively, 7-10% and 24.8-28.1% 20 years after brain injury. The prevalence of suicide attempts was 0.8-1.7% at the end of follow-up. The highest rates of suicidal ideation and depression were registered after 5 years form TBI. Patients with head injury presented a greater risk of suicide attempts, suicidal ideation and depression than general population</td>
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<tr>
<td>Patient Health Questionnaire (PHQ-9) was used to assess depression and suicidal ideation. Previous suicide attempts were self-reported by patients. Patients were evaluated at 1, 2, 3, 10, 15 and 20 years after brain injury</td>
<td>PHQ-9 was used to evaluate suicidal ideation. Suicide attempts were assessed with an interview. Severity of TBI and extracranial injuries were evaluated respectively with Abbreviated Injury Scale head score and with Injury Scale (non-head). Measures were assessed at 1st, 2nd and 5th year after TBI</td>
<td>8.2% of subjects presented with suicide ideation without suicide attempts. 3.0% committed at least one suicide attempt during 5 years after TBI. There was a relationship between severe extracranial injury and suicide ideation (OR = 2.73 CI 95%, 1.55-4.82; p value = 0.001), and between use of alcohol and drugs and suicide ideation (OR = 1.69 CI 95%, 1.11-2.86; p value = 0.015)</td>
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<td>Hopelessness and suicide ideation were assessed using the Beck Hopelessness Scale (BHS) and the Beck Scale for Suicidal Ideation (BSS)</td>
<td>35% patients had moderate-severe levels of hopelessness, 23% had suicidal ideation and 17.4% attempted suicide after TBI. No relationship was found between injury severity and suicidality</td>
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<tr>
<td><strong>Suicidal ideation</strong></td>
<td><strong>Study</strong></td>
<td><strong>Sample</strong></td>
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<tr>
<td>Wisco et al., 2014</td>
<td>824 male and 825 female U.S. veterans</td>
<td>To evaluate the relationship between TBI history and suicidal ideation in a group of U.S. veterans</td>
</tr>
<tr>
<td>Mackelprang et al., 2014</td>
<td>Recruitment phase of a clinical trial</td>
<td>559 patients admitted to Harborview Medical Center (Seattle) for TBI between June 2001 and March 2005</td>
</tr>
<tr>
<td>Bethune et al., 2016</td>
<td>871 patients in an urban tertiary care ED enrolled at 3 months post injury, between 1998 and 2012</td>
<td>To clarify psychosocial and injury features contributing to suicidal ideation (SI) after concussion or mTBI and the time it takes to develop</td>
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<tr>
<td>DeBeer et al., 2017</td>
<td>Observational study</td>
<td>145 Iraq/Afghanistan veterans within the Central Texas Veterans Health Care System</td>
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<tr>
<td><strong>Suicidality</strong></td>
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<tr>
<td>Brenner, Ignacio et al., 2011</td>
<td>Observational retrospective study</td>
<td>7,850,472 veterans who received care between fiscal years 2001 to 2006: 49,626 with a history of TBI (12,159 with concussion or cranial fracture and 39,545 with cerebral contusion/traumatic intracranial hemorrhage), and 389,053 patients without TBI</td>
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<tr>
<td>Bryan, Clemans, Hernandez et al., 2013</td>
<td>Observational study</td>
<td>158 military personnel as outpatients TBI clinic in Iraq: 135 (85.4%) with diagnosis of mTBI and 23 (14.6%) without</td>
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<tr>
<td>Juengst et al., 2014</td>
<td>74 patients with TBI (acute cerebrospinal fluid (CSF) levels of TNF-α: n = 37 vs n = 15 controls; acute serum levels of TNF-α: n = 48 vs n = 15 controls; chronic serum levels of TNF-α: n = 48 vs n = 15 controls)</td>
<td>To measure the association between high level of Tumor Necrosis Factor-α (TNF-α), disinhibition and suicidal behaviour</td>
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<td><strong>Suicidality</strong></td>
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<tr>
<td>Bryson et al., 2017</td>
<td>Observational study</td>
<td>42 college students self-reported a history of TBI (42 controls matched)</td>
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<td>Material and methods</td>
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<tr>
<td>TBI history was assessed using a structured interview. The prime-MD Patient Health Questionnaire was used to evaluate depressive symptoms. The Mini-International Neuropsychiatric Interview, English version 5.0 (M.I.N.I.) was used to evaluate suicidality</td>
<td>TBI was significantly associated with suicidal ideation among male (RR = 1.55), but not female, veterans. In addition, multiple TBI and TBI with loss of consciousness were more strongly associated with suicidal ideation. Depressive symptoms and PTSD were associated with greater risk of ideation in both groups (male and female)</td>
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<td>PHQ-9 was used to evaluate suicidal ideation. A structured telephone interview was conducted at month 1-6-8-10 and 12 after brain injury</td>
<td>25% of patients reported suicidal ideation during the first year after brain injury. Rate of ideation was highest (10%) during months 2 and 8. Patients with history of previous suicide attempts presented a risk 5 times more to have suicidal ideation after injury than patients without a history of a suicide attempt (OR: 4.81; 95% CI: 2.83-8.17)</td>
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<td>Psychiatric (DSM-IV, MMSE, General Health Questionnaire) and social-demographic (clinical interview) assessments at 3 and 6 months after injury. The Rivermead Post-Concussion Disorder Questionnaire (RPDQ) to record the post concussion syndrome symptoms</td>
<td>SI emerged in 6.3% of patients at 3 months and in 8.2% at 6 months. It was independently associated with speaking English as a second language and injury mechanism (motor vehicle crashes/passenger) at 3 and 6 months, and with history of depression and marital status at 3 months only</td>
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<td>Defense and Veterans Brain Injury Center Brief Traumatic Brain Injury Screening Tool, Pittsburgh Sleep Quality Index, Beck Scale for Suicide Ideation</td>
<td>Sleep quality influenced the effect of TBI history on current suicidal ideation (indirect effect = 0.0082); individuals with history of TBI suffered worse sleep quality, which was also associated with increased suicidal ideation</td>
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<tr>
<td>ICD-9 (Diagnosis of TBI), National Death Index (vital status or dates/causes of death)</td>
<td>Veterans with a history of TBI were 1.55 times more likely to die by suicide than those without a history of TBI. Those with concussion/cranial fracture were 1.98 times more likely to die by suicide and cerebral contusion/intracranial hemorrhage were 1.34 times more likely to die by suicide, compared to those without an injury history. The presence of psychiatric disorders or demographic factors didn’t explain this increased risk</td>
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<tr>
<td>4-item Suicidal Behaviors Questionnaire–Revised, 5-item Depression subscale of the Behavioral Health Measure-20, PTSD Checklist–Military Version, Insomnia Severity Index, 2008 TBI Task Force’s criteria of the Department of Defense and Department of Veterans Affairs</td>
<td>Depression and its interaction with PTSD symptoms were significantly associated with increased suicidality among patients with diagnosis of mTBI. Decreased probability for any suicidality was correlated with a longer duration of loss of consciousness</td>
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<tr>
<td>TNF-α levels were collected for 12 months after TBI. Frontal System Behaviour Scale (FrSBe) Disinhibition Subscale and PHQ-9 were used to assess respectively disinhibition and suicidal behavior</td>
<td>Acute CSF level of TNF-α was associated with suicidal behaviour at 12 months from TBI (p = 0.014). Acute and chronic serum TNF-α level was not related with suicidal behaviour but was significantly associated with disinhibition at 6 months post-injury (respectively p = 0.009; p = 0.029). Disinhibition was associated with suicidal behaviour at 6 and 12 months (respectively p = 0.045; p = 0.033)</td>
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<tr>
<td>Depression Anxiety Stress Scale – 21, Interpersonal Needs Questionnaire, Acquired Capability for Suicide Scale, Suicidal Behaviors Questionnaire–Revised</td>
<td>Higher suicide risk emerged in individuals with a TBI than those without, even accounting for the relative influence of 2 strong suicide risk factors (i.e., depression, perceived burdensomeness, thwarted belongingness, and acquired capability). The interaction of perceived burdensomeness, acquired capability and thwarted belongingness (IPTS) was significantly associated with suicide risks</td>
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### Suicidality

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<thead>
<tr>
<th>Author, year</th>
<th>Study</th>
<th>Sample</th>
<th>Aims</th>
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</thead>
<tbody>
<tr>
<td>Palladino et al., 2017</td>
<td>103 homeless veterans with TBI</td>
<td>To evaluate the associations between suicide risk and physical, psychological, social and military characteristics among homeless veterans with TBI</td>
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### NEGATIVE FINDINGS

#### Completed suicide

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
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<tbody>
<tr>
<td>Shavelle et al.; 2001</td>
<td>2,320 subjects who had TBI at the age of 10 or more and with a mental disability after TBI followed-up between 1988 and 1997</td>
<td>To assess causes of death in patients with previous TBI vs in general population</td>
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#### Attempted suicide

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Aims</th>
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</thead>
<tbody>
<tr>
<td>Brenner et al., 2017</td>
<td>309 veterans seeking homeless services: 282 with a history of TBI and 27 without a history of TBI</td>
<td>To find out any difference in negative psychiatric results among veterans seeking homeless services, with and without a history of traumatic brain injury (TBI)</td>
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#### Suicidal ideation

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Aims</th>
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</thead>
<tbody>
<tr>
<td>Stanley et al., 2016</td>
<td>149 military service members referred to a TBI clinic within a military hospital in Iraq during a 6-month span in 2009</td>
<td>To determine if the relationship between mild TBI and suicide risk is statistically accounted for by anger and depression symptoms</td>
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#### Suicidality

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<thead>
<tr>
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<tbody>
<tr>
<td>Barnes et al., 2012</td>
<td>92 male veterans in treatment for PTSD between 2006 and 2010 at a Midwestern Veterans Affairs Medical Center; 46 of these patients had sustained an mTBI</td>
<td>To investigate whether mTBI increases suicide risk beyond the risk associated with PTSD alone</td>
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#### Treatment

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<tr>
<th>Study</th>
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<th>Aims</th>
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<tr>
<td>Simpson &amp; Tate, 2011</td>
<td>17 patients with severe TBI (aged 18 or older at injury and current &lt; 65 years) and moderate/severe levels of hopelessness and/or suicide ideation (BHS-Beck Hopelessness Scale)</td>
<td>To evaluate the efficacy of a psychological treatment (CBT therapy) to reduce the hopelessness after severe TBI</td>
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**TBI:** Traumatic Brain Injury; **PHQ-9:** Patient Health Questionnaire
### Traumatic brain injury and suicide risk

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<tr>
<th>Material and methods</th>
<th>Follow-up</th>
<th>Results</th>
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<tbody>
<tr>
<td>TBI-4 Questionnaire and Ohio State University TBI Identification Method (OSU TBI-ID) were used to find positive subjects for TBI. MINI International Neuropsychiatric Interview (MINI) was used to investigate the presence of psychiatric disorders including suicidal ideation.</td>
<td>1 year (December 2010-September 2011)</td>
<td>Veterans with high risk of suicide reported significantly more frequently the following TBI related symptoms than those with no or low risk: blurred vision (81.8 vs 45.7%), seizures (36.4 vs 4.3%) and difficulty with memory/problem-solving (81.8 vs 37%) and managing stress (63.6 vs 27.2%). Veterans with PTSD had 8 times the odds of being at high risk for suicide.</td>
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<td>Subjects were identified from a database with people who received assistance from the California Department of Developmental Services. Death information were extracted from annual computer register.</td>
<td>9 years</td>
<td>TBI subjects presented higher risk of death than general population (SMR = 3.1; CI 95% 2.5-3.7). 3% of patients had attempted suicide before TBI. 2 suicides occurred during the follow-up period.</td>
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<tr>
<td>The Ohio State University TBI-Identification Method (structured interview); the MINI international neuropsychiatric interview (short, structured diagnostic interview)</td>
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<td>Veterans with a history of TBI received significantly more psychiatric diagnoses (p = 0.0003), and showed higher risk for suicide (p = 0.007) than those without a history of TBI.</td>
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<tr>
<td>Mild TBI diagnosis was confirmed by a licensed clinical psychologist or physician during a clinical interview. Suicide risk was assessed utilizing the Suicidal Behaviors Questionnaire (SBQ-R). Anger was assessed utilizing the mood scale module of the Automated Neuropsychological Assessment Metrics (ANAM). Depression symptoms were assessed utilizing the Behavioral Health Measure-20 (BHM-20)</td>
<td>6 months</td>
<td>The relationship between mild TBI and suicide risk is fully mediated by anger and depression symptoms: mild TBI significantly predicted anger; anger significantly predicted depression symptoms and depression symptoms significantly predicted suicide risk.</td>
</tr>
<tr>
<td>PTSD Scale assesses DSM-IV-TR PTSD diagnostic criteria; SCID-I to detect current and/or lifetime presence of Axis I psychiatric disorders. Self-report measures: BDI-II for assessing depressive symptoms; the PCL-S (PTSD Checklist Stressor Specific Version) instructs patients to rate the severity of their PTSD symptoms in relation to a specific traumatic stressor.</td>
<td></td>
<td>No significant differences emerged in the assessed risk factors suggesting that, if PTSD and mTBI are associated with greater suicide risk relative to PTSD alone, the added risk is attributable to PTSD symptom severity.</td>
</tr>
<tr>
<td>Participants were aged between 18 and 65 years, experienced post traumatic amnesia more than 1 day and moderate/severe hopelessness (evaluated with the Beck Hopelessness Scale) and/or suicide ideation (evaluated with the Beck Scale for Suicide Ideation)</td>
<td>3 months</td>
<td>The treatment group improved with a reduction of 6 BHS points, whereas the wait-list group increased scores by 1 BHS point. Was also observed a significant reduction in suicide ideation scores in the treatment group.</td>
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The interplay between cannabis use and suicidal behaviours: epidemiological overview, psychopathological and clinical models

Summary

Objectives
The clinical and psychopathological relationships between substance use and suicidal behaviours are deserving growing attention. Understanding and identifying factors that may be associated with suicidal behaviours can help clinicians to early detect high-risk individuals.

Methods
We conducted a narrative review, summarising main epidemiological data from longitudinal studies, on the potential association between cannabis use and suicidal behaviours. In addition, we discuss possible psychopathological models that may explain and disentangle this clinical relationship.

Results
Individuals who use cannabis, the most common psychoactive drug apart from alcohol and nicotine, may have higher risk of suicidal behaviours. Despite the mixed findings, evidence seems to suggest that an early and heavy cannabis use may be associated with suicidal ideation, attempt, and completion.

Conclusions
Findings from our review show that it is likely that cannabis is associated with increased rates of suicidal behaviours. This relationship could be explained by the reciprocal influence of cannabis on severity of depression, psychotic features, and impulsivity. Cannabis may play a key role in the complex clinical pathways that link mental disorders and suicide-related behaviours. Nevertheless, various potential mechanisms and contributing factors to this association remain to be investigated.

Key words
Cannabis • Suicide • Epidemiology • Psychopathology

Introduction
According to the World Health Organization, suicide is a global phenomenon, representing the 17th leading cause of death in 2015. In the European Union, out of the 4.9 million deaths reported in 2014, 58,000 (1.2%) were due to intentional self-harm. In addition, evidence from the National Vital Statistics System show that between 1999 and 2014 age-adjusted suicide rates in the United States raised from 10.5 to 13.0 per 100,000 individuals in the general population. Thus, suicide represents a public health problem, and it seems correlated with different clinical, psychological, biological and environmental risk factors, although no effective predictive algorithms for clinical practice are available. Nevertheless, understanding and identifying factors that may be associated with suicidal behaviours could help clinicians to early detect high-risk individuals and assist them in screening for treatment.
In recent years, the possible relationship between substance use and suicidal behaviours has been investigated. Mood and substance use disorders are the most frequent mental disorders among suicide decedents worldwide. In addition, cannabis, following nicotine and alcohol, is the most commonly used psychoactive substance both in the United States and in Europe, with particularly high misuse rates among young people. Mixed results have been produced by studies analysing the possible detrimental effect of cannabis on health, making difficult to clarify whether, how, and to what extent cannabis is harmful. Negative effects are heterogeneous and may include a range of consequences in terms of brain development, mental disorders, use of other illicit drugs, school performance and lifetime achievement. In particular, cannabis misuse may explain a portion of the complex interplay between mental illness and suicidality. Individuals who have attempted suicide show structural and functional brain changes similar to those found in cannabis users. Moreover, high rates of cannabis use are common among individuals suffering from any mental disorders. For example, data from the NESARC study indicated that rates of cannabis use and cannabis use disorder among individuals with 12-month mental illness were 9.9 and 4.0%, respectively, as compared with 1.6 and 0.4% among individuals without any mental illness. In particular, the likelihood of having a cannabis use disorder for individuals with 12-month mental illness was over three times higher, after adjusting for sociodemographic characteristics and other substance use disorders. Potential effects of cannabis on suicidality have been analysed in different mental disorders, including major depression, anxiety, bipolar, and psychotic disorders. Consistently, toxicology reports have shown high cannabis rates amongst suicide decedents by non-overdose methods, and chronic, heavy cannabis use has been found to be associated with suicidal ideation, attempt, and completion. A relatively recent meta-analysis estimated that chronic cannabis use could predict suicidality. In particular, cannabis use was associated with any suicidal behaviours, including suicidal ideation (Odds ratio [OR] = 1.43; 95% Confidence Interval [CI]: 1.13-1.83), suicide attempts (OR = 2.23; 95% CI: 1.24-4.00), and suicide death (OR = 2.56; 95% CI: 1.25-5.27). Nevertheless, the lack of homogeneity in the measurement of cannabis exposure and, at least partially, of systematic controlling for known risk factors, temper these findings. Consistently, a systematic review of epidemiological evidence on adverse effects of cannabis use, has pointed out that it is still unclear whether a regular cannabis use may increase the risk of death, including it due to suicide. An epidemiological understanding is certainly required to clarify the nature of the clinical relationship between cannabis use and suicidal behaviours, as well as significance, consistency, and strength of this association. In particular, epidemiological research has attempted to establish whether a causal relationship may be postulated, clarifying the role of associated psychopathology, common among both cannabis users and suicidal individuals. In addition, it should be clarified whether certain mediators or moderators (the so-called third factors) might better explain the association between cannabis use and suicidal behaviours. These clinical, environmental, genetic factors may have an independent effect on both behaviours, thus confounding and influencing the association. In this paper, we provide a narrative overview on the potential association between cannabis use and suicidal behaviours. In particular, we review findings of main longitudinal studies published in this field, discussing possible psychopathological models that may explain and disentangle this clinical relationship.

Methods
We conducted a narrative review including main population-based longitudinal studies. Studies had to analyse the direction of the association between cannabis use and any suicidal behaviours (suicidal ideation, attempts, completion), as well as the possible interplay of this relationship on individual psychopathological characteristics. We excluded studies selecting only special populations, such as individuals with mental disorders or those with substance use disorders. We searched on PubMed for articles written in English and indexed during the last 10 years (ranging from January 2008 to May 2018). Our search strategy included the following terms: (Cannabis or Marijuana) and (Suicide or Suicidal) and (Longitudinal or Cohort or Prospective).

Results
Our search strategy identified a preliminary pool of 80 studies. Among these, seven longitudinal studies analysing the association between cannabis use and different suicidal behaviours, met our inclusion criteria. We found that most of studies reported a significant association between cannabis use and subsequent suicidal behaviours. An integrative analysis of participant-level data from three large, long-running, longitudinal studies conducted in Australia and New Zealand tested the association between the maximum frequency of cannabis use before the age 17 and various young adult psychosocial sequelae, including suicide attempts. After adjustment for confounders, daily cannabis users during adolescence had an increased odds of suicide attempts (adjusted OR = 6.83; 95% CI: 2.04 to 22.90), along with
other adverse outcomes, including reduction in school proficiency and risk of cannabis dependence or other illicit drugs use. Moreover, data from the Young in Norway longitudinal study, a population-based sample of 2,033 individuals followed up over a 13-year period, from their early teens to their late twenties, showed that exposure to cannabis by itself, though not leading to depression, was associated with later suicidal thoughts and attempts. Consistently, the Mexican Adolescent Mental Health Survey, estimating the prospective associations between substance use and incident suicide-related behaviours, showed that an early and a high frequency of cannabis use were associated with both suicide ideation and attempt. In addition, data gathered over the course of the Christchurch Health and Development Study, based on 938 individuals born in an urban region of New Zealand, estimated that using cannabis several times a week led to suicidal ideation in susceptible males, though, suicidal ideation did not lead to cannabis use in either males or females. Gender differences were found also from waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) based on 31,549 participants. This study showed that daily cannabis use was associated with an increased incidence of suicidality among men (adjusted OR = 4.28; 95% CI: 1.32 to 13.82), but not among women (adjusted OR = 0.75; 95% CI: 0.28-2.05). On the other hand, suicide ideation or attempts were associated with subsequent cannabis use among women (adjusted OR = 2.34; 95% CI: 1.42 to 3.87) but not among men (adjusted OR = 1.10; 95% CI: 0.57 to 2.15).

Other studies did not show any relationship between cannabis use and suicidal behaviours. The prospective cohort of the Collaborative Study of the Genetics of Alcoholism (COGA), based on 3,277 individuals, reported that an early cannabis use was unrelated to the onset of suicidal ideation or suicide attempt. Similarly, no effect of suicidal ideation or suicide attempt on the onset of cannabis use was found. In addition, an important longitudinal study investigating more than 50,000 men conscripted for Swedish military service, found 600 cases of suicides or deaths from undetermined causes at a 33-year follow-up. Findings showed that, despite a crude effect of cannabis use on risk of suicide was found (crude OR = 1.62; 95% CI: 1.28 to 2.07), this association was not confirmed after adjustment for relevant confounders (adjusted OR = 0.88; 95% CI: 0.65 to 1.20). The authors concluded that it is unlikely that cannabis use – either directly or because of mental health problems – may have a strong effect on completed suicide risk. Although there was a significant association between cannabis use and suicide, this relationship was likely to be attributable to correlated psychological and behavioural features.

Discussion

Summary and interpretation of findings

Over the years, epidemiological evidence has produced conflicting results, making it complex to identify a valid and reliable clinical model for subjects who use cannabis and have a greater risk of suicide ideation or attempt. In this narrative review, we pointed out that cannabis may be associated with increased rates of suicidal behaviours, despite mixed findings are available from different longitudinal studies. Heterogeneity of findings across studies could obviously involve methodological differences, in terms of study design, index population, follow-up duration, assessment methods. In addition, it should be considered that, in terms of toxicology, cannabis is a complex compound, with different active agents (phytocannabinoids) leading to various psychotropic effects. Delta-9-tetrahydrocannabinol (THC) explains most of the psychotopic and psychotomimetic effects of cannabis, while cannabidiol (CBD) may have anxiolytic, mood stabilizing, and antipsychotic effects. For this reason, future, prospective, cohort studies should benefit from specific biochemical analyses of different phytocannabinoids concentration to clearly characterize possible dose-response effects between cannabis use and adverse outcomes, including suicidality. Moreover, epidemiological research did not consider different methods for cannabis consumption, e.g., joints, bowls, bongs, edibles or drinks, despite these may potentially impact on related acute and chronic effects of cannabis, as well as on patterns of drug use. Thus, the lack of a sufficient amount of longitudinal studies taking into account cannabis potency and routes of administration does not allow estimating these factors could influence the individual risk of suicide. Consistently, the possible role of cannabis legal status as an environmental factor that can prevent or shape life consequences for cannabis users should be considered. Country-level legalization or prohibition of cannabis represent key environmental factors that may influence outcomes of cannabis use, including those related to mental health and risk of suicide. Legislation changes in several countries may thus provide “natural” experiments on the effects of general population exposure to cannabis, giving the unique opportunity to monitor the related effects on mental health. Studies that attempted to analyse the relationship between country-level cannabis legalization/prohibition and rates of suicide, can be taken as an example of this approach. A relatively recent study estimated the association between cannabis use and completed suicide, showing that the legalization of medical cannabis does not affect suicide rates. No association between the number of “medical cannabis” registrants (used
as a proxy measure of cannabis use) and completed suicide was found after controlling for multiple known, potential confounders. Consistently, relatively recent data from the National Vital Statistics System’s Mortality Detail Files, analysed pre- and post-legalization trends in US states where medical cannabis was legalized. After adjustment for economic conditions, state policies, and state-specific linear time-period trends, the association between legalizing medical cannabis and suicides was not statistically significant. However, suicide rates decreased after medical cannabis legalization as compared with states that did not legalize it. In particular, although estimates for women were less precise, legalization was associated with a significant suicide rate reduction among men aged 20 to 29 years and those aged 30 to 39 years, respectively.

**Psychopathological implications**

Despite epidemiological research produced mixed results and the lack of sufficient evidence to support the hypothesis of an independent role of cannabis on suicide risk, it is important to identify psychopathological models that may at least partially explain the perceived association found in crude models. Subjects misusing cannabis may have an increased risk of psychopathological conditions, possibly leading to a higher risk of suicidal behaviours (suicidal ideation, suicide attempt, completed suicide). On the other hand, cannabis use may be the consequence of pre-existing clinical conditions, independently correlated with increased suicidality. Cannabis, along with alcohol and other substances, may represent one of the facilitators of the clinical progression from non-structured suicidal thoughts to emergent suicide ideation and attempts. Recent findings actually support the hypothesis that cannabis users are vulnerable to perceived burdensomeness and thwarted belongingness, preliminarily confirming that difficulties in interpersonal functioning may serve as potential pathways through which daily cannabis use may lead to greater suicide risk.

From a clinical perspective, it should be considered that different psychopathological links may explain the interplay between cannabis use and suicidal behaviours (Fig. 1).

First, subjects experiencing depressive features, particularly those with pre-existing dysthmic traits or experiencing hopelessness, may use cannabis to relieve symptoms. This perspective is certainly consistent with the self-medication hypothesis, postulating that

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**FIGURE 1. Relationship between cannabis use and suicidal behaviours: psychopathological models.**

[Diagram showing the relationship between cannabis use and suicidal behaviours, including depressive symptoms, psychotic features, impulsivity, and parasuicidal traits.]
individuals may use illicit substances in order to relieve symptoms such as affective dysregulation, apathy, and anhedonia. According to this model, cannabis use would occur in a context of self-regulation vulnerability and individual difficulties in controlling subjective emotions, affects, relationships, and self-care. Moreover, a relationship between cannabis use and suicidal behaviours has been highlighted in subjects with additional risk factors, including stressful life events, interpersonal problems, poor social support, lonely lives, and feelings of hopelessness. This can represent the first step of a vicious circle in which cannabis use might impair, regardless of temporary improvement, depressive symptoms, increasing the degree of anhedonia and apathy. It has been reported that subjects with lifetime depression, under the influence of cannabis, more often experience sadness, anxiety and paranoia, being less likely to report happiness or euphoria. Consistently, negative symptoms are considered key features of depression in cannabis users, characterizing the so-called “amotivational syndrome”, which combines affective flattening and loss of emotional reactivity.

In particular, hopelessness may represent the most important clinical and psychopathological mediator of the complex interplay between depression, suicide risk and cannabis use. Nevertheless, evidence that cannabis use itself may independently trigger depressive symptoms are only partially convincing. For example, a three-year-follow-up longitudinal study, including 8,598 Swedish men and women, aged 20-64, did not show any association between cannabis use and incidence of depression/anxiety. Consistently, a recent longitudinal study showed that in mid-adolescence, anhedonia – an important psychopathological trait indicative of inability to experience pleasure and linked with suicide-related behaviors - might be correlated with subsequent increase of cannabis use, despite, conversely, cannabis use did not appear to be associated with subsequent anhedonia. On the other hand, a recent study reported that the monozygotic twin using cannabis was more likely to report both major depression and suicidal ideation, as compared with twin who used cannabis less frequently. Nevertheless, it has been argued that cannabis use is probably related to both depression and suicidal behaviours, through a constellation of mechanisms, involving genetic predisposition as well as social and environmental factors.

In particular, shared genetic influences seem to underlie the association of early-onset cannabis use with both depression and suicidality. Second, psychotic symptoms also play a role as potential mediators of the clinical association between cannabis use and suicidal behaviours. Both neurobiological models and epidemiological evidence support the role of cannabinoids as a possible risk factor for psychosis, showing that cannabis might influence, in a dose-dependent manner, the onset of schizophrenia and other psychotic disorders. A concomitant increase in the severity of positive symptoms can be expected as an acute and chronic effect of THC, inducing psychotomimetic symptoms, delusions and auditory hallucinations, which may be the core signal of suicidal risk in individuals suffering from psychotic disorders. Consistently, a relatively recent meta-analysis has shown that a continued cannabis use after the psychosis onset, may predict, along with other adverse outcomes, more severe positive symptoms as compared with individuals who discontinued cannabis use or never used it. In addition, cannabis can have an indirect effect on the overall symptoms’ severity and on the individual suicide risk, since cannabis use is one of main determinants of medication non-adherence. A third important element is the effect of cannabis on impulsivity. It is known that elevated impulsivity may facilitate the transition from suicidal thoughts to suicidal behaviours. Consistently, cannabis use is associated with changes in impulse control and hostility in daily life. Despite the unsolved issue as to whether impulsivity is a trait preceding cannabis consumption or, the other way, cannabis itself exacerbates impulsivity, reduced prefrontal volumes and differences in white matter integrity have been identified in cannabis users. This might explain the likelihood of impulsive and non-planned suicidal attempts in subjects with mental disorders misusing cannabis. Indeed, data from two community-based twin samples from the Australian Twin Registry showed that cannabis use is associated with unplanned suicide attempts, but not with planned ones, even after controlling for other substance use disorders. Finally, illicit substance use is common among subjects with personality disorders, especially antisocial and borderline ones. Recent cross-sectional data from the Norwegian Institute of Public Health Twin Study of Mental Health showed that subjects with antisocial or borderline personality disorders are more likely to use cannabis or suffering from a cannabis use disorder. In particular, it has been shown that the shared genetic risk between depression and cannabis dependence may be largely explained by genetic effects of antisocial personality disorder. Thus, the clinical relationship between cannabis use and suicidality in some personality disorders can be considered a false association, since both substance use and suicidal tendencies are likely to be direct consequences of individual traits, rather than linked through a causal or bidirectional relationship. In addition, it should be considered that individuals with personality disorders might be vulnerable to parasuicidal behaviours and manipulative/impulsive
suicidal threats and/or gestures, with low lethality and lack of medical consequences, rather than suicidal behaviours. 

Conclusions
Over the years, disentangling psychopathological issues underlying the relationship between co-occurring substance use disorders and behaviours has represented a key challenge of research in psychiatry. Despite mixed findings deriving from main epidemiological evidence, our review shows that cannabis use may be clinically associated with an increased risk of suicide. However, the various mechanisms as well as contributing factors to this association remain to be clarified. Cannabis seems to have a role in the complex clinical pathways that link mental disorders and suicide-related behaviours. Cannabis may influence or trigger psychopathological features associated with increased suicidality. The association between cannabis use and suicidal behaviours may be due to an impairment on depressive symptoms, psychotic features, and impulsivity, which may have bidirectional links with cannabis use. In addition, personality traits and characteristics may independently cause both cannabis use and suicidal behaviours, thus determining a false association. Nevertheless, it is likely that the psychopathological relationship between cannabis use and suicidal behaviours cannot be explained by a single clinical model, even taking into account the possible role of overlapping genetic influences. Future research should consider the possible association between increasing potency of cannabis and suicidality, the potential anxiolytic, antidepressant, antipsychotic effects of CBD, as well as the possible influence of various routes for cannabis consumption.

Conflict of Interest
The authors have no conflict of interest to declare.

References


Hypersexuality: the controversial mismatch of the psychiatric diagnosis

Summary
Hypersexuality is characterized by intrusive fantasies and thoughts regarding sex, excessive sexual behaviours, and the inability to control one’s own sexuality, resulting in an impairment of relational and social life. While several clinical histories and empirical research consider hypersexuality as a disorder, the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not include hypersexuality as a psychopathological category in se. This has generated controversy among clinicians and researchers and a mismatch with the 11th revision of the International Classification of Diseases (ICD-11). However, different theoretical models are related to hypersexuality, i.e. the compulsivity model, the impulsivity model and the addiction model. This paper addresses the psychopathology of hypersexuality, including treatment and related comorbid conditions.

Key words
Hypersexuality • Comorbidity • Treatment • ICD-11 • DSM-5

Introduction
Sexual behaviour represents a fundamental aspect of human life, mainly involving pleasure, reproduction and couple relationships. Sexual physiology consists of several phases according to the gender and problems can occur in some cases. The most common sexual problems are erectile dysfunction and premature ejaculation in males and anorgasmia or sexual pain in females 1. In some cases, the main cause of a sexual impairment is hypoactive sexual desire disorder, i.e. lack of libido, that causes a decrease of sexual activity. On the contrary, hypersexuality includes excess of sexual activities, the obsession toward sex and its consequences. Hypersexual behaviours include excess of compulsive masturbation, pornography, sexual behaviour with consenting adults, cybersex or telephone sex use and strip clubs attendance 2.

In the last years, the debate was on whether to include hypersexuality within the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), with some proposals based on diagnostic criteria, but to date the psychiatric nosography has not considered hypersexuality a mental disorder per se. On the contrary, the World Health Organization has recently proposed to include hypersexuality within the last version of the International Classification of Diseases (ICD-11) as a disorder of sexual compulsive behaviour (compulsive sexual behaviour disorder, CSBD) 3. This generates a mismatch and controversy for the clinical and diagnostic praxis. Is hypersexuality a disorder for psychiatrists and clinical psychologists? In 2010, prominent American psychiatrist M.P. Kafka proposed the criteria to detect hypersexuality 4, but the American Psychiatric Association (APA) still does not include this condition as a category of mental disorder, although the debate is currently open 5. However, the impossibility to diagnose hypersexuality according to DSM-5 criteria does not mean that this condition does not exist, since several empirical data
and the clinical practice demonstrate a large pathologi-
cal spectrum characterizing this particular sexual con-
dition 6. The aim of the current paper is to highlight the
main theoretical models and the state of art of hyper-
sexuality in the field of psychopathology.

Theories of hypersexuality
Theoretical debate concerning the hypersexuality
started with Freud’s psychoanalytic theories. In par-
ticular some authors in this field discussed about the
relationship between life instinct and death instinct in
sexual addiction 7. From this perspective, hypersexual/
addicted subjects attempt to antagonize depressive
states and death anxiety with the life instinct through
sexual activities, although in a deregulated way. Hence,
hypersexual behaviours can be bona fide considered a
defensive behaviour against death anxiety 8.

However, other theoretical models were developed
based on different aspects leading to hypersexual dis-
order: the compulsive sexual behaviour, the sexual im-
pulsivity, and the sexual addiction.

Compulsivity model
Coleman described and defined hypersexuality as a
compulsive sexual behaviour through a parallelism
with the phenomenology of obsessive-compulsive dis-
order (OCD), characterized by repetitive and intrusive
thoughts and then the repetition of sexual experiences.
These experiences are described by an increase of
arousal before – and a decrease after – a sexual act 9.

According to this model, thoughts and images consti-
tute the obsession, while the acting constitutes the com-
pulsion. However, this psychopathological mechanism
in hypersexuality is ego-syntonic 6.

Impulsivity model
According to this model, the hypersexual behaviour is
due to the failure to resist to sexual drive, and to the
incapacity to delay the sexual gratification 6. Based on
the impulsivity model, the hypersexuality is thus caused
by impulse dyscontrol, although this proposal has been
largely criticized. Many hypersexual subjects, in fact,
carefully plan their sexual activities and behaviours.
Moreover, the reward system related to the pleasure ex-
perience would reinforce the hypersexual behaviour 10.

However, according to some studies, sexual impulsivity
and sexual compulsivity are factors characterizing hy-
persexuality together and not separately 10.

Addiction model
The addiction model is considered the most valid to ex-
plain the hypersexual disorder. The parallelism between
hypersexuality and the common addiction disorders
was made in the past 11. The symptomatology concerns
the increase of sexual activity together with the devel-

opment of the disorder, while abstinence symptoms as
depression, anxiety, and blame are associated to the
decrease of sexual conducts 11. Moreover, as in other
forms of addiction, hypersexual subjects spend a par-
ticular amount of time looking for novel sexual partners
and compromise their social and relational life, without
taking into account potential negative consequences as
the sexually transmitted diseases.

ICD-11 versus DSM-5
The categorial approach towards mental disorders re-
gards both the ICD and the DSM classifications, how-
ever the ICD proposed to include hypersexuality as a
condition in its last version (ICD-11). Hypersexuality has
an estimated prevalence of 2-6%, with males being the
most affected 12 13. This high prevalence, in absence of
specific diagnostic criteria, drove some clinicians and
epidemiologists to categorize and propose hypersexu-
ality as a distinct disorder. In particular, the World Health
Organization proposed to describe hypersexuality as a
compulsive sexual behaviour disorder (CSBD), describ-
ing it in the ICD-11 as follows:

Compulsive sexual behaviour disorder is characterized
by a persistent pattern of failure to control intense, re-
petitive sexual impulses or urges resulting in repetitive
sexual behaviour. Symptoms may include repetitive
sexual activities becoming a central focus of the per-
son’s life to the point of neglecting health and personal
care or other interests, activities and responsibilities;
numerous unsuccessful efforts to significantly reduce
repetitive sexual behaviour; and continued repetitive
sexual behaviour despite adverse consequences or
deriving little or no satisfaction from it. The pattern of
failure to control intense, sexual impulses or urges and
resulting repetitive sexual behaviour is manifested over
an extended period of time (e.g., 6 months or more),
and causes marked distress or significant impairment
in personal, family, social, educational, occupational, or
other important areas of functioning. Distress that is en-
tirely related to moral judgments and disapproval about
sexual impulses, urges, or behaviours is not sufficient to
meet this requirement 14.

Moreover, an additional controversial aspect is the posi-
tion of CSBD among the impulse control disorders to-
gether with pyromania, kleptomania and intermittent ex-
ploding disorder, as also the various substance impulse
control disorders 14. According to the ICD-11 classifica-
tion, the only conditions to be excluded when diagnos-
ing CSBD are paraphilic disorders. The ICD-11 made
also a further specification concerning the terminology:
hypersexuality or hypersexual disorder is better defined
as compulsive sexual behaviour disorder.
On the other hand, hypersexuality was considered for inclusion as a psychiatric disorder within the section of sexual dysfunctions of the DSM-5. The DSM-5 Working Group on Sexual and Gender Identity Disorders proposed possible detailed criteria. Also in this case, as for the ICD-11, the clinicians of DSM-5 considered the possible differential diagnosis with paraphilic disorders. Both ICD-11 criteria as putative DSM-5 criteria isolate hypersexuality from paraphilias. However, hypersexuality is not a pathological category of DSM-5 for several reasons, including insufficient evidence, studies or clinical trials on hypersexual subjects, and the potential misuse of this delicate diagnosis in forensic settings.

Hypersexuality and comorbid disorders

Hypersexuality is very often present along with different comorbid disorders, that make the diagnostic process more complex and question the official nosography. In fact, hypersexual disorder was found in comorbidity with other psychiatric and physical conditions, particularly in males, such as anxiety and mood disorders, substance use disorder, attention-deficit hyperactivity disorder (ADHD) 

Moreover, some studies, and that hypersexuality correlates with narcissistic, borderline, antisocial, avoidant, obsessive-compulsive, and passive-aggressive personality disorders; a high comorbidity with paranoid personality disorder was also found. To make the differential diagnosis, it is necessary to distinguish hypersexuality from paraphilic disorders. Comparing to paraphilias, hypersexual subjects and hypersexual behaviours do not concern inanimate objects, animals, parts of the body, etc. However, paraphilic patients can also develop hypersexual disorder along with elements of compulsivity, obsession and distress. Finally, hypersexual behaviours should also be distinguished from other medical conditions, neuropsychi-
atric diseases, neurodegenerative disorders and from iatrogenic effects of some medications. 

**Treatments**
Following the idea of hypersexuality as a mental disorder, some possible treatments can be considered along the pharmacological and psychotherapeutic continua. The first includes the noradrenergic and serotoninergic reuptake inhibitors, or simply selective serotonin reuptake inhibitor. On the other hand, also opiate agonists were experimentally verified for compulsive sexual behaviour in a retrospective study. Psychological therapies for hypersexuality are mainly follow cognitive-behavioural approaches, although psychodynamic psychotherapy focused on trauma and the family of origin have also been considered useful. Moreover, different styles of group or couple therapy were also found to be useful. Mindfulness has proven to be effective in people seeking help for hypersexual behaviour. In any case, it is also important the treatment of comorbid conditions, such as substance abuse, mood and anxiety disorders. This aspect represents a crucial point to take into account for the treatment of hypersexual subjects.

**Conclusions**
If most of social media recently claimed that “hypersexuality is a mental disorder that regards the compulsive sexual behaviour”, based on our article the issue remains controversial. The psychiatric community sees the hypersexuality as a pathological condition, and different psychological treatments were empirically proven. Therefore, many psychiatrists and clinical psychologists prompt to include hypersexuality in the psychiatric nosography, although some doubts still persist. The first doubt concerns the differential diagnosis. Is hypersexuality an isolated disorder? Or the sexual addiction is a consequence of another mental disease, as manic phases of bipolar disorder or the effect of substance abuse? The compulsive sexual behaviour can be considered a psychotic sign or the onset of a first episode of psychosis in the young while an iatrogenic effect of Parkinson’s therapy in the elderly. However, these comorbid conditions could be considered into the diagnostic process to detect a primary diagnosis excluding the other consequent pathologies.

In other words, if hypersexuality is not better accounted for by another mental disorder, it could be considered a category per se. This is the case of many mental diseases as addiction and eating disorders. In this regard, when two pathologies are present together, we talk of dual diagnosis. Therefore, it is crucial to take into account the concept of dual diagnosis involved also in hypersexual disorder when we adopt a categorial diagnostic method.

In conclusion, we believe that when individuals use sex, sexual behaviour and sexual activities as a therapy for another disorder, such as anxiety or depression, that could be considered as an index of discomfort. In the same manner, when a subject suffering from a specific mental disorder, such as bipolar disorder or schizophrenia, the hypersexual behaviour can be considered a manifestation of those primary diagnoses. If APA will include hypersexuality as a disorder, it is important to define a criterion that clearly specifies whether the disorder is present alone or in comorbidity, as it has been partially proposed. On the other hand, many theories and hypothesis try to explain the origin and the correct definition of hypersexuality according to different approaches, although all studies conclude that more research and clinical studies are necessary to be able to categorize hypersexuality as a specific disorder.

**Conflict of Interest**
The authors declare no conflict of interest.
Hypersexuality: the controversial mismatch of the psychiatric diagnosis


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